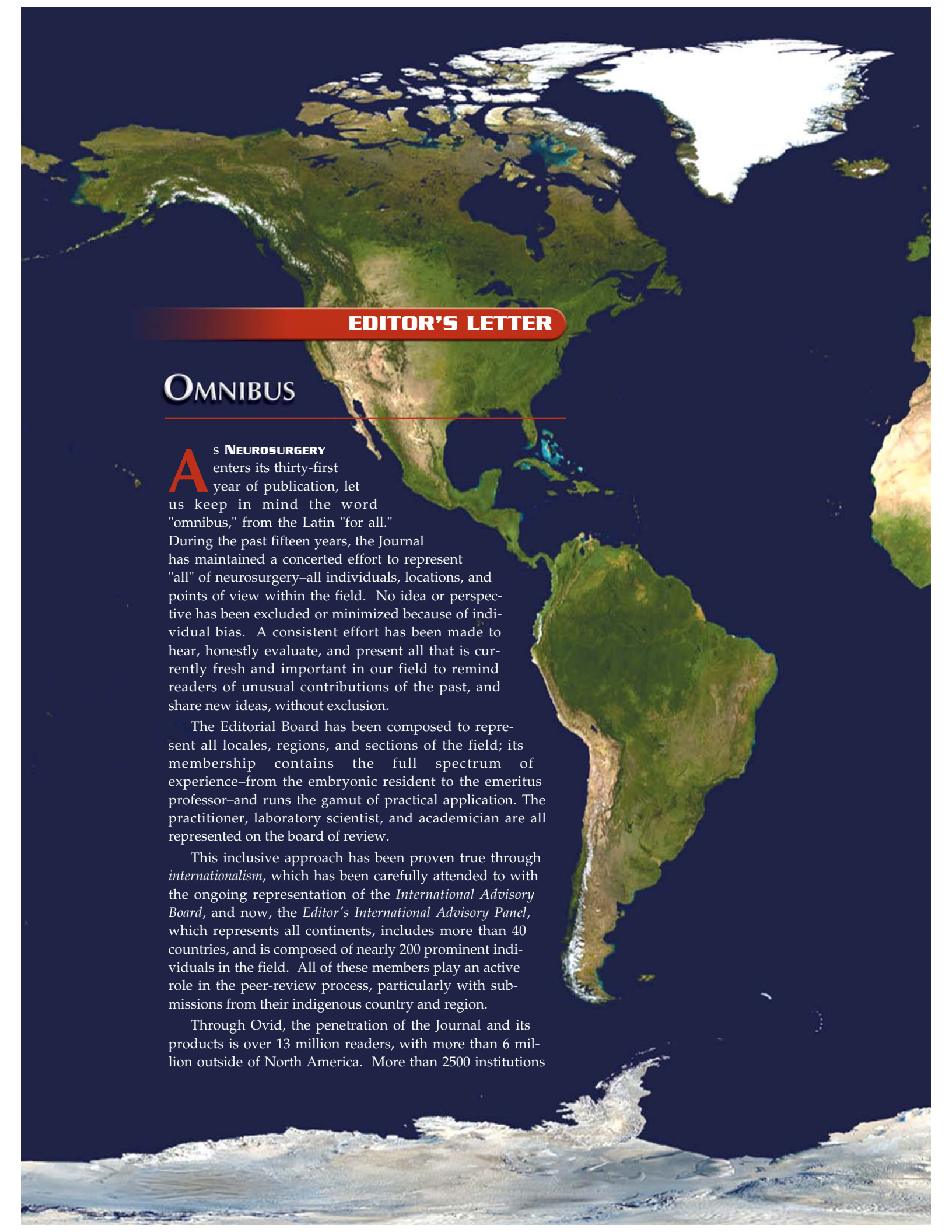


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OMNIBUS

2008 ANNUAL MEETING INSIDE
CNS Joint Meeting with the
Brazilian Society of Neurosurgery



EDITOR'S LETTER

OMNIBUS

As **NEUROSURGERY** enters its thirty-first year of publication, let us keep in mind the word "omnibus," from the Latin "for all." During the past fifteen years, the Journal has maintained a concerted effort to represent "all" of neurosurgery—all individuals, locations, and points of view within the field. No idea or perspective has been excluded or minimized because of individual bias. A consistent effort has been made to hear, honestly evaluate, and present all that is currently fresh and important in our field to remind readers of unusual contributions of the past, and share new ideas, without exclusion.

The Editorial Board has been composed to represent all locales, regions, and sections of the field; its membership contains the full spectrum of experience—from the embryonic resident to the emeritus professor—and runs the gamut of practical application. The practitioner, laboratory scientist, and academician are all represented on the board of review.

This inclusive approach has been proven true through *internationalism*, which has been carefully attended to with the ongoing representation of the *International Advisory Board*, and now, the *Editor's International Advisory Panel*, which represents all continents, includes more than 40 countries, and is composed of nearly 200 prominent individuals in the field. All of these members play an active role in the peer-review process, particularly with submissions from their indigenous country and region.

Through Ovid, the penetration of the Journal and its products is over 13 million readers, with more than 6 million outside of North America. More than 2500 institutions



have licenses to the **NEUROSURGERY-ONLINE** platform, which is robust and truly international with millions of international visits per year.

At this time, more than sixty percent of the several thousand yearly submissions to **NEUROSURGERY** are from outside of North America, with publication rates for international authors being approximately the same as those from their North American colleagues. Review of each issue's table of contents shows the flavor of internationalism that has been established in the Journal.

In the past decade, I have represented the Journal in virtually every continent and world region, and it is apparent that, with a number of exceptions, as the world is flattening, so too is neurosurgery in the intellectual sense. Through the convenience of air travel, the presence of international journals, international meetings, and the Internet, information is being made readily available to all and ideas are flourishing and being universally shared. Thus, there is both an information deluge and a knowledge revolution.

Economics play a key role in local and regional availability of "modern" capabilities, but knowledge and the appreciation of the current status of the field is moving rapidly toward universality.

In this evolving process, the Journal's theme is and will remain "omnibus": for all, representing all, and involving all who wish to participate. I am convinced that this policy is largely responsible for the great success and popularity the Journal currently enjoys.

Michael L.J. Apuzzo
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MESENCHYMAL STEM CELL AND GENE THERAPIES FOR SPINAL FUSION

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THE IDEAL GRAFT material to promote spinal fusion should possess osteoconductive, osteoinductive, and osteogenic properties. Although autogenous bone graft has all three qualities and is the standard for comparison, research has focused on finding alternatives that have similar efficacy but not the morbidities associated with graft donor sites. Efforts have focused on various osteoconductive scaffolds and introduction of osteoinductive proteins, including bone morphogenetic protein. Recently, interest in using osteoprogenitor cells, or osteogenesis, for spinal fusion has increased. Bone marrow aspiration allows the introduction of mesenchymal stem cells and ultimately osteoblasts to promote fusion. Preclinical studies suggest that the addition of osteoprogenitor cells to various osteoconductive materials results in a fusion rate similar to that of autograft. There is growing recognition that local gene therapy has the benefit of delivering therapeutic genes that encode novel osteoinductive proteins. Gene delivery offers an alternative to local implantation of recombinant protein, which typically requires high doses of the protein to result in a sufficient osteoinductive response. The findings of animal studies demonstrate that gene therapy results in sustained and regulated production of desired osteoinductive proteins and is efficacious in promoting spinal fusion; however, before treatment in humans can be undertaken, obstacles such as the safety profile, host immune response, transfection rates with insufficient transgene expression, and imprecise control of the timing of transgene expression must be overcome. In this review, the authors summarize the latest research efforts under way to promote spinal fusion with osteoprogenitor cells and gene therapy and discuss the clinical implications of these treatments.

KEY WORDS: Bone morphogenetic protein, Gene therapy, Mesenchymal stem cells, Osteogenesis, Spinal fusion

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Molecular biology research into spinal fusion demonstrates that this process is complex and multifactorial (53). Growing knowledge of molecular and cellular biology provided by in vitro and animal models has provided new targets to promote fusion (42, 53). Typically, harvesting of iliac crest (IC) bone and decortication at the site of the future fusion is the standard to promote fusion. This process has been very successful because autologous bone graft has the osteoconductive, osteoinductive, and osteogenic properties necessary to promote fusion (7). An ideal graft material demonstrates each of these properties: an osteoconductive material that serves as a scaffold or matrix for bone growth; an osteoinductive agent that induces bone growth by growth factors or proteins that recruit and stimulate osteoblasts to form bone;

and an osteogenic capacity that results in new bone growth directly by osteoblast cells (7).

Recently, advances reported in the spine literature have identified new graft materials as alternatives to the standard of harvesting IC bone graft (ICBG) to avoid the donor site morbidities commonly reported in as many as 30% of patients (31, 53). The most common complication of ICBG harvesting is postoperative pain at the donor site; patients may also describe local tenderness and localized sensory loss (22, 75). In one series of 300 patients undergoing anterior or posterior ICBG harvesting, IC morbidity, including pain (52 patients), wound dehiscence (8 patients), meralgia paresthetica (4 patients), hematoma requiring evacuation (3 patients), and iliac spinal fracture (2 patients), occurred in 25.3% of the patients (80). In addition to these complications, Silber et al. (83) also described reports of ambulation difficulty, extended antibiotic use, and persistent drainage in their large series of patients. Similarly, in two large series of patients requiring anterior or posterior ICBG harvest-

ABBREVIATIONS: IC, iliac crest; ICBG, iliac crest bone graft; BMP, bone morphogenetic protein; MSC, mesenchymal stem cell; VB, vertebral body; DNA, deoxyribonucleic acid

ing, 38 to 41% of patients reported pain 6 months postoperatively, and 19 to 31% of patients continued to report pain more than 2 years postoperatively (29, 79).

Although newer graft materials avoid the complications of IC donor site morbidity, they must demonstrate equivalent or better rates of fusion to ultimately replace this standard. Allograft materials possessing osteoconductive and osteoinductive qualities are well described. Varied osteoconductive scaffolds have been studied, including collagen and bioabsorbable carriers, demineralized bone matrix, hydroxyapatite, and calcium phosphate ceramic materials (47, 81, 85). These graft materials are combined with osteoinductive or osteogenic components or both to result in fusion. Similarly, osteoinductive proteins have received significant attention, as studies have shown great efficacy and fusion rates similar to or better than those associated with ICBG with the use of bone morphogenetic protein (BMP) (17, 23, 47, 61, 85). A recent meta-analysis of randomized clinical trials that compared the use of BMP with traditional methods for spinal fusion concluded that BMP offered a slightly but statistically significantly greater efficacy than traditional techniques when clinical and radiological outcomes were evaluated (61). Although the greater operative expense of BMP was initially used as an argument against its widespread use (16, 28, 71), cost-analysis studies comparing the use of BMP with use of ICBG have shown that the overall expense over a longer term is similar (1, 28, 71). Preliminary results suggest that the upfront price of BMP is likely entirely offset by reductions in the use of other medical resources (1, 28, 71), including those for the prevention of pain and complications associated with autogenous IC bone graft, and reduction of the costs associated with fusion failures (1).

With the increasingly widespread use of BMP for spinal fusion, further demonstrations of efficacy compared with the alternatives (including ICBG), and the potential for reduced costs as a result of advancing manufacturing technologies and market forces, the use of BMP has the potential to become the standard for spinal fusions. However, some limitations associated with the use of BMP need to be resolved. For example, high doses of BMP are currently used to produce significant osteoinduction because a single dose may not induce a sufficient response in all patients (68). The adverse reactions associated with the use of BMP, including those related to inflammation and soft tissue edema, may occur in a dose-dependent manner (4). The recombinant growth factors currently approved for human use have been associated with local inflammatory reactions including postoperative radiculitis (78) and soft tissue edema in the lumbar spine and clinically significant postoperative neck swelling with its use for anterior cervical fusion (4, 16, 52, 67, 82, 84, 86). BMP has also been frequently associated with heterotopic bone formation, and there are examples of bone growth in the spinal canal contributing to symptomatic neurological findings (52, 91). Although there is agreement that BMP results in an increased incidence of heterotopic bone formation with and without epidural compression for posterior spinal fusions, there is not a consensus in the literature about whether this is always clinically important (32, 40, 91).

Other reported complications with the use of BMP include vertebral osteolysis after posterior lumbar interbody fusion (50) and significant graft subsidence with interbody fusions, resulting in a loss of graft structural support (87). The fusion rate with BMP is high, but it has only been approved and demonstrated safe by the United States Food and Drug Administration for very specific lumbar spinal fusion procedures. For example, BMP-2 is approved only for anterior lumbar fusion in conjunction with lordotic threaded cages, and there is a significant amount of off-label use (91). Also, the current method of BMP delivery with an osteoconductive scaffold is not ideal for a minimally invasive percutaneous injection. Overall, issues concerning BMP use include postoperative inflammation and edema, hyperostosis, osteoclast activation (76), the need to further define dosing to promote fusion and minimize adverse reactions, and the need to improve bioavailability with new carriers and delivery methods. Thus, there remain limitations associated with the use of BMP, suggesting the need to explore the use of alternative growth factors, other delivery methods with more regulated dosing, and autologous cells promoting osteogenesis.

Recently, the study of gene- and stem cell-based therapy has expanded, and researchers have found that both have potential benefits that may overcome some of the limitations described above and may enable them to become viable alternatives. The use of adult mesenchymal stem cells (MSC) for bone regeneration has gained focus because multipotential cells can be isolated from various sources, including bone marrow and adipose and muscle tissues, and can be differentiated into the osteogenic lineage to promote bone fusion (26, 33, 38, 44, 81). Another strategy for bone fusion includes the delivery of genetically manipulated cells or vectors that express therapeutic levels of osteoinductive proteins for set time periods to enhance bioavailability and limit the adverse effects of overdosing (44).

Researchers have expanded their exploration of the use of autologous osteoprogenitor cells for spinal fusion. New products for use in humans combine bone marrow aspirate containing these osteoprogenitor cells with an osteoconductive matrix (8, 46, 63). Unfortunately, these treatments have not been widely successful because fresh bone marrow aspirate that has not undergone any treatment or culturing is not as effective at promoting osteogenesis because of low numbers of MSCs and osteoprogenitor cells (13, 14, 19–21, 30). Thus, new methods are being developed to increase the number of osteoprogenitor cells to promote spinal fusion (30, 43, 45, 57, 58). Overall, studies of stem cells in humans are in the early stages (27), although a growing number of reports demonstrate the benefits of osteoprogenitor cells for spinal fusion in preclinical models, as discussed in this review.

As mentioned above, local gene therapy is another new approach for spinal fusion (11), in which the goal is to deliver therapeutic genes that encode novel osteoinductive proteins, resulting in appropriate levels of protein to facilitate fusion. Gene delivery offers an alternative to local implantation of osteoinductive proteins because it is difficult to deliver an adequate amount of protein in a single dose, and high and uncontrolled doses may be associated with increased adverse reac-

tions (4). In humans, larger amounts of recombinant protein and longer periods of action are needed to achieve fusion than in lower animals (10). Gene therapy allows the continuous expression of osteoinductive proteins in target cells for either short or long periods. Research into gene therapy for spinal fusion remains in the preclinical stage, but studies demonstrate its efficacy with several different genes and modes of gene delivery.

In this review, we summarize the latest research efforts under way to promote fusion with osteoprogenitor cells and gene therapy. Although several reviews have been published in the past 10 years on the use of MSCs (13, 14, 20, 35, 81) or gene therapy (18, 69, 77, 92) for spinal fusion, there has been continued research progress in these areas in the past several years, and this article reviews these important studies. This article is a current and comprehensive review that will aid the busy spine surgeon in understanding the biology, clinical implications, and current limitations of the use of MSC and gene therapy for the promotion of spinal fusion.

OSTEOGENESIS

Researchers have begun targeting bone marrow to take advantage of the benefits of osteogenesis to improve spinal fusion. Specifically, MSCs have been targeted because of their capacity to differentiate into different cells, including those in the osteogenic lineage. The osteogenic potential of bone marrow was described by Burwell (15) in 1964 and Friedenstein et al. (25) in 1968, and today it is well known that bone marrow contains two populations of pluripotent progenitor cells: hematopoietic stem cells, which give rise to all circulating blood elements, and MSCs, which are capable of differentiating into bone, cartilage, tendon, and muscle.

In clinical practice, bone marrow aspirates used to enhance spinal fusions are obtained from the IC more often than from the vertebral body (VB) (74). VB bone marrow, however, is readily available at the operative site and takes less time to obtain, can be easily collected (i.e., during pedicle screw preparation), does not require a separate incision, and avoids the donor site morbidity associated with IC and bone graft harvesting. Risbud et al. (74) evaluated the osteogenic potential of cells taken from these two sites on operative patients. Compared with IC marrow, VB marrow had a higher frequency of progenitor cells and higher alkaline phosphatase activity, which represents osteogenic differentiation. Progenitor cells isolated from both locations responded in a similar manner to osteogenic stimuli and expressed common immunophenotypes and antigens of cells committed to the osteogenic phenotype. The authors concluded that progenitor cells from the lumbar VB exhibit a similar osteogenic potential and would be suitable for osseous graft supplementation for spinal fusion procedures. McLain et al. (55) also compared the aspiration of marrow from the VB and IC from patients undergoing posterior lumbar fusion; progenitor cell concentrations were a statistically significant 71% higher at the VB than at the IC in matched controls. There was no difference associated with most other variables, including VB level, side aspirated,

depth of aspiration, or sex, but there was an age-dependent decline in cellularity for IC aspirates.

Interestingly, the number of MSCs in bone marrow is very low and is estimated at 1 per 100,000 of all cells present in the marrow (14). Thus, fresh bone marrow that has not undergone any treatment or culturing is not as effective at promoting osteogenesis because of low numbers of MSC and osteoprogenitor cells (13, 14, 19–21, 30, 62). Additionally, improper aspiration technique, including not changing the position of the needle or aspirating more than 2 mL of bone marrow from a single location, results in increased dilution with whole blood (45, 57).

One strategy that has been used in the clinical environment is the use of selective cell retention to increase the number of MSCs that can be delivered from a bone marrow aspirate. This technique relies on an affinity column to select anchorage-dependent (osteogenic) cells while allowing hematopoietic cells to pass through, resulting in a severalfold increase in the number of osteoprogenitor cells compared with that in native bone marrow (30, 45, 57, 58). In canine models of lumbar fusion, selective cell retention has resulted in concentrations of MSCs that are two- to threefold greater in a graft matrix than when the unconcentrated bone marrow aspirate alone is used (58, 59). The result was a higher fusion rate and greater fusion volume in animals with grafts enriched with concentrated bone marrow aspirates when compared with animals receiving bone graft alone or graft with unconcentrated aspirate. The benefit of this technique is that it can increase the number of osteoprogenitor cells at the time of surgery without the need for weeks of cell culturing. One method for selective retention of connective tissue progenitors has been made clinically available in the Collect Graft Preparation system (Dupuy, Raynham, MA), although no clinical outcomes have been published on this technique (55).

Another strategy to increase the number of osteoprogenitor cells is to purify and culture-expand MSCs from animals and humans. Cell culture *ex vivo* can result in a significant increase in the number of progenitor cells, and these can be used as graft material to promote bony fusion (14, 56). It may also be necessary to induce and differentiate the MSCs into osteogenic osteoblasts with the addition of osteogenic factors before implantation to form bone tissue *in vitro* and *in vivo* (9, 39, 41, 54, 56, 65). Studies confirm that culture-expanded animal and human bone marrow osteoprogenitor cells contribute more effectively than freshly prepared marrow to the repair of segmental defects in cortical bone (13, 14, 19–21, 30, 58, 62). However, culture expansion adds costs and has risks such as contamination as well as the obvious need for additional time to grow the cultures.

As a recent example, Nakajima et al. (62) demonstrated that osteogenic differentiation of MSCs was more effective at promoting fusion than use of undifferentiated MSCs (see *Table 1* for a summary of animal studies using MSC therapy to promote spinal fusion). They investigated the effectiveness of graft material for spinal fusion using a rabbit posterolateral spinal fusion model. The lumbar spine was harvested, and the fusion mass was evaluated radiographically, by a manual palpation test, and by histological analysis at 6 weeks after surgery.

TABLE 1. Animal models of mesenchymal stem cells for spinal fusion^a

Series (ref. no.)	Animal	Type of fusion	Graft material	Final evaluation	Fusion rate	Observations
Nakajima et al., 2007 (62)	Rabbit	Posterolateral lumbar spine	MSCs that were cultured for osteogenic differentiation compared with undifferentiated MSC and IC autograft	6 wk	Fusion achieved in osteogenic MSC (4/5, 80%), MSC (2/6, 33%), and IC autograft (4/6, 67%)	Osteogenic MSC and IC resulted in new mature bone formation as observed histologically, while undifferentiated MSC resulted in less mature bone growth
Minamide et al., 2005 (56)	Rabbit	Posterolateral lumbar spine	Collagen gel + HA particles + differentiated bone marrow cells from IC (100 versus 1 million) compared with autologous IC graft (control)	6 wk	100 million cells resulted in solid bone formation (5/7, 71%), 1 million cells resulted in no fusion (0/7, 0%), control group (4/7, 57%)	Critical number of osteoprogenitor cells are needed for bone formation, similar fusion rate for 100 million bone marrow cells and standard IC
Kai et al., 2003 (41)	Rabbit	Interbody lumbar spine	Calcium phosphate ceramic + bone marrow stromal-derived osteoblasts compared with autologous IC graft (control)	3 mo	Solid fusion in experimental group (6/6, 100%), control group (4/6, 67%)	Fusion masses in the experimental group were significantly stronger with biomechanical testing and with increased bone formation on histological analysis
Wang et al., 2005 (89)	Rhesus monkeys	Interbody lumbar spine	Calcium phosphate ceramic + osteoblast-induced MSC compared with autologous IC graft (control)	3 mo	Fusion in experimental group (4/6, 67%), control group (5/6, 83%)	MSC bone volume was significantly lower, but there was no difference in biomechanical stiffness, poorer fusion in the MSC group due to reduced potential for bone regeneration in primates and low density of cells
Gupta et al., 2007 (30)	Sheep	Posterolateral lumbar spine	Tricalcium phosphate + osteoprogenitor cells using SCR compared with autologous IC graft (control)	6 mo	Fusion in experimental group (33%), control group (25%)	Histology of fused samples showed denser bone formation in the SCR-enriched grafts than in the controls
Cui et al., 2001 (21)	Athymic rats	Posterolateral lumbar spine	Collagen gel + cloned osteoprogenitor cells from mouse bone marrow or mixed marrow cells	6 and 9 wk	Spinal fusion in animals receiving cloned cells (8/8, 100%), 4/8 (50%) in mixed marrow cells	Compared with mixed marrow cells, cloned osteoprogenitor cells produce a larger amount of mature osseous tissue at an earlier time point

^a MSC, mesenchymal stem cell; IC, iliac crest; HA, hydroxyapatite particles; SCR, selective cell retention technology.

Fusion was achieved in four of five rabbits in the osteogenic differentiated MSC group, two of six in the undifferentiated MSC group, and four of six in the autologous group. In the osteogenic MSC and autograft groups, new bone formation was observed histologically, whereas in the undifferentiated MSC group, less mature bone formation was present in the grafted fragments. Overall, MSCs that have been cultured with osteogenic differentiation medium are more effective in the formation of new bone in experimental spinal fusion.

In another rabbit model of posterolateral lumbar spinal fusion, Minamide et al. (56) demonstrated that the number of differentiated MSCs is also relevant to achieve spinal fusion. The authors cultured fresh bone marrow cells from the IC of each animal for 2 weeks in a standard medium and for 1 week in dexamethasone, Type I collagen gel, and porous hydroxyapatite particles. These cells were later used as graft material (with the collagen gel and hydroxyapatite particles), resulting in high-quality bone fusion (at 6 wk). It has been shown that

exposure to or culturing with porous hydroxyapatite particles or dexamethasone enhances the differentiation of MSCs into osteogenic cells (55, 74). In this study (56), implantation of greater numbers of bone marrow cells (100 million) resulted in solid fusion with mature bone formation in five of seven animals, whereas implantation of fibrous tissue containing only 1 million bone marrow cells resulted in no fusion (0 of 7), illustrating that a critical number of osteoprogenitor cells must be present for fusion (54, 56, 74).

Results from several other animal studies support the idea that osteogenic MSCs from cultured bone marrow cells combined with an appropriate delivery vehicle (osteoconductive bone graft substitute) may serve as an alternative to autogenous bone grafting, with equivalent or better rates of spinal fusion (19, 30, 41, 65, 74). The autologous graft was from the IC in all of these studies. In the study described above (56), fusion with cultured bone marrow cells occurred at a similar rate (5 in 7) to fusion with autologous bone (4 in 7). Kai et al. (41) demonstrated in a rabbit lumbar intervertebral fusion model that use of bone marrow stroma-derived osteoblasts combined with a porous calcium phosphate ceramic composite resulted in successful fusion in 100% of animals (6 of 6 animals) compared with 66.6% of animals (4 of 6 animals) receiving autograft at 12 weeks. Also, fusion masses in the animals implanted with the bone marrow stroma-derived osteoblasts were statistically significantly stiffer and stronger on biomechanical testing and had a qualitative increase in bone formation on histological analysis compared with those of animals in the allograft group.

Further studies have been undertaken in larger animals with similar results. Some authors have argued that more studies are needed in larger animals that more closely resemble humans (primates) because of the diminished potential for bone regeneration compared with phylogenetically lower animals (89). Wang et al. (89) showed comparable fusion rates for a rhesus monkey interbody fusion model for osteoblast-induced MSC-calcium phosphate ceramic composite (4 of 6 animals, 66.6%) compared with autogenous bone graft (5 of 6 animals, 83.3%) at 3 months. In contrast to the results of other studies, the bone volume for the MSC group was significantly lower than that of the autograft group, but there was no significant difference in biomechanical stiffness. The worse fusion in the MSC group in this study was attributed to the diminished potential for bone regeneration in primates compared with lower animals as well as the low density of cell suspension. Gupta et al. (30) found equivalent fusion rates for osteoprogenitor-enriched tricalcium phosphate (33%) compared with autogenous bone graft (25%) in a sheep posterolateral lumbar spine model, but in this study, the osteoprogenitor group produced denser bone. The authors noted that the overall low fusion rate for the osteoprogenitor group may have been due to the low number of osteoprogenitor cells (30).

As mentioned above, studies demonstrate that the presence of high numbers of osteoprogenitor cells enhances bone formation. Thus, in the clinical setting, higher cell densities may be required to promote bone fusion (89). Options to meet this increased need include use of the selective cell retention method or other new technologies, aspiration of more bone

marrow from several locations, improvement of cell culture, or use of allogeneic MSCs (89). Allogeneic cells provide a readily available source of cells that survive transplantation, recipients demonstrate good immunological reconstitution, and the cells can be used without need for immunosuppressant therapy (9, 39, 41, 89).

Osteogenesis by the differentiation of cloned osteoprogenitor cells is an alternative to ex vivo expanded marrow cells that may be more effective (21). In a study by Cui et al. (21), D1-BAG osteoprogenitor cells, which were cloned from a mouse bone marrow cell, combined with mixed marrow stromal cells were most efficacious in producing posterior spinal fusion (in eight of eight rats tested) at 6- and 9-week observation intervals. The D1-BAG cells are pluripotent and capable of osteogenesis, and unlike MSCs, they are cloned from a single cell. Mixed marrow stromal cells alone and controls resulted in fusions in 4 (50%) of 8 cases and 0 (0%) of 8 cases, respectively. The authors noted that, compared with mixed marrow stromal cells alone, cloned osteoprogenitor cells produced a larger amount of mature osseous tissue, resulted in earlier bone growth, and underwent osteogenesis without a cartilaginous phase (21). In contrast, fresh marrow and culture-expanded stromal cells, which contain chondrogenic and osteogenic cells, repair bone defects by endochondral ossification (7, 21).

Although the bone marrow is the best source of MSCs, it is thought that other locations in the body contain stem cells capable of osteogenic differentiation (81). For example, subcutaneous adipose tissue is a readily available source of multipotential stromal cells (33). Adipocytes can share common functions with stromal stem cells, osteoblasts, and hematopoietic supportive cells and function directly in osteoblastic lineages (26). When adipose tissue-derived stromal cells are exposed to osteogenic factors, they display osteoblastic gene markers and mineralize their extracellular matrix (33). Other cell types, including periosteal and muscle cells, have also been used to induce bone formation (38, 89).

Overall, the results of these studies suggest that osteoprogenitor cells may result in a solid bone fusion at a similar rate as autograft. Not surprisingly, the results were not as great in larger animals, likely because of diminished potential for bone regeneration compared with phylogenetically lower animals. More studies are needed in animals that more closely resemble humans (primates). Additionally, development of techniques to maximize the number of osteoprogenitor cells in an efficient manner at the time of surgery will be one important issue in making these research protocols clinically feasible and efficacious in humans. An ideal and clinically practical treatment with MSCs would need to maximize the number of osteoprogenitor cells at surgery without the need for cell culturing or a separate surgery for cell harvesting. Other potential options would be to obtain somatic cells in a minimally invasive fashion before surgery that can be "reprogrammed to pluripotency with defined factors" (66), differentiated to the osteogenic lineage, and cultured as needed for use at the time of surgery. Allogeneic cells remain an option, but, as mentioned above, it is also possible to use non-bone marrow multipotential stromal

cells, including those from subcutaneous adipose tissue, that are capable of osteogenic differentiation, can be harvested and cultured before surgery, or can be harvested at the time of surgery. The use of cloned mesenchymal cells also appears to be an appealing method to promote osteogenesis without the need for additional procedures. Overall, in addition to demonstrating efficacy in promoting fusion at a rate similar to rates of the alternatives, these techniques will need to demonstrate that they are safe in humans before widespread clinical use. Currently, MSCs are being evaluated in clinical trials for multiple indications, including amyotrophic lateral sclerosis, lysosomal storage diseases, corticosteroid-refractory graft-versus-host disease, myocardial infarction, osteogenesis imperfecta, and periodontitis (27), which will help establish their safety profile in humans.

GENE THERAPY

Local gene therapy is another new treatment approach for spinal fusion (11) in which the goal is to deliver therapeutic genes that encode novel osteoinductive proteins that result in adequate levels of protein for bone formation. It is possible to deliver the genes with MSCs, thus increasing the chance of fusion with osteogenic cells. Gene delivery offers an alternative to local implantation of osteoinductive proteins and thereby avoids the difficulty of delivering an adequate amount of recombinant protein in a single dose, as well as the side effects associated with the current use of larger doses. Because the response to bone protein is dose dependent, a minimum threshold must be overcome before bone formation is induced. Further difficulties in humans are the need for larger amounts of recombinant protein and longer time of exposure for fusion to occur than in lower animals (10). Gene therapy allows the continuous or regulated expression of osteoinductive proteins in target cells for either short or long periods. In animal studies comparing the use of recombinant BMP protein with BMP-producing marrow cells, bone formation from the transduced bone marrow cells has been more robust (51, 90).

Vectors used for gene therapy include naked deoxyribonucleic acid (DNA), liposomes, and plasmids, which contain the complementary DNA of the gene of interest, or viral vectors, which have much higher transduction efficiencies (68). Typically, the nonviral vectors including plasmids maintain the DNA extrachromosomally and, thus, have a decreased risk of insertion into the host DNA. They also do not have the immunological problems associated with many viral vectors, but they have low in vivo transfection efficiency. The most commonly tested viral delivery vehicle for gene therapy for bone healing has been the adenovirus, which is very efficient in cell transfection to a variety of cells (68). Recombinant adenoviral vectors can be produced at high levels, infect a variety of cell types, and maintain more genetic material than other viruses. In these vectors, the transgene remains episomal, meaning that the therapeutic gene expression is stopped when the genetically modified cell divides; thus, the protein is expressed only when it is needed and not indefinitely. Because the adenovirus is highly immunogenic, however, some

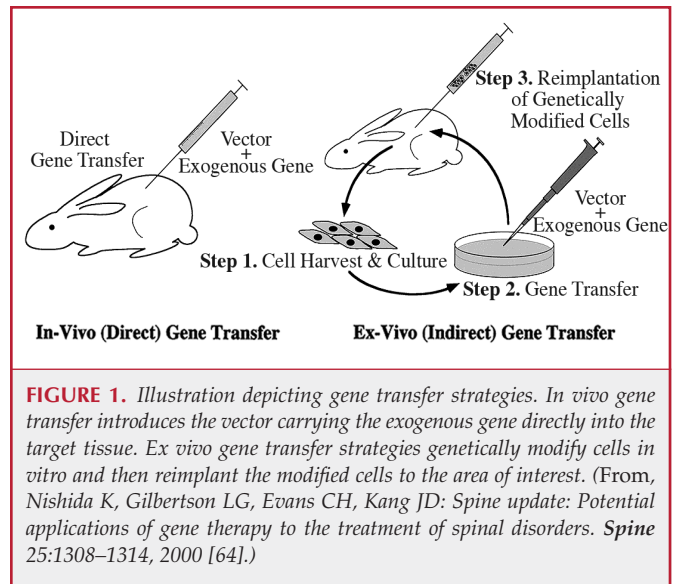


FIGURE 1. Illustration depicting gene transfer strategies. *In vivo* gene transfer introduces the vector carrying the exogenous gene directly into the target tissue. *Ex vivo* gene transfer strategies genetically modify cells *in vitro* and then reimplant the modified cells to the area of interest. (From, Nishida K, Gilbertson LG, Evans CH, Kang JD: Spine update: Potential applications of gene therapy to the treatment of spinal disorders. *Spine* 25:1308–1314, 2000 [64].)

immune responses can actually remove the transduced cell, which decreases gene expression. Newer formulations of adenovirus vectors have undergone removal of many viral antigens to minimize this challenge. For localized gene therapy, either an *ex vivo* or an *in vivo* approach can be used (Fig. 1). *Ex vivo* approaches are ideal because they allow selection of the cell that is transduced (and thus delivery of a carrier, an osteogenic cell, and osteoinductive proteins), they have higher rates of transduction, and no viral or DNA complexes are directly injected (less antigenic) into the host. This should result in less of an inflammatory and immune response. Of note, some of the gene therapies with BMP have resulted in significant bone growth or fusions only in immunosuppressed rats, and this result may be attributable to the host animals' immune response (36, 60). Interestingly, in the studies described below, there were no descriptions of animals undergoing gene therapy demonstrating signs of systemic or local toxicity or a clinically relevant immune response.

Bone growth and spinal fusion with *ex vivo* gene therapy has been demonstrated in several rat studies. Dumont et al. (24) percutaneously injected athymic rats in the paraspinous region with human MSCs transduced *ex vivo* with recombinant, replication-defective adenovirus containing *BMP-9* (*Ad-BMP-9*) or a control gene (see Table 2 for summary of animal studies using gene therapy to promote spinal fusion). Both radiological and histological analysis demonstrated large volumes of bone and fusion after *Ad-BMP-9*-transduced MSC injection. This treatment is unique because it did not require the addition of osteoconductive agent or allograft bone for fusion. In another example of *ex vivo* gene therapy, Peterson et al. (68) placed human bone marrow cells infected with *Ad-BMP-2* on a collagen sponge on the spines of athymic mice and obtained 100% fusion (eight of eight). A 100% fusion rate was also found by Hasharoni et al. (34), who injected MSCs that conditionally expressed *BMP-2* under the control of tetracycline into athymic

TABLE 2. Animal models of gene therapy for spine fusion^a

Series (ref. no.)	Animal	Location and mode of implantation	Graft material	Final evaluation	Fusion rate	Observations
Dumont et al., 2002 (24) ^b	Athymic rats	Percutaneous injection in the paraspinal region	Human MSCs transduced ex vivo with adenovirus containing <i>BMP-9</i> or a control gene	8 wk	Spine fusion (16/16, 100%), control (0/0, 100%)	Both CT and histological studies demonstrated large volumes of bone at the <i>BMP-9</i> injection sites
Peterson et al., 2005 (68)	Athymic mice	Implantation at posterolateral lumbar spine	Collagen sponge with 5 million HBMCs transduced with adenovirus containing <i>BMP-2</i> or control gene	12 wk	Spine fusion (8/8, 100%), control (0/15, 0%)	Fusion confirmed with radiographic evaluation, manual palpation, and histology.
Hasharoni et al., 2005 (34) ^b	Athymic mice	Implantation at paraspinal muscles at posterior lumbar spine	MSCs genetically engineered to conditionally express rhBMP-2 under the control of tetracycline	8 wk	Bone formation seen at 4 weeks, increasing further by 8 weeks. A minimum of 7 days of <i>BMP-2</i> expression was necessary for bone formation.	Bone formation was followed by CT and histological studies. There was more bone volume formation with longer duration of <i>BMP-2</i> expression.
Hidaka et al., 2003 (37)	Rats	Implantation at posterior lumbar spine	Bone marrow cells genetically modified by Ad vector-encoding BMP-7 or control gene on an allograft scaffold	8 wk	With <i>Ad-BMP-7</i> , there was radiologic fusion in 70% and mechanical fusion in 80% of animals, and no fusion (0%) in the controls	Fusion masses showed normal trabecular bone and resulted in decreased range of motion
Boden et al., 1998 (11)	Athymic rats	Implantation into the posterior thoracic and lumbar spine	Transfected bone marrow cells with the plasmid, <i>pCMV2-LMP-1</i> or control gene with a devitalized bone matrix	4 wk	Fusion was (9/9, 100%) rats receiving marrow cells with active <i>LMP-1</i> , and (0/0, 0%) with marrow cells without active <i>LMP-1</i>	Fusion evaluated by manual palpation, radiographs, and nondecalcified histology
Riew et al., 1998 (73) ^b	Rabbits	Implantation into intertransverse lumbar spine	Adenoviral vector carrying the human BMP-2 gene to transduce marrow-derived mesenchymal stem cells	NA	Production of new bone formation (1/5, 20%).	Demonstrable on both radiographic and histologic examination
Lee et al., 2006 (49)	Rabbits	Implantation into intertransverse lumbar spine	Kidney cells transfected with <i>CMV-BMP2</i> vectors with transfected cells encapsulated and suspended in a fibrin scaffold	12 wk	(6 rabbits; 4 fused, 67%, 2 moderate bone growth, 33%), No fusion with the same cells and surgical gelatin sponge	Fibrin gel is a biocompatible and biodegradable matrix that can encapsulate the transfected cells and adhere to the spine for effective gene therapy
Viggeswarapu et al., 2001 (88)	Immuno-competent rabbits	Implantation into posterolateral lumbar spine	Carrier matrix with bone marrow cells transfected with adenovirus <i>LMP-1</i> or a control gene	5 wk	All of the animals (10/10, 100%) with <i>Ad-LMP-1</i> induced a solid, fusion mass, control without the <i>LMP-1</i> gene induced no bone formation (0/10, 0%)	Biomechanical and histological testing of the <i>Ad-LMP-1</i> -treated specimens revealed findings that were consistent with a high-quality spinal fusion

(continues)

TABLE 2. Continued

Series (ref. no.)	Animal	Location and mode of implantation	Graft material	Final evaluation	Fusion rate	Observations
Riew et al., 2003 (72) ^b	Pigs	Implantation into anterior thoracic disc space	Mesenchymal stem cells isolated and expanded in culture, and transduced with an adenovirus with <i>BMP-2</i> gene or a control gene	6 wk	Anterior spinal fusion (6/6, 100%) in the disc spaces treated with <i>Ad-BMP2</i> transduced stem cells, (0/6, 0%) in the six control disc spaces	Fusion determined by CT and histological examination; histological examination demonstrated bridging bone from end plate to end plate in <i>BMP-2</i> group
Helm et al., 2000 (36) ^c	Athymic rats	Percutaneous injection into lumbar paraspinal musculature	In vivo (without cells) injection of <i>BMP-9</i> adenoviral vector	16 wk	Massive bone growth in all animals (100%)	CT and histological analysis demonstrated massive bone induction leading to solid spinal arthrodesis, without nerve root compression or side effects
Alden et al., 1999 (2) ^c	Athymic rats	Percutaneous paraspinal injection at the lumbosacral junction	In vivo injection of <i>BMP-2</i> adenoviral vector or same vector with a control gene	12 wk	Fusion on all sites treated with <i>Ad-BMP-2</i> (100%) and 0% with control gene	Ectopic bone formation on CT and histological examination in all sites treated with <i>Ad-BMP-2</i> . Bone seen adjacent to the spinous processes, laminae, and transverse processes.
Lu et al., 2007 (52) ^d	Athymic rats	Implantation at posterolateral intertransverse process lumbar spine	Open implantation of DBM carrier with adenovirus coding for <i>Nell-1</i> (<i>Ad-Nell-1</i>) or a control gene	6 wk	<i>Ad-Nell-1</i> in a DBM carrier had significantly higher rates of spinal fusion over controls: 70% vs. 20% by palpation, CT, and histology	Histological assessment of bone quality and maturity revealed more mature, higher quality bone in all the <i>Nell-1</i> treated specimens relative to controls
Zhu et al., 2004 (93) ^d	Immuno-competent rats	Implantation at posterolateral lumbar spine	Allograft plus adenovirus vectors encoding <i>BMP2</i> and <i>BMP7</i> or, as controls, each vector alone	8 wk	Coadministration of <i>Ad-BMP-2</i> and <i>Ad-BMP-7</i> resulted in a significantly greater number of mechanically stable fusions (73% compared with 8% for <i>BMP2</i> alone and 16% for <i>BMP7</i> alone)	Coadministration resulted in a twofold higher mineralization rate and bone volume in the fusion mass compared with single <i>BMP</i> gene transfer
Bright et al., 2006 (12) ^d	Immuno-competent rats	Percutaneous injection of posterolateral and interbody lumbar spine	Delivery of plasmid carrying <i>BMP-7</i> DNA with collagen compared to <i>BMP-7</i> protein injection	4 wk	Bone formation occurred after the delivery of <i>BMP-7</i> plasmid DNA and collagen (50-75%), but was less frequent than with injection of <i>BMP-7</i> protein and collagen (100%)	Bone formation was evaluated by manual palpation, radiographs, and histology. Lower fusion rates were due to the low dose of plasmid and low protein production
Laurent et al., 2004 (48) ^c	Immuno-competent rabbits	Percutaneous injection of intertransverse lumbar spine	Adenoviral vector containing <i>BMP-6</i> gene or control gene	14 wk	Solid fusion at the site of <i>Ad-BMP-6</i> injection (4/5, 80%), controls with no fusion (0/5, 0%)	Fusion confirmed with gross inspection, histopathological, and CT. Anatomically precise fusion can be accomplished by percutaneous administration of gene therapy

^a HBMC, human bone marrow cell; MSC, mesenchymal stem cell; rhBMP-2, recombinant human bone morphogenetic protein-2; Ad, adenovirus; BMP, bone morphogenetic protein; CT, computed tomography; DBM, demineralized bone matrix.

^b Cells with osteoconductive scaffold.

^c In vivo gene therapy without use of cells or scaffold.

^d In vivo gene therapy without use of cells but with scaffold.

mice. This study is valuable because it demonstrates a method to control the duration of *BMP* expression. The authors found bone formation at 4 weeks, which increased further by 8 weeks. A minimum of 7 days of *BMP-2* expression was necessary for bone formation, and there was more bone volume formation with longer duration of *BMP-2* expression.

Hidaka et al. (37) placed bone marrow cells modified with an adenovirus vector encoding *BMP-7* and an allograft at a site of posterior fusion in rats. Marker gene expression was maximal on Day 3, was present at Day 7, and returned to background levels by Day 14. With *Ad-BMP-7* treatment, there was radiological fusion in 70% and mechanical fusion in 80% of animals, whereas there was no fusion (0%) in the controls with allograft without the addition of the *BMP-7* gene or without the addition of bone marrow cells. Fusion masses showed normal trabecular bone and resulted in decreased range of motion. This study shows that *BMP-7* is expressed when it is needed and has a predictable end point.

Boden et al. (11) transfected bone marrow cells with the plasmid *pCMV2-LMP-1* (LIM mineralization protein-1 gene, which encodes for an intracellular protein that induces the expression of several bone growth factors including BMPs) and implanted the cells with a devitalized bone matrix into the thoracic and lumbar spine of athymic rats. High-quality spinal fusion was obtained in 9 (100%) of 9 rats receiving marrow cells with active *LMP-1*, whereas 0 (0%) of 9 rats (4 with lumbar implants and 5 with thoracic implants) had fusion with bone matrix and marrow cells without active *LMP-1*. *LMP-3* is also under investigation, and in vivo and in vitro studies suggest that it promotes new bone formation more vigorously than *BMP-2* (70). Targeting the *LMP* genes is ideal because they produce an intracellular protein and thus circumvent limitations seen with secreted and extracellular osteoinductive factors. It also results in the expression of multiple different BMP proteins.

Similar ex vivo gene therapy studies have been performed in rabbits. Riew et al. (73) used adenoviral vector carrying the human *BMP-2* gene to transduce marrow-derived MSCs in rabbits, resulting in some bone growth without clear fusion. Lee et al. (49) demonstrated spinal fusion (6 rabbits; 4 fused, 2 moderate bone growth) using kidney cells transfected with *CMV-BMP-2* vectors in rabbits only when the transfected cells were encapsulated and suspended in a fibrin scaffold, whereas no fusion occurred when the cells were delivered on a fibrin sponge. The authors noted that fibrin scaffold is a natural matrix, is easily obtained from patients, allows cells to adhere to the spine, provides cell support for incorporation of new cells, and may be ideal for gene therapy.

Viggeswarapu et al. (88) studied the *LMP-1* gene, which produces an intracellular protein that results in the expression of several osteoinductive proteins. They implanted a carrier matrix with bone marrow cells transfected with adenovirus *LMP-1* in immunocompetent rabbits. In all the animals (100%) that had received cells infected with *Ad-LMP-1*, a solid, continuous spinal fusion mass was induced at 5 weeks, whereas in the controls without the *LMP-1* gene, little or no bone formation was induced. Of note, when peripheral blood cells were

used instead of bone marrow cells and a collagen-ceramic composite sponge was used as the carrier, fusion still occurred in all cases (100%). The findings of biomechanical and histological testing of the *Ad-LMP-1*-treated specimens were consistent with a high-quality spinal fusion. In comparison to studies with BMP and adenovirus, the use of *Ad-LMP-1* in this study involved a much smaller dose of adenovirus (100,000 times less), required very short infection times (10 min), and did not require MSC or culture expansion. Thus, the authors noted that this procedure is performed easily and rapidly and could be completed in the operating room.

Riew et al. (72) described the use of *Ad-BMP-2*-transfected autologous MSCs for anterior intradiscal fusion in 3 pigs. After thoracoscopic discectomy, MSCs transfected with *Ad-BMP-2* were injected into 2 disc spaces on each pig. All 6 treatment levels demonstrated fusion, with continuous bone from endplate to endplate, whereas the controls did not have bone growth. Histological examination demonstrated bridging bone from endplate to endplate in all 6 disc spaces that had been treated with implantation of *Adv-BMP2*-transduced stem cells, whereas the 6 control disc spaces had no bridging bone. Overall, the study demonstrated that the *Ad-BMP2*-transduced MSCs produced BMP-2 protein and induced anterior spinal fusion in all disc spaces in this pig model. The authors noted that, although many technical and practical challenges remain, it may eventually be possible to use similar techniques to achieve anterior spinal fusion in humans.

In contrast to many of the studies mentioned above, the authors of several studies describe direct injection (in vivo) of adenovirus or plasmid with encoded genes without any cells and with or without the use of an osteoconductive scaffold. Helm and Gazit (35) directly (percutaneously) injected *Ad-BMP-9*, and Alden et al. (2) injected *Ad-BMP-2* into athymic rats, relying on vector transfection of host cells (in vivo gene therapy). Bone growth was demonstrated in all animals in both studies. Lu et al. (52) evaluated a novel osteoinductive growth factor, *Nell-1*, which acts more specifically on osteoblasts than BMPs (which affect other cells), is regulated by a gene controlling bone formation, and accelerates osteogenic differentiation. Athymic rats underwent an open fusion with *Ad-Nell-1* and demineralized bone matrix, and after 6 weeks, direct injection of *Ad-Nell-1* resulted in a statistically significantly higher rate of fusion (70%) than the same implant without the *Nell-1* gene (20%). Histological evaluation revealed mature, higher-quality bone in the treatment group.

Interestingly, Zhu et al. (93) found that coadministration of *Ad-BMP-2* and *Ad-BMP-7* resulted in a significantly greater number of mechanically stable fusions (73% compared with 8% for *BMP-2* alone and 16% for *BMP-7* alone) and also a twofold higher mineralization rate and bone volume in the fusion mass compared with single *BMP* gene transfer. They implanted immunocompetent rats with allograft and hemostatic foam with adenovirus vectors encoding *BMP-2* and *BMP-7* or each separately. They also found that combined gene transfer accelerates osteoblastic differentiation in vitro. The poor fusion rate with individual *BMP* genes may have been due to a host immune response in the immunocompe-

tent animal, which has been shown to interfere with *Ad-BMP*-mediated bone formation or to the lack of presence of osteoprogenitor cells. Similarly, combining *BMP-2* and *BMP-7* may have overcome these effects. Bright et al. (12) evaluated in vivo nonviral transfection of host cells including muscle cells with plasmid carrying *BMP-7* complementary DNA in immunocompetent rats with a collagen carrier. Although bone formation resulted with *BMP-7* plasmid DNA with collagen, no single-level fusions occurred, and the authors noted that this was likely because the dose of plasmid was too low and protein production was inadequate. Finally, in a rabbit model of spinal fusion, Laurent et al. (48) directly injected *Ad-BMP-6* percutaneously into immunocompetent animals, and four of five demonstrated a solid fusion at the site of *Ad-BMP-6* injection at 14 weeks.

In conclusion, preclinical studies demonstrate that gene therapies have the ability to deliver osteogenic molecules to precise anatomic locations at therapeutic levels for sustained periods of time (5). Both in vivo and ex vivo transduction of cells can induce bone formation (5). Some hurdles must be overcome, however, before these treatments can be clinically applicable in humans. The ability to circumvent the host immune response, to develop adequate transfection rates resulting in sufficient transgene expression, and to have appropriate control of the timing of transgene expression must all be developed (3). Further preclinical testing will be needed to directly compare the different osteoinductive genes and methods of gene delivery including cell type or vector and determine the effective doses for bone formation and the safest treatment option for humans. The most clinically appealing treatments, in vivo gene therapies, bypass the need for cell harvesting and in some cases do not require an osteoconductive scaffold to induce fusion. Ex vivo strategies would require two operative interventions and increased costs, whereas direct transfer of osteogenic genes offers an alternative that is more clinically expeditious (6). Interestingly, these treatments were often administered through a single, percutaneous injection to a precise location. Overall, regulating gene expression of an osteoinductive protein on a precise timeline, as needed for bone formation, and then turning off the expression to limit side effects is ideal and may offer a benefit over current implantation of osteoinductive proteins. Although gene transfer can produce therapeutic and sustained levels of osteoinductive proteins to achieve osteogenesis in a variety of animal models, the most important issue delaying the move from preclinical to human testing is safety, and issues regarding toxicity, cancer risk, and the influence on the host immune response will need to be fully explored and limited before clinical testing can begin.

CONCLUSIONS

Using osteoprogenitor cells and gene therapy for spinal fusion has shown benefit in preclinical evaluations. As with any animal study of fusion, however, the benefit of using these methods in humans may not be as great. Several studies suggest that humans may require increased numbers of osteoprogenitor cells and increased osteoinductive protein expression to

have the positive benefits seen in animals. More studies using osteoprogenitor cells and gene therapy are needed in larger animals, including primates, that more closely resemble humans. For osteogenesis-promoting procedures to become clinically applicable in addition to demonstrating safety, it will be necessary to develop techniques to rapidly increase the number of osteoprogenitor cells for implantation after bone marrow aspiration or to take advantage of other methods including cloned osteoprogenitor cells. Currently, gene therapy is further away from clinical testing, mostly because of issues regarding safety. Once gene therapy can be proven to be safe for use even for diseases, such as spine degeneration, that are not life threatening, it will also be necessary to overcome obstacles including the host immune response, transfection rates with insufficient transgene expression, and imprecise control of the timing of transgene expression.

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COMMENTS

Gottfried and Dailey provided a superb review of the state-of-the-art in progenitor cell and gene therapy treatment alternatives for spine fusion. They clearly outlined what we know and what we do not know regarding this potentially very productive area of laboratory and clinical research and clinical application. This review should provide the foundation from which to move forward in this new frontier.

Edward C. Benzel
Cleveland, Ohio

Gottfried and Dailey provided an excellent review of an important topic. Unfortunately, most efforts to improve the outcome after spinal fusion have failed; a nonunion rate of 15 to 20% is typically reported even with the use of fixation and iliac crest grafting.

In addition, an iliac crest graft is not always available and, furthermore, can be associated with morbidity. Simplifying techniques for obtaining bone healing, therefore, are important.

The use of bone marrow aspirate has been touted clinically, on the basis of preclinical studies. To date, I am unaware of any prospective or randomized trial demonstrating improved outcomes over iliac crest

bone grafting. However, there are several anecdotal reports indicating excellent results, and bone marrow aspirate is certainly associated with less morbidity than taking an iliac crest bone graft. Therefore, it will continue to be popular until proven otherwise.

Gene therapy, on the other hand, remains purely experimental. Again, clinical evidence of efficacy is uncertain at present. However, there is enough basic science literature to suggest that ultimately this may be a direction in which we go.

In the meantime, use of bone marrow aspirate using techniques described by Gottfried and Dailey certainly represents an effective alternative on the basis of the translational efforts reported. Furthermore, the authors have certainly presented avenues of future research and clinical effort.

I am sure that all of us involved in spine surgery will read this review very critically and will use it as a guide to monitor future developments.

Dennis Maiman
Milwaukee, Wisconsin

Gottfried and Dailey have nicely reviewed the current state of the art of osteobiological strategies for improving rates of bony arthrodesis, with a discussion on experimental genetic therapies to this end. Given the frequency of spinal fusions in the developed world, the review is timely and demonstrates the potential broad applicability of these strategies, in theory. There have certainly been a number of developments over the past decade that would make one less optimistic about the applicability of genetic therapies, at least in their current form. 1) The increasing use of a variety of bone morphogenetic proteins (BMP) has led to a general view that protein-based biological therapies can be highly effective in hostile local environments that would otherwise inhibit bone fusion. The large number of available molecules in the transforming growth factor- β superfamily will probably yield other candidates that will be used clinically. 2) This experience with existing BMPs has drawn attention to the significant costs associated with the use of expensive technology (sometimes rather wantonly), increasing medical treatment costs, and has produced associated scrutiny of the economics of surgical intervention. 3) Newer biomaterials that limit systemic exposure to any biological adjuvants for bone fusion while locally improving the fusion environment have been developed. 4) Concerns regarding the safety of such powerful technologies for diseases such as arthritis are increasing, as evidenced by the recent death (and subsequent threats of litigation) of a patient treated with gene therapy for rheumatoid arthritis in a clinical trial (1).

What could emerge as a potential use for the next iterations of these technologies would be the biological capabilities for reconstitution of skeletoligamentous structures. Given the ever-increasing human life span, we see more and more "healthy" patients who are essentially crippled from a musculoskeletal standpoint. These individuals, who have normal intellectual and neurological function and healthy vital organs, may find themselves incapacitated from arthritic degeneration and skeletal decompensation. The ideal strategy for these patients would not be joint fusion per se but rather replacement and reconstitution of a devitalized and nonfunctioning mechanical endoskeleton. Although seemingly unattainable, such strategies have already been used successfully in a limited fashion (2). Thus, it is critical that spinal neurosurgeons stay abreast of these interesting scientific developments.

Michael Y. Wang
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1. Wang MY: Gene therapy for arthritis: Death raises ethical and scientific issues. *Neurosurgery* 61:N7, 2007.

2. Warnke P, Springer IN, Witfang J, Acil Y, Eufinger H, Wehmoller M, Russo PA, Bolte H, Sherry E, Behrens E, Terheyden H: Growth and transplantation of a custom vascularised bone graft in a man. *Lancet* 364:766-770, 2004.

Gottfried and Dailey presented a thorough review of mesenchymal stem cell and gene therapies for spine fusion. In this work the authors summarize the latest research efforts underway to promote spine fusion with osteoprogenitor cells and gene therapy and discuss the clinical implications of these treatments. The problems with autografts relate primarily to their availability and the morbidity associated with harvest. BMP-2 has proven to be a safe and efficacious substitute for autografts, but BMP-2 has been associated with a unique set of potential complications including the induction of local inflammatory reactions, osteolysis, and heterotopic bone formation. Although infrequent, these adverse events underscore the need for further advancements in this field.

The use of adult mesenchymal stem cells for bone regeneration is of interest because multipotential cells can be isolated from a number of sources including bone marrow and adipose and muscle tissues. Mesenchymal stem cells can be differentiated into the osteogenic lineage to promote bone fusion, and the ongoing work in this field is promising.

Implantation of genetically manipulated cells or vectors that express biologically effective levels of osteoinductive proteins over time may enhance bioavailability and limit adverse effects from overdosing. This local gene therapy research has primarily focused on BMP-2, but investigations on factors are beginning.

Although the benefits of this work will not be realized for some time, this exciting field represents the future of spinal fusion.

Vincent C. Traynelis
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Over the past several decades, concepts related to the restoration of function have generated considerable excitement in neurosurgery. This is due in part to the identification of novel cellular and molecular adjuvants to our current armamentarium to treat disease, as well as to the potential broadening of the spectrum of disease that are "neurosurgical." Although the neurosurgical literature is rich in contributions addressing restoration of neurological function by cellular and molecular means, it is important to consider that a significant percentage of the neurosurgical endeavor involves the structure and function of the spine. Indeed, neurosurgery can be loosely defined as the surgical treatment of the nervous system and its coverings. In this review, the authors report on the current state-of-the-art in development of cellular and molecular adjuvants for spinal fusion, focusing on mesenchymal stem cells and gene therapies. Although the development of sophisticated methodologies to fuse bone may seem to represent a rudimentary goal, with the "holy grail" being the regeneration of all components of the spine, it is an important first step that is consistent with currently accepted treatments for spinal disorders, with potential advantages over currently available methods. Indeed, the structural components of the spine, including bone, cartilage, ligament, and muscular elements, combine with biomechanical considerations to constitute a marvelously complex functional amalgam. Thus, the likelihood of "growing a new spine" is equally as unlikely as that of "growing a new brain." However, there is little doubt in this reviewer's mind that increased knowledge about the processes of osteogenesis and regeneration of cartilage and soft tissue will expand our ability to utilize these cellular and molecular adjuvants to improve the lives of neurosurgical patients with spinal disorders.

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CHALLENGING TRADITIONAL BELIEFS: MICROSURGERY FOR ARTERIOVENOUS MALFORMATIONS OF THE BASAL GANGLIA AND THALAMUS

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OBJECTIVE: Arteriovenous malformations of the basal ganglia and thalamus are often managed with radiosurgery or observation, without consideration of microsurgery. Given the devastating effects of hemorrhage from these lesions, the accumulating evidence that they bleed more frequently than their lobar counterparts should prompt more creative thinking regarding their management.

METHODS: A review of the endovascular, microsurgical, and radiosurgical literature for arteriovenous malformations of the basal ganglia and thalamus was performed, with close attention to surgical approaches, obliteration rates, and procedure-related complications.

RESULTS: A complete resection rate of 91% and a mortality rate of 2.4% were found across surgical series of these lesions. These contrast with a 69% rate of complete obliteration and a 5.3% mortality rate (from latency-period hemorrhage) found when compiling results across the radiosurgical literature.

CONCLUSION: Given an appropriate surgical corridor of access, often afforded by incident hemorrhage, arteriovenous malformations of the basal ganglia and thalamus should be considered for microsurgical extirpation with preoperative embolization. In experienced hands, this approach presents an expeditious and definitive opportunity to eliminate the risk of subsequent hemorrhage and resultant morbidity and mortality.

KEY WORDS: Arteriovenous malformations, Basal ganglia, Embolization, Microsurgical excision, Operative approach, Thalamus

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Buried in eloquent diencephalic white matter and rooted by a deep perforator supply, arteriovenous malformations (AVM) of the basal ganglia and thalamus represent some of the most challenging lesions encountered in neurosurgery and are often deemed “inoperable” (23, 42, 54, 70). The advent of radiosurgery provided an ostensibly safer, less invasive alternative to microsurgery. However, AVMs of the basal ganglia and thal-

amus have shown greater resistance to radiosurgical cure compared with most other AVMs (3, 72, 100), and permanent radiation-induced side effects are higher for these lesions (3, 4, 39, 72, 84, 103), a factor that adds to the morbidity and mortality of latency-period hemorrhage. Recent work by Stapf et al. (95) has shown an annual hemorrhage rate of 34% for previously hemorrhaged, deep-seated lesions with exclusively deep venous drainage. These character-

ABBREVIATIONS: AVM, arteriovenous malformation; C, caudate head lesion; DTI, diffusion tensor imaging; GK, gamma knife; GOS, Glasgow Outcome Scale; HA, headache; HCP, hydrocephalus; HP, hemiparesis; HS, hemisensory deficit; ICV, internal cerebral vein; ITG, inferior temporal gyrus; LA, linear accelerator; MFG, middle frontal gyrus; MRI, magnetic resonance imaging; NBCA, n-butylcyanoacrylate; OFG, orbitofrontal gyrus; PVA, polyvinyl alcohol; RAH, recurrent artery of Heubner; STG, superior temporal gyrus; T, thalamic lesions; VF, visual field deficit

istics are common among AVMs of the basal ganglia and thalamus, reinforcing the danger of waiting 1 to 2 years for lesion obliteration. In contrast, microsurgery is an expeditious, definitive alternative for select cases. In this article, we review the endovascular, radiosurgical, and microsurgical literature, highlighting that certain malformations, with appropriate surgical routes of access and patient characteristics, are best treated by microsurgery coupled with preoperative embolization.

NATURAL HISTORY

Numerous studies have shown that approximately 10% of cerebral arteriovenous malformations are located in the basal ganglia and thalamus (13, 17, 52, 95). Although 50% of all AVMs present with hemorrhage (7, 32, 36, 57, 58, 59, 95, 97), higher rates of 72 to 91% (21, 53, 84) have been cited for the subgroup of basal ganglia and thalamic lesions (Table 1). Table 1 summarizes data from retrospective studies that either initially followed patients before intervention (21) or selected out a group to observe from a larger cohort with these lesions. The consistent finding of an annual hemorrhage rate of 10 to 11% (21, 53, 84) contrasts sharply with the classically quoted 2 to 4% annual rate (10, 67). On the one hand, the 10 to 11% rate may be somewhat inflated, as most patients had already bled, a factor known to increase the risk of subsequent hemorrhage (57, 95, 117). On the other hand, most of these patients had large lesions, a factor which has been shown to decrease hemorrhage rates (24, 36, 93, 95), potentially because of decreased feeding artery pressures (93). Indeed, in studies by Matsushima et al. (53) and Sasaki et al. (84), patients chosen for observation were more likely to have larger lesions and less likely to have pre-

sented with hemorrhage. Notwithstanding nidus size, Stapf et al. (95) predict a 15% annual hemorrhage rate for patients with deep-seated lesions that have already bled. This further increases to 34% if the drainage is exclusively deep (95), a characteristic common among ganglionic and thalamic AVMs (50, 52, 53). Furthermore, Tew et al. (103) have noted that AVMs in the basal ganglia and thalamus have a greater proclivity to develop venous hypertension and to drain into a single vein, factors known to increase the risk of developing hemorrhage (1, 43, 55, 61, 96). Overall initial rupture morbidity for AVMs has been quoted at 30 to 50% (10, 13, 29, 32, 51, 83), with a mortality rate of 10% (24, 32, 51, 83). Intuitively, one would expect these rates to increase for lesions located in eloquent areas and with the potential for intraventricular extension (75, 112). In fact, 85.5% of patients who presented with hemorrhage in the study by Fleetwood et al. (21) were hemiparetic or hemiplegic. In another study of 42 patients with supratentorial deep arteriovenous malformations managed with radiosurgery, 88% presented with hemorrhage and 62% had motor deficits (3). In Lee's (47) series of 8 patients with thalamic AVMs all presenting with hemorrhage, 6 experienced hemiparesis and hemianesthesia. In the series of small thalamocaudate AVMs by Solomon and Stein (91), 21 of 22 patients initially presented with hemorrhage. Three were left with a mild hemiparesis, 2 with hemianopsia, and 6 with a disturbance of memory function. In the cohort observed by Sasaki et al. (84), 62.5% of patients with subsequent hemorrhage died. Combining the data for observed cohorts in the studies by Matsushima et al. (53) and Sasaki et al. (84), 10 (43%) of 23 patients died as a result of subsequent hemorrhage over a mean follow-up period of 8 years. Thus, in summary, these lesions are more likely to

TABLE 1. Retrospective studies of arteriovenous malformations of the basal ganglia and thalamus

Series (ref. no.)	No. of patients	Size distribution	Hemorrhage on presentation (%)	Annual follow-up hemorrhage rate (%) ^a	Annual mortality from hemorrhage (%)
Fleetwood et al., 2003 (21)	96	35% <3 cm 54% 3–6 cm 9% >6 cm	72	10	
Matsushima et al., 1988 (53)	18	33% <2.5 cm 28% 2.5–5 cm 39% >5 cm	78		
<i>Observed cohort^b</i>	8	13% <2.5 cm 38% 2.5–5 cm 50% >5 cm	63		5
Sasaki et al., 1998 (84)	101	77% <3 cm 17% 3–6 cm 6% >6 cm	91		
<i>Observed cohort^b</i>	15	47% <3 cm 13% 3–6 cm 40% >6 cm	67	11	7

^a The condition of patients in the observed cohort of Matsushima et al. (53) on follow-up examination was described as either "working" or "dead;" thus, an annual follow-up hemorrhage rate could not be reliably derived.

^b A subgroup in the studies of Matsushima et al. (53) and Sasaki et al. (84) was selected out for observation only.

present with hemorrhage, hemorrhage more frequently, and have greater morbidity and mortality with each bleed.

VASCULAR ANATOMY

Crucial to effective treatment of AVMs of the basal ganglia and thalamus is a thorough understanding of their vascular supply and drainage. *Table 2* subdivides these malformations by location, summarizing arterial supply and venous drainage as described by de Oliveira et al. (16). In general terms, lateral AVMs based in the lentiform nucleus are supplied by lateral lenticulostriate vessels, insular and cortical branches of the medial cerebral artery, and, variably, the anterior choroidal artery (50, 52, 53). Venous drainage is often both superficial and deep. Anteromedial lesions are generally supplied by medial lenticulostriate vessels from the M1 and A1 segments, with rostroventral malformations often supplied by the recurrent artery of Heubner (50, 52, 53, 109). Drainage is often exclusively deep via caudate veins emptying into the internal cerebral vein. In the report by Solomon and Stein (91) of 22 thalamocaudate AVMs, most were supplied by the posterior choroidal and/or the posterior pericallosal arteries. Some ($n = 9$) were supplied by the anterior pericallosal artery and a few ($n = 4$) were supplied by the anterior choroidal artery. All lesions drained toward the midline, 21 to the deep venous system, and one drained superiorly to the superior sagittal sinus. Angiographically, only 3 lesions

were supplied by thalamoperforator arteries; however, intraoperatively, the deep aspect of almost all lesions was supplied by small penetrators (91). In Lee's (47) series of 8 thalamic AVMs, all were reported to be supplied by thalamoperforators, and 7 were fed by the posterior choroidal, 4 by the anterior choroidal, and 2 by the lenticulostriate arteries. All AVMs had deep venous drainage. The ubiquitous deep perforator supply to these lesions is notoriously difficult to coagulate intraoperatively (39, 44, 99), and they must often be followed into eloquent tissue to achieve hemostasis (18). Thus, it is not surprising that perforator supply to an AVM is known to significantly increase surgical morbidity, worsen overall outcome, and increase the frequency of hyperemic complications (7). Some series have shown deep venous drainage to increase surgical risk (34, 92); however, this finding is not consistent in the literature (7). In the senior author's (HHB) personal experience, deep venous drainage has not increased surgical risk (7). In fact, at times, it has facilitated the early phases of surgery by not encumbering the dissection field, a convenience during the extirpation of periventricular lesions (6, 39).

SURGICAL APPROACHES AND OUTCOMES

An ideal surgical approach would provide a wide, perpendicular view of the malformation while traversing noneloquent brain or a subdural or subarachnoid corridor. It would additionally entail minimal retraction and a short, direct

TABLE 2. Arterial supply and venous drainage according to arteriovenous malformation location as described by de Oliveira et al. (16)^a

Location	Arterial supply	Venous drainage
Lateral		
<i>Anterior</i>	M1, M2, occasionally A1	Deep sylvian vein and/or superficial sylvian vein
<i>Middle</i>	M2, occasionally M1, A1	Superficial sylvian vein and/or Labbé, Trolard
<i>Posterior</i>	M2, M3, occasionally lateral, posterior, choroidal	Superficial, occasionally deep if lateral posterior choroidal supply
Medial		
<i>Anterior (caudate head)</i>	M1, A1	ICV
<i>Middle, superior to ICV</i>	Lateral, posterior, choroidal; occasionally posterior, thalamoperforators	ICV
<i>Middle, inferior to ICV</i>	Medial, posterior, choroidal; anterior and posterior thalamoperforators	ICV
<i>Posterior (pulvinar)</i>	Medial and lateral posterior choroidal, thalamogeniculate	Basal vein or ICV
Anteroinferior^b		
<i>Medial to carotid bifurcation</i>	A1, A2, RAH, anterior communicating artery	Basal vein
<i>Lateral to carotid bifurcation</i>	M1, RAH	Basal vein
Superior^c	M2, M3, occasionally M1	Deep
Mixed (large)	Multiple sources	Superficial and deep

^a ICV, internal cerebral vein; RAH, recurrent artery of Heubner.

^b Anteroinferior malformations are in the region of the anterior perforated substance.

^c Superior lesions are those in deep cerebral white matter surrounding the ventricles.

approach to the lesion. Hemorrhage frequently affords the opportunity to operate through such a direct transcortical route that would have otherwise required traversing functional, healthy cortex. A hematoma often dissects the AVM from surrounding tissue (18, 84, 103, 108), enhancing exposure of the contour and depth of the lesion and requiring less manipulation of surrounding parenchyma. It is not surprising that by compiling the data from surgical series (Tables 3–6), 89% of patients (189 of 212) had preoperatively bled. Impressively, the overall complete resection rate across these reports is 91% (193 of 212 patients; range, 67–100%), with an overall surgical mortality rate of 2.4% (5 of 212 patients). In fact, one death occurred in the case of a patient who arrived moribund (103), and another occurred after an incompletely resected lesion hemorrhaged postoperatively (47). Thus, this

mortality rate is a conservative estimate, particularly for completely excised lesions. These impressive results of microsurgery are based on a carefully selected patient population, generally young patients with small lesions that had hemorrhaged, often causing significant preoperative neurological deficits. For example, Tew et al. (103) did not operate on any patients who were neurologically intact after hemorrhage. In addition, exceptional surgical skill afforded these results; they are not universally reproducible.

Lateral AVMs

Facilitated by the presence of a sylvian hematoma, lesions lateral to the internal capsule may be approached via the sylvian fissure, allowing for early control of lenticulostriate feeders. As shown in Table 4, this is the historical approach of

TABLE 3. Summary of preoperative hemorrhage rates and operative results from larger surgical series of arteriovenous malformations of the basal ganglia and thalamus that did not subdivide, results by location^a

Series (ref. no.)	No. of patients	Preoperative condition	Preoperative hemorrhage	Complete resection	Early postoperative condition ^b	Outcome/long-term complications attributed to surgery ^b
de Oliveira et al., 1997 (16)	18; 2 preoperative embolization 1 preoperative radiation	39% intact	89%	83%	78% unchanged 17% new deficits 5.6% mortality	95% improved 67% fully intact 0% permanent morbidity 5.6% mortality
Sasaki et al., 1998 (84)	15; 1 preoperative embolization		100%	100%	33% new dysphasia 33% new VF 20% new HP	93% independent 67% premorbid job 33% VF 20% HP 6.7% dysphasia 0% mortality
Shi and Chen, 1987 (87)	16	88% HP, 63% HS, 31% dysphasia, 25% VF, 12.5% intact	100%	93%	75% unchanged or improved 19% new or increased deficits 6.3% mortality	88% unchanged/improved 6.3% permanent morbidity (HP) 6.3% mortality
Tew et al., 1995 (103)	39	0% intact	91% ^c	97%	67% improved 18% unchanged 13% worse 2.6% mortality	85% unchanged/improved 13% permanent morbidity 7.7% HP 5.1% VF 5.1% dysphasia 2.6% memory deficit 2.6% mortality

^a VF, visual field deficit; HP, hemiparesis; HS, hemisensory deficit.

^b In the studies of Sasaki et al. (84) and Tew et al. (103), the given percentages for new, specific deficits could not be summed to afford procedural morbidity rates as multiple deficits may have been present in one patient.

^c Hemorrhage rate for entire series of 65 vascular malformations of the basal ganglia and thalamus (includes 51 arteriovenous malformations, of which 39 were excised, and 14 cavernous malformations).

TABLE 4. Summary of lesion characteristics, operative approach, and results for surgical series of arteriovenous malformations primarily lateral to the internal capsule^a

Series (ref. no.)	No. of patients	Lesion size (cm)	Preoperative condition	Preoperative hemorrhage	Approach	Complete resection	Early postoperative condition	Outcome/long-term complications attributed to surgery
Liu and Lee, 2001 (50)	3	<3 in 2 3–6 in 1	100% HP, 33% HS, 33% VF	100%	2 transsylvian, 1 OFG	100%	67% worse HP 33% unchanged	33% improved 33% preoperative HP level 33% permanent morbidity (HP) 0% mortality
Malik et al., 1988 (52)	3	2.5–4	100% HP, 67% dysphasia, 33% VF	67%	1 ITG, 1 OFG, 1 MFG	100%	67% worse HP 33% improved	100% improved 100% premonitory job 33% fully intact 0% permanent morbidity 0% mortality
Matsushima et al., 1988 (53)	4	<2.5 in 3 2.5–5 in 1	0% intact	100%	Transsylvian	100%	50% improved 50% unchanged	100% premonitory job 50% improved 0% permanent morbidity 0% mortality
Viale et al., 1980 (107)	3	All <1.3	67% intact, 33% HP	100%	Transsylvian	100%	33% improved 33% unchanged 33% worse HP	0% permanent morbidity 0% mortality
Yamada et al., 1998 (116)	4			100%	Transsylvian, transinsular	100%	50% unchanged 50% worse HP	

^a HP, hemiparesis; HS, hemisensory deficit; VF, visual field deficit; ITG, inferior temporal gyrus; OFG, orbitofrontal gyrus; MFG, middle frontal gyrus.

choice, with a 100% resection rate and no surgical mortality in our reviewed series. Tew et al. (103) also advocated this approach for striatal AVMs, adding that a subtemporal exposure may be used in conjunction for easier control of the vascular supply from lateral posterior choroidal branches. In the series by Sasaki et al. (84), patients without preoperative weakness from lentiform AVMs were significantly more likely to experience postoperative paresis after transsylvian extirpation. In fact, postoperative weakness is the one ostensible shortcoming of this approach, suggesting caution in considering neurologically intact patients for surgery. In contrast, patients with fixed, significant preoperative hemiparesis are good surgical candidates with “little to lose.” It should be noted that, with the exception of the series of Yamada et al. (116) in which the authors do not clarify which lesions were embolized, adjunctive endovascular embolization was not used in any of the series listed in Table 4. Malik et al. (52) have used transfrontal

routes to these lesions. They advocate an approach via the orbital gyrus for lesions close to the middle cerebral artery involving the anterior perforated substance and an incision in the middle frontal gyrus for deeper malformations. Their one case of long-term operative morbidity occurred in a patient without previous hemorrhage. Her lentiform lesion was approached via the inferior temporal gyrus after an initial transsylvian phase to ligate feeders. The patient experienced worsening hemiparesis, hemianopsia, and dysphasia. The authors mention that previous hemorrhage would have likely facilitated a more facile transinsular approach for this lesion (52). de Oliveira et al. (16) specifically subclassify antero-inferior malformations in the region of the anterior perforated substance. They successfully extirpated 2 such lesions via a transsylvian route without subsequent long-term operative morbidity or mortality. They emphasized the crucial importance of a preoperative hematoma to guide the approach (16).

TABLE 5. Summary of lesion characteristics, operative approach, and results for surgical series of arteriovenous malformations primarily medial to the internal capsule^a

Series (ref. no.)	No. of patients and lesion type	Lesion size (cm)	Preoperative condition	Preoperative hemorrhage	Complete resection	Early postoperative condition ^b	Outcome/long-term complications attributed to surgery
Drake, 1979 (18)	4 T, 1 C			40% ^c	100%	20% morbidity (mild HP, HS)	20% permanent morbidity 0% mortality
Lee, 1993 (47)	8 T		75% HP 75% HS 50% memory deficit 38% VF	100%	88%	63% unchanged 13% new memory deficit 13% new HP, 13% mortality	88% premorbid job 13% permanent morbidity (memory deficit) 13% mortality
Liu and Lee, 2001 (50)	3 C, 10 T	<3 in 9 3–6 in 4	7.7% HP 7.7% HS, 7.7% VF	85%	100%	14% memory deficit 7.7% HP	7.7% permanent morbidity (HP) 0% mortality
Malik et al., 1988 (52)	3 C	2.5–5	67% intact 33% mild HP 33% dysphasia	100%	100%	67% unchanged 33% dysphasia 33% neglect	100% intact 100% premorbid job 0% permanent morbidity 0% mortality
Matsushima et al., 1988 (53)	2 C	All <2.5	0% intact	100%	100%	100% unchanged	100% premorbid job/status 0% permanent morbidity 0% mortality
Sisti et al., 1993 (89)	6 T	All <3		94% ^d	83%		0% permanent morbidity 0% mortality
Solomon and Stein, 1987 (91)	22	All <2.5	27% memory deficit, 14% mild HP, 9% VF	95%	82%	36% new memory deficit 18% new VF 14% new HP 14% new HS 5% new Parinaud's	100% premorbid job 36% memory deficit 18% VF 9% HS 0% mortality
Waga, 1986 (108)	4 C, 4 T	All <2	50% HP, 38% intact, 13% ataxia	100%	100% (C), 75% (T)	25% improved 50% unchanged 13% confusion/disoriented (C) 13% HP, HS, neglect, memory deficit (T)	88% premorbid job/status 25% permanent morbidity 13% confusion/disoriented 13% mild neglect 0% mortality
Wilson et al., 1979 (113)	3	All <2	67% intact, 33% HP (T), 33% HS (T)	100%	100%	33% intact (C) 67% worse HP (T)	67% unchanged/improved 33% permanent morbidity (HP) 0% mortality
Yamada et al., 1998 (116)	12 T			100% ^e	100%	0% morbidity	0% mortality

^a T, thalamic lesions; C, caudate head lesions; HP, hemiparetic; HS, hemisensory deficit; VF, visual field deficit; MFG, middle frontal gyrus; OFG, orbitofrontal gyrus; AVMs, arteriovenous malformations.

^b In the study of Solomon and Stein (91), the given percentages for new, specific deficits could not be summed to afford procedural morbidity rates, as multiple deficits may have been present in one patient.

^c Conservative estimate, as the bleed history of the three other lesions was not described.

^d Hemorrhage rate for thalamic lesions was not reported; this rate is for all 67 AVMs in this study.

^e Hemorrhage rate for all thalamic AVMs were not reported. This rate is based on the three lesions discussed in detail.

TABLE 6. Summary of lesion characteristics, operative approach, and results for surgical series of large arteriovenous malformations of the basal ganglia and thalamus^a

Series (ref. no.)	No. of patients	Lesion size (cm)	Preoperative condition	Preoperative hemorrhage	Approach	Complete resection	Early postoperative condition	Outcome/long-term complications attributed to surgery
Juhász, 1978 (40)	3	All 5		100%	Transcortical ^b	67%	67% worse- ned (1 HCP) 33% unchanged	33% permanent morbidity 0% mortality
Lawton et al., 1995 (46)	6 ^c 10 opera- tions 3 preoper- ative emb- olizations	<3 in 1 3–6 in 2 >6 in 3	50% GOS score of 1 33% GOS score of 3 17% GOS score of 4	83%		67%	50% improved 33% unchanged 17% worsened	83% GOS score of 1 17% GOS score of 2 17% permanent morbidity 0% mortality
Mizoi et al., 1995 (56)	2 2 preopera- tive emboli- zations	6.5 and 7	100% HP 100% dysphasia 50% VF	100%	Transsylvian, transinsular	100%	100% worse HP	100% improved 0% permanent morbidity 0% mortality
U, 1985 (104)	4 11 opera- tions 2 preoper- ative emboliza- tions	All >4	75% HP 25% obtunded 25% VF 25% dysphasia	25%	Transsylvian	75%	25% improved 50% unchanged 25% mortality	25% intact 50% unchanged 0% permanent morbidity 25% mortality
U et al., 1992 (105)	12 26 opera- tions 4 preoper- ative embo- lizations	<2 in 2 2–4 in 4 >4 in 4	67% HP 17% intact 8.3% coma- tose 8.3% HS 8.3% dysphasia 8.3% memory deficit	67%	Transcortical MFG	75%	33% improved 42% unchanged 25% worsened (2 HP)	17% intact 25% permanent morbidity (HP) 0% mortality

^a GOS, Glasgow Outcome Scale (where 1 is good recovery and 5 is death); HP, hemiparesis; HA, headaches; VF, visual field deficit; MFG, middle frontal gyrus; HCP, hydrocephalus successfully managed with ventriculoperitoneal shunting.

^b A lesion in the caudate head and anterior limb of the internal capsule was excised via the middle frontal gyrus. A lesion involving both the basal ganglia and thalamus was excised via a combined middle frontal gyrus and transparietal approach. The final lesion was partially excised via a transtemporal approach.

^c These selected results from a larger series are for patients that did not have previous microsurgery or any adjunctive or prior irradiation.

Medial AVMs

Lesions medial to the internal capsule are generally managed via a transventricular approach after frontal corticotomy if a hematoma is present, or by an interhemispheric approach with callosotomy (Table 7). Although a transcortical route is more direct, the risk of postoperative neuropsychological deficits (11, 78) and seizures (40, 109) has swayed surgeons toward the interhemispheric transcallosal approach (15, 88)

when no hematoma exists, as it has been shown to be quite safe (13, 16, 88). Furthermore, this approach allows for early identification and control of feeders emanating from the anterior cerebral artery (75). Waga et al. (109) initially espoused a transfrontal approach for lesions of the caudate head. Although their first 2 patients with caudate AVMs underwent transfrontal extirpation without complication, their third patient developed long-term, significant confusion, disorientation, and apathy.

TABLE 7. Surgical approach to lesions primarily medial to the internal capsule^a

Series (ref. no.)	Anterior (caudate head)	Middle	Posterior (pulvinar)
de Oliveira et al., 1997 (16)	Transsulcal via postero-superior frontal sulcus ^b	Transcallosal	Transsplenial or open tentorium and approach through isthmus of cingulate gyrus
Drake, 1979 (18)	Transcallosal	Transfrontal ^c	STG or transsplenial ^d
Lee, 1993 (47)	Transcallosal		Transcallosal
Malik et al., 1988 (52)	Transfrontal (2 MFG, 1 OFG)		
Matsushima et al., 1988 (53)	1 transfrontal (MFG), 1 transcallosal		
Solomon and Stein, 1987 (91)	Transcallosal	Transcallosal	Transcallosal
Tew et al., 1995 (103)	Transcallosal		Transcallosal ^e
Waga, 1986 (108)	3 transfrontal, 1 transcallosal		Transcallosal
Wilson et al., 1979 (113)	1 transfrontal (MFG)		2 transparietal
Yamada et al., 1998 (116)		Transcallosal ^f	Excise part of parahippocampus, approach through velum interpositum

^a STG, superior temporal gyrus; MFG, middle frontal gyrus; OFG, orbitofrontal gyrus.

^b The authors felt a transcallosal approach would entail excessive retraction.

^c A ruptured arteriovenous malformation in the anterior thalamus was excised transfrontally.

^d One other thalamic lesion was excised via a subtemporal approach facilitated by a temporal lobe clot cavity.

^e A transcallosal approach was used for small midline lesions. Larger lesions expanding laterally into the temporal horn were approached transcortically (parieto-occipital).

^f Lesions of the mediodorsal thalamus were approached transcallosally. In all 5 cases, an associated venous aneurysm facilitated the approach.

Attributing this result to their frontal corticotomy, they subsequently used an anterior transcallosal approach successfully for their fourth patient with head of the caudate AVM (109). All 4 thalamic lesions in their series were approached transcallosally, allowing for early control of posterior choroidal feeders (108,109). Solomon and Stein (91) advocated the interhemispheric transcallosal approach for their full series of 22 thalamo-caudate AVMs. A 1- to 2-cm callosotomy was performed with subsequent ipsilateral sectioning of the fornix, affording immediate access to the blood supply on the medial surface of the AVM, an inherent advantage to this midline approach (75, 91). Although this series (91) and those of Waga (108) and Drake (18) reported no functional impairment from posterior callosotomy, psychometric testing of patients has demonstrated a visual disconnection syndrome (91). Lee (47) also used an interhemispheric approach; however, he retracted in the parieto-occipital region, emphasizing that fewer bridging veins are encountered along this route. Postoperatively, 1 of 7 patients with completely excised AVMs exhibited a new memory deficit; otherwise, there was no significant surgical morbidity. However, the one patient with an incompletely excised lesion experienced fatal postoperative hemorrhage, underscoring the danger of partially treated AVMs. Interestingly, Heros (31) successfully excised 2 AVMs of the medial temporal lobe with extension into the basal ganglia and thalamus via an approach through the inferior temporal lobe. Neither patient experienced new neurological deficits postoperatively. He emphasized that lesions limited to the posterolateral portion of the thalamus or

the inferior portion of the basal ganglia are particularly safe candidates for surgical extirpation. They are correlated angiographically with primary supply by the anterior choroidal artery and laterally oriented branches of the posterior cerebral artery. Their primary venous drainage is into the basal vein of Rosenthal and the medial sylvian veins. This arterial supply and venous drainage pattern underscores the ideal, direct nature of a transtemporal approach (31, 109). Drake (18) has shown that approaches to lesions in the nondominant hemisphere via small incisions in the superior temporal gyrus between the upper and lower optic radiations may prevent postoperative visual field deficits. Although new postoperative visual field deficits are always a possibility with a temporal approach (5), none were experienced by any patients in a series of trigonal AVMs approached transtemporally reported by Batjer and Samson (8). Heros (31) advocates a subtemporal approach for inferiorly located lesions, affording clean exposure of the posterior cerebral artery and anterior choroidal artery in the ambient cistern and minimizing the potential for damage to the optic radiations. Facilitated by the presence of a temporal lobe clot cavity, Drake (18) used this approach to successfully excise a lesion in the deep base of the basal ganglia and thalamus without long-term surgical morbidity. Coupled with the successful excision of a hemorrhaged AVM in the anterior thalamus via a transfrontal approach in his series (18), these results again emphasize the surgical advantage that can be afforded by a preexisting hematoma. The contralateral interhemispheric transcallosal approach (62, 81, 88) is another alter-

native, popularized by Lawton et al. (45) in a surgical series of 32 deep lesions, 2 of which were thalamic AVMs. This route may be particularly advantageous for dominant hemisphere lesions. The patient is positioned with the lesion side up, allowing gravity to hold open the interhemispheric fissure. The authors propose that this more lateral approach increases exposure and minimizes retraction on the medial hemisphere, as the falx aids in retraction. Although no procedural morbidity was observed for the 2 thalamic AVMs, subsequent radiosurgery was required for complete obliteration in each case (45). Including the results of Heros (31) and Lawton et al. (45) with those in *Table 5*, the overall complete resection rate was 89% for surgical small medial lesions. Although they did not clarify their complete resection rate for these lesions in particular, de Oliveira et al. (16) excised 10 thalamocaudate AVMs, with no long-term surgical morbidity and one death. This mortality occurred as a result of a thalamic venous infarction and massive bleeding into the thalamus. Including all of these series, this case results in a combined mortality rate of 2.1%, with the other death resulting from a postoperative hemorrhage from residual AVM (47).

Large AVMs

Although the AVMs in the aforementioned series were generally small, some studies have been composed of primarily larger lesions (*Table 6*). In his early report, Juhász (40) recognized the need to extirpate deep lesions presenting with hemorrhage. One patient in his series had 6 bleeds from an AVM primarily in the caudate head and anterior limb of the internal capsule. He successfully excised it via an approach through the middle frontal gyrus. Postoperative hydrocephalus from obstruction of the foramen of Munro was successfully treated with ventriculoperitoneal shunting (40). U (104) and U et al. (105) reported impressive multistaged surgical excisions of 16 AVMs of the basal ganglia and thalamus, 10 of which were greater than 4 cm. The patients in these series presented more often with progressive neurological deficits and less frequently with hemorrhage than other studies, possibly because such large malformations are more likely to initially present symptomatically without having hemorrhaged. After his first and only mortality, U (104) changed from a transsylvian approach to a transfrontal, transventricular route to improve lateral exposure, in addition using barbiturate coma and hypothermia. He would stop procedures when excessive pulsation or oozing around the operative site did not abate, an initial sign of what he termed “autoregulation breakthrough” swelling or hemorrhage. U (104) felt that these modifications allowed for better control of potential intraventricular hemorrhage, decreased cerebral metabolic demands (to allow for better tolerance of potential complications), and decreased prevalence of hyperemic complications. This cautious approach seen only in U’s series may be attributable to the fact that he was excising larger lesions than most other groups. Normal perfusion pressure breakthrough—overly rapid distribution of blood to surrounding vasculature incapable of autoregulation because of prolonged hypoperfusion—is correlated with AVM size (7, 94).

With the modifications of U et al. (105), the prevalence of this phenomenon decreased from 3 times in the first 11 operations to once in the subsequent 26 operations. Mizoi et al. (56) demonstrated successful extirpation of 2 giant (6.5-cm and 7-cm) AVMs of the basal ganglia after multistaged (4 and 6 sessions, respectively) embolization. They used an extended, transsylvian transinsular approach, feeling that it posed less risk of damage to pyramidal tracts than the transfrontal, transventricular approach espoused by U (104) and U et al. (105). Tew et al. (103) advocated combining the transsylvian approach with a transcallosal approach for these larger lesions. Like the route used by U (104) and U et al. (105), this allows for control of potential intraventricular hemorrhage. Although Sasaki et al. (84) noted decreased visual morbidity for the interhemispheric approach to thalamic AVMs, larger lesions may necessitate a transcortical route to facilitate lateral exposure (18, 75, 98, 108, 109). Tew et al. (103) advocated the consideration of a parieto-occipital transcortical-transventricular route. Alternatively, as seen in the senior author’s (HHB) experience with trigonal AVMs (8), an approach via the middle temporal gyrus for lesions projecting lateral to the P2-P3 junction is an attractive choice to limit surgical morbidity. When considering the delayed exposure of the posterior cerebral artery and choroidal vessels, such an approach may seem unappealing. However, in the series by Batjer and Samson (8), interhemispheric approaches to lesions extending lateral to the P2-P3 junction led to permanent visual field deficits in 4 of 6 patients. New visual field deficits, likely attributable to occipital lobe retraction during their interhemispheric approach, were even seen in 4 of 22 patients in a series by Solomon and Stein (91) of small thalamocaudate AVMs.

ENDOVASCULAR APPROACHES AND OUTCOMES

Most of the recent series describing management of AVMs of the basal ganglia and thalamus have used adjunctive endovascular embolization (16, 46, 56). *Table 8* summarizes results of series specifically addressing embolization of these lesions. Seven of 70 embolized AVMs demonstrated complete angiographic obliteration, with 8 patients (11%) experiencing permanent morbidity attributable to the embolization procedure and one death (1.4%). The challenge of embolizing delicate lenticulostriate feeders may explain the wide range of procedural morbidity rates in these studies. Not surprisingly, Hartmann et al. (30) have specifically shown that deep venous drainage and eloquent AVM location are independently associated with new treatment-associated deficits after embolization. Several measures have been used to lower procedural morbidity. Many have advocated the use of intra-arterial sodium amytal to guide embolization (35, 69, 76, 79, 82). In a series of 50 embolized AVMs, Purdy et al. (76) observed significantly improved results in both the number and severity of neurological deficits and hemorrhage when sodium amytal was used. Among the series in *Table 9*, all except that of Sasaki et al. (84) cite the use of sodium amytal. Rauch et al. (80) also demon-

TABLE 8. Results from series specifically describing embolization of arteriovenous malformations of the basal ganglia and thalamus^a

Series (ref. no.)	Total patients	Patients embolized (%)	Preembolization condition	Preembolization hemorrhage (%)	Embolization agent	Complete obliteration	Early post-embolization condition	Outcome/ complications attributed to embolization
Hurst et al., 1995 (35)	14	100	50% HP 14% intact	3 4	100% NBCA	15%	29% improved 14% new deficits	36% improved 14% permanent morbidity: 14% thalamic pain syndrome, 7% HP 0% mortality
Paulsen et al., 1999 (69)	38	92	39.5% intact	18.4	71% NBCA 14% PVA 14% NBCA plus PVA	2.9%	23% new deficits: 14% new VF, 8.6% new HP	11% permanent morbidity 5.7% HP 5.7% VF 0% mortality
Richling and Bavinski, 1991 (82)	18	89	39% progressive deficits	61	100% NBCA	25%	13% new deficits	0% permanent morbidity 0% mortality
Sasaki et al., 1998 (84)	5	100		100		0%	60% new deficits 20% intact 20% mortality	40% permanent morbidity 20% mortality

^a HP, hemiparesis; NBCA, *n*-butylcyanoacrylate; PVA, polyvinyl alcohol; VF, visual field deficit.

TABLE 9. Hemorrhage rates and resultant morbidity and mortality in the first 2 years after radiosurgery for arteriovenous malformations of the basal ganglia and thalamus

Series (ref. no.)	No. of patients	No. of patients with follow-up hemorrhage	Annual hemorrhage rate	Morbidity	Mortality
Andrade-Souza et al., 2005 (3)	42	6	9.5% yr 1, 4.7% yr 2	17% major, 17% minor	50%
Nicolato et al., 2002 (63)	21	2	8% overall	50% major	50%
Pollock et al., 2004 (72)	40	7	9.8% yr 1, 5.6% yr 2	0%	71%
Sasaki et al., 1998 (84)	66	3	3.3% yr 1, 1.7% yr 2	33% major	0%

strated the utility of added neurophysiological monitoring, as only half of cases with positive amyntal tests were identified clinically in their series. Furthermore, morbidity can be lowered by staging embolization, waiting 1 to 2 weeks between sessions (60). Hopkins advocates limiting embolization to a maximum of 2 pedicles per session (LN Hopkins, personal communication). Hurst et al. (35) attributed their procedural morbidity to difficulty in identifying thalamogeniculate vessels. These feeders to the posterolateral thalamus have been shown to be an etiological factor in Dejerine-Roussy syndrome (25). In addition, false-negative results to amyntal testing were attributed to either high flow into the AVM preventing perfusion into the desired vessels or reflux of the embolic agent into adjacent vessels (35). Paulsen et al. (69) noted that all of their complications occurred before the implementation of somatosensory evoked potential monitoring. Including transient deficits, 2 of their first 6 patients embolized with polyvinyl alcohol via guidewire-

directed microcatheters experienced postembolization complications. Only 2 of their next 24 patients embolized with *n*-butylcyanoacrylate (NBCA) via less traumatic flow-directed microcatheters had complications. After the addition of somatosensory evoked potential monitoring, procedural morbidity was reduced to 0% (69). Accumulating operating experience is an additional, potential contributing factor to this gradual improvement. Promisingly, advancements in the field of endovascular neurosurgery are likely to further improve the utility and outcomes of embolization. Improved penetration achievable with Onyx (27, 37, 101, 102) may make these lesions significantly easier to embolize. NBCA is limited by the unpredictability of intranidal flow and polymerization rate (60,106). In contrast, Onyx is less adhesive and polymerizes more slowly, allowing for controlled, longer injection times (37, 60, 106). This allows the endovascular surgeon to pause during injections and assess nidus occlusion and draining vein status by means

of contrast injection. The injection can be ceased if reflux into arterial feeders or venous migration is noted (106). More areas of the AVM nidus can be embolized from a single pedicle when Onyx is used (37), and vessels embolized with Onyx often seem less fragile intraoperatively, potentially from less inflammation and the absence of polymerization heat as seen with NBCA (111). In their early experience with Onyx embolization of 23 AVMs, Jahan et al. (37) reported one case of long-term, procedure-related morbidity occurring for a Spetzler-Martin Grade III lesion of the basal ganglia. The authors cite that Onyx likely refluxed into a branch of the anterior choroidal artery supplying normal parenchyma, resulting in a permanent hemiparesis. They noted that vasospasm of the desired artery to be embolized may have contributed to this complication and thus recommend slower injection of dimethyl sulfoxide to help prevent potential future occurrences. One other AVM in their series was in the basal ganglia; it was a Spetzler-Martin Grade IV lesion, embolized without procedure-related long-term complications (37). Many institutions, including our own, view a complementary role of Onyx and NBCA in deep AVM embolization (60, 106). NBCA is lightweight, allowing for the use of less traumatic, softer microcatheters with greater flow directability. Van Rooij et al. (106) noted that NBCA is particularly useful for lesions with a plexiform nidus and en passant feeders. In addition, they found that in very small pedicles, it was difficult to visualize Onyx and, thus, reflux may go unseen. Mounayer et al. (60) used NBCA if the distal segment of an arterial feeder could not be occluded because of reflux of Onyx. In their series of 94 patients undergoing AVM embolization with Onyx or NBCA, Mounayer et al. (60) had a 20% procedure-related long-term morbidity rate and a 10% procedure-related mortality rate in their subgroup of 10 AVMs in the basal ganglia. One patient with a subthalamic AVM embolized with Onyx experienced ophthalmoplegia caused by an ischemic event. Another with a lesion in the internal capsule suffered from significant hemiparesis resulting from hemorrhage after NBCA embolization. Their one death occurred as a result of catheter perforation of a vessel wall during Onyx embolization of a thalamic AVM (60).

RADIOSURGICAL RESULTS

Although the role of embolization remains adjunctive (77), radiosurgery is frequently the reflexive approach to treating AVMs of the basal ganglia and thalamus. However, accumulating evidence in the literature suggests a relative radioresistance of these lesions (3, 72, 100). Across radiosurgical series devoted exclusively to AVMs of the basal ganglia and thalamus, 116 (69%) of 169 patients had complete obliteration after one treatment (Table 10) (3, 64, 72, 84). The wide range of obliteration rates across these series may be explained by the differential use of preradiosurgical treatments, different lesion sizes, and the varied use of magnetic resonance imaging instead of angiography to denote complete obliteration. Seventeen (10%) of 169 patients experienced permanent complications from radiation of their deep AVMs, a rate greater than that quoted

for cortical lesions (3, 10, 72, 84). Given the eloquence of adjacent tissue, radiation-induced hemodynamic alterations and edema are intuitively more likely to present symptomatically. Tew et al. (103) emphasized that microvessels supplying the internal capsule are particularly susceptible to radiation injury. Eleven of 33 patients in the general radiosurgical series of Steinberg et al. (100) had histological evidence of perivascular parenchymal necrosis after treatment. One long-term study of a variety of cerebral arteriovenous malformations treated with radiosurgery, including several in the basal ganglia and thalamus, noted delayed cyst formation in 23% of patients (119). Other long-term studies demonstrate cases of angiographic recurrence (31, 44) and the development of intracranial neoplasms (22, 86) after radiosurgery. The major drawback of stereotactic radiosurgery is the latency period. Results in Table 9 demonstrate annual hemorrhage rates after radiosurgery equal to or less than those of the natural history of these deep-seated lesions. However, resultant morbidity and mortality from hemorrhages of these lesions as their luminal diameters dwindle is high. This may be explained by larger hematomas from ruptures of smaller AVMs (93). Regardless, when combining the studies in Table 9, we see that 9 (5.3%) of 169 patients in radiosurgical series died as a result of hemorrhage during the latency period (3, 10, 72, 84). Curiously, unusually high rates of resultant mortality from latency-period hemorrhage have also been seen in several general radiosurgical studies (74, 100, 118). In the series by Pollock et al. (74) of "operable" arteriovenous malformations, 2 of 5 patients died as a result of latency-period hemorrhage. In the study by Steinberg et al. (100) of large arteriovenous malformations undergoing radiosurgery followed by surgical excision, 2 of 5 patients died as a result of latency-period hemorrhage. Finally, in a study by Yamamoto et al. (118), 3 of 6 patients died as a result of hemorrhage during the latency period. Despite these drawbacks, Lawton et al. (46) and Sasaki et al. (84) demonstrated improved treatment outcomes after the introduction of radiosurgery. This less invasive approach can be performed on an outpatient basis with less periprocedural morbidity, allowing for an expeditious return to regular activities and employment. Furthermore, improper targeting, a significant cause of incomplete obliteration (73), is likely to abate in frequency with accumulating operator experience, and the potential use of radiosensitizers may also improve obliteration rates in the future (65, 68). Emphasizing improved ease of coagulation and decreased surgical blood loss, some studies have used microsurgery after radiosurgical obliteration of deep, inoperable portions of large AVMs (12, 20, 100), underscoring that these 2 treatment modalities are not strictly competitive. In light of these known and emerging attributes of radiosurgery, it is clear that radiosurgery is attractive as primary therapy for truly inoperable lesions.

DISCUSSION

Arteriovenous malformations are complex, heterogeneous lesions; the application of facile algorithms and rigid dogma to their management is bound to be fraught with perilous pitfalls.

TABLE 10. Studies devoted to radiosurgical management of arteriovenous malformations of the basal ganglia and thalamus^a

Series (ref. no.)	Radiation	No. of patients	Previous treatment	Median maximal dose (Gy)	Median marginal dose (Gy)	Median size (cm)	Previous condition	Previous hemor- rhage	Obliter- ation rate	Early morbidity	Median follow-up (range)	Permanent radiation- induced morbidity	Total long- term morbidity and mortality ^b
Andrade- Souza et al., 2005 (3)	LA	42	12 emboli- zation 4 surgery	22.4	16.2	1.8	62% paretic 29% intact	88%	62%	19%	39 mo (25–90)	12%, 4.8% worse HP 2.4% VF 2.4% tremor 2.4%	17% morbidity 7.1% mortality
Nicolato et al., 2002 (63)	GK	21		38.7 ^c	21.6 ^c	All <3		91%	81%	8%	All >2 yr	4% Parinaud's	8% morbidity 4% mortality
Pollock et al., 2004 (72)	GK	40	1 surgery 1 embo- lization 2 radiation	36	18	2.6		62% ^d	40% 55% after 2 treat- ments	18%	45 mo (3–121)	18% morbidity 13% mortality	18% morbidity 13% mortality
Sasaki et al., 1998 (84)	GK	66	10 emboli- zation 3 emboli- zation, surgery 6 surgery			83% <3 53% <2	23% intact	94%	86%	13%	20 mo ^c	5% morbidity: 6.7% dependent 0% mortality	6.7% morbidity: 6.7% dependent 0% mortality

^a LA, linear accelerator; GK, gamma knife; VF, visual field deficit.^b Includes both radiation-induced and morbidity and mortality attributable to latency-period hemorrhage.^c Mean values.^d These values are for the entire cohort of patients in the study: 40 with arteriovenous malformations in the basal ganglia and thalamus and an additional 16 with brainstem arteriovenous malformations.

AVMs of the basal ganglia and thalamus are often deemed “inoperable” (23, 42, 54, 70), but the literature contains numerous examples of successful extirpation of these lesions with acceptable morbidity and mortality (*Tables 3–6*). Perhaps the most vital contributions to these accomplishments are appropriate preoperative planning and patient selection. At our institution, we approach these lesions with a multidisciplinary team composed of multiple neurovascular surgeons, including those with expertise in radiosurgery and endovascular embolization. The role of the endovascular surgeon is particularly important in the management of these malformations. With the theoretical exception of single-pedicle AVMs, the role of embolization is adjunctive (77), as partial embolization does not protect against subsequent hemorrhage (35, 69, 82). Although embolization of thalamoperforator and small lenticulostriate feeders may be challenging (30), the afforded dry dissection plane is highly desirable. Without embolization, a strong arterial supply can lead to rupture of small, fragile vessels at the periphery of the lesion which can draw the surgeon farther into eloquent tissue to achieve hemostasis, increasing surgical morbidity (18).

The current state of perforator and deep AVM nidus embolization continues to evolve. Advances in flow-guided microcatheter and microwire technology have enabled distal navigation into small intracranial arterial branches (14). Even with current catheter technology, vessel size limits cannot be clearly defined. Essentially, almost any perforator, including the anterior choroidal artery (37), can be embolized if sufficient purchase is achieved (LN Hopkins, personal communication). Controlled, longer injection times and the ability to embolize more nidus from one pedicle afforded by Onyx make it an attractive complement to NBCA (37, 60,106). When reflux cannot be tolerated and when access mandates the softest flow-directed microcatheters,

NBCA can be used (37,106). As Paulsen et al. (69) saw decreasing procedure-related morbidity rates with time in their series, it is likely that accruing embolization experience with the combination of Onyx and NBCA and careful staging will lead to decreasing complications. Although radiosurgery is often the treatment of choice for these lesions, the efficacy of adjunctive embolization has recently come under critical scrutiny, with one article citing decreased obliteration rates for various AVMs receiving radiosurgery with embolization as compared with radiosurgery alone (2). This result will undoubtedly meet with considerable controversy. It is necessary to emphasize the fact that delayed recanalization and collateral vascularization are conceptually more likely to occur when embolization is combined with radiosurgery as compared with combination with an expeditious and definitive surgical extirpation. Although the overall surgical resection rate of 91% is for a carefully selected patient population, this rate includes large lesions and has an accompanying conservative mortality estimate of 2.4%. This contrasts with the 69% rate of complete obliteration and 5.3% mortality rate (from latency-period hemorrhage) observed across radiosurgical series (3, 10, 72, 84). It is difficult to compare morbidity rates for these lesions, as surgical morbidity is known to decrease with time (33) and radiosurgical morbidity is more likely to accrue with time (85, 119). One must combine accumulating permanent deficits from radiation with the morbidity and mortality of latency-period hemorrhage when weighing the risks of radiosurgery. Furthermore, these risks accompany a nondefinitive approach (3, 10, 72, 84) and, thus, must be compounded if a second radiosurgical treatment is undertaken. The absence of hemorrhage after successful complete surgical extirpation of AVMs underscores its role as the “gold standard” of obliterative therapy for these lesions (33). *Table 11* delineates criteria that

TABLE 11. Comparison of factors favoring surgical treatment to those favoring radiosurgical treatment of arteriovenous malformations of the basal ganglia and thalamus^a

	Consider microsurgery	Consider radiosurgery
AVM characteristics	Ruptured ^b	Unruptured
	Surgically accessible ^b	Surgically inaccessible
	Small nidus	
	Venous outflow obstruction	
	Exclusive deep venous drainage ^c	
	Associated aneurysms	
Patient characteristics	Deep perforators can be embolized	
	Fixed neurological deficit	Neurologically intact
	Young age	
Surgeon's experience	Poor follow-up	
	Highly experienced ^b	

^a AVM, arteriovenous malformation.

^b Crucial for consideration of microsurgery.

^c The increased rupture risk for lesions with exclusively deep venous drainage favors a more expeditious treatment approach (microsurgery). The neurosurgeon's personal preference will dictate whether this feature is an intraoperative impediment. In the senior author's (HHB) experience, deep venous drainage is, at times, a convenience, as it does not encumber the early dissection field (6, 40).

favor the consideration of microsurgery for AVMs involving the basal ganglia and/or thalamus. Factors that increase the risk of rupture from these already hemorrhage-prone malformations such as history of hemorrhage (26, 38, 57, 71, 95, 117), exclusively deep venous drainage (19, 43, 55, 61, 95, 96), venous outflow obstruction (56), and small nidus size (24, 36, 41, 57, 58, 51, 93, 95, 110), as well as associated aneurysms, should prompt strong consideration of microsurgical intervention. Indeed, surgery allows for immediate and definitive treatment of both aneurysms and AVMs (9, 89). Crucial to the success of such an intervention is an appropriate corridor of access. Classical anatomic routes such as the transcallosal approach for medial lesions with good ventricular presentation are always a consideration. In addition, although hemorrhage may encourage surgical intervention, it can also facilitate it by creating a surgical route to the lesion (18, 47). Similarly, although smaller AVM size may increase the risk (24, 36, 41, 56, 57, 58, 59, 93, 95, 110) and resultant volume (93) of hemorrhage, surgical risk concomitantly decreases (44, 92), particularly when the AVM is compact. An AVM's specific vascular anatomy can also dictate surgical approach and operability. If an extensive deep perforator supply cannot be embolized, the potential surgical risk to critical parenchyma favors radiosurgical intervention. Anterior thalamoperforator supply may suggest hypothalamic involvement, similarly making the lesion a poor candidate for microsurgical resection (47). Often accompanying incident hemorrhage, a pre-existing neurological deficit also encourages surgical extirpation. There is "less to lose" and a significant amount to gain in terms of decreasing future mortality. Appeasing patient expectations becomes easier with these patients as opposed to those with asymptomatic lobar AVMs. As mentioned earlier, Sasaki et al. (84) noted that new or worsening postoperative hemiparesis was significantly associated with patients with no preoperative motor deficit and lentiform AVMs, and Tew et al. (103) did not operate on any patient whose neurological system was intact. Increasing age is an important factor to consider in these cases as remaining years for rupture dwindle and surgical risk increases. The only case of mortality in the series by U (104) was in a 60-year-old patient with a large AVM. The option of conservative (observational) management should not be forgotten for these lesions, particularly in older patients with large lesions (39). Given the proclivity to use multimodality therapy for these lesions, conflicting reports exist regarding the possibility of increased risk of developing hemorrhage after partial treatment of such AVMs (28, 38). We recently submitted 2 examples of successful complete surgical extirpation of deep AVMs after embolization (EAM Duckworth, BA Gross, HH Batjer, submitted for publication). Both patients were young, with a history of hemorrhage, and each had a convenient surgical corridor of access to their respective lesions (Figs. 1 and 2). Neither patient experienced long-term morbidity from surgery. As advocated by others (39, 48, 103), we recommend extirpation subacutely, allowing time for resolution of transient deficits and for hematoma organization. We feel that aggressive, staged, preoperative embolization is crucial for these lesions, as large and/or previously untreatable lesions may be made amenable to surgical resection. We also

advocate the use of intraoperative electrophysiological monitoring and frameless stereotaxy (89, 90). The successful intraoperative use of diffusion tensor imaging (DTI) for supratentorial gliomas (64) underscores the potential future of intraoperative imaging for deep AVMs. Thus far, reports have detailed use of DTI preoperatively for arteriovenous malformations (114, 115). Though susceptibility artifacts from surrounding hematomas may limit its utility for hemorrhaged AVMs (114), as familiarity with DTI improves, this limitation may be overcome. Okada

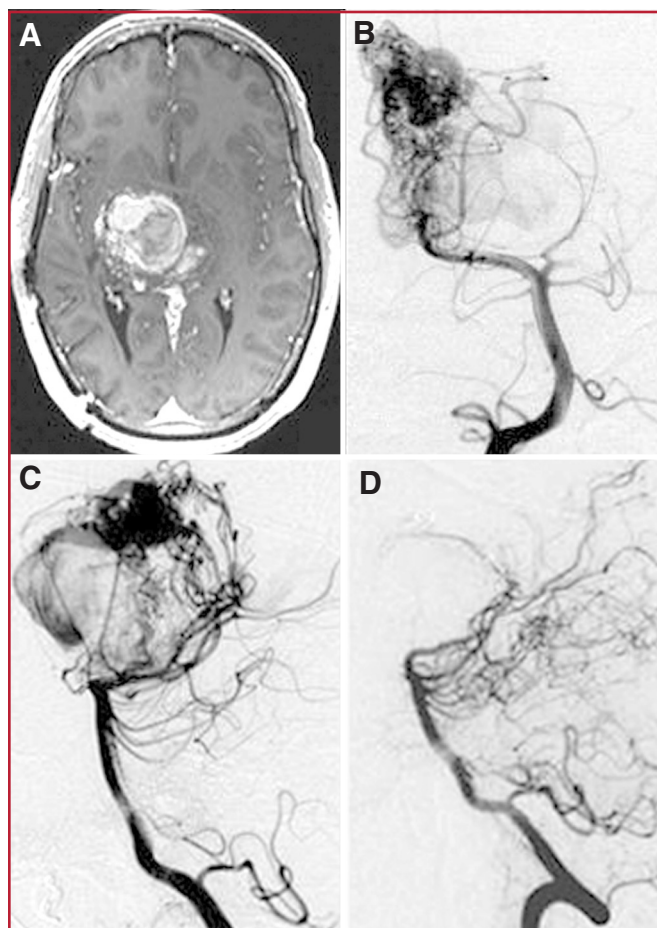


FIGURE 1. A 26-year-old man with a history of hemorrhage from a thalamic arteriovenous malformation, subsequent hematoma evacuation, and failed radiosurgery presented to our institution with worsening of his fixed left-sided hemiparesis and new-onset diplopia. Contrast-enhanced T1-weighted magnetic resonance imaging scans demonstrated a persistent 2.5-cm arteriovenous malformation with an associated large thrombosed varix (A). Anteroposterior (B) and lateral (C) digital subtraction angiography demonstrating its prominent thalamoperforator supply and deep venous drainage. Successful n-butylcyanoacrylate embolization of 3 thalamoperforate pedicles was complicated by thalamic hemorrhage, leaving the patient with long-term, mild, medically manageable residual autonomic instability. Subsequent microsurgical extirpation was performed without complication, as the previous hematoma and corticectomy tract provided a corridor of access via the superior parietal lobule. Complete obliteration was achieved, as demonstrated by postoperative digital subtraction angiography (D).

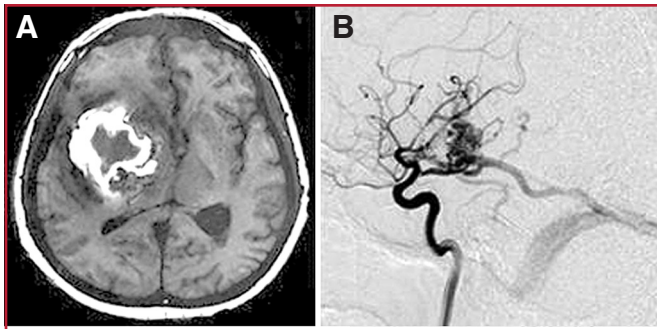


FIGURE 2. An 18-year-old man with fixed homonymous hemianopsia and left-sided spastic hemiparesis from a previous hemorrhage of his deep-seated arteriovenous malformation presented to our institution after failed radiosurgery and rebleeding. **A**, magnetic resonance imaging demonstrating dissection of the sylvian fissure by the hematoma, presenting our corridor of access for resection. **B**, digital subtraction angiography demonstrating both superficial and deep venous drainage from this 2.5-cm lesion. **C**, after successful embolization of a thalamoperforate feeder with 70% lipiodol and 30% n-butylcyanoacrylate, complete surgical extirpation was achieved without morbidity via a transsylvian, transinsular approach, as demonstrated by postoperative digital subtraction angiography.

et al. (66) used DTI preoperatively with adjunctive intraoperative subcortical motor evoked potentials; no patients in their series (including one with a parietal AVM) developed long-term weakness postoperatively. In summary, careful case selection for microsurgical extirpation is crucial. Radiosurgery has earned its place as an appropriate approach for deep-seated lesions without safe surgical access. However, patients with corridors of access to the lesion, often via a hematoma cavity, become good candidates for microsurgery, particularly if they already have fixed neurological deficits. It is the most definitive mode of approach, eliminating the risk of subsequent hemorrhage.

CONCLUSION

Arteriovenous malformations of the basal ganglia and thalamus are more likely to present with hemorrhage, have greater annual hemorrhage rates, and have greater associated morbidity and mortality with each bleed than their lobar counterparts. A multidisciplinary approach that considers observation, microsurgery, embolization, and radiosurgery, alone or in combination, is imperative to the effective management of these lesions. Incident hemorrhage, preexisting neurological deficit, small AVM size, and young age are factors that favor the consideration of microsurgical extirpation, provided the highly skilled surgeon is afforded with—and well versed in—appropriate corridors of access to these challenging lesions.

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COMMENTS

This article is an excellent review of the pertinent literature regarding surgical and radiosurgical treatment of arteriovenous malformations (AVMs) of the thalamus and basal ganglia. Gross et al. espouse a compelling argument in favor of surgical resection in appropriately selected patients with these deep seated malformations in highly eloquent brain locations. The history of previous hemorrhage and the ability to achieve partial embolization are important predictors of successful surgical resection. As noted, there is a high incidence of recurrent hemorrhage in these deep malformations, and even though radiosurgery is less invasive, the 10% annual rebleeding rate and significant risk of radiation-induced complications support the surgical option.

Although I agree with the authors' rational approach supporting surgical treatment, I am still in favor of radiosurgery for the majority of AVMs of the thalamus and basal ganglia. Several of the important points made in this discussion are worth underscoring. It should first be emphasized that the senior neurosurgeon in this report is a highly experienced vascular neurosurgeon, and his results and surgical abilities may not be generalizable. Surgical treatment should not be considered as a primary treatment option for unruptured lesions in the basal ganglia and thalamus. Previous hemorrhage that has already produced a neurological deficit, created a corridor of safe surgical approach, and partially dissected the AVM from surrounding eloquent tissue are essential elements for choosing microsurgery over radiosurgery. The other critical factor is the availability of an endovascular approach to the deep perforator supply. If the deep choroidal and/or lenticulostriate supply to the malformation cannot be embolized, further neurological deficit is likely from deep dissection of these arterial feeders. An active lenticulostriate supply at the time of surgery suggests that the internal capsule is at risk during the resection.

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Gross et al. reviewed the literature on the treatment and outcome of patients with deep-seated AVMs. They argued that because of their poor natural history, certain lesions are best treated by surgical resection. They also reviewed operative approaches based on the anatomic location of the lesion. Surgical results are compared with published series on AVMs treated with radiosurgery. Gross et al. rightly emphasized that certain deep lesions are amenable to surgical cure and should not be universally considered inoperable.

Radiosurgery and microsurgery are complementary modalities. In patients with a neurological deficit, we favor surgical resection for deep lesions when a hematoma has created an operative corridor. We favor radiosurgery for small (<3 cm) lesions in asymptomatic patients.

Infrequently, the two modalities can be combined in the same patient. Radiosurgery is applied for the deep, relatively inaccessible portion of a lesion, followed by delayed resection of the residual AVM. This strategy does not eliminate the risk of hemorrhage during the latency period before resection. However, it may help reduce the approach-related morbidity associated with extirpation of the deep portion of the lesion.

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Gross et al. provide a concise review of AVMs of the diencephalon, challenging the conventional belief that these lesions are inoperable. As discussed, with experience and skill such as those possessed by the senior author, microsurgical resection of selected lesions may be performed safely with results that are superior to those achieved with radiosurgery. The natural history, vascular anatomy, surgical approaches, and results of both surgical and radiosurgical treatment modalities were reviewed in detail. Several important points were made that deserve reiteration. Deep venous drainage, often seen in these AVMs, can be protective during surgical expatriation and, when possible, preoperative embolization is a useful adjunct to surgical management. These lesions have a tendency to present with hemorrhage more frequently than other AVMs and often are associated with a greater morbidity and mortality.

These are challenging lesions even in the most skilled hands. Neurologically intact patients presenting with these AVMs are often best managed by observation or radiosurgery. This is an excellent and thorough review.

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Gross et al. describe the highly successful rate of complete obliteration with low morbidity that they achieved with surgery for selected small AVMs at the boundaries of the basal ganglia and thalamus and also in conjunction with the insular cortex as the central core or insular lobe region (2–5). However, we do not consider the lower complete obliteration rate and higher morbidity with radiosurgery as being comparable with the results achieved with surgical resection owing to the fact that basal ganglia and thalamic lesions centrally located near or intermingled with the internal capsule or thalamus with perforators as the arterial supply are often treated by radiosurgery, increasing the rate of failure and complications related to it. On the other hand, these central lesions are seldom approached surgically, leading to the higher complication rate in the radiosurgical group. For this reason, we still consider radiosurgery to be the treatment of choice for these AVMs and reserve the use of surgery for small peripherally located lesions.

A difficult decision remains for borderline AVMs when surgery and radiosurgery are both options. In these patients, the latency period of approximately 3 years to achieve complete obliteration with radiosurgery must be strongly considered. Age, previous and number of hemorrhagic episodes, and pretreatment deficits are also as important as the experience of the surgeon in consideration of the treatment modality (3).

We divide insular lobe region AVMs as follows:

- 1) The lateral aspect or insular cortex. If restricted to its surrounding white matter called the extreme capsule, these lesions are able to be approached surgically, especially if they are located at the first or

middle third of the insular shield. The posterior third are in close proximity to the optic radiations and the posterior, retro, and sublenticular portions of the internal capsule, with a high risk of damage to these structures.

- 2) The anteroinferior portion on the insular lobe, the perforated substance. These AVMs can be approached surgically.
- 3) The medial boundary of the insular lobe. This region can be divided into the anterior portion, where the head of the caudate nucleus can harbor a small surgical lesion, the middle part subdivided in the middle superior part represented by the ventricular surface of the thalamus, where an AVM is also able to be resected, the inferior middle part, and the third ventricle walls, which usually has poor results with surgery.
- 4) The posterior region, the pulvinar of the thalamus. This region also has the potential to allow surgical resection of lesions as the atrium acts as a natural corridor if the lesion is at the surface of that region.
- 5) The superior region, located around the lateral ventricular walls. AVMs in this region can be surgically resected in selected patients.

The mixed type of AVMs include a mixture of more than one type described above and are often represented by large lesions for which surgery has little value in most patients. Central lesions involving the lentiform nucleus, the internal capsule, and deep thalamus are often treated nonsurgically. In some of our patients, we also observed the importance of previous bleeding leading to dissection planes, in which the hematoma acts as a corridor to the lesion making some "inoperable" AVMs operable.

We do agree that endovascular procedures are an adjuvant modality, playing no role as the single treatment (3). However, the concept that the risk of incomplete obliteration of AVMs is increased if embolization is performed before radiosurgery is not shared by us. The recanalization after an endovascular procedure is well known. However, the risk of misplacing the target in radiosurgery planning owing to recanalization of some feeders or the nidus of an AVM is decreased by delaying radiosurgery planning up to 3 months after the last nidus embolization by which time recanalization often already occurred. We observed similar or even better results with prior embolization before radiosurgery.

We have operated on 56 insular lobe AVMs in the past 20 years. We achieved an obliteration rate similar to that described in this article. There was a good outcome in 49 (87.5%) patients with no neurological deficits, 6 (11%) patients had a fair outcome with development of additional deficits but maintenance of Karnofsky scale scores of more than 70, and 1 (1.4%) patient died. We had no patient with complete deficit or aphasia (3).

As described by Gross et al., we believe that a multidisciplinary team is the appropriate treatment for these complex and challenging insular lobe region AVMs (1–4).

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In this article, Gross et al. reviewed the literature on the results of endovascular, radiosurgical, and microsurgical treatment for basal ganglia and thalamic AVMs. They described the natural history of these entities, and pointed out the poorer results with deep-seated AVMs. They then reviewed vascular anatomy and surgical approaches, subdivided for the various types and locations of these deep-seated AVMs, and finally reviewed endovascular approaches and outcomes and results of radiosurgery.

I found the discussion very useful because it included many appropriate remarks frequently not acknowledged adequately in other publications, such as "one must combine accumulating permanent deficits from radiation with the morbidity and mortality of late hemorrhage when weighing the risks of radiosurgery." The most important contribution of this review is that it highlights the different outcomes and higher risks with this subgroup of AVMs along with the fact that it would be a mistake to apply rigid dogmas and algorithms in their management. Because of the extensive amount of literature reviewed, a certain complexity is evident, which makes the reading of the article somewhat difficult. However, this occurs commonly with this type of review and cannot be easily avoided.

The article contains an important message that is well presented. The final conclusion is that more of these AVMs might be suitable for microsurgery, although the place of embolization and radiosurgery in treatment of these lesions is not disputed.

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INTRAOPERATIVE MAGNETIC RESONANCE IMAGING AT 3-T USING A DUAL INDEPENDENT OPERATING ROOM-MAGNETIC RESONANCE IMAGING SUITE: DEVELOPMENT, FEASIBILITY, SAFETY, AND PRELIMINARY EXPERIENCE

OBJECTIVE: A twin neurosurgical magnetic resonance imaging (MRI) suite with 3-T intraoperative MRI (iMRI) was developed to be available to neurosurgeons for iMRI and for independent use by radiologists.

METHODS: The suite was designed with one area dedicated to neurosurgery and the other to performing MRI under surgical conditions (sterility and anesthesia). The operating table is motorized, enabling transfer of the patient into the MRI system. These two areas can function independently, allowing the MRI area to be used for nonsurgical cases. We report the findings from the first 21 patients to undergo scheduled neurosurgery with iMRI in this suite (average age, 51 ± 24 yr; intracranial tumor, 18 patients; epilepsy surgery, 3 patients).

RESULTS: Twenty-six iMRI examinations were performed, 3 immediately before surgical incision, 9 during surgery (operative field partially closed), and 14 immediately postsurgery (operative field fully closed but patient still anesthetized and draped). Minor technical dysfunctions prolonged 10 iMRI procedures; however, no serious iMRI-related incidents occurred. Twenty-three iMRI examinations took an average of 78 ± 20 minutes to perform. In three patients, iMRI led to further tumor resection because removable residual tumor was identified. Complete tumor resection was achieved in 15 of the 18 cases.

CONCLUSION: The layout of the new complex allows open access to the 3-T iMRI system except when it is in use under surgical conditions. Three patients benefited from the iMRI examination to achieve total resection. No permanent complications were observed. Therefore, the 3-T iMRI is feasible and appears to be a safe tool for intraoperative surgical planning and assessment.

KEY WORDS: Intraoperative magnetic resonance imaging, Twin neurosurgical-magnetic resonance imaging suite

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Since the pioneering neurosurgical studies of Black et al. (1) at Brigham and Women's Hospital in the mid-1990s (12), intraoperative magnetic resonance imaging (iMRI) has evolved according to medical priorities and institutional constraints. The iMRI

suite developed by the Black group was used to perform magnetic resonance imaging (MRI) during surgery using a dedicated MRI suite in which surgery took place within the magnet. This arrangement permitted the use of imaging during neurosurgical procedures,

ABBREVIATIONS: iMRI, intraoperative magnetic resonance imaging; IQ, image quality; MRI, magnetic resonance imaging; OR, operating room; SNR, signal-to-noise ratio

providing the surgeon with nearly real-time neuronavigation. Such accuracy was not possible with the concomitantly developed neuronavigation systems that used only preoperative imaging (10, 22) because of perioperative anatomic shifts in brain anatomy.

Since then, iMRI suite development has followed two general concepts. The first concept, developed by two groups, is based on continuously refreshed images (1, 6). The suite developed by Black et al. allowed the surgeon access to the patient during the imaging procedure through the 56-cm-wide gap of the open-bore. T2-weighted images were updated every 2 seconds. Every instrument used in the operating room (OR) had to be MRI-compatible. The second and more widely developed alternative concept was to perform iMRI discontinuously during interruptions of the surgical procedure by either bringing the MRI machine to the patient or vice versa (2, 7–9, 14, 17, 18, 20, 21, 23). This latter concept evolved in two main directions, toward either MRI systems with a higher magnetic field strength of 1.5- or 3-T (7, 8, 18, 21) or lighter devices (2, 14). The light and mobile PoleStar N10 (Odin Medical Technologies, Yokneam, Israel), running at 0.12-T, was designed to be used in a familiar OR environment; however, a compromise was made on image quality (IQ), which was considered to be poor in 12% of the cases and excellent in only 45% (14). Moreover, the device's functionality "imposed restrictions on patient positioning" (14, p 615), leading to practical surgical limitations. The main modifications made to the second-generation PoleStar N20 were: 1) a slight increase in basic magnetic field strength (0.15 T); 2) a slight widening of the interpolar gap to 27 cm; and 3) a larger image field of view (14). The main advantage of using the mobile ultra-low-field iMRI system was that it could be used with standard, non-MRI-compatible instruments (including the table) because the field strength fell below the critical threshold for use in an operating area; no significant attraction is felt within 1 ft of the poles (14).

High-field iMRI was developed (7, 8, 18) not only to provide surgery with diagnostic anatomic and functional iMRI, but also in such a way as to not adversely affect established surgical nursing and anesthetic techniques. To achieve this, it was necessary for imaging to take place at various stages of the procedure rather than in real time. The main constraint of all iterative, noncontinuous modalities is the need to interrupt the surgical procedure to safely transfer the patient to the MRI system (7, 8) or the mobile MRI system to the patient (18), which requires careful training. However, these configurations allow the neurosurgeon to endure minimized constraints during surgery and to use conventional surgical tools beyond the 5-G line.

A multidisciplinary working group was created that included architects, engineers, technicians, radiologists, anesthesiologists, nurses, and neurosurgeons, who conceived and built an original MRI-neurosurgical facility equipped with a state-of-the-art 3-T system. This facility was designed to meet the demands of diagnostic, research, intraoperative imaging, and high surgical comfort standards. This concept and the first 21 patients treated in this facility are reported here.

PATIENTS AND METHODS

Definition of the Requirements and Constraints

Because the 3-T iMRI provides greater IQ, the first global goal of the project was to establish the use of MRI with such field strength in the operating facility. Because of the danger of permanent magnetic attraction, the precautions needed to protect against external electromagnetic interferences, the difficulty in finding highly specialized staff, and the difficulty in defining a cost-effective solution, the second global goal of this project was to enable the two rooms (the OR and the MRI room) to function independently of one another. The target was to recoup costs by maximizing the use of the 3-T MRI system as well as contain costs by enabling the use of standard surgical equipment in the OR.

Keeping these two goals and their consequences in mind, the exploratory group analyzed the requirements imposed on architectural design by the main medical disciplines that would be involved in the daily use of this equipment, the technical constraints linked to specific equipment in the OR and MRI room, and the specific constraints of the layout of the building. All of these constraints are presented in *Table 1*.

MRI Device

The MRI scanner (Achieve 3T; Philips Medical Systems, Best, The Netherlands) runs under Release 2.1 software and is equipped with high-power 80 mT/m (Quasar) gradients; it is 2 m wide, 1.8 m long, and weighs 4.6 tons. It should be noted that the entire MRI department is situated on the ground floor. The cooling system of the magnet does not have any interface with the patient; the magnet is cooled by its own loop of cooled water connected to the hospital network.

The working space of the magnet can be defined by the 60-cm aperture of the body coil. This aperture is similar at its bore and its center. There is no true working space because the cylinder-shaped system is dedicated to standard clinical imaging and not to intraoperative procedures such as the PoleStar system or the pioneering double doughnut designed by GE (Boston, MA) in the mid-1990s.

This magnet is used for research projects 90% of the time. The neurosurgeons benefit from specified time slots during which they can request its use for intraoperative imaging. For compatibility with the Mayfield head clamp, two flexible surface coils are positioned on both sides of the patient's head.

Architecture and Site Description

Architectural Setup

The suite consists of an OR (surface area, 50 m²) and an MRI scanner room (surface area, 33 m²) separated by an air lock (surface area, 15 m²) (*Fig. 1*). The distance from the center of the OR to the center of the MRI room is 12 m (*Fig. 2*).

In this project, we had to consider various parameters of the existing building. Some were very positive, such as the two neighboring departments (Neuroradiology and Neurosurgery), whereas some existing parameters presented disadvantages that we had to manage, e.g., the two different building modules required to adapt the architecture of the OR, principally moving the surgical activity from the center of the OR to the axis of the magnet (*Fig. 2*).

Electromagnetic Compatibility

To make the MRI scanner available to the remainder of the hospital and to satisfy the neuroradiologists' demands to preserve IQ, we

TABLE 1. System and integration requirements^a**Neurosurgery**

Smooth transfer of the patient
The transfer table has to allow as many neurosurgical positions as possible
Enough space available around the table position to install all the medical equipment needed for transfer or surgery
Have the option to perform surgical procedures in the MRI room

Anesthesiology

Be able to control/monitor vital parameters and ventilate the patient in all places and at all times during the procedures, regardless of which type of MRI system is installed

Nursing and biotechnology

Fluid access to the various storage areas and the operating field
Equipment technically and physically easy to manipulate

Neuroradiology

Protecting against the dangers linked to magnetic force by prohibiting any ferromagnetic object within a 0.5-mT field line of the magnet
Preserve image quality by prohibiting any ferromagnetic object within a 0.1-mT field line of the magnet; maintaining a homogeneous magnetic field: the magnet needed to be placed as symmetrically as possible to the building structure; no potential sources of electromagnetic interferences can be permitted within the Faraday cage
Prevent helium leakage into the OR: need for the air pressure in the OR to be slightly higher than in the MRI room
Allow the MRI system to be available for diagnostic use as well as for perioperative imaging

Hygiene

The main goal identified by hygienists was for the air quality in the MRI room to be equivalent to that in the OR: 25 air renewals per hour, absolute terminal filtration, positive pressure is required in the MRI room when it is being used as an OR
The operating field sterility needs to be maintained when moving between rooms
It has to be as easy to clean all surfaces in the MRI room as in an OR

Architecture

The MRI system is situated in a building extension built on a different module than the remainder of the hospital; therefore, it was not possible to align the operating room with the MRI room
Respect various building requirements related to an operating environment for the OR or the MRI room

Acoustic

The acceptable noise level in an OR is extremely low, approximately 40 dB. However, the noise level reached by a 3-T MRI during image acquisition is extremely high, >100 dB for certain sequences. For this shared resource project to succeed, the OR needs to be shielded from the noise generated during image acquisition in the neighboring room

^a MRI, magnetic resonance imaging; OR, operating room.

installed the OR outside the 0.1-mT field line of the magnet. The distance between the MRI scanner and the OR obviates the need for MRI-compatible surgical instruments in the OR. However, before patient transfer to the MRI scanner, everything but MRI-compatible devices must be removed from the patient and the table to avoid the projectile effect and prevent imaging artifacts. The radiofrequency waves emitted and received by the MRI scanner (128 MHz) are limited to the MRI room by a Faraday cage.

Hygiene and Air Flow Regulation

To obtain an air quality in the MRI room equivalent to that of the OR and to meet building standards for an operating block, we designed the MRI room as an OR, with the same pulsating ceiling system that allowed laminar distribution, the same types of safe power supplies, and the same easy-to-clean surfaces. The strict air quality standards that are required when the MRI system is used in the intraoperative

mode are not required when the system is used in the research and diagnostic modes. Therefore, it is necessary to prevent air blending when the rooms are working independently. This is achieved by controlling the direction of airflow, which should move from sterile environments to non-sterile environments.

This pressure control problem can be summarized by the following expression: $P[\text{operating room}] > P[\text{magnet room}] > P[\text{MRI department}]$. We used conventional pressure control technology to meet these requirements but also created two independent ventilation systems without any interconnection in their distribution networks or air processing systems. The link necessary to maintain desired pressures on either side is provided through airflow management electronics in both the pulsation and suction groups and in the compensation flaps. The running parameters of the system include a temperature setting at $21 \pm 3^\circ\text{C}$, and moisture is controlled by the system to remain between 45 and 55%.

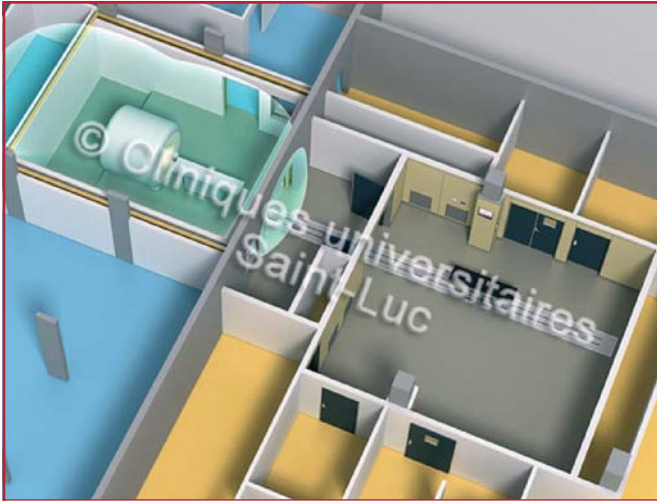


FIGURE 1. Diagram of the magnetic resonance imaging (MRI) department (blue), the operating department (OR) (yellow), and the OR-MRI suite (gray). The three-dimensional blue volume shows the 0.1-mT limits, and the green one shows the 0.5-mT limits.

Air Lock

According to the relative position of the two rooms (concrete shell) and the fire department's requirements, an air lock between the two rooms had to be designed to be sure that, in case of fire, smoke in one



FIGURE 3. Photograph of the double casing that reduces noise transferred to the OR by the 3-T MRI machine.

room could not contaminate the other room (Figs. 1 and 2). Notably, this air lock creates a buffer zone for pressure control and finalizes the acoustic insulation. In daily use, the most important function of this air lock is to serve as a physical barrier to secure both rooms and to protect OR users against hazards presented by the magnetic field.

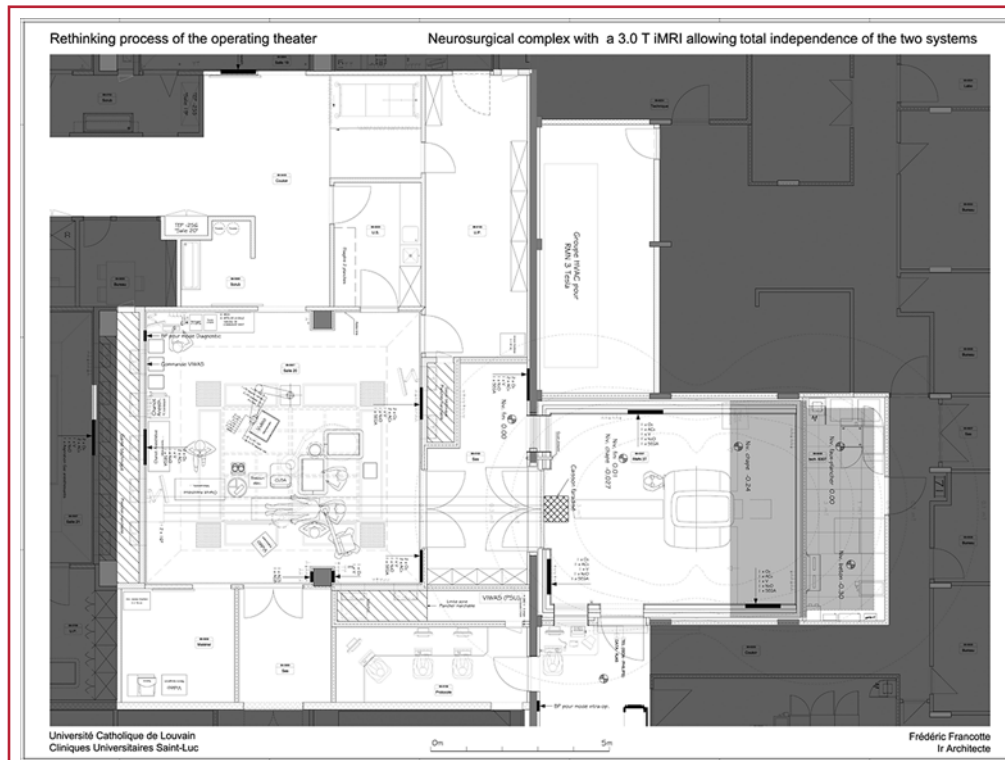


FIGURE 2. Floor plan of the OR-MRI suite with graphic scale.

Acoustics

Because the acceptable level of noise in an OR is low (40 dB) and given the confines of the existing building, the MRI machine was placed on an acoustic insulator, an acoustic door was installed, acoustic glazing was used to fill openings in the concrete shell, and a double casing was built around the Faraday cage (Fig. 3).

Security Procedures

To minimize the risk of injury to patients and staff during an intraoperative imaging procedure, we designed an access control system for the OR. When the surgeon does not need the twin neurosurgical-MRI suite, the door between the MRI room and the OR (i.e., the operating door) is locked and the alternative MRI access door (the research door) is not; however, when the neurosurgeon needs iMRI, the research door is locked and the operating door is not. To further alert the staff about the potential hazards associated with the MRI process, we installed a blue light to indicate that a proce-

ture is ongoing and a sound alert that signals when someone enters the OR. Before performing the first iMRI, the members of the work group offered proper training to all staff associated with these procedures (neurosurgery and 3-T MRI) and created protocols delineating standard operating procedures.

Surgical Integration

Ergonomics and Lighting

We wanted to develop a system that did not require any specific physical abilities to operate and manipulate. Using the Maquet system was one part of the solution, but to increase flexibility in the OR, we placed a boom arm next to the pulsating ceiling to give the surgeons access to power and medical fluids.

We wanted to enable the performance of surgical procedures during MRI, so we had to guarantee an ergonomic position for the neurosurgeon. Therefore, we designed a 30-cm pit in the floor of the MRI room, as was done in Minneapolis (21). Added to the 70-cm height of the machine table, this provided a 100-cm work level. For procedures in the MRI room, we installed surgical lighting (1200 lux) generated outside the Faraday cage and brought in by fiberoptics (Starflex Lightgen150W HIT; Zumtobel Lighting GmbH, Dornbirn, Austria). For future evolutions, medical fluid sockets were installed in the MRI room so that 3-T MRI-compatible devices could be used inside the MRI room.

Surgical Equipment

For each procedure, the VectorVision neuronavigation system (BrainLAB, Munich, Germany) and the Pentero microsurgical microscope (Zeiss, Jena, Germany) are used. The patient's head is fixed in the Doro Radiolucent Headrest system with MRI-compatible disposable cranial pins (Pro Med Instruments GmbH, Freiburg, Germany), whose arm is fixed to the same tabletop during surgery and iMRI. The Budde Halo Retractor System (Integra LifeSciences Corp., Plainsboro, NJ) and conventional surgical and microsurgical tool sets are used.

Anesthetic Technique

Anesthesiologists manage three separate challenges during a 3-T iMRI procedure. First, the patient must be prepared carefully, draped, and positioned in such a manner as to allow MRI to be performed. Second, MRI-compatible patient monitoring is necessary. The monitoring equipment (Veris-Medrad, Inc., Warrendale, PA), built into a special MRI-compatible trolley, can be pushed with the patient into the MRI suite. This equipment is adapted for patients on neuroanesthesia for intracranial procedures and allows simultaneous electrocardiographic monitoring (three or five leads), invasive blood pressure monitoring, pulse oximetry, capnography, inspired and expired concentrations of anesthetic gases and O₂, and patient temperature. This monitoring equipment uses primarily fiberoptic technology and is appropriate for both adult and pediatric patients. The electrocardiograph machine is connected to special MRI-compatible electrodes (Invisatrace-ConMed Corp., Utica, NY). The third challenge is to perform the anesthesia in an MRI-compatible manner. During the surgical part of the operation, total intravenous anesthesia based on propofol, sufentanil, or remifentanyl and muscle relaxant was administered. Inhalational anesthesia (sevoflurane or isoflurane) is used for the transfer into and the time in the MRI scanner. The breathing circuit is a coaxial circuit (Universal F2, 150–300 cm; King Systems Corp., Noblesville, IN) connected to a ventilator. This allows easy disconnection for transfer to the ambulatory system, a KAB CO₂ absorber (King Systems Corp.), which allows the patient to be ventilated manually as well as providing inhalational anesthesia during patient transfer.



FIGURE 4. Photograph of the Maquet table in the direction of the MRI room.

Once in the MRI scanner, the patient is reconnected to a ventilator that remains in the air lock, outside the MRI room; therefore, purchase of an expensive MRI-compatible ventilator is not required. The anesthesiologist also remains outside the MRI room and monitors the patient visually through a window and via data relayed from a monitoring system inside the MRI room. Once the MRI scan is completed, the patient is returned to the OR for further surgery or reversal of anesthesia or is transferred anesthetized to the intensive care unit.

Patient Transfer

The distance between the two rooms required that we develop a system for transferring the patient from one room to the other. We chose a special operating table (Vascular Interventional Workplace for Advanced Surgery; Maquet, Rastatt, Germany) with a weight limit of



FIGURE 5. Photograph of the tabletop, designed by the Center for Research in Mechatronics at Université Catholique de Louvain, on the Maquet table at the interface between the air lock room and the MRI room.

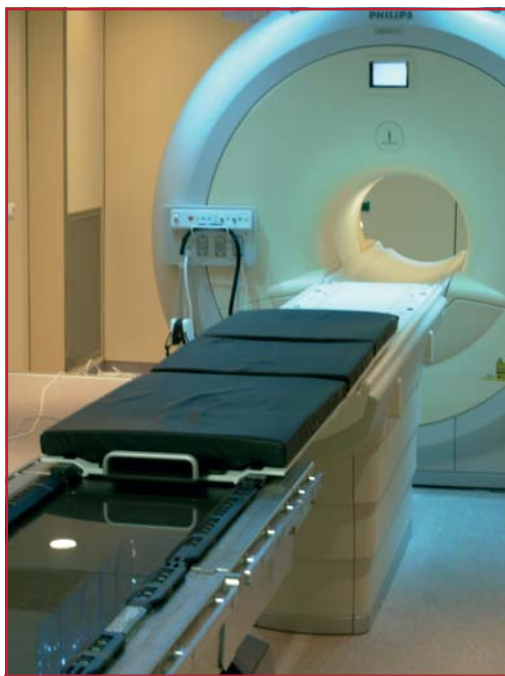


FIGURE 6. Photograph of the sliding of the tabletop from the Maquet table to the MRI table.

150 kg that can move on tracks from the OR to the entrance of the MRI room and that can assume any surgical position required for cranial and spinal neurosurgery. This table is set in the horizontal position for imaging procedures and is mechanically buffered to protect the patient's head from vibrations (Fig. 4). The rails are completely integrated in an aluminum box, and the spacings needed to support the feed are covered by a rubber band moving with them.

The patient lies on an MRI-compatible tabletop made of white polyoxymethylene that was manufactured by the Center for Research in Mechatronics at the Université Catholique de Louvain. This transfer tray slides from the Maquet table to an MRI tabletop, manufactured by the same team, which enters the MRI machine and positions the patient's head at its isocenter (Figs. 5 and 6). An MRI-compatible Mayfield headholder is fixed on the sliding tabletop.

Imaging Protocols

All intraoperative brain images are acquired using the same pair of standard medium-sized flexible surface coils (M-Flex coil; Philips Medical Systems). Pulse sequence data are optimized to obtain the best IQ for all sequences. The main tradeoff is an increase in acquisition time. The chosen option is to preserve the highest IQ possible despite the use of a nonquadrature receiving system and the lack of parallel imaging in this receiver configuration. Initially, priority was given to the fast spin echo technique because it theoretically lowers susceptibility artifacts. However, using gradient echo, even with the echo planar imaging technique, failed to demonstrate a prohibitive increase in metallic artifacts in the intraoperative setting. Therefore, three different T1-weighted sequences were tailored for different purposes: 1) a spin echo (2', 4") sequence with 24 slices of 5-mm thickness for common use covering the whole brain; 2) a gradient echo or fast-field echo (2', 33") sequence with thinner 3-mm slices; and 3) a three-dimensional fast-field echo sequence with 1-mm slices for multiplanar or coregistration purposes.

T1- and T2-weighted fast spin echo (1', 33"), fast fluid-attenuated inversion recovery (2', 56") sequences were all included in the initial basic MRI protocol. However, echo planar imaging-gradient echo T2* (14") was added shortly thereafter because of the importance of detecting and delineating acute bleeding areas in the operative area. Echo planar imaging, spin echo, diffusion-weighted (29'), and time-of-flight phlebogram were added in an "à la carte" mode. Diffusion-weighted imaging is performed in all cases in which tumor extension is accurately delineated by the technique on preoperative workup or acute ischemic damage has to be ruled out. Phlebograms are obtained when normal patency of the major venous channels adjacent to surgical area has to be assessed. When needed, the use of fat suppression is feasible and does not result in overall IQ degradation. Basic principles for intraoperative imaging are applied as follows: to obtain pre- and postcontrast T1- and T2-weighted information in strictly similar slice locations (in axial transverse plane for most cases); to obtain T2-weighted information in at least two orthogonal planes (mainly axial transverse and coronal); and to obtain postcontrast images in all cases of glioma resection even when no contrast enhancement has been observed on preoperative MRI workup.

Patients and Data Collection

We prospectively collected data from the first 21 consecutive patients (11 men, 10 women) who were scheduled for cranial neurosurgery and iMRI between March and June 2006. Patient ages ranged from 3 to 80 years (average, 51 ± 24 yr), and patient weights ranged from 11 to 105 kg. Patient diagnoses were glioma (six patients), meningioma (three patients), schwannoma (one patient), pituitary adenoma (three patients), intraventricular tumor (two patients), metastasis (three patients), and epilepsy (three patients) (Table 2).

To facilitate iMRI interpretation, the neuroradiologist was systematically informed of the surgical technique and of the perioperative surgeon's assessment before the iMRI procedure to reinforce the accuracy of the online and real-time interpretation of the intraoperative images.

Additionally, the radiological team gave a second and final collegial interpretation of the iMRI 24 to 48 hours after the procedure. We called this delayed interpretation. The definition of the resection quality was as follows: total, 100%; near total, 95% or greater; subtotal, 80% to 95%; partial, less than 80%.

For each patient, the surgical goal and the surgeon's assessment at the end of surgery were pronounced before iMRI was performed. Patients who underwent tumor resection had a follow-up computed tomographic examination (Brilliance 16Power; Philips Medical Systems) performed within 1 (high-grade) to 3 months (low-grade) and a follow-up MRI examination between 2 and 6 months. All events and dysfunctions that occurred between the interruption and resumption of surgery (the entire iMRI procedure) were noted, as was any significant loss of time (Table 3). For the last 10 patients of the series (11 examinations), we recorded the precise timing of each phase of the iMRI procedure (Fig. 7).

RESULTS

We used the twin neurosurgical-MRI suite for 21 patients. Twenty-six iMRI examinations were carried out, of which 3 were immediately presurgical (only children), 9 were intrasurgical (partial head closure before iMRI), and 14 were immediately postsurgical (head fully closed, but patient still anesthetized and sterilely draped). Five patients had two iMRI procedures during the same intervention, and three had additional tumor resection immediately after iMRI, of whom two had partial head closure and one was already completely closed (Table 2).

TABLE 2. Characteristics of the population^a

Patient no.	Age (yr)/sex	Weight (kg)	BMI	Pathology	Location	Side	Position	iMRI no.	iMRI			Ad Res	Results	Results
									Pre-incision	Head partially closed	Head completely closed			
1	3/F	11	11.22	MRE	Frontotemporo- oparietal	R	Dorsal	01	+					
2	80/F	66	29.72	Meningioma	Frontal	B	Dorsal	02			+		TFD + MST	
3	56/F	77	24.24	Colloid cyst	Intraventricular		Dorsal	03			+		TR	
4	58/M	83	25.61	Adenoma hCG, LH	Pituitary		Dorsal	04			+		TR	
5	60/F	55	20.2	Carcinoma metastasis	Parietal	R	Ventral	05			+		TR	
6	38/M	85	28.4	Meningioma G III	Frontal	R	Dorsal	06			+		Near TR	+
7	21/M	65	21.71	MRE	Frontotemporo- oparietal	R	Dorsal	07			+		Near TR	TR
8	70/F	105	40	Glioblastoma	Frontal	R	Dorsal	08			+		TFD + MST	
9	67/M	78	26.06	Oligoastrocytoma G II	Temporoinsular	R	Dorsal	09			+		TR	
10	9/F	40	19.02	MRE	Precentral	R	Dorsal	10			+		TR	
11	43/M	90	31.14	Astrocytoma G III	Frontotemporo- oparietal	L	Dorsal	11			+		MST	
12	74/F	100	35.85	Meningioma	Precentral	R	Dorsal	12			+		TR	
13	75/M	74	22.83	Schwannoma ^b	Temporal	L	Dorsal	13			+		TR	
14	49/M	72	23.51	Astrocytoma G III	CPA	L	Ventral	14			+		Partial resection (75%)	
15	55/F	85	30.11	Carcinoma metastasis	Precentral	R	Dorsal	15			+		Near TR ^c	+
16	2/M	12	14.49	Choroid plexus papilloma	Frontal	L	Dorsal	16			+		Near TR	+
17	43/F	63	21.29	Oligodendroglioma G III	Temporal horn	L	Dorsal	17			+		TR	
18	53/M	92	25.48	Glioblastoma	Frontal	R	Dorsal	18			+		TR	
19	75/M	103	29.45	Carcinoma metastasis ^d	Frontal	R	Dorsal	19			+		TR	
20	61/F	74	27.85	Adenoma ACTH	Frontal extradural	B	Dorsal	20			+		TR	
21	75/M	73	24.67	Adenoma NF	Pituitary		Dorsal	21			+		TR	
22					Pituitary		Dorsal	22			+		Sub-TR	

^a BMI, body mass index; iMRI, intraoperative magnetic resonance imaging; Ad Res, additional resection; MRE, medically refractory epilepsy; R, right; TFD, total frontal disconnection; MST, multiple subpial transections; B, both; TR, total resection; hCG, human chorionic gonadotropin; LH, luteinizing hormone; G, grade; L, left; CPA, cerebellopontine angle; ACTH, adrenocorticotropin; Sub-TR, subtotal resection; NF, nonfunctional.

^b Extrameatal largest diameter of 30 mm.

^c Near total resection followed by an additional resection without a second iMRI but checked 2 days later, confirming the TR.

^d Extra-axial metastasis of a basocellular tumor.

TABLE 3. Intraoperative magnetic resonance imaging procedural dysfunctions and their duration^a

Patient no.	Location	OR waiting for MRI (min)	Blocked transfer table (min)	Blocked MRI table (min)	Unplugged coil (min)	Coil position artifact (min)	Head too high (artifact) ^b	Metal artifact	MRI bug software (min)
4	Pituitary						+		
5	Parietal							+	
9	Frontal	30							
11	Frontal						+		
12	Temporal						+		
14	Frontal	17			15	26			
15	Frontal			10					
16	Temporal		2						
17	Frontal								20
18	Frontal				12				
20	Pituitary	14							
21	Pituitary	28					+		10
Total		4	1	1	2	1	4	1	2

^a OR, operating room; MRI, magnetic resonance imaging.

^b When a coil touched the wall of the MRI tunnel, an artifact was observed, but it did not prevent MRI interpretation.

^c The star-holder remained attached to the headholder.

Procedure

All patients were anesthetized, monitored with MRI-compatible electrodes installed dorsally (n = 19) or ventrally (n = 2), and positioned without restraints for surgery, with the head held in a three-pin MRI-compatible headholder. To avoid any electrical loop that could lead to skin burns in a contact zone during MRI, each limb was draped and electrically isolated from the rest of the body. Once the neurosurgical procedure was thought to be completed, patients were temporarily (n = 9) or completely (n = 14) closed, depending on the surgeon's assessment. For partial closure, a large gelatin foam sponge (Gelfoam; Pharmacia & Upjohn Co., Kalamazoo, MI) covered the exposed brain, two or three stitches were placed to stretch the dura mater, and two or three large stitches were placed on the scalp, the whole partial

closure being done in less than 5 minutes. The reopening of such a partial closure would take less than 2 minutes.

The surgical wound was protected by sterile compresses and adhesive tape. The drapes were cut around the patient's head and body. The BrainLAB reference star-holder was detached from the headholder, and the whole headholder system and head were repositioned above the plane of the surgical table to allow insertion of the mobile table extension. The nonsterile MRI flexible surface coils were then fixed on the patient's head with regular tape.

Once the surgical team was ready, the motorized surgical table on rails was moved to the MRI facility. A trained senior neuroradiologist interpreted intraoperative images immediately after acquisition. The surgeon evaluated whether additional resection was appropriate when residual tumor was

clearly delineated. If not, when necessary, patients were re-draped, and a complete head closure was performed (n = 9). If additional surgery was indicated, the operating field was reopened, and tumor resection was completed. If needed, the additional tumor resection was followed by a second iMRI examination (n = 2).

Safety and Reliability

All involved personnel were thoroughly trained to avoid accidents owing to ferromagnetic objects entering the MRI

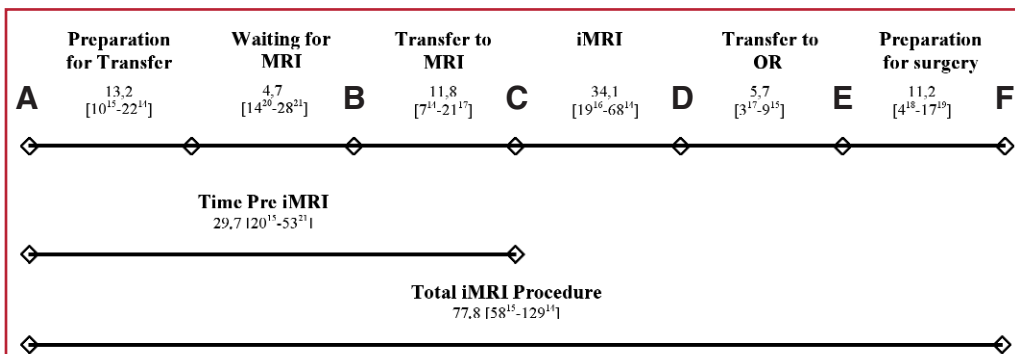


FIGURE 7. Timeline of intraoperative MRI (iMRI) procedure: mean [min^{case} – max^{case}] (minutes). **A**, end of surgical closure; **B**, departure of surgical table; **C**, closure of MRI doors; **D**, opening of MRI doors; **E**, stop of the surgical table; **F**, restarting of surgery.

facility; no such events have occurred. Similarly, no accidents have occurred during patient transfer between the OR and MRI room. We carefully avoided placing wire loops on patients' skin to prevent burns caused by electromagnetically induced eddy currents (also named Foucault currents). Nevertheless, one patient experienced a second-degree burn of the intergluteal sulcus that we attributed to conductive moisture caused by local sweating. The patient had been placed on an absorbent pad with a plastic underlay that we suspected had caused excessive sweating. This kind of pad was not used subsequently. Similarly, another patient placed in the ventral decubitus position experienced chest burns attributed to the covering on the cushions that were used. We ceased using these types of cushions, and no additional burns were observed. Indeed, conducting perspiration induced by prolonged contact between skin and polyacrylate (or vinyl) materials (synthetic tissues and drapes) have been responsible for superficial burns caused by eddy currents. Discontinuing their use has resulted in the disappearance of such a drawback in subsequent patients so far.

Every planned iMRI procedure was successfully completed. The technical dysfunctions that did occur were minor and were attributed to the learning curve required to master the technical tricks and widgets of the OR-MRI suite. A senior MRI technician was present in the suite for only the two initial procedures (Table 3).

Each type of technical problem that we encountered occurred only once or twice, except for the head being too high in the MRI tunnel (four times). Any metal artifact that we encountered did not disturb the MRI interpretation, and the two incidents that did occur did not lead to any loss of time because the patient's head did not need to be repositioned. Other MRI-related dysfunctions were solved by online collaboration with the radiological team. In the beginning, the surgical table frequently became blocked, but this did not cause

significant delay. A technical check of the table revealed an internal problem that was easily solved, and no further table blockage occurred.

Timeline

For the last 10 patients, we recorded the time taken for each phase of the iMRI procedure (Fig. 7). The time required to perform the whole procedure ranged from 58 minutes in Patient 15 to 129 minutes in Patient 14, in whom three dysfunctions occurred, accounting for 58 minutes of delay (Table 3). On average, the procedure took 78 ± 20 minutes, with an average of 34.1 minutes for the MRI itself. Avoidable delays occurred when the OR had to wait for the MRI room to be converted to surgical conditions (Table 3); this happened in four cases, three of them in the second half of this series. Delays were attributed to surgery taking less time than projected, calling for MRI room preparation less than an hour before the end of the surgery, or the radiologist's program delay with the 3-T MRI in research mode. These issues account for the wide time range (10–43 min) observed for the transfer preparation.

Surgical Results, Assessments, and Additional Tumor Resection

The impact of iMRI on the surgical assessment for this series of patients was also prospectively studied (Table 4). One patient who benefited from epilepsy surgery was excluded from this aspect of the study because only multiple subpial transections based on electrocorticography were performed. Perioperative iMRI interpretation concluded that tumor or dysplastic cortex removal or lobar disconnection was complete in 14 of 20 cases, including all intraventricular tumors ($n = 2$) and lobar disconnections ($n = 2$), 2 of 3 meningiomas, 2 of 3 pituitary adenomas, 5 of 6 gliomas, and 1 of 3 metastases. The iMRI scans of one meningioma, one vestibular schwannoma, and one pitu-

TABLE 4. Intraoperative magnetic resonance imaging results and additional resection^a

Tumors (n = 18) and other pathology	First iMRI				Additional resection	Second iMRI total
	Total	Near total	Subtotal	Partial		
Primary (n = 15)						
Glioma (n = 6)	5	1 ^b			1 ^b	None ^c
Meningioma (n = 3)	2	1				
Schwannoma (n = 1)				1		
Pituitary adenoma (n = 3)	2		1			
Intraventricular (n = 2)	2					
Metastasis (n = 3)	1 ^d	2			2	2
Medically refractory epilepsy (n = 3) ^e	2					
Total (n = 20)	14	4	1	1	3	2

^a iMRI, intraoperative magnetic resonance imaging.

^b Patient 14: histology of the residue showed a slight tumoral infiltration.

^c MRI control done within 48 hours demonstrated a total removal.

^d Extra-axial metastasis.

^e Patient 10 had 54 multiple subpial transections; the iMRI was performed to rule out multiple subpial transection-related complications.

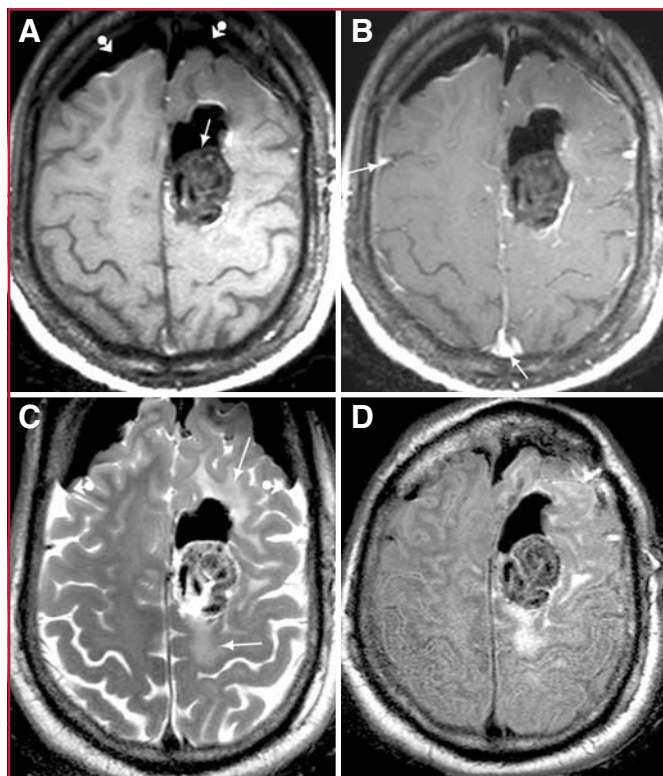


FIGURE 8. Patient 14. Example of iMRI scans at 3-T. The patient is a 49-year-old man with anaplastic World Health Organization Grade III glioma with partial wound closure; all views are in a similar slice location. **A**, pre-contrast T1-weighted image. Air within the frontal subarachnoid spaces (ball arrowheads) and Gelfoam plug in resection area (arrow) owing to intrasurgical conditions are present. Thin linear areas of spontaneous hypersignal intensity are seen at some places along the margins of the resection cavity, corresponding to absorbable hemostat mixed with hemorrhagic debris. Overall image quality (IQ) is excellent except for mild blurring of the right parietal area. **B**, postcontrast T1-weighted image. Only normal intravascular arteriolar/venous enhancement occurs after paramagnetic contrast agent perfusion (arrows). No focus of tumor enhancement is seen. **C**, T2-weighted image. Edematous hyperintense white matter changes adjacent to the resection cavity are visible (arrows); this white matter was not visible on previous T1-weighted views. Layers of rolled Gelfoam plug are more visible, and delineation between hyperintense cerebrospinal fluid and hypointense air-filled subarachnoid areas is sharp (ball arrowheads). **D**, fluid-attenuated inversion recovery image showing similar features of tissue contrast as in the previous T2-weighted view, but with no signal intensity of the cerebrospinal fluid. Blurring of parietal areas is increased compared with previous images.

itary macroadenoma were interpreted intraoperatively as near total, partial, and subtotal, respectively, and no additional resection was performed. For these three cases, the surgeon considered that additional resection could be not performed with a favorable benefit-to-risk ratio.

In 3 of 20 cases, the iMRI interpretation led to a modification of the surgical assessment with additional tumor resection. One patient (Patient 14) (Fig. 8; Table 2) who presented with a Grade

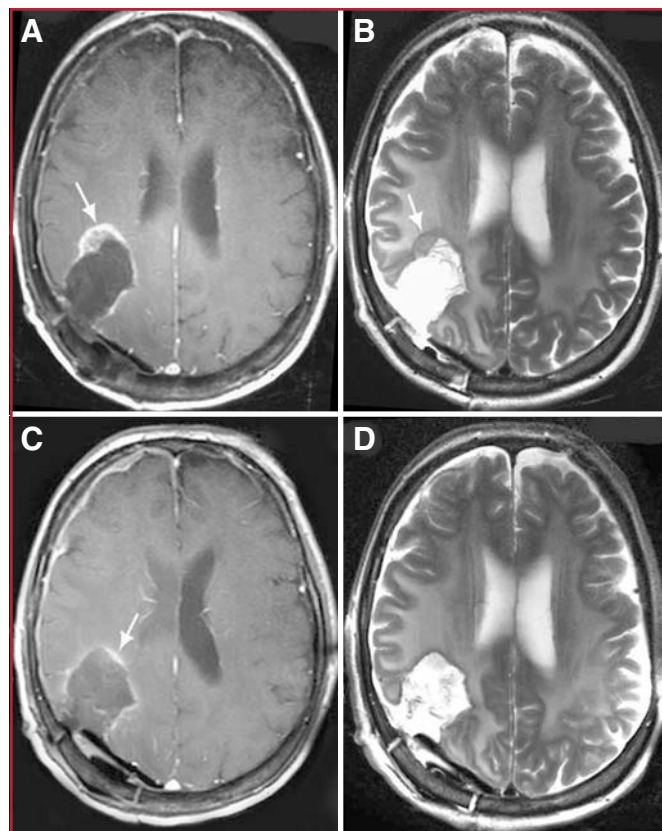


FIGURE 9. Patient 5. Example of monitored additional surgery after iMRI. The patient is a 55-year-old woman with an intracerebral metastasis of breast carcinoma; all views are in a similar slice location. **A** and **B**, images from the first iMRI. **C** and **D**, images from the second iMRI after additional resection. **A**, postcontrast T1-weighted image after the initial phase of resection showing a thin area of enhanced residual tumor at the anterior margin of the resection cavity (arrow). **B**, corresponding T2-weighted image showing the tumor residue as an area of decreased signal intensity (arrow). **C**, postcontrast T1-weighted image after additional resection showing disappearance of enhanced residue. Only a small linear enhanced focus was considered dubious but most probably compatible with benign reactive change (arrow) (probably related to absorbable hemostat and hemorrhagic debris). **D**, corresponding T2-weighted image showing complete disappearance of the tumor residue.

III glioma in the precentral region had an iMRI scan interpreted as near total resection. The removal was completed with a resection and was shown to be total by a 24-hour postoperative MRI. The residue histology showed slight tumor infiltration. The two patients with intra-axial metastasis had a near total tumor resection followed by a post-iMRI residue resection with a second iMRI perioperatively interpreted as total (Patient 5, Fig. 9; Patient 15, Fig. 10). In both cases, the surgeon macroscopically identified the tumor residue.

The surgical goals and surgical assessments were collected before the iMRI scan was done and were compared with iMRI

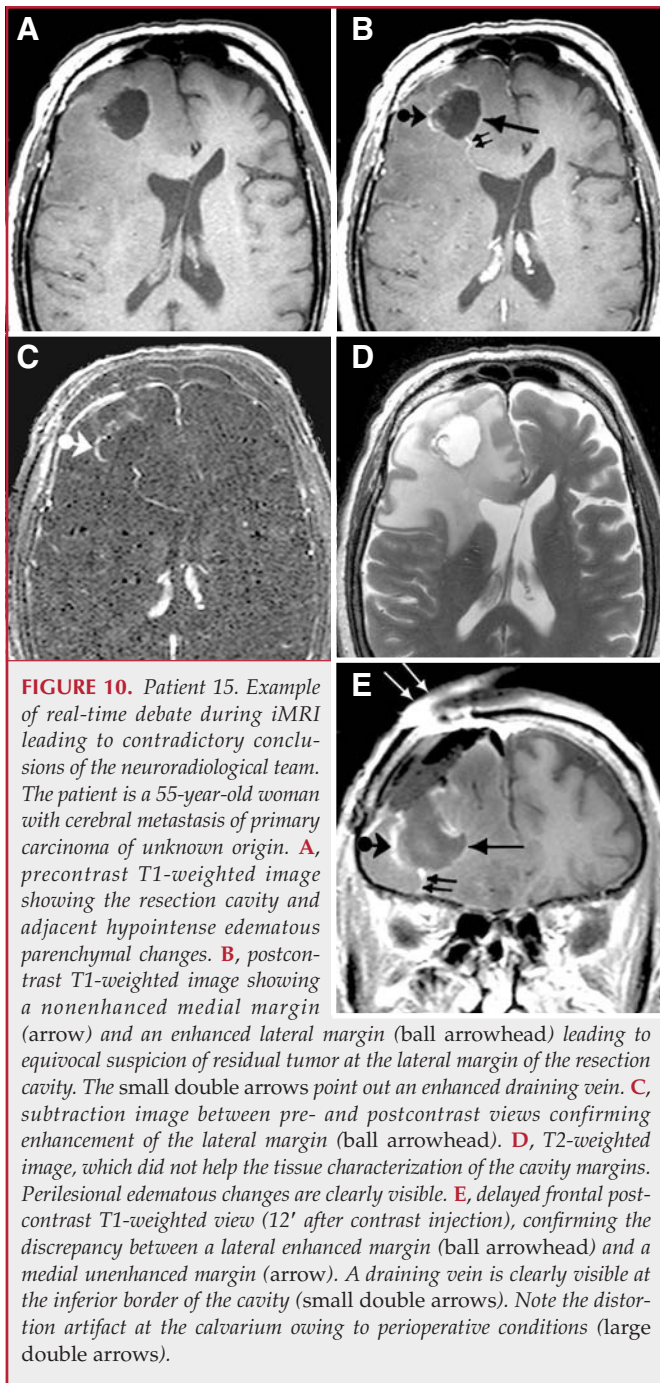


FIGURE 10. Patient 15. Example of real-time debate during iMRI leading to contradictory conclusions of the neuroradiological team. The patient is a 55-year-old woman with cerebral metastasis of primary carcinoma of unknown origin. **A**, precontrast T1-weighted image showing the resection cavity and adjacent hypointense edematous parenchymal changes. **B**, postcontrast T1-weighted image showing a nonenhanced medial margin (arrow) and an enhanced lateral margin (ball arrowhead) leading to equivocal suspicion of residual tumor at the lateral margin of the resection cavity. The small double arrows point out an enhanced draining vein. **C**, subtraction image between pre- and postcontrast views confirming enhancement of the lateral margin (ball arrowhead). **D**, T2-weighted image, which did not help the tissue characterization of the cavity margins. Perilesional edematous changes are clearly visible. **E**, delayed frontal post-contrast T1-weighted view (12' after contrast injection), confirming the discrepancy between a lateral enhanced margin (ball arrowhead) and a medial unenhanced margin (arrow). A draining vein is clearly visible at the inferior border of the cavity (small double arrows). Note the distortion artifact at the calvarium owing to perioperative conditions (large double arrows).

interpretation (Table 5). When the surgeon wanted to perform a total tumor removal or lobar disconnection ($n = 18$), he considered the resection or disconnection total in 17 cases, 4 (24%) of which were actually interpreted as near total on iMRI. One of these patients (Patient 6) (Table 2) had no further surgery. The three other patients were those described in the preceding paragraph.

DISCUSSION

Why Use a 3-T Magnet? Better Spatial Resolution

Spatial resolution is based on the theoretical linearity of the relationship between the strength of the magnetic field and the signal-to-noise ratio (SNR). Without changing any other conditions, the SNR increases as the field strength increases. This allows a choice between shorter acquisition time for the same IQ and improved IQ, in terms of spatial resolution, without increasing acquisition time (3, 4, 21).

For surgical purposes, spatial resolution is the most important parameter affecting the quality of surgical resection. A better SNR also allows a better recognition of deep gray, thalamic, and subthalamic nuclei (15). Even if the gain obtained by shifting from 1.5- to 3-T is not exactly double in terms of time and SNR, the IQ of the brain, the nerves, and the vessels is noticeably improved (11). Other advantages of high-field-strength imaging are the ability to acquire three-dimensional isotropic images (voxels of equal size) in a reasonable acquisition time and the ability to study a volume in any possible plane with the same spatial resolution.

The choice of a 3-T MRI magnet for coupling imaging and surgery was based on the assumption that over the next 7 years, day-to-day imaging practices in the university hospital setting will gradually move from 1.5- to 3-T (19). Our aim is to offer IQ inside the OR similar to that available outside it.

Using a 3-T MRI scanner is associated with some well-known disadvantages that can be managed by choosing the appropriate technical options and adapting specific procedures: 1) increasing radiofrequency energy deposition (specific absorption rate): the use of gradient echo, inversion recovery, and other new sequences with hyperechoes; 2) altering the contrast: namely, the increase of T1 with lesser contrast between white and gray matter in the T1 ponderation; 3) stronger susceptibility effect and metallic artifacts: the use of new coils and acquisition parameters with algorithms like BSENSE (sensitivity encoding), BmSENSE (modified SENSE), BPILS (parallel imaging with localized sensitivities); this stronger susceptibility can also be an advantage in detecting hemosiderin deposition and bleeding lesions containing deoxyhemoglobin; 4) more moving artifacts: the use of adapted sequences and preference for gradient echo sequences to spin echo sequences; 5) larger chemical shift, e.g., use of sequences with fat saturation.

The iMRI procedures that we performed caused two second-degree skin burns that healed without additional sequelae. The single case of wound infection was not attributed to the iMRI procedure because the infection was due to a secondary reopening of the wound caused by a transient movement disorder. Because no other complications associated with the iMRI occurred, we conclude that use of the twin neurosurgical-MRI suite at 3-T is safe, and intraoperative procedures should continue.

The design of the OR-MRI suite allows normal neurosurgical procedures to be performed without any MRI-linked restrictions. The high standards set for surgeon comfort are counterbalanced by the complexity of a multiphase transfer procedure. Indeed, eight different types of transfer-associated dysfunctions were encountered, which disturbed 12 of the procedures. Six types of

TABLE 5. Intraoperative magnetic resonance imaging results compared with surgeon's goal^a

Surgeon's goal	First impression		First iMRI				Additional surgery and second impression				Second MRI	
	Total	Subtotal	Total	Near total	Subtotal	Partial	Total	Near total	Subtotal	Partial	iMRI	24 h postop
											Total	Total
Total (n = 18)	17	1 ^b	13	4 ^c		1 ^b	3				2	1
Subtotal (n = 2)		2	1 ^d		1							

^a iMRI, intraoperative magnetic resonance imaging; postop, postoperatively.

^b Patient 13 had a 75% resection and did not have additional surgery because the schwannoma was too adherent.

^c Among these four patients, only Patient 6 did not have additional surgery because the surgery took 11 hours.

^d Patient 8: the surgeon did not expect to perform a total resection before surgery, but the iMRI interpretation was wrong.

dysfunctions occurred no more than twice: blocked transfer table (resolved by technical inspection of the table), blocked MRI table (unrelated to the iMRI procedure), unplugged coil (the disconnection between the plug and the coil wire was systematically checked), coil position artifacts (owing to overlap or close contacts between the coils), metal artifacts (the removal of the starholder was double checked), and MRI software bug (unrelated to the iMRI procedure). The two remaining dysfunctions were a prolonged waiting period (14–30 min) between the end of the surgery and the availability of the MRI room and the head being positioned too high to fit into the MRI tunnel. The prolonged waiting period depended on the anticipated remaining surgical time and the constraints of the neuroradiological team. This potential waiting period remains the most unpredictable aspect of the procedure. We solved the head position problem by disconnecting the headholder from its base if the head was too high. Regardless of the type of dysfunction that occurred, every planned iMRI procedure was completed successfully. We consider these dysfunctions to be part of the learning process because, for the next 100 patients, the main problem that occurred occasionally was the prolonged waiting period.

Historically, iMRI has been developed in conjunction with neuronavigation systems designed to be used within the flow of surgery with MRI-compatible surgical rooms and tools. The goal was to obtain live brain images during surgery; therefore, it was crucial to have a simple and fast imaging procedure that allowed repeated iMRI. Currently, this need is filled by various neuronavigation systems and iMRI can be used as a quality control system that allows for additional tumor resection. In our experience, repeating an iMRI scan was rarely needed and was only done twice. The iMRI procedure is time-consuming, which is the main drawback of the suite that we developed; the procedure adds an average of 78 ± 20 minutes to the normal surgical time. The average time needed for MRI is 34 minutes, and the average total transfer time is 43 minutes, with a minimum of 32 minutes (Patients 15 and 20). However, considering the potential added benefit for the patient, this additional time seems reasonable. Interestingly, Schwartz et al. (14a) reported that a craniotomy performed under iMRI conditions lasted an average of 1 hour and 42 minutes longer than under conventional conditions, owing mainly to the setup in the double doughnut magnet. Similarly, Martin et al. (7) calculated that tumor resection performed with iMRI took approximately one-third

longer than in a conventional operating room. Finally, the use of the PoleStar N10 was calculated to lengthen surgical time by 1.7 hours compared with conventional surgery (13).

General considerations, issued from routine diagnostic imaging, about the benefits of increasing the basic magnetic field B₀, fully applied to the obtained intraoperative images. Mainly, a higher SNR allows either shorter acquisition time at constant IQ or improved IQ (mainly higher spatial resolution) in a similar acquisition time. We were committed to preserving a similar IQ of iMRI when compared with routine diagnostic imaging. Sensitivity encoding (SENSE) parallel imaging option was used, resulting in significant time savings. Overall, in this study, the intraoperative IQ was rated similar to that of conventional imaging except in the deepest areas, where a slight loss of SNR was observed because of the use of the surface coil instead of quadrature bird cage head coils.

In this preliminary study, we decided to perform iMRI in every brain surgery except brain biopsies. Indeed, the time needed for iMRI would have been as long as the time needed for the biopsy, which seemed unacceptable to us. This study included only three pituitary adenomas that required no further surgery after iMRI. We could not discern any trends with regard to the usefulness of 3-T iMRI for this particular pathology. Three patients (16.6%) undergoing tumor resection required an additional surgical removal. These results are in line with the lowest rate of required additional surgery reported in the literature, which ranges from 16% (13) to 67% (16). Analysis of the glioma surgeries shows that, of the six patients with glioma who underwent operations in this study, only one (16%) required further tumor resection, a rate lower than the 28% published by Nimsy et al. (8), but our series of gliomas is too small to reach statistical significance.

Surprisingly, two of the three patients with metastasis required additional surgery. Thus, metastasis accounts for the highest rate of additional surgery in our study, which is close to the highest rate of additional surgery reported in the literature (67%). This was unexpected because brain metastases are known to be well-delineated tumors. One possible explanation for this is that one of these patients had undergone gamma knife radiosurgery for the metastasis before surgery. This preliminary procedure could have made it difficult for the surgeon to identify the tumor margin. However, this group is also too small to allow us to draw any meaningful conclusions.

The interpretation of the 3-T iMRI is crucial to the neurosurgeon's decision-making process. Surgical information provided to the neuroradiologist facilitated interpretation of the iMRI. However, in five (21%) of 23 intra- and postsurgical MRI scans, the interpretation changed, illustrating how challenging interpreting iMRI can be. Nonspecific peritumoral enhancement after gadolinium injection is known to be difficult to interpret with lower-field iMRI (5). The accuracy in the definition of tumor remnant versus nonspecific enhancement is a major limit of iMRI regardless of the intensity of the magnetic field used; however, the 3-T iMRI should be able to overcome this limitation. At 3-T, intraoperative spectroscopic and perfusion studies of the margin of the tumor resection cavity are technically possible within a clinically acceptable period; we are currently evaluating the accuracy of these tools for defining the putative tumor remnant.

CONCLUSIONS

The OR-MRI suite at 3-T was developed by a multidisciplinary team. The concept of two independent surgical rooms, one with a 3-T MRI machine, separated by an air lock chamber that could be linked when iMRI is needed, proved to be safe and practicable, albeit time-consuming. The IQ allowed thorough analysis of the tumor resection margins, providing us with the tools needed to distinguish tumor tissue from nonspecific gadolinium enhancement. Our initial experience suggests that iMRI at 3-T is safe and feasible and can influence the extent of surgery for glioma and metastasis, but larger studies are needed to draw firm conclusions.

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COMMENTS

Jankovski et al. provided a comprehensive description of their early experience with a 3-T intraoperative magnetic resonance imaging (iMRI) unit. In the first part of their report, they provided a stepwise account of their conception, planning, and construction of an MRI suite designed so that the unit can be shared for diagnostic ambulatory patient scanning. They addressed important considerations including room layout, safety, ergonomics, surgical instrumentation, anesthesia modifications, and imaging protocol design. In doing so, they provided general insight into the multitude of factors that must be weighed for institutions considering new iMRI installations.

In the second part of their report, Jankovski et al. summarized their initial experience with iMRI for a variety of intracranial pathological

lesions including meningiomas, colloid cysts, astrocytomas, pituitary tumors, and metastases. The number of patients is small and their experience is nascent: so far they reported that iMRI led to additional resection in three patients (14.3%). Interpretation is limited by the lack of uniform postoperative MRI assessment and long-term clinical outcomes. Perhaps more important than the numbers, they provided details about dysfunctions and delays that illustrate the learning curve and time required to incorporate this technology successfully into the operating room (OR). The most useful iMRI system is the one that gets the most use. A 3-T magnet may have some technical advantages over a 1.5-T magnet in terms of imaging. However, choosing a 3-T system introduces problems that may make the system less useful in practice as 3-T magnets are more expensive, have a larger footprint, and require more elaborate shielding and safety measures. The higher fixed costs of the machine and installation may increase the motivation for shared usage, which maximizes the opportunity to increase revenue from non-operative scanning. In this study, Jankovski et al. found that shared usage came at the cost of reduced throughput for the surgeons. Intraoperative scans were delayed while the scanner was in use. It is notable that for many patients only a postoperative image was obtained, suggesting significant barriers (real or perceived) to obtaining "on-the-fly" scans. Practical use of a 3-T system is further encumbered by additional safety considerations. They noted two patients with thermal injuries owing presumably to current loops from skin-to-skin contact. The burn risk can be addressed by careful positioning and thorough inspection before each scan, although these procedures take additional time.

Overall, this study highlights the need for detailed cost-benefit analysis when one is considering 3-T versus 1.5-T technology for iMRI. Image quality is only one part of the equation. In the end, practical considerations were paramount in our decision to install a dedicated 1.5-T system at our institution.

The current study contributes to the growing literature on the role of high-field (1.5-T or 3.0-T) iMRI in neurosurgical procedures (1–4). It is now imperative to ask for what pathological conditions and presentations does iMRI provide true clinical benefit?

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Jankovski et al. provide an illustrative report on a multidisciplinary installation of a 3-T iMRI unit. They present valuable information concerning issues such as shielding, hygiene, safety, and electromagnetic compatibility, information that might prove to be of special value to anyone planning to introduce high-field MRI to the OR. This report indicates how meticulously such a setup must be prepared to satisfy the needs of all involved parties. In addition, all of the demonstrated efforts to contain costs are imperative to convince the hospital administration to invest in this technology.

As we observe a trend toward the use of 3.0-T MRI in routine diagnostic imaging, the question as to what extent intraoperative imaging acquired with either a 0.15- or 3.0-T system influences patient outcome remains unanswered. Seemingly, neurosurgery follows the common trend of technology evolving faster than its benefits can be evaluated. As this trend will not be reversed, combined efforts will have to be made to rate the clinical impact of image-guided surgery in general and of iMRI in particular.

It is obvious that higher field strength enhances the spectrum of intraoperative imaging capabilities, extending to areas such as functional MRI, spectroscopy, real-time navigation, and vascular imaging. For the near future, however, intraoperative 3.0-T installations will remain restricted to a very few centers; thus, lower-field units provide an accessible and also sensible solution for most institutions, at least in the near future. In our experience, the image quality delivered by a PoleStar N20 (0.15-T) system must be rated as good in far more cases than have been stated by Jankovski et al. Current data demonstrate that this system generates reliable information about the extent of tumor resection in high-grade as well as in low-grade gliomas.

Still, to promote iMRI and to eventually establish it as a standard of care, the promise of the technology must first be proven. The newly founded International Intraoperative Imaging Society will certainly help to reach that goal.

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Jankovski et al. report on implementation and preliminary experience with a 3-T iMRI suite. A total of 21 patients underwent 3-T intraoperative MRI, and in 9 patients actual iMRI with the head only partially closed was performed. Although several low-field and an increasing number of high-field iMRI setups have been established in recent years, only a few reports on ultra-high-field iMRI, which has been pioneered at a few sites, are available. This article adds highly valuable information on the feasibility of ultra-high-field iMRI.

It will be of special interest to see the actual differences in the application of 1.5-T iMRI. What are the potential benefits of going to ultra-high-field iMRI? Is it better resolution of the border zone in gliomas or better visualization of detailed structures in the cavernous sinus during transsphenoidal surgery of pituitary tumors? Or is it the potential for much improved functional imaging capabilities with a better resolution in functional MRI and diffusion tensor imaging or even improved magnetic resonance spectroscopy (which still has not been shown to actually work intraoperatively)?

A 3-T imaging system offers a better signal-to-noise ratio, which could also be used to further shorten intraoperative imaging time. With our intraoperative 1.5-T system applying parallel imaging techniques, we need only about 15 minutes with an additional maximum of 5 minutes in total for moving the patient from the operating position into the scanner and back again until surgery continues, even for complicated procedures. For the application of intraoperative imaging, a smooth integration into the surgical workflow is crucial. The reported iMRI examination times of 78 ± 20 minutes with a maximum of 129 minutes are really unacceptable in a routine setting. Extreme cases of a waiting time of half an hour for the scanner to be available for intraoperative use may be attributed to the implementation phase and might be avoided in the future.

Sophisticated integration of multimodal navigation with intraoperative imaging including automatic registration of the pre- and intraoperative image data to update the navigation system during surgery, allowing highly reliable multimodal navigation throughout the whole

procedure without any brain shift handicaps, seems to be mandatory to achieve extended resections with low rates of neurological deficits.

Jankovski et al. should be encouraged to investigate the potential benefits of intraoperative 3-T scanning especially compared with standard 1.5-T scanning: it will be very interesting to see how the full potential of a 3-T MRI system can be actually used in an operating room environment with advanced anatomic, structural, functional, and metabolic imaging in the future.

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In this study from the University of Louvain in Brussels, Jankovski et al. presented a novel solution to the desire for iMRI. Instead of pursuing one of the commercially available systems and planning how to convince hospital administration to commit well over 1 million dollars to iMRI, they built one themselves—and not just any iMRI system, but one with a 3-T magnet. This project was only feasible as a shared resource system, in which the scanner is used for diagnostic imaging when it is not in use during surgery. Three years passed between conception to the first operation being done. The various technical and engineering issues relating (among others) to anesthesia, the sterile field, acoustic noise, air flow and pressure, and the magnetic environment were methodically solved. Of note is the fact that construction was done as part of an OR remodeling project; hence, use of iMRI does not require the surgeon to move to the radiology department or to a separate and unfamiliar OR complex.

The Louvain approach separates the OR completely from the magnet. Thus, surgeons can operate without any constraints in terms of equipment (although an MRI-compatible headholder is needed). To achieve intraoperative imaging, patients are moved on a mobile table on tracks to the MRI room entrance. From there they are transferred using an MRI-compatible plastic tabletop onto the scanner. Most of the time, the scanner is used for diagnostic imaging and thereby becomes a revenue source for the hospital.

Still, despite the ingenuity of the solution and the careful engineering described, the benefit of this elaborate technology remains unclear. In their early experience, Jankovski et al. reported using iMRI in 21 patients, with only two scans being acquired per operation. It may be that the 77 minutes average time it took to complete a patient transfer and image lessened the surgeons' zeal for acquiring intraoperative images. In only 3 of 20 patients undergoing tumor resections (18 patients) or epileptic foci (2 patients) did imaging lead to further resection. In 3 other patients residual tumor was identified on imaging but deemed not safely resectable. The authors also point out the vagaries of image interpretation in 5 patients; the neuroradiologists changed their reports upon their postoperative "second look" at the scans.

Surgery in the 3-T environment is not risk free. Two patients sustained second-degree burns, presumably because of looped wires that heated up during placement in the magnet, and as the authors noted "the behavior of the medical staff must be adapted to prevent any objects from becoming dangerous projectiles."

Dr. Raftopoulos's group has shown ingenuity and stamina in bringing this project to fruition. No doubt with further experience they will smooth over some of the technical obstacles to routine actual intraoperative imaging. We should withhold any skepticism regarding the need for such high-field iMRI, and the need for elaborate patient transfers, pending follow-up reports and objective analyses from these and other centers.

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In this article, Jankovski et al. reported on the development and initial clinical use of an interventional MRI system based on a 3-T magnet. The patient is moved to the magnet for imaging according to their configuration, which allows the technology to be shared between diagnostics and surgery. This is important, given the cost of purchasing, installing, and maintaining an interventional MRI system. At the time of article submission, the system had been used to evaluate surgical procedures in 21 patients. The main limitation of the reported configuration remains the need to move the patient with its associated risk and impact on OR time. This limitation may have in part restricted the case mix to predominantly central nervous system neoplasia.

Although preliminary and somewhat limited, the application of surgical planning iMRI may have allowed diagnostic images to be updated and craniotomy placement to be optimized. Jankovski et al. demonstrated the application of interdissection imaging for additional tumor resection in three patients. Perhaps related to moving the patient, technical difficulties were encountered in 10 imaging studies, which were interpreted by Jankovski et al. as a learning curve.

More than 10 years ago, we developed an iMRI system that was based on a moveable 1.5-Tesla magnet (1–3). The philosophy of moving the magnet allowed a patient-focused environment and enabled the sharing of technology between diagnostics and surgery. The system has been used as an adjunct to neurosurgery in some 1000 procedures that have included the full spectrum of neurosurgical procedures. Similar to Jankovski et al., we performed surgical planning imaging after the induction of anesthesia and patient placement to optimize craniotomy placement. In 20% of 202 patients with low-grade gliomas and 30% of 66 patients with pituitary adenomas, interdissection images showed unsuspected residual tumor. Among 139 patients treated surgically for temporal lobe epilepsy, interdissection images showed unsuspected residual tissue in 19%. Because of radiofrequency coil design, spinal applications have been restricted to the upper cervical spine for which 23% of 36 patients showed unsuspected residual tumor degenerative tissue.

In 89 patients with vascular pathological lesions, the benefit was restricted mainly to craniotomy placement. Quality assurance imaging performed after wound closure but before reversal from anesthesia confirmed that surgical objectives had been achieved and defined acute complications. In only one patient with a glioma was the surgical wound reopened for removal of hematoma.

Limitations related to iMRI include increased OR time (on average 90 minutes in our series), disruption of the surgical rhythm for image acquisition, and cost. Despite these, we have found that the benefits offset these challenges. Similar to Jankovski et al., we are upgrading our present iMRI system to a 3-Tesla system with a 70-cm working aperture. The large working aperture and the ability to acquire images rapidly and drape the magnet rather than the patient should collectively decrease imaging time. To offset cost, it will become increasingly necessary for intraoperative or interventional MRI technologies to be shared between health care departments.

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SURGERY FOR CONVEXITY MENINGIOMAS

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OBJECTIVE: Meningiomas that occur over the convexity of the brain are the most common meningiomas, but little has been published about their contemporary management. We aimed to analyze a large series of convexity meningiomas with respect to surgical technique, complication rates, and pathological factors leading to recurrence.

METHODS: We retrospectively reviewed 163 cases of convexity meningiomas operated on in our institution by the senior author (PMB) between 1986 and 2005. The median follow-up time was 2.3 years (range, 1–13 yr).

RESULTS: Convexity tumors represented 22% of all meningiomas operated on. There was a female:male ratio of 2.7:1. Median age was 57 years (range, 20–89 yr). Image-guided surgery was used on all cases in the last 5 years. The 30-day mortality rate was 0%. The incidence of new neurological deficits was 1.7%, and the overall complication rate was 9.4%. The pathology of the tumors was benign in 144 (88.3%), atypical in 16 (9.8%), and anaplastic/malignant in 3 (1.8%). In six of the cases designated “benign,” there were borderline atypical features. The 5-year recurrence rate for benign meningiomas was 1.8%, atypical meningiomas 27.2%, and anaplastic meningiomas 50%. The two cases of benign tumor recurrences involved tumors with borderline atypia and high MIB-1 indices. The borderline atypical cases had a 5-year recurrence-free survival rate of only 55.9%, more closely approximating that of tumors designated “atypical.”

CONCLUSION: Convexity meningiomas can be safely removed using modern image-guided minimally invasive surgical techniques with a very low operative mortality. Benign convexity meningiomas having a Simpson Grade I complete excision have a very low recurrence rate. The recurrence rates of atypical and malignant tumors are significantly higher, and borderline atypical tumors should be considered to behave more like atypical rather than benign lesions. Longer-term follow-up data are needed to more accurately determine the recurrence rates of benign meningiomas.

KEY WORDS: Convexity, Meningioma, Minimally invasive surgery, Recurrence, Simpson grade

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In their seminal monograph of 1938, Cushing and Eisenhardt stated that “. . . it is apparent that sub-varieties of the meningiomas, because of their differences in behavior, would have to be distinguished.” Since then, it has been well established that the chance of meningioma recurrence is dependent on both the extent of resection and the biological aggressiveness of the tumor (3, 5, 10, 22). Features that have been associated with recurrence include male sex, lack of calcification, non-cranial base location, high MIB-1 index, loss of chromosome 1p, and vascular endothelial growth factor expression (8, 9, 24, 25). The relative contribution of histopathological grade and Simpson grade is often unclear, because many studies did not look at these variables independently.

ABBREVIATIONS: MRI, magnetic resonance imaging; RFS, recurrence-free survival

Furthermore, comparing recurrence rates with historical studies is problematic because of the nonstandard and changing definitions of what constitutes atypical and malignant pathological features as well as progress in imaging technology and changes in surgical techniques, including navigation.

Because convexity meningiomas can be “completely” excised, they offer a good opportunity to examine the phenomenon of recurrence. The few modern studies that included a subgroup of benign, completely excised meningiomas have found a small but consistent incidence of recurrence. Jääskeläinen et al. (5) found a recurrence rate of 3% for completely removed benign tumors at 5 years, 9% at 10 years, and 21% at 25 years. The 5-year recurrence rates were significantly higher for higher-grade tumors: 38% for atypical and 78% for anaplastic. Mirimanoff et al. (15) studied 45 convexity meningiomas and also found a recurrence rate of 3%. Yamasaki et al. (25) reported a rate of 11.1% after a follow-up period of 3 years

in 54 patients. In their review of 9000 patients in the National Cancer Data Base, McCarthy et al. (14) found a rate of 20.5% for completely resected benign tumors, but their study was self-reportedly inaccurate as a result of vague definitions of recurrence. A recent review of 100 completely resected benign meningiomas by Maiuri et al. (12) found that MIB-1 index, mitotic index, and progesterone receptor absence were significantly correlated with tumor recurrence. We retrospectively reviewed a series of convexity meningiomas operated on in our institution over the past 20 years by a single surgeon to better understand the relationship among extent of resection, histopathology, and long-term prognosis of these tumors.

PATIENTS AND METHODS

Patient Population

Data for this study were obtained from the Brigham & Women's Hospital Department of Neurosurgery brain tumor database as well as clinical records and imaging data available on an integrated computer records system. All cases for which records were available with the pathological diagnosis of meningiomas operated on by the senior author (PMB) from 1989 to 2006 were reviewed retrospectively, and those patients who had tumors with a convexity location were specifically studied. Only strictly convexity tumors were included; tumors with any origin from the sinuses, cranial base, falx, tentorium, sphenoid wing (except for lateral sphenoid wing/"pterional" tumors without extension into the medial sphenoid wing or the anterior or middle cranial fossae), and all posterior fossa tumors were excluded. Although there is a "gray area" in terms of defining what is "high convexity" versus "parasagittal," we considered a tumor with only minimal attachment to the dura of the sinus, or the draining veins, that was able to be detached easily and completely during surgery, a convexity tumor rather than a parasagittal tumor. Any tumor whose location could not be accurately determined from the data was also excluded. Patients with multiple meningiomas, neurofibromatosis, and concurrent malignant brain tumors such as metastases or high-grade gliomas were also excluded.

Follow-up data were obtained from the clinical records of the Brigham & Women's Hospital and partner hospitals. Data on the age, sex, pathology, date of diagnosis, and last known contact dates were available on all patients. Data on maximum tumor diameter based on radiology, specific tumor location, and details of the surgical procedure were available on the vast majority of patients. Histopathological data available for all patients from the clinical records were reviewed. For survival analysis, the date of death or the date of last known contact was taken as the survival time. For recurrence analysis, the recurrence time was defined as presence of a new enhancing tumor on the computed tomographic scan or magnetic resonance imaging (MRI) scan or, in the absence of imaging data, a second procedure (surgery or radiotherapy) for the same tumor location. Data on radiation and chemotherapy were also obtained from the clinical records when available.

Operative Techniques

Operations were performed through standard craniotomies using microsurgical techniques in all cases. Routine antibiotics, dexamethasone, antiseizure prophylaxis, and diuretics were used. Over the course of 2 decades, various technological advances have been introduced. Initially, lesions were localized with rough guidance from preoperative

computed tomographic scans, necessitating large flaps. The Codman-Roberts-Wells stereotactic frame (Codman/Johnson & Johnson, Raynham, MA) was used in a few cases. Frameless stereotactic guidance was introduced in the mid-1990s and assisted by the establishment of the Surgical Planning Laboratory at the Brigham & Women's Hospital. The current frameless navigation system was developed by GE and is an electromagnetic-based system (GENav system; General Electric Medical Systems, Schenectady, NY). With the advent of accurate image-guided localization, our preference has been for minimal shave, linear incisions, and small craniotomies, all of which can be very accurately achieved using the navigation system, with the aim of minimizing morbidity, healing time, and cosmetic disruption. In 1995, the introduction of intraoperative MRI-guided surgery was made possible by the installation of a GE Signa 0.5-T "double-donut" surgical suite. This has been used more predominantly for low-grade glioma resections rather than meningiomas, however.

The aim of every operation for convexity meningioma was to achieve complete macroscopic resection of the tumor, including the dural attachments and any involved surrounding bony structures. This usually necessitated taking a margin of dura of approximately 5 mm surrounding the tumor. Very rarely, a Simpson Grade I resection was not possible because of dural attachments around the sinuses or draining venous channels, in which case a Grade II resection (coagulation of the dura) was achieved. In a few cases, the contact yttrium-aluminum-garnet laser was helpful. The very large tumors that were not able to be removed *en bloc* were generally debulked initially using the Cavitron ultrasonic surgical aspirator (Valleylab, Boulder, CO) or Bovie loop cautery (Bovie Medical Corp., St. Petersburg, FL). Careful attention was paid to the arachnoid plane at the tumor-brain interface to make sure that no residual tumor was left behind and to achieve proper hemostasis. The dura was closed with a pericranial graft when possible or an artificial dural substitute. A variety of artificial dural substitutes have been used over the years, more recently, AlloDerm (LifeCell, Branchburg, NJ). Cranioplasty was performed if tumor invasion of bone necessitated removal of bone with a large resulting defect. Postoperatively, the patients were cared for in the neurosurgical intensive care unit for an average of 1 day before returning to the ward. The average length of hospital stay has diminished from 5 days in the 1990s to 3.5 days in 2006.

Statistical Analysis

Analysis of survival and recurrence-free survival (RFS) was performed by comparing computer-generated curves estimated by the Kaplan-Meier method (7). Comparison of survival data was done using a log rank method with XLStat statistical software (Addinsoft, New York, NY). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Of the total 732 patients with meningiomas operated on over the past 20 years by the senior author (PMB), 163 (22%) had convexity tumors. The median age at diagnosis was 57 years (range, 20–89 yr). There were 43 men (27.2%) and 120 women (72.8%), giving a female:male ratio of 2.7:1. There was a higher proportion of men in the atypical and malignant group, with a female:male ratio of 1:1.

The distribution of tumors by location is shown in Figure 1. The majority of tumors were found in the frontal lobe, followed by the parietal, temporal, and occipital lobes. There were 85 left-sided and 80 right-sided tumors. The median maximum

tumor diameter was 3.5 cm (range, 0.5–7.5 cm).

The range of presenting complaints is shown in *Table 1*. Headache was, by far, the most common symptom, followed by seizures and hemiparesis. Thirty-two patients were asymptomatic; their tumors were found incidentally on imaging. The most common reasons for surveillance scans were a history of carcinoma (11 patients), lymphoma (one patient), or a family history of tumors (one patient). Two patients had a history of irradiation during childhood.

One hundred seventy-two operations were performed in this group of patients. All operations were craniotomies with a view to a “curative” procedure. Simpson Grade I resections were achieved in the vast majority of cases for which the operative records were available (95% of cases). Forty-eight cases were done using the image-guided frameless stereotactic navigation system. This particular system was introduced in 1999; in the past few years, the use of this system has become standard on convexity meningioma cases. Eleven cases in this series were performed in the intraoperative MRI suite, the first in 1996. Only two procedures were done on “awake” patients (monitored sedation anesthesia) to allow cortical stimulation testing for tumors in eloquent areas.

The pathology of the tumors was benign in 144 cases (88.3%), atypical in 16 (9.8%), and anaplastic in three (1.8%). In six cases, the pathology was reported as benign but with “borderline atypical” features. The median age of patients with benign histology was 56 years, whereas the median age for those with atypical or malignant tumors was 72 years.

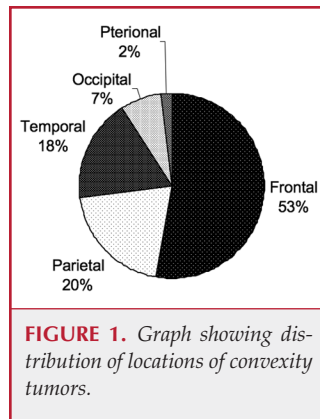


FIGURE 1. Graph showing distribution of locations of convexity tumors.

TABLE 2. Morbidity

Morbidity	No. of patients (%)
New neurological deficit	3 (1.8)
Infection	
All types	5 (3)
Cranium/scalp	3 (1.8)
Brain/meninges	1 (0.6)
Urinary tract	1 (0.6)
Cardiac	2 (1.2)
Deep venous thrombosis	2 (1.2)
Seizure	2 (1.2)
Hematoma	1 (0.6)
Delayed hydrocephalus	2 (1.2)

Surgical Morbidity and Mortality

No deaths occurred within 30 days of surgery. There were 11 deaths during the total follow-up period in our series. Ten of these were in patients aged 65 years or older, and none were meningioma- or surgery-related.

There were three cases (1.7%) of new neurological deficit; all were cases of increased hemiparesis in patients who had presented with motor deficits preoperatively. These three cases also involved large tumors (>4 cm maximum diameter), and two were in elderly patients (aged 72 and 84 yr) with invasive tumors. Overall, the complication rate was 9.4% (*Table 2*). The rate of major morbidity was 5.5%. There was one case of intracranial hematoma after resection of a 5-cm left frontal meningioma, which required evacuation at 2 days postoperatively. There were five cases of postoperative infection, making the overall rate of infection 2.9%. Three of these were deep infections involving the scalp and craniotomy and necessitating removal of the bone flap and replacement at a later date. There were two cardiac complications, which occurred in the 65 years or older group; all three infected craniotomies, however, occurred in the younger than 65 years age group as well as two-thirds of the new neurological deficits. There was no significant difference in the morbidity between the younger than 65 and older than 65 age groups in this series.

Survival and Recurrence Rates

The median follow-up time was 28 months, with a maximum of 158 months (13 yr). Seventy-five patients (46%) were followed for 3 years or more. All recurrences found in the series had follow-up imaging available. The Kaplan-Meier survival curve data are shown in *Figure 2*. The 5-year actuarial survival rate for all patients in the study was 90% (*Fig. 2*).

There were seven recurrences in our series, making the overall recurrence rate during the follow-up period 4.3%. Among the patients who had recurrences, there were five women and two men. The overall actuarial 5-year RFS rate, including all histological grades, was 85% (*Fig. 2*). The median time to recurrence was 14 months; the mean time to recurrence was 28

TABLE 1. Presenting symptoms

Presenting symptoms	No. of patients (%)
Headache	64 (39)
Seizures	33 (20)
Asymptomatic	32 (20)
Motor weakness	15 (9.2)
Confusion/memory loss	15 (9.2)
Sensory alteration	8 (5)
Dysphasia	7 (4.3)
Tumor growth on imaging	5 (3)
Dizziness/syncope	5 (3)
Depression/personality alteration	5 (3)
Palpable cranial mass	4 (2.5)
Visual disturbance	4 (2.5)

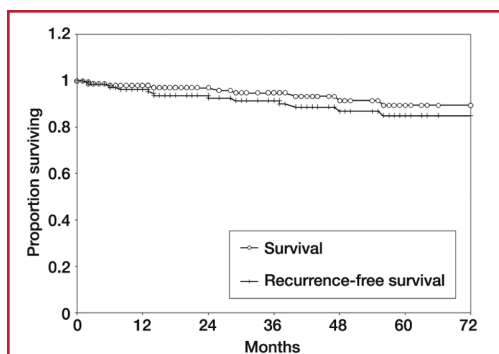


FIGURE 2. Graph showing Kaplan-Meier survival and recurrence-free survival curves for all convexity meningiomas of all grades.

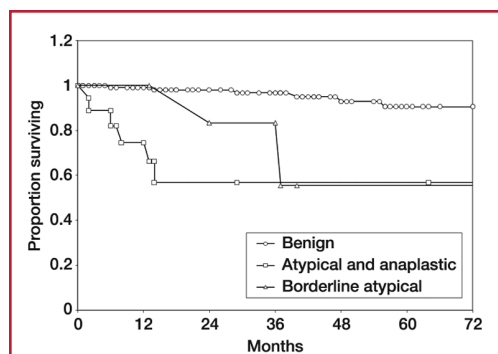


FIGURE 3. Graph showing Kaplan-Meier recurrence-free survival curves for benign, atypical/malignant, and borderline atypical meningiomas.

months (range, 6–94 mo). Four recurrent tumors were treated by repeat surgery followed by radiotherapy, and three were treated by radiation alone (Table 3).

Among the benign tumors, there were only two recurrences, both within 5 years of first surgery, making the recurrence rate 1.8%. Of note, however, is that both of these recurrences were reported as having “borderline atypia.” One of these had a MIB-1 index of 17% and was of a clear cell type, which has been associated with a higher chance of recurrence (20). The other case showed a MIB-1 index of greater than 10% and had progressed to frankly atypical histopathology at the time of the second operation.

The 5-year recurrence rates for atypical tumors and anaplastic tumors were 27.2% and 50%, respectively. The rate for anaplastic tumors may be inaccurate because it is based on only three patients in our series. One of these anaplastic cases was a recurrence from an originally benign meningioma previously treated at another institution. Another patient who had an anaplastic meningioma operated on in 1998 and then treated with proton beam radiotherapy has not had a recurrence to date.

The RFS Kaplan-Meier data subdivided by histopathological grade and considering the tumors with borderline atypia separately from those with purely benign histology are shown in

Figure 3. Atypical and malignant tumors have been included together. The 5-year RFS for benign tumors was 90.5%, and that for atypical/malignant tumors was 56.8%. As expected, the atypical/malignant tumor survival rate differed significantly from the rate in patients with benign tumors ($P < 0.0001$). Interestingly, however, the RFS for those benign tumors with borderline atypia seemed to follow the benign curve initially before trending toward the atypical/malignant curve; the 5-year RFS for these tumors was 55.6%, very similar to that of atypical/malignant tumors (Fig. 3). The borderline atypical tumor curve was statistically significantly different from that of benign tumors ($P = 0.0276$), but not significantly different from that of the atypical/malignant tumors ($P = 0.1258$).

In addition to the tumors that recurred within the timeframe of our series, three patients had operations on tumors that had previously been operated on at another institution. One of these cases was initially a benign tumor operated on in 1993 that had a small convexity recurrence on the MRI scan that proved to be a malignant meningioma after second resection. The second case was an atypical meningioma, and the third case was considered benign but with a high MIB-1 index of 10 to 13%. Each of these cases was treated with radiotherapy after second resection.

TABLE 3. Recurrent patients and treatment modality^a

Patient no.	Age (yr)	Year of first operation	World Health Organization grade ^b	RT initial tumor	Time to recurrence (mo)	Repeat surgery?	RT for recurrence
1	67	1997	1+	No	24	No	SRS
2	37	1997	2	No	94	Yes	SRS (18 Gy)
3	38	2002	1+	No	37	Yes	RT
4	62	2004	2	No	8	No	IMRT
5	72	2004	3	RT (66 Gy)	14	Yes	RT (45 Gy)
6	22	2005	2	No	6	No	Proton beam
7	72	2005	2	No	13	Yes	IMRT

^a RT, conventional fractionated radiotherapy; SRS, stereotactic radiosurgery; IMRT, intensity-modulated radiotherapy.

^b 1+ refers to benign with some atypical features, such as a high MIB-1 index.

Radiation and Chemotherapy

Fifteen patients (9%) underwent radiation therapy in a variety of modalities (Table 3). Our approach was to irradiate all anaplastic meningiomas after the first operation, but for other histological grades, cases were selected on an individual basis. Of the 16 patients with atypical meningiomas, three received adjuvant radiation after initial surgery. These tumors have not recurred within the time period of our study, whereas four patients who did not receive adjuvant radiation after the initial operation subsequently went on to have radiation for recurrent tumors (Table 3). Two patients with recurrent borderline atypical tumors were treated with adjuvant radiation. One was a recurrent lesion with a high MIB-1 index (10–13%), and the other tumor was thought to have invasive features at surgery. Although we have used hydroxyurea for recurrent meningiomas in other locations, no chemotherapy was used for any patients in this series with convexity tumors.

DISCUSSION

As far as we are aware, this is the largest study of convexity meningiomas in the literature. Convexity meningiomas accounted for 22% of our total series of meningiomas, which is consistent with previous reports (15). Our series confirmed the findings of previous authors, who reported a 2.7:1 ratio of women to men, except in higher-grade tumors, in which it is 1:1 (11). The proportion of atypical tumors was slightly higher in our series compared with historical studies, most likely because of the clarification of the designation “atypical” and its introduction into the World Health Organization scheme in the 1990s, although complete consensus has still not been reached about meningioma grading (5, 11). Approximately one-fifth of tumors were found incidentally; however, headache as a presenting symptom in some cases was likely not meningioma-related, so this may be an underestimate of how many tumors were genuinely “asymptomatic.”

Overall, the rate of complications was quite small. The 30-day mortality rate was zero, and the 1-year mortality rate was only 1.8%. This emphasizes the fact that surgical removal of convexity meningiomas is generally a safe procedure. Modern image-guided surgery has helped to minimize the size of the craniotomy, reduce postoperative pain and potential complications, as well as assist the surgeon in identifying important structures to preserve, such as veins. It should be noted, however, that we saw a small incidence of infection of 2 to 3%, which highlights the need to be constantly vigilant with surgical technique, sterility, and the use of perioperative antibiotics. Although techniques such as intraoperative MRI and cortical stimulation under conditions of monitored sedation anesthesia have been used, we have not found them to be as helpful as in the treatment of diffuse parenchymal lesions, such as low-grade gliomas.

Recurrence

Although benign meningiomas are generally considered a curable disease, this is not always the case. In his original study in 1957, based on clinical criteria of recurrence, Simpson (22)

found that 13 of the recurrences occurred after Grade I and II benign tumors were “completely” removed. Because true Simpson Grade I resections can only realistically be achieved with convexity meningiomas, our current series effectively represents a comparison of the recurrence rates by histological grading, keeping the extent of resection variable constant.

We found 5-year recurrence rates of 1.8% for benign tumors and 44% for atypical/malignant tumors; these rates are very similar to those of Jääskeläinen et al. (5) and Mirimanoff et al. (15). A limitation of our study, however, was that although 46% of patients were followed for 3 years or more, only seven patients were followed for 10 years or more, and a much longer time might be needed to reveal the true rate of recurrence of benign meningiomas that have been completely excised.

Additionally, if the benign tumors in our series are separated into those that are completely benign and those that have some atypical features, the recurrence rate for the benign group becomes zero, whereas the “borderline atypical” group has a 5-year recurrence rate of 33%, which is in the same range as the atypical tumors (27.2%). It should be noted that the recurrence rate in our borderline atypical group is based on only a small number of cases, but we found that the RFS curve for tumors with benign but borderline features is intermediate between that of benign and atypical/malignant tumors (Fig. 3).

We found only one patient in our series who had progressed in tumor grade at the time of recurrence. Although progression has been reported in meningiomas (1), a number of other studies have confirmed a lack of histological change in recurrent benign meningiomas (12, 21). It is notable that both recurrent borderline atypical tumors in our series had a high MIB-1 index (17% and >10%). The MIB-1 labeling index, which is an immunohistochemical measure of Ki-67 antigen expression, a proliferation marker, has been associated with meningioma recurrence (8, 12, 21, 24). It has previously been suggested that the MIB-1 index may be useful to distinguish borderline atypical meningiomas (17, 19). There is no consensus, however, on appropriate cutoffs for the MIB-1 labeling index, and these results should all be viewed with some caution, because MIB-1 staining levels are nonstandardized and can vary significantly between different laboratories. A level of more than 10 to 12% has been significantly associated with the risk of recurrence in the literature (4, 9, 24). Takahashi et al. (23) found that a MIB-1 index of more than 5%, even in the presence of a low mitotic index (<4 per 10 high-power fields), was strongly predictive of a short progression-free course. As noted by Schiffer et al. (21), recurrent tumors appear to already have an initial higher proliferation capacity, as measured by the MIB-1 index, even when of benign histology, suggesting that increasing tumor aggressiveness is not an important cause of recurrence. Simpson (22) identified three possible causes of recurrence: inadequate resection, multifocality of tumor cells in the dura, and de novo tumor formation. He felt that the most likely reason was unrecognized spread of tumor cells at the time of operation, particularly through the falx or the tentorium. A more widespread dural multifocality of disease beyond the margin of the tumor itself has been postulated by others as well (2, 13, 21). Residual tumor

cells in thickened arachnoid membrane have also been proposed as a source of recurrence (6, 21). The fact that even benign, completely excised tumors still recurred in his series led Simpson (22) to state, "It is more profitable to consider these recurrences . . . as failures in surgery" (22). To deal with the problem of recurrence, some authors have suggested the necessity of an additional margin of 2 cm around the tumor (the so-called "Simpson grade zero"), although there are no long-term data to show whether this approach is successful (2, 10).

Because there were no recurrences in those tumors that were completely benign in our series, we suggest that these tumors can potentially be cured by a traditional Simpson Grade I complete resection using a dural margin of approximately 5 mm. However, for borderline atypical and higher-grade meningiomas, this may not be adequate. Palma et al. (18) reported that a standard Simpson Grade I resection was enough to eliminate even atypical and anaplastic meningiomas for up to 19 years, and in our study, there was one example of an anaplastic convexity meningioma that has so far not recurred after a Simpson Grade I resection and adjuvant radiotherapy, but this appears to be the exception. Overall, for convexity meningiomas, in which complete resection is likely to be achieved, the histopathological grade appears to be the most important correlate of the risk of recurrence.

Radiation Therapy

There is controversy about the indications for postoperative radiation therapy. This has been further complicated in the past few years by the options of radiosurgery versus standard fractionated radiotherapy, including intensity-modulated radiation therapy, which have been shown to achieve good tumor control. Modha and Gutin (16), in their 2005 review, suggested that all anaplastic tumors and atypical tumors subtotally excised with brain invasion or a MIB-1 index of 4.2% or more should be treated with fractionated radiotherapy. However, for the "gray zone" tumors that have only some atypical criteria, or for benign lesions with invasive features, they suggested observation if completely excised or fractionated radiotherapy if the MIB-1 is 4.2% or more (16). Given our findings that tumors with borderline atypia and high MIB-1 indices, even if completely excised, eventually behave more like "true" atypical tumors, we would support this philosophy. In lieu of radiotherapy, we would perform extremely cautious follow-up with regular contrast-enhanced MRI scanning.

Management of Asymptomatic Tumors

We generally adopted a more aggressive treatment philosophy to convexity meningiomas, preferring to remove them rather than observe with follow-up imaging over a long period of time. In a recent article by Yano et al. (26), only 6.4% of asymptomatic tumors (in all locations) became symptomatic and 37% of tumors showed growth on imaging during a period of observation (median follow-up, 3.9 yr). Because of this, these authors and others have suggested that an initial period of observation is warranted for all asymptomatic lesions, particularly for smaller tumors and in older patients in whom the surgical morbidity is

higher. One drawback of this approach, however, is that atypical and malignant lesions can be missed, with the subsequent delay in surgery making the operative risk higher and possibly affecting the long-term outcome. Additionally, the question of how long to follow patients under observation, especially in the younger age group, is unknown. Do patients require yearly or biennial MRI studies for the rest of their life? A true appreciation of the lifetime growth potential of meningiomas might require a much longer follow-up period than 3 to 5 years.

Extrapolating from the results of Yano et al. (26) that there is an approximately 1.6% chance per year (6.4% over 4 yr) of a meningioma becoming symptomatic, for an otherwise healthy 60-year-old person who might be expected to live another 20 years, there would be a 28% chance of this lesion becoming symptomatic in their remaining lifetime. Similarly, there would be an 86% risk of tumor growth in this time period. Noting that the operative morbidity is in the range of 4 to 10%, this would seem to favor removing the lesion while it is still small, before it has a chance to become symptomatic. Noting that the study of Yano et al. included meningiomas in all locations, this principle should be even more applicable to convexity meningiomas, which in our series had 0% surgical mortality, 5.5% major morbidity, and a 1.8% recurrence rate for benign tumors.

CONCLUSIONS

We retrospectively studied 163 convexity meningiomas completely resected at one institution by a single surgeon with a median follow-up of 28 months. The 5-year recurrence rate was 1.8% for benign tumors and 44% for atypical/malignant meningiomas. When borderline atypical cases were considered separately, the recurrence rate of purely benign tumors was 0%. The RFS rates at 5 years were 90.5% for benign tumors, 56.8% for atypical tumors, and 55.6% for borderline atypical cases. It should be emphasized that, given our relatively short follow-up for this indolent disease, the long-term recurrence rates may be higher. The tumors that had borderline atypia were notable for having a high MIB-1 index. This subgroup of ostensibly benign meningiomas should be viewed as being more aggressive; this might alter the clinical decision-making in terms of adjuvant therapy and follow-up until better markers and pathological grading systems for meningiomas are developed.

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COMMENTS

This study by a renowned group in the field is interesting not only from a surgical standpoint but also for its scientific implications. Meningiomas are the most fascinating brain tumors in the field of neurosurgery. The aim of every operation is to achieve complete macroscopic

resection of the tumor including dural attachment and, when involved, adjacent bony structures also, realizing a Simpson Grade 1 complete excision. Because true total resection can only be achieved with convexity meningiomas, these tumors could be considered a sort of “experimental model” for a comparison of recurrence rates with histological grade, keeping the variable of extent of resection constant. Morokoff et al. evaluated the role of histology, remembering that a complete consensus has still not been reached about meningioma grading. In their series, benign convexity meningiomas have a very low recurrence rate in contrast with the higher recurrence rates of atypical and malignant tumors, whereas borderline/atypical tumors should be considered to behave more like atypical rather than benign lesions. Morokoff et al. found recurrence rates at 5 years for benign tumors of 1.8% and for atypical/malignant tumors of 44%, whereas the borderline/atypical group had a recurrence rate of 33%. Because even benign completely excised tumors still recur, many researchers searched for other causes: multifocality of the tumor cells in the dura, residual tumor cells in thickened arachnoid, and lack of additional resection of the dural tail around the tumor. Finally, surgery and histopathological grade seem to be the most important risk factors for recurrence.

Although surgery is the most important therapeutic modality for meningioma management, observation and radiation therapy have important roles in the decision-making process approach to these tumors. I agree completely with the policy of Morokoff et al. concerning the management of asymptomatic tumors, the problems of meningiomas in elderly patients, and the indications for postoperative radiotherapy.

Of particular interest in this is the exploration of the roles of surgery and science. On these bases, Morokoff et al. stress the problem of trying to match surgery with biology in managing these remarkable tumors. Thus, they emphasize the importance of the science (epidemiology and genetics and a meningioma model using neurofibromatosis 2 knockout, low-release polymer therapy) and the surgery (image-guided surgery and brain mapping).

The take-home message of this study is that, although “benign” tumors, meningiomas create a series of problems concerning decision-making, management, and long-term follow-up. Finally, with their abundant experience in this field, Morokoff et al. have brought the problem of recurrence of meningiomas, which has not yet been solved, to the attention of the neurosurgical community.

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This retrospective series dealt with microsurgical removal of convexity meningiomas in 163 patients at a single institution operated on by a single surgeon. Three tumors were actually recurrent meningiomas initially treated at another institution.

Current surgical strategy is to use neuronavigation, making possible a targeted linear skin incision as well as a small craniotomy. Complete resection was achieved by taking a 5-mm margin of dura surrounding the tumor in most patients. Very large tumors not able to be removed *en bloc* were debulked initially using the Cavitron (Valleylab, Boulder, CO) ultrasonic surgical aspirator or Bovie loop cautery (Bovie Medical Corp., St. Petersburg, FL). Attention was paid to staying in the arachnoid plane at the tumor-brain interface. Dura closure was achieved with a pericranial graft or an artificial substitute, and cranioplasty was performed if there was a large bone defect owing to tumor invasion. The average length of hospital stay was only 3.5 days in 2006.

Mortality and morbidity were remarkably low: the 30-day mortality was 0, the 1-year mortality was 1.8%, and none of the 11 deaths during follow-up was directly related to the meningioma or the surgery. Only 1.7% (three patients), showed a new deficit, i.e., worsening of a preexisting hemiparesis, after surgery. All three patients with a new deficit

had tumors larger than 4 cm and two of them were older than 71 years and had invasive tumors. There was only one (0.6%) hematoma and a 2.9% rate of infection.

The median follow-up time was 28 months with a reported Simpson Grade I resection in the majority of patients; the overall recurrence rate was 4.3%. Among the benign tumors, the recurrence rate was only 1.8% (i.e., two patients, with both of them having tumors showing borderline atypia) as opposed to 44% among those with atypical/malignant tumors (5-year rates). For higher-grade meningiomas, the numbers are too small to report exact recurrence rates or survival curves. The data confirm, however, that after complete removal, recurrence is mainly a matter of the presence of atypical, malignant, or borderline histological features. Despite the limited time of follow-up, another significant finding was that meningiomas showing borderline atypical features seemed to behave much more like atypical tumors than benign tumors.

Most important, this work provides data showing removal of convexity meningiomas is, in the best hands, a procedure with exceedingly low mortality and morbidity. These results are crucial for making treatment decisions in patients with convexity meningiomas.

**Juergen Beck
Volker Seifert**
Frankfurt, Germany

In this article, the authors presented a large series of patients with convexity meningiomas, who underwent operations and were subsequently followed. The complication rates were extremely low, and recurrence was noted mainly with atypical and malignant meningiomas. However, I do not agree with the policy of Morokoff et al. of operating on all patients with asymptomatic meningiomas of the convexity, especially when they are 3 cm or less in dimension. These tumors can be followed with magnetic resonance imaging after 3 months and 6 months and then once yearly thereafter. I have many patients under such follow-up schedules, and very few have required an operation.

Laligam N. Sekhar
Seattle, Washington

The ideal management of benign intracranial tumors is tumor control with limited morbidity. Although resection is frequently performed for meningiomas of the cranial base to reduce mass effect and less commonly to confirm the diagnosis, total removal is often not possible without damaging the adjacent neurovascular structures. Conversely, as shown in this large series, complete tumor removal of convexity meningiomas is normal, and the neurological morbidity associated with these operations was less than 2%. Over the years we have performed radiosurgery for a small number of convexity meningiomas, typically in elderly patients with recurrent tumors. It seems that the chance of symptomatic parenchymal imaging changes is far greater for these patients compared with patients having radiosurgery for cranial base meningiomas. On the basis of this experience, we continue to favor tumor removal over radiosurgery for the majority of patients with convexity meningiomas.

Bruce E. Pollock
Rochester, Minnesota

Since the pioneering work of Simpson, the recurrence of surgically resected meningiomas has been discussed by several authors. In this article, Morokoff et al. concentrated on convexity meningiomas, which are among those for which complete resection (including the dura) is possible and feasible.

The pros of this article are as follows: It includes a large series of consecutive patients (163 operated on in 20 years); it is a single institution-single surgeon series; demographic characteristics, diagnostic material, and pathological material have been well studied and reviewed; and the results are excellent, with 0% 30-days mortality and a very low complication rate.

Morokoff et al. confirm what it is known from the literature. 1) The patient population shows a dominance of female sex in those with benign meningiomas, although among those with anaplastic meningiomas, the male-to-female ratio is 1:1. 2) The recurrence of completely removed meningiomas is significantly higher and earlier for tumors with atypical (even borderline atypical) and anaplastic features. However, the definition of atypical might be different among different laboratories, and therefore this result must be accepted with caution. The MIB-1 index is possibly the most significant element. 3) Postoperative management of atypical meningiomas is still controversial. Morokoff et al. suggested close follow-up, instead of immediate postoperative radiotherapy.

Unfortunately, Morokoff et al. cannot report the final word about recurrence rate at 5 and 10 years because only 46% of their patients have been followed-up for more than 3 years and only seven patients have been followed-up for more than 10 years (the median follow-up time was 28 months). The other drawback is that the study is retrospective. However, it seems reasonable to share the conclusion of Morokoff et al. that benign meningiomas removed completely (Simpson grades I or 0) do not recur or have a very low risk of recurrence at 10 years. With a mortality of 0% and a low complication rate, surgery is indicated even in patients with asymptomatic lesions, particularly because the "wait and scan" policy might miss atypical tumors that should be removed.

Morokoff et al. provided an excellent review of 163 patients undergoing surgery for convexity meningiomas over a 10-year period. They documented results that would be expected from high-quality neurosurgery and noted the limitations in the interpretation of the recurrence rate, as this was a retrospective study with a mean follow-up of 2.3 years with one patient who has been followed for more than 10 years. Nevertheless, they have provided interesting data on the recurrence of these tumors, with a 5-year recurrence rate for benign meningiomas of 1.8%, for atypical meningiomas of 27.2%, and for anaplastic meningiomas of 50%. It is essential when one is comparing recurrence rates with the work of Simpson to remember that his study was undertaken 20 years before the introduction of computed tomographic scanning, and the definition of recurrence was based on clinical grounds only.

I agree with the "more aggressive treatment philosophy" for convexity meningiomas of Morokoff et al. In general I advise surgery if the convexity tumor is greater than 2 cm in diameter and growing or there is underlying cerebral edema, and/or the patient is symptomatic. Tumors larger than 3 cm should be resected, unless the patient is very elderly or frail. Morokoff et al. have shown that these tumors can be removed with minimal morbidity, and their interpretation of the results of Yano et al. (1) show that there is an 86% chance of tumor growth in a 60-year-old patient who is expected to live for another 20 years.

This is a valuable study with a thoughtful analysis of the data.

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PREDICTORS OF PERITUMORAL EDEMA AFTER STEREOTACTIC RADIOSURGERY OF SUPRATENTORIAL MENINGIOMAS

OBJECTIVE: Anecdotal evidence suggests that radiosurgical ablation of parasagittal meningiomas may be associated with increased risk of subsequent edema. Potential predictors of postradiosurgical peritumoral edema, including parasagittal tumor location, tumor size, and treatment dose, were evaluated.

METHODS: We retrospectively reviewed records of 102 patients with 111 supratentorial meningiomas treated with CyberKnife (Accuray, Inc., Sunnyvale, CA) stereotactic radiosurgery (SRS). A median marginal dose of 18.0 Gy (range, 11.3–25.0 Gy) was delivered in 1 to 5 sessions (fractions). Potential predictors of posttreatment symptomatic edema were evaluated using Fisher's exact test.

RESULTS: Of the 102 patients followed for a mean of 20.9 months (range, 6–77 mo), 15 (14.7%) developed symptomatic edema after SRS. Nine of 31 with parasagittal meningiomas (29.0%) and 6 of 80 with nonparasagittal supratentorial meningiomas (7.5%) developed symptomatic edema ($P = 0.0053$). Compared with patients with meningiomas in nonmidline supratentorial locations, patients with parasagittal meningiomas were more than 4 times as likely to develop symptomatic edema after SRS (odds ratio, 4.1; 95% confidence interval, 1.5–11.5). The 6-, 12-, and 18-month actuarial rates of symptomatic edema development were significantly greater for patients with parasagittal meningiomas than for patients with nonparasagittal meningiomas (17.8 versus 1.3%, 25.4 versus 5.8%, and 35.2 versus 7.8%, respectively).

CONCLUSION: Patients with parasagittal meningiomas are at greater risk of developing peritumoral symptomatic edema after SRS. Close follow-up after SRS may be particularly important in such patients. These results highlight the need to pursue strategies that could decrease the incidence of postradiosurgical edema in patients with parasagittal meningioma.

KEY WORDS: CyberKnife, Edema, Meningioma, Parasagittal, Radiosurgery

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Stereotactic radiosurgery (SRS) has emerged as an effective surgical tool for managing a broad spectrum of intracranial meningiomas. Actuarial 5- and 10-year tumor control rates of 93% have been reported (3). Overall, treatment-related complications have been reported in approximately 9% of patients (3, 13). The range of complications includes radiation necrosis, cranial nerve deficit, motor deficit, hydrocephalus, vascular occlusion, and development of peritumoral edema.

ABBREVIATIONS: CT, computed tomographic; MRI, magnetic resonance imaging; SRS, stereotactic radiosurgery

The delayed occurrence of adjacent edema is a well-known risk of using radiosurgery to manage intracranial meningiomas. It has been proposed that this complication, which occurs in 6 to 35% of patients (2, 7, 9, 10, 16), may be related to several risk factors, including tumor location, volume, and the total radiation dose; in particular, a midline position may be more prone to this phenomenon (7, 8). However, information regarding potential predictors of edema with a detailed comparison of edema rates between parasagittal and other supratentorial meningiomas is limited (2, 5).

The present study sought to determine the incidence of symptomatic postradiosurgical

peritumoral edema in a cohort of patients with supratentorial meningiomas. Several proposed risk factors were evaluated systematically. Emphasis was placed on the risk of developing edema in patients with either parasagittal meningiomas or meningiomas in other midline supratentorial locations that are in close proximity to a venous sinus.

PATIENTS AND METHODS

A retrospective review of all patients who underwent CyberKnife (Accuray, Inc., Sunnyvale, CA) radiosurgery for supratentorial meningiomas at Stanford University between January 2001 and December 2006 was conducted. One hundred eleven tumors in 102 patients with a minimum follow-up period of 3 months were identified and included in the analysis.

A parasagittal meningioma was defined as a lesion that, in some part, was in direct contact with the wall of and/or within the sagittal sinus. Midline, supratentorial, parasinus meningiomas were defined as those with direct contact with a midline venous sinus and included parasagittal, falx, and pineal region meningiomas. Indications for meningioma radiosurgery included symptomatic presentation, interval tumor growth, mass effect, residual tumor, and patient treatment preference. Radiographic interval tumor growth was documented in approximately 30% of the patients in our study.

Treatment Planning

Computed tomographic (CT) scans with 1.25-mm-thick, contrast-enhanced, contiguous axial images of the brain were acquired. In 20% of the cases, the meningioma was felt to be suboptimally visualized on contrast CT scans alone. In such cases, a gadolinium-enhanced magnetic resonance imaging (MRI) scan using 2.0-mm contiguous slices was also obtained and fused to the CT scan. The boundary of the tumor and surrounding critical anatomy were delineated on contiguous slices using standard radiosurgical contouring tools. After specifying both a minimum and a maximum target dose, as well as doses to critical structures,

an optimal treatment plan was arrived at by means of an inverse planning algorithm. A representative treatment plan with the isodose distribution overlaid onto the respective CT scan is depicted in Figure 1.

Given their tight interrelationship, decisions on the total dose and number of sessions was the product of a complex individualized calculus. A multisession radiosurgical approach (2 to 5 sessions) was generally pursued for larger-volume meningiomas or those with an unusually lengthy dimension adjacent to a region of critical anatomy (e.g., anterior visual pathways) or in cases with a previous history of conventional radiation therapy. In the current series, 76 meningiomas were treated in a single session, 11 were treated in 2 sessions, 16 were treated in 3 ses-

sions, 2 were treated in 4 sessions, and 6 were treated in 5 sessions. The tumor volume for those meningiomas undergoing multisession radiosurgery was significantly higher than for those lesions treated with single-session radiosurgery (9.3 versus 3.9 cc; $P < 0.001$). The dosing for single-session radiosurgery paralleled the recommendations described in published reports involving gamma knife radiosurgery (11). In cases of multisession radiosurgery, the linear quadratic formulation was used to select a single-session, biologically effective dose of radiation (4). For purposes of analysis and comparison of treatment doses between patients, the dose used in multisession radiosurgery was converted to a single-session equivalent dose. This conversion was accomplished using the linear-quadratic equation with α/β of 3.0 (15). The single-session equivalent median marginal dose was 18.0 Gy (range, 11.3–25.0 Gy) and the median maximum dose was 22.2 Gy (range, 14.0–38.7 Gy). The mean marginal single-session equivalent dose for patients who underwent multisession radiosurgery was 1385 cGy, and the mean marginal dose for patients who were treated in one session was 1848 cGy. The mean conformality index (prescription isodose volume/target isodose volume) for all patients was 1.48 ± 0.33 .

Radiosurgical Procedure

Each patient was positioned supine on the radiosurgical table and then immobilized in a previously constructed thermoplastic mask. Importantly, the function of the mask is merely to restrict motion; this device has no involvement in the process of target localization. The latter is accomplished by comparing digitally reconstructed x-rays generated from the CT scan with real-time orthogonal digital cranium x-rays obtained periodically before and throughout CyberKnife radiosurgery. Only after the treating physicians confirmed the visual fidelity of the image-guided targeting process was the intended radiosurgical plan delivered. On completion of each radiosurgery session, patients were routinely given a 4-mg tablet of dexamethasone.

Postradiosurgical follow-up typically included clinic visits and serial MRI scans at 6 months and 1, 2, and 3 years, with all subsequent evaluations at 2-year intervals. Radiographic presence of peritumoral edema was defined as an increased area of hyperintensity on T2-weighted MRI in adjacent white matter. Patients were classified as having symptomatic edema if they had radiographic evidence of increased peritumoral edema and presented with new-onset, moderate to severe headache, neurological deficit, or seizure. A definitive pathological diagnosis of radiation necrosis was not made in any of the study patients, and we did not examine any potential relationship between patients with possible radionecrosis and edema compared with patients who had edema alone. Patients who developed symptomatic edema after radiosurgery were followed every 6 to 12 weeks with clinical examinations and MRI scans until symptoms resolved.

Statistical Analysis

Univariate analysis of potential predictors of posttreatment edema, such as tumor volume, dose, maximum dose, and tumor location (parasagittal versus nonparasagittal, midline versus nonmidline), was performed using Fisher's exact test. It should be noted, however, that performing multiple comparisons increases the odds of finding spurious associations. To aid interpretation, tumor location (parasagittal versus nonparasagittal) was evaluated as a predictor of symptomatic postradiosurgery peritumoral edema in a univariate Kaplan-Meier analysis using the log-rank test. Actuarial rates of edema were determined using the product-limit method of Kaplan and Meier. Cox proportional hazards models were used to determine the risk of edema development in patients with parasagittal meningiomas and meningiomas in other supratentorial, midline, parasinus locations.



FIGURE 1. CyberKnife (Accuray, Inc., Sunnyvale, CA) radiosurgery treatment plan for a meningioma (marginal dose of 18 Gy delivered to the 81% isodose line in one session).

RESULTS

One hundred two patients with 111 supratentorial meningiomas were included in this analysis. The mean age of patients at radiosurgery was 59.8 years (range, 24–86 yr). Sixty-one (59.8%) of the 102 patients were women. Twenty-two (21.6%) patients had a preexisting neurological deficit. None of the patients in our study had symptomatic edema before radiosurgery, and none of the patients were taking daily glucocorticoids at the time of radiosurgery. A previous surgical resection had been performed in 50 (45.1%) of the 111 tumors. Twelve of the tumors in this series were confirmed to be atypical or malignant on histological examination. Moreover, 8 (7.2%) tumors had been treated previously with conventional fractionated radiotherapy.

Of the 102 patients followed for a mean of 20.9 months (median, 15.2 mo; range, 6–77 mo), 15 (14.7%) patients developed symptomatic edema after stereotactic radiosurgery. The median time to onset was 7 months (range, 4–20 mo). Only 2 patients developed edema more than 14 months after SRS.

Table 1 depicts patient, tumor, and radiosurgical characteristics and the association of these factors with the rate of subsequent edema formation. Only tumor location significantly affected the likelihood of edema development. Of note, the degree of dose conformality was not associated with development of symptomatic edema ($P = 0.1$). Meanwhile, the volumes of parasagittal meningiomas and nonparasagittal tumors were similar (mean volume, 6.7 versus 5.2 cc; $P = 0.19$, t test). Nine (29.0%) of 31 parasagittal meningiomas and 6 (7.5%) of 80 nonparasagittal supratentorial tumors developed postradiosurgery peritumoral edema ($P = 0.0053$). The 9 parasagittal meningiomas that developed postradiosurgery symptomatic edema were widely distributed along the course of the sagittal sinus (anterior third of the sagittal sinus, 2 tumors; middle third, 4 tumors; and posterior third, 3 tumors). Compared with patients who had meningiomas in other supratentorial locations, patients with parasagittal meningiomas were 4.1 times more likely to develop symptomatic edema after radiosurgery (hazard ratio, 4.1; 95% confidence interval, 1.5–11.5; $P = 0.0076$). The 6-, 12-, 18-, and 24-month actuarial rates of symptomatic edema development were significantly greater for patients with parasagittal meningiomas compared with nonparasagittal meningiomas (17.8 versus 1.3%, 25.4 versus 5.8%, 35.2 versus 7.8%, and 35.2 versus 10.9%, respectively; $P = 0.0038$, log-rank test) (Fig. 2). The Kaplan-Meier curves comparing the rates of symptomatic edema development are presented in Figure 3.

The effect of a supratentorial, midline parasinus location on the risk of developing symptomatic edema was also examined. Excluding parasagittal meningiomas, our study had 11 patients with midline parasinus meningiomas, 2 of whom developed symptomatic postradiosurgery edema. The risk of developing symptomatic edema after treatment of nonparasagittal, midline parasinus meningiomas was 18.2% compared with 5.8% for nonmidline tumors. However, because of the very small number of these tumors, this difference did not reach statistical significance ($P = 0.38$). After pooling all midline parasinus tumors

(parasagittal, falcine, and pineal), midline parasinus meningiomas were 4.7 times more likely to develop symptomatic edema than nonmidline supratentorial tumors (hazard ratio, 4.7; 95% confidence interval, 1.5–14.7; $P = 0.0083$).

Of the 15 patients who developed peritumoral symptomatic edema after stereotactic radiosurgery, 11 were symptomatic enough to require prolonged use (2–9 mo) of glucocorticoids. Figure 4 demonstrates the typical pattern of postradiosurgical peritumoral edema. These patients were typically started on dexamethasone (4 mg every 6 h) subsequent dosing was titrated to symptoms and neurological deficits. Meanwhile, 4 patients were managed conservatively and merely followed with serial MRI scans. The specific symptoms associated with peritumoral edema included a new motor deficit in 8 patients, new-onset moderate to severe headache in 8 patients, seizure in 4 patients, memory deficit in 3 patients, and visual deficit in 2 patients. Seizures abated in all 4 patients once steroids were begun. Edema improvement and symptom resolution was seen in 14 of the 15 patients. One patient, who was more recently diagnosed with peritumoral edema, remains on glucocorticoids.

DISCUSSION

In this study, the overall incidence of peritumoral symptomatic edema after CyberKnife SRS was 14.7%. This rate is similar to the previously reported rates after gamma knife SRS; Kan et al. (8) and Kobayashi et al. (9) reported that posttreatment peritumoral symptomatic edema developed in 17 and 13.8% of patients, respectively. In contrast, another large single-institution gamma knife series of 194 patients documented a posttreatment peritumoral symptomatic edema rate of 23.6% (2). Of note, we were unable to provide an accurate estimate of the rate of asymptomatic postradiosurgery edema, nor could we assess whether symptomatic edema was preceded by asymptomatic edema. In the present investigation, the median time to onset of symptomatic edema was 7 months. This is also consistent with the peak time to edema (6–8 mo) as reported by Kondziolka et al. (10) in a multicenter outcomes study of parasagittal meningiomas treated by using the gamma knife. At our institution, patients routinely receive 4 mg of dexamethasone immediately after each radiosurgery session. Given the delayed nature of postradiosurgery edema, the current research does not indicate that we should change this policy.

The cause of postradiosurgical peritumoral edema in meningiomas is not known. Meanwhile, a number of risk factors have been proposed, including large tumor size, parasagittal location, history of previous surgery, history of previous irradiation, previous neurological deficit, atypical abnormality, marginal tumor dose, maximum dose, and radiation delivery in a single fraction (1, 6, 7, 10, 17). However, our analysis of these potential risk factors revealed only the location of the meningioma to be predictive of subsequent peritumoral symptomatic edema formation. The 2-year actuarial rate of symptomatic edema was 35% for parasagittal tumors and 11% for nonparasagittal supratentorial tumors. Compared with patients who had nonmidline supratentorial tumors, patients who had parasagittal meningiomas were

TABLE 1. Patient, tumor, and radiosurgical characteristics and their association with the rate of subsequent symptomatic edema formation

Variable	No edema (n = 96 tumors) (%)	Edema (n = 15 tumors) (%)	P value
Age (yr)	59.1 ± 13.5	63.0 ± 15.3	0.301
Sex			0.778
Women	53 (86.9)	8 (13.1)	
Men	34 (82.9)	7 (17.1)	
Previous surgery			0.784
No	52 (85.3)	9 (14.7)	
Yes	44 (88.0)	6 (12.0)	
Previous irradiation			0.295
No	90 (87.4)	13 (12.6)	
Yes	6 (75.0)	2 (25.0)	
Previous neurological deficit			0.736
No	76 (87.4)	11 (9.9)	
Yes	20 (83.3)	4 (16.7)	
Tumor location			0.0053 ^a
Parasagittal	22 (71.0)	9 (29.0)	
Supratentorial nonparasagittal	74 (92.5)	6 (7.5)	
Tumor location			0.0036 ^a
Midline parasinus	31 (73.8)	11 (26.2)	
Nonmidline	65 (94.2)	4 (5.8)	
Tumor volume (cc)			0.270
<3	43 (91.5)	4 (8.5)	
3–6	21 (77.8)	6 (22.2)	
>6	32 (86.5)	5 (13.5)	
Treatment dose (cGy) ^b			0.876
<1600	28 (87.5)	4 (12.5)	
1600–1800	47 (87.0)	7 (13.0)	
>1800	21 (84.0)	4 (16.0)	
Maximum dose (cGy) ^b			0.415
<2000	29 (90.6)	3 (9.4)	
2000–2400	44 (81.5)	10 (18.5)	
>2400	23 (92.0)	2 (8.0)	
Fractionation			0.381
No	64 (84.2)	12 (15.8)	
Yes	32 (91.4)	3 (8.6)	
Pathological findings			1.000
Typical	85 (85.9)	14 (14.1)	
Atypical	11 (91.7)	1 (8.3)	

^a Statistically significant.^b Radiation doses of multisession radiosurgery are presented as single-session equivalent dose.

more than 4 times as likely to develop symptomatic edema after SRS. In addition, meningiomas in other midline than parasinus locations had a higher rate of symptomatic edema than nonmidline meningiomas (18.2 and 5.8%, respectively). Although this difference did not reach statistical significance because of the small number of nonparasagittal midline tumors, after pooling these tumors with the parasagittal meningiomas, the difference was

statistically significant and the effect estimate increased (i.e., the odds ratio increased from 4.1 to 4.7). These findings suggest that patients with nonparasagittal, midline parasinus meningiomas may also be at increased risk of developing postradiosurgery symptomatic edema.

To date, publications using similar definitions of symptomatic edema have reported highly variable rates of symptomatic per-

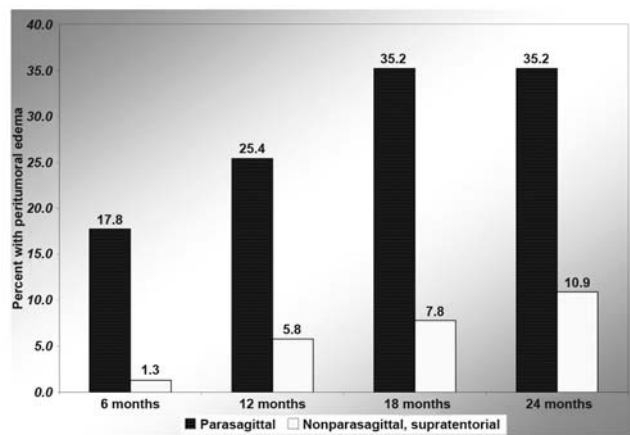


FIGURE 2. Bar graph showing actuarial rates of development of symptomatic edema after stereotactic radiosurgery of parasagittal and nonparasagittal meningiomas.

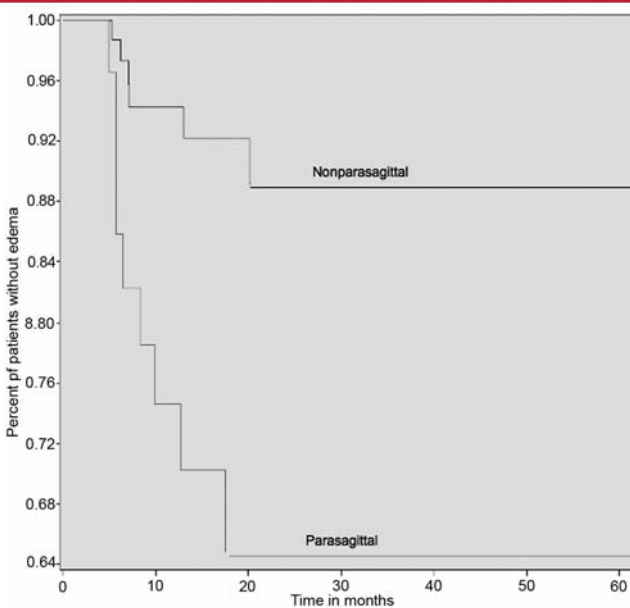


FIGURE 3. Kaplan-Meier analysis of freedom from symptomatic peritumoral edema after radiosurgery, stratified by meningioma location (parasagittal versus nonparasagittal).

itumoral edema. Kalapurakal et al. (7) reported worsening peritumoral edema in all 11 (100%) patients with parasagittal meningiomas and 4 (12.5%) of the 32 patients with nonparasagittal tumors. Chang et al. (2) reported postradiosurgery symptomatic edema in 40% of patients with parasagittal meningiomas, 18.2% of patients with convexity meningiomas, and 1.8% of patients with basilar meningiomas. Meanwhile, Singh et al. (16) found parasagittal location as the only predictor of peritumoral edema and reported symptomatic edema in 4 (25%) of 16 patients with

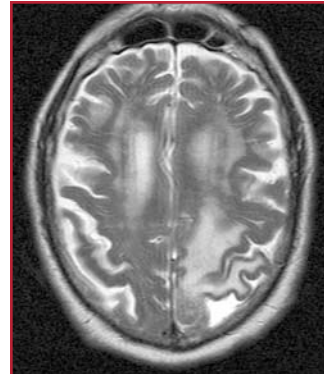


FIGURE 4. Axial T2-weighted magnetic resonance imaging scan of the brain showing postradiosurgical peritumoral edema in a patient with a parasagittal meningioma.

parasagittal meningiomas. Finally, in a multicenter study of parasagittal meningiomas, Kondziolka et al. (10) reported a 16% incidence of posttreatment symptomatic edema, but a comparison with other tumor sites was not performed. We cannot readily explain the much higher rate of postradiosurgery symptomatic edema in our series compared with the study by Kondziolka et al. (35 versus 16%). Although it would seem reasonable to attribute some of this difference to a higher median marginal dose of 18 Gy, we could

not find a relationship between dose and the likelihood of edema in our analysis. Meanwhile, other above-referenced series have observed similar (or even higher) rates of symptomatic edema development among parasagittal meningioma patients managed with radiosurgery.

Edema Management and Sequelae

After sufficient time, generally in conjunction with glucocorticoids, the symptoms of peritumoral edema resolved in all of our patients. However, it is noteworthy that four patients with only a moderate amount of peritumoral edema whose symptoms were restricted to less severe headaches could be successfully managed without steroids. Given the systemic side effects of prolonged high-dose glucocorticoid exposure, it would seem advisable at least to consider such a conservative approach in affected patients. Kondziolka et al. (10) and Singh et al. (16) reported similar symptom resolution in all their patients with peritumoral edema who were treated with steroids. In contrast, Kalapurakal et al. (7) reported 5 patients with parasagittal meningiomas that developed panhemispheric edema that did not fully resolve with aggressive steroids; in fact, one of the 5 patients in this series died as a result of uncal herniation. Despite this reported fatality, the majority of the published experience is consistent with the present observation that peritumoral symptomatic edema can usually be managed successfully with glucocorticoids alone. However, such treatment is obviously less than ideal, given the severe and protean side effects associated with prolonged steroid use.

Potential Mechanism of Injury

Although SRS is not known to damage normal venous sinuses (16), the striking increase in risk observed with the treatment of parasagittal meningiomas makes it tempting to argue in favor of a primary venous cause for postradiosurgical symptomatic edema. Radiation could theoretically cause the observed phenomenon by damaging small collateral bridging veins draining into the adjacent venous sinuses and perhaps

inducing localized thrombosis (16). The resulting edema would stem from the backward transmission of increased hydrostatic pressure into the peritumoral cortex. Meanwhile, Kan et al. (8) have detected increased levels of hypoxia-regulated angiogenesis factors in patients with meningiomas who develop edema after SRS, and have proposed another but perhaps complementary theory for peritumoral edema. Specifically, angiogenesis factors might increase the permeability of tumor blood vessels, which in turn could predispose a treated meningioma to swell. Such swelling could potentially obstruct draining cortical veins and thereby raise the hydrostatic pressure in upstream vessels, the permeability of which would already be compromised by the same hypoxia-induced angiogenesis factors found in meningiomas. Perhaps more detailed imaging of pre- and postradiosurgical venous anatomy using magnetic resonance venography could be used to investigate such venous outflow problems as a factor in postradiosurgical edema. In addition, future research into the cause of edema may involve dose-volume histogram analysis of sinuses.

CONCLUSIONS

The utility of documenting the increased risk of symptomatic postradiosurgical edema among parasagittal meningioma is twofold. First, the better recognition of the potential for complications can allow for more nuanced surgical decision making in a specific case of parasagittal meningioma. Second, the relatively large risk of symptomatic peritumoral edema after SRS of parasagittal and other midline parasinus meningiomas cries out for effective strategies for decreasing the likelihood of such a complication; a dose of greater than 6 Gy per fraction has been reported in one small study as a significant predictor of edema in parasagittal tumors (7). In this regard, is it possible that multisection radiosurgery which, with meningioma, appears to have comparable efficacy to single-session treatment, achieve this objective? The fact that conventionally fractionated radiotherapy is infrequently associated with symptomatic edema lends some, albeit limited, support to such a notion (7, 14). In the present study, 15.8% of patients who were treated in a single session developed symptomatic edema, compared with only 8.6% treated in 2 to 5 fractions. Although this difference does not rise to statistical significance, the power of our study was inadequate to detect a meaningful difference (12). Nevertheless, it is possible that a multisection approach could limit the amount of damage to draining veins and thereby decrease the incidence of symptomatic peritumoral edema. Future studies may seek to investigate such an approach.

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COMMENTS

In this report, Patil et al. evaluated the response to radiosurgery using their CyberKnife technique on a series of supratentorial meningiomas. Their aim was to compare the onset of symptomatic edema in patients with parasagittal versus nonparasagittal meningiomas. The article is limited by a relatively short median follow-up, as the window for observation of radiation-induced parenchymal effects probably extends to 3 years.

Indeed, they found that parasagittal tumors had more adverse effects, with 29% of their patients developing symptomatic edema. This rate for patients with smaller meningiomas (larger ones would probably have been resected) may seem somewhat high. Were there specific factors that could explain this? First, the median tumor margin dose was 18 Gy. This dose is high and has not typically been used by most centers for many years. The majority of meningiomas at our center receive 12 to 16 Gy, and 16 Gy would be used for a small tumor in a less critical location. On the other hand, they did study the dose response and did not find this to be important among their patients. Second, for 80% of their patients radiosurgical planning was done with computed tomography alone. This raises the question of how selective the radio-

surgical plan was to the tumor margin. Computed tomographic scanning just does not show the tumor contours as well as magnetic resonance imaging.

Third, some meningiomas just release more cytokines than others. Some patients have edema before any surgery and others do not. This factor was not assessed. Fourth, the location along the sagittal sinus may be relevant, and perhaps middle third or posterior third tumors would do worse. This was not the case in this series. Fifth, tumor volume is always important in radiosurgery. The mean volume was approximately 6 mL and was similar between the two groups. Finally, they included 12 patients with atypical or malignant meningiomas, and 7% of their patients had prior radiotherapy. The effects on these subgroups were not detailed under Results.

Patil et al. commented that a limited fractionated regimen may be one approach to lessen their rate of symptomatic edema, but this remains unknown. Another approach is to reduce the radiosurgery dose and ensure that plans use high-resolution magnetic resonance imaging obtained under precise stereotactic conditions. I think most centers would agree with the conclusion that parasagittal meningiomas are associated with an increased rate of edema (probably true after radiosurgery or resection). The challenge is for all of us to continue to improve our outcomes.

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Patil et al. present a single-center retrospective review of 102 patients with 111 supratentorial meningiomas treated with CyberKnife stereotactic radiosurgery to determine factors associated with symptomatic postradiosurgical edema. They noted an actuarial 2-year risk of 35% for patients with parasagittal meningiomas compared with 11 % for patients with nonparasagittal meningiomas. All symptomatic patients were successfully treated with corticosteroid treatment. Multivariate analysis showed tumor location as the only significant factors for development of symptomatic edema. They reviewed possible causes for this finding and proposed the use of fractionated radiosurgery to reduce the risk of this complication for patients with parasagittal meningiomas.

The increased incidence of postradiosurgical edema in patients with parasagittal meningiomas after stereotactic radiosurgery is not a new discovery. A point not emphasized in this series was the chance of symptomatic edema (11%) for patients with nonparasagittal meningiomas, which is far greater than typically discussed after radiosurgery of cranial base meningiomas, whose primary risk is cranial nerve deficits. Although modification of the radiosurgical technique (decreased dose prescription, more conformal planning, dose fractionation) may reduce the chance of this complication, changing the criteria for radiosurgery for these patients would also improve outcomes. In this series, 80 of 111 tumors (72%) were nonparasagittal tumors and 73 (66%) were less than 6 mL in volume. A complete surgical resection (Simpson Grade 1) could probably have been accomplished for the majority of this group of patients with meningiomas (mean age, 60 years), with a low risk of postoperative morbidity.

Although radiosurgery is an attractive alternative to surgical resection for both the patient and surgeon, these results should lead us to carefully evaluate our management decisions for these benign tumors, especially when they are surgically accessible. For large tumors involving a major sinus, the use of combined surgical resection and radiosurgery has become a widely accepted and used practice.

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In their article, Patil et al. have brought to our attention an observation noted by others but not previously appreciated for its importance with regard to parasagittal and midline tumor locations. The number of events is fairly small, that is, symptomatic cerebral edema after stereotactic radiosurgery. They might have separated out the 79 patients who had single fraction versus fractionated treatment when they compared their findings to those for gamma knife radiosurgery (single fraction). With regard to tumor volume, the percentage of patients developing symptomatic edema was not found to be significant, but of the patients with tumor volumes less than 3 cc, how many of them were less than 1 or 2 cc? Would cytoreductive surgery to a volume of less than 1 cc be recommended before considering stereotactic radiosurgery be a reasonable paradigm? Because of the small number of events, definite conclusions cannot be reached. The authors speculate on the possible causes of the edema after stereotactic radiosurgery, but it is likely that the mechanism(s) of cell kill is different between single and fractionated irradiation therapy. In considering the findings and observations of Patil et al., it is probably an issue that should be discussed with the patient as part of the informed consent process.

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A multicenter retrospective study led by Douglas Kondziolka some years ago demonstrated a quite high rate of toxicity after radiosurgery in patients with parasagittal meningiomas (1). In a group of 185 patients treated with a mean peripheral dose of 15 Gy and with a median follow-up of 3.5 years, this series reported that 16% of patients experienced a symptomatic transient edema with neurological clinical worsening in 9%. Interestingly, in this material the risk was significantly higher in patients with previously resected meningiomas, in patients harboring a deficit before radiosurgery, and in patients with larger tumors (especially tumors larger than 7.5 ml). Patil et al. provide us with an interesting report about increased risk of parasagittal meningiomas after radiosurgery. Thus, it is not a new observation. However, the demonstration of this fact when compared with results for non-midline meningiomas is new. The claim that, taken together, the data show that there is an increased risk with midline meningiomas is interesting. However, owing to the small size of this population, the authors have failed to demonstrate a higher risk in the subgroup of nonparasagittal midline meningiomas. In fact, such a demonstration is of interest both for practical reasons (patient information and indication selection) and for a better understanding of the underlying physiological mechanism of this phenomenon. In the present series 29% of the patients with parasagittal meningiomas experienced symptomatic edema, which is clearly a higher rate than the 16% in Kondziolka et al. (1). Patil et al. gave few explanations regarding this very high toxicity rate. Is it related to the marginal dose, which was a bit higher, to the fractionation, to the fact that 80% of tumors were targeted only on computed tomographic scans, or to technology? It would have been interesting if they had attempted to clarify these issues. Usually, when such a discrepancy is observed between two series, one may suspect that there is one or several parameters differentiating these two series and accounting for those differences. Being able to understand these hidden parameters is always very fruitful and useful for future practice and development of future strategies. Nevertheless, it must be emphasized that small, growing parasagittal meningiomas that had not been previously operated on and are invading a patent

sagittal sinus can be treated very safely and efficiently by radiosurgery if performed with state-of-the-art techniques.

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1. Kondziolka D, Flickinger J, Perez B: Judicious resection and/or radiosurgery for parasagittal meningiomas: Outcomes from a multicenter review. Gamma Knife Meningioma Study Group. *Neurosurgery* 43:405–413, 1998.

In this article, Patil et al. reported on the extent to which they observed symptomatic edema after CyberKnife radiosurgery in patients with supratentorial meningiomas. This group treated 102 patients with 111 supratentorial meningiomas. The median prescription dose was 18 Gy. Patients were treated using one- to five-fraction schemes; patients with larger meningiomas predominantly underwent multisession radiosurgery. Overall, 14.7% of patients developed symptomatic edema following radiosurgery. Patients with parasagittal and midline parasinus (defined in this study as parasagittal, falx, and pineal) meningiomas were more likely to develop symptomatic edema after radiosurgery.

Patil et al. have added to the current understanding of symptomatic edema after radiosurgery and identification of risk factors associated with this phenomenon. Interestingly, despite the use of fractionation, the overall risk of edema in this series is comparable to that in previously reported radiosurgical series in which single-fraction delivery was used.

Fortunately, symptomatic edema can typically be managed with a brief course of corticosteroids. At the University of Virginia, steroids given perioperatively do not seem to alter the risk of delayed radiosurgically induced edema. Given this observation and the potential morbidity associated with steroids, we have halted the routine administration of steroids at the time of gamma knife surgery for benign intracranial tumors. It is even rarer yet that a patient with a meningioma who has symptomatic edema and is receiving steroids progresses further and requires a surgical resection. For patients with moderate- to large-volume parasagittal meningiomas and preexisting T2-weighted changes on magnetic resonance imaging, a cytoreductive operation before radiosurgery seems intuitively pleasing so as to avoid tipping the scales and thereby pushing a patient's edema from asymptomatic to symptomatic.

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New Orleans. Image courtesy of Earth Sciences and Image Analysis Laboratory, NASA Johnson Space Center, (<http://eol.jsc.nasa.gov>).

THE ROLE OF STEREOTACTIC RADIOSURGERY FOR INTRACRANIAL HEMANGIOBLASTOMAS

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OBJECTIVE: To evaluate the role of stereotactic radiosurgery (SRS) in the management of recurrent or residual intracranial hemangioblastomas, we assessed tumor control, survival, and complications in 32 consecutive patients.

METHODS: We retrospectively reviewed records of 32 consecutive hemangioblastoma patients (74 intracranial tumors) who underwent gamma knife SRS. The median patient age was 43.8 years (range, 21.3–79.4 yr). Thirty-one patients had undergone previous surgical resections. Nineteen patients had sporadic lesions (22 tumors), and 13 patients had von Hippel-Lindau disease-associated hemangioblastomas (52 tumors). The median SRS target volume was 0.72 mL (range, 0.08–16.6 mL), and the median marginal dose was 16.0 Gy (range, 11–20 Gy).

RESULTS: At a median of 50.1 months (range, 6.0–165.4 mo), seven patients had died from disease progression, and one patient had died secondary to heart failure. The overall survival after radiosurgery was 100%, 94.4%, and 68.7% at 1, 3, and 7 years, respectively. Follow-up imaging studies demonstrated tumor control in 68 tumors (91.9%). The progression-free survival after SRS at 1, 3, and 5 years was 96.9%, 95.0%, and 89.9%, respectively. Factors associated with an improved progression-free survival included von Hippel-Lindau disease-associated hemangioblastoma, solid tumor, lower tumor volume, and greater marginal dose.

CONCLUSION: SRS is an important tool in the management of hemangioblastomas and is associated with a high tumor control rate and a low risk of adverse radiation effects.

KEY WORDS: Gamma knife, Hemangioblastoma, Stereotactic radiosurgery, von Hippel-Lindau disease

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Hemangioblastomas are rare benign tumors of the central nervous system that often occur in the posterior fossa (3). They present as highly vascular, solid, or cystic neoplasms. Hemangioblastomas of the brain can present as sporadic lesions or as a manifestation of von Hippel-Lindau (VHL) disease (5, 7, 15). Although they occur throughout the cerebrospinal axis, multifocal hemangioblastomas associated with VHL predominate in the posterior fossa (20).

In most patients (>75%), the hemangioblastoma is a sporadic, single lesion involving the cerebellum, brainstem, or upper cervical spinal cord (10). These tumors usually occur in young

adults with a slight male predominance. Approximately 20 to 25% of patients with intracranial hemangioblastomas have VHL (9).

Surgical resection is the usual treatment of choice for most symptomatic hemangioblastomas (13). However, vascularity or critical location often makes complete resection impossible. In patients with multiple hemangioblastomas, complete resection of all tumors is not feasible. Conventional radiation therapy (RT) has been used for residual, recurrent, or inaccessible tumors (14, 16). Progression of symptomatic tumors may lead to neurologically worse outcomes.

Although surgical resection and radiation therapy both have a role in the treatment of hemangioblastomas, the role of stereotactic radiosurgery (SRS) has not been well defined (4, 8, 11, 12, 20). We reviewed our updated

ABBREVIATIONS: MRI, magnetic resonance imaging; RT, radiation therapy; SRS, stereotactic radiosurgery; VHL, von Hippel-Lindau.

experience in 32 patients who had 74 tumors treated by SRS with use of the gamma knife. We assessed tumor control, patient survival, adverse radiation effects, and other variables that could affect outcomes.

PATIENTS AND METHODS

Patient Population

Between June 1990 and October 2006, 32 hemangioblastoma patients underwent primary (21 patients) or adjuvant SRS (11 patients) at the University of Pittsburgh (Table 1). There were 21 men and 11 women with a median age of 43.8 years (range, 21.3–79.4 yr). The major presenting clinical features were cerebellar signs (25 of 32 patients), lower cranial nerve dysfunction (12 of 32 patients), or serial progression on imaging (2 of 32 patients). The Karnofsky Performance Scale score varied from 60 to 100 (median, 80). Thirty-one patients had undergone previous surgical resection of their hemangioblastomas, and one patient was diagnosed by magnetic resonance imaging (MRI) and angiography. Pathology review was performed at the referring hospital in 8 patients and at our medical center in 23 patients. All pathological data

were reviewed by neuropathologists. Pathological grading was performed according to the World Health Organization classification of hemangioblastoma. Thirteen patients (40.1%) with 52 tumors had established stigmata of VHL disease, whereas the other 19 patients (59.3%) with 22 tumors had sporadic intracranial hemangioblastomas.

Twenty-one patients with 59 tumors received SRS at the time of tumor progression identified by imaging. Tumor progression was defined as an increase in tumor volume at the time of follow-up MRI. The median duration between last surgical removal and recurrence was 22.4 months (range, 3.8–122 mo). Eleven patients with 15 tumors received adjuvant SRS for residual tumors after surgical removal. The median duration between last surgical removal and SRS for residual tumor was 2.4 months (range, 1.1–34.5 mo).

Radiosurgery Technique

Radiosurgery was performed with the Model U, B, C, or 4-C Leksell Gamma Knife (Elekta, Inc., Atlanta, GA). The procedure began with application of a Model G Leksell stereotactic frame with the patient under conscious sedation and receiving local scalp anesthesia. After a fiducial system was attached to the frame, all patients underwent high-resolution MRI. A three-dimensional localizer sequence that included axial, coronal, and sagittal images was performed first. The tumor was then imaged with a three-dimensional spoiled gradient recalled volume acquisition at steady state. T2-weighted magnetic resonance images obtained via the fast spin echo technique also were acquired to assess the infiltrative tumor volume or reactive (edema) changes. The images were exported to a computer workstation via the hospital ethernet for dose planning. In all patients, the radiosurgery target volume was defined as the enhancing tumor volume.

The mean and median tumor volumes were 2.43 and 0.72 mL, respectively (range, 0.08–16.6 mL). A median of 2 isocenters (range, 1–13 isocenters) was used for dose planning. The median prescription dose delivered to the margins of tumor was 16.0 Gy (range, 11–20 Gy). The prescription isodose was 50% in 64 lesions. Maximum dose varied from 22 to 40 Gy (median, 30 Gy). All patients received an intravenous dose of 20 to 40 mg methylprednisolone after radiosurgery, and all were discharged from the hospital within 24 hours.

All patients were evaluated with MRI at intervals of 3 to 6 months after radiosurgery. All living patients had a minimum of 6 months' follow-up. Twenty patients had a follow-up of 24 months or longer. The median follow-up time after SRS was 50.1 months (range, 6.0–165 mo), and the mean follow-up time after diagnosis was 132.2 months (range, 6.0–363 mo). Follow-up MRI scans were compared with the intraoperative images, and tumor dimensions were measured in the axial, sagittal, and coronal planes. A complete response was defined as the complete disappearance of enhancing tumor volume, partial response was defined as shrinkage of more than 50% of the tumor volume, stable disease was defined as 25% or less change in tumor volume, and progressive disease was defined as more than 25% increase in size of enhancing or nonenhancing tumor volume.

Statistical Analysis

For statistical analysis, we constructed Kaplan-Meier plots for survival and progression-free survival using the dates of diagnosis, first surgery, first SRS, follow-up MRI studies, and death or last follow-up. Progression-free survival and overall survival time were calculated from the day of the first SRS with the use of the Kaplan-Meier method. Univariate analysis was performed on the Kaplan-Meier curves using the log rank statistic, with $P < 0.05$ set as significant. The Wilcoxon rank-sum test was used to analyze the relationship between the tumor volumes of sporadic and VHL-associated hemangioblastomas.

TABLE 1. Patient characteristics in 32 patients with 74 lesions^a

Characteristics	Sporadic	VHL	Entire series
No. of patients	19	13	32
No. of lesions	22	52	74
Median age (range)	50.6	40.2	43.8 (21.3–79.4)
Male	14	7	21
Female	5	6	11
Previous surgery	18	13	31
Single	17	5	22
Multiple	2	8	10
Location			
Cerebellar hemisphere	10	40	50
Vermis	10	7	17
Brainstem	0	2	2
Cerebellopontine angle	1	0	1
Cavernous sinus	1	0	1
Clinoid	0	1	1
Supratentorial	0	2	2
Solid	17	49	66
Cystic	5	3	8
Mean/median target volume, mL (range)	5.22/4.10	1.25/0.54	2.43/0.72 (0.08–16.6)
Mean/median margin dose, Gy (range)	15.9/15.0	15.7/16.0	15.8/16.0 (11–20)
Mean/median maximum dose, Gy (range)	30.6/30.0	30.3/30.6	30.4/30.0 (22–40)

^a VHL, von Hippel-Lindau disease.

Standard statistical processing software (SPSS, version 15.0, Chicago, IL) was used. This retrospective study was approved by the University of Pittsburgh Institutional Review Board. All chart reviews and data analyses were conducted before December 30, 2007.

RESULTS

At the time of this assessment, 24 patients (75%) were alive, and 8 patients (25%) had died. Three of the eight who died had VHL disease. Two sporadic hemangioblastoma patients died from heart failure. Three sporadic hemangioblastoma patients and one VHL patient died from unknown causes. One VHL patient died 28 months after SRS as the result of a rapid tumor progression at multiple brain and cervical spine sites. Another VHL patient died 32 months after SRS as the result of rapid tumor progression of a cervical spinal cord hemangioblastoma. These eight patients died at an average of 74.9 months after radiosurgery (range, 12.5–165 mo). At the time of this analysis, 24 patients were surviving at a median of 56.7 months after radiosurgery (range, 6.0–163 mo). The median survival time was 165.4 months. The overall survival after initial diagnosis was 100, 95.8, and 85.4% at 1, 5, and 10 years, respectively. The overall survival after radiosurgery was 100, 94.4, and 68.7% at 1, 3, and 7 years, respectively. The overall survival of sporadic hemangioblastoma patients after SRS was 100, 100, and 50% at 3, 5, and 7 years, respectively. The overall survival of VHL patients after SRS was 90.9, 90.9, and 77.9% at 3, 5, and 7 years, respectively.

After radiosurgery, local tumor progression was observed in six tumors (four sporadic hemangioblastomas and two VHL-associated hemangioblastomas). Three of these patients underwent surgical resection, two underwent stereotactic cyst aspiration, and one was managed conservatively with imaging follow-up. Two patients underwent stereotactic cyst aspiration once (8.1 and 36.8 mo after SRS). The solid tumor components (mural nodules) were unchanged in volume after SRS. After simple stereotactic cyst aspiration, both patients had control of residual solid and cystic components at the time of last follow-up (55.5 and 62.6 mo after SRS). Follow-up imaging showed stable appearance (no change in volume) in 30 tumors (40.5%). A reduction in tumor volume was identified in 36 tumors (48.6%), and complete resolution was seen in two tumors (Table 2).

During the follow-up period, 10 (31.2%) of 32 patients developed new tumors at other brain locations. Two of the 10 patients who had sporadic hemangioblastomas developed

recurrent tumors within the previous resection cavity (which was not included in the radiosurgery dose plan) 6.8 and 54.7 months after SRS. Eight of 10 patients who had VHL-associated hemangioblastomas developed new tumors at other brain or spinal regions at a median of 43.7 months (range, 14.0–121.8 mo) after SRS. Actuarial rates of freedom from new tumor development after SRS at 1, 5, and 10 years were 96.7, 65.4, and 39.2%, respectively. Actuarial rates of freedom from new tumors of sporadic hemangioblastoma patients after SRS at 1, 5, and 10 years were 94.4, 81.0, and 81.0%, respectively. Actuarial rates of freedom from new tumor development of VHL patients after SRS at 1, 5, and 10 years were 100, 55.6, and 18.5%, respectively. The median recurrence-free survival time was 116.0 months. Sporadic hemangioblastoma was associated with better freedom from new tumor development ($P = 0.0472$). Three VHL-associated hemangioblastoma patients who had progression at other brain sites outside the radiosurgery treatment volume (two, seven, and four tumors) underwent repeat radiosurgery for all new tumors 3.8, 4.5, and 13 years, respectively, after initial SRS. The remaining two patients who developed new tumors at other brain sites outside the radiosurgery treatment volume elected for conservative management and follow-up imaging. Three patients had spinal hemangioblastomas. One patient underwent spinal CyberKnife SRS (Accuray, Sunnyvale, CA). Two patients elected to continue observation. The progression-free survival after SRS for all hemangioblastomas was 96.9, 95.0, 89.9, and 85.9% at 1, 3, 5, and 10 years, respectively (Table 3).

Statistical Analysis

We performed univariate analysis using the log rank test to assess factors that influence the length of overall and progression-free survival. The following variables were assessed: sex (male or female), age (≥ 50 yr or < 50 yr), radiosurgery target volume (≥ 3.2 ml or < 3.2 ml), marginal dose (≥ 15 Gy or < 15 Gy), tumor type (solid or cystic), VHL-associated hemangioblastoma

TABLE 2. Tumor grade and imaging response after radiosurgery^a

Imaging response	Sporadic	VHL	Entire series
Complete resolution	0	2	2
Tumor regression	9	27	36
Stable tumor	9	21	30
Tumor progression	4	2	6

^a VHL, von Hippel-Lindau disease.

TABLE 3. Survival based on sporadic or von Hippel-Lindau disease-associated hemangioblastoma^a

	Sporadic	VHL	Entire series
Survival rate, %	84.2	76.9	81.3
OAS, %			
1 yr	100	100	100
5 yr	100	90.9	94.4
10 yr	50.0	77.9	68.7
Recurrence rate, %	81.8	96.2	91.9
PFS, %			
1 yr	95.5	97.4	96.9
3 yr	88.6	97.4	95.0
5 yr	44.3	97.4	89.9

^a VHL, von Hippel-Lindau disease; OAS, overall survival; PFS, progression-free survival.

TABLE 4. Results of univariate analysis for 32 patients with 74 lesions treated with a single radiosurgery, with progression-free survival measured from date of radiosurgery^a

Characteristics	P value
Age (<50 yr)	0.4774
Sex	0.0515
VHL versus sporadic tumor	0.0018 ^b
Solid tumor versus cystic tumor	<0.0001 ^b
Target volume (<3.2 ml)	<0.0001 ^b
Margin dose (≥15 Gy)	0.0021 ^b
Residual versus new and recurrent tumor	0.0694

^a VHL, von Hippel-Lindau disease^b Statistically significant difference.

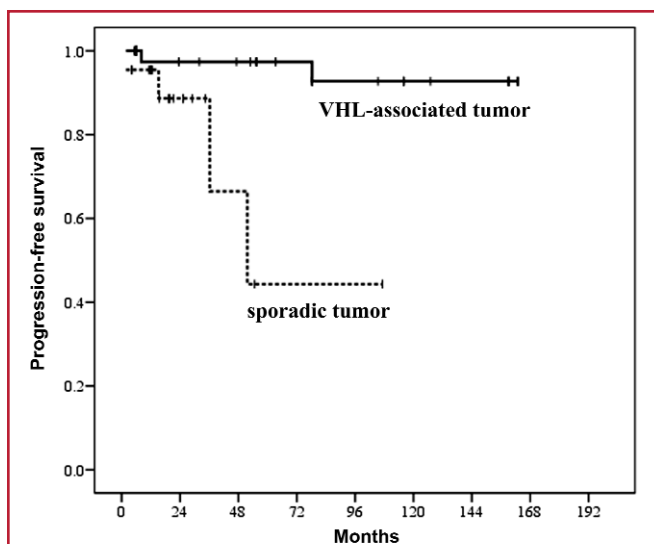
or sporadic hemangioblastoma, Karnofsky Performance Scale score (≥80 or <80), single or multiple lesions, and timing of SRS (SRS for tumor recurrence or SRS for residual tumor or as initial treatment). VHL-associated hemangioblastoma, smaller tumor volume, and greater margin dose were associated with better progression-free survival (Table 4).

VHL Disease-associated Hemangioblastoma

Two (3.8%) of 52 VHL-associated hemangioblastomas showed progression in the SRS volume. In contrast, 4 (18.2%) of 22 patients with sporadic hemangioblastomas exhibited progression in SRS volume. VHL-associated hemangioblastoma had a 1-, 3-, and 5-year progression-free survival of 97.4% for each. Sporadic hemangioblastomas had a 1-, 3-, and 5-year progression-free survival of 95.5, 88.6, and 44.3%, respectively (Fig. 1). Sporadic hemangioblastoma was significantly associated with worse progression-free survival ($P = 0.0018$). The mean tumor volumes of VHL-associated hemangioblastomas and sporadic hemangioblastomas were 1.25 and 5.04 mL, respectively. The tumor volume of sporadic hemangioblastomas was significantly larger than that of VHL-associated hemangioblastomas ($P = 0.0016$).

Tumor Characteristics

Two (3.1%) of 65 patients with a solid tumor showed progression in the SRS target volume. One patient with sporadic hemangioblastoma underwent surgical removal 52 months after SRS, and one with VHL-associated hemangioblastoma underwent stereotactic cyst aspiration 8.1 months after SRS. Four (44.4%) of nine patients with a mixed cystic and solid tumor showed progression in the SRS target volume. The median time to progression of mixed cystic and solid tumors was 25.2 months (range, 1.8–78.3 mo). One patient with VHL-associated hemangioblastoma had conservative follow-up. Two patients with sporadic hemangioblastomas underwent stereotactic cyst aspiration 15.2 and 36.8 months after SRS. One patient with sporadic hemangioblastoma underwent additional surgical removal 8 months after SRS. One patient who under-

**FIGURE 1.** Kaplan-Meier curves comparing progression-free survival after stereotactic radiosurgery (SRS) for sporadic hemangioblastomas versus von Hippel-Lindau (VHL) disease-associated hemangioblastomas. VHL disease was significantly associated with better progression-free survival ($P = 0.018$).

went stereotactic cyst aspiration 15.2 months after SRS died from disease progression at 75.9 months after SRS. The remaining patients were still alive at the time of last follow-up. Patients with solid tumors had 1-, 3-, and 5-year progression-free survivals of 98.0, 98.0, and 94.9%, respectively. Patients with mixed cystic and solid tumors had 1-, 3-, and 5-year progression-free survivals of 88.9, 76.2, and 61.0%, respectively (Fig. 2). Patients with solid tumors had significantly better progression-free survivals ($P < 0.0001$).

Tumor Volume

In the entire series, 6 (30%) of 20 lesions with a tumor volume of 3.2 mL or more progressed in SRS volume; the median time to progression was 25.7 months. The mean and median tumor volumes with progression after SRS were 7.59 and 6.90 mL (range, 4.32–12.4 mL). In contrast, none of the 54 lesions with a tumor volume of less than 3.2 mL exhibited local progression in SRS volume. Kaplan-Meier plots, generated for progression-free survival (Fig. 3), showed that lesions with a volume of 3.2 mL or more had 1-, 3-, and 5-year progression-free survivals of 89.4, 82.5, and 56.6%, respectively. Lesions with a target volume of less than 3.2 mL had 1-, 3-, and 5-year progression-free survivals of 100% for each. A target volume of less than 3.2 mL was significantly associated with better progression-free survival ($P < 0.0001$).

Marginal Dose

Twenty-one lesions (28.4%) received a marginal dose of less than 15 Gy, and 53 lesions (71.6%) received 15 Gy or more. Four (19.0%) of 21 lesions treated with a marginal dose of less

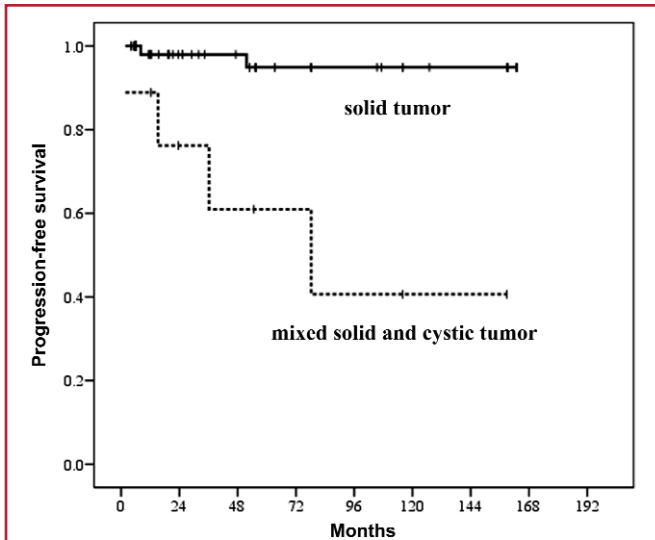


FIGURE 2. Kaplan-Meier curves comparing progression-free survival after SRS for solid versus mixed (solid and cystic) hemangioblastomas. Solid hemangioblastomas were significantly associated with better progression-free survival ($P < 0.0001$).

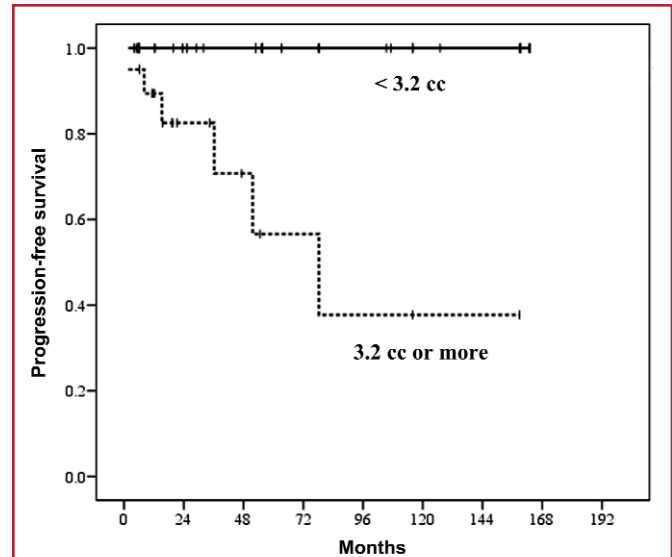


FIGURE 3. Kaplan-Meier curves of progression-free survival after SRS for hemangioblastoma patients with target volumes of ≥ 3.2 mL versus < 3.2 mL. The target volume of < 3.2 mL was significantly associated with better progression-free survival ($P < 0.0001$).

than 15 Gy exhibited in-field progression. In contrast, only 2 (3.8%) of 53 lesions treated with 15 Gy or more exhibited in-field progression. The marginal dose of 15 Gy or more had 1-, 3-, and 5-year progression-free survivals of 100, 100, and 96.7%, respectively. The marginal dose of less than 15 Gy had 1-, 3-, and 5-year progression-free survivals of 87.9, 79.9, and 68.5%, respectively (Fig. 4). The marginal dose of 15 Gy or more was significantly associated with better progression-free survival ($P = 0.0021$). Other variables (sex, age, residual versus new and recurrent tumor) were not significantly associated with better progression-free survival (Table 4).

Adverse Radiation Effects

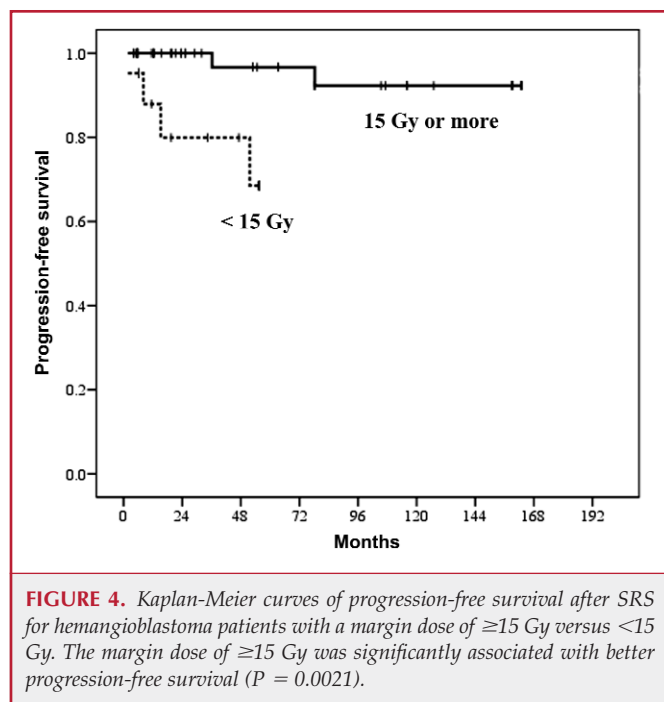
One patient (3.1%) who had a VHL-associated hemangioblastoma and received 12 Gy at the margin developed increased peritumoral T2 signal changes on MRI but no new symptoms. This patient was successfully managed with oral corticosteroids.

DISCUSSION

Intracranial hemangioblastomas are highly vascular and well-circumscribed tumors (15). Hemangioblastomas are considered World Health Organization Grade 1 tumors of uncertain origin and are composed of stromal cells and abundant capillaries. Approximately 20 to 25% of hemangioblastomas are associated with VHL disease (8). Sporadic hemangioblastomas occur predominantly in the cerebellum, whereas VHL-associated hemangioblastomas are found in the cerebellum, brainstem, and spinal cord (2). In our series, 20 of 22 sporadic hemangioblastomas were located in the cerebellum, but one

involved the cavernous sinus and one developed in the cerebellopontine angle. One sporadic hemangioblastoma patient with a large tumor involving the cavernous sinus underwent SRS 3 months after partial surgical removal. VHL-associated hemangioblastomas were found in the cerebellum (47 of 52 tumors), the brainstem (2 tumors), clinoid region (1 tumor), and the cerebrum (2 tumors). Three patients also had spinal VHL-associated hemangioblastomas.

When hemangioblastomas are located in critical areas, complete resection may be difficult. The highly vascular nature of some hemangioblastomas may benefit from preoperative embolization before surgical removal (6, 18, 19). Complete surgical resection is often curative, whereas subtotal resection results in predictable recurrences (14). Conway et al. (5) reported 40 hemangioblastoma cases and noted that partial resection led to recurrence in eight patients (20%) and additional morbidity in six patients (15%). Wang et al. (21) reported 39 hemangioblastoma patients who underwent radical surgical resection. Postoperatively, 11 patients deteriorated after surgery, and 2 patients died. Ammerman et al. (1) reported the long-term natural history of VHL-associated hemangioblastomas. Despite measurable growth in almost all hemangioblastomas (97% of patients), only 41% of patients became symptomatic. Forty-five percent of the hemangioblastomas that eventually produced symptoms were not among the tumors that were apparent on the initial MRI study. Depending on location (brainstem and cerebellum), the hemangioblastoma size and/or tumor and cyst growth rates predicted symptom development and the need for treatment ($P < 0.05$). Because hemangioblastomas exhibit a stuttering growth pattern (mean growth period, 13 mo), and frequently remain asymptomatic, continued observation may



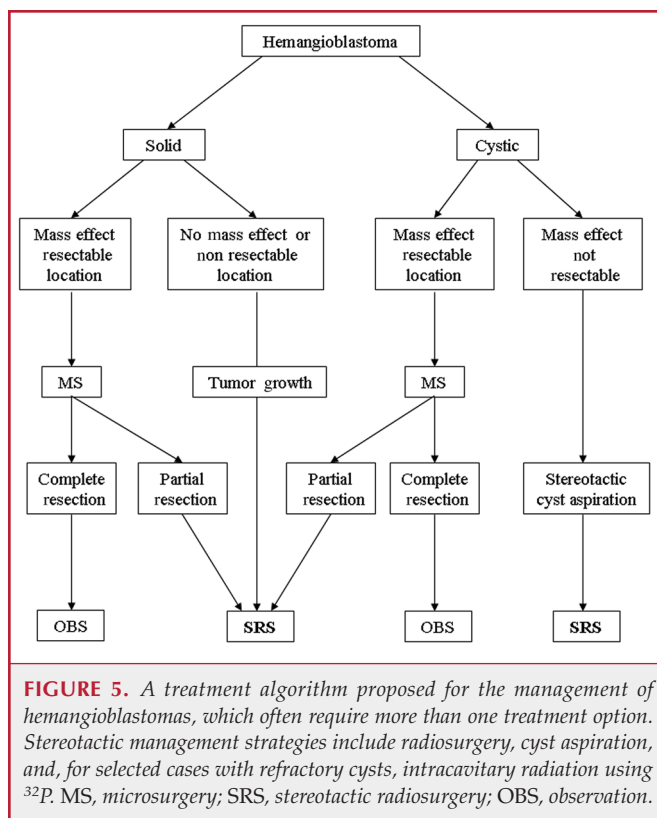
be possible for long intervals. In our series, 8 of 10 patients who had VHL-associated hemangioblastomas developed new tumors at a median of 43.7 months.

Fractionated Radiation Therapy

Smalley et al. (14) treated 27 hemangioblastoma patients with fractionated RT after incomplete surgical removal. The recurrence-free survival rates at 5, 10, and 15 years were 76, 52, and 42%, respectively. Local control was significantly better in patients receiving 50 Gy compared with those treated with lower doses (57 versus 33%). RT may be administered after resection. In our series, there were no patients who had undergone previous RT. The progression-free survival after SRS for all hemangioblastomas was 89.9 and 85.9% at 5 and 10 years, respectively. These data suggest that local control rate after SRS may be enhanced, compared with RT. However, no prospective trial has been performed.

SRS

In Figure 5, we suggest a potential treatment algorithm for patients with hemangioblastoma. In this concept, SRS is applied most commonly for residual tumors that could not be completely removed or for patients with deep-seated tumors that are deemed a high risk for microsurgery. Stereotactic aspiration of deep-seated cystic tumors can precede SRS in selected cases. Intracavitary radiation by stereotactic implantation of ^{32}P may be used to reduce cyst filling in refractory hemangioblastoma cysts. Previously published reports also describe the potential role of SRS in the management of hemangioblastoma. Patrice et al. (12) reported an 86% actuarial rate of tumor control at 2



years after SRS (Table 5). Niemelä et al. (10) reported 11 hemangioblastoma cases and showed a reduction in the treated volume in six tumors at a median 30 months after SRS. Chang et al. (4) reported that, in 13 patients (with 29 hemangioblastomas) who underwent linear accelerator radiosurgery, a higher dose improved results. In our previous multi-institutional study, the actuarial 5-year survival was 75.1% and the 5-year actuarial tumor control rate was 75.2%. Tumor control was related to smaller tumor volume and greater radiosurgical dose (18 Gy) (8). Wang et al. (22) reported 35 patients with 93 hemangioblastomas treated with gamma knife SRS. The 5-year progression-free survival was 71%, and the actuarial survival rate was 82.9%. Tago et al. (17) reported actuarial 5- and 10-year control rates of 96.2%. In the present series, the progression-free survival after SRS for all hemangioblastomas was 89.9% at 5 years.

VHL Disease

In our series, sporadic hemangioblastoma was significantly associated with worse progression-free survival than VHL-associated hemangioblastoma ($P = 0.0018$). This unexpected result may be related to differences in tumor volumes. Tumor volumes of sporadic hemangioblastomas were significantly larger than those of VHL-associated hemangioblastomas ($P = 0.0016$). We suspect that growing VHL-associated hemangioblastomas are recognized sooner because of close MRI follow-up, prompting earlier intervention. We believe that small,

TABLE 5. Summary of stereotactic radiosurgery for hemangioblastomas from previous publications^a

Series (ref. no.)	No. patients/ tumors	Mean follow-up, mo	Mean tumor volume or diameter	Mean mar- gin dose, Gy	5-year OAS	5-year PFS
Patrice et al., 1996 (12)	22/38	24.5	0.97 mL	15.5	88% (2-yr)	86% (2-yr)
Niemelä et al., 1996 (10)	10/11	43	13.5 mm	20	67.5%	100%
Chang et al., 1998 (4)	13/29	43	1.6 mL	23.2	92.3% (overall)	96.6% (overall)
Pan et al., 1998 (11)	13/20	29	20 mm	18.4	92.3% (overall)	69.2% (overall)
Wang et al., 2005 (22)	35/93	66	13 mm	17.2	69.0%	82.9% (overall)
Tago et al., 2005 (17)	13/38	36	0.23 mL	20	80.8%	96.2%
Present series	32/74	61.4	0.72 mL	16	94.4%	89.9%

^a OAS, overall survival; PFS, progression-free survival.

asymptomatic hemangioblastomas, as often are noted in VHL patients, are best observed until documented growth is confirmed by imaging or symptoms develop.

Tumor Characteristics

Wang et al. (22) reported six hemangioblastomas with associated cysts. Although solid tumors and cysts were irradiated, enlarging cysts in two patients required evacuation at 3 and 4 months, respectively. Two cysts in two other patients shrank at 18 and 24 months but increased at 22 months and 3 years, respectively. In the remaining two cystic hemangioblastomas, small cysts disappeared or shrank during the follow-up period (22). In our series, hemangioblastomas with cystic components had significantly worse progression-free survival ($P < 0.0001$). Four (44.4%) of nine patients with a mixed cystic and solid tumor showed progression in the SRS target volume. Three of four patients underwent additional surgical procedures (two had stereotactic cyst aspiration, and one had surgical removal). One of four patients had conservative follow-up. One patient who underwent stereotactic cyst aspiration 15.2 months after SRS died from disease progression 75.9 months after SRS. All other patients were still alive at the time of last follow-up. Because SRS does not quickly reduce mass effect, it may not be effective for treating large symptomatic cystic hemangioblastomas. In selected patients, stereotactic cyst aspiration or even intracavitary radiation using ³²P (for refractory cysts) followed by SRS of the remaining mass may enhance local tumor control.

Marginal Dose

Patrice et al. (12) indicated that a greater radiosurgical dose and a smaller tumor volume significantly contributed to a higher tumor control rate. Chang et al. (4) also described the importance of higher dose. In our series, a target volume of less than 3.2 mL was significantly associated with better progression-free survival ($P < 0.0001$), and a marginal dose of 15 Gy or more was significantly associated with better progression-free survival ($P = 0.0021$). Better progression-free survival was associated with smaller tumor volumes, higher margin dose, and solid tumor configuration.

CONCLUSION

SRS is an effective and safe strategy during multimodal management of hemangioblastomas. As a minimally invasive option, it may be especially valuable for treatment of multiple VHL-associated hemangioblastomas.

Disclosure

L. Dade Lunsford, M.D., Douglas Kondziolka, M.D., and Ajay Narajan, M.Ch., are consultants with Elekta AB.

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COMMENTS

Kano et al. review a series of patients treated with radiosurgery for hemangioblastomas. We have achieved similar control rates for these tumors at our institution and have also noted that cystic tumors were more difficult to control than solid tumors. Furthermore, we also had experiences with the need for cyst aspiration after radiosurgery for a hemangioblastoma but found that this was required only during the first year after radiosurgery. Presumably cyst fluid production may decrease or stop once the actual tumor nodule has been destroyed with radiosurgery. A remaining question is how to manage small asymptomatic tumors in patients with multiple hemangioblastomas as part of their von Hippel-Lindau (VHL) disease. Many of these tumors remain stable in size on serial magnetic resonance imaging scans, and it is difficult to predict which of these small tumors would become the next symptomatic lesion.

Steven D. Chang
Stanford, California

In this article, Kano et al. retrospectively review their experience with gamma knife radiosurgery for patients with hemangioblastomas. Thirty-two patients underwent gamma knife radiosurgery for a total of 74 tumors. Nineteen patients had sporadic hemangioblastomas, and 13 had VHL disease-associated tumors. In this study, the majority of the

hemangioblastomas analyzed (70%) were in patients with VHL disease. Median tumor volume was small at 0.72 mL.

Progression-free survival (PFS) rates at 1 year, 3 years, and 5 years after radiosurgery were 96.9, 95, and 89.9%, respectively. Factors associated with improvements in PFS included VHL disease, solid compared with cystic tumors, small tumor volume, and increased margin dose.

For patients with a growing and symptomatic hemangioblastoma, surgical resection should be the treatment of choice. Radiosurgery represents a reasonable treatment option for patients with hemangioblastomas that demonstrate growth and are either surgically inaccessible or for which the patient is unwilling to undergo resection. In those patients with small and asymptomatic hemangioblastomas, observation with serial neuroimaging is reasonable. This option is particularly appealing for patients with VHL disease, given the well-defined natural history of this disease (1).

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Kano et al. update their experience from the University of Pittsburgh on the radiosurgical management of patients with intracranial hemangioblastomas. Their results and conclusions are in line with those of previous publications on this topic. Of note, new tumor formation was frequent for both patients with sporadic tumors (19% at 5 years) and patients with VHL disease (45% at 5 years), and the failure rate noted for patients with cystic tumors (40% at 2 years) emphasizes the limited role of radiosurgery for patients with this tumor morphology. The recommendation that patients with small, asymptomatic tumors be observed until tumor growth is confirmed by serial imaging is reasonable, considering the natural history information provided.

Bruce E. Pollock
Rochester, Minnesota

In this retrospective study Kano et al. analyze the records of 32 consecutive patients with hemangioblastomas (31 of 32 operated on previously) harboring 74 intracranial lesions, who were treated by gamma knife radiosurgery in one of the leading centers of the world. In 19 of 32 patients (22 tumors), tumors were sporadic forms, whereas 13 of 32 patients (52 tumors) had typical VHL syndromes. Average tumor volume was rather small (0.72 mL), the mean surface dose was 16 Gy, and the average follow-up was 61.4 months. Results were rewarding, either in terms of PFS (5-yr PFS of 89.9%) and overall survival (5- and 10-yr survival of 94.4 and 68.7%, respectively) or in terms of quality of life. Adverse radiation effects were minimal.

The main favorable prognostic factors were limited (<3.2 mL) tumor volume, absence of cystic components, and higher (>15 Gy) edge dose. However, the predictive relevance of VHL versus sporadic disease remains controversial. Indeed, Kano et al. stated that “VHL disease-associated hemangioblastomas” showed improved PFS (Fig. 1 of the article). In terms of mere PFS, i.e., effective local tumor control, the observation sounds understandable and may probably be explained by some well-known peculiarities of VHL-associated hemangioblastomas: smaller volumes allowing higher dosages, less frequent cystic components, and so on.

However, the statistical evaluation on the basis of these numbers (19 sporadic forms that entail 22 lesions versus 13 VHL disease-related with 52 lesions) seems weak. Furthermore, if we check the 1-, 5-, and 10-year survival rates for VHL/sporadic diseases, there is no significant difference. Finally, in considering the natural history of hemangioblastomas, the overall follow-up is not conclusive. Nevertheless, given this particular topic, the rarity of the disease, and the non-negligible problems that have to be tackled in treating these patients, the experience reported by this extremely experienced team represents an important contribution to an intriguing debate.

Massimo Gerosa
Verona, Italy

This is an important contribution to the literature because of the relatively large number of hemangioblastomas treated by radiosurgery. In this report Kano et al. describe 32 patients with recurrent or residual intracranial hemangioblastomas treated with radiosurgery. Conclusions are difficult to extract from this report, however, because two different disease processes are conflated: sporadic intracranial hemangioblastoma and VHL disease-associated hemangioblastoma. The first is a benign, World Health Organization Grade I solitary tumor cured by surgical resection; the second is a relentless systemic disease with multiple and often innumerable intracranial tumors. Let us try to tease apart the data presented in this report for each disease entity separately.

Successful surgical extirpation of sporadic hemangioblastomas is so commonplace as to no longer be reportable (3). The vast majority of sporadic hemangioblastomas are eminently accessible within the cerebellar hemispheres. There are a few reports in the literature concerning the challenge of hemangioblastoma in the cerebellopontine angle, but these are rare occurrences with equally favorable outcomes (1). The successful surgical treatment of sporadic hemangioblastomas makes it hard to understand why radiosurgery was chosen for the 19 tumors in this report rather than repeat surgical resection. Clearly, the referral patterns of a busy gamma knife unit play an important role with referred patients expecting to be treated with radiation or refusing any further surgical attempts. This study cannot answer the truly burning question of which is the better treatment for subtotally resected sporadic hemangioblastomas (of which this report must contain the largest series in the literature): complete surgical resection versus radiosurgery. If radiation is chosen, this study offers valuable insight into which tumors are most likely to respond: the smaller and more solid ones, which lend themselves best to treatment with doses ≥ 15 Gy. The larger mean volumes of the sporadic hemangioblastomas in this series result in the anomalous finding of shorter PFS compared with the VHL-associated tumors. Patients with cystic tumors greater than 3.2 mL in volume should be advised that surgery will probably offer more chance of cure.

The data reported here for the VHL-associated tumors are provocative because of the excellent PFS reported. The fact that 52 tumors were treated in 13 patients with VHL disease leads us to believe that these tumors were the preponderance of the ones chosen for treatment solely because of progression on serial imaging. Overall these tumors were smaller, supporting this conclusion. The burning question in this population is different from that of the population with sporadic tumors. For these patients we want to know whether radiosurgery for small, asymptomatic but growing tumors is better than no treatment at all. Second, if treatment is chosen, is surgery better than radiation? The recent publication (in all fairness not available to Kano et al.) of a large series of patients with VHL-associated hemangioblastomas from the National Institutes of Health provides data in support of conservative treatment or surgical treatment but not in favor of radiation (2). The National Institutes of Health series included 80 patients, virtually all of whom (96%) underwent surgery for symptomatic tumors. Postoperative magnetic resonance imaging confirmed gross total resection in all patients and, more importantly, no recurrence at a mean follow-up of 60 months. As for radiation, the National Institutes of Health series included four patients who had undergone prior radiosurgery that resulted in symptomatic tumor growth or progressive edema. The mean time to surgery after radiosurgery was 110 months with a range of 10 to 196 months. The patients in the current study of Kano et al. were followed for a mean of only 61.4 months. We would expect further radiosurgical failures with more complete and prolonged follow-up.

This series provides useful information on dosing, technique, and expected results when radiosurgery is used to treat hemangioblastomas. Unfortunately, it still does not answer the question of which patients should be selected for radiosurgical treatment when surgery remains a safe and extremely effective treatment for these tumors.

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DIFFUSION TENSOR TRACTOGRAPHY: CORTICOSPINAL TRACT FIBER REDUCTION IS ASSOCIATED WITH TEMPORARY HEMIPARESIS IN BENIGN EXTRACEREBRAL LESIONS

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OBJECTIVE: Benign extracerebral lesions such as meningiomas may cause hemiparesis by compression and deviation without infiltrating the white matter. We used magnetic resonance diffusion tensor imaging and diffusion tensor tractography to investigate the effects of benign extracerebral lesions on the corticospinal tract (CST).

METHODS: Thirteen patients with extracerebral lesions (11 benign meningiomas and 2 benign cysts) underwent magnetic resonance diffusion tensor imaging and diffusion tensor tractography of the CST using fiber assignment by continuous tractography. The CST was reconstructed and assessed by comparing the ipsilateral and unaffected contralateral fibers. The tumor volume, relative fractional anisotropy, fiber deviation, relative fiber number, and relative fiber per voxel were compared between patients without and with temporary presurgical hemiparesis.

RESULTS: Seven patients without hemiparesis and five patients with temporary hemiparesis were analyzed; one patient had permanent weakness and was excluded from analysis. There was no significant difference in the tumor volume, relative fractional anisotropy, presence of cerebral edema, or CST deviation between groups. In patients with temporary hemiparesis, the median relative fiber number (mean, 0.35 ± 0.32) and relative fiber per voxel (mean, 0.49 ± 0.14) were significantly reduced compared with patients without hemiparesis (0.92 ± 0.55 , $P = 0.04$; and 0.96 ± 0.28 , $P < 0.01$, respectively).

CONCLUSION: In patients with benign extracerebral lesions, reduction in fiber number and fiber per voxel, but not fiber deviation, correlated with temporary hemiparesis. Clinical recovery was possible even if the CST fibers detected by diffusion tensor tractography were reduced by benign extracerebral lesions.

KEY WORDS: Diffusion tensor imaging, Fiber tracking, Magnetic resonance imaging, Tractography, White matter tracking

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Intracranial neoplasms cause a variety of deleterious effects on the brain. The presence of cerebral edema, malignant infiltration of normal brain tissue, and bulk displacement of vital structures may lead to loss of normal brain function (11). White matter invasion

ABBREVIATIONS: CST, corticospinal tract; DTI, diffusion tensor imaging; DTT, diffusion tensor tractography; FA, fractional anisotropy; FN, fiber number; FpV, fibers per voxel; MRI, magnetic resonance imaging

by malignant tumor may result in destruction and disruption of fiber bundles, and animal models of glioblastoma have demonstrated tumor infiltration and migration along blood vessels and white matter fiber tracts (12, 21). However, compression or pressure effects on fiber bundles without tumor infiltration can also lead to significant loss of neuronal transmission, demyelination, and axonal loss, with resultant disability (27). A method with which to visualize the cerebral white matter and to distinguish permanent fiber tract destruction

from the other reversible effects on the fiber tracts would therefore be desirable to assist with presurgical planning.

Magnetic resonance diffusion tensor imaging (DTI) provides a new noninvasive method for studying white matter architecture in vivo (15). By applying magnetic field gradients in six or more directions, the diffusivity of the random, thermally driven motion (diffusion) of water molecules can be represented by an ellipsoid. This diffusion ellipsoid is mathematically described by a tensor, whose three eigenvalues and eigenvectors correspond, respectively, to the three diameters and directions along the major axes. In the white matter, the highly organized axons covered by myelin sheaths cause the water movement to be anisotropic, with the direction of maximum diffusivity coinciding with the white matter fiber tract orientation (15, 26). Using the diffusion principle, white matter fiber bundles such as the corticospinal tract (CST), visual pathways, corpus callosum, association tracts, and other white matter tracts can be tracked using magnetic resonance diffusion tensor tractography (DTT) methods (2–6, 9, 13, 15, 17, 31, 41). DTI has also been used to study brain tumors, and some authors have found deviated (6, 7, 14, 15, 17, 19, 20, 37, 38) and infiltrated (6, 15, 38) white matter fibers in malignant neoplasms. However, the relative contribution from deviation as opposed to infiltration is variable and difficult to define, especially in malignant neoplasms. Compared with malignant intracranial brain neoplasms, benign extracerebral lesions such as meningiomas may also result in hemiparesis by compression and deviation of the white matter tracts, but they do not cause malignant infiltration and destruction (19). It may therefore be useful to study benign neoplasms that may deviate but do not infiltrate the brain to understand the contribution of the nondestructive effects on the white matter tracts. We used DTI and DTT to compare the effects of benign extracerebral lesions on the CSTs in patient groups without and with hemiparesis.

PATIENTS AND METHODS

Patients

Thirteen patients (1 man and 12 women; age range, 47–78 yr; mean, 59.3 ± 7.41 yr) with benign extracerebral lesions diagnosed on preoperative magnetic resonance imaging (MRI) underwent DTI and DTT of the CST as part of a larger clinical trial of DTI in intracranial neoplasms. The final diagnosis after surgery was 11 meningiomas (World Health Organization Grade I) and 2 arachnoid cysts (Patients 3 and 9). The study was approved by the institutional review board, and all patients provided signed statements of informed consent. Baseline preoperative motor power, defined using the Medical Research Council motor scoring system, was recorded, and postoperative motor power was assessed 6 months after surgery.

MRI

All patients underwent presurgical conventional MRI as well as DTI on either 1.5-T (NVi; General Electric, Milwaukee, WI) or 3-T (Intera; Philips, Best, the Netherlands) clinical MRI systems. Conventional MRI sequences included at least T1- and T2-weighted fast spin echo and contrast-enhanced sequences, with some patients also undergoing fluid-attenuated inversion recovery and gradient-recalled echo imaging. DTI was performed using diffusion-weighted, single-shot, echo-planar imaging

with the following parameters: repetition time, 4000 to 10,000 milliseconds; echo time, 65 to 100 milliseconds; one to six excitations; 3- to 5-mm slice thickness with a gap of 0 to 1.5 mm; acquisition matrix, 128×128 or 256×256 ; field of view, 21 to 24 cm; sensitivity encoding factor, 0 to 2.7; and b values, 800 to 1000 s/mm² along 6 to 25 noncollinear directions.

Image Processing

Two observers (CCTL, DL-HC) that were blinded to the clinical details analyzed the conventional MRI and DTI studies by consensus reading. Tumor volume was calculated using the ellipsoid formula by measuring the maximum diameters on three orthogonal planes on post-contrast three-dimensional volumetric data. Using DtiStudio software (Version 2.4; Johns Hopkins University, Baltimore, MD) (16), fiber assignment by continuous assignment was performed in a manner similar to methods described previously (24, 25, 36). The software calculates the three eigenvalues and eigenvectors of the diffusion tensor on a voxel-by-voxel basis and by fractional anisotropy (FA), a measure of the strength of directionality of diffusion. The principal eigenvector, measuring the main direction of water diffusion, is assumed to represent the local fiber direction, and the fiber trajectory is initiated from seed voxels and propagated in both directions based on the principal eigenvector. Voxels with FA values greater than 0.25 were chosen by the software as seed voxels, and tracking was terminated when a voxel with an FA value of less than 0.15 was reached or the bending angle was greater than 55 degrees (33). On the basis of prior anatomic knowledge of fiber projections, tracts belonging to CSTs on each side of the brain were selected by placing regions of interest (8, 9, 23, 29, 35) on axial images at two distant portions of the tract: 1) in the rostrocaudal axis in the ipsilateral anterior pons, as seen on the DTI color maps; and 2) in the entire ipsilateral hemisphere at the level of the central sulcus (29). Fibers that were clearly not part of CSTs were deleted manually.

Fiber tracking results of the CSTs were visualized using the three-dimensional triplanar view and three two-dimensional orthogonal views in the DtiStudio software (16). Each CST was studied as a whole fiber, and there was no topographical selection to distinguish the upper and lower extremities. The entire CST on the side of the lesion was inspected visually to determine whether it was involved in the peritumoral vasogenic edema and whether it was compressed visibly and asymmetrically deviated in its course compared with the unaffected normal side. The number of CST fibers that passed through each voxel was automatically measured by the software, including the total number of fibers (FN) and the average number of fibers per voxel (FpV), which is a measure of the fiber density of the selected fiber bundle (33). To standardize these fiber measurements over different acquisition parameters, each fiber bundle of the CST ipsilateral to the tumor or cyst was normalized to the unaffected normal CST on the contralateral side (28), yielding measurements of relative FA, relative FN, and relative FpV.

Statistical Analysis

Patients were divided into two groups on the basis of presurgical hemiparesis. Grouped data in patients without and with hemiparesis were compared with presence of cerebral edema in the CST and deviation of CSTs using Fisher's exact test for nonparametric values. The volume of tumor, relative FA, relative FN, and relative FpV of CSTs were compared between groups using the Mann-Whitney *U* test. Statistical significance was established at $P < 0.05$.

RESULTS

The clinical and MRI results of patients with benign extracerebral tumors are listed in Table 1. Seven patients (Patients

TABLE 1. Clinical findings and magnetic resonance diffusion tensor imaging and tractography findings of corticospinal tracts in 13 patients with extracerebral lesions^a

Patient no.	Age (yr)/sex	Clinical findings	Diagnosis	MRI DTI/DTT findings of CSTs						
				Pre-surgical power	Tumor volume (cm ³)	CST edema ^b	Relative FA	CST deviated	Relative FN	Relative FpV
1	62/F	Headache	Right parietal meningioma	5/5	2.9	No	1.02	No	1.44	0.79
2	57/F	Headache, anosmia visual	Olfactory groove meningioma	5/5	28.1	No	1.00	No	1.52	0.72
3	61/F	Expressive dysphasia, memory disturbances	Left parieto-occipital arachnoid cyst	5/5	163.0	No	0.98	Anterior	0.71	1.03
4	47/F	Headache	Right parietal meningioma	5/5	45.1	Yes	0.89	Anterior	1.19	1.08
5	58/F	Transient amnesia	Left frontal meningioma	5/5	82.1	Yes	0.64	Posterior	1.17	1.40
6	52/F	Behavioral changes, expressive dysphasia	Left frontal parietal meningioma	5/5	102.3	Yes	0.84	Posterior	0.30	1.10
7	56/M	Seizures	Right frontal meningioma	5/5	18.8	Yes	0.75	Posterior and inferior	0.14	0.58
8	54/F	Dementia, left hemiparesis	Right frontal meningioma	4+/5	108.2	No	0.78	Posterior	0.90	0.73
9	55/F	Right hemiparesis	Left frontoparietal prosencephalic cyst	4+/5	56.9	No	0.96	Lateral	0.14	0.46
10	68/F	Headache, right hemiparesis	Left parietal meningioma	4/5	35.2	No	0.94	Anterior	0.12	0.42
11	62/F	Left hemiparesis	Right frontal meningioma	4/5	63.7	Yes	0.83	Lateral	0.37	0.36
12	61/F	Memory disturbances, headache, right hemiparesis	Left frontal meningioma	4/5	60.9	Yes	0.99	Medial	0.21	0.49
13 ^c	78/F	Focal seizures, right hemiparesis	Left parietal parasagittal meningioma	2/5	16.7	Yes	0.96	No	0.84	1.22

^a MRI, magnetic resonance imaging; DTI, diffusion tensor imaging; DTT, diffusion tensor tractography; CSTs, corticospinal tracts; FA, fractional anisotropy; FN, fiber number; FpV, fiber per voxel.^b CST is involved in the peritumoral vasogenic edema.^c Excluded from statistical analysis. See text.

1–7) did not have motor weakness, and six (Patients 8–13) presented with hemiparesis. Six months after surgical resection, all but one of the patients recovered full motor power (Patient 13). This patient had a meningioma that was located on the motor cortex, but the CST was not visibly deviated or reduced. She remained hemiplegic after surgery and was excluded from further statistical analysis.

The statistical comparisons between patients without and with temporary hemiparesis are listed in *Table 2*. Median tumor volume in patients without hemiparesis (mean, 63.2 ± 56.3 cm³) was not statistically smaller than in patients with temporary hemiparesis (mean, 65.0 ± 26.6 cm³; $P = 0.32$). The CST was affected by cerebral edema in four of seven patients without hemiparesis (Patients 4–7) and two of five patients with temporary hemiparesis (Patients 11 and 12), without a statistically significant difference between the two study groups ($P = 0.50$) in the proportion of those in whom the CST was affected by edema. Mean relative FA in patients without hemiparesis (0.87 ± 0.14) was slightly lower, and its median was not significantly higher than in patients with temporary hemiparesis (mean, 0.90 ± 0.09 ; $P = 0.50$). However, the median relative FA in CSTs affected by tumor edema (mean, 0.86 ± 0.12) was significantly lower ($P = 0.047$) than in those not affected by edema (mean, 0.95 ± 0.09) in both groups.

Comparing the DTT, the CST was visibly compressed and deviated in five of seven patients without hemiparesis (Patients 3–7) (*Fig. 1*) and in all five with temporary hemiparesis (*Fig. 2*), without a statistically significant difference between the two study groups ($P = 0.32$) in the proportion of those displaying fiber tract deviation. In the group of patients without hemiparesis, the relative FN of CST fibers ranged from severely reduced (0.1) to increased (1.5), and averaged 0.92 ± 0.55 (mean $\pm$ standard deviation). Among patients with temporary hemiparesis, the relative FN of CST fibers was always reduced (0.1–0.9) and averaged 0.35 ± 0.32 , the median of which was significantly lower than in patients without hemiparesis ($P = 0.04$). Similarly, the median relative FpV in patients with temporary hemiparesis (mean, 0.49 ± 0.14 ; range, 0.1–0.9) was lower than in patients

TABLE 2. Comparisons between patients without and with hemiparesis^a

Parameter	Without hemiparesis (n = 7)	With hemiparesis (n = 5)	P value
Tumor volume (cm ³)	63.2 ± 56.3	65.0 ± 26.6	0.32
CST edema ^b	4	2	0.50
Relative FA	0.87 ± 0.14	0.90 ± 0.09	0.50
CST deviated	5	5	0.32
Relative FN	0.92 ± 0.55	0.35 ± 0.32	0.04 ^c
Relative FpV	0.96 ± 0.28	0.49 ± 0.14	<0.01 ^c

^a Data are represented as mean ± standard deviation, or number of cases. CST, corticospinal tract; FA, fractional anisotropy; FN, fiber number; FpV, fiber per voxel.

^b CST is involved in the peritumoral vasogenic edema.

^c Statistically significant.

without hemiparesis (mean, 0.96 ± 0.28 ; range, 0.6–1.4) at a higher significance level ($P < 0.01$).

DISCUSSION

We found that decreased relative FN and FpV, but not deviation of the CST, correlated with temporary hemiparesis in patients with benign extracerebral lesions. In those patients with a space-occupying mass that compressed and deviated but did not infiltrate or destroy the CST, fiber bundles that were detected by DTT were reduced quantitatively. DTI has been used to study the effects of neoplasms on the white matter of the brain, with several authors using voxel-based quantitative parameters of anisotropy, diffusivity, and tensor orientation for tissue characterization such as tumor cellularity, gliomatous infiltration into the peritumoral edema, and tumor grading (15, 20, 32, 37, 38). Fiber tracking methods based on DTI have also been studied, as the ability of these intuitive and visually pleasing tractography images to map anatomic interconnections would be desirable in patients with neoplasms for presurgical evaluation (2–7, 9, 10, 13–15, 17, 19, 31, 41). However, quantitative tissue characterization of fibers affected by malignant neoplasms that infiltrate, destroy, or otherwise affect the white matter have been more challenging. Some authors have used quantitative DTT measures such as FN and FpV to measure the CST fibers in normal individuals and patients with malignant neoplasms (29, 30, 33). These quantitative measurements of fiber bundle density may be expressed as the average of the number of fibers passing each pixel or voxel, over a selected set of voxels, either as a two-dimensional region of interest or a three-dimensional volume of interest, respectively (30, 33). Roberts et al. (30) proposed a fiber density index, representing the number of fibers per pixel averaged over a two-dimensional region of interest, and found that the fiber density index of CSTs was significantly reduced on the side ipsilateral to glioblastomas compared with the contralateral side (30). Stadlbauer et al. (33), using the measurement FpV, representing the number of fibers per voxel averaged over a

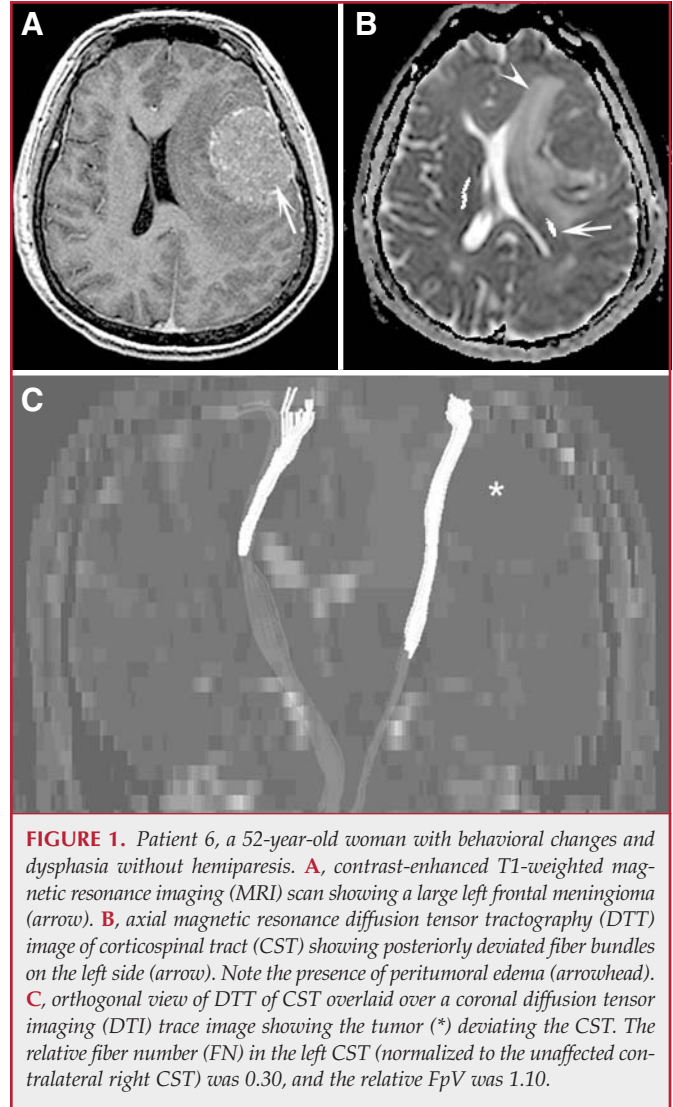


FIGURE 1. Patient 6, a 52-year-old woman with behavioral changes and dysphasia without hemiparesis. **A**, contrast-enhanced T1-weighted magnetic resonance imaging (MRI) scan showing a large left frontal meningioma (arrow). **B**, axial magnetic resonance diffusion tensor tractography (DTT) image of corticospinal tract (CST) showing posteriorly deviated fiber bundles on the left side (arrow). Note the presence of peritumoral edema (arrowhead). **C**, orthogonal view of DTT of CST overlaid over a coronal diffusion tensor imaging (DTI) trace image showing the tumor (*) deviating the CST. The relative fiber number (FN) in the left CST (normalized to the unaffected contralateral right CST) was 0.30, and the relative FpV was 1.10.

three-dimensional volume of interest (33), also showed reduction in the pyramidal tract in patients with gliomas. Using the latter measurement, we found that temporary hemiparesis correlated to both relative FN and relative FpV, with better significance level and standard deviation for FpV. This may suggest that fiber density measures per voxel might be more useful than merely counting the number of fibers in a white matter tract that has been compressed but not infiltrated by an external tumor such as the extracerebral lesions in our patients.

We also found that compression and deviation alone, without reduction in fibers, may not correlate with clinical motor weakness. Although all patients with temporary hemiparesis showed fiber deviation, and two patients without hemiparesis did not, this difference between groups was not statistically significant. This finding suggests that in addition to fiber tract deviation, reduction in the FpV or FN as visualized by DTT was necessary to cause temporary hemiparesis, and that devi-

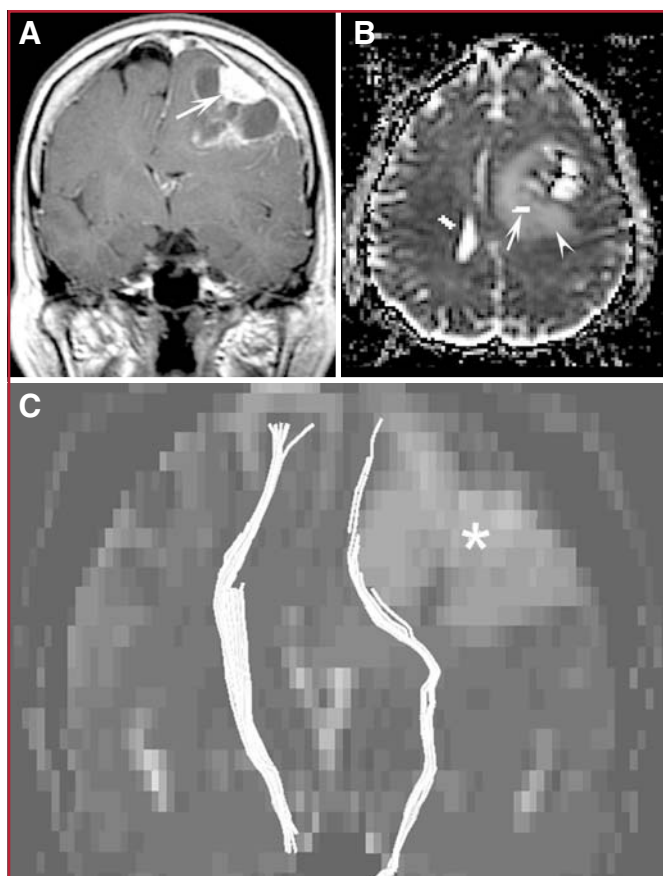


FIGURE 2. Patient 12, a 61-year-old woman with headache, memory disturbance, and right hemiparesis. **A**, contrast-enhanced coronal MRI scan showing a large frontal meningioma (arrow). **B**, axial DTT image showing medial deviation of the left CST (arrow) by the meningioma with peritumoral edema (arrowhead). **C**, orthogonal view of DTT of CST overlaid over a coronal DTI trace image showing the tumor (*) and the deviated and reduced left CST fiber tracts. The measured relative FN was 0.21, and the relative FpV was 0.49.

ation of the CST without reduction may not be helpful in predicting clinical effects. Other groups have found that patients with CSTs deviated by gliomas may not have weakness (3, 39), but, to our knowledge, these findings have not been reported before in benign extracerebral lesions.

Although, as a group, there was no difference in the presence of edema and the median FA between patients with temporary hemiparesis and those without, we found significantly decreased relative FA in the subgroup of patients whose CST was affected by the presence of cerebral edema, but not in those patients without cerebral edema. This suggests that there is a relationship between edema and a decrease in FA and would be consistent with prior studies that showed that cerebral edema was associated with a decrease in FA (3, 18) and production of edema by a meningioma (34).

Among our patients with hemiparesis, all (except Patient 13) recovered full motor capabilities 6 months after surgical resection,

implying that even if the number of CST fibers detected by DTI were reduced by benign extracerebral lesions, they were not permanently destroyed, and clinical recovery was possible. This is consistent with prior studies that have also found that preoperatively decreased FA, deviated CST, and hemiparesis caused by benign intra-axial lesions could be reversed after surgery (20), and the FA of the CST was probably decreased below the threshold of detection used by fiber tracking software (1). The CSTs in these patients were most likely affected temporarily by extrinsic pressure effects, bulk displacement, vasogenic edema, and other effects of the benign extracerebral tumor or cyst that may result in temporary clinical hemiparesis without gross CST infiltration or destruction. Thus, in patients with reduced DTT, surgical resection need not be precluded, as hemiparesis may be reversible. This observation in benign lesions may also have clinical implications for the application of DTI in presurgical planning to help interpret the results in malignant neoplasms, where the effects on the white matter may be more complex. In malignant tumors, the relative contribution to reduction in fibers by benign or reversible mechanisms as opposed to irreversible tumor destruction or infiltration may be difficult to ascertain. Thus, it may not be safe to proceed with aggressive surgical resection in reduced or “disappearing” fiber bundles detected on DTT. Although fiber tracking is an intuitive and visually appealing method with which to study the white matter fiber tracts (2–6, 9, 13, 22, 31, 40, 41), these limitations must be borne in mind when interpreting the results for presurgical planning.

Our study is limited by the small number of patients in each group, which especially hampers meaningful statistical analysis. Furthermore, the DTI data were acquired using scanners at two different field strengths and parameters, and the number of fibers reconstructed is probably affected by these differences. We therefore could not compare absolute values but attempted to limit these effects by normalizing all measurements to the contralateral side, which we assumed to be normal, as there were no abnormal clinical or conventional MRI signs. We also could not perform DTI at 6 months, when the hemiparesis had recovered, to measure whether FpV had returned to normal. Larger, better statistically powered, longitudinal studies in patients with noninfiltrative tumors, preferably with clinical stratification and controlling for variability of acquisition parameters, might be helpful in the future. The effects of acquisition and fiber tracking algorithm parameters on the values of FN and FpV have not been studied widely, and thus their use may be clinically limited or superseded by better methods of measurement. Patient 13, the patient without deviation or reduction of CST fibers but who nevertheless developed permanent hemiparesis because of direct tumor effects on the motor cortex, also illustrates the important principle that the DTI studies in patients should not be considered in isolation but as part of the entire motor network, including cortex and fiber tracts.

CONCLUSION

In patients with benign extracerebral lesions, the effects of reversible compression can lead to reduction in FN and FpV.

Reduced markers of DTT, but not fiber deviation, are associated with temporary hemiparesis. Although DTT may have the potential to be a useful tool in presurgical planning in patients with a neoplasm, these studies should be interpreted with caution.

Disclosure

CCTL is a member of the General Electric Medical Systems Information Technology Medical Advisory Board and is on the speakers bureau of General Electric and Philips Medical Systems.

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COMMENTS

The ability to predict neurological improvement after surgery for an extra-axial tumor can be subjective. Ng et al. offer diffusion tensor tractography (DTT) as a method to do this on the basis of the observation of estimated fiber density. Although there are many factors that can influence functional recovery and many are not addressed by this report, further investigation with tractography may prove to be helpful. It is not obvious to the reader how this report will influence surgical decision making, but it is hoped that future work will add to the clinical utility of this technique.

Joseph M. Piepmeier
New Haven, Connecticut

Ng et al. studied diffusion tensor imaging (DTI) and DTT to investigate the effects of benign extracerebral lesions on corticospinal tracts. Seven patients without hemiparesis and five patients with hemiparesis who had benign masses deviating the corticospinal tract were compared by measuring tumor volume, relative fractional anisotropy, fiber deviation, relative fiber numbers, and relative fibers per voxel. They concluded that reduction in fiber number and relative fibers per voxel but not in fiber deviation correlated with temporary hemiparesis.

With rapid advances in image analysis software and postprocessing techniques, this kind of study will become more popular. It would have been more interesting if the authors had addressed topographic considerations regarding the region of interest in that most patients with hemiparesis have various degrees of motor weakness and differences between the upper and lower extremities. In addition, follow-up data after mass removal are needed to confirm the conclusion of this study to determine whether fiber numbers and relative fibers per voxel values are restored.

Dong Gyu Kim
Seoul, Korea

Ng et al. have described an approach to identifying subtle changes in corticospinal white matter tracts in patients with benign extracerebral lesions, using magnetic resonance DTI/DTT. Their main findings suggest that reduced fiber numbers and fiber density (per voxel) on DTI/DTT correlate with temporary, reversible hemiparesis. Interestingly, these clinical findings were not attributed to the extent of fiber deviation. Their conclusions ultimately argue for the role of DTI/DTT in the preoperative planning of affected patients, particularly those with malignant lesions being considered for (potentially) aggressive surgical resection.

More importantly, however, this article reflects the tremendous diagnostic and prognostic potential associated with ongoing technological developments in radiographic imaging. Specifically, DTI/DTT is becoming increasingly popular as a noninvasive technique for the unique study of white matter architecture. Abnormal white matter integrity is associated with numerous congenital and acquired conditions. At present, our understanding of the link between the type (and severity) of neurological deficit and the degree of underlying white matter change remains limited, at best. However, with the advent of DTI/DTT and other related imaging modalities, it will become increasingly possible to characterize the extent of white matter injury and the clinical significance this holds for eventual patient outcome. It is also speculated that improved visualization of white matter fibers, in combination with current neuronavigation techniques, will allow the surgeon to avoid these eloquent tracts and lead to improved surgical accuracy, while protecting the patient from subsequent deficits. Finally, the ability to track and compare even minimal white matter changes in the pre- and postoperative setting will probably enhance the surgeon's capacity for detecting disease progression, perhaps even before the onset of new or worsened clinical deficits.

We anticipate that current imaging modalities will continue to evolve to better capture the anatomical and functional correlates of disease arising in the nervous system. Ng et al. have demonstrated this concept in their work, describing an interesting technique that will probably become increasingly important in the years to come.

Demitre Serletis
James T. Rutka
Toronto, Canada

DTI and white matter tractography using DTI are promising techniques for estimating the course, extent, and connectivity patterns of the white matter structures in the human brain. DTI has been used to study the effects of neoplasms using quantitative parameters of anisotropy, diffusivity, and tensor orientation to characterize tumor cellularity, gliomatous infiltration into the peritumoral edema, and tumor grade. Because fractional anisotropy eigenvector analysis was first shown to be able to delineate discrete white matter tracts, the past decade has predictably been characterized by a proliferation of studies exploring the potential clinical utility of this technique. This process has shown slow, intermittent progress (at least in terms of practical clinical application), as the vision inevitably encountered limitations, both foreseen and unforeseen, connatal to this technique. This contribution by Ng et al. is one of the small necessary pieces in this larger puzzle. As they note, although fiber tracking methods based on DTI have yielded intuitive and visually pleasing tractography images, quantitative tissue characterization of fibers in adjacent white matter affected by tumors has been more challenging. Whereas the immediate direct clinical utility of these results is limited, the conclusions offered by this succinct study do indeed contribute to the trajectory of this research. The limitations of this contribution, such as the small number of patients studied, are well acknowledged by the authors. What may have been the biggest limitation, as the authors and reviewers all agree, is the lack of a follow-up DTT study after recovery of hemiparesis. Another limitation inherent to any quantitative DTT analysis is the absence of histological confirmation that parameters such as fiber index, fiber number, and fibers per voxel determined by DTI/DTT actually correspond to number of in vivo white matter fibers; i.e., are these parameters actually a reflection of something else? Regardless, it is clear empirically that these parameters have *some* physiological meaning. Therefore,

all of the issues discussed in this work and previous contributions to this area of research are likely to prove ultimately meaningful as well.

Paul E. Kim
Neuroradiologist
Los Angeles, California

This is an early study using tractography in patients undergoing surgery for compressive extra-axial tumors. Such studies will help

our understanding of how these lesions affect fiber tracts both in terms of displacement and compression, and how these effects translate into clinical meaning pre- and postoperatively. Translating such studies into and assessing clinical utility will only become apparent with further studies in this area. Nevertheless, this is an elegant article that hints at the potential of this exciting imaging technique, which can only improve technically in the future.

Neil Kitchen
London, England



Cairo. Image courtesy of Earth Sciences and Image Analysis Laboratory, NASA Johnson Space Center, (<http://eol.jsc.nasa.gov>).

TRANSCEREBELLAR STEREOTACTIC BIOPSY FOR LESIONS OF THE BRAINSTEM AND PEDUNCLES UNDER LOCAL ANESTHESIA

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OBJECTIVE: For certain brainstem lesions, a diagnostic biopsy is required for treatment planning. We reviewed the indications, safety, and diagnostic effectiveness of a transcerebellar stereotactic biopsy using local anesthesia and sedation.

METHODS: We retrospectively reviewed hospital records for all adult patients with symptomatic lesions of the pons and/or cerebellar peduncle who underwent an awake transcerebellar stereotactic biopsy at our institution over a 7-year period. Our technique features several modifications from the standard method and was performed under local anesthesia with patients in the semi-sitting position.

RESULTS: Our rate of diagnostic success (92%) was comparable to those in other published reports. However, only 5 (42%) of 12 biopsy-derived diagnoses were consistent with those predicted from preoperative magnetic resonance imaging. There were no deaths, and the only neurological complication was a cranial nerve palsy. Diagnoses in the 13 cases included infiltrative glioma (4), metastases (3), lymphoma (2), encephalitis (1), and reactive astrogliosis (1).

CONCLUSION: Tissue diagnosis of lesions in the brainstem and cerebellar peduncles continues to be a significant challenge, with the potential for major morbidity. With appropriate patient selection, however, awake transcerebellar biopsy is a safe and effective procedure that can change clinical management and provide important prognostic information.

KEY WORDS: Brainstem tumor, Pontine glioma, Stereotactic biopsy, Transcerebellar

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The popularity of brainstem tumor biopsies has fluctuated during the past 3 decades. In the 1980s, technical advances in neurosurgery pushed the practice of brainstem tissue diagnosis toward widespread use. This trend continued until several studies questioned its necessity, particularly in the pediatric population (3). It was reported that characteristic magnetic resonance imaging (MRI) features were sufficient to diagnose diffuse brainstem gliomas without the need for a surgical biopsy (2, 3, 14). Radiographic classification schemes were proposed to predict clinical prognosis in the absence of histological evidence (15).

ABBREVIATIONS: CI, confidence interval; CRW, Cosman-Roberts-Wells; MRI, magnetic resonance imaging

More recently, brainstem and deep-brain stereotactic biopsies are re-emerging as an essential step in the management of many primary brain tumors. In children, some authors advocate a surgical biopsy to obtain tissue when the radiographic features are not consistent with a diffuse pontine glioma (35). Similarly, in adults, it is increasingly apparent that the heterogeneity of brainstem lesions complicates the ability to diagnose and prognosticate on the basis of imaging alone (14, 22, 37, 39, 40, 44). Furthermore, limited insight into the cytoarchitecture, cellular composition, and origin of pediatric and adult brainstem gliomas means that tissue collection could accelerate the understanding of the disease (23, 33, 34).

Once considered surgically inaccessible, the brainstem contains vital nuclei and long fiber tracts that are vulnerable to serious neurologi-

cal deficits if damaged (20). Transfrontal, transtentorial, and transcerebellar routes are used to access various targets within the brainstem (1, 4, 10, 13, 19, 21, 22, 26, 27, 37, 44). For lesions located in the middle two-thirds of the pons, a transcerebellar approach (13) traverses the middle cerebellar peduncle and offers the shortest possible trajectory. This route avoids the ventricle and crosses only one pial surface. Additionally, its entry point at the pontine tegmentum poses the least risk of disrupting the longitudinal fibers of the motor and sensory tracts.

We reviewed our experience with awake transcerebellar stereotactic biopsies. Our objective was to determine the safety and efficacy of this biopsy technique.

PATIENTS AND METHODS

Clinical Data Collection

We retrospectively reviewed the records of all patients who underwent awake transcerebellar biopsy for lesions of the brainstem and middle cerebellar peduncle by a single surgeon (MWM) at the University of California, San Francisco, over a 7-year period. All patients were 21 years of age or older and presented with symptomatic lesions of the pons or middle cerebellar peduncle. None had conditions that could be definitively diagnosed by clinical and radiographic data alone.

Clinical data, abstracted from hospital and outpatient clinic records, included age at the time of biopsy, sex, preoperative Karnofsky Performance Scale score, medical history, date of diagnosis, presenting symptoms, and duration of symptoms. Dictated surgical reports were reviewed to determine the date of biopsy, stereotactic trajectory (transcerebellar versus transfrontal), total operating time, number of passes with the stereotactic biopsy probe, and any intraoperative complications. Predicted differential diagnoses were determined from review of preoperative neuroradiology reports and neurosurgical records. Lesion location was recorded after review of the preoperative MRI scans and computed tomographic images. Formal pathology reports were reviewed to establish frozen section and final pathological diagnoses. The occurrence of postoperative complications, form of definitive treatment, and survival outcome were determined, when possible, from neurosurgical and oncology clinic and hospital records. The term “early postoperative complications” refers to those occurring during the initial hospitalization after biopsy, and the designation “late postoperative complications” refers to those arising after discharge from acute in-hospital care.

Awake Transcerebellar Biopsy Technique

All stereotactic biopsies were performed in the semi-sitting position using the Cosman-Roberts-Wells (CRW) frame, which was placed as low as possible in relation to the occiput. Four modifications were made to previously reported techniques (13). The first was to place the frame close to the skin of the side of the biopsy to minimize the mechanical limitations when rotating the frame’s arc into position for biopsies (Fig. 1). Target coordinates were based on computed tomographic or magnetic resonance axial images obtained after the frame’s placement. In all cases, computerized, image-based neuronavigation (Radionics OAS, Burlington, MA; or Stealth, Medtronic Sofamor Danek, Minneapolis, MN) was used for planning by marking entry and target positions as well as devising trajectory. A biopsy trajectory was plotted so that it crossed the center of the middle cerebellar peduncle and intersected with the target. The coordinates of the planned trajectory’s point of intersection with the skin were extrapolated to estab-

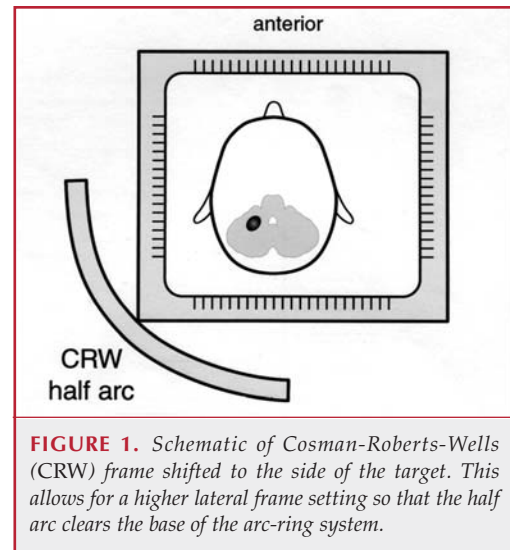


FIGURE 1. Schematic of Cosman-Roberts-Wells (CRW) frame shifted to the side of the target. This allows for a higher lateral frame setting so that the half arc clears the base of the arc-ring system.

lish the precise surgical entry point. Defining this entry point ensures that the biopsy probe will pass along its planned trajectory through the middle cerebellar peduncle.

Once the patient was transported to the operating room, the antero-posterior, lateral, and vertical coordinates of the target were entered into the phantom base of the arc-ring CRW system. The depth to the target was set on the biopsy needle after localization was confirmed to be correct. Then the anterior-posterior, lateral, and vertical coordinates for the entry point were entered into the phantom base, and the arc-ring was adjusted using its two degrees of freedom centered about the target. Adjustment was completed when the biopsy needle could pass through the entry point en route to the target, thus setting the desired trajectory from preoperative treatment planning. A half-arc was used to the side of the approach to avoid the interference the full arc encounters with the base when up-angled trajectories are used.

When the arc was in place, local anesthetic and intravenous sedation were given with patients in the semi-sitting position. In no case was general anesthesia or intubation required. The skin entrance point was marked using the predetermined entry point coordinates from the CRW frame. Although a few early patients had burr holes placed for cranial access, later procedures were adapted to use twist drills to reduce the risk of air emboli. A second modification was to select a large twist drill to avoid deflection off the sloping occipital bone when drilling at the entry point. The CRW coordinates were then adjusted to the lesion target point. Our third modification was to use a 5-mm Nashold biopsy needle instead of the standard 9-mm opening. This allows for up to three passes to ensure tissue diagnosis. A fourth and final modification, once the needle was advanced to the level of the spinal trigeminal tract at the border of the pons and middle cerebellar peduncle, was to administer a bolus of propofol to the patient to avoid otherwise severe facial pain (Fig. 2). Before this point in the procedure, a combination of midazolam (Versed; Roche Pharmaceuticals, Nutley, NJ) and intravenous sufentanyl was used for sedation, as necessary. After the procedure, most patients were discharged on postoperative Day 1.

Statistical Analysis

Biopsy specimens were sent in formalin to the pathology department for analysis. A procedure was considered successful if there were no

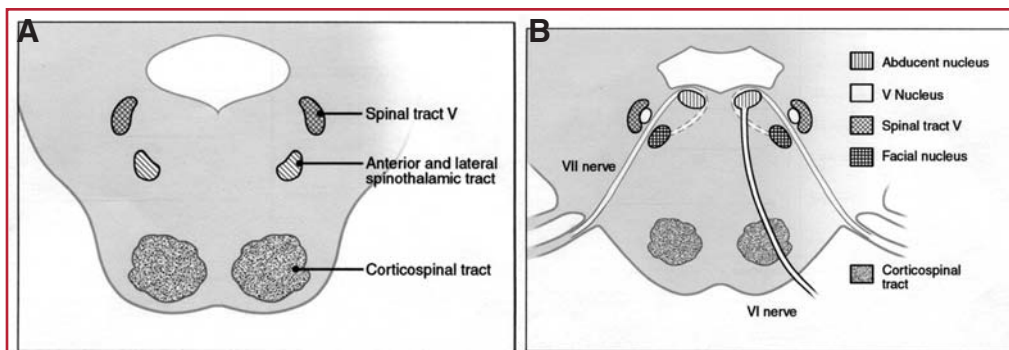


FIGURE 2. **A**, schematic showing transverse section through the lower third of the pons, indicating position of the spinal tract of the trigeminal nerve (V) and the lateral spinal thalamic tract. For lesions within the pons, these pathways will be in the trajectory through the middle cerebellar peduncle, necessitating transient deepening of anesthesia during the procedure. **B**, schematic showing transverse section through the lower pons just above its junction with the medulla. Presence of sixth and seventh nerve fibers in the trajectory stresses the importance of using a short opening (5 mm) sidecut biopsy needle.

intraoperative or postoperative complications, the biopsy was obtained through the planned transcerebellar route, and a definitive diagnosis was established. Exact two-tailed 95% confidence intervals (CIs) based on the binomial distribution were calculated for the percentages of nondiagnostic biopsies, procedure-related deaths, and intraoperative and postoperative complications.

RESULTS

The clinical and pathological findings for 13 patients (10 men; median age, 52 yr; age range, 34–77 yr) who underwent awake transcerebellar biopsy are summarized in Table 1. Symptoms at presentation had been noted from 10 days to 12 months before diagnosis and included long tract signs such as hemiparesis, ataxia, and gait difficulty; cranial nerve dysfunc-

tion signs such as diplopia, facial weakness, poor facial sensation, dysarthria, vertigo, and hearing loss; and symptoms of raised intracranial pressure such as nausea, vomiting, headache, and lethargy. Preoperative imaging identified lesions within the pons ($n = 3$), pons and upper medulla ($n = 1$), middle cerebellar peduncle ($n = 6$), and pons and middle cerebellar peduncle ($n = 3$). One patient with a middle cerebellar peduncle mass and another with a combined pontine-middle cerebellar peduncle mass had separate supratentorial lesions, suggesting metastatic cancer.

However, the preoperative workup failed to reveal the primary tumor site in either patient, and a biopsy was necessary to establish tumor histology. In both cases, the brainstem lesion was more surgically accessible, because of location and size, than the supratentorial lesion. For both patients, however, all preoperative workup failed to reveal a primary tumor.

One patient had his procedure aborted intraoperatively because of an air embolism after placement of the suboccipital burr hole. This patient then underwent a successful transfrontal biopsy in the supine position that did not require replacement of the head frame. This was the only intraoperative complication (1 of 14 patients; 95% CI, 0.2%–34%), and the patient was excluded from subsequent analyses of postoperative complications and diagnostic procedure rates.

TABLE 1. Patient profile and biopsy results^a

Patient no.	Age (yr)/sex	KPS score	Sign/symptom	Location of lesion	Biopsy route	Expected diagnosis	Actual diagnosis
1	48/M	60	Hemiparesis	Pons	TC	Glioma	Grade II astrocytoma
2	52/M	70	Hemiparesis	Pons	TC	Infection versus glioma	None possible
3	62/M	70	Diplopia	Pons, medulla	TC	Glioma	Grade II astrocytoma
4	62/F	70	Ataxia	Pons	TC	Glioma	Metastatic lung carcinoma
5	45/M	70	Ataxia	Bilateral MCP	TC	Glioma versus inflammatory lesion	Chronic encephalitis
6	77/M	70	Lethargy	Pons, right MCP	TC	Metastasis (unknown primary)	Metastatic lung carcinoma
7	56/M	70	Headache	Left MCP	TC	Lymphoma versus metastasis	Malignant B-cell lymphoma
8	34/M	60	Nausea/ vomiting	Left cerebellar MCP	TC	Glioma	Grade II astrocytoma
9	36/M	70	Ataxia	Right MCP	TC	Necrosis versus recurrent glioma	Grade III astrocytoma
10	34/F	70	Hemiparesis	Left MCP	TC	Glioma	Reactive benign astrogliosis
11	52/F	70	Vertigo	Left MCP	TC	Metastasis (unknown primary)	Metastatic lung carcinoma
12	47/M	70	Facial numbness	Pons, left MCP	TC	Recurrent glioma versus necrosis	Grade III astrocytoma
13	70/M	70	Hemiparesis	Pons, right MCP	TC	Glioma	Malignant B-cell lymphoma

^a KPS, Karnofsky Performance Scale; TC, transcerebellar; MCP, middle cerebellar peduncle.

Among all awake transcerebellar biopsies, our nondiagnostic biopsy rate was 7.6% (1 of 13 patients; 95% CI, 0.2%–36%). Twelve biopsies (92%) were diagnostic (Table 1): 5 (38%) for glioma, 3 (20%) for metastases, 2 (15%) for lymphoma, 1 (8%) for encephalitis, and 1 (8%) for nonneoplastic reactive astrogliosis. Interestingly, only 5 (42%) of the 12 diagnostic specimens were consistent with the diagnosis predicted on the basis of preoperative imaging. Two of these five patients had metastatic disease (Fig. 3), and the three others had Grade II or III astrocytomas.

The mean postoperative recovery time was 1.4 days (range, 1–4 d). Patients with glioma and lymphoma received postoperative radiation and/or chemotherapy. Those with metastases all had primary lung tumors. The two patients with nonneoplastic diagnoses underwent serial radiographic studies and did not receive the cytotoxic therapy that was anticipated preoperatively. One patient who had a nondiagnostic biopsy of a pontine lesion underwent empiric postoperative radiation for a presumed glioma. None of the 13 biopsied patients required any additional neurosurgical intervention.

The postoperative complication rate was 8% (1 of 13 patients; 95% CI, 0.2–36%). The one early postoperative complication (in Patient 2) was a complete sixth cranial nerve palsy ipsilateral to a pontine biopsy site, which occurred just after passage of the biopsy needle into the pons. Because the patient demonstrated an obvious new deficit intraoperatively, only one specimen was sampled, and the procedure was consequently nondiagnostic. A postoperative computed tomographic scan did not reveal any pontine hemorrhage, but the deficit was permanent. No patient experienced a late postoperative complication secondary to the biopsy, and there were no deaths in this series (95% CI, upper limit of 25%).

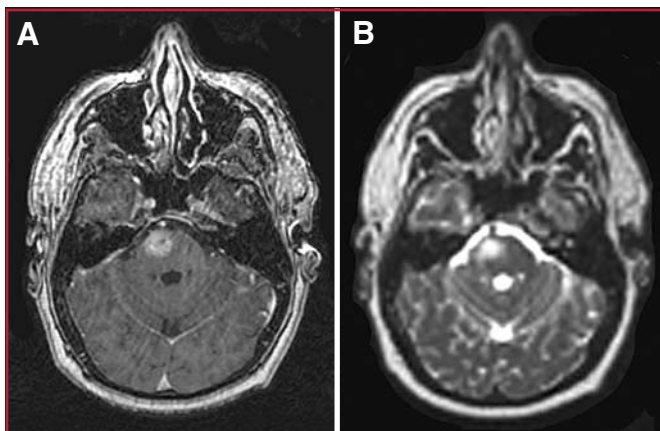


FIGURE 3. **A**, axial T1-weighted magnetic resonance imaging (MRI) scan with contrast; **B**, axial T2-weighted MRI scan demonstrating a contrast-enhancing mass of the ventral pons. The patient is a 77-year-old male with a several-month history of constitutional symptoms and a left hemiparesis. Awake transcerebellar stereotactic biopsy revealed metastatic lung cancer.

DISCUSSION

Advantages of an Awake Biopsy

Our experience suggests that an awake transcerebellar biopsy using a stereotactic head frame in a semi-sitting position is a safe and effective alternative to an open transfrontal approach. Although this study employed a frame-based approach, we used frameless stereotaxy in a subsequent patient cohort (not reported) and found this transition straightforward to implement but less desirable, because the patients required general anesthesia. In children, we have preferred the use of frameless stereotaxy, because most patients will require general anesthesia. Although the convenience of intraoperative imaging using MRI neuronavigation justifies this transition in many cases (4, 18, 31, 36, 45), a role remains for the traditional frame-based approach, particularly when anesthesia resources, operating room time, and hospital space are a significant concern (42).

The modifications we made to the standard surgical technique for transcerebellar stereotactic biopsies have distinct advantages. Although many surgeons prefer that patients be prone, which requires general anesthesia (1, 13, 27, 37), the semi-sitting position requires only a local anesthetic (19). This reduces cardiac and pulmonary risks and shortens both procedure and postoperative recovery times. An awake procedure also allows for patients to be monitored intraoperatively for neurological deficits. In our opinion, this is particularly important for brainstem biopsies, where monitoring of the patient's neurological findings can allow the surgeon to avoid potentially devastating injury. In our series, only one patient had a postoperative neurological deficit, a sixth nerve palsy; this was noted intraoperatively, and the procedure was then aborted. Although this did not avoid the deficit, it allowed us to avert additional adverse effects.

Risk of Air Embolus

The risk of air embolus with burr hole cranial access in the semi-sitting position is not trivial. However, in the only case where this became a concern, we were able to easily reposition the patient for a successful transfrontal biopsy without adverse sequelae. In subsequent patients, after switching to the twist drill for cranial access, there were no complications related to our positioning, as the risk of air embolus was minimized by the fact that the skin incision was only large enough to admit the twist drill (diameter of approximately 5 mm). Although there are a few reports of prone or laterally positioned transcerebellar biopsies under local anesthesia (22, 26, 43), it is our experience that most patients cannot tolerate such procedures without intubation, as the positioning can be both uncomfortable and psychologically unnerving. Additionally, a lateral position also significantly increases the complexity of the operative setup, as the Mayfield attachments are in a posterior position on the CRW base ring.

Avoiding the Spinal Trigeminal Tract

The ability to reproducibly evoke painful perceptions by stereotactic electrical stimulation has been well documented in

studies of specific thalamic nuclei (28). Because of the spinal trigeminal tract's proximity to the entry point for a trans cerebellar brainstem biopsy, severe facial pain can occur when the needle is passed near this region (Fig. 2). In some cases, the severity of this facial pain can be intolerable and ultimately will force the surgeon to abort the procedure (26). To avoid this complication, our patients received a bolus of propofol just before we traversed the medial cerebellar peduncle and pontine tegmentum. The timing of this bolus can be refined by preoperatively measuring the distance from the entry point to the position of the trigeminal fiber tracts. With this technical modification, none of our patients experienced facial pain during their biopsies.

Comparative Analysis of Neurological Complications

To date, there are eight major studies in the literature that include awake or asleep trans cerebellar stereotactic biopsies of brainstem or posterior fossa lesions (1, 13, 19, 22, 26, 27, 37, 44). These reports often combined adult and pediatric patients, and grouped trans cerebellar approaches with transfrontal or transtentorial approaches (13, 19, 26, 44). In total, we identified 73 reported trans cerebellar biopsies in 45 adults and 20 children. Table 2 provides a comparative summary of these cases.

Owing to the air embolus described above, our intraoperative complication rate was 7.1% ($n = 1$), which falls within the range of 7 to 12% reported by others (1, 6, 9, 13, 19, 22, 26, 27, 37). Our postoperative complication rate of 7.6% ($n = 1$; 95% CI, 0.2–36%) is also within the published range of 0 to 25%. Similarly, our morbidity profile compares favorably to the general brainstem biopsy literature, irrespective of the surgical approach: among all reported studies using a transtentorial or transfrontal approach, there were 26 postoperative complications (7%; 95% CI, 5–11%) and 2 deaths (0.6%; 95% CI, 0.07–2%) in 360 cumulative patients (4, 5, 13, 16, 17, 19, 24–27, 32, 37, 38, 44).

Our only postoperative neurological complication was a sixth nerve palsy that occurred during a pontine biopsy. In this case, the damage likely resulted from direct injury to fibers of the sixth cranial nerve, illustrating the proximity of the abducent nucleus and nerve fibers to the origin of the middle cerebellar peduncle (Fig. 2B). Although there are no other reports of permanent injury to the sixth cranial nerve from trans cerebellar biopsies, Guthrie et al. (22) described a patient with temporary postoperative diplopia. In considering the regional anatomy of the pons, the sixth cranial nerve (and perhaps the seventh cranial nerve) is at risk during any trans cerebellar approach, and, therefore, their potential injury should be discussed with the patient. However, in contrast to the transfrontal approach (five reported cases of hemiparesis or sensory symptoms versus none for the trans cerebellar approach), trans cerebellar biopsies should not endanger other cranial nerve nuclei or the more anterior motor and sensory fiber tracts (16, 25, 37, 44). One exception, though, is the spinal trigeminal tract carrying fibers for facial pain and temperature sensation. These fibers run longitudinally through the dorsolateral pons, traversing the level of the middle cerebellar peduncle (Fig. 2A).

TABLE 2. Summary of stereotactic brainstem and/or posterior fossa biopsy series^a

Series (ref. no.)	TCSB /total cases (%) ^b	Intraoperative complications		Postoperative complications ^c		Nondiagnostic biopsies		Deaths	
		TCSB	Total	TCSB	Total	TCSB	Total	TCSB	Total
Current study	13/14 (92.8%)	1/14 (7.1%)	1/14 (7.1%)	1/13 (7.7%)	1/14 (7.1%)	1/13 (7.7%)	1/14 (7.1%)	0	0
Coffey and Lunsford, 1985 (13)	2/1 (18.2%)	0	0	0	0	0	0	0	0
Steck and Friedman, 1995 (44)	2/24 (8.3%)	0	0	UK	3/24 (12.5%)	UK	1/24 (4.2%)	UK	1/24 (4.2%)
Rajshekhkar and Chandy, 1995 (37)	2/72 (2.8%)	0	0	UK	5/72 (6.9%)	UK	1/72 (1.4%)	0	0
Kondziolka and Lunsford, 1995 (26)	8/40 (20%)	1/8 (12.5%)	1/40 (2.5%)	0	1/40 (2.5%)	UK	1/40 (2.5%)	0	0
Abernathey et al., 1989 (1)	26/26 (100%)	0	0	0	0	0	0	0	0
Guthrie et al., 1989 (22)	4/4 (100%)	0	0	1/4 (25%)	1/4 (25%)	0	0	0	0
Giunta et al., 1988 (19)	17/22 (77.3%)	2/17 (11.8%)	2/22 (9.1%)	1/17 (5.9%)	1/22 (4.5%)	2/17 (11.8%)	2/22 (9.1%)	0	0
Kratimenos and Thomas, 1993 (27)	12/56 (21.4%)	0	0	UK	2/56 (3.6%)	1/12 (8.3%)	4/56 (7.1%)	0	0

^a TCSB, trans cerebellar stereotactic biopsy; UK, unknown.

^b Includes all cases reported in each study (transfrontal and/or transtentorial approaches, as well as TCSB).

^c Includes morbidity and mortality.

Diagnostic Accuracy

Our nondiagnostic biopsy rate of 7.6% ($n = 1$; 95% CI, 0.2–36%) is slightly greater than that of other published transcerebellar biopsy series (range, 0–7%) (Table 2). This may be due to a true difference in diagnostic accuracy or an artifact of low sample size, as other studies did not specify their CIs. In total, only three nondiagnostic biopsies have been reported in the literature with the transcerebellar approach (19, 27).

Indications

The pathological variability of adult brainstem lesions is greater than that observed in children. The broad differential diagnoses are infarction, demyelinating disease, ependymoma, cryptic vascular malformation, abscess, radionecrosis, tuberculoma, epidermoid cyst, granuloma, metastatic adenocarcinoma, and lymphoma (1, 11, 12, 27, 29, 37). As a result of such diversity, preoperative diagnoses of these lesions based solely on radiographic studies are unreliable. In one report of 12 adult and pediatric patients, 50% of the tissue diagnoses differed from image-based diagnoses (13). In another study, 14 (25%) of 56 adults and children with brainstem lesions had tissue diagnoses that differed significantly from those predicted by radiological criteria. Multimodal imaging does little to improve this lack of concordance with histology, as one study of 26 adults imaged with both MRI and positron emission tomography revealed only a 63% correlation with their biopsy-proven diagnoses (30).

MRI examination is considered diagnostic for diffuse pontine gliomas, which occur primarily in children. The question of whether brainstem glioma biopsies can change management in children, however, remains unanswered. Although MRI scans may reliably categorize pediatric brainstem lesions as tumor versus nontumor, they remain inaccurate in predicting tumor grade and histological subtype, particularly in brainstem gliomas (7, 8, 41). For this reason, the reliance on imaging for the diagnosis of pediatric brainstem tumors has been questioned (7, 30, 35, 40). In our series, MRI scans carried a 58% diagnostic error rate. Although this may speak to the heterogeneity of adult brainstem lesions, it also casts doubt on the predictive value of nontissue diagnosis at any age. The safety of brainstem biopsies, as demonstrated in our series and others, suggests that obtaining pathological tissue for analysis should be considered before treatment. This approach, unquestioned in other anatomic areas before the start of therapy, will also be required increasingly in the future as treatment strategies tailored to tumor phenotype are implemented.

CONCLUSIONS

The awake transcerebellar biopsy is a relatively well-tolerated and effective method of establishing a diagnosis in adults with brainstem and/or cerebellar peduncle lesions. Clinical data and radiographic appearance may not be sufficient to accurately predict the cause of such lesions. Although complications from brainstem biopsies are rare, they can be cata-

strophic or result in permanent impairment because of the high density of fibers and nuclei within the brainstem. Despite these inherent risks, successful brainstem biopsies can change clinical management and provide important prognostic information. Our findings demonstrate that a transcerebellar biopsy of pontine or deep brain lesions can be routinely successful in the sitting position and under local anesthesia.

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COMMENTS

Sanai et al. describe modifications to the procedure of transcerebellar stereotactic biopsy of the brainstem, previously described by others, that improve safety and comfort, including use of the semi-sitting position under local anesthesia and use of a twist drill hole rather than a burr hole to minimize the associated risk of air embolism. One particularly interesting modification is the use of a propofol bolus during manipulation of the spinal trigeminal tract to minimize face pain. The reported tolerable risks (one neurological complication of sixth nerve palsy) and acceptable diagnostic yields may increase the use of this underutilized approach for appropriate patients with diagnostic issues involving the brainstem. Given the number of diagnostic changes occurring as a result of the biopsy (7 of 12 patients), it would seem the risks of this procedure outweigh the risks of radiation without a diagnostic pathological specimen. However, for patients with multiple lesions, of which some are supratentorial, it is likely that the latter would be more approachable with less risk in most instances.

Robert E. Gross
Atlanta, Georgia

This is an excellent article by Sanai et al. describing their technique and experience with frame-based stereotactic biopsy of adult brainstem tumors via the transcerebellar route. I still think that brainstem biopsies are required only infrequently and that the patients' history, presentation, and clinical and radiographic workup can most often make the diagnosis without tissue. For example, Sanai et al. had 3 patients with lung cancers in this series of 13 patients. I cannot remember ever needing to do a biopsy to prove metastasis.

The transfrontal approach gives reasonable access down to the level of the mid-pons and is, I think, less challenging for both surgeon and patient. In addition to facial pain, I have had patients undergoing the transcerebellar approach experience vertigo or diplopia intraoperatively. The propofol bolus for the needle pass is a terrific idea.

Philip H. Gutin
New York, New York

Sanai et al. report their technique for performing awake transcerebellar stereotactic biopsies in 13 patients. They use a semisitting position, a half-arc Cosman-Roberts-Wells frame, and a modified biopsy needle (smaller opening). They also use a bolus anesthetic to avoid the pain commonly encountered with manipulation of the trigeminal nuclei/pathways. Their technique seems to be practical and successful. As they note, we published a technique for awake transcerebellar biopsies in 1991. We use a standard Cosman-Roberts-Wells frame and a standard biopsy needle, inserted via a twist drill hole and requiring only a stab wound skin incision. The patient is comfortably placed in the lateral position, not the semi-sitting position, which probably reduces or eliminates the risk of air embolus, as was encountered in this series. The precise biopsy trajectory and all frame coordinates are determined via intraoperative computer programming developed at the University of Florida.

William Friedman
Gainesville, Florida

Sanai et al. provide an excellent retrospective review of their experience with awake transcerebellar stereotactic biopsies of lesions in adults involving the pons and cerebellar peduncles. Radiographic studies have been relied upon heavily in many patients in an attempt to make diagnoses of brainstem lesions, and, therefore, subsequent treatment has been planned on the basis of these interpretations without tissue diagnosis. Sanai et al. provide data showing that only 42% of the diagnostic specimens in their patient cohort were consistent with the diagnoses predicted by preoperative imaging, supporting an increased role for biopsies in both diagnosis and subsequent treatment planning. In addition, Sanai et al. nicely elaborate on use of the Cosman-Roberts-Wells frame with their four modifications to increase the safety and effectiveness of this procedure. We agree that performance of this technique with the patient awake, when feasible, is optimal for monitoring for any new neurological deficits during the procedure, as significant morbidity or mortality can result from brainstem biopsies. Finally, they briefly mention the use of frameless stereotaxy for these biopsies in a subsequent patient cohort, and it would be interesting to see a future report on their results, in terms of diagnostic rate and intraoperative/postoperative complications, as these patients require general anesthesia.

James L. Frazier
Alfredo Quinones-Hinojosa
Baltimore, Maryland

“What has been will be again, what has been done will be done again; there is nothing new under the sun”—Ecclesiastes 1:9–14

About 20 years ago we reported a series of 26 patients who underwent stereotactic biopsy of pontine lesions with the use of an approach that traversed the cerebellar hemisphere and middle cerebellar peduncle (1). In 1995 I was going to report my series of 132 pontine lesions in patients who underwent this procedure between 1984 and 1993. I did not do this because (in my opinion) even in 1995 it was neither a new idea nor new information. In fact Erik Backlund's group had reported a series of patients operated on with this approach in 1987 (2), 2 years before we did! Of particular note: Mathisen et al. described performing these procedures in adult patients in the sitting position under local anesthesia. Aside from differences in stereotactic instrumentation, the method described in the present article is identical.

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Sanai et al. review their transcerebellar brainstem biopsy experience. They considered that clinical data and radiographic appearance were not sufficient to predict the cause of the lesions in most patients with only a minority of the lesion diagnoses predicted on the basis of preoperative data. Their experience indicates that brainstem biopsies can be safely carried out and may be indicated more often than is currently believed for diagnostic effectiveness.

They believe their article introduced several novel operative principles and nuances. I do not feel that this article contains any new technical information. I randomly pulled two early textbooks from the 1980s, and both had a few chapters discussing transcerebellar brain-

stem biopsy (5, 13). Whether patients are awake or asleep or in the prone or semi-sitting position, it has all been done before and written about in detail. All you have to do is look back far enough and go to textbooks. I have taught the technique for transcerebellar and transfrontal brainstem biopsies throughout the last three decades. The keys are seeing the target and trajectory to avoid vascular structures, only penetrating the pia once and avoiding ependymal surfaces, obtaining specimens from a minimum of tissue, and confirming the pathological lesion before withdrawing (4).

I preferred performing transcerebellar brainstem biopsies with the patient in the lateral decubitus position. This was always easily tolerated, never caused an air embolism, and simply required the Cosman-Roberts-Wells to be rotated 90° so the base is down. The 5-mm side-biting biopsy cannula was standard even back then. To prevent the drill bit from sliding, the guide tube can be placed right up against the bone. We used local anesthesia in adults and held the option of using general anesthesia for children. One advantage of the patient being awake is the quicker detection of problems such as numbness or weakness so that the procedure can be stopped before severe complications occur. The use of a propofol bolus defeats that purpose. Rarely, low dose sufentanil was used for comfort. Brainstem hemorrhage is a rare but significant problem whether patients are intubated or breathing on their own, and there is not much that can be done about an expanding brainstem hematoma: prevention by scrupulous screening and by operating with meticulous precision is the best defense.

A small clinical series of 13 patients does not have the statistical power to justify any conclusions about a low complication rate or diagnostic efficacy. A missed diagnosis, an air embolism, and a sixth nerve palsy are complications.

Stereotactic brainstem biopsy studies from the last century with twice as many or more patients confirmed the safety (<1% morbidity and mortality) and efficacy (> 95% diagnostic) in 180 patients (1–3, 6–11, 14). This century's data so far are little different, but still the data are insufficient for a scientific conclusion (12). Whereas a number of us have great experience with stereotactic brainstem biopsies, this is not the case for the general neurosurgical readership and the real question is what is the risk-to-benefit ratio. This ratio has shifted back and forth. Early computed tomographic imaging allowed these targets to be reached, and the benefit clearly was on the side of biopsy. Magnetic resonance imaging and modern imaging technology have shifted it back to noninvasive diagnostics. This study has nothing to offer on how to manage children. In adults, there are good reasons to perform biopsies in few selected patients. The 13 patients in 7 years and the frequent alterations in diagnosis indubitably reflect the uncommon need for biopsy and the bias in the selection process. Whether or not brainstem biopsies have a significant impact remains to be determined. We need a definitive study.

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Cape Town. Image courtesy of Earth Sciences and Image Analysis Laboratory, NASA Johnson Space Center, (<http://eol.jsc.nasa.gov>).

DELAYED VISUAL DEFICITS AND MONOCULAR BLINDNESS AFTER ENDOVASCULAR TREATMENT OF LARGE AND GIANT PARAOPHTHALMIC ANEURYSMS

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OBJECTIVE: Paraophthalmic aneurysms may exert mass effect on the optic apparatus. Although surgical clipping and endovascular coiling of these aneurysms can be complicated by immediate postoperative visual deterioration, endovascular coil embolization has the unique risk of visual complications later (>24 h) in the perioperative period.

METHODS: Six patients with a delayed onset of vision loss after technically successful coil embolization of paraophthalmic region aneurysms were identified. All available clinical, angiographic, and cross sectional imaging for these patients, in addition to histopathological data, were reviewed.

RESULTS: Six patients who underwent endovascular treatment of paraclinoid aneurysms at our institutions developed delayed postoperative visual decline. Four were treated with combination hydrogel-coated and bare platinum coils, one with hydrogel-coated coils, and one with bare platinum coils. Three patients presented with some degree of visual impairment caused by their aneurysms. Catheter angiography performed after the visual decline revealed no etiology in any of the cases. Magnetic resonance imaging was performed in all patients and was unremarkable in two. At follow-up, two had improved, three remained unchanged, and one patient died before any follow-up assessment of her vision.

CONCLUSION: Both acute and delayed visual disturbances can present after the endovascular treatment of carotid artery paraophthalmic aneurysms. Delayed visual deterioration can be observed up to 35 days after embolization. Although the cause is still undefined, it is likely that the more delayed visual deterioration can be attributed to progression of mass effect and/or perianeurysmal inflammatory change. Our case series raises the possibility that this phenomenon may be more likely with HydroCoil (HydroCoil Embolic System; MicroVention, Aliso Viejo, CA). This possibility should be taken into account by neurointerventionists when selecting a coil type to treat large paraophthalmic aneurysms.

KEY WORDS: Bare platinum coil, Blindness, Coiling, Cranial neuropathy, HydroCoil

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Cerebral aneurysms are common lesions, with autopsy studies suggesting an adult population prevalence of 1 to 5% (23). Before the early 1990s, the vast majority of treated aneurysms were performed with the use of surgical clipping. However, since 1995, when the Food and Drug Administration approved Guglielmi detachable coils, more than 100,000 patients have undergone endo-

vascular aneurysm treatment (24). Paraophthalmic aneurysms may compress the optic apparatus and present clinically with visual deterioration. The proximity of these aneurysms to the optic apparatus accounts for the risk of acute visual complications after both endovascular and surgical clipping (1). Visual complications after the clipping of paraophthalmic aneurysms usually are evident immediately after open surgery. However, both acute and delayed (>24 h) visual deterioration may be observed after coil

ABBREVIATIONS: ICA, internal carotid artery;
MRI, magnetic resonance imaging

embolization. We present six cases of delayed visual impairment after the coil embolization of paraophthalmic aneurysms.

PATIENTS AND METHODS

Six patients who presented with a delayed onset of vision loss after technically successful coil embolization of periorbital region aneurysms were identified at our two institutions. All available clinical, angiographic, and cross sectional imaging for these patients, in addition to histopathological data, were reviewed.

RESULTS

Six patients experienced delayed visual deterioration after endovascular coil embolization (Table 1). Three of the six patients presented with symptoms related to mass effect on the optic apparatus. Four of the patients had been treated with HydroCoil (HydroCoil Embolic System; MicroVention, Aliso Viejo, CA) and bare platinum, one with HydroCoil alone, and one with bare platinum alone. In one patient, the monocular vision loss and contralateral hemianopia was gradual during a 24-hour period and was associated with headache. A second patient developed rapidly progressive monocular blindness at 48 hours without additional symptoms. In four patients, the visual deterioration occurred much later in the recovery period (7–35 d). On magnetic resonance imaging (MRI), two patients had T2 signal changes in the optic nerve and enhancement of the optic chiasm and nerve, whereas a third patient had evidence of mass effect from the aneurysm on the optic apparatus. MRI studies in two patients were unremarkable, demonstrating no significant peri-

aneurysmal enhancement or signal abnormality within the adjacent brain parenchyma.

All six patients were treated with corticosteroids after their vision deteriorated. At follow-up, two had improved, three remained unchanged, and one patient died before any follow-up assessment of her vision.

ILLUSTRATIVE CASES

Patient 1

A 69-year-old right-handed woman presented at an outside institution with decreased peripheral vision and was found to have an unruptured large (17- × 22- × 13-mm) paraophthalmic aneurysm in the right internal carotid artery (ICA). She underwent failed surgical clipping and a subsequent muslin wrap. During intraoperative angiography, the patient sustained an embolic left posterior cerebral artery infarct, which left her with a right homonymous hemianopsia. The patient was referred to our institutions for endovascular treatment and presented to us with short-term memory deficits, progressive vision loss, and hydrocephalus. A baseline ophthalmological examination revealed bilateral optic nerve compression from the aneurysm that limited her visual perception to the appreciation of hand motion only at 20/400 in each eye. The patient underwent ventriculoperitoneal shunting with some subjective improvement in her visual symptoms. After pretreatment with aspirin and clopidogrel, she underwent successful stent-assisted coiling with HydroCoils and bare platinum coils (Fig. 1).

Two weeks after the procedure, the patient presented with visual deterioration. She was found to have no light reflex, with pupils measuring 7 mm bilaterally and unresponsive visual evoked potentials bilaterally. Her left optic nerve had good color; however, her right optic nerve showed mild atrophy, both of which were unchanged from her previous examination. MRI revealed T2 signal changes within the basal

TABLE 1. Patient data and outcome for six patients^a

Patient no.	Age (yr)/sex	Aneurysm size (mm)	Coil type	Stent-assisted coiling?	HydroCoil length (cm)/total coil length (%)	HydroCoil packing density/total packing density ^b	Presented with visual symptoms?	Time to visual deterioration (d)	Visual outcome	Response to corticosteroids
1	69/F	17 × 22 × 13	B	Yes	267/373 (71.6%)	50.6%/54.4%	Yes	14	Blind (bilateral) ^c	Died
2	40/F	26 × 23 × 22	H	Yes	570/570 (100%)	47.8%	No	30	Hand motion only (left eye)	Improved
3	18/M	20 × 16 × 10	B	No	180/270 (66.7%)	48.7%/54.8%	Yes	2	Light perception (left eye)	No change
4	55/F	14 × 14 × 13	B	No	85/296 (29%)	30.8%/46.2%	No	2	Blind (left eye)	No change
5	68/F	23 × 16 × 8	B	Yes	135/291 (46.4%)	32.3%/41.2%	No	21	Inferior quadrant-anopia (right eye)	No change
6	44/F	21 × 19 × 18	P	Yes	0/806 (0%)	0%/23.8%	Yes	7	20/400 (bilaterally), temporal field cut (left eye)	Improved

^a B, both HydroCoil and bare platinum coils; H, HydroCoil; P, bare platinum coil.

^b Packing density was calculated using software found at www.angiocalc.com.

^c Patient 1 developed blindness 14 days after the procedure; however, she died from a fatal stroke 5 weeks after the procedure.

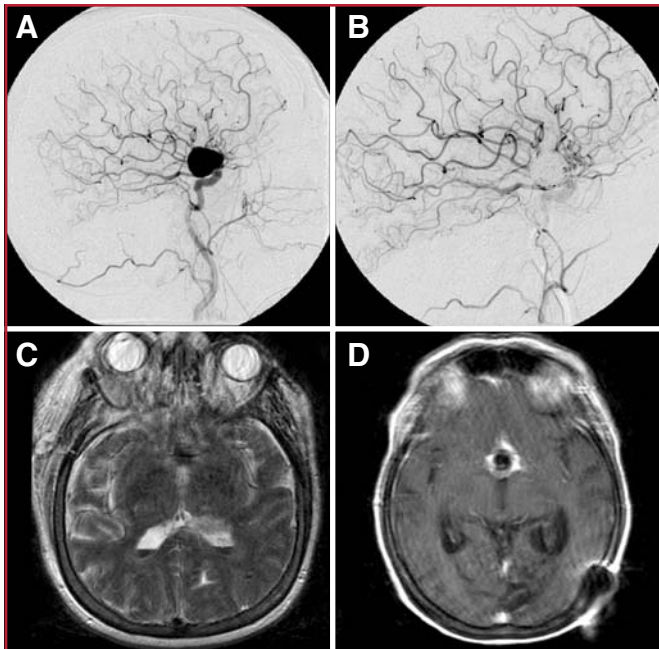


FIGURE 1. **A** and **B**, pre- (**A**) and postoperative (**B**) lateral angiograms significant for a coiled large right internal carotid artery aneurysm and a patent ophthalmic artery. **C** and **D**, magnetic resonance images. The pre-embolization T2-weighted image (**C**) shows minimal perianeurysmal edema. After muslin wrapping and coil embolization, the postgadolinium T1-weighted image (**D**) shows enhancement surrounding the hypointense coil mass.

forebrain surrounding the aneurysm dome with a thick and intense perianeurysmal cuff of contrast enhancement. Angiography revealed a patent right ophthalmic artery (Fig. 1). She was started on corticosteroids for a presumed inflammatory etiology for these findings.

Three weeks later, the patient developed respiratory distress and neurological deterioration, and she subsequently died. Noninvasive imaging had demonstrated an occluded right ICA and a large right middle cerebral artery infarct. A review of her outpatient medications revealed that aspirin and clopidogrel had been discontinued (after her presentation with perioperative vision loss), likely leading to the thrombosis of her indwelling right ICA Neuroform stent (Boston Scientific, Fremont, CA). On autopsy, a foreign body giant cell reaction was identified surrounding the aneurysm and extending along the leptomeninges of the right sylvian fissure. Macrophage and T-cell lymphocyte infiltrates were identified within the adventitia of the aneurysm wall and adjacent to both optic nerves, which adhered densely to the aneurysm. No inflammatory infiltrate was identified within the lumen of the coiled aneurysm. Subacute infarcts of both optic nerves were noted, along with acute hemorrhage within the left optic nerve. The right ICA was thrombosed in the segment containing the stent, with acute infarction of the right frontal and temporal lobes. Cerebrospinal fluid collected at the time of the autopsy was significant for increased cellularity with lymphomononuclear cells.

Although these changes are suggestive of an aneurysmal-based inflammatory process as a cause for the associated visual deterioration, the clinical picture is obscured to a large extent by the history of an attempted surgical clipping and subsequent muslin wrapping. It is possible that the previous muslin wrapping contributed significantly to the subsequent leptomeningeal inflammatory process and subsequent

visual deterioration. The development of hydrocephalus and visual compromise in this patient after the muslin wrapping and before endovascular treatment raises the suspicion that a significant inflammatory response to the muslin had been developing before the attempted coiling. The phenomenon of chronic inflammatory reactions to muslin wrapping with delayed visual deterioration was first described by Carney and Oatey (5) and, subsequently, by a number of other investigators (3, 9, 10, 13, 17, 19).

Patient 2

A 40-year-old woman presented with hyperprolactinemia, hypothyroidism, and adrenocorticotrophic hormone deficiency caused by stalk disconnection syndrome. Imaging revealed a giant (26- × 23- × 22-mm), partially thrombosed ICA aneurysm located just distal to the left ophthalmic artery origin. The patient's vision was normal, and she was started on hormone replacement therapy, including corticosteroids. Two months later, the aneurysm was treated by stent-assisted coiling with HydroCoil. The procedure was complicated by immediate right visual field loss secondary to a small left occipital lobe infarct, likely attributable to an intraprocedural thromboembolism. Her vision improved over the course of 24 hours, and she was discharged from hospital 2 days later without any visual defect.

A month later, she developed rapidly progressive monocular vision loss in the left eye; her vision deteriorated to perception of hand movements only. On examination, the left optic disc was pale with inflammatory characteristics. The right eye was normal. MRI revealed communicating hydrocephalus (Fig. 2) as well as high T2 signal in the left optic nerve with gadolinium enhancement of the chiasm, the adjacent left optic nerve, and the aneurysm wall (Fig. 3). A laboratory examination of her cerebrospinal fluid was normal. A neurophysiological evaluation with cortical visual evoked potentials confirmed a left optic neuropathy. The patient was treated by cerebrospinal fluid diversion (ventriculoperitoneal shunt) and high doses of corticosteroids. At 6 months' follow-up, her left eye vision has improved, and MRI has shown a reduction in the chiasmal T2 signal abnormality and contrast enhancement.

Patient 3

An 18-year-old man presented with a 3-month history of blurred vision in the left eye. The ophthalmological examination was normal, but imaging revealed a 20- × 15- × 15-mm left carotid ophthalmic

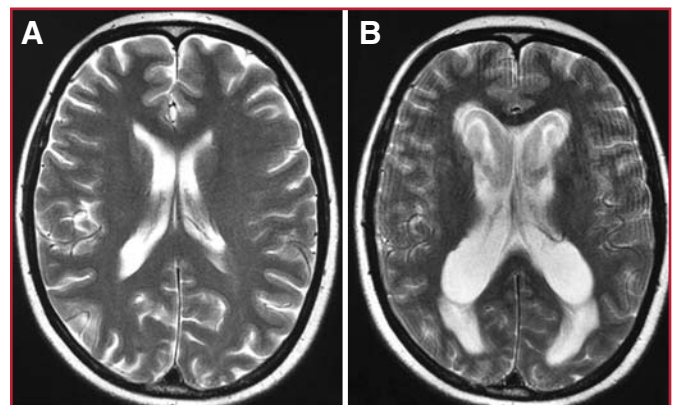


FIGURE 2. Pre- (**A**) and postoperative (**B**) T2-weighted magnetic resonance images showing a significant increase in ventricular size after endovascular coiling.

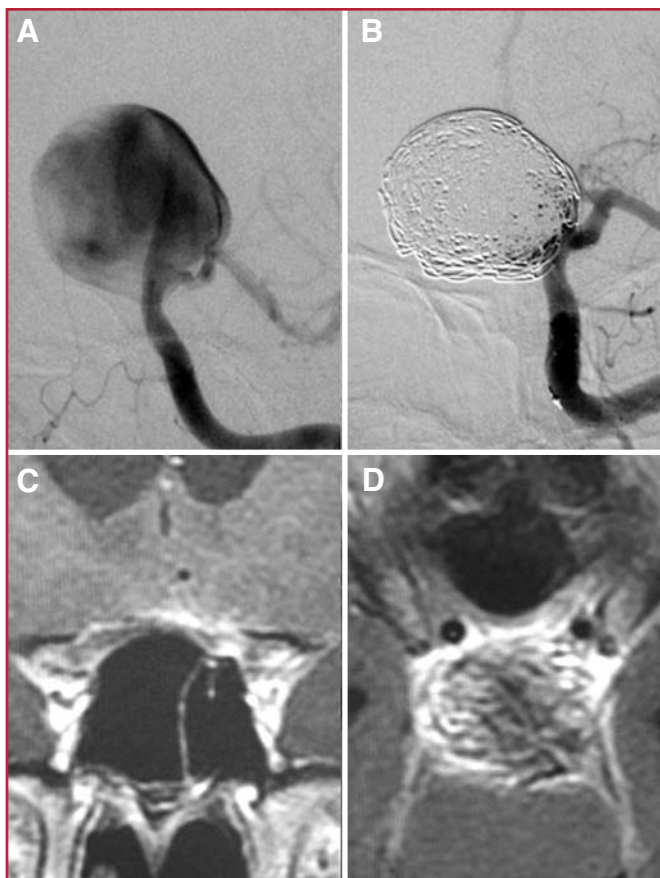


FIGURE 3. **A** and **B**, pre- (**A**) and postoperative (**B**) left internal carotid artery angiograms showing near-complete coil embolization of the giant aneurysm. **C** and **D**, magnetic resonance images. Postembolization coronal (**C**) and axial (**D**) T1-weighted images with gadolinium showing intense perianeurysmal enhancement with compression on the optic chiasm.

aneurysm. He was treated by endovascular coiling with a combination of bare platinum coils and HydroCoils. The procedure was uncomplicated, and his postprocedure vision was initially normal. Two days later, vision in his left eye deteriorated, and MRI suggested local compression of the optic nerve with T2 hyperintensity in the left optic nerve (Fig. 4). Treatment with corticosteroids was started, but after a further 48 hours, his vision remained at finger counting only, and transethmoidal decompression of the optic nerve was performed without effective improvement. On follow-up at 9 months, his vision in the left eye remains at the level of light perception only.

DISCUSSION

Paraophthalmic ICA aneurysms, because of their direct proximity to the optic apparatus, are unique with respect to the risk of visual deterioration after both surgical and endovascular treatment (1, 16, 20). Although few data exist, the risk of this complication seems to occur in 5 to 10% of patients, regardless of the treatment strategy. Andaluz et al. (1) reported that 3 (7.9%) of 38 patients who underwent surgical clipping of para-

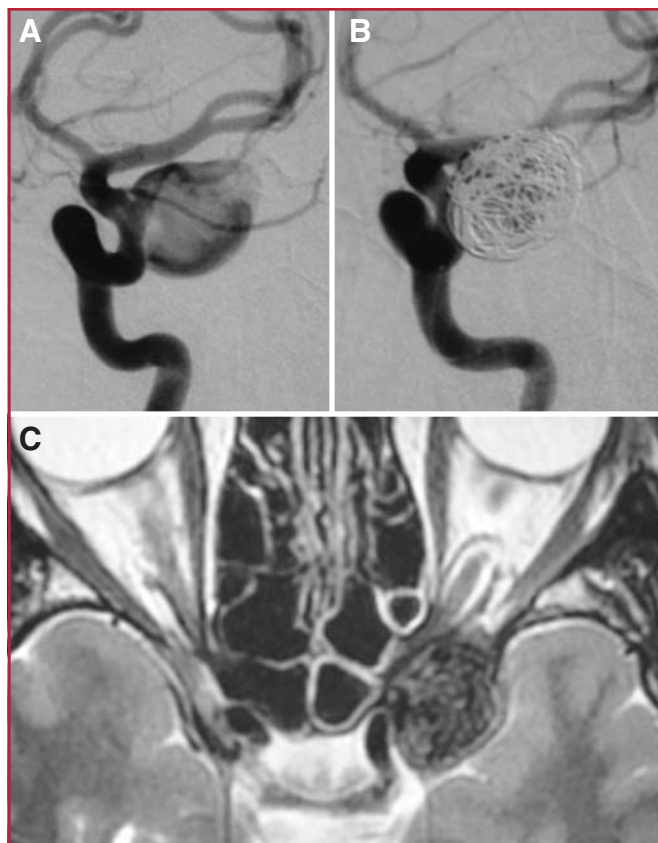


FIGURE 4. **A** and **B**, pre- (**A**) and postoperative (**B**) left internal carotid artery angiograms showing near-complete coil embolization of the aneurysm. **C**, postembolization axial T2-weighted magnetic resonance image showing significant mass effect on the left optic nerve and hyperintensity within the left optic nerve.

clinoid aneurysms experienced new visual field deficits, and 1 (8.3%) of 12 patients who underwent endovascular embolization had an acute onset of blindness requiring immediate surgical decompression of the optic nerve. Vargas et al. (22) reported 19 patients who underwent endovascular treatment of giant aneurysms and who were symptomatic with vision loss. Of these patients, 18 were improved or unchanged, and 1 (5.3%) experienced further visual deterioration after treatment.

Categorization of the new-onset visual deficits or blindness after endovascular treatment of paraclinoid aneurysms can be based on the etiology, timing, and acuity of the symptom onset. Deficits that occur abruptly and are maximal at onset are likely thromboembolic, related to direct retinal infarcts via the ophthalmic artery or posterior communicating artery to posterior cerebral artery emboli and leading to occipital lobe infarcts and cortical blindness. These events are most common during the procedure or in the immediate periprocedural period (7). These ischemic deficits typically do not improve with time or respond to corticosteroid therapy and may require emergent intervention to save vision.

Progressive visual changes, as observed in our series, typically occur hours to weeks after the procedure. Unlike the thromboembolic events, which have an abrupt and maximal onset, these changes have a slower, more progressive onset and are likely secondary to evolving mass effect from aneurysm thrombosis and/or perianeurysmal inflammation and edema (15, 21, 25). The severity of edema, the anatomic configuration of the aneurysm, its relationship to the optic apparatus, and the degree of mass effect and visual compromise before the embolization likely dictate the ultimate outcome of the visual deficits in these patients. These visual disturbances may stabilize or improve with administration of corticosteroids.

The workup of patients presenting with visual changes after coil embolization of paraophthalmic aneurysms can be simplified on the basis of presentation. Patients who present with abrupt, maximal-at-onset vision decline within hours to days after the procedure likely have a thromboembolic etiology. Immediate catheter angiography may be performed in these cases to identify an occluded ophthalmic artery, which may be amenable to therapeutic revascularization, depending on the time frame. However, for patients presenting with a slow, progressive deterioration in their vision, MRI is often useful to evaluate for mass effect and/or edema. If present, corticosteroids or decompressive surgery may be of benefit.

Five of the six aneurysms in our series were embolized, at least partially, with HydroCoil. Embolization with the HydroCoil has been associated with postprocedure headaches (8), worsening cranial neuropathy (8), aseptic meningitis (6, 8, 14), and delayed hydrocephalus (2, 8). These sequelae are postulated to be secondary to perianeurysmal inflammation and mass effect on adjacent structures, particularly the cranial nerves and dura mater. However, although these phenomena have been reported to occur in association with the use of HydroCoils, similar findings also are observed after the embolization of aneurysms with bare platinum (11, 12) and polyglycolic-poly-lactic acid-coated coils (14, 18). In the current series, the HydroCoil component of the coil mass could be contributing to perianeurysmal edema and inflammation. This inflammatory process, even in the absence of significant mass effect on MRI, could conceivably cause delayed visual loss.

Cantón et al. (4) found that aneurysm packing densities of up to 93% with HydroCoil did not increase intra-aneurysmal pressures, suggesting that mass effect-related symptoms may be minimized by not overpacking (>100% packing density), a phenomenon that can be achieved with HydroCoil but not bare platinum. In fact, improvement in cranial neuropathies caused by decreased mass effect and aneurysmal pulsatility has been noted in association with low packing density (<50%) embolization, regardless of the coil type (4, 8). In the present series, no aneurysm was packed to a density greater than 55% (Table 1).

Because the present series does not represent an all-inclusive, prospective study at either institution, it is possible (although not probable) that additional periophthalmic aneurysms were treated with other coil types and that delayed blindness resulted but was not captured in this retrospective

evaluation. It is also certainly true that many other periophthalmic aneurysms were treated at both institutions with HydroCoil (and other coil types) over the same time period without resulting in blindness. As such, no precise estimate of the rate at which these complications occur can be provided. The present data are therefore not sufficient to draw any firm conclusions as to a relationship between HydroCoil use in these aneurysms and delayed blindness. At the same time, we do raise the possibility that this phenomenon of delayed blindness, although observed with other coil types as well, may be more likely with HydroCoil.

CONCLUSION

Both acute and delayed visual disturbances can present after the endovascular treatment of carotid artery paraophthalmic aneurysms. Delayed visual deterioration can be observed up to 35 days after embolization. It is likely that the more delayed visual deterioration can be attributed to progression of mass effect and/or perianeurysmal inflammatory change. In our series, this complication occurred exclusively after the treatment of large paraophthalmic aneurysms, half of which had initially presented with mass effect or visual disturbance. In this series, five of six patients underwent coiling with HydroCoil, which raises significant concerns that delayed vision loss may be more likely with the use of HydroCoil than other coil types. This possibility should be taken into account by neurointerventionists when selecting a coil type to treat large periophthalmic aneurysms.

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COMMENTS

Turner et al. presented a small case series of subacute to chronic visual loss in patients with paraophthalmic aneurysms undergoing endovascular treatment. In this series of six patients, they described different patterns of visual loss in presumed association with the treatment of the aneurysms by coiling. Although four of the six patients had been treated exclusively with HydroCoils (HydroCoil Embolic System; Microvention, Aliso Viejo, CA), one patient had been treated with a bare platinum coil alone and one patient was treated with a combination of coils.

An important complication in the endovascular treatment of aneurysms of the ophthalmic region is also described. This timely contribution emphasized other recent publications describing similar results in the endovascular treatment of aneurysms of that region (1). Interestingly, Turner et al. point out that mass effect may not be the only cause for visual loss, especially in the delayed setting. Indeed, Schmidt et al. made this suggestion as well, especially in light of the fact that several of the patients in the series presented 24 hours later with pyrexia (unpublished data), which seems to correlate with various laboratory studies. It is unclear in this limited series and in other published series as to whether the problem is truly a consequence of the HydroCoils. Given the combined assessment of several articles, HydroCoils per se may not be the cause. Rather, the presence of a large thrombus burden may be the true cause.

A better understanding of the pathobiological basis of aneurysm therapy, be it endovascular or microsurgical, is necessary. Future case series and in vitro analyses will certainly help provide the needed answers to effect safe, definitive treatments for aneurysms.

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Turner et al. reported a case series of six patients with delayed monocular blindness after endovascular treatment of paraclinoid aneurysms. Three of these patients presented with a history of some visual deterioration preoperatively and five of six of the patients were treated with HydroCoils. They concluded that this phenomenon is related to both the mass effect and inflammatory reactions after the use of HydroCoils. One of the fundamental principles in treating many neurosurgical problems is relieving the mass effect. This is important in a wide range of neurological disorders ranging from acute epidural hematomas, spinal compression from disc or tumors, or compression of the brain stem in cranial base tumors. It is therefore surprising that the authors would not expect this result as these were mostly large paraclinoid aneurysms with mass effect on the optic apparatus, and therefore visual loss would occur regardless of the type of coils used. In my practice in which I coil a large number of paraophthalmic aneurysms, I manage large aneurysms and treat those with clinical evidence of optic nerve compression with intradural clinoid removal and microsurgical clipping to prevent early and delayed visual deterioration.

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Turner et al. reported their experience with six patients who underwent endovascular treatment of paraclinoid aneurysms and developed delayed postoperative visual field deficits or decline. In four of the patients, a hydrogel-coated coil was used along with a bare platinum coil, and one patient had a hydrogel coil alone.

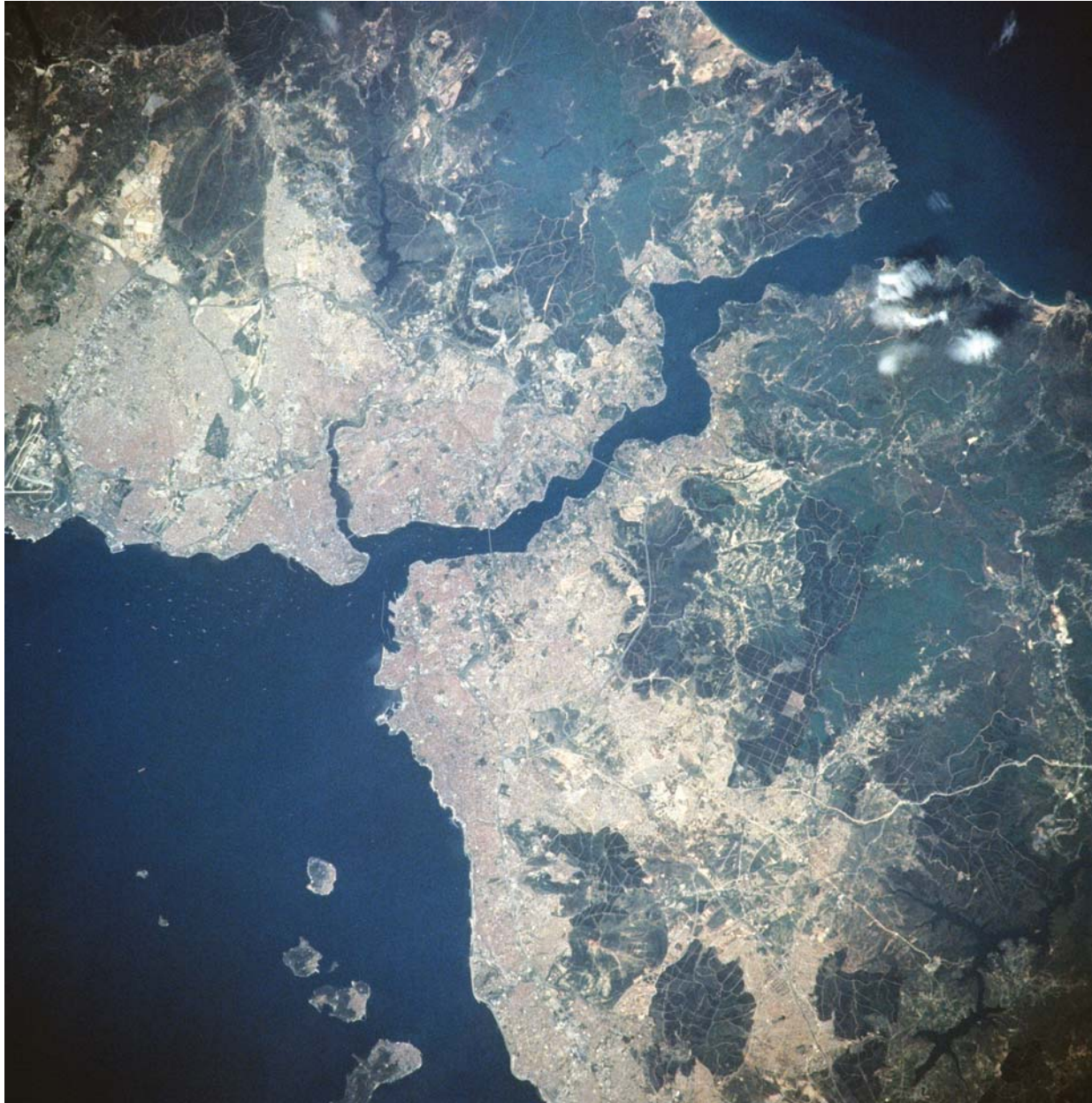
Hydrogel has been implicated in a significant perivascular inflammatory response, which clearly may have led to the delayed visual loss in these patients. Even with bare platinum and thrombosis of the lesion, an inflammatory response can occur, often with swelling, edema formation of the lesion, and compression of the optic apparatus. After surgical manipulation, visual loss is often acute and is detected immediately upon the patient's emergence from anesthesia; however, I think

there is a need to be aware of this possibility in an endovascularly treated group. Perhaps these patients should be treated more aggressively with large doses of steroids in a prophylactic fashion. Oftentimes, however, the use of steroids is more for the treating physician than for an actual change in the course of the disease.

As Turner et al. stated in their article, these deficits, when they occur, may require urgent surgical decompression. This certainly could make the case for considering surgical intervention for large lesions such as

these; however, six patients is quite a small number for the numerator, and I am sure the denominator needs to be considered as well. If visual loss associated with endosaccular occlusion is raised as an issue, then the numerator and denominator for surgical intervention should be intellectually examined as well.

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Istanbul. Image courtesy of Earth Sciences and Image Analysis Laboratory, NASA Johnson Space Center, (<http://eol.jsc.nasa.gov>).

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RESULTS OF ENDOVASCULAR TREATMENT OF TRAUMATIC INTRACRANIAL ANEURYSMS

OBJECTIVE: To present results of early angiographic diagnosis and endovascular treatment of traumatic intracranial aneurysms (TICA).

METHODS: From June 2002 to December 2006, diagnostic angiography was performed on patients with moderate to severe traumatic brain injury that involved a cranial base fracture or a penetrating brain injury with a tract from the penetrating agent that entered at the pterional area, went through the middle cerebral artery candelabra, and crossed the midline. TICAs were treated by various endovascular techniques during the same angiographic procedure.

RESULTS: Thirty-four patients with traumatic brain injury underwent angiography (25 penetrating brain injuries, nine blunt injuries); 13 TICAs were diagnosed (10 penetrating brain injuries, three blunt injuries). The Glasgow Coma Scale score at diagnosis ranged from 5 to 15. Angiography was performed for screening in eight patients and for clinical indications in five patients; 11 TICAs were diagnosed before rupture. Seven aneurysms were located on branches of the middle cerebral artery, two on pericallosal branches of the anterior cerebral artery, and four on the internal carotid artery. No recanalization was detected in 12 patients. One patient treated with a bare stent and coiling had a growing intracavernous pseudoaneurysm; therefore, internal carotid artery occlusion with extracranial-intracranial microvascular bypass was performed. Six patients refused angiographic follow-up, but computed tomographic angiography has failed to show recanalization. No patient presented with delayed bleeding (mean follow-up, 2.6 yr). There were no procedure-related complications or mortality.

CONCLUSION: Early angiographic diagnosis with immediate endovascular treatment provided an effective approach for TICA detection and management. Endovascular therapy is versatile and offers a valuable alternative to surgery, allowing early aneurysm exclusion with excellent results.

KEY WORDS: Cerebral aneurysm, Embolization, Intracranial hemorrhage, Subarachnoid hemorrhage, Traumatic brain injury

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A traumatic intracranial aneurysm (TICA) is considered a rare entity, constituting less than 1% of all aneurysms in large series (2, 5, 17). Management of patients with a TICA is controversial, with the cause, mechanism of development, and optimal timing for diagnostic angiography subject to debate. Aneurysmal screening with computed to-

graphic angiography (CTA) has been suggested by some authors (4, 12, 20, 34, 40).

Epidemiological and etiological data reported in the literature are contradictory. A TICA can occur after both blunt and penetrating head trauma and is more frequently described in the pediatric population (1, 7, 16, 39). The reported TICA incidence varies

ABBREVIATIONS: ACA, anterior cerebral artery; CCF, carotid-cavernous fistula; CT, computed tomography; CTA, computed tomographic angiography; GOS, Glasgow Outcome Scale; ICA, internal carotid artery; MCA, middle cerebral artery; PBI, penetrating brain injury; TBI, traumatic brain injury; TICA, traumatic intracranial aneurysm

widely, ranging from 3.2% in civilian penetrating craniocaudal injuries (26) to 42% of patients with gunshot wounds and missile head injuries (19). Patients may present with a variety of signs and symptoms, depending on the aneurysm location and the extent of other traumatic injury. Delayed intracranial hemorrhage is typical in these patients and is associated with a significant mortality rate, as high as 50% (2, 11, 14, 15, 17).

There is consensus in the literature that a TICA is often associated with a poor prognosis and should be diagnosed as soon as possible to prevent delayed intracranial traumatic hemorrhage and high rates of morbidity/mortality related to bleeding (3, 7, 14, 17, 18, 22). Until recently, a TICA was generally treated by open surgery or managed conservatively. Although reported results of surgical treatment are better than those after conservative management, mortality is still high, at 18 to 29% (14, 16, 26, 29). Recent reports of endovascular treatment of TICAs have shown promising results, with no reported mortality and very low or no morbidity in early reports (10, 13, 18, 23, 28, 30, 38).

There are no guidelines regarding indications, timing, or screening protocols for patients with traumatic brain injury (TBI) who could potentially harbor a TICA. Several authors indicate that those with cranial base fractures in the area of the carotid canal (38) and those with penetrating brain injury (PBI) who have a tract from the penetrating agent (bullet, shrapnel, stylet) entering at the pterional area, going through the middle cerebral artery (MCA) candelabra, and crossing the midline structures are candidates for early cerebral angiography (1, 3, 4, 6, 15). In the past 5 years, we have adopted a policy of early diagnostic angiography for TBI patients whose injuries fit these descriptions, with immediate endovascular treatment of a TICA during the same angiographic session when appropriate.

In this article, we present results of early angiographic diagnosis and endovascular treatment using various techniques, including glue, coils, or stents for 13 patients with TICAs.

PATIENTS AND METHODS

Hadassah University Hospital is a tertiary referral center serving a population of approximately 800,000 and providing the sole Level I trauma service to the greater Jerusalem region.

From June 2002 to December 2006, we accumulated data prospectively on diagnostic angiography procedures in patients with moderate to severe TBIs and endovascular treatment of patients with TICAs. During this period, we performed 34 angiographic studies in head-injured patients, including 25 with PBIs and nine with blunt head injuries. Angiography was performed on the basis of clear clinical indications or as a screening procedure in PBI patients with a tract from the penetrating agent entering the pterional area and passing through the MCA candelabra across the midline. A TICA was diagnosed in 13 patients (Table 1). Ten were admitted in poor condition with Glasgow Coma Scale scores of 5 to 11 immediately after terrorist bombings (three patients), combat explosions (four patients), gunshot wounds (two patients), or a fall from a height (one patient) (Table 1, Patients 1–10). These 10 patients were treated according to the Advanced Trauma Life Support trauma protocol. Head computed tomography (CT) and emergent surgical procedures were performed, including wound debridement when necessary, decompressive craniectomy (four patients), and

ventriculostomy and/or intracranial pressure monitoring (10 patients). Patients were stabilized in the neurosurgical intensive care unit.

Screening angiography was performed 1 to 3 days after injury in eight TICA patients (Patients 1–8). These patients all had PBIs, and all met the criteria cited above. Angiography was performed as soon as patients were stabilized.

A screening angiogram was not obtained in Patient 9, although he met these criteria. This was a 6-month-old infant who sustained a gunshot wound inflicted by a bullet fired into a moving vehicle in which he was a passenger. Because he arrived at our Emergency Department in generally poor condition and remained unstable during his hospitalization in the pediatric intensive care unit, we decided to postpone screening angiography in this infant. Six days after injury, he developed a delayed intracranial hematoma. Angiography was performed at this point, revealing a false aneurysm on a second-generation branch of the right pericallosal artery.

Patient 10 presented with a closed head injury and cranial base fracture after sustaining a fall from a height. He remained comatose, and repeat head CT studies revealed the formation of multiple right hemispheric infarctions in the frontal and occipital lobes. We therefore performed cerebral angiography on Day 7, which revealed a right internal carotid-cavernous aneurysm.

Patients 11 and 12 had been involved in motor vehicle accidents and sustained cranial base fractures related to their closed head injuries. They were referred from other hospitals in a late posttraumatic period, 21 and 30 days after trauma, respectively, when they developed symptoms suggestive of a carotid-cavernous fistula (CCF), which led to the decision to obtain an angiogram.

Patient 13, a 5-year-old child, had been accidentally stabbed with an umbrella through her upper left eyelid while playing. Her visual function was preserved. She was somnolent, but in good general condition. Emergent CT revealed basal subarachnoid hemorrhage centered on the intracranial portion of the left internal carotid artery (ICA), a straightforward indication for immediate angiography, which revealed a left ICA transitional aneurysm.

All in all, angiography was performed on a screening basis in eight patients (Patients 1–8). In five other patients, indications for cerebral angiography were intracranial hemorrhage (Patients 9 and 13), symptoms suggestive of CCF (Patients 11 and 12), and multiple infarctions with vascular territorial spread (Patient 10).

RESULTS

Thirteen consecutive TICAs were diagnosed in 13 patients (10 males, three females; mean age, 18.4 yr; age range, 6 mo to 31 yr) (Table 1). Among the 34 TBI patients who underwent angiography, 10 (40%) of 25 PBI patients and 3 (33.3%) of 9 patients with blunt trauma had TICAs.

Aneurysms were found in 8 (32.0%) of 25 PBI patients at the first screening angiography (Patients 1–8) and in 2 PBI patients with clear clinical indications for angiography (Patients 9 and 13). Among 15 PBI patients with a negative result on the first angiogram, a second angiogram was obtained 2 weeks to 1 month after admission. No additional aneurysms were diagnosed in these screening studies.

A TICA was also diagnosed in three blunt head trauma patients who underwent angiography because of clinical indications 7, 21, and 30 days after injury (Patients 9, 11, and 12, respectively).

TABLE 1. Patients presenting with traumatic intracranial aneurysms^a

Patient no.	Age (yr)/sex	Type of trauma	Incident	GCS score at angio	CT findings	Immediate treatment	Indication for angio	Day angio	Aneurysm location, size	Repair	Outcome
1	31/M	PBI: missile wound	Bus bombing	Coma/7	Contusion, swelling	ICP monitoring, wound debridement	Screening	3	2nd-generation branch L MCA; 2 mm	NBCA, 33% parent artery	Angio f/u: AEC, GOS score 4
2	17/F	PBI: missile wound	Bus bombing	Coma/7	Contusion, swelling	ICP monitoring, wound debridement	Screening	2	R pericallosal, 2 mm	Coils, aneurysm obliteration	CTA f/u: AEC, GOS score 5
3	16/M	PBI: missile wound	Bombing	Stupor/11	Contusion, swelling	ICP monitoring, wound debridement	Screening	2	2nd-generation branch L MCA, 2 mm	NBCA, 25% parent artery	Angio f/u: AEC, GOS score 5
4	19/M	PBI: missile wound	Battle explosion	Stupor/9	Contusion, swelling	Decompressive craniectomy, ICP monitoring	Screening	1	2nd-generation branch L MCA, 2 mm	NBCA, 33% parent artery	Angio f/u: AEC, GOS score 5
5	23/M	PBI: missile wound	Battle explosion	Stupor/10	Contusion, swelling	Decompressive craniectomy, ICP monitoring	Screening	2	2nd-generation branch L MCA, 2 mm	NBCA, 25% parent artery	CTA f/u: AEC, GOS score 4
6	21/M	PBI: missile wound	Battle explosion	Coma/7	Contusion, swelling	Decompressive craniectomy, ICP monitoring	Screening	2	2nd-generation branch R MCA, 3 mm	NBCA, 33% parent artery	Angio f/u: AEC, GOS score 4
7	29/M	PBI: missile wound	Battle explosion	Coma/5	Contusion, swelling	Decompressive craniectomy, ICP monitoring	Screening	2	2nd-generation branch R MCA, 2 mm	NBCA, 33% parent artery	Angio f/u: AEC, GOS score 4
8	20/M	PBI: GSW, transfrontal midline cross	GSW	Coma/7	Contusion, swelling	ICP monitoring, wound debridement	Screening	2	2nd-generation branch R MCA, 3 mm	NBCA, 33% parent artery	CTA f/u: AEC, GOS score 4
9	0.5/M	PBI: GSW, transfrontal midline cross	GSW	Coma/7	Contusion, swelling	ICP monitoring, wound debridement	Delayed ICH due to TICA rupture	6	2nd-generation branch R pericallosal, 3 mm	NBCA, 33% parent artery	Angio f/u: AEC, GOS score 5
10	13/M	Fall: closed trauma	Fall from height	Coma/6	Contusion, swelling, cranial base fracture, R hemispheric frontal and occipital infarctions 7 d post-trauma	ICP monitoring	R frontal, occipital infarctions	7	R ICA cavernous, 4 mm	Bare stent, coils, aneurysm obliteration	CTA f/u: AEC, GOS score 4

(continues)

TABLE 1. Continued

Patient no.	Age (yr)/sex	Type of trauma	Incident	GCS score at angio	CT findings	Immediate treatment	Indication for angio	Day angio	Aneurysm location, size	Repair	Outcome
11	22/F	MVA: closed trauma	MVA	Coma/10	SDH, EDH, multiple contusions, swelling, cranial base fracture	EDH evacuation, decompressive craniectomy	Exophthalmos, CN dysfunction, CT findings suggestive of CCF	21	L ICA cavernous, 12 mm	Covered stent graft, aneurysm obliteration	CTA f/u: AEC, GOS score 3
12	23/M	MVA: closed trauma	MVA	Normal/15	Contusion, swelling, cranial base fracture	ICP monitoring	Exophthalmos, CN dysfunction, CT findings suggestive of CCF	30	L ICA cavernous, 14 mm	Bare stent, coils; recanalization at angio f/u, ICA coil occlusion and EC-IC bypass	Asymptomatic GOS score 5
13	5/F	PBI: stab wound; transorbital-transcavernous	Stab with umbrella	Confusion/13	SAH	Wound debridement	SAH caused by TICA rupture	1	L ICA cavernous, 2 mm	Bare stent, coil, aneurysm obliteration	Angio f/u: AEC, GOS score 4

^a AEC, aneurysm excluded from circulation; angio, angiography; CCF, carotid-cavernous fistula; CN, cranial nerve; CT, computed tomography; CTA, computed tomographic angiography; EC-IC, extracranial-intracranial; EDH, epidural hematoma; f/u, follow-up; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; GSW, gunshot wound; ICA, internal carotid artery; ICH, intracranial hemorrhage; ICP, intracranial pressure; L, left; MCA, middle cerebral artery; MVA, motor vehicle accident; NBCA, *n*-butylcyanoacrylate; PBI, penetrating brain injury; R, right; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage; TICA, traumatic intracranial aneurysm.

Aneurysms were located on branches of the MCA in seven patients (53.8%), on pericallosal branches of the anterior cerebral artery (ACA) in two (15.4%), and on the ICA in four (30.8%).

Aneurysms ranged in diameter from 2 to 14 mm (mean, 4.08 mm; median, 2.0 mm). Lesions detected at screening angiography were all 2 to 3 mm, whereas the aneurysm diameter was 12 and 14 mm in Patients 11 and 12, respectively. A TICA was diagnosed in these patients at the time of transfer to our center, 21 and 30 days after being in motor vehicle accidents, when clinical symptoms suggestive of CCF developed (Table 1). Patient 11 was treated with a covered stent graft for aneurysm obliteration and achieved a Glasgow Outcome Scale (GOS) score of 3 after inpatient rehabilitation. Patient 12 was treated with a bare stent and coils and later underwent ICA coil occlusion and extracranial-intracranial bypass when recanalization was detected at follow-up angiography. He is now asymptomatic, with a GOS score of 5.

Endovascular treatment was performed immediately after diagnosis during the same angiography session in all 13 patients. Eight peripheral aneurysms (61.5%), including seven on MCA branches and one on a pericallosal ACA branch, were occluded with *n*-butylcyanoacrylate glue embolization (Patients 1 and 3–9). Poor neurological condition in these eight patients precluded performance of the amyntal test. Glue was injected selectively into the injured branch, achieving occlusion of both the aneurysm and its feeding branch without compromising any major vessels. In one patient, a 2-mm aneurysm on a right pericallosal branch was obliterated with coils (Patient 2).

Four ICA aneurysms (33.2%) were treated by stent implantation after complete angiographic evaluation of the circle of Willis in three patients and balloon test occlusion for assessment of collateral circulation in one. In three patients (23.1%), balloon-expandable bare stents were implanted, followed by coiling, as described previously (27). In one patient (7.7%, Patient 11) a balloon-expandable stent graft was used. All four patients tolerated the procedure well. Aneurysms were completely excluded in three patients (23.1%, Patients 10, 11, and 13), and subtotal occlusion was achieved in one (7.7%, Patient 12).

Due to their head injuries, all patients had preexisting neurological deficits and abnormalities on head CT; however, after endovascular surgery, no new infarction was seen on imaging studies and clinical assessment did not reveal any new neurological deficits in these patients. There was no procedure-related morbidity or mortality, and no patient developed delayed bleeding at a mean clinical follow-up of 2.6 years (range, 0.5–4.2 yr) after treatment. Groin complications were avoided in all patients who underwent angiography. All femoral artery punctures were performed under ultrasound

guidance to ensure single-wall puncture. After the procedure, all patients were managed with classic manual compression, compressive bandages, and 6-hour immobilization. Rehabilitation was indicated in all 13 trauma patients because of neurological deficits caused by their head injuries. Five patients achieved a GOS score of 5, seven reached a GOS score of 4, and one has stabilized with a GOS score of 3.

Follow-up angiography was performed 6 months after treatment in eight patients (61.5%). There were no angiographic abnormalities in seven patients who had peripheral aneurysms. The patient treated with a covered stent demonstrated an excellent angiographic result. The ICA was patent, and the aneurysm remained fully excluded (Patient 11). Two of three patients treated with bare stents and coils remained stable with no evidence of ICA stenosis or aneurysm recanalization at follow-up CTA (Patient 10) or angiography (Patient 13); however, aneurysmal recanalization was seen on the 6-month follow-up angiogram in the third patient (Patient 12). Endovascular coil occlusion of the ICA was then performed, followed by superficial temporal artery-MCA microvascular bypass. Five patients (38.5%) who refused angiographic follow-up were followed by periodic CTA with no evidence of recurrence.

ILLUSTRATIVE CASES

Patient 6

A 21-year-old man was admitted to the emergency department in poor condition after sustaining a penetrating head injury and multiple wounds in a combat explosion. He arrived in a deep coma (Glasgow Coma Scale score of 5), with brain matter extruding through the right temporal scalp wound. He was intubated in the emergency department. Cranial CT showed right frontotemporal hemorrhagic contusions with mass effect and multiple bone and metal fragments in the temporal lobe. Emergent surgical debridement and decompressive craniectomy were performed, and a left ventriculostomy was placed for intracranial pressure monitoring. The patient's neurological condition improved to a Glasgow Coma Scale score of 8. Because the missile trajectory passed through the right MCA candelabra, it was decided to perform cerebral angiography to rule out vascular injury. As soon as the patient was stabilized, the second day after trauma, cerebral angiography was performed, revealing a small traumatic pseudoaneurysm arising from a secondary branch of the right MCA (Fig. 1, A and B).

Endovascular Procedure

At the beginning of the procedure, the patient received a heparin bolus (6000 IU) that was flushed with saline and heparin (1 U heparin per milliliter of isotonic sodium chloride solution at a rate of 100 mL/h) with the use of a rotating hemostatic valve. A 6-French guiding catheter (Guider Softip; Boston Scientific, Boston, MA) was inserted via the femoral artery and positioned in the right cervical ICA. Selective angiography was performed, and the targeted MCA segment was outlined in multiple projections. The aneurysm diameter measured 3 mm. An Excelsior SL-10 microcatheter (Boston Scientific) over a tapered 0.010-in guidewire (Transend; Boston Scientific) was used to selectively microcatheterize the injured temporal branch. Selective angiography through the microcatheter showed the traumatic aneurysm with marked contrast stagnation (Fig. 1, C and D). The aneurysm and the

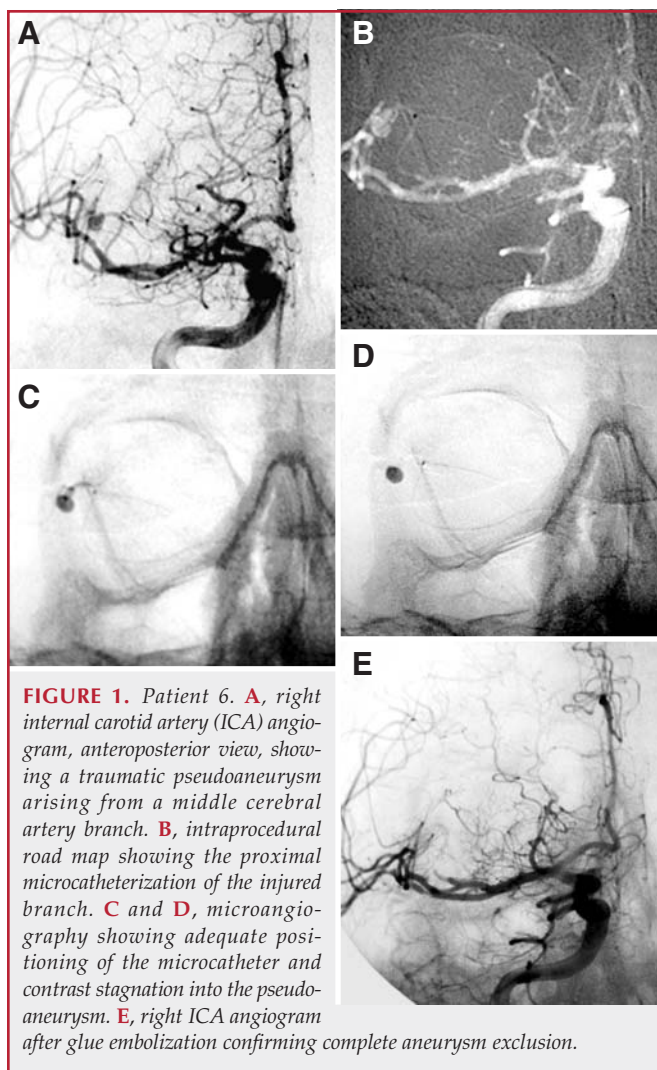


FIGURE 1. Patient 6. **A**, right internal carotid artery (ICA) angiogram, anteroposterior view, showing a traumatic pseudoaneurysm arising from a middle cerebral artery branch. **B**, intraprocedural road map showing the proximal microcatheterization of the injured branch. **C** and **D**, microangiography showing adequate positioning of the microcatheter and contrast stagnation into the pseudoaneurysm. **E**, right ICA angiogram after glue embolization confirming complete aneurysm exclusion.

second-generation parent vessel were completely occluded with 66% diluted *n*-butyl-2-cyanoacrylate glue (Histoacryl; B. Braun, Melsungen AB, Melsungen, Germany) and mixed iodized oil (Lipidoil; Byk Gulden, Konstanz, Germany) (Fig. 1, D and E). The patient continued to improve clinically and was discharged to a rehabilitation facility. Cranioplasty was performed 1 year later, and the patient now lives an independent life with minor cognitive and motor limitations (GOS score of 4).

Patient 11

A 22-year-old woman was admitted to the emergency department of another hospital in a coma after sustaining a severe head injury in a motor vehicle accident. She had left eye proptosis and epistaxis that was controlled with nasal packing. Admission CT revealed signs of cranial base fracture, acute epidural and subdural left-sided hematomas with midline shift, and diffuse subarachnoid hemorrhage. She was taken to the operating room immediately, where the epidural and subdural hematomas were evacuated. Because of cerebral edema, the bone flap was not repositioned, leaving a large craniectomy defect. She remained comatose for a long period with gradual improvement.

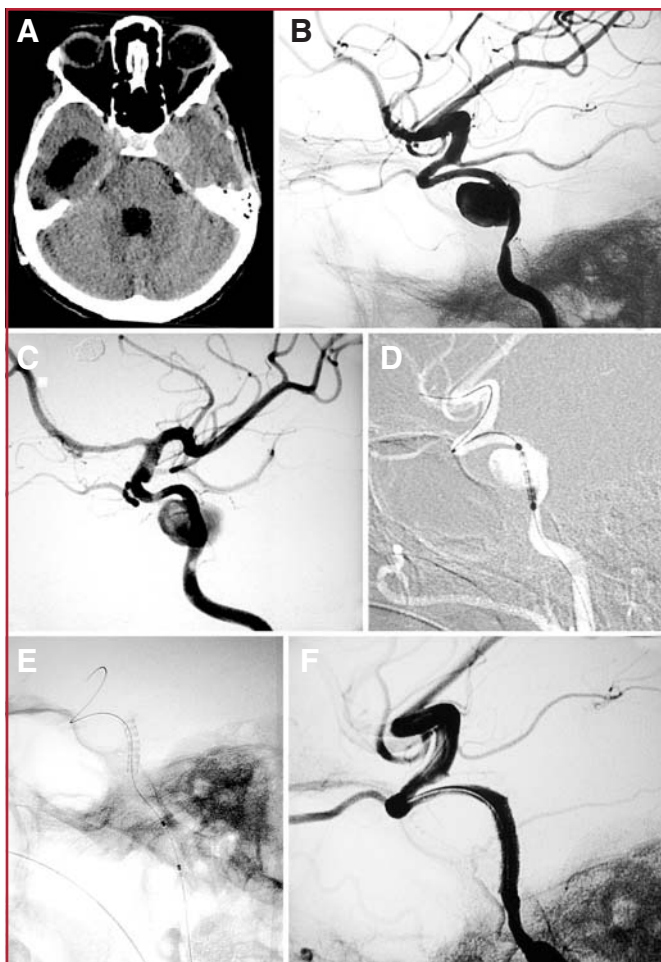


FIGURE 2. Patient 11. **A**, postenhanced computed tomography, axial cut, demonstrating a left intracavernous mass, suggestive of an aneurysm. **B** and **C**, lateral (**B**) and oblique (**C**) views of a right internal carotid artery (ICA) angiogram showing the traumatic cavernous aneurysm and the focal petrocavernous dissection, causing arterial stenosis. **D**, intraprocedural road map during stent graft positioning. **E**, radioscopic view of the implanted stent. **F**, lateral view of a right ICA angiogram showing complete exclusion of the traumatic aneurysm and repair of the proximal arterial dissection.

Repeat head CT revealed formation of an intracavernous mass, suggestive of aneurysm (Fig. 2A). As soon as she stabilized, she was transported to our hospital for endovascular treatment. On admission, she was stuporous, with prominent left-sided proptosis and ophthalmoplegia. Cerebral angiography revealed a focal dissection with stenosis of the petrocavernous segment of the ICA, followed by a large cavernous aneurysm (Fig. 2, B and C). Primary collateral circulation was not adequate for carotid sacrifice, and thus a reconstructive technique was chosen.

Endovascular Procedure

The procedure was performed with the patient under general anesthesia. At the start of the procedure, she received a heparin bolus (8000 IU) and an abciximab loading dose appropriate for her body weight. An 8-French guiding catheter (Guider Softip) was inserted via the

femoral artery and positioned in the left cervical ICA. The targeted carotid segment was outlined in multiple projections followed by rotational three-dimensional angiography. The aneurysm diameter measured 12 mm and presented a wide neck; the parent vessel diameter was 3.2 mm (Fig. 2, B and C). An Excel microcatheter (Boston Scientific) over a tapered 0.014-in Transend guidewire was used to selectively catheterize the distal MCA. The microcatheter was exchanged for a balloon-expandable covered stent (Jomed; Abbott Laboratories, Abbott Park, IL). The stent was centered at the aneurysm opening but was also intended to cover the proximal dissection (Fig. 2, D and E). After stent placement, the aneurysm was completely excluded from the circulation, the dissection was repaired, and the arterial stenosis was corrected (Fig. 2F). The patient's postoperative course was uneventful, and she demonstrated gradual improvement in awareness and cognitive function. She was discharged to a rehabilitation facility, where her proptosis and ophthalmoplegia resolved with recovery of visual function. A ventriculoperitoneal shunt was later inserted for management of posttraumatic hydrocephalus. Four months after treatment, she remains with a patent ICA and no signs of aneurysm recanalization on follow-up CTA. No morbidity resulted from the endovascular treatment, but the patient has significant limitations to daily function (GOS scale of 3) because of sequelae of her traumatic injury. She is awaiting cranioplasty.

DISCUSSION

A TICA is a rare lesion, constituting 0.15 to 0.40% of intracranial aneurysms (38). Early diagnosis of a TICA can be challenging with CT (19, 26, 38), which is now the preferred screening modality for TBI patients (4, 35). Mortality as high as 50% as a result of rupture during the first 1 to 3 weeks in untreated lesions has been reported (3, 7, 14, 17, 18, 22, 24, 38). Because some portion of TBI patients do not have an appropriate imaging evaluation, the actual rate of hemorrhage in TICAs is most likely unknown. Surgical treatment may be complicated because of the nature of the lesion as well as the extent of traumatic injuries (3, 15, 38).

We present our results of early angiographic diagnostics and endovascular treatment in the same session for 13 cases of TICAs. Between June 2002 and December 2006, we performed angiography as a screening examination or because of clinical indications in 34 TBI patients, including 25 with PBIs and nine with closed head injuries. We detected 13 TICAs, 10 in cases of PBI (gunshot wound, shrapnel injuries, stab wound) and three in blunt head-injured patients with cranial base fractures.

Our series includes patients who were in both good and difficult clinical conditions, presenting with Glasgow Coma Scale scores ranging from 5 to 15. Their TICAs were of varying mechanisms and were located at the ICA as well as peripheral branches of the MCA and ACA. What is common to all of these cases was awareness of possible aneurysm formation, angiographic diagnostics soon after arrival at our medical center, and immediate endovascular treatment.

Based on findings from early posttraumatic angiography, TICAs were diagnosed and treated before symptoms appeared in 8 (61.5%) of these 13 patients and before rupture in 11 (84.6%). We had no procedure-related morbidity or mortality. Twelve patients (92.3%) had achieved GOS scores of 4 to 5 an

average of 2.6 years after aneurysm occlusion. Early treatment averted the possibility of disastrous consequences and most likely contributed to good outcomes in some of these patients.

A TICA was diagnosed only after the left ICA aneurysm had grown to 12 mm in one patient who was transferred to our medical center with clinical suspicion of CCF 21 days after a motor vehicle accident. This patient's endovascular treatment was successful with no procedure-related morbidity, but she only reached a GOS score of 3 because of other sequelae of her traumatic injuries. A second patient with clinical signs of CCF and with CT evidence of a cranial base fracture was also diagnosed with a TICA after transfer to our medical center 30 days after injury. Angiography revealed a 14-mm left ICA aneurysm. This patient has been fortunate to reach a GOS scale of 5; however, this large aneurysm recanalized after initial occlusion with a bare stent and coils. Retreatment with ICA coil occlusion and extracranial-intracranial bypass provided a good outcome.

Epidemiology and Cause

The true incidence of traumatic intracranial aneurysms is unknown. In the few studies in which a large number of trauma patients were screened with angiography, the reported incidence ranges from 3.2 to 3.6% (1, 26) to 5.7% (3), and even 42% (19). The nature of the trauma and the timing of angiography also vary in these studies.

Although several authors have discussed the causes and classification of posttraumatic aneurysms (3, 5, 7, 8, 14, 24, 29, 38), the mechanisms of formation in various types of traumatic injury are poorly understood. A TICA is often related to blunt head injury, and in some reports the incidence is higher in pediatric than adult patients (7, 24). Conversely, there are major series describing TICAs in adult patients resulting from missile injuries and gunshot wounds (1–3, 6, 16, 19, 26) or transcranial stab wounds (22). Most probably, there are different TICA subentities.

Blunt trauma occurs frequently in pediatric patients. Because the cranium is softer and the cerebral content may be more mobile in children, shearing forces may cause greater harm to more delicate and vulnerable vessels in this population (7, 9, 15, 39). There are no widely accepted screening recommendations for this patient contingent. Angiography is recommended if intracranial hemorrhage develops in the late posttraumatic period (4, 26, 32, 39) and after massive or delayed epistaxis (38).

Another accepted mechanism for TICAs is the development of an intracavernous aneurysm after a cranial base fracture, similar to traumatic CCF development (24, 29, 38). We present three patients with TICAs resulting from such a mechanism (Patients 10–12). Although diagnostic angiography is not indicated in all patients with cranial base fractures, special attention is appropriate when fractures involve the area of the sphenoid sinus and carotid canal (33, 38).

Patients with penetrating missile and gunshot wounds comprise a separate category. The incidence of TICAs in this subgroup is controversial (2, 4, 6, 19, 26), but there is agreement that the most probable mechanism is direct injury to intracra-

nial vessels by fragments from missiles, bullets, or bone. We have seen an increasing number of civilian and combat casualties in recent years, and based on our experience, we now perform screening angiography in patients with a missile tract passing through the MCA candelabra and crossing the midline structures. Others have reported similar angiographic screening criteria in head-injured patients (1, 3, 4, 6, 15, 38). These cases represent the majority of TICAs in our series: 9 (69.2%) of 13 patients. Screening angiography is performed on a semi-emergent basis, after immediate treatment of life-threatening complications according to Advanced Trauma Life Support guidelines; in a significant proportion of cases, it is performed before aneurysmal bleeding occurs.

Most traumatic aneurysms can be defined as false aneurysms resulting from a full-thickness arterial tear (15, 16, 24, 35, 36, 38), with high bleeding and rebleeding rates. False aneurysms or pseudoaneurysms are, in fact, a cavity of encapsulated hematoma communicating with the arterial lumen. It is noteworthy that pseudoaneurysms show delayed emptying on angiography (Fig. 1, C and D) (15, 16, 29).

Presentation and Management

In the pre-CT era, angiography was used for first-line diagnosis in head-injured patients, making early identification of TICAs likely. However, aneurysmal injury is easily overlooked when CT is the primary screening tool in trauma patients, especially when the surgeon's attention is focused on other traumatic injuries (19, 29). Clinical symptoms, including late deterioration due to unexplained intracranial hemorrhage, neurological deterioration ranging from headache and lethargy to coma, massive epistaxis, and cranial nerve palsy, are often the first indication of a TICA today (15, 24).

CTA has been suggested for the diagnosis of aneurysms (4, 12, 20, 34, 40); however, we prefer to use catheter angiography. CTA has limited sensitivity for detection of small (≤ 3 mm) aneurysms (34, 40). In addition, CTA requires administration of a 80- to 100-mL bolus of intravenous contrast, which poses risks in trauma patients who may have compromised renal function. For patients at high risk of a TICA who have negative findings on CTA, we would proceed to angiography for confirmation, with additional use of contrast. When a TICA is found on CTA, we would also go on to angiography for endovascular treatment in most patients. Thus, for the initial screening examination, we find it preferable to rely on catheter angiography, the "gold standard," with its superior spatial and contrast resolution, lack of interference from bony structures, and the possibility to perform endovascular treatment in the same procedure.

The timing of angiography is also subject to debate. Isolated cases of normal initial angiography with detection of traumatic aneurysm at a subsequent study are reported, and some authors suggest that first angiography should be performed approximately 10 days to 2 weeks after injury to avoid missed diagnoses (2, 3, 22, 24). However, other authors have reported that TICAs may manifest on angiography as early as 2 hours after injury (16) and that 50% of ruptures occur within 1 (38) to

3 weeks after primary injury (14); thus, diagnostic angiography, when indicated, should be performed soon after injury (6, 19, 26, 38). Our experience supports this approach. We performed repeat angiography 2 weeks to 1 month later in 15 (40.0%) of 25 PBI patients at risk of a TICA after the first study was negative, and we found no new aneurysms at the second study.

Fleischer et al. (14) reported that TICA patients who were managed conservatively presented a much higher mortality rate than patients managed surgically (41% versus 18%), and other reports from case series also report mortality as high as 50% in untreated TICA patients (1, 11, 17, 21, 29, 31). Although there is consensus that aggressive treatment is warranted, some disagreement lingers on the subject of timing. One study (3) found that as many as 19% of TICAs spontaneously disappear and recommended angiographic monitoring with surgical removal only when lesions show signs of growth. However, the balance of opinion is that high mortality associated with untreated aneurysms mandates urgent surgical or endovascular treatment (3, 7, 14, 17, 18, 38). Repeat angiography is recommended when a significant delay occurs between diagnosis and intervention (14, 16).

TICAs present a surgical challenge because of their unusual locations, thin walls, and poorly defined necks (3, 15, 38). Levy et al. (26) suggest that aneurysms of traumatic origin exhibit a greater propensity for intraoperative rupture than congenital lesions because of the presence of dense arachnoid adhesions. As most TICAs are pseudoaneurysms, clipping without sacrifice of the parent artery may not be possible (3, 16, 25). In these cases, trapping or excision of the aneurysm has become the accepted technique (7, 17, 18, 39). Surgery is further complicated because many patients have multiple cerebral and other injuries and are in poor clinical condition. Therefore, surgical treatment is associated with significant morbidity and a reported mortality of 18 to 29% (14, 16, 26, 29).

For these patients, endovascular approaches have emerged as valid therapeutic alternatives (10, 13, 18, 23, 28, 30, 38). The endovascular route uses blood vessels as channels to reach the aneurysm, providing a less invasive approach than open surgery. This technique avoids craniotomy, brain retraction, and cerebral dissection, as well as external manipulation of the vasculature during surgery. Thus, other complications related to craniotomy, such as epilepsy or wound infection, are avoided. Early reports of outcomes after endovascular treatment of TICAs show no mortality and no or very little morbidity (38). It should be noted that these reports have been published in recent years and emanate from leading academic centers, whereas reports of surgical outcomes are older and represent a broader spectrum of clinical environments, making direct comparison of outcomes difficult.

Ideally, the goal of endovascular therapy is to achieve complete aneurysm occlusion with parent artery preservation. On occasion, the diameter of the parent vessel may be too narrow to allow passage of a microcatheter to the aneurysm, the configuration of the aneurysm may not be amenable to coil placement, or conditions may be encountered that make occlusion of the parent vessel the preferred treatment. Coils and liquid

embolic agents have been used for this purpose. Occlusion is a decision that is always made with reluctance, and only after weighing all the alternatives. However, we have not seen new postprocedural neurological deficits or new infarctions in TICA patients when occlusion of the parent vessel was the only available treatment option. Surgical management may also require occlusion of the parent vessel in many of these patients because aneurysms of traumatic origin often lack a clear neck to enable safe and effective clipping (1–3, 14).

Coils are preferred in peripheral aneurysms that arise from vessels of a caliber larger than 1.5 mm, and it has to be remembered that the smallest available detachable coil is 2 mm in diameter, thus placing these coils in a 1-mm artery may not be safe or feasible. Although glue is less predictable than coils for embolization, it can penetrate the aneurysm and effectively occlude the parent vessel, abolishing the chance of undesired retrograde filling of the aneurysm by collaterals.

In our series of 13 TICAs, eight patients had peripheral aneurysms arising from small MCA or ACA branches that cannot be selectively occluded by coils. Endovascular treatment was performed with glue obliteration of the aneurysm together with its feeding artery in all seven patients in whom the TICA was located in tertiary branches of the MCA, and in one patient in whom the aneurysm was found on a second-generation ACA branch.

Although the current treatment of peripherally located traumatic aneurysms often involves endovascular occlusion of the parent artery, in selected cases, primary coiling may allow aneurysm exclusion with parent vessel preservation (10). In this series, coils were used in one TICA of a pericallosal artery with favorable aneurysm anatomy (i.e., high dome-to-neck ratio), without incorporation of the parent vessels. The embolization technique in this case did not differ from the technique used for embolization of saccular aneurysms (37).

In comparison with peripheral aneurysms, intracavernous ICA lesions are technically more challenging with both open surgery and endovascular techniques. In these patients, collateral circulation must be evaluated with complete angiographic assessment of the circle of Willis and possibly with balloon test occlusion in cases in which ICA sacrifice is contemplated. Bare stents or stent grafts are used for exclusion of these aneurysms from flow. In one patient in this series (Patient 12), a bare stent with coiling did not prevent aneurysm recanalization. In a second procedure, we occluded the ICA and performed a microvascular bypass, achieving permanent aneurysm exclusion.

In the trauma setting, careful patient selection must precede a decision to manage vascular injuries with stent placement. Prolonged antithrombotic therapy is mandatory after stent placement, and this therapy may interfere with the performance of other surgical procedures that these patients usually require. During the endovascular procedure, the most convenient antithrombotic treatment is abciximab, the single available intravenous agent. After the procedure, it may be substituted by parenterally administered aspirin or clopidogrel (Plavix; Bristol-Myers Squibb/Sanofi Pharmaceuticals, New York, NY).

Based on discussions in the literature, several subsets of trauma patients appear to be at highest risk of developing a TICA. We find that patients with gunshot, shrapnel, and stab wounds and those with blunt head injury associated with cranial base fracture are at increased risk of developing a TICA and are thus candidates for early angiographic screening. We believe that screening is particularly important for patients with any type of penetrating head injury when the tract courses through areas with a high density of cerebral vasculature, such as sylvian and interhemispheric fissures. Given the accessibility and safety of angiography in the armamentarium of the trauma center, we advocate an activist approach, with early angiographic screening of trauma patients with injuries such as those described here. Eleven (84.6%) of 13 aneurysms in our series were obliterated before they bled, including eight that were treated before they became symptomatic, preventing disastrous sequelae and most likely providing improved outcomes.

There is still much argument regarding what type of surgical procedure is optimal. In our series, 12 of 13 patients were treated exclusively by means of endovascular techniques, using glue, coiling, or stents. In one patient, ICA occlusion along with extracranial-intracranial bypass was needed after recanalization. We did not have any serious complications related to the procedures. We find that the endovascular approach may have advantages over open surgery. The fact that treatment can be performed as a continuation of the diagnostic procedure, in the same session, is an added advantage.

CONCLUSION

We recommend early angiographic diagnosis and endovascular treatment of TICAs. In our series, excellent immediate and midterm outcomes were obtained after endovascular treatment of 13 TICAs using multiple techniques (coiling, glue injection, and expandable bare and covered stents). We conclude that the endovascular approach offers a valuable alternative to surgery for the treatment of TICAs. Different techniques can be selected for specific cases allowing the early treatment of TICAs with excellent results.

Disclosure

None of the authors has any financial interest or other conflict of interest related to any company whose products are mentioned in this article.

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COMMENTS

Cohen et al. related their experience in the management of 13 patients with traumatic intracranial aneurysms (TICA). As they correctly noted, a multitude of endovascular techniques are frequently required for the treatment of these often complex lesions. These lesions can affect not only arteries in proximity to the cranial base but also arteries in the distal cerebral vascular tree. For this reason, endovascular techniques are often uniquely suited for the management of these lesions.

For these distally located traumatic aneurysms, parent vessel sacrifice either via glue or coil embolization is often required for definitive treatment. Nonetheless, these patients frequently are badly injured and already demonstrate deficits related to the particular arterial injury. For this reason, parent vessel sacrifice often does not produce any new neurological deficit after treatment. More proximal lesions may be difficult to treat in a deconstructive fashion and can require reconstruction with either stent-supported coiling or covered stenting. Cohen et al. articulately describe their endovascular approach and delineate a screening process whereby all patients with suspicious traumatic intracranial injuries are assessed for aneurysms.

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Cohen et al. bring an interesting contribution to the neurointerventional literature by presenting an article on endovascular therapeutic management of posttraumatic intracranial aneurysms and pseudoaneurysms. Both of these need to be treated as an emergency owing to their high incidence of rupturing with catastrophic clinical consequences. Cohen et al. showed in-depth knowledge of different delivery systems and embolic materials and explained their decision-making process regarding the selection of endovascular

devices by evaluating location, size, and regional vascular anatomy related to the aneurysm.

This type of posttraumatic intracranial aneurysm is seldom seen in the civilian population unexposed to war but when identified it should be treated urgently. Surgical management of these types of aneurysms should be only considered when the endovascular approach is not indicated. Surgical manipulation becomes a very difficult task in patients with edematous brain resulting from trauma. Surgical clipping of a traumatic aneurysm carries a high incidence of aneurysm rupture owing to traumatic dissection of the arterial wall. Surgical identification of peripheral aneurysms can also be a very challenging task. Sometimes, the involvement of arteries supplying eloquent brain areas requires surgical bypass before surgical or endovascular sacrifice of the parent artery.

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Cohen et al. presented a series of 13 TICAs encountered at a single institution over a 4.5-year period. The aneurysms varied in location (proximal versus peripheral) and causative mechanism (blunt trauma with cranial base fracture, gunshot wounds, shrapnel injury, stab wounds, and iatrogenic injuries from surgery). Whereas some came to attention because of hemorrhage, others were detected on the basis of angiographic screening alone. The variety of treatments rendered (endosaccular coil occlusion, parent vessel sacrifice with liquid embolic agents, covered stent deployment, and others) showcases the versatility of endovascular strategies for the management of TICAs and highlights the importance of tailoring care to specific clinical situations.

Cohen et al. provided compelling arguments for angiographic surveillance in selected patients with head trauma, particularly when the trajectory of a penetrating injury traverses the sylvian or interhemispheric fissures. In this series, TICAs in eight patients were detected on the basis of vigilant monitoring alone, without any overt signs of the aneurysm. What is not reported, however, is the number of angiograms that revealed no abnormalities. The diagnostic yield of this practice, therefore, remains unknown. Furthermore, the optimal timing of angiography is unclear. In this series, all studies were done 1 to 7 days after injury, but it is possible that additional TICAs would be discovered with more delayed imaging. Thus, the true incidence is unknown. Unfortunately, computed tomographic angiography may not sufficiently evaluate the distal vasculature to exclude a small TICA or pseudoaneurysm; therefore, invasive catheter angiography is still required.

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Cohen et al. described a prospective series of 13 patients who underwent prompt endovascular treatment of TICAs, most of which were caused by deeply penetrating missile injuries. Two main subgroups of lesions requiring different treatments emerged: proximal lesions, which may be obliterated with preservation of the parent vessel, and lesions distal to the first cerebral artery segments, which usually require vessel sacrifice by liquid embolic agents. Using this endovascular approach, they reported zero mortality and commendably low levels of morbidity with only a single patient being functionally dependent at a mean 2.6 years of follow-up. Their results are impressive, given the natural history of these lesions without intervention. Longer-term follow-up of these treated lesions is also warranted.

Issues that we think should be kept in mind when dealing with these lesions are the following: 1) Occlusion of a pseudoaneurysm without parent artery sacrifice carries higher risk than coiling a true aneurysm and may be associated with higher rehemorrhage rates. 2) When feasible, parent artery sacrifice is the most definitive treatment for these lesions. Unfortunately, this is not always feasible. 3) Balloon test occlusion and possible bypass should be considered if parent artery sacrifice would result in clinically significant infarction. 4) Stents (especially low porosity or covered stents) may play an increasingly important role in the management of this condition. Rapid advances in stent technology may eventually make it feasible to reconstruct the vessel intraluminally and avoid vessel sacrifice. 5) Imaging follow-up is necessary to rule out potentially dangerous recanalization.

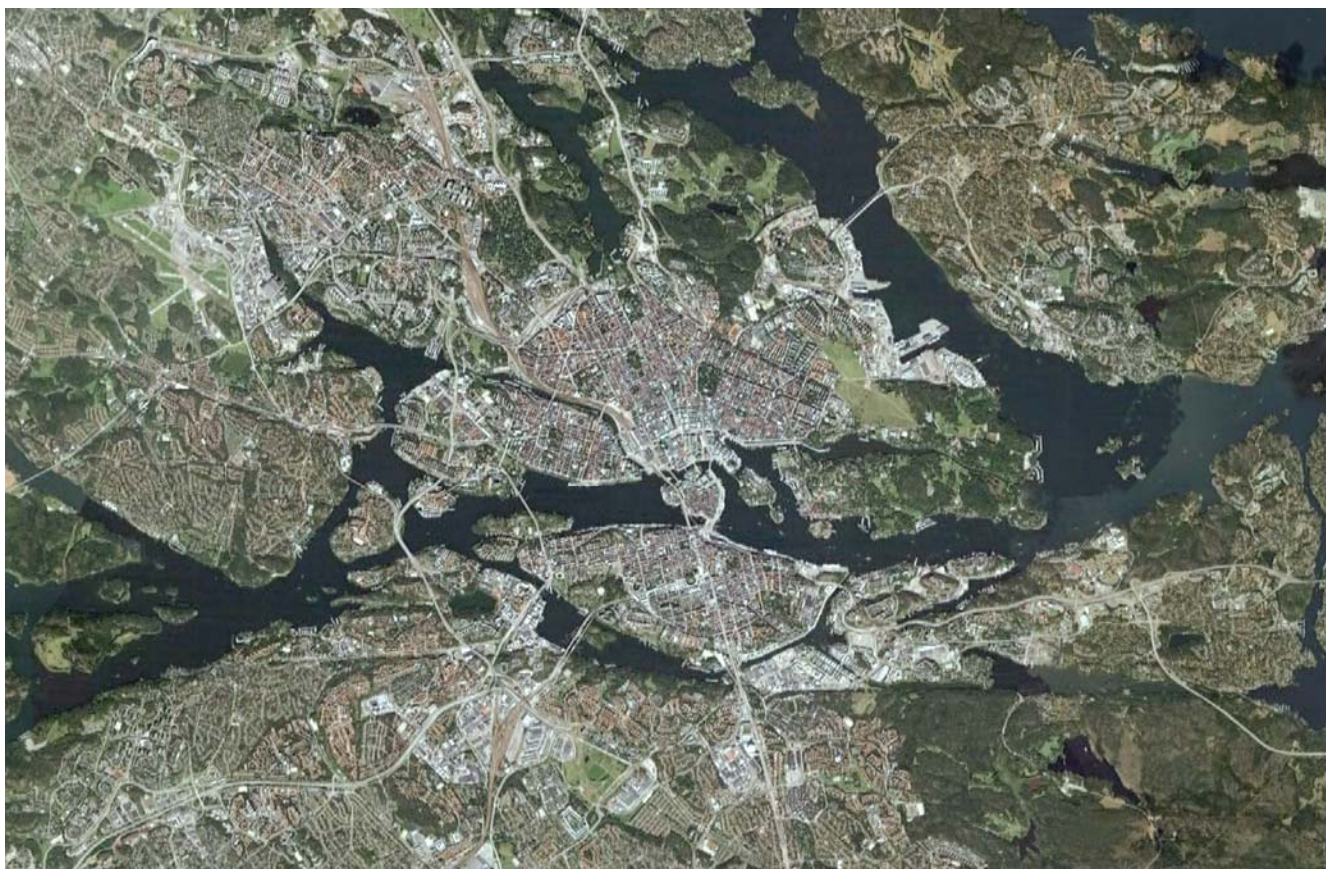
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The combination of recent advances in endovascular therapy with the unfortunate situation of frequent combat casualties from the Gulf War and other campaigns has made TICAs an increasingly significant topic. The importance of the current work is to help the reader

better understand the incidence of TICAs in the population of patients with traumatic brain injury, appropriate screening methods, and treatment options. On the basis of their earlier experience and reports within the literature, Cohen et al. adopted a policy of performing screening angiography on traumatic brain injured patients with "cranial base fractures in the area of the carotid canal" or penetrating injuries to the "pterional area . . . , MCA [middle cerebral artery] canelabra, [or] crossing midline structures." This report describes the results for 34 patients who met these criteria over a 4.5-year period. Thirteen TICAs were identified from this relatively small group, and this prevalence highlights the importance of screening angiography for patients with the above-mentioned injuries. Endovascular treatment was done at the time of diagnosis and required a broad range of techniques. By the time of publication, aneurysm regrowth had occurred in one patient, requiring recoiling and surgical bypass.

Cohen et al. have contributed to our understanding of TICAs by analyzing their experience with this difficult vascular pathological lesion. We look forward to their long-term follow-up of these patients. Perhaps in the future, early identification and treatment will significantly reduce morbidity and mortality from this condition.

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LANGUAGE REORGANIZATION IN APHASICS: AN ELECTRICAL STIMULATION MAPPING INVESTIGATION

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OBJECTIVE: The purpose of this investigation was to determine whether clinical speech deficits after brain injury are associated with functional speech reorganization.

METHODS: Across an 18-year interval, 11 patients with mild-to-moderate speech deficits underwent language mapping as part of their treatment for intractable epilepsy. These "aphasics" were compared with 14 matched "control" patients with normal speech who also were undergoing epilepsy surgery. Neuroanatomic data were compared with quantitative language profiles and clinical variables.

RESULTS: Cortical lesions were evident near speech areas in all aphasia cases. As expected, aphasic and control patients were distinguished by quantitative language profiles. The groups were further distinguished by the anatomic distribution of their speech sites. A significantly greater proportion of frontal speech sites was found in patients with previous brain injury, consistent with frontal site recruitment. The degree of frontal recruitment varied as a function of patient age at the time of initial brain injury; earlier injuries were associated with greater recruitment. The overall number of speech sites remained the same after injury. Significant associations were found between the number of the speech sites, naming fluency, and the lesion proximity in the temporal lobe.

CONCLUSION: Language maps in aphasics demonstrated evidence for age-dependent functional recruitment in the frontal, but not temporal, lobe. The proximity of cortical lesions to temporal speech sites predicted the overall extent of temporal lobe speech representation and performance on naming fluency. These findings have implications for neurosurgical planning in patients with preoperative speech deficits.

KEY WORDS: Aphasia, Dominant hemisphere, Language mapping, Plasticity

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A clear understanding of the anatomic location of essential speech sites is critical if one is to confidently avoid postoperative speech deficits when performing dominant hemisphere surgery. Electrical stimulation mapping has become a standard technique to identify those sites in individual patients. With the use of this technique, the organization of speech sites has been well characterized in adults (43) and children (42). However, little is known about how language organization is affected by damage to eloquent speech areas (5, 30, 54). Such information is valuable for neurosurgeons who encounter patients with preoperative language deficits.

ABBREVIATION: COWA, Controlled Oral Word Association Test

Recent functional imaging and electrophysiological studies suggest that language organization is altered in response to lesions that damage speech areas in adults. Taken as evidence for functional reorganization, cortical language activity may increase locally around the lesion periphery (32) or may shift to more distant areas in the frontal (12, 50, 51) or temporal lobes (1). In addition to the location of language-related cortical activity, the temporal patterns of electrographic language activity also change in response to lesions (20, 26, 49). Such functional changes have been attributed to treatment during the recovery phase of aphasia (13) and may portend a better prognosis (28). These findings are reminiscent of the functional reorganization observed after injury to the central nerv-

ous system in a number of animal models (3, 4, 8, 21, 33, 34, 37–39, 58).

In the present investigation, we sought to compare speech organization between patients with and without preoperative speech deficits. To the best of our knowledge, this is the first published series to compare stimulation mapping between patients with preoperative speech deficits and those with normal speech. We report findings that are consistent with theories of functional reorganization in the frontal lobe after cortical damage. We found no evidence of functional reorganization in the temporal lobe, despite the fact that all patients had some degree of temporal lobe damage. However, significant relationships were found in the temporal lobe among the number of the speech sites, naming fluency, and the proximity of the cortical lesion. These findings have important implications for those who study the functional organization of the dominant hemisphere and are discussed in light of cerebral plasticity literature.

PATIENTS AND METHODS

Patients

The study population in this investigation consisted of a series of patients presenting with clinical language deficits between January 1, 1985, and December 31, 2003. All patients in this series underwent surgical procedures for the treatment of epilepsy or lesions associated with seizures. Patients with obvious language deficits documented during a preoperative neurological examination performed by the senior author (GAO) were considered “aphasic.” The majority of patients demonstrated expressive aphasia symptoms, although patients varied in the degree and type of specific language deficits. To be enrolled in this investigation, the following inclusion criteria were applied: 1) patients must have been free from preexisting language deficits before a defined neurological insult; 2) the timing and type of neurological insult must have been documented; 3) patients must have completed comprehensive preoperative neuropsychological evaluations, including quantitative language assessments; and 4) patients must have sufficient language function to permit reliable intraoperative language mapping (i.e., a confrontational naming baseline performance rate of greater than 70%). Patients who did not meet these criteria were excluded.

The aphasic population was compared with a “control” population matched on operative age, sex, language dominance, and side of surgery. In all cases, the operative indication was medically intractable epilepsy secondary to mesial temporal lobe sclerosis. Control patients demonstrated no evidence of preoperative language deficits, nor were cortical lesions present on preoperative imaging. The University of Washington Human Subjects Division approved Confidentiality Agreements for the use of clinical data presented in this research investigation.

Neuropsychological Testing

As part of the preoperative evaluation for epilepsy surgery at the University of Washington, patients undergo formal neuropsychological evaluations performed by licensed academic neuropsychologists (DLD, CBD). Patients undergo a thorough, well-validated battery of neuropsychological measures. For the purposes of this study, we were most interested in tests tapping general intellectual functioning and language performance. General intellectual functioning was assessed with the use of

the Wechsler Adult Intelligence Scale (Revised or Third Edition) (55, 56). Language assessment included the Aphasia Screening Test from the Halstead-Reitan Neuropsychological Battery (27), the Controlled Oral Word Association Test (COWA) (7), and a standard semantic fluency paradigm (i.e., Animal Naming) (6, 48). The Aphasia Screening Test is purported to be the most widely used of the aphasia tests (48) and includes a range of test items chosen to reflect most basic language functions. The COWA and the animal-naming task represent measures of generative verbal fluency. The COWA is a letter fluency task that requires the patient to state as many words as possible beginning with a given letter of the alphabet in a specified time period (i.e., three 1-min trials with different letters). The Animal Naming task is a semantic fluency paradigm requiring the patient to generate exemplars of a specified category within an allotted time span. Performance below the published normative ranges signals the presence of a language disturbance. These tests were used to confirm the clinical suspicion of language deficits.

Electrical Stimulation Mapping

Mapping of speech cortex was performed extraoperatively with subdural grids or intraoperatively during craniotomy with the patient awake. The standardized confrontation naming task was identical in both instances. All aphasic patients (100%) and 8 (57%) of 14 control patients underwent extraoperative mapping. Extraoperative mapping consisted of first identifying rolandic cortex, followed by language mapping. During language mapping, the threshold for afterdischarges was determined for each electrode pair (separated by 1 cm), and stimulus intensities were adjusted to the maximal intensity that did not produce afterdischarges. These currents typically ranged from 1.5 to 10 mA (40) for both extraoperative and intraoperative mapping techniques. Stimulation consisted of 2.5-millisecond biphasic square-wave pulses in 4-second trains at a frequency of 60 Hz. For extraoperative mapping, standard 64-contact electrode grid (1 cm inter-electrode distance) centered on the sylvian fissure covered areas of suspected language sites and seizure onsets. Electrode selection commenced in pseudo-random order, provided that each contact was stimulated at least once before any individual contact was stimulated a second time, and provided that no two adjacent sites were stimulated back-to-back. This was done to minimize the effects of stimulating the same cortical area multiple times in succession. All stimulated contacts were within the limits of the craniotomy. The location of speech sites was documented and labeled at the time of grid removal with sterile numbered markers. The location of these sites was then photographed.

Six (43%) of 14 control patients underwent intraoperative mapping. The intraoperative stimulation mapping technique for the localization of essential language cortices has been described in detail previously (41, 43). In brief, initial anesthesia (propofol) was administered to allow a large frontotemporoparietal craniotomy to be fashioned. Local analgesics (0.5% lidocaine and 0.25% bupivacaine [Marcaine; AstraZeneca Pharmaceuticals, Wilmington, DE]) were applied along the scalp and dural incisions for patient comfort upon waking. Once the cortex was exposed, anesthesia was discontinued, and the patient was allowed to awaken fully. No other medications were administered until after stimulation mapping, which was usually performed 3 to 4 hours after the operation was begun. Rolandic cortex was identified by stimulation, and the threshold for afterdischarges was established with electrocorticography.

Language mapping in the exposed cortex followed. Sites for stimulation were selected to sample the full extent of the cortical exposure in approximately 1-cm intervals and were labeled with sterile numbered tags. Sites were stimulated in pseudorandom fashion as with extraoperative mapping. Stimulation was delivered from a constant-current stimulator with 1-mm ball-tip bipolar electrodes separated by 5 mm. Four-second trains were applied, using the largest current that did not

evoke afterdischarges. The stimulation sites, averaging 22.8 ± 9.9 sites per patient, were identified with sterile numbered markers, and the location of these markers was recorded photographically.

The language paradigm consisted of the standard confrontation object naming paradigm (43). Two separate raters recorded the patients' responses on score sheets. In addition, patient responses were recorded on audiotape. Errors consisted of anomic episodes, the production of nonsense words, and the use of incorrect object names (e.g., using the word "fork" to name a "spoon"). Baseline error rates for each patient were calculated during nonstimulation trials from the ratio of incorrect to total responses. Each stimulation site was tested at least three times during baseline and test conditions; all sites were tested at least once before repeating any individual site, and no site was tested twice in succession. To make statistical inferences reliable, patients had to demonstrate at least 70% accuracy during baseline testing. Baseline error rates were statistically compared with the stimulation-induced error rate for each anatomic site by use of the Fisher's exact test. The Fisher's exact test was chosen because it makes no assumptions about the expected proportion of correct or incorrect responses. The χ^2 test was used to compare group and lobe differences. Essential speech sites were those where electrical stimulation produced reliable, statistically significant differences in error rate during confrontational naming when compared with the patient's baseline naming performance. Objects that could not be named during any trial (including at least three baseline trials) were omitted from analysis.

Statistical Analysis

All patient data were coded with a four-digit patient number. A third, blinded investigator reviewed each audiotape and verified score sheet accuracy, without knowledge of preoperative language abilities. Stimulation mapping data and neuropsychological scores were then collated into a common spreadsheet. Statistical analyses were performed with SPSS software (SPSS, Inc., Chicago, IL). Sites statistically associated with stimulation-induced errors were then identified on intraoperative photographs. The location of these sites was anatomically categorized on the basis of their relationship to the major hemispheric fissures and veins. When obvious cortical lesions were evident, the relationship between the nearest lesion margin and the closest essential language site was measured.

RESULTS

Patient Demographics

Aphasic and control populations were matched on clinical demographics (Table 1). Eighteen patients were retrospectively identified with preoperative language deficits. Of these, 11 satisfied the inclusion criteria outlined previously. Seven patients performed at less than the minimum necessary to undergo reliable language mapping (i.e., greater than 30% error rate on object naming). The study group thus consisted of eight male and three female originally right-handed patients. Their mean age at the time of operation was 35 ± 7 years. Aphasic patients had a variety of speech deficits (Table 2). Four of the 11 patients exhibited purely expressive aphasia, characterized by impaired speech fluency and naming deficits with intact comprehension. Two of these patients retained some repetition capability (Table 2). Two patients experienced deficits in naming and milder deficits in generative fluency tasks and preserved repetition. These patients were considered anomic aphasics. Five

TABLE 1. Patient clinical variables^a

Clinical variable	Aphasia (mean $\pm$ SD)	Control (mean $\pm$ SD)	t score	P value
Age (yr) at operation	34 $\pm$ 7.1	35.1 $\pm$ 9.7	-0.168	NS
Age (yr) at brain injury	23.9 $\pm$ 10	18.3 $\pm$ 10.1	1.351	NS
Symptom duration (yr)	10.0 $\pm$ 7.9	14.2 $\pm$ 10.7	-1.125	NS
Education (grades)	12.0 $\pm$ 2.1	12.8 $\pm$ 1.9	-1.047	NS

^a There were no differences between aphasics and matched control patients on demographic variables. Means and standard deviations (SD) shown. NS, not statistically significant.

patients exhibited deficits in semantic fluency, naming, and the rate of speech. Two of these patients also had deficits in articulation and literacy skills (Table 2, dysphasia/dysfluency).

The control group consisted of 14 patients (4 men, 10 women) with a mean age of 35 ± 10 years. Twelve of the control patients were right handed, and two were left handed. All patients were left hemisphere dominant for speech, as assessed by sodium amobarbital testing. Mean symptom onset (i.e., age at time of brain insult), duration of illness, age at operation, and education are presented in Table 1. For consistency across patients, symptom onset and illness duration data were gathered with respect to clinical seizures. It must be noted, however, that speech deficits were present immediately after brain injury. No patient experienced new speech deficits after surgery. There were no significant differences between the aphasia group and the matched control group for the aforementioned variables.

Cortical lesions were evident intraoperatively in all aphasia patients during left hemisphere craniotomy (Fig. 1). Scalp and subdural recordings demonstrated that seizure foci were associated with cortical lesions in all cases. Lesions associated with speech disturbances included the following: focal contusions (e.g., after traumatic brain injury) in eight patients (73%), astrocytoma in one patient (9%), subarachnoid hemorrhage with focal cerebrovascular accident in one patient (9%), and penetrating injury in one patient (9%). The lesion location was classified by lobe of involvement. The temporal lobe was involved in every instance (100%). Six (55%) of the 11 aphasics demonstrated isolated temporal lobe lesions, two aphasic patients demonstrated frontotemporal lesions (18%), and the remaining three aphasics (27%) demonstrated frontotemporo-parietal lesions. The control group had no apparent cortical lesions intraoperatively.

Quantitative Speech Differences

Aphasic and control patients were distinguished by language performance. Aphasics demonstrated objective speech deficits on a battery of sensitive language tests, including the Verbal

TABLE 2. Diagnosis and speech disorders of aphasics^a

Patient no.	Age (yr)/sex	Handedness	Diagnosis	Etiology	Speech disorder
1	36/M	R	Epilepsy	SAH/CVA	Expressive aphasia ^b
3	32/M	R	Epilepsy	Glioma	Dysphasia
4	25/M	R	Epilepsy	TBI	Dysphasia with anomia
5	32/M	R	Epilepsy	TBI	Dysphasia/dysfluency
6	37/M	R	Epilepsy	TBI	Expressive aphasia ^b
7	42/F	R	Epilepsy	TBI	Expressive aphasia
8	30/M	R	Epilepsy	TBI	Anomic aphasia
9	39/F	R	Epilepsy	TBI	Anomic aphasia
10	45/M	R	Epilepsy	TBI	Dysphasia
11	34/F	R	Epilepsy	GSW	Expressive aphasia
13	33/F	R	Epilepsy	TBI	Aysphasia/dysfluency

^a R, right; SAH/CVA, subarachnoid hemorrhage/cerebrovascular event; TBI, traumatic brain injury; GSW, gunshot wound. Eleven aphasic patients were included in this investigation. Their diagnosis, etiology of brain injury, and speech disorder are listed.

^b Two patients with expressive aphasias who exhibited only mild forms of impaired repetition. These patients fall on the diagnostic spectrum between classic expressive aphasia and transcortical motor aphasia.

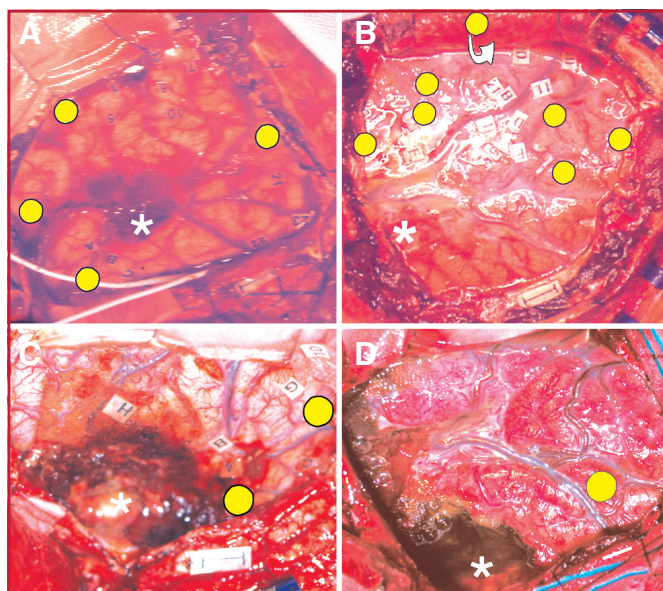


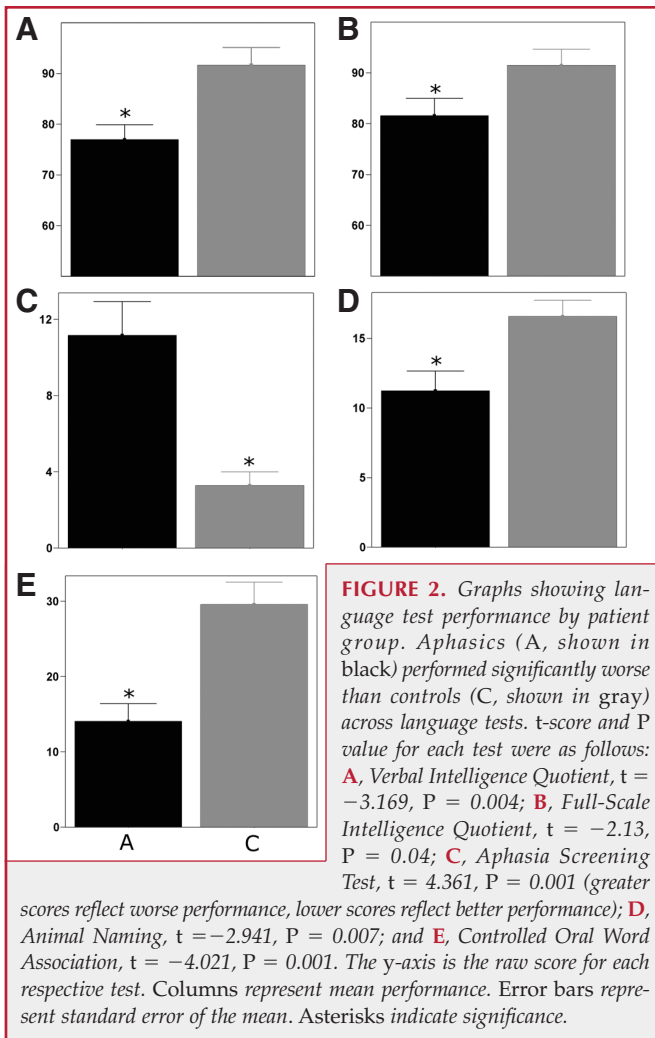
FIGURE 1. Intraoperative photographs showing speech sites in patients with language deficits. Speech sites (yellow circles) are shown in relation to the cortical lesions (*). **A**, a 42-year-old woman who experienced a traumatic brain injury and cortical contusion. Mapping demonstrated a speech site on the frontal operculum in a typical location, as well as a speech site more dorsally on the inferior frontal gyrus. **B**, a 33-year-old man who sustained a traumatic brain injury. Mapping demonstrated multiple speech sites along the frontal operculum (arrow). **C** and **D**, temporal lobe speech sites at varying distances from the lesion margin. **C**, a 39-year-old woman with traumatic brain injury. The photograph illustrates the evacuated cavity from a cerebral contusion. **D**, a 36-year-old man with subarachnoid hemorrhage. The photograph depicts the resection cavity after resection of epileptic focus. Size bars represent 1 cm.

Intelligence Quotient, Full-Scale Intelligence Quotient, the Aphasia Screening Battery, COWA, and Animal Naming (Fig. 2). For individual patients, performance across these tests was significantly intercorrelated (Table 3). For example, Verbal Intelligence Quotient scores and COWA scores were significantly related (bivariate Pearson correlation coefficient $r = 0.58$, $P < 0.002$). Although “aphasic” patients demonstrated objective language deficits, these deficits were mild to moderate in severity and were not so severe as to preclude intraoperative language mapping. As described under Patients and Methods, patients must have achieved at least 70% baseline naming accuracy during intraoperative testing to make statistical inferences for determining essential speech sites reliable.

Aphasic patients demonstrated objective speech deficits during intraoperative confrontation naming. Intraoperative naming proficiency was assessed by first determining the baseline performance during confrontational naming. Both aphasics and controls performed well on this simple language task, achieving mean scores greater than 95%. Nevertheless, controls significantly outperformed aphasics ($99.2 \pm 1.2\%$ versus $96.0 \pm 4.3\%$, $t = -2.577$, $P = 0.018$). Intraoperative naming performance was highly correlated with Verbal Intelligence Quotient ($r = 0.56$, $P < 0.005$), Full-Scale Intelligence Quotient ($r = 0.42$, $P < 0.05$), the Aphasia Screening Battery ($r = -0.59$, $P < 0.005$), COWA ($r = 0.47$, $P < 0.05$), and Animal Naming ($r = 0.53$, $P < 0.01$). Performance on all of these tests was independent of such clinical variables as the duration of illness, age of symptom onset, and age at time of surgery for both groups.

Differences in Cortical Speech Representation

The cortical distribution of speech sites distinguished aphasic patients from matched controls. Essential speech sites were significantly redistributed in aphasics, with proportionally



more frontal lobe, and fewer temporal lobe, sites than matched controls. In the aphasic group, 19 (40%) of 47 essential language sites were found in the temporal lobe, whereas in the control group, 35 (78%) of 45 essential language sites were found in the temporal lobe ($\chi^2 = 11.618$, $P < 0.001$). Aphasics had proportionally more frontal lobe sites than controls (21 of 47 versus 11 of 45, respectively; $\chi^2 = 4.15$, $P < 0.05$) (Fig. 3). These additional frontal lobe sites were observed dorsal to the frontal operculum, predominantly occurring along the superior border of the inferior frontal gyrus, as well as along the middle frontal gyrus. This redistribution of speech sites was independent of frontal lobe lesion involvement.

Aphasic patients with lesions involving the frontal lobe averaged 2.2 ± 1 frontal sites and 2.2 ± 1.5 temporal sites, whereas aphasics without frontal lobe lesion involvement averaged 1.7 ± 2.4 frontal and 1.3 ± 1.5 temporal lobe sites (not statistically significant). Of note, the overall number of essential sites found in aphasic and control patients was the same despite the reorganization of sites in aphasics (47 versus 45, respectively), which suggests that the overall extent of dominant-hemisphere speech representation remained constant. Aphasic patients averaged 4.3 ± 2.6 language sites per patient, whereas controls averaged 3.4 ± 3.1 sites ($t = 0.734$, not statistically significant). Hence, cortical lesions near the eloquent speech cortex that produce clinical speech deficits were associated with a redistribution of essential speech sites favoring the frontal lobe.

The redistribution of frontal speech sites varied as a function of the age of the patient at the time of the initial brain insult. The observed number of frontal lobe sites was inversely related to the age of symptom onset ($r = -0.71$, $P = 0.014$). Figure 4A illustrates the linear association between age of brain insult and the number of frontal lobe sites. Aphasic patients with "early" insults had more frontal speech sites than those with "late" insults (3.5 ± 1.9 versus 1.0 ± 1.2 , respectively; $t = 2.745$, $P = 0.02$) (Fig. 4B). The number of frontal lobe sites was

TABLE 3. Language tests that are significantly intercorrelated^a

Neuropsychological variables	OR naming	VIQ	FIQ	Aphasia battery	COWA
VIQ	-0.585 0.003				
FIQ	0.417 0.05	0.936 0.001			
Aphasia Battery	-0.585 0.003	-0.67 0.001	-0.626 0.001		
COWA	0.474 0.02	0.577 0.002	0.502 0.01	-0.61 0.001	
Animal Naming	0.526 0.01	0.631 0.001	0.572 0.002	-0.488 0.01	0.535 0.005

^a OR naming, intraoperative naming performance; VIQ, Verbal Intelligence Quotient; FIQ, Full-Scale Intelligence Quotient; COWA, Controlled Oral Word Association test (also known as "F.A.S." test). A correlation matrix of language tests demonstrates that language performance across tests was significantly intercorrelated. Pearson's *r* shown as top number in each cell. *P* value shown as bottom number. The Aphasia Battery score represents error rates; greater values represent worse performance, whereas lower values represent better performance.

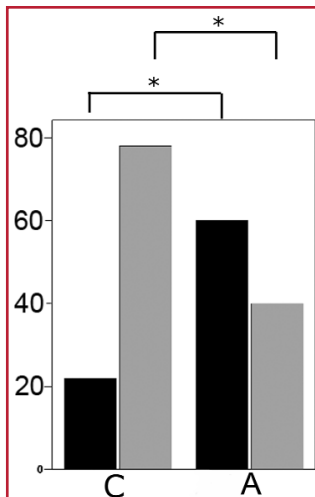


FIGURE 3. Graph showing reversal of speech site distribution. The proportion of speech sites found in the frontal lobe (black) and temporal lobe (gray) is shown on the y-axis. The typical proportion of speech sites found in the frontal and temporal lobes is reversed in patients with temporal lobe lesions involving eloquent speech areas. Aphasics (A) had proportionally fewer temporal lobe sites than controls (C) (*, $\chi^2 = 11.618$, $P < 0.001$) and proportionally more frontal sites (*, $\chi^2 = 4.15$, $P < 0.05$). Columns represent comparisons between control and aphasic groups.

gin. At least one speech site was within 2.5 cm of the lesion margin in every case. Interestingly, the distance between the lesion and the nearest language site was negatively correlated with the number of temporal lobe sites ($r = -0.642$, $P < 0.05$). No relationship was found between this distance and the number of frontal lobe sites language sites (not statistically significant) or the overall number of sites (not statistically significant).

To characterize this relationship further, patients were categorized into three groups on the basis of lesion proximity. The “adjacent” group consisted of patients with a speech site located within 1 cm of the lesion ($n = 5$). The “near” group consisted of patients with a speech site between 1 and 1.5 cm from the lesion ($n = 2$). This distance corresponds to the outer limit of the depolarization effects of electrical stimulation used to induce transient anomia during language mapping (24, 43). The “remote” group consisted of patients with a speech site farther than 1.5 cm from the lesion ($n = 4$). Analyses of variance were completed to explore possible group differences on neuroanatomic and neuropsychological data.

Considering neuroanatomic variables first, the number of temporal lobe sites was significantly different among the three groups

also inversely related to the age of the patient at the time of surgery ($r = -0.68$, $P = 0.021$). The number of frontal sites was independent of the duration of illness. Identical analyses were run on temporal lobe speech sites and failed to reveal any associations between the number of sites and the age of brain insult, age at time of surgery, or duration of illness. Control patients, who had no history of speech disturbances, demonstrated no significant relationships relating speech sites and clinical variables.

Lesion Proximity to Speech Cortex Predicts the Number of Essential Speech Sites in the Temporal Lobe

The distance between the cortical lesion and the nearest temporal language site was measured with intraoperative photographs. Essential language sites were located on average 1.1 ± 1 cm from the lesion margin (range, 0.1–2.5 cm). Nine (82%) of 11 aphasic patients had a language site within 2 cm of the lesion margin.

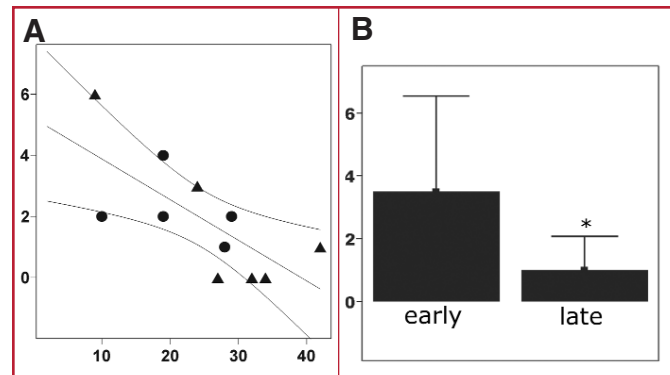


FIGURE 4. Graphs showing that frontal lobe sites decline with age of brain insult. **A**, the number of frontal lobe sites plotted as a function of the age of the patient at the time of initial brain insult. The number of sites was significantly inversely correlated with age of brain insult ($r = -0.71$, $P = 0.014$). This finding was independent of frontal lobe lesion involvement. Circles, patients with frontal lobe involvement; triangles, patients without frontal lobe involvement. Lines represent linear regression with 95% mean prediction interval ($r^2 = 0.51$, $F = 9.266$, $P = 0.014$). **B**, comparison between early and late brain injury patients. The mean number of frontal lobe sites is shown for patients with “early” brain injury (19 yr of age or younger) and for those with “late” brain injury (older than 19 yr of age). $t = 2.745$; *, $P = 0.02$. Error bars represent standard deviation.

(analysis of variance $F_{2,10} = 7.161$, $P = 0.01$). The “adjacent” and “near” groups had a significantly greater number of temporal lobe speech sites than the “remote” patients (Bonferroni post hoc tests: “adjacent” versus “remote,” $P = 0.03$; “near” versus “remote,” $P = 0.04$; a priori contrast “adjacent” and “near” versus “remote,” $P = 0.005$). “Adjacent” and “near” patients were not significantly different from each other. “Remote” patients consisted of patients whose lesions were farther than 1.5 cm from the nearest speech site. These data, therefore, suggest that fewer temporal lobe sites are found in patients whose sites are more than 1.5 cm from a focal cortical lesion (Fig. 5). Patients with at least 1.5 cm of separation between the lesion and language sites had 0.25 ± 0.5 temporal lobe sites ($n = 4$), whereas those with less than 1.5 cm of separation had 2.6 ± 1.1 temporal lobe sites ($n = 7$; $t = 3.819$, $P = 0.004$). There were no differences between these groups in the number of frontal lobe sites or overall number of sites.

Considering neuropsychological variables, naming fluency was significantly different among the three groups. Patients in the “near” group outperformed other patients on naming fluency (analysis of variance $F_{2,10} = 8.960$, $P = 0.009$; a priori contrast “near” versus “adjacent” and “remote,” $P = 0.006$) (Fig. 6). Post-hoc Bonferroni tests also revealed significantly worse performance in the “adjacent” group compared with the “near” group ($P = 0.009$). The “adjacent” and “remote” groups did not significantly differ on naming fluency performance. These findings suggest that aphasic patients perform better on naming fluency when their lesion is near (i.e., 1–1.5 cm) speech sites than when the lesion is either immediately adjacent to, or apparently quite distant from, speech areas. A possible explanation for the neuroanatomic and neuropsychological findings is discussed herein.

DISCUSSION

The purpose of this investigation was to determine whether clinical speech deficits after brain injury were associated with functional speech reorganization. Such information is valuable for neurosurgeons who encounter patients with language deficits in preoperative consultation. To answer this question, we compared intraoperative language maps between epilepsy patients with and without preoperative speech deficits. The major findings in this investigation were the following: 1) insults to eloquent speech areas altered the distribution of speech sites by increasing frontal lobe—but not temporal lobe—speech representation; 2) this functional reorganization of the frontal lobe varied as a function of the age of the patient at the time of initial brain insult; and 3) the proximity of the lesion to the temporal lobe speech areas predicted both patient performance on generative naming fluency as well as the number of temporal lobe speech sites found during mapping.

Lesion-induced Differences in Cortical Speech Representation: The Frontal Lobe

Frontal lobe speech representation expanded into the superior border of the inferior frontal gyrus and middle frontal gyrus after injury to eloquent speech areas. This finding supports the hypothesis that the frontal lobe retains the ability to functionally adapt to eloquent cortex injury into early adulthood. Several potential models of functional reorganization could explain these findings. First, the appearance of reorganized frontal speech areas may reflect the unmasking (15) of diffuse language networks. Damage to an essential language node

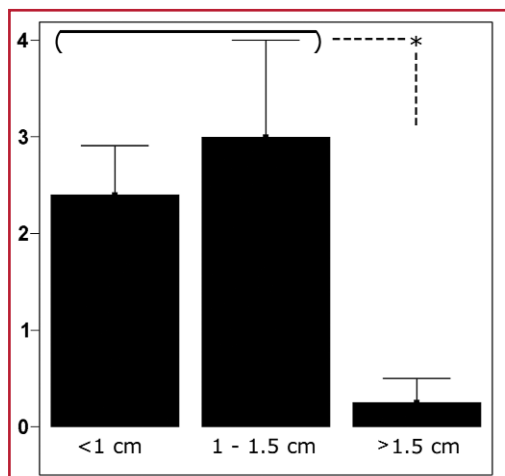


FIGURE 5. Graph showing temporal lobe sites by lesion proximity. The number of temporal lobe sites varied as a function of the distance between the lesion and the nearest speech site. Patients with lesions beyond 1.5 cm from the nearest speech site (i.e. “remote” lesions) had significantly fewer sites (analysis of variance, $F_{10,2} = 7.161$; *, $P = 0.01$). Columns represent mean value, error bars represent standard deviation.

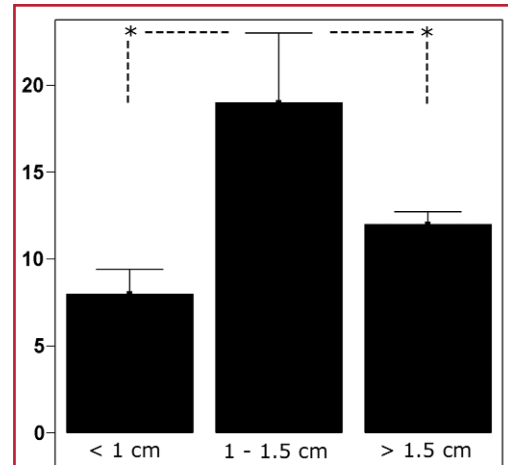


FIGURE 6. Graph showing naming fluency by lesion proximity. Performance on the Animal Naming test is shown across lesion proximity groups as in Figure 5. Patients with “near” lesions (i.e., between 1 and 1.5 cm) significantly outperformed the other patients (analysis of variance, $F_{10,2} = 8.960$; *, $P = 0.009$).

in this model would result in a shift of the functional load of speech processing to portions of the network previously involved in, but not essential for, speech. These unmasked nodes would then become apparent at the time of language mapping. Alternatively, this functional reorganization of frontal speech areas may signify recruitment of areas not previously involved in speech processing. Such functional reshaping has been described after glioma resections in eloquent cortex (16). Finally, behavioral adaptation, such as the use of alternative linguistic strategies to compensate for speech deficits, could engage alternate cortical pathways that emerge as new speech nodes. Although the data collected here support the capacity for frontal lobe functional reorganization, the data do not establish a definitive mechanism of plasticity.

Convergent lines of evidence support the ability of the adult brain to undergo functional reorganization. Evidence from functional imaging studies, including positron emission tomography and functional magnetic resonance imaging, demonstrates reorganization of linguistic functions within the left hemisphere after brain injury (5, 30, 54). For example, frontal lobe lesions alter language activity patterns, resulting in recruitment of additional frontal (12, 50, 51) and temporal (1) language representation. Electrophysiological evidence of spatial and temporal reorganization occurs during the aphasic patient’s recovery from brain injury (20, 26, 49). Functional reorganization is found in amputees with phantom limb pain (19) and focal hand dystonia (17). String instrument musicians, with expert use of their fingers, demonstrate functional reorganization of somatosensory cortices (18).

The potential for functional reorganization has also been convincingly demonstrated in animal models. Cortical reorganiza-

tion occurs in primates after lesions (58), including focal infarcts (37, 39) and sensory deafferentation (21, 33, 34). Cortical plasticity in the mature brain also occurs in response to advanced behavioral training (3, 4, 8, 38). The capacity of the central nervous system for plastic adaptation, to at least a limited extent, has been demonstrated in both human and animal studies.

Extent of Frontal Lobe Recruitment Is a Function of the Age of Brain Injury

The degree of frontal lobe recruitment varied as a function of the age of the patient at the time of brain insult. Brain damage at earlier ages was associated with the development of significantly more frontal lobe sites. Meanwhile, the duration of patient illness did not influence the degree of frontal lobe recruitment, which suggests that the capacity of the frontal lobe to functionally reorganize may decline with age.

This finding is consistent with other investigations of brain plasticity. The degree of recovery of function after damage to the central nervous system is dependent upon the age of the individual when the lesion is acquired (10). Coined the Kennard effect (31), the developing brain has a greater capacity for plasticity than the adult state. This plasticity is confirmed in studies of children who undergo hemispherectomy for intractable epilepsy (53, 57). Children undergoing resection early in life manifest marked functional recovery after surgery when compared with those patients undergoing resection at an older age (11, 29, 35, 52, 57).

Differences in the rate of maturation of white matter provide one possible explanation for functional adaptation in the frontal lobe but not the temporal lobe. The average age at onset of brain injury in this population was 24 years, with the earliest occurring at 9 years of age. It is well described that white matter maturation continues into early adulthood, particularly in the frontal regions (14, 22, 44, 46). Regional differences in myelination rates may underlie the development of different cognitive functions (36), as well as regional differences in the response to insult. For instance, working memory performance is strongly associated with white matter development in the superior and inferior left frontal lobe (36). Similarly, measures of brain growth and cortical gray matter density suggest persistent growth in the frontal lobe, but not the temporal lobe, through early adulthood (47). Taken together, these factors suggest that regional differences in brain maturation occur into early adulthood and may explain the regional differences in functional adaptation to focal insult found here. Further study in this area is clearly warranted.

Lesion-induced Differences in Cortical Speech Representation: The Temporal Lobe

Unlike the frontal lobe, temporal lobe speech representation was reduced after injury to eloquent language areas. This finding is perhaps not surprising given that each of the cortical lesions in this series involved the temporal lobe. Within the temporal lobe, lesions were highly variable in both location and size, which is consistent with other reports of highly variable lesions that result in speech deficits (2). In fact, aphasic syndromes may result from lesions that spare perisylvian areas (2). This result also is not surprising, given that the location of

essential speech areas is highly variable and may occur at locations distant from the classic language areas (43).

Lesion Proximity Predicts Temporal Lobe Sites and Naming Fluency

A relationship was observed between the organization of speech centers and the proximity of the lesion in the temporal lobe. Using the number of essential speech areas as a measure of the extent of speech representation, we found an inverse relationship between the extent of temporal lobe speech representation and the proximity of the lesion. Temporal lobe speech representation was maximal when the lesion was located "adjacent to" or "near" speech areas (i.e., within 1.5 cm). Conversely, when the lesion was "remote" (i.e., greater than 1.5 cm), the temporal lobe speech representation was diminished. Stratifying patients based on the lesion's proximity to speech sites confirmed this observation; a significant reduction in the number of temporal lobe sites was found when the lesion was farther than 1.5 cm from speech centers ($P = 0.004$). Lesion proximity modulates the extent of temporal lobe speech representation.

Stratifying patients by lesion proximity also revealed significant differences in naming fluency across the groups. In this analysis, one might hypothesize that naming fluency would improve as the distance between the cortical lesion and nearest speech center increased. As expected, patients with "adjacent" lesions performed worse than those with lesions "near" speech areas. Unexpectedly, however, patients with "remote" lesions performed as poorly as patients with "adjacent" lesions (Fig. 6), with no significant difference between "adjacent" and "remote" performance. Lesion proximity modulates naming fluency.

It is easy to understand how a lesion immediately adjacent to speech sites might disrupt naming abilities. It is perhaps less obvious how lesions that are apparently quite distant from speech areas might disrupt naming abilities. To answer this question and to reconcile the finding of modulated speech site representation described previously, consider the illustrations shown in Figure 7. Three potential lesion locations are considered against the background of a typical pattern of temporal lobe speech representation. Lesion proximity is measured as the distance between the lesion and the closest essential speech site (Fig. 7, black circles). In Figure 7A, a lesion occurs in very close proximity (i.e., "adjacent") to a temporal lobe speech site without destroying it. In this case, it is easy to see how significant speech symptoms might result from the lesion's encroachment upon an essential speech site. Note that the total number of temporal lobe sites (i.e., 3) remains unchanged. In Figure 7B, the lesion occurs at a moderate distance from a speech site (i.e., "near"). This lesion might produce subtle speech symptoms by encroaching upon the outer limits of the functional radius of a speech site, which is known to be approximately 1 to 1.5 cm (23–25, 43). In this case, the number of sites also remains unchanged (i.e., 3). In Figure 7C, the lesion completely destroys the speech site, leaving no functional evidence of its preexisting location. The nearest speech site is seemingly far from the lesion (i.e., "remote"). In this instance, speech symptoms obviously result from the destruction of the speech site. When one tallies the remaining

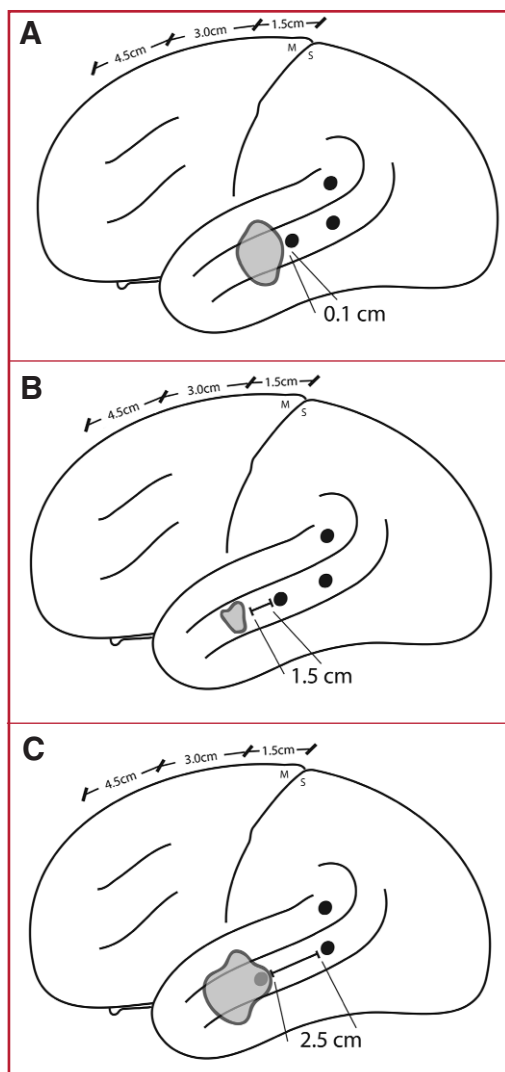


FIGURE 7. Drawings illustrating model relationship between temporal lobe sites and lesion proximity. Three potential lesions are illustrated against the background of a typical pattern of temporal lobe speech representation. Lesion proximity to the nearest speech site (black circles) is measured. **A**, an “adjacent” lesion occurring within 1 cm of a speech site without destroying it. Significant speech symptoms result from the lesion’s encroachment upon the speech site. Note that the total number of temporal lobe sites remains unchanged (i.e., 3). **B**, a “near” lesion occurring at a moderate distance from a speech site (i.e., between 1 and 1.5 cm). This lesion produces mild speech symptoms by damaging only the outer limits of a speech site. The number of sites remains unchanged. **C**, the “remote” lesion, destroys the speech site, leaving the next closest speech site intact. Significant speech deficits result from the destruction of the speech site. Only two temporal lobe sites remain, and the distance between the lesion and next closest speech site is greater than 1.5 cm. M, motor cortex; S, somatosensory cortex.

temporal lobe sites, the number has decreased to two. Hence, the apparent extent of temporal lobe speech representation has decreased. Considering all three examples together, the number of temporal lobe sites is an inverse function of the distance between the lesion and the nearest speech site, thus mirroring the results documented in our patient sample.

Further support for this model comes from the neuropsychological data. The model predicts that patients with a speech site that has been destroyed would perform poorly (cf. Group C, represented in Fig. 7C). Similarly, those with a lesion immediately adjacent to, but not destroying, a speech site would also perform poorly (cf. Group A, represented in Fig. 7A). However, patients with lesions along the outer functional limits of a speech site would perform comparatively better than the other two groups because all speech sites are relatively preserved (cf. Group B, represented in Fig. 7B). The result predicted by this model is precisely what was found in our sample (Fig. 7). The model parsimoniously accounts for the relationships between both the anatomic data and the behavioral data presented here. It serves as a testable hypothesis against which data from other brain mapping techniques, such as functional imaging, may be compared.

A final word must be said regarding functional reorganization. The degree to which spatial reorganization of speech areas is associated with clinical improvement remains unclear. Most studies have focused on changes in perilesional activation. Some researchers report a correlation between clinical improvement and the magnitude of perilesional language activity (32). Such activity has been associated with treatment-induced adaptation (13). Additionally, favorable outcomes have been related to reactivation of perilesional areas in longitudinal studies of aphasics (28). Yet, it remains undetermined whether perilesional activity represents focal reorganization, functional sparing, or restoration of typical activity patterns (45). Our findings suggest the presence of reorganization in frontal areas in response to lesions involving the dominant temporal lobe.

Study Limitations

Several important factors must be considered when analyzing these results. First, this investigation was structured to address the practical clinical question: Are speech deficits after brain injury associated with functional speech reorganization in a neurosurgical population? Our purpose was not to strictly identify the neuroanatomic correlates of specific aphasic syndromes, nor was it to compare patients with isolated frontal lesions versus those with isolated temporal lesions. This limited study population is heterogeneous in lesion etiology, focus, and magnitude of speech deficits. In this regard, this population mirrors clinical neurosurgical practice populations. Second, the aphasics studied here had mild-to-moderate speech deficits; severe speech deficits preclude language mapping and are not included in this investigation. Third, the nature of electrical stimulation mapping allows for data to be collected only during a brief period of time in the course of the patient’s disease. These data are cross sectional. The relationship between the presence of eloquent cortex lesions and altered speech maps must therefore be inferred. Inferences about causality are indirect and must be interpreted with caution.

Finally, every attempt was made to map the full extent of cortex exposed through large frontotemporoparietal craniotomies. The possibility that additional sites were located beyond the limits of the craniotomy, or in the opposite hemisphere, cannot be ruled out in these investigations. Future investigations should include functional mapping methods, such as functional magnetic resonance imaging, as other investigators have noted contralateral language activation in stroke (50) and tumor populations (9).

CONCLUSION

The purpose of this investigation was to determine whether clinical speech deficits after brain damage were associated with functional speech reorganization. We found evidence for function reorganization in the frontal lobe but not the temporal lobe. This reorganization varies as a function of the age of the patient at the time of brain injury. In the temporal lobe, the spatial relationship between the lesion and speech areas predicts naming fluency and the number of temporal lobe speech areas found. We offer an anatomic model to explain these findings. Collectively, these findings are important for planning neurosurgical resections in patients with preoperative speech deficits. Particular care should be applied to identify speech areas in these patients.

Disclosures

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COMMENTS

This is a fascinating study which supports the contention that functional reorganization of language cortex can occur following injury to language-dominant cortical regions. Of note is the plasticity profile of the frontal lobe, especially as it relates to patient age at the time of initial brain injury. It certainly would have been interesting to know whether there is a cutoff, in terms of age, at which the degree of functional reorganization wanes. Also, it would be important to know whether the size of the cortical injury affects the degree of reorganization, and perhaps in the future functional imaging will elucidate these important mechanisms and pathways. That said, I would agree with the authors that this data will be important in terms of future planning of patients with preoperative speech problems undergoing surgery within and around the temporal as well as the frontal lobe in the dominant hemisphere.

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This article presents a relatively extensive experience with cortical language mapping in epileptic patients with speech deficits associated with structural lesions. The investigative team is well established and experienced, and the mapping methodology and analysis are rigorous. As one would expect, the number of language sites in the diseased temporal lobe is decreased relative to a set of matched controls. The interesting observation concerns the increased number of sites in the frontal lobe, consistent with neural reorganization, or plasticity. Similar adaptation in nonlinguistic domains has been demonstrated in animal models as well as humans. It is a bit unclear what role might be played by the variable extent of exposure (and, consequently, the consistency of assessed cortex), particularly frontally, in this retrospective analysis, but the findings remain intriguing and provocative. The sampling afforded by noninvasive imaging methodologies, which are rapidly being refined, will address this issue, and the present study should encourage and further enable future work in this hot area.

David W. Roberts
Lebanon, NH

Extensive experience with intra-operative mapping of cerebral localization of language has given the authors the opportunity to study the reorganization of cortical speech areas in 11 aphasic patients who had structural lesions in the speech areas of their temporal lobes. The data indicate that their speech areas migrated to areas adjacent to the lesions. The study provides concepts for planning cortical resections in patients with aphasia and structural lesions: speech function may have migrated to adjacent cortex, particularly adjacent frontal lobe, and mapping of speech loci prior to resection is indicated in these patients.

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INTRACRANIAL ELECTROENCEPHALOGRAPHY WITH SUBDURAL GRID ELECTRODES: TECHNIQUES, COMPLICATIONS, AND OUTCOMES

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OBJECTIVE: Intracranial subdural grid monitoring is a useful diagnostic technique for surgical localization in patients with intractable partial epilepsy. The rationale for the present study was to assess the morbidity of intracranial recordings and the surgical outcomes.

METHODS: We retrospectively reviewed the clinical data for 189 unique patients undergoing 198 intracranial subdural grid monitoring sessions between 1996 and 2004 at a tertiary epilepsy center.

RESULTS: The mean age of patients undergoing monitoring was 28 ± 14 years. An average of 63 ± 23 electrodes were inserted. The mean duration of monitoring was 8 ± 4 days. Localization of an epileptogenic zone occurred in 156 sessions (79%) resulting in 136 resections (69%). There were 13 major complications (6.6%), including five infections and six hematomas. Three patients (1.5%) developed permanent deficits related to implantation. Sixty-two (47%) of 136 patients undergoing resection were seizure-free after resection. An additional 38 patients (28%) had a significant reduction in seizures. The mean follow-up was 51 ± 30 months. The duration of monitoring, bone flap replacement, number of electrodes, and perioperative corticosteroids were not associated with infection or complication.

CONCLUSION: Subdural grid monitoring for identification an epileptogenic focus is high yield, revealing a focus in 79% of monitoring sessions. Complications rarely result in permanent morbidity (1.5%). Surgical outcome indicated that 74% of patients experienced a favorable reduction in seizure tendency.

KEY WORDS: Epilepsy, Invasive electroencephalography, Subdural grid

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There are approximately two million Americans with epilepsy currently on antiepileptic drug therapy (4). Interestingly, 75% of the cost of epilepsy in the United States is accounted for by the one-fifth of patients in this group who are medically refractory (4). Partial or localization-related epilepsy is often responsible for medically intractable seizures (7). In partial seizure disorders, whether or not a lesion is apparent on magnetic resonance imaging (MRI), intracranial monitoring can aid in the identification of potential candidates for surgically responsive

epilepsy. There are several methodologies available for chronic intracranial electroencephalography (iEEG) to localize the epileptogenic zone, i.e., the site of seizure onset and initial seizure propagation. They include subdural strips, depth electrodes, or subdural grids (3, 4, 6, 8, 11, 13–17, 19, 22). Subdural grids offer a larger area of neocortical coverage compared with strips or depth electrodes, and they may be used for functional mapping. The implantation of a subdural grid requires a larger craniotomy and may have an increased risk of adverse effects owing to several factors,

ABBREVIATIONS: CT, computed tomography; EEG, electroencephalography; iEEG, intracranial EEG; MRI, magnetic resonance imaging; SPECT, single-photon emission CT

such as increased number of electrodes, as previously reported (1, 5, 6, 11, 13–16, 19, 22).

Invasive monitoring rates at adult epilepsy centers range from 25 to 50% of patients undergoing surgery for epilepsy (20). Despite this frequent use, there is still a paucity of data pertaining to technique, complications, and outcome, especially since the initial articles reporting the technique. Therefore, we undertook a review of a large cohort of 189 patients who underwent 198 craniotomies with placement of subdural grids for iEEG accrued over a relatively short period of time, 1996 to 2004.

PATIENTS AND METHODS

Subjects

All adult and pediatric patients undergoing implantation of subdural grid electrodes between 1996 and 2004 were identified from our surgical coding database of patients who underwent extraoperative video iEEG monitoring at the Mayo Clinic, Rochester, MN. There were a total of 189 patients who underwent invasive monitoring sessions in 198 unique admissions. Pediatric patients were included.

Data Collection

All charts were retrospectively reviewed by one of the authors (JJVG). Data were collected with regard to bone flap replacement, duration of monitoring, complication, shift, number of electrodes, and outcome.

Presurgical Workup

All patients were referred for invasive monitoring after extensive evaluation by our institutional epileptologists. Before admission for subdural grid monitoring, patients had undergone noninvasive techniques to localize the epileptogenic region, such as outpatient electroencephalography (EEG), inpatient prolonged video EEG monitoring, structural neuroimaging (MRI, functional neuroimaging, subtraction ictal single-photon emission computed tomography [SPECT] coregistered to MRI), positron emission tomography, magnetic resonance spectroscopy, and neuropsychological testing. MRI was performed in all patients with 1.5- or, later, 3-T magnets according to epilepsy protocol technique as described by Jack (12). These studies and clinical history/seminology were presented at our multidisciplinary epilepsy surgical conference, with neurologists, neuroradiologists, and neurosurgeons present to discuss surgical options and approach. The indication for invasive monitoring was to determine candidacy for directed surgery/resection of epileptic focus in patients who were not well localized on other noninvasive tests.

Surgical Method

Subdural grid insertion was performed under general anesthesia; craniotomy and dural opening were performed in all cases. Placement of grids, strips, and, often, depth electrodes were guided by noninvasive testing, according to the recommendations of the attendants at the epilepsy surgery conference (Fig. 1). Depths were placed using stereotactic guidance with image fusion of MRI and SPECT images. All grids, strips, and depth electrodes were from Ad-Tech Medical Instrument Corp. (Racine, WI). The electrode cables were tunneled away from the incision to the skin in separate stab incisions per lead, and the dura was reapproximated. Bone flap replacement during monitoring was left to the consultant's clinical discretion. This was often based on the violence

of seizures, or, in the case of very young children who were unable to protect their own craniotomy defect (see Results), the bone flap was often replaced and secured with metal prostheses. Postoperatively, the patients were monitored in the intensive care unit with continuous video EEG. Postoperative spiral computed tomography (CT) was performed to confirm electrode locations and rule out occult hemorrhage in all cases. Prophylactic antibiotics, either cefazolin or vancomycin, were given as scheduled intravenous dosing while grids were in place and for three doses after removal. Dexamethasone use was sporadic perioperatively (see Results). Head dressings were applied postoperatively and were left in place throughout monitoring. Anticonvulsants were often tapered by our epileptologists, with variable rates of taper. Prolonged seizures (>5 min) were treated with intravenously administered lorazepam in crescendo dosing. If seizures were well localized, resection of the epileptic tissue ensued unless the ictal onset zone corresponded to eloquent areas on cortical mapping or the patient declined further surgery, which occurred in one instance (0.5%). When monitoring failed to reveal the ictal onset zone, the patient underwent grid removal, wound irrigation, and primary closure without resection.

Autologous Bone Procurement (Bone Flap Storage)

In 145 patients, a craniotomy flap was made in the usual fashion. This was then transferred sterile to the back scrub table. An autologous bone procurement kit (Allo-Source, Centennial, OH) was used. The bone flap was soaked in bacitracin solution, wrapped in a sterile towel, placed in a sterile labeled bag and then in a sterile labeled inner container and, subsequently, a labeled outer container. This was then transferred to our

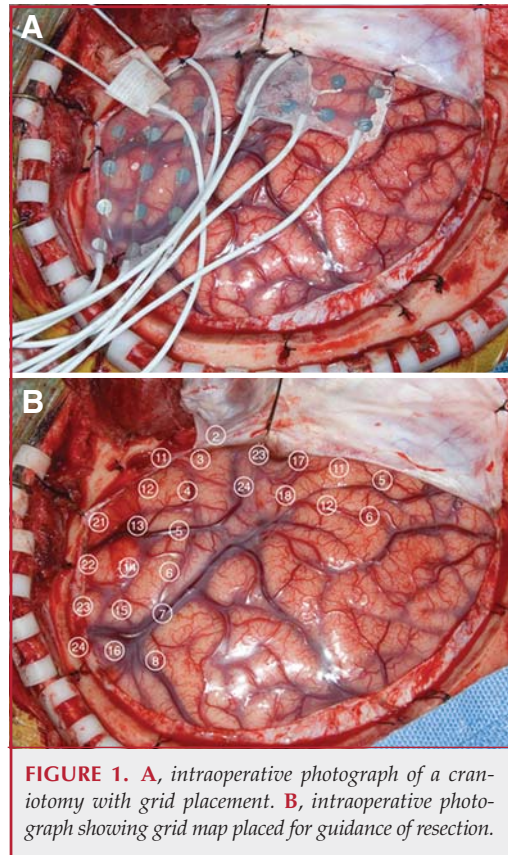


FIGURE 1. A, intraoperative photograph of a craniotomy with grid placement. B, intraoperative photograph showing grid map placed for guidance of resection.

bone bank freezer. The freezing and storage temperature was -40°C . The bone flap was taken out before replacement and allowed to thaw at room temperature in isotonic saline 60 minutes before reimplantation. It was also soaked in bacitracin solution. These handling provisions are guided by the American Association of Tissue Banking.

Outcome Assessment

Outcome was assessed using the modified guidelines recommended by Engel et al. (9). This assessment is briefly summarized: Class I, free of seizure or with aura only; Class II, rare disabling seizures since surgery or nocturnal seizures only, seizure frequency is at least at 90% reduction in absolute number in regard to nondisabling seizures; Class III, worthwhile improvement defined as greater than 50% reduction in seizures to 90% reduction in regard to nondisabling seizures; Class IV, no worthwhile improvement. These assessments were based on the last known follow-up; for most patients (82%), follow-up was longer than 2 years. We arbitrarily grouped modified Engel Classes I and II together to represent a favorable outcome category and Engel Classes III and IV as an unfavorable outcome category.

Statistical Analysis

JMP 6.0 software (SAS Institute, Inc., Cary, NC) was used for statistical analysis. Data pertaining to bone flap replacement, duration of monitoring, complication, shift, number of electrodes, and outcome were included in Bonferroni analysis, and all other correlations were determined by post hoc analysis. Univariate associations with complications and outcomes were assessed using χ^2 or Fisher's exact tests, as appropriate. Variables with P values of <0.10 were then included in a multivariable logistic regression model; significance was set at $P < 0.05$ or with the Bonferroni correction when applicable. Our study was approved by the Mayo Clinic's Institutional Review Board, and patients gave consent to participate.

RESULTS

Demographics

Between July 1996 and December 2004, we identified 198 intracranial seizure monitoring sessions, all with at least one grid insertion and craniotomy. Demographic information is represented in Table 1. There were 146 adult and 52 pediatric (younger than 18 yr of age) patients who underwent monitoring sessions. The average age was 28 ± 14 years (range, 1–73 yr). There were 94 female and 104 male patients. Previous epilepsy surgery had been performed in 55 patients (28%).

Preoperative Workup

MRI showed focal findings in 129 of 198 sessions. Purely nonlesional monitoring sessions occurred in 69 (48%) of 143 sessions, the 55 previous resections were excluded from this group. Subtraction ictal SPECT suggested a seizure onset zone in 155 of 184 sessions; iEEG was concordant with subtraction ictal SPECT in 108 (70%) of these 155 sessions. A positron emission tomography scan was performed in only 40 cases.

Surgery

Craniotomy was performed in all patients; 101 (51%) were right sided, 87 (44%) were left sided, and 10 (5%) were bilateral. Additional burr holes were created in 46 cases. There were $1.3 \pm$

TABLE 1. Demographic data for 198 craniotomies with subdural grid monitoring for seizure localization^a

Characteristic	Data
Age, yr $\pm$ SD (range)	28 ± 14 (1–73)
No. (%) of children (≤ 18 yr)	52 (26)
Sex (M/F), no.	104/94
Side of electrode coverage, no. (%)	
Right	101 (51)
Left	87 (44)
Both	10 (5)
Lobe, no. (%)	
Frontal	143 (72)
Temporal	155 (78)
Subtemporal	57 (29)
Parietal	97 (49)
Occipital	25 (13)
Interhemispheric	51 (26)
Implants	
No. of grids ^b (range)	1.3 ± 0.5 (1–3)
No. of strips (range)	2.3 ± 2.1 (0–10)
No. of cables (range)	9.5 ± 4.7 (3–20)
No. of patients also with depths (%)	44 (22)
No. of electrodes (range)	63 ± 23 (24–144)
No. of additional burr holes (%)	46 (23)

^a SD, standard deviation.

^b There were 146 patients with 1 grid, 52 patients with 2 grids, and 1 patient with 3 grids.

0.5 subdural grids (range, 1–3 subdural grids) implanted per surgery. The absolute number of grids implanted was as follows: grid array (number): 8×8 (37), 8×6 (43), 8×4 (38), 8×2 (5), 6×6 (45), and 6×4 (84). Strips supplemented grid coverage with the average number of 2.3 ± 2.1 strips (range, 0–10 strips) per surgery. The absolute number of strips implanted was as follows: strip array (number): 8×1 (225), and 4×1 (228). Depth electrodes supplemented monitoring in 44 patients (22%). There were on average 63 ± 23 electrodes (range, 24–144 electrodes) along with 10 ± 5 cables (range, 3–60 cables) used per surgery. Electrodes were placed with frontal lobe coverage in 143 patients, temporal coverage in 155, occipital coverage in 25, interhemispheric coverage in 51, and parietal coverage in 97. The bone flap was replaced during intracranial monitoring in 53 patients. There were no recognized events of delayed bone resorption after reimplantation. Length of hospitalization was 12 ± 5 days (range, 5–28 d).

Monitoring

Results are summarized in Table 2. Focal identification of the seizure focus occurred in 156 patients; 136 of these patients went on to resection. Nineteen foci were nonresectable because the seizure focus was located in eloquent brain, and one patient

TABLE 2. Results of 198 invasive electroencephalographic monitoring sessions^a

Characteristic	No.
Monitoring data	
Mean length of hospitalization, $d \pm SD$ (range)	12 $\pm$ 5 (5–28)
Duration of monitoring, $d \pm SD$ (range)	8 $\pm$ 4 (2–24)
Fever ($\geq 38.4^{\circ}\text{C}$), no. (%)	39 (20)
Leukocytosis (>10.5 white blood cells), no. (%)	82 (41)
No. receiving perioperative corticosteroids (%)	87 (44)
Characteristic, no. (%)	
Focal identification of epileptic focus	156 (79)
Resection of epileptic focus	136 (69)
Previous resective surgery for epilepsy	55 (28)
Replacement of bone flap during monitoring	53 (28)
Localizing seizures on antiepileptic medication	64 (33)
Shift appreciated on postoperative CT ≥ 3 mm	26 (13)
Primary seizure type, no. (%)	
Simple partial	10 (5)
Complex partial	59 (30)
Complex partial with secondary generalization	117 (59)
Pure generalized seizures	2 (1)
Multiple seizure types	10 (5)
Complications, no. (%)	
Infection	5 (2.5)
Osteomyelitis	2 (1)
Empyema	2 (1)
Abscess	1 (0.5)
Hematoma	6 (3)
Status epilepticus	9 (4.5)
Deep vein thrombosis	3 (1.5)
Permanent deficit	3 (1.5)
Death	0 (0)

^a SD, standard deviation; CT, computed tomography.

refused resection. Return to the operating room for readjustment or reinsertion of grids occurred 14 times; no patient underwent a third adjustment. Postoperative head CT was obtained for all patients. Midline shift on postoperative head CT, defined as greater than 3 mm, was identified on 26 postoperative scans. The seizures recorded during the monitoring sessions were ultimately categorized into types; 10 simple partial, 59 complex partial only, 117 complex partial with secondary generalization, 2 with primary generalized seizures, and 10 with simple partial, complex partial, and complex partial with secondary generalization. During monitoring per session, 9 $\pm$

15 partial seizures (range, 0–100 partial seizures) and 1 $\pm$ 4 generalized seizures (range, 0–23 generalized seizures) occurred. Corticosteroids, most commonly dexamethasone, were used perioperatively in 87 patients (44%).

Complications

Major complications occurred in 13 patients (6.6%) overall; three (1.5%) of these occurrences represented residual morbidity. There were no deaths. Of these 13 major complications, there were five infections (2.5%), six symptomatic hematomas (3.0%), and two occurrences of postimplantation edema necessitating earlier than expected reoperation.

Bleeding

In total, 17 patients (8.6%) had observed hematomas at reoperation, the majority of which were asymptomatic blood collections either around or under the grids. These were not considered complications. Six patients required expedited surgical care for their symptomatic hematoma. These six hematomas occurred in patients with deteriorating neurological examinations, CT demonstrating hematoma, and some with significant midline shift. The majority of these hemorrhages occurred in patients with multiple implantations or a history of craniotomy. In two patients, the surgeon thought that tearing of a bridging vein was the cause. A dramatic example is provided in *Figure 2*. There was one case in which a permanent deficit was incurred. This patient underwent implantation and was noted on postoperative CT to have a significant subdural hematoma along with an intraparenchymal hematoma (there were no other intraparenchymal hematomas in this series). The patient was returned to the operating room immediately, the electrodes were removed, and the hematoma was evacuated. The postoperative pathology revealed

**FIGURE 2.** Computed tomography imaging scan showing a postoperative epidural hematoma requiring emergent evacuation.

amyloid angiopathy. Fortunately, the patient's immediate postoperative aphasia and right hemiparesis have improved significantly. Last, there were also two patients who required expedited care because of edema underneath the grid. In these two patients, the bone flap had been replaced at the time of implantation.

Infection

Fever higher than 38.4°C developed in 39 patients during monitoring, with five confirmed infections (2.5%) related to subdural grid insertion. Two of these patients had osteomyelitis requiring bone flap removal, two had epidural/subdural space infections, and one patient had an abscess. Clinical infection developed on average postoperatively, 21 ± 31 days after initial implantation; all clinical infections became apparent after grid explantation. The most common microorganism cultured was coagulase-negative *Staphylococcus* ($n = 3$); other significant infections cultured were *Staphylococcus aureus* (one patient) and *Enterobacter* (one patient). There was one patient who developed a subdural empyema requiring surgical removal and who sustained a permanent left-sided sensory deficit.

Other Complications

Status epilepticus, defined as seizure activity lasting longer than 5 minutes on EEG, occurred in nine patients (4.5%), and all were treated with medication. One patient had a prolonged episode of status epilepticus that was initially medication-resistant and lasted 20 minutes. Head CT did not demonstrate hemorrhage. Postictally, she had a mild expressive aphasia that persisted. Two days after this event, the patient underwent resection of a posterior frontal seizure focus. Her mild expressive aphasia

has persisted. Finally, we noted three patients with hypercoagulable disorders (deep vein thrombosis), one of whom was discovered by presentation in a manner consistent with air-to-arterial gradient compromising pulmonary embolism. All of these disorders were discovered after explantation and were treated with anticoagulation without complications.

Histopathology

Gliosis was the most common pathology type, representing 90 (66%) of 136 resections. Tumor on pathology accounted for 20 (15%) as a group. The next most common were focal abnormalities of cortical development ($n = 16$, 12%). See Table 3 for specific numbers and types of histopathology.

Outcome

Sixty-two (47%) of 136 patients undergoing resection were seizure-free after resection (Engel Class I), and an additional 38 patients (28%) had a significant reduction in seizures (Engel Class II) (9). Only 18% experienced no significant reduction in seizure frequency or severity (Engel Class IV) (9). See Table 4 for surgical outcomes by area of resection. Notably, in 55 patients with previous resection, 45 underwent further resection. Their surgical outcomes were 44% Engel Class I ($n = 20$), 27% Engel Class II ($n = 12$), 11% Engel Class III ($n = 5$), and 18% Engel Class IV ($n = 8$) (Table 5). Further breakdown in outcome by histopathology is provided in Table 3.

Statistical Analysis

Duration of monitoring did not correlate with infection ($P = 0.44$) or complication ($P = 0.80$). However, monitoring for

TABLE 3. Postoperative histopathology and outcome of 136 patients undergoing resection of epileptic focus after intracranial electroencephalography^a

Histopathology	No. of patients	Engel classification, no. (%)			
		Class I	Class II	Class III	Class IV
Gliosis	90	40 (44)	22 (24)	9 (10)	19 (21)
Tumors ($n = 20$)					
Low-grade glioma	7	3 (43)	3 (43)		1 (14)
High-grade glioma	7	2 (29)	3 (43)	1 (14)	1 (14)
DNET	4	2 (50)	2 (50)		
Meningioma	1	1 (100)			
Tuber	1	1 (100)			
Focal malformation of cortical development	16	7 (44)	6 (38)	1 (6)	2 (13)
Mesial temporal sclerosis	3	3 (100)			
Infarct	3	3 (100)			
Rasmussen encephalopathy	2				2 (100)
Arachnoid cyst	1		1 (100)		
Vascular malformation	1		1 (100)		
Total	136	62	38	11	25

^a DNET, dysembryoplastic neuroepithelial tumor.

TABLE 4. Postoperative seizure outcome in 136 resections after grid intracranial electroencephalography, by seizure frequency

Engel class	No. (%)
I: seizure-free or aura only	62 (47.0)
II: significant improvement	38 (28.0)
Sum of I and II (good outcome)	100 (73.5)
III: improvement	11 (8.1)
IV: no significant reduction	25 (18.3)
Sum of III and IV (poor outcome)	36 (26.5)

TABLE 5. Postoperative seizure outcome in 136 resections after grid intracranial electroencephalography, by locus of cortical resection

Locus of cortical resection	Engel classification, no. (%)				
	Class I	Class II	Class III	Class IV	Total
Temporal	23 (52)	11 (25)	2 (5)	8 (18)	44
<i>Mesial temporal</i>	12 (60)	4 (20)	0 (0)	4 (20)	20
<i>Neocortical</i>	11 (46)	7 (29)	2 (8)	4 (17)	24
Extratemporal	42 (46)	25 (27)	9 (10)	16 (17)	92
<i>Frontal</i>	31 (43)	19 (26)	8 (11)	14 (19)	72
<i>Parietal</i>	5 (45)	3 (27)	1 (9)	2 (18)	11
<i>Occipital</i>	6 (67)	3 (33)	0 (0)	0 (0)	9

longer than 7 days was more common with bone flap replacement ($P = 0.01$). Complication and infection rates were not increased by bone flap replacement ($P = 0.29$ and $P = 0.68$, respectively) or the use of perioperative corticosteroids ($P = 0.80$ and $P = 0.14$, respectively). The side of surgery ($P = 0.25$), age younger than 18 years ($P = 0.31$), and the number of cables ($P = 0.44$), grids ($P = 0.12$), electrodes ($P = 0.89$), and strips ($P = 0.15$) did not affect complication rates; furthermore, there was no trend in correlation, as in other studies (11). The use of depth electrodes has been reported as being associated with complications (11); there was no correlation in our study ($P = 0.06$).

DISCUSSION

This retrospective study encompasses the results of 198 consecutive craniotomies for invasive EEG monitoring over an 8-year period. The demographics of our patient population were similar to those of most published studies (1, 5, 6, 11, 13–16, 19, 22). Our findings are unique, however, because of the relatively large size and rapid rate of accrual. Hamer et al. (11) accumulated the same number of iEEG sessions over an 18-year period; however, during this period, there were significant changes in surgical technique and medical management, including tunneling of electrode leads and prophylactic antibiotic use, which are now standard of care at most centers. Notably, in our series,

there were no major changes in grid type (Ad-Tech), surgical or medical technique, or monitoring protocol. Therefore, this may be a more accurate representation of modern iEEG.

Technique

One controversial issue regarding iEEG is how the placement of electrodes affects the brain and seizure characteristics and whether it is likely responsible for complications (10). The Monro-Kellie doctrine predicts that volume changes in the cranial cavity from brain swelling and implantation of foreign objects will directly affect intracranial pressure and perfusion pressure, which may affect the local environment and in turn may affect seizure type, frequency, and complications. We routinely placed the craniotomy flap in cold storage during monitoring to prevent complications from its replacement unless unable to do so clinically. In addition, we frequently used perioperative corticosteroids to reduce brain swelling.

In reviewing the several large series available to us, it is evident the craniotomy bone flaps are most often replaced during monitoring (2, 11, 22). This has caused concern in our group that this will lead to complications, putting the bone flap at risk of osteomyelitis, altering iEEG characteristics, or causing patients to become lethargic from grid mass effect. Therefore, except in patients at high risk of craniotomy defect trauma, such as those with violent seizures and those of young age, our technique has evolved to placing the bone flap in cold sterile storage until it is returned for grid explantation. Notably, in the largest comparable series with the same number of monitoring sessions, six patients lost their bone flap to osteomyelitis, compared with two in our series (11). In addition, in published series in which bone flap replacement is routine, there is a retrospectively reported correlation of complications with the number of electrodes, grids, and cable number, suggesting that mass effect from insertion affects this rate. However, we noted no such correlation in our study (6, 11, 13, 14, 16, 22). Some institutions have taken to drilling down the internal table of the bone flap before bone flap replacement during monitoring to accommodate the electrode implantation. We do not perform this practice at our institution. Anecdotally, we have seen several osteomalacic bone flaps from thinning of the inner table and have performed cranioplasty to repair these.

In our series, those individuals with craniotomy bone flap replacement were more likely to have shift on postoperative CT of 3 mm or more. The duration of monitoring was also increased with craniotomy flap replacement, suggesting that it affects seizure characteristics. However, bone flap replacement was not associated with a higher rate of complications. Despite this, it did not affect whether the patient underwent surgery and subsequent resection, indicating that it likely did not interfere with localization or outcome after resection. This information has led us to recommend that the craniotomy flap should be left off during monitoring unless contraindicated by violent seizures, in which case, we are concerned about trauma to the unprotected cortex. We believe this for several reasons. First, our series did not find that leaving the craniotomy flap off during monitoring incurred patient morbidity. Second, replace-

ment of the craniotomy flap correlated with longer monitoring sessions, and we believe it to be beneficial to the patient to be monitored for as short a time as possible. Third, the number of electrodes and the side of surgery did not correlate with complications, as they did in other studies; this may be directly related to leaving the craniotomy flap off for monitoring. Fourth, it is our impression that patients are less lethargic or ill.

Corticosteroids are largely avoided secondary to a perceived risk of increased infection as well as a possible impact on suppression of seizure activity (2). Johnston et al. (13) and Araki et al. (2) demonstrated symptomatic improvement in their patient populations, which were largely pediatric, with routine corticosteroid use perioperatively, without an increase in infectious complications. In addition, Hamer et al. (11) noted a decrease in complications after the institution of routine perioperative corticosteroids; however, they were uncertain as to whether this decrease was secondary to more experience (there were fewer complications as time went on) or other changes in technique. This issue has not been addressed in a large or general population such as ours. In a post hoc analysis, we have found no change in infection rates in our 44% of patients receiving corticosteroids compared with those not receiving corticosteroids; in fact, there were relatively fewer infections in those receiving corticosteroids. These data are limited by their retrospective nature, and a randomized trial would be needed to establish a protective role of corticosteroids. Furthermore, complications were not correlated with the use of perioperative corticosteroids. Therefore, we believe that the use of corticosteroids can be left to the surgeon's preference without negatively affecting the patient, although we did not look at the medical complications associated with corticosteroid use, such as gastrointestinal ulcers.

Complications

The major complication rate reported here ($n = 13$, 6.6%), with a 1.5% persistent morbidity along with the types of complications, is comparable to those of other reports (11, 13, 22). Infection was concurrent with the only prospective data collection regarding its risk with subdural grids: 2.5% in our series and 7.9% in that of Wiggins et al. (22). In the largest retrospective study by Hamer et al. (11), an infection rate of 12.1% was reported; however, technique was changed mid-study, which reduced this rate. Furthermore, in that study, there was a 5% permanent deficit along with one death. We report a 1.5% permanent deficit rate with no deaths, which is concordant with the findings of Wiggins et al. (22). Notably, complications were not correlated with the length of time that the subdural electrodes were in place or with the number of cables, grids, or electrodes, which is in contrast to several published studies (11, 13, 22).

Outcome

Outcome can vary with the institution because patient demographics and techniques may vary. In our implanted group, 79% of sessions identified a responsible epileptogenic zone, and 69% of sessions led to resection of that focus. Our grid iEEG popula-

tion as a whole represents a unique and difficult population at a tertiary referral center with medically and, in 55 patients, surgically intractable epilepsy. A relatively high proportion of our patients (28% [55 total patients]) had undergone a previous resection before implantation. Siegel et al. (18) reported seizure outcomes in the largest series ($n = 64$) of subsequent resective surgeries after failed initial epilepsy surgery. In this group, only 34% were Engel Class I and 36% were Engel Class IV, demonstrating that members of this group had a particularly poor prognosis. In addition, the majority of resections in this series were extratemporal (68%), and, as noted in our pathology report, only three patients had postoperative pathology consistent with mesial temporal sclerosis. Furthermore, a relatively high proportion of our patients (48%) had no lesion on MRI. In 49 patients implanted with subdural grids, of whom only five were nonlesional (10%), Lee et al. (14) noted that of these five, three were Engel Class IV, representing a difficult population. Zentner et al. (23) noted that 60 patients with extratemporal epilepsy, 52% of whom had nonneoplastic lesions and 20% of whom had no lesions, were seizure-free at follow-up. Finally, intracranial monitoring is a negative prognostic indicator for seizure-free status after resection (21). Despite this difficult population, 47% of patients were seizure-free at last follow-up, and good seizure (Engel Classes I and II) control was obtained in 74% of patients with a mean follow-up of 50.6 ± 29.8 months. This suggests that iEEG has a high yield in identification of a focus for seizures and is highly effective in terms of outcome, even in cases of previous resections and extratemporal nonlesional epilepsy.

CONCLUSIONS

Subdural grid monitoring for identification of epileptogenic foci is high yield, even in challenging epilepsy populations. We prefer sterile storage of the bone flap during routine monitoring with grid iEEG, except in patients with violent seizures. This practice does not reduce the yield of iEEG or increase complication rates. Patients appear to tolerate implantation better. Furthermore, corticosteroid use, the number of electrodes, and the duration of monitoring do not seem to negatively influence complications or results, despite previously reported associations.

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COMMENTS

The successful surgical treatment of epilepsy requires the exact identification and localization of the seizure focus. Despite advances in “noninvasive” methodologies, the presurgical workup in selected patients continues to involve the placement of subdural and depth electrodes. In this article, Van Gompel et al. reviewed a large contemporary series of 189 patients who underwent placement of subdural electrodes as part of their preoperative workup. They described their technique, outcomes, and complications and considered additional lessons learned compared with previous series. Their results confirm that the technique of subdural electrode placement for intracranial electroencephalography is safe and effective.

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In this study Van Gompel et al. provided a lot of information regarding success rates in morbidity after grid implantation in a very large series of patients. The study population contained 26% pediatric patients and a high proportion of patients who had undergone previous resection and may thus be different from other study populations. The focus was on patients with partial epilepsy, with mixing those with temporal and extratemporal epilepsy. This article contains useful data and is therefore of great interest for epilepsy surgery groups. Incidentally, the mean duration of implantation, the detection rate of foci (79% in this series), and the incidence of hematomas are similar to experiences in our own center. It is clear that the technique of grid implantation is very useful but has certain risks. However, it obviously helps in the detection of many lesions not precisely identifiable with noninvasive recording and thus makes epilepsy surgery more precise and successful. A specific feature of this series is that the surgeons chose to leave out the bone flap in most patients. The article contains a very good discussion of the reasons that one might be doing this and presents results from other series in which this was not done. Van Gompel et al. described some useful findings, i.e., that the use of corticosteroids, the number of implanted electrodes, and the duration of monitoring do not seem to negatively influence the results or the complications. The main message is that serious permanent complications are rare. Overall, this is a very useful study.

Hans Clusmann
Johannes Schramm
Bonn, Germany

Van Gompel et al. have effectively summarized their experience with invasive intracranial electroencephalographic (iEEG) monitoring as a diagnostic tool and surgical adjunct in the management of patients with refractory epilepsy. This retrospective review of 189 patients over the relatively short span of 8 years provides a welcome addition to the current literature on the subject, owing to the accurate account of their surgical technique and subsequent patient outcomes. Of note, the epileptogenic zone was successfully localized with iEEG in 79% of monitored patients; 69% of patients underwent surgical resection, with 74% achieving Engel Class I/II outcomes after surgery. Permanent morbidity owing to complications was low (1.5%) and no deaths were reported, supporting the fact that this technique poses minimal long-term risks to patients.

Invasive monitoring in the workup of the patients with medically intractable epilepsy has become the “gold standard” when other noninvasive tests have failed to identify a focal lesion for resection. The technique was first attempted at the Montreal Neurological Institute by Penfield in 1939, using single-contact epidural electrodes introduced through a burr hole exposure. Since then, iEEG has matured as a diagnostic and surgical tool, largely owing to recent enhancements in equipment design (e.g., grids, strips, and depth electrodes), more accurate neurophysiological recording capabilities, and sophisticated signal analysis methodologies. Shorter monitoring periods have become the norm (often <1 week), and complication rates are typically low.

The article by Van Gompel et al. offers a refreshing update of this all-important technique and confirms its role in the surgical management of patients with epilepsy. Interestingly, their storage of the bone flap during the monitoring period is interesting and may merit consideration by certain readers. Ultimately, we feel that iEEG will continue to evolve and play an increasingly important role in the management of patients with refractory epilepsy.

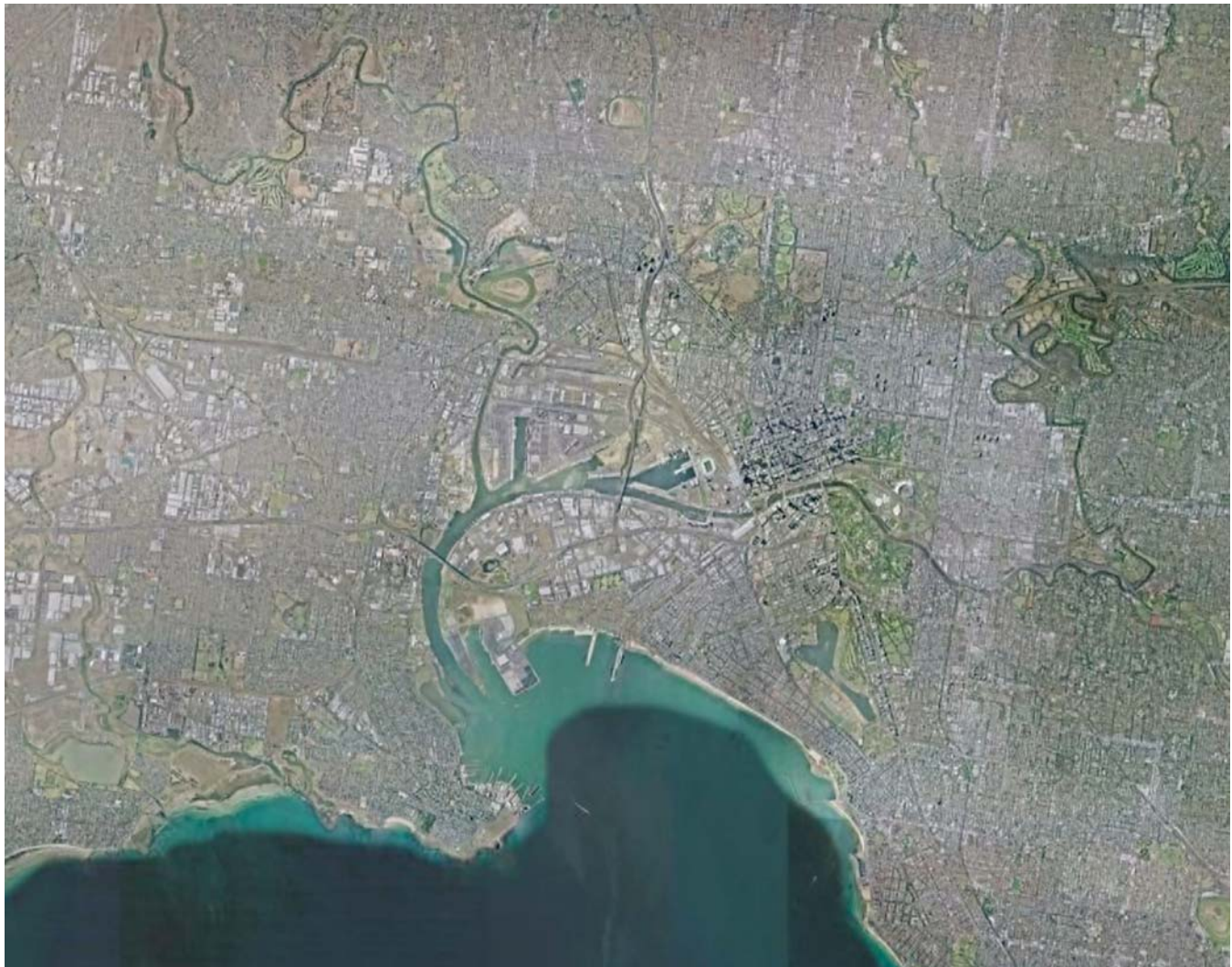
Demitre Serletis
James T. Rutka
Toronto, Canada

This is an important article describing the use of subdural grids and strips in both children and adults with intractable epilepsy. Van Gompel et al. described nicely the benefits and risks of such implantation. The benefits are the following: 1) It was possible to localize a seizure focus in 79% of patients; 2) 74% of patients had resolution or significant improvement in their seizures after resection of a focus; and 3) although not discussed in this article, the ability to map cortex under the grid for eloquent areas using cortical stimulation is an important consideration, especially in children. On the risk side, there was a significant complication rate of 6.6%, primarily infection or hematoma formation, with a 1.5% incidence of permanent deficits.

There are several features of this article that deserve comments. First, it is notable that there appeared to be little problem with cerebrospinal fluid leakage, an issue that has occasionally plagued us and requires earlier removal of the grids than planned. Second, the concept of leav-

ing out the bone flap is strange to us. At the Brigham and Women's and Children's Hospitals, we have not left the bone flap out in our subdural grid placements and have not noted any adverse effects of leaving it in place in more than 200 patients; we do leave it untethered by plates after the initial placement. Finally, the median length of time of 8 days for leaving grids in place is greater than we generally like to see; we try to remove them at 1 week if possible. However, it does not seem that the longer time at the Mayo Clinic increased the infection risk. Placement of grids and strips is an extremely powerful technique for localizing a seizure focus and at our institution has replaced depth electrode insertion in most cases. This article by Dr. Meyer's group suggests why this is an important and safe technique for localizing a seizure focus in patients of all ages.

Peter M. Black
Boston, Massachusetts



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VISUAL FIELD DEFECTS IN SELECTIVE AMYGDALOHIPPOCAMPECTOMY FOR HIPPOCAMPAL SCLEROSIS: THE FATE OF MEYER'S LOOP DURING THE TRANSSYLVIAN APPROACH TO THE TEMPORAL HORN

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OBJECTIVE: Meyer's loop, the most vulnerable part of the optic radiations during approaches to the temporomedial region, extends to the tip of the temporal horn and is often encountered in epilepsy surgery. The risk of damaging Meyer's loop during transsylvian selective amygdalohippocampectomy peaks while accessing the temporal horn through its roof by opening the inferior limiting sulcus of the insula. In this prospective study, we sought to evaluate and identify the incidence of visual field deficits in a homogeneous group of patients who had temporal lobe epilepsy with hippocampal sclerosis and who underwent transsylvian selective amygdalohippocampectomy.

METHODS: We studied 30 patients who were referred for epilepsy surgery for intractable complex partial and/or secondary generalized seizures and evaluated according to a non-invasive protocol. All patients underwent selective amygdalohippocampectomy for temporal lobe epilepsy with hippocampal sclerosis using the standard transsylvian approach. Visual field deficits were examined preoperatively in 30 patients, by either a confrontation method ($n = 18$) or standard Goldmann perimetry ($n = 12$) and post-operatively in all patients using standard Humphrey digital perimetry.

RESULTS: Visual field examination was normal in all patients before surgery. Humphrey perimetric measurement revealed visual field deficits in 11 patients (36.6%) after surgery.

CONCLUSION: We have shown that there is a considerable risk of having visual field deficits after standard transsylvian selective amygdalohippocampectomy owing to the interruption of the anterior bundle of the optic radiation fibers, which most likely occurs while opening the temporal horn through the inferior limiting sulcus of the insula.

KEY WORDS: Amygdalohippocampectomy, Epilepsy, Epilepsy surgery, Microsurgical anatomy, Optic radiation, Temporal lobe, Visual field

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Meyer's loop is formed by the anterior bundle of the optic radiation fibers that travels forward from the lateral geniculate body (LGB) toward the tip of the temporal pole in the roof of the temporal horn of the lateral ventricle. Meyer's loop, the most vulnerable part of the optic radiations during approaches to the temporal horn and temporomedial region, is often encountered in epilepsy surgery (15). Damage to the anterior bundle of

the optic radiation fibers (Meyer's loop) frequently results in superior homonymous quadrantanopic visual field deficits (VFD) after anterior temporal lobectomy (ATL) (in 50–90% of cases) (12–25). It is clear that the extent of the resection has an impact on the risk of VFD (1).

There have been conflicting reports regarding the incidence of VFD after transsylvian selective amygdalohippocampectomy (TSAH), although minimal invasiveness to Meyer's

ABBREVIATIONS: ATL, anterior temporal lobectomy; LGB, lateral geniculate body; MRI, magnetic resonance imaging; TLE-HS, temporal lobe epilepsy with hippocampal sclerosis; TSAH, transsylvian selective amygdalohippocampectomy; VFD, visual field deficit

loop would be expected owing to avoidance of neocortical corticectomy and resection on the temporal lobe, along with a more medial trajectory of the approach (32). In 1995, Renowden et al. (20) reported a VFD in the form of contralateral incomplete quadrantanopia, indicating damage to Meyer's loop, in 50% of their patients who underwent TSAH for temporal lobe epilepsy with hippocampal sclerosis (TLE-HS). In contrast, Yaşargil et al. (31) recently reported that only 2 of their 173 patients who underwent TSAH for TLE-HS had a VFD, and both of these patients had postoperative hematomas.

Several recent publications on microsurgical anatomy revealed the course of Meyer's loop by applying a fiber dissection technique and delineated the probable fate of this anterior bundle of optic radiation fibers in the transsylvian approach to the mediobasal temporal lobe (5, 22, 23). In this prospective study, we sought to evaluate and identify the incidence of VFD in a homogeneous group of patients who had TLE-HS and who underwent TSAH.

PATIENTS AND METHODS

All patients were referred for epilepsy surgery for intractable complex partial and/or secondary generalized seizures and evaluated according to a noninvasive protocol including ictal video electroencephalographic monitoring and neuropsychological and psychiatric examinations. Cranial magnetic resonance imaging (MRI) revealed only hippocampal sclerosis in all patients, without any additional abnormality. The definition of hippocampal sclerosis with reference to MRI was atrophy on T1-weighted images and hyperintensity on T2-weighted and fluid-attenuated inversion recovery MRI sequences.

All patients underwent TSAH, which was performed by the senior author (EO) using a pterional transsylvian approach, as described by Yaşargil et al. (32). The approach involved opening the sylvian fissure and exposing the anterior third of the insula down to the inferior limiting sulcus and the initial 2 cm of the M2 segment (24). Next, the bifurcation of the middle cerebral artery at the limen insulae was examined, and the inferior trunk of the middle cerebral artery was elevated away from the inferior limiting sulcus in most of the cases. A 1.5- to 2-cm incision directed downward and medially was completed beginning at the region of the limen insulae and extending back to the anterior part of the inferior limiting sulcus of the insula. The removal of the lower and lateral parts of the amygdala immediately below the incision provided entry into the temporal horn. The incision along the inferior limiting sulcus provided exposure of the head and the initial part of the body of the hippocampus and the choroid plexus on the floor of the temporal horn. The initial part of the choroidal fissure could be opened through the tenia fimbriae in all cases. The branches of the anterior choroidal artery and the P2 segment of the posterior cerebral artery that pass to the hippocampal sulcus were obliterated and cut. An incision around the hippocampus and the uncus recess was extended downward into the collateral and rhinal sulci, located below the temporal lobe. The head and body of the hippocampus, located approximately 1 cm behind the inferior choroidal point, and part of the parahippocampal gyrus were removed *en bloc* in all cases. The posterior part of the parahippocampal gyrus was removed with the help of suction to the posterior edge of the resection plane, located at the level of the lateral mesencephalic sulcus. Self-retaining brain retraction was not used in any part of the operation.

VFDs were examined preoperatively in 30 patients by either a confrontation method ($n = 18$) or standard Goldmann perimetry ($n = 12$) and postoperatively in all patients by standard Humphrey digital perimetry. There were 18 men and 12 women; 21 patients underwent left TSAH, and 9 patients underwent right TSAH. Their mean age was 31.6 years (range, 12–57 yr). Mean age at seizure onset was 13.1 years (range, 1.5–25 yr). A χ^2 test was used in the statistical analyses.

RESULTS

Visual field examination was normal in all patients before surgery. Humphrey perimetric measurement revealed VFDs in 10 patients (36.6%) after surgery (Fig. 1, C and D). However, all patients but one were unaware of the VFD. This patient had an additional third nerve palsy that resolved a few months after surgery. As expected, all VFDs were superior quadrantanopias in various degrees. Ten of 21 patients with left TLE-HS and 1 of 9 patients with right TLE-HS developed VFDs after TSAH ($P > 0.05$).

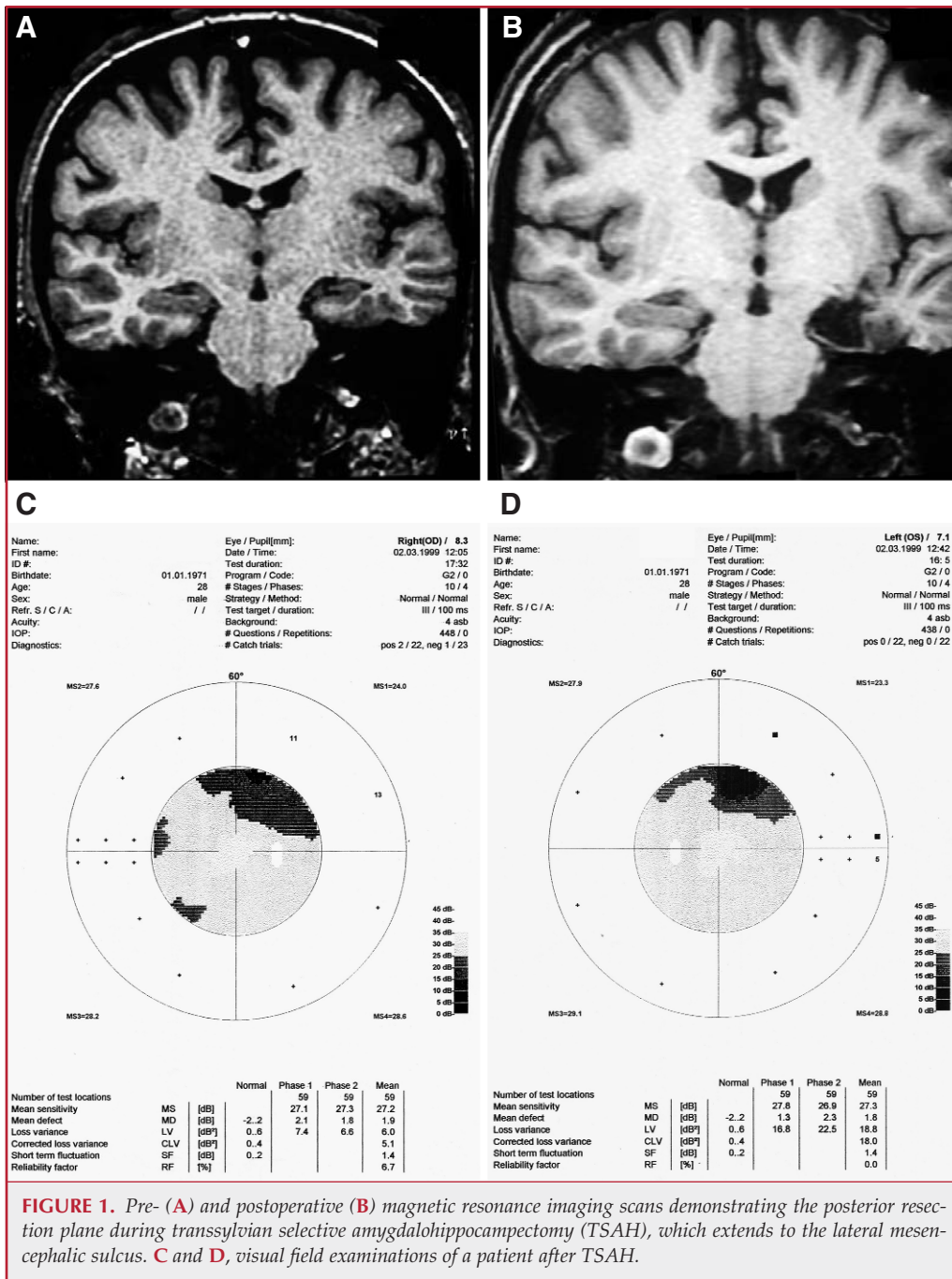
The postoperative follow-up period was 5.6 years (range, 1–11 yr). At the last follow-up evaluation, 23 patients were in Engel Class I, 6 patients were in Class II, and 1 patient was in Class IV according to Engel's outcome classification (10). However, all patients with VFDs were seizure-free after surgery (mean length of follow-up after surgery, 5.4 yr; range, 2–9.5 yr). There was no significant difference between Class I and non-Class I patients with regard to the presence of quadrantanopia ($P > 0.05$).

DISCUSSION

Meyer's Loop: Microsurgical Anatomy and Implications for TSAH

The geniculocalcarine tract arises from the LGB, passes through the retrolenticular and sublenticular portions of the internal capsule, and forms the optic radiations to reach the striate cortex, located on the medial surface of the occipital lobe (4, 29). The anterior bundle of the optic radiation fibers travels forward from the LGB toward the tip of the temporal pole in the roof of the temporal horn of the lateral ventricle. The anterior bundle then turns back, forming Meyer's loop, and passes posteriorly along the roof and lateral surface of the temporal horn. The fibers eventually pass below the atrium and occipital horn to reach the lower lip of the calcarine sulcus.

The demonstration of ATL as an efficient treatment option for complex partial seizures increased the number of studies evaluating the anatomy of Meyer's loop in the past 50 years (27). The incidence of VFDs after ATL ranges from 50 to 70% (16, 25) to 90 to 100% (2, 11, 13). There has been controversy about the course of Meyer's loop and its relationship with the temporal horn of the lateral ventricle. The anterior limit of Meyer's loop has been at the center of debate and is estimated to be anywhere from 20 to 60 mm posterior to the temporal pole. Previously, it was thought that the anterior limit of



It is known that the anterior bundles of the optic radiation convey the fibers of the superior quadrants of the retina, and damage to the anterior bundle inevitably results in partial or complete homonymous superior quadrantanopia (4, 29). Because of the lack of consensus on the location and configuration of the anterior extension of Meyer's loop in previous anatomic studies, conflicting results have been reported on the length of a safe area that can be resected during ATL. Initially, Penfield (18) stated that lesions less than 60 mm from the temporal tip were not likely to produce a field defect. In 1958, Falconer and Wilson (11) suggested that the location of the anterior limit of Meyer's loop is at about 45 mm from the tip of the temporal pole. Bjork and Kugelberg (2) estimated the anterior limit to be between 30 and 40 mm. In 1968, Marino and Rasmussen (16) reduced the length of the safely resected area and reported that the smallest defect occurred with a resection of 40 mm. More recent studies have evaluated the anterior limit of Meyer's loop using MRI and automated perimetry rather than intraoperative estimates of resection size. Krolak-Salmon et al. (14) estimated the anterior limit of Meyer's loop to be between 20 and 30 mm. In 2004, Nilsson et al. (17) concluded that the presence of VFDs was correlated with the involvement of the superior temporal gyrus between 18 and 36 mm from the temporal pole.

Meyer's loop does not reach the tip of the temporal horn in most cases. However, recent reports on microsurgical anatomy questioned this concept and revealed that Meyer's loop, in fact, extends to the tip of the temporal horn (5, 8, 19, 22, 23). The studies on quantitative assessment of Meyer's loop using MRI scans after ATL seem to concur with these findings and position the anterior extent of Meyer's loop approximately 24 mm from the tip of the temporal pole (1).

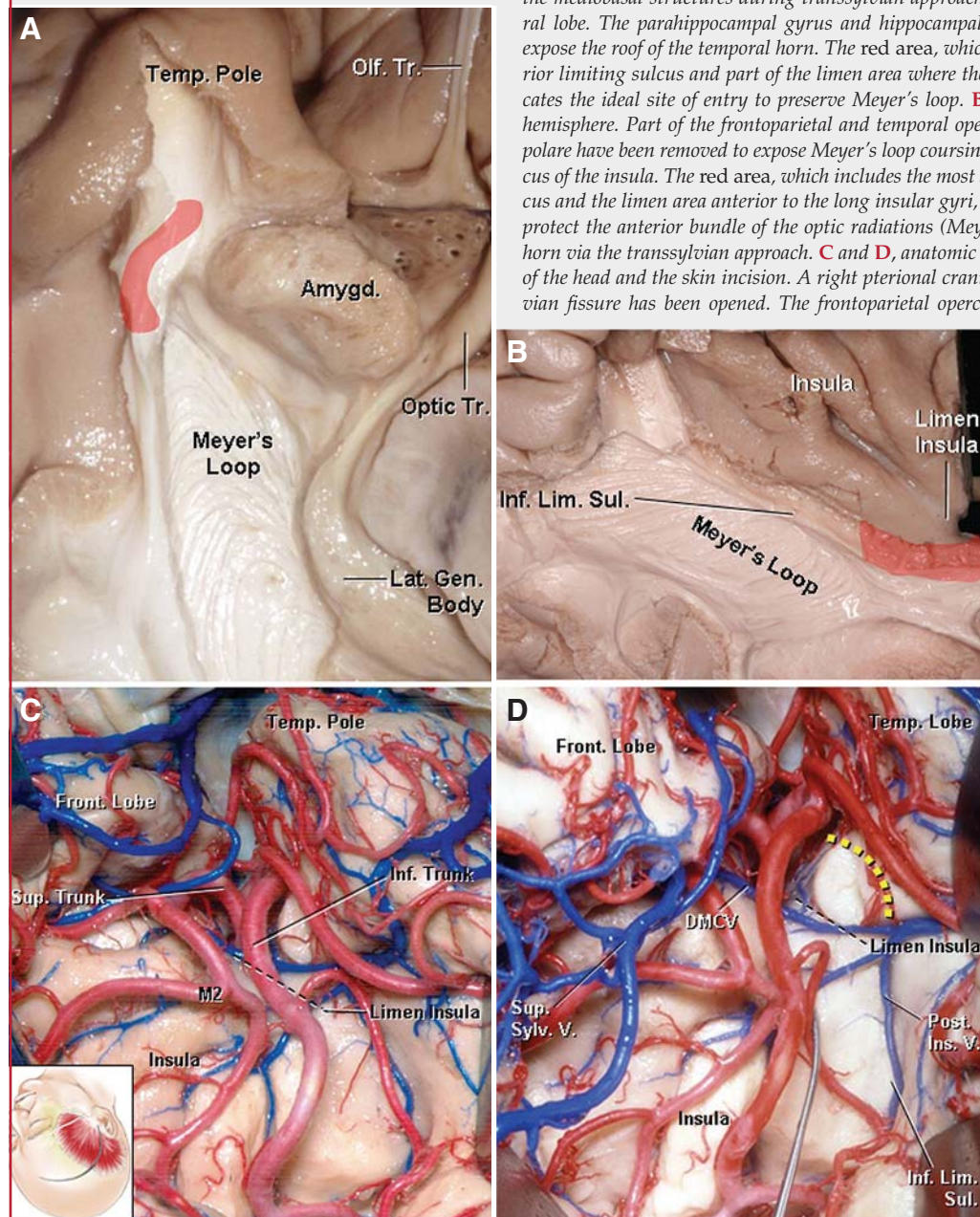
In a recent report, Barton et al. (1) evaluated the relationship of visual field loss to sagittal resection length during ATL and described the functional anatomy of Meyer's loop. Using MRI data, the authors placed the anterior limit of Meyer's loop 24 mm from the temporal pole for the nasal field and 28 mm from the temporal field. Importantly, the mean position of the tip of the temporal horn was 32 mm from the temporal pole, implying that Meyer's loop extends 4 to 8 mm beyond the ventricle on

average (1). All of these recent findings regarding the relationship between the anterior limit of Meyer's loop and the tip of the temporal pole as well as the temporal horn are in agreement with the studies on microsurgical anatomy. The anatomic studies clearly demonstrate that Meyer's loop passes forward along the roof of the temporal horn and reaches its anterior tip in all cases; however, evaluation of the medial extension of the anterior part of Meyer's loop toward the anterior part of the inferior limiting sulcus of the insula is more complicated, and this part

seems to display significant variability (Fig. 2, A and B) (5, 8, 19, 22, 23).

Visual impairment in the upper quadrant can, therefore, be expected when the roof of the temporal horn is opened to access the temporomedial structures, as in the case of TSAH. The risk of damaging Meyer's loop during TSAH peaks when accessing the temporal horn through its roof by an opening through the inferior limiting sulcus of the insula (Fig. 2, A and B). The incision to enter the temporal horn in TSAH has

FIGURE 2. A and B, anatomic dissections demonstrating the relationship between Meyer's loop and the safe zone of entry to the temporal horn to access the mediobasal structures during transsylvian approaches. A, inferior view of the right temporal lobe. The parahippocampal gyrus and hippocampal head and body have been removed to expose the roof of the temporal horn. The red area, which includes the initial 0.5 cm of the inferior limiting sulcus and part of the limen area where the long gyri of the insula converge, indicates the ideal site of entry to preserve Meyer's loop. B, superolateral view of a right cerebral hemisphere. Part of the frontoparietal and temporal operculum and the planum temporale and polare have been removed to expose Meyer's loop coursing anteriorly on the inferior limiting sulcus of the insula. The red area, which includes the most anterior part of the inferior limiting sulcus and the limen area anterior to the long insular gyri, indicates the ideal site of entry that can protect the anterior bundle of the optic radiations (Meyer's loop) while accessing the temporal horn via the transsylvian approach. C and D, anatomic dissections. C, inset shows the position of the head and the skin incision. A right pterional craniotomy has been completed, and the sylvian fissure has been opened. The frontoparietal operculum has been retracted to expose the



short and long gyri of the insula, the superior and inferior trunks of the middle cerebral artery (MCA), and the limen area. D, the inferior trunk of the MCA has been retracted to expose the inferior limiting sulcus of the insula through which the temporal horn is reached during TSAH. The incision (yellow broken line) on the most anterior edge of the inferior limiting sulcus and extending into the temporal site of the arch-shaped limen insula reaches the temporal horn through the amygdala and carries almost no risk of damaging Meyer's loop. The site of this incision corresponds approximately to the incision used in the transsylvian-transcisternal approach for selective amygdalohippocampectomy. The posterior insular vein passes anteriorly on the inferior limiting sulcus of the insula to join the deep middle cerebral vein at the level of the limen insula. Amygd., amygdala; DMCV, deep middle cerebral vein; Front., frontal; Gen., geniculate; Inf., inferior; Ins., insular; Lat., lateral; Lim., limiting; M2, insular segment of the middle cerebral artery; Olf., olfactory; Post., posterior; Sul., sulcus; Sup., superior, superficial; Sylv., sylvian; Temp., temporal; Tr., tract; V., vein.

been described as being from 12 to 20 mm in length and along the anterior part of the inferior limiting sulcus of the insula (32). In a recent publication, Choi et al. (5) examined Meyer's loop in relation to TSAH and demonstrated that it is not possible to preserve the anterior bundle of the optic radiations through an incision extending behind the initial 5 mm of the inferior limiting sulcus of the insula. The authors also defined a safe zone below the floor of the sylvian fissure, an incision directed inferiorly at the level of the limen insulae and the adjacent 5 mm of the inferior limiting sulcus, through which the temporal horn can be accessed via TSAH with a lower risk of damaging Meyer's loop. The amygdala is located in the base of this safe zone.

VFDs in Amygdalohippocampectomy

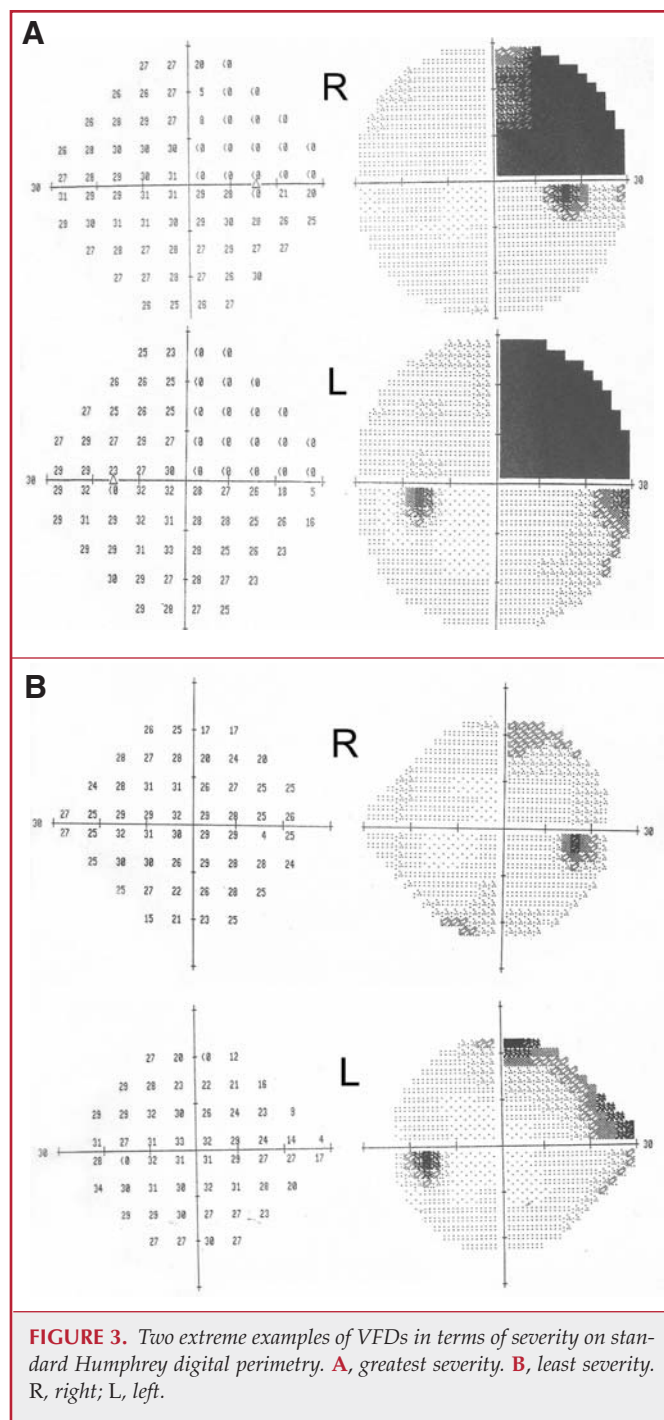
In accordance with these reports, a previous study demonstrated no significant difference between the frequency of VFDs produced after a modified ATL along the superior temporal gyrus through a transsylvian approach, and amygdalohippocampectomy through the middle temporal gyrus (9). That comparison study included not only patients with hippocampal sclerosis, but also patients with tumors on the uncus, amygdala, or hippocampus (9). Renowden et al. (20) demonstrated gliosis in the anterior temporal lobe on MRI scans resulting from wallerian degeneration in patients who underwent TSAH for TLE-HS. The significance of this study lies in the fact that, even though the surgeons opened the temporal horn through an incision beginning less than 2.4 cm behind the tip of the temporal pole and extending it less than 2 cm in all cases, wallerian degeneration was shown in the optic radiation fibers after TSAH (20). Half of the patients who underwent TSAH had a VFD that was homonymous superior quadrantanopia. The same authors also noted that white matter changes would have been observed in the T2 relaxation times or magnetization transfer in the remaining half of the patients after TSAH had these been measured in the study (20). Our results support the findings of these previous studies and reveal that even a relatively limited and anterior incision along the limen insulae area and inferior limiting sulcus during TSAH carries a significant risk of an interruption along the anterior bundle of optic radiations. Our incision for opening the temporal horn began anteriorly on the limen insulae area and did not exceed 2 cm in any patient. However, 36.6% of our patients had superior quadrantanopia on postoperative examination.

Contrary to these data, Yaşargil et al. (31) stated that they avoided the anterior bundle of optic radiations in almost all cases, although they performed an incision along the anterior portion of the inferior limiting sulcus of the insula. The low incidence of deficits in these patients has been explained by the fact that the trajectory of the TSAH may reach the temporal horn through the amygdala on the medial side of Meyer's loop and is directed posteriorly below the optic radiation into the hippocampus and medial temporal lobe (22). Although it is not clear why we could not spare Meyer's loop in 11 of 30 patients in our series, this may be the scenario in cases in which we preserved the optic radiations.

Although the same surgical technique and the site of entry to the temporal horn were used in all of our patients, not all patients had the same VFDs, and most had no deficits. These data and those of previous studies imply that a significant variability exists between each individual's organization of the anteromedial extension of Meyer's loop, the part that is intimately related to the anterior part of the inferior limiting sulcus of the insula (9, 20). The presence of variability on the medial and anterior extension of Meyer's loop may explain the diverse severity of the VFDs after TSAH in our series (*Fig. 3, A and B*). After removing the lateral parts of the amygdala through the incision at the level of the limen insula along the anterior part of the inferior limiting sulcus, as proposed by Yaşargil et al. (32), and Wieser and Yaşargil (28), the exposure of the TSAH is directed medially to avoid anteromedial extensions of Meyer's loop. However, in those cases in which Meyer's loop extends more medially at its anterior part, determining the correct medial trajectory to the temporal horn through the amygdala during TSAH will not be able to preserve the anterior loop of the optic radiations.

Another argument is that VFDs may occur after TSAH owing to spasm affecting the branches of the anterior choroidal artery that supply the optic tract and LGB (30, 32). This argument has been questioned because of the fact that the VFDs were very uncommon even after surgical obliteration of the anterior choroidal artery for parkinsonism. Cooper (6, 7) performed surgical occlusion of the anterior choroidal artery for parkinsonism in 50 patients. The artery was clipped twice, once at its origin and once at the distal part of the cisternal segment. Although the author reported 20% morbidity and 6% mortality in this group, only one patient developed homonymous quadrantanopia (6, 7). The extremely low incidence of VFDs secondary to anterior choroidal artery occlusion can be explained by the presence of the abundant number of anastomoses between the anterior choroidal artery and the branches of the posterior communicating and posterior cerebral arteries along the optic tract and the region of the LGB (21; Tanriover N, Ulu MO, Rhoton AL Jr, Sam B, Uzan M, Ozyurt E, in preparation). All of the postoperative VFDs observed in our patients were superior quadrantanopias, suggesting an interruption of Meyer's loop rather than the optic tract, where most of the branches of the anterior choroidal artery penetrate.

Entering the temporal horn through a more anteromedial incision, the transsylvian-transcisternal approach, has been described by Vajkoczy et al. (26) to preserve Meyer's loop during TSAH. This approach consists of entering the temporal horn through the planum polare on the medial side of the limen and entering the amygdala, located in the anterior segment of the uncus, from that trajectory (*Fig. 2, C and D*). The anterior uncus area and lower and lateral parts of the amygdala are initially removed in this approach by using subpial suction, which provides entry into the temporal horn. This route through the sylvian fissure and basal cisterns leaves the lateral and basal temporal cortices intact, and access through the roof and lateral wall of the temporal horn is also avoided, thus preserving the optic radiations. The drawback of the transsylvian-



transcisternal approach is the difficulty in visualizing and opening the choroidal fissure (3). Comparison of the VFDs produced after entry to the temporal horn through an incision on the inferior limiting sulcus during standard TSAH and those occurring after the transsylvian-transcisternal approach, with a more anteromedial incision, has not been published. However,

recent work on microsurgical anatomy, which directs special attention to the location of optic radiations, supports the role of the transsylvian-transcisternal approach in preserving the optic radiations (5, 22, 23).

Only one of our 11 patients was aware of the deficit, whereas the others were totally unaware of the situation. It seems that VFDs in the form of quadrantanopia after TSAH, similar to those occurring after ATL, may not have an important impact on the quality of life, especially when the patients are seizure-free. The patients usually do not notice their deficit. The only problem that arises in relation to this minor deficit is driving. Authorities prohibit driving if there is considerable VFD, the amount of which may differ from country to country. Manji and Plant (15) reported that 54% of their patients had VFDs using monocular Goldmann perimetry and 42% of their patients failed to fulfill the criteria to obtain a driver's license. Using the Esterman method (Humphrey perimetry) to evaluate the field defects in the same study reduced the frequency of VFDs and the number of patients failing to meet the criteria for obtaining a driver's license (15). According to the same criteria and considering the seizure outcome together with postoperative VFDs after TSAH, only 36% of our patients would have fulfilled the criteria to obtain a driver's license (15). The patients with TLE-HS would not be able to drive unless they became seizure-free; however, becoming seizure-free will not be sufficient to obtain a driver's license in the case of VFDs. Therefore, the risk of developing a VFD after TSAH for drug-resistant TLE may need to be discussed clearly with the patients, especially in those countries where driving has an important impact on the quality of life.

We have shown that there is a considerable risk of developing VFDs after standard TSAH caused by the interruption of the anterior bundle of the optic radiation fibers, which most likely occurs while opening the temporal horn through a 1.5- to 2-cm incision beginning at the region of the limen insulae and extending back to the anterior part of the inferior limiting sulcus of the insula. Further clinical studies are needed to determine whether moving the posterior limit of the incision more anteriorly during TSAH would reduce the risk of postoperative VFDs, because one of the goals of the approach is to enter the temporal horn below the roof, thus avoiding Meyer's loop.

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COMMENTS

Yeni et al. reported their series of selective amygdalohippocampectomy (SAH) via a pterional craniotomy using the anterior transsylvian approach in 30 patients with medication-resistant temporal seizures. The overall surgical outcome was very good and long-term results demonstrate success. The patients had no major neurological or cognitive deficits. However, postoperative visual field evaluations revealed that 11 patients (36.6%) had a homonymous superior quadrantanopia. We agree with Yeni et al. that this represents a high rate of visual deficit using the pterional transsylvian approach for SAH. However, their explanation of this visual deficit rate in their series is, in our opinion, rather simplistic. A more detailed analysis of the experience of the surgical team, the surgical trajectory, and the surgical methodology should be performed when one is assessing a single variable that can be influenced by multiple factors in a retrospective case series.

In the conclusion of their article, Yeni et al. left many aspects of the procedure open. The question arises as to why in 19 of 30 patients, apparently operated on by the same team, no visual defect occurred. The latter finding raises two important questions: 1) Were the operations performed by the same or different surgeons and 2) Were the patients with the deficits operated on earlier in the series (a learning curve factor)?

From a microsurgical anatomic and technical standpoint, a number of elements are important to clarify in the description of this technique. The procedure as described by the senior commentator (MGY) is a transsylvian trajectory that strictly avoids the use of self-retaining retractors. Therefore, it is important to raise the question: Was the self-retaining rigid brain retractor system applied to elevate the temporal lobe laterally and upward? This issue is especially important because of the fact that there are variations in the size, shape, and course in the vascular and parenchymal structures of the mesial-basal temporal lobe and consequently, extended unintentional lateral and posterior resection can lead to potential deficits. From the standpoint of postoperative assessment, were diffusion and diffusion tensor magnetic resonance imaging studies obtained, particularly in those 11 patients with postoperative visual field defects?

The so-called “standard transsylvian amygdalohippocampectomy” is a broad term, as there are several essential steps to consider and to appreciate in this delicate procedure. Since 1973, Yaşargil has applied the anterior transsylvian transamygdalar approach (1, 2). The sylvian fissure is opened anterior to the venous confluence. The interopercular sulcus, between the lateral fronto-orbital and superior temporal gyri, is dissected down to the sylvian fossa at the level of the middle cerebral artery bifurcation. Following the M1 segment of the middle cerebral artery in the distal to proximal direction, the entire proximal sylvian fossa is opened in an inside-outside fashion and the M1 segment and the internal cerebral artery, their branches, and their courses are identified. A pial incision is made lateral to the M1 segment between the temporal polar and anterior temporal arteries, beginning on the anterior point of the inferior peri-insular sulcus just at the level of the limen insulae and moving from distal to proximal (not backwards, as incor-

rectly mentioned by Wieser in 1982 [reference 28 in the article]) in a length of 10 to 15 mm over the cortical region of the amygdala. This approach was inaccurately described as a transsylvian transinsular approach by some colleagues. The descriptions and illustrations of this approach by Yaşargil since 1985 demonstrate clearly that this is a transsylvian transamygdalar approach. Initially, an attempt can be made to explore the temporal horn by an anterior-inferior approach, using bipolar forceps for dissection. As the temporal horn often collapses after release of cerebrospinal fluid from the basal cisterns and is difficult to target immediately, a more efficient tactic is to first remove the lateral amygdala using rongeurs or a suction system (1). During the process of piecemeal subpial suction of the amygdala, the cural cistern will be reached, in which the anterior choroidal artery and its branches, the basilar vein, and optic tract will be seen through the transparent pia-arachnoid layers. The next step is removal of the piriform cortex until the ambient cistern is reached, which allows identification of the IIIrd cranial nerve, the P1 and P2 segments and branches, the lateral aspect of the ipsilateral cerebral peduncle, and the entrance to the tip of the temporal horn in an anterior-medial-inferior axis. The dorsolateral wall of the temporal horn with several layers of fiber systems, in particular Meyer's loop, remains untouched during the entire procedure.

In Yaşargil's experience while in Zurich, the anterior two-thirds of the hippocampus and parahippocampus were removed *en bloc* to be able to perform biochemical studies. In Little Rock only the pes hippocampus is removed *en bloc* for histological studies and the posterior part of the hippocampus and parahippocampus undergo resection using the ultrasonic aspirator.

Yaşargil's publications have specifically stated and illustrated that the temporal horn is entered from an antero-medial-inferior transamygdalar trajectory rather than from the roof, and this trajectory is well illustrated in Figs. 7–15 in the article by Yaşargil et al. (1). The proposed modifications to the transsylvian amygdalohippocampectomy mentioned by Yeni et al. are not novel and have previously been well delineated (1).

The anterior transsylvian cisternal approach and transamygdalar selective amygdalohippocampectomy are performed with application of high-quality cotton sponges in increasing sizes, placed at each end of the sylvian fissure. They maintain a temporary atraumatic retraction of the fissure during dissection. Since the description of this approach by the Yaşargil in 1973, the rigid self-retaining brain retraction system has never been used to avoid any compression of the neopallial cortex and subcortical eloquent structures.

The availability of diffusion tensor magnetic resonance imaging tractography studies proves that the proximal transsylvian cisternal and transamygdalar approach permits selective removal of the anterior two-thirds of the hippocampus and parahippocampus without endangering the fiber systems of the optic radiation, anterior commissure, inferior-fronto-occipital fascicle, and neopallial connection of the uncinate fascicle.

Yaşargil mentions that numerous colleagues who have trained with him have also been able to avoid visual field defects in their series using the anterior transsylvian approach for selective amygdalohippocampectomy when performed as described above.

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Yeni et al. contributed valuable information to the epilepsy surgery literature. Ever since the introduction of the transsylvian amygdalohippocampectomy, authors have debated the relative merits of this approach compared with a more standard approach that transgresses the neocortex. The critical outcome variables have been language, memory, visual field deficits, and, of course, seizure control and stroke. This current article adds to a growing body of literature showing that not only is seizure control comparable (5), but also differential effects on language, memory, and now visual fields are not as dramatic as may have been thought (1, 2, 4). Hence, an amygdalohippocampectomy is equally effective, regardless of the approach, and the morbidity is comparable, as long as one minimizes the amount of neocortical disruption either through a small transcortical incision, a limited anterior temporal tip resection, or a posterior subtemporal approach.

What is most intriguing about this article is the variability in visual field deficits after uniform surgery. The variability in the anatomic location of Meyer's loop raises the possibility that one may be able to tailor the approach on the basis of the patient's unique anatomy. The technology now exists to perform preoperative optic radiation mapping with functional magnetic resonance imaging, and these data can be loaded into stereotactic planning computers to assist in surgical planning (3). I encourage the authors to take the next step to map the optic radiations and attempt to reduce visual field deficits prospectively.

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In this article Yeni et al. reviewed the incidence of visual field defects in the transsylvian approach for SAH. It contains very few original data, which are in themselves neither new nor surprising. A large part of the article is devoted to reviewing the literature and speculating on other types of approaches that may (or may not) lower the incidence of visual field defects. In Figure 2D of the article, the incision line used by the authors is shown by the dotted yellow line. With this approach, 11 patients of 30 patients had field defects. In our large SAH series, we open the inferior sulcus limitans more posteriorly, approximately 15 mm posterior to the limen insulae and usually do not open the temporal horn by a transamygdalar approach, but we enter the temporal horn at the posterior border of the amygdala, approximately at the level of

1. Yaşargil MG, Türe U, Yaşargil DC: Impact of temporal lobe surgery. *J Neurosurg* 101:725–738, 2004.

the choroidal point. Taking this difference into account, it is quite surprising that we have a rate of quadrantanopias that is not much different from the one in this series. In quite a number of articles, the fiber tracts of Meyer's bundle have been dissected or studied, and sometimes authors have chosen to describe in millimeters the distance from the tip of the temporal lobe to the most anterior aspect of Meyer's loop. Obviously this was done in the hope that if the surgeon knew about the extent and variation of Meyer's loop, injury would be prevented. As Yeni et al. correctly point out in their discussion, there obviously is a wide variation in the course of the fibers in Meyer's loop, and I am convinced that the kind of static anatomic description of the position of Meyer's loop is of no great help and that all descriptions in millimeters of distance are more or less useless. I think this is true for several reasons: first, not all damage to Meyer's loop is by direct transgression of its fibers, the damage may also be caused by damage to its vascular supply, by retraction of the lobe in the lateral direction, or by the necessity to perform a more liberal resection in those instances in which a small tumor or another lesion in the amygdaloid body or particularly in the head of hippocampus requires a more lateral reaching retraction. Any discussion about avoidance of visual field defects in the transylvian approach to the temporal horn should therefore be restricted to those patients in whom only the amygdala and hippocampus are to be removed. If one wants to avoid damage to the roof of the lateral ventricle, the ideal approach direction for entering the temporal horn is directly from the anterior, i.e., from the direction of where the orbit is placed, and that is obviously impossible. It is doubtful that it will ever be possible to have a selective amygdalohippocampectomy that reaches further backward than just 1 cm behind the choroidal point without visual field defects in a certain proportion of patients. However, this does not mean that I feel this kind of study is completely useless.

We neurosurgeons should always try to improve our outcomes. However, the impact of this study would have been greater if Yeni et al. had not only described the incidence of visual field defects in their series but had also initiated a second series in which they tried an alternative approach and would then have possibly been able to demonstrate a different incidence of field defects with a different approach. In the current version, the question of whether moving the site of entry into the temporal horn actually improved the rate of visual field defects cannot be answered. One positive item of note, although it may be due to the low number of cases: they did not observe hemianopia. Hemianopia is also possible in SAH and constitutes a serious side effect of this approach. We feel the rare cases of hemianopia are more likely to be caused by damage

to small vessels when arteries in the hippocampal fissure are coagulated and transected. These small vessels exit from perimesencephalic larger arteries such as the posterior cerebral artery or the anterior choroidal artery, and it may be that one inadvertently damages a tiny vessel that is supplying the optic tract or even the lateral geniculate body. Because a sacrifice of the vessel in the hippocampal sulcus is unavoidable in hippocampal resection, this source of visual field defects cannot be abolished by changing the entry into the temporal horn; it can only be avoided by even more careful dissection in the fissure of the hippocampus.

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Resection of the mesial structures of the temporal lobe continues to be a highly successful treatment for temporal lobe epilepsy owing to mesial temporal sclerosis. Traditionally, the surgical technique involved anterior temporal lobectomy with resection of the amygdala, the head and body of the hippocampus, and the parahippocampal gyrus, along with varying amounts of neocortex. Over the past several decades, increasingly specific techniques tailored for the preservation of neocortex have evolved to become standard in many centers, motivated principally by the potential for improved neuropsychological outcomes. One benefit of the transylvian approach for SAH relates to improved visual field outcomes from preservation of the anterior extent of Meyer's loop. In this article, Yeni et al. evaluated the fate of Meyer's loop in 30 patients with temporal lobe epilepsy treated with the transylvian approach for SAH. All of the procedures were performed by a senior neurosurgeon with well-accepted techniques. The patients were evaluated for visual field deficits both pre- and postoperatively. Interestingly, the results show that despite standard surgical technique, almost 40% of the patients demonstrated varying amounts of visual field deficits. The risk of injury to Meyer's loop is highest during access of the temporal horn through the inferior limiting sulcus of the insula. This study demonstrates that there may be considerable variability in the anteriomedial extension of Meyer's loop, as evidenced by more than 60% of patients having no postoperative visual deficits, as well as the variability of the visual deficits in those who experienced them. Further study is necessary to further define safe corridors, either in terms of general microsurgical trajectories or in terms of a specific definition of Meyer's loop by preoperative imaging.

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OUTCOME OF EXTRATEMPORAL EPILEPSY SURGERY EXPERIENCE OF A SINGLE CENTER

OBJECTIVE: Our aim was to determine the surgical outcome in adult patients with intractable extratemporal epilepsy and follow it over time.

METHODS: We retrospectively studied the operative outcome in 218 consecutive adult patients with extratemporal lesions who underwent resective surgical treatment for intractable partial epilepsy in the Bethel Epilepsy Center, Bielefeld, Germany, between 1991 and 2005. Patients were divided into three groups according to the 5-year period in which the surgical procedure took place.

RESULTS: Group I (1991–1995) consisted of 64 patients. The postoperative Engel Class I outcome was 50% at 6 months, 44.4% at 2 years, and 45.2% at 5 years. Group II (1996–2000) included 91 patients. Engel Class I outcome was 57.1% at 6 months, 53.8% at 2 years, and 53.5% at 5 years. In Group III (2001–2005), there were 63 patients. Engel Class I outcome was 65.1% at 6 months, 61.3% at 2 years, and 60.6% at 5 years. Short duration of epilepsy, surgery before 30 years of age, pathological findings of neoplasm, and well-circumscribed lesions on the preoperative magnetic resonance imaging scan were good prognostic factors. Poor prognostic factors were one or more of the following: psychic aura, generalized tonic-clonic seizure, versive seizure, history of previous surgery, and focal cortical dysplasia. On multivariate analysis, only the presence of well-circumscribed lesions on preoperative magnetic resonance imaging predicted a positive outcome ($P = 0.001$).

CONCLUSION: Our results indicate that extratemporal epilepsy surgery at the Bethel Epilepsy Center has become more effective in the treatment of extratemporal epilepsy patients over the years, ensuring continuous improvement in outcome. This improvement can be attributed mainly to more restrictive patient selection.

KEY WORDS: Epilepsy surgery, Extratemporal, Long-term outcome

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Epilepsy surgery is now widely accepted for the management of medically intractable localization-related epilepsy (34). Although results of extratemporal resection in adult patients with focal epilepsy have been reported previously, many of the studies included only a small number of patients and took place before magnetic resonance imaging (MRI) was widely implemented. Most reports include patients with both extratemporal and temporal lobe epilepsy of diverse causes (33, 36, 40). Results reported at the Second International Conference on Epilepsy Surgery suggest that the outcome

of seizure control has improved in patients with temporal lobe resections but is only stable in patients with extratemporal resections (10, 33). Recent developments in epilepsy surgery have increased the need for more follow-up studies (37). Whereas several studies have estimated the outcome of extratemporal epilepsy surgery, little attention has been paid to any changes in the extratemporal outcome over time. This report addresses the following questions: Has extratemporal epilepsy surgery outcome altered over time? What is our current state of extratemporal epilepsy surgery outcome? What are the characteristics of patients with the best outcome? What variables correlate with good long-term outcome? Our study includes only adult patients with extratemporal epilepsy who

ABBREVIATION: CI, confidence interval; MRI, magnetic resonance imaging

had surgery in an era that could benefit from MRI. They were under the care of the same neurologists and surgeons throughout the time periods in question. Although previous studies found that the response to epilepsy surgery during the first year of follow-up is a reliable indicator of long-term outcome (8, 41), we followed the progress of most of the patients for 5 years (4.1 ± 1.5 yr) postoperatively.

PATIENTS AND METHODS

We retrospectively reviewed the records of all adult patients (≥ 16 yr of age) who underwent epilepsy surgery at the Bethel Epilepsy Center, Bielefeld, Germany, from 1991 to 2005. There were 243 consecutive patients. We excluded patients who only underwent biopsy, patients with Rasmussen's encephalitis (a progressive disease with special criteria), patients who did not have electroencephalographic video monitoring, and patients who had unclear extratemporal resections. Nine patients had normal brain tissue in resected pathological specimens. Our study includes 218 patients divided into three groups according to the time period of operation: Group I patients were operated on from 1991 through 1995, Group II patients were operated on from 1996 through 2000, and Group III patients were operated on from 2001 through 2005.

Patient Characteristics

Group I consisted of 64 patients (29.3%); 41 patients were male (64%), and 23 were female (36%). The mean age at epilepsy onset was 11.7 ± 10.8 years (range, 0.08–51.0 yr; 95% confidence interval [CI], 8.8–15.0 yr). The mean age at surgery was 29.3 ± 11.3 years (range, 16–57 yr; 95% CI, 25–32 yr). The mean duration of epilepsy was 17.5 ± 9.8 years (range, 1–38 yr; 95% CI, 14.2–19.6 yr); and the mean duration of follow-up was 4.9 ± 0.5 years (range, 1–5 yr).

Group II was composed of 91 patients (41.7%); 50 patients were male (55%), and 41 were female (45%). The mean age at onset of epilepsy was 13.2 ± 9.3 years (range, 1–52 yr; 95% CI, 10.9–14.6 yr). The mean age at surgery was 28.1 ± 10.1 years (range, 16–59 yr; 95% CI, 26.1–30.4 yr). The mean duration of epilepsy was 14.9 ± 9.0 years (range, 0.83–44 yr; 95% CI, 13.2–17.0 yr); and the mean duration of follow-up was 4.9 ± 0.5 years (range, 2–5 yr).

Group III included 63 patients (29%); 38 patients were male (60%), and 25 were female (40%). The mean age at onset was 17.4 ± 15.9 years (range, 0.04–65.0 yr; 95% CI, 13.6–21.2 yr). The mean age at surgery was 32.2 ± 13.7 years (range, 16.0–69.0 yr; 95% CI, 29.1–35.6 yr). The mean duration of epilepsy was 13.8 ± 13.8 years (range, 0.91–65.4 yr; 95% CI, 11.4–17.9 yr); and the mean duration of follow-up was 2.5 ± 1.3 years (range, 1–5 yr).

The clinical characteristics of these patients, as well as detailed differences among the groups, are summarized in *Table 1*. The foregoing values are given as the mean number of years $\pm$ standard deviation.

Preoperative Evaluation

Preoperative workup for epilepsy surgery candidates includes recording the patient's history and carrying out a physical examination, neuropsychological evaluation, visual field test, and MRI examination, as well as inpatient video electroencephalographic monitoring and invasive monitoring with some patients for delineation of eloquent cortical areas. In our study, 75 patients (34.4%) underwent invasive monitoring in the form of subdural grids: 38 (59.3%) in Group I, 30 (32.9%) in Group II, and 7 (11.1%) in Group III.

Neuroimaging Modalities

Until 1998, a 1-T MRI scanner was used, and later a 1.5-T MRI scanner was available. A specific protocol for epilepsy patients was followed, using functional MRI, Wada test, positron emission tomography, and single-photon emission computed tomography (interictal and ictal) for the majority of the patients and additionally conducting MRI angiography in a few cases.

Surgical Procedure and Postoperative Evaluation

All patients underwent resective surgery in the form of lesionectomy, cortical resection, or lobectomy. There were a total of 34 patients (16.3%) who had surgery in the central area: 12 patients (18.7%) from Group I, 12 (13.1%) from the Group II, and 10 (15.8%) from Group III. Four patients (11.7%) had incomplete resections because of overlapping of the motor area and underwent combined lesionectomy with multiple subpial transections.

The same surgical team carried out all operations. Subdural grid or strip electrodes were used for invasive monitoring. Intraoperative electrocorticography was routinely used, except for patients with extraoperative invasive monitoring. Postoperative inpatient evaluation routinely included MRI and electroencephalography after 6 months and 2 years.

Data Collection

Research data in this study were drawn from four main sources: the patient's medical records, the postoperative routine follow-up program, additional outpatient appointments, and telephone and mail questionnaires. Families were consulted in many cases, especially for patients with mental retardation or with psychological problems. In 10 patients (4.5%), the data were missing after 2 years' follow-up. Another five patients (2.25%) died: one (0.4%) died in status epilepticus, and four (1.8%) died as a result of other medical causes. Histopathological information was extracted from histopathological reports in the patients' files. In our analysis, there were pathological findings in the resected specimen in 209 cases (95.9%), and no pathological findings in 9 cases (4.1%).

Outcome Evaluation

Seizure outcome was classified by using the modified seizure classification of Engel. Engel Class I patients were seizure-free; or they had only nondisabling, simple, partial seizures; or they had some disabling seizures after surgery but had been free of disabling seizures for at least 2 years; or generalized convulsions occurred only after withdrawal of antiepileptic drugs. Engel Class II patients rarely had seizures ($>85\%$ reduction). Engel Class III patients experienced worthwhile improvement, with a greater than 50% reduction in seizure frequency. Engel Class IV patients experienced no significant reduction in seizure frequency.

Outcome in relation to preoperative MRI pathological findings was correlated with well-circumscribed lesions (neoplastic, vascular, and cystic lesions) or less-well-circumscribed lesions (cortical dysplasia, malformation of cortical development, and gliosis) based on the MRI shape of the lesions. For all patients, preoperative MRI was reevaluated visually in the case conference by two epileptologists and an epilepsy neurosurgeon to determine whether the appearance of a lesion was well circumscribed or less well circumscribed.

Statistical Analysis

Categorical data of patients were compared by using the two-tailed Fisher's exact test. Mean numerical variables were compared using the Student's independent *t* test. The χ^2 test and the rank-sum test were used for univariate analyses. We additionally examined the independent effect of the variables as possible predictors of surgical outcome.

TABLE 1. Characteristics of 218 patients who underwent surgery over a 15-year period^a

Variable	Group I (%)	Group II (%)	Group III (%)	Total (%)
Mean age at onset (yr)	11.7 ± 10.8	13.2 ± 9.3	17.4 ± 15.9	14.0 ± 12.1
Mean age at surgery (yr)	29.3 ± 11.3	28.1 ± 10.1	32.2 ± 13.7	29.6 ± 11.7
Mean age at second surgery (yr)	28.0 ± 9.7	32.3 ± 10.1	29.0 ± 14.1	30.3 ± 10.0
Mean duration of epilepsy (yr)	17.5 ± 9.8	14.9 ± 9.0	13.8 ± 13.7	15.7 ± 10.8
Mean duration of follow-up (yr)	4.9 ± 0.5	4.9 ± 0.5	2.4 ± 1.1	4.2 ± 1.4
Febrile convulsion	2 (3.1)	3 (3.2)	2 (3.1)	7 (3.2)
Family history	1 (1.5)	3 (3.2)	3 (4.3)	7 (3.2)
Head trauma	4 (6.2)	7 (7.6)	3 (4.3)	14 (6.4)
Previous surgery	14 (21.8)	25 (27.4)	17 (26.9)	56 (25.6)
Prenatal infarction	3 (4.6)	8 (8.7)	4 (6.3)	15 (6.8)
MCD	5 (7.8)	5 (5.4)	3 (4.7)	13 (5.9)
CNS infections	1 (1.5)	5 (5.4)	4 (6.3)	10 (4.5)
Aura	50 (78.1)	66 (72.5)	43 (68.2)	159 (72.9)
Unclassified seizure	2 (3.1)	4 (4.3)		6 (2.7)
Simple motor seizure	7 (10.9)	5 (5.4)	5 (7.9)	17 (7.7)
Complex partial seizure	34 (53.1)	43 (47.2)	18 (28.5)	95 (43.6)
Generalized seizure	15 (23.4)	23 (25.2)	31 (49.2)	69 (31.6)
Combined seizure form	8 (12.5)	14 (15.3)	9 (14.2)	31 (14.2)
Pathological finding				
Neoplasm	22 (34.4)	29 (31.90)	28 (44.4)	79 (36.2)
FCD	24 (37.5)	30 (33.0)	14 (22.2)	68 (31.2)
Vascular	6 (9.4)	6 (6.6)	12 (19.0)	24 (11.0)
Gliosis	4 (6.3)	14 (15.40)	3 (4.8)	21 (9.6)
No abnormality	5 (7.8)	4 (4.4)		9 (4.1)
Cystic lesion	1 (1.6)	2 (2.2)	3 (4.8)	6 (2.8)
MCD		2 (2.2)	1 (1.6)	3 (1.4)
Sclerosis	1 (1.6)	1 (1.1)	1 (1.6)	3 (1.4)
Atrophy		2 (2.2)	1 (1.6)	3 (1.4)
Inflammation	1 (1.6)	1 (1.1)		2 (0.9)

^a MCD, malformation of cortical development; CNS, central nervous system; FCD, focal cortical dysplasia.

through binary logistic regression analysis by using the SPSS statistical program (Version 11.0; SPSS, Inc., Chicago, IL). The magnitude of the association between selected variables and surgical outcome was measured by the crude and adjusted odds ratio. Results were considered significant for values of $P \leq 0.05$. Cox multivariate stepwise regression was used to evaluate the predictors for Engel Class I outcome.

RESULTS

Overall Outcome

Engel Class I outcome was found in 125 patients (57.3%) at the 6-month follow-up, in 121 patients (56.0%) at the 1-year follow-up, in 115 patients (53.2%) at the 2-year follow-up, and in 94 patients (51.9%) at the 5-year follow-up. The statistical difference among the groups with regard to Engel Class I out-

come was $P = 0.375$ at 6 months, $P = 0.125$ at 1 year, $P = 0.03$ at 2 years, and $P = 0.230$ at 5 years. Figure 1 shows the percentage of Engel Class I over time in all groups. Numbers and percentages of different Engel classes in all groups are summarized in Table 2.

The outcome for Group I was as follows: 32 patients (50.0%) were in Engel Class I at the 6-month follow-up, 31 patients (49.2%) at 1 year, 28 patients (45.2%) at 2 years, and 28 patients (44.4%) at 5 years. After 5 years of postsurgical follow-up, 77.4% of the patients had a favorable outcome (Classes I–III), and 22.6% had no significant changes (Class IV).

In Group II, an Engel Class I outcome was found in 52 patients (57.1%) at the 6-month follow-up, in 51 patients (56.0%) at 1 year, in 49 patients (53.8%) at 2 years, and in 46 patients (53.5%) at 5 years. After 5 years of postsurgical follow-

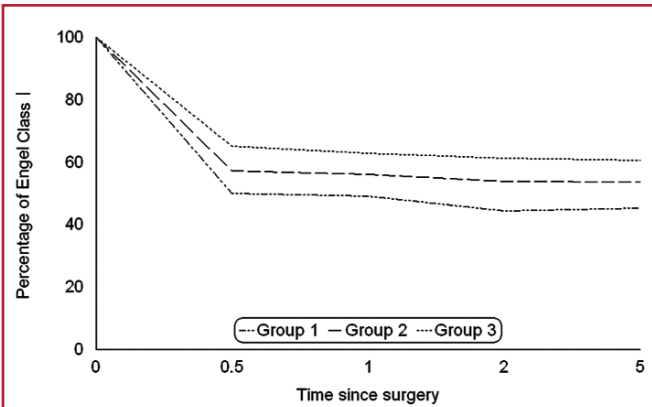


FIGURE 1. Graph showing the percentage of patients in the three groups in Engel Class I at different time points. The line representing Group III also represents the current state of the outcome in extratemporal epilepsy surgery.

up, 87.2% of the patients had a favorable outcome, and 12.8% had no changes.

For Group III, an Engel Class I outcome was found in 41 patients (65.1%) at the 6-month follow-up, in 39 patients (62.9%) at 1 year, in 38 patients (61.3%) at 2 years, and in 20 patients (60.6%) at 5 years. At the 5-year follow-up, 90.9% of

TABLE 2. Numbers and percentages of patients in the different Engel classes at 6 months and 1, 2, and 5 years

Engel Class	Group I (%)	Group II (%)	Group III (%)	Total (%)
At 6 mo				
I	32 (50.0)	52 (57.1)	41 (65.1)	125 (57.3)
II	9 (14.1)	10 (11.0)	6 (9.5)	25 (11.5)
III	7 (10.9)	14 (15.4)	7 (11.1)	28 (12.8)
IV	16 (25.0)	15 (16.5)	9 (14.3)	40 (18.3)
At 1 yr				
I	31 (49.2)	51 (56.0)	39 (62.9)	121 (56.0)
II	10 (15.9)	11 (12.1)	9 (14.5)	30 (13.9)
III	8 (12.7)	15 (16.5)	6 (9.7)	29 (13.4)
IV	14 (22.2)	14 (15.4)	8 (12.9)	36 (16.7)
At 2 yr				
I	28 (44.4)	49 (53.8)	38 (61.3)	115 (53.2)
II	17 (27.0)	12 (13.2)	10 (16.1)	39 (18.1)
III	7 (11.1)	16 (17.6)	7 (11.3)	30 (13.9)
IV	11 (17.5)	14 (15.4)	7 (11.3)	32 (14.8)
At 5 yr				
I	28 (45.2)	46 (53.5)	20 (60.6)	94 (51.9)
II	10 (16.1)	10 (11.6)	5 (15.2)	25 (13.8)
III	10 (16.1)	19 (22.1)	5 (15.2)	34 (18.8)
IV	14 (22.6)	11 (12.8)	3 (9.1)	28 (15.5)

patients had a favorable outcome, and 9.1% had no significant postsurgical changes.

Outcome in Relation to Resection Location

Frontal Lobe

In Group I, 25 patients (39.1%) had frontal lobe resections. Engel Class I outcome was found in 13 patients (52.0%) at the 6-month postoperative follow-up, in 13 (52.0%) at 1 year, in 11 (44.0%) at 2 years, and in 11 (44.0%) at 5 years. At the 5-year follow-up, 68% of patients had a favorable outcome (Classes I–III), and 32% had no significant changes (Class IV) (Fig. 2).

In Group II, there were 37 patients (40.7%) with frontal lobe resections. Engel Class I outcome was found in 21 patients (56.80%) at 6 months, in 21 patients (56.80%) at 1 year, in 19 patients (51.40%) at 2 years, and in 18 patients (54.50%) at 5 years. At the 5-year follow-up, 93.9% of patients had a favorable outcome, and 6.1% had no significant postsurgical changes.

In Group III, 33 patients (52.4%) had frontal lobe resections. Engel Class I outcome was found in 23 patients (69.7%) at 6 months, in 22 patients (66.7%) at 1 year, in 21 patients (63.7%) at 2 years, and in 11 patients (61.1%) at 5 years. At the 5-year follow-up, 88.2% of patients had a favorable outcome, and 11.8% had no significant changes.

The outcome in patients who were operated on in the motor area was slightly less favorable than the outcome for those operated on in other areas of the extratemporal cortex. Engel Class I was found in 17 patients (50%) at the 6-month follow-up, in 16 patients (47.1%) at 2 years, and in 11 patients (45.8%) at 5 years.

Posterior Cortical Resections

In Group I, 31 patients (48.4%) had posterior cortical epilepsy resections. Engel Class I outcome was found in 18 patients (58.1%) at the 6-month postoperative follow-up, in 17 patients (56.7%) at 1 year, in 16 patients (53.3%) at 2 years, and in 15

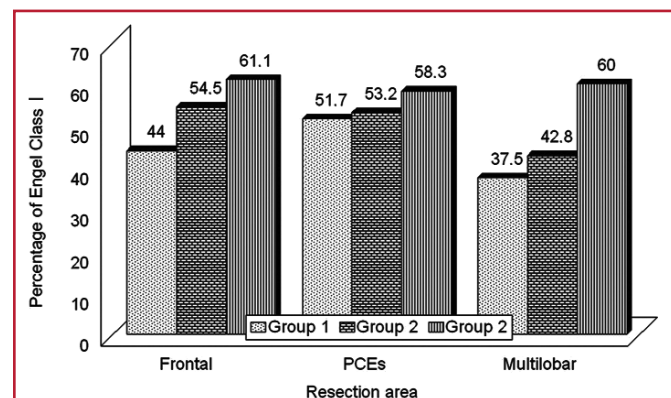


FIGURE 2. Bar graph showing the percentage of patients in the three groups in Engel Class I at the 5-year follow-up, categorized on the basis of the type of resection area. PCE, posterior cortical epilepsy.

patients (51.7%) at 5 years. At the 5-year follow-up, 89.7% of these patients had a favorable outcome, and 10.3% had no significant postsurgical changes.

In Group II, 47 patients (51.6%) underwent resections of the posterior cortex. Engel Class I outcome was found in 27 patients (57.4%) at 6 months, in 27 patients (57.4%) at 1 year, in 26 patients (55.3%) at 2 years, and in 25 patients (53.2%) at 5 years. At the 5-year follow-up examination, 85.1% of patients had a favorable outcome, and 14.9% had no significant postsurgical changes.

In Group III, 25 patients (39.7%) had posterior cortical resections. Engel Class I outcome was found in 15 patients (60.0%) at the 6-month postoperative follow-up, in 15 patients (60.0%) at 1 year, in 14 patients (58.3%) at 2 years, and in 7 patients (58.3%) at 5 years. At the 5-year follow-up, 81.7% of patients had a favorable outcome, and 8.3% had no significant postsurgical changes.

We had 11 patients with purely parietal lobe resections and 6 patients with purely occipital lobe resections. Engel Class I was found in 8 patients (72.7%) at the 2-year follow-up and in 6 patients (70%) at the 5-year follow-up in the parietal group. In patients who had purely occipital resections, 4 (66.7%) were in Engel Class I at the 2- and 5-year follow-ups.

Multilobar Resections

In Group I, 8 patients (12.5%) had multilobar resections. At 2 and 5 years, 3 patients (37.5%) were in Engel Class I. In Group II, 7 patients (7.7%) underwent multilobar resections. Engel Class I outcome was found in 3 patients (42.8%) at 2 and 5 years. In Group III, 5 patients (7.9%) had multilobar resections. Engel Class I outcome was found in 3 patients (60.0%) at 2 and 5 years. At the 5-year follow-up, 88.3% of the patients in Group I, 87.5% of the patients in Group II, and 88.3% of the patients in Group III had a favorable outcome.

Outcome in Relation to the Preoperative MRI Pathological Findings

In Group I, 31 patients (48.4%) had well-circumscribed lesions, and 33 patients (51.6%) had less-well-circumscribed lesions. Engel Class I outcome for the patients with well-circumscribed lesions after 6 months and 1, 2, and 5 years was found in 17 patients (54.8%), 16 patients (51.6%), 15 patients (50%), and 14 patients (48.3%), respectively. Engel Class I outcome for the patients with less-well-circumscribed lesions after 6 months and 1, 2, and 5 years was found in 15 patients (45.5%), 14 patients (42.4%), 13 patients (39.3%), and 13 patients (39.3%), respectively. At the 5-year follow-up, 86.7% of the patients with well-circumscribed lesions and 77.1% of those with less-well-circumscribed lesions had a favorable outcome.

In Group II, 37 patients (40.7%) had well-circumscribed lesions, and 54 patients (59.3%) had less-well-circumscribed lesions. Engel Class I outcome for the well-circumscribed lesions after 6 months and 1, 2, and 5 years was found in 25 patients (67.6%), 24 patients (64.9%), 23 patients (62.2%), and 22 patients (61.1%), respectively. Engel Class I outcome for the

patients with less-well-circumscribed lesions after 6 months and 1, 2, and 5 years was found in 31 patients (57.4%), 29 patients (53.7%), 24 patients (44.4%), and 25 patients (50.0%), respectively. At the 5-year follow-up, 83% of the patients with well-circumscribed lesions and 80% of those with less-well-circumscribed lesions had a favorable outcome.

In Group III, 42 patients (66.7%) had well-circumscribed lesions, and 21 patients (33.3%) had less-well-circumscribed lesions. Engel Class I outcome for those patients with well-circumscribed lesions after 6 months and 1, 2, and 5 years was found in 32 patients (76.2%), 31 patients (73.8%), 30 patients (71.4%), and 17 patients (70.8%), respectively. Engel Class I outcome for patients with less-well-circumscribed lesions after 6 months and 1, 2, and 5 years was found in 12 patients (57.1%), 11 patients (55.0%), 10 patients (50%), and 5 patients (55.6%), respectively. At the 5-year follow-up, 100% of the patients with well-circumscribed lesions and 90% of those with less-well-circumscribed lesions had a favorable outcome.

Engel Class I outcome showed significant differences among patients with regard to well-circumscribed and less-circumscribed lesions on MRI ($P = 0.03$) (Fig. 3).

Outcome According to Pathological Findings

At the 2-year follow-up, Engel Class I was found in 50 patients (64.1%) with neoplasms, in 15 patients (62.5%) with vascular lesions, in 25 patients (37.3%) with focal cortical dysplasia, in 10 patients (47.6%) with gliosis, and in 4 patients (44.4%) with no pathological lesions (Fig. 4). The numbers and percentages of the patients in Engel Class I at the 6-month and 1-, 2-, and 5-year follow-ups are summarized in Table 3. Although there was a significant difference at the first-year follow-up ($P = 0.012$) between the lesional and nonlesional groups and an apparent improvement in the percentage of Engel Class I over time, this result is considered not conclusive because of the small number of patients in the nonlesional group.

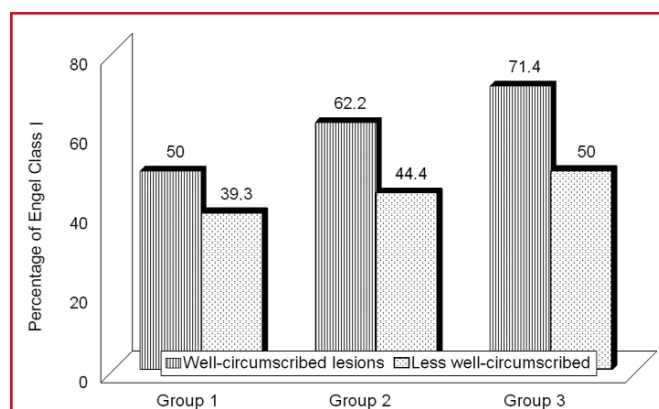


FIGURE 3. Bar graph showing the percentage of patients in the three groups in Engel Class I at the 2-year follow-up, categorized on the basis of the type of lesion on preoperative magnetic resonance imaging (MRI) (well-circumscribed or less-well-circumscribed).

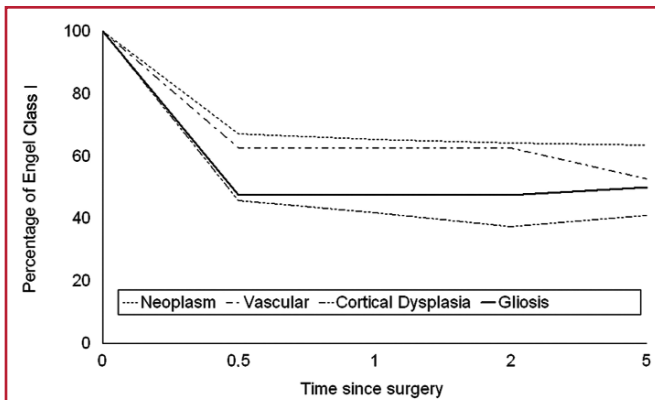


FIGURE 4. Line graph showing the percentage of patients in Engel Class I over time in the entire sample, categorized on the basis of different types of abnormality.

TABLE 3. Numbers and percentages of patients in Engel Class I at 6 months and 1, 2, and 5 years in most frequent pathological categories in the entire sample

Abnormality type	6 mo (%)	1 yr (%)	2 yr (%)	5 yr (%)
Neoplasm	53 (67.1)	51 (65.4)	50 (64.1)	40 (63.5)
Cortical dysplasia	31 (45.6)	28 (41.8)	25 (37.3)	25 (41.0)
Vascular	15 (62.5)	15 (62.5)	15 (62.5)	10 (52.6)
Gliosis	10 (47.6)	10 (47.6)	10 (47.6)	8 (50.0)
No abnormality	3 (33.3)	3 (33.3)	4 (44.4)	4 (44.4)

Prognostic Factors (Univariate and Multivariate Analysis)

In our study, the univariate analysis showed (Table 4) that there was a significant correlation of good outcome with each of the following findings: a well-circumscribed lesion on the preoperative MRI scan (Fig. 5), short duration of epilepsy (Fig. 6), early surgical interference, and a neoplasm in the resected specimen. There was a significant correlation of poor outcome with each of the following findings: a psychic aura, versive seizures, tonic-clonic seizures, history of previous surgery, and focal cortical dysplasia in the resected specimen. Table 4 lists the results of the univariate analysis in the entire sample.

In the Cox multivariate stepwise regression analysis, only the presence of a well-circumscribed lesion on the preoperative MRI scan could predict the long- and short-term outcome ($P = 0.001$; hazard ratio, 0.523; 95% CI, 0.361–0.756). All of the other factors that correlated with the outcome in the univariate analysis were unable to provide predictive value for the outcome in the Cox multivariate stepwise regression analysis.

Postoperative Complications

In Group I, 8 patients (13.5%) had various types of complications; 5 patients (8.4%) had permanent disabilities, and 3

TABLE 4. Univariate analysis for significant variables^a

Variables	P value	HR	95% CI
Well-circumscribed lesion on MRI	0.03	0.658	0.489–0.885
Invasive monitoring	0.0360	1.78	1.01–3.12
Psychic aura	0.0100	1.96	1.34–2.86
Versive seizure	0.012	2.870	1.261–6.532
Tonic-clonic seizures	0.024	2.56	0.05–6.19
History of previous surgery	0.045	2.033	1.017–4.061
FCD in abnormality	0.021	2.980	1.180–7.526
Neoplasm in abnormality	0.031	1.54	1.06–2.23
Duration of epilepsy (yr)			
≤ 5 (n = 37) (reference)			
> 5 (n = 181)	0.044	0.631	0.404–0.987
Age at surgery (yr)			
≤ 30 (n = 119) (reference)			
> 30 (n = 99)	0.042	0.349	0.127–0.964

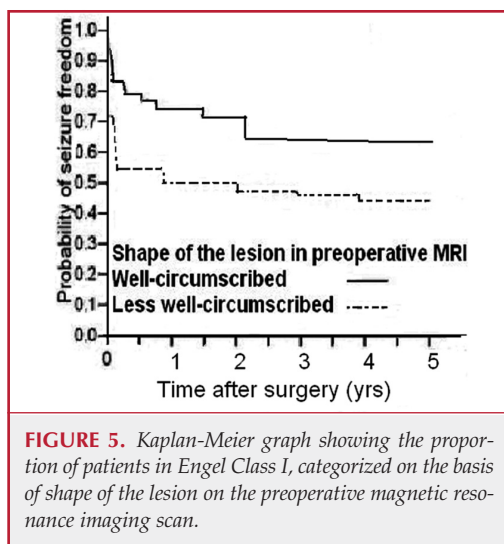
^a HR, hazard ratio; CI, confidence interval; MRI, magnetic resonance imaging; FCD, focal cortical dysplasia.

patients (5%) had transient morbidity. In Group II, 9 patients (10.3%) had complications; 4 patients (4.5%) had permanent disabilities, and 5 patients (5.5%) had transient morbidity. In Group III, 4 patients (6.3%) had complications; 1 patient (1.5%) had a permanent disability, and 3 patients (4.7%) had transient morbidity. Figure 7 shows the type of complications and the number of patients in the entire sample.

DISCUSSION

A considerable amount of literature has been published on the outcome of extratemporal epilepsy surgery. These studies showed a great difference in the outcome attributable to different types of lesions, different types of surgery, and the absence of a standard surgical procedure for extratemporal epilepsy surgery compared with temporal lobe epilepsy surgery. Unlike most researchers, we focused on the changes of extratemporal epilepsy surgery outcome over time and factors that play a role in causing these changes. Our patients were divided into three groups on the basis of their year of surgery to detect outcome changes over time and changes in the characteristics of the patients who were selected for surgery. The patients were followed for 5 years postoperatively. Engel Class I outcome progressed between 1991 and 2005 from 45.2% to 61.3% at the 2-year follow-up and from 44.4% to 60.6% at the 5-year follow-up. This change in the outcome is statistically significant at the 2-year follow-up ($P = 0.03$).

Published results show various outcome figures: Zentner et al. (43) reported 54% in Class I, Mathern et al. (20) reported 46%, Wyllie et al. (42) reported 35%, and Spencer et al. (35) reported 56% in a multicenter study. Generally, the reports pub-



lished over the last 15 years have varied from 35 to 80% (2, 11, 14, 34, 35, 40, 44).

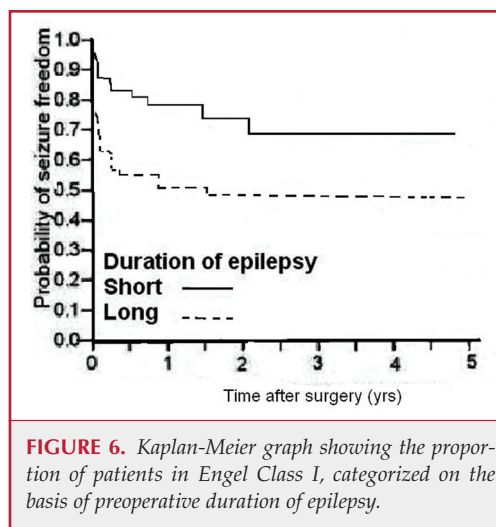
From the previous reports, it is not clear whether the outcome of extratemporal epilepsy surgery has progressed over time. At the Second International Conference on Epilepsy Surgery, it was suggested that outcomes for extratemporal epilepsy surgery had not changed since the time of the first Congress 6 years previously. This report (12, 46) from 1993 included patients operated on before the era of high-resolution MRI and the advancement of operative techniques. Tellez-Zenteno et al. (37) reported that outcome in the studies included combined temporal and extratemporal resections that improved more readily than purely temporal resections because of the improvement in outcome of the extratemporal resections. Our results are in line with studies showing more improvement in outcome of extratemporal resections.

Frontal Lobe Surgery Outcome

Previous reports showed great variation in the outcome after frontal lobe surgery: larger studies reported 50 to 55% favorable outcomes (11, 32, 38). However, seizure-free outcome was reported to reach 80% for specific subgroups of frontal lobe epilepsy surgery (12, 15, 19, 32, 44). Our results show a progressive increase of Engel Class I over time; Engel Class I had increased from 44% to 63.7% by the 2-year postoperative follow-up. By the 5-year follow-up, Engel Class I had increased from 44% to 61.1%. Some authors reported that frontal lobe epilepsy surgery improved over time (15, 16, 28). Our results are in accordance with previous reports and support this improvement of frontal lobe epilepsy surgery outcome.

Posterior Cortical Epilepsy Outcome

Our results show a continuous improvement of Engel Class I in posterior cortical epilepsies over time. Engel Class I increased from 53.3% to 55.3% after 2 years and from 51.7% to 58.3% after 5 years. In pure parietal lobe resection, Engel Class

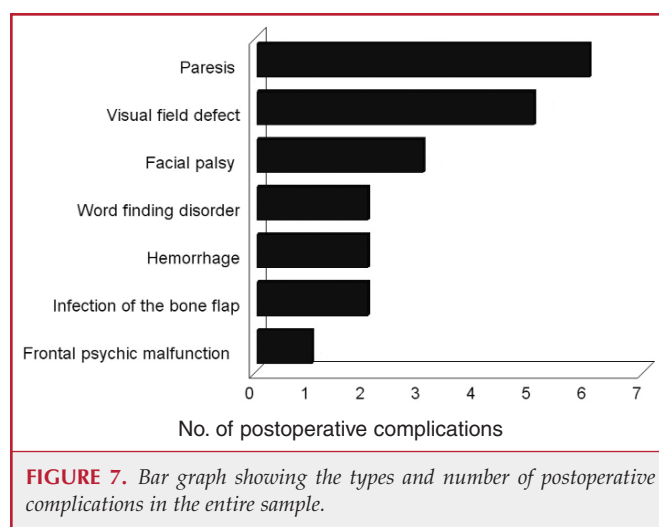


I reached 72.2% and 66.7%, respectively, over the same time periods in pure occipital lobe surgery.

Posterior cortical epilepsies in previous series range from 40 to 80% (2, 16, 19, 43). Recently, Kun Lee et al. (18) reported that 61.5% of patients were seizure-free after occipital lobe surgery. Dalmagro et al. (9) reported a 65.11% seizure-free rate, a percentage that is a little higher than our results. The reason for this difference may be that 20.6% of our patients had a previous history of surgery, a factor found to be associated with poor outcome in our study.

Multilobar Epilepsy Surgery Outcome

Multilobar epilepsy surgery showed some improvement despite the fact that this group had the least favorable outcomes in our study. Engel Class I changed from 37.5% to 60% at 2 and 5 years postoperatively. Devinsky et al. (10) reported 31% Class I and 23% Class II after multilobar epilepsy surgery, including operations on the eloquent cortex. However, the outcomes after



multilobar epilepsy surgery in most previous reports have ranged from 40 to 60% (14, 19, 25). Our results show agreement with the latest published reports. Multilobar epilepsy surgery has the lowest number of patients and the poorest outcome.

Outcome in Relation to Pathological Findings

In well-circumscribed lesions, Engel Class I outcome progressed from 50% to 71.4% after 2 years and from 48.3% to 70.8% after 5 years. In less-well-circumscribed lesions, Engel Class I progressed from 39.3% to 50% after 2 years and from 39.3% to 55.6% after 5 years. There were significant differences in Engel Class I outcome among groups ($P = 0.004$). Previous results show that for patients with less-well-circumscribed lesions, the seizure-free outcome rate is approximately 47 to 72% (1, 9, 17, 29), and for patients with well-circumscribed lesions, the seizure-free outcome rate is in the range of 70 to 80% (10, 13, 28, 29, 31). Our results are in agreement with the newer literature and support the thesis that lesional epilepsy surgery in well-circumscribed lesions has a better outcome.

Duration of Epilepsy and Age of Onset

In our study, we found a statistically and clinically significant correlation between Class I outcome and the duration of epilepsy before surgery ($P = 0.024$). Patients who were operated on within 5 years from epilepsy onset had a lower rate of recurrence compared with patients operated on after more than 5 years. The difference is clear in *Figure 6*, but short duration of epilepsy failed to predict the outcome. The difference between univariate and multivariate analysis indicates that the duration of epilepsy affects the outcome through other factors.

The relationship between good outcome and the duration of presurgical epilepsy is a controversial subject. Some authors have observed that the age at onset, age at time of surgery, and duration of epilepsy were not prognostic factors and therefore had no relationship to the outcome (1, 13, 34). Other authors, however, did find a significant correlation between the shorter preoperative duration of epilepsy and improved outcome. Trevathan and Gilliam (39) reported that early intervention is associated with good outcome in children and adults. Siegel et al. (30) reported good outcome after a second operation, which was related to the short duration of epilepsy. Cohen-Gadol et al. (8) reported a correlation between short duration of epilepsy and good outcome among patients with extratemporal resections. Some authors have reported a relationship between short duration of epilepsy and good outcome with certain abnormalities such as focal cortical dysplasia (17, 29). Our results strongly indicate a relationship between good outcome and short duration of epilepsy among patients with extratemporal epilepsy.

Long-term Outcome

Our results show little and insignificant differences in Engel Class I outcome between follow-up results gathered 2 and 5 years postoperatively. The majority of seizure recurrences in all groups occurred in the first 2 years after surgery. Earlier studies established the first 2-year outcome as a reliable indicator for long-term outcome, but most of these reports dealt with tempo-

ral lobe epilepsy surgery (24, 27, 41). Spencer et al. (34) reported no significant difference between temporal and extratemporal resections in the postoperative remission after 2 years of follow-up. Our study shows that the stability of outcome seen 2 years after surgery can be extended to extratemporal epilepsy surgery.

Complications

Our results show a progressive decrease in the complication rate in both permanent and transient morbidity over time, starting in Group I with 8.4% and reaching 1.5% in Group III. Previous reports showed that the complication rates for epilepsy surgery are generally low (3, 4, 6, 22). In 1997, Behrens et al. (3) reported 5.4% as the total rate of neurological complications, with 3.03% causing transient morbidity and 2.33% causing permanent morbidity. Rydenhag and Silander (26) reported minor complications in 8.9% and major complications in 3.1% of patients. Schramm et al. (28) reported transient neurological deficits of 4% and a permanent deficit rate of 2% after frontal lobe epilepsy surgery. Devinsky et al. (10) reported complications in 7.6% of patients.

Patient Selection

The improvement of Group III's outcome reflects the advancement in patient selection as a consequence of accumulated experience gained by the preoperative and operative teams. The third group had the shortest duration of epilepsy before surgery, early adult onset of epilepsy, midlife operation time, the highest number of well-circumscribed lesions (69.6%), and the lowest number of less-well-circumscribed lesions (30.4%). Only 11.1% of the patients had invasive monitoring, compared with 59.3% of the patients in Group I, and all of the patients had lesional epilepsy.

These results intensively point to the role of patient selection in increasing the probability of a good outcome, as some authors have already reported (5, 7, 21, 23). We recommend that patients with extratemporal epilepsy be well selected and referred to presurgical evaluation as early as possible.

CONCLUSION

This study shows the improvement of the outcome of extratemporal epilepsy surgery over time and supports the efficacy of epilepsy surgery to control medically intractable seizures. This development is attributable to appropriate patient selection, accurate presurgical delineation of the epileptic focus, high-resolution MRI, and the experience of the preoperative and surgical teams. This study shows that the outcome of extratemporal epilepsy surgery after 2 years can be used to predict the long-term outcome. The aforementioned information may be important in the decision-making process regarding referral to surgery and tapering of anticonvulsant medications postoperatively.

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COMMENTS

This very large retrospective study reported the results regarding seizure control rates in a consecutive series of more than 200 patients undergoing extratemporal epilepsy surgery between 1991 and 2005. Patients were grouped according to the respective date of surgery in three cohorts. Elsharkawy et al. found that seizure control rates improved over time from about 47% to 60% in this series. Although retrospective in nature, this outcome study provides some important information regarding surgery for extratemporal epilepsy. One strength of the study is the large number of patients. Other important information is the decline in the incidence of Engel Class I seizure-free outcome over 5 years, which is roughly equivalent to a loss of 1% seizure-free patients per year.

Our impression from our own patient groups and from observing the literature over the last 15 years is comparable to the main findings from this report: there seems to be clear improvement in seizure-free outcome with surgery for extratemporal lobe epilepsy. A seizure-free outcome of more than 60% is seen in recent groups using better magnetic resonance imaging technology, whereas 15 or 20 years ago the seizure-free outcome was frequently only approximately 50% (with variations according to various etiologies and locations). This series also confirms multiple findings from our own group and from other authors that patients with neoplasms have a better outcome than those with other causes; the same is true after surgery for temporal lobe epilepsy.

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Medical disciplines are celebrated for their successes, defined by their challenges, and haunted by their failures. Epilepsy surgery, a long and deep partnership between the fields of neurosurgery and neurology, has pockets of progress punctuating a field with little movement. Advances in neuroimaging and neurophysiology/invasive electrode monitoring have expanded the diagnostic arsenal. Novel stimulation and direct-to-brain drug delivery paradigms form an exciting pipeline to future therapies. Yet, it is frustrating to review Penfield's outcomes from 50 years ago and wonder just how far we have come.

This well-documented, consecutive case series between 1991 and 2006 from the Elsharkawy and the Bethel clinic team reported the outcome of extratemporal lobe epilepsy over a 15-year period. They identified a trend that all epilepsy centers would love to see. Looking at three consecutive blocks of 5 years, surgical success consistently improved over time. Although some of the improvement may relate to improved diagnostic and surgical tools, improved patient selection appeared to be the main factor. Their data support this conclusion. Two year postoperative Engel Class I outcome was highest in patients with well-circumscribed lesions such as tumors and vascular lesions (>60%). In contrast, comparable outcomes were lower among patients with focal cortical dysplasia (37%), gliosis (48%), or no pathological lesion (44%). The percentage of patients with tumors and vascular pathological lesions who underwent surgery rose over the past 15 years, whereas those with focal cortical dysplasia, gliosis, and no pathological lesions declined. Further, the sooner epilepsy surgery was

performed after the onset of seizures, the better the outcome. The duration of epilepsy among patients undergoing operations declined over the 15-year period.

Unilateral temporal lobe epilepsy and extratemporal lobe epilepsy resulting from localized lesions are the success stories of epilepsy surgery, with seizure-free rates of more than 60%. In highly selected groups (e.g., patients with mesial temporal sclerosis on their nondominant side and concordant seizure onsets), seizure-free rates exceed 80%. Among the estimated 500,000 patients in the United States and 10,000,000 patients worldwide with medically refractory partial epilepsy, less than one-third have unilateral temporal lobe epilepsy or extratemporal epilepsy with well-circumscribed lesions. What about the other two-thirds?

The trend at the Bethel Epilepsy Center to more carefully select candidates for surgery and identify those who have a better chance of achieving seizure freedom parallels the approach at many centers around the world. Improved outcome reflects improved patient selection. But improved outcome for whom? And for the two-thirds who are not offered surgery, is it really better patient selection? Perhaps the goal should be to seek a lower percentage of seizure-free outcomes. Our target population should be widened, away from the "sweet center" of unilateral temporal lobe and extratemporal epilepsy with localized lesions, to include those who are less likely to achieve seizure freedom.

The field of epilepsy surgery focuses on seizure-free outcome as the marker of success. But have we ignored palliation, the opportunity to improve quality of life through a reduction of seizure frequency and medication burden? For the majority of patients with medically refractory partial epilepsy who are "not good candidates for epilepsy surgery," we need to reconsider our definition of a "good candidate." How did we come to decide that seizure freedom was synonymous with surgical success?

Epilepsy surgery shares with cerebral tumor and other neurosurgical procedures a spectrum of disease substrates and a range of respective acceptable outcomes. These outcomes range from permanent alleviation of the disease to palliation or prolongation of the time to recurrence of the disease process. What all of these therapies share is the intention to improve the patient's quality of life. Yet epilepsy surgery, unlike tumor surgery, is perceived as failing unless seizures are completely controlled. Restricting epilepsy to only certain patients, in whom complete success is assured, is analogous to restricting tumor surgery to only benign or low-grade neoplasms. Evaluating success solely on the basis of seizure resolution may deny therapy to patients who may gain worthwhile improvement otherwise. As epilepsy surgery becomes better refined are patients being excluded from consideration?

Who are these patients with refractory partial epilepsy whose seizures are frequent enough to restrict their lives, who have tried multiple antiepileptic drugs and drug combinations with failed results, and who live with ongoing seizures and side effects? For many, epilepsy is a progressive disorder, with deteriorating cognitive and behavioral function and increased rates of suicide and sudden unexplained death. Memory, attention, mental processing speed, executive and language functions, and social skills can all decline as a result of years of seizures pounding on the brain. Depression, anxiety disorders, and psychosis all become more frequent with chronic epilepsy. Perhaps most startling are the rates of sudden unexplained death. Among patients with refractory epilepsy who are considering surgery, the yearly rate of sudden unexplained death in epilepsy is approximately 0.63% (5). Over a decade, that is a 6.3% rate that does not include deaths from other causes. We need to reexamine the benefits as well as the risks of the status quo.

Epilepsy surgery is definitely not for everyone with refractory partial epilepsy. Many patients have multiple or widespread foci that overlap with functional cortex. Surgery could leave a permanent deficit without any benefit. Yet some patients with two or even three seizure foci can benefit when one or two main foci are resected. Seizure frequency and severity may be reduced by 50% or more (2). This is hardly a cure, but surely it is a better place, and, for some, it can be potentially life-saving. Our challenge is not only to increase the frequency of seizure-free outcomes but also to help patients who cannot currently achieve seizure freedom.

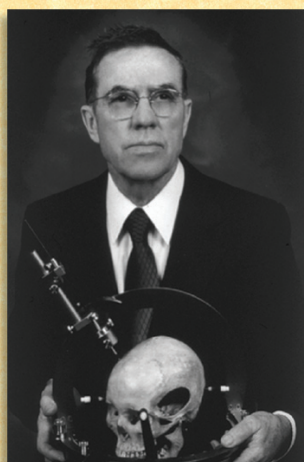
The field of epilepsy surgery needs to move beyond the myopic focus on seizures. Yes, well-designed studies have examined deficits in naming and short-term verbal memory after dominant temporal resections (3). Yet, what do we know about real-life executive and social functions after frontal lobe resections? The answer is not much. More recent studies have addressed employment, quality of life, and mood (3, 8, 10). However, we have ignored or avoided questions that Penfield raised a half-century ago concerning the epileptic substrate that he believed caused adverse interictal effects.

The nociferous cortex is defined as dysfunctional epileptogenic tissue that fails to perform its normal functions and impairs the function of other brain areas (4). Penfield and Jasper (7) introduced the concept of nociferous cortex in describing the dramatic behavioral improvements after hemispherectomy in an aggressive boy: "Among patients who have large areas of abnormality in one hemisphere, abnormal behavior may appear, together with advancing mental retardation. The behavioral abnormality is often a more important complaint than the seizures themselves. Radical complete excision may correct the abnormal behavior, stop the seizures, and allow improvement in the patient's mental state" (7, pp 841–842). How do we systematically identify both deficits and improvements after epilepsy surgery? What can we do to predict postoperative cognitive and behavior changes before surgery? Restricted epileptogenic foci can be nociferous. For example, nondominant anterior temporal lobectomy can improve verbal memory (6). Temporal lobectomy can improve metabolic functions ipsilateral and contralateral to the seizure focus, cortically and subcortically (6). Preoperative depression and anxiety often resolve after anterior temporal lobectomy (1, 2).

This article highlighted the capacity of excellent surgical centers to improve outcomes through diagnostic and therapeutic advances as well as more restrictive patient selection. It also highlighted the need to address the problems faced by those patients with epilepsy who do not meet more rigorous selection criteria and raises the question: As epilepsy surgery becomes better refined, are patients who would benefit from surgery being excluded from consideration?

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NEUROPSYCHOLOGICAL EFFECTS OF SHUNT TREATMENT IN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

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OBJECTIVE: To prospectively evaluate the effects of shunting on the neuropsychological performance of patients with idiopathic normal pressure hydrocephalus (INPH), to compare their performance with that of healthy individuals, and to estimate the predictive utility of putatively important factors.

METHODS: A consecutive series of 47 patients with INPH underwent neurological, radiological, and neuropsychological examinations before and 3 months after shunt surgery. The same neuropsychological tests, measuring simple and target reaction times, dexterity, memory and learning, working memory, and aspects of executive functioning, were also administered to 159 healthy individuals.

RESULTS: Performance on all neuropsychological tests, except Simple Reaction Time and Digit Span, significantly improved after surgery, with more severe functional deficits showing greatest improvement. Age, education, duration, vascular comorbidity, sex, and onset symptom all failed to predict the neuropsychological effects of treatment. Despite improvement 3 months after shunt surgery, INPH patients were still outperformed by healthy individuals.

CONCLUSION: Most of the wide range of neuropsychological functions that are affected by INPH are markedly improved by shunt treatment, but not completely restored.

KEY WORDS: Idiopathic normal pressure hydrocephalus, Neuropsychology, Outcome, Performance, Prospective study, Shunt surgery, Treatment effect

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Idiopathic normal pressure hydrocephalus (INPH) is a condition of disturbed cerebrospinal fluid (CSF) dynamics, the causes of which are not known. It is clinically characterized by progressive impairment of gait and balance, cognitive deterioration, and urinary incontinence in conjunction with an enlarged ventricular system and normal intracranial pressure.

The success rate of shunt surgery in reported series has ranged from 30 to 96% (22, 31, 45, 56). Reported long-term effects of shunting also vary considerably between studies (26–50%) (30, 36, 53). The neuropsychological characteristics of INPH and the cognitive effects of shunting have been much debated during recent years (17, 37). Reported improvement in neuropsychological functions

after surgery have ranged from no statistically significant improvement to improvement rates of 70% (27, 44, 47, 51).

We recently showed that the preoperative neuropsychological deficits in INPH are wide-ranging, interrelated, associated with neurological signs, and aggravated by vascular comorbidity (24). The aims of this prospective study were to evaluate the effects of shunting on neuropsychological performance in INPH patients and to estimate the predictive utility of putatively important factors.

PATIENTS AND METHODS

Patients

Fifty-six consecutive patients with INPH were preoperatively examined and reevaluated postoperatively at the Hydrocephalus Research Unit, Sahlgrenska University Hospital, between January 1, 1999, and December 31, 2006.

ABBREVIATIONS: CSF, cerebrospinal fluid; HI, healthy individual; INPH, idiopathic normal pressure hydrocephalus

The diagnosis of INPH was based on the presence of typical gait disturbance (6, 46, 50), either organic mental symptoms (35, 54) or urinary incontinence (2), enlarged ventricles on computed tomography or magnetic resonance imaging scans (Evans' index >0.30), a lumbar CSF pressure below 18 mmHg, and an open aqueduct as evidenced by magnetic resonance imaging and/or radionuclide cisternography. The diagnosis also required an insidious onset and no evidence of antecedent causes of secondary hydrocephalus.

A neurological examination was performed according to standard procedures at our unit (6, 34, 55) and included the assessment of dementia (by means of the Mini-Mental State Examination [18]), gait, balance, incontinence, and daily hours of sleep. Vascular risk factors (hypertension, diabetes, and cardiovascular disease) were registered as present or not present. A neuropsychological examination was also performed (24).

All patients subsequently received ventriculoperitoneal shunts and were re-examined 3 months postoperatively using the same methods.

The valves used were Delta shunts (Medtronic PS Medical, Goleta, CA) (i.e., fixed valves, $n = 18$), Strata programmable valves ($n = 27$) (Medtronic PS Medical), and Codman Hakim programmable valves (Johnson & Johnson Co., Raynham, MA) ($n = 11$). In cases of unsatisfactory clinical improvement after surgery, the valves were checked using either the radionuclide shunt function test (58) or a computerized infusion test. Dysfunctioning valves were replaced, and in cases of working shunts associated with little or no clinical improvement, valves were adjusted to enhance treatment response.

Valve opening pressure was adjusted in 10 patients (lowered in 9 and raised in 1), and consequently, the postoperative examination was postponed for 3 months. Of these, four patients had a full-scale re-examination; three patients were clinically improved after several adjustments but could not be reexamined according to the protocol; and three patients had undetermined outcome and no complete reexamination was performed. Thus, the latter six patients were excluded. Eight patients experienced shunt-related problems. Of these, two had subdural hematomas and were reexamined according to the protocol 3 months after treatment (one revision, one adjustment), and five patients had mechanical shunt problems which required reoperation. Of the latter five patients, three were reevaluated according to the protocol, whereas two experienced repeated complications and were excluded because they could not be neuropsychologically reevaluated. One patient was excluded owing to uncertain shunt function at the time of reexamination. Thus, nine patients were excluded owing to lack of complete reexaminations, leaving 47 patients in the study.

A comparison group comprising 159 healthy individuals (HI) with a comparable age distribution was recruited from senior associations and church organizations. Participants voluntarily underwent neuropsychological testing in the spring of 2006. Individuals with neurological disorders were excluded, whereas those with stable medical conditions (e.g., successfully treated diabetes, hypertension, or hypothyreosis) and/or minor psychiatric disorders (e.g., mild symptoms of anxiety or depression and/or self-reported use of antidepressants [selective serotonin reuptake inhibitors only] or mild tranquilizers) were included. Information regarding the presence of vascular risk factors among the HIs was not recorded. Demographic characteristics of patients and HIs are shown in Table 1, and the preoperative clinical characteristics of the patients are presented in Table 2.

Neuropsychological Methods

All of the INPH patients were examined by the same neuropsychologist (PH). The formal testing was preceded by a clinical interview to acquaint the patient with the clinician and the situation. The following

tests were administered: Simple Reaction Time, Target Reaction Time, Grooved Pegboard, Tracks Task, Rey Auditory Verbal Learning Test, Swedish Stroop Test, and Digit Span.

Simple Reaction Time is a computerized task developed at our unit that measures mean reaction time. The patient is instructed to fixate on a white cross on a black screen and to press the space bar as quickly as possible when the screen turns white. There are 20 screen changes, and the length of the fixation intervals varies randomly between 2 and 6 seconds (this task was not included in the assessment of HIs).

Target Reaction Time measures mean reaction time in milliseconds for 20 randomly appearing targets. The fixation conditions are identical to those in the previous task, and the patient is also instructed to press the space bar as quickly as possible when the screen turns white (target), but to avoid pressing if it turns red (nontarget). The same number of nontargets and targets are presented in each session, and the order of presentation is randomized. The two reaction time tasks were developed using E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA) and were administered on standard computers.

The Grooved Pegboard (Lafayette Instrument Co., Lafayette, IN) measures manual dexterity as time to fit 25 pegs into holes with randomly positioned slots. The test is performed first with the dominant hand, followed by a trial with the nondominant hand. The score represents the time in seconds to complete both trials.

The Tracks Task, originally constructed by Alan Baddeley (4) as the motor half of a dual task, measures motor speed in a task requiring the patient to cross squares in an order indicated by connecting lines (the score is the number of squares in 1 minute).

The Rey Auditory Verbal Learning Test (48) assesses verbal learning and memory. Scores represent the total number of words recalled over five learning trials and the number of words remembered after 30 minutes.

The Swedish Stroop Test (23) measures naming speed, response selection, and inhibition. It requires the patient to name the colors (blue, red, green, or yellow) of 100 rectangles as fast as possible, and then to name the printed color of 100 incongruent color words (e.g., the word "blue" printed in red). The scores are the number of seconds to complete each trial (color naming and interference) and the difference in seconds between the two trials (reflecting the extra time needed to select the correct response in the interference condition).

TABLE 1. Demographic characteristics of idiopathic normal pressure hydrocephalus patients and healthy individuals^a

Demographic characteristics	INPH (n = 47)	HI (n = 159)
Age, median (range)	73 (24–84)	73 (50–87)
Sex, male/female (%)	47/53	46/54
Education (yr), median (IQR)	11 (7–14)	13 (10–17)
Living conditions (%)		
At home without assistance	60	100
At home assisted by spouse or relatives	21	
At home assisted by home service	6	
Service flat	6	
Nursing home or hospital	6	

^a INPH, idiopathic normal pressure hydrocephalus; HI, healthy individual; IQR, interquartile range.

TABLE 2. Symptoms, signs, and comorbidity in idiopathic normal pressure hydrocephalus^a

Gait disturbance (100%)	No. or %
0 Normal	0%
1 Insecure but unaided	60%
2 Cane	15%
3 Bimanual support	17%
4 Living support	6%
5 Wheelchair	2%
Balance disturbance (100%)	
0 Normal	0%
1 Unstable	30%
2 Romberg <60 s	8%
3 Romberg <30 s	43%
4 Unable	19%
Incontinence (100%)	
0 Normal	20%
1 Urgency	24%
2 Occasional leakage	22%
3 Always diapers	28%
4 Double incontinence	6%
Cognition	
MMSE, median (range)	25 (7–29)
Daily need of sleep	
Time (h), median (range)	9.5 (6–18)
Comorbidity (%)	
Hypertension	21%
Cardiovascular disease	26%
Diabetes	11%
Combinations	43%

^a MMSE, Mini-Mental State Examination.

The Digit Span Test, from the Wechsler Adult Intelligence Scale III (Harcourt Assessment, Inc., San Antonio, TX), assesses short-term or working memory by means of forward and backward repetition of series of digits. Scores correspond to the number of digits in the longest series under each condition. A summary score (Wechsler Adult Intelligence Scale score) is also calculated and represents the total number of correctly repeated series under both conditions.

The rationale for the selection of the specific instruments has been described earlier (24). Owing to changes in examination routines through the years, not all of the patients were assessed with all of the above tests (actual numbers are presented in Table 3). The HI group was tested in neutral settings by one of four psychology students, who were trained and supervised by PH.

Statistical Analysis

Nonparametric statistical methods were used in all analyses of ordinal variables and of continuous quantitative variables as a result of

nonsymmetrical distributions and/or substantially larger variances among patients than among the HIs. The Spearman rank correlation coefficient (ρ) was used to estimate associations between variables. The Wilcoxon-Mann-Whitney U test was used for comparisons between INPH patients and HIs and between subgroups of patients, whereas the Wilcoxon signed-rank test was used for comparisons between pre- and postoperative results of the INPH patients.

The predictive utility of the selected variables was estimated by means of ρ or the Wilcoxon-Mann-Whitney U test, depending on the nature of the variables. The Bonferroni-Holm step-down test (25, 26) was applied to adjust for multiple pairwise comparisons.

The numerical differences between pre- and postoperative measurements were used for the classification of patients as improved, unchanged, or worsened (Table 3). The performance of patients before and after surgery, as well as the magnitude of postoperative changes, is expressed as percentage of the median performance of the HIs. To establish the proportional performance of patients relative to HIs on tests with time scores (Target Reaction Time, Grooved Pegboard, and the Stroop variables), the values were recalculated as units per second. It should be noted that median values of individual changes (Table 3; Fig. 2) are not mathematically identical to the differences between pre- and postoperative median values of the total group of INPH patients (Fig. 1). Statistical analyses were performed with SPSS 13.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

The INPH patients showed statistically significant improvement in all applied tests except for the Simple Reaction Time, Digit Span forward, and the Digit Span Wechsler Adult Intelligence Scale score (Table 3). The greatest proportion of patients showed improvement on the Stroop (82–91%) and Grooved Pegboard (86–90%) tests, whereas the lowest proportion of patients improved on the Digit Span forward (26%) and backward (44%) tests.

The preoperative performance of INPH patients was below that of HIs on all tests, ranging from 38 to 88% of the median performance of HIs. After surgery, the median performance of INPH patients improved on all tests except for Digit Span and ranged from 62 to 94% of the median performance of HIs (Fig. 1).

Functions that were more severely impaired before surgery tended to improve more than milder deficits. There was a significant negative correlation ($r_s = -0.80$, n [i.e., the number of tests] = 9, $P < 0.05$) between the median preoperative performance levels of the different tests and their median magnitude of improvement after treatment (Fig. 2).

The proportions of improved, unchanged, and worsened results on the individual tests and clinical variables are presented in the rightmost column in Table 3. Information regarding the number of individuals who improved on each of the nine neuropsychological measures (Figs. 1 and 2) is presented in Table 4.

The patterns of associations between the neuropsychological variables was different for the INPH patients pre- and post-surgery than for the HI group. Several significant correlations between the tests findings in the INPH patient group (both pre- and postoperatively) were not seen in the HI group. The strength of the majority of inter-test correlations was lower

TABLE 3. Neuropsychological performance and neurological signs in idiopathic normal pressure hydrocephalus patients before and after shunt surgery and test results for healthy individuals (not included in the statistical analyses)^a

	HI (n = 159)	INPH before surgery	INPH 3 mo after surgery	INPH difference	P value	Change I/U/W
Neuropsychological test results, median (IQR)						
MMSE (n = 46)		25.5 (23–28)	28 (25–29)	1 (0–3)	<0.001 ^b	74/6/20
Reaction time, ms						
Simple (n = 43)		285 (246–342)	266 (236–317)	12 (–23 to 59)	0.12 ^b	56/0/44
Target (n = 41)	462 (428–498)	527 (483–706)	492 (420–658)	43 (–8 to 109)	<0.001 ^b	74/0/26
Tracks (n = 42)	80 (76–90)	58 (51–72)	66 (54–78)	7 (0–13)	<0.0001 ^b	74/12/14
Grooved Pegboard (n = 41)						
Dominant hand	78 (69–91)	121 (104–163)	106 (88–127)	16 (5–44)	<0.0001 ^b	86/2/12
Nondominant hand	93 (80–113)	162 (117–259)	135 (98–186)	26 (5–52)	<0.0001 ^b	86/2/12
Sum of both hands	172 (151–201)	293 (234–394)	240 (190–312)	42 (16–92)	<0.0001 ^b	90/0/10
Digit Span (n = 40)						
Forward	6 (5–7)	5 (5–6)	6 (5–6)	0 (0–1)	0.11 ^b	26/58/16
Backward	4 (4–5)	4 (3–4)	4 (3–4)	0 (0–1)	<0.01 ^b	44/46/10
WAIS score	13 (11–15)	10 (8–12)	10 (9–13)	1 (–1 to 1)	0.02 ^b	57/16/27
Rey AVLT (n = 46)						
Sum of trials 1–5	42 (35–50)	28 (20–34)	35 (24–42)	6 (2–11)	<0.0001 ^b	85/2/13
Delayed recall	8 (6–11)	3 (1–5)	5 (2–8)	1 (1–4)	<0.001 ^b	66/18/16
Stroop tasks, time (s)						
Color naming (n = 25)	67 (60–75)	98 (84–130)	85 (71–106)	12 (5–18)	<0.001 ^b	88/4/8
Interference task (n = 22)	128 (108–150)	249 (144–305)	166 (124–264)	38 (5–78)	<0.01 ^b	91/0/9
Response selection (n = 22)	62 (46–77)	135 (58–198)	81 (49–148)	25 (8–74)	<0.01 ^b	82/0/18
Neurological signs, median (IQR)						
Gait						
Clinical grading (n = 47)		2 (2–4)	2 (1–3)		<0.0001 ^c	60/38/2
10 m, no. of steps (n = 43)		24 (18–39)	18 (16–22)	4 (1–14)	<0.0001 ^b	90/5/5
10 m, time (s) (n = 43)		14 (10–24)	10 (9–13)		<0.0001 ^b	79/14/7
Balance (n = 46)		3 (1–3)	1 (1–3)		<0.001 ^c	35/63/2
Incontinence (n = 46)		3 (2–5)	1 (1–2)		<0.0001 ^c	68/28/4
Hours of daily sleep (n = 42)		9.5 (8–12)	8 (7–9)	1 (0–3)	<0.0001 ^b	53/40/7

^a HI, healthy individual; I, improved; INPH, idiopathic normal pressure hydrocephalus; IQR, interquartile range; MMSE, Mini-Mental State Examination; U, unchanged; W, worse; WAIS, Wechsler Adult Intelligence Scale; AVLT, Auditory Verbal Learning Test.

^b Wilcoxon signed rank test.

^c Sign test.

postsurgery, and the matrix thus coincided more closely with that of the HI group (Table 5).

The changes in test performance and the changes in the clinical variables of gait, incontinence, and hours of sleep were also subjected to correlation analyses. There were significant associations between reduction of sleep and improvement in dexterity, learning, and color naming ($r_s = 0.34, 0.33$, and 0.52 , respectively), and between the improvement in gait and the Stroop variables of Interference and Selection ($r_s = 0.60$ and 0.54 for the time, $r_s = 0.55$ and 0.49 for the number of steps).

Among the background variables of age, education, and disease duration, age correlated significantly with the magnitude of improvement on the Grooved Pegboard and Stroop color naming tests, whereas education was negatively correlated with improvement on the Grooved Pegboard test. No other statistically significant correlations were found (Table 6).

The predictive utility of the categorical variables, including vascular risk factors (presence/absence, $n = 20$ and $n = 27$, respectively), onset symptom (gait disturbance/cognitive deterioration, $n = 13$ and $n = 11$), and sex (male = 22/female = 25),

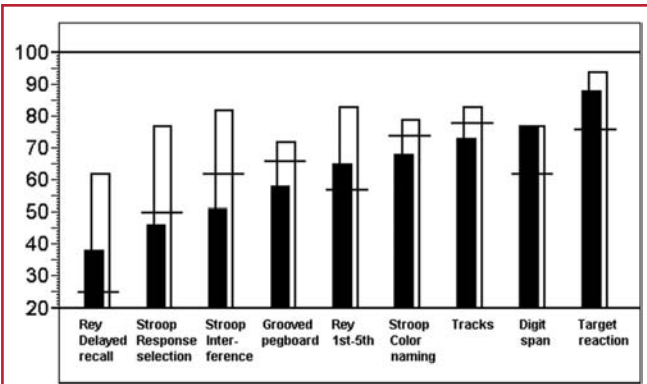


FIGURE 1. Graph showing performance before (black bars) and 3 months after shunt surgery (white bars), expressed in percentages of median performance for healthy individuals (HI) (100%). The 5th centile for HI on each variable is represented by a short horizontal line. Only tests with data from HI and patients with idiopathic normal pressure hydrocephalus (INPH) are included. The Grooved Pegboard and Digit Span tests are represented by the composite scores.

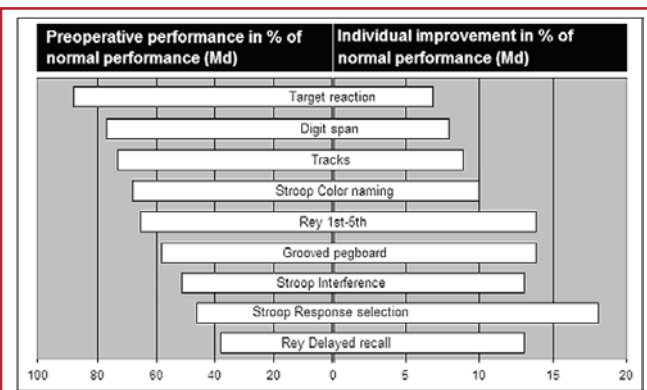


FIGURE 2. Graph showing performance of INPH patients before surgery and the magnitude of change, both are expressed in percentages of median performance of HIs. Md, median.

was also evaluated. There were no statistically significant differences between the subgroups.

DISCUSSION

In INPH, the CSF dynamic disturbance and its corollaries, the expansion of the ventricular system, and the resultant blood flow decrements and metabolic disturbance of the circumventricular tissue (1, 11, 12, 33, 41) affect several subcortical structures and subcortical-cortical circuits. Consequently, neurological functions like movement, tonus, and posture, but also more complex functions (e.g., purposeful acquisition and retention of new information, willed planning, initiation and monitoring of motor or mental processes, problem-solving, decision-making,

TABLE 4. Number of idiopathic normal pressure hydrocephalus patients (n = 47) showing improvement on 0 to 9 of the neuropsychological variables

	No. of improved tests									
	0	1	2	3	4	5	6	7	8	9
No. of patients	2	1	1	4	7	11	10	5	3	3

etc.) that depend on the integrity of the constituents of functional networks and their connections, may be impaired. The simultaneous presence of gait disturbance, cognitive deterioration, and incontinence seen in most hydrocephalic patients suggests a common pathophysiological mechanism (34, 37). This notion is reinforced by neuropsychological studies showing that multiple and diverse functions are affected by INPH, including vigilance; psychomotor speed; attention and concentration; memory and learning; visuoperceptual, spatial, and constructive ability; arithmetic, reading, and writing; problem-solving; conceptualization; abstract reasoning; and executive functions (5, 13–15, 28, 29, 38, 40, 42, 43, 51, 52, 54). Further evidence stems from reports on strong and frequent associations not only between neuropsychological tests, but also between such tests and assessments of gait and balance disturbance, incontinence, and increased daily sleep (24, 40). The presence of vascular risk factors and vascular lesions affecting the same subcortical regions have been shown to increase the severity of neuropsychological deficits seen in INPH (24) and to reduce the benefit of shunt surgery (7, 49).

Neuropsychological Changes after Shunt Surgery

Most of the tests applied in this study discriminate well between INPH patients before surgery and HIs (24). In the present study, we found that the same tests also distinguished between pre- and postoperative performance (Table 3).

Furthermore, there was a negative correlation between preoperative performance levels and the magnitude of improvement on different tests. A reasonable explanation for this is that functions that are more heavily dependent on the integrity of the structures and circuits that are most affected by metabolic (as opposed to structural) changes as a result of INPH are those that will also improve more after the abolition of the CSF dynamic disturbance causing these changes. This view is supported by the immediate response to the CSF tap test (57).

However, our findings also clearly demonstrate that the neuropsychological functions are not fully restored and that the INPH patients were still outperformed by HIs on all of the tests included in Table 5 (Wilcoxon-Mann-Whitney, all P values < 0.05), except for the Target Reaction Test. We find it likely that these remaining deficits reflect irreversible changes attributable to hydrocephalus, some of which have been described in neuropathological studies (3, 11, 12).

Our own clinical expectations and the information we provide to INPH patients and their relatives before surgery should be tem-

TABLE 5. Correlation matrices for idiopathic normal pressure hydrocephalus patients before and after surgery and for healthy individuals^a

	TR	Tracks	GP	DS	R1–5	Rdel	SC	SI	SS
INPH before surgery									
Target Reaction	1								
Tracks	−0.51 ^b	1							
Grooved Pegboard	0.55 ^{b,d}	−0.73 ^{b,d}	1						
Digit Span	−0.34 ^{c,d}	0.61 ^{b,d}	−0.46 ^b	1					
Rey 1st–5th	−0.40 ^{b,d}	0.81 ^{b,d}	−0.62 ^{b,d}	0.55 ^{b,d}	1				
Rey delayed		0.64 ^{b,d}	−0.42 ^{b,d}	0.44 ^{b,d}	0.73 ^b	1			
Stroop color	0.75 ^{b,d}	−0.82 ^{b,d}	0.91 ^{b,d}	−0.59 ^{b,d}	−0.71 ^{b,d}		1		
Stroop interference	0.64 ^b	−0.60 ^b	0.79 ^b		−0.62 ^{b,d}		0.88 ^b	1	
Stroop selection	0.60 ^b	−0.56 ^b	0.75 ^b		−0.60 ^b		0.84 ^b	0.99 ^{b,d}	1
INPH after surgery									
Target Reaction	1								
Tracks	−0.54 ^{b,d}	1							
Grooved Pegboard	0.44 ^b	−0.60 ^b	1						
Digit Span		0.54 ^b	−0.47 ^{b,d}	1					
Rey 1st–5th	−0.36 ^c	0.60 ^b	−0.45 ^b	0.45 ^b	1				
Rey delayed		0.41 ^b	−0.33 ^c	0.40 ^c	0.79 ^{b,d}	1			
Stroop color	0.60 ^b	−0.68 ^b	0.83 ^b	−0.49 ^c	−0.51 ^c		1		
Stroop interference	0.65 ^{b,d}	−0.68 ^b	0.84 ^{b,d}	−0.48 ^{c,d}	−0.62 ^{b,d}		0.90 ^{b,d}	1	
Stroop selection	0.66 ^{b,d}	−0.67 ^{b,d}	0.83 ^{b,d}		−0.63 ^{b,d}		0.85 ^{b,d}	0.98 ^b	1
Healthy individuals									
Target Reaction	1								
Tracks	−0.35 ^b	1							
Grooved Pegboard		−0.49 ^b	1						
Digit Span				1					
Rey 1st–5th		0.30 ^b	−0.32 ^b		1				
Rey delayed			−0.35 ^b		0.77 ^b	1			
Stroop color		−0.42 ^b	0.31 ^b				1		
Stroop interference		−0.37 ^b	0.34 ^b	−0.46 ^b			0.63 ^b	1	
Stroop selection				−0.42 ^{b,d}				0.91 ^b	1

^a TR, Target Reaction; GP, Grooved Pegboard; DS, Digit Span; R1–5, Rey 1st to 5th; Rdel, Rey delayed; SC, Stroop color; SI, Stroop interference; SS, Stroop selection; INPH, idiopathic normal pressure hydrocephalus.

^b $P < 0.01$.

^c $P < 0.05$.

^d Correlation coefficients that are equal to or larger than corresponding coefficients in the other two conditions. Other values represent nonsignificant correlations and/or coefficients of < 0.30 .

pered in accordance with these findings. The few studies of neuropsychological effects of shunt treatment in INPH have generally presented positive effects. However, the ways of defining change have differed among authors. To compare our findings with some of the more well-known reports, we subjected our data to the same analyses as those used in other studies. Raftopoulos et al. (45) used the ratio between the postoperative result and the sum of the pre- and postoperative results (i.e., post/[pre + post]) to calculate the “percent change.” They found 14 (66.6%) of their 21 patients to be improved 1 year after surgery (defining improve-

ment as a quotient exceeding 0.55). The corresponding proportion in our study is 80.8% (38 of 47 patients). Two more recent studies have used an improvement criterion corresponding to a positive change of 1 standard deviation of HI on 50% of the tests, or a 4-point change on the Mini-Mental State Examination at least 3 months after surgery. The proportions of successful cases in these series were 52% (22 of 42 patients) (51) and 60% (6 of 10 patients) (16), respectively. The corresponding proportion in our group of patients was 51% (24 of 47 patients), i.e., similar to the finding in the larger of the two series.

TABLE 6. Changes in neuropsychological test results and their relations to age, education, and disease duration

Neuropsychological test	Age	Education	Duration
Target Reaction	−0.07	−0.04	0.18
Tracks	0.14	−0.06	0.00
Grooved Pegboard	0.60 ^a	−0.36 ^b	0.08
Digit Span	0.22	0.29	0.00
Rey 1st–5th	0.04	0.25	−0.10
Rey delayed	0.12	0.01	−0.28
Stroop color	0.51 ^b	−0.12	0.19
Stroop interference	0.32	−0.18	0.11
Stroop response selection	0.27	−0.16	0.02

^a $P < 0.01$.^b $P < 0.05$.

Associations among Deficits before and after Surgery

There were many pronounced correlations among the different neuropsychological tests, particularly in relation to preoperative assessments. A probable explanation for this is the multiregionality of the disease process, which contributes to the variability of all the functions tested and thereby creates or strengthens associations among them. This phenomenon has been labeled “dedifferentiation.” This term is used in research concerning cognitive development and refers to development from a relatively undifferentiated state of early childhood through a gradual differentiation of intellectual functions and then, at a much later stage, to an increasing dedifferentiation of advanced aging (10).

The dedifferentiation in INPH is not restricted to neuropsychological performance. We have recently presented findings regarding associations between neuropsychological test results and the severity of gait and balance disturbance, incontinence, and increased daily sleep among INPH patients before surgery (24). Similarly, associations between cognitive impairment and gait disturbance have been presented by others (40).

If INPH is, in fact, associated with a dedifferentiation of functions, then treatment by CSF diversion should be expected to revert this development and lead to a functional redifferentiation. We found that several normally disparate functions improved after surgery (Table 3), and, as expected, there was some degree of redifferentiation of function (Table 5). However, because of the incomplete restoration, the postsurgery correlational pattern is still far from that of HIs.

Evaluation of Putative Predictors of Treatment Effect

INPH patients with vascular comorbidity, as suggested by the presence of hypertension, cardiovascular disease, and/or diabetes, performed significantly worse at baseline than patients without such ailments. The influence of vascular risk factors in INPH has been discussed by others (9, 20, 32), and a

reduced effect of shunt treatment in INPH patients with cerebrovascular disease has been reported (7, 49). As mentioned earlier, we found no evidence that vascular comorbidity negatively affects the magnitude of improvement in neuropsychological functioning. Instead, it continues to contribute to the deficits remaining postoperatively. Stated differently, patients with vascular risk factors show the same degree of improvement as patients without vascular comorbidity, but they have significantly poorer results on most of the neuropsychological tests 3 months after shunt surgery (data not shown).

Similarly, we did not find any significant effect of onset symptom or sex on neuropsychological improvement after shunt treatment. Women outperformed men on the Rey auditory variables, both before and after surgery. Regarding onset symptom, no baseline differences in neuropsychological function were found between patients reporting gait disturbance versus cognitive deterioration as the primary onset symptom (24), and the magnitude of improvement was similar in the two groups; hence, no significant differences were found in neuropsychological performance after surgery. In previous studies, dementia preceding gait disturbance in the course of INPH has been shown to predict a poor response to shunt treatment (8, 19, 21). These studies lack explicit criteria for dementia, which makes comparisons uncertain. Patients reporting cognitive deterioration as their first symptom in our sample described memory problems and/or concentration difficulties; i.e., they did experience cognitive problems but were not demented before the onset of gait symptoms. None of the quantitative background variables of age, education, or disease duration were found to be of any practical use in predicting neuropsychological effects of shunt surgery in INPH.

Sample Representation and Study Design

All adults in the western part of Sweden who are diagnosed with chronic hydrocephalus are referred to our unit for evaluation and treatment. The diagnostic criteria used here are in agreement with the evidence-based clinical criteria recently presented by Relkin et al. (46), with two exceptions. First, we set no requirements regarding assessment of the nature and severity of cognitive impairment, apart from the routine neurological examination and an interview with relatives. Secondly, we chose to include all adult patients—regardless of age—on the basis of clinical findings. Although the use of an arbitrary age limit may enhance the diagnostic certainty in a studied sample, it may exclude patients who would benefit from shunt treatment. In the present sample, two patients were less than 40 years of age and thus younger than recommended in the guidelines (46). However, both of them showed clinically significant improvement regarding gait, dexterity, and neuropsychological performance after surgery.

We think that the patients included in this study are representative of patients with INPH. It is unfortunate that we were forced to exclude nine patients owing to a lack of evaluated effects of shunt revisions or valve adjustments. The advent of adjustable valves and the development of increasingly practical adjustment devices have made it possible to optimize treatment response by changing valve settings. When repeated adjustments were

required (or when patients had multiple complications), it was not logistically possible to organize complete reevaluations in accordance with the study protocol. However, since many patients experience significant improvement only after more than one adjustment, we have recently initiated a double-blind study to evaluate the effects of repeated adjustments and to try to predict the optimal settings on the basis of early examinations.

Three aspects of our study design need to be discussed. First, patients may continue to improve well beyond 3 months after surgery, suggesting the existence of less dramatic and more slowly evolving effects than the rapid metabolic changes discussed earlier. This is supported by recently reported findings of an increased proportion of symptomatically improved patients from 33% at 3 months to 60% at 6 months (39). Hence, in some instances, our evaluations of the magnitude of neuropsychological change may underestimate the effect of shunt treatment as well as the proportion of improved patients.

Second, for the sake of comprehensibility, we chose to transform pre- and postoperative results, as well as changes after surgery, into percentages of normal performance (i.e., median values of HIs). Admittedly, estimates of the magnitude of change resulting from repeated exposure to the test procedures alone would be of great value, since it would make it possible to differentiate between the effects of training, chance, and treatment. We have initiated studies of the effects of repeated neuropsychological assessments (3 mo apart) on performance in healthy volunteers, but data are not yet available.

Third, this study is concerned with the statistical ascertainment of beneficial neuropsychological changes owing to shunt treatment. It does not, however, show the practical consequences of these changes, i.e., the effect on the quality of life or day-to-day-functioning of our patients. In an ongoing study, we have included ratings of activities of daily living and quality of life by raters who are blind to other investigations, including the neuropsychological assessment, and we hope to be able to report the results in the near future.

CONCLUSIONS

In this prospective study of 47 INPH patients, we found significant improvements in the results of neuropsychological tests measuring target reaction, dexterity, learning and memory, working memory, and naming speed and response selection, as well as in clinical symptoms, after 3 months of shunt treatment. None of six candidate variables (age, education, disease duration, vascular comorbidity, sex, and onset symptom) predicted these neuropsychological changes. The strength of the associations between normally disparate functions was reduced after surgery, reflecting the significant, yet incomplete, recovery from multiregional pathological changes.

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COMMENTS

The experience reported by Hellström et al. confirms clearly that patients with idiopathic normal pressure hydrocephalus (INPH) can hope to experience a significant improvement of their neuropsychological deficit after shunting. In my current clinical practice I inform these patients and their families that there is a probability of cognitive improvement in about two of three patients. Hellström et al. reported an even higher rate of 80.8%. However, this improvement rate depends on the methodology used to consider when these observed changes are significant. Indeed, if a positive change of 1 standard deviation on 50% of the tests is considered, the improvement rate is then around 50%. So I think to announce a chance of cognitive improvement in two of three patients remains reasonable information to be given to our patients.

Another important point in this article is that cognitive deterioration as a primary onset symptom is associated with similar clinical improvement after shunting. Indeed, memory problems and attention difficulties are different from dementia and as primary onset symptoms do not predict a poor response to shunting.

I regret the absence of data regarding a 12-month follow-up. It would have been interesting to know what evolution at 12 months this encouraging 80% neuropsychological improvement could have.

Christian Raftopoulos
Brussels, Belgium

Hellström et al. presented a well-controlled prospective cohort study evaluating the neurocognitive response to ventricular cerebrospinal fluid (CSF) shunting for INPH. Whereas gait disturbance has been reported to be the most shunt-responsive of the classic INPH triad, neuropsychological symptoms of INPH are frequently more refractory to CSF shunting. In the current study, Hellström et al. successfully demonstrated both statistical and clinically significant improvements in neuropsychological tests of target reaction time, manual dexterity, motor speed, verbal learning and memory, and naming speed, response selection, and inhibition 3 months after surgery. Only simple reaction time and digit span (short-term or working memory) failed to improve after CSF shunting.

The value of this study is the well-controlled, prospective study design, using a well-matched cohort of non-INPH patients. The results presented here are encouraging and demonstrate that with appropriate patient selection, neurocognitive improvement can be expected in the majority of INPH patients, despite the failure to return to normal. This study also demonstrated that cognitive improvement can be expected in INPH patients with more marked neuropsychological deficits. It should be highlighted, however, that six patients requiring valve pressure adjustments (probably for lack of a clinical response) were excluded. This exclusion probably falsely elevated the response rate reported here. However, even with inclusion of these six patients as

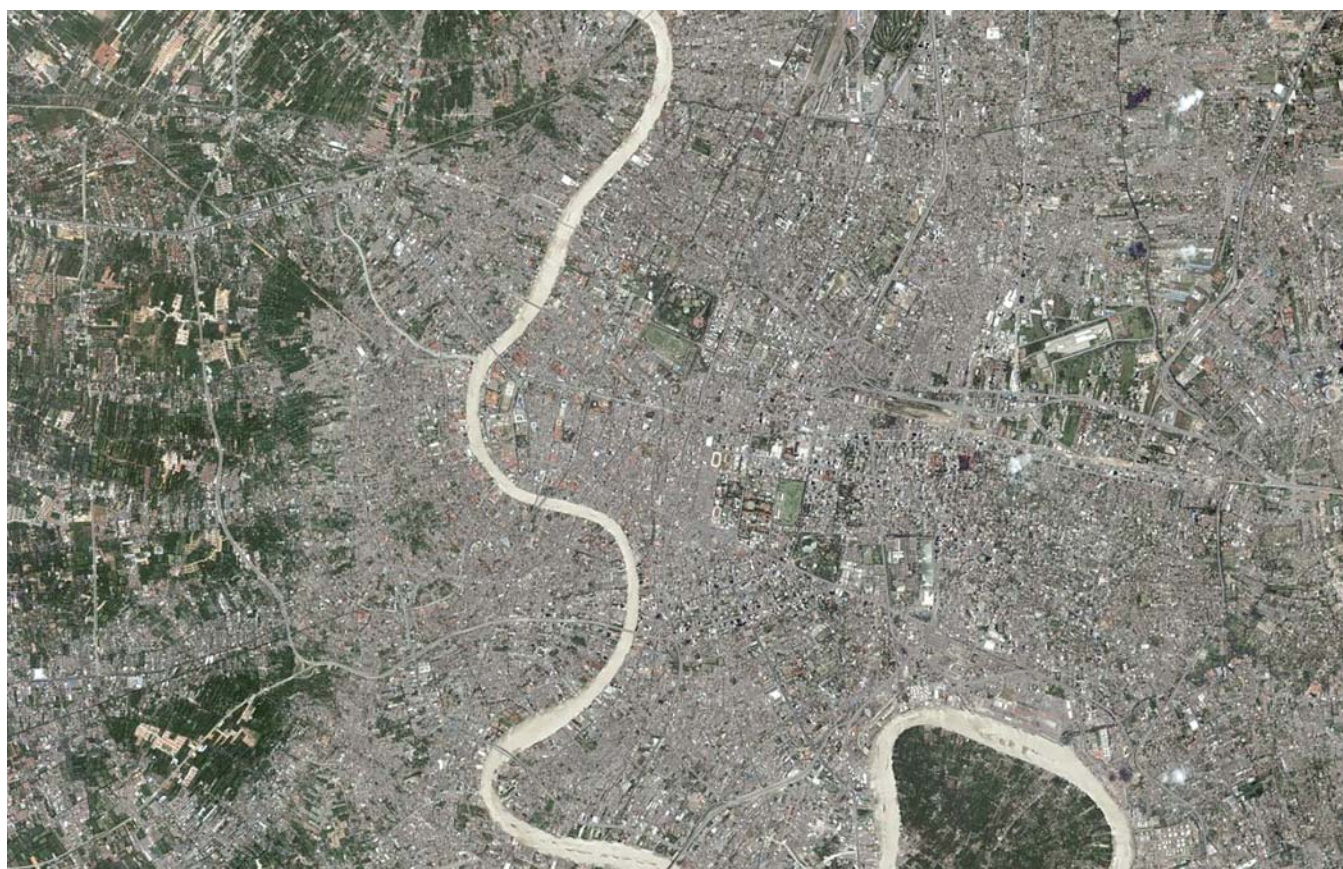
neuropsychological treatment failures, improvement occurred in the majority of patients.

The most important factor affecting the efficacy of CSF shunting for INPH remains patient selection. The high incidence of improvement reported here by Hellström et al. is probably in part attributable to their rigorous selection criteria. This article is a worthwhile contribution to the INPH literature.

Matthew J. McGirt
Baltimore, Maryland

This is a report about the neuropsychological outcome of 47 consecutively treated patients with INPH. Patients were treated over an approximately 5-year period. Although I do not regularly insist on ancillary confirmative diagnostic tests such as cisternography, lumbar drainage, or more complex evaluations of resistance to absorption, I never planned to publish my case results. Here, a relatively small number of patients had only cisternography and no other tests, which may be a weakness in the minds of some readers. Perhaps more importantly, there is no information about evaluations of quality of life. Nonetheless, I think the article provides useful information for **NEUROSURGERY** readers.

Howard M. Eisenberg
Baltimore, Maryland



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VERTEBRAL BODY REPLACEMENT SYSTEMS WITH EXPANDABLE CAGES IN THE TREATMENT OF VARIOUS SPINAL PATHOLOGIES: A PROSPECTIVELY FOLLOWED CASE SERIES OF 60 PATIENTS

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OBJECTIVE: Vertebral body reconstruction after corpectomy has become a common surgical procedure. The authors describe a prospectively followed case series of patients treated with expandable cages for various indications.

METHODS: Sixty patients underwent single or multilevel corpectomy for degenerative stenosis (13 patients), herniated disc (7 patients), deformity (14 patients), traumatic fracture (3 patients), infection (1 patient), or tumor (22 patients). Six different expandable vertebral body systems were used in the cervical spine (41 patients), thoracic spine (15 patients), and lumbar spine (4 patients). All patients were evaluated clinically and radiographically.

RESULTS: Thirty-nine patients underwent single-level corpectomy, 18 patients underwent two-level corpectomy, and 3 patients underwent three-level corpectomy. Anterior reconstruction alone was performed in 30 patients; circumferential reconstruction was performed in 30 patients, 9 of whom underwent reconstruction through a posterior approach only. At the time of the final follow-up examination (mean, 9 mo), the Nurick grade improved significantly. Ninety-five percent of the patients maintained or improved their Frankel score and 67% had good clinical results. The regional angulation was corrected significantly (4.0 ± 9.0 degrees, $P = 0.002$), and the segment height increased significantly (3.5 ± 8.0 mm, $P = 0.002$). Bony fusion was achieved in 93% of the cases. Subsidence was documented in nearly half of the patients (1.4 ± 2.0 mm) and was reduced after circumferential fusion (0.9 ± 1.9 mm, $P = 0.08$). Eighteen patients (30%) had complications and 12 patients (20%) underwent revision surgery.

CONCLUSION: Expandable vertebral body replacement systems can provide solid anterior column constructs with restoration of height and sagittal alignment. Favorable clinical outcome was shown in most patients, although the complication and reoperation rates are rather high.

KEY WORDS: Corpectomy, Deformity, Expandable cage, Metastasis, Spinal reconstruction

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Corpectomy has become a common surgical procedure for spinal metastasis, deformity, instability, degenerative stenosis, infection, and trauma (1, 8, 9, 15, 16). Autogenous bone grafts such as iliac crest or fibula have been used to reconstruct the anterior column despite donor site morbidity; pseudarthrosis and graft dislodgement are well

known complications (6, 11, 21). Ideally, a vertebral body replacement system should be stable, resist axial load-bearing, have a large interbody-bone interface to facilitate fusion and prevent migration, and restore height and sagittal alignment (4). Titanium mesh cages have been developed, which eliminate the need for autogenous tricortical bone grafts. However, optimal placement of a nonexpandable spacer can be demanding and challenging. In an attempt to overcome the technical problems of nonexpandable cages, various expandable cages have been developed that can be adjusted in situ to the height of the corpectomy defect. These devices have

ABBREVIATIONS: ADD, anterior distraction device; CT, computed tomography; MRI, magnetic resonance imaging; TPS, telescoping plate spacer

already been used successfully for various indications (2, 5, 10, 13, 19, 22, 24–28).

In the present prospectively followed case series, we report our experience with 60 patients who underwent single- or multilevel corpectomy with insertion of expandable vertebral body replacement systems in the cervical, thoracic, and lumbar spine. This study evaluates the surgical techniques, complications, and outcomes of patients treated with 6 different implant systems. To our knowledge, this is the largest series of patients treated with expandable cages.

PATIENTS AND METHODS

Patient Population

Between October 2004 and November 2007, 60 consecutive patients—including 28 men and 32 women with a mean age of 54 years (range, 16–80 yr)—underwent single- or multilevel corpectomy with implantation of an expandable cage. All but 2 surgical procedures were performed by the authors. The indications for corpectomy were stenosis in 13 patients, 2-level disc herniation in 7 patients, kyphotic deformity in 14 patients, traumatic fracture in 3 patients, spinal metastasis in 22 patients, and spinal tuberculosis in one patient, and were localized in the cervical (41 patients), thoracic (15 patients), and lumbar spine (4 patients). The mean duration of symptoms was 51 weeks (range, 0–336 wk) and consisted of neck or back pain in 9 patients, radiculopathy in 10 patients, and myelopathy in 39 patients. Two patients had radiographic tumor progression without symptoms (*Table 1*).

TABLE 1. Demographic data of 60 consecutive patients

	No. of patients (%)
Sex	
Male	28 (46.7)
Female	32 (53.3)
Mean age (yr)	54 (range, 16–80)
Diagnosis	
Stenosis	13 (21.7)
Herniated disc	7 (11.7)
Deformity	14 (23.3)
Fracture	3 (5)
Tumor	22 (36.7)
Tuberculosis	1 (1.7)
Spinal localization	
Cervical	41 (68.3)
Thoracic	15 (25)
Lumbar	4 (6.7)
Symptoms	
Neck or back pain	9 (15)
Radiculopathy	10 (16.7)
Myelopathy	39 (65)
Asymptomatic	2 (3.3)

Symptoms were assessed using the Frankel classification and Nurick grading scale (7, 17). Patients' perceived recovery was measured by the 7-point Likert scale; complete recovery and almost-complete recovery were determined to be good results.

Radiographic Evaluation

Magnetic resonance imaging (MRI), computed tomography (CT), and conventional x-ray scans were available pre- and postoperatively in all patients. The regional angulation was determined by measuring the angle between the normal endplate above and below the affected segment. Kyphosis was documented as "positive" and lordosis as "negative" angulation. The segment height was evaluated by measuring the height of the involved vertebral segment, including the 2 adjacent intervertebral discs. In all patients, dynamic x-rays and CT scans were performed 3 months postoperatively to document stability, fusion, subsidence, and possible hardware displacement. Fusion was defined as solid consolidation on CT scan, and no sign of implant dislocation on flexion/extension radiographs. MRI was performed 3 to 6 months after surgery to evaluate adequate decompression of the involved neural structures.

Implant Characteristics

In the present study, we implanted 6 different expandable vertebral body replacement systems for reconstruction of the corpectomy defect.

- 1) The telescoping plate spacer (TPS) (Interpore Cross International, Irvine, CA) is a rectangular stand-alone device (15 mm wide by 15 mm deep) that is designed for C3 to T3 vertebral body replacement. The end pieces are fixed with 0 degrees of caudal surface and 10 degrees of cranial surface. The flanges prevent the TPS from impelling dorsally and contain two 15-degree and two 45-degree holes for screw fixation. The implant has a large contact area due to open sidewalls and can be packed with bone. The distractor is attached to the TPS implant and, when inserted, the height can range from 22 to 29 mm for one-level corpectomy, and from 34 to 50 mm for 2-level corpectomy.
- 2) The anterior distraction device (ADD); (Ulrich Medical, Ulm, Germany) is used for reconstructing the anterior column of the cervical and upper thoracic spine from C3 to T3. ADD is available in 3 outer diameters (12, 14, and 16 mm) with 0-degree (or 6-degree) fixed angulation of the cranial end piece and 0-degree fixed angulation of the caudal end piece. The small central cavity can be filled with bone. An expansion instrument is inserted into a bore of the distraction ring, and the cage is distracted by counterclockwise rotation of the ring. The distraction ranges extend from 10 to 13 mm to 39 to 65 mm. Additional anterior plating is necessary.
- 3) The winged anterior distraction device (ADDplus; Ulrich Medical), has the advantage of an integrated plate system that reduces the risk of migration and sinking in. The implant is anchored with expandable osmium screws. There are 4 different implant heights with an outer diameter of 12 mm; the small central cavity can be filled with bone. The distraction mechanism is similar to the ADD, and the height ranges from 13 to 18 mm and 40 to 65 mm. The angle of the integrated plate is fixed and varies from 0 to 18 degrees.
- 4) The obelisc vertebral body replacement (Ulrich Medical), is designed for reconstruction of the anterior thoracic and lumbar spine. Obelisc has a standard external diameter of 20 mm, and the central cavity can be filled with bone. The end pieces are available in 3 diameters (20, 24, and 26 mm) with different angles (0, 5, and 10 degrees). There are 6 different sizes, and the distraction height

ranges from 20 to 28 mm and 76 to 132 mm. The implant is fixed to the inserter and the device is expanded by counterclockwise rotation. Additional anterior or posterior fixation is necessary.

- 5) The VLIIFT vertebral body replacement system (Stryker, Kalamazoo, MI) is designed for reconstruction of the corpectomy defect of the thoracolumbar spine (T1 to L5). The device is designed to be inserted through an anterior approach, but a circumferential reconstruction through a single posterior approach is possible. The diameter of the implant is 18 or 22 mm, and the central part can be packed with bone. The end caps of the 18 mm are available in 0, 3, or 8 degrees. The 22-mm implant end caps are also available in 15 degrees to restore lumbosacral sagittal alignment. There are 4 different sizes, which vary from 20.5 to 27.5 mm and 37 to 60.5 mm. Extension pieces can be placed on both ends of the VLIIFT to build a longer construct, which can increase the height to 90.5 mm. An expander is used to insert and distract the implant by counterclockwise rotation. Additional anterior or posterior internal fixation is required.
- 6) The Cervilift expandable cage (Deltacon GmbH, Werneck, Germany) is designed for cervical vertebral body replacement. The diameter of the implant is 11 or 14 mm, the central part can be filled with bone, and the end caps are available in 0, 3, and 5 degrees. There are 2 sizes, which vary from 13 to 20 mm and 18 to 30 mm. Extension pieces of 5 or 10 mm can be placed on both ends to increase the height of the implant. Insertion and expansion of the implant is similar to VLIIFT. Supplemental plate fixation is necessary.

The criteria for choosing the type of vertebral body replacement system were based on the localization of pathology, surgical approach, and implant characteristics. In all patients, the central part of the implants was filled with allograft bone.

Statistical Analysis

Student's paired 2-tailed *t* tests were used to compare pre- and postoperative Nurick grades, regional angulations, and segment heights. Pearson's χ^2 tests were used to calculate differences in outcome assessments between groups. Results are presented as the means $\pm$ standard deviations. A *P* value less than 0.05 was considered statistically significant. Statistical analysis was performed with SPSS software (version 15; SPSS Inc., Chicago, IL).

RESULTS

Clinical Results

The mean follow-up period was 9 months (range, 1–28 mo). Eight patients died after a mean survival time of 9.9 months (range, 1–27 mo); cause of death was progression of disease in 6 patients, respiratory insufficiency in 1 patient, and sepsis due to lower limb infection in 1 patient.

One-level corpectomy was performed in 39 patients, 2-level corpectomy in 18 patients, and 3-level corpectomy in 3 patients (Fig. 1). In 30 patients, an anterior reconstruction was performed without posterior instrumentation. Circumferential reconstructions were performed in 30 patients, in 9 of whom a posterior approach only was used (Fig. 2). The distribution of implants used was ADD in 1 patient, ADDplus in 16 patients, obelisc in 3 patients, TPS in 27 patients, VLIIFT in 11 patients, and Cervilift in 2 patients. The mean duration of surgery was 340 minutes (range, 100–950 min), and the mean blood loss was 1728 mL (range, 100–16000 mL) (Table 2).

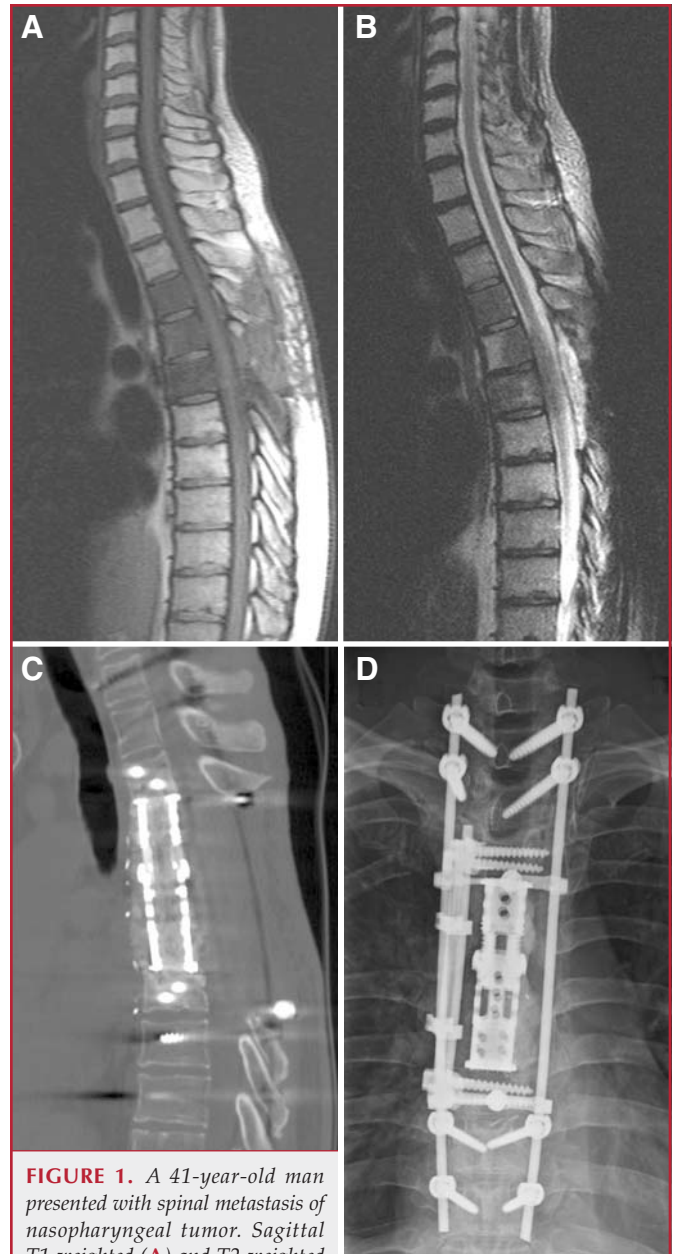


FIGURE 1. A 41-year-old man presented with spinal metastasis of nasopharyngeal tumor. Sagittal T1-weighted (A) and T2-weighted (B) magnetic resonance imaging scans showing metastasis from T4 to T6 extending posteriorly. Transthoracic 3-level corpectomy with implantation of VLIIFT (Stryker, Kalamazoo, MI) and additional anterior fixation at T3 to T7 was performed. Second-stage posterior surgery included resection of posterior elements at T4 to T6, and pedicle screw fixation at T1 to T9. Postoperative sagittal computed tomography (C) and anteroposterior x-ray (D) showing solid fusion with stable circumferential construction.

The mean preoperative Nurick grade was 1.9 ± 1.7 , which improved significantly to 1.0 ± 1.6 postoperatively ($P < 0.001$). The majority (95%) of patients maintained or improved their Frankel score. Forty (67%) patients had good clinical results according to the Likert scale (Table 3).

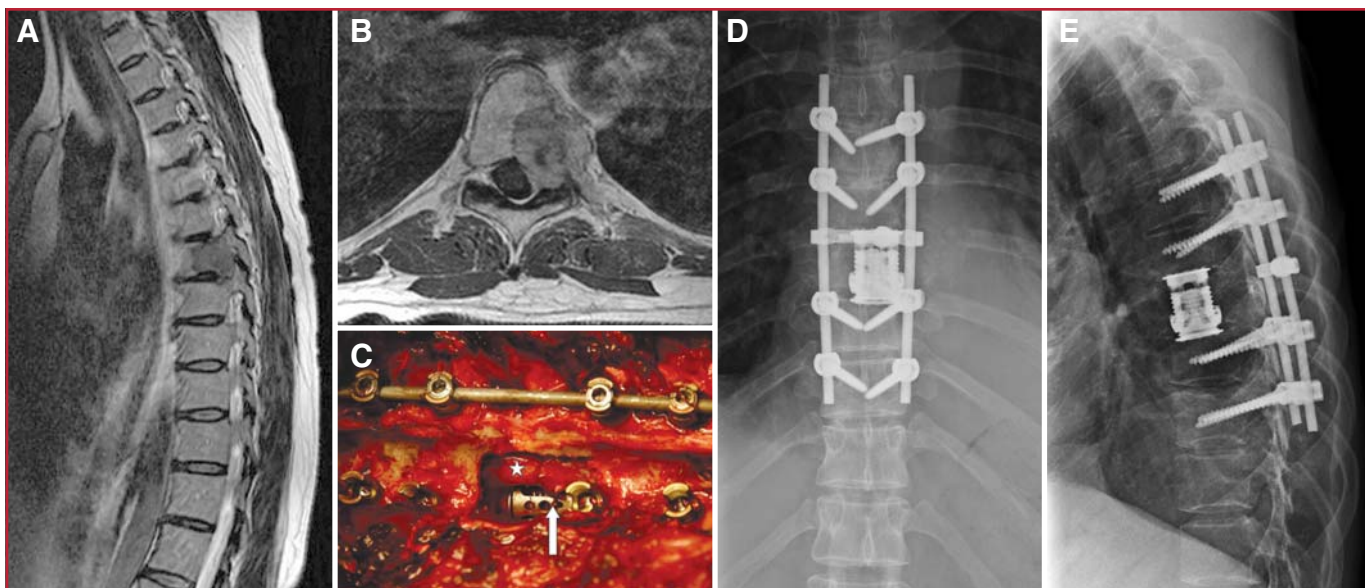


FIGURE 2. A 38-year-old woman with solitary spinal metastasis of leiomyosarcoma. Sagittal T2-weighted (A) and axial T1-weighted (B) magnetic resonance imaging scans showing posterolateral located metastasis of T7. Left-sided costotransversectomy and partial corpectomy were performed, followed by posterolateral insertion of VLIIFT and pedicle screw fixation at

T5 to T9. C, rhizotomy of the nerve root at T7 (arrow) was necessary to insert the cage; the spinal cord is marked with a star. D and E, postoperative x-rays showing solid circumferential fixation at T5 to T9 through a single-stage posterior approach.

Radiographic Results

The mean preoperative regional angulation was 7 ± 12.2 degrees, which was significantly corrected to 3.3 ± 13.9 degrees ($P = 0.002$) (Fig. 3). The mean segment height increased from 27.4 ± 14.8 mm and 30.8 ± 16.8 mm, which was also statistically significant ($P = 0.002$) (Fig. 4). Bony fusion was achieved in 93% of the patients. The fusion rate decreased to 87% whenever fusion was based on the intention-to-treat principle, and hardware failures with consequent revision surgery were considered as fusion failures. There was no relation between nonunion and type of implant ($P = 0.7$). Cage subsidence was documented in nearly half of the patients (42.6%). The mean subsidence of all patients was 1.4 ± 2.0 mm. In patients treated with anterior reconstruction alone, the mean subsidence was 2.0 ± 2.1 mm; in those with circumferential fusion, the mean subsidence was 0.9 ± 1.9 mm. This difference did not reach statistical significance ($P = 0.08$). There was no significant difference between type of implant and subsidence rate ($P = 0.53$). The subsidence rate between 1-level, 2-level, or 3-level corpectomy was not statistically significant ($P = 0.52$). In all patients, postoperative MRI scans documented adequate decompression of neural structures.

Surgery-related Complications

Perioperative complications occurred in 18 patients (30%) (Table 2). Hardware displacement was observed in 5 patients. Three patients had progressive dysphagia because of anterior displacement of a screw (1 patient) or anterior migration of the

implant (2 patients). The patients recovered completely after removal of the screw or repositioning of the cage, respectively (Fig. 5A). In one patient, the implant was under-distracted and had no contact with the adjacent endplates. However, consolidation in and around the cage was documented, and the construct was shown to be stable on dynamic radiographs. In one patient, the caudal screw was placed too steeply and crossed the adjacent intervertebral disc without clinical consequences.

Rebleeding occurred in 2 patients. One patient developed an acute hypotensive shock due to cage migration and consequent rupture of the aorta. Immediate surgery with hardware removal, suturing of the vascular rupture, and second-stage implantation of a smaller cage resulted in complete recovery. The other patient developed progressive tetraplegia due to an epidural hematoma with spinal cord compression. The patient recovered without neurological deficit after acute evacuation of the hematoma and re-implantation of the distractable cage in a later stage.

Neurological deficit occurred in 3 patients. One patient developed a right-sided C5 palsy, which resolved completely after 6 months. One patient had L1 radiculopathy, and 1 patient developed partial paresis of 1 leg. Both patients died due to disease progression and, as far as we know, the neurological deficit was unchanged. Transient vocal cord paralysis occurred in 1 patient.

Three patients developed progressive kyphosis; 2 of them were reoperated with additional posterior instrumentation. One patient experienced a deep infection with consequent hardware removal. Two patients developed cerebrospinal fluid

TABLE 2. Summary of surgical procedures and complications^a

	Patients (%)
Corpectomy	
1-level	39 (65)
2-level	18 (30)
3-level	3 (5)
Approach	
Anterior	30 (50)
Anterior and posterior	21 (35)
Posterior	9 (15)
Mean blood loss (mL)	1728 (range, 100–16000)
Mean duration of surgery (min)	340 (range, 100–950)
Implanted device	
ADD	1 (1.7)
ADDplus	16 (26.7)
Obelisc	3 (5)
TPS	27 (45)
VLIFT	11 (18.3)
Cervilift	2 (3.3)
Complications (total)	18 (30)
Hardware displacement	5 (8.3)
Rebleeding	2 (3.3)
Neurological deficit	3 (5)
Vocal cord paralysis	1 (1.7)
Cerebrospinal fluid leakage	2 (3.3)
Infection	2 (3.3)
Progressive angulation	3 (5)
Reoperations	12 (20)

^a ADD, anterior distraction device; TPS, telescoping plate spacer

leakage; reexploration and dural reconstruction was necessary in both cases. In total, 12 (20%) patients underwent reoperation for implant-related complications.

DISCUSSION

Removal of one or more vertebral bodies followed by spinal column reconstruction continues to evolve. Traditionally, implantation of autologous tricortical iliac bone graft was the “gold standard” to reconstruct the corpectomy defect. We presented the results of 60 patients treated with 6 different expandable cage systems throughout the spinal column. To our knowledge, this is the largest series on vertebral body replacement.

Correct positioning of non-expandable cages can be challenging. Some distraction forces and shaping of the endplates may be necessary to insert a rigid implant. Even then, the position of the implant can be inadequate; endplates can weaken with consequent subsidence, and restoring sagittal alignment can be

TABLE 3. Pre- and postoperative Frankel grade and Nurick grade and postoperative patients' perceived recovery

	No. of patients preoperatively (%)	No of patients postoperatively (%)
Frankel grade		
A	3 (5)	0
B	1 (1.7)	4 (6.7)
C	5 (8.3)	4 (6.7)
D	22 (36.7)	9 (15)
E	29 (48.3)	43 (71.7)
Nurick grade		
0	20 (33.3)	38 (63.3)
1	10 (16.7)	7 (11.7)
2	10 (16.7)	6 (10)
3	8 (13.3)	1 (1.7)
4	6 (10)	2 (3.3)
5	6 (10)	6 (10)
Likert scale		
Complete recovery		19 (31.7)
Almost-complete recovery		21 (35)
Some recovery		5 (8.3)
Unchanged		10 (16.7)
Some worsening		1 (1.7)
Serious worsening		2 (3.3)
Worse than ever		2 (3.3)

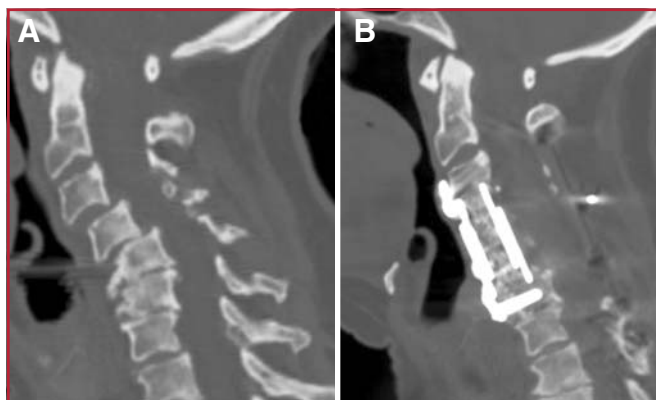


FIGURE 3. **A**, a 67-year-old woman presented with “staircase deformity” and severe cervical spondylogenic myelopathy. The patient underwent cervical traction to achieve better alignment, followed by corpectomy of C4 and C5 with insertion of a telescoping plate spacer (TPS) cage and additional posterior fixation from C2 to T1. **B**, postoperative sagittal computed tomographic reconstruction showing solid fusion with improvement of segmental angulation from 18 to 0 degrees kyphosis.

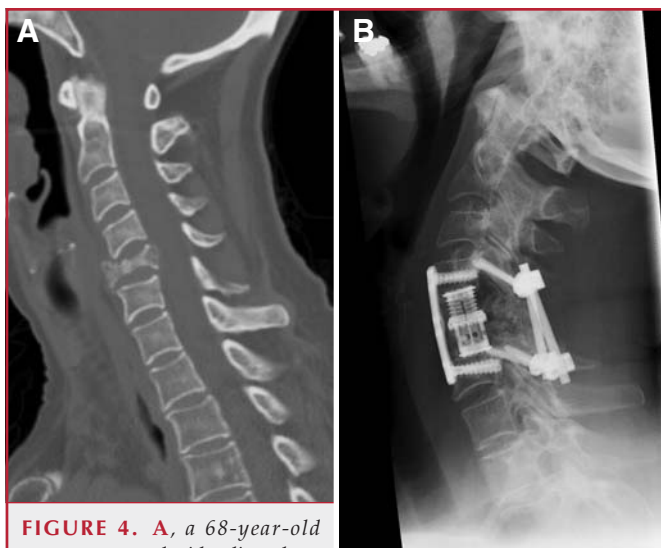


FIGURE 4. **A**, a 68-year-old woman presented with solitary lung metastasis with destruction of C5. **B**, corpectomy of C5 with implantation of Cervilift (Deltacon GmbH, Werneck, Germany) and additional plating, and resection of posterior elements followed by lateral mass screw fixation was performed from C4 to C6. The segment height increased from 16 to 23 mm.

insufficient (12). One of the main advantages of expandable cages for vertebral body replacement is easy, non-distracted insertion of the cage. The height can be adjusted to the corpectomy defect in situ, and correction of deformity and restoring height can be achieved. Similarly, in the present study we have achieved a mean improvement of segment height by 3.5 mm and sagittal correction by 4.0 degrees. However, one of the pitfalls of expandable cages is over-distraction. The mechanical properties of the implant allow smooth and easy distraction, and the surgeon should not maneuver against too much resistance to prevent traction injury of the segmental nerves. In our series, one patient developed transient C5 palsy because of overdistraction, which has been documented previously (20).

The fusion rate in our study was high and in accordance with the literature (2, 5, 13, 19, 26, 28). There was no relation between occurrence of non-union and type of implant. The central cavity of the ADD, ADDplus, and obelisc is relatively small, with consequent limited interbody-bone interface. However, consolidation around the implants was visible, and signs of instability were not observed. TPS, VLIFT, and Cervilift have a better implant-bone interface because of the large central cavity that can be filled with bone.

In the present case series, implant subsidence was documented in nearly half of the patients, which was remarkably high in terms of our relatively short follow-up period. It is possible that the adjacent end plates were cleaned and flattened too rigorously, or the endplates were weakened primarily, since most of the cases involved spinal metastasis. Coumans et al. (5) investigated 15 patients who underwent placement of TPS. No patient showed subsidence, and their mean follow-up was short as well. Auguste et al. (2) documented a significant sub-

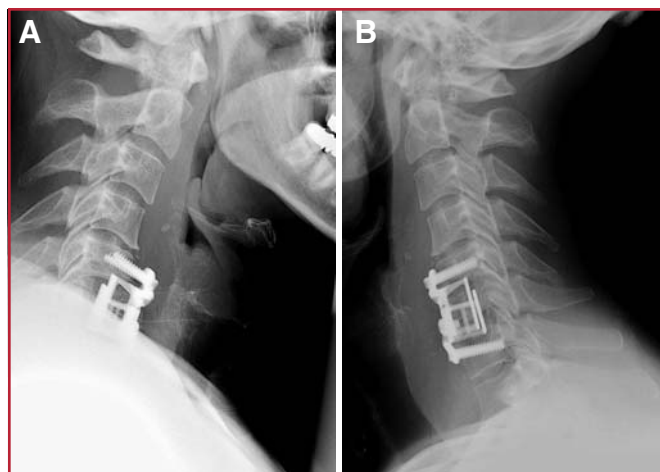


FIGURE 5. **A**, lateral fluoroscopic image of a 51-year-old man with anterior stenosis at C5 to C7 who was treated with corpectomy at C6 and implantation of TPS. The central gutter was too narrow with consequent anterior position of the implant. **B**, during reexploration the next day, the posterior part of the vertebral defect was extended in the lateral direction and the implant was repositioned.

sidence rate in 22 patients treated with Synnex expandable cages (Synthes Spine, West Chester, PA). In accordance with Auguste et al. (2), we observed a correlation between additional posterior instrumentation and reduced subsidence rate, although this was not statistically significant.

The complication and reoperation rates in our series are remarkably high and will be discussed in more detail. Surprisingly, hardware displacement was the most documented complication. Expandable cages were developed for easier use and less effort in spinal column reconstruction. However, some basic biomechanical principles and spinal surgical experience are recommended. In our series, all 5 patients with hardware displacement were operated during the first period, and 2 procedures were performed by surgeons who had no experience in vertebral body reconstruction. All these cases involved TPS cages. The TPS has a rectangular shape; therefore, the central gutter in the vertebral body has to be drilled straight or somewhat divergent to insert the implant properly and prevent anterior displacement (Fig. 5). The other implants used are rounded and, therefore, the carpentry can be less precise. In addition, TPS has fixed end caps that require accurate preparation.

Another biomechanical complication we documented in 3 patients was progressive kyphosis. Two of them had multilevel degenerative stenosis with kyphosis and underwent 2-level corpectomy with circumferential spondylodesis. However, the posterior construct involved the same vertebral segments as the anterior construct, and progressive kyphosis developed at the adjacent cervicothoracic junction (Fig. 6). Secondary surgery with extension of the posterior construct to the upper thoracic spine was necessary, which would have been prevented if the primary construct were made longer.

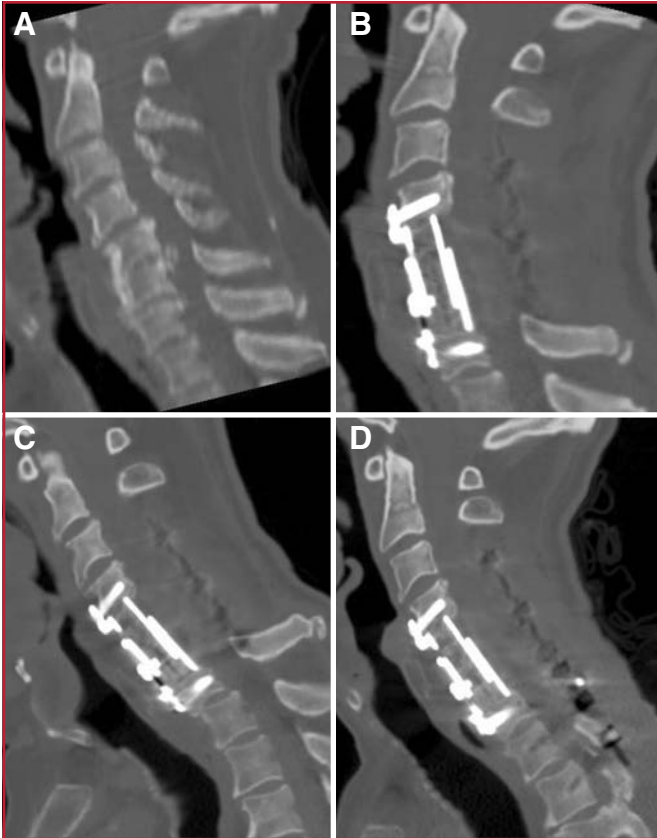


FIGURE 6. **A**, sagittal computed tomographic reconstruction of a 73-year-old male with spondylotic myelopathy based on stenosis at C4 to C7 with anterior and posterior compression. **B**, corpectomy at C5 to C6 with TPS implantation and posterior decompression at C3 to C6 with lateral mass screw fixation at C3 to C6 were performed. **C**, 1 year postoperatively, anterolisthesis with kyphosis at the cervicothoracic junction was demonstrated. **D**, posterior revision surgery with additional pedicle screw fixation and extension of the construct to T2 were performed.

In our study, more than one-third of the patients had spinal metastasis, and half of the cases with complications involved metastasis. This might bring our complication rate into perspective. Patients with spinal metastasis are at high risk regarding complications because of steroid use, previous radiotherapy, weight loss, or metastasis elsewhere. Therefore, it is of utmost importance to estimate a patient's life expectancy a priori when considering extensive spinal surgery with instrumentation (3).

Spinal metastases often require corpectomy through an anterior approach followed by posterior column resection and subsequent instrumentation. This circumferential reconstruction is often demanding and is associated with significant risks (14, 18, 23). In 9 patients, we performed a corpectomy with circumferential reconstruction through a single posterior approach, which has been described before (22, 24, 25). Wide unilateral costotransversectomy allowed extracavitary decompression of the dura across the midline to the contralateral pedicle. Depending on the pathology, resection of the vertebral body

was approached unilaterally or bilaterally, which obviated the transcutaneous-associated risks. However, rhizotomy of 1 segmental nerve root could be necessary to insert the smallest nondistracted expandable cage (Fig. 2C). Neurological deficit after rhizotomy of a single spinal thoracic nerve root is usually limited due to extensive overlap of distributions, as shown in our patients. In cases of lumbar spine involvement, the implant can be inserted horizontally and then rotated vertically when in position. This can allow insertion of the implant without sacrificing the nerve root (24).

The present case series has several limitations. The mean follow-up period of 9 months is short, particularly in the light of the high complication and subsidence rates. It would appear necessary to have longer duration of follow-up to determine if any late complications have occurred as well, and to evaluate long-term subsidence. Secondly, the patient population is heterogeneous, various pathologies were treated, and different expandable implants were used. However, in our opinion, the basics of vertebral body replacement and reconstruction remain the same in all of our cases. Finally, we presented a case series, and this study was not designed to compare expandable cages with other forms of reconstruction, such as the traditional bone grafting with plating.

In the present series, we have implanted 6 different expandable vertebral body replacement systems. Each device has its pros and cons. The main advantage of TPS, VLIFT, and Cervilift is the large central part of the implant with the possibility of bone filling. This is limited in ADD, ADDplus, and obelisc. The disadvantage of TPS is the fixed end cap and the bulky square shape of the implant. The carpentry of the end plates and remaining vertebral body to prevent anterior displacement can be challenging. In the upper thoracic spine, insertion of VLIFT can be problematic because of the relative large diameter; therefore, we prefer the smaller Cervilift or ADDplus in this region. Cervilift, ADD, obelisc, and VLIFT require supplemental instrumentation, but direct connection to these implants is not possible. TPS and ADDplus, on the other hand, have an integrated wing fixation to the adjacent vertebral bodies, which eliminates the need for additional plating. All implants lack the possibility to restore a large 3- or more level corpectomy defect without 1 or 2 extension pieces. In such a construct, however, the biomechanical properties might be questionable.

CONCLUSION

Vertebral body resection with implantation of expandable cages can be performed in the cervical, thoracic, and lumbar regions for the treatment of various spinal pathologies. The main advantage is in situ adjustment to the height of the corpectomy defect, which eliminates the need for extensive carpentry. Different devices are available, and all have the potential of restoring height and correction of sagittal alignment. In the present prospectively followed case series of 60 patients, the construct appears stable, although the subsidence rate is high. The neurological function improves significantly, and the

majority of patients have good clinical results. However, the complication rate and incidence of revision surgery are high.

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COMMENTS

The material used to replace a vertebral body after a corpectomy has changed from autograft, allograft, and methylmethacrylate to fixed cages to the current use of expandable cages. Arts and Peul used six different types of expandable cages to replace vertebral bodies removed for a variety of reasons. They found the ability to expand the cages helpful, especially when they were placed from a posterolateral approach.

Their relatively high complication rate (21.7%) emphasizes the fact that surgical experience is needed to ensure good outcomes after placement of spinal cages. However, their patient population included 22 patients with primary or secondary tumors, and surgical treatment in such patients is known to be associated with a high complication rate.

Compared with the previous devices, expandable cages are elegant and offer many advantages. Nonetheless, most of the devices occupy the space at the endplates where placement of graft material is usually preferred. The cages are also expensive. This article emphasizes the pros and cons of these cages.

Volker K.H. Sonntag
Phoenix, Arizona

Arts and Peul provided a relatively large clinical series that assessed use of expandable cage vertebral body replacement systems for a variety of spinal pathological lesions. Their assessment and their experience provide valuable insight for the complex spine surgeon. Most notably, the complication rate is not insignificant. With this in mind, the advantages and disadvantages of such a clinical strategy can be appropriately determined preoperatively. They have provided an honest and meticulous report.

Edward C. Benzel
Cleveland, Ohio

Arts and Peul reported their experience with expandable cages for reconstruction of the anterior column in 60 prospectively followed patients. The cohort is very heterogeneous in that the pathological lesions were varied, cervical, thoracic, and lumbar procedures were included, and six different types of expandable cages were used. All cages were filled with allograft. Fusion was determined using dynamic

films and computed tomography, and the rate is stated to be 93%. Unfortunately, the imaging was performed at 3 months postsurgery which is too soon to verify a true arthrodesis.

Expandable cages can be very helpful in the thoracic and lumbar regions, but they offer less advantage in the cervical spine compared with other techniques. In this study, 68% of the subjects had cervical cages placed.

Perhaps the most important finding is the complication rate of 30%. Although some of these were fairly minor, a number of them were very serious. It is notable that although only one-third of the patients in this study were treated for spinal metastasis, this subgroup accounted for half of all complications. The discussion reviews a number of important points that should help minimize adverse events and should be carefully read by all interested in using these devices.

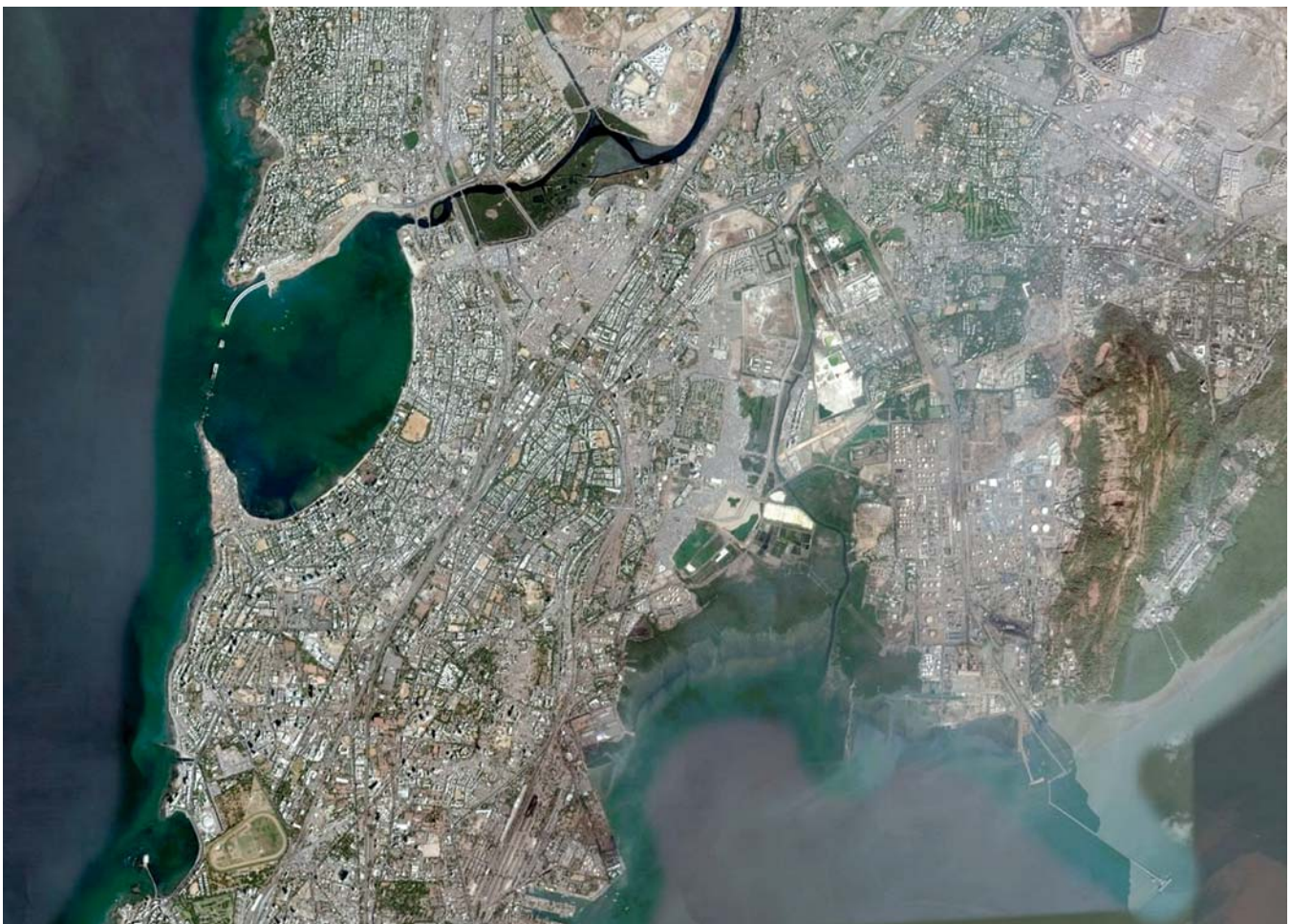
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Arts and Peul presented their extensive case series of patients (N = 60) who underwent vertebral body reconstruction with expandable

metallic cages. A number of different devices from three separate manufacturers were used, but all of the prostheses were similar in design and application. The results were quite acceptable with a 93% radiographic fusion rate, and a number of complications were encountered owing to the severity of pathological lesions treated.

The introduction of these devices has significantly expanded the surgical armamentarium. These cages have made anterior column reconstruction after a posterolateral corpectomy much more feasible, as they can be lengthened in situ after insertion ventral to the spinal cord. However, they have substantial metallic bulk and thus create significant artifacts on postoperative magnetic resonance imaging. In addition, in the United States, these devices add a large implant cost to the surgical procedure compared with allograft or static mesh cages. Whether their added expense can be justified in all patients remains to be proven, and in my practice their use has been limited to those challenging situations in which their in situ expansion capabilities are truly beneficial.

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RADIOLOGICAL FINDINGS AND CLINICAL COURSE OF CONUS LIPOMA: IMPLICATIONS FOR SURGICAL TREATMENT

OBJECTIVE: A significant variety in morphology of conus lipomas may underlie differences in clinical presentation of the patients and controversy in surgical management. We retrospectively studied 58 patients with conus lipomas at our institutions. The purpose of this study was to infer the clinical course from the radiological findings and to provide information for decision-making in planning for surgical treatment.

METHODS: The patients underwent untethering surgery between 1984 and 2005. There were 35 transitional and 23 dorsal lipomas. The age at surgery ranged from 1 month to 50 years (median, 4 yr). Preoperative clinical history, radiological findings, and postoperative results were analyzed.

RESULTS: Fifteen patients were asymptomatic, and 43 patients were symptomatic preoperatively. Twenty-one patients presented with motor deficits of the lower extremities. In seven patients, motor deficits appeared early, before 1 year of age. Massive lipomas compressing the cord or herniation of the spinal cord into the subcutaneous tissue were characteristic findings of such early deterioration. Motor deficits were present in 73% of patients with lipomas extending to the lumbar level, whereas 88% of patients with lipomas confined to the sacral level had only urinary deficits. During a mean postoperative follow-up period of 7.9 years, 4 (27%) of the 15 asymptomatic patients developed urinary and/or motor deficits, and 12 (28%) of the 43 symptomatic patients showed further neurological deterioration.

CONCLUSION: This study demonstrates that the location and morphology of conus lipomas influence the neurological presentation of the patients. Early prophylactic surgery is a reasonable treatment option if early deterioration is predicted by imaging studies.

KEY WORDS: Conus lipoma, Lumbosacral spinal lipoma, Occult spinal dysraphism, Surgical treatment, Tethered cord

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Lumbosacral spinal lipoma is a common form of spinal cord disorder associated with occult spinal dysraphism. Neurological or urinary deficits often appear after birth (16, 20, 27). The literature indicates that surgical treatment is effective in controlling the symptoms (1, 3, 4, 6, 7, 10–13, 17, 18, 20, 21, 23, 24, 29–31). However, the long-term postoperative results in conus lipomas have not been satisfactory, as compared with filum lipomas (25, 28). Conservative management until the development of symptoms was recently reported in asymptomatic patients with conus lipomas

(22). Indeed, some groups of patients have urinary and motor deficits since childhood, whereas some patients develop symptoms in adulthood (14). A significant variety in the morphology of the lipoma-spinal cord complex may underlie differences in the clinical presentation of the patients and may contribute to the controversy in management.

In this investigation, we retrospectively studied 58 patients with conus lipomas who underwent surgical treatment at our institutions. The purpose of this study was to infer the clinical course from the radiological findings and to provide information for decision-making in planning the surgical treatment.

ABBREVIATION: MRI, magnetic resonance imaging

PATIENTS AND METHODS

Patients

Fifty-eight patients were operated on between 1984 and 2005. Patients with a history of surgical treatment of the conus lipoma at other institutions were excluded. There were 25 male patients and 33 female patients, ranging in age from 1 month to 50 years (mean, 11.5 yr; median, 4 yr) at the time of surgical treatment (Fig. 1). According to the modified Chapman classification (21), there were 35 transitional and 23 dorsal lipomas. Preoperatively, 15 patients were asymptomatic except for skin lesions, and 43 patients exhibited urinary deficits and/or motor deficits of the lower extremities. One patient had been operated on for atresia ani. All patients were examined preoperatively and postoperatively in the urological service. Preoperative radiological examinations included plain x-rays, computed tomography of the spine, and magnetic resonance imaging (MRI) (54 patients) or computed tomographic myelography (4 patients). Syrinx formation rostral to the lipoma was noted in 12 patients (21%). The analysis was focused on the age at onset of urinary or motor deficits from the clinical records, the spinal level of the conus lipoma from imaging studies, and the postoperative clinical course.

Surgery

Surgery was performed with the patient in the prone position under general anesthesia. The surgical procedures included one- to three-level laminectomy or laminoplasty rostral to the lamina defect, opening of the intact dura, and detachment of the spinal cord lipoma from the surrounding dural and subcutaneous tissues. The lipoma at the conus medullaris was partially removed, and the pia was approximated at several points with 8-0 nylon sutures. After the spinal cord/lipoma was restored in the spinal canal, the dural defect was repaired with a freeze-dried dura or artificial dura (Gore-Tex; W.L. Gore & Associates, Inc., Flagstaff, AZ). For intraoperative monitoring, evoked electromyography was recorded from the anal sphincter and gastrocnemius muscles after 0.8- to 1.0-mA bipolar stimulation.

RESULTS

Age at Onset of Motor Deficits

Twenty-one patients (36%), ranging in age from 1 month to 48 years (median, 22 yr), presented with motor deficits of the lower extremities, such as motor weakness, atrophy of the muscles, or foot deformity, at the time of surgery. These patients also had urinary deficits of various degrees. The age distribution at the onset of motor deficits could be classified into two age groups (Fig. 2). Fourteen (67%) of the 21 patients developed motor deficits between 7 and 44 years of age (mean, 17.8 yr; median, 16.5 yr). The other seven patients (33%) exhibited motor deficits before 1 year of age. One of them had a unilateral foot deformity at birth, but the other six patients developed motor weakness after birth (range, 1–12 mo; mean, 6.8 mo; median, 7 mo). Two of these six patients had massive lipomas compressing the spinal cord in the spinal canal (Fig. 3). The other four patients had a herniated spinal cord with a lipoma from the lamina defects (Fig. 4). All four patients with a herniated spinal cord had dorsal-type lipomas, and three of the lipomas were associated with myelocystoceles. No other patients in our series had a herniated spinal cord.

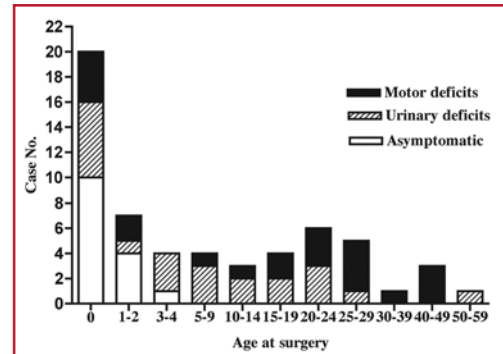


FIGURE 1. Bar graph showing the number of cases and age distribution at the time of surgery in 58 patients with conus lipomas. Black, shaded, and white bars indicate patients with motor deficits of the lower extremities, patients with urinary deficits alone, and asymptomatic patients, respectively. Note that all asymptomatic patients are younger than 4 years of age.

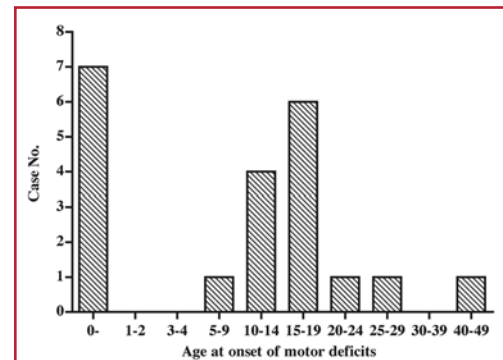


FIGURE 2. Bar graph showing the number of cases and age at onset of motor deficits in 21 patients. There are two peaks (before 1 yr and late teens) of the age at onset.

When a “massive lipoma” is defined as a lipoma extending into the lumbar spinal canal and compressing the spinal cord tissue on the posterior aspect of the vertebral bodies, such lipomas were identified in 4 of the 43 symptomatic patients and in 3 of the 15 asymptomatic patients in our series. Two of the symptomatic patients showed early motor deterioration, and the other two patients had only urinary problems. Because five patients with urinary problems (two patients) or no deficits (three patients) underwent “prophylactic” untethering surgery at 1 to 9 months of age (mean, 4.8 mo), the further natural clinical course, including motor deterioration, cannot be evaluated. Massive lipomas may be one of the risk factors for early motor deterioration because of possible mechanical compressive effects on the spinal cord. Five of the six patients showed syrinx formation. Preoperative serial MRI examinations revealed progressive enlargement of the syrinx (Figs. 3 and 4) in three of them.



FIGURE 3. Serial magnetic resonance imaging (MRI) scans of the lumbosacral spine in a patient who underwent surgical treatment at the age of 7 months. This patient developed progressive motor weakness of the lower extremities at 2 months. T1-weighted MRI scans at 8 days (**A**) and 5 months (**B**) of age display progressive compression of the spinal cord in the spinal canal by a massive lipoma. Syrinx formation is noted at 5 months.

Age at Onset of Urinary Deficits

Forty-three patients (74%), ranging in age from 1 month to 50 years (median, 13 yr), presented with urinary deficits at the time of surgery. Thirty-two patients showed urinary symptoms such as incontinence, difficulty in voiding, pollakiuria, or repeated urinary infection. In the other 11 patients, neurogenic bladder was diagnosed or suspected at the urological examination. The age distribution at onset of urinary deficits or diagnosis of neurogenic bladder is shown in *Figure 5*. Twenty-six patients (60%) had urinary deficits by 4 years of age, whereas the other 17 patients (40%) developed urinary deficits between 8 and 47 years of age. Of the 22 patients who had urinary deficits without motor problems of the lower extremities, 17 (77%) had exhibited urinary deficits by 4 years of age (*Fig. 5*).

Urinary or Motor Deficits and Lipoma Level

The spinal level of the conus lipoma was determined from the radiological findings (mostly MRI scans) in 43 symptomatic patients. The rostral end of the lipoma and the age at onset of symptoms were plotted graphically (*Fig. 6*). The levels of lipomas were not related to the age at onset of the symptoms. However, in 26 patients, the rostral end of the lipoma existed at or above the L5–S1 level. Nineteen (73%) of them presented with motor deficits of the lower extremities, whereas the other seven patients (27%) showed only urinary problems. Seventeen patients had the lipoma at or below the S1 level. Fifteen (88%) of these 17 patients had urinary problems without motor

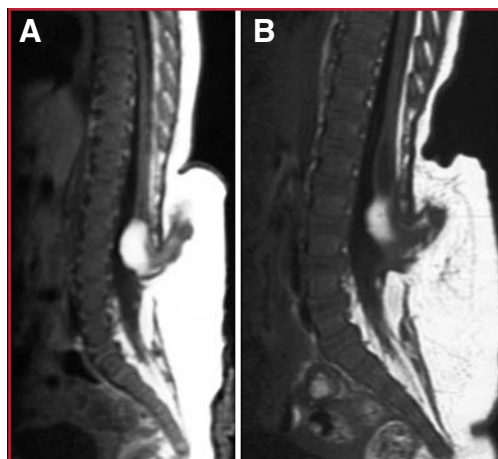


FIGURE 4. Serial MRI scans of the lumbosacral spine in a patient who underwent surgical treatment at the age of 9 months. This patient developed motor weakness of the lower extremities at 7 months. T1-weighted image at 3 days (**A**) shows the lipoma and the spinal cord herniated into the subcutaneous lipoma. T1-weighted image at 8 months (**B**) reveals development of syrinx immediately rostral to the lipoma.

deficits. The difference in the number of patients with motor deficits between these spinal level groups was determined to be statistically significant by the χ^2 test ($P < 0.0001$).

Type of Lipoma

There were 30 transitional and 13 dorsal lipomas in the 43 symptomatic patients (69.8% and 30.2%, respectively). The rostral end of the lipoma extended to the lumbar level in 13 of 30 transitional lipomas and in all 13 dorsal lipomas. The other 17 transitional lipomas existed at the sacral level. Neurologically, motor deficits were noted in 12 transitional and 9 dorsal lipomas. Twenty-two patients with urinary deficits alone had 18 transitional and 4 dorsal lipomas. Thus, there were more transitional lipomas in the patients with urinary deficits alone, whereas dorsal lipomas were more common in the patients with motor deficits. However, the difference of the lipoma type (transitional or dorsal) between these two patient groups was not significant ($P = 0.078$, χ^2 test). In the 15 asymptomatic patients, there were 5 transitional and 10 dorsal lipomas (33.3% and 66.7%, respectively).

Postoperative Results

For the 15 asymptomatic patients, untethering surgery was performed at the age of 2 months to 4 years (median, 8 mo). Three patients had the syrinx immediately rostral to the lipoma, and two of them underwent syringosubarachnoid shunt surgery. Postoperatively, two patients (13%) developed a subcutaneous cerebrospinal fluid collection after surgery, and one of them needed reoperation for dural repair.

Postoperative follow-up periods ranged from 6 to 222 months (mean, 116.5 mo [9.7 yr]). During the follow-up period,

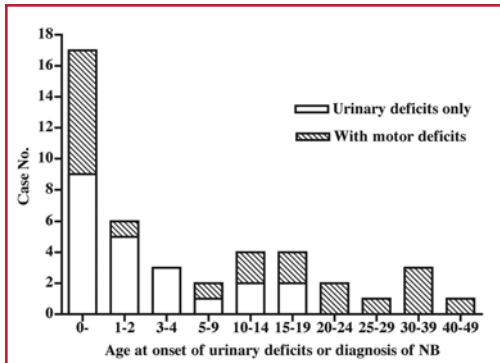


FIGURE 5. Bar graph showing the number of cases and age at onset of urinary deficits or diagnosis of neurogenic bladder (NB) at urological examination in the 43 symptomatic patients. Shaded bars indicate patients with urinary and motor deficits. White bars represent patients exhibiting only urinary deficits.

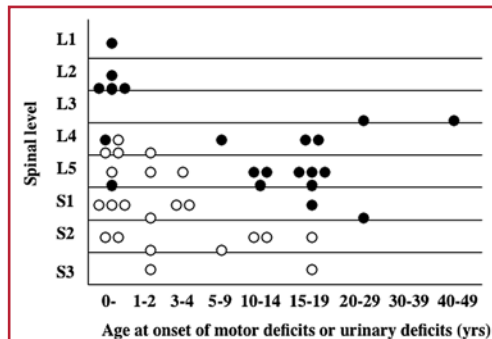


FIGURE 6. Plotted graph showing the spinal level of the rostral end of the lipoma and age at onset of motor deficits (black dots, 21 patients with motor deficits) or urinary deficits (white dots, 22 patients with urinary deficits only) in 43 symptomatic patients.

four patients (27%) with three transitional lipomas and one dorsal lipoma developed urinary (one patient) or urinary and motor deficits (three patients) 1 to 15 years after surgery. Three of them underwent a second untethering operation 10 to 15 years after the first operation. The other 11 patients (73%) remained asymptomatic, with a mean follow-up of 9.2 years (range, 6–222 mo).

For the 43 symptomatic patients, untethering surgery was performed at the age of 1 month to 50 years (median, 13 yr). Nine patients had a syrinx, and three of them underwent syringosubarachnoid shunt surgery. Postoperatively, a subcutaneous cerebrospinal fluid collection occurred in 10 patients (23%). Four of them required surgical repair of the dura mater. Decreased anal tonus and worsened urinary state were noted in four patients. Two patients experienced a temporary worsened urinary state. One patient showed temporary motor weakness of the legs and worsened lumbar pain after surgery.

Thus, seven patients (16%) displayed neurological or urological deterioration immediately after surgery, although these deficits improved gradually with time.

Postoperative follow-up periods ranged from 2 to 262 months (mean, 87.7 mo [7.3 yr]). During the follow-up period, 12 patients (28%) with 10 transitional and 2 dorsal lipomas showed neurological or urological deterioration (five motor deficits, four motor and urinary deficits, and three urinary deficits) 1 to 12 years after surgery, and 6 of them underwent reoperation 1 to 14 years after the first operation. Nineteen patients (44%) were unchanged, whereas 12 patients (28%) showed improvement of the symptoms (motor deficits in six, motor and urinary deficits in one, and urinary deficits in five). No patients achieved complete recovery from their deficits.

DISCUSSION

Natural Clinical History

Previous clinical studies have shown that the proportion of asymptomatic patients decreased progressively with age in lumbosacral spinal lipomas (13, 16, 20, 27). It is supposed that the tethering effects of the spinal cord associated with growth of the spinal column or daily body motion and/or spinal cord compression by the lipoma are responsible for the delayed deterioration (21, 26). However, it is difficult to predict when the deterioration will occur in each patient.

In the present study, the onset of symptoms was determined from the clinical record to determine the natural history of each patient from birth to the time of surgery. Although this method may not provide the accurate time of onset, our results revealed that there were two peaks in the age of patients for development of motor deficits (Fig. 2). The MRI findings of the patients whose onset was at the first peak suggest that early motor deterioration was probably attributable to compression of the spinal cord by the massive lipoma extending into the lumbar spinal canal (Fig. 3) or acute tethering effects (bent or stretched) on the lower spinal cord associated with herniation of the spinal cord (Fig. 4). Syrinx formation might have had additional effects on neurological deterioration in these patients (15, 19); five of them showed syrinx formation immediately rostral to the lipoma. Such MRI findings may indicate significant mechanical stress on the spinal cord.

In contrast to motor deficits, the age at onset of urinary deficits showed only one peak in the first year after birth. This may include patients with congenital defects of urinary function. However, at least 40% of the patients developed late urinary deficits in this series. Elucidation of the mechanisms of urinary deterioration will need further studies, including prospective analysis.

Effects of Location and Type of Lipoma

The present study also revealed that the location of the lipoma was related to the neurological deficits of the patients. In our 43 symptomatic patients, 73% of the patients with lumbar extension lipomas had motor deficits in the legs, and 50%

of patients with massive lipomas showed early motor deterioration before 1 year of age (19 of 23 patients and 2 of 4 patients, respectively). All of the patients with a herniated spinal cord showed early motor deterioration (four patients). Eighty-eight percent of the patients with sacral lipomas presented with urinary deficits without motor problems (15 of 17 patients). Motor deficits were significantly more common in patients with lipomas extending to the lumbar level. In contrast, patients with lipomas confined to the sacral level more frequently presented with only urinary deficits. The difference in the level of compression or tethering of the spinal cord may explain such differences in neurological presentation. It is interesting that, in this series, all of the lipomas confined to the sacral level were of the transitional type. Such patients may develop urinary deterioration early after birth without showing motor problems of the lower extremities. Thus, radiological evaluation of the morphology of the conus lipoma may be helpful for predicting neurological deterioration.

The type of lipoma has been discussed in the literature (2, 5, 8) with relation to the difficulty of untethering surgery. For example, Arai et al. (2) reported that untethering surgery could be performed for dorsal lipomas without risk, whereas the surgery for transitional lipomas was accompanied by surgical risk. A higher frequency of retethering in transitional lipomas was also reported (8). In our series, transitional lipoma occurred in 13 (81%) of the 16 patients (4 asymptomatic and 12 symptomatic patients) who showed late postoperative deterioration. Thus, our series also indicates differences in surgical results according to the type of lipoma.

Few reports have described the relationship between the spinal level and clinical presentations of the lipomas. In 2002, Dorward et al. (9) reported the possibility of two different patient groups in lumbosacral lipomas. In one group, the lipomas tended to lie in the lumbar region, and the patients showed relatively late urological deterioration. The other group consisted of patients with large sacral lipomas who presented with early urological deficits. Their observation is consistent with our results in that the location of the lipoma significantly influences the clinical presentation of the patient.

Effects of Surgical Treatment

Although early untethering surgery has been advocated for patients with lumbosacral spinal lipomas, prophylactic surgery for asymptomatic patients with conus lipomas is still controversial. According to several relatively large series of conus lipomas (23, 28, 31), 13 to 24% of asymptomatic patients who underwent surgical treatment showed late neurological deterioration, with mean follow-up periods of 5.2 to 6.3 years. However, Pierre-Kahn et al. (28) reported a late deterioration rate of 47% (15 of the 32 asymptomatic patients) if the analysis was performed at more than 5 years' follow-up (5–23 yr; mean, 8.7 yr). In our series, 27% of the asymptomatic patients showed late deterioration after surgery, with a mean follow-up of 9.7 years. According to a recent report (22), during the conservative management protocol for asymptomatic patients with conus lipomas, 13 (25%) of the 53 patients showed neurological deterioration

at a mean follow-up of 4.4 years (range, 12 mo–9 yr). Further studies will be needed to determine the role of prophylactic surgery for patients with conus lipomas, because the clinical course and postoperative results may be significantly influenced by the type and location of the lipoma.

For symptomatic patients with conus lipomas reported in the literature, 26 to 67% of patients were improved after surgery, whereas 18 to 41% showed late deterioration at a mean follow-up of 5.2 to 6.6 years (23, 28, 31). In our series, postoperative results (28% improved) were rather disappointing. A relatively higher proportion of older patients (19 of 43 symptomatic patients were older than 17 yr) in our series might account for a part of the unsatisfactory results because of a delay in diagnosis and treatment.

CONCLUSION

According to our study, conus lipoma is not a uniform clinical entity. There is a high-risk patient group that will develop neurological deterioration soon after birth. Factors for early motor deterioration may include massive lipomas extending into the lumbar spinal canal and compressing the spinal cord on the posterior aspect of the vertebral bodies, or herniation of the spinal cord into the subcutaneous lipoma through the dysraphic area. Conus lipomas confined to the sacral level may include a group with early urological deterioration. Understanding the relationship between the morphology of conus lipomas and the possible clinical course will be important for determining the management of these patients. Early prophylactic surgery is a reasonable treatment option if imaging studies demonstrate significant mechanical stress on the spinal cord.

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COMMENTS

Koyanagi et al. reviewed a series of 58 patients with lipomas of the conus and cauda equina between 1984 and 2005 to span the magnetic resonance imaging era. This is a detailed analysis.

Of the 58 patients who were reviewed, 35 had a transitional type and 23 had a dorsal plate lipoma. Excluded from this series were patients who had fatty filum and previous surgery. Fifteen patients were asymptomatic but had skin abnormalities, and 43 had urinary/motor symptoms. A terminal syrinx was noted in 12 individuals.

Of the patients, 60% had urinary symptoms, and these patients were usually younger than age 4. Lumbosacral lipomas produced motor deficits and tended to be dorsal plate. The lipomas that were confined to the sacral spinal canal usually presented with urinary deficits and were transitional. The conclusion of Koyanagi et al. was that symptomatic patients usually presented between the ages of 2 months and 4 years and a delayed surgical procedure resulted in less recovery. They felt that the size of the mass with cord compression and a tethering effect were factors responsible for early motor deficits that were seen in patients younger than 1 year of age. An interesting finding was that asymptomatic patients showed late deterioration as in other series, and recovery was less than otherwise expected. Hence, they proposed that prophylactic surgery is desired.

This is an important detailed analysis that should be taken into consideration when one is considering surgical procedures for such affected children.

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When confronted with a child or adult with a conus lipoma, the neurosurgeon must address several important issues within the context of a single question: should I operate on this patient? In general, the tendency among neurosurgeons experienced in the management of spinal lipomas has been to operate on patients whether they are symptomatic or not. This tendency is also reflected in the present series in which one-fourth of the patients who underwent operations were asymptomatic at the time of surgery. The rationale has always been that both asymptomatic and symptomatic individuals have a high likelihood of neurological deterioration at some point in the future. Indeed, in this series, more than 80% of the patients developed motor and/or urological deficits at some time either pre- or postoperatively. It is noteworthy that 94% (33 of 35) of patients with transitional lipomas showed deterioration compared with 61% (14 of 23) with dorsal lesions. This finding suggests that there is a relatively greater indication for prophylactic surgery with transitional lipomas. Such a conclusion must, however, be qualified by the fact that untethering this type of lipoma is not only technically more challenging but also somewhat riskier by virtue of the intimate relationship between neural elements and the fibrolipomatous mass. In addition, the congenital dural defect is larger and extends anterior to the neural foramina on one or both sides. The greater technical difficulty of adequately untethering transitional lipomas is suggested in this study by the higher likelihood of postoperative deterioration.

If there were no risk involved and the likelihood of preventing neurological deterioration approached certainty, prophylactic surgery for all patients would be a reasonable approach. As one might anticipate, neither goal has been fulfilled despite the obvious skill and attention to detail of the surgeons involved in the care of the patients in the present series. We are indebted to them for sharing their substantial experience with us and carefully documenting their results and observations.

Paul H. Chapman
Boston, Massachusetts

Koyanagi et al. provided observations from a relatively large clinical analysis that associate morphological and anatomic findings with risk of neurological deterioration in patients with conus lipomas. As an example, early surgery may be indicated in minimally symptomatic or asymptomatic patients with large or dorsal lipomas. They have suc-

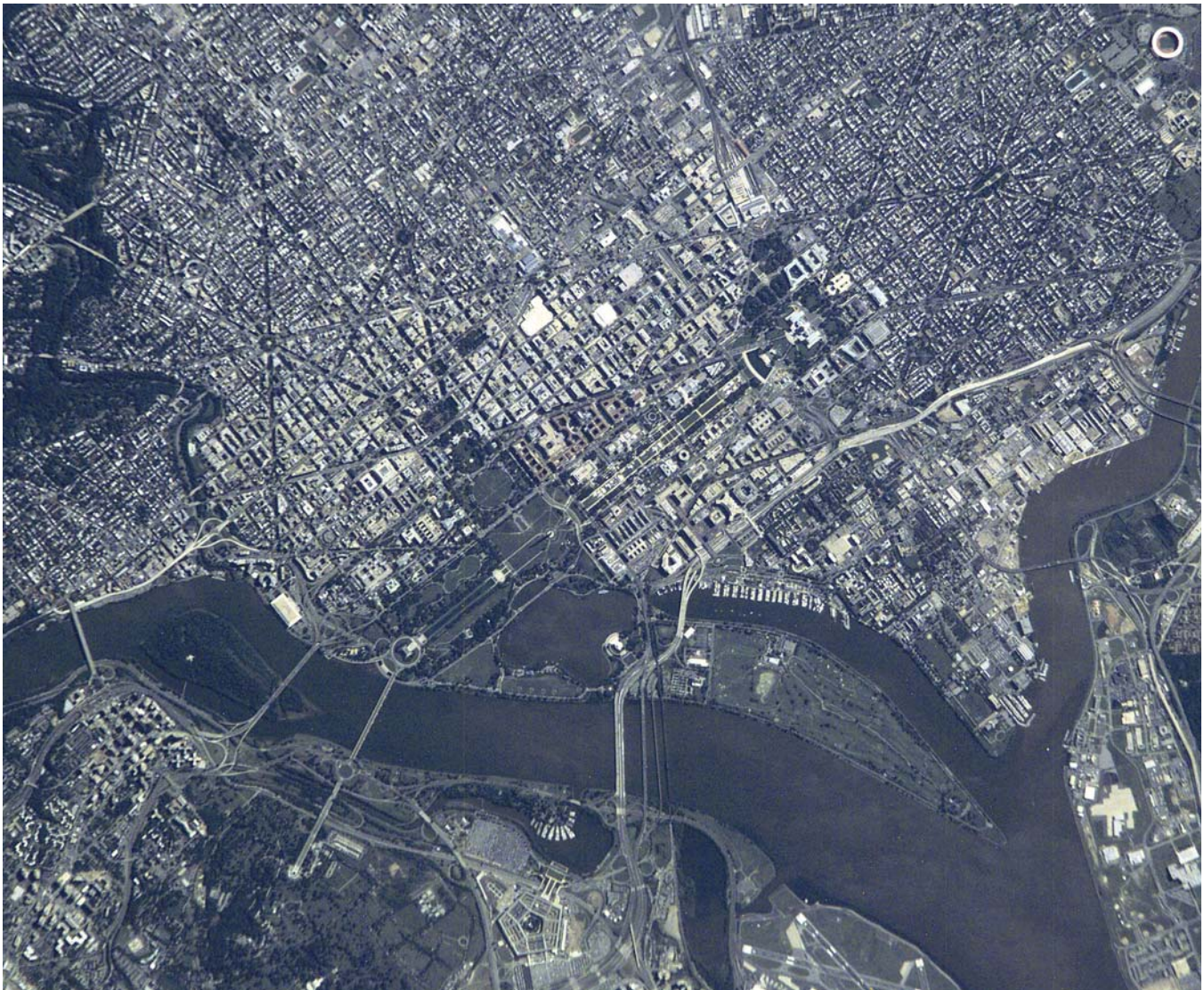
cessfully compiled information so that clinical decisions may be made more accurately.

Edward C. Benzel
Cleveland, Ohio

Koyanagi et al. assembled a large case series ($n = 58$) of lumbosacral lipomas treated surgically. The sample is impressive and consists of a mixture of both pediatric and adult patients. Their indication for surgery in adults was definitive, as they underwent surgery only if there was leg weakness or bowel/bladder dysfunction. Based on their longi-

tudinal tracking of this cohort, they recommended that large lesions compressing the spinal cord be resected, even if asymptomatic. This recommendation seems intuitive but the decision to resect had always been based more on clinical judgment and opinion than on scientific data. Nevertheless, the conclusion that I would draw is that patients harboring these lesions need to be followed closely to detect the early signs of neurological deterioration, which can occur many years after the initial diagnosis.

Michael Y. Wang
Miami, Florida



Washington, D.C. Image courtesy of Earth Sciences and Image Analysis Laboratory, NASA Johnson Space Center, (<http://eol.jsc.nasa.gov>).

CONTRALATERAL C7 TRANSFER VIA THE PRESPINAL AND RETROPHARYNGEAL ROUTE TO REPAIR BRACHIAL PLEXUS ROOT AVULSION: A PRELIMINARY REPORT

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OBJECTIVE: We sought to investigate a shorter and safer route for contralateral C7 transfer.

METHODS: Eight male patients were treated from December 2005 to November 2006. Their ages ranged from 22 to 43 years (average, 30 yr). Five patients had total brachial plexus avulsion. The operative delay was from 2 to 6 months (mean, 4 mo). The bilateral scalenus anterior muscles were transected before a prespinal and retropharyngeal tunnel was made. The contralateral C7 nerve root was used to repair the upper trunk or the infraclavicular lateral cord and posterior cord of the injured side via this route, with the use of direct neurorrhaphy or nerve grafting.

RESULTS: The length of the harvested contralateral C7 nerve root was 4.67 ± 0.52 cm in the first five patients. The nerve graft was 6.25 ± 0.35 cm long for repairing supraclavicular brachial plexus and 8.56 ± 0.45 cm long for repairing infraclavicular brachial plexus. The length of the harvested contralateral C7 nerve root averaged 6.85 cm in the last three patients, two of whom had direct neurorrhaphy to the C5 and six residual nerve roots; in the other patient, a nerve graft 3 cm in length was used. Transient contralateral sensory symptoms were reported in most patients. In all cases, shoulder abduction and elbow flexion recovered by 12 months postoperatively.

CONCLUSION: Transection of the bilateral scalenus muscles can reduce the length of the nerve graft and allow the C7 nerve to be transferred more smoothly and safely through the prespinal and retropharyngeal route; this method also favors nerve regeneration and functional recovery.

KEY WORDS: Brachial plexus repair, Contralateral C7 nerve root, Nerve graft, Root avulsion, Vertebral body

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Contralateral C7 (cC7) nerve root transfer was first introduced by Gu et al. (5) in 1986. It has been applied primarily in the repair of brachial plexus avulsion (2–4, 7, 8). cC7 nerve root transfer requires nerve grafting to bridge the donor and injured nerves. Commonly used bridging nerves include the vascularized ulnar nerve or free sural nerve, which is transferred via a route through a subcutaneous tunnel in the neck and chest to the contralateral side. In 2002, McGuinness and Kay (6) reported one case of cC7 nerve root transfer accomplished by passing the nerve through the prespinal and retropharyngeal space to repair the median nerve of an infant who had obstetric brachial plexus palsy (Tassin type IV). They made a

curved incision in the neck, dissected from anterior to posterior, and retracted bilateral sternomastoid muscles and carotid sheath laterally and esophagus/trachea medially to form a route to pass the C7 nerve through the prespinal and retropharyngeal space.

This route involves extensive dissection and may cause more damage to the vessel and esophagus/trachea. In this work, we introduce our modified technique to pass the C7 nerve through the prespinal and retropharyngeal space by severing bilateral anterior scalenus muscles and forming a transverse prevertebral tunnel by bilateral mobilization. Eight patients have been treated since December 2005, including six cases of supraclavicular brachial plexus repair and two cases of infraclavicular brachial plexus repair. Direct neurorrhaphy was achieved in two patients. In the other six

ABBREVIATION: cC7, contralateral C7

patients, conventional nerve grafting of various lengths was used. The initial follow-up results are reported in this article.

PATIENTS AND METHODS

General Data

From December 2005 to November 2006, eight male patients with brachial plexus root avulsion underwent this procedure. Their ages ranged from 22 to 43 years (average, 30 yr). Five patients had sustained total brachial plexus avulsion, and the other three patients had C5–C7 avulsion with C8 and T1 postganglionic injury. Six of the eight patients had accessory nerve and phrenic nerve injuries to different extents; the function of the accessory nerve was normal in the other two patients. The average interval between injury and operation was 4 months (range, 2–6 mo). All cases had follow-up for 12 months after surgery (*Table 1*).

Operative Approach

We used bilateral supraclavicular transverse incisions for exploration of the brachial plexus on both the injured and uninjured sides. Brachial plexus avulsion was confirmed by visual observation and intraoperative somatosensory evoked potentials on the injured side. The upper trunk and its divisions were found supraclavicularly in six patients. In the other two patients, the lateral and posterior cord could be dissected out only infraclavicularly because of retraction of the plexus.

The C5, C6, C7, C8, and T1 spinal nerve roots were exposed on the uninjured side. The phrenic nerve was carefully exposed along the surface of the scalenus anterior muscle and protected. The scalenus anterior muscle was then severed. The C7 nerve root was identified by visual observation. In the first five patients, we transected C7 at the trunk division level and, in the last three patients, we cut it at the division cord retroclavicularly to obtain more length. Then, the C7 nerve root was dissected proximally close to the intervertebral foramen, and the length of the C7 nerve root was measured. The anterolateral aspect of the C7 vertebral body was dissected bluntly. The esophagus was easily found anterior to the vertebral body. A space was then developed between the anterior vertebral body and the posterior border of the esophagus.

The same technique was used on the opposite side to establish a prespinal and retropharyngeal route (*Fig. 1*). A plastic tube was used to measure the needed length of nerve graft through this route. In cases in which the sural nerve was harvested as grafting material, five to seven strands of the sural nerve were sutured as one band, according to the needed length, before it was sewn to the cC7 nerve root (*Fig. 2*). The distal end of the before nerve or C7 nerve root was put into a plastic tube and secured with a stitch. The plastic tube was pulled through the tunnel. The distal ends of the grafted nerve were sutured to the upper trunk or its divisions, the suprascapular nerve, the infraclavicular lateral cord, or the posterior cord. Direct neurorrhaphy of C5 and C6 nerve roots was obtained in the last two patients (*Fig. 3*). After hemostasis, the incision was closed. Cessation of water and food intake was necessary in the first 4 days after operation.

In three patients, we performed two operations. One patient received an accessory nerve transfer to the suprascapular nerve via a dorsal approach; another patient underwent free gracilis muscle transplantation to reconstruct finger flexion; and a third patient first received an accessory nerve transfer to the suprascapular nerve via a dorsal approach and then underwent prespinal C7 transfer to repair C5 and C6.

RESULTS

In this clinical group, the length of the harvested cC7 nerve root was 4.67 ± 0.52 cm in the first five patients. The nerve graft for repairing the supraclavicular brachial plexus was 6.25 ± 0.35 cm and for repairing the infraclavicular brachial plexus was 8.56 ± 0.45 cm. In the last three patients, the length of the harvested cC7 nerve root averaged 6.85 cm, including two cases of direct neurorrhaphy to the residual nerve root of C5 and C6 on the injured side and one case of repairing the upper trunk of the brachial plexus by a nerve graft that was 3 cm in length.

All operations were uncomplicated, with no injury to the esophagus, major blood vessels, pleura, or thoracic duct during or after the operation. All patients had different degrees of tingling sensations in the contralateral radial three fingers at 3 to 4 weeks after the surgery. Five of the eight patients complained of tingling in the contralateral fingers when coughing or eating, which gradually subsided in 2 to 3 weeks. The sensory symptoms had almost complete resolution in 3 months. At 3 months' follow-up, all patients had tingling sensations on the contralateral fingers with percussion on the injured cervical area. At 7 months' follow-up, compound muscle action potentials could be recorded in the biceps, deltoids, and infraspinatus or triceps with stimulation at Erb's point on the uninjured side in all patients; however, no clinical movements were noticed. At 12 months' follow-up, we could observe early motor and sensory function recovery in the patients, to different extents (*Table 1*).

Illustrative Case

Patient 1, a 27-year-old man, had paralysis of the right upper limb caused by a motor vehicle accident 4 months earlier. On physical examination, there was no shoulder abduction or elbow extension and flexion. Muscle strength was measured using the modified British Medical Research Council grading system: trapezius: grade M1; deltoid,

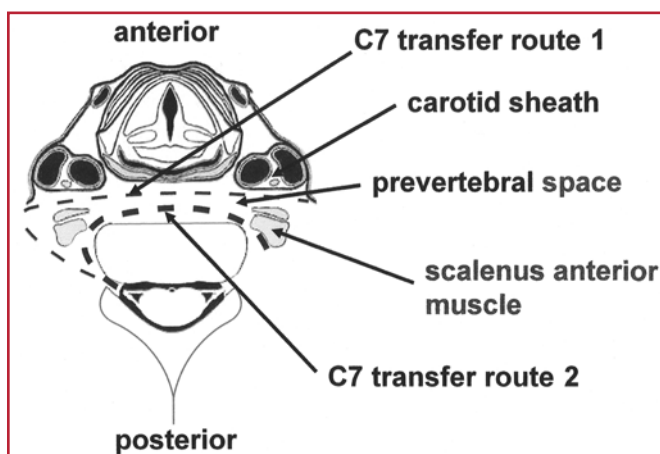


FIGURE 1. Diagrammatic cross section of the neck illustrating our route of contralateral C7 (cC7) nerve root transfer through the transversely configured prespinal and retropharyngeal space after bilateral resection of scalenus anterior muscles (Route 2). Route 1 is the McGuinness and Kay method (6).

TABLE 1. Patient data^a

Patient no.	Age (yr)	Injury date/ operation date	Diagnosis	Contralateral C7 transfer/other transfer	Results of nerve transfer (electrophysiology/clinic)	
					7 mo postoperatively	12 mo postoperatively
1	27	08.09.2005/ 12.29.2005	C5, C6, C7 avulsion C8, T1 PGD, PNP/SANP	C7-GSN (7.2 cm × 3 strands)-ADUT C7-GSRN (7.2 cm × 2 strands)-PDUT C7-GSN (7.2 cm × 1 strand)-SSN	CMAP/NMUP in Bic, Del, lfr; NMFR C5, C6, S2	SA, 30-45°; EF, 80° Bic, M3+; Del, M3-; lfr, M4-; C5, C6, S3-S4
2	42	10.30.2005/ 01.06.2006 (FS) 05.15.2006 (SS)	C5-T1 avulsion PNP/SANP	FS: C7-GSN (8 cm × 2 strands)-ADUT C7-GSN (8 cm × 2 strands)-PDUT C7-GSN (10 cm × 2 strands)-RN (IA) SS: FFGT	CMAP/NMUP in Bic, Del, Tri; NMFR C5, C6/RN, ≤S2	SA, 30°; EF, 80°; EE, 170°; FF, 10° Bic, M4-; Del, M3-; Tri, M4; TGM, M3-; Med, S3; MN, S4-; AN, S3; RN, S3+
3	36	11.09.2005/ 01.11.2006	C5-C7 avulsion C8, T1 PGD, PNP/SANP	C7-GSN (8 cm × 2 strands)-LC C7-GSN (8 cm × 4 strands)-PC	CMAP/NMUP in Bic, Del, Tri; NMFR Med/MN/AN/RN, ≤S2	SA, 30°; EF, 80°; EE, 170° Bic, M4; Del, M3-; Tri, M4; Med, S3; MN, S4-; AN, S3; RN, S3+
4	22	10.25.2005/ 03.13.2006 (FS) 07.13.2006 (SS)	C5-T1 avulsion PNP/NSANP	FS: C7-GSN (8 cm × 2 strands) + GSRN (8 cm × 1 strand)-LC C7-GSN (8 cm × 3 strands)-PC SS: SAN-SSN (PAT)	CMAP/NMUP in Bic, Del, Tri; NMFR Med/MN/AN, ≤S2	SA, 40°; EF, 75°; EE, 160° Bic, M4-; Del, M3-; Tri, M4-; Med, S3; MN, S4-; AN, S3; RN, S3+
5	25	01.29.2006/ 04.05.2006	C5-T1 avulsion NPNP/SANP	C7-GSN (6.5 cm × 3 strands)-ADUT C7-GSN (6.5 cm × 3 strands)-PDUT	CMAP/NMUP in Bic, Del, Tri; NMFR C5, C6, ≤S2	SA, 35°; EF, 85° Bic, M3+; Del, M3-; C5, C6, S3-S4
6	25	06.10.2006/ 10.19.2006	C5, C6 avulsion C7-T1 PGD, PNP/SANP	AD of C7-C5 (DA) PD of C7-C6 (DA)	CMAP/NMUP in Bic, Del, lfr; NMFR C5, C6, ≤S2	SA, 45°; EF, 80° Bic, M3+; Del, M3-; lfr, M3, C5, C6, S4
7	28	08.10.2006/ 10.23.2006	C5-T1 avulsion PNP/SANP	AD of C7-GSRN (3 cm × 3 strands)-PDUT PD of C7-GSRN (3 cm × 3 strands)-ADUT	CMAP/NMUP in Bic, Del; NMFR C5, C6, ≤S2	SA, 40°; EF, 85° Bic, M4-; Del, M3, C5, C6, S3-S4
8	32	05.06.2006/ 09.28.2006 (FS) 11.06.2006 (SS)	C5-T1 avulsion PNP/NSANP	FS: SAN-SSN (PAT) SS: AD of C7-C5 (DA) PD of C7-C6 (DA)	CMAP/NMUP in Bic, Del, lfr; NMFR C5, C6, ≤S2	SA, 35°; EF, 80° Bic, M4-; Del, M3-; lfr, M3-; C5, C6, S4

^a AD, anterior division; ADUT, anterior division of upper trunk; AN, axillary nerve; Bic, biceps; CMAP, compound muscle action potential; DA, direct anastomosis; Del, deltoid; EE, elbow extension; EF, elbow flexion; FF, finger flexion; FFGT, functional free gracilis transplantation to reconstruct finger flexion (intercostal nerve as donor nerve); FS, first stage; GSN, grafted sural nerve; GSRN, grafted superficial radial nerve; IA, infraclavicular anastomosis; lfr, infraspinatus; LC, lateral cord; Med, median nerve; MN, musculocutaneous nerve; NMFR, no motor function recovery; NMUP, nascent motor unit potentials; NPNP, no phrenic nerve palsy; NSANP, no spinal accessory nerve palsy; PAT, posterior approach transfer; PC, posterior cord; PD, posterior division; PDUT, posterior division of upper trunk; PGD, postganglionic damage; PNP, phrenic nerve palsy; RN, radial nerve; S, sensation; SA, shoulder abduction; SAN, spinal accessory nerve; SANP, spinal accessory nerve palsy; SS, second stage; SSN, suprascapular nerve; TGM, transplanted gracilis muscle; Tri, triceps.

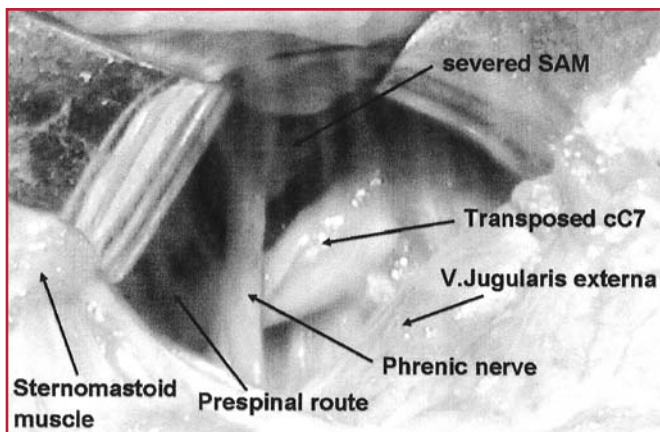


FIGURE 2. The distal end of the nerve graft was placed into a plastic tube whose proximal end was secured to the epineurium of the C7 nerve root. The nerve graft was then passed to the ipsilateral side by pulling the tube posterior and medial to the phrenic nerve. The adjacency of the c7 nerve and phrenic nerve on the uninjured side is shown in this illustration. SAM, scalenus anterior muscle; V., vein.

supraspinatus, infraspinatus, biceps: grade 0; triceps: grade 1; the muscles of flexion of the wrist and fingers: grade 3; the muscles of extension of the wrist and fingers: grade 2; and hand intrinsics: grade 2. Horner's sign was negative. Electromyography was consistent with brachial plexus injury: the injury of the C5 nerve root was both preganglionic and postganglionic, that of the C6 and C7 nerve roots was preganglionic, and that of the C8 and T1 nerve roots was postganglionic. The spinal accessory nerve and phrenic nerve also were injured.

Under general anesthesia, the right brachial plexus was explored, and preganglionic and postganglionic injury of the C5, C6, and C7 nerve roots

and postganglionic injury of the C8 and T1 nerve roots were found. The findings also were confirmed by intraoperative somatosensory evoked potentials, with nerve root stimulation and contralateral scalp recording. The injured brachial plexus nerves in this patient were repaired by transferring the c7 nerve root via the prespinal and retropharyngeal route by the use of sural nerve grafting. The harvested length of the c7 nerve root was 5.8 cm. We harvested 29 cm of the right sural nerve and 15 cm of the right superficial radial nerve.

A total of six strands of nerves were used for grafting. One grafted nerve was sutured to the suprascapular nerve, three grafted nerves were sutured to the anterior divisions of the upper trunk, and two grafted nerves were sutured to the posterior division of the upper trunk. After surgery, the patient had tingling in the contralateral index and middle fingers when eating; this resolved 17 days postoperatively.

Electromyography at 7 months postoperatively recorded compound muscle action potentials in the deltoid, infraspinatus, and biceps with contralateral Erb's point stimulation. Nascent motor unit potentials also were observed in these muscles. The clinical examination showed the presence of pinprick sensation on the lateral upper arm but no motor function of the shoulder and elbow. Flexion of the wrist and finger improved from M4- to M4+.

At 12 months postoperatively, this patient had 30 to 45 degrees of shoulder abduction and 80 degrees of elbow flexion. Strength of the biceps was M3+, deltoid M3-, infraspinatus M4-, triceps M4, extension of wrist and finger M4-, and flexion of wrist and finger M4+. A nerve conduction study recorded compound muscle action potentials in the biceps, deltoid, and infraspinatus; electromyography revealed reduced recruitment in these muscles (Figs. 4-6), and the recovery of sensory function was approximately S3 to S4 (British Medical Research Council grading system).

DISCUSSION

Since Gu et al. (5) introduced c7 nerve root transfer to repair brachial plexus injury in the 1980s, this procedure has been

adopted and modified; for example, it is used for ipsilateral C7 nerve root transfer in pediatric patients (1, 2, 9, 11). A reversed pedicle ulnar nerve graft typically was used, passing through the anterior neck, chest, and axilla via the subcutaneous passage to connect the injured nerves, such as the median nerve or the radial nerve (10). Free or vascularized sural nerve grafts also were commonly used via the same subcutaneous route. The subcutaneous route usually has a length of at least 18 cm. The harvested sural nerves could only be used in groups of three or four strands. Theoretically, the prespinal and retropharyngeal route for c7 nerve root transfer is the shortest route. In our group, the c7 nerve root

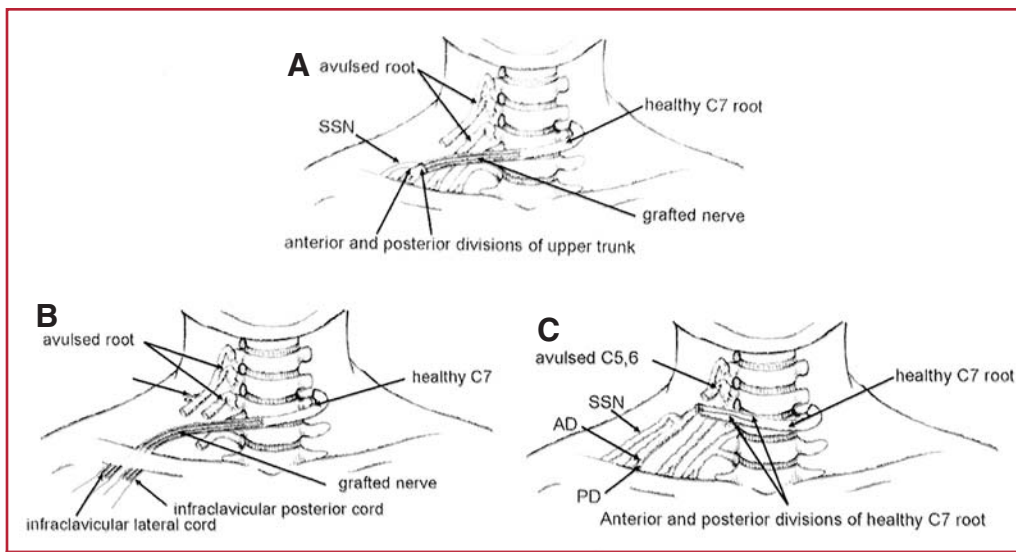


FIGURE 3. Diagrams showing the repair technique. **A**, the c7 nerve root was used to repair the supraclavicular nerves (the recipient nerves are the suprascapular nerve (SSN), anterior division of upper trunk (AD), and posterior division of upper trunk (PD), respectively). **B**, the c7 nerve root was used to repair the lateral and posterior cords infraclavicularly. **C**, direct repair of the upper trunk by c7 nerve root transfer.

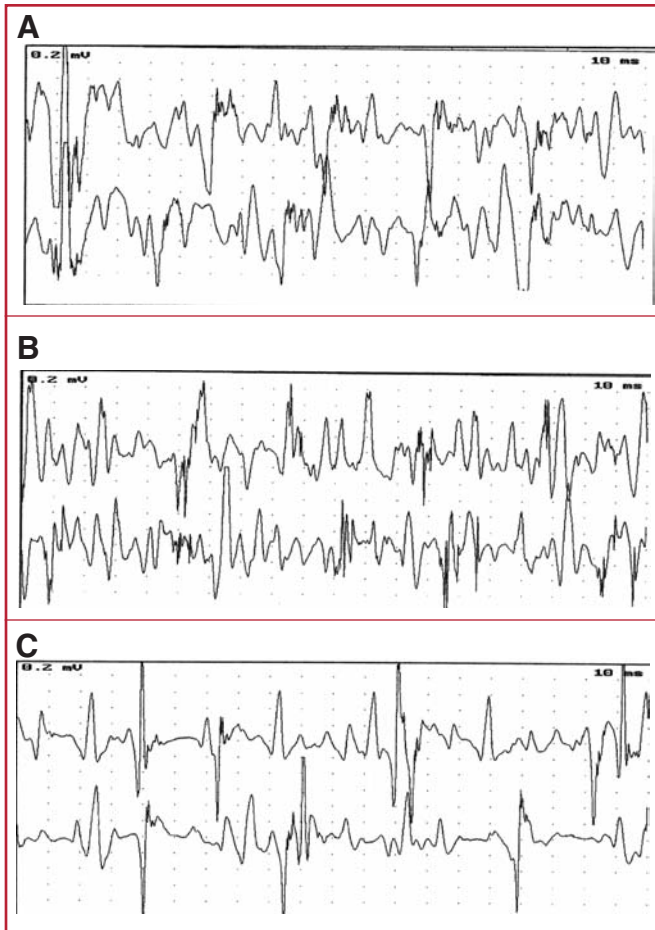


FIGURE 4. Patient 1. Twelve-month postoperative electromyographic follow-up of the biceps (A), deltoid (B), and infraspinatus (C) detected motor units in all three muscles and revealed reduced recruitment. Parametric setting: sensitivity, 0.2 mV; scanning speed, 10 milliseconds/d.

could reach one-third of the vertebral body on the injured side in the first five patients. In the last two patients, direct neurorrhaphy to the residual C5 and C6 roots was possible because of the slim stature of the patients and preganglionic damage. In the other six patients, only short bridging by 3-to 6-cm nerve grafts was necessary, so grafted sural nerve could be woven into five to six strands and C7 donor fibers could therefore be fully used to restore function to the shoulder and elbow. We believe that our approach greatly shortens the distance needed for nerve regeneration and should facilitate recovery of function.

The cervical region is anatomically complex. To further improve the safety, usability, and outcome, we designed an alternative route to the McGuiness and Kay method (6) by making a transverse supraclavicular incision bilaterally, using the C7 vertebral body as a landmark, and cutting the bilateral scalenus anterior muscles, making a transversely prevertebral tunnel by bilateral mobilization, and passing the nerve via this route to repair the injured nerves. First, our approach provides

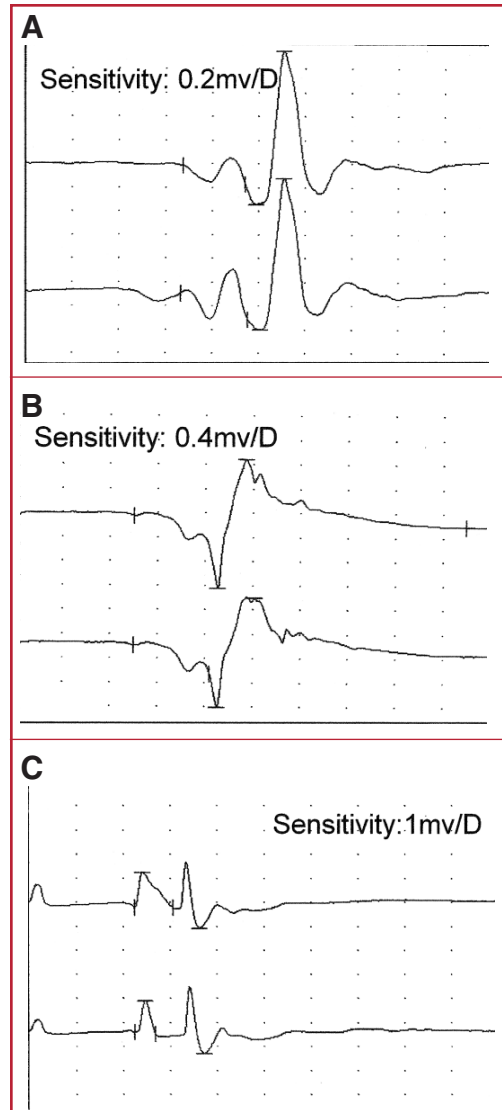
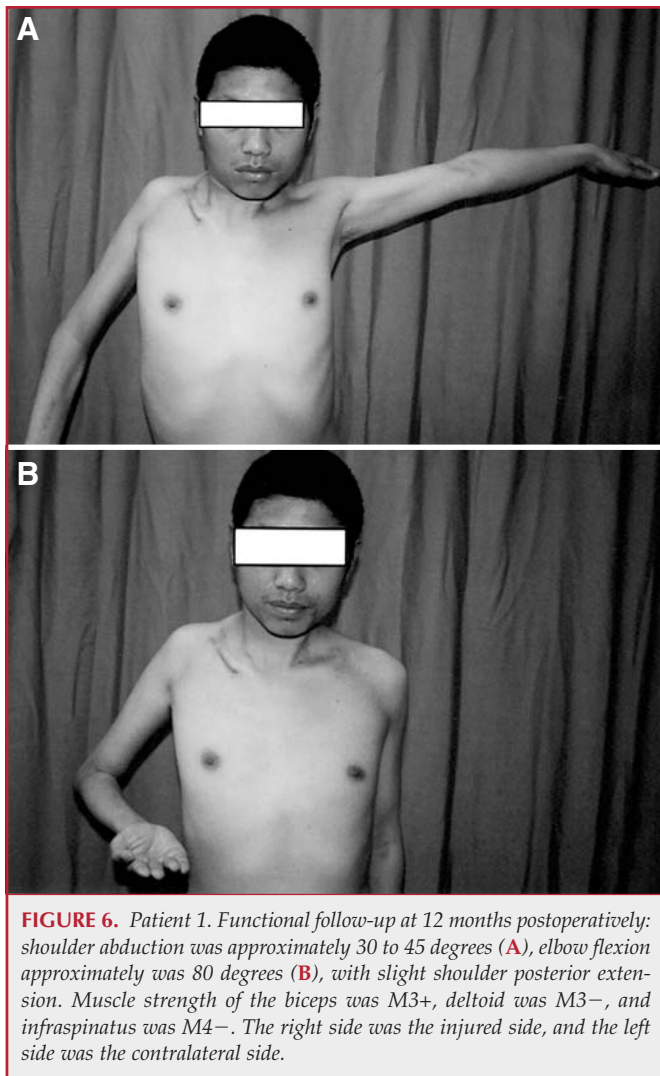


FIGURE 5. Patient 1. Twelve-month postoperative evoked potential follow-up of the biceps (A), deltoid (B), and infraspinatus (C) showed that the latency of compound muscle action potentials in these muscles were 16.7 milliseconds, 12.46 milliseconds, and 11.17 milliseconds, respectively, when stimulating the supraclavicular brachial plexus on the uninjured side. The amplitudes were 1.28 mV, 1.95 mV, and 2.24 mV, respectively. Parametric setting: time span, 5 milliseconds; width of impulse, 2 milliseconds; intensity, 36 mA.

adequate exposure of the anterior region of the vertebral body without the need to dissect the carotid sheath or other important structures in the neck. Second, the transferred nerve is protected, and potential compression by the scalenus anterior muscle can be avoided. Third, the operative procedure is easy and safe, and a prespinal and retropharyngeal route can be estab-



lished typically within 30 minutes by using our method. Therefore, we consider our approach more convenient and safer than that of McGuinness and Kay.

Caution should be taken for protection of the contralateral phrenic nerve during the procedure, because the ipsilateral phrenic nerve is often damaged from the antecedent injury. We expose the scalenus anterior muscle and free the phrenic nerve and each nerve root first, before severing the scalenus anterior muscle. The C7 nerve root should be reversed to the posteromedial aspect of the phrenic nerve and immediately anterior to the vertebral body to avoid compression of the phrenic nerve (Fig. 2).

Securing the C7 nerve root with the plastic catheter is important, as the avulsion of grafted nerves would affect the surgical results. Cessation of water and food intake in the first 4 days after operation is also important because it may prevent rupture of the neurorrhaphy, facilitate nerve healing, and alleviate the finger numbness caused by swallowing.

We noticed better functional recovery of elbow flexion than shoulder abduction in our patients. This could be a result of the fact that more donor nerves were sutured to the anterior division of the upper trunk or C6 roots. We also considered neurotization of the supraspinatus by using other donor nerves, such as the spinal accessory nerve, which might be more beneficial for shoulder abduction. Further follow-up and more research will be necessary to find the optimal distribution of donor nerves and to compare this approach with the traditional subcutaneous route.

Disclosure

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COMMENTS

In this preliminary report, Xu et al. described the prepsal and retroesophageal routing of the contralateral C7 spinal nerve for transfer to repair brachial plexus injuries in eight patients. This article adds to the literature by the group from Shanghai, who have already made several major contributions on the contralateral C7 transfer technique. In the current report, the technique of resecting the anterior scalene muscle bilaterally is emphasized to shorten the distance for transfer (Fig. 1 of the article). In turn,

this translates to the need for either relatively short (3–8 cm) nerve grafts or in some cases, allows for a direct transfer. The advantage over the substantially longer grafts (sural or vascularized ulnar) when a subcutaneous route is used for the contralateral C7 transfer seems intuitive. Theoretically, the technique described should produce improved outcomes in patients. Unfortunately, the current report does not contain sufficient patient follow-up to conclude this and should be considered preliminary. I found the 7-month electromyographic and somatosensory evoked potential data unconvincing, and although the 12-month data are promising, the example is from a single case. Also, in the clinical illustration shown, biceps recovery seems to be adequate, but the shoulder movements in abduction and exorotation illustrated in the figure provided are not compelling. I, therefore, eagerly look forward to longer-term follow-up and a more detailed report regarding this patient cohort and perhaps a larger series in the future.

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For patients with complete brachial plexus avulsion with associated accessory and phrenic nerve injury, there are few therapeutic options. Previously described procedures by Xu et al. require use of a graft and a route through the subcutaneous tunnel in the neck and thorax of the uninjured side. This method had associated complications related to extreme graft length and risks to associated vascular structures, total operative time, and cosmetic result.

Xu et al. have improved their previous technique and present a novel surgical technique. The indications are clearly outlined: avulsion of the upper and middle trunks with associated injury to accessory and phrenic nerves. This technique addresses previous limitations of the standard method of repair: shorter graft length, thus improving the chance for neural regeneration and functional recovery, a nerve graft able to provide the demand of rebuilding function to the injured limb, decreased risk to associated vascular structures via a safer and shorter route, and improved cosmetic result. The case illustration provides hopeful outcomes.

Xu et al. presented this technique as part of a two-stage procedure. Stage I was contralateral C7 nerve root transfer via a prespinal and postesophagus route, and Stage II was free gracilis muscle transplantation to reconstruct the flexion function of the wrist and fingers. Although the authors presented a thorough review of the indications for the procedure and associated complications, the article is limited in its review of the cohort's results, either electrodiagnostically or clinically. In addition, there are no follow-up data regarding whether patients advanced to Stage II of the procedure.

Despite these limitations, Xu et al. provide a potentially hopeful procedure to a population with limited surgical treatment options geared toward functional recovery.

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Xu et al. presented a logical technique to shorten the distance that a nerve graft must travel when the contralateral C7 nerve is to be connected to the supra- or infraclavicular plexus on the opposite, injured side. This shortened distance not only seems to allow the use of free sural grafts, as opposed to the vascularized ulnar nerve graft that is commonly used with a contralateral C7 transfer, but also perhaps improves outcomes because of the shorter distance. Complications including bilateral phrenic nerve palsies, damage to the sympathetic chain, paresthesias when the esophagus contracts against the donor C7

nerve fascicles, and any residual deficits in the donor arm remain of concern but seem quite acceptable on the basis of the current series.

Excluding newborns, the contralateral C7 technique often requires cocontraction of the donor C7 musculature to activate movement in the injured arm. Over time, these cocontractions become less obvious; however, even many years postoperatively, it still often requires the donor arm to be extended at the elbow with a concurrent clenching of the fist with or without wrist extension. This conscious effort limits the spontaneous functionality of the injured arm. Patients are glad they can move their arms, but anecdotal interviews reveal that they frequently do not use the injured arm during activities of daily living. Continued optimization of the contralateral C7 technique, including the variation presented by Xu et al., may eventually lead to improved functional outcomes.

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This is a preliminary report of a technical innovation developed by Dr. Gu and his group at Huashan Hospital. Dr. Gu initially introduced the contralateral C7 nerve transfer in 1986 for severe brachial plexus avulsion injuries, and others have reported varying degrees of success with this technique. McGuinness and Kay reported a prespinal route for the nerve grafts, which shortened the lengths of the grafts. Gu and his group have simplified this prespinal approach by transecting the anterior scalene muscles bilaterally and bluntly developing the prevertebral plane for passage of the grafts. By extending the dissection even farther proximally and distally on the healthy C7 spinal nerve, they were even able to perform direct neurorrhaphy to the avulsed contralateral C5 and C6 spinal nerves in two thin patients.

This technical innovation results in shorter nerve grafts (and occasional elimination of grafts) and should improve outcomes, although the results in this series are preliminary with relatively short follow-up. This technique requires less dissection of neck structures than the technique earlier reported by McGuinness and Kay. If the results and complications ultimately prove to be favorable, the challenge for the peripheral nerve surgeon will be deciding how and when to incorporate this technique into a comprehensive strategy for optimal reconstruction of the severely damaged brachial plexus.

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Complications affecting the esophagus or trachea with such a procedure, although possible, did not occur in this series. Several patients had transient sensory symptoms on the donor side but no weakness. In the illustrative case in which grafts went to the suprascapular nerve and to the anterior and posterior divisions of the upper trunk, there was significant recovery of shoulder abduction to 30 and 45 degrees and elbow flexion to 80 degrees. Perhaps transfer of the accessory nerve to the suprascapular nerve and intercostal nerves to musculocutaneous nerve would have given as good as or better results but perhaps not. Only three of eight patients had some usable follow-up, so this is more of a technical article than one on outcomes using the procedure. At any rate, the procedure shortens the grafts needed for a contralateral transfer, and that is good because the cross chest procedures with long grafts have not been very successful in many other surgeons' hands.

As a small aside, in my experience, major inputs to latissimus dorsi are C6 as well as C7 so care must be taken in using this as a "bellwether" muscle."

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CXCR4 EXPRESSION IS ELEVATED IN GLIOBLASTOMA MULTIFORME AND CORRELATES WITH AN INCREASE IN INTENSITY AND EXTENT OF PERITUMORAL T2-WEIGHTED MAGNETIC RESONANCE IMAGING SIGNAL ABNORMALITIES

OBJECTIVE: With the objective of investigating the utility of CXCR4, a chemokine receptor known to mediate glioma cell invasiveness, as a molecular marker for peritumoral disease extent in high-grade gliomas, we sought to characterize the expression profile of CXCR4 in a large panel of tumor samples and determine whether CXCR4 expression levels within glioblastoma multiforme might correlate with radiological evidence of a more extensive disease process.

METHODS: Freshly resected tumor tissue samples were processed for immunohistochemical and quantitative polymerase chain reaction analyses to identify and quantify expression levels of CXCR4 and its corresponding ligand CXCL12. T1 postcontrast and T2-weighted magnetic resonance imaging brain scans were used to generate voxel signal intensity histograms that were quantitatively analyzed to determine the extent and intensity of peritumoral signal abnormality as a marker of disseminated disease in the brain.

RESULTS: CXCR4 expression was markedly elevated in Grade III and IV tumors compared with Grade II gliomas. Significantly, when patients with glioblastoma multiforme were segregated into two groups based on CXCR4 expression level, we observed a statistically significant increase in the intensity and extent of peritumoral magnetic resonance imaging signal abnormalities associated with CXCR4 high-expressing gliomas.

CONCLUSION: Our data confirm that high-grade gliomas robustly express CXCR4 and demonstrate a correlative relationship between expression levels of the CXCR4 receptor and the magnetic resonance imaging-based finding of a diffuse and more extensive disease process in the brain. CXCR4 expression status may, therefore, prove useful as a marker of disseminated disease in patients with glioblastoma multiforme.

KEY WORDS: Brain tumor, CXCR4, Glioma

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Gliomas are the most common type of primary brain tumor and, according to the World Health Organization convention, are divided into four clinical grades (I–IV) on the basis of tumor histopathology (11). Grade I tumors represent a distinct subset of neoplasms occurring predominantly in children and young adults and are characterized

as relatively benign lesions with well-demarcated margins and lending themselves to surgical cure. In contrast to this, Grades II, III, and IV gliomas are generally tumors of adulthood and reflect a spectrum of increasingly infiltrative and aggressive disease. These tumors have poorly defined margins and invade directly adjacent brain parenchyma, thereby preclud-

ABBREVIATIONS: GBM, glioblastoma multiforme; MRI, magnetic resonance imaging; RNA, ribonucleic acid; SEM, standard error of the mean

ing complete surgical resection. Despite recent advances in adjuvant radio- and chemotherapeutic regimens, current clinical treatment protocols fail to eliminate residual infiltrative tumor foci in their entirety. Additionally, invasive nests of tumor cells are associated with the initiation of neovascular angiogenesis and disruption of the blood-brain barrier via the release of vasomodulatory cytokines. Taken together, these factors contribute to a rapid dissemination of the disease process beyond the confines of the original radiologically identifiable tumor mass, eventually resulting in near-universal tumor recurrence and, ultimately, death. Whereas patients with Grade II tumors can survive for 7 to 15 years, a diagnosis of a Grade IV glioma, or glioblastoma multiforme (GBM), carries a median survival prognosis of approximately 9 months (17). GBM also represents the most infiltrative spectrum of this disease and is frequently associated with significant involvement of peritumoral parenchyma as evidenced by the presence of extensive T2 signal abnormalities on magnetic resonance imaging (MRI). Indeed, postmortem analyses in GBM-affected brains have demonstrated the presence of tumor cells deep in the contralateral hemisphere (15). Current therapeutic regimens do not adequately address the disseminated disease burden associated with infiltrative gliomas, and there is, therefore, an urgent need to develop novel treatment approaches to specifically target the invasive capacity of these tumors.

The clinical evaluation of patients with high-grade gliomas centers on the use of T1-weighted MRI sequences obtained after the administration of a gadolinium-based contrast agent to demarcate the boundaries of what is generally considered to be the surgically targetable main tumor mass. Additionally, T2-weighted imaging is used to assess the extent of the peritumoral disease process. T2-weighted signal abnormalities surrounding the T1-weighted postgadolinium-enhancing lesion are attributable to multiple facets of a progressively disseminating disease process that is inexorably extending its effects throughout the brain. In this context, our definition of glioma-associated disseminated disease would include the presence of microscopic infiltrative disease (8), foci of tumor-induced neovascularization, and generalized vasogenic edema resulting from cytokines elaborated by invasive glioma cells. As such, the extent and intensity of T2-weighted signal abnormalities can serve as a quantifiable reflection of a disseminated neoplastic disease process in the brain.

Fundamental to the objective of developing effective translational therapies for this disease are the requirements for a better understanding of the biological mechanisms that govern glioma cell dispersal. Concurrently, it is critical to develop clinical imaging tools to link the presence and activity of specific biological mechanisms that drive tumor invasion and angiogenesis with an evaluation of the extent of neoplastic disease in patients with high-grade gliomas. In this context, we previously characterized the cell surface chemokine receptor CXCR4 as an important mediator of glioma cell invasiveness *in vitro* and *in vivo* (5), whereas others have reported its role in GBM neovascularization (1). In this report, we now detail an extensive analysis of CXCR4 expression in a large set of human glioma tissue

samples and report a strong correlation between increasing histological grade and CXCR4 expression levels. Furthermore, we report a novel association within GBM between CXCR4 expression levels and an increased extent and intensity of preoperative T2-weighted peritumoral MRI signal abnormalities. In conjunction with our earlier report detailing the mechanistic role of CXCR4 in mediating glioma cell dispersal, these findings underscore the clinical relevance of CXCR4 based on its association with increasing invasive tumor grade and imaging-related evidence of a more disseminated disease process in the brain. Our study indicates that, in addition to further supporting the previously described roles for CXCR4 as a mediator of invasion and neovascularization, tumor CXCR4 expression levels can be used to segregate patient sets into distinct groups based on evidence of extended peritumoral disease process on T2-weighted MRI. This provides a valuable link between a routinely used clinical evaluation tool and a signaling mechanism that governs the biological aggressiveness of these tumors.

MATERIALS AND METHODS

Sample Collection and Processing

Tumor and nonneoplastic (epilepsy) brain samples were obtained intraoperatively from patients undergoing open craniotomy for resection of intracranial lesions. Patients provided consent through a Vanderbilt Institutional Review Board-approved protocol. For putative tumor specimens, tissue was sampled intraoperatively from within what was clinically judged to be the main tumor lesion (which in the case of suspected GBM comprised the T1 postcontrast-enhancing mass). After intraoperative frozen-section pathology analysis confirming a likely diagnosis of glioma, tissue was sampled from radiographically confirmed postcontrast-enhancing regions of the brain and transported on ice to the research laboratory. For each patient, several (2–10, depending on the amount of resected sample available) tumor fragments measuring roughly between 25 and 250 mm³ each were pooled together to average out for operative sampling heterogeneity and processed collectively for ribonucleic acid (RNA) extraction, as previously described (5). Similarly, multiple tissue fragments were embedded in paraffin for subsequent histological and immunohistochemical analyses. Grossly necrotic tissue was not used for either RNA isolation or histological analysis. Final tissue diagnoses were confirmed using hematoxylin and eosin stains on paraffin-embedded specimens.

Quantitative Polymerase Chain Reaction

Isolated RNA was processed for complementary deoxyribonucleic acid generation as described (5) and then subjected to triplicate multiplex real-time quantitative polymerase chain reaction amplification for CXCR4 and CXCL12 nucleotide sequences using predesigned *Taqman* probe and primer sets (Applied Biosystems, Norwalk, CT) in an ABI 7300 thermal cycler (Applied Biosystems). 18S ribosomal RNA was used as an internal control amplification target. Threshold cycles were determined for each amplification run as described (5) and normalized against sequence-specific plasmid-generated standard curves. Run-to-run (i.e., interassay) variability was eliminated by including, within each run, a constant calibrator sample. Data from four temporal lobe samples from patients undergoing surgery for intractable epilepsy were averaged and used as nonneoplastic controls against which expression levels for all patient samples were expressed.

Immunohistochemistry

Paraffin-embedded tissue sample blocks were sectioned using a microtome, and, after routine antigen retrieval processing, slide-mounted sections were immunoprobed using primary antibodies against CXCR4 and CXCL12 (R&D Systems, Minneapolis, MN) as well as factor VIII (Dako, Carpinteria, CA) and neuron-specific enolase (Chemicon, Temecula, CA). Slides were then either probed with fluorescent secondary antibodies (Jackson ImmunoResearch Laboratories, Inc., West Grove, PA) or processed for colorimetric development (Vector Laboratories, Burlingame, CA) per standard methodology.

Imaging Methodology and Analyses

Data were obtained from preoperative scans acquired using a General Electric Genesis Signa (Waukesha, WI) or a Philips Intera Achieva (Cleveland, OH) system. All analyzed scans were obtained 1 to 4 days before initial tumor resection from patients who were treatment- (i.e., radio- and chemotherapy) naive. Both scanner magnets from which images were derived were rated at 1.5 T. The General Electric fast spin echo scan used the following parameters: repetition time = 4000 milliseconds, echo time = 106.3 milliseconds, slice thickness/gap = 3/3 mm, field of view = 240 mm, matrix = 256×256 . The Philips spin echo sequence was: repetition time = 6715 milliseconds, echo time = 110 milliseconds, slice thickness/gap = 3/3 mm, field of view = 230 mm, matrix = 512×512 . Preoperative scans were performed in the axial plane after administration of contrast.

T1- and T2-weighted images for 22 patients were analyzed using an automated process with the Matlab software package as described below so a correlation with CXCR4 expression levels could be made. First, we demarcated the boundaries of contrast enhancement on postcontrast T1-weighted images. Once these images were aligned to their respective T2-weighted maps, the area corresponding to T1 enhancement was subtracted from the T2 images. To account for scaling differences over patients, normalization of the signal intensities was performed. We divided the intensity value for each voxel by the maximum signal intensity value located in the cerebrospinal fluid in the non-tumor hemisphere to complete this normalization. Histograms were then formed from the tumor-bearing hemisphere of the T2-weighted image using bins sized to contain 1% of the normalized signal intensity for each patient. For each of 100 bins, there existed a count of the number of voxels for the given signal intensity range. All histograms (i.e., those generated for diseased as well as non-tumor-bearing hemispheres) were independently normalized for differing patient-to-patient brain volumes by dividing the number of voxels at any particular signal intensity by the total number of voxels within that

specific analyzed hemisphere. Using this methodology, the distribution of voxel signal intensities across each histogram ceases to be a function of hemisphere volume as the area under each independent histogram is forced to a uniform value (arbitrarily designated as 1 in our calculations). Finally, histograms were averaged across groups.

RESULTS

CXCR4 is significantly overexpressed in human high-grade gliomas. Our earlier work identified CXCR4 overexpression as a key mediator of glioma cell invasiveness in a panel of primary and cell line-based glioma cultures and in a rodent brain tumor model (5). With the aim of placing these findings in a clinical context, we surveyed 80 primary human gliomas spanning World Health Organization Grades II, III, and IV for CXCR4 expression levels. Using quantitative real-time polymerase chain reaction, we calculated the CXCR4 message level for each tumor relative to the average CXCR4 expression level determined from four nonneoplastic temporal lobe samples that were surgically resected from patients with intractable epilepsy. As illustrated in Figure 1, we found that CXCR4 expression in Grade II gliomas ($n = 18$) was very close to that found in control samples ($n = 4$): 1.05 ± 0.2 fold, average $\pm$ standard error of the mean (SEM). In contrast, Grade III tumors ($n = 24$) and GBMs ($n = 38$) expressed significantly more CXCR4 message: 2.54 ± 0.47 fold ($P = 0.021$; Wilcoxon rank-

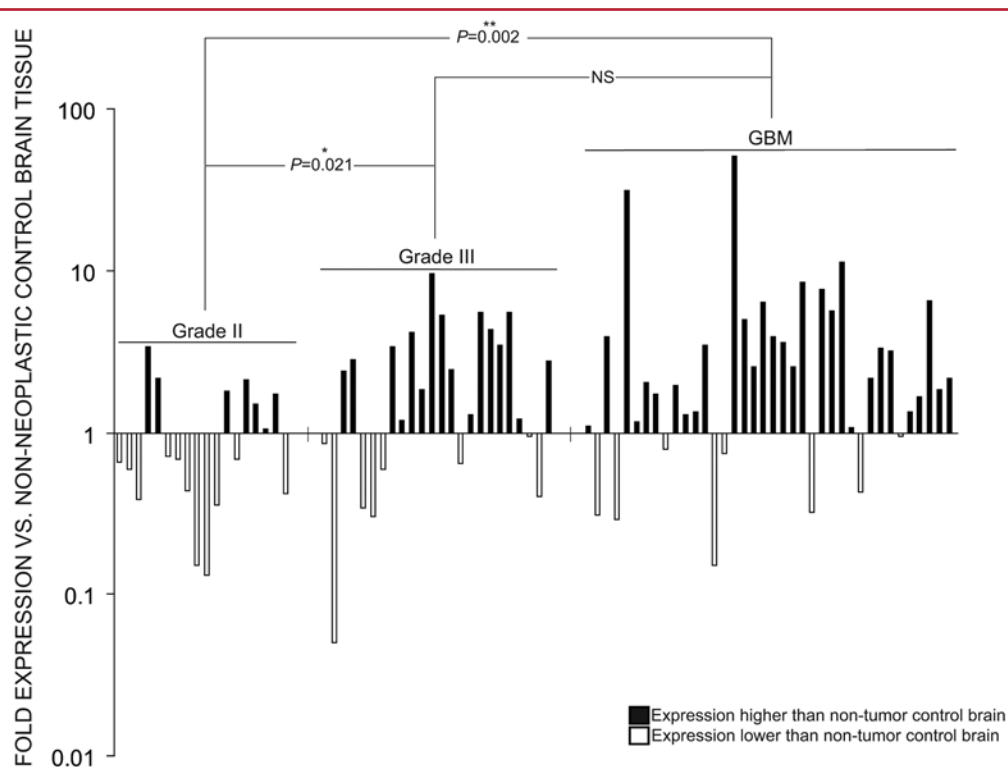


FIGURE 1. Graphic illustration of CXCR4 expression levels as determined by quantitative polymerase chain reaction in a survey of 80 human gliomas. NS, not significant; GBM, glioblastoma multiforme.

sum test) and 4.85 ± 1.51 fold ($P = 0.002$), respectively. These results clearly indicate the significant overexpression of CXCR4 within human high-grade gliomas and, in particular, GBMs.

GBMs demonstrate neoplastic cell expression of CXCR4 and neuronal production of CXCL12. After confirming that GBMs expressed markedly elevated levels of CXCR4 transcript, we wished to confirm expression at the protein level. To this end, we immunohistochemically probed a panel of five human GBM specimens and observed robust expression of CXCR4 protein in neoplastic cells. The pattern of localization was predominantly nuclear in all analyzed samples (representative fields are shown in Fig. 2, A and B), a pattern of CXCR4 staining in paraffin-embedded tissue that has been reported previously in nonsmall cell lung cancer (25). In a random sampling of five high-power fields from five slide-mounted hematoxylin-counterstained GBM specimens (also selected randomly from our patient pool), we observed that $66 \pm 11\%$ of visible nuclei stained positive for CXCR4. CXCR4 expression in a subset of Grade III gliomas ($n = 4$) and GBMs ($n = 6$) was also confirmed by Western immunoblot (not shown). Given that we and others have previously identified CXCL12 as a potent activator of CXCR4-mediated glioma cell proliferation (3) and invasiveness (5), we sought to identify cell populations within GBMs that expressed CXCL12, as the endogenous presence of ligand would provide a strong mechanistic context to the

markedly elevated CXCR4 expression profile that we observed. Indeed, immunohistochemical profiling of GBM tissues from the same five samples previously analyzed for CXCR4 expression did reveal strong expression of CXCL12 in these same tumors. This was found to be localized predominantly within endothelial cells (representative panels are shown in Fig. 2, C and E) as well as in overrun neurons (Fig. 2, D and F).

MRI scans of patients with CXCR4-overexpressing GBMs demonstrated a marked increase in intensity and extent of peritumoral T2 signal abnormality. In preclinical *in vitro* and *in vivo* experimental models, we previously demonstrated that CXCR4 mediates the adoption of an invasive phenotype by GBM tumor cells (5). Given our subsequent observation of significantly elevated CXCR4 transcript in a large number of human GBM specimens, we sought to ascertain whether CXCR4 expression levels might correlate with clinical evidence of increased tumor dissemination. For this purpose, we examined postgadolinium T1- and T2-weighted preoperative MRI scans of the patients from whom we had collected tumor tissue samples for quantitative CXCR4 expression level analysis. Of the 38 GBM specimens that we had collected, we identified 22 patients as being treatment-naïve (i.e., the tissue sample that we obtained was harvested before the initiation of radiation or chemotherapy in these patients), whereas the remaining 16 patients represented tumor recurrences with a history of adju-

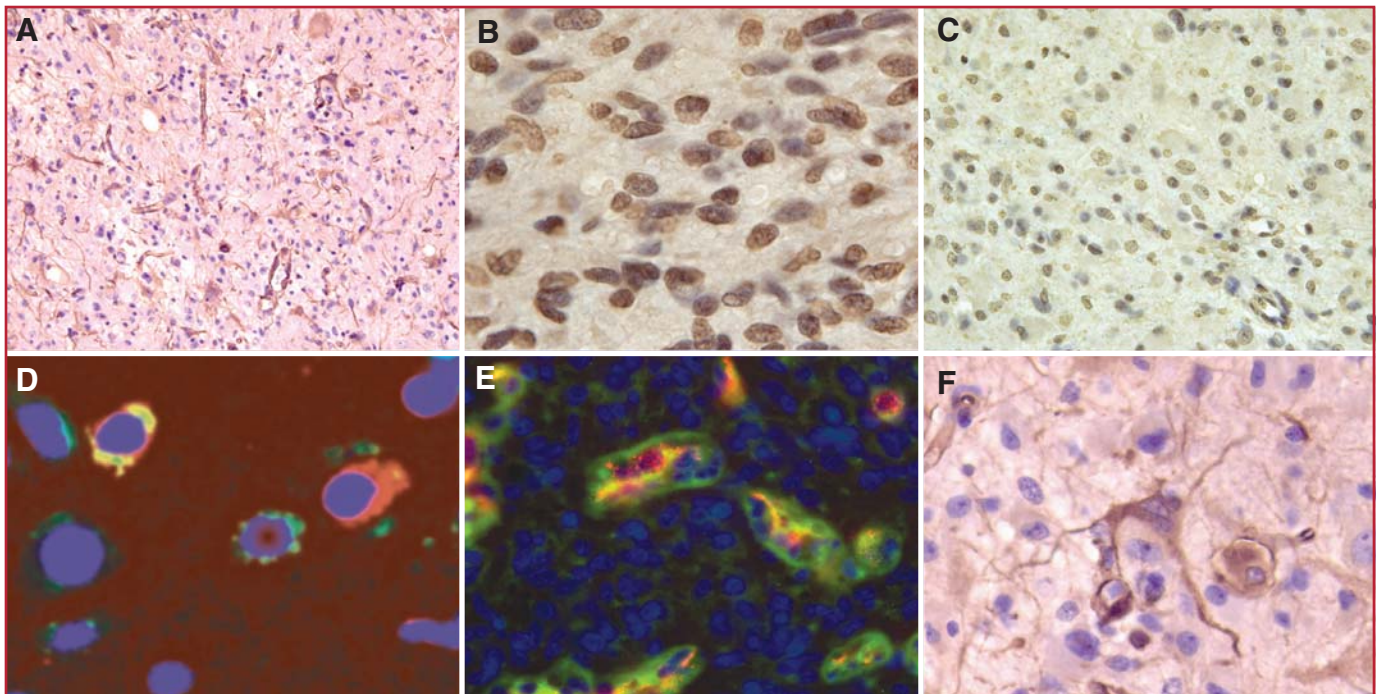


FIGURE 2. Immunohistochemistry revealing the presence and localization of CXCR4 and CXCL12 expression in human glioblastoma multiforme (GBM). **A** and **B**, immunoprobings of paraffin-embedded GBM tumor tissue sections revealing robust expression of CXCR4 protein. **C** and **D**, CXCL12 protein also readily detectable in GBM tissue specimens and observed both within vascular endothelium and pyramidal neurons. **E**,

CXCL12 (green) colocalization with factor VIII-expressing endothelial cells (red) confirmed using immunofluorescence. **F**, fluorescent staining with neuron-specific enolase (red) in combination with CXCL12 (green), confirming the presence of CXCL12-expressing neurons within GBM parenchyma. (**A**, **C**, and **E**, original magnification, $\times 200$; **B**, **D**, and **F**, original magnification, $\times 400$.)

TABLE 1. Details of measured CXCR4 levels, tumor volume, and tumor location in glioblastoma multiforme patients analyzed by magnetic resonance imaging^a

Analyzed GBM group and patient no.	CXCR4 level	Volume (cm ³) of T1 postcontrast-enhancing lesion	Location
CXCR4-low (avg)		76.88 ± 15.59	
1	0.29	41.98	Frontal
2	0.31	105.80	Frontal
3	0.43	7.23	Posterior frontal
4	1.07	39.30	Inferior frontal
5	1.1	72.00	Frontotemporal
6	1.17	164.56	Temporal
7	1.3	90.77	Parieto-occipital
8	1.66	196.63	Frontal
9	1.73	41.32	Temporal
10	1.82	12.70	Posterior frontal
11	1.95	97.20	Parietal
CXCR4-high (avg)		79.04 ± 18.17	
12	2.01	156.06	Frontal
13	2.52	52.02	Inferior frontal
14	3.17	135.68	Parietal
15	3.27	9.20	Parieto-occipital
16	3.47	112.66	Frontal
17	3.57	87.41	Temporal
18	5.56	128.12	Frontal
19	6.39	35.10	Temporal
20	8.49	77.57	Temporal
21	31.5	5.20	Temporal
22	50.89	46.66	Temporal

^a GBM, glioblastoma multiforme.

vant treatments. For our imaging analyses, we excluded the patients who had received previous radiation and/or chemotherapy given the expected nonspecific changes that are known to occur in brain MRI after such treatments. The remaining 22 patients were arranged in ascending order of CXCR4 expression level (as determined by quantitative polymerase chain reaction). We observed a continuous distribution

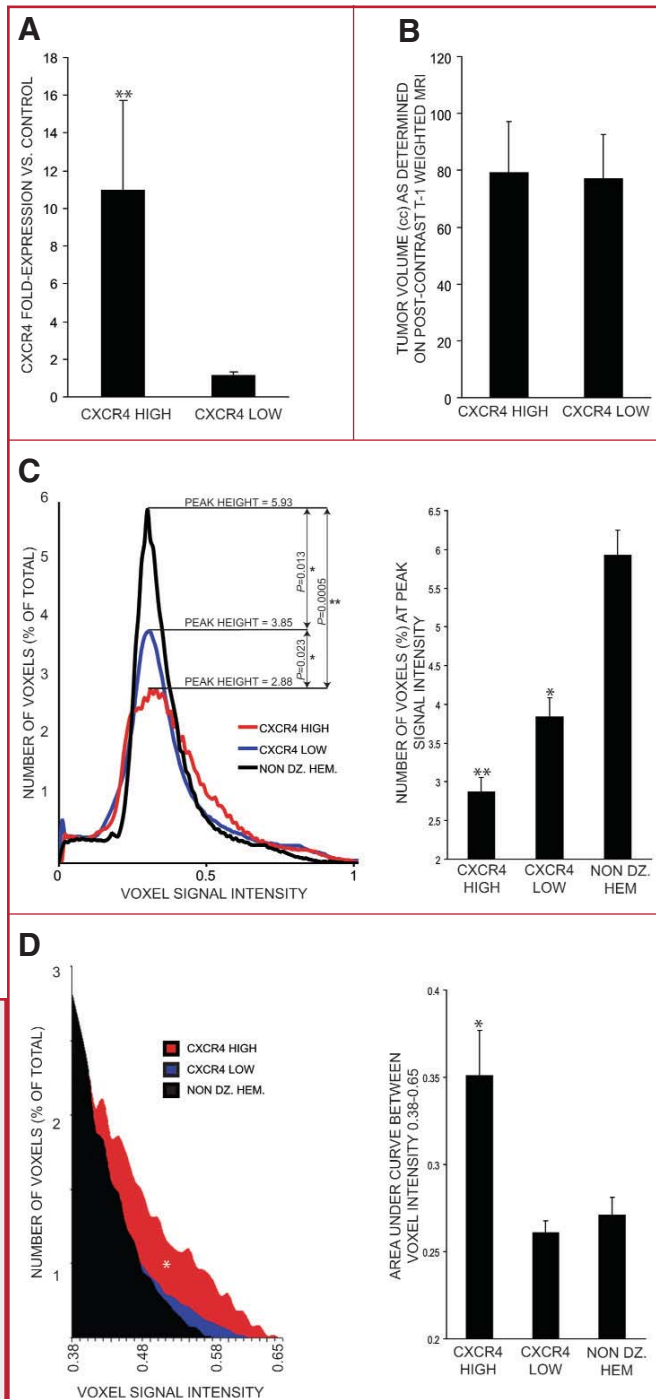


FIGURE 3. Quantitative histogram analysis of T2-weighted magnetic resonance imaging (MRI), revealing significantly increased intensity and extent of peritumoral signal in CXCR4-high GBM patients. **A**, study patients divided into CXCR4-high and CXCR4-low groups based on quantitative polymerase chain reaction-measured levels of receptor expression. **B**, both groups demonstrate nearly equivalent gross tumor volumes as measured on T1 postgadolinium MRI scans. **C** and **D**, quantitative histogram analysis of T2-weighted MRI scans from the same patients (after digital subtraction of T1 postgadolinium-enhancing lesions), revealing marked increases in both intensity (indicated by decreased peak height in **C**) and extent (indicated by increased area under the curve in **D**) of T2 signal abnormality in CXCR4-high GBM patients compared with CXCR4-low patients or control subjects. NON DZ. HEM, non-tumor-involved contralateral hemisphere from three CXCR4-high and three CXCR4-low patients. Asterisks indicate significance.

TABLE 2. Details of preimaging corticosteroid administration in glioblastoma multiforme patients analyzed by magnetic resonance imaging^a

Analyzed GBM group and patient no.	Corticosteroids					CXCR4 level	Area under the curve (0.38–0.65)	P value (t test)
	Use (yes/no)	Type	Dose (mg/d)	Length of use (no. of days before MRI)	Cumulative preimaging dose (mg)			
CXCR4-low (avg)					127.3 ± 29.3 ^b			
1	Y	Dexamethasone	40	3	120	0.29	0.2576	
2	Y	Dexamethasone	24	4	96	0.31	0.2491	
3	Y	Dexamethasone	10	8	80	0.43	0.2489	
4	Y	Dexamethasone	24	4	96	1.07	0.2385	
5	Y	Dexamethasone	8	0	0	1.1	0.2768	
6	Y	Dexamethasone	16	12	192	1.17	0.2469	
7	Y	Dexamethasone	16	7	112	1.3	0.2768	
8	Y	Dexamethasone	40	8	320	1.66	0.2549	
9	N				0	1.73	0.2996	
10	Y	Dexamethasone	16	9	144	1.82	0.2894	
11	Y	Dexamethasone	24	10	240	1.95	0.2339	
CXCR4-high (avg)					122.4 ± 28.9			0.91
12	Y	Dexamethasone	24	10	240	2.01	0.4262	
13	Y	Dexamethasone	16	5	80	2.52	0.2702	
14	N				0	3.17	0.2756	
15	Y	Dexamethasone	24	3	72	3.27	0.4382	
16	Y	Dexamethasone	24	4	96	3.47	0.4774	
17	Y	Dexamethasone	No data	18	No data	3.57	0.2883	
18	Y	Dexamethasone	40	4	160	5.56	0.2857	
19	Y	Dexamethasone	24	8	192	6.39	0.3217	
20	Y	Dexamethasone	40	3	120	8.49	0.3893	
21	Y	Dexamethasone	24	11	264	31.5	0.4514	
22	N				0	50.89	0.2368	

^a In individual patients, corticosteroid use bore no correlation with CXCR4 expression level ($P = 0.69$; Spearman rank correlation test). GBM, glioblastoma multiforme; Y, yes; N, no; MRI, magnetic resonance imaging.

^b Standard error of the mean.

of CXCR4 expression level in these samples (Table 1), and in the absence of a clear bimodal data set, we chose to arithmetically divide the patients into two equal groups of 11 patients each, with the higher CXCR4 expressors denoted as the CXCR4-high group and the lower CXCR4-expressing patients designated as the CXCR4-low group.

The average CXCR4 expression in the CXCR4-high group was 10.99 ± 4.72 fold (average $\pm$ SEM) versus nonneoplastic sample controls (as detailed in Materials and Methods), whereas expression in the CXCR4-low group was 1.17 ± 0.18 fold (Fig. 3A). This difference was highly significant ($P < 0.001$; Mann-Whitney test). Before further analysis, we confirmed that, with the exception of one patient for whom data were not available, all patients received similar summative doses of corticosteroid therapy as routinely used in patients diagnosed with intracranial space-occupying lesions. (For detailed corti-

costeroid dose information, see Table 2.) In the CXCR4-low patient group, corticosteroid administration ranged from 0 to 40 mg/d over a course of 3 to 12 days before preoperative MRI scanning. In the CXCR4-high group, doses ranged from 0 to 40 mg/d over a course of 3 to 18 days before preoperative MRI scanning. The average cumulative corticosteroid dose administered before MRI scanning was 127.3 ± 29.3 mg in the CXCR4-low group (average $\pm$ SEM) versus 122.4 ± 28.9 mg in the CXCR4-high group ($P = 0.91$; t test). We also confirmed that the corticosteroid dose bore no correlation with CXCR4 expression level ($P = 0.69$; Spearman rank correlation test).

Postgadolinium T1-weighted scans were then used to calculate the volume of the contrast-enhancing lesion for each patient. As illustrated in Figure 3B, this revealed nearly identical average T1-weighted contrast-enhancing tumor volumes in the CXCR4-high (79.04 ± 18.17 cm³ [average $\pm$ SEM]) and

CXCR4-low ($76.88 \pm 15.59 \text{ cm}^3$) patient groups (Fig. 3B). As described in Materials and Methods, an analysis of voxel (i.e., three-dimensional pixel) signal intensity was then performed for each patient using the T2-weighted axial scan series for that same patient. Signal intensity was normalized within each patient by assigning a value of 1.0 unit to the brightest voxel located within any of the axial slices analyzed for that patient. This voxel was confirmed to lie within cerebrospinal fluid in each case. All remaining voxels in each patient's entire T2-weighted axial series were assigned decreasing signal intensity values (with a resolution of 0.01 unit) in relation to the identified 1.0-unit control voxel. After this, the three-dimensional volume correlating with tissue that demonstrated postgadolinium enhancement on corresponding T1-weighted MRI was digitally removed from the rasterized T2-weighted MRI scan. The resulting map then consisted of an entire axial T2-weighted MRI series of the brain minus the T1-weighted post-contrast-enhancing lesion. In this manner, we restricted our analysis to peritumoral signal abnormalities and removed signal contamination emanating from what would be considered the main (and surgically targetable) tumor mass.

These modified T2-weighted MRI scans (comprising the entire axial series for the ipsilateral diseased cerebral hemi-

sphere) for each patient were used to generate histograms of voxel signal intensity versus the number of voxels normalized for hemisphere size to account for differences in brain volumes across patients. The average profiles generated from the CXCR4-high and CXCR4-low patient groups demonstrated statistically significant differences. For control purposes, we generated histograms from the non-tumor-bearing cerebral hemispheres of three CXCR4-high and three CXCR4-low patients. As demonstrated in Figure 3C, the diseased cerebral hemispheres from both CXCR4-high and CXCR4-low patients displayed significantly decreased peak height compared with nondiseased hemispheres on voxel signal intensity histograms. These peaks all fell within an intensity range of 0.3 to 0.4 unit, which correlated with nondiseased brain parenchyma (Fig. 4). Although we thought that using contralateral non-tumor-involved brain from our own patient sample represented the optimal age- and condition-matched control group, we also analyzed T2 histograms from an additional control group comprising brain magnetic resonance images from 11 otherwise healthy student volunteers (data not shown). For analytic purposes, it should be clarified that the presence of fewer voxels at peak intensity is reflective of less normal tissue, whereas a greater area under the curve represents more abnormal tissue.

Although this descriptive methodology can appear counterintuitive, when analyzing our voxel-intensity histograms, we chose to remain consistent with the conventions of the imaging literature.

Significantly, the histograms from CXCR4-high and CXCR4-low patients also demonstrated significantly depressed peak height compared with this additional control group, and there was no statistical difference between the histogram plots derived from the nondiseased contralateral hemispheres of our glioma patients and those obtained from healthy volunteers. These results indicated that depressed peak height from tumor-bearing cerebral hemispheres (from both CXCR4-high and CXCR4-low patients) represented a marked decrease in the amount of normal tissue present in the analyzed hemispheres from these patients. Significantly, we observed a striking difference in peak height between CXCR4-high and CXCR4-low

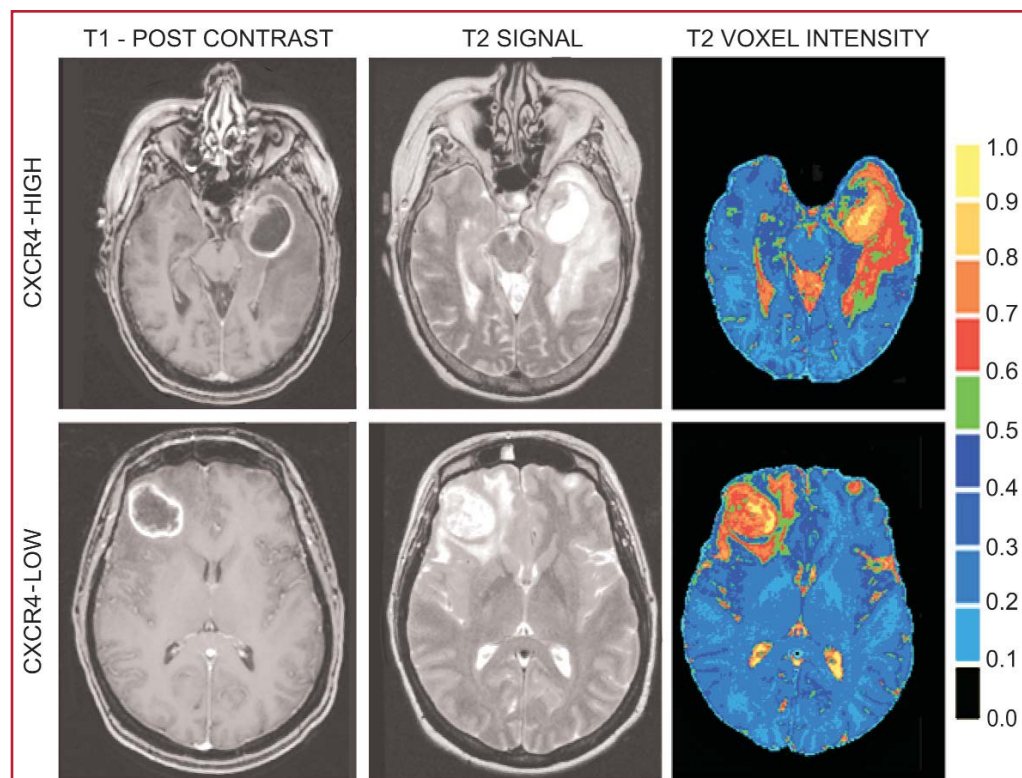


FIGURE 4. CXCR4 expression level correlated with the extent and intensity of T2-weighted magnetic resonance imaging signal. As illustrated by scans from a representative patient from each group (CXCR4-high and CXCR4-low), despite similar T1 postcontrast tumor volumes, marked increases in T2-weighted signal abnormalities in patients whose tumor tissue revealed elevated CXCR4 expression can be observed.

patients (2.88 versus 3.85% of normalized total voxels, $P = 0.02$; Wilcoxon test) (Fig. 3C). This indicated that, in GBM patients, the number of normal peritumoral voxels in CXCR4-high patients was significantly lower than that in CXCR4-low patients, thereby indicating that CXCR4-high tumors were affecting/involving brain tissue (which fell outside the confines of the T1-weighted postgadolinium-enhancing lesion) to a more significant extent than CXCR4-low tumors.

To further elucidate this, we focused on a specific portion of the histogram signal intensity plot between the values of 0.38 and 0.65 unit of normalized signal intensity. This range was confirmed as predominantly covering the spectrum of signal between normal nondiseased brain parenchyma and cerebrospinal fluid. This analysis revealed that, within this signal intensity range, CXCR4-low GBM-bearing patient brain hemispheres contained a similar number of voxels as control nondiseased patient brain hemispheres (28.9 and 27.1%, respectively; $P = 0.14$; Wilcoxon test) (Fig. 3D). Significantly, however, CXCR4-high patients displayed a markedly greater number of voxels (37.7%) within this signal intensity range, clearly indicating that CXCR4-high GBMs were creating high-signal voxel abnormalities within peritumoral brain parenchyma to a much greater extent than CXCR4-low tumors ($P = 0.036$; Wilcoxon test) (Fig. 3D). Based on these quantitative and highly sensitive analytic techniques, we concluded that CXCR4-high GBMs were associated with an increased extent and intensity of peritumoral T2-weighted signal abnormalities compared with CXCR4-low tumors.

To further illustrate these results, we generated visual representations wherein axial T2-weighted MRI slices were overlaid with a colorimetric voxel signal intensity gradient (with a resolution of 0.1 unit per color change). Figure 4 displays representative single slices from a CXCR4-high patient and a CXCR4-low patient. Evidence of diffuse increases in peritumoral T2-signal abnormalities, as revealed by our quantitative analysis described above, could be readily visualized on analysis of colorimetrically graded axial MRI scans.

DISCUSSION

CXCR4 is a seven-domain transmembrane G protein-coupled receptor and was initially characterized on the basis of its ability to stimulate the differentiation and chemotaxis of hematopoietic progenitor cells and as a coreceptor for human immunodeficiency virus entry into CD4⁺ T lymphocytes (19). In recent years, significant evidence has elucidated additional roles for CXCR4, and its secreted protein ligand CXCL12, in directing stem cell differentiation and migration in multiple organ systems (19). This is clearly demonstrated by the observation that CXCR4 knockout mice are embryonic lethal with massive defects in neural tube formation, cardiogenesis, and gastrointestinal development (13, 16). Additionally, the role of CXCR4 in cancer has also received increasing attention. Numerous reports detail the expression and functional mediation of tumor cell proliferation and migration by CXCR4 in models of breast (14), colon (31), prostate (6), pancreatic (24), and lung (26) cancer. In the context of brain tumors, we (5) and

others (3, 22, 32) have detailed the ability of CXCR4 to affect glioma growth and invasiveness in vitro and in vivo. Rubin et al. (22) described the use of a small-molecule CXCR4-specific inhibitor to significantly impair the growth of human U87 glioblastomas in nude mice. Recently, Redjal et al. (20) reported that CXCR4 inhibition markedly sensitizes glioma cell lines to in vitro chemotherapy. In conjunction with additional evidence establishing a role for the CXCL12/CXCR4 axis in glioma neovascularization (1, 23, 30) and a demonstration by our group of CXCR4-mediated regulation of cancer stem cell-like cell proliferation in human GBM-derived cell cultures (unpublished data), these developments readily establish the clinical relevance of targeting CXCR4 in patients with malignant glioma. Furthermore, our growing understanding of CXCR4 as a potentiator of GBM dissemination in the brain may allow us to use CXCR4 expression quantitation as a marker for the assessment of patient-specific disease behavior and ultimately prognosis. Such analyses in patients with osteosarcoma (12), colon cancer (10), and melanoma (9) have revealed a clear correlation between CXCR4 expression and clinical outcome. In this study, our limited sample size of 22 treatment-naïve GBM patients did not permit us to investigate a link between pretherapeutic tumor CXCR4 expression levels and patient prognosis. However, our results do establish a robust connection between CXCR4 expression and radiographic evidence of increased disease dissemination as observed on T2-weighted MRI, a routinely employed and readily available imaging modality used in the management of patients with brain tumors.

Although there is considerable excitement about, and movement toward, the implementation of multiparametric imaging modalities to better identify and characterize neoplastic disease in the brain, in this study, we chose to use traditional T2-weighted MRI in combination with a highly quantitative analysis of whole-hemisphere voxel signal intensities. As detailed under Materials and Methods, this involves the use of an automated software platform to digitally assign normalized intensity values to each analyzed voxel and then plot these data into averaged histograms. Such histogram-based assessment has been used previously for whole-brain or hemisphere-based analysis in patients with multiple sclerosis to quantitate sizable yet subtle signal abnormalities (27, 28). In addition, comparisons of the peak height on these histograms have demonstrated decreases in mean signal diffusivity using scans obtained from cases of patients with migraine headaches (21), subtle early changes in the brain parenchyma of patients with acute lymphoblastic leukemia (29), and diffusion and magnetization transfer changes in cases of Alzheimer's disease (4). Overall, in addition to being objective and user-independent, histogram generation and analysis are fast and simple to implement (28).

The generation of peritumoral T2 signal abnormalities associated with high-grade gliomas is attributable to multiple mechanisms. Key among these is the presence of invading tumor cells and associated foci of neovascularization. Additionally, the elaboration of multiple cytokines by these infiltrative nests of tumor and endothelial cells contributes to the generation of vasogenic edema. As such, we believe that

our use of quantitative peritumoral T2 signal abnormality analysis was a well-suited method for investigating whether CXCR4 expression levels in GBM patients could be indicative of increased extent and intensity of peritumoral disease involvement in the brain. Indeed, the presence of increased T2-weighted peritumoral signal abnormalities portends a worse clinical prognosis in patients with GBM (7, 18). In relation to analysis of T2 signal variability, Aghi et al. (2) previously reported an operator-dependent analytic methodology for interpretation of peritumoral imaging changes in patients with GBM. This involved manual assignment of a border sharpness coefficient value based on an observer's on-screen assessment of the T2 signal at the margin of a visualized tumor. In contrast, our data use an operator-independent and fully quantitative methodology based on the automated assignment of voxel signal intensities using a wide dynamic range of 100 units spanning the extent from no signal to brightest signal.

CONCLUSION

In this study, we have now identified expression levels of the CXCR4 receptor, known to control activity of a key cellular signaling mechanism mediating multiple aspects of glioma biology, as a correlative marker for disseminated disease in the brains of GBM patients. These findings provide a critical bridge between currently used diagnostic tools and the molecular biology of these tumors. In conjunction with our earlier mechanistic descriptions (5) of CXCR4 signaling in gliomas and those of others (1, 3, 22, 32), these current results further support the use of CXCR4 inhibitors in the clinical treatment of malignant glioma. More specifically, our findings argue strongly for such therapy in cases in which quantitative analysis of peritumoral tissue using T2-weighted MRI reveals increased diffuse signal abnormalities, as this is highly likely to correlate with CXCR4 overexpression and therefore potentially treatment-responsive tumors.

Disclosure

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COMMENTS

In this study, Stevenson et al. reported interesting findings correlating the expression of the CXCR4 chemokine receptor with histological grade of gliomas and the degree of T2-weighted signal abnormalities on a preoperative magnetic resonance imaging (MRI) scan. For the correlation of CXCR4 expression and histological grade, they looked at 80 primary glioma samples. However, for the correlation studies with MRI T2 characteristics, they only looked at 22 cases. Although the finding that CXCR4 correlates with MRI characteristics is intriguing, the numbers are too small at this time to validate the correlation of CXCR4 with MRI analysis and further studies are needed.

Overall, this study makes some assumptions that are as yet unproven, which makes the conclusions of the article preliminary. Even if CXCR4 was a good correlate of histological grade, many previous studies have shown that histological grade of gliomas does not translate into clear differences in MRI findings beyond the areas of contrast enhancement. It is still unclear how much of the T2 changes around enhancing tumors are consistent with infiltrating tumor versus peritumoral edema. This has been a challenge for neuroradiologists. Furthermore, it is still not known how the differences in T2 MRI findings translate to clinical outcome. Unfortunately, this study does not correlate CXCR4 expression and MRI abnormalities with patient survival or response to treatment, which would be a much more interesting (and clinically relevant) analysis.

Nevertheless, this is an interesting study with some provocative preliminary findings. Further studies will be needed to better characterize the clinical value of CXCR4 in determining the biological behavior, imaging characteristics, and clinical outcome of gliomas.

Linda M. Liau
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Stevenson et al. presented an interesting glioblastoma study showing a correlation between the expression of chemokine receptor CXCR4 and the extent of T2 abnormality surrounding the contrast-enhancing portion of the tumor on MRI. The tumors have significantly different areas of hyperintensity on T2-weighted imaging based on whether they have been categorized into a high or low CXCR4 expression group. This supports earlier in vitro and in vivo animal studies documenting a link between CXCR4 and glioma cell proliferation and invasiveness (1–4).

Study samples were divided into “low” and “high” groups at the midpoint of a continuous distribution making the “distinct groups” somewhat arbitrarily defined. Although the high and low portions of the CXCR4 expression spectrum are clearly different, the degree of correlation between expression levels and invasiveness is unclear. It would be helpful to know whether the relationship displays a linear or sigmoidal pattern, as this relationship would be important for translation into a therapeutic strategy.

Although a broad definition of “glioma-associated disseminated disease” is reasonable for this study’s analysis, it limits the conclusions that may be drawn. CXCR4 expression may correlate most significantly with the degree of edema rather than the degree of microvascular proliferation or tumor cell infiltration. Although this alone represents an interesting finding, CXCR4 expression does not necessarily correlate with increasingly invasive tumors. However, reviewed in the context of previous studies correlating CXCR4 and microvascular proliferation in mouse tumors (1) and CXCR4 with “glioma cell dispersal” in animal models and human cells in vitro (3, 4), this work further supports an important in vivo role for CXCR4 in human glioma invasiveness. Further studies are still needed to characterize this relationship. More importantly, this study provides support for adding a targeted anti-invasion agent aimed at CXCR4 to the glioma therapy armamentarium.

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True mediators of glioma invasion remain elusive in the field of neuro-oncology. As usual, there are a lot of suspects, which could result in a targeted therapeutic approach to abrogate the invasive profile of gliomas. Stevenson et al. produced another convincing set of data implying that the chemokine receptor CXCR4 is indeed a worthy component of the glioma invasiveness profile. They went one step further and characterized the expression profile of this receptor in relation to imaging findings and observed, as expected, that CXCR4 expression was elevated in high-grade gliomas compared with their lower-grade counterparts. They also found a significant increase in the T2 abnormality on MRI imaging, which serves as a surrogate marker of invasion, potentially

in relation to CXCR4 expression. Certainly a prospective analysis with biopsy samples taken from T2 and fluid-attenuated inversion recovery signals correlated with CXCR4 expression profiles will be needed to verify that these two parameters are correlated, as opposed to coincidental. That said, it will, of course, be even more interesting to determine whether or not blocking CXCR4 reduces the invasive component of gliomas seen both in *in vivo* systems as well as using imaging. Stevenson et al. are encouraged to continue their experimental work with this invasion-related target and to specifically link it to imaging parameters that may be useful as surrogate biomarkers of glioma invasion.

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Gliomas are infiltrative neoplasms of the central nervous system. Although most glial tumors develop a focal mass lesion, with rare exception local therapies (e.g., surgery) that are effective for removing tumor mass fail to provide curative benefit as a large volume of neoplastic cells is left behind in the peritumoral infiltrated central nervous system parenchyma. Regional therapies, including fractionated radiotherapy and chemotherapy, are directed to treating the volume of tumor cell-infiltrated parenchyma not removed with surgery, but these therapies also are not curative. This infiltrative component of gliomas ultimately results in progressive neurological morbidity and death and therefore needs to be the focus of basic laboratory investigation and therapeutic development.

In this report, Stevenson et al. have made an important association between the presence of a chemokine receptor, CXCR4, on the surface of resected glioblastoma tumor specimens and the presence of progressive T2/fluid-attenuated inversion recovery changes on MRI that are manifested by glioma cell invasion and release of proinflammatory and proangiogenic molecules. The expression of CXCR4 on glioblastoma multiforme cells has been established previously and linked to the release of proinflammatory cytokines and vesicle-associated membrane protein, resistance to chemotherapy, and a worsened prognosis by oth-

ers (1, 4, 5). Stevenson et al. had previously shown (2) *in vitro* that CXCR4 expression is linked to an invasive phenotype, and thus the current work represents an association between their prior mechanistic work and a well-recognized clinical observation, that of the MRI changes associated with progressive infiltrative disease. One implication from this study is that one can subdivide glioblastoma multiforme on the basis of expression of CXCR4 and that those tumors that express this cytokine receptor are more likely to have an invasive phenotype. Other studies (3) also have demonstrated unique subgroups of glioblastoma multiforme on the basis of genotype or phenotype; how these findings will translate into individualized therapies is not yet clear. That said, given the association between glioma infiltration and progressive neurological morbidity, identification of key molecules associated with glioma cell invasion probably will lead to development of new therapeutic molecules that can slow or stop the inevitable progression of this disease.

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KRIT1 MODULATES β 1-INTEGRIN-MEDIATED ENDOTHELIAL CELL PROLIFERATION

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OBJECTIVE: Using ribonucleic acid interference on cultured cell lines, we examined the role of Krev interaction trapped 1 (krit1) and integrin cytoplasmic domain-associated protein-1 α (icap1 α) in β 1-integrin-mediated cell proliferation.

METHODS: Upon depletion of either krit1 or icap1 α in the HeLa cells, umbilical vein endothelial cells, and microvascular endothelial cells, we examined the cell number and proliferation changes in the cells, followed by the evaluation of β 1-integrin-mediated mitogen-activated protein kinase signal pathway and microscopic study.

RESULTS: Depletion of krit1 reduces cell number and decreases endothelial cell proliferation. Examination of β 1-integrin signaling downstream of focal adhesion kinase reveals decreased phosphorylation along the extracellular signal-regulated kinase/mitogen-activated protein kinase pathway. Depletion of icap1 α , a protein known to interact with krit1, has similar effects, suggesting synergistic function. We also show that krit1 colocalizes with icap1 α in both the nucleus and the cytoplasm; however, most of icap1 α is found in the nucleus and most of krit1 is found in the cytoplasm at steady state. On depletion of krit1, icap1 α decreases in the cytoplasm and is no longer detected in the nucleus.

CONCLUSION: Both krit1 and icap1 α act concordantly to play a critical role in β 1-integrin-mediated cell proliferation. Our data further suggest that krit1 both stabilizes and shuttles icap1 α and thus modulates its regulation of β 1-integrin-mediated signal transduction.

KEY WORDS: β 1-integrin, Cerebral cavernous malformations, icap1 α , krit1, Ribonucleic acid interference, Signal transduction

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Cerebral cavernous malformations (CCM) are abnormal collections of vascular sinusoids found in the central nervous system in 0.5% of the population (5, 14). Patients with cerebral cavernous malformations have a prospective hemorrhage risk of approximately 3% per lesion per year and a new-onset seizure rate of 2.4% per year (13). Familial CCM is an autosomal dominant disorder that accounts for

a large percentage of patients with CCMs (15). This disease is genetically heterogeneous, with loci at 7q (CCM1), 7p (CCM2), and 3q (CCM3) (4, 6, 8, 12). *KRIT1* mutations account for cases linked to the CCM1 locus on 7q (10, 17, 22), whereas mutations in a phosphotyrosine-binding protein, malcavernin, and in apoptosis-related protein, PDCD10, account for cases linked to the CCM2 (11) and CCM3 loci (1).

ABBREVIATIONS: ANOVA, analysis of variance; CCM, cerebral cavernous malformations; cDNA, complementary deoxyribonucleic acid; ERK, extracellular signal-related kinase; FAK, focal adhesion kinase; G3PDH, glyceraldehyde-3-phosphate dehydrogenase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HA, HA.11 antibody; HUVEC, human umbilical vein endothelial cells; icap1 α , integrin cytoplasmic domain-associated protein-1 α ; JNK, Jun N-terminal kinase; krit1, Krev interaction trapped 1; MAP, mitogen-activated protein; MEK, ERK kinase; mRNA, messenger ribonucleic acid; PBS, phosphate-buffered saline; PCNA, proliferating cell nuclear agent; RAF, v-raf-1 murine leukemia viral oncogene homolog; RNAi, ribonucleic acid interference; siRNA, small interference ribonucleic acid; VEGF, vascular endothelial growth factor; XTT, 2,3-Bis(2-methoxy-4-nitro-5-sulphophenyl)-2H-tetrazolium-5-carboxanilide

The molecular relationship of *KRIT1* mutations to cerebral cavernous malformations remains unclear. Krev interaction trapped 1 (krit1) was identified in a two-hybrid screen through interaction with krev1/rap1a, a small Ras family GTPase (18). This implicated krit1 in GTPase-mediated signaling, leading to the hypothesis that it might function as a tumor suppressor (22). However, after the identification of additional coding exons at the 5' end of the *KRIT1* gene (7, 16, 21), we showed that full-length krit1 (unlike the N-terminally truncated version) does not interact with krev1 (20). Instead, full-length krit1 interacts with integrin cytoplasmic domain-associated protein-1 α (icap1 α), a modulator of β 1-integrin-mediated signal transduction (19, 20). In this article, we show that krit1 plays a pivotal role in β 1-integrin-mediated endothelial cell proliferation. Depletion of krit1 by ribonucleic acid interference (RNAi) inhibits endothelial cell proliferation and decreases phosphorylation along the extracellular signal-regulated kinase/mitogen-activated protein (ERK/MAP) kinase signaling pathway. This constitutes one of the major signal transduction pathways in angiogenesis. Finally, we show that krit1 and icap1 α are present in both the nucleus and cytoplasm, with predominant steady-state localization of krit1 in the cytoplasm and icap1 α in the nucleus. Depletion of krit1 leads to decreased levels of icap1 α in the cytoplasm and to undetectable levels in the nucleus.

MATERIALS AND METHODS

Cell Culture

HeLa cells were cultured in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum and an antibiotic-antimycotic mixture (GIBCO BRL, Carlsbad, CA). Human umbilical vein endothelial cells (HUVEC) were cultured in EGM2, and human microvascular endothelial cells were cultured in EGM2-MV medium (Clonetics, Walkersville, MD).

RNAi

Small interference RNA (siRNA) duplex oligo targeting AAGAUGGGCAGAGA AGCAUCA (RNAiHKA) on the human full-length *KRIT1* RNA was used. SiRNA duplex oligo targeting AAUCCGGAUGGUGUGUACGA (RIICPA1) on the human *ICAP1* RNA was used. These gene-specific siRNA duplex targeting sequences were blasted through the National Center for Biotechnology Information nucleotide database and found to be specific to the targeted genes. All gene-specific siRNA oligos and control siRNA duplex Luciferase GL2 duplex oligos were synthesized at Dharmacon, Inc. (Lafayette, CO). Duplex siRNA oligonucleotides were applied at a final concentration of 10 μ mol/L in the presence of Oligofectamine (Invitrogen, Carlsbad, CA) using the instructions supplied by the manufacturer.

Cell Proliferation Assay

Cell counts and proliferation assays were carried out using a hemacytometer and the (2,3-bis [2-methoxy-4-nitro-5-sulfophenyl]-5-[[phenylamino] carbonyl]-2H-tetrazolium hydroxide) (XTT)-based colorimetric assay from Roche (Indianapolis, IN) in HUVEC and HeLa cell lines. For siRNA treatment, 10⁵ HUVECs or HeLa cells were seeded into each well, and cell counts were performed at 3 days after RNAi treatment. For XTT (2,3-Bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetra-

zolium-5-carboxanilide) assays, absorbance was measured on Day 6 after RNAi treatment at Day 1 and Day 4. Absorbance for the XTT assays was read at 490 to 650 nm.

Cellular Fractionation

Per dish, cells were scraped into 1 mL of phosphate-buffered saline (PBS) and pelleted at 1000 rpm for 10 minutes. Pellets were resuspended in fractionation buffer (10 mmol/L Tris, pH 8.0; 140 mmol/L NaCl; 1.5 mmol/L magnesium chloride; and 0.5% NP-40). Pellets were gently vortexed on ice for 5 minutes, and centrifuged at 500 $\times$ g for 5 minutes. Supernatants (cytosolic fraction) were removed and saved. Remaining nuclear pellets were resuspended in inositol-hexaphosphate buffer, gently vortexed, and pelleted for 5 minutes at 500 $\times$ g. This was repeated 3 times and nuclear pellets were resuspended in an appropriate volume of inositol-hexaphosphate buffer containing 1% polyoxyethylene sorbitan monopalmitate Polyoxyethylene (20) Monolaurate (Tween-20, Sigma-Aldrich, St. Louis, MO) and 0.5% sodium deoxycholate (nuclear fraction).

Antibodies and Immunocytochemistry

Raf-1 (E-10), pERK (E-4), ERK2 (C-14), pJNK (G-7), JNK2 (D-2), pp38 (D-8), p38 (A-12), proliferating cell nuclear antigen, and β -actin (C-2) primary antibodies were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). The antibody pRaf-1 (ser259) was purchased from Cell Signaling Technology (Beverly, MA). Dr. Chang and Dr. Block kindly donated icap1 α antibodies for this research. The HA (HA.11) antibody was purchased from Covance, Inc. (Richmond, CA), the V-5 antibody was purchased from Invitrogen (Carlsbad, CA), and the neomycin antibody was purchased from Cortex Biochem (San Leandro, CA). Cells were split onto microscope cover slides, and cultures were grown for 24 hours. Slides were then washed with cold PBS, fixed with 3.7% paraformaldehyde in PBS for 20 minutes, and permeabilized in 0.1% Triton X-100 in PBS for 15 minutes. Sections were then blocked with 1% bovine serum albumin in PBS for 30 minutes, followed by incubation with primary antibody for 60 minutes and finally by secondary antibody for 60 minutes. They were then mounted with antifade agent (Molecular Probes, Eugene, OR).

Western Blot

Cell lysates were equally mixed with twofold protein loading buffer, heated at 100°C for 5 minutes, and centrifuged briefly before loading onto sodium dodecyl sulfate polyacrylamide gel electrophoresis (4–12% polyacrylamide), then transferred to nitrocellulose. Blots were blocked in 5% nonfat milk in PBS with 0.1% Tween 20. Blots were incubated with primary antibody, washed 3 times, and then incubated with secondary antibody conjugated with horseradish peroxidase. Proteins were detected using chemiluminescence and autoradiography. For RNAi assays, cells were lysed in lysis buffer (0.5 mmol/L ethylenediamine tetra-acetic acid, 150 mmol/L sodium chloride, 20 mmol/L N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid, 0.2% NP-40, and 1 mmol/L dithiothreitol), and protein concentrations of the treatment lysates were measured with the RC DC Protein Assay kit (Bio-Rad Laboratories, Inc., Hercules, CA). Equal amounts of protein for each treatment were loaded onto sodium dodecyl sulfate polyacrylamide gel electrophoresis.

Northern Blot

Poly-A RNAs from HeLa cells (1 μ g) were separated electrophoretically in a 1% agarose 3-(N-morpholino)propanesulfonic acid gel with 10% formaldehyde denaturing buffer, and transferred to a GeneScreen Plus membrane (NEN Life Science Products, Boston, MA). Hybridization to P32-labeled probes (Random Primed

DNA Labeling Kit; Boehringer Mannheim, Indianapolis, IN) was carried out at 42°C for 24 hours using UltraHyb solution (Clontech, Palo Alto, CA). Probes included a full-length human *krit1* complementary deoxyribonucleic acid (cDNA) fragment, a full-length human *icap1 α* cDNA fragment, and a glyceraldehyde-3-phosphate dehydrogenase cDNA control probe (Clontech). The membrane was stripped between subsequent hybridizations. Developed autoradiographs were scanned using InstantImage electronic radiography (Packard, Meriden, CT).

Plasmid Construction and Transfections

For construction of recombinant plasmids, all polymerase chain reaction amplifications were carried out with Platinum DNA Polymerase High Fidelity (Invitrogen) as specified by the manufacturer. All final constructs were sequenced to verify insert orientation and sequences. For the full-length N-terminally HA-tagged human *KRIT1* construct (HA-*KRIT1*: 1–736), primers were used as previously reported (20). For the C-terminal V5-tagged full-length human *KRIT1* construct (V5-*KRIT1*: 1–736-V5), primers HK02F2 (5-TACACCATGG GAAATCCA-

GAAA-3) and KRIT005R (sequence above) were used. For the C-terminal V5-tagged *ICAP1 α* construct (V5-*ICAP1 α* : 1–200-V5), primers were used as previously reported (21). All mammalian expression constructs were fashioned by subcloning the appropriate polymerase chain reaction product into pcDNA3.1/V5/HIS-TOPO (Invitrogen). HeLa transfections were completed using HeLa Monster reagent (PanVera, Madison, WI) with the directions provided by the manufacturer. For transfection, 10 μ g of plasmids was used per 10-cm-diameter dish.

Confocal Microscopy

Samples were acquired with the Nikon PCM 2000 confocal laser scanning microscope system (Nikon, Melville, NY), using COM-PIX software on a desktop computer. A krypton-argon laser exciting at 488- and 568-nm wavelength was used to obtain optical sections. Narrow-band emission filters (525 and 605 nm) were used to eliminate channel cross-talk, and a pin-hole aperture was set to obtain 0.5 μ m Z-plane sections (as determined by full-width, half-maximum-intensity values). Slides were imaged with a 60-fold oil immersion planar apochromatic objective lens through a Nikon E-800 Eclipse microscope.

Subcellular Localization and Fluorescence Microscopy

HeLa cells were grown on coverslips in 35-mm dishes at 3×10^3 cells per coverslip, siRNA treated, and then transfected with 3 μ g of plasmid expressing C-terminal *icap1 α* -V5 construct. Twenty-four hours after transfection, anti-V5 antibody was applied. Hoechst dye 33258 (Sigma, Perth, Australia)

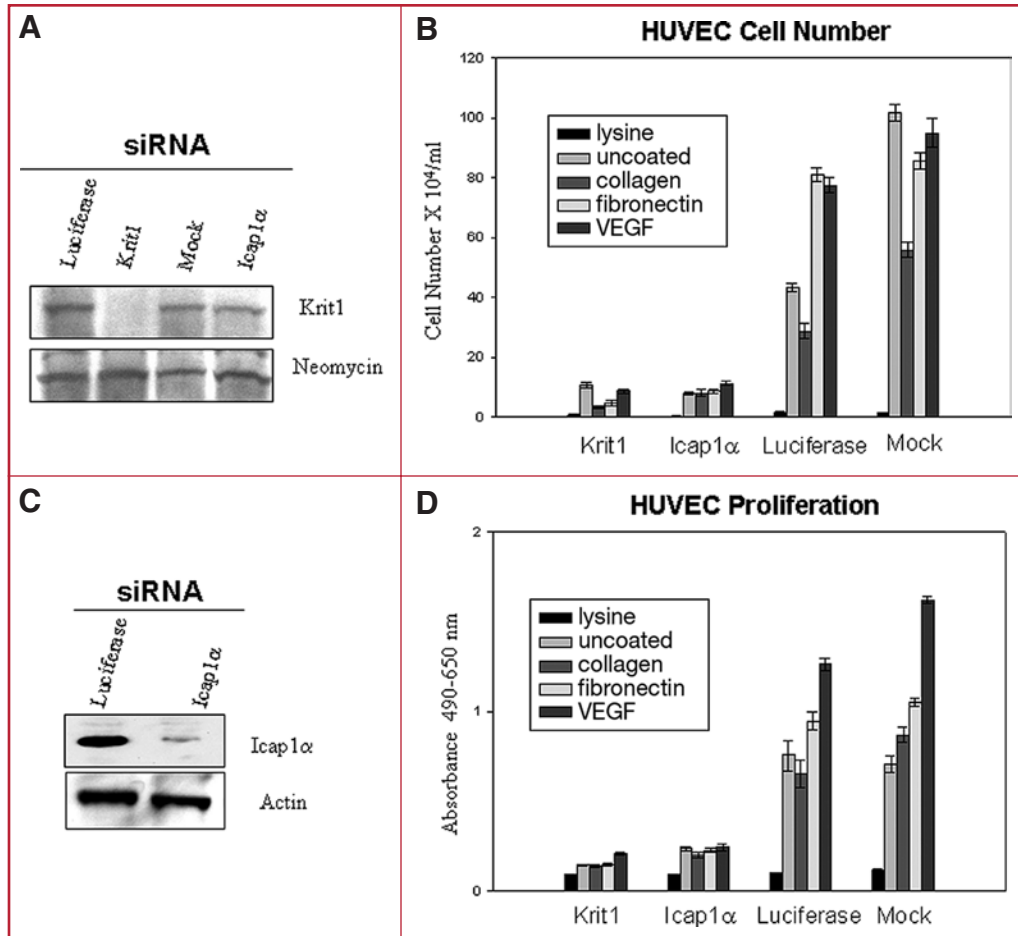


FIGURE 1. Small interference ribonucleic acid (siRNA) abolishes Krev interaction trapped 1 (*krit1*) and integrin cytoplasmic domain-associated protein-1 α (*icap1 α*) expression in human cells and leads to decreased HeLa and vascular endothelial cell proliferation. **A**, Western blot shows specific depletion of *krit1* protein in the *krit1* siRNA lane in HeLa compared with the luciferase, *icap1 α* , and mock control siRNA lanes. An anti-V-5 antibody was used to detect *krit1*-V5 protein expression. Neomycin in the vector backbone was used to assess transfection efficiency and as an internal expression and loading control. **B**, histogram showing that depletion of *krit1* and *icap1 α* decreases human umbilical vein endothelial cells (HUVEC) number on the different cellular environments (from left to right: lysine-coated, uncoated, collagen-coated, fibronectin-coated, and 10-fold increase of vascular endothelial growth factor [VEGF] in the media). **C**, depletion of endogenous *icap1 α* expression in HeLa in *icap1 α* siRNA lane compared with the luciferase control lane using an anti-*icap1 α* monoclonal antibody. An anti-actin antibody was used as a loading control. **D**, histogram showing that depletion of *krit1* and *icap1 α* inhibits HUVEC proliferation on the different cellular environments (from left to right: lysine-coated, uncoated, collagen-coated, fibronectin-coated, and 10-fold increase of VEGF in the media). Absorbance values (index for cell proliferation capacity) in this 2,3-Bis(2-methoxy-4-nitro-5-sulphophenyl)-2H-tetrazolium-5-carboxanilide assay are significantly smaller in the *krit1* and *icap1 α* siRNA-treated cells compared with luciferase and mock siRNA-treated controls.

for nuclear staining and phalloidin (Invitrogen) for cytoskeletal staining were incubated with secondary antibody to distinguish cellular localization via differential fluorescence patterns under fluorescence microscopy. For leptomycin (Sigma, St. Louis, MO) treatment, 5 ng/ml was used to treat cells for 3 hours before fixing cells.

Statistical Analysis

One-way analysis of variance (ANOVA) was used to detect the differences in the mean values among the treatment groups. All pairwise comparisons were calculated with a Tukey test. All error bars are standard error of the mean.

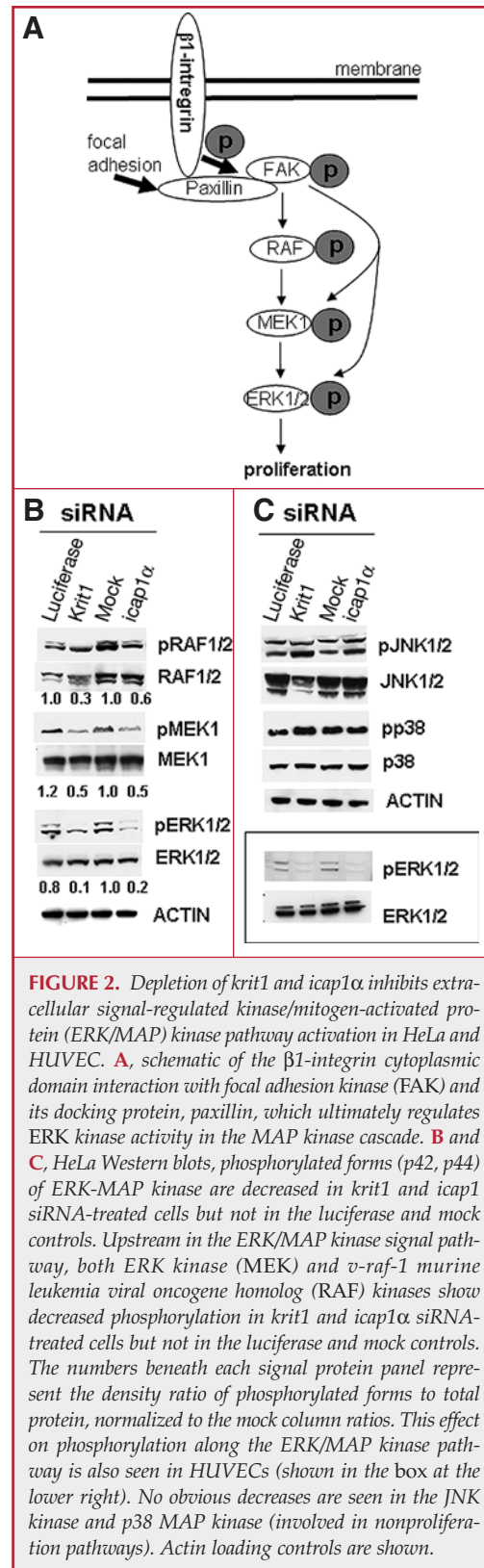
RESULTS

krit1 and icap1 α siRNAs Effectively Deplete krit1 and icap1 α Protein

Western blot data in HeLa cells show that krit1 protein expression is dramatically decreased by a krit1-specific siRNA. Protein depletion of icap1 α by an icap1 α -specific siRNA was also confirmed by Western blot analysis (Fig. 1). Identical results were observed on Northern and Western blot analysis of siRNA-treated HUVECs and human microvascular endothelial cells (data not shown).

Depletion of krit1 or icap1 α Decreases Cell Number and Proliferation

Depletion of krit1 significantly decreases HeLa cell number (one-way ANOVA: $F = 138.42$; $P < 0.001$, $n = 3$) when compared with siRNA controls. Tukey tests for pairwise comparison show that there are significant differences between the krit1 and icap1 α siRNA-treated HeLa cells and each of the controls ($P < 0.002$, $n = 3$). Likewise, significant decreases in HUVEC number were also observed on uncoated (one-way ANOVA: $F = 689.89$, $P < 0.0001$, $n = 6$), collagen-coated (one-way ANOVA: $F = 162.55$, $P < 0.0001$, $n = 6$), and fibronectin-coated plates (one-way ANOVA: $F = 551.09$, $P < 0.0001$, $n = 6$), as well as a 10-fold increase of vascular endothelial growth factor (VEGF) in the media (one-way ANOVA: $F = 269.61$, $P < 0.0001$, $n = 6$) (Fig. 1). Tukey tests for pairwise comparison show even more significant differences between the krit1 and icap1 α siRNA-treated HUVECs and each of the controls ($P < 0.0001$, $n = 6$). Interestingly, the magnitude of the changes between the icap1 α and krit1 siRNA-treated HUVECs compared with luciferase siRNA-treated HUVECs (the control) are very different on the different cellular environments: 4- to 5.6-fold decrease on uncoated plates, 3.7- to 9-fold decrease on collagen-coated plates, 9- to 17-fold decrease on fibronectin-coated plates, and 7- to 9-fold decrease on the VEGF-increased media. Although RNAi directed against an irrelevant target decreased cell number, RNAi directed against krit1 or icap1 α had a significantly accentuated effect (HUVECs: $P < 0.0001$, $n = 6$; HeLa cells: $P < 0.002$, $n = 3$). This decreased cell number could be the result of decreased cell proliferation, increased cell death, or a combination of both. In this article, we focus our investigation on cell proliferation in this aspect because of space limitations. Therefore, the effect of depletion of krit1 and icap1 α on cell proliferation



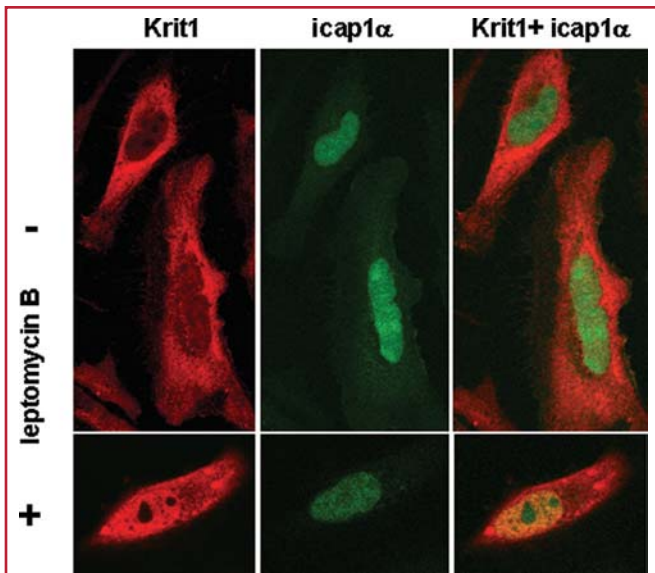


FIGURE 3. Cellular localization of *krit1* and *icap1α* before (–) and after (+) treatment with leptomycin B. **A**, confocal microscopy showing that *krit1* is seen predominantly in the cytoplasm in cells, but that *krit1* accumulates in the nucleus following leptomycin treatment (as detected using N-terminal Hemagglutinin-tagged *krit1* proteins). **B**, *icap1α* shows the complementary distribution, with the majority of the protein being sequestered in the nucleus. Further nuclear accumulation is evident after treatment with leptomycin. **C**, superimposition of these images demonstrates colocalization of *krit1* and *icap1α* in both the nucleus and cytoplasm.

was consequently explored using an XTT assay. Our results show that depletion of either *krit1* or *icap1α* significantly inhibits HeLa cell proliferation (one-way ANOVA: $F = 191.43$, $P < 0.001$, $n = 6$) compared with controls; Tukey tests for pairwise comparison show significant differences between *krit1* and *icap1α* siRNA treatment with each of the siRNA controls ($P < 0.001$, $n = 6$). When either *krit1* or *icap1α* was depleted, the same inhibitory effects on cell proliferation of HUVECs were also observed on different cellular environments: uncoated (one-way ANOVA: $F = 54.2$, $P < 0.0001$, $n = 6$), collagen-coated (one-way ANOVA: $F = 31.2$, $P < 0.0001$, $n = 6$), and fibronectin-coated plates (one-way ANOVA: $F = 33.34$, $P < 0.0001$, $n = 6$), as well as the VEGF-increased media (one-way ANOVA: $F = 14.7$; $P < 0.0001$, $n = 6$) (Fig. 1). Tukey tests for pairwise comparison show

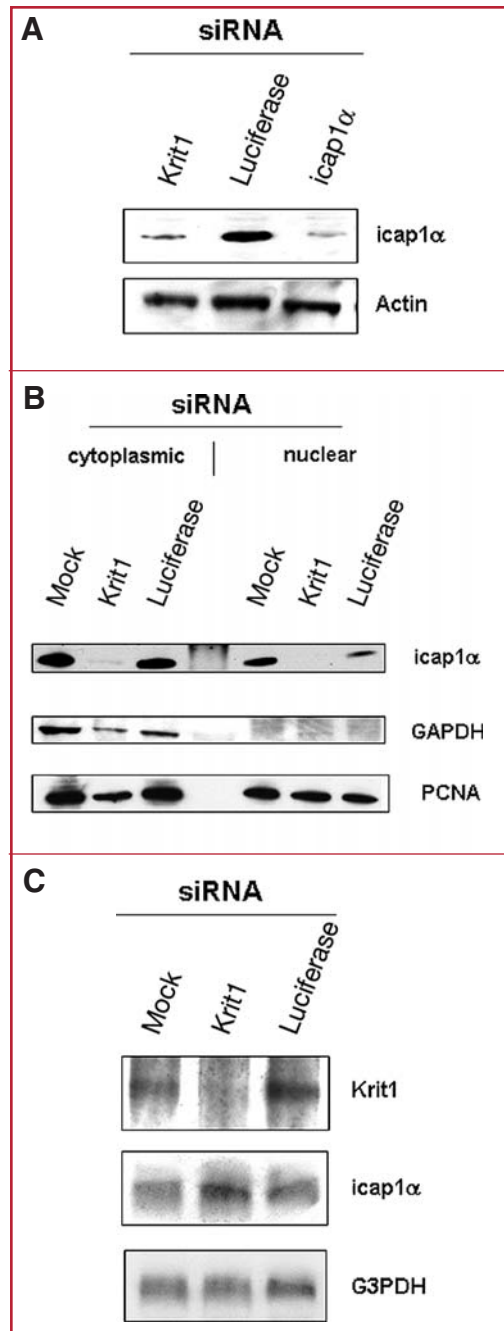


FIGURE 4. Cellular fractionation and the effect of *krit1* depletion on *icap1α* protein levels by Western analysis. Western blot analysis for *icap1α* levels show that both *icap1α* and *krit1* siRNA decrease *icap1α* levels (**A**). This is expected with *icap1α* siRNA, but the concordant effect of *krit1* depletion suggests that *krit1* may stabilize *icap1α*. Actin is shown as a loading control. Northern analysis following *krit1* depletion (**B**) shows stable *icap1α* messenger ribonucleic acid (mRNA), thus supporting the idea that *icap1α* protein is degraded in the absence of *krit1*. Here, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is shown as a loading control. Cellular fractionation and Western blot analysis (**C**) demonstrate a decrease in

icap1α levels in the cytoplasm after *krit1* depletion as above. However, no *icap1α* is detectable in the nuclear fraction following *krit1* depletion, thereby suggesting that *icap1α* depends on *krit1* for nuclear import. In mock and irrelevant (luciferase) siRNA, *icap1α* is present in both the cytoplasm and the nucleus. GAPDH, present only in the cytoplasm, is shown as a fractionation control, as is proliferating cell nuclear antigen (PCNA), known to be present in the cytoplasm and nucleus (with cytoplasmic preference as culture density increases) (19). In the subcellular fractionation experiments, a V5-tagged *icap1α* construct was used. G3PDH, glyceraldehyde 3-phosphate dehydrogenase.

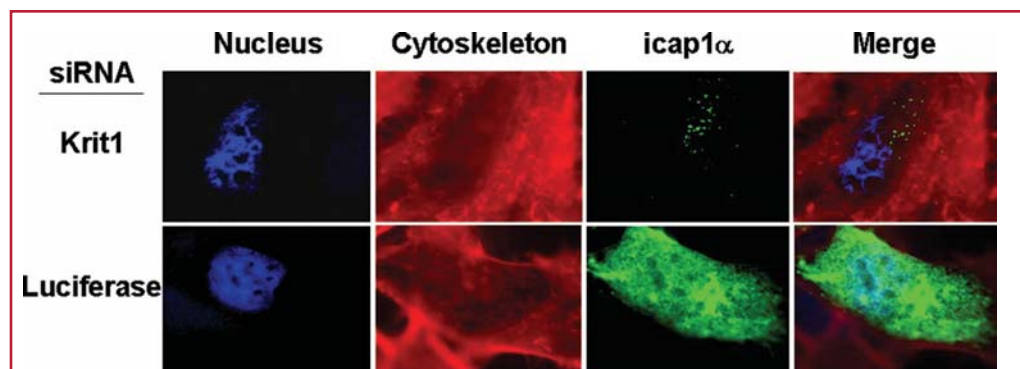


FIGURE 5. Effect of krit1 depletion on icap1 α by fluorescence microscopy. HeLa cells studied by fluorescence microscopy after krit1 depletion and siRNA control treatments confirm the impression from cellular fractionation and Western analysis; icap1 α (seen both in the nucleus and cytoplasm in mock siRNA cells) is seen only faintly in the cytoplasm in cells depleted of krit1. Hoechst dye33258 and phalloidin were used for nuclear and cytoskeletal stainings, respectively. A V5-tagged icap1 α construct was used.

even more significant differences between the krit1 and icap1 α siRNA-treated HUVECs and each of the controls ($P < 0.0001$, $n = 6$). Although HUVECs grow poorly on the lysine-coated plates, significant decreases in cell number and proliferation of the krit1 and icap1 α siRNA-treated HUVECs compared with controls were observed (data not shown). Intriguingly, similar trends in the changes in cell proliferation between the icap1 α and krit1 siRNA-treated HUVECs compared with luciferase siRNA-treated HUVECs (the control) were also observed on the different cellular environments: 1.3- to 2-fold decrease on uncoated plates, 1.6- to 3-fold decrease on collagen-coated plates, 1.8- to 3.6-fold decrease on fibronectin-coated plates, and 2.1- to 3.1-fold decrease on the VEGF-increased media (Fig. 1).

Depletion of krit1 and icap1 α Leads to Decreased Activation of the ERK/MAP Kinase Pathway

β 1-integrin stimulation of cellular proliferation is largely mediated through the ERK/MAP kinase signaling cascade. We hypothesized that the effects seen on depletion of either krit1 or icap1 α manifest attenuation of this signal. In keeping with this hypothesis, we observed a significant decrease in phosphorylation of factors along the ERK/MAP kinase pathway, including v-raf-1 murine leukemia viral oncogene homolog (RAF)1/2, ERK kinase 1 (MEK1), and ERK1/2. This was indicative of a specific perturbation rather than generalized alteration of cellular metabolism, as evidenced by preserved phosphorylation along the Jun N-terminal kinase (JNK) and p38 MAP kinase (MAPK) pathways (Fig. 2).

krit1 and icap1 α Cycle through the Nucleus

In transiently transfected HeLa cells studied with confocal microscopy, krit1 distributes in both the cytoplasm and nucleus, although it is localized predominantly in the cytoplasm. By comparison, icap1 α is highly concentrated in the nucleus but also distributes in the cytoplasm. Both krit1 and icap1 α are enriched in the nuclear compartment on treatment with leptomycin (an

inhibitor of the major nuclear export pathway), suggesting that both proteins shuttle between the nucleus and the cytoplasm (Fig. 3).

Depletion of krit1 Leads to a Decrease in icap1 α and Blocks Its Nuclear Import

In HeLa cells, both icap1 α and krit1 depletion decreased icap1 α protein levels by Western blot analysis. Northern analysis after siRNA-mediated silencing of krit1 expression revealed no decrease in icap1 α messenger ribonucleic acid (mRNA) levels. After cellular fractionation, icap1 α can be detected in both the cytoplasm and nucleus. Depletion of krit1 leads to a decrease in icap1 α levels in the cytoplasm, and no icap1 α can be detected in the nuclear fraction (Fig. 4). This suggests that icap1 α is stabilized by krit1 and may depend on krit1 for nuclear import. Confocal immunohistochemistry confirmed both a reduction in the abundance and nuclear localization of icap1 α on depletion of krit1 (Fig. 5).

DISCUSSION

A prior study posited that krit1 sequesters cytoplasmic icap1 α and thus down-regulates β 1-integrin-mediated signaling (20). This hypothesis was largely based on the observations that both β 1-integrin and krit1 use a NPXY motif to bind icap1 α and that they compete for binding in vitro. In this scenario, decreased krit1 expression, as occurs in CCM, would enhance icap1 α binding to β 1-integrin and enhance signaling. Also inherent in this view is the prediction that loss of function of krit1 or icap1 α should exert counterregulatory effects, with an increase or decrease in β 1-integrin signaling, respectively. In contrast, we have found that loss of function of either protein attenuates signaling (Fig. 2). These data suggest that krit1 and icap1 α act cooperatively and that CCM may manifest decreased rather than increased β 1-integrin signaling. We also demonstrated the more negative impacts on endothelial cell number and proliferation on depletion of either protein on the fibronectin, a specific β 1-integrin extracellular receptor. This further implies the direct involvement of both proteins in β 1-integrin signaling (Fig. 1). Our data are consistent with recent zebrafish data that *san*, a zebrafish krit1 ortholog, regulates the expression level of endothelium-specific genes and/or the number of vascular endothelial cells (9). It has been shown that overexpression of icap1 α in the cytoplasm has the capacity to physically disrupt focal adhesions (3). These data suggest that regulated recruitment of icap1 α to the cell membrane in proximity to focal adhesions may be critical for the maintenance of cellular architecture as well as regulation of β 1-integrin-mediated signaling.

Our data are consistent with a model in which krit1 contributes significantly to this regulation by both stabilizing and transporting icap1 α into and out of the nucleus and eventually targeting it to focal adhesions. The key initial observation in support of this model was the preferential and discordant predominant compartmentalization of the two proteins; krit1 is predominantly cytoplasmic but shuttles between compartments, a finding that parallels its strong nuclear localization (residues 46–51; KKRRKK) and nuclear export (residues 551–562; LITLASLL) sequences. In contrast, icap1 α is predominantly nuclear and has a weak nuclear localization sequence (KKRH at residues 6–9) and no readily identifiable nuclear export sequence. Nuclear enrichment of both proteins on treatment with leptomycin B would be explained if trafficking of icap1 α between the nuclear and cytoplasmic compartments depends on krit1. Moreover, by virtue of FERM (F, 4.1 protein; E, ezrin; R, radixin; M, moesin; a protein domain functioning as membrane-cytoskeleton linkers) and ankyrin-repeat domains, krit1 could contribute to the targeting of icap1 α to its site of intended function at the cell membrane and, more specifically, focal adhesions. In this view, targeting functions mediated by krit1 titrate icap1 α 's ability to interact with and thus regulate β 1-integrin as we previously suggested (23). This is in keeping with the cooperative functions of krit1 and icap1 α in modulating β 1-integrin-mediated signaling revealed by RNAi-mediated silencing experiments. Our hypothesis was further supported by the recent data that kri-1, a krit1 ortholog in *Caenorhabditis elegans*, is required for DAF-16/FOXO transcription factor nuclear localization (2).

The disruptive role of icap1 α to focal adhesion formation (3) has raised the possibility that krit1 may critically regulate the abundance and localization of icap1 α . Our data suggest that krit1 is both a positive and a negative regulator of icap1 α -mediated modulation of β 1-integrin signaling. It may exert positive regulation by stabilizing and shuttling icap1 α from the nucleus to the cytoplasm, thereby facilitating icap1 α and β 1-integrin interaction and the propagation of proliferation signals from the extracellular matrix. It may exert a negative regulatory influence by limiting the level of icap1 α available to interact with β 1-integrin through nuclear sequestration. In this view, krit1 titrates icap1 α -mediated endothelial cell proliferation using regulatory cues and mechanisms that remain to be fully explored.

KRIT1, the CCM1 gene, when mutated, leads to the formation of vascular malformations in the brain and spinal cord. These lesions consist of endothelium-lined channels containing blood. How suppression of β 1-integrin signaling and, more specifically, cellular proliferation contributes to the formation of vascular lesions in CCM remains speculative. One model posits that the focality of lesions observed in CCM reflects somatic loss of function of the second allele in individuals who have inherited one germline mutation. It remains to be determined whether the lesional expansions of endothelial cells manifest a cell-autonomous loss of critical function or an indirect and non-productive response to the failed proliferation of a distinct cell population that is devoid of krit1 function. Clearly, additional studies are needed to understand the relevance of these in vitro

findings and to interrogate the role of krit1 in other β 1-integrin-mediated signal transduction cascades that govern diverse processes, including cell migration and survival.

Disclosures

This work was supported by the Center for Inherited Neurovascular Disease (www.cind.org), the Salisbury Family Foundation, the Fondazione Agarini (DR), and the Howard Hughes Medical Institute (HCD).

CONCLUSION

In summary, we found that both krit1 and icap1 α act concordantly to play a critical role in β 1-integrin-mediated cell proliferation. However, continuing efforts are certainly needed to link the perturbed β 1-integrin-mediated signal cascades in vascular endothelial cells and human phenotype of cerebral vascular lesions in CCM conditions. We strongly believe that understanding the role of CCM genes in β 1-integrin-mediated signaling and vascular endothelial cell function is a critical first step in the development of diagnostic and nonsurgical therapeutic strategies for this devastating clinical condition.

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COMMENTS

This study addressed the cellular mechanism of KRIT1 (gene product of the CCM1 gene) in endothelial cells. The functional impact of this gene on endothelial cell biology remains only partially elucidated. The authors have used RNA interference (RNAi) methodology to demonstrate the effect of KRIT1 depletion on endothelial cell proliferation and integrin cytoplasmic domain-associated protein-1a (icap1a) expression in the cytoplasm and nucleus, hence supporting its role in β 1-integrin signal transduction. This is an important step in demonstrating potential mechanisms of disease. Future studies will need to

link these cellular changes to the ultimate vascular phenotype of dilated and leaky capillaries, which are thought to trigger the genesis of cerebral cavernous malformations (CCM).

This research complements other recent reports relating KRIT1 to endothelial cell tube formation and the genesis of leaky endothelial phenotype. It is still not known whether this effect on endothelial cells is sufficient for lesion genesis, or if other factors, such as hemorrhage and inflammation, play a role in ultimate lesion formation. These studies are important in starting to dissect the ultimate mechanism of disease and may ultimately open new venues for therapeutic manipulation.

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Zhang et al. have attempted to increase our understanding of the biology of cavernous malformations. Familial CCMs may arise from mutations in different genetic loci including 7q (CCM1), 7p (CCM2), and 3q (CCM3). Cases linked to the CCM1 locus on 7q have mutations in the *KRIT1* gene. At present, the molecular relationship of *KRIT1* mutations to CCMs has not been elucidated. In the present study, Zhang et al. attempted to define the role of krit1 (and a modulator protein of β 1-integrin-mediated signal transduction known to interact with krit1, icap1 α in β 1 integrin-mediated cell proliferation).

Zhang et al. used several different cell lines including HeLa cells, umbilical vein endothelial cells and microvascular endothelial cells. Using RNAi, the authors depleted krit1 which reduced cell number and diminished endothelial cell proliferation. As β 1-integrin stimulation of cellular proliferation is mediated largely through the extracellular signal-regulated kinase/mitogen-activated protein kinase signaling cascade, they examined the effects of krit1 depletion on this pathway finding that krit1 depletion did indeed decrease activation of this pathway. Depletion of icap1 α with RNAi had similar effects, suggesting a synergistic role with krit1. They also demonstrated that krit1 colocalizes with icap1 α in both the nucleus and cytoplasm (and both shuttle between the compartments), although icap1 α is found predominantly in the nucleus and krit1 predominantly in the cytoplasm at steady state. Depletion of krit1 decreases icap1 α in the cytoplasm and blocks its nuclear import, suggesting that icap1 α is stabilized by krit1 and may depend upon krit1 for nuclear import.

These elegant experiments provide new insight concerning the basic function of krit1 and icap1 α . However, further investigation is clearly needed. Zhang et al. did not actually use cerebral endothelial cell lines and whether or not these observations remain applicable to the cerebral circulation is unknown. The limitations of RNAi approaches are well known. Furthermore, they did not show their data, owing to space limitations, concerning a possible role of cell death to the observed decrease in cell numbers seen with RNAi treatment.

Overall, these are carefully conducted experiments that attempt to preliminarily elucidate how mutations in the *KRIT1* gene may contribute to the development of cavernous malformations. They certainly provide impetus for future investigation. As Zhang et al. point out, defining the biology of CCMs is a necessary step in the development of novel diagnostic and less invasive therapeutic strategies for this condition. We look forward to future contributions from this group and others that contribute to our understanding of the biology of CCMs.

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THE HARVARD NEUROSURGICAL SERVICE AT THE CHILDREN'S HOSPITAL BOSTON AND BRIGHAM & WOMEN'S HOSPITAL, 1912–2007

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THE HARVARD NEUROSURGICAL Service at Brigham and Women's Hospital and Children's Hospital Boston has a distinguished history, beginning in 1912 when Dr. Harvey Cushing became surgeon-in-chief at the Peter Bent Brigham Hospital. After Cushing left in 1932, the Children's Hospital had a dominant role, with the creation and development of pediatric neurosurgery under Franc D. Ingraham, Donald Matson, John Shillito, and Keasley Welch. In 1987, the service at Brigham and Women's Hospital began to grow with the appointment of Dr. Peter Black as chief. In 2000, it became a department. In 2002, the clinical services at the two institutions were large enough to separate, with Dr. Black continuing as academic chair of both. By 2005, the Brigham and Women's Hospital service had 10 neurosurgeons with brain tumor, cerebrovascular, spine, and intensive care unit divisions; the Children's service had 5 neurosurgeons under Dr. Michael Scott. There were also six full-time scientists in the group. Despite reporting on more than 2500 cases a year, the combined service continued to have a strong academic program. This was helped by a residency with two required research years, an academic day each week, faculty committed to research, strong scientific collaborations, and contributions from many visiting neurosurgeons and research fellows. In its first 94 years, the service has been a strong force in clinical, educational, political, and research efforts in neurosurgery.

KEY WORDS: Children's Hospital, History of medicine, History of neurosurgery, Peter Bent Brigham Hospital, Cushing

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In the late 19th century, the Boston restaurateur Peter Bent Brigham left a substantial bequest to found a hospital that would provide care for indigent patients of Suffolk County. The bequest lay fallow for 20 years; ultimately, its trustees purchased the Ebenezer Francis estate. This estate was sufficient not only for the Peter Bent Brigham Hospital (PBBH) but also for the Harvard Medical School, which moved there at the same time, and for Children's Hospital. This created the union of medical school and hospitals that continues to this day (1, 11, 35, 75).

THE CUSHING YEARS, 1912–1932

When the Dean of the Harvard Medical School scoured the country for an appropriate surgeon-in-chief for the new hospital, one major candidate emerged: Dr. Harvey Cushing, a student of William Halsted at Johns Hopkins and former graduate of Harvard (Fig. 1). He accepted the post of Chief of Surgery at the as yet unbuilt hospital in 1910 and moved to

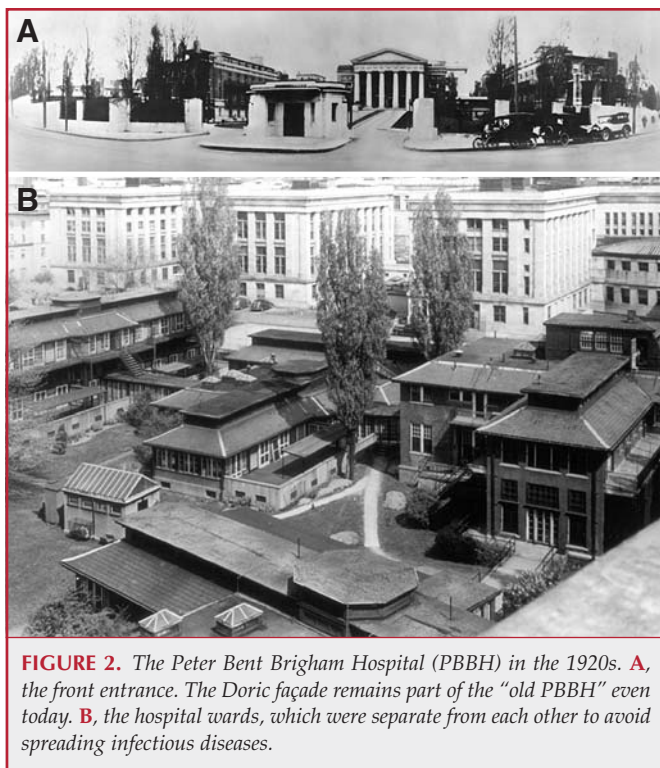


FIGURE 1. Harvey Cushing, founder of modern neurosurgery, *Neurosurgery's Man of the Twentieth Century*, and the first surgeon-in-chief at the Peter Bent Brigham Hospital (PBBH) beginning in 1912.

Boston with his family in the fall of 1912. Neurosurgery came to the Harvard Medical School in January 1913, when the PBBH finally opened its doors (Fig. 2).

Cushing was a graduate of Yale College and Harvard Medical School. He had spent 1 year as a house officer at the Massachusetts General Hospital and then 4 residency years at the Johns Hopkins Hospital, joining their surgical staff in 1901. Dr. Halsted, under whom Cushing worked, set the stage for the meticulous surgical technique for which Cushing became known and which was passed down through his trainees.

ABBREVIATIONS: BWH, Brigham and Women's Hospital; CSF, cerebrospinal fluid; PBBH, Peter Bent Brigham Hospital



By the time Cushing left Hopkins for the Brigham Hospital, he had 100 publications to his credit, 69 of which had to do with neurosurgery, neurology, or neuroendocrinology (56). The most significant of these were probably his 1912 monograph titled “The pituitary body and its disorders,” in which he described the condition of pituitary basophilism we now call Cushing’s disease (16); a 1910 article titled “Concerning a definite regulatory mechanism of the vasomotor center which controls blood pressure during cerebral compression,” which described the increase of blood pressure that follows increased intracranial pressure (the so-called “Cushing reflex”) (13); and a 1903 article that revolutionized anesthesia, titled “On routine determinations of arterial tension in operating room and clinic” (14).

The Chief of Medicine on the opening of the Peter Bent Brigham Hospital was Henry Christian, a physician who focused on cardiology. It was agreed at that time by the two chiefs that each would retire at age 63, which seemed a long way away at the time; Cushing was then only 43. He and Christian ran the hospital with Burt Wolbach, Chief of Pathology, and Carrie Hall, Chief of Nursing.

With Cushing on the surgical staff were several men who performed primarily general surgery: Drs. Cheever, Conrad, Jacobson, and, later, Dr. Eliot Cutler, who was to become Cushing’s successor. “Consultants” such as Dr. W.C. Quimby in Urology represented other surgical specialties.

Cushing had no neurosurgical residents as such, only carefully selected general surgery residents. The list of their names, as compiled by Dr. Edward Laws, sounds today like a “Who’s Who” of neurosurgery (Table 1) (54). Two were to remain as

important neurosurgical figures in Boston: Dr. Gil Horrax remained as the chief associate until Cushing’s retirement and then went to the Lahey Clinic and Deaconess Hospital, training Jim Poppen and others; and Dr. Franc Ingraham went across Shattuck Street and began pediatric neurosurgery at the adjacent Children’s Hospital.

During his 22 years at Brigham, Cushing observed, documented, and published an amazing quantity and variety of material (6, 55). Just before his arrival, he had written “Observations on the phenomenon of choked disc, with the role of decompressive craniotomy” (28) and published his technique of using silver “clips” for control of bleeding from vessels inaccessible to ligature (15). In 1914, he published his studies on the cerebrospinal fluid (CSF) pathways (17). In 1917 came the first article on acoustic tumors (18). In 1917, his section on fractures of the cranium appeared in Keene’s *Textbook of Surgery*, establishing neurosurgery as a surgical discipline (19).

In 1920, he published an article about a series of 332 gasserian ganglion operations for the treatment of trigeminal neuralgia (20). During the 1920s, he also described the use of radiation for treating malignant gliomas (68). In 1923, he published a clinical study of intracranial aneurysms (21), and the following year, he joined Percival Bailey in a study of medulloblastoma cerebelli, a common childhood tumor (27). That same year, with Loyal Davis, he reported three cases of choroid plexus papilloma (29). In 1925, he and Davis wrote about experiences with blood replacement during or after major intracranial operations (30). It is interesting that during one such intraoperative transfusion, the medical student beneath the drapes, pumping blood into the patient from the donor present in the same room, was drenched when the tubing exploded. The student was overheard by Cushing to mutter, “There must be a better way!” Cushing later called him into his office and challenged him to find such a way. The student was Carl Walter, and it was Walter who later developed the first blood bank in America at the Brigham, using sterile glass flasks to store and deliver donated blood. Ultimately, the system of plastic bags manufactured by his Fenwal Co. saved many lives in battlefield situations. Dr. Walter went on to join the surgical staff of Brigham, and many of us had the opportunity of taking his course on canine surgery and later working with him in the operating room and clinic of the hospital.

In 1925, Cushing wrote on chronic subdural fluid collections (22) and, in the same year, published his Pulitzer Prize-winning biography of Sir William Osler (23). In 1926, Cushing invited Dr. W.T. Bovie, a physicist with the Harvard Cancer Commission whose laboratory was at the nearby Huntington Hospital, to bring his homemade electrocoagulation unit to Brigham for a trial. The scene was more than electrifying, and it is well described by Cushing himself. A student blood donor fainted, and a new assistant left the operating room in horror (25, 40). However, the ability to stop bleeding with this device was a major advance in surgery, and Cushing began calling back all his patients known to have residual tumors that had previously been inoperable because of bleeding (25). Soon the Liebel Flarsheim Co. of Cincinnati made a model that could be mass-produced. The neurosurgical operative load increased in part

TABLE 1. Cushing's neurosurgical trainees at the Peter Bent Brigham Hospital (as collected by ER Laws, Jr [54])^a

Year(s) in training	Name	Career
1913	Charles E. Dowman, Jr.	Neurosurgery, Atlanta, GA
1913–1914	Charles Bagley, Jr.	Prof., Neurosurgery, Univ. of Maryland
1913–1914	Carl W. Rand	Prof., Neurosurgery, USC, Los Angeles
1913–1916	Gilbert Horrax	Prof., Neurosurgery, Lahey Clinic
1914–1917	Edward B. Towne	Prof., Surgery, Stanford University
1914–1917	Samuel C. Harvey	Prof., Surgery, Yale Univ.
1918–1919	Wilder Penfield	Prof., Neurosurgery, Montreal Neurol. Inst.
1918–1920	Howard W. Fleming	Neurosurgery, San Francisco, CA
1918–1920	Jay Keegan	Prof., Neurosurgery, Univ. of Nebraska
1919–1928	Percival Bailey	Prof., Neurosurgery, Univ. of Chicago
1920–1921	Charles E. Locke, Jr.	Chief, Neurosurgery, Cleveland Clinic
1921–1922	Paul Martin	Neurosurgery, Brussels, Belgium
1922–1923	Kenneth G. McKenzie	Prof., Surgery, Univ. of Toronto, Canada
1922–1925	William P. Van Wagenen	Prof., Neurosurgery, Univ. of Rochester
1923	J. Paterson Ross	Prof., Neurosurgery, St. Bart's, London, England
1923–1924	Norman M. Dott	Prof., Neurosurgery, Edinburgh, Scotland
1923–1924	Loyal Davis	Prof, Neurosurgery, Northwestern Univ.
1923–1925	R. Glen Spurling	Prof., Neurosurgery, Univ. of Louisville
1923–1926	Leo M. Davidoff	Prof., Neurosurgery, Mt. Sinai
1923–1928	Tracy J. Putnam	Prof., Neurosurgery, NY Neuroscience Institute
1925–1926	Francis C. Grant	Prof., Neurosurgery, Univ. of Pennsylvania
1925–1926	Jean Morelle	Neurosurgery, Louvain, France
1925–1927	A.J. McLean	Neurosurgery, Portland, OR
1925–1928	Franc D. Ingraham	Assoc. Prof., Neurosurgery, Peter Bent Brigham & Children's Hospital
1926–1927	William J. German	Prof., Neurosurgery, Yale Univ.
1926–1927	Sir Hugh W.B. Cairns	Prof., Neurosurgery, Oxford Univ.
1927	Edgar Fincher	Prof., Neurosurgery, Emory Clinic
1927–1928	Cobb Pilcher	Prof., Neurosurgery, Vanderbilt Univ.
1927–1929	Ignaz Otjenick	Neurosurgery, Amsterdam, The Netherlands
1927–1929	Richard Meagher	Neurosurgery, New York
1928–1929	W. Gayle Crutchfield	Prof., Neurosurgery, Univ. of Virginia
1928–1929	Dimitriu Bagdasar	Prof., Neurosurgery, Bucharest, Romania
1929–1930	Eric Oldberg	Prof., Neurosurgery, Univ. of Illinois
1930	Richard U. Light	Neurosurgery, Kalamazoo, MI
1930–1932	Bronson Ray	Prof., Neurosurgery, Cornell Univ.

^a Assoc., Association; Inst., Institution; Prof., professor; Univ., university

because of this Bovie apparatus. That same year, Cushing and Bailey presented their seminal classification of tumors of the glioma group (26), and beginning in 1927, with his observations on acromegaly, Cushing continued publications on the pituitary body and hypothalamus (24).

Cushing retired in 1932. It was only in 1938, well after his retirement, that perhaps his best known book, *Meningiomas*, was published (31). Dr. Louise Eisenhardt, a secretary and his

revered pathologist whom he had convinced to go medical school, was instrumental in finishing this work.

Throughout the Brigham years, Cushing established and maintained a new low in morbidity and mortality for neurosurgical cases, including an infection rate unparalleled even by today's standards (11). This was attributed to the open ventilation of the Brigham operating rooms and wards with many changes of air per hour, and Cushing's meticulous technique

and personal attention to details, not only of the surgery and postsurgical care, but also forbidding unnecessary talking in the operating room to reduce the danger of droplet infection of the open wound (77). After every operation, he retired to his dressing room and made sketches of the procedure. These can be found in his publications and were of great use to Mildred Coddington, his medical artist, who was not always successful in getting the view she wanted of what was going on at the depths of the wound. Black et al. (9) have presented Cushing's artistic abilities in a volume of his surgical art.

Cushing was not only a remarkable surgeon and scientist, but was also a dedicated teacher. He founded the Society of Neurological Surgeons in 1920 and taught many of the great neurosurgeons of his generation. In 1932, a group of neurosurgeons held their first meeting at the PBBH, and, with his permission and to his delight, named their new society the Harvey Cushing Society; this organization was subsequently renamed the American Association of Neurological Surgeons and is one of the major neurosurgical organizations in the world today. Michael Bliss, the recent Canadian biographer of Cushing, has claimed that Cushing helped to make the United States the world center of surgical excellence (11).

Cushing was also a great writer and artist; he wrote about his experiences in the First World War, about medicine as a career, and about his cases. He wrote 10 books, including a biography of William Osler that won him the Pulitzer Prize (11, 23). He was interested in the history of medicine and particularly in medical books. He was the fourth generation of physician bibliophiles in his family, and his interest grew as he came in contact with men such as Sir William Osler, William Welch, Howard Kelly, and S. Weir Mitchell (76). His wonderful collection now resides in the Sterling Medical Library at Yale Medical School, along with the collections of Arnold Klebs and John Fulton. It is remarkable how one man could do all these things and do them so well. He set a model of excellence in clinical surgery, research, and teaching that has become a measuring stick for later generations of surgeons (55).

THE EARLY INGRAHAM YEARS, 1929–1949

Before Cushing's arrival, general pediatric surgeons operated on an occasional myelomeningocele patient at Children's Hospital. After 1913, children in need of neurosurgical procedures were transferred to the PBBH for operation by Cushing and then returned to the Children's Hospital. As Cushing's reputation spread, such cases were referred directly to the Brigham as well. By 1926, Cushing had operated on 1108 brain tumor patients; 154 of those were under the age of 15, and 24 were under the age of 5. Recognizing the need for a subspecialty of pediatric neurosurgery, in 1929 Dr. Cushing asked Dr. Franc Ingraham to start a Department of Neurosurgery at Children's Hospital.

Dr. Ingraham was born in 1898 in Minneapolis, graduated from Harvard Medical School in 1925, and took his surgical residency at the PBBH (Fig. 3). He spent 1 year there under Cushing and then was sent to visit Walter Dandy at Johns



FIGURE 3. Franc D. Ingraham, student of Cushing's and founder of pediatric neurosurgery; the first neurosurgeon-in-chief at Children's Hospital Boston, beginning in 1929.

Hopkins Hospital. Dandy had been one of Cushing's House Officers but was at odds with Cushing at this time. Dandy would not allow Dr. Ingraham near the operating room, and Ingraham therefore returned to Boston early. After another year with Cushing, he went to Oxford, where he worked in Sherrington's laboratory with John Fulton, who was later to become his brother-in-law through marriage into the Wheatland family of Boston.

In 1929, Dr. Ingraham published three experimental papers on sympathectomy (36, 41, 64). He did no academic work for 9 years after

that. According to Mrs. Ingraham, this was a period when Dr. Ingraham was having a terrible time with asthma. He went to Baltimore to have a radical sinus exenteration, which left him anosmic, but not until the availability of penicillin and then of corticosteroids was he able to resume his normal pace of activity. There were many occasions when she was with him in hospitals, away from home, when he very nearly died. Questions were raised as to whether he should try to pursue his career, but he persisted.

Not unlike Dr. Cushing, Dr. Ingraham quickly acquired a following of men who either worked in the laboratory or as clinical fellows. Many of these went on to become well-known neurosurgeons in their own right: Eben Alexander, Orville Bailey, Bruce Humphreys, Hannibal Hamlin, John Lowrey, Donald Matson, Robert McLaurin, and others. With their help, Dr. Ingraham collected, studied, diagnosed, and operated on children with many of the conditions so commonly known to us now but which at that time were little known, belatedly recognized, and poorly treated: subdural hematoma, hydrocephalus, diastematomyelia, craniosynostosis, dermal sinus tract, choroid plexus papilloma, and other brain tumors (42, 45, 47, 50, 52). These men did their own diagnostic studies, followed the children postoperatively, and wrote and spoke well about what they were doing. It was a frontier in pediatric neurosurgery comparable to that which Harvey Cushing had enjoyed a generation before, during his Brigham years, and it made Children's Hospital Boston the founding institution for the entire subspecialty of pediatric neurosurgery.

In 1938, Dr. Ingraham began a reinvigorated career with an article on "Intraspinal tumors in infancy and childhood" (42). In 1943, he published the first of a series of 5 articles on "Spina bifida and cranium bifidum," a total of 546 cases, in the *New England Journal of Medicine*; these appeared later as a monograph (52). In 1944, Ingraham and Matson coauthored "Subdural hematoma in infancy" (45). This was a 41-page doc-

umentation of 147 patients, with detailed data on the cause, diagnostic steps, and therapy. The significance of vascularized membranes was stressed, as well as the constrictive effect of a less vascular inner membrane. The service continued to see about one case a year in which enormous effusions were present with thick, highly vascularized membranes that were producing high-protein fluid and could bleed spontaneously. Sometimes the situation could be corrected only by craniotomy and excision of the membranes (74).

During this period, there was also considerable activity in the Neurosurgical Research Laboratory, across the street in the Carnegie Building, where researchers were investigating the use of human fibrinogen and thrombin in the production of hemostatic agents and devices and attempting to prevent scarring, both in neurosurgery and general surgery (2–5, 43, 44, 48, 49).

Drs. Eben Alexander and Donald Matson were both in the Class of 1939 at Harvard Medical School. They took their surgical internship at the PBBH and then spent time with Dr. Ingraham at Children's Hospital until called to duty during World War II. Both returned to neurosurgery after the war. Dr. Alexander subsequently went on to the Bowman Gray School of Medicine in 1949, where he ultimately became head of the Department of Neurosurgery and a major contributor to American neurosurgery until his death in 2004.

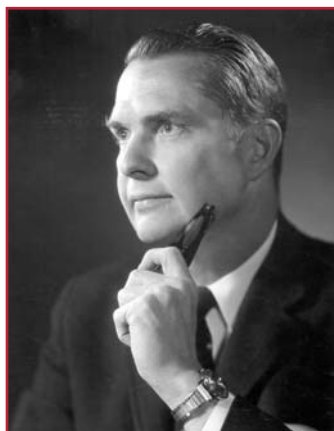


FIGURE 4. Donald Matson, the first Franc D. Ingraham Professor of Neurosurgery at the Harvard Medical School. He died prematurely of Creutzfeldt-Jakob disease, whose source was never found.

Dr. Matson (Fig. 4) was in the Army from 1943 to 1946. During that tour, his experiences prompted the Surgeon General to ask him to publish his work on missile injuries of the brain and spinal cord, now available as two monographs (59, 60). He returned to Dr. Ingraham in 1946 as a research fellow, alternating research and clinical duties with Dr. Alexander. Matson spent a year as resident at Duke under Barnes Woodhall and, with Guy Odom, as a fellow at the Lahey Clinic under James Poppen, and he then returned in 1948 to a partnership with Dr. Ingraham on the attending staffs of both Children's Hospital and PBBH.

THE PBBH AFTER CUSHING, 1933–1949

At the PBBH, Cushing reached the age of 63 in 1932 and agreed to retire as he had planned. The hospital named Eliot Cutler, one of his trainees, as his successor. Cushing returned from a trip to Europe to find that he had been moved out of his office, with quarters in a room in the surgical laboratory. He moved to Yale, largely at John Fulton's insistence, as the

Sterling Professor of History. Fulton later wrote a definitive biography of Cushing and remained one of his closest friends (35). The precise details of Cushing's departure are somewhat controversial (11), but it appears that he was not very happy with Harvard and the PBBH. He took with him his brain tumor specimens, pathology registry, books and journals, and his pathologist, Louise Eisenhardt. His patient notes have recently formed the source of a wonderful book by Cohen-Gadol and Spencer (12). During his final 7 years at Yale, he continued publishing, with his cardinal volume with Louise Eisenhardt, *Meningiomas*, as his greatest contribution during this time (31).

Remaining behind at the PBBH was Cushing's operating room orderly, Adolph Watska, who is well remembered by those who saw him walking his dachshunds on Shattuck Street and for his collection of cuckoo clocks and his Duesenberg convertible. Adolph appears with his white hat in a movie made by resident Richard Light about Cushing's 2000th brain tumor (AANS Archives). Adolph never wore a mask but did agree to pinch one between his lips for the movies, as he walked in to perform his customary, frequent, intraoperative swabbing of the floor. He worked in the operating room until the 1950s. In 1952, Adolph died of a massive myocardial infarct as he pushed a dental patient into Cushing's old galleried Operating Room 2. One of us (JS) heard the crash. Attempts at resuscitation by all present were in vain.

Cushing also left behind Mildred Codding, his medical artist since 1930. She had trained under artist Max Brodel at Hopkins and had come to Boston at Cushing's request. After Cushing left, she did major work for Cutler and other members of the Harvard surgical staffs at Brigham and elsewhere in Boston. Her last work, long after her "retirement," was *An Atlas of Pediatric Neurosurgical Operations*, published with Drs. John Shillito and Donald Matson in 1982 (74). After that work was completed, she retired to her home on Cape Cod, where she enjoyed sketching the surroundings and exhibiting at local galleries. She died there in August 1991.

After Cutler's appointment, the old neurosurgical team dissolved and moved elsewhere, and the caseload of neurosurgical patients dropped precipitously. Cutler felt that he could operate in any body cavity, but he was particularly interested in cardiac surgery. Dr. Ingraham provided neurosurgical services for Brigham as well as Children's Hospital. In part, this was because asthma had prevented him from serving in the war, which involved with many other PBBH surgeons from the hospital, including Eliot Cutler, who became a four-star general. World War II thus began the tradition of a service primarily run through the Children's Hospital that served both institutions.

Eliot Cutler succumbed to prostate cancer in 1948, and shortly thereafter Francis D. Moore was appointed as his successor as surgeon-in-chief at PBBH. Moore was happy to have his classmate, Donald Matson, and Dr. Ingraham become the neurosurgeons for Brigham, but there was no real neurosurgical group at PBBH. Most of the caseload of the combined service was at Children's Hospital, and that at Brigham was never very large.

This situation allowed for the strong growth of other neurosurgical services in Boston, including the Lahey Clinic under Dr. Gil Horrax and his student Dr. James Poppen, and the Massachusetts General Hospital under Dr. J.C. White and, later, Dr. William Sweet.

Children's Hospital and PBBH were covered by one neurosurgical service housed at Children's Hospital, and the residency program was centered there. Until the 1990s, when the greatly increased caseload made it impractical, the attending and resident staffs made daily rounds, operated, and were on call at both hospitals.

TABLE 2. Alumni of the service, 1939–2007

Name	Year(s) of residency or fellowship
Donald D. Matson, M.D.	1939–1942, 1948–1969
Eben Alexander, Jr., M.D.	1939–1942, 1946–1947
Albert Farley, M.D.	1949–1950
Edgar A. Bering, M.D.	1949–1952
Anthony Susen, M.D.	1949–1953
Robert L. McLaurin, M.D.	1950–1951
E. Bruce Hendrick, M.D.	1953–1954
Hal Tucker, M.D.	1954–1955
Fred D. Fowler, M.D.	1955–1956
John Shillito, Jr., M.D.	1955–1957
Ernest S. Matthews, M.D.	1956–1959
Walter C. Cotter, M.D.	1957–1958
Robert W. Schick, M.D.	1958–1960
John T. Garner, M.D.	1959–1962
Francis X. Rockett, M.D.	1960–1964
August W. Geise, M.D.	1961
David L. Kelly, M.D.	1962–1963
Erich S. Wisiol, M.D.	1962–1963
Larry K. Page, M.D.	1962–1966
Ronald Birkenfeld, M.D.	1963
Michael J. Jerva, M.D.	1963–1965
Edward L. Katz, M.D.	1963–1967
Alan D. Rosenthal, M.D.	1964–1968
Donlin M. Long, M.D., Ph.D.	1965
Howard M. Eisenberg, M.D.	1966–1970
John M. Tew, M.D.	1967–1968
Edwin G. Fischer, M.D.	1967–1971
A. Loren Amacher, M.D.	1968–1969
Robin I. Davidson, M.D.	1968–1971
J. Gordon McComb, M.D.	1969–1973
John W. Walsh, M.D., Ph.D.	1970–1974
James E. McLennan, M.D.	1970–1975
J. Parker Mickle, M.D.	1972–1976
Thomas Arkins, M.D.	1974–1978
Dennis L. Johnson, M.D.	1975–1977
Joe Ordia, M.D.	1975–1979

INGRAHAM, MATSON, AND SHILLITO, 1949–1971

From 1949 to 1971, pediatric neurosurgery really began to flourish at Children's Hospital while there was relatively little neurosurgical activity at the PBBH. Ingraham and Matson and their residents and fellows studied series of patients with all known conditions amenable to neurosurgery and brought them to the attention of the general practitioners and pediatricians to facilitate earlier recognition and proper treatment. These experiences were collected in the text, *Neurosurgery of Infancy and*

TABLE 2. Continued

Name	Year(s) of residency or fellowship
Clarence S. Greene, M.D.	1977–1980
David C.Y. Kung, M.D.	1979–1980
Robert M. Beatty, M.D.	1979–1984
Stephen Ofori-Kwakye, M.D.	1980–1984
Gregory W. Hornig, M.D.	1981–1986
John R. Adler, M.D.	1982–1987
Luis M. Zavala-Roman, M.D.	1983–1985
Robert Peterson, M.D.	1983–1988
Richard C. Ellenbogen, M.D.	1984–1989
Clifford M. Gall, M.D.	1986–1991
Matthew R. Moore, M.D.	1987–1992
Sumeer Sathi, M.D.	1988–1995
Philip A. Starr, M.D., Ph.D.	1989–1995
Patrick A. Juneau III, M.D.	1990–1992
Simcha J. Weller, M.D.	1990–1996
P. Langham Gleason, M.D.	1991–1995
Faith Barnett, M.D., Ph.D.	1991–1996
Thomas Moriarty, M.D., Ph.D.	1991–1997
Marc S. Schwartz, M.D.	1992–1997
Craig van Horne, M.D., Ph.D.	1992–1998
John K. Park, M.D., Ph.D.	1993–1998
Kai U. Frerichs, M.D., Ph.D.	1993–2000
Subu N. Magge, M.D.	1993–2000
Steven P. Leon, M.D.	1994–2000
Adel Malek, M.D., Ph.D.	1994–2001
Claudia Martin M.D.	1996–2000
Peng (Roc) Chen, M.D.	1996–2003
Deepa Soni, M.D.	1996–2006
Kadir Erkmen, M.D.	1997–2004
Chima O. Ohaegbulam, M.D.	1998–2005
Stephanie Greene, M.D.	2000–2004
Alexandra J. Golby, M.D.	2001–2002
Ian T. Johnson, M.D.	2001–2006
Bryan Figueroa	2002–2007
Jon Slotkin	2002–2007

Childhood, first published in 1953 (46). Also in 1953, the service developed a residency program centered at Children's Hospital. The list of residents and visiting fellows is long and noteworthy (Table 2) and, not unlike Cushing's, reads like a "Who's Who" of neurosurgery here and abroad. At the 50th anniversary of the American Board of Neurological Surgery in 1980, the Children's and Brigham service had more Board members than any other center. Through their many friends in neurosurgical circles, Ingraham and Matson arranged profitable exchanges with other training programs, taking on residents from elsewhere who needed some pediatric experience, and sending one of their own men away for a year to augment the adult experience at Brigham. Trainees such as Bob McLaurin, Bruce Hendrick, Hal Tucker, Fred Fowler, Joseph Galicich, David Kelly, Alan Rosenthal, Donlin Long, Howard Eisenberg, John Tew, Gordon McComb, Parker Mickle, Dennis Johnson, John Adler, Richard Ellenbogen, and others went on to become heads of neurosurgical training programs, chiefs of departments, or pediatric neurosurgeons in their communities. There was later a regular collaboration with the Massachusetts General Hospital in Boston, from which neurosurgical residents in that program came to Children's for their pediatric experience. One of us (JS) started as a general surgical resident under Dr. Francis Moore in 1952 (Fig. 5). He became a neurosurgical resident in 1955 and, after a year in Memphis with Dr. Francis Murphey, was asked to join Dr. Ingraham's neurosurgical staff in 1958, where he remained until retirement in 1995.

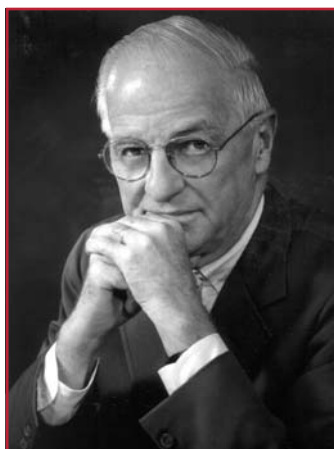


FIGURE 5. Dr. John Shillito, interim neurosurgeon-in-chief and widely respected pediatric neurosurgeon

During the post-war period and into the 1950s, a major challenge for neurosurgery was that there was no completely successful treatment for hydrocephalus. Don Matson revived the idea of shunting CSF into the urinary bladder (57). By the early 1950s, he had developed the lumboureteral shunt, connecting the lumbar subarachnoid space to the urinary tract (58). He found that neither the shunt nor the ipsilateral kidney functioned adequately, but when the kidney was sacrificed, the shunt would work well. There were no alternative shunts, and untreated hydrocephalus was

then, as now, a potentially fatal condition; such heroics were justifiable at the time. Matson's residents learned how to remove a child's kidney, prepare the ureter, bend a length of polyethylene tubing in boiling water, and secure it in the subarachnoid space, tunneling it through the paraspinal muscles, to which the waiting ureter was stitched in such a fashion as to allow the shunt to move with the child's growth. The only valve was the natural one at the ureterovesical junction.

Bladder catheterization was forbidden from then on, lest retrograde infection occur. If a small child became dehydrated from unrelated causes, the remaining kidney could restrict fluid loss, but the continuing loss of CSF would lead to rapid and serious depletion if not immediately treated with intravenous hydration, and some children were lost because of inadequate rapid fluid replacement. If the child's hydrocephalus was not of the "communicating" variety, with free flow from ventricles to spinal subarachnoid space, we could make it so by creating a ventriculocervical shunt and then a lumboureteral shunt; the so-called "leapfrog" shunt, which obviated the need for lengthening with a child's growth, or simply by shunting from ventricle directly to ureter.

The lumboureteral shunt indirectly led to two Nobel Prizes for Children's and Brigham scientists. When John Enders, a Children's Hospital investigator, was trying to grow human poliovirus to create a vaccine, he found that it was incredibly delicate. There was no good tissue for it until he found that kidney tissue from shunted patients allowed the virus to grow; Enders received the Nobel Prize in 1954 for the discoveries that led to polio vaccination. After the first successful kidney transplantation by Dr. Joseph Murray at Brigham Hospital in 1954, the need for kidneys became demanding. Several of those removed from older children for the Matson shunt, as it came to be called, were sent from the Children's operating room to the team waiting at the Brigham, for successful transplantation into an appropriate recipient. In 1990, Dr. Murray shared a Nobel Prize with Dr. E. Donnall Thomas of Seattle for work on organ transplantation.

Some of these lumboureteral shunts worked for many years, occasionally presenting problems caused by downward herniation of the cerebellar tonsils (34). By this time, other techniques had been improved, and revision was possible, although tricky, because of ventricles that had become tiny as a result of prolonged, successful shunting. While others around the country were developing valved shunt systems, Matson collaborated with Vannevar Bush of the Massachusetts Institute of Technology in the development of a one-way valve for hydrocephalus. This consisted of a slim, gold-plated device with a magnetically seated ball valve for insertion between a lateral ventricle and the bloodstream, usually via the jugular vein. The pressure maintained by the system could be established at operation by passing the valve through a strong magnetic field and, by trial and error, achieving the amount of resistance desired. This technique was not in use for very long. As with many of our shunts in those days, the problem often lay with the stiffness of the polyethylene tubing and its propensity to cause clot formation in the bloodstream. The advent of Silastic tubing (Dow Corning, Auburn, MI) made a huge difference.

A second major contribution of Matson and the Children's group was in craniopharyngioma surgery. Craniopharyngiomas of childhood presented an insurmountable problem for the surgeon until the use of corticosteroids made operation feasible. Ingraham, Matson, and McLaurin reported the use of cortisone and adrenocorticotrophic hormone in such surgery in 1952 (51); they had begun using corticosteroids in 1950. Matson's interest attracted many such cases, and he soon learned how difficult

and risky reoperation was after subtotal removal performed elsewhere. For that reason, he became a strong advocate of total removal at the first operation, although advising that the decision regarding the feasibility of such an approach could only be evaluated at operation (51, 61, 62).

With surgeon Andrew Jessiman and others at Brigham, Matson performed many total hypophysectomies in an effort to control breast cancer and its pain (53). Residents remember long delays during surgery when blood levels for circulating hormones were repeatedly checked at various stages of the procedure for evidence of residual function (33).

For repair of cranial defects, the technique of tantalum cranioplasty was frequently employed (39), and, as many residents have never forgotten, part of the evening before such a procedure was spent pounding out a sheet of tantalum on the positive and negative steel molds of a 12-year-old girl's cranium, fitting the contour to the region of the patient's cranium to be repaired. At surgery, a bevel was created around the bony defect, onto which the plate was laid; it was held in place by tantalum glazier's points, which were seated into the edge of the bevel. These were long, tedious procedures, with many punctured gloves, usually worn doubled.

Craniosynostosis was an early interest of the department. In 1947, Ingraham, Matson, and Alexander published the technique of applying polyethylene film to craniectomy margins to delay fusion of the openings by new bone formation from the dura (50). Early operation was always advised to take advantage of the rapid growth of the brain during the first year of life (47).

In the mid-1960s, the late plastic surgeon Paul Tessier of Paris visited our hospitals as the guest of Dr. Joseph Murray, then Chief of Plastic Surgery at Brigham and Children's Hospital, to demonstrate his techniques for the correction of congenital craniofacial anomalies. Our neurosurgical team would collaborate by starting the craniotomy, exposing the brain, and then turning over the procedure to the plastic surgical team. About 12 hours later, we would be called back to help put things together again. There were some striking results, but in the early cases, the long exposures of the intracranial contents occasionally led to severe edema, and retraction of the brain sometimes led to late intracortical hemorrhages (72).

IMAGING

Until the 1970s, neurosurgical diagnostic techniques were invasive, uncomfortable, or dangerous for the patient, and they left much to be desired in both localization and identification of the lesion. Cerebral arteriography was carried out via percutaneous carotid puncture and was initially limited to one exposure per injection. Then homemade multiple-cassette holders were improvised, and one could hear the call "Pull!!" as the operator directed a technician to remove the first and then subsequent film holders. Angiograms were done in adults under local anesthesia in most cases; children required general anesthesia.

Air studies included the pneumoencephalogram. This entailed removing most or all of a patient's CSF through a lum-

bar puncture while the patient was supported in a sitting position, and substituting either air, or preferably oxygen, to fill the ventricles and subarachnoid spaces to provide contrast with the surroundings. Getting the gas into the ventricular system was tricky, and gas filling the subarachnoid spaces could be accompanied by intense headache. Films were then made with the patient in various positions to coax the gas into the desired portion of the ventricular system. It was a nasty procedure at best and could not be used safely in the presence of an intracranial mass lesion, for removal of supporting CSF could permit dangerous shift of the intracranial contents. In such cases, air could be placed directly into the ventricles through a burr hole or, in infants, through a percutaneous puncture at the corner of a patent anterior fontanelle, just far enough from the midline to avoid hitting a vein bridging from the cortex to the sagittal sinus. This was easy if hydrocephalus was present, but because the possibility of an obstructing lesion in the ventricular system, or impinging upon it, could not always be appreciated before the study, preparations were frequently made for surgery to follow immediately after the completion of the study, should the offending tumor be found. This compressed diagnostics and operation into the same day, which could be an anxious time for all concerned.

The electroencephalogram was a valuable tool, and in some cases, it obviated the need for such contrast studies. Dr. Alexander Nadas, the Chief of Cardiology at Children's Hospital, would often call the neurosurgeons to state that he had a patient with cyanotic congenital heart disease who had developed neurological signs and whose electroencephalogram showed phase reversal in such-and-such an area. Would the neurosurgical staff please come and drain the abscess? Almost without exception, Dr. Nadas was right, and placement of a burr hole over the site so indicated would allow aspiration of many milliliters of purulent material. Various materials might be inserted into the cavity to watch it shrink with time and to reaspirate as necessary. Depending on its location, its capsule might later be excised (63).

If a lesion was calcified, it was possible to define it more sharply by a technique called lateral tomography, in which the radiating source and the film were in motion during exposure. All other objects were blurred except those exactly at the fulcrum of the move. By moving that point from left to right through a suspect area, much greater definition of fine objects was obtained. This was particularly useful when looking for residual calcification, such as in a craniopharyngioma, which was easily masked by overlying bony prominences at the base of the cranium.

Owing to the often vague localization of intracranial mass lesions, neurosurgeons were trained to make very wide exposures of the area involved so that they could examine the surface of the brain carefully, as well as above and below it, palpating suspicious gyri until they located the target as much by touch as by vision.

Spinal problems were localized by iodophenylundecylic acid (Pantopaque) myelography, the oily dye necessitating insertion via a large-bore lumbar puncture needle. Tilting the patient

up and down rolled the material throughout the spinal canal. At the completion of the study, efforts were made to remove as much of the dye as possible, for it could become sequestered and cause inflammation later. This naturally removed a good bit of CSF as well, and that, coupled with the puncture hole from a no. 18 needle, often led to headache prolonged by continued seepage of CSF after removal of the needle.

In those early years, there were no neuroradiologists, and the residents in neurosurgery, or occasionally in neurology, were expected to carry out these procedures. Following the tenets outlined by Cushing, Drs. Ingraham and Matson evaluated all such studies, and trained their residents to do so. Diagnostic studies were reviewed by the team on the day they were made. Weekly teaching sessions included not only radiology, which was supervised by the attending staff, but also electroencephalogram, neurology, or pathology. With the help of staff members in each field, such as general radiologists Merrill Sosman and Ed Neuhauser, trainees learned to make their own diagnoses and to formulate a plan of action.

The x-ray conferences at Children's Hospital were hosted by Miss Mehitabel ("Hetty") Millar, who provided tea and cookies served on "astrocyte" china. For years, the astrocyte was Dr. Ingraham's trademark. The design was on office china, on the neckties given graduating residents, and on gifts from the Chief at special occasions. Hetty served as the department secretary and ultimate source of authority during the reigns of Drs. Ingraham and Matson. She "broke in" Dr. Shillito when he arrived on the staff in 1958 and later remained as his loyal secretary until she retired in the 1970s.

Soon neuroradiologists appeared on the scene at both hospitals to perform and interpret imaging procedures, not without reluctance on the part of some of the attending staff. Dr. Roy Strand joined the Children's Hospital staff and spent many years working with the group, to be joined later by Dr. Patrick Barnes. At the PBBH, Dr. Herbert Abrams, an accomplished arteriographer, took over the department. Later, Dr. Calvin Rumbaugh and Dr. Amir Zamani and their teams educated the neurosurgeons in radiology and served them well.

In the early 1970s, brain imaging began to allow major changes in neurosurgery. The first EMI scanner (made by Electric and Musical Industries, Ltd., London, England, producer of the Beatles' records) arrived at Children's Hospital. This first computed axial tomography, or "CAT," scanner could be used for cranial studies only, and water bags had to be applied to each side of a patient's head to permit better visualization. The device was given space in the nearby Carnegie Laboratory Building, across the street from the hospital, although connected by a bridge. If the need for a scan arose after hours, residents had to trundle the patient down by elevator to the second-story ramp, braking hard as the litter sped downhill to the other building, then ride up on another elevator to the fourth floor. Taking a child to have a "CAT scan" proved anxiety-producing at any time of day, and the name was shortened to "CT" quite soon.

Later equipment became so much more accurate and easier to use that the demand was extremely high. The initial expense

of the scanners and the high charge for each study prompted the state to step in, and for many months, we were required to fill out long forms, testifying to the reasons for use of the scanner, and what previous, less expensive steps, had been taken. Finally, that chore went away. Scanners could soon handle other areas of the body, even full body width. A new temporary problem arose. The general radiologists decided that the orientation of the scan should be as if they were looking from below. Ever since the first cranial scan was obtained, the orientation had been the opposite, as though looking from the top of the head, which was the neurosurgeon's point of view. Some confusion arose, with many heated arguments at national meetings. Ultimately, the general radiologists view prevailed, and left became right!

After years of improvement in computed tomographic scanners, the first nuclear magnetic resonance scanner appeared. Again, there was a naming problem. The term "nuclear" implied something radioactive, and the "NMR" soon became the "MRI," for magnetic resonance imaging. Neurosurgeons learned to view all these studies, but usually now with a radiologist's help, because the complexity of the scanning techniques required special knowledge. Brain imaging, however, became an important tool at these hospitals, a tradition that has been amplified substantially in the past 20 years with the surgical planning laboratory at Brigham Women's Hospital.

During these busy years, many men and women from abroad came either as visitors, simply to observe, or as fellows or residents. Many did laboratory or clinical research, as well as helping with the clinical load. Some of their names appear as coauthors of many publications during this period: Hiroshi Araki, Roberto Aranabar, Nurhan Avman, Jorge Ayala, Jean-Paul Chodkiewicz, Gustavo Gutniski, Bjarni Hahnson, Kaarlo Heiskanen, Karl Hovind, Werner Isler, Kimjuro Iwata, Takeo Kuwabara, Gregorio Mariscal, Shuro Nishimura, Khosrov Parsa, Osamu Sato, Peter Schurr, Sabina Strich, Noe Vargas, and many others.

In the 1960s, major changes occurred in the service. Dr. Ingraham retired in 1964, and died of a myocardial infarction in 1965. Dr. Matson became the Chief of Neurosurgery and the first Ingraham Professor of Neurosurgery at the Harvard Medical School. Neurosurgery was a department at Children's Hospital and a division of surgery at Brigham. Larry Page, a resident who graduated from the program in 1964, joined the attending staff from 1965 to 1970, and in addition to duties in Boston, assumed care of neurosurgical patients at Beverly Hospital, where Dr. Ingraham had for years been consultant, since he spent summers in nearby Manchester. The other faculty helped out there as the need arose. In 1964, Dr. Francis Rockett, a former graduate of the program, joined the staff as consultant, with his primary efforts at Newton Wellesley Hospital.

In 1967, the service was honored by the election of Dr. Matson as President-Elect of the Harvey Cushing Society (which had become the American Association of Neurological Surgeons), and Dr. Shillito as President-Elect of the Congress of Neurological Surgeons. Shortly thereafter, Dr. Matson began

noticing unusual symptoms: twitching of the legs, loss of control of the volume of his voice, and unsteadiness. When he walked to the podium to accept his new post, some of his friends noted this ataxia, and ribbed him later about too much celebrating. There continued a steady progression of symptoms, which eluded diagnosis, being ascribed to an unusual form of arteritis. So determined were the staff to rule out something correctible, such as a cerebellar tumor, that we put the poor man through a most uncomfortable air study, which was not helpful. He gradually lost his ability to hear and speak, developed multiple cranial nerve signs, and ultimately died at the PBBH in May 1969 of brainstem failure. Autopsy showed areas of softening and infarction of the brain, and some minor arteritis.

Only many months later was a consultation sent to Dr. Carlton Gadjusek, then of the National Institutes of Health, National Institute of Neurological Diseases and Blindness, an expert in diseases such as scrapie in sheep and kuru in cannibalistic tribes of the South Pacific. He came to the Brigham, took some of Matson's fixed and frozen brain tissue (38), and after passage of the tissue through three primates, twice, established the diagnosis of Creutzfeldt-Jakob disease (37). At the time, this was thought to be transmissible only by inoculation. However, a wide search of hospital records and Dr. Matson's travel contacts, led vigorously by his classmate, Dr. Francis Moore, showed no apparent source.

Dr. Matson never saw the printed version of the second edition of *Neurosurgery of Infancy and Childhood*, which he and many associates at Children's Hospital, especially Dr. Howard Eisenberg, had worked so hard to complete. The book was published later in 1969, after Matson's death (61).

Dr. Shillito assumed the role of Acting Chief of Neurosurgery and, with Dr. Page's help, took care of the patients at Children's and PBBH, as well as covering the small service at the Beverly Hospital. The group also covered the State Cancer Hospital at Pondville, MA, and the West Roxbury Veterans Administrations Hospital. Through the latter relationship, Dr. Shillito was asked to provide an academic connection for the neurosurgical service at the Boston Veterans Administration Hospital on the retirement from Tufts of Dr. Bertram Selverstone, so that the Tufts residency program could continue. A year or more later, on the appointment of Dr. Ben Stein as Dr. Selverstone's successor, the Boston Veterans Administration neurosurgical service was returned to Tufts. Help was obtained from another of our graduates, Dr. Edward Katz, who joined the service in 1969, and from Dr. William Heisey. All of us managed to cover all these bases while the search went on for Dr. Matson's successor.

Dr. Shillito made several contributions to pediatric and adult neurosurgery during his time at Children's and Brigham Hospitals. He did intracranial embolectomies on adults and children who had developed their symptoms while in the hospital (70). He described a syndrome of carotid arteritis in children and proposed a possible causative mechanism (69). With Dr. Matson, he reviewed 519 cases of craniosynostosis and found that frequently there occurred new suture, normal in

appearance but occurring in an unnatural location (71, 73). Dr. Matson asked Dr. Shillito if he would finish the work he had begun with Mildred Coddington—an atlas of operative procedures. Ms. Coddington and Dr. Shillito decided to limit the work to his pediatric operations, and the atlas was published 12 years later (74).

DR. KEASLEY WELCH, 1971–1985

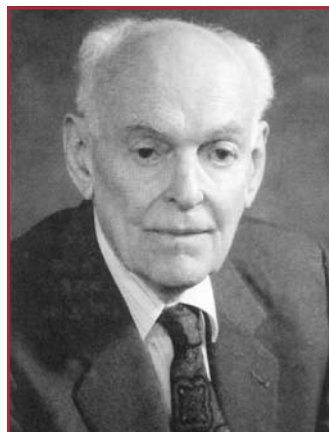


FIGURE 6. Dr. Keasley Welch, the second Franc D. Ingraham Professor of Neurosurgery at the Harvard Medical School. He was chair of the service from 1971 to 1986.

In 1970, Dr. Keasley Welch of Denver, CO, was appointed the second Franc D. Ingraham Professor of Neurosurgery and neurosurgeon-in-chief at Children's Hospital; he came to Boston in 1971 (Fig. 6). He brought with him Dr. Ken Winston, who had been his chief resident in Denver, and soon added Dr. Garry Fischer, a former Children's Hospital resident. Dr. Page soon moved to Miami, where he continued his practice, principally in pediatric neurosurgery. Dr. Welch's special interest was in hydrocephalus, and most of his publications during his tenure were on that topic. Among

them was a classic work, *The Physiology and Pathophysiology of the Cerebrospinal Fluid*, with Dr. Hugh Davson of Cambridge University in England (32).

In the early 1980s, the PBBH was amalgamated into an affiliation with the Robert Breck Brigham Hospital, an arthritis and orthopedic center nearby, the Boston Lying-In Hospital, and the Parkway Divisions of the Boston Women's Hospital. The new hospital was first called the Affiliated Hospitals Center but was later called the Brigham and Women's Hospital, established in 1980. It was built just across the street from the Bader 3 neurosurgery office windows at Children's Hospital. This tower was completed and connected to the "Pike," which ran the length of the old PBBH, as well as to Children's Hospital by a bridge; it was the first step of a rebuilding program that has included a new research building (the Thorn building) in 1990, a new building for Women and Newborns (the Connors Center) in 2000, and a replacement of the old wards with modern outpatient and diagnostic services. The hospital is now continuing to expand with the creation of a cardiovascular building this year.

The Children's Hospital opened a beautiful new in-patient facility adjacent to its existing structures in 1988, and our neurosurgical ward was moved from the adjacent "Division 33," just down the hall from our office suite, to much more functional quarters in a much less convenient location. The office suite itself was also moved recently.

DR. PETER BLACK, 1987–2007

Dr. Welch retired as Chief of Neurosurgery at the two hospitals in 1985, in poor health because of emphysema. Dr. Peter Black, who had rotated through the Children's service during his Massachusetts General Hospital training and taken a fellowship year in hydrocephalus physiology with Dr. Welch and Dr. Antonio Lorenzo, was selected as the third Franc D. Ingraham Professor of Neurosurgery at Harvard Medical School, Chairman of the Department of Neurosurgery at the Children's Hospital, and Neurosurgeon-in-Chief at both Children's Hospital and Brigham and Women's Hospital (Fig. 7). Dr. Black had a particular interest in brain tumors in children and adults; during his tenure, he and his laboratory and associates published over 500 original papers and 10 books. In 2006, he completed his 5000th brain tumor operation.



FIGURE 7. Dr. Peter Black, the third Franc D. Ingraham Professor of Neurosurgery at the Harvard Medical School. He chaired the service from 1987 to 2007, especially building the Brigham and Women's Hospital (BWH) department.

As part of building the service in the first 2 years, Dr. Black added to the staff Dr. Eben Alexander III, son of Dr. Eben Alexander, Jr., and Dr. R. Michael Scott, the son of Dr. Michael Scott, Chair of Neurosurgery at Temple University, who was recruited from Tufts to Harvard as Director of Clinical Neurosurgery at Children's Hospital. Soon after, there were further additions: Dr. Philip Stieg, who trained at Southwestern University in Dallas, for vascular neurosurgery; Dr. Liliana Goumnerova of the Hospital for Sick Children in Toronto for pediatric tumor neurosurgery; and Dr. Joseph Madsen from the Massachusetts General Hospital for pediatric neurosurgery and epilepsy surgery. Dr. Shillito stayed on. Dr. Winston went to Denver Children's Hospital to become Chief of Pediatric Neurosurgery, and Dr. Fischer became Chief of Neurosurgery at the New England Deaconess Hospital until his recent retirement.

Dr. Shillito retired in 1995, and a Shillito Pediatric Fellowship was created and announced at a special affair, which many associates and former patients attended during the Congress of Neurological Surgeons meeting in Boston in 2000. Since then, a graduate neurosurgeon is selected every year by a national search to spend a year as the Shillito Junior Staff Associate at Children's Hospital.

In 1993, Dr. Eugene Rossitch from Duke University joined the staff to perform complex spine surgery. He was a great surgeon and historian of medicine, coauthoring several publications with other members of the staff (8, 65–67). Tragically, he drowned while rescuing his 8-year-old son from the surf in Florida in November 1994. To carry on complex spine instru-

mentation, Dr. Eric Woodard came on staff from private practice in 1996, having trained at Emory University. Under his guidance, the spine program grew considerably, with over 350 cases a year. Dr. Robert Friedlander was recruited from the Massachusetts General Hospital in 1999 to perform vascular neurosurgery and laboratory work in apoptosis. Dr. Kai Frerichs, a neurosurgeon who trained in endovascular neurosurgery, became a member of the cerebrovascular team in 2001.

In 2000, neurosurgery became a department at Brigham and Women's Hospital, allowing the development of tumor/functional, cerebrovascular, and spine sections within it. By 2005, the tumor/functional section had four faculty members: Dr. Black; Dr. Craig van Horne, who did movement disorder surgery; Dr. Alexandra Golby from Stanford, who did cortical mapping and epilepsy; and Dr. Mark Johnson from the University of Washington in Seattle, who did brain tumor and pain work. The spine section had three surgeons: Dr. Eric Woodard, Dr. Marc Eichler from Washington University in St. Louis, and Dr. Sagun Tuli from the University of Toronto. The vascular section had four members: Dr. Arthur Day from Gainesville, Dr. Robert Friedlander, Dr. Dong Kim, and Dr. Kai Frerichs. When Dr. Stieg left to become Chief of Neurosurgery at Cornell in 2001, Dr. Arthur Day was recruited to head the vascular and residency programs. He significantly grew the stroke practice by creating a multidisciplinary group that included interventional radiology within neurosurgery. In 2007, he became chief of the service. Dr. Dong Kim from the University of Texas in Houston joined the service in 2003 to develop the neuroscience intensive care unit, again creating a multidisciplinary group to care for acutely ill patients. Several other neurosurgeons spent part of their early postgraduate development with the service, including Dr. John Park, now the Director of Neurosurgical Oncology at the National Institutes of Health, and Drs. Nicole Moayeri and Kim Harbaugh, both of whom later moved with their families to other sites. In 2005, Dr. Elizabeth Claus joined our tumor section, and in 2006, Dr. William Gormley joined the intensive care unit group.

The pediatric group under Dr. Scott grew during this time to include Dr. Liliana Goumnerova, Dr. Joseph Madsen, Dr. Mark Proctor, Dr. Peter Black, and, most recently, Dr. Ed Smith. With the growth in caseload and administrative and regulatory responsibilities, it was almost impossible to continue the tradition of one clinical service at both hospitals, although the academic initiatives continue to be merged. In 2004, the services divided, with separate neurosurgeons-in-chief. Dr. Scott became interim and then permanent Neurosurgeon-in-Chief at Children's Hospital and was also the first incumbent in a Children's Hospital chair named for the Fellows family.

The years 1987 to 2007 had steady expansion of the BWH service (Fig. 10). Faculty members served on national and international groups in leadership roles, including the Congress of Neurological Surgeons, American Association of Neurological Surgeons, Society of University Neurosurgeons, Society of Neurosurgeons, World Federation of Neurological Societies, American Board of Neurological Surgery, Neurosurgical Society of America, American Academy of Neurological Surgery, and Residency Review Committee. The volume of



FIGURE 8. The intraoperative magnetic resonance imaging device at BWH on the occasion of the 1000th craniotomy. Beside Dr. Black are Dr. Ferenc Jolesz, initiator of the GE Signa concept, and Dr. Amir Zamani, Chief of Neuroradiology at BWH.



FIGURE 9. The neuroscience group in front of the old PBBH entrance in 2005.

clinical cases grew, especially in brain tumors, cerebrovascular disease, pediatric neurosurgery, and spine.

Several programs were particularly important:

1) The intraoperative imaging program with Dr. Ferenc Jolesz, Dr. Peter Black, Dr. Eben Alexander, Dr. Phil Stieg, and many others. Dr. Black carried out the world's first resection of a brain tumor with real-time intraoperative imaging in 1995; subsequently, more than 1000 craniotomies were performed in the GE Signa System (GE Healthcare, Milwaukee, WI) (Fig. 8) (10).

2) The linear accelerator radiosurgery program started by Ken Winston, Wendell Lutz, and Robert Saunders and carried on by Jay Loeffler of radiation oncology, Eben Alexander III,



FIGURE 10. BWH today. New facilities have replaced the old wards, and patient towers for women's health, cardiac disease, and general care dominate the present environment.

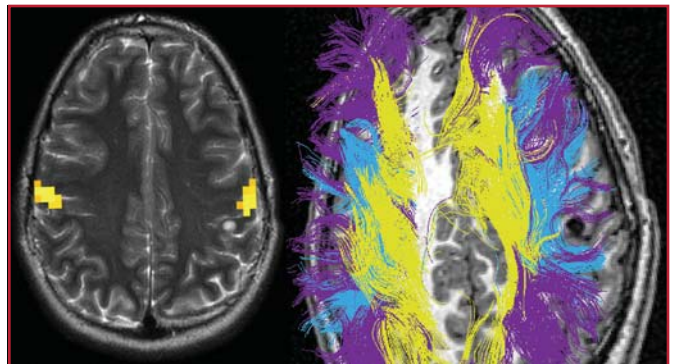


FIGURE 11. An example of functional magnetic resonance imaging and diffusion tensor imaging from the Golby laboratory in conjunction with the surgical planning laboratory under Ron Kikinis.

Peter Black, and others. The program included the world's first dedicated radiosurgery linear accelerator for radiosurgery and the first stereotactic radiotherapy; it developed many principles now used throughout the world.

3) Multidisciplinary programs in adult and pediatric tumor surgery, cerebrovascular disorders, spine surgery, epilepsy surgery in children and adults, and hydrocephalus. These became part of a neuroscience initiative whose 2005 members are pictured in Figure 9.

4) Collaboration with the surgical planning laboratory under Ron Kikinis, which pioneered many postprocessing magnetic resonance imaging capabilities, including segmentation, diffusion tensor imaging, and registration of magnetic resonance imaging by surface registration. Recently, functional magnetic resonance imaging for surgical planning has been an added initiative with Dr. Alexandra Golby (Fig. 11).

5) Intraoperative imaging for children: the world's first intraoperative magnetic resonance imaging device in a pediatric hospital was installed in Children's Hospital in 2006.

6) Translational research laboratories in apoptosis, brain tumors, spinal cord injury, brain regeneration, and functional imaging.



FIGURE 12. *The Neurosurgery Department at Children's Hospital Boston and BWH in 2006.*

7) Significant contributions to the management of moyamoya disease, low-grade gliomas, cranial base meningiomas, hydrocephalus, and antiangiogenic therapy for malignant tumors.

8) The world's first Comprehensive Meningioma Center, created with the help of Mr. Steven Haley and the Brain Science Foundation.

During the years 1995 to 2005, the caseloads both at Brigham and Women's Hospital and Children's Hospital increased tremendously. The faculty and staff also grew (Fig. 12). In recent years, neurosurgeons on the service have performed more than 1500 operative cases annually at Brigham and Women's Hospital and 900 at Children's Hospital. Growth was especially seen in pediatric cases and tumor, spine, and vascular cases at Brigham and Women's Hospital.

An important component of growth was the development of active translational laboratories, with two-thirds of our faculty doing funded peer-reviewed research as a major initiative. The service has averaged 30 to 50 original articles and includes 7 Ph.D.s, as well as its M.D. staff. The research budget of the group was more than \$6 million in 2006.

The educational program remained central to the mission of the service during that time. The comprehensive teaching program has included a residency with 2 residents a year; more than 20 medical students a year, including many from other countries; noncategorical fellows; postgraduate fellows in tumor, pediatric, vascular, and spine neurosurgery; and didactic courses in brain tumors, neurosurgery as neuroscience, and sports injury. The service hosts many visiting neurosurgeons from around the world. The faculty is very involved in medical education and includes members of the American Board of Neurological Surgery and Residency Review Committee, a recent Honored Guest of the Congress of Neurological

Surgeons (7), and members of most neurosurgical societies. As well as having comprehensive interdisciplinary programs in tumor, epilepsy, pain, spine, and cerebrovascular disease, the service has a heavy emphasis on minimally invasive, image-guided neurosurgery. Despite the demands of clinical work, it holds Thursday as an academic day and continues to require 2 years of resident research, during which no clinical duties are assigned.

The period after 2006 was marked by a number of changes at the Brigham and Women's Hospital that are beyond the scope of this article. Dr. Arthur Day became Neurosurgeon-in-Chief at Brigham and Women's Hospital as Dr. Black turned to his responsibilities as president-elect of the World Federation of Neurological Societies. Dr. Edward Laws was recruited to develop the pituitary and peripheral nerve programs, and several other young surgeons were being recruited to join the faculty to strengthen and enhance its work. These will form a new and exciting chapter for this department.

THE FUTURE

Since 1912, the Harvard neurosurgical service at Children's Hospital and Brigham and Women's Hospital has had an important role in neurosurgery. Initially, with Harvey Cushing, it was the matrix for the creation of adult neurosurgery; Franc Ingraham had a similar role in pediatric neurosurgery. Programs in image-guided, minimally invasive neurosurgery; cerebrovascular surgery, including endovascular surgery; functional imaging; brain tumor surgery and science; and translational research distinguish this center. With its strong tradition of clinical, teaching, and research excellence, it will hopefully continue to be a major contributor to world neurosurgery in the years to come.

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COMMENTS

If only by virtue of its creator, Harvey Cushing, the Harvard neurosurgery program has for almost a century had a huge impact on the field of neurosurgery worldwide. Cushing was by all rights a towering figure, but as a consequence of his dominating and at times tempestuous personality, many other surgical disciplines at the Brigham and

Women's Hospital harbored ambivalent feelings toward the division of neurosurgery long after his "retirement." During my own residency in the 1980s, more than 50 years after Cushing's departure, there existed in many corners of the Brigham an almost palpable antipathy that was directed toward a strong adult neurosurgery program. It was during this long period of time that the pediatric service, characterized by Drs. Ingraham, Matson, and Shillito's perfectionist natures (in the Cushing tradition), came to dominate the program. However, under Dr. Black's recent leadership a rebalancing of pediatric and adult neurosurgery has finally occurred and, in the process, much of the Brigham's adult neurosurgical legacy has been restored. Because of the Harvard Neurosurgical Service at the Children's and Brigham and Women's Hospitals' unique culture and its immediate proximity to Harvard Medical School, this program is destined to make important contributions to neurosurgery well into the future.

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The two professors from Harvard provided us with a fascinating journey through one of the most renowned neurosurgical services worldwide. The father of modern neurosurgery, Harvey Cushing, started what would become one of the most intellectually vibrant and surgically talented centers in our field. This article provides data that the Brigham and Children's Neurosurgical Team have contributed to the benefit of mankind in unique ways from 1913 to the current day. So, the questions that may pique the interest of the reader are why did this happen and why at the Brigham and Boston Children's Hospitals? I think the answers have to include the amazing leadership, energy, and vision first demonstrated by Cushing. It starts there, but clearly does not end there. Cushing's drive and inspiration are still arguably palpable throughout our field, even today. The neurosurgical service in Boston is simply one group that can honestly claim Cushing as the originator of their inspiration. Apparently, Cushing's students followed a pattern of passing this legacy of expectations and performance to the next generation in Boston. The other reasons for success seem to be the inherent nature and colocation of these three special institutions: the Harvard Medical School, the Brigham and Women's Hospital, and Boston Children's Hospital. Geography should never be underestimated. These two hospitals and the medical school have been synergistic in attracting and fostering a certain sort of trainee and mentor that has persisted to this day. Thus, the robust and long-standing infrastructure is exclusively designed and dedicated to advancing a particular medical/surgical field. The efficacy of that drive and lineage has been etched into the expectations of all who go there. Second, there seems to be a huge premium placed on pursuing cutting edge clinical practice or research, and thus support for it is described in this article. And last, the need for excellent surgical skills is still one of the requisites to succeeding at hospitals uniformly replete with talented surgeons of every subspecialty. The reader senses that the competition and collaboration across disciplines is ingrained at these institutions. The example of cross-fertilization that was most striking to me is that of Boston Children's neurosurgeons removing kidneys to create shunts. Those displaced kidneys subsequently led in part, to the burgeoning field of transplantation, and Joe Murray's subsequent Nobel Prize for his pioneering work in that field. I suspect the combination of the forces of history, geography, and expectations have contributed to the recurrent successes in the field of neurosurgery at these institutions.

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STEREOTACTIC NEUROSURGERY IN THE UNITED KINGDOM: THE HUNDRED YEARS FROM HORSLEY TO HARIZ

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THE HISTORY OF stereotactic neurosurgery in the United Kingdom of Great Britain and Northern Ireland is reviewed. Horsley and Clarke's primate stereotaxy at the turn of the 20th century and events surrounding it are described, including Mussen's development of a human version of the apparatus. Stereotactic surgery after the Second World War is reviewed, with an emphasis on the pioneering work of Gillingham, Hitchcock, Knight, and Watkins and the contributions from Bennett, Gleave, Hughes, Johnson, McKissock, McCaul, and Dutton after the influences of Dott, Cairns, and Jefferson. Forster's introduction of gamma knife radiosurgery is summarized, as is the application of computed tomography by Hounsfield and Ambrose. Contemporary contributions to the present day from Bartlett, Richardson, Miles, Thomas, Gill, Aziz, Hariz, and others are summarized. The current status of British stereotactic neurosurgery is discussed.

KEY WORDS: Atlas, Computed tomography, Functional neurosurgery, History, Radiosurgery, Stereotactic frame, Stereotactic neurosurgery

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*Pigmaei gigantum humeris impositi
plusquam ipsi gigantes vident
[If I have seen further it is by standing
on the shoulders of giants]*

—Sir Isaac Newton (136)

In debates over the paternity of the discipline of neurosurgery, Sir Victor Horsley frequently vies with Harvey Cushing and notable others, including the Englishman Sir Rickman Godlee and the Scot Sir William MacEwen (19, 87, 89, 95, 120, 137, 167). Yet, it is a truth universally acknowledged, even west of the Atlantic, that stereotaxis (as he named it back then) was invented in London by the Englishman. Although Dittmar, in Germany, had used a guided probe to transect the rodent medulla in 1873 (33) and the Russian Zernov had described an encephalometer enabling brain surface localization in 1889 (181), neither technique enabled targeting with respect to a fixed three-dimensional Cartesian coordinate system.

ABBREVIATIONS: CT, computed tomography;
EMI, Electric and Musical Industries

Sir Victor Alexander Haden Horsley (1857–1916) (Fig. 1A) studied medicine in University College London before training surgically there. He was the first neurophysiologist who was also a neurosurgeon, pioneering a Great British tradition of such hybrid scholars that were particularly prevalent in the stereotactic community (137). His uniquely deft approach to neurosurgery, derived from experiments on more than 100 primates, made a reputation such that when tenure became available at the National Hospital for the Paralyzed and Epileptic in Queen Square in 1886, “the Staff intended to have Horsley and nobody else” (140, p 27).

Like Sir Isaac Newton two centuries before him, Robert Henry Clarke (1850–1926) (Fig. 1B) read mathematics at Cambridge University. He then undertook medicine at St. George's Hospital in London before surgical training in Glasgow. He returned to London to work with Horsley in the late 1880s (30). Throughout the following decades, Horsley became intellectually consumed by the experimental challenges of cerebral localization of motor function, following the seminal work of Hughlings Jackson and others.

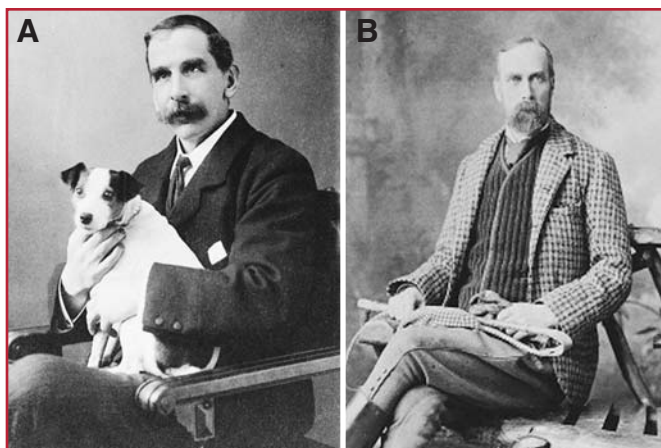


FIGURE 1. **A**, Sir Victor Alexander Haden Horsley; **B**, Robert Henry Clarke. (Courtesy of the Wellcome Library, London.)

After Clarke developed aspiration pneumonia after aspirin inhalation in the early 1890s, he traveled to Egypt to convalesce. While there, legend has it that while gazing up at the stars and contemplating his place in them, he conceived an apparatus through which probing intracranial instruments could be inserted; the apparatus could be clamped to an animal's head by laterally placed skull pins, bars attached to plugs inserted into the external auditory meatus, and further bars resting upon the nose and orbital margins, which would fix the device to a Cartesian coordinate system. He presented his idea to Horsley on his return to England soon afterward (155). A decade later, in 1905, they commissioned James Swift, a machinist at Palmer & Company in London, to construct the first machine from brass, "Clarke's stereoscopic instrument employed for excitation and electrolysis," comprising frame, carrier, and needle holder and costing £300 (Fig. 2) (159). Results from experimental use of the first instrument for targeting electrolytic lesions in the deep cerebellar nuclei of rhesus macaques were published in 1906 (26). In 1908, Horsley and Clarke described the apparatus and its use in greater depth, coining the term "stereotaxic" from the Greek words *stereos* (meaning "solid") and *taxis* (meaning "arrangement") (82). "By this means any cubic millimetre in the brain can easily be identified, recorded, and referred to" (26, p 1799).

Although Clarke suggested that the apparatus might be useful in humans, neither he nor Horsley pursued the idea, and they acrimoniously ceased collaboration shortly afterward. Nevertheless, the apparatus, including its proposed use in humans, was patented by Clarke in 1914, and he devoted much time to improving it. A rectilinear modification enabling needle inclination at different angles in an equatorial frame enabling 360 degrees of movement was described by 1920 (Fig. 2) (23). Three others used the original apparatus in London for experimental work: first, the visiting American surgeon Ernest Sachs, who studied the optic thalamus (154), and then the neurologist S.A. Kinnier Wilson, who studied the basal ganglia of 25 monkeys using the "Clarke-Horsley machine" (179).

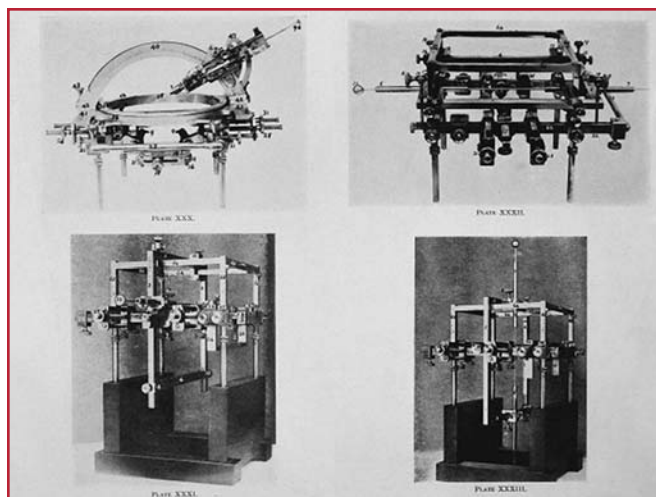


FIGURE 2. Clarke and Horsley's 1905 primate stereotactic apparatus, showing also Clarke's 1920 equatorial modification (top left). (Courtesy of the Wellcome Library, London.)

Clarke's original instrument was last applied by F.J.F. Barrington, a London urologist who used it to study the effect of brain lesions upon feline micturition (12). Barrington died suddenly in 1956. Among the contents of his laboratory, "in true British fashion, was a biscuit tin" (120a, p 33). It contained a number of pieces first thought to be the original apparatus but later found to be only parts. After many inquiries, a technician in the Royal Veterinary College where Barrington had once worked produced a mahogany box containing the original model, and it was returned to University College London in 1970. It now resides in the Science Museum in London, having been promoted from closed storage to prominent display by the senior author (TZA) in 2000 (Fig. 3). Two further apparatus designs were made for Clarke by machinists Goodwin and Velacott, also of Palmer & Company in London, and exported to the United States for animal research soon after the First World War; one of them was sent to Johns Hopkins with the proviso that the Baltimore institution would publish Clarke's stereotactic atlas (39).

Translation of Horsley-Clarke stereotaxy to humans was considered not only by Clarke, but also by one of Horsley's students, the Canadian Aubrey Mussen. Mussen purchased one of the original Horsley-Clarke contraptions secondhand for £100 while working at the National Hospital in London from 1905 to 1906, returning to McGill University with it and subsequently publishing results from studies of the hypoglossal nuclei that Horsley traversed with his deep cerebellar lesions (130). Mussen designed further stereotactic instruments with Clarke, including a "cyclotome," a probe used to make disk-shaped incisions along its axis, and a "spherotome," used to cut spherical volumes, to which the leukotome of António Egas Moniz bears much resemblance (23).

Having returned to London in 1914, Mussen designed and had commissioned a modification of the Horsley-Clarke appa-



FIGURE 3. The senior author (TZ) with one of the original Horsley-Clarke frames in 2000.

ratus for use in humans, completed around 1918, again in brass, and most likely again manufactured by Palmer & Company (Fig. 4). In the frame, electrode holders slid along horizontal graduated bars or vertical corner posts, enabling orthogonal approaches to intracranial structures in anteroposterior and lateral directions. The apparatus required a human brain atlas, and Mussen envisaged its use to thermocoagulate tumors using “Galvanic current . . . through a 5 mm trephine in the skull and puncturing the dura without exposing the brain at all” (17, p 1245). In the 2 decades that followed, Mussen neither completed the human atlas nor convinced neurosurgical colleagues to take up use of his frame (90). He wrapped the unused British-made apparatus in newspaper dating from the 1940s and placed it in his attic (43).

Sachs, Wilson, and Barrington all had loan of the original Horsley-Clarke frame after Horsley’s original experiments.

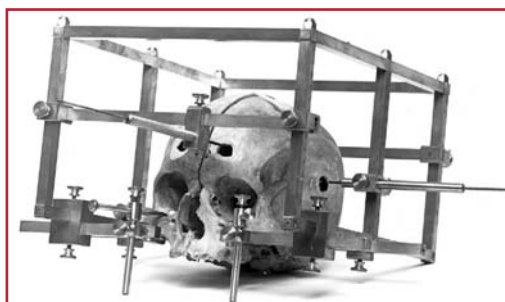


FIGURE 4. Mussen’s human stereotactic instrument, circa 1918 (from, Picard C, Olivier A, Bertrand G: *The first human stereotaxic apparatus. The contribution of Aubrey Mussen to the field of stereotaxis. J Neurosurg* 59:673–676, 1983 [148]).

Sachs and Mussen used Clarke’s second and third frames, respectively, for animal experiments in North America throughout the 1920s, (131, 156), as did others during the following decade. However, the key challenges in translating experimental animal stereotaxy into a clinical tool were twofold. First, there was great variability between human cranial landmarks and cerebral structures and, second, humans could not be killed like animals to enable confirmatory histology to determine accurate targeting and, thus, experimental validity.

Three decades after Horsley and Clarke’s work, Spiegel and Wycis devised an apparatus for stereotactic neurosurgery in humans, publishing their achievement in 1947 (164). The North Americans established “stereotactic” as the preferred term, fusing the Greek *stereos* with the Latin word *tactis*, the pluperfect passive form of the verb *tangere* (meaning “to touch”). Their major advances were, first, to create a frame tailored to the individual cranium by means of a plaster cranial cap and, second, to align their frame not just to the cranium but also to brain landmarks such as the calcified pineal gland and the foramen of Monroe by means of intra-operative pneumoencephalography, hence their naming their device a “stereoecephalotome.”

Post-war Innovation

Should you scratch deeply enough a man of pioneering spirit, the chances are that you will draw Scottish blood.

—Harvey Cushing (153, p 423)

British stereotactic surgery remained quiescent for half a century after Horsley, spanning the two World Wars, the discipline only reaching the clinic after word spread of Spiegel and Wycis’ invention. At first, primary applications were for treating psychiatric disorders, and, later, clinical usage diffused to movement disorders in the 1950s and chronic pain in the 1960s.

Ahead of the rest, two Scottish pioneers and an English crusader emerged, each a clinical polymath but with a discrete focus to their research endeavors. In London, Geoffrey Knight developed stereotactic subcaudate tractotomy for psychiatric disorders, treating hundreds of patients, while the doyen of the London establishment, Sir Wylie McKissock, used a free-hand approach. In Edinburgh, John Gillingham embraced stereotactic surgery for multiple clinical indications, designing his own stereotactic frame. In turn, he inspired his associate Ted Hitchcock, first at Edinburgh and then in Birmingham, to pioneer stereotactic approaches to the brainstem and high cervical spinal cord.

Francis John Gillingham (1916–) (Fig. 5) trained in St. Bartholomew’s Hospital in London before entering the neurosurgical faculty at Edinburgh in 1950. Gillingham spent 12 years as first assistant to Norman McOmish Dott, one of the great triumvirate alongside Sir Hugh Cairns in Oxford and Sir Geoffrey Jefferson in Manchester, the apostles of Cushing who definitively established neurosurgery as a specialty in Great Britain (40, 153, 160). Like his mentor, Dott, Gillingham was a brilliant and pioneering aneurysm surgeon (48, 171). He was also a passionate educator who introduced the concept of sub-



FIGURE 5. Francis John Gillingham (left) preparing for a stereotactic thalamotomy in 1968 (from, *Housepian EM: Stereotactic surgery: The early years. Neurosurgery* 55:1210–1214, 2004 [85]).

specialty fellowships to British neurosurgical training (49), but his greatest contribution was to stereotactic surgery.

Gillingham's introduction to stereotactic surgery came from the Parisian neurosurgeon Gerard Guiot. Guiot had recently visited Edinburgh to learn aneurysmal surgery from Dott and Gillingham, and they had become friends. Guiot's 1953 telegram to Gillingham read "I have something interesting to show you—come over," (50, p 139). Gillingham obeyed, and 4 days were then spent performing freehand pallidotomies to treat parkinsonism by means of a subfrontal approach to the anterior perforated substance, with interruption of the ansa lenticularis and with the patient under local anesthesia, as described by Fenelon and Thiebaut after the seminal discoveries of Cooper (27, 38, 58).

Gillingham returned convinced, treating two patients in Edinburgh in 1955 and 1957, respectively, and reporting long-term improvements in tremor, rigidity, and quality of life. However, wishing to avoid the demanding subfrontal approach, if possible, he adapted Guiot's stereotactic method (57). In 1960, he published results from stereotactic "thermal electrocoagulation lesions of the globus pallidus, internal capsule and thalamus either separately or in combination" (50, p 1395) in a further 58 patients who underwent operations between 1957 and 1959 (53). In addition to the globus pallidus and internal capsule, he began targeting the ventrolateral thalamus for refractory tremor on the basis of work by Hassler (61). "Of these [60] patients 53, or 88%, had tremor and/or rigidity abolished or significantly reduced without complications" (53, p 1402).

Gillingham drew several conclusions from his early clinical results. On targeting, he wrote that "The best type of lesion . . . would seem to be the double one, made at the same time in the ventro-lateral nucleus of the thalamus and in the globus pallidus 16 mm from the mid-line, both lesions bordering on the internal capsule. . . . Bilateral lesions in the treatment of bilateral Parkinsonism, provided they are small and strategically placed, would seem to be eminently practicable . . . usually with an interval of three to six months between the two operations" (50, p 1401). On his modification of Guiot's stereotactic

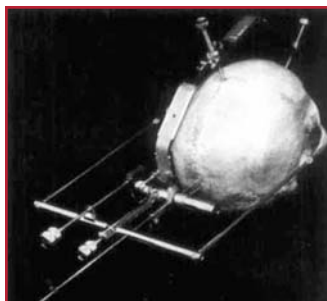


FIGURE 6. The Guiot-Gillingham stereotactic apparatus, in which a posterior rather than a coronal approach is used (from, Gillingham FJ, Watson WS, Donaldson AA, Naughton JA: *The surgical treatment of parkinsonism. Br Med J* 2:1395–1402, 1960 [49]).

apparatus, he felt "that the merits of this method lie in the relatively short operative procedure and in its accuracy and simplicity. Its principles are based on the fact that the globus pallidus and thalamus bear a reasonably constant anatomic relationship to the anterior and posterior commissures, the intercommissural line, and the mid-sagittal plane of the head . . ." (50, p 1396) "The method used has evolved progressively, and is unique, in allowing the creation of lesions in the globus pallidus, internal capsule, or thalamus with one

electrode track at different depths" (53, p 1402).

In their stereotactic apparatus design, Guiot and Gillingham favored operative principles to prioritize patient comfort, not restricting the patient's movements by clamping the head and attempting to obviate the need for multifarious calculations. Guiot planned a parasagittal approach in which he used intra-operative encephalography to delineate the midline and intercommissural point. Gillingham favored an occipitoparietal entry to avoid the striate arteries and horizontal patient positioning to reduce putative brain shift. Thus, the Guiot-Gillingham stereotactic apparatus was devised (Fig. 6). Radiopaque midline markers were used for the procedure, and a 1-mm steel ball was placed in each 5-mm lesion for subsequent charting. The ball was seen to fall through the necrotic lesion over a period of weeks, elegantly providing an estimate of its size. The frame's conception preceded Hassler's discovery of the thalamus as a target for tremor, and Gillingham attributed to serendipity that his posterior approach enabled multiple targets to be lesioned in a single pass (50).

Despite impressive clinical outcomes, Gillingham noted some inaccuracy to his lesions in the context of Brierley and Beck's demonstration that relationships between basal ganglia structures and commissural landmarks were highly variable (21, 47). David Whitteridge, his neurophysiologist colleague at Edinburgh, had demonstrated to him in 1961 how microelectrode recordings could distinguish between gray and white matter and thus delineate the lateral geniculate nuclei in the cat (46). He immediately saw their utility for distinguishing functionally between deep brain structures, and, with his colleague Michael Gaze, he developed the technique for humans, as did Guiot (59). Fundamental physiological insights were gained in the quest to improve lesion accuracy and clinical efficacy, including spontaneous rhythmic discharge in the thalamus, which was found to be synchronous with tremor (Fig. 7) (42). With the use of microelectrode recordings, target localization could be done accurately with a margin of error of less than 1 mm.

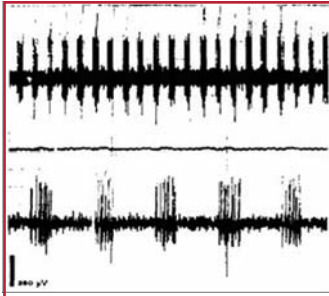


FIGURE 7. Spontaneous rhythmic activity synchronous with tremor recorded from the human thalamus. The record at the bottom is a sped-up version of the one at the top. The middle record is taken from an accelerometer on the wrist (from, Gillingham FJ: *Neurosurgery. Br J Surg* 53:833–836, 1966 [46]).

formed (91). Ten-year follow-up in the post-levodopa era of a second 60-patient parkinsonian cohort of Gillingham's that underwent surgery between 1965 and 1967 showed a decline in efficacy for bradykinesia but consistent relief of tremor and rigidity (94). He remained engaged in academic neurosurgery well into his ninth decade, authoring insightful reviews of stereotactic surgery for Parkinson's disease (51).

As Gillingham became Dott's protégé, so Ted Hitchcock became Gillingham's. Edward Robert Hitchcock (1929–1993) studied medicine at Birmingham and trained in neurosurgery at Oxford before joining the Edinburgh staff at the then-recently-opened Western General Hospital in 1965. While there, he received unique exposure to Gillingham's stereotactic surgery, which attracted international visitors like Guiot and Housepian (85). In the late 1960s, Hitchcock's own interest was chronic pain and, in particular, developing his idea of percutaneous high spinal stereotactic commissural myelotomy. This procedure aimed to divide the decussating spinothalamic tracts but reduce the risks of respiratory paralysis conferred by open cordotomy through a targeted lesion, primarily aimed at chronic pain that was attributable to neoplasia. It required access below the plane of a versatile frame; thus, he invented his

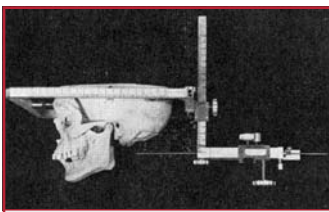


FIGURE 8. Hitchcock's stereotactic apparatus for brainstem and cervical spine surgery (from, Hitchcock E, Lewin M: *Stereotactic recording from the spinal cord of man. Br Med J* 4:44–45, 1969 [72]).

own target-centered arc system, which was attached to a hollow square aluminum base ring that was secured to the cranium by three-point fixation (Fig. 8). Vertical and horizontal bars determined probe length and laterality. The system was first used both for surgery and for microelectrode recording in the spinal

cord by a percutaneous approach using portable x-rays (62, 63, 72). Hitchcock reported initial results of good or complete pain relief in 13 of 19 patients at follow-up periods ranging from 1 week to 4 years (66). A stereotactic pontine approach to spinothalamic tractotomy and to the trigeminal nucleus for anesthesia dolorosa was also applied (64, 65, 74, 78, 80), as were approaches to the thalamus and dentate nucleus to treat dystonia and, in particular, the spasticity of cerebral palsy (54). The rationale behind the stereotactic pontine spinothalamic approach was to provide good analgesia with minimal risks to respiration, micturition, and upward gaze (65). Hitchcock wrote of his apparatus in the early 1970s that "the design and construction make this one of the most accurate, adaptable and simplest of modern stereotactic instruments" (161, p 104).

Hitchcock became Professor of Neurosurgery at Birmingham in 1978, succeeding Brodie Hughes (1913–1989), who was also a stereotactic surgeon of some repute (86, 119). Hitchcock put his stereotactic frame to many further clinical uses, including biopsy of supratentorial, infratentorial, and high spinal tumors and intraventricular masses (71, 73, 76), foreign body removal (70), real-time clipping of otherwise inoperable arteriovenous malformations (161), and image-guided craniotomies (68); in the 1980s, he also used it in the planning and treatment stages of radiosurgery (79). These many varied clinical indications in brain and spine earned him the nickname "Columbus of the brain" in the local clinical neuroscience community. At the Midland Hospital for Neurology and Neurosurgery, he used his stereotactic expertise to establish a program at first for adrenal medullary transplantation and, in the late 1980s, for fetal mesencephalic transplantation in Parkinson's disease, performing the procedure on 55 patients and gaining fundamental insights into its mechanisms (69, 75, 77, 109).

Neurosurgery for psychiatric disorders in Great Britain mirrored treatment in the United States, its popularity following Freeman and Watts' simplification of Moniz's procedure in the 1940s (41, 128). Its most assiduous British proponent was the London neurosurgeon, Sir Wylie McKissock (1906–1994), founder of the Neurosurgical Department at Atkinson Morley's Hospital in Wimbledon (150). The illustrious McKissock favored a freehand approach to the frontal lobe from above (96). He described the rostral leukotomy in 1951 as a rejoinder to Freeman and Watt's transorbital "ice-pick" leukotomy, which he considered to contravene "established aseptic surgical principles" (126, 127, p 92). McKissock's immense practice, covering swathes of South England, and his reputation for extraordinary surgical speed inculcated a peripatetic service, as he visited other hospitals in his car with his surgical instrument set in the boot, drawing parallels with Freeman (13, 35). It is suggested that McKissock alone may have performed one-quarter of the 10,365 procedures performed in the United Kingdom from 1942 to 1954, as reported by Tooth and Newton in 1961 (172).

Geoffrey Cureton Knight (1906–1994) of Hammersmith and Brook Hospitals in London and Woolwich saw, more readily than McKissock, the merits of stereotactic approaches over freehand techniques in reducing the morbidity and mortality of neurosurgery for psychiatric disorders, and, indeed, the two



FIGURE 9. Anteroposterior x-ray of Geoffrey Knight's stereotactic subcaudate tractotomy showing yttrium seeds in situ for brachytherapy (from, Knight GC: Bifrontal stereotactic tractotomy: An atraumatic operation of value in the treatment of intractable psychoneurosis. *Br J Psychiatry* 115:257–266, 1969 [103]).

therapy as an ablative tool, implanting radioactive yttrium (^{90}Y) to create a flat lesion approximately 20 by 20 by 7 mm (Fig. 9) (103–105).

The treatment proved effective and endured 4 decades amid the demise of other psychosurgical treatments. Knight's group described the treatment of 1300 patients with "nonschizophrenic affective disorders," 40 to 60% going on to live normal or near-normal lives with a reduction in suicide rates from 15% to 1% (20, 81). Long-term outcomes were published by the psychiatrist Bridges and the London neurosurgeon John Bartlett, Knight's successor beginning in 1972. After the retirement of Knight, the unit was named the Geoffrey Knight Unit for Affective Disorders to emphasize Knight's appreciation of the fundamental importance of psychiatric evaluation, both in diagnosis and in full consideration of medical treatments before offering surgery. In 1996, the unit moved to the Maudsley Hospital, Professor Checkley succeeded Dr. Bridges as its psychiatrist, and ^{90}Y production ceased. Bartlett adapted a Leksell frame arc (Elekta, Stockholm, Sweden) compatible with modern neuroimaging using concepts that underlay the McCaul device. Radiofrequency lesioning replaced radioisotope implantation (121, 122).

It is a tribute to Knight that the Atkinson Morley Hospital's neurosurgeon Alan Richardson (1926–1998), profoundly influenced by McKissock—as all around the great man were—adapted a stereotactic approach for his psychiatric procedures (96). Together with his psychiatrist colleague Desmond Kelly, he combined Knight's subcaudate tractotomy with a cingulotomy to invent the procedure of limbic leukotomy in the early 1970s (Fig. 10) (92, 93). It is interesting to note that cingulotomy for psychiatric disorders was first performed in 1948 in Oxford by Sir Hugh Cairns, albeit freehand, before the advent of stereotactic surgery (178). Both Knight's subcaudate tractotomy and Richardson's limbic leukotomy continue to be per-

debated such issues in 1959 (100, 127). After his freehand experience (106), Knight created the procedure of stereotactic subcaudate tractotomy in 1961, using a modified stereotactic device that his London colleague, the Scottish neurosurgeon Ian Reay McCaul (1916–1989), reported in 1959 (119, 125). His first few hundred orbital undercuttings led him to conclude that lesions extending posteriorly under the caudate were most efficacious and that the last 2 cm were key (101, 102). Knight used bony landmarks on lateral x-rays and, later, air encephalography to guide him. In addition, he used brachy-

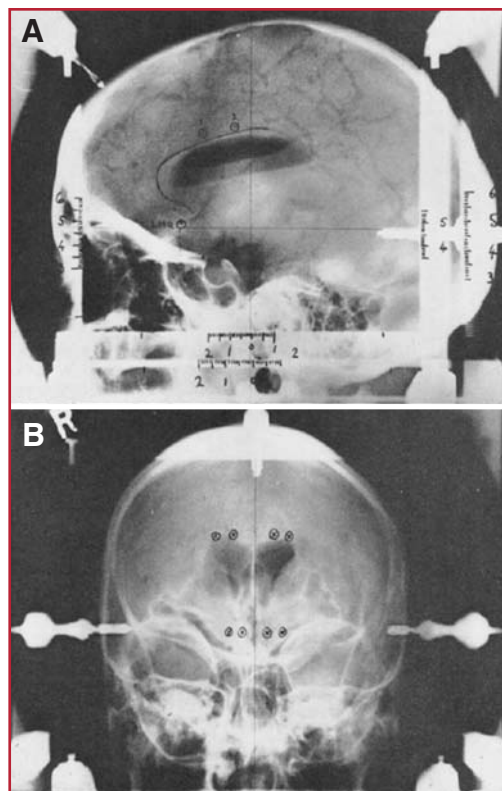


FIGURE 10. Desmond Kelly and Alan Richardson's stereotactic limbic leukotomy. The lateral (A) and anteroposterior (B) air ventriculograms illustrate cingulate lesion sites above and medial frontal lesion sites below. The lateral x-ray (A) also shows the corpus callosum marked and crosshairs over the base of the anterior clinoid process—the lower medial lesion site is 1 cm anterior and superior to this landmark (from, Kelly D, Richardson A, Mitchell-Heggs N: Stereotactic limbic leukotomy: Neurophysiological aspects and operative technique. *Br J Psychiatry* 123:133–140, 1973 [92]).

formed worldwide, including in the United Kingdom and North America, in carefully selected cases that are refractory to medical treatment (22, 37, 107).

Stereotactic neurosurgery was embraced by Dott's unit in Edinburgh and, after Cairns, Pennybacker appointed Sid Watkins to establish an Oxford service, but other regions also were keen to commence it. In Manchester, Jefferson's successor, Richard Johnson, appointed John Dutton to undertake a high volume of ablations for parkinsonism and other stereotactic procedures throughout the 1960s using a Leksell frame. Soon after, John Gleave (1925–2006) established a stereotactic service in Cambridge, also using a Leksell frame, treating parkinsonism with cryosurgery, and developing a side-cutting stereotactic biopsy cannula (123, 177). Other British neurosurgeons, such as McCaul, made and modified stereotactic frames. Of particular note was the frame of Alfred Michael Bennett (1920–1996) and his use of a sphere inserted into a burr hole to aid targeting (15,

18). Bennett's apparatus was popular locally, being used by Sid Watkins and later David Thomas in London, among others (36, 144). Most designs were less radical and, therefore, perhaps less memorable than those of Gillingham and Hitchcock. However, far from echoing the designs of the English cartoonist William Heath Robinson, these innovative neurosurgeons taught and inspired experimental endeavors in the generations that followed. Several of the ventures amounted to little, but the ones that yielded fruit have changed the specialty forever, transforming many patients' lives in the process.

Atlases

Of necessity to enable their targeting, Horsley and Clarke also produced the first stereotactic atlas, a monkey version appearing in their 1908 publication. Later publications were by Clarke, at first for the cat, in collaboration with the British ophthalmic surgeon E. Erskine Henderson in 1912, and later by Clarke alone for the rhesus macaque in 1920 (23–25). Both atlases comprised 2-mm-thick brain slices. The latter atlas showed sections of monkey brain at calibrated intervals with a scale giving slice thickness and height from the base of the apparatus. Sections were registered by a Cartesian coordinate system to the skull landmarks of the inferior orbital rim and both external auditory canals, to which the frame was fixed. Zero axes were the plane between these structures axially, the midsagittal plane, and the coronal plane between both external auditory meati orthogonal to both other planes.

There is no doubt that human brain atlases produced outside Great Britain, in particular by Spiegel and Wycis, Schaltenbrand and Bailey, and Talairach, transformed stereotactic functional neurosurgery. Schaltenbrand detailed anatomic nuclei with an emphasis on the thalamus and adjacent deep brain structures that is now indispensable to deep brain stimulation for movement disorders, and Talairach revealed the vasculature relevant to epilepsy surgery (157, 163, 166). Nevertheless, another "Columbus of the brain," the British neurosurgeon Sid Watkins, made rigorous contributions.

Eric Sidney Watkins (1932–) was charged by Joe Pennybacker with the task of starting stereotactic neurosurgery at the Radcliffe Infirmary in Oxford in the 1950s. He was initially dissatisfied with the variability of basal ganglia structures with respect to the frequently uncalcified and, thus, radiolucent pineal gland using the Spiegel and Wycis atlases, but the Schaltenbrand and Talairach atlases appeared shortly after and were of aid to him. Initially, the globus pallidus and ansa lenticularis were targeted for parkinsonian rigidity, tremor, and dystonia, and then the lateral thalamus was targeted in the 1960s. An interest in creating his own atlas developed in the early 1960s from a desire to commence the therapy of thalamotomy for pain combined with concern about the adequacy of available atlases to accurately enable targeting based on anatomy alone in the absence of subjective or physiological guidance. Encouragement came from neurosurgical colleagues John Andrew and Valentine Logue, who were also keen to commence such treatment in London.

Another atlas that became available was that of Brierley and Beck, who sectioned 40 brains in 3- to 5-mm slices, relating them in a proportional hypothesis for thalamic nuclear determination to anterior and posterior thalamic limits and the midthalamic point and describing great individual variations (21). However, Watkins found the atlas to be limited clinically, because the use of simultaneous positive and air ventriculography using air in the ambient cisterns to outline the pulvinar nuclei and thus the thalamic limits was not consistently reproducible.

At the National Hospital for Nervous and Mental Diseases, with Sid Watkins nearby at the Royal London Hospital, John Andrew produced in 1969 a greatly enlarged atlas with drawings defining in detail deep brain nuclei, including the thalamus and its relations (5). The atlas was based upon 38 formalin-fixed brains. It measured the position of the thalamic centromedian nucleus with the use of 1-mm coronal slices with reference planes between the posteroinferior margin of the foramen of Monro and the posterior commissure and the midpoint between the ventricular surfaces of the anterior and posterior commissures. Its utility lies in the presentation of statistical data in a graphic form together with stereotactic coordinates superimposed on simple line drawings of the thalamus.

In 1978 at the London Hospital, Fari Afshar detailed brainstem and cerebellar nuclei, again under Sid Watkins' supervision (1). The impetus for the Afshar atlas came from an interest in attempting to ameliorate spasticity in cerebral palsy by ablation of the cerebellar dentate nucleus. Approximately 30 brains were prepared by the use of positive-contrast ventriculography with the skull and brain mounted in a stereotactic frame in order to accurately correlate structures with coordinates. Again, formalin fixation of 1-mm slices was performed. A modified Mulligan stain was used, and each section was magnified with drawings made by a camera lucida. Reference planes were the fourth ventricular floor and fastigium and the midsagittal plane. As before, variability profiles were quantified, and standard deviations were presented.

Both Watkins atlases are rich resources that are still used to help ratify localization and, indeed, the Afshar atlas continues to augment heated debates regarding the targeting of the novel functional neurosurgical treatment of deep brain stimulation of the pedunculopontine region for Parkinson's disease (124).

Watkins has commented on the major difficulties in measurement caused by distortion related to fixation and shrinkage, with past atlases suffering from approximately 10% shrinkage. To reduce shrinkage to 2 to 5%, he used Corsellis' technique—a 10-day formalin suspension after removing brain and skull *en bloc* minus the frontal and facial bones (28). To appease undertakers' disgust at the cosmetic consequences, each cadaver's scalp was replaced over a plaster of Paris prosthesis fixed to a broom handle on a nail inserted into the cervical canal. Nevertheless, cremation of the augmented cadavers remained suboptimal, precipitating a strike among undertakers serving the London Hospital by the time Afshar's posterior fossa atlas reached its completion (175).

The British Engineer

There must be a beginning of any great matter, but the continuing unto the end until it be thoroughly finished yields the true glory.

—Sir Francis Drake, [1540–1596; Drake to Walsingham, Cape Sagres, Portugal. May 17, 1587 (Letter)]

By the late 1970s, British stereotactic functional surgery was a decade on from its first successes, having declined with the advent of neuropsychopharmacology. Levodopa was introduced to relieve Parkinson's disease (29), and chlorpromazine and monoamine oxidase inhibitors were found to ameliorate schizophrenia and depression, respectively. Thus, case series showing good relief after lesional surgery for chronic pain paled against the background of new analgesics and peripheral neuromodulatory therapies. Stereotactic approaches to tumors had been established but were found challenging by many neurosurgeons who were not steeped in the subspecialty. Although Watkins lived life in the fast lane (176), becoming medical advisor to Fédération Internationale de l'Automobile Formula One racing (176), Hitchcock continued to innovate and, alongside Bartlett and Richardson, continued using psychiatric procedures for medically refractory depression, obsessive-compulsive disorders, and anxiety; however,

the still-fallow field awaited advances in other domains. Enter the British engineer.

Sir Godfrey Newbold Hounsfield (1919–2004) (*Fig. 11*) joined Electric and Musical Industries (EMI) in Hayes, Middlesex, in 1951, having previously been a radio mechanic and then a radar mechanic in the Royal Air Force before obtaining a diploma from Faraday House Electrical Engineering College in London. At EMI, he worked first on radars and guided weapons and then on the first all-transistor computers. During a weekend ramble in 1967, he conceived what later became the first EMI scanner and the technique of computed tomography (CT),



FIGURE 11. Sir Godfrey Hounsfield at the controls of the Electric and Musical Industries scanner in Atkinson Morley's Hospital in London (from, Petrik V, Apok V, Britton JA, Bell BA, Papadopoulos MC: Godfrey Hounsfield and the dawn of computed tomography. *Neurosurgery* 58:780–787, 2006 [147]).

which he described humbly as “a realization that you could determine what was in a box by taking readings at all angles through it,” (176a, p 226).

By recording multiple pictures from a rotating photon source, a series of slices could be photographed, and a three-dimensional image could then be reconstructed from the slices. After initial successful experiments with a cylindrical phantom containing radiopaque objects in his Hayes laboratory using x-rays, Hounsfield forged a collaboration with James

Ambrose (1923–2006), a radiologist at Atkinson Morley's Hospital, to translate the device's utility to humans. McKissock gave the endeavor his blessing (13). Hounsfield set to work on bullocks' heads obtained from a kosher slaughterhouse in East London to obviate the traumatic intracranial hemorrhage observed after conventional slaughter (147). Ambrose interpreted the early scans and suggested the use of sodium iothalamate contrast to highlight tumors (4). His early interpretations and predictions formed the basis of contemporary diagnostic neuroradiology (2, 3). The scan of the first patient, in 1971, revealed a cyst in the brain (83). In 1979, Hounsfield was awarded the Nobel Prize for Physiology or Medicine together with Allan Cormack, the Cape Town physicist whose mathematical theories Hounsfield had realized (84).

The advent of CT reawakened the use of stereotactic surgery in Britain. Several neurosurgeons began to experiment with CT-compatible apparatus, both imported (usually Leksell) and that of Gillingham and Hitchcock (50, 67). Magnetic resonance imaging followed shortly after, again with frames being modified as required. After a quiescent decade, the late 1980s augured a renaissance. Alongside the emerging limitations of drug therapies for movement disorders, which resurrected the clinical indications for functional neurosurgery, great advances came from increasing computer power, enabling the fusion of more spatially robust CT information with the greater soft tissue detail of magnetic resonance imaging and comparison with computed brain atlas images. In Britain, the current generation of senior stereotactic neurosurgeons was gaining their clinical training and conducting their first research, some in classical stereotactic methods abroad, some by subspecialty fellowships in Britain, thanks to Gillingham's enduring influence upon neurosurgical programs, and others by animal experiments true to the hybrid scientist-surgeon mold of Horsley. The stage was set for 2 decades of rapid advances in stereotactic neurosurgery.

Radiosurgery

Lars Leksell's genius showed not only in his frame design (111), in which he used the novel arc-quadrant principle, but also in his insight that focused radiation could be used as the tool. Many intersecting radiation beams focused toward a target would result in a high cumulative radiation dose, with radiation intensity declining rapidly with distance from the “isocenter.” Thus, a deep brain structure could be lesioned noninvasively by focused radiation. The technology could be applied to acoustic neuromas, arteriovenous malformations, and other discrete pathologies. Radiosurgery was born in 1951 (112).

Britain acquired one of the first gamma knives in 1985, as did Argentina just 3 years after the Falklands War. David Forster achieved incredible feats in leading the campaign to fund the device on the British National Health Service, building the infrastructure over 2 years to host it and ultimately purchasing the first custom-made unit in 1985. The National Center for Stereotactic Radiosurgery was refurbished in 1991, and its cobalt sources were renewed. Andras Kemeny, Matthias Radatz, and Jeremy Rowe are the neurosurgeons at the unit,

receiving approximately one-half to two-thirds of all radiosurgery referrals from all over the United Kingdom. Approximately 500 cases a year are performed, a third of cases treated being arteriovenous malformations, with small- to medium-sized acoustic neuroma treatment having increased from 10% to one-third during the period 1994 to 2001. In addition, approximately 100 meningiomas and other cranial base or recurrent tumors are treated per year. Other indications for treatment include trigeminal neuralgia, pituitary tumors, and metastases, although the latter two indications are treated in smaller proportions than outside the United Kingdom, reflecting more conservative referral patterns (152). For similar reasons, few epilepsy and functional cases have been performed.

Several neurosurgical centers use linear accelerators to perform radiosurgery, each performing up to 40 cases per year. A gamma knife was also acquired in 1998 by the Cromwell Hospital in London, which is run privately by Christer Lindquist. The hospital's gamma knife has treated 1000 patients since installation and was recently upgraded.

Functional Neurosurgery

Seminal European catalysts in the crucible of *fin de siècle* British stereotactic surgery were without doubt Benabid's application of thalamic deep brain stimulation to Parkinson's disease in 1987 and Laitinen's resurrection of Leksell's pallidotomy in 1992 (14, 110). Functional neurosurgery was resurrected at the Radcliffe Infirmary in Oxford 4 decades after Watkins' departure under the headship of Mr. Chris Adams (7). At Oxford and Charing Cross Hospital in London, as we had already established with Alan Crossman in Manchester by the early 1990s, at the same time as DeLong's team across the Atlantic, that lesions made to the subthalamic nucleus in primates reversed the motor symptoms of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism (10, 11, 16), we undertook stereotactic surgery of this target and others (8, 9, 116, 141, 142, 146). At the same time, we continued nonhuman primate research into establishing the pedunclopontine nucleus as a potential target for gait freezing and postural instability (88, 129, 133, 134). The subthalamic nucleus is now the target of choice for Parkinson's disease surgery, and initial clinical results of targeting the pedunclopontine nucleus show great promise (99, 151, 158, 165).

Other translational research at the University of Oxford and Imperial College London included invasive deep brain electrophysiological insights into tremor and dystonia (115, 117, 174), the use of single-photon emission tomography (145), magnetoencephalography (108), and diffusion tensor imaging (6, 132) to study deep brain stimulation, and research into deep brain stimulation for pain and blood pressure control and brainstem control of exercise (55, 56). We have used deep brain stimulation to treat 70 patients with dystonia (180) and 60 patients with chronic pain (138), and we perform one-fifth of Britain's movement disorders surgery.

In Bristol, Professor Steven Gill has continued the Great British tradition of innovation, creating a stereotactic frame convenient for radiosurgery under Professor David Thomas'



FIGURE 12. The faculty of the International Workshop on Functional Neurosurgery for Movement Disorders and Mental Illness & Commemoration of the 150th Anniversary of the Birth of Sir Victor Horsley, London, 2007. (Courtesy of Professor Marwan Hariz.)

supervision in London (97, 162) and performing several clinical firsts, including glial cell-derived neurotrophic factor infusion and pedunclopontine nucleus stimulation for patients with Parkinson's disease (45, 118, 143, 149). With a current Hunterian Professor of the Royal College of Surgeons, Mr. Nik Patel, he continues to drive the field forward.

After the retirement last decade of Mr. John Miles in Liverpool, whose tremendous pain practice still left time for several innovations (31, 32, 139), Professor David Thomas also recently retired as the Gough-Cooper Professor of Neurosurgery at the National Hospital of Neurology and Neurosurgery at Queen Square. He had devoted 3 decades to the improvement of stereotactic surgical techniques with and without frames (34, 98, 168–170). Britain recently welcomed Professor Marwan Hariz at Queen Square as the first Edmond J. Safra Chair of Functional Neurosurgery, establishing a biennial international workshop that, like its host, is truly unique for its conviviality and candor (Fig. 12).

In 2008, a century on from Horsley's first experiments, almost all of the 34 hospitals conducting neurosurgery in Great Britain and Northern Ireland have consultants able to offer stereotactic surgery. One-third of these hospitals have subspecialty-trained stereotactic surgeons who offer functional procedures. Most of these surgeons are affiliated with universities and are conducting clinical or translational research, or both. From Cardiff to Cambridge to Liverpool to Newcastle and beyond, far from being the reserve of the eccentric scientist-surgeons looked upon with suspicion by the rest of the neurosurgical fraternity, stereotactic surgery has become an established clinical subspecialty and academic discipline in its own right.

The Past as Prologue

The empires of the future are the empires of the mind.

—Sir Winston Churchill
(1943, speaking at Harvard)

The Society of British Neurological Surgeons, formed in 1929, has recently begun devoting specific sections to stereo-

tactic and functional neurosurgery at its meetings. Its journal, the *British Journal of Neurosurgery*, is currently edited by Mr. Thelekat Varma, assisted by Mr. Paul Eldridge, both of whom are experts in stereotactic surgery. Another society with a focus on pain that welcomes stereotactic neurosurgeons, the Neuromodulation Society of the United Kingdom and Ireland, was founded in 2001. Such factors prove good indicators of the definitive establishment of the subspecialty in the United Kingdom.

The current and future status of neurosurgical training in Great Britain is uncertain, with a recent move to enable entry to a 7-year "run-through" residency in the specialty commencing with neurosciences exposure after 2 "foundation years" of internships, usually comprising less than a year of general surgical experience (60, 135). A 1-year subspecialty year follows the 7-year residency; academic experience during training is potentially discouraged in all but a handful of trainees, who are appointed to "integrated academic training." It is too early to predict whether such moves will promote or stifle the rich British tradition of surgeon-scientists. As has been observed, "one disappointing area at present is the reluctance of United Kingdom trainees to commit themselves to a career in academic neurosurgery, the majority preferring the seemingly more secure and definitely better remunerated posts in the National Health Service" (127a, p 158).

Further challenges to British neurosurgical training include a European Working Time Directive limiting doctors' hours to a 48-hour week beginning in 2009, which increases the tensions between training and service (114). Standards have remained constant during the past decade (113) and may be augmented by the structure of competence-based progression implemented by Professor Alan Crockard (60). However, we maintain that stereotactic neurosurgeons must, first and foremost, be excellent general neurosurgeons who are well versed in the anatomy of their procedures and able to deal with potential complications, and that they must be masters of the cantatas before they attempt the fugues. Seventy-seven years after Dott first clipped an aneurysm (171), few new British consultants have ever done so. Fewer still have performed functional procedures, but, perhaps they will do so within half the time since Dott, because they all may have stereotactic surgery in their repertoire by the end of their training.

Gildenberg has commented that there are several tenets of the field of stereotactic surgery (44): that there is a need to be innovative—a better way to do something may be more apparent to the most junior member of the team rather than the most senior; that stereotactic surgeons work as a community and not in isolation; that stereotactic surgery is, to a large extent, a basic science. Although not appealing to the neurosurgeon interested only in a better way to cut, it is exciting to one appreciating the associated basic science. Finally, there is awe and appreciation for the insight and courage of the true pioneers in the field. The British school exemplifies such principles. It is hoped that its practitioners will continue to hold true to them in the current era of excitement and beyond.

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COMMENTS

Pereira et al. have provided a detailed and interesting historical perspective on how stereotactic surgery advanced in Great Britain during the past century. Not only is the pertinent time line presented, but also the style provides the reader with some appreciation of the personalities and motivation of the major players. Not only is there agreement that the seeds of stereotactic concepts were planted in the laboratory of Sir Victor Horsley, but also he is also generally acknowledged to be the father of modern day functional neurosurgery. The examples of cross-fertilization of ideas freely shared and the handing of the torch to suc-

cessive generations are still the patterns on which stereotactic and functional neurosurgery continue to advance.

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This is an excellent historical review of stereotactic neurosurgery in the United Kingdom. I feel blessed that I was given the opportunity to live through some of the history recounted here, fortunate to have known many of the people referred to in this article, and honored to call some of them friends. And I have heard oral, admittedly anecdotal, versions of that history that render it all the more colorful. I will start with this story John Gillingham told me:

He and his good friend, Gerard Guiot, were inspired by the work of Fenelon who was placing a coagulation probe above the optic tract to lesion the ansa lenticularis in awake patients with Parkinson's disease and tremor. Fenelon had developed this technique after Russell Meyers had established that the ansa lenticularis was the key to the management of tremor. However, Meyers' transventricular approach to the ansa had a 10% mortality!

Gillingham and Guiot adopted Fenelon's technique but noted that, at the awake craniotomy, retraction of the frontal lobe to properly visualize the optic tract stretched the lenticulostriate arteries. They then discussed stereotactic lesioning of the ansa; Guiot proposed a coronal approach.

Neither Gillingham nor Guiot spoke the other's language very well. Gillingham communicated with Guiot by speaking English with a French accent; Guiot drew pictures when his English failed him. So, Guiot, a talented artist, drew anatomic cross sections of the anatomy on a blackboard for Gillingham in order to illustrate the surgical approach.

Gillingham admired the drawing and its anatomic sophistication and then said: "Gerard, my friend, you have forgotten something very important in this drawing: the blood vessels!" "Tu as raison!" Guiot answered, "You are right!"

It was at that moment that both saw the wisdom of approaching the ansa lenticularis target from the posterior. They developed the frame as described in this article. Guiot went on to target the medial pallidum, then ventrolateral (ventro-oralis posterior/ventral intermediate nucleus), and this approach was perfect for the neurophysiologic localization methods he developed with Albe Fessard. Gillingham used the approach to lesion the pallidum then the pallidothalamic fibers in the anterior portion of the internal capsule's posterior limb. The only substantive difference between Guiot's and Gillingham's frames was that Guiot's frame directed the lesioning probe at a fixed 6-degree medial trajectory (to account for the obliquity of the internal capsule); Gillingham's frame directed the probe parallel to the midline. Both understood, very early on, the importance of electrophysiologic target corroboration.

As an aside: when Russell Meyers learned of the posterior approach to the ansa and pallidum he declared: "Leave it to the French and Brits to approach a problem from behind!"

Robert Henry Clarke's contribution was not necessarily the development of a stereotactic frame (as Pereira et al. note: probe positioning devices had been used for about 30 years before that). However, incorporating a navigational Cartesian coordinate system to the frame may have truly been an original concept. They suggested that Clarke received his inspiration from the start during a trip to Egypt. My understanding was that he found himself in Alexandria, the home of Claudius Ptolemy (100–178 AD), astronomy, cartography, and navigation. For centuries geographical location has been defined by a coordinate system: latitude and longitude; a concept easily abstracted to intracranial navigation.

I doubt that Horsley and Clark's falling out stemmed from a simple row over the adaptation of the stereotactic concept to humans

(although I would like to believe this). Their acrimony started before this, possibly when Horsley was knighted. What started as friendship and collaboration, degenerated into jealousy, mistrust, and bickering. As Horsley's fame grew, Clarke became ever more resentful and sour with his own descent into obscurity.

Americans credit E.A. Spiegel with the first human subcortical stereotactic procedure in 1947. However, Spiegel was in communication with Clarke in the early 1920s and tried to have a stereotactic frame constructed by Palmer & Company. But the price of £300 was too steep for him at the time. Of particular interest is that each of Spiegel's versions of human stereotactic devices bore striking similarities to the devices pictured in Clark's 1920 monograph. Indeed, in 1912, Clarke submitted to the British Patent Office a patent application a device for a human stereotactic instrument.

Certainly British stereotactic neurosurgery has a rich history of innovation, and I could go on and on with stories; John Gillingham, Ted Hitchcock, David Thomas, and others were great raconteurs. But it is important for us to realize that the United Kingdom is an island only in geography. For the past 100 years British stereotactic surgeons and scientists have generously shared their techniques and innovations with the rest of the world (I recall John Gillingham, on a visit to Texas, bringing me one of his semimicroelectrodes so that I could copy it.) When the practice of stereotactic neurosurgery had virtually died in America with the advent of L-dopa, stereotactic techniques survived in England (as well as in France, Sweden, and Germany) and were passed on to young neurosurgeons from around the world.

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With his appointment in 1884 as Professor-Superintendent of the Brown Institution, a veterinary research facility, Victor Horsley embarked on a landmark series of experiments to delineate the functions of the cerebral hemispheres of primates. In collaboration with Charles Beevor and E.A. Schafer, he extended the pioneer work of David Ferrier using both ablations and electrical stimulations. The development of Robert Clarke's apparatus allowed Horsley to make lesions in the deep cerebellar nuclei without violating the overlying cerebellar cortex. He did not live to see adaptation of the frame to human subjects, nor could he have envisioned the enormous impact that this innovation would have on the field of neurological surgery in the century that followed. In this informative article, Pereira et al. mentioned Wylie McKissock's criticism of the ice-pick leucotomy procedure. This transorbital approach was adopted by Walter Freeman, a neuropsychiatrist. His early collaborator was James Watts, a neurosurgeon trained by Charles Frazier and Otfried Foerster. Watts in essence agreed with McKissock and as a consequence severed his relationship with Freeman. He wrote the following in a second edition of their book: "It is Walter Freeman's opinion that transorbital lobotomy is a minor operation. It is my opinion that any procedure involving cutting of brain tissue is a major surgical operation, no matter how quickly or atraumatically one enters the intracranial cavity. Therefore, it follows logically, that only those who have been schooled in neurosurgical technics and can handle complications which may arise should perform the operation (1)."

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RUPTURE OF A PSEUDOANEURYSM OF THE POSTERIOR MENINGEAL ARTERY AT ITS ANOMALOUS ORIGIN FROM THE POSTEROINFERIOR CEREBELLAR ARTERY: CASE REPORT

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OBJECTIVE: The posterior meningeal artery (PMA) normally arises from the vertebral artery; however, its origin varies considerably as the result of its embryological development. This gains clinical significance when associated with vascular pathology.

CLINICAL PRESENTATION: A 65-year-old man presented to his local hospital with a sudden-onset, severe headache. Computed tomography of the head revealed diffuse subarachnoid hemorrhage, mostly in the left posterior fossa. A computed tomographic angiogram demonstrated an anomalous origin of the PMA from the posteroinferior cerebellar artery (PICA). Cerebral angiography showed the PICA to be enlarged, with a reduced caliber at the takeoff of the PMA, which is consistent with possible dissection.

INTERVENTION: The patient was taken to the operating room for trapping of the dissecting segment of the PMA. A clip was placed across the PMA at its origin from the PICA, and the vessel was coagulated and transected. The PICA was wrapped in muslin gauze.

CONCLUSION: The variable origin of the PMA and PICA may be the result of the persistence of embryological anastomoses between the arteries, with regression of the normal channel. Physical stress at the junction of the anomalous PMA and the PICA may have contributed to the abnormality of the PMA, consistent with possible dissection. Because the PMA has multiple anastomoses with the arteries of the falx cerebri, the proximal PMA may be occluded with no compromise to its vascular territory.

KEY WORDS: Aneurysm, Posterior meningeal artery, Posteroinferior cerebellar artery, Subarachnoid hemorrhage

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The origins of the posteroinferior cerebellar artery (PICA) and posterior meningeal artery (PMA) vary considerably as a result of their embryological development. The PMA is clinically important because it may supply posterior fossa lesions, including meningiomas, hemangioblastomas, and arteriovenous malformations (8). The PMA normally arises from the V3 segment of the vertebral artery, at or just below the foramen magnum, supplying the falx cerebelli and the medial aspect of the dura underlying the occipital bone (5). Anatomic variations of the origin of the PMA, in which the artery arises from the PICA, have been described. In three of the four cases in the literature, this anomaly was found incidentally (3, 8). One report describes a ruptured aneurysm at the PICA-PMA bifurcation (4). We report the case of a

patient presenting with subarachnoid hemorrhage from a pseudoaneurysm of the PMA that was treated by microsurgical trapping.

CASE REPORT

While playing bridge at home, a 65-year-old man with a history of hypertension developed a sudden, severe headache across his entire head, accompanied by neck pain. He experienced "dry heaves" but had no loss of consciousness or neurological deficits. He presented to his local hospital, where he underwent computed tomography of the head, which demonstrated a diffuse subarachnoid hemorrhage, with the majority of the blood in the left posterior fossa. There was no hydrocephalus or midline shift. The patient was placed on mannitol and dexamethasone (Decadron; Merck, Whitehouse Station, NJ), and he was admitted to the intensive care unit. A cerebral angiogram was inconclusive for intracranial aneurysm; however, an abnormality was suspected in the region of the left PICA origin. Verapamil and nimodipine were started on postbleed Day 5. A computed tomographic angiogram demonstrated an extradural origin of the left PICA from the

ABBREVIATIONS: PICA, posteroinferior cerebellar artery; PMA, posterior meningeal artery; VA, vertebral artery

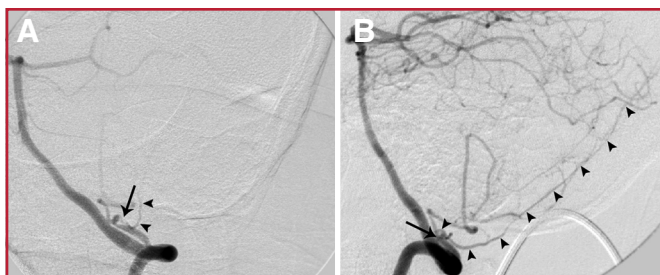


FIGURE 1. **A**, angiogram showing the posterior meningeal artery (PMA) (arrowheads); it appears to be narrowed proximally (arrow) and which is consistent with possible dissection. **B**, left vertebral angiogram demonstrating the anomalous origin of the PMA from the lateral medullary segment of the posteroinferior cerebellar artery (PICA) (arrow). The PMA is identified by its straight course (arrowheads).

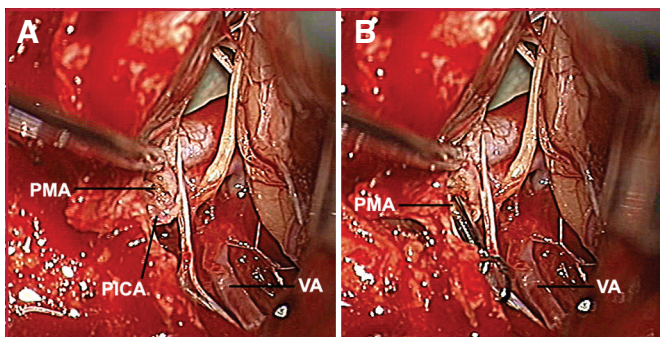


FIGURE 2. **A**, intraoperative photograph showing the PMA arising from the PICA. VA, vertebral artery. **B**, intraoperative photograph showing the PMA, which was coagulated and clipped immediately after its origin from the PICA, with no impingement of the PICA.

ipsilateral vertebral artery and an anomalous origin of the PMA from the PICA just distal to the site of dural penetration. The angiogram showed the PICA to be enlarged and to have a reduced caliber at the takeoff of the PMA, consistent with possible dissection (Fig. 1A). Both the PICA and PMA were noted to have tortuous courses; however, no aneurysm was observed (Fig. 1B).

The patient was taken to the operating room for microsurgical exploration of the left vertebral artery, PICA, and PMA. A left suboccipital craniotomy was performed. The vertebral artery was directly visualized as it pierced the dura, and the tortuous course of the PICA was identified. The PMA branch was identified coursing to the dura. The PMA appeared to have a thickened wall as it entered the dura; however, it was unclear whether this was part of a pathological process or the normal appearance as the vessel penetrated the dura. A 5-mm clip was placed across the PMA, close to its origin from the PICA. The vessel was coagulated and transected (Fig. 2). The PICA was pulsatile and showed no sign of compromised flow. The PICA was then wrapped with muslin gauze, out of concern for possible dissection of the proximal PICA. Postoperatively, the patient awoke with no neurological deficits. An angiogram obtained on postoperative Day 3 revealed surgical clip obliteration of the origin of the left PMA without evidence of dissection or residual opacification (Fig. 3). The patient was discharged on postoperative Day 8, and at a follow-up

evaluation 1 month after discharge, he was neurologically intact.

DISCUSSION

Including our patient, there are only five reported cases of an anomalous PMA originating from the PICA, and in only two of these, this anomaly has led to vascular pathology (3, 4, 8). In the previous case described by Okuno et al. (4), a saccular aneurysm at the PMA-PICA bifurcation was microsurgically clipped, with no compromise of either vessel.

The PMA, at times identified as the artery of the falx cerebelli, usually originates from the vertebral artery extradurally, but it has been identified with some frequency to branch from the ascending pharyngeal artery or the occipital artery (2, 9). There are reports of single cases in which the PMA arises from the hypoglossal or carotid arteries and three previous cases of a PICA origin. This considerable variation results from the embryological development of the PMA.

The arteries along the posterior part of the hindbrain maintain a plexiform conformation late in development, as seen in Stage 6 (20–24 mm) embryos (6). The PMA arises from the anastomosis in the first cervical space, and its origin depends on the hemodynamic dominance of the arteries in the area of the posterior hindbrain (1). The persistence of the lateral basilovertbral anastomosis may be exhibited in the adult by the wide variation in the origins of the PICA and PMA. The PMA may arise from the PICA by persistence of an embryological channel with regression of the usual proximal channel from the vertebral artery (4, 8).

Intracranially, the PMA courses straight, along the falx cerebelli. It divides at the level of the occipital protuberance, with branches supplying the inferior tentorium cerebelli and the posterior part of the falx cerebri. As the PMA is fixed to the dura, physical stress at the junction of the anomalous PMA to the PICA might have contributed to the PMA abnormality with possible dissection in our patient.

The PMA has multiple anastomoses with the arteries of the falx cerebri, including the middle meningeal artery and meningeal branches of the posterior cerebral artery (1, 2, 7). This abundant blood supply allows the proximal PMA to be occluded with no compromise to the falx cerebelli, as was demonstrated in our patient.

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FIGURE 3. Left vertebral angiogram demonstrating clip positioned at the origin of the PMA from the PICA (arrow). No residual filling of the PMA is observed.

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COMMENTS

This case report is a reminder to us to continue to be vigilant when looking for causes of subarachnoid hemorrhage (SAH). Aronson et al. nicely describe an unusual case of a patient with a SAH resulting from a pseudoaneurysm of anomalous origin of the posterior meningeal artery (PMA) from the posterior inferior cerebellar artery. This is one of the few reported cases of an anomalous origin of the PMA and the second patient in whom the anomalous origin was associated with a pathological condition. Aronson et al. showed diagnostic and surgical skill in the treatment of this unusual cause of SAH.

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Aronson et al. report a patient with a pseudoaneurysm of the posterior PMA causing a SAH, and the PMA anomalously originated from the posterior inferior cerebellar artery of extradural origin. Although the reported case is rare in terms of the source of the SAH, possible anomalous origins of the PMA also from branches of the external carotid artery or the internal carotid artery should be considered in the treatment of various lesions adjacent to the posterior fossa dura and tentorium. Because the endogenous revascularization of the distal posterior inferior cerebellar artery (PICA) territory via collateral circulation from the PMA has been reported in a patient with a dissecting aneurysm of the PICA after endovascular occlusion of the lesion and parent artery (1), the role of PMA should be kept in mind

not only as a feeder of vascular lesions or tumors but also as a potential collateral vessel.

Kazuhiko Nozaki
Otsu, Japan

1. Tsutsumi M, Kazekawa K, Aikawa H, Iko M, Kodama T, Nii K, Matsubara S, Etou H, Sakamoto K, Tanaka A: Development of unusual collateral channel from the posterior meningeal artery after endovascular proximal occlusion of the posterior inferior cerebellar artery. *Neurol Med Chir (Tokyo)* 47:503–505, 2007.

Aronson et al. report a patient, who had a SAH while playing bridge. The source of the SAH was a pseudoaneurysm of the intradural PMA, which had an anomalous origin from the PICA in association with a possible dissection. This was treated successfully by trapping of the proximal PMA.

There have only been five cases, including the one here, describing this kind of vascular anomaly and only two were associated with a symptomatic aneurysm. Thus, there is an element of originality in this report, which is very well written and illustrated. From reading this, I learned that the PMA may be the site for a symptomatic aneurysm and that playing bridge is not entirely without danger.

Bernhard Meyer
Munich, Germany

Aronson et al. describe an unusual occurrence of an SAH in a 65-year-old man from a pseudoaneurysm of the PMA. The PMA had an anomalous origin from the PICA, arising from this vessel just distal to the site of dural penetration. The posterior meningeal artery was clipped, coagulated, and transected and the PICA was wrapped with muslin. The authors theorize that physical stress at the junction of the PMA with PICA may have been the cause of this pseudoaneurysm. The angiogram provided does show a decrease in the diameter of PICA just before the take off of the PMA, but I am not convinced that I see a definite pseudoaneurysm. I suspect this decrease in PICA diameter correlates with the site of dural penetration of this vessel. The patient did well and experienced no further episodes of subarachnoid hemorrhage.

It seems unlikely that an acute physical stress of the anomalous PMA origin from PICA occurred during a game of bridge. Perhaps the patient's partner trumped a trick that was already won, causing the patient to snap his head up in disbelief! Alternatively the SAH from this vessel anomaly may have been the result of chronic vessel stress from years of head movements and traction on this vessel anomaly.

Carl B. Heilman
Boston, Massachusetts

THE DEVELOPMENT OF RING-SHAPED CONTRAST ENHANCEMENT IN A CASE OF CEREBELLAR DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOR: CASE REPORT

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OBJECTIVE: Dysembryoplastic neuroepithelial tumor (DNT) occurs rarely in the cerebellum. We describe a rare case of cerebellar DNT that developed contrast enhancement after long-term observation and discuss the underlying mechanism and clinical relevance of this unusual phenomenon.

CLINICAL PRESENTATION: A 34-year-old woman with known cystic cerebellar lesions presented with increased frequency of vertigo and new onset of truncal ataxia. Magnetic resonance imaging revealed new contrast enhancement in the dominant cystic lesion of the cerebellar vermis without any change in size and shape or evidence of edema.

INTERVENTION: The lesions were resected under magnetic resonance imaging guidance. Histological assessment revealed populations of small, round cells in a microcystic background containing "floating" neurons, diagnostic of DNT. Microvascular proliferation and pigmented neurons were also present.

CONCLUSION: This is the first report of the development of contrast enhancement in a previously nonenhancing case of cerebellar DNT. The acquisition of ring-shaped contrast enhancement may be associated with microvascular proliferation, but otherwise no evidence of malignant progression. In addition, this case presents the novel pathological finding of pigmented neurons in DNT.

KEY WORDS: Cerebellum, Contrast enhancement, Dysembryoplastic neuroepithelial tumor, Microvascular proliferation

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Dysembryoplastic neuroepithelial tumors (DNT) are thought to arise during embryogenesis. Clinically, they are indolent lesions that are usually found in cortical regions of young adults and present with partial seizures (4). Radiographically, they appear hypodense on computed tomography, hypointense on T1-weighted magnetic resonance imaging (MRI) scans, and hyperintense on T2-weighted MRI scans (6). Contrast enhancement is variable, occurring in 18 to 33% of cases (4, 16, 17). We report a patient with a previously nonenhancing lesion in the cerebellar vermis that developed ring-shaped contrast

enhancement concurrent with new localizing symptoms after 9 years.

Case Report

Clinical Presentation and Examination

A 34-year-old professional equestrian presented with an indolent cystic lesion in the cerebellum that had initially caused headaches and spells of vertigo 9 years before the present evaluation. Fifteen months previously, she had reported increased frequency of vertigo up to 3 episodes per week, each lasting a few seconds to 1 hour and associated with nausea and unsteadiness. In addition, she experienced headaches that were migrainous in nature, which responded to regular nocturnal doses of nortriptyline. There were no other pertinent symptoms during this time, and her neurological and systemic examination was normal. An MRI scan of the brain during this period showed no significant interval

ABBREVIATIONS: DNT, dysembryoplastic neuroepithelial tumor; MRI, magnetic resonance imaging

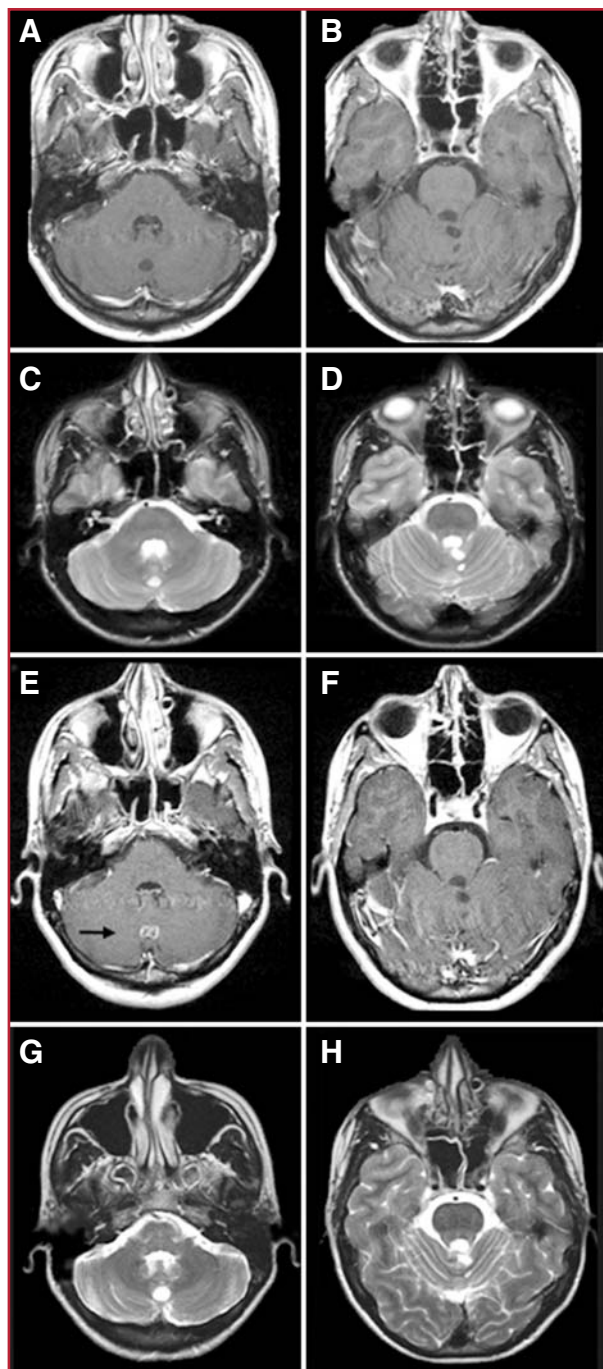


FIGURE 1. Magnetic resonance imaging (MRI) scans demonstrating the development of a cystic enhancing lesion in the cerebellar vermis over 20 months. The T1- (**A** and **B**) and T2-weighted (**C** and **D**) images demonstrate cystic nonenhancing lesions in the vermis with no significant edema. Twenty months later, the dominant cystic lesion in the posterior cerebellar vermis (arrow) developed new ring-like gadolinium enhancement on T1-weighted images (**E** and **F**) with no significant increase in size or edema shown on T2-weighted imaging (**G** and **H**).

change in the size or appearance of the small cystic areas in the cerebellar vermis, as compared with 4 years previously (Fig. 1, A–D). Other investigations into the cause of her vertiginous episodes, including magnetic resonance angiography of the neck and brain, electroencephalography, and electronystagmography were unremarkable.

Five months before the present evaluation, the patient had experienced an episode of altered consciousness during horseback riding. Witnesses reported her to be “riding around lost” for a period of 5 minutes, of which she had no memory. After this episode she experienced constant headache of varying intensity and the new onset of truncal ataxia, which caused her to fall off her horse on numerous occasions. Repeat MRI scans showed a 1 × 1 cm lesion in the cerebellar vermis posteriorly, a 0.8 × 0.8 cm lesion in the anterior vermis, and two additional small lesions lateral to the midline (Fig. 1, E–H). These lesions had been present on the previous MRI scans and were similarly hypointense on T1-weighted scans and hyperintense on T2-weighted scans. However, the new MRI scan revealed a new finding: the dominant lesion in the posterior cerebellar vermis demonstrated ring-shaped enhancement with gadolinium (Fig. 1E). There was no evidence of perilesional edema, increased mass effect, or calcification. Subsequent magnetic resonance spectroscopy revealed normal spectra of chemicals. Serology for cysticercosis and cryptococcal antigen was negative, making the possibility of infection by these agents unlikely.

In view of the new symptoms affecting this patient’s equestrian career, as well as the uncertain pathological nature of the lesion and the development of contrast enhancement, the patient was offered surgical biopsy and resection under intraoperative magnetic resonance guidance.

Surgery

A midline suboccipital craniotomy was performed with the patient in the prone position. The cystic lesions were identified with intraoperative MRI scans after injection of gadolinium. During surgery, the dominant lesion in the posterior vermis was found to contain yellow fluid and appeared different from the anterior cysts, which contained soft, gray, multinodular gelatinous tissue. The small non-contrast enhancing parasagittal lesions to the left of the midline were macroscopically consistent with solid tumor.

The patient had an uncomplicated postoperative course. At the 9-month follow-up examination, the patient was free of headache, vertigo, ataxia, or any other neurological symptoms experienced preoperatively and had restarted work as a horseback riding instructor. Postoperative MRI performed 3 months after the operation demonstrated no recurrence of the enhancing vermian lesion (Fig. 2).

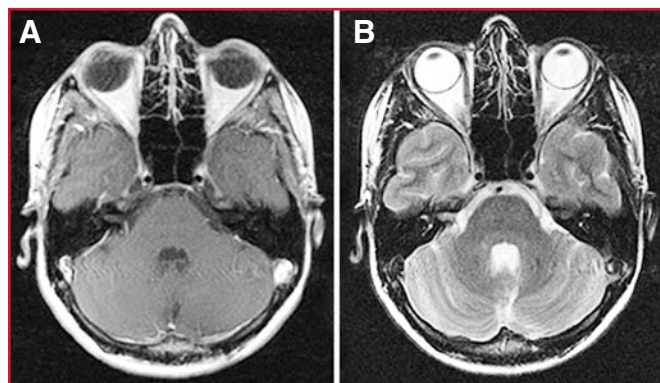


FIGURE 2. T1- (**A**) and T2-weighted (**B**) MRI scans taken 3 months after the operation showing no recurrence of the enhancing lesion.

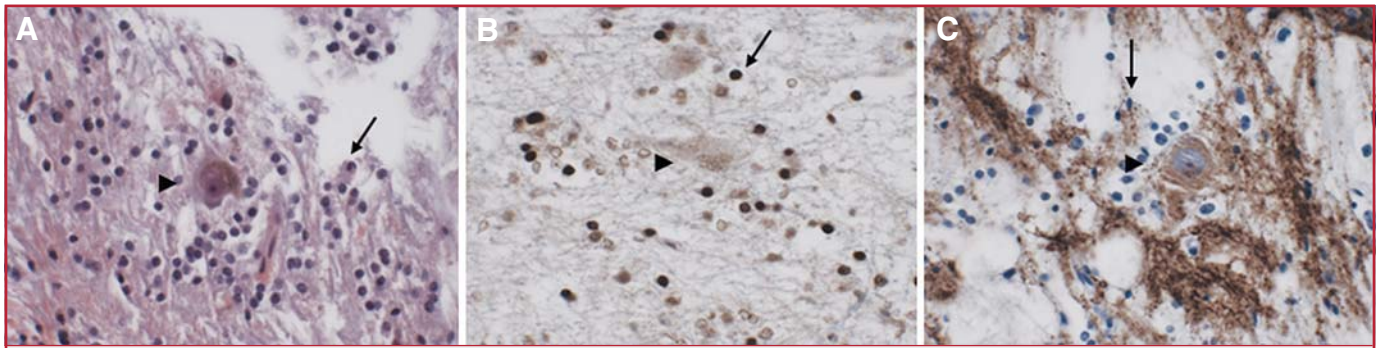


FIGURE 3. Histopathology of dysembryoplastic neuroepithelial tumor, with large, pigmented ganglion cells (arrowheads) and small oligodendroglia-like cells (arrows). **A**, hematoxylin and eosin stain; **B**, immunostain.

Immunostain for Olig2, marking nuclei of some small cells but no ganglion cells; **C**, immunostain for synaptophysin, positive along the cytoplasmic membrane of both cell types. Original magnification, $\times 400$ (**A–C**).

Neuropathology

The dominant lesion was composed of mostly small, round cells in a microcystic background containing “floating neurons,” some of which contained cytoplasmic neuromelanin-type pigment (Fig. 3). This pigment was negative on Perl’s iron stain. The small, round cells were predominantly oligodendrocyte-like cells, immunostaining extensively for Olig-2 and occasionally with neuronal marker NeuN. Punctate staining for neurofilament (SMI-31) and synaptophysin was noted in the background neuropil. Background astrocytes stained positively for glial fibrillary acidic protein. In some areas, tumor cells had a bipolar “piloid” appearance, with the unusual finding of microvascular proliferation (Fig. 4). The MIB-1 proliferative index in tumor cells was 1%, confirming low-grade histology. There was no histological evidence of previous hemorrhage (i.e., hemosiderin-laden macrophages, astrogliosis or fibrosis, or extracellular iron depositon Perl’s stain).

DISCUSSION

Dysembryoplastic neuroepithelial tumor is a slow-growing, intracranial, mixed neuronal-glia neoplasm characterized by cortical location, multinodular architecture, and heterogeneous cellular composition (4). Only five reported cases have involved the cerebellum (7, 10, 12, 13, 18). These patients typically presented with recurrent episodes of ataxia or vertigo as young adults (there was one report of a 10-year-old child) with an otherwise normal neurological examination. There was one report of cerebellar DNT associated with Arnold-Chiari Type I malformation (18), and one case of DNT that was multifocal, also affecting the right temporal lobe (12).

The radiographical features of DNT have been extensively characterized (6, 14). DNTs are hypodense on computed tomography examination, and demonstrate decreased signal on T1-weighted MRI and increased signal on T2-weighted MRI. Contrast enhancement is well-recognized in supratentorial DNTs, often appearing as multiple rings rather than homogeneous enhancement (3, 17). Stanescu Cosson et al. (17) found contrast enhancement in 21% of cases of supratentorial DNT, and Shin et al. (16) found these changes in one third of cases. Our patient is the first reported case of cerebellar DNT to show

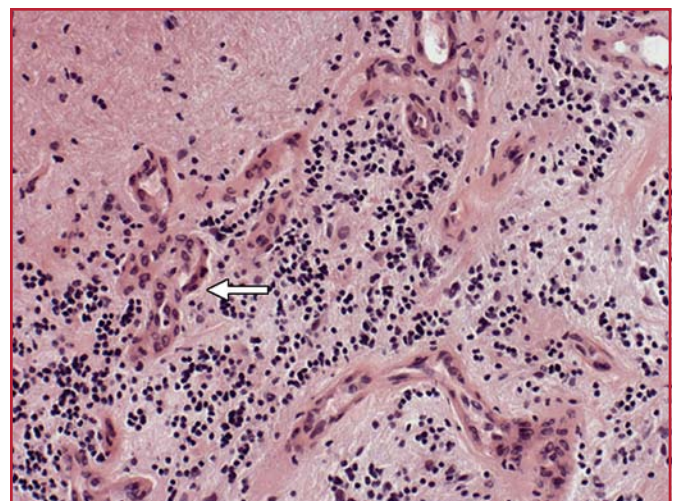


FIGURE 4. Histopathology showing the interface between tumor (right) and normal cerebellum (top left), where there is increased vascular density as well as microvascular proliferation (arrow). Original magnification, $\times 400$.

contrast enhancement. Notably, the contrast enhancement developed after many years of long-term observation and coincided with an episode of altered consciousness, increasing vertiginous symptoms, and new-onset truncal ataxia. The new contrast enhancement, in conjunction with these increased neurological symptoms, stood as important reasons to remove the tumor surgically at this time.

One mechanism underlying contrast enhancement is thought to be related to ischemic and/or hemorrhagic changes (3). Although the dominant lesion in our case was noted to contain xanthochromic fluid at surgery, there was no histological evidence of old or recent hemorrhage, making the latter explanation unlikely in our case. Instead, the histopathological finding of microvascular proliferation may be the underlying substrate for the contrast enhancement in this case. The microvascular network in DNT is well recognized to vary considerably from sim-

ple to exuberant glomeruli-like vessels (3). The presence of hamartomatous or calcified vessels is not uncommon (2, 3, 5). Such abnormally developed vessels may have altered vascular permeability as well as altered vascular bed perfusion, leading to ring-like localization of contrast agent. They may also be the source of microhemorrhages, although these were not present in this case.

In 2006, Jensen et al. (8) reported a patient who developed contrast enhancement after 15 years of follow-up MRI scans that showed a stable, nonenhancing DNT in the medial temporal lobe. The patient experienced medically intractable epilepsy for several years, although the patient's seizures grew progressively worse in the year preceding her eventual surgery. The authors postulated that the new enhancement in the medial temporal lobe could be the result of increased seizure activity, similar to enhancement seen in cases of epilepsy with non-neoplastic causes (8). However, no literature data were given by these authors for the later observation, and contrast enhancement is not characteristic of highly epileptogenic lesions such as focal cortical dysplasia of Taylor (1). Other theories for the development of contrast enhancement in DNT include malignant transformation or progression from simple to complex form. Malignant transformation is unlikely because the MIB-1 proliferative index of the resected tumor was less than 1%, and progression to complex type of DNT with formation of new glial nodules and multinodular architecture is improbable because there was no significant increase in size of the lesion. Moreover, most complex DNT do not show contrast enhancement (3).

As an additional point, this case demonstrates the finding of neuromelanin-like pigment in the "floating" neuron component of the DNT, which, to our knowledge, has not been described previously. These cells must be a tumor-derived element, as no such cell types exist in the cerebellum normally, and may indicate the functional capability of tumor cells to secrete catecholamines or other neurotransmitters. Unfortunately, insufficient tumor tissue remains in the blocks for testing of this hypothesis.

CONCLUSION

This case report demonstrates that DNT in the cerebellum may develop contrast enhancement on MRI over time. Histologically, these radiographical findings were associated with microvascular proliferation. The new contrast enhancement may coincide with worsening symptoms relating to the affected brain location and may be used as a factor in the surgical management of this type of brain tumor. This case study also offers the first report of pigmented ganglion cells in DNT.

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COMMENTS

There are a number of unusual features of this case report presented by Tailor et al.: 1) The cerebellum is an unusual location for a dysembryoplastic neuroepithelial tumor (DNT). (This probably is a DNT, although the presence of "floating neurons" may be mimicked by entrapment of normal neurons by a variety of tumors. Unfortunately, there is no confirmatory molecular test for DNT as yet.) 2) The development of contrast enhancement in a DNT is unusual in the absence of infarction, hemorrhage, or more aggressive tumor proliferation, none of which was histologically present in this patient (although sampling error of the tissue reviewed could be an explanation). 3) The development of new symptoms not clearly mechanistically associated with a tumor in this location in the absence of significant mass effect.

The take-home points of this article are as follows: 1) The development of contrast enhancement in a previously nonenhancing primary brain tumor is generally a bad sign: something has changed in the tumor vessels, allowing extravasation of the contrast material. This finding often heralds progression to a more malignant tumor and, with or without new symptoms, should prompt further investigation, either biopsy or resection. 2) A well-defined molecular characterization of DNT is sorely needed to aid in confirming the diagnosis of true DNT in such patients.

Gene H. Barnett
Cleveland, Ohio

The authors described a rare cerebellar DNT that developed contrast enhancement after long-term observation. This case report adds to the wide spectrum of tumor characteristics that fulfill the criteria for DNT, although there must be some doubt as to whether the lesion itself was related to the symptoms as described. The mechanism for the contrast enhancement in this patient is not clear, although the histological finding of microvascular proliferation might be the underlying “substrate” for the enhancement.

This is an excellent case report and furthers our expanding knowledge of DNT.

Andrew H. Kaye
Melbourne, Australia

This case report is interesting from a double point of view: it draws attention to the fact that DNTs may be located in the cerebellum and confirms that in DNTs the development of contrast enhancement in a previously nonenhancing tumor is not a sign of malignant transformation.

Only five cases of cerebellar DNT have been reported previously. DNTs are, however, probably more frequent in this location than previously believed. As illustrated by this patient, DNTs may be composed of pilocytic astrocytes and oligodendroglial-like cells and may thus histologically resemble pilocytic astrocytomas. However, including at the time of diagnosis pilocytic astrocytomas of the cerebellum typically show homogeneous contrast enhancement. The hypothesis of a DNT should thus be considered when such a tumor does not show contrast enhancement. This differential diagnosis is important from a prognostic point of view because, particularly in infants and young children, pilocytic astrocytomas may behave as slow-growing tumors, and in a minority of the patients, intra-axial metastases may be observed at distance from the primary tumor site. Of note, DNTs are not slow-growing tumors, as is said in this article. In the adult brain, the tumors that occur during embryogenesis usually behave as stable lesions.

Ring-like contrast enhancement in a previously nonenhancing tumor has previously been reported in DNT located in the supratentorial cortex. Its occurrence is, in our experience, related to hemorrhagic and/or ischemic changes that induce microangiogenesis (1). The newly formed tumor blood vessels typically occur under the form of arcades of glomeruli-like capillaries. These latter correspond to the ring(s) of con-

trast enhancement seen on imaging. In the patient reported by Taylor et al., no hemorrhagic changes were observed histologically but, interestingly, they reported that during surgery the dominant lesion in the posterior vermis, the one in which contrast enhancement occurred, was found to contain a yellow fluid. This finding strongly suggests that hemorrhagic changes did occur in this part of the tumor. As in this observation, such changes may occur without an increase in the size of the lesion; it is noteworthy, however, that they may lead to an impressive increase in volume of the tumor and major mass effect (1). This is one of the reasons that, in our opinion, surgical removal of a DNT should be considered at the time of diagnosis.

The present case report is the first report of a DNT that comprises ganglion cells with neuromelanin-like pigment. We emphasize that, although the neuronal population of DNTs is sometimes described under this term, these tumors, contrary to gangliogliomas, do not contain ganglion-like cells. Although in the World Health Organization classification, DNTs have been included in the generic category of glioneuronal tumors, it is likely that the neurons seen in DNTs are not tumoral, but correspond to neurons included in this tumor at the time of its development during embryogenesis. In these tumors, neurons may be present in an ectopic situation. Because the magnetic resonance imaging pictures in this report suggest that the anterior “cyst” (which contained soft gray multinodular gelatinous tissue) was in close contact with the brainstem, it is tempting to hypothesize that the pigmented neurons in question may correspond to those normally present in this structure.

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This is the first case report of a cerebellar DNT with contrast enhancement, a radiographic feature sometimes found in DNTs arising supratentorially. Although intriguing, the evidence for a causal relationship between the dramatic worsening of the patient's symptoms and the development of contrast enhancement on imaging is inconclusive because the patient had a nonenhancing magnetic resonance imaging scan when her condition began deteriorating 15 months before presentation. The absence of histological signs of hemorrhage suggests that contrast enhancement is due to microvascular proliferation rather than bleeding.

An additional observation, the presence of pigmented “floating” neurons on histopathological examination, is noteworthy although of unclear significance. The interesting features of this case report should alert clinicians to further study their significance in other rare occurrences of cerebellar DNTs that may arise.

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INTRAMEDULLARY SPINAL CORD METASTASIS FROM BLADDER CARCINOMA: CASE REPORT

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OBJECTIVE: Intramedullary spinal cord metastases are rare complications of systemic cancer. Although the majority of these metastases spread from lung cancer, they have been seen to arise from a variety of other primary sources. The authors report the second known case of an intramedullary spinal cord metastatic lesion arising from primary bladder carcinoma.

CLINICAL PRESENTATION: A 74-year-old man presented with an 8-day history of rapidly progressive Brown-Séquard syndrome, with weakness in his left lower extremity and decreased pain and temperature sensation in his right lower extremity. The patient's history was significant for high-grade urothelial carcinoma that had been treated 6 months earlier with radical cystectomy. A magnetic resonance imaging scan showed an enhancing intramedullary lesion at T1–T2.

INTERVENTION: The patient underwent laminectomies, and removal of his intramedullary lesion was attempted. Intraoperative pathology revealed that the lesion was metastatic in nature, and the decision was made to perform a subtotal resection. Pathology later confirmed that the lesion was consistent with a less differentiated form of his bladder primary. Postoperatively, the patient experienced minimal improvement in his symptoms, and he was subsequently treated with fractionated external beam radiotherapy. The patient died 7 weeks after undergoing surgery for his spinal cord lesion.

CONCLUSION: The occurrence of metastatic primary bladder cancer in the intramedullary spinal cord has been reported in the literature only once previously. Despite the lack of similar cases, the acute onset of Brown-Séquard syndrome was highly suggestive of a metastatic lesion. A review of relevant literature is provided.

KEY WORDS: Bladder carcinoma, Intramedullary tumor, Metastases, Spinal cord

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Intramedullary spinal cord metastases (ISCM) are considered to be quite rare; they account for 1 to 3% of all intramedullary spinal cord lesions (5). The majority of intramedullary metastases are from lung cancer, representing approximately 50% of these lesions. Intramedullary metastases have also been frequently reported to arise from primary lesions such as breast carcinoma, melanoma, lymphoma, renal cell carcinoma, colorectal carcinoma, and unknown primary tumors (5, 7–9, 16, 17). Despite the long list of primary neoplasms that may metastasize to the spinal cord, ISCM that originate from bladder carcinoma are virtually nonexistent. To our knowledge, there has been only one previous report of a patient with a primary bladder carcinoma that metastasized to an intradural intramedullary location

(13). We report a case of an intramedullary metastasis from bladder carcinoma.

CASE REPORT

A 74-year-old man presented with a history of approximately 1 month of dysuria and incomplete voiding. He was initially treated for prostatitis before eventually developing gross hematuria 5 months after initial presentation. A cystoscopy discovered a round, lobular tumor affixed to the base of the bladder. An excisional biopsy performed at that time revealed a high-grade urothelial carcinoma characterized by solid-nodular growth through the bladder wall, invading into the perivesicular tissue. Nests and sheets of mitotically active, mildly pleomorphic cells were seen (*Fig. 1*). The patient then underwent a radical cystectomy with creation of an ileal conduit. Surgical pathology confirmed the previous diagnosis; the distal ureters, prostate, seminal vesicles, and 18 lymph nodes all showed no evidence of malignancy. Based on this diagnosis, the patient was treated conservatively without adjuvant therapy.

ABBREVIATIONS: H & E, hematoxylin and eosin; ISCM, intramedullary spinal cord metastasis

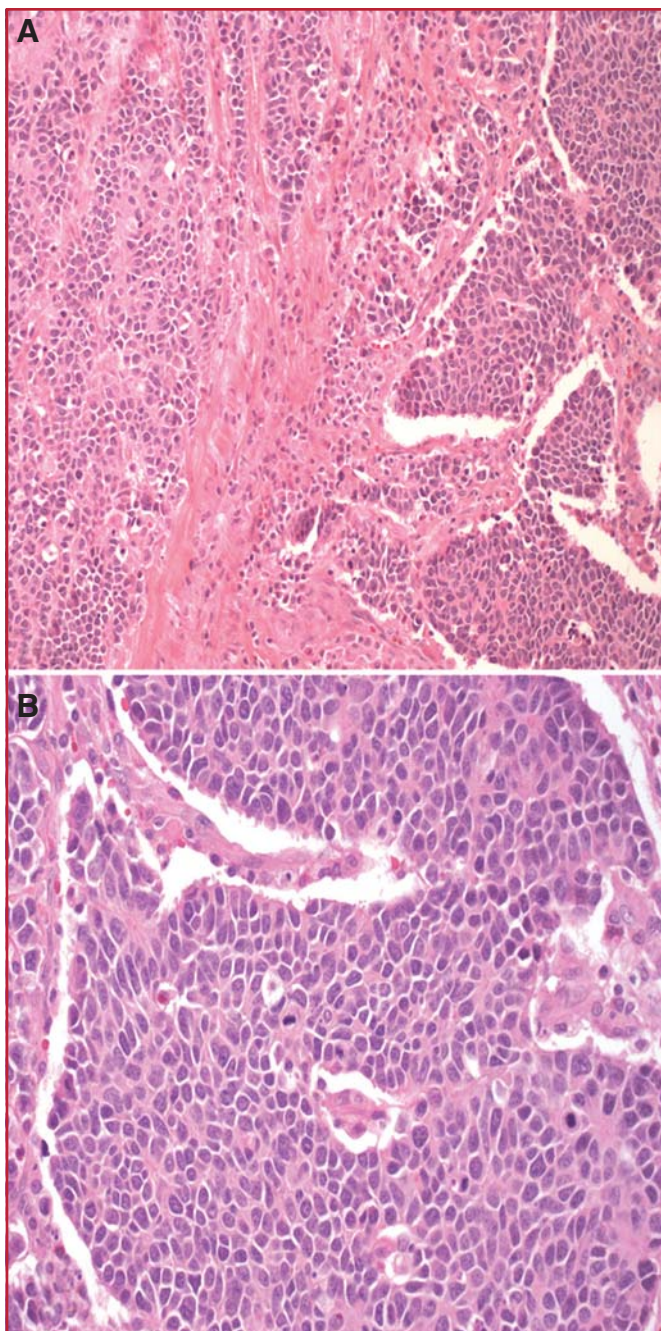


FIGURE 1. Representative histological sections of the primary tumor affixed to the base of the bladder. Micrographs of the tumor at low (**A**, original magnification, $\times 100$) and intermediate power (**B**, original magnification, $\times 200$), displaying a high-grade urothelial carcinoma characterized by nests and sheets of mitotically active, mildly pleomorphic cells. Hematoxylin and eosin (H & E) stain.

The patient presented to the University of Virginia 6 months after the radical cystectomy after experiencing 8 days of progressive left lower-extremity weakness and several episodes of fecal incontinence. On physical examination, the patient displayed a classic Brown-

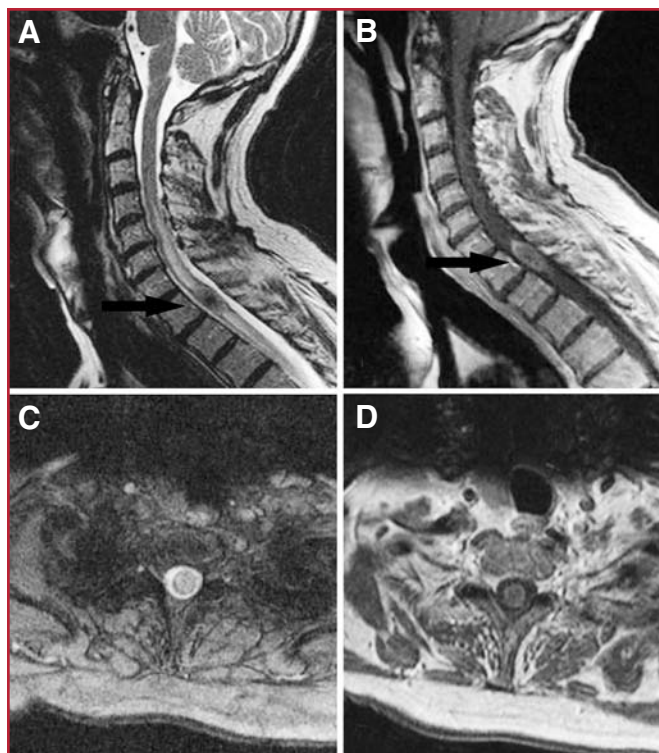


FIGURE 2. Preoperative magnetic resonance imaging scans displaying an enhancing intramedullary mass lesion with significant peritumoral edema. **A** and **B**, T2- (**A**) and T1-weighted postgadolinium (**B**) sagittal images displaying the tumor (black arrows) located between the first and second thoracic vertebrae. **C** and **D**, T2- (**C**) and T1-weighted postgadolinium (**D**) axial images displaying the intramedullary location of the metastatic lesion.

Séquard syndrome, with 2/5 strength and loss of posterior column function throughout his left lower extremity and decreased pain and temperature sensation in his right lower extremity. A magnetic resonance imaging scan of the entire neuraxis revealed an enhancing intramedullary lesion at T1–T2, measuring $0.8 \times 0.8 \times 2.7$ cm with significant peritumoral edema (Fig. 2). A magnetic resonance imaging scan of the brain revealed two small enhancing lesions in the left frontal lobe and left temporal lobe. A computed tomographic scan of the chest, abdomen, and pelvis showed no other evidence of metastatic disease.

The patient was taken to the operating room for a planned resection of his intramedullary lesion. Intraoperatively, the lesion was noted to be infiltrative, with no discernible plane between normal spinal cord and the tumor. When the intraoperative pathology specimen showed that the lesion was metastatic in nature, the decision was made to perform a subtotal resection by internally debulking the tumor, sparing the patient any further loss of function.

Histological examination of the lesion showed a highly cellular proliferation of pleomorphic epithelioid cells with a nest-like to sheet-like growth pattern, present within a background of hemorrhage and necrosis. Neoplastic cells are characterized by significant nuclear atypia, with hyperchromatic nuclei and an overall high nuclear-to-cytoplasmic ratio (Fig. 3). The overall morphological features are those of a metastatic, poorly differentiated carcinoma. Immunohistochemical stains con-

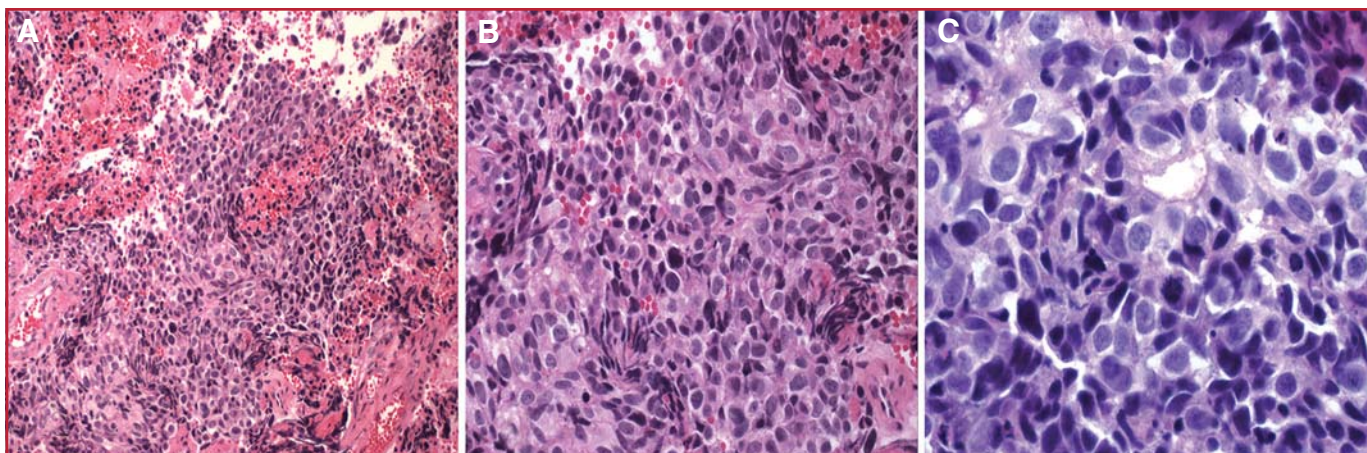


FIGURE 3. Representative histological sections of the intramedullary spinal cord tumor. **A**, micrograph of the tumor at low power (original magnification, $\times 100$) displaying a poorly differentiated carcinoma characterized by a highly cellular proliferation of pleomorphic epithelioid cells with a nest-like to sheet-like growth pattern. These cells are present within a background of

hemorrhage and necrosis. **B** and **C**, micrographs of the tumor at intermediate (**B**, original magnification, $\times 200$) and high power (**C**, original magnification, $\times 400$) displaying neoplastic cells characterized by significant nuclear atypia, with hyperchromatic nuclei and an overall high nuclear-to-cytoplasmic ratio. H & E stain.

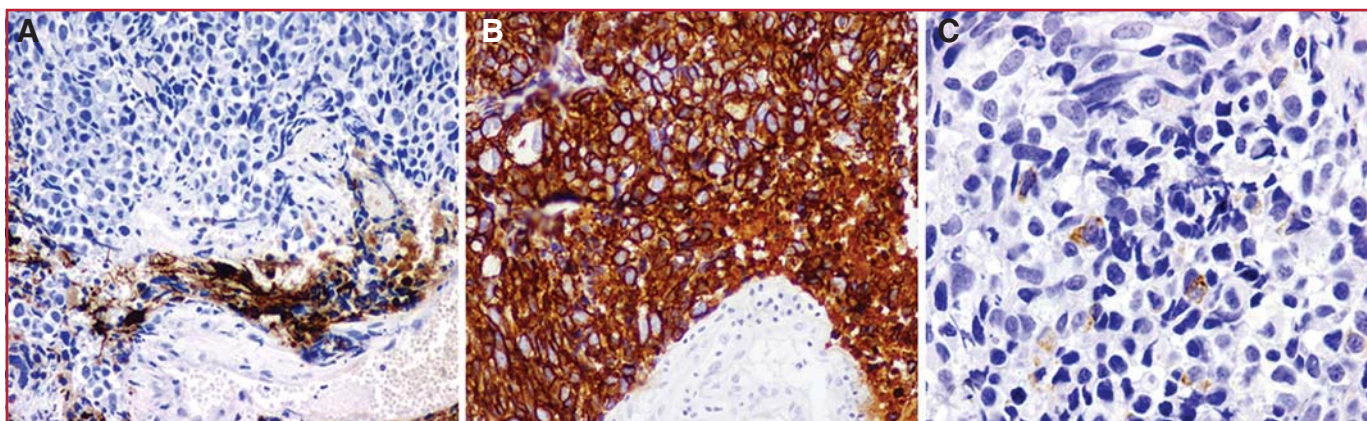


FIGURE 4. Immunohistochemical stains of the intramedullary spinal cord tumor. **A**, the tumor cells are negative for glial fibrillary acidic protein, whereas reactive astrocytes at the periphery of the metastatic lesion are positive (glial fibrillary acidic protein immunohistochemistry; original magnification,

$\times 200$). **B** and **C**, the tumor is strongly and diffusely positive for cytokeratin 7 (**B**, cytokeratin 7 immunohistochemistry; original magnification, $\times 200$) and focally for cytokeratin 20 (**C**, cytokeratin 20 immunohistochemistry; original magnification, $\times 400$).

firmed the epithelial nature of the neoplasm (Fig. 4). The tumor cells were strongly and diffusely positive for cytokeratin 7 and focally positive for cytokeratin 20. In addition, the tumor cells were negative for glial fibrillary acidic protein; a primary glial neoplasm could therefore be ruled out. Although the spinal lesion appeared significantly less differentiated than the primary bladder tumor, it showed morphological similarities to the primary bladder lesion, yielding the final diagnosis of metastatic bladder carcinoma.

Postoperatively, the patient demonstrated minimal improvement in his clinical symptoms. During his hospital stay, he underwent gamma knife radiosurgery for the metastatic brain lesions. Approximately 2 weeks postoperatively, he began fractionated external beam radiation therapy to the thoracic lesion. Over a 19-day period, he was treated with a total of 3000 cGy given in 10 fractions to the region from C5 to T3. Three weeks after completion of his radiation and less than 2

months after his surgical resection, the patient died of systemic disease while under hospice care.

DISCUSSION

Metastasis to the intramedullary spinal cord rarely occurs with systemic cancer. Autopsy series have reported its prevalence in cancer patients as ranging from 0.9 to 2.1% (3, 6), whereas clinically significant ISCM have been reported in 0.1 to 0.4% of cancer patients (5). Lung cancer is the most common source of ISCM, comprising approximately 50% of reported cases (5, 10, 13, 14, 18). Breast carcinoma is another less frequently seen source, accounting for 8 to 14% of ISCM. Other primary sources for ISCM include renal cell

carcinoma, melanoma, colorectal carcinoma, and lymphoma (5, 13, 14).

ISCM from the bladder are extremely rare, with only one previously reported case in the literature (13). Bladder carcinoma accounts for 2% of all cancers (12), and the frequency of metastases has been reported to be 67% (1). In 2003, Anderson et al. (1) reported their experience in treating 359 patients with bladder carcinoma. They observed six patients (2%) with epidural spinal cord metastases, and four patients (1%) with brain metastases. They did not, however, see any patients with ISCM, and their review of the literature yielded no cases of ISCM from the bladder.

Although the radiographic evidence suggested a primary spinal cord lesion such as an ependymoma, the patient's clinical presentation with rapid progression of symptoms was highly suggestive of a metastatic lesion (2, 15). The most common symptom associated with ISCM is weakness (5, 14). In their series of 40 patients, Schiff and O'Neill (13) reported that 92.5% of patients had motor deficits at the time of diagnosis. In addition, 45% of patients had either a true Brown-Séquard syndrome or a pseudo-Brown-Séquard syndrome. Despite radiographic imaging that did not unequivocally suggest a metastatic lesion, our patient presented with a true Brown-Séquard syndrome, a finding that often portends an ISCM in cancer patients (11, 13). In addition to his ISCM, our patient had evidence of brain metastases, an occurrence that Schiff and O'Neill (13) observed in 57.5% of patients with ISCM. Other series have reported even higher rates of brain metastases (10). Although the vast majority of patients with ISCM often have other locations of systemic spread, only 8 to 11% of patients have been found to have multiple intramedullary lesions (13, 14).

As no prospective trials on treatment have been performed, treatment of ISCM has primarily been based on anecdotal experience. External beam radiation therapy is the most effective treatment option, but its effectiveness depends primarily on the radiosensitivity of the tumor, the duration of symptoms, and the degree of preoperative neurological deficit (17). To avoid the sequelae of external beam radiation therapy, stereotactic radiosurgery can be used as an alternative to treat individual metastatic lesions. However, the current literature only reports effectiveness of this treatment modality with primary vascular tumors (19). Surgical management has led to improved neurological function in patients with rapidly progressive neurological deficits (9). However, as aggressive metastatic lesions typically have unidentifiable margins, the goal of surgery must be to decompress the spinal cord while, at the same time, maintaining residual neurological function (4). Focal radiation can then be used as an adjunct to treat residual disease within the resection cavity (13).

CONCLUSION

ISCM are rare complications of systemic cancer. Such lesions arising from bladder carcinoma are virtually nonexistent. Despite the paucity of these lesions, our patient experienced the

rapid onset of a Brown-Séquard syndrome in the setting of recently treated cancer. A clinical presentation such as this should be considered highly suggestive of an ISCM, despite the rare association between bladder carcinoma and ISCM.

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COMMENTS

Crowley et al. report the case of a patient who developed an intramedullary spinal cord metastasis from bladder carcinoma.

The poorly differentiated nature of this tumor and acute onset of the patient's symptoms provide insight as to the aggressive nature of this tumor in this particular patient. Unfortunately, because the patient died of systemic disease only 7 weeks after treatment, no follow-up imaging was obtained to determine the efficacy of the treatment for this spinal cord lesion.

Steven D. Chang
Stanford, California

This is a case report of a patient with a history of bladder carcinoma, who presented with an undifferentiated intramedullary spinal cord tumor. The tumor was an enhancing intramedullary lesion at T1–T2 that the authors concluded was metastatic bladder carcinoma. Metastatic bladder carcinoma to the spinal cord is extremely rare and probably reportable. The spinal cord tumor was subtotally resected in this patient, and histopathological examination showed a highly undifferentiated neoplasm, with markers positive for bladder carcinoma and negative for glial fibrillary acidic protein.

More extensive immunohistochemical analysis and/or genetic characterization of the bladder and spinal cord tumors would be interesting. Nevertheless, this is a well-written, nicely documented case report.

Linda M. Liau
Los Angeles, California

This is a nice case presentation of a rare occurrence, intramedullary spinal cord metastasis (ISCM) from a systemic cancer. Crowley et al. reported an almost unique case (actually the second in the English literature, but the first one with a complete illustration) of ISCM from

bladder carcinoma. The case is well described and the literature discussion is complete. In my opinion, the most interesting feature of this article is the clinical one. Crowley et al. stressed that a Brown-Sequard syndrome in a patient with cancer should suggest a possible diagnosis of ISCM. Beyond all of the neuroradiological appearances, this is a critical point in choosing a therapeutic strategy.

Alessandro Ducati
Turin, Italy

Crowley et al. presented a patient with ISCM from bladder carcinoma. Although the pathological lesion is unusual, the report highlights two important management decisions regarding ISCM. First, many of these tumors are associated with additional neuraxis tumors, including brain metastasis, as seen in this patient, and leptomeningeal tumor. Complete brain and spine imaging is important before treatment decisions, as it may provide a diagnosis of metastatic disease, obviating the need for open spine biopsy. Second, ISCM is often unresectable without incurring additional neurological deficits. Despite their potential for being well encapsulated, these tumors typically invade the spinal cord and are difficult to dissect from normal tissue planes. ISCM tumor resections are very different from resection of intramedullary spinal ependymomas. The judgment to perform a biopsy and irradiate seems prudent in light of the high probability of significant spinal cord injury with attempted resection. Radiation offers the best chance of local tumor control and the possibility of neurological salvage.

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INTRA-ABDOMINAL VASCULAR INJURY DURING TROCAR-ASSISTED VENTRICULOPERITONEAL SHUNTING: CASE REPORT

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OBJECTIVE: Laparoscopic trocar injury is a relatively well-described complication of cholecystectomies and gynecological procedures. However, this type of injury has not been reported in association with adult neurological surgery. To increase awareness of this very serious risk, we report a case of intra-abdominal vascular injury during a shunt procedure involved with a common neurosurgical procedure.

CLINICAL PRESENTATION: A 76-year-old man with no previous abdominal surgical history presented with probable normal pressure hydrocephalus.

INTERVENTION: After an appropriate preoperative workup confirming probable normal pressure hydrocephalus, the patient consented to placement of a ventriculoperitoneal shunt with a programmable valve. During placement of the distal catheter using an abdominal trocar, the aorta was punctured inadvertently, necessitating emergency laparotomy for vascular repair.

CONCLUSION: An abdominal trocar should be used with caution in ventriculoperitoneal shunt surgery. Even with meticulous technique, vascular injury can occur with any trocar-based abdominal procedure. The neurosurgeon who uses this technique must be prepared to initiate emergent vascular access and repair, with a vascular surgery team available should such an injury occur. Alternatively, open placement of peritoneal catheters avoids blind peritoneal instrumentation and is an effective method for minimizing potentially catastrophic vascular injuries.

KEY WORDS: Trocar, Vascular injury, Ventriculoperitoneal shunt

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Trocar injury is a well-described complication of laparoscopic abdominal and gynecological surgery (5, 7, 19). One study reports an incidence of 0.18% for trocar and Veress needle injuries during laparoscopy (18). Other reports in the literature estimate that the incidence of major vessel injury in laparoscopic procedures may range from 0.04 to 0.5% (13). Despite improved safety with optical access trocars (2), there are still serious risks and injuries associated with them. Laparoscopic trocars are the most common devices in malpractice injury claims associated with laparoscopic procedures (5). Although cholecystectomy is the procedure most frequently associated with trocar injuries (5), all types of surgery using trocars present serious risks, particularly to major vessels. We present the case of an adult normal pressure hydrocephalus patient who sustained an intraoperative aortic puncture caused by trocar use. To our knowledge, this is the first reported adult case of major vascular injury caused by trocar puncture during

the placement of a ventriculoperitoneal shunt (VPS). We emphasize the risk associated with the use of trocars, the importance of precision in their placement, and the need for rapid hemostatic control in the event of vascular injury.

CASE REPORT

A 76-year-old man presented with symptoms of normal pressure hydrocephalus, including balance difficulty, urinary frequency, and short-term memory problems for more than 1 year. After an appropriate workup in conjunction with the Department of Neurology, including video-monitored gait testing during a lumbar spinal fluid drainage trial, the patient consented to placement of a ventricular peritoneal shunt with a programmable valve. A left-sided shunt was chosen ipsilateral to a prominent left-sided arachnoid cyst. The ventricular catheter and valve were placed uneventfully, and the distal catheter was tunneled to the left upper quadrant of the abdomen. Spontaneous flow of cerebrospinal fluid was visualized from the distal catheter.

At this point, the abdominal trocar was used to place the distal catheter into the peritoneal cavity. The trocar and obturator were placed through a left upper quadrant small anterior rectus sheath opening

ABBREVIATION: VPS, ventriculoperitoneal shunt

and advanced to the deep rectus fascia. The posterior rectus sheath and peritoneum were then "bunched up" in the surgeon's left hand while these structures were penetrated with the trocar at an angle parallel to the operating room floor toward the contralateral iliac crest. On removing the obturator portion of the trocar, bright red pulsatile blood was visualized. A probable aortic injury was recognized immediately, and the obturator was replaced. An emergent laparotomy was performed with the assistance of a transplant surgeon who was immediately available. Subsequently, a vascular surgeon primarily repaired the visualized abdominal aortic puncture. During the laparotomy and repair, the decision was made to remove the already placed proximal shunt system because of concerns over infection risk.

Multiple transfusions were required, but the patient survived the procedure. He developed multiorgan dysfunction from his intraoperative shock. However, after prolonged hospital care, the patient improved to the point at which he was oriented and conversant and being evaluated for inpatient rehabilitation. Unfortunately, he developed aspiration pneumonia, experienced a cardiopulmonary arrest, and remained significantly debilitated thereafter. He died in a skilled nursing facility 9 months postoperatively. In retrospect, this patient had a very thin abdomen with a prominent lumbar lordosis, placing the abdominal aorta unusually close to the anterior abdominal wall.

DISCUSSION

First described in 1993 (1), trocar-based distal shunt catheter placement has been reported with increasing frequency. Although all published reports describe a high degree of safety, with no major morbidity, these are mostly small retrospective series. Roth et al. (17), at the University of Kentucky, used a 2-mm laparoscope together with either a venous introducer kit or a 5-mm direct-view trocar. From 1998 to 1999, they successfully placed distal catheters in 27 shunt patients, 16 of whom had undergone previous abdominal surgery. Kirshtein et al. (10) subsequently reported 28 laparoscopic procedures in 24 patients aged 6 to 80 years, two-thirds of whom had previously undergone abdominal surgery. They reported one distal infection, one distal malfunction, and a mean operative time of 63 ± 34.9 minutes. The largest series, which was recently reported by Li et al. (12), detailed 56 adult patients (aged 17–65 yr) from China using an abdominal pneumoperitoneum technique. The authors modified the laparoscopic approach to require 2 small incisions. They reported no major complications and 100% successful initial implantation, but required 4 distal revisions in the first 6 months for obstructed or kinked catheters.

Despite the relative infrequency of major vascular injury associated with trocar use, the possibility of life-threatening complications does exist. Complications of laparoscopic trocar access include vascular injury, gastrointestinal complications, dehiscence and hernia, wound infection, port-site metastasis, and extraperitoneal gas (13). Most trocar-related fatalities are attributable to vascular injury (5). One group found that despite the time that has passed since the introduction of laparoscopic procedures and consideration of the initial learning curve of the techniques required, the rate of bleeding complications remains substantial (15).

Although most trocar injuries are associated with cholecystectomies, any type of abdominal or pelvic surgery risks trauma to major vessels (6). Pring (16) reported an aortic injury

using a Hasson trocar during open access laparoscopic appendectomy. The distal abdominal aorta and the large pelvic vessels are especially vulnerable to injury during trocar insertion into the abdomen. In a report of 9 major retroperitoneal vascular injuries during laparoscopic cholecystectomies and appendectomies, 3 were located in the abdominal aorta (8). Two cases were recently reported in the French literature of iatrogenic puncture of trunk vessels during emergency shunt procedures in children, resulting in hemorrhagic shock (4). Aside from this report, however, there is a paucity of literature describing such complications associated with neurological surgery.

The growing popularity of laparoscopic procedures of all types warrants serious consideration of the risks involved with trocars. Although the benefits of laparoscopy are incontrovertible, surgeons must be cognizant of the possibility of vascular injury and establish mandatory preparations for emergency situations accordingly. Given that this type of injury is well recognized with cholecystectomy and gynecological operations but minimally documented in neurological surgery, all neurological surgeons who use trocars should be aware of the risks and proper insertion techniques. In the event of iatrogenic major vessel injury, vascular surgeons should be accessible for emergency hemostatic control and repair. Unless hemostatic control is obtained or a team skilled in laparoscopic suture is available, surgeons should be ready to convert to an open procedure (14).

Trocar vascular injury is well recognized in the general surgical and laparoscopic literature. Although not previously reported in an adult patient in the neurological surgery literature, this type of injury is not unique to our institution. Discussions between neurosurgical colleagues at several other institutions and the senior author (GMM) confirmed other trocar-related major abdominal vascular injuries in VPS operations. Given the small but very real risk of potentially catastrophic abdominal vascular injury using an abdominal trocar to access the peritoneal cavity, we have discontinued this technique in routine adult hydrocephalus patients. Consistent with this view, Sigman et al. (21) suggest that blind access to the peritoneal cavity for laparoscopy be abandoned altogether in favor of an open approach because of a lack of advantages and the increased risk of serious visceral and vascular injury, despite the relative infrequency of those injuries.

Technical adjustments may increase the safety of minimally invasive abdominal approaches. Insufflating the abdomen with air with a Veress needle to induce pneumoperitoneum before trocar placement theoretically lessens the risk of vascular injury by increasing the distance between the abdominal wall and the retroperitoneal major vessels. However, insufflation has not eliminated major vessel injuries in the laparoscopic surgery literature (9). In fact, it has been suggested that the increased intra-abdominal pressure that results from insufflation may actually delay diagnosis of major vessel injury because of compression of the bleeding vessels (8, 11, 20). The type of trocar used may also play a role in risk. One study suggests that radially expanding (blunt) trocars are less likely to result in intraoperative or postoperative complications compared with conventional trocars (3). Whichever technique is used, trocar-assisted distal shunt catheter placement must have a near-zero

vascular complication rate. To our knowledge, injuries to the aorta or vena cava have not been reported in routine VPS placement using a minilaparotomy.

It is difficult to make a compelling argument for the routine use of an abdominal trocar in uncomplicated adult hydrocephalus patients. The primary advantages of minimally invasive surgical approaches in general are the minimization of surgical exposure, postoperative pain, and hospitalization time, without increasing surgical risk. Although use of an abdominal trocar may slightly shorten the VPS abdominal surgical time and requires a smaller incision, it does not lessen hospitalization time or dramatically alter abdominal discomfort in our experience. It can be easier on the surgeon but not necessarily the patient. The trocar surgical technique used in our patient had been similarly applied at our institution without complication in well over 100 adult VPS patients in the 5 years before this complication. However, as the saying goes, "It only takes one."

We recommend that neurosurgeons continue to use an open approach to place the peritoneal end of shunt systems in routine adult hydrocephalus patients who are not obese and do not have a complicated abdominal surgical history. Typically, this approach requires a small incision and is associated with minimal postoperative discomfort. In our opinion, it is reasonable to consider using laparoscopic techniques in special circumstances, such as the patient who has undergone multiple operations, the previously infected patient, or the obese patient requiring a large minilaparotomy exposure. Neurosurgical training or collaboration with experienced laparoscopic surgeons is recommended. Prospective evaluation of large series of laparoscopic distal catheter techniques is required to determine the safety of this minimally invasive approach, given the low anticipated incidence of major vessel injury.

CONCLUSION

Abdominal vascular injury is a serious risk of all trocar-based procedures, including distal shunt catheter placement. Laparoscopic insufflation techniques do not prevent this complication. Neurosurgeons using trocars to place abdominal VPS catheters must be prepared for the possibility of such injuries in the event that they do occur.

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COMMENTS

In this case report Danan et al. described a patient with abdominal aortic injury owing to trocar-assisted placement of the peritoneal end of a ventriculoperitoneal shunt. Although the aortic injury was repaired, multiorgan failure ensued and the patient ultimately died of aspiration pneumonia 9 months later. This patient highlights one of the risks associated with using trocars to access the peritoneal cavity. I have always favored the minilaparotomy approach and will continue to do so.

Carl B. Heilman
Boston, Massachusetts

This is an important contribution to the literature, highlighting the necessity of reporting our complications along with our successes. Moreover, it raises the question as to the rationale and impetus for adopting new surgical techniques. Some may argue that laparoscopy is a "minimally invasive" alternative to minilaparotomy. Having seen many patients with abdominal incisions greater than 5 cm in length, who were operated on elsewhere, there may be some unfortunate truth to this. In my experience, a routine muscle-sparing minilaparotomy can usually be easily performed with a <2.5 cm incision, with minimal cosmetic impact and very low morbidity and discomfort.

A purported advantage of laparoscopy is the ability to redirect the peritoneal catheter away from intraperitoneal adhesions. In my personal experience of well over 1000 adult shunt operations, this "requirement" has arisen twice. For adult patients with a history of peritoneal adhesions, significant abdominal surgery, or infection, an ultrasound-

guided percutaneous approach ventriculoatrial shunt is an excellent alternative. The single neck incision is only about 5 mm long and well-hidden in a skin crease. Moreover, peritoneal adhesions increase the risk of bowel perforation with laparoscopic trocar placement.

There are other issues not addressed in this report, including additional equipment costs (disposables) and training and laparoscopic certification for neurosurgeons performing the laparoscopy. Although Danan et al. stated that they had experience of more than 100 successful procedures before this fatal outcome, if this had been their second case, there could be far different medicolegal ramifications.

Is there a justification for laparoscopic-assisted ventriculoperitoneal shunt placement? I think one of the biggest problems with the minilaparotomy approach is withdrawal and coiling of the peritoneal catheter within the subcutaneous pocket created by the approach. Turner et al. (1) described a laparoscopic technique in which the shunt tunneler penetrated the peritoneum, under laparoscopic guidance, at a site separate from the laparoscopy-associated incisions. Avoidance of preperitoneal catheter placement is a second advantage of laparoscopy. Both of these complications tend to occur more often in obese patients, and therefore, I agree with the authors that selected patients may benefit. Parenthetically, ventriculoatrial shunt placement is also an excellent alternative for most adult obese patients.

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1. Turner RD, Rosenblatt SM, Chand B, Luciano MG: Laparoscopic peritoneal catheter placement: Results of a new method in 111 patients. *Neurosurgery* 61 [Suppl]:167-172, 2007.

This article is timely as the trend to perform more and more procedures with minimally invasive techniques (often interpreted by patients as no-risk procedures) continues to grow. I appreciate the courage and character of Danan et al. in sharing this complication. This should be a sobering example for all of us, especially as some are advocating for a few of these procedures to be done in ambulatory surgery centers. The literature review was excellent, and I, for one, will be more sober-minded when performing such maneuvers.

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Frequently, the most valuable scientific publications deal with unexpected findings and outcomes because they force us to understand the aberration and possibly change our practices. Danan et al. described a highly relevant complication of laparoscopic peritoneal placement in ventriculoperitoneal shunting. This is the first such report and is important because the choice of surgical techniques must be made against the background information of potential complications, and thus, such information should be accessible in the scientific literature.

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Danan et al. presented a well-written case report and brief review of the literature regarding vascular injury during trocar placement in laparoscopic procedures. This is an important complication that neurosurgeons should be aware of, particularly those in search of indications for minimally invasive techniques. However, we are not sure that their report expands on or enhances the large amount of previously published literature already available on this topic. Other than the indication for laparoscopy being related to a neurosurgical diagnosis, the uniqueness of this patient is elusive. Hollow viscous and vascular

injuries sustained during trocar insertion during laparoscopic surgery are relatively rare but are well-described morbidities associated with this surgical modality. The literature has been inundated with case reports and clinical trials from many different surgical specialties as well as multidisciplinary topic reviews and consensus statements (1-8). To date the available body of evidence does not support the use of any single fail-safe initial entry technique ("blind" puncture with or without pneumoperitoneum versus a "Hasson" cut-down method) or a specific device (shielded trocar versus optical-access trocar) for all patients, and all have a small, but real, associated complication rate.

The conclusions and recommendations of Danan et al. are also somewhat misguided and inaccurate. They recommend using an open approach to place the peritoneal end of shunt systems in adult patients with routine hydrocephalus who are not obese and do not have a complicated abdominal surgical history. These patients have, in fact, the lowest risk of a complication of laparoscopic trocar insertion and stand to reap the benefits of the laparoscopic approach (including incisional cosmesis, improved visualization, and low incisional hernia rate) with the least morbidity and fewest number of trocars necessary. For patients with a history of prior abdominal surgery, very small or very thin patients, or patients with abdominal skin that cannot be adequately stabilized manually, laparoscopy is still a viable option, but alternatives to blind trocar insertion should be used. In addition, for these patients, entry in the left upper quadrant (Palmer's point) traditionally has been shown to be a safe first-line option to eliminate major vessel injury and injury to bowel or omentum that might adhere to previously made midline abdominal incisions, lower transverse abdominal incisions, or right upper quadrant incisions. These sites are most often used for incisions during common general surgical and gynecological procedures.

We firmly agree that collaboration with an experienced laparoscopist is a good idea at least until a neurosurgeon is able to gain enough clinical experience to feel comfortable with his or her laparoscopy skills. We also concur that a general and/or vascular surgeon should at least be available to respond to the operating room in the case of an identified complication.

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CHIARI I MALFORMATION AS A CAUSE OF TRIGEMINAL NEURALGIA: CASE REPORT

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OBJECTIVE: Trigeminal neuralgia (TN) is usually associated with vascular compression of the trigeminal nerve, but some cases are associated with central lesions such as tumors, aneurysms, or arteriovenous malformations. In this article, we report the 19th case of TN associated with Chiari I malformation and review clinical outcomes and pathophysiology.

CLINICAL PRESENTATION: A 63-year-old right-handed man initially presented in 1993 with left-sided lancinating facial pain in the V2 distribution of the trigeminal nerve; the pain was triggered by certain movements, tactile stimulation, or a hot shower. Magnetic resonance imaging revealed a Chiari I malformation associated with a syrinx from C1 to C3.

INTERVENTION: The patient underwent uncomplicated suboccipital craniectomy, C1 laminectomy, and duraplasty for Chiari decompression. Postoperatively, his pain resolved over a period of 1 year.

CONCLUSION: Chiari I malformation has been found to be associated with TN in 19 cases in the English-language literature. In patients refractory to medical treatment, suboccipital decompression leads to resolution of pain in about two-thirds of patients. Potential mechanisms for the pathogenesis of TN in the setting of Chiari I malformation are discussed. Chiari I malformation is important to consider as a rare cause of TN that responds to surgical therapy.

KEY WORDS: Arnold-Chiari malformation diagnosis, Arnold-Chiari malformation surgery, Decompression, Trigeminal neuralgia diagnosis, Trigeminal neuralgia surgery

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Trigeminal neuralgia (TN) is defined as a sudden, usually unilateral, severe but brief, recurrent stabbing pain in the distribution of one or more branches of the trigeminal nerve (25). The incidence of TN is 4.7 per 100,000 persons (20). Although most cases of TN are associated with vascular compression of the trigeminal nerve or are idiopathic, some cases are associated with central lesions such as tumors or, rarely, aneurysms or arteriovenous malformations. Although many general references do not include Chiari I malformation as a cause of TN, there are case reports in which TN occurs in the setting of a Chiari I malformation, and surgical treatment of the Chiari I malformation has been found to

relieve TN. Here, we present what, to our knowledge, is the 19th such case reported in the English-language literature. In addition, we propose a potential mechanism for the etiology of TN in this patient.

CASE REPORT

A 63-year-old right-handed man initially presented in 1993 with left-sided lancinating facial pain in the V2 distribution of the trigeminal nerve; pain was triggered by certain movements, tactile stimulation, or a hot shower. He complained of occasional aching, numbness, or soreness in this area as well. The neurological examination showed hyperesthesia in all three distributions of the left trigeminal nerve, with the worst component being in the maxillary division. Magnetic resonance imaging (MRI), performed on the initial evaluation, was reported to have shown a vessel loop contacting the left trigeminal nerve. The patient was diag-

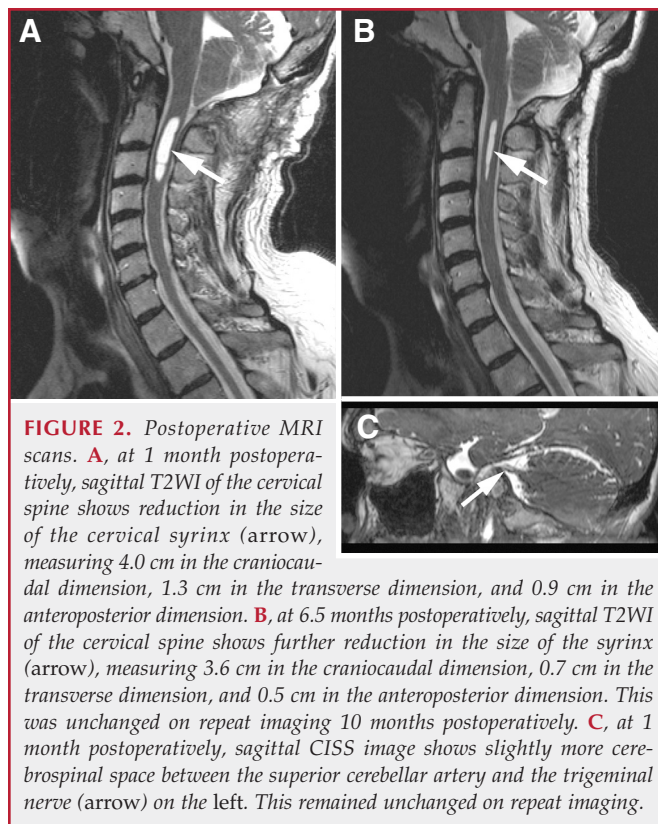
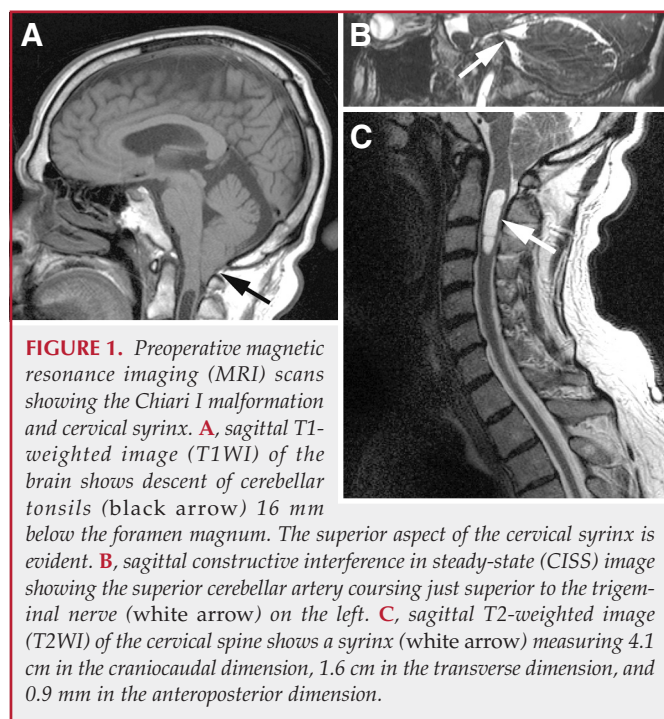
ABBREVIATIONS: CISS, constructive interference in steady-state; MRI, magnetic resonance imaging; TN, trigeminal neuralgia

nosed with TN and was treated for approximately 10 years with up to 1600 mg/d of carbamazepine, until worsening of his facial pain prompted a referral to neurosurgery for consideration of microvascular decompression in January 2005. The preoperative neurological examination showed a mild decrease in light-touch, pin-prick, and temperature sensation on the left side of the patient's face, as well as slight gait unsteadiness. There were no other pertinent signs or symptoms related to a syrinx. Preoperative evaluation included an MRI scan, which showed a Chiari Type I malformation with a cervical spine syrinx, as well as the superior cerebellar artery coursing just superior to the trigeminal nerve (Fig. 1). Review of his initial MRI from 1993 did show evidence of the Chiari I malformation and syrinx, but this study was not available to us.

The patient underwent uncomplicated suboccipital craniectomy, C1 laminectomy, and duraplasty for Chiari decompression on January 28, 2005. Intraoperatively, descent of the tonsils to C1 with compression of the medulla was observed. The tonsils were extended to an equal extent on both sides. Postoperatively, the patient's examination continued at baseline, and he reported that his pain was mostly better. His pain continued to improve, and he was able to wean his carbamazepine to 600 mg/d by 2 weeks postoperatively and then to 200 mg/d by 6 months postoperatively. One year after surgery, the patient was off of carbamazepine and all pain medicines, and he continues to be pain-free, without the use of pain or antiepileptic medications, as of December 2007. Postoperative MRI scans at 1 month, 6.5 months, and 10 months after surgery demonstrated progressive reduction in the size of the syrinx (Fig. 2, A and B). A slight increase in cerebrospinal fluid space between the superior cerebellar artery and trigeminal nerve is present (Fig. 2C).

DISCUSSION

TN that is not caused by a structural lesion is initially treated medically. The first-line agent is carbamazepine, which has a



patient response rate of approximately 70% (7, 21, 28, 44). Many other anticonvulsant medicines are also used for TN. The indication for surgery in this situation is symptoms refractory to medical therapy, for which microvascular decompression is performed (2).

The presence of a symptomatic accessible mass lesion is also an indication for surgery. Such symptomatic lesions are termed, by the International Association for the Study of Pain, "secondary trigeminal neuralgia from central nervous system lesions" (25). Cushing (10) first reported that mass lesions can cause TN. Current series show that 0.8 to 5.7% of patients with TN or facial pain harbor tumors affecting the trigeminal nerve (4, 9, 37).

In a series of 215 patients who underwent posterior fossa craniotomy for section of the trigeminal nerve for treatment of TN, Dandy (11) described two cases in which TN was associated with congenital malformations at the base of the cranium. His description of a malformation with reduced intracranial space and cerebellar tonsillar herniation fits the modern definition of a Chiari I malformation. The illustration from this initial report is shown in Figure 3. Since this time, 16 additional patients have been reported in the English language for which TN or facial pain is associated with a Chiari I malformation, and they are summarized in Table 1 (8, 14, 15, 29, 31, 34, 37, 40, 41). Of the 18 cases, 15 patients experienced pain typical of TN, whereas 3 were reported to have facial pain. Treatment by sub-

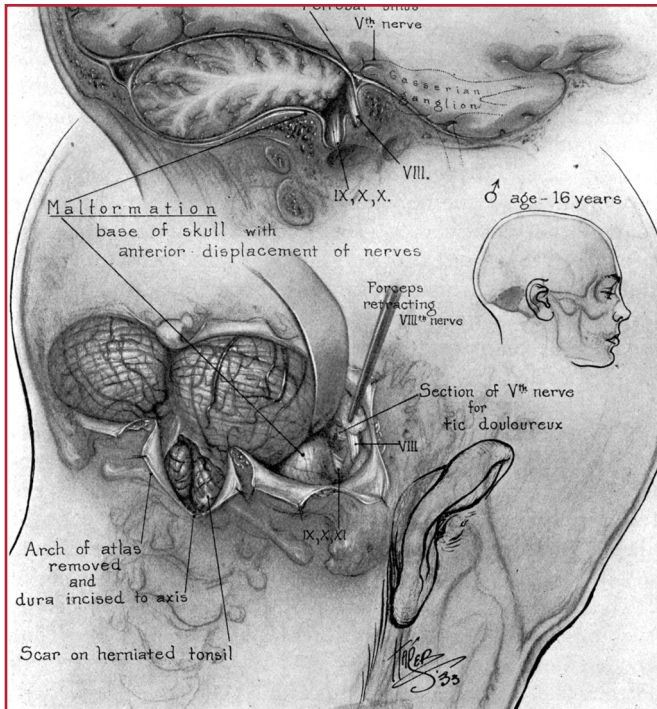


FIGURE 3. Illustration from Walter Dandy's initial description of trigeminal neuralgia (TN) in the setting of a Chiari I malformation. Removal of the arch of C1 and incision of the dura revealed tonsillar herniation. The trigeminal nerve root was sectioned for TN symptoms (from, Dandy WE: Concerning the cause of trigeminal neuralgia. *Am J Surg* 24:447-455, 1934. Copyright 1934, with permission from Excerpta Medica, Inc. [11]).

occipital craniectomy with or without laminectomies, duraplasty, or tonsillar aspiration was performed in 13 of the 18 patients. Postoperatively, nine of these 13 patients (approximately two-thirds) were pain-free. Two additional patients were pain-free after additional microvascular decompression, whereas the two remaining patients experienced improved or bearable, but residual, pain.

Of the five patients who did not undergo suboccipital craniectomy, two with hydrocephalus experienced complete relief of symptoms after ventriculoperitoneal shunting or third ventriculostomy. Another was pain-free with carbamazepine treatment, and data are not available for the other two patients. The patient described here had lancinating pain characteristic of TN, as well as hyperesthesia and occasional aching, numbness, or soreness that is not typical of TN. As of December 2007, the patient continues to have no pain without taking pain or antiepileptic medications.

The mechanism by which Chiari I malformation could cause TN is not clear. Four mechanisms have been proposed: 1) symptoms of TN could be caused by vascular compression at the nerve root entry zone, which could be affected by hydrocephalus or anatomic factors related to the Chiari I malformation, such as a small posterior fossa; 2) the Chiari I malformation could lead to stretching of the trigeminal nerve, resulting in demyelination; 3)

the TN may suffer from microischemic changes; and 4) direct brainstem compression may result in symptoms of TN.

The following discussion explores these suggested mechanisms, drawing on available data on the pathophysiology of TN and Chiari I malformations. The first two hypotheses are appealing because of their consistency with the body of data supporting vascular compression and subsequent demyelination of the trigeminal nerve root entry zone as the cause of typical TN (11, 17, 18, 37). Similarly, nerve root specimens from multiple sclerosis patients with TN also show demyelination in the nerve root entry zone. Taken together, these observations support the hypothesis that nerve root entry zone demyelination and the resulting ectopic generation of spontaneous nerve impulses with ephaptic conduction to neighboring axons are the common mechanism by which various pathological processes cause TN (5, 6, 12, 19, 23, 24, 32, 33, 36, 38, 39). Although constructive interference in steady-state (CISS) images in this patient show the superior cerebellar artery just superior to the trigeminal nerve, there are no reports with histopathological evidence that the Chiari I malformation leads to stretching or demyelination of the trigeminal nerve.

The third proposed mechanism that microischemic changes cause TN in the setting of a Chiari I malformation seems plausible, but no direct support for this hypothesis has been reported. Several case reports indicate that, central lesions such as a small infarction or a cavernous malformation of the nerve root entry zone or pons rarely may cause TN, showing that ischemia can cause TN in other clinical settings (1, 16, 22, 27, 30, 35, 42).

Regarding the fourth hypothesis, that the Chiari I malformation causes TN as the result of mass effect on the brainstem, one might expect to observe histopathological changes in the trigeminal nucleus in such cases. However, we are not aware of post-mortem studies in any patient with TN and a Chiari I malformation. Additionally, although the authors of many studies detail the gross and microscopic findings of syrinxes in Chiari I malformations, relatively few reports exist on the microscopic parenchymal findings in the Chiari I malformation (3, 43). Typical histological parenchymal findings associated with syringomyelia include the existence of vascular dilation, fibrosis, or simple hyalinization of the walls of blood vessels. In the spinal cord parenchyma, there may be a proliferation of Schwann cells, termed schwannosis, although this finding is not specific (43). The relationship between these features and TN associated with Chiari I malformations remains unestablished. Although central processes such as increased excitation and decreased inhibition in the trigeminal nuclear complex likely contribute to TN, whether brainstem compression could contribute to such processes through demyelination of intramedullary trigeminal fascicles or cellular effects remains unexplored (13).

Pathological findings have been reported in a 60-year-old woman with Chiari I malformation and multiple, mostly left-sided neurological findings but no trigeminal pain. Relevant neurological findings included decreased tactile and pain sensation in the left face and nearly absent left-sided corneal reflex (3). Autopsy showed an elongated medulla oblongata with

TABLE 1. Patients reported as having trigeminal neuralgia or facial pain associated with a Chiari I malformation^a

Series (ref. no.)	No. of patients	Age (yr)/sex	Pain	Other symptoms	Neurological findings	Syrinx	Vasc comp on MRI	Previous CBMZ	Treatment	Vasc comp at surg	Dural graft	Success	Postop pain med	F/U
Dandy, 1934 (11)	2	Yg	TN (both patients)	N/S	N/S	N/S	N/A	N/A	TN section	N/S	N/S	N/S	N/S	N/S
Pascual et al., 1992 (29)	1	N/S	Atypical unilateral TN	Trigeminal neuropathy	N/S	N/S	N/S	Poor response	Amitriptyline	N/A	N/A	Good relief	N/A	N/S
Sindou et al., 1995 (37)	9	N/S	TN for all	N/S	N/S	N/S	N/S	N/S	Suboccipital crani, C1 lami; 5/9 cured; 2/4 with additional MVD relief; 2 others with improved pain	N/S	No	Pain-free, normal exam	N/S	N/S
Storrs and Roberts, 1996 (40)	1	31/M	Trigeminal dyesthesia RV1–3, then also LV2	Generalized head-aches	B ↓ facial sensation, ↓ R corneal reflex	No	N/S	N/S	Suboccipital decompression, C1 lami	N/S	N/S	Pain-free, all symptoms resolved	N/S	2 yr
Rosetti et al., 1999 (34)	1	66/M	TN, LV3	None	↓ sensation LUE, LLE; loss of L brachio-radialis/bicipital DTRs	Yes	No	Efficacy ↓ to nothing over 11 yr	Suboccipital crani, duraplasty, tonsillar aspiration	No	Yes	Pain-free, normal exam	None	1.5 yr
Peñarrocha et al., 2001 (31)	1	45M	Lower L continuous pain, made worse by physical effort; LV2 “pain crisis”; L hemifacial pain	See “Pain” column	↓ pain/ temp in L lower face, predominantly periorally	Yes	N/S	CBMZ/ergotamine improved crises but continuous pain persisted	Suboccipital crani, transverse microincisions in outer layer of dura	N/S	No	Pain-free, normal exam	None	2 yr
Chakraborty et al., 2003 (8)	1	38/F	TN, LV1–3	“Whooshing” feeling, neck stiffness	Normal	No	N/S	CBMZ, gabapentin, baclofen with limited effect	Foramen magnum decompression	N/S	N/S	Pain-free, normal exam	None	N/S

(continues)

TABLE 1. continued														
Series (ref. no.)	No. of patients	Age (yr)/sex	Pain	Other symptoms	Neurological findings	Syrinx	Vasc comp on MRI	Previous CBMZ	Treatment	Vasc comp at surg	Dural graft	Success	Postop pain med	F/U
Gnanalingham et al., 2005 (15)	1	31/M	TN, RV3	None	Normal	No	N/S	CBMZ with some effect for 21 mo, then failed	VPS	N/S	N/A	Pain-free	None	3 mo
Teo et al., 2005 (41)	1	38/F	TN, RV3	Hand tingling	Mildly positive Rhomberg	No	No	CBMZ, also gabapentin, with some effect	Third ventriculostomy	N/A	N/A	Pain-free	None	3 mo

^a MRI, magnetic resonance imaging; CBMZ, carbamazepine; vasc comp, vascular compression; surg, surgery; postop, postoperative; med, medication; F/U, follow-up; Yg, young; TN, trigeminal neuralgia; N/S, not stated; N/A, not applicable; crani, craniectomy; lami, laminectomy; MVD, microvascular decompression; exam, examination; R, right; L, left; B, both sides; ↓, decrease; LUE, left upper extremity; LLE, left lower extremity; DTRs, deep tendon reflexes; temp, temperature; VPS, ventriculoperitoneal shunt.

flattening of its right side from tonsillar herniation, as well as reduced size of the left half of the medulla. Multiple nuclei and tracts in the medulla showed a decrease in size. In particular, the right corticospinal tract showed demyelination, and the left trigeminal complex was hypoplastic. This patient was not reported to have had facial pain, but the brainstem pathology described makes a central pathogenesis for TN symptoms in the setting of a Chiari I malformation seem plausible. In a similar vein, axial morphology of nonneoplastic spinal cord cavities has been shown to correlate with histopathology and clinical findings (26). Evaluation of this hypothesis will await postmortem analysis in a patient with TN associated with a Chiari I malformation.

We propose a novel mechanism by which the presence of a cervical syrinx with a Chiari I malformation may contribute to TN symptoms. Concordant with hypotheses 1 and 2, detailed previously, a cervical syrinx indirectly may result in vascular compression or stretching of the trigeminal nerve at the nerve root entry zone. On the other hand, a syrinx may affect the brainstem directly. Given that the sensory fibers arising from the trigeminal nucleus descend down to the level of C2 and then course rostrally before they exit the brainstem, it is possible that the presence of a syrinx may impact the excitability of these fibers. In the patient described in this report, it is of interest to note that his TN decreased in parallel with the reduction of the volume of the syrinx (Fig. 2, A and B). This is clearly an association and not a direct proof. Also, this mechanism is only relevant in cases in which a syrinx is present. In two previous reports of TN and Chiari I malformation, identification of a syrinx has been reported (31, 34).

CONCLUSION

TN is usually caused by vascular compression, but a small percentage of cases result from mass lesions such as tumors or vascular malformations. Chiari I malformation is important to consider as a rare cause of TN that responds to surgical therapy. MRI evaluation of patients with TN is necessary to detect these treatable lesions.

Disclosure

This work was presented at the New England Neurosurgical Society Annual Meeting on June 9, 2006.

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COMMENTS

Papanastassiou et al. presented a patient with a Chiari I malformation, cervical syrinx, a superior cerebellar artery near the trigeminal nerve, and trigeminal neuralgia (TN), which was improved after foramen magnum decompression. Eighteen other occurrence of Chiari I malformation and TN from the literature are reviewed.

The question is whether to do a foramen magnum decompression or another neurosurgical procedure (microvascular decompression, needle rhizotomy, or gamma knife radiosurgery) when TN is associated with a Chiari I malformation. Of the 19 patients, the follow-up interval is available for only six patients: all reported relief of TN, but follow-up for 2 patients treated only for hydrocephalus was 3 months and follow-up for the other 4 patients treated with foramen magnum decompression (3 also had a syrinx) was from 1.5 to 2.9 years. The question as to the best way to treat these patients remains open, but it would seem from the data, on the basis of the relatively short follow-up, that foramen magnum decompression is a reasonable option, especially if there is also a syrinx.

Ronald Brisman
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An association of TN and Chiari I malformation has been reported previously but is quite rare. Even rarer is its association with syringomyelia. In this report, Papanastassiou et al. described the case of a 63-year-old man who presented with a long-standing history of left TN in association with a Chiari I malformation and syringomyelia. The possible mechanisms of TN were felt to include vascular compres-

sion of the trigeminal nerve within the volumetrically small posterior cranial fossa, direct compression of the brainstem, and secondary effects of syringomyelia such as vascular compression, stretching of the trigeminal nerve at the root entry zone, and intramedullary damage of the descending tract of the trigeminal nucleus. The latter hypothesis would have been stronger if there were magnetic resonance imaging scans with thin axial sections showing the anatomic relationship of the syrinx to the left dorsolateral quadrant of the spinal cord between C2 and the lower brainstem. Regardless of the exact cause of TN, the patient was significantly improved after a standard posterior fossa decompression for Chiari I malformation and was pain free and not taking medications at the 1-year follow-up. Postoperative magnetic resonance imaging scans demonstrated a reduction of syrinx size and a slight increase in the cerebrospinal fluid space between the left superior cerebellar artery and ipsilateral trigeminal nerve, but there was insufficient evidence to establish a direct correlation with pain relief. Overall, this is a useful case report that adds to the small but important body of literature dealing with the association of Chiari I malformation and TN.

Thomas H. Milhorat
Manhasset, New York

Papanastassiou et al. presented an interesting rare symptom of Chiari I malformation with TN. The patient did have a cervical syrinx. He underwent posterior fossa decompression with duraplasty, and his postoperative magnetic resonance imaging scan showed progressive reduction in the size of the syrinx.

The sensory loss in trigeminal distribution to pain and temperature has been reported in large series. However, TN with the hyperesthesia documented in this individual is a rare phenomenon.

Arnold H. Menezes
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This case report of TN in a patient presenting with syringomyelia caused by a Chiari I malformation is interesting because TN was relieved by simple occipitocervical decompression that subsequently produced a decrease in the size of the cervical syrinx. In their article,

Papanastassiou et al. also provided a fruitful discussion on possible anatomic mechanisms of the neuralgia.

In their discussion they seem to favor the role of the syrinx. It would have been useful to have an axial section of the cervical spinal cord to see whether the syrinx was (even slightly) lateralized or strictly median and symmetrical. We have noticed on the constructive interference in the steady state oblique sagittal view that the trigeminal root was angulated at the crossing of the upper petrous ridge.

We have seen a patient with TN who had such a syrinx; we also have seen 9 cases of TN with Chiari I malformations without any significant associated syringomyelic cavity. Four of these 10 patients were cured by simple posterior cervico-occipital decompression; the other 6 underwent secondary additional microvascular decompression, which showed arterial compression (the superior cerebellar artery) in 3 and a pure venous compression in the 3 others, namely the inferior transverse pontine vein. In all 6 patients, the cerebellopontine cistern was "virtual" owing to the small size of the posterior fossa and the trigeminal nerve was found compressed, squeezed between the pons and the posterior aspect of the petrous pyramid. In the three patients with the transverse pontine vein as the compression, the vein was making a groove at the inferior aspect of the root just after its exit from the porus of Meckel's cave. At this point the root was segmentally atrophic and of a grayish color owing to focal demyelination. The vein was coagulated and divided. In all 6 of these patients, secondary microvascular decompression relieved the trigeminal pain.

More generally, we did notice in our series, although we did not study this aspect in a quantifying way, that in the younger population with TN, the posterior fossa was frequently of small capacity, with virtual cisterns including cisterna magna. At surgery, the cerebellopontine angle was found to be "crowded," with a trigeminal root squeezed between the brainstem and petrous wall and vessel(s) packed along the root, with a special emphasis on the inferior transverse pontine vein engrooved in the root. Only a sufficiently wide "keyhole" craniotomy and systematic careful checking of the whole root, from the brainstem to the porus of Meckel's cave, will ensure that nothing compressing the root is missed.

Marc P. Sindou
Lyon, France

INTRACRANIAL PLACEMENT OF A NEW, COMPLIANT GUIDE CATHETER: TECHNICAL NOTE

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OBJECTIVE: We describe our initial experience with the use of a novel, compliant guide catheter designed for placement within the cranial vasculature in a series of seven patients who were treated for various intracranial pathologies.

CLINICAL PRESENTATION: Seven patients were deemed to have either tortuous supra-aortic, intracranial, and/or extracranial vasculature or to require additional microcatheter support as the result of lesion location.

INTERVENTION: The patients were treated, in part, with the 6-French Neuron delivery catheter (Penumbra, Inc., San Leandro, CA) at the authors' two institutions. The guide catheter was positioned in various distal locations within the intracranial internal carotid artery or external carotid artery. Three patients were treated for unruptured intracranial aneurysms, 2 patients for intracranial atherosclerosis, 1 patient for an arteriovenous malformation, and 1 patient for a pseudoaneurysm.

CONCLUSION: All lesions were successfully treated through a microcatheter advanced in a coaxial fashion through the guide catheter. There were no complications related to the positioning of the catheter. Distal intra- or extracranial placement of a specially designed, compliant guide catheter can be performed safely and may improve access and microcatheter stability in patients with tortuous vessels or difficult-to-reach lesions.

KEY WORDS: Endovascular, Guide catheter, Interventional, Intracranial

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As medical technology advances, an increasing number of intracranial lesions, once deemed unsuitable for endovascular treatment, are being addressed through interventional techniques. Despite these technological breakthroughs, access to intracranial pathology through tortuous vasculature has often been a limiting factor in certain patients (1, 3–7, 10, 11). Indeed, the success of neurointerventional procedures has often hinged on the dual requirements of adequate access to the lesion and appropriate support of the microcatheter during treatment. To address this issue, the 6-French Neuron delivery catheter (Penumbra, Inc., San Leandro, CA) was developed to enable distal catheterization of the intracranial vasculature with added stability and support of the microcatheter.

ABBREVIATIONS: AVM, arteriovenous malformation; ICA, internal carotid artery; MCA, middle cerebral artery

PATIENTS AND METHODS

From July to September 2007, 3 patients presented for elective internal carotid artery (ICA) aneurysm treatment, 2 patients presented for the treatment of intracranial atherosclerosis, 1 patient presented for staged embolization of a right frontal arteriovenous malformation (AVM), and 1 patient presented for embolization of an internal maxillary artery pseudoaneurysm (Table 1). Two patients were treated for right-sided ICA aneurysms, and 1 patient was treated for a left-sided ICA aneurysm. Two patients underwent angioplasty and/or stent placement for a right-sided M1 segment stenosis. The AVM was embolized in 2 stages before surgical resection. One patient underwent embolization of a pseudoaneurysm of the internal maxillary artery. The average age of the patients was 51.3 years (range, 27–72 yr). There were 3 women and 4 men in the series. Patient charts and angiograms were reviewed in a retrospective manner.

The Neuron delivery catheter was used in each of the 7 cases and placed within the distal intracranial or extracranial vasculature. In 5 cases requiring intracranial placement, the Neuron delivery catheter was either advanced over a wire or exchanged after

TABLE 1. Clinical summary of patients treated^a

Patient no.	Age (yr)/sex	Pathology	Catheter position	Treatment	Complications
1	44/F	Aneurysm	Vertical segment of petrous ICA	Coiling	None
2	40/F	Aneurysm	Vertical segment of petrous ICA	Coiling	None
3	56/F	Aneurysm	Vertical segment of petrous ICA	Coiling	None
4	72/M	Intracranial stenosis	Vertical segment of cavernous ICA	Angioplasty	None
5	65/M	Intracranial stenosis	Vertical segment of cavernous ICA	Angioplasty and stent	None
6	55/M	AVM	Vertical segment of cavernous ICA	Glue embolization	None
7	27/M	Pseudoaneurysm	Internal maxillary artery	Embolization	None

^a ICA, internal carotid artery; AVM, arteriovenous malformation.

routine diagnostic angiography and positioned at the cranial base, after placement of a 6-French sheath in the femoral artery. Various microcatheters and wires were advanced in a coaxial fashion through the catheter and positioned distally in the intracranial vasculature. The Neuron delivery catheter was then advanced over the microcatheters to their ultimate position in either the petrous or cavernous segment of the ICA. In 1 case, the Neuron delivery catheter was directly positioned in the cavernous ICA using a 0.038-inch glidewire (Terumo Medical Corp., Somerset, NJ). The intracranial lesions were treated through the microcatheters. There were no complications related to the Neuron delivery catheter or thromboembolic complications during any of these cases.

The Neuron delivery catheter (Fig. 1) is designed with a compliant 6- or 12-cm tip to allow for intracranial placement. The 115-cm catheter is composed of a 6-French support zone tapered to a distal, flexible 5-French tip with an inner diameter of 1.35 mm. The delivery catheter accommodates a 3.5-French Neuron select catheter (Penumbra, Inc.). The inner diameter of the 3.5-French catheter is 0.558 mm, and it accommodates a 0.018-inch wire. We have found that the combination of the Neuron delivery catheter over the Neuron select catheter over a 0.018-inch wire is insufficient to easily catheterize the supra-aortic vessels. Thus, we have mostly relied on catheter exchanges to position the Neuron delivery catheter in the proximal target vessel. We then proceeded with navigation of the catheter into the cranial circulation over a 0.035-inch wire or over a microcatheter and microwire combination.

With particularly tortuous supra-aortic vessels, additional support is often necessary to facilitate the exchange of catheters. In these instances, we prefer to position the diagnostic catheter more distally in the cervical vasculature over a guidewire before the exchange. Also, stiffer exchange wires may be necessary to maintain this position during the exchange and to prevent the wire from “backing out” of position.

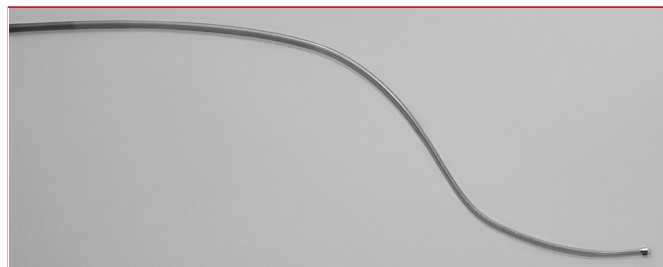


FIGURE 1. Photograph of the distal tip of the Neuron delivery catheter. (Courtesy of Penumbra, Inc., San Leandro, CA).

ILLUSTRATIVE CASES

Patient 1

A 72-year-old right-handed man was transferred from another institution for treatment of a focal stenosis of the right M1 segment. Previously, he had experienced a right middle cerebral artery (MCA) stroke with left-sided hemiparesis. After an extensive preoperative work-up, a right MCA stenosis was identified. The patient was started on an antiplatelet medication regimen consisting of 325 mg of aspirin and 75 mg of clopidogrel (Plavix; Bristol-Myers Squibb/Sanofi Pharmaceuticals, New York, NY). Despite medical management, he continued to have transient ischemic attacks.

After a lengthy discussion with the patient and his family, the decision was made to proceed with angioplasty of the right M1 segment stenosis. Digital subtraction angiography of the right ICA was performed with a 5-French diagnostic catheter positioned in the proximal ICA (Fig. 2). Because of tortuous supra-aortic vessels, we elected to use the Neuron delivery catheter to increase microcatheter support for the procedure.

The diagnostic catheter was exchanged for a Neuron delivery catheter over an exchange length wire. The Neuron catheter was then advanced over a Terumo glidewire until it was positioned in the vertical segment of the cavernous ICA. A microwire was advanced in a coaxial fashion through the guide catheter, carefully navigated across the stenosis, and positioned within a distal MCA branch. Next, an angioplasty balloon was passed over the wire, positioned across the stenosis, and gently inflated. Postangioplasty angiography revealed improvement in the MCA patency. There were no complications during the procedure, and the patient was ultimately discharged to a rehabilitative hospital for continued therapy.

Patient 2

A 55-year-old right-handed man underwent preoperative staged embolization of a right frontal AVM (Fig. 3). The AVM was fed predominantly by branches originating from the anterior cerebral artery with additional supply from several branches of the MCA. Angiography was initially performed with a 5-French diagnostic catheter. The patient had a tortuous cervical ICA that prevented positioning a guide catheter near the cranial base (Fig. 4). A catheter exchange was then performed with the Neuron delivery catheter in the proximal ICA. A microcatheter and wire were advanced in a coaxial fashion through the Neuron catheter and initially positioned within the ICA terminus. The Neuron catheter was then advanced over the microcatheter and wire combination and positioned in the vertical portion of the cavernous segment of

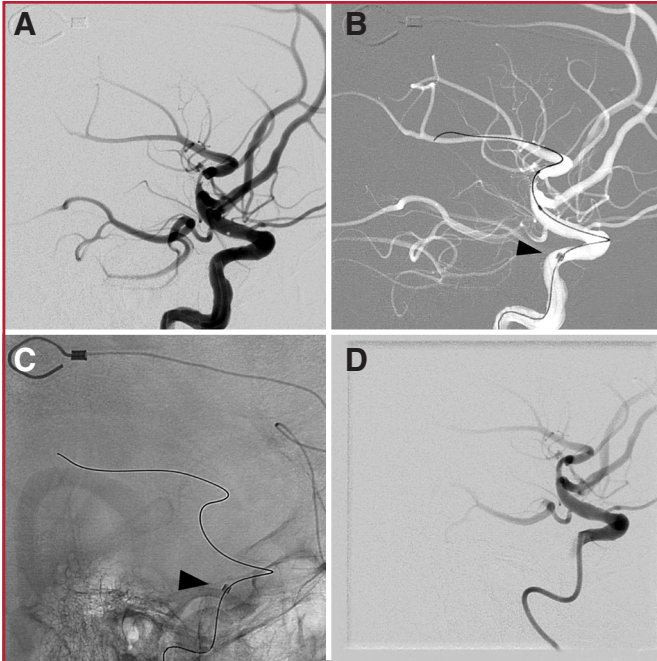


FIGURE 2. Patient 1. **A**, right internal carotid artery (ICA) angiogram, lateral view, demonstrating high-grade stenosis of the M1 segment. **B**, right ICA angiogram, lateral road map view, with the Neuron delivery catheter positioned in the cavernous segment of the ICA (arrowhead). A balloon angioplasty catheter is positioned over the region of stenosis (microcatheter markers) in the proximal middle cerebral artery (MCA), and a wire is positioned in the distal MCA. **C**, unsubtracted lateral view of the Penumbra Neuron catheter (arrowhead) and wire. **D**, postangioplasty angiogram performed through the Neuron catheter. (Courtesy of the Barrow Neurological Institute).

the ICA. The flow-directed microcatheter over a wire was used to catheterize distal branches of the anterior cerebral artery and MCA for further embolization. There were no complications during the procedure or changes in the patient's neurological status after the procedure. After the staged embolization, the patient underwent successful resection of the AVM.

DISCUSSION

Appropriate access and positioning of catheters are essential requirements for the success and safety of neurointerventional procedures. The increased degree of vessel tortuosity encountered in older patients makes access and catheter stability an important issue in their treatment. Cai et al. (4) treated 63 patients older than 70 years of age for ruptured and unruptured aneurysms. Ten patients required direct carotid puncture, and 1 patient required a brachial artery approach as the result of vessel tortuosity. In 3 of their patients, selective embolization of the aneurysm failed.

Technical limitations related to access also affected 2 of 36 patients selected for angioplasty and stent placement to treat intracranial stenoses and dissections in a study by Lylyk et al.

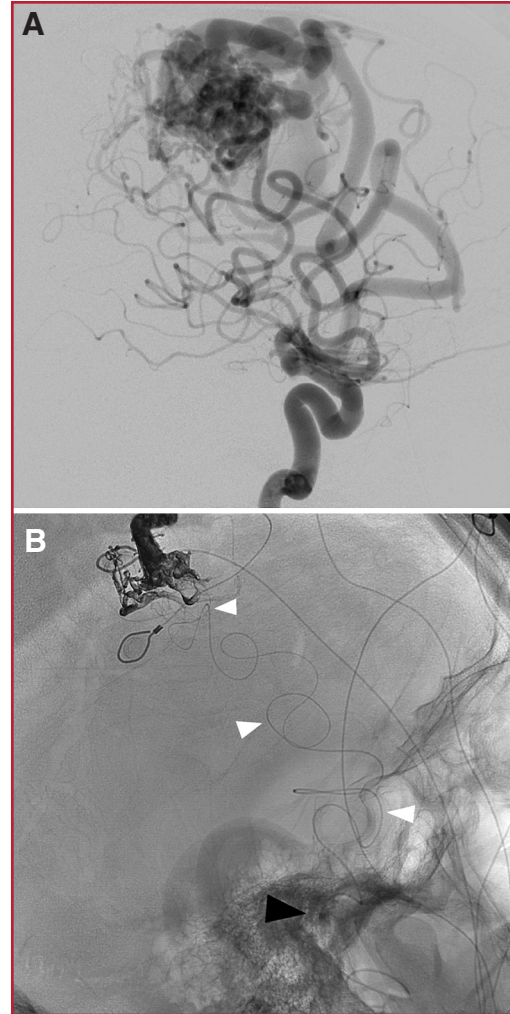


FIGURE 3. Patient 2. **A**, right ICA angiogram, lateral view, demonstrating a large frontal/parietal arteriovenous malformation. **B**, unsubtracted lateral view of the Penumbra Neuron delivery catheter positioned in the cavernous segment of the ICA (black arrowhead). The course of the microcatheter is delineated by the white arrowheads. (Courtesy of the Barrow Neurological Institute).

(7). They were unable to target stenotic regions of the supraclinoid ICA because of the anatomy of the cervical ICA and the anterior bend of its cavernous segment. Eckard et al. (6) encountered difficulty with catheter stability in a 60-year-old man with severe stenosis involving the distal left ICA. Their initial attempts at passing a 4- × 18-mm balloon-mounted, Velocity stent (Cordis, Miami, FL) through a 6-French, 90-cm Arrow sheath (Arrow International, Reading, PA) positioned in the proximal left ICA was confounded by vessel tortuosity. Several attempts to advance the stent/balloon catheter toward the stenosis caused the guide sheath to back out into



FIGURE 4. Patient 2. Angiogram, right anterior oblique view, showing a tortuous C1 segment of the right ICA. (Courtesy of the Barrow Neurological Institute).

the aortic arch. Ultimately, they were able to cross and treat the stenosis by stabilizing the guide sheath with a Stiff Shaft Glidewire (Terumo Medical Corp.) in what they termed the “stiff guide” technique.

During coil embolization of an aneurysm, the guide catheter is typically placed in the cervical vessel (2). In patients with tortuous vessels, advancement of the microcatheter can push the guide catheter toward the aortic arch and out of the cervical vessels. Replacement with a stiffer guide catheter is often necessary, thereby increasing the risk of vessel injury or dissection or leading to termination of the procedure. However, the Neuron delivery catheter can be placed in a distal position in the intracranial vasculature to provide additional support of the microcatheter during an interventional procedure. The more distal placement of the guide catheter decreases the extent of the microcatheter exposed to the vessel wall and limits the potential for friction to build up between the microcatheter and vessel. The opportunity for the microcatheter to “jump” forward and create unintended and potentially disastrous consequences may be reduced (8). Furthermore, a more distal position of the guide catheter may allow neurointerventional surgeons to visualize the tip of the guide catheter during the treatment of intracranial lesions.

Placement of a guide catheter into the intracranial circulation has been described in the literature for treatment of acute thromboembolic events (9). In 25 patients with tandem thromboembolic occlusions of the ICA and MCA, Nedeltchev et al. (9) used an 8-French guide catheter, with or without a 120-cm Tracker 38 infusion catheter (Boston Scientific/Target, Fremont, CA), to bypass and aspirate thrombus in the ICA and MCA. The guide catheter was advanced as far as the horizontal segment of the petrous ICA, whereas the infusion catheter was advanced into the proximal M1 segment. Use of the guide catheter in this manner completely blocked blood flow in the patient and created negative pressure to facilitate aspiration of thrombi from the intracranial vessels. Obviously, this technique is not feasible or generally recommended during other interventional treatments, such as coil embolization of aneurysms, stenting of intracranial atherosclerosis, or embolization of dural arteriovenous fistulae, AVMs, or intracranial tumors.

We have described several scenarios in which a guide catheter positioned within the intracranial vasculature may assist in neurointerventional procedures. It is important to note that there are some limitations. The inner diameter of the catheter limits the ability to simultaneously advance a second microcatheter in cases such as balloon remodeling during aneurysm treatment. Also, as stated, we have had little success in using this system as initially designed (with the 6-French Neuron delivery catheter over the 3.5-French Neuron select catheter over a 0.018-inch wire). In general, the 0.018-inch wire is not robust enough to select the supra-aortic vessels easily.

CONCLUSION

A novel, specially designed, intracranial guide catheter has the potential to improve support and stability of a microcatheter during neurointerventional procedures. The tapered and compliant catheter tip is supple and flexible, potentially minimizing the risk of vessel injury during intracranial placement. The decision to use this catheter rests in the hands and judgment of the neurointerventionalist surgeon. We have found this catheter to be useful in selected cases in which additional microcatheter support is required during attempts to access particularly distal intracranial lesions or during attempts to overcome difficulties related to tortuous proximal vessels. Ultimately, the use of this type of catheter may increase the success and safety of otherwise difficult interventional treatments.

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COMMENTS

Park et al. described their experience using a novel guide catheter, the Neuron guide catheter (Penumbra, Inc., San Leandro, CA), in seven different neuroendovascular procedures. In one patient, the guide was placed in the cavernous internal carotid artery. We share their positive impression in using this catheter to gain stable access in tortuous cervical arteries, although we have not seen a need to navigate beyond the petrous carotid or vertebral V4 segment. A major advantage of this guide catheter is the ability to keep it in view while maneuvering devices intracranially. As they demonstrate, the 6-cm length floppy tip covers most situations, and the catheter can be exchanged into the more proximal vessel and subsequently advanced coaxially over the microcatheter-microguidewire construct. Its inability to accommodate a second catheter (such as for balloon remodeling) is a limitation that the manufacturer should address.

Michael C. Hurley
Bernard R. Bendok
Chicago, Illinois

Park et al. shared their experience with the compliant guide catheter that can be placed quite distally within the proximal intracranial circulation. Catheter support is often problematic, particularly in patients with tortuous anatomy, and distal support is often advantageous in the treatment of multiple pathological lesions. This is a straightforward evaluation of a new system that allows one to do that, and certainly this system has absolute technical advantages and is a primary illustration of how technology is improving.

Robert H. Rosenwasser
Philadelphia, Pennsylvania

Park et al. presented their initial experiences with a new guiding catheter that is soft and supple enough to safely navigate into the intracranial circulation. Although limited, the initial experiences sug-

gested that this device will help to improve accessibility to distal, very tortuous vasculature, which can be quite difficult and carries a significant risk of vessel dissection or perforation. It is well-known by this readership that establishing a stable position for the guide catheter is very important in achieving the appropriate distal positioning of microcatheters for endovascular procedures.

The guide catheter provides the necessary support, or buttress, for the softer, more supple microcatheters in the proximal circulation, thus helping to vector the forces to advance the microcatheter to more distal portions of the cerebral vasculature. In the setting of highly tortuous proximal vasculature, this buttress effect is compromised when the guide catheter is placed proximal to the tortuosity and might result in loss of a safe microcatheter position. Of course, placement of such a catheter beyond the cranial base can certainly increase the risk of carotid injury. As Park et al. state, judicious use of this catheter is required to maximize the benefits of this new device to the field of neurointerventional surgery while minimizing its risks.

Charles J. Prestigiacomo
Newark, New Jersey

In this article, Park et al. described the contribution of a new guiding catheter (Neuron) in the endovascular treatment of intracranial lesions in patients with tortuous brachycephalic arteries. It is particularly useful in delivery of intracranial stents or catheterization of distal aneurysms such as anterior communicating or anterior cerebral artery aneurysms. Interventional neuroradiologists at the UCLA Medical Center have had the opportunity to use this delivery catheter in similar intracranial lesions and unanimously agree with their very positive overall impression.

There is a place in our present endovascular armamentarium for the Neuron catheter. Its use in specific patients will decrease overall iatrogenesis. This is particularly true in deployment of intracranial stents (for aneurysms or stenotic lesions).

Fernando Viñuela
Interventional Neuroradiologist
Los Angeles, California

This article is typically without interest if you just look at the title and think about the subject. If you are not confronted, on a daily basis, with this very primitive and trivial procedure called catheterization of brain vessels, then you cannot understand the importance of this technical note. Everything is “theoretically” possible in terms of navigation in the brain circulation with only one limitation, which is the stability of the guiding catheter system for coaxial catheterization. Up to now, none of the guiding catheter systems was really dedicated to brain navigation when the vessels of the aorta are tortuous. It is probably not that difficult for the industry to develop a guiding catheter compared with new “magic coils” or very sophisticated stents. I think that this article provided crucial information. Not only does it provide an essential tip for safe and efficient catheterization, but it also emphasizes the courage of a company to put some money on a so-called “zero interest” item, which is in fact absolutely essential. For many years interventional neuroradiologists were crying out, without any effect, for such an intracranial guiding catheter, and finally it has happened. I thank the company behind this device because it is a real breakthrough for endovascular therapy.

Jacques Moret
Paris, France

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[p 380] **Mesenchymal Stem Cell and Gene Therapies for Spine Fusion**

Oren N. Gottfried, Andrew T. Dailey

Question 1: Which of the following is a current limitation of the use of mesenchymal stem cells to promote spinal fusion in humans?

- A. Cultured osteoprogenitor cells are less effective at promoting bone fusion than cells from fresh bone marrow aspirate
- B. Selective cell retention of osteogenic cells renders them less effective than cells from bone marrow aspirate
- C. Bone fusion with mesenchymal cells is only effective in immunocompromised animals
- D. Vertebral bone marrow has fewer osteoprogenitor cells than iliac crest marrow
- E. Techniques to differentiate and increase number of osteogenic cells in culture at the time of surgery

[p 393] **Challenging Traditional Beliefs: Microsurgery for Arteriovenous Malformations of the Basal Ganglia and Thalamus**

Bradley A. Gross, Edward A.M. Duckworth, Christopher C. Getch, Bernard R. Bendok, H. Hunt Batjer

A 22-year-old man is diagnosed with a right basal ganglia arteriovenous malformation (AVM) after suffering from a thalamic and parietal lobe hemorrhage. He undergoes a small craniotomy for evacuation of hematoma and is then treated with radiosurgery. He is left with a residual spastic hemiparesis and epilepsy. He presents 4 years later (age 26) with diplopia, headache, and worsening left-sided motor function. His imaging demonstrates a right thalamic 2.5 cm AVM nidus with an associated 4-cm thrombosed varix underneath an area of cortical encephalomalacia at his prior craniotomy site.

Question 1. Which of the following is the most appropriate management?

- A. Embolization

- B. Stereotactic radiosurgery
- C. Microsurgery
- D. Embolization and stereotactic radiosurgery
- E. Embolization and microsurgery

Question 2. Which are the most important factors determining the hemorrhage risk of an *untreated* brain AVM?

- A. AVM size, venous drainage pattern, eloquence of brain
- B. Infratentorial location, number of draining veins, deep perforator supply
- C. Deep location, deep venous drainage, history of prior hemorrhage
- D. Sex, diffuse AVM morphology, border-zone location

[p 476] **Results of Endovascular Treatment of Traumatic Intracranial Aneurysms**

José E. Cohen, John M. Gomori, Ricardo Segal, Alex Spivak, Emil Margolin, Gil Sviri, Gustavo Rajz, Shifra Fraifeld, Sergey Spektor

Question 1: A 2-year-old boy was admitted to the emergency room after sustaining an accidental frontal gunshot wound. He was intubated and admitted to the Department of Neurosurgery with Glasgow Coma Scale score of 8. His head computed tomographic (CT) scan is shown in Fig. 1, A and B (go to sans.cns.org to view figures). Wound debridement was performed, and intracranial pressure (ICP) monitoring revealed pressure of 15 to 25 mmHg. The optimal next step in the care of this patient will be:

- A. Neurointensive care management to control ICP
- B. Emergent craniotomy with hematoma evacuation
- C. Cerebral computerized tomography with 3-D angiographic reconstruction
- D. Diagnostic digital subtraction angiography
- E. Cerebral magnetic resonance imaging with angiographic protocol

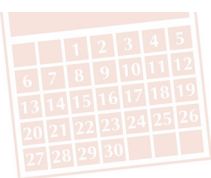
Objectives: Participating surgeons will improve their ability to recognize and treat a wide variety of disorders relevant to neurological surgeons. They will have greater insight into their existing knowledge base, and will use their performance on SANS to tailor their subsequent educational efforts. In addition, users will be better prepared for certification and recertification examinations in neurological surgery.

Target Audience: This activity is primarily intended for neurosurgeons and neurosurgeons-in-training.

Accreditation: This activity has been planned and implemented in accordance with the essential areas and policies of the ACCME through the Sponsorship of the CNS. The CNS is accredited by the ACCME to provide CME for physicians.

Credit: CME will be assigned on an annual basis. 1 CME hour will be given for every 10 questions completed.

Disclaimer: The information contained within the Program is intended solely for educational purposes. The questions and critiques presented herein are intended to inform neurosurgeons of the medical knowledge, surgical technique, and decision making, and other experiences of the physicians who have contributed to the Program. In view of the possibility of human error, however, and in recognition of the fact that medical knowledge continuously evolves, neither the CNS, the contributors, editors or any other individual who has been involved in the preparation of the Program represents or warrants that the information contained herein is, in every respect, accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from use of the information included in the Program. As with any source of medical information, you are encouraged to confirm the information presented herein with other sources.



CALENDAR OF EVENTS

Full contact information is available online only

Listings for this section need to be submitted at least 3 months in advance. Please include a telephone number and/or a fax number.

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INTERNATIONAL / GENERAL NEUROSURGERY

AUGUST 30, 2009 – SEPTEMBER 4, 2009	XIV World Congress of Neurological Surgery of the World Federation of Neurosurgical Societies	Boston, MA	CONTACT: American Association of Neurological Surgeons TEL: (888) 566 AANS EMAIL: support@abstractsonline.com WEB SITE: www.aans.org/wfns2009
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SPINE / PERIPHERAL NERVE

OCTOBER 6–8, 2008	International Conference on Spine Surgery and Rehabilitation	Milan, Italy	TEL: +39 051 765357 FAX: +39 051 765195 EMAIL: info@csrcongressi.com WEB SITE: www.csrcongressi.com
NOVEMBER 1–2, 2008	Spine Deformity Symposium	Ft. Lauderdale, FL	CONTACT: AO North America TEL: (800) 769 1391 WEB SITE: www.aona.org
NOVEMBER 1–2, 2008	Current Practices and Emerging Technologies in Spine Surgery	Ft. Lauderdale, FL	CONTACT: AO North America TEL: (800) 769 1391 WEB SITE: www.aona.org
NOVEMBER 22–23, 2008	The Aging Spine	Philadelphia, PA	CONTACT: AO North America TEL: (800) 769 1391 WEB SITE: www.aona.org
JULY 17–19, 2009	Spine 2009	Tamil Nadu State, India	CONTACT: Kailai Rajan EMAIL: dkailairajan@dataone.in

STEREOTACTIC / FUNCTIONAL

OCTOBER 5–8, 2008	XVIII Congress of the European Society for Stereotactic and Functional Neurosurgery	Rimini, Italy	TEL: +39 051 765357 FAX: +39 051 765195 EMAIL: emarzaloni@csrcongressi.com WEB SITE: www.essfn2008.csrcongress.com
OCTOBER 20–28, 2008	Gamma Knife Perfexion Course	Cleveland, OH	CONTACT: Martha Tobin TEL: (216) 445 3449 EMAIL: tobinm@ccf.org
OCTOBER 22–24, 2008	Advanced Gamma Knife Course	Charlottesville, VA	CONTACT: Jason Sheehan, MD TEL: (434) 924 8129 FAX: (434) 243 6726 EMAIL: jps2f@virginia.edu WEB SITE: www.healthsystem.virginia.edu/ internet/neurosurgery/gkcourse/home.cfm
DECEMBER 1–5, 2008	Gamma Knife Perfexion Course	Cleveland, OH	CONTACT: Martha Tobin TEL: (216) 445 3449 EMAIL: tobinm@ccf.org
MARCH 7, 2009	Contemporary Stereotactic Radiosurgery on the Central Nervous System: A Primer and Update	Los Angeles, CA	CONTACT: Mairead C. Rusch TEL: (323) 442 8860
OCTOBER 22–25, 2008	Neurocritical Care Society 6th Annual Meeting	Miami Beach, FL	CONTACT: Tami Page TEL: (952) 646 2034 FAX: (952) 545 6073 EMAIL: info@neurocriticalcare.org WEB SITE: www.neurocriticalcare.org

MINIMALLY INVASIVE NEUROSURGERY

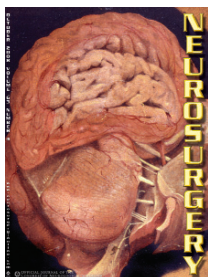
OCTOBER 23–24, 2008	Clinical Course on High Definition (HD) Imaging in Neuroendoscopy and Endoscopic-assisted Skull Base Surgery	Greifswald, Germany	CONTACT: Henry Schroeder EMAIL: Henry.Schroeder@uni-greifswald.de WEB SITE: www.medizin.uni-greifswald.de/neuro_ch/
DECEMBER 11–12, 2008	Clinical Course on High Definition (HD) Imaging in Neuroendoscopy and Endoscopic-assisted Skull Base Surgery	Greifswald, Germany	CONTACT: Henry Schroeder EMAIL: Henry.Schroeder@uni-greifswald.de WEB SITE: www.medizin.uni-greifswald.de/neuro_ch/

PEDIATRICS

OCTOBER 12–16, 2008	International Society for Pediatric Neurosurgery	Cape Town, South Africa	CONTACT: Dr. Graham Fieggen TEL: +27 21 4066213 FAX: +27 21 4066555 EMAIL: graham.fieggen@uct.ac.za WEB SITE: www.ISPN2008.org
JANUARY 23–24, 2009	Consensus Conference on Pediatric Neurosurgery	Rome, Italy	EMAIL: CPN2009@ptsroma.it WEB SITE: www.ptsroma.it/cpn2009
MARCH 15–18, 2009	First World Congress on Spina Bifida Research and Care	Orlando, FL	CONTACT: Jeffrey Blount, MD EMAIL: Jeffrey.Blount@ccc.uab.edu WEB SITE: http://medicalconference.spinabifidaassociation.org
MARCH 15–19, 2009	4th Fred J. Epstein International Symposium on New Horizons in Pediatric Neurology, Neurosurgery and Neurofibromatosis	Eilat, Israel	CONTACT: Hannah Baum TEL: +97 23 517 5150 EMAIL: newhorizons@targetconf.com WEB SITE: www.fredhorizons.com

SPECIAL TOPICS

OCTOBER 18–25, 2008	Research Update in Neuroscience for Neurosurgeons	Woods Hole, MA	CONTACT: Dr. Issam A. Awad TEL: (303) 315 1310 FAX: (303) 315 1331 EMAIL: issam.awad@uchsc.edu WEB SITE: www.societyns.org
NOVEMBER 9–11, 2008	Goodman Oral Board Preparation Neurosurgery Review by Case Management	Houston, TX	CONTACT: Vanessa Garlisch TEL: (857) 378 0500 EMAIL: epm@aans.org WEB SITE: www.aans.org
JANUARY 29, 2009– FEBRUARY 8, 2009	Chicago Review Course in Neurosurgery	Chicago, IL	CONTACT: Maria T. Pena TEL: (773) 296 6666 EMAIL: mpena@chcagoreviewcourse.com WEB SITE: www.chicagoreviewcourse.com
FEBRUARY 6–8, 2009	Managing Coding and Reimbursement Challenges in Neurosurgery	Las Vegas, NV	CONTACT: Heather Hodge TEL: (847) 378 0500 EMAIL: emp@aans.org WEB SITE: www.AANS.org
MARCH 20–21, 2009	Managing Coding and Reimbursement Challenges in Neurosurgery	New Orleans, LA	CONTACT: Heather Hodge TEL: (847) 378 0500 EMAIL: emp@aans.org WEB SITE: www.AANS.org
MAY 17–19, 2009	Goodman Oral Board Preparation Neurosurgery Review by Case Management	Houston, TX	CONTACT: Vanessa Garlisch TEL: (847) 378 0500 EMAIL: emp@aans.org WEB SITE: www.AANS.org
JUNE 26–27, 2009	Managing Coding and Reimbursement Challenges in Neurosurgery	Chicago, IL	CONTACT: Heather Hodge TEL: (847) 378 0500 EMAIL: emp@aans.org WEB SITE: www.AANS.org
JULY 17–18, 2009	Managing Coding and Reimbursement Challenges in Neurosurgery	Washington, DC	CONTACT: Heather Hodge TEL: (847) 378 0500 EMAIL: emp@aans.org WEB SITE: www.AANS.org



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OCTOBER 2008 VOLUME 63 NUMBER 4

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Collice

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Gene and Cell Delivery to the Degenerated Striatum: Status of Pre-clinical Efforts in Primate Models

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Acute Relative Adrenal Insufficiency Following Aneurysmal Subarachnoid Hemorrhage

Weant

Angiographic Balloon Test Occlusion and Therapeutic Sacrifice of Major Arteries to the Brain

Sorteberg

Clinical and Angiographic Outcome Following Endovascular Management of Giant Intracranial Aneurysms

Jahromi/Levy

Intracranial Aneurysm Perforation during Endosaccular Coiling: Impact on Clinical Outcome, Initial Occlusion, and Recanalization Rates

Kwon/Han

Neurosurgical Treatment for Aneurysm Remnants or Recurrences after Coil Occlusion

Lejeune/Thines

Thrombophilic Risks Factors in Patients with Cranial and Spinal Dural Arteriovenous Fistulas

Gerlach/Seifert

Extent of Surgical Resection Is Independently Associated with Survival in Patients with Hemispheric Infiltrating Low-grade Glioma

McGirt/Quiñones-Hinojosa/Brem

Pituitary Hormonal Loss and Recovery after Transsphenoidal Adenoma Removal

Fatemi/Kelly

Sequential Salvage Chemotherapy for Recurrent Intracranial Hemangiopericytoma

Chamberlain

Radiation Tolerance Limits of the Brainstem

Sharma/Kondziolka

Stereotactic Radiosurgery and Fractionated Stereotactic Radiotherapy for the Treatment of Nonacoustic Cranial Nerve Schwannomas

Showalter/Andrews

Cervical Disc Arthroplasty Compared with Fusion in a Workers' Compensation Population

Steinmetz/Traynelis/Resnick

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Wan/Tator

Reoperation for Suboptimal Outcomes after Deep Brain Stimulation Surgery

Ellis/Okun

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Kumar/North

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The Identification of Deleted in Liver Cancer-1 (DLC1) as a Candidate Meningioma Tumor Suppressor

Hankins/Helm

EXPERIMENTAL STUDIES

Advanced Magnetic Resonance Imaging of Cerebral Cavernous Malformations: I. High Field Imaging of Excised Human Lesions

Shenkar/Batjer/Awad

Advanced Magnetic Resonance Imaging of Cerebral Cavernous Malformations: II. Imaging of Lesions in Murine Models

Shenkar/Awad

Perfluorocarbon Emulsions Improve Cognitive Recovery Following Lateral Fluid Percussion Brain Injury in Rats

Zhou/Sun/Bullock

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Sir Victor Horsley's Contributions to Gunshot Wounds of the Head

Cybulski

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Ayberk

Microvascular Decompression in Hemifacial Spasm Resulting from Cerebellopontine Angle Lipoma: Case Report

Barajas

TECHNICAL CASE REPORT

Surgical Management of a Paraclinoid Aneurysm Containing a Displaced Neuroform Microstent: Technical Case Report

Thomas