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Clinical Management of Intramedullary Spinal Ependymomas in Adults

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Intramedullary ependymomas are the most common spinal cord tumor in adults, representing one third of all central nervous system (CNS) ependymomas and approximately 60% of all intramedullary tumors [1–10]. They occur throughout life but more frequently in the middle adult years [3,9]. Men and women are equally affected [9,11]. Approximately 65% have associated syringes, particularly when presenting in cervical locations [12]. Although the cervical cord represents only 22.5% of spinal cord tissue, approximately 68% of spinal cord tumors arise from or extend into the cervical cord [3,9,13].

Clinical presentation and diagnosis

Arising from ependymal cells lining the central canal, these well-circumscribed slow-growing tumors are centrally located and cause symmetric expansion of the spinal cord [1]. Patients typically complain of dysesthesia correlating to the level of the tumor for months to years before diagnosis. Other presenting symptoms include paresthesia, radicular pain, bowel and bladder dysfunction, and other sensory disturbances [1–3,5,6,9,11,14–19]. Decline in neurologic symptoms may occur after intratumoral hemorrhage [11]. Motor impairment usually only occurs late in the disease progression as the expanding tumor thins the surrounding spinal cord to a few millimeters [15]. This differs from intramedullary astrocytomas, which tend to present with neuraxis pain and progressive motor dysfunction over a shorter time course [15].

Intramedullary spinal cord tumors are best evaluated with MRI [20,21]. Intramedullary ependymomas are classically centrally located lesions with sharply defined rostral and caudal margins. They are isointense on T1-weighted MRI and slightly hyperintense on T2-weighted MRI [20,21]. Signal heterogeneity can occur with cyst formation, necrosis, or hemorrhage, however [20]. Hypointensity at the tumor margin is often attributable to hemosiderin [1,20]. Almost all intramedullary ependymomas enhance with contrast but to a lesser degree than cerebral ependymomas [21].

Tumor-related cysts are common and are classified into three types: cystic tumors from tumor necrosis and hemorrhage, syrinx formation from disturbances of cerebrospinal fluid (CSF) formation, and rostral and caudal cysts as reactive products of cord tumors [21]. Tumor-associated cysts appear hypointense on T1-weighted MRI and hyperintense on T2-weighted MRI [21]. These cysts are centrally located and cause symmetric expansion of the spinal cord [21]. Tumor-associated syringes share similar MRI characteristics to CSF and are present in more than 50% of

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intramedullary ependymomas [1], which is more common compared with the incidence of syringes associated with intramedullary astrocytomas [1,21]. Most rostral and caudal cysts are also hypointense on T1-weighted MRI and hyperintense on T2-weighted MRI; however, they have a signal intensity slightly different from that of CSF [21].

Although a wide variety of pathologic processes may arise from or secondarily involve the spinal cord as a mass lesion, primary glial tumors account for at least 80% of intramedullary tumors in most published series [5,13,15,22–24]. In addition to ependymomas, these include astrocytomas, gangliogliomas, oligodendrogliomas, and subependymomas.

Approximately 3% of CNS astrocytomas arise within the spinal cord [25]. These tumors occur at any age but seem to be most prevalent in the first three decades of life. Nearly 60% of these tumors occur in the cervical and cervicothoracic region [8], and 20% have associated syringes [12]. Hemangioblastomas account for 3% to 8% of intramedullary neoplasms [26]. These tumors arise at any age but are rare in early childhood. Associated syringes are common [12]. Most are dorsal or dorsolaterally located. Radiographic distinction between intramedullary tumors is often difficult [20,21].

Inclusion tumors and cysts, metastases, nerve sheath tumors, neurocytoma, and melanocytoma account for much of the remainder of intramedullary mass lesions. Metastatic lesions can also be found in an intramedullary location, with the lung and breast being the most common sources.

Approximately 4% of apparent intramedullary spinal cord tumors turn out to be nonneoplastic lesions [27]. An acute or subacute clinical course is characteristic, and evidence of systemic involvement further suggests the diagnosis. Lipomas are the most common dysembryogenic lesion and account for approximately 1% of intramedullary tumors.

Pathologic findings

Intramedullary ependymomas appear as a grossly soft red or grayish-purple somewhat friable mass [9,11,21]. Cystic degeneration and hemorrhage are common in these vascular tumors [21]. Although unencapsulated, these glial-derived tumors are usually well circumscribed and do not infiltrate adjacent spinal cord tissue. Microscopically, tumor cells appear as cuboidal or columnar cells in perivascular pseudorosettes. True rosettes can also be present [9].

A variety of histologic subtypes may be encountered. The cellular ependymoma is the most common, but epithelial, tanycytic (fibrillar), malignant, subependymoma, myxopapillary, or mixed examples may occur. The myxopapillary subtype is almost exclusively observed in the filum terminale or conus and, as such, is classified as an extramedullary tumor [28]. Nearly all are histologically benign [1,3,7,11,15,22,29]. The proliferative activity of intramedullary ependymoma is significantly lower than that of intracranial ependymoma using MIB-1 immunohistochemistry. Proliferative indices greater than 2.0% may be associated with risk of recurrence [30].

Association with neurofibromatosis type 2

Neurofibromatosis (NF) is an autosomal dominant genetic disorder associated with tumors of the CNS [31]. Type 2 NF (NF-2) is rare, occurring in 1 in every 40,000 individuals [32], and is caused by a mutation of a tumor suppressor gene called ''merlin'' or ''schwannomin'' on chromosome 22 [33–35]. Patients with NF-2 have a high incidence of several CNS tumors, including acoustic neuromas and meningiomas [36]. Several authors have also noted an association between NF-2 and intramedullary ependymomas [36–40]. Patients with NF-2 represent approximately 2.5% of patients with intramedullary spinal cord tumors yet only 0.03% of the population [38]. In addition, in one small study, 71% of patients with intramedullary ependymomas and no evidence of NF were shown to possess mutations in the NF-2 gene [41].

Surgical objectives

The goals of surgery for intramedullary ependymoma are gross total resection and preservation of neurologic function [1,11,13,15,16,22,23]. Gross total resection is usually sufficient to achieve long-term tumor control or cure in these low-grade lesions [1,42]. The most important factor in achieving the surgical objective is the plane between the tumor and the spinal cord. This interface can only be accurately assessed through an adequate myelotomy that extends over the entire rostral caudal extent of the tumor (Fig. 1). Although the presence of a syrinx may improve the chances of a gross total resection by facilitating surgical manipulation of the tumor, it cannot be

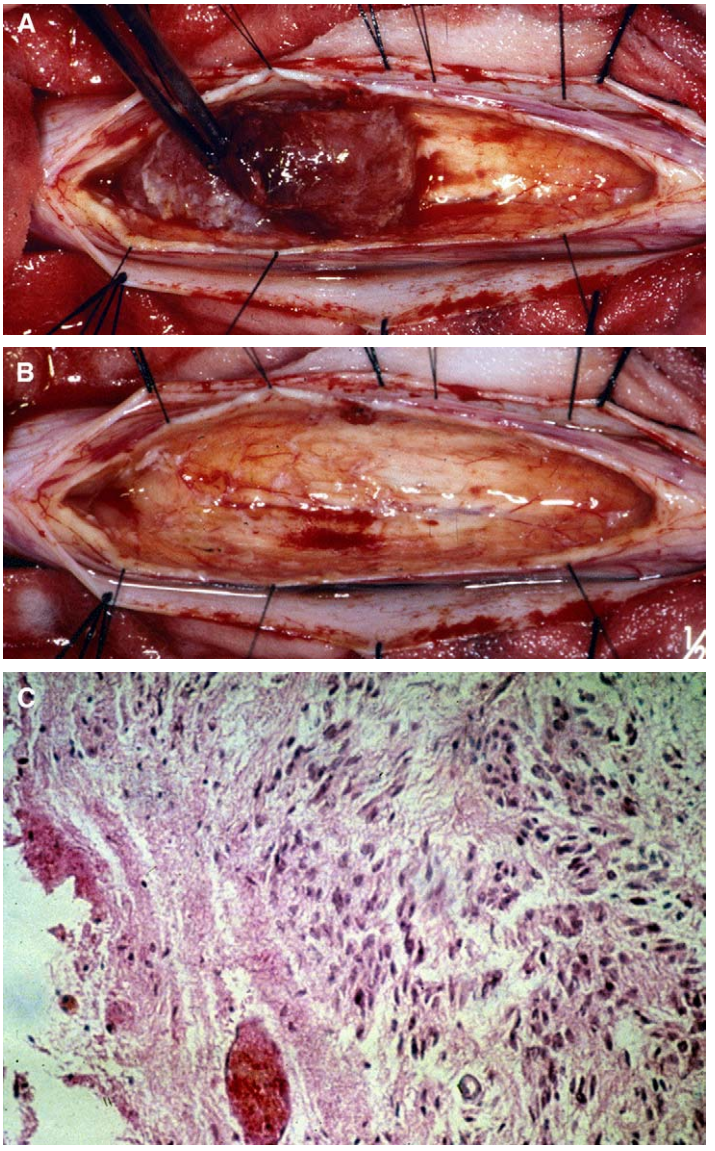

Fig. 1. Intraoperative vies of initial (*A*) and complete (*B*) resection of ependymoma. Microscopic correlate of well defined plane between normal spinal cord and ependymoma is shown in *C*.

used as an independent predictor of outcome [1,12,17].

Ependymomas, although unencapsulated, are noninfiltrative lesions that typically cause compression of the adjacent cord parenchyma and display a distinct plane [42]. Gross total removal is the treatment of choice in these cases for optimum disease control [1,11,13,15,16,22,23]. An intraoperative biopsy can be useful in certain circumstances but should not be used as the sole criterion dictating the surgical objective. First, interpretation of tiny biopsy fragments often is inaccurate or nondiagnostic and may consist of only peritumoral gliosis, which may be erroneously interpreted as an infiltrating astrocytoma [3]. Second, it is difficult if not impossible to assess the nature of the tumor/spinal cord interface accurately through a tiny myelotomy [3]. Biopsy results, however, may be particularly helpful in some circumstances; for example, identification of a histologically malignant tumor independently signals an end to the procedure, because surgery is

of no benefit for malignant intramedullary neoplasms [22,43,44]. In other cases in which the tumor/spinal cord interface may not be apparent, confident histologic identification of an ependymoma reassures the surgeon that a plane must exist and that surgical removal should continue.

Surgical technique

The technique of tumor removal is determined by the surgical objective, tumor size, and gross and histologic characteristics of the tumor. If no plane is apparent between the tumor and surrounding spinal cord, it is likely that an infiltrative tumor is present. A biopsy is obtained to establish a histologic diagnosis. If an infiltrating or malignant astrocytoma is identified and is consistent with the intraoperative findings, further tumor removal is not warranted. In most cases, however, a reasonably well-defined benign glial tumor is identified. Ependymomas appear with a smooth, reddish-gray, glistening tumor surface that is sharply demarcated from the surrounding spinal cord. Large tumors may require internal decompression with an ultrasonic aspirator or laser. Intraoperative ultrasonography may also aid in determining extent of tumor and morphology [3,15].

In contrast to the ependymoma, most benign astrocytomas present with varying degrees of circumscription. Approximately one third of these patients have benign infiltrative tumors without an identifiable tumor mass. A biopsy for diagnosis becomes the only viable surgical objective. Occasionally, an astrocytoma may be so well developed as to mimic an ependymoma. Nevertheless, there is rarely as defined a plane with astrocytomas as is typically seen with ependymomas. The surgeon must rely on his own judgment and experience. Obviously, if gross tumor is easily identified, continued removal is reasonable. Changes in motor sensory evoked potentials [14,45] or uncertainty of spinal cord/tumor interface should signal an end to tumor resection [14].

Postoperative management

Early mobilization is encouraged to prevent complications of recumbency, such as deep venous thrombosis and pneumonia [46]. Paretic patients are particularly vulnerable to thromboembolic complications. Compression stockings are routinely used, and subcutaneous heparin is begun on the second postoperative day in these patients at a dose of 5000 U every 12 hours [47]. Orthostatic hypotension may occasionally occur after removal of upper thoracic and cervical intramedullary neoplasms. This is usually a self-limiting problem that can be managed with liberalization of fluids and more gradual mobilization. A posterior fossa syndrome occasionally occurs after removal of a high cervical intramedullary neoplasm. This is effectively managed with steroids, although a lumbar puncture may be required to rule out meningitis. Complications related to wound dehiscence, infection, and CSF leak are much more common in patients who have undergone prior surgery or radiation therapy [16,48]. These complications rarely resolve with conservative therapy, and early return to the operating room is imperative to avoid exacerbation [16].

Early and aggressive use of physical and occupational therapy can optimize functional recovery. Despite confident gross total resection, benign intramedullary tumors present a continued risk of recurrence [1,10]. Long-term clinical and radiographic follow-up is warranted in these patients [42]. Early postoperative MRI 6 to 8 weeks after surgery establishes the completeness of resection and serves as a baseline against which further studies can be compared. Serial gadolinium-enhanced MRI scans are obtained yearly, because radiographic tumor recurrence usually precedes clinical symptoms [1,3].

Functional outcome

Most surgical series indicate that the strongest predictor of postoperative functional outcome is preoperative functional ability [1,5,11,15,16,22,23,42]. Significant improvement of a severe or long-standing preoperative neurologic deficit rarely occurs, even after technically successful surgical excision [1]. Surgical morbidity is also greater in patients with more significant preoperative deficits. Pre- and postoperative functional or neurologic status is typically evaluated by use of a grading scale, such as the McCormick, Neurick, or Frankel scales [1,3,5,17]. The ratio of the tumor width to the largest cord width at the tumor site is also associated with pre- and postoperative neurologic grade [17].

In general, most patients note sensory loss in the early postoperative period, most likely as a result of the midline myelotomy, transient edema, or vascular compromise [15,16]. These complaints are more subjective than objective in nature and can be significant even with little or

no objective deficit. These deficits usually resolve within 3 months [5,17], although they may not return to their preoperative baseline [16].

Additional surgical morbidity is directly related to the patient's preoperative status, the location of the tumor, and the presence of spinal cord atrophy and arachnoid scarring [5,12,16,22,23]. Patients with significant or long-standing deficit rarely demonstrate any significant recovery and are more likely to worsen after surgery. A shorter duration of preoperative symptoms, however, may favor improvement even in patients with a significant preoperative deficit [5]. Thoracic location has also been correlated with a decline in postoperative function [3,5,23,42], perhaps because of a more tenuous blood supply in this region. Appreciation of spinal cord atrophy and arachnoid scarring may indicate chronic spinal cord compression and predict poor functional outcome [5,12]. Preservation rather than restoration of neurologic function is the reasonable expectation for intramedullary tumor surgery. The greatest benefit and most minimal risk of surgery for intramedullary tumors are therefore derived in those patients who are only minimally symptomatic [3,11,15,16,22,42].

Adjuvant therapy

For intramedullary ependymomas, long-term outcome and risk of recurrence are dependent primarily on the extent of initial tumor resection. Gross total resection of benign intramedullary ependymomas provides better long-term tumor control or cure compared with subtotal resection and radiation therapy [5,6,11,15,23]. Most authors agree that radiation therapy is unnecessary after gross total resection [6,11,12,15,22,48].

Although many authors report a 100% recurrence-free survival after gross total resection [11,49], other authors report a 5% to 10% recurrence rate [1,6,22,49]. Ependymomas are slow-growing tumors, and late recurrence can occur, even up to 12 years after surgery [50]. Subtotal resection, conversely, has a high recurrence rate [1]. Even 99% removal can lead to tumor recurrence in up to 30% of patients in spite of postoperative radiation therapy, whereas subtotal resection can lead to significant recurrence in up to 50% to 70% of patients [22,50]. In the event of tumor recurrence, reoperation and another attempt at gross total resection should be considered [3,22,51].

The evidence to support postoperative radiation after subtotal resection is largely based on studies with small patient populations, limited follow-up, and inadequate or no matched controls treated without radiation therapy. Despite these limitations, the accumulated data in these series suggest that radiation may be beneficial [22,44,50,52,53]. Reports of 5- and 10-year recurrence-free survival, however, vary widely from 60% to 100% with fractionated external beam doses of greater than 40 Gy [50,52]. At doses less than 40 Gy or at 15 years, recurrence rates approach 70% to 90% [50,52]. The presence of a dose-response curve is controversial. Doses less than 40 Gy are clearly too low [52,54], but local failures have been reported with doses up to 55 Gy when the risk of myelopathy becomes significant with conventional fractionation [50,53]. Craniospinal radiation is only indicated for the rare patient who presents with multifocal disease [6,50,54]. Although the outcome is worse for this subgroup, good control rates have been reported [50,52]. Patients who present with focal disease usually have local recurrence and do not manifest late dissemination [51,55]. We recommend adjuvant radiation for malignant ependymomas and the rare benign lesion that cannot be totally resected.

Salvage chemotherapy in patients who fail surgery and radiotherapy is largely unexplored. A pilot study using etoposide, a topoisomerase II inhibitor, to treat recurrent intramedullary ependymomas resulted in 3 patients with progressive disease, 2 patients with a partial response, and 5 patients with stable disease. Overall, the median disease-free progression was 15 months and the overall median survival was 17.5 months. This drug seemed to be well tolerated, with modest toxicity [51,55]. Further trials are needed to determine the efficacy of this potential therapy for recurrent and refractory intramedullary ependymomas.

Summary

Intramedullary ependymomas are rare tumors but comprise most intramedullary glial neoplasms in the adult. These tumors are benign slow-growing lesions, and gross total surgical resection can be safely achieved in most patients, providing long-term cure. The extent of surgical resection is the strongest predictor of long-term survival. Adjuvant therapy is indicated for the rare malignant or disseminated tumor or after subtotal resection. Preoperative functional status is a strong predictor in postoperative functional outcome. Therefore, early diagnosis and surgical intervention before

symptomatic progression are critical to the successful treatment of these tumors.

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