Outcomes After Surgical Treatment of Intradural-Extramedullary Spinal Cord Tumors: A Review

Lorenzo Rinaldo[1], Brandon A. McCutcheon[1], Panagiotis Kerezoudis[1], John H. Shin[2], Ankit I. Mehta[3], Michelle J. Clarke[1], Adetokunbo A. Oyelese[4], William E. Krauss[1], Mohamad Bydon[1]

[1]Department of Neurosurgery, Mayo Clinic, Rochester, MN, USA
[2]Department of Neurosurgery, Massachusetts General Hospital & Harvard Medical School, Boston, MA, USA
[3]Department of Neurosurgery, University of Illinois at Chicago, Chicago, IL, USA
[4]Department of Neurosurgery, the Warren Alpert Medical School of Brown University, the Rhode Island Hospital and Hasbro Children's Hospital, Providence, RI, USA

ABSTRACT

Intradural-extramedullary (ID-EM) tumors are the most common type of neoplasm found within the spinal canal. Most of these lesions are either meningiomas or spinal nerve sheath tumors, both of which are generally histologically benign. As such, ID-EM tumors have historically been a surgical disease. Herein, we provide an overview of the literature examining outcomes of the surgical management of these conditions, with a focus on those factors that confer both a positive and negative prognosis.

KEY WORDS: Intradural tumor, spinal cord tumor, tumor

INTRODUCTION

Intradural-extramedullary (ID-EM) tumors are the most commonly observed intradural spinal tumors, comprising over 60% of tumors found within the spinal canal (Aghayev et al., 2011; Chamberlain et al., 2011; Engelhard et al., 2010). While consisting of a heterogeneous group of pathological entities, the vast majority of these lesions are one of three types: meningiomas, schwannomas, or neurofibromas (Klekamp and Samii, 2007). In a survey of United States cancer registries the relative incidence of these tumors was found to be roughly the same (Engelhard et al., 2010). Other less commonly observed ID-EM tumors include lipomas, metastases, paragangliomas, sarcomas, spinal nerve sheath myxomas, and vascular tumors (Abul-Kasim K et al., 2008).

Fortunately, the more common tumors are typically benign, and thus surgical excision represents the possibility of a curative result (Aghayev et al., 2011; Chamberlain et al., 2011). Surgical outcomes have generally been quite positive, with multiple studies quoting gross total resection rates approaching 100% with minimal morbidity and mortality regardless of histologic subtype (Albanese et al., 2002; Riad et al., 2013). Moreover, multiple studies have found the likelihood of neurologic improvement after surgery to be high regardless of the level of preoperative neurologic dysfunction, reinforcing the primacy of surgical therapy in the management of these conditions (Ahn et al., 2009; Albanese et al., 2002). Despite the effectiveness of surgery, however, it is important to remember that these lesions are often benign and slow growing. As such, the potential benefit from surgical excision may not always exceed the risks associated with intradural surgery, particularly for patients with significant comorbidities or a lesion associated with challenging anatomy. These factors should be considered before attempting a gross total resection or even a palliative

procedure. A clearer understanding of both the clinical and histological characteristics associated with tumor progression and recurrence is needed for optimal clinical decision-making in these circumstances. Herein, we shall review the surgical outcomes and prognostic features of the more commonly seen primary ID-EM spinal cord tumors, as well as a brief discussion of metastases to this compartment. In addition, we shall discuss the role of radiosurgery as well as recent advances in the use of minimally-invasive surgical techniques in the management of these lesions.

Surgical Outcomes of Intradural-Extramedullary Spinal Cord Tumors

As stated above, most ID-EM neoplasms are either meningiomas or nerve sheath tumors, the latter of which consists of both schwannomas and neurofibromas. These two larger subgroups will be considered separately, as each presents a unique set of clinical challenges. In addition, we will discuss the incidence and treatment of these tumors in the setting of Neurofibromatosis Types 1 and 2. Finally, we will discuss the epidemiology and surgical outcomes of intradural-extramedullary metastases.

Meningiomas

Potentially the most common ID-EM tumor, spinal meningiomas occur predominantly in women and are located most often in the thoracic region (Gezen et al., 2000; Karsy et al., 2006; Riad et al., 2013; Sandalcioglu et al., 2008). Similarly to their intracranial counterparts, spinal meningiomas arise from the meningothelial arachnoid cap cells within the spinal dura (Karsy et al., 2015). The most common presenting symptom of these tumors is pain, classically at night, within or around the area of the lesion (Klekamp and Samii, 2007). The second most common symptom is neurologic dysfunction, which is generally correlated to the degree to which the tumor occupies the spinal canal (Ahn et al., 2009).

Following the trend observed with ID-EM tumors in general, most institutional case series examining the surgical management of spinal meningiomas report rates of gross total resection above 95% with a very low incidence of morbidity and mortality (Gezen et al., 2000; Gottfried et al., 2003; Riad et al., 2013; Sandalcioglu et al., 2008). These outcomes justify the general consensus that complete surgical excision should be the goal of surgery whenever possible. Even with a gross total resection (Simpson Grade 1 or 2), however, long-term studies with an average follow-up time of greater than 10 years have found a recurrence rate ranging from 6% to 9.7% (Nakamura et al., 2012; Solero et al., 1989). As one would expect, recurrence rates are significantly higher in instances of subtotal resection (Simpson Grade ≥ 3; Heald et al., 2014; Nakamura et al., 2012).

Interestingly, there is controversy regarding the benefits of pursuing radical resection of spinal meningiomas, i.e., pursuing a Simpson Grade 1 versus Grade 2 resection. A study by Heald and colleagues found no difference in recurrence rates between Grade 1 and 2 resections, calling into question the tendency towards "heroic" surgical efforts (Heald et al., 2014). A possible explanation for this may simply be subtotal microscopic resection, as in a study by Nakamura and colleagues histological examination of dural margins from Grade 1 resections with a negative MRI often revealed evidence of residual tumor (Nakamura et al., 2012). Dural margins may indeed be a key component to the pathophysiology of recurrence. In patients receiving subtotal resections (Simpson Grade 4), failure to remove the dural attachment was associated with a significantly shorter recurrence-free survival time regardless of the amount of tumor debulking (Fukushima et al., 2013). More studies are needed in order to determine optimal treatment strategies when radical resection is not possible or dangerous. Regardless, while the evidence is limited to individual case reports, outcomes after reoperation for recurrent meningiomas have been positive (Choi et al., 2012; Nadkarni et al., 2005), and thus recurrence does not preclude the possibility of a favorable outcome.

Beyond extent of resection, a number of other factors have been associated with worse prognosis in patients with spinal meningiomas. In one study, the psammomatous histologic subtype was associated with neurologic decline after tumor resection, as well as worse neurologic outcome overall compared to other histologic variants (Schaller et al., 2005). Given the relatively increased malignant potential of psammomatous meningiomas compared to the other subtypes (Bruner et al., 1998), this finding suggests that a measure of the degree of cellular anaplasia may assist in predicting long-term outcomes of patients with these neoplasms. Within the relatively recent past, the immunohistochemical quantification of proliferative potential through labeling of the marker Ki-67 has been investigated as a means to predict the natural history of resected meningiomas, with respect to risk of both

recurrence and malignant degeneration (Abry et al., 2010; Roser et al., 2004). While a general trend towards increased labeling indices has been seen in both recurrent and higher grade tumors, the significance of this trend has yet to be established. For example, in a comparison of spinal and intracranial tumors, Ki-67 indices were significantly higher in intracranial meningiomas despite no difference in observed recurrence rates (Roser et al., 2006). A more in depth understanding of the molecular basis of recurrence and degeneration is needed in order to determine the proper role for labeling indices in determining the prognosis of spinal meningiomas.

Studies examining the surgical outcomes of anaplastic spinal meningiomas are lacking. Given the rarity of spinal tumors and anaplastic meningiomas in general, anaplastic spinal meningiomas are likely to be exceedingly rare, making the study of outcomes after surgical resection difficult. Complete surgical excision of these lesions is likely to be a major determinant of survival, as in studies of intracranial anaplastic meningiomas 5-year survival rates were significantly higher in patients receiving a gross total resection (Aizer et al., 2015; Moliterno et al., 2015). More work is needed to determine the natural history of anaplastic spinal meningiomas after surgical resection.

Nerve Sheath Tumors

Nerve sheath tumors comprise the other major subset of ID-EM neoplasms, accounting for approximately 25% of intradural tumors in adults and 14% in pediatric patients (Abdul-Kasim et al., 2008). The two most common nerve sheath tumors are schwannomas and neurofibromas. While schwannomas arise exclusively from schwann cells, the histologic heterogeneity of neurofibromas suggest that they can arise from a number of different cells within the spinal nerve sheath (Burger et al., 1991). Despite their morphologic and histologic similarities, these tumors can be reliably differentiated on the basis of immunohistochemical staining patterns (Fine et al., 2004; Gray et al., 1990). The distinction between these tumors is important, as significant differences in clinical presentation and natural history have been observed between them.

Similarly to spinal meningiomas, the most common presenting symptom for both schwannomas and neurofibromas is pain, followed by both motor and sensory neurologic symptoms (Safaee et al., 2015; Safavi-Abbasi et al., 2008). Unlike meningiomas, however, neither of these tumors are more likely to occur in females (Safaee et al., 2015; Safavi-Abbasi et al., 2008). In addition, they exhibit unique localization patterns within the spinal canal, with studies showing schwannomas to occur more frequently in the thoracic and lumbar regions and neurofibromas to be located more commonly in the cervical region (Safaee et al., 2015; Seppälä et al., 1995; Seppälä et al., 1995). The treatment of nerve sheath tumors, regardless of location, is nevertheless primarily surgical, with routinely good outcomes seen after surgical excision (Nanda et al., 2015; Safavi-Abbasi et al., 2008). Prior reports have demonstrated that cervical location was associated with lower rates of gross total resection compared to other spinal regions. This observation may explain the increased recurrence rates of neurofibromas relative to schwannomas, given the former's tropism for the cervical spine (Safaee et al., 2015). Advances in surgical technique will hopefully continue to increase the likelihood of a gross total resection of cervical lesions (Acosta et al., 2007; Fernandes et al., 2014; Lot and George, 1997).

Nerve sheath tumors have been associated with lower rates of gross total resection relative to spinal meningiomas (Gezen et al., 2000; Gottfried et al., 2003; Halvorsen et al., 2015; Riad et al., 2013; Safaee et al., 2015; Sandalcioglu et al., 2008). This difference is potentially explained by the often intimate involvement of these tumors with spinal nerve roots. Intraoperative sacrifice of nerve roots may increase gross total resection rates while producing acceptable neurologic consequences. One study of cervical neuromas with a root preservation rate of only 28% achieved a gross total resection rate of 96%, albeit with 4% of patients experiencing worsening of preoperative neurologic deficits (Lot and George, 1997). In another study, sequelae of nerve root sacrifice were exclusively minor, and were mostly sensory with only a few motor deficits (Safavi-Abbasi et al., 2008). Debilitating motor weakness is nevertheless a possibility after nerve root sacrifice, with risk factors for severe deficits including preoperative neurologic deficits, extradural extension of the tumor, and, notably, a diagnosis of schwannoma (Celli, 2002; Nanda et al., 2015). Intraoperative neurophysiologic monitoring is undoubtedly helpful for minimizing the risk of severe postoperative neurologic deficits, with one study showing that use of intraoperative monitoring modified surgical strategy in 7.35% of cases and was associated with good outcome, suggesting that use of this technology may have prevented neurologic injury in some cases (Ghadirpour et al., 2015).

Approximately 2.5% of nerve sheath tumors are malignant, a subgroup formally classified as Malignant Peripheral Nerve Sheath Tumors (MPNSTs; Sordillo et al., 1981). In contrast to their benign counterparts, the prognosis of MPNSTs is poor, with recorded 5-year survival rates as low as 16% (Ducatman et al., 1986; Wong et al., 1998). A recent analysis of the SEER database found that of 690 patients with spinal nerve sheath tumors, 64 (9%) had MPNSTs. These tumors present significant surgical challenges. In one study, only 76% underwent a surgical procedure and only 39% received a gross total resection. In the same study, however, both gross total resection and partial resection conferred a survival benefit compared to biopsy alone, suggesting that surgery has a significant role to play in the management of these conditions. Moreover, 5-year survival rates for spinal MPNSTs were 65% overall and even higher for those patients receiving surgical intervention (Stadler et al., 2014).

Neurofibromatosis Type 1 and 2

A discussion of ID-EM tumors is incomplete without mention of these tumors in the setting of Neurofibromatosis Type 1 and Type 2 (NF1 and NF2). Patients with these conditions can develop numerous nerve sheath tumors at an early age, particularly in NF1, and also carry a predisposition towards the development of meningiomas (Ferner et al., 2007; von Deimling, 1995). NF1 and NF2 are caused by inactivation of the tumor suppressor gene neurofibromin on chromosome 17q11.2 and of the gene Merlin on chromosome 22q12.2, respectively (Rouleau et al., 1993; Wallace et al., 1990). In imaging studies, spinal tumors were found in 1.6% (23/1400) of patients with NF1 and a surprising 89% (65/73) of patients with NF2 (Mautner et al., 1995; Thakkar et al., 1999). The proportion of tumors classified as ID-EM was 33% and 49% in NF1 and NF2, respectively, with the majority of tumors classified as intraforaminal for both conditions (Mautner et al., 1995; Thakkar et al., 1999).

Importantly, these tumors may follow a different clinical course when occurring in the setting of a neurocutaneous disorder compared to those seen in the general population. In one study, despite comparable radiographic characteristics and extent of surgical resection, the neurologic symptoms of patients with NF2 were on average unchanged after tumor excision, whereas patients with sporadic nerve sheath tumors tended to experience neurologic improvement. Moreover, 5-year recurrence rates were 39.2% and 10.7% in patients with and without NF2, respectively, and 100% of tumors had recurred in patients with NF2 by 9 years (Klekamp and Samii, 1998). Other studies not differentiating between types of Neurofibromatosis also found increased recurrence rates and lower rates of gross total resection in patients with these disorders (Halvorsen et al., 2015; Safaee et al., 2015). In contrast, however, one study of 32 patients presenting with spinal neurofibromas demonstrated that the clinical presentation, gross total resection rates, and recurrence rates were similar between patients with and without NF1 (Seppälä et al., 1995). In a separate report in which schwannomas were overrepresented, no difference in recurrence rates was seen between patients with and without NF1 (Klekamp and Samii, 1998). Of note, however, neurofibromas in the setting of NF1 are more likely to undergo malignant degeneration into MPNSTs (Dimou et al., 2009; Ziadi and Saliba, 2010). Further investigation into the molecular differences between spinal tumors occurring in patients with Neurofibromatosis and sporadic tumors will undoubtedly yield a better understanding of the factors predictive of a good outcome for spinal tumors in general.

Intradural-Extramedullary Metastases

ID-EM metastases are extremely rare entities, accounting for an estimated 6% of all spinal metastases (Ghosh et al., 2001). They warrant discussion in the present context, however, as a review of the literature suggests an important role for surgical resection in the management of these lesions.

While evidence is limited to individual case reports and small institutional case series, ID-EM metastases are typically epithelial in origin, with the most common primary sites being the lung, breast, kidney, prostate, and gastrointestinal tract (Kim et al., 2009; Schick et al., 200; Xiong and Zhong, 2015). The primary mechanism of spread to the intradural compartment is likely hematogenous, and particularly for intraperitoneal tumors may often occur through Batson's plexus, which sends collateral branches from the epidural to intradural space. Increases in intra-abominal pressure secondary to large masses may facilitate the spread of metastases across these valveless vessels (Batson, 1945). Alternative routes of spread include invasion via the perineural lymphatics (Coutinho and Teixeira., 1976) and seeding from CSF dissemination (Ghosh et al., 2001).

The clinical presentation of ID-EM metastases is similar to that of primary ID-EM neoplasms, with pain and neurologic dysfunction being the most common presenting symptoms (Jost et al., 2009; Schick et al., 2001). In addition,

a number of case reports have described ID-EM metastases precipitating cauda equina syndrome, which in some cases occurred as the initial manifestation of malignancy (Kim et al., 2009; Kotil et al., 2007; Lin et al., 2010; Xiong et al., 2015). Of note, all patients treated with decompression and excision of the lesion experienced a rapid return of neurologic function (Kim et al., 2009; Kotil et al., 2007; Xiong et al., 2015). Though cauda equina syndrome secondary to an ID-EM metastasis is an exceedingly rare event, practitioners should be aware of this potential complication, particularly for malignancies associated with paraneoplastic syndromes known to cause neurologic dysfunction. Without a sufficient index of suspicion, physicians may incorrectly localize the cause of neurologic deficits and miss the opportunity for effective intervention (Lee et al., 2012).

The prognosis of patients with ID-EM metastases is very poor, with mean survival times of 5-7.3 months having been reported in institutional case series (Hoover et al., 2012; Schick et al., 2001; Wostrack et al., 2012). Though surgical resection was not shown to extend survival, debulking of these lesions was nevertheless shown to result in substantial improvements to patient pain levels, neurologic functioning, and quality of life in a majority of cases (Hoover et al., 2012; Wostrack et al., 2012). In addition, one series found the likelihood of symptomatic improvement to be independent of the extent of resection (Wostrack et al., 2012). Surgical complication rates were generally very low and almost all patients eventually passed away from causes related to systemic disease (Hoover et al., 2012; Schick et al., 2001; Wostrack et al., 2012). Surgical resection of ID-EM metastases should thus be given strong consideration, particularly in patients severely debilitated by pain or neurologic dysfunction. Moreover, for a select group of patients in whom the primary tumor has been controlled, surgical excision may even prolong survival (Kim et al., 2009; Kotil et al., 2007).

The Role of Stereotactic Radiosurgery in Management of ID-EM Tumors

Given its curative potential for most ID-EM tumors, surgical intervention has been and should continue to be the first line of therapy for these conditions. However, for those lesions not amenable to total resection or for those that have recurred, stereotactic radiosurgery (SRS) may provide a useful adjunct to traditional treatment strategies. In a study of 58 patients with a total of 110 spinal neurogenic tumors, SRS provided symptomatic relief in all patients initially presenting with pain and a local control rate of 95.4% for benign tumors (Shin et al., 2015), demonstrating SRS to be a viable treatment option when surgical resection is not feasible. For MPNSTs, however, the efficacy of SRS is much less clear. While the same study found mixed results when employing SRS to treat MPNSTs, an analysis of the SEER database found that patients receiving radiotherapy for MPNSTs had significantly lower survival rates compared to those that did not receive SRS. In addition, survival rates were lower in patients that received SRS and surgery compared to those that received surgery alone (Stadler et al., 2014), suggesting that radiation may further the malignant degeneration of these lesions. For unclear reasons, patients with neurofibromatosis may be particularly sensitive to this phenomenon, as the survival rate of NF1 patients receiving SRS for treatment of a MPNST was significantly lower than that of patients with sporadic MPNSTs, which could potentially be explained by the negative effects of radiation (Shin et al., 2015). This concern has also been raised with respect to meningiomas, as a previous study found that in patients with NF2, 5% of intracranial meningiomas treated with SRS underwent malignant degeneration (Baser et al., 2000). A more recent study of NF2 patients, however, observed zero instances of malignant transformation of meningiomas after SRS treatment, concluding that SRS was a safe and effective treatment for meningiomas in patients with NF2 (Liu et al., 2015). The generalizability of these results to spinal meningiomas has yet to be established. More work is needed to determine both the efficacy and safety of SRS for both neurogenic tumors and meningiomas, particularly in the setting of Neurofibromatosis.

Minimally Invasive Spine Surgery and ID-EM Tumors

While traditional open approaches for resection of ID-EM tumors have been associated with favorable outcomes, they typically require bilateral laminectomies at the targeted vertebral level(s). As a result, these techniques frequently demand that the neurosurgeon perform simultaneous spinal fusion in order to mitigate the risk of subsequent spinal instability (Wong et al. 2015; Zhu et al. 2015).

Recent reports in the degenerative spine literature have demonstrated reduced blood loss and length of stay through the use of minimally invasive approaches (MIS; Fessler and Khoo 2002; Khoo and Fessler 2002). Given these advantages, as well as the potential for reduced spinal instability, case reports began to emerge describing the application of minimally invasive approaches to resection

of ID-EM tumors (Gandhi and German 2013; Iacoangeli et al. 2012). Recently, a multi-institutional retrospective review of 45 patients with ID-EM spinal tumors demonstrated that a MIS approach was associated with reduced estimated blood loss, length of stay, and incidence of CSF leak without compromising the rate of gross total resection (Wong et al. 2015). Additional retrospective reviews have had comparable results, demonstrating similar rates of gross total resection between MIS and open approaches while providing further evidence that MIS approaches are associated with reduced total blood loss during surgery (Raygor et al., 2015; Zhu et al. 2015). These results suggest that MIS is a viable surgical approach for the management of ID-EM tumors, and may potentially be superior to traditional methods in certain circumstances. The decision to employ MIS techniques to treat these conditions will likely continue to depend largely on surgeon comfort and be made on a case-by-case basis.

CONCLUSION

A review of the literature has revealed that the results of surgical therapy for ID-EM spinal tumors have generally been quite positive. A further understanding of the predictors of both positive and negative prognosis after surgical therapy of these tumors, as well as refinement of the role of radiosurgery and advances in surgical technology, will hopefully lead to the continued betterment of patient outcomes.

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Address correspondence to: Mohamad Bydon, Department of Neurosurgery, Mayo Clinic, 200 First Street SW, Rochester, Minnesota, USA

Phone: 507 284 52 06

email: Bydon.mohamad@mayo.edu