4

Primary Spinal Cord Tumors

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The first successful resection of a spinal cord tumor was performed by Victor Horsley in 1887 (Stein and McCormick, 1996). The diagnosis and treatment of intramedullary spinal cord tumors was first described in detail by Elsberg in 1925 (Stein and McCormick, 1996), and Greenwood reported the first large modern series in 1967. Since then, numerous radiographic, microsurgical, and electrophysiologic advances have enabled the clinician to better manage patients with these challenging tumors. Today a skilled and knowledgeable surgeon is able to cure many patients harboring such tumors. Despite these improvements, much remains to be learned about the optimal management of patients with spinal cord tumors.

EPIDEMIOLOGY

Very few reliable epidemiologic data on primary intraspinal tumors are found in the literature, with most series consisting of authors' personal experiences, which are often biased by referral patterns. The few existing population-based studies indicate that the annual incidence of these tumors ranges from 0.5 to 1.4 per 100,000 (Helseth and Mork, 1989; Sasanelli et al., 1983). The majority of the tumors included in these series consist of meningiomas and schwannomas, which are not discussed in this chapter. Classifications of spinal tumors are frequently made on the basis of their anatomic location, as depicted in Table 4–1. Approximately 25% of intraspinal tumors in adults and the majority of these tumors in children are intramedullary. Of the true intramedullary spinal cord tumors, the vast majority are gliomas, with ependymomas occurring most frequently in the adult population and astrocytomas accounting for about 60% of pediatric intramedullary tumors (Nadkarni and Rekate, 1999; Cristante and Herrmann, 1994; O'Sullivan et al., 1994; Epstein et al., 1992; Cooper, 1989). Most spinal gliomas are low grade, with glioblastomas representing only 7.5% of all intramedullary gliomas (Ciappetta et al., 1991; Cohen et al., 1989; Helseth and Mork, 1989).

Hemangioblastomas, which occur sporadically or are associated with von Hippel-Lindau syndrome, are the third most common intramedullary tumor type to occur in adults and represent only approximately 4% of intramedullary tumors (Hoff et al., 1993; Trost et al., 1993; Solomon and Stein, 1988). In contrast to the gliomas, which occur with approximately equal incidence in both sexes, hemangioblastomas occur more frequently in males (Cristante and Herrmann, 1999; Cooper, 1996; Murota and Symon, 1989). Even less frequently encountered tumors in this location include gangliogliomas, primitive neuroectodermal tumors, lipomas (usually associated with congenital defects), ganglioneurocytomas, and neurocytomas (Constantini and Epstein, 1996; Tatter et al., 1994). Myxopapillary ependymomas, histologic variants of ependymomas, are most commonly found in the filum terminale. These tumors infrequently invade the thecal sac, are usually well circumscribed, and are often completely resectable. All of these factors account

Table 4–1 Classification of Spinal Tumors by Location

Location	Tumor
EXTRADURAL	Metastatic (carcinoma, lymphoma, melanoma, sarcoma), chordoma, epidermoid, teratoma, dermoid, lipoma
INTRADURAL	
Extramedullary	Nerve sheath tumors (schwannoma), epidermoid, teratoma, dermoid, lipoma, neurenteric cyst
Intramedullary	Astrocytoma, ependymoma, hemangioblastoma

for the generally favorable outcome that patients harboring these rare tumors can expect (Freeman and Cahill, 1996).

RADIOLOGY

Magnetic resonance imaging (MRI) is the radiographic method of choice in the diagnosis of primary spinal cord tumors. All MRI studies done on suspected intramedullary tumors should include T_1- and T_2-weighted images as well as images taken after the administration of a contrast agent. Computed tomography (CT) with myelography, which was the diagnostic tool of choice for intramedullary tumors in the 1970s and 1980s, continues to be used when MRI is not available. Although CT with myelography can reliably identify the presence of spinal cord pathology, it is an invasive test and does not define the spinal cord anatomy as well as MRI. In addition, in the presence of a complete spinal block, it may be necessary to perform a C1–C2 puncture to define the rostral extent of the tumor.

More recently, emphasis has been placed on making a pathologic diagnosis from MRI characteristics, with particular attention paid toward differentiating astrocytomas from ependymomas. Despite the improving quality of MRI and our increasing experience with this diagnostic modality, the only way to ascertain a definitive diagnosis is by obtaining a surgical specimen of the tumor. Furthermore, the surgical resectability of these tumors is not reliably predicted by their MRI characteristics.

In general, intramedullary ependymomas appear isointense on T_1-weighted images. All have a hyperintense signal on T_2-weighted images and are enhanced after administration of a contrast agent (Fine et al., 1995). The enhancement borders are sharply defined, and the tumor is characteristically found to

be centrally located in an expanded spinal cord (Epstein et al., 1993) (Fig. 4–1). Hemosiderin is often found at the periphery of cervical ependymomas (Fine et al., 1995).

Astrocytomas similarly show diffuse cord enlargement on T_1-weighted images, with increased signal on T_2-weighted images (Epstein et al., 1993); however, contrast enhancement in astrocytomas is often heterogeneous and the borders are often irregular (Epstein et al., 1993; Dillon et al., 1989). Furthermore, astrocytomas are less frequently associated with a syrinx than are ependymomas or hemangioblastomas (Samii and Klekamp, 1994). Regardless of the pathology, the more rostral the tumor, the more likely it is to be associated with a syrinx (Samii and Klekamp, 1994).

Hemangioblastomas are isointense or slightly hyperintense on T_1-weighted images. Classically, they are known to contain an intensely enhancing tumor nodule surrounded by edema and are associated with a cyst or a syrinx (Xu et al., 1994; Hoff et al., 1993). Spinal angiography in hemangioblastomas will often demonstrate the compact tumor nodule, feeding arteries, and main draining vein and is useful for diagnosing these tumors as it most clearly defines the regional vascular anatomy (Spetzger et al., 1996). Spinal angiography can also be used therapeutically for preoperative embolization (Tampieri et al., 1993), but is not indicated if MRI characteristics are suggestive of an astrocytoma or ependymoma.

CLINICAL PRESENTATION

The clinical presentation for primary spinal cord tumors usually involves an indolent course. The most common presenting symptoms include pain along the spinal axis, sensory disturbances, motor weakness, and gait disturbance. Bowel and bladder as well as

Figure 4–1. Pre- and postoperative T_1-weighted images of a patient with cervicothoracic region ependymoma, after contrast injection. Preoperative study (left) demonstrates a relatively well-circumscribed enhancing intramedullary lesion associated with syrinx and spinal cord enlargement. Postoperative MRI (right) shows complete excision of intramedullary tumor and almost complete resolution of syrinx.

sexual dysfunction are considerably less frequent but well-described symptoms found on presentation (Lee et al., 1998). Radicular pain occurs in approximately 10% of patients and is usually limited to one or two cervical, thoracic, or lumbar dermatomes (Constantini and Epstein, 1996).

On examination, variable motor deficits, sensory disturbances, reflex changes, and long tract findings may be detected (Lee et al., 1998). In the pediatric population, these tumors may additionally present with torticollis and progressive kyphoscoliosis (Constantini et al., 1996; Rossitch et al., 1990).

The duration of symptoms before presentation for astrocytomas and ependymomas varies depending on the series. Cooper (1989), in a review of 51 patients, reported means of 7.7 and 6.4 years of symptoms before surgery for astrocytomas and ependymomas, respectively. Others report a shorter range of several months to several years for both of these tumor types (Jyothirmayi et al., 1997; Minehan et al., 1995; Waldron et al., 1993). In contrast, malignant gliomas

have a much shorter prodrome of only several weeks to several months before presentation (Cristante and Herrmann, 1994). In addition, patients with these malignant tumors may present with headaches, and of these patients ultimately 50% to 60% will develop concurrent hydrocephalus (Ciappetta et al., 1991; Cohen et al., 1989). Even patients with a more benign pathology can develop hydrocephalus, albeit at a significantly lower frequency. The pathophysiology of the development of hydrocephalus in these patients is thought to be related either to markedly increased protein concentration in the cerebrospinal fluid or to dissemination of tumor in the subarachnoid space, as seen with malignant gliomas (Rifkinson-Mann et al., 1990).

As stated previously, the only definitive way to make a pathologic diagnosis is to evaluate tissue from the tumor. However, by combining the patient's clinical presentation with imaging information, it is frequently possible to predict whether a particular intramedullary tumor is benign. In general, when a pa-

tient presents with a mild neurologic deficit and significant cord enlargement is seen on MRI, the tumor's histology will be benign. If, however, the patient presents with a severe neurologic deficit with only modest cord enlargement, then the tumor is likely to be malignant.

Hemangioblastomas have presenting features similar to other intramedullary tumors and are symptomatic for a mean of approximately 2 years before presentation (Cristante and Herrmann, 1999). In addition, these tumors have been reported to present acutely, mimicking a typical intracranial subarachnoid hemorrhage, or with acute onset of paraplegia secondary to hemorrhage into the tumor (Yu et al., 1994; Cerejo et al., 1990).

SURGERY

General Considerations

Surgery for primary spinal cord tumors is one of the most technically challenging procedures performed by neurosurgeons. These tumors are rare, and, as a result, no practice guidelines have been established for their optimal treatment. It is the authors' opinion, however, that surgery is indicated for virtually all patients who are found to have radiographic evidence of an intramedullary tumor, with the exception of the rare patient who is medically unable to tolerate an operation. Patients who do not have neurologic deficit may be followed very closely but should undergo surgery at the earliest hint of neurologic dysfunction or of radiographic evidence of tumor enlargement. Even patients who have a complete neurologic deficit below the spinal level of the tumor should undergo surgery to establish a diagnosis and prevent the onset of neurologic deficits at a higher spinal level, particularly if the tumor extends above T4.

The goals of surgery are to establish a diagnosis and to resect the maximal amount of tumor possible without causing any deterioration in the patient's neurologic condition. These goals can be attained by always establishing adequate exposure and meticulously minimizing manipulation of the spinal cord. Intraoperative ultrasonography should be used before the dura is opened to ensure that sufficient bone has been removed to permit safe resection of the tumor. Ultrasonography is also useful in planning the place-

ment of the myelotomy and confirming that there is no residual tumor once the resection has been completed (Epstein et al., 1991). Available instruments that facilitate the resection of these tumors include the Cavitron ultrasonic aspirator (CUSA) and the laser.

Ependymomas have a distinct surgical plane between the tumor and the spinal cord, and thus a total resection is often feasible, although internal debulking is frequently required to prevent excessive retraction of the spinal cord (Hoshimaru et al., 1999; Epstein et al., 1993) (Fig. 4–2). Hemangioblastomas also display a clear interface between the tumor and normal tissue; however, the surgeon is advised to refrain from internally debulking these vascular tumors (Cristante and Herrmann, 1999; Murota and Symon, 1989).

Conversely, astrocytomas normally do not have a distinct plane of demarcation between the tumor and spinal cord and must be debulked internally, with the surgeon using his or her discretion as to when to stop the resection (Fig. 4–3). If a frozen section is sent for diagnosis intraoperatively, particular care must be used, as tanycytic ependymomas can easily be mistaken for astrocytomas. Detailed descriptions of the resection of these tumors are beyond the scope of this chapter and are well described elsewhere (Cooper, 1996; Stein and McCormick, 1996).

The role of intraoperative somatosensory evoked potential (SSEP) monitoring during resection of intramedullary tumors is unclear, and no statistically valid evidence exists to support use of this technique (Cooper, 1996). Nevertheless, most surgeons performing this operation use SSEP monitoring. Problems with SSEP monitoring for intramedullary tumors include the frequently abnormal responses seen before the resection is started. In addition, the delay inherent in this monitoring system will often indicate that injury has occurred only after it has become irreversible. Furthermore the system monitors sensory pathways and does not reflect the integrity of the motor pathways.

Motor evoked potential (MEP) monitoring is a newer technique that directly measures the integrity of motor pathways and is being used at an increasing number of medical centers. Preliminary studies indicate that this technique provides good functional outcome prognosis in adults, but it has not yet been determined whether it improves surgical outcome
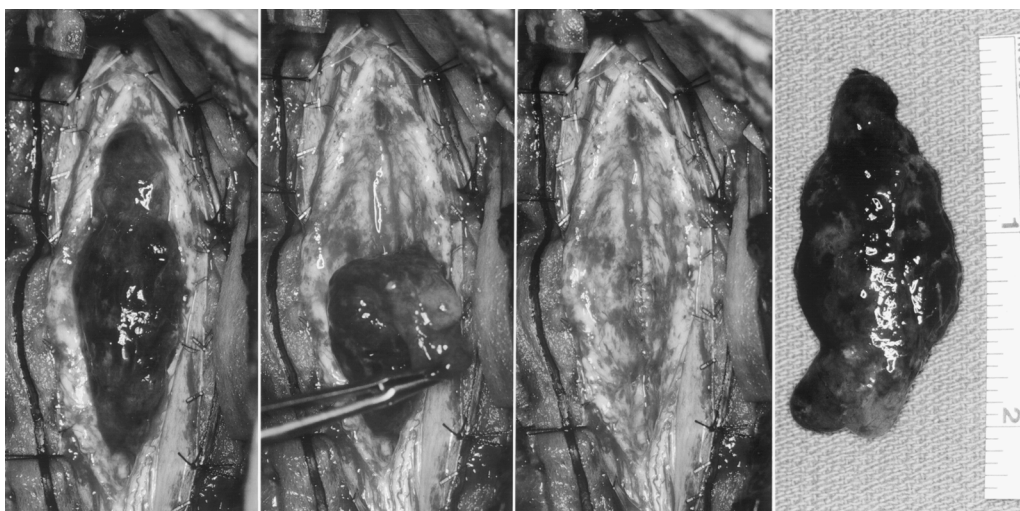
Figure 4–2. Serial intraoperative photographs (from left to right) of the patient in Figure 4–1 show the characteristic features of an ependymoma. After a dorsal midline myelotomy, a typical well-circumscribed, beefy-red-appearing mass is observed. After tedious dissection using the operating microscope, the tumor is gradually being lifted off the normal spinal cord. The tumor specimen, which has been removed in toto, measures almost 2 inches in length.

Figure 4–3. Pre- and postoperative MR images (after gadolinium injection) of a patient with anaplastic astrocytoma of the conus region. Despite the relatively well-circumscribed radiographic appearance of the tumor on preoperative MR images (left), intraoperative explorations revealed infiltration of the conus with no distinct surgical plane. Thus, as seen on the postoperative MR image (right), residual tumor infiltrating the spinal cord was not removed to avoid causing any neurologic deficit.

(Morota et al., 1997). This monitoring technique is less useful in pediatric patients because of the nature of their immature nervous systems (Morota et al., 1997).

Surgical Complications

The postoperative course of patients with intramedullary tumors is frequently characterized by a transient deterioration in neurologic condition, lasting from a few days to months before recovery occurs (Samii and Klekamp, 1994). Some investigators do not report any motor deterioration in the immediate postoperative period in patients with benign gliomas, even after aggressive resection (Epstein et al., 1992). Patients with severe preoperative disability are more likely to deteriorate as a result of surgery (Constantini and Epstein, 1996). Patients who have a syrinx associated with their tumor tend to recover more rapidly (Samii and Klekamp, 1994).

Loss of proprioception is a common complication that can be very debilitating, even in the presence of preserved motor function. The development or progression of kyphoscoliosis can occur postoperatively, especially in the pediatric population, and may necessitate a second operation for fusion and instrumentation. Cerebrospinal fluid leaks and concomitant meningitis may also occur despite meticulous surgical technique, particularly if the region has been irradiated previously.

RADIATION THERAPY

In general, when radiotherapy is employed, approximately 50 Gy are administered to the involved site (with rostral/caudal margins of at least 3 cm) in 16 to 20 fractions over a 4 to 5 week period (Shirato et al., 1995). There has not yet been any prospective, randomized study demonstrating the efficacy of radiation therapy in treating primary spinal cord tumors. However, until a more definitive study is done, generalizations can be drawn from the many retrospective series that exist.

In the treatment of benign ependymomas, prior studies show that postoperative radiotherapy is not indicated if a gross total resection of the tumor has been achieved (Ohata et al., 1999; Lee et al., 1998; McLaughlin et al., 1998; Shirato et al., 1995; Clover

et al., 1993; Epstein et al., 1993; Waldron et al., 1993; Wen et al., 1991; Whitaker et al., 1991; McCormick et al., 1990). The same studies recommend radiotherapy when there is residual tumor. Some also recommend postoperative radiotherapy if the tumor has been removed in a piecemeal fashion (McLaughlin et al., 1998; Wen et al., 1991), whereas others vehemently disagree (Epstein et al., 1993). Despite the recommendations above, it must be emphasized that no definitive study has demonstrated a benefit of radiation exceeding that of clinical follow-up and reoperation for residual tumor (Lee et al., 1998).

Most reported series recommend postoperative radiotherapy in the treatment of low-grade astrocytomas, regardless of the degree of surgical resection (McLaughlin et al., 1998; Jyothirmayi et al., 1997; Minehan et al., 1995; Shirato et al., 1995; Huddart et al., 1993; Cooper, 1989). Others suggest that close observation without radiotherapy is a better alternative, with either reoperation or radiotherapy should the tumor recur (Innocenzi et al., 1997; Brotchi et al., 1992; Epstein et al., 1992). All malignant gliomas of the spinal cord are treated with postoperative radiotherapy, although there is no clinical evidence for the efficacy of this treatment.

There is no evidence to support the use of either pre- or postoperative radiotherapy in the treatment of hemangioblastomas (Murota and Symon, 1989). The hazards of administrating radiotherapy in the pediatric population have been well described (Duffner et al., 1993). As a result, postoperative radiation treatment should not routinely be used in this cohort of patients with primary spinal cord tumors except for the treatment of malignant tumors or in the setting of recurrence (Goh et al., 1997; Przybylski et al., 1997; Constantini et al., 1996).

CHEMOTHERAPY

The adjuvant role of chemotherapy in the treatment of malignant primary spinal cord tumors is even less well defined than that of radiation therapy. Several small retrospective series that have examined the optimal management of these lesions recommend chemotherapy, although it is unclear whether this therapeutic modality changes the uniformly poor outcome associated with these tumors (Ciappetta et al., 1991; Cohen et al., 1989). More recently, limited trials using experimental chemotherapeutic regimens in pe-

diatric populations have shown some limited success (Allen et al., 1998; Lowis et al., 1998; Doireau et al., 1999). The exact role that chemotherapy has in the treatment of intramedullary tumors thus remains uncertain, and no clear guidelines for its use can be established at the present time.

OUTCOME

Of patients with astrocytomas of the spinal cord, 50% to 73% survive 5 years and 23% to 54% survive for 10 years (reviewed by Abdel-Wahab et al., 1999). The histologic type and grade of the tumor are the most important features in predicting prognosis (Abdel-Wahab et al., 1999; McLaughlin et al., 1998; Innocenzi et al., 1997; Jyothirmayi et al., 1997; Huddart et al., 1993). Among the low-grade astrocytomas, patients with pilocytic tumors had significantly improved survival rates (81% at 5 years) compared with those with fibrillary tumors (15% at 5 years) (Minehan et al., 1995). Prognostically significant clinical features were the length of history of the disease and the patient's pre- and postoperative neurologic status, with both a longer disease history and good neurologic status predicting a favorable outcome (Innocenzi et al., 1997; Cristante and Herrmann, 1994; Samii and Klekamp, 1994). Some series report an association between female gender and a favorable prognosis (Abdel-Wahab et al., 1999; Huddart et al., 1993). The extent of surgical resection in patients with low-grade astrocytomas was found by most to not have a significant impact on survival (Abdel-Wahab et al., 1999; Jyothirmayi et al., 1997; Minehan et al., 1995; Huddart et al., 1993; Sandler et al., 1992; Cooper, 1989). However, in a retrospective review of intramedullary astrocytomas, Epstein et al. (1992) suggest that radical resection of these tumors does improve patient outcome, although no control group was provided. Biopsy of these lesions carries the same risk as more aggressive resection. Furthermore, there is no correlation between increased postoperative radiation doses and improved survival (Jyothirmayi et al., 1997; Minehan et al., 1995; Wen et al., 1991).

All patients with malignant astrocytomas have a very poor prognosis, with overall median postoperative survival times in the range of 6 months to 1 year (Innocenzi et al., 1997; Cohen et al., 1989). Furthermore, surgery on these patients does not halt the decline in their neurologic function (Epstein et al.,

1992). Neither a greater extent of surgical resection nor the administration of radiotherapy or chemotherapy have been shown to improve outcome (Epstein et al., 1992; Ciappetta et al., 1991; Cohen et al., 1989).

The overall 10 year survival for patients with intramedullary ependymomas ranges from about 50% to 95% and is better than that observed for astrocytomas (Abdel-Wahab et al., 1999; Waldron et al., 1993). The most important factors in determining long-term outcome for patients with ependymomas include whether total surgical resection is attained, the preoperative neurologic status of the patient, and the histologic grade of the tumor (Hoshimaru et al., 1999; Whitaker et al., 1991; Cooper, 1989). Several groups report 100% long-term survival in patients undergoing radical resection of ependymomas without postoperative radiotherapy (Epstein et al., 1993; McCormick et al., 1990). Patients with incomplete resection of primary spinal ependymomas have an approximately 62% 10 year survival rate when treated with postoperative radiation (Whitaker et al., 1991). The survival rates of ependymoma patients who undergo subtotal resection or biopsy and do not receive radiotherapy are not known.

The incidence of intramedullary hemangioblastomas is very low, and as a result outcome analysis for these tumors is lacking. One study examining recurrence rates of hemangioblastomas that had been surgically treated found that recurrence was correlated with younger age, association with von Hippel-Lindau syndrome, and the presence of multicentric tumors of the nervous system at the time of presentation (de la Monte and Horowitz, 1989). Investigations of neurologic outcome after surgical resection of these tumors report long-term clinical improvement in 40% to 72% of patients (Cristante and Herrmann, 1999; Murota and Symon, 1989).

Outcome in the pediatric population appears to be similar to that in adults, and patients with ependymomas have the longest recurrence-free survival (Goh et al., 1997; Przybylski et al., 1997). As in adults, the histologic grade of the tumor and the patient's preoperative neurologic condition are the most frequently identified prognostic indicators (Nadkarni and Rekate, 1999; Bouffet et al., 1998). Children with malignant gliomas generally have poor survival; however, a small minority of these children with anaplastic astrocytomas survive longer than 10 years (Merchant et al., 1999).

CONCLUSION

The management of patients with primary spinal cord tumors remains a formidable challenge to the clinician. These tumors are very rare, and the presenting symptoms will often initially mimic more common benign pathologies. Even after the diagnosis has been made, the ideal treatment of these tumors remains somewhat controversial. Overall, the tumors are best treated with aggressive surgical resection early in the course of the disease and performed by a surgeon experienced with all aspects of their management.

The exact role of postoperative adjunctive therapy is controversial, but certainly there is no role for radiotherapy after total resection of an ependymoma. There remains much room for improvement in treating patients with malignant primary spinal cord tumors, and clearly new therapies will have to be found to deal with these devastating tumors.

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