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Treatment of Pituitary Tumors

Surgery

Michael Buchfelder

Department of Neurosurgery, University of Erlangen-Nüremberg Medical School, Erlangen, Germany

Following a century of technical developments and refinements, a variety of standard operation techniques to date are available for the surgical treatment of pituitary tumors. The vast majority of the lesions can be dealt with satisfactorily utilizing transsphenoidal approaches. The goal of surgical treatment is rapid eradication of the tumor mass, decompression of visual pathways, and elimination of hormonal oversecretion while preserving the normal gland and avoiding potential surgical complications. The tumor's size, extension, and configuration and the magnitude of hormonal oversecretion, are the essential factors that decide whether all the goals can be reached. Another important factor is the individual skill and experience of the surgeon. Still, several lesions that are mainly developed outside of the sella require transcranial approaches, of which the pterional and subfrontal routes are the most widely used. With microsurgical techniques and standard approaches, mortality is far below 1% and morbidity is remarkably low. The most favorable surgical results are obtained with microadenomas, which in the MR image are depicted as distinct low intensity lesions. Only recently has the recovery of pituitary function following surgery been convincingly demonstrated. With the extended transsphenoidal approaches, lesions become accessible that previously have been considered contraindications for transsphenoidal surgery. The introduction of new technical gadgets such as neuronavigation, endoscopy, and intraoperative imaging open new avenues and, even more, widen the spectrum of accessible lesions. Indications for surgery, the preoperative workup, surgical techniques, results, limitations, and new technical developments are briefly reviewed in this article.

Key Words: Complications; pituitary adenomas; technical developments; transcranial approach; transsphenoidal approach; surgical indications; surgical results.

*This paper is dedicated to Prof. Dr. Rudolf Fahlbusch on his 65th birthday.

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Author to whom all correspondence and reprint requests should be addressed: Prof. Dr. med. M. Buchfelder, Neurochirurgische Klinik mit Poliklinik der Universität Erlangen, Schwabachanlage 6, D-91054, Erlangen, Germany. E-mail: buchfelder@nch.imed.uni-erlangen.de

Surgical Indications

It is generally accepted that symptomatic pituitary adenomas require treatment. Thus, once visual compromise has occurred, surgical decompression of the visual pathways is usually recommended unless the compression can be resolved by medical treatment. However, unless the lesion is a prolactinoma, the most rapid and reliable relief from optic nerve and chiasmal compression is being achieved by surgery. In nonsecreting, hormonally inactive pituitary tumors, no competitive treatment of the space-occupying lesion is available to date. Thus, surgery remains the mainstay in their treatment. Hormonal oversecretion in patients suffering from Cushing's disease, Nelson's syndrome, thyrotropinomas, and acromegaly is generally considered an indication for surgery *(7,14,26,43)*. In ACTH-secreting tumors medical therapy is certainly not a long-term alternative therapy, and, thus, once the diagnosis is made, surgery should be scheduled. In growth hormone– and TSH-secreting tumors alternative medical therapy is currently being discussed *(29)*. However, surgery is still generally considered the most rapidly acting and cheapest long-term solution for most patients. Unless visual compromise or hormonal oversecretion are present, documented hypopituitarism can also be considered an indication for surgery because pituitary function may be improved following decompression of the gland by selective tumor resection *(39)*. A conservative approach is usually recommended in incidentally detected lesions. However, progression of a tumor, which is clearly documented in the MRI, is another good reason to surgically intervene. After all, surgical results are dependent on the size and extension of the lesion and thus, an earlier intervention in a progressive disease is certainly preferrable. The mere documentation of an incidentally detected intrasellar lesion is per se not considered an indication for surgery. In such cases, a rather conservative approach including of course long term radiological and endocrinological observation is strongly advised. The primary therapy of prolactinomas is usually considered medical therapy with dopamine agonists. Non-responders and those, who do not sufficiently tolerate the drugs are certainly still surgical candidates, even if the underlying lesion is a prolactinoma. In macroprolactinomas satisfactory size reduction and stable prolactin levels are the aims of therapy, whilst in microprolactinomas stable persistent normoprolactinaemia should

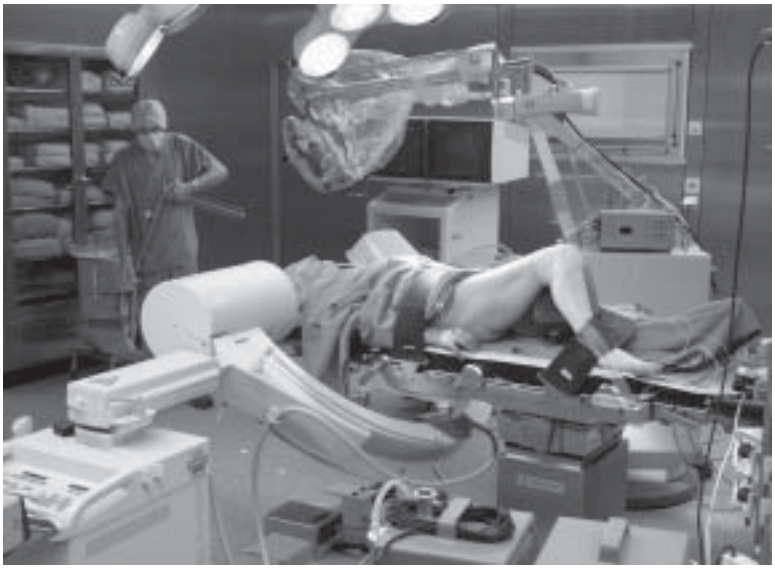

Fig. 1. Patient's position and operating room setup for "classical" transsphenoidal surgery of pituitary tumors as used by the author.

be achieved. Recently, the excellent short and long-term normalization rates in microprolactinomas observed by several groups were considered a basis to suggest transsphenoidal surgery as an alternative first-line therapy for patients with microprolactinomas *(15)*, just as it was recommended in the past. On the other hand, a primary medical treatment with somatostatin analoges was advocated as a competitive therapy to surgery for growth hormone secreting tumors and thyrotropinomas. Reoperations should be strongly considered if a resectable lesion has not been excised satisfactorily by the primary intervention, certainly also in recurrent disease, if adjunctive medical or radiation therapy failed to achieve control of the adenoma and in symptomatic progressions of residual tumors.

Preoperative Workup

Generally, the minimal imaging technique required is a proper MR scan that depicts the tumor in T1-weighted images before and after the application of contrast medium, at least in the sagittal and coronal planes. This 3D dataset can also be used for planning neuronavigation. Other sequences may be additionally required in an individual case. A skull X-ray is no longer mandatory. In selected cases a coronal CT scan is helpful, because it provides much more information about the structure and segmentation of the paranasal sinuses. Endocrinological investigations should provide information about the function of the various axes of the anterior pituitary. The prolactin level is a particularly crucial parameter, because in cases of excessive elevation of prolactin, a prolactinoma is suspected and, consequently, any surgical intervention needs to be discussed mentioning alternative medical treatment with dopamine agonists to the patient. Hypopituitarism requires adequate perioperative substitution therapy. Endocrine evaluation also needs to reveal potential hormonal activity of the lesions and to document the magnitude of hormonal oversecretion. At least in patients with acromegaly and prolactinomas, this has been shown to be a prognostic factor for the outcome of surgery in terms of normalization. In all suprasellarly extending lesions, an ophthalmological evaluation should be performed, consisting of perimetry and testing of visual acuity. Furthermore, the general health of the patient should be assessed with respect to the chance that he or she will tolerate the surgery without any problems.

Surgical Techniques

From a variety of historical attempts to reach pituitary tumors, only a few standard approaches elapsed. Today, the transsphenoidal route is used predominantly as a highly versatile approach. Certainly, more than 90–95% of pituitary adenomas can be dealt with it. However, there are many variations possible, which start with the positioning of the patient *(14)*. While some surgeons, like ourselves, prefer to operate on a patient in supine position *(7)* with the head slightly extended (Fig. 1), others favor a semisitting position *(25,26)*. Radiofluoroscopic control is the most commonly used procedure for navigation and intraoperative imaging. This surgery can be performed with and without dissection of the septal mucosa. Creation of a submucous tunnel, such as in septal corrective surgeries, can be perfomed following either a sublabial or medial nasal incision. Then, the medial nasal mucosa is unilaterally being detached from the cartilaginous and osseous nasal septae, respectively. A nasal speculum is inserted to keep the mucosal tunnel open *(7,26,45)*. Alternatively, a direct endonasal approach to the sphenoid sinus can be chosen *(24,45)*. At this stage the operating microscope is usually brought into place. The vomer, which serves as an excellent midline

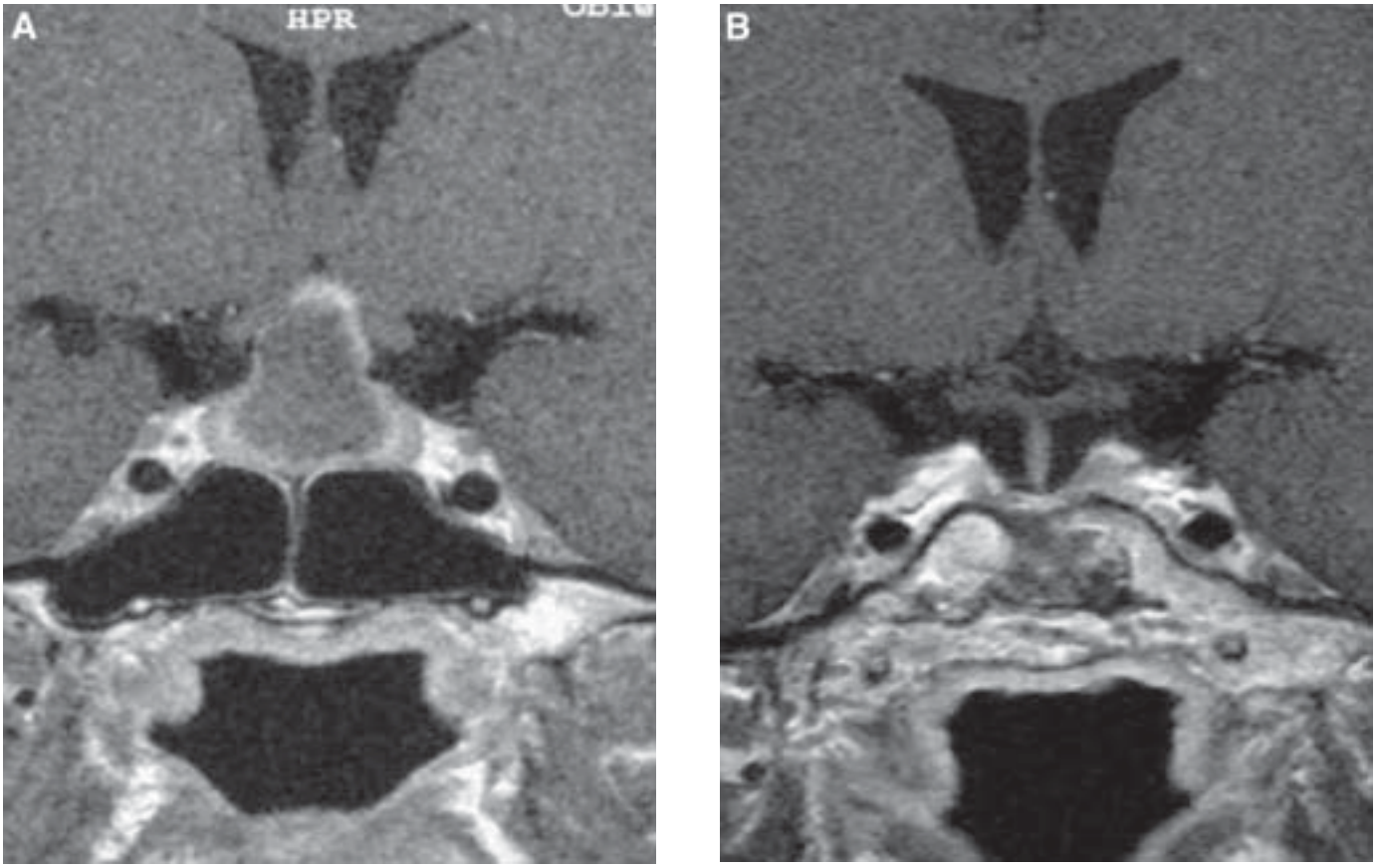

Fig. 2. (**A**) Pre- and delayed postoperative (**B**) coronal T1-weighted MR images of an intra- and suprasellar pituitary adenoma. Note the considerable change of the deformed anterior pituitary's position that is first supported by the tumor and after surgery descends down to the bottom of the sella. The "secondary empty sella" is the ideal postoperative finding after transsphenoidal resection of such a tumor.

orientation, is exposed and opened with forceps and drill. The septations of the sphenoid sinus are resected. Usually at this stage the sellar floor is visualized through the sphenoid sinus (transsphenoidally). Incomplete pneumatization of the sphenoid requires extensive drilling. Once the sellar floor is resected, the basal dura of the pituitary fossa may be incised, thus allowing a soft tumor to protrude through this opening. Variously shaped curettes and microforceps are used to resect the tumor. The deformed nomal pituitary is identified by its yellowish color, firmer consistency, and vascular surface structure and is preserved. The extent and radicality of tumor resection can be estimated by inspection and palpation of the tumor cavity, by visualization of the cavernous sinus bilaterally, and, in larger tumors with suprasellar extension, by the arachnoid that descends into the intrasellar space *(7,14,26)*. The size of the tumor is per se not a critical factor. However, the wider the connection between intra- and extrasellar tumor portions, the easier is the resection of a large adenoma. The delayed postoperative MRI documents the morphological quality of resection of such a tumor (Fig. 2). Even in invasive tumors, extensive and sometimes total resection can be achieved. Invaded mucosa of the sphenoid sinus can be resected, invaded bone of the skull base can be drilled away, and tumor portions with invasion into the cavernous sinus can be traced gently, once the perforation site has been identified. Clearly, if there is tumor in the MRI that extends laterally from the carotid artery, this portion will persist after transsphenoidal surgery (Fig. 3). With focused radiotherapy available, there is no longer justification to attack such residuals aggressively *(34)*.The most perfect overview of an adenoma cavity after selective adenomectomy is usually achieved in moderately sized microadenomas. In small microadenomas which escape radiological detection, the gland must be sectioned multiply in order not to miss the tiny tumor. This is a specific surgical problem encountered in many cases with Cushing's disease. The normal size of the gland, the vascularization of the basal dura, and the proximity of the cavernous sinus and carotid arteries make it a technically demanding enterprise. Even with utmost experience and optimal technical equipment there are still pituitary adenomas that cannot be resected completely. In the past, tumor extension to the planum sphenoidale was considered a contraindication for transsphenoidal surgery. This is no longer the case. With the extended transsphenoidal approach, which implies opening of the tuberculum sellae, even suprasellar meningiomas and pituitary stalk lesions can be treated through the nasal route *(16,26,30)*. The additional use of the endoscope

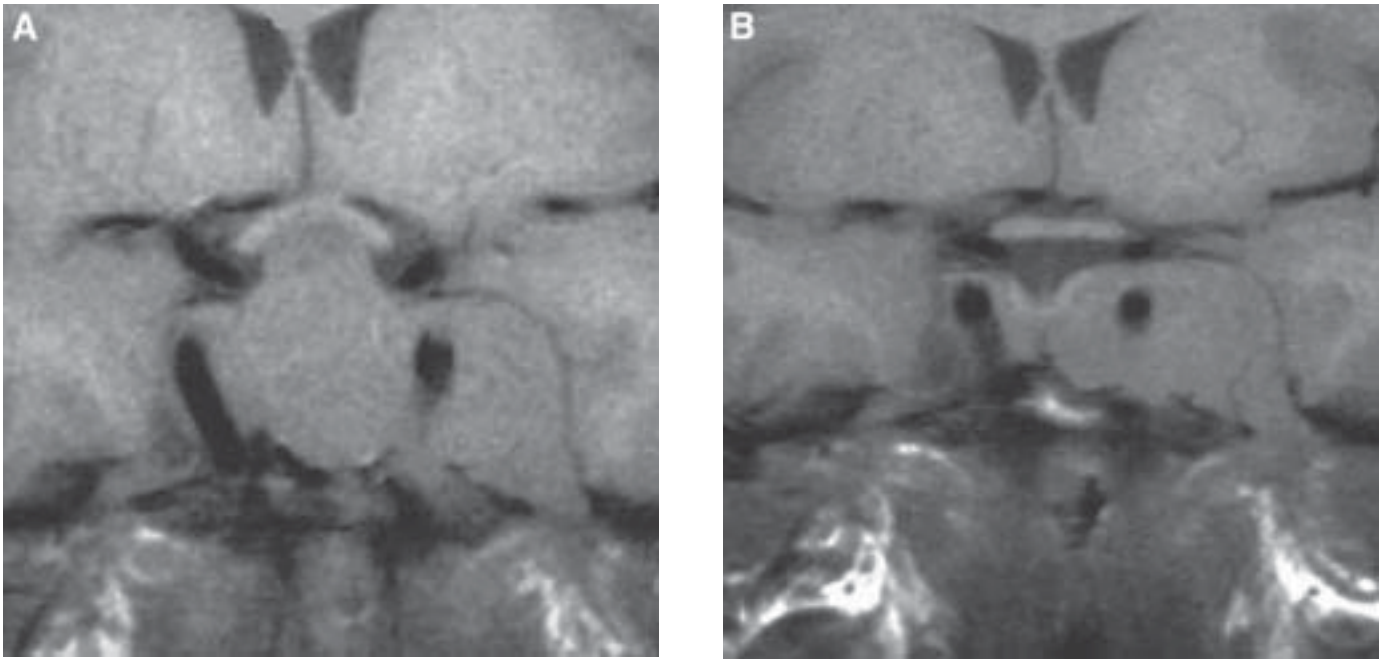

Fig. 3. Once tumor extension to lateral of the carotid artery occurs, such as in this large intra- and parasellar adenoma (**A**), the lesion is generally considered not completely resectable. The invasive tumor portion within the cavernous sinus, encasing the carotid artery, usually persists after transsphenoidal surgery (**B**).

opens new avenues for the visualization of such lesions. Thus, the indication to perform transcanial surgery is handled more and more restrictively. However, to date a suprasellar tumor that has no or very little intrasellar component is still being operated on using transcranial surgery by most of the expert neurosurgeons. Either a pterional or subfrontal approach can be used. The lateral, frontotemporal craniotomies are usually preferred. Essentially, brain protection is achieved by drainage of CSF. Once the brain is slack, self-retaining retractors can be put into place. The visual pathways and the major arteries of the anterior cerebral circulation are dissected and the tumor is then stepwise resected through corridors either medially between the optic nerves or laterally between the optic nerve and the carotid artery *(14)*. Some additional insight can be gained by opening the sphenoid sinus and anterior sellar floor. In tumors extending into the third ventricle, a translamina terminalis approach is advisable. For this variation, a basal bifrontal midline approach, which initially requires dissection of olfactory nerves, offers some advantage, because it allows controlled manipulation under excellent view backwards to the basilar artery bifurcation and, thus, total resection of even large and extensive suprasellar tumors in many cases. The bone flaps are repositioned and secured in place.

Surgical Results

The surgical results may be evaluated in terms of the radicality of tumor resection in the early period after the operation and the avoidance of recurrences during long-term follow-up. Moreover, the success rate should also imply the avoidance of complications. The surgical success rate and prognostic factors can excellently be demonstrated by considering the normalization rates for growth hormone secretion in acromegaly. In the past, surgeons reported their operative results utilizing hormonal criteria that to date cannot be equated with the secretion dynamics of the respective hormones in normal individuals *(41,43)*. It is obvious that the normalization rates claimed by surgeons strongly depend on the criteria of normalization used in an individual series. If one considers the outcome after primary transsphenoidal surgery utilizing the remission criteria established by a consensus conference *(23)*, there is a strong relationship of tumor size and normalization of excessive hormonal secretion. While in microadenomas remission rates between 72% and 87% are reported in recent reports, the normalization rates drop to between 50% and 56% in macroadenomas *(19,31,38)*. For the total series, that may be differently composed, normalization rates between 54% and 70% were reported *(19,31,38,45)*. The enclosed or invasive character of an adenoma is another crucial prognostic parameter. Furthermore, the magnitude of the growth hormone excess plays a significant role. While 89.5% of the patients whose growth hormone levels were less than 10 ng/mL before surgery had a satisfactory surgical outcome, the outcome of patients with serum levels above 200 ng/mL was very poor in a previously reported series *(19)*. Intraoperative measurements of growth hormone have been pro-

posed to monitor the radicality of tumor resection utilizing a biochemical marker *(1)*. If it makes a difference whether the tumors are pretreated by somatostatin analogs or not, has been discussed controversially and as yet has not been finally clarified *(4,13,32)*. Certainly, the outcome after reoperations is much less favorable than that of primary procedures. However, although several authors report on success rates around 20% *(19,35)*, Kurosaki et al. *(33)* achieved recognizable 67% following redo procedures. Real recurrences are relatively rare, once remission has been achieved. However, even if the stringent criteria are used, the reported recurrence rate ranges from 0% to 8.4% during follow-up periods ranging from 0.5 to 30 yr in the individual patients *(3,17)*. Prognostic factors that suggest a long-term recurrence and account for recurrent acromegaly are very low basal as well as glucose-suppressed post-operative growth hormone levels *(22,40)* and lacking or only minor increase after TRH or other stimulating agents *(5)*. Another factor that determines surgical success is independent from the characteristics of the tumor—it is the surgeon's experience. In this respect we can all learn from our British colleagues who convincingly showed that with gaining experience in an individual center over time the surgical success rate increases and the failure rate decreases *(2)*. If in a department the number of surgeons who operate on patients with pituitary tumors is reduced, more individual experience can be gained and the surgical success rate is dramatically increased *(12)*. Similar observations are made in patients suffering from Cushing's disease. Because almost half of these tumors escape radiological detection in the MRI, there is a tendency to submit the resective patients to specialized centers. A wide range of remission rates has been reported by expert neurosurgeons. The outcome seems to be more favorable if a circumscript tumor is detected in preoperative imaging. A remission rate of 74% at 5 yr seems to be a reasonable estimate of operative success in the author's opinion *(10)*. In hormonally inactive adenomas we lack the most sensitive parameters that allow us to decide precisely on complete or incomplete excision of the tumor. Here, the delayed postoperative MRI is the most sensitive parameter for the estimation of total tumor resection. However, for various reasons, postoperative images might be difficult to interpret. In the past, one got the impression that following pituitary tumor operations, pituitary function could either be preserved or get worse *(43)*. However, more recent investigations revealed that actually in a considerable number of patients deficient partial functions of the pituitary can recover following successful surgery, particularly when pituitary adenomas are treated *(36,39,42)*. This applies for any one axis of the anterior pituitary and also for combined deficiences. Total hypopituitarism, however, is unlikely to recover. Also, following transcranial surgery more patients aquire additional defects than actually recover. Because pituitary function may be improved with tumor resection using highly selective techniques, deficient function may to date even be considered an indication for surgical treatment *(39)*.

Complications

While Harvey Cushing had abandoned the transnasal approach and even advised others against the use of transsphenoidal in favor of transcranial surgery, for the high complication rate he had experienced, in recent years the low mortality and morbidity are generally considered major assets of this approach. To date, mortality is well below 1% *(11)*. Anterior pituitary insufficiency and diabetes insipidus occur in up to 20% of cases. However, as mentioned above, in a significant number of patients, anterior pituitary function is improved following selective adenomectomy. Serious complications, such as CSF-leaks, putride infection, lesions of major arteries, hypothalamic injury, subarachnoid hemorrhage, and loss of vision do occur, but are relatively rare (<1% to 5%). Thus, transsphenoidal surgery is considered a relatively safe procedure *(7,8,11,26,43)*. Recent estimates of the total complication rate suggested that more extensive previous experience of the surgeon is associated with a lesser likelihood of occurrence of complications, irrespective of whether the surgery is performed in a classical microsurgical fashion *(11)* or endoscopically *(8)*. However, avoidance of nasal septum dissection seems to increase the patient's comfort and to minimize rhinological complications *(45)*.

Still, transcranial surgery necessitates direct dissection of brain, vascular structures and visual pathways and thus bears a considerably higher complication rate. Because the selection of patients suitable for one or the other approach is highly variable, but only a minority undergo a craniotomy, this factor also implies an unfavorable selection bias that should be considered when complication rates of transnasal operations and transcranial approaches are being compared *(14)*.

New Technical Developments

Just like in other surgical specialities, a variety of novel technical developments have been made available also for operations around the pituitary gland. The endoscopic technique was widely used by ENT surgeons and has relatively recently been adopted by pituitary surgeons. The endoscope allows limitations of the classical microsurgical technique to be overcome. In the latter, the straight beam of light is largely restricted within the nasal tunnel kept open by the speculum. Introduction of an endoscope into the sphenoid sinus allows a more panoramic visualization of the anatomy, an excellent orientation, and an additional control of the radicality of tumor resection. The visual field of the surgeon is considerably extended. This technique is referred to as "endoscope-assisted microsurgery" *(21)* and widely adopted (Fig. 4). However, in several centers, endoscopists

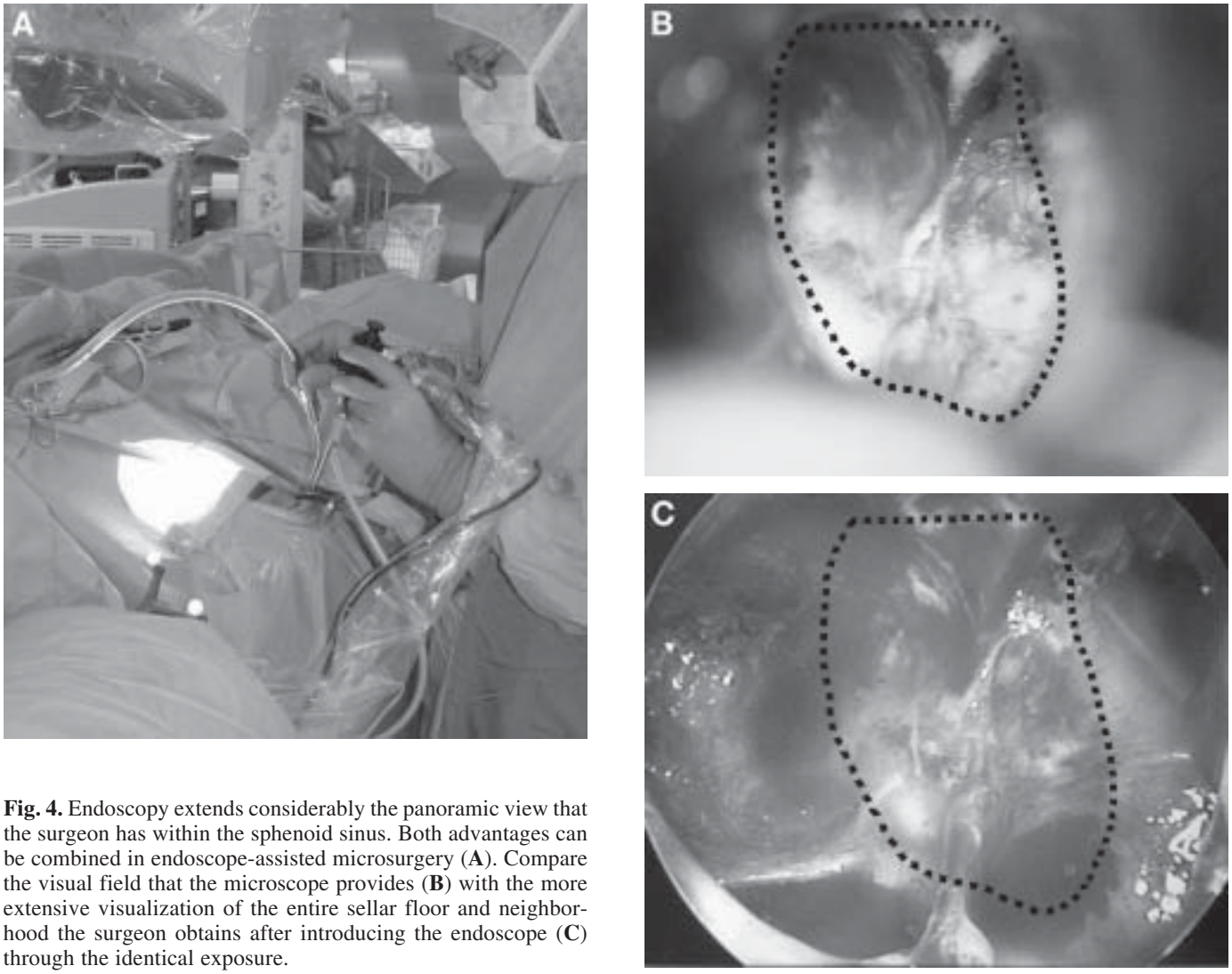

Fig. 4. Endoscopy extends considerably the panoramic view that the surgeon has within the sphenoid sinus. Both advantages can be combined in endoscope-assisted microsurgery (**A**). Compare the visual field that the microscope provides (**B**) with the more extensive visualization of the entire sellar floor and neighborhood the surgeon obtains after introducing the endoscope (**C**) through the identical exposure.

developed fully endoscopic procedures that no longer require septal dissection and the use of a speculum *(9,27)*. A direct perinasal route is chosen and a sphenoidotomy is performed *(24)*. Rather than an operating microscope, a monitor is used. Patients appreciate the comfort, and a shorter hospital stay is advertised. However, to date, comparable remission rates such as with open microsurgical procedures have not been convincingly documented. Disadvantages of the endoscopic technique include a new learning curve with a technically somewhat different procedure during which the surgeon controls his or her instruments from a screen rather than from lenses needs to be established. The operating time is extended. The three-dimensional view, which the operating microscope allows, is lost and the colour information is inferior to that obtained with the microscopic technique *(21)*.

Neuronavigation is widely used in the entire field of microneurosurgery and has also been applied to pituitary operations. The three-dimensional dataset provided by preoperative imaging is related to the patient's surface characteristics. Critical structures such as the tumor shape or the brain supplying major arteries can be segmented and superimposed onto the surgical field utilizing specific operating microscopes *(18,21,28)*. Alternatively, pointers allow the identification of locations found in the operative situs in the respective MR. Thus, additional anatomical orientation is gained. Image guided surgery can be particularly helpful in specific situations such as anatomic variations of the brain supplying major arteries. In the past kinks and coils of the carotid arteries into the sella were considered a major problem. Other potential applications are incomplete or lacking pneumatization of the sphenoid sinus (Fig. 5), reoperations in which anatomical landmarks that could allow precise localization were lost and, of course, teaching and training purposes. Still, however, the majority of pituitary operations are performed under fluoroscopic control.

The microdoppler system, which is widely used in neurovascular microsurgery, can also be considered a useful technical tool for pituitary operations. It allows the carotid arteries to be localized within the cavernous sinus or within

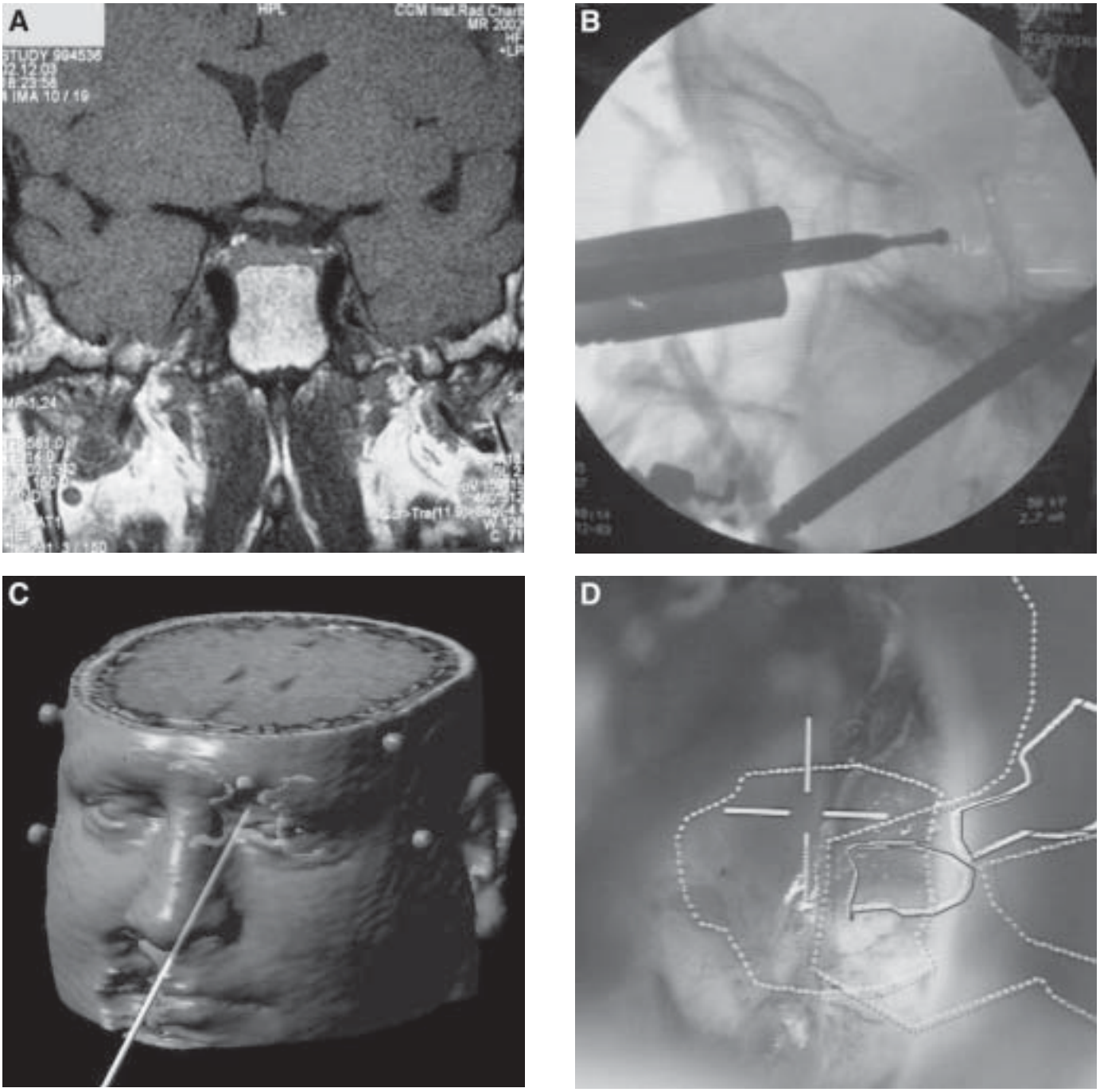

Fig. 5. Neuronavigation is a useful technology, particularly in anatomic variations, such as incomplete pneumatization of the sphenoid sinus (**A**). When the microadenoma is located in the lateral compartment of the sella, extensive drilling is required, which flouroscopy cannot sufficiently guide, because it does not provide information about the coronal plane (**B**). In such cases, segmentation of crucial structures, such as the adenoma and the major arteries allows targeting the lesion (**C**) and superposition of the outlines onto the operative field (**D**).

parasellar tumor. Thus, the likelihood of an arterial lesion is further minimized *(44)*.

Intraoperative imaging is another issue that deserves mention. Dedicated MR scanners have been developed for intraoperative imaging and diagnostic scanner systems have been modified for intraoperative use. Although in an ideal case of an intra- and suprasellar adenoma, the elevated arachnoid descends into the sella in only one smooth arachnoidal plane, many adenomas are not ideal in this sense. In these the arachnoid descends in multiple folds. Even if each of the folds is probed separately, there might be tumor hidden below any one of the arachnoidal pouches. Both low- and high-field MR systems are able to detect such residual tumor intraoperatively and thus allow the radicality of tumor excision to

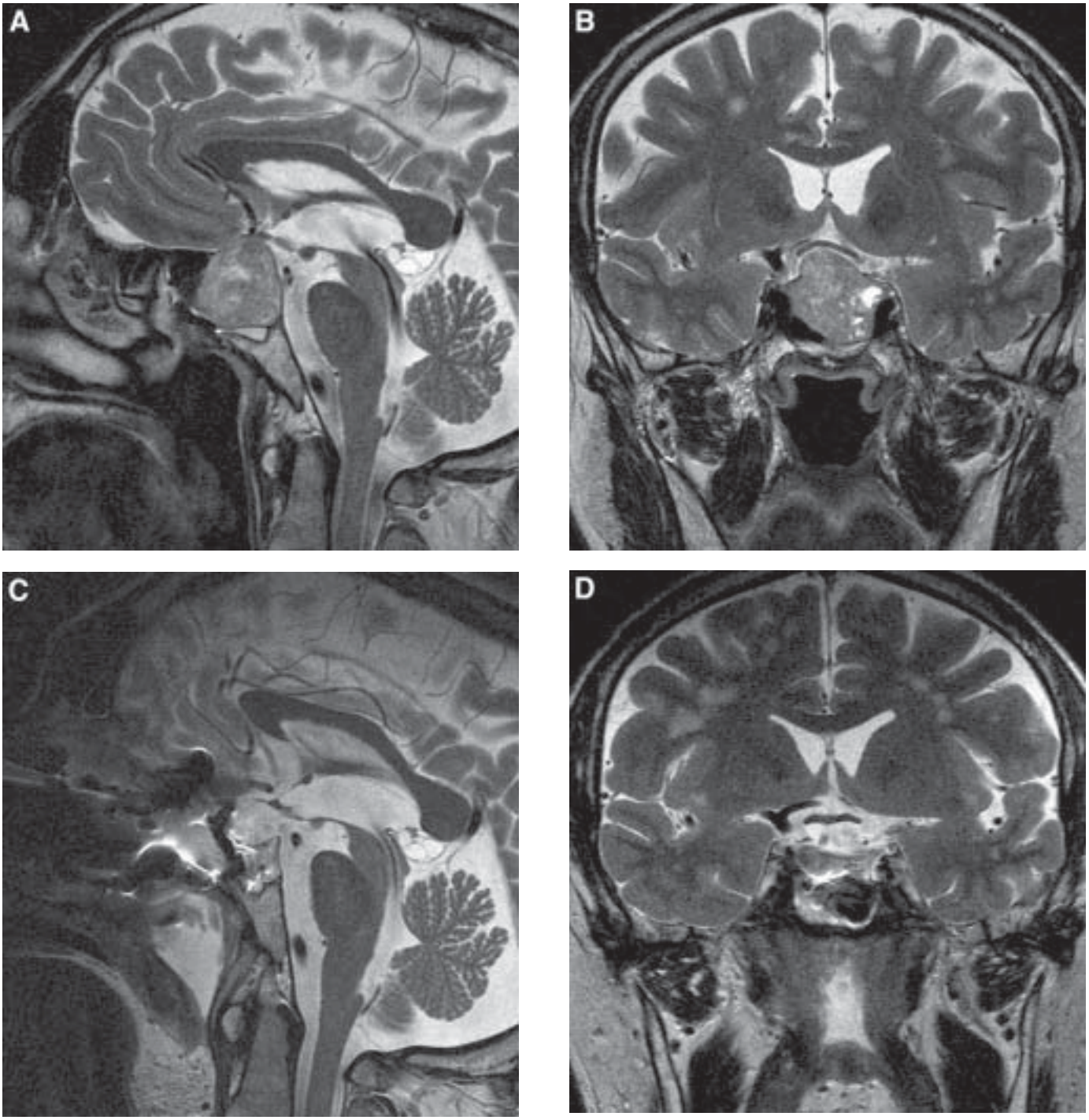

Fig. 6. Intraoperative MR imaging provides information about the extent of tumor resection already at the time of surgery. Particularly, high-field (1.5 T) systems allow intraoperative images to be obtained that are comparable to the delayed postoperative ones, such as in this 58-yr-old patient with an intra- and suprasellar adenoma. Preoperative images depict the lesion in sagittal (**A**) and coronal (**B**) planes. After tumor resection, intraoperative images depict the decompression of optic pathways as well in sagittal (**C**) and coronal (**D**) planes.

be improved, particularly in large tumors *(6,20)*. Furthermore, only high-field systems can also depict the parasellar structures with sufficient image quality and thus allow one to decide upon total removal of intra- and parasellar lesions. In a modern high-field system intraoperative images can be obtained that correspond perfectly to the delayed postoperative scans (Fig. 6), which constitute the standard of postoperative imaging *(37)*. The relatively high costs of the devices and the necessity to, at least partially, rebuild the operating room to make it suitable for the MR are clearly disadvantages of this technology.

In summary, while all these new technical developments increase the comfort of the surgeon and widen the spectrum of surgically accessible lesions in the sellar region, for none

of these novel technologies it has convincingly been shown that the surgical results obtained are improved or the complication rate is decreased. Thus, just as with the classical equipment, the factors defined by the tumor's growth characteristics and location and the individual experience and technical skills of the surgeon are still the main determinants of the surgical outcome for any individual patient.

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