Intramedullary spinal cord tumors: a review of current and future treatment strategies

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Intramedullary spinal cord tumors have low incidence rates but are associated with difficult treatment options. The majority of patients with these tumors can be initially treated with an attempted resection. Unfortunately, those patients who cannot undergo gross-total resection or have subtotal resection are left with few treatment options, such as radiotherapy and chemotherapy. These adjuvant treatments, however, are associated with the potential for significant adverse side effects and still leave patients with a poor prognosis. To successfully manage these patients and improve both their quality of life and prognosis, novel treatment options must be developed to supplement subtotal resection. New research is underway investigating alternative therapeutic approaches for these patients, including directed, localized drug delivery and nanomedicine techniques. These and other future investigations will hopefully lead to promising new therapies for these devastating diseases.

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Intramedullary spinal cord tumors (IMSCTs) are rare neoplasms of the CNS and have been a significant clinical challenge due to the lack of a clear standard of care, limited therapeutic options, and challenges of drug delivery. IMSCTs account for 2%–4% of all CNS tumors, with ependymoma being the most common in adults and astrocytomas being the most common in children and adolescents. Overall, ependymomas are the most frequent IMSCTs, followed by astrocytomas and then miscellaneous tumors including hemangioblastomas, gangliogliomas, germinomas, primary CNS lymphomas, and melanomas (Table 1). Although rare, IMSCTs can also develop as a result of metastasis from a primary malignancy.

While most IMSCTs are benign, low-grade (WHO Grades I and II) tumors, many vary in histology and 7%–30% of astrocytomas are considered malignant. IMSCTs can be found in any location throughout the length of the spinal cord; however, they are most common at the cervical level (33%), followed by the thoracic (26%) and lumbar (24%) levels. The higher incidence of IMSCTs at the cervical level may be related to the higher level of gray matter present at that level. MRI is recommended for the identification and evaluation of IMSCTs, with intensities and contrast-enhancement varying depending on the tumor type and signal.

The most common presenting symptom of IMSCT is back pain, which may be diffuse or radicular in nature. Diagnosis is especially difficult in children, where IMSCTs may remain asymptomatic for a long period of time or cause nonspecific complaints. The character of the pain varies, but is commonly reported to worsen at night. IMSCTs can also impinge on somatosensory and motor systems, causing dys- and paresthesias, spasticity, and weakness. Loss of bowel and bladder function can also occur at a later stage and is the least common presenting symptom. Symptoms in children may be perceived as clumsiness or attributed to...
trivial injuries, and scoliosis is present in one-third of patients.\textsuperscript{28}

Evidence-based treatment of IMSCTs (Table 2) primarily involves resection, with radiotherapy and chemotherapy often reserved for tumor recurrence, high-grade and infiltrative tumors, or when resection is contraindicated. Preoperative neurological status and tumor histology are considered the best predictors of outcome, with tumor histology shown to be predictive of extent of resection, functional neurological outcomes, and recurrence.\textsuperscript{30} Resection is generally considered a good predictor of outcome. Recent studies, however, have shown that surgical intervention for the management of astrocytoma is associated with higher rates of long-term neurological complications with no derived benefit for patients.\textsuperscript{7}

The standard of care for most cases of IMSCT is resection, which has improved with the development of modern neurosurgical instrumentation, use of the operating microscope, as well as the measurement of intraoperative motor and somatosensory evoked potentials. However, resection of IMSCT is generally dependent on the presence or absence of a clear plane of dissection. While ependymomas typically have a clear plane between the tumor and spinal cord parenchyma, astrocytomas tend to be more infiltrative, lacking a good plane of dissection.\textsuperscript{14} This limits the ability for gross-total resection (GTR) for intramedullary astrocytomas, as any attempt at GTR may damage spinal pathways, leading to postoperative neurological deficits involving both motor and sensory systems.

Adjuvant radiotherapy is recommended when resection is contraindicated, or for high-grade tumors that are not amenable to GTR. The role of radiotherapy, though, is controversial, as there have been reports that suggest a positive outcome while others suggest no benefit despite its routine use in the clinical setting.\textsuperscript{60} Additionally, radiotherapy can have several adverse effects, including radiation myelopathy, impaired spine growth, spinal deformities, radiation necrosis, vasculopathy, changes to the normal spine parenchyma, and a 25% risk of secondary tumors in 30 years.\textsuperscript{6,10} These longer-term consequences can be particularly adverse in children and adolescents.

Since children are more sensitive to the adverse effects of IMSCTs, the role of chemotherapy has gained further appreciation. Chemotherapy has historically been used only when resection and adjuvant radiotherapy were contraindicated or unsuccessful.\textsuperscript{10} Some of the limitations of chemotherapeutic agents include the inability of large molecules to bypass the blood–spinal cord barrier (BSCB),

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Incidence</th>
<th>Location</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ependymoma</td>
<td>Most common (50–60% of IMSCTs)</td>
<td>Cervical &gt; thoracic &gt; lumbar</td>
<td>Good</td>
</tr>
<tr>
<td>Myxopapillary ependymoma</td>
<td>Rare</td>
<td>Filum terminale &amp; conus medullaris</td>
<td>Excellent</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>Second most common</td>
<td>Cervical &gt; thoracic &gt; lumbar</td>
<td>Poor</td>
</tr>
<tr>
<td>Hemangioblastoma</td>
<td>Very rare; increased incidence in VHL disease patients</td>
<td>Cervical &gt; thoracic &gt; lumbar</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

**TABLE 2. Intramedullary spinal cord tumors**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Treatment</th>
<th>Evidence-Based Classification*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ependymoma</td>
<td>Primary: resection</td>
<td>Class I, Level of Evidence: C</td>
</tr>
<tr>
<td></td>
<td>Secondary: RT</td>
<td>Class IIa, Level of Evidence: C</td>
</tr>
<tr>
<td></td>
<td>Secondary: chemo</td>
<td>Class IIb, Level of Evidence: C</td>
</tr>
<tr>
<td>Myxopapillary ependymoma</td>
<td>Surgical resection</td>
<td>Class I, Level of Evidence: C</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>Primary: resection</td>
<td>Class IIb, Level of Evidence: C</td>
</tr>
<tr>
<td></td>
<td>Secondary: RT</td>
<td>Class IIa, Level of Evidence: C</td>
</tr>
<tr>
<td></td>
<td>Secondary: chemo</td>
<td>Class IIb, Level of Evidence: C</td>
</tr>
<tr>
<td>Hemangioblastoma</td>
<td>Surgical resection</td>
<td>Class I, Level of Evidence: C</td>
</tr>
<tr>
<td>GCT</td>
<td>Primary: resection</td>
<td>Class I, Level of Evidence: C</td>
</tr>
<tr>
<td></td>
<td>Secondary: RT (germinomas)</td>
<td>Class IIa, Level of Evidence: C</td>
</tr>
<tr>
<td></td>
<td>Secondary: chemo (non-germinomatous GCT)</td>
<td>Class IIa, Level of Evidence: C</td>
</tr>
<tr>
<td>Ganglioglioma</td>
<td>Surgical resection</td>
<td>Class I, Level of Evidence: C</td>
</tr>
<tr>
<td>CNS lymphoma</td>
<td>Intrathecal chemo</td>
<td>Class IIb, Level of Evidence: C</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Primary: resection</td>
<td>Class I, Level of Evidence: C</td>
</tr>
<tr>
<td></td>
<td>Secondary: RT</td>
<td>Class IIb, Level of Evidence: C</td>
</tr>
</tbody>
</table>

Chemo = chemotherapy; RT = radiotherapy.
* The American Heart Association Evidence-Based Scoring System.
Intramedullary Spinal Cord Tumors

Ependymomas

Ependymomas are rare, unencapsulated glial tumors of the brain, but they represent the most common form of IMSCT in adults and account for approximately 50%–60% of all intramedullary tumors.43 Ependymomas develop from ependymal cells, which are the epithelial-like cells lining the ventricles of the brain as well as the central canal of the spinal cord. Histologically, ependymomas can be classified into 4 types: myxopapillary ependymoma (WHO Grade I), subependymoma (WHO Grade I), ependymoma (WHO Grade II), and anaplastic ependymoma (WHO Grade III). Myxopapillary ependymomas account for up to 50% of ependymoma cases, typically arise from the filum terminale, and are usually located in the cauda equina while the other 3 subtypes follow the normal distribution of IMSCTs and are most often found in the cervical or thoracic spinal cord. All types appear to show heterogeneous enhancement with contrast, and cyst formation and syrinx are common especially at the cervical level.1 Cysts form in both the rostral and caudal directions from the enhancing mass.

In most cases, ependymomas have an easily identified plane of dissection, and thus GTR is the primary form of treatment. There are several studies showing that the extent of resection is a strong predictor of overall survival, with 90%–100% of patients showing improvement following complete resection.20 However, GTR is not achieved in most patients due to most ependymomas being located in areas that, if resected, would decrease neurological function.6 GTR in cases of myxopapillary ependymomas has been controversial, but a recent study found that GTR is associated with lower overall recurrence compared with subtotal resection (STR), but also states that there is no evidence whether GTR contributes to better functional outcome in patients.17 While adjuvant radiotherapy is not recommended for completely resected tumors, it has been traditionally used following STR, recurrent tumors, or when surgery cannot be performed. The benefit of radiotherapy has also been contested, with some studies reporting a 5-year survival rate of 70% for patients receiving adjuvant irradiation compared with 20% for patients treated with surgery alone.6 More recent studies suggest that radiotherapy is not associated with lower overall recurrence regardless of the extent of resection.17

While there are few data supporting the use of chemotherapy in the treatment of ependymoma, the high incidence of these tumors in children makes it an important option for therapeutic development. Chemotherapy has, for the most part, been studied in recurrent intracranial ependymoma and has been shown to have a modest effect; however, its role in IMSCTs remains to be elucidated.8 In the 2002 study by Chamberlain,4 the topoisomerase-2 inhibitor etoposide was well tolerated and had a partial response in 2 of 10 treated patients (20%). The small number of patients limits the study but highlights the fact that more studies need to be done on various chemotherapeutic agents, like etoposide.

**TABLE 3. The authors’ proposed management strategy for IMSCTs**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ependymoma</td>
<td>Attempt GTR based on plane of dissection &amp; intraop neuromonitoring; if STR performed, add adjuvant RT</td>
</tr>
<tr>
<td>Myxopapillary ependymoma</td>
<td>Attempt GTR based on plane of dissection &amp; intraop neuromonitoring</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>Assess plane of dissection &amp; perform STR (biopsy); if there is significant residual tumor or recurrence, add RT</td>
</tr>
<tr>
<td>Hemangioblastoma</td>
<td>Preop spinal cord angiography for possible embolization of vascular feeders; GTR w/ a good plane of dissection</td>
</tr>
<tr>
<td>GCT</td>
<td>Assess CSF for germ cell markers (hCG, AFP, PLAP); RT</td>
</tr>
<tr>
<td>Ganglioglioma</td>
<td>GTR; if there is recurrence, consider RT</td>
</tr>
<tr>
<td>CNS lymphoma</td>
<td>High-dose methotrexate &amp; temozolomide; diagnosis made w/ biopsy</td>
</tr>
<tr>
<td>Melanoma</td>
<td>GTR; postop RT</td>
</tr>
</tbody>
</table>

AAFP = alpha-fetoprotein; hCG = human chorionic gonadotropin; PLAP = placental alkaline phosphatase.
Astrocytomas

Intramedullary astrocytomas are glial tumors responsible for approximately 60% of all spinal cord tumors in children and adolescents, despite affecting patients of all ages. Most spinal cord astrocytomas are low grade (WHO Grade II) and generally considered to be less aggressive than those in the brain. Of a total of 86 studied astrocytoma cases, Raco et al. found 48% to be WHO Grade II, followed by 31% to be WHO Grade I, and 21% to be WHO Grade III to IV. WHO Grade I lesions represent pilocytic astrocytomas, a slow-growing tumor associated with cyst formation. Some studies have suggested that pilocytic astrocytomas represent the most common subtype in children, though these studies are limited by their sample sizes. Grade III and IV astrocytomas carried a poor prognosis with a mean survival of 15.5 months. These lesions are the most aggressive and infiltrative class of astrocytomas.

The presentation of these lesions varies, with pain being one of the earliest symptoms similar to ependymomas. Since these lesions tend to affect pediatric populations, certain symptoms in children are indicative of astrocytoma. These include children complaining of pain at night that wakes them up, abdominal pain, motor deficits or regression, and scoliosis. Combined together, presentation in children is often nonspecific and may require extensive diagnostic workup to rule out other etiologies before suspecting astrocytoma.

On MRI, astrocytomas are difficult to distinguish from other types of intramedullary tumors. While usually hypo- or isointense on T1-weighted images and hyperintense on T2-weighted images, their asymmetry and slightly off-center location may help distinguish them from other tumor types. Similar to ependymomas, astrocytomas show heterogeneous enhancement with contrast that makes it hard to distinguish between ependymomas and astrocytomas based on MRI alone. For this reason, biopsy and histology might be considered the best methods for distinguishing astrocytomas from ependymomas and planning treatment options.

Astrocytomas typically lack a clear plane of dissection and demonstrate a much more infiltrative nature than ependymomas. For this reason, GTR is often not achieved, and astrocytomas are associated with a poorer prognosis. In the study by Raco et al., 0% of WHO Grade III to IV astrocytomas were able to undergo GTR, while only 12% of WHO Grade II tumors were completely resected. In a study by Babu et al., a total of 46 patients underwent laminectomy over the regions with solid tumor, and maximal resection was attempted while monitoring sensory and motor evoked potentials. The study found that 37% of patients had a worse postoperative neurological outcome compared with baseline before operation. This is most likely due to the infiltrative nature of the tumor, which risks damage to the normal spinal cord parenchyma during resection. In current practice, attempting GTR is not recommended; however, partial resection or STR can be attempted. This increases the likelihood of recurrence as microscopic remnants of the tumor may remain in the spinal cord parenchyma following resection. Karikari et al. noted that 47.6% of patients with primary spinal cord astrocytomas had a recurrence, all of whom had originally undergone STR. This is much higher than the rate of recurrence for ependymomas of 7.3%.

If recurrence of astrocytoma does occur, radiotherapy is the next course of treatment. However, the use of radiotherapy for astrocytomas, especially low-grade astrocytomas, is controversial since they commonly affect children and adolescents. All of the risks associated with radiotherapy, combined with the frequent inability
to achieve GTR, point toward chemotherapy as a viable option for treating astrocytomas. This is especially true when surgery and radiotherapy have been unsuccessful. Studies of chemotherapeutic agents for astrocytomas are very limited, and further studies are warranted. Some studies have suggested a possible therapeutic value for the DNA-alkylating drug temozolomide. Chamberlain et al.9 showed that temozolomide treatment led to 27% progression-free survival at 2 years with a median survival of 23 months. As temozolomide has shown some efficacy in treating intracranial astrocytomas, such as glioblastoma, it has been used in treating astrocytomas within the spinal cord as well10,40. Despite this modest benefit, there were also associated systemic toxicities, including constipation, fatigue, neutropenia, lymphopenia, and thrombocytopenia in several patients.9 These adverse effects associated with standard chemotherapy treatments are dependent on the systemic toxicity associated with the agents used. Thus, to develop effective treatments for astrocytoma, larger studies on chemotherapy, as well as therapies that localize drug delivery to specific spinal cord segments, are necessary.

Hemangioblastomas

Intramedullary hemangioblastomas are rare, benign tumors of mesenchymal origin that originate from the vascular system within the spinal cord. Intramedullary hemangioblastomas account for 3%-4% of all IMSCTs and are the third most frequent after ependymomas and astrocytomas.33 Hemangioblastomas most commonly present in the posterior fossa (83%); however, approximately 13% are found within the spinal cord.48 While they do not develop from the intrinsic cells of the spinal cord, their close association with the vasculature that nourishes the spinal cord can lead to the rare development of intramedullary tumor. For this reason, they tend to possess a high degree of vascularity and angiogenesis during growth.

Hemangioblastoma is strongly associated with von Hippel-Lindau (VHL) disease, and approximately 10%-30% of patients diagnosed with spinal cord hemangioblastoma will also have VHL disease.10 Patients with VHL disease typically present with multiple hemangioblastomas in addition to other abnormalities such as renal cell carcinoma, pheochromocytoma, pancreatic cysts, and others.48 The presence of multiple hemangioblastomas along with these other abnormalities may thus point toward VHL disease. In patients with VHL disease, gene mutation results in the absence of VHL protein, leading to enhanced transcription of several genes, including vascular endothelial growth factor (VEGF), which perhaps contributes to the development of vascular tumors such as hemangioblastomas.39

Intramedullary hemangioblastomas tend to develop in the dorsal portion of the spinal cord and thus present with progressive sensory deficits, particularly proprioceptive deficits.10 Due to the high vascularity of the tumor, there is also a risk of hemorrhage. Although rare, hemorrhage from hemangioblastoma can be subarachnoid hemorrhage (73%) or intramedullary hemorrhage (27%).64 Unlike astrocytomas, hemangioblastomas can be differentiated from ependymomas using MRI by the presence of hypervascularity along with tumor enhancement.10 Further, more, due to the altered vasculature within the spinal cord, unusual enlargement of the spinal cord may be observed due to edema.43

Similar to other IMSCTs, resection is the primary treatment for intramedullary hemangioblastomas. Hemangioblastomas typically exhibit a clear dissection plane that allows for GTR.10 Due to the vascularity of the lesion, resection does pose a risk of intraoperative bleeding; however, recent studies have shown that hemorrhage from feeder arteries is generally not an issue due to techniques such as preoperative embolization and temporary artery occlusion.66 Therefore, resection appears to be the best option for patients with hemangioblastoma.

The use of radiotherapy in the treatment of hemangioblastomas is very limited, while chemotherapy has been studied even less. Antiangiogenic therapy using the VEGF receptor-2 inhibitor SU5416 was shown to be somewhat effective in patients with VHL disease.39 In contrast, the use of the monoclonal antibody bevacizumab to inhibit the VEGF receptor was shown to be ineffective, resulting in increased tumor invasiveness following antiangiogenic therapy.63 Taken together, this may imply that some hemangioblastomas might show responsiveness to angiogenesis inhibitors, while others may not, depending on the level of upregulation of the VEGF gene.

Germ Cell Tumors

Germ cell tumors (GCTs) of the CNS are made up of cells similar to the germinal cells that develop in the gonads. GCTs represent approximately 1% of brain or spinal cord tumors in Europe and the United States, with higher rates of incidence in other geographical regions such as Japan (3%) and East Asia (12.5%).4 The rates of primary intramedullary GCTs are even lower. There are 2 types of GCT: nongerminomatous GCT and germinoma. Patients with primary intramedullary germinomas typically present with sensory and motor deficits of the lower extremities.38 MRI typically shows an expanding mass (often at the lower thoracic level), contrast enhancement with T1- and T2-weighted MRI can vary, and focal spinal cord atrophy may be an important sign.38

Germinomas have been shown to be radiosensitive, with some studies suggesting 5-year survival rates of 65%-95% with irradiation alone.6 Germinomas are sensitive to chemotherapy as well.6 In contrast, nongerminomatous GCTs show little sensitivity to radiotherapy alone and are often treated in combination with chemotherapy.6 Since intracranial germinomas seem to be responsive to the chemotherapeutic drugs cisplatin and etoposide, attempts have been made to treat intraspinal germinomas in the same manner.32 A recent study by Kinoshita et al.32 found that in a patient with multiple spinal cord germinomas, this combination therapy was effective in reducing tumors at multiple levels. Other studies have suggested that combination therapy will allow for a reduction in the necessary radiation dose and still lead to complete remission.4 Thus, chemotherapy might provide an alternate option in the treatment of intramedullary germinomas that could avoid the negative side effects associated with radiation treatment.
Gangliogliomas

Gangliogliomas are rare tumors from both neuronal and glial origins that are composed of glial and ganglion cells. Most gangliogliomas are intracranial in the supratentorial space, with intramedullary spinal cord gangliomas being very rare. They are typically benign, slow-growing tumors (WHO Grade I or II), although malignant transformation has been shown and is presumed to involve the glial component of the tumor. Of interest, a recent study on 27 infratentorial gangliogliomas found that there were 2 distinct categories: 59% were classic gangliogliomas, and the remaining 41% were described as having a high similarity to pilocytic astrocytomas but with the addition of some cells of ganglion cell origin.

Intramedullary gangliogliomas are usually located within the cervical level, larger than other types of IMSCTs, and difficult to distinguish on MRI. Yang et al. found that 39% of patients with intramedullary ganglioglioma also presented with obvious scoliosis, which may be indicative of this type of lesion. These tumors tend to mostly affect the pediatric population, and in a recent study of 348 children were found to affect mostly older children and young teenagers.

Similar to most IMSCTs, resection is the primary treatment of choice. GTR for spinal gangliogliomas is achieved at a much higher rate (83.3%) compared with intracranial tumors. However, due to the large size of these tumors and the fact they are often located in the cervical spinal cord, attempting GTR can be risky. Thus, STR may be a more effective treatment in regards to minimizing neurological dysfunction following resection, although more studies need to be done. Adjuvant and postoperative radiotherapy are typically not recommended, except in some cases of recurrence, and the use of chemotherapy has only been extrapolated from its use for intracranial gangliogliomas. Despite these treatments, spinal gangliogliomas have a higher relative risk of recurrence than both cerebral and brainstem gangliogliomas and have a 10-year survival rate of 83%.

CNS Lymphoma

Intramedullary spinal cord lymphoma is a rare form of primary lymphoma and can occur anywhere in the CNS. It can originate in the spinal cord, accompany tumors in other locations throughout the CNS, or occur as a part of systemic lymphoma. It is usually an aggressive non-Hodgkin lymphoma of B-cell origin. T1-weighted MRI shows homogeneous contrast enhancement in an enlarged area of the spinal cord, while diffusion-weighted and T2-weighted MRI demonstrate hyperintensity. Due to its lack of localization, the primary treatment for intramedullary lymphoma and other lymphomas of the neuraxis is the chemotherapeutic agent methotrexate; however, recurrence is common and often occurs within 2 months. High-dose methotrexate-based therapy has been shown to be effective in elderly patients suffering from primary CNS lymphomas, and even more so when combined with alkylating agents such as temozolomide. Thus, the development of chemotherapeutic agents for the treatment of primary CNS lymphoma is especially appealing, given that its diffuse nature makes resection and radiotherapy more challenging.

Melanoma

Primary melanomas of the spinal cord are very rare and account for about 1% of all melanomas, with diagnosis dependent on the absence of melanoma outside of the CNS and histological confirmation of pigmented tumors. Patients with primary intramedullary melanoma will experience similar symptoms as other intramedullary tumors. However, melanomas often develop more rapidly than other IMSCTs, so the progression of symptoms will be rapid. On MRI, distinguishing intramedullary melanomas from other IMSCTs is difficult; however, their patterns on T1- and T2-weighted images are different from other IMSCTs and may prove useful. Melanomas typically display hyperintensity on T1-weighted images due to the presence of melanin, while T2-weighted images are generally hypo- or isointense.

While resection is the primary treatment option for intramedullary melanoma, GTR is difficult and most patients will require postoperative radiotherapy. Nishihara et al. used a combination of whole-brain and local radiation therapy, intrathecal injections of interferon-β, and chemotherapy with dacarbazine following the resection of a primary spinal melanoma and demonstrated the control of progression and prolonged survival. With that said, the rarity of these types of tumors make it very difficult to evaluate therapeutic options and potential at a statistically significant level.

Intramedullary Metastases

Although intramedullary metastases are considered rare, they affect 0.4% of all patients with cancer and represent 1%–3% of intramedullary tumors. They are most commonly derived from primary tumors found in the lung (49%), breast (15%), and lymphoma (9%). The prognosis of patients diagnosed with intramedullary metastases is generally very poor, and thus prompt diagnosis and treatment are often crucial for survival. Recent studies have shown a median survival time of 4 months with 0 patients achieving complete remission. Resection may be attempted, but the lack of a clear plane of dissection often prevents achievement of GTR.

Some studies have shown the potential for the use of long-course radiotherapy, but the progressive deterioration of quality of life and neurological function pose clear limits. There have been a few reports on the use of chemotherapy in the treatment of intramedullary metastases in the literature, which show mixed results of efficacy. Hata et al. reported the improvement of intramedullary metastasis from lung adenocarcinoma after 2 weeks and complete response following the administration of the epidermal growth factor receptor (EGFR) inhibitor gefitinib following radiotherapy and other chemotherapeutic agents. Thus, while this particular case might have only demonstrated improvement due to an EGFR inhibitor-sensitive tumor and metastasis, the potential for chemotherapeutic agents in the treatment of intramedullary tumors warrants continued investigation.

Discussion

IMSCTs represent a rare but significant cause of neu-
ological morbidity and mortality and affect patients of all ages. GTR remains the primary goal of treatment for most types of IMSCTs. While tumors such as ependymomas and hemangioblastomas might exhibit a clear surgical plane of dissection, more infiltrative tumors, such as astrocytomas, do not have such a plane, making complete resection impossible. When a plane of dissection is absent, resection is often associated with poor outcomes, despite advances in microsurgical techniques and electrophysiological monitoring during the procedure. Radiotherapy is often the second line of treatment when resection is contraindicated or unsuccessful. However, the adverse effects of radiation are often undesirable and contribute to decreased quality of life. Chemotherapy has not been well studied for the treatment of IMSCTs, despite the therapeutic potential demonstrated in similar intracranial tumors.

The localized nature of intramedullary tumors, the lack of a clear standard of care, and the failure of current treatment regimens to produce significant results has led to the development of novel, site-specific treatment strategies (Table 2). Additionally, despite progress being made in the fields of convection-enhanced delivery (CED), ultrasound, and ultrasonic disruption of the blood-brain barrier; these methods have not yet seen the same application in spinal cord tumors. There are, however, some preclinical studies demonstrating the utility of CED and focused ultrasound for delivery to the spinal cord.

Some of the main obstacles of chemotherapy include bypassing the BSCB, lack of adequate penetration into the spinal cord parenchyma, and off-target effects associated with systemic drug administration. Intrathecal drug delivery has provided the ability to bypass the BSCB, but penetration of spinal cord parenchyma remains an issue. Furthermore, since intrathecal delivery does not localize to the tumor and has unhindered access to the CNS due to CSF flow, there can often be unwanted CNS side effects. Because of inherent physiological properties, such as CSF pulsations, CSF volume, heart rate, and respiratory rate, the dispersion of chemotherapeutic agents throughout the CNS can be accelerated. Consequently, there is an increasing interest in developing therapies capable of directed, localized drug delivery.

Unfortunately, the vast majority of new research is focused on the treatment of brain tumors, rather than spinal cord tumors. The results of these studies should, theoretically, apply to spinal cord tumors as well. Areas of new research have largely focused on 4 methods for enhancing local drug delivery: 1) enhancing drug permeability through the blood-brain barrier; 2) temporary disruption of the blood-brain barrier (e.g., ultrasound); 3) interstitial delivery of drugs (e.g., CED); and 4) the use of implantable polymer wafers. Several methods for enhancing drug permeability have been investigated. These include modifying drugs with molecules known to initiate receptor-mediated transcytosis via the transferrin receptor and lipoprotein receptor-related protein-1. Percutaneous drug elution can also be enhanced by coating agents with polymers such as polysorbate-80 and poly(ethylene glycol). Disruption of the blood-brain barrier can be achieved in several ways, including focused ultrasound with microbubbles, osmotic agents such as mannitol, and blood vessel modulators such as RMP-7. Interstitial drug delivery occurs via the direct injection of drugs via the stereotactic placement of a catheter with convection-enhanced (bulk flow) drug delivery. Lastly, the introduction of drug-eluting polymers has allowed the implantation of small polymer wafers adjacent to tumors in order to deliver drugs in a controlled, sustained fashion.

One area of research increasingly being investigated in the field is the utilization of nanomedicine for the direct administration of therapeutic drugs. This is especially relevant for various tumors and provides the potential to bypass several obstacles encountered in regard to localization and penetration of the spinal cord parenchyma. Unfortunately, much like the treatments discussed above, the vast majority of new research has been aimed at brain tumors rather than spinal cord tumors. However, there have been promising results from nanomedicine approaches to brain tumors. For instance, Schneider et al. show that the use of drug-loaded nanoparticles can be targeted to specifically bind glioblastoma cells via conjugation with the protein fibroblast growth factor-inducible 14 (Fn14). These nanoparticles successfully penetrated brain parenchyma, but specifically bound glioblastoma cells, without significant off-target effects. Additionally, the nanoparticles showed reduced nonspecific binding of the brain extracellular matrix. By specifically targeting cancer cells, as demonstrated via Fn14 conjugation in the Schneider et al. study, it is possible that nanoparticles that specifically target cancer cells could be effectively used to deliver drugs to remote tumor cells that otherwise escape resection.

To expand the study of nanomedicine to the treatment of IMSCTs, the development of both good in vitro assays as well as animal models of these tumors is essential. Fortunately, these models are available for use and have been demonstrated in both rats and rabbits using immortalized cell lines as well as using cells derived from human glioblastoma tissue. Unique to the treatment of the spinal cord is the ability to use magnetic guidance to direct nanoparticles via an externally placed magnet on a patient’s back. In fact, recent in vitro studies using a human spine model have shown the ability to achieve effective drug delivery using external magnetic guidance of intrathecally delivered gold-coated nanoparticles. Further studies by the same group demonstrated that magnetic guidance of these particles resulted in a 181% increase in the site-specific delivery of nanoparticles compared with unguided particles. The development of drug delivery systems, such as these that allow for the precise localization of chemotherapeutic drugs, may represent a novel approach to treating these types of tumors (Fig. 1). This would overcome some of the obstacles faced by current chemotherapy treatments and perhaps create a better option for patients who would otherwise have a poor prognosis.

Conclusions

IMSCTs are rare but represent a very difficult to treat pathology. While most of these tumors are amenable to some extent of resection, the majority of them will require some form of adjuvant therapy, either radiation therapy or...
chemotherapy. Unfortunately, the efficacy and safety of radiation therapy and chemotherapy are not well agreed upon and are often not beneficial for these patients. Consequently, it is imperative that novel treatments be developed to help manage these devastating tumors. One interesting area of ongoing research in developing new treatments is nanomedicine and the ability to develop localizable, targeted therapies for these tumors. While there is a significant amount of work left to be done in this field, the early results achieved with cell targeting and the magnetic guidance of nanoparticles seem promising for the future applications of this technology.

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**Author Contributions**

Conception and design: Mehta. Acquisition of data: Mehta, Tobin, Geraghty. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: Mehta, Geraghty, Engelhard, Linninger. Approved the final version of the manuscript on behalf of all authors: Mehta.

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