Intensive Care Research (2022) 2:76–95
https://doi.org/10.1007/s44231-022-00014-3

REVIEW ARTICLE

Characterization and Treatment of Spinal Tumors

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Received: 12 May 2022 / Accepted: 3 September 2022 / Published online: 8 September 2022

Abstract
The prevalence of spinal tumors is rare in comparison to brain tumors which encompass most central nervous system tumors. Tumors of the spine can be divided into primary and metastatic tumors with the latter being the most common presentation. Primary tumors are subdivided based on their location on the spinal column and in the spinal cord into intramedullary, intradural extramedullary, and primary bone tumors. Back pain is a common presentation in spine cancer patients; however, other radicular pain may be present. Magnetic resonance imaging (MRI) is the imaging modality of choice for intradural extramedullary and intramedullary tumors. Plain radiographs are used in the initial diagnosis of primary bone tumors while Computed tomography (CT) and MRI may often be necessary for further characterization. Complete surgical resection is the treatment of choice for spinal tumors and may be curative for well circumscribed lesions. However, intralesional resection along with adjuvant radiation and chemotherapy can be indicated for patients that would experience increased morbidity from damage to nearby neurological structures caused by resection with wide margins. Even with the current treatment options, the prognosis for aggressive spinal cancer remains poor. Advances in novel treatments including molecular targeting, immunotherapy and stem cell therapy provide the potential for greater control of malignant and metastatic tumors of the spine.

Keywords Spinal tumors · Management · Updated care · Critical care

1 Introduction

Tumors of the spine consist of extradural (vertebral) tumors, extramedullary spinal cord tumors (EMSCTs), and intramedullary spinal cord tumors (IMSCTs) (Table 1).

Extradural spinal tumors are the most common tumors of the spine (50%) [1]. Extradural spinal tumors are characterized as either primary or secondary tumors. Secondary tumors comprise 97% of all vertebral spinal tumors because the spinal column is very vascular and in close proximity to lymphatic drainage [2]. Additionally, 70% of cancer patients have metastases in the spine [3]. In particular, adenocarcinomas from the breast, lung, kidneys, prostate, thyroid, and colon are prone to vertebral metastasis [3–5]. Primary extradural tumors are exceedingly rare. The majority of primary extradural spinal tumors are hemangiomas and enostoses which have an incidence of 11–14% [2]. Primary tumors are often encountered incidentally and present asymptomatically. The vast majority of primary spinal tumors do not require treatment.

EMSCTs are tumors that develop in the subdural space, but outside of the spinal cord. EMSCTs are the second most common spinal tumor (40%) [1]. These tumors arise from leptomeninges or nerve roots [6]. The most common EMSCTs are Schwannomas (29%) followed by meningiomas (25%) and gliomas (22%) [7]. EMSCT patients present with lower back pain that is worse at night and/or when supine [7].

IMSCTs are tumors that develop from the glial cells in the spinal cord. These tumors can be found anywhere along the spinal cord. IMSCTs have low incidence rates at just 2–4% of all CNS tumors [1, 6, 8]. 80% of IMSCTs are gliomas [6]. The most common glioma causing IMSCTs are ependymomas followed by astrocytomas. Most IMSCTs are benign and present with back pain most commonly at night and/or when supine [9, 10].

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Table 1 Characteristics and treatment of extramedullary spinal cord tumors (EMSCTs) and intramedullary spinal cord tumors (IMSCTs)

Tumor	Relative frequency	Imaging characteristics	Treatment	Prognosis
Extramedullary spinal cord tumors (EMSCTs)				
Meningioma	Second most common EMSCT	Iso- or hypointense on T1 Mildly hyperintense on T2 Well-circumscribed Dural tail sign seen with contrast Calcification may be present on CT	1st line: surgical resection 2nd line: adjuvant radiotherapy for recurrent tumors	Surgery curative in most cases
Schwannoma	Benign NST make up the most common EMSCT	Iso- or hypointense on T1 Heterogenous, hyperintense signal with ringlike enhancements and fascicular sign on T2 Well-circumscribed	1st line: gross total surgical resection 2nd line: stereotactic radiosurgery for recurrent tumors or when surgery contraindicated 2nd line: chemotherapy may be used in syndromic disease	Surgery is curative in most cases
Neurofibroma		Iso-or hypointense on T1 with target sign Homogeneous, hyperintense signal on T2 with fascicular sign	1st line: gross total surgical resection in symptomatic tumors 2nd line: chemotherapy in syndromic disease	Surgery is curative in most cases however potential for malignant transformation with incomplete resection
Malignant Nerve Sheath Tumor	Rare	Iso- or hypointense T1 Hyperintense T2 Heterogenous, well-circumscribed in most cases	1st line: surgical resection 2nd line: adjuvant radiotherapy for high grade tumors 2nd line: chemotherapy for unresectable tumors	Poor
Lipoma	Very rare	Hyperintense T1 Hypointense T2	1st line: gross total surgical resection	Stabilized with subtotal excision
Paraganglioma	Very rare	Isointense T1 Iso- or Hyperintense T2 with salt and pepper lesions Calcification may be present on CT Intense focal uptake of ^{123}I MIBG	1st line: gross total surgical resection	Excellent following GTR of benign lesions. Few reports of surgical outcomes in metastatic spinal paragangliomas
Epidermoid Cyst	Very Rare	Hypointense T1 Hyperintense T2 Variable appearance	1st line: gross total surgical resection	Surgery is curative in most cases
Dermoid cyst	Very rare	Hyperintense T1 Hypointense T2 Variable appearance	1st line: gross total surgical resection	Surgery is curative in most cases
Intramedullary spinal cord tumors (IMSCTs)				
Astrocytoma	2nd most common	Iso- or hypointense on T1 Hyperintense on T2 Can appear as heterogeneous enhancing or nonenhancing mass Cysts may be present	1st line: Gross total resection 2nd line: adjuvant radiotherapy indicated for high grade tumors 2nd line: chemotherapy indicated for recurrent tumors	Poor

Table 1 (continued)

Tumor	Relative frequency	Imaging characteristics	Treatment	Prognosis
Ependymoma	most common IMSCT	Iso- or hypointense on T1 Hyperintense on T2 Homogenous enhancement Tumoral and polar cyst, and cap sign usually present	1st line: gross total resection 2nd line: adjuvant radiotherapy indicated for high grade tumors or cases where complete resection is not possible	Prognosis correlated with extent of resection
Gangliоglioma	Exceedingly rare	Hypointense on T1 Hyperintense on T2 Heterogeneous enhancement Tumoral cyst usually present Calcification may be present on CT	1st line: gross total resection 2nd line: chemotherapy indicated for high grade tumors	Good
Hemangioblastoma	Rare	Isointense on T1 Hyperintense on T2 with flow voids seen in larger tumors Homogenous enhancement Well circumscribed Prominent feeding vessels with enlarged draining veins seen on angiography	1st line: gross total resection for symptomatic tumors	Excellent however recurrence possible in patients with von Hippel–Lindau disease

2 Extramedullary Tumors

The differential diagnosis for EMSCTs includes meningiomas, nerve sheath tumors, lipomas, paragangliomas, epidermoids, and dermoids.

2.1 Clinical Diagnosis of IMSCTs

Spinal meningiomas are one of the most common extramedullary tumors accounting for 25% of all spinal neoplasms [11]. Although they are found along the entire length of the spine, meningiomas most commonly occur posterolateral and 64–87% in thoracic spine [12]. Meningiomas are mostly benign tumors arising from arachnoid cells in the meninges and are connected to the inner layer of the dura mater [13]. Histologically, meningiomas show lobules lined by thin collagenous septa. Psammoma bodies can be seen in many cases where meningioma cells form a whorled pattern surrounding calcified tissue. Certain genetic syndromes such as neurofibromatosis type 2 (NF2), PTEN syndrome, and Gorlin syndrome have been associated as risk factors for developing meningiomas [14].

Nerve sheath tumors are the most common intradural extramedullary spinal cord tumor in adults and have an incidence of 0.26 cases per 100,000 in the United States [15]. The tumors consist mostly of schwannomas and neurofibromas.

Neurofibromas are benign nerve sheath tumors composed of proliferating Schwann cells [16]. However, they differ from schwannomas in that they also contain additional cell types such as mast cells, perineural cells, and fibroblasts. Neurofibromas show fusiform expansion of the parent nerve fascicle when under gross examination. Neurofibromas can be subdivided into three morphological forms: diffuse, solitary, plexiform [17]. Diffuse neurofibromas usually form a plaque-like appearance of the skin [18]. Plexiform neurofibromas form multinodular enlargements giving the lesions their characteristic "bag of worms" appearance. Solitary neurofibromas present as small polypoid masses. Spinal neurofibromas arise in 38% of patients with neurofibromatosis type 1 (NF1) [19]. Although these patients will present with a variety of symptoms due to the involvement of multiple organ systems in NF1, diagnosis can be made from the classic clinical triad of skeletal deformity, mental deficiency, and cutaneous lesions [20].

Schwannomas are benign, encapsulated peripheral nerve sheath tumors composed predominantly of neoplastic Schwann cells [16]. The classic form of the tumor has a histological appearance containing two basic patterns,

Antoni A and Antoni B. zones. Antoni A zones are characterized by areas of increased cellularity with nuclear palisading patterns called Verocay bodies. Antoni B zones are areas of hypocellularity featuring varied macrophage infiltration.

Schwannomas usually present as a solitary, slow growing, small mass that is mobile to palpation except at the point of nerve attachment [20]. Large tumors can present with radicular pain and neurological symptoms. Although schwannomas are usually sporadic, multiple schwannomas can be seen in neurofibromatosis type 2 (NF2) and in multiple schwannomatosis syndromes [17].

2.2 Diagnosis and Treatment of IMSCTs

Magnetic resonance imaging (MRI) is the imaging modality of choice for spinal meningiomas because the size, location, and axial position can be identified [21]. The lesion is usually either iso- or hypointense on T1 and mildly hyperintense on T2 weighted MRI. Accumulation of gadolinium contrast media in the region adjacent to the dura can present with a "dural tail" sign noted in 60–70% of spinal meningiomas [22]. The dural tail is a nonspecific finding signifying reactive fibrovascular tissue. CT myelography can be used in conjunction with MRI to identify the presence of calcification in the lesion or in cases where MRI is contraindicated. Spinal angiography is often utilized before surgical intervention of spinal meningiomas in the thoraco-lumbar spine to identify the artery of Adamkiewicz in relation to the lesion [21]. Spinal angiography is also used in certain cases preoperatively for the embolization of tumor-feeding vessels to reduce intraoperative bleeding and tumor volume.

MRI is the imaging modality of choice to diagnose nerve sheath tumors of the spine. However, neurofibromas and schwannomas are often indistinguishable by imaging [23]. Both tumors are well defined masses that are hypointense to isointense on T1-weighted MRI and hyperintense on T2. Since larger schwannomas will often occur with cystic degeneration, a heterogeneous signal intensity with ringlike enhancements on T2 MRI may be present [22]. The heterogeneity of schwannomas on T2 reflects the histological pattern of the tumor with regions of loosely arranged cells intertwined with zones of compact cells [23]. Schwannomas are also more likely to display a hypointense rim on MRI, known as the fascicular sign, which correlates with its fibrous capsule. Neurofibromas may show a characteristic target sign on T1 MRI caused by a ring of hyperintense myxoid tissue surrounding a hypointense core of fibrous tissue. CT may be indicated for tracking chronic changes such as scalloping of nearby bone and widening of the neural foramina [24].

The current standard of care for spinal meningiomas is surgical resection with the goal of total removal of the tumor and decompression of the spine [25]. The tumor will generally show a favorable response to surgical excision displaying a low postoperative recurrence rate (3–15%). Complete surgical resection is preferred since recurrence rates are associated with the extent of resection. The completeness of surgical resection can be evaluated using the Simpson Grading System with each subsequent grade demonstrating less invasive resection, increasing the chance for recurrence [26]. Simpson grade I resection, which is the total removal of the tumor and adjacent dura and bone, is usually the surgical goal when treating spinal meningiomas. However, the extent of resection must be balanced with an increased risk of operative morbidity. In fact, recent studies have challenged the use of the Simpson grade as a quantitative measure of prognosis in spinal meningiomas. Behling et al., reported no difference in progression-free survival (PFS) between Simpson grades I–III with the largest prognostic effect occurring at grade IV [27]. Although incomplete resection remains a prognostic factor, further studies are needed to determine the effect of radical resection of the dural attachment.

Adjuvant radiotherapy in addition to surgery has been reported in the management of recurrent and atypical/anaplastic tumors [28]. However, a common limitation in these studies is the lack of long-term follow-up that would show the overall survival rate (OS). Additional studies assessing the outcomes in the long-term treatment of atypical and anaplastic meningiomas are needed to assess the role of radiotherapy in the management of spinal meningiomas.

Despite limited evidence, there has been some interest in using systematic therapies to treat recurrent meningiomas not responsive to surgery or radiotherapy [29]. Graillon et al., found that everolimus–octreotide, sunitinib, and bevacizumab demonstrated probable activity that would justify their use in the treatment of high-grade meningioma [29].

The current treatment options for nerve sheath tumors depend on factors such as clinical symptoms, relation to genetic syndromes, and degree of malignancy. The treatment of choice for symptomatic nerve sheath tumors is surgical resection while patients with asymptomatic tumors are observed for signs of growth and symptom development [15]. Fernandes et al., showed that microsurgical gross total removal (GTR) of spinal nerve sheath tumors was both a safe and effective form of treatment with surgical morbidity and recurrence rates of only 3.3% [30]. In the treatment of schwannomas, the affected nerve is separated from the tumor after dissection of the epineurium, ultimately preserving its function [20]. Neurofibromas, however, cannot be separated from the nerve without difficulty, so complete resection of the tumor may lead to sacrifice of the nerve. Neurological deficits can be an inevitable outcome of microsurgical resection of nerve sheath tumors due to the intimacy of the tumor with functional neural elements [19]. Safaee et al., followed the outcomes of patients with spinal nerve sheath tumors

treated with surgery and found that the rate of worsening or new sensory symptoms was 15% and the rate of weakness was 3%.

Although microsurgical resection is the primary treatment for benign nerve sheath tumors, early data shows that stereotactic radiosurgery (SRS) may be indicated in patients with recurrent disease or for whom surgery may be contraindicated [31]. Shin et al., followed 65 cases of benign nerve sheath tumors with an average follow-up time of 44 months [32]. The local control rate was 95.4%. Other case series have documented comparable results with high local control rates, strengthening the evidence of SRS as a standard-of-care alternative to surgical resection [33, 34]. However, due to the slow growth rate of benign nerve sheath tumors, studies with longer follow-up are needed to determine the potential for late recurrence.

The treatment of nerve sheath tumors in relation to syndromic diseases such as NF1, NF2, and schwannomatosis is more complex, because the goal is to control symptoms and local disease [11, 26, 35]. The major nerve sheath tumor present in patients with NF1 is the plexiform neurofibroma (pNF) [36]. There have been over 20 clinical trials testing systemic therapies either targeting the Ras-regulated pathway or the tumor environment in treating pnFs in patients with NF1. Some of the drugs tested in the trials include Sorafenib, Tipifarnib, and Pirfenidone [36]. The nerve sheath tumor most common in NF2 is the schwannoma [35]. The systemic therapies developed for patients with NF2 have so far focused on vestibular schwannomas due to the morbidity the tumor causes in this set of patients [36]. Most of these trials have assessed RTK inhibitors such as everolimus, lapatinib, and sorafenib with mixed results. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), has been shown to be efficacious in decreasing tumor size [35, 36]. Patients with schwannomatosis have a predisposition for developing multiple schwannomas [36]. The current treatment for schwannomatosis is surgery with the goal of pain and symptom control caused by the tumor compressing surrounding tissue.

Nerve sheath tumors may rarely present as a malignant well-circumscribed, rapidly enlarging mass [23]. They are treated with GTR and adjuvant radiotherapy. Chemotherapy is indicated in recurrent lesions. The prognosis for malignant nerve sheath tumors is poor with 50% local recurrence and 33% metastasis to the bone and lung.

2.3 Additional EMSCTs

Other EMSCTs include lipomas, paraganglioma, epidermoids, and dermoids. These tumors are rare and comprise 5% of the EMSCTs [11]. Lipomas of the spine are one of the most common congenital spinal defects encountered in pediatric neurosurgery [37]. These lesions are diagnosed by MRI, appearing hyperintense on T1 and hypointense on T2. The treatment of spinal lipomas depends on the severity and location of the tumor. In 2019, Pang et al. demonstrated that PFS was higher with total resection of complex dysraphic lipomas than partial resection [38]. In addition, the investigators show that PFS is higher with prophylactic total resection of asymptomatic dorsal and transitional lipomas than conservative treatment (no surgery). However, GTR is not feasible in many cases because lipomas closely attach to the spinal parenchyma.

Spinal paragangliomas are benign, well-encapsulated, hypervascular neuroepithelial tumors usually located in the lumbar and sacral vertebrae [39]. Although most paragangliomas are nonfunctional, functional tumors secrete excess catecholamines. As the initial diagnostic choice, MRI displays well-demarcated isointense lesions on T1 and isointense or slightly hyperintense "salt and pepper" lesions on T2. Paraganglioma can also be visualized on CT as a homogenous mass with calcification. ^{123}I MIBG scintigraphy can be used to diagnose paragangliomas that are unidentifiable on MRI or CT. GTR along with preoperative embolization to limit blood loss is the treatment of choice for spinal paraganglioma [39–41].

Spinal dermoids and epidermoids are rare neoplasms accounting for less than 1% of pediatric spinal tumors and are frequently associated with an underlying dysraphic malformation [42]. Their diagnosis and optimal treatment are a point of controversy. In 2009, van Aalst et al. correlated the clinical, radiological, and intraoperative findings of dermoids and epidermoids to their histopathological characteristics [43]. The investigators reported no difference between clinical presentation and imaging on treatment outcome. The intraoperative diagnosis correlated with the histopathological findings in less than 50% of the cases. Although the tumors can have a variable appearance on MRI, typically epidermoids are hypointense on T1 and hyperintense on T2. Dermoids are generally hyperintense on T1 and hypointense on T2 although considerable overlap on imaging exists between the two tumors [44]. Although the primary treatment in dermoids and epidermoids is surgery, radical resection is cautioned due to the concern for neurological injury caused by the tumor capsule adherence to the spinal cord and nerve roots [42, 44]. In a recent study, Siller et al. reported a higher rate of GTR along with reduced postoperative neurological decline using intraoperative neurophysiological monitoring [45].

3 Intramedullary Tumors

The differential diagnosis for IMSCTs includes astrocytomas, ependymomas, hemangioblastomas, and gangliogliomas.

3.1 Clinical Diagnosis of IMSCTs

Spinal cord astrocytomas (SCA) are intramedullary neoplasms that make up 6–8% of spinal cord tumors [46, 47]. They comprise 30–40% of intramedullary tumors in adults and 80–90% of intramedullary tumors in children making them the most common pediatric spinal cord tumor [48, 49]. SCAs are primarily located in the thoracic spine in adults and cervical/cervicothoracic spine in children [48]. The tumors primarily affect younger patients since the average age of presentation is 29 ± 18 [47].

SCAs are glossy, gray, red tumors with poorly defined margins [50]. SCAs are usually located eccentric to the central canal [13, 51]. Histologically, astrocytomas show a biphasic architecture of loose cystic zones with myxoid material and compact fascicular zones with piloid processes [51]. Astrocytomas can be subdivided into pilocytic (WHO grade I), fibrillary (WHO grade II), anaplastic (WHO grade III), and glioblastoma multiforme (WHO grade IV) [48, 49, 52, 53]. Pilocytic astrocytomas are well circumscribed, and unlike other forms of astrocytomas, tend to displace rather than infiltrate the spinal cord [53]. They are described histologically as compact bipolar piloid cells associated with eosinophilic Rosenthal fibers [13]. Diffuse infiltrating astrocytomas can dedifferentiate from diffuse fibrillary astrocytomas to hypercellular anaplastic astrocytomas with increased mitosis to glioblastoma astrocytomas with palisading necrosis and microvascular proliferation [51]. Astrocytomas may be associated with NF-1 [50].

Spinal ependymomas are the most common primary intramedullary tumor representing approximately 45–60% of the lesions [54–56]. The patient population is usually 30–40 years old with men and women affected equally [57]. Although ependymomas can be found at any spinal level, they most commonly occur at the cervical spine and filum terminale [49, 56].

Ependymomas are encapsulated, vascular, yellow or reddish gray tumors that arise from ependymal cells that line the central canal [48–50]. Compared to astrocytomas, ependymomas are located more centromedullary, tending to blend with the spinal cord [50]. Ependymomas have a mean extension of three to four segmental levels, whereas astrocytomas average five to six segmental levels. The WHO classification divides ependymomas into five histological subtypes categorized into three grades [56–58]. Grade I ependymomas are benign in their appearance and compromise subependymoma and myxopapillary ependymomas [57]. Grade II ependymomas are described as a well-circumscribed mass composed of cells forming perivascular pseudorosettes [59]. The variants of grade II ependymomas include clear cell, papillary, and tanycytic ependymoma. The grade II lesions are known as "classic" ependymomas accounting for 55–75% of spinal ependymomas [57]. Grade III ependymomas, known as anaplastic ependymomas, are characterized by abundant mitosis, pleomorphic nuclei, pseudopalisading necrosis, and microvascular proliferation [58].

3.2 Diagnosis and Treatment of IMSCTs

MRI is the imaging modality of choice for SCAs [50, 52]. On MRI, astrocytomas are hypointense or isointense on T1-weighted imaging and hyperintense on T2 [52, 53]. Pilocytic and glioblastoma astrocytomas tend to appear as enhancing masses from the spinal cord parenchyma while diffuse and anaplastic astrocytomas appear as non-enhancing masses [51]. Cysts, a common finding in pilocytic astrocytomas, have peripheral contrast enhancement [51, 52].

The imaging modality of choice for spinal ependymomas is MRI [13]. From a diagnostic standpoint, MRI has enabled advances in tumor localization and characterization, decreasing the time from the onset of symptoms to diagnosis from 24–36 months to 14 months [53, 60] On MRI, spinal ependymomas appear hypointense or isointense on T1 and hyperintense on T2 [57]. Tumoral and polar cysts are common features seen on imaging [48]. Hemorrhage at the margins helps to differentiate ependymomas from astrocytomas on imaging [48, 59].

The relative rarity of SCA makes the accumulation of data for large patient series difficult. For this reason, there is currently no consensus management for SCAs [46, 61]. Usually, SCAs are treated by surgical resection and decompression [52]. However, it is difficult to achieve GTR because of the proximity of the tumor to axonal tracts in the spinal cord [61]. Histological grading of SCAs, which affects the infiltrative tendency of the tumor, is the most important prognostic factor in achieving GTR [61]. Pojskic et al. achieved GTR in four patients with low grade SCAs [47]. They reported favorable postoperative recovery with marked improvement in neurological functioning. Other studies show that aggressive resection in low grade SCAs lead to an increase in PFS [62–64]. However, GTR of high grade SCAs may not always be feasible with reports citing the possibility of GTR in grade IV tumors at 0% and grade III tumors at 12% [52]. Butenschoen et al. found that surgical resection did not correlate with OS in patients with infiltrating astrocytomas WHO II–IV [65]. The goal for surgery in patients with infiltrating SCA is to acquire histological tissue for biopsy or for tumor debulking in patients with preoperative deficits. These tumors tend to expand the cord and can make a nice plane once dura excised.

Postoperative radiotherapy has been shown to increase survival in patients with astrocytomas WHO II–IV [50]. Techniques such as stereotactic radiosurgery and image-guided radiotherapy can ensure delivery of a therapeutic dose while sparing healthy tissue [64]. Currently there is

no unanimous evidence for the optimal timing and dose for radiation [63]. However, some studies support a minimum dosage of 40 Gy.

The role of chemotherapy in the treatment of SCAs has been a source of controversy [52, 64]. There are small case series showing promising results of temozolomide as a potential treatment for low-grade SCAs [63].

Surgical resection is the treatment of choice for spinal ependymomas. The goal of surgery is GTR while preserving healthy tissue [57]. Kaner et al. conducted a retrospective study following the postoperative outcomes of patients with spinal ependymomas treated with GTR [66]. They found that the extent of resection was a major prognostic factor. Other studies also show a significant association between GTR and PFS [56, 67].

Adjuvant radiation is an effective treatment for anaplastic ependymomas and grade II ependymomas with subtotal resection (STR) [13]. Although the data is not clear over the use of adjuvant radiotherapy in GTR of spinal ependymomas, patients will sometimes receive postoperative radiation due to the tumor's propensity to infiltrate healthy brain tissue [68]. The role of radiotherapy in the treatment of grade I ependymoma has not been established. A retrospective study of spinal ependymoma patients, after multivariate analysis, found a positive correlation between postoperative radiotherapy with PFS and local control [69]. Dosage ranging from 5400 cGy in 30 fractions to 5940 cGy in 33 fractions has been tested in treatment protocols [58].

The use of chemotherapy in the treatment of spinal ependymomas remains unclear. One prospective study evaluated the effect of oral etoposide treatment on adults with low grade intramedullary ependymomas [57]. The clinical trial did not reach phase II, so the efficacy of etoposide compared to other treatments is currently unknown.

3.3 Additional IMSCTs

Other IMSCTs include hemangioblastomas and gangliogliomas. Hemangioblastomas are the third most common IMSCT representing 2–6% of intramedullary tumors [70]. Although the majority of cases are sporadic, 40% of hemangioblastomas can occur as a manifestation of von Hippel Lindau disease. Hemangioblastomas are benign, highly vascularized lesions primarily located on the cervical spine [70]. The lesions appear isointense on T1 and hyperintense on T2 with vascular flow voids in lesions greater than 15 mm. GTR is the primary treatment for hemangioblastomas along with preoperative embolization to prevent bleeding. The postsurgical recurrence rates for sporadic and von Hippel Lindau hemangioblastomas have been reported to 7.9% and 22% respectively [70].

Spinal gangliogliomas are a slow growing glial tumor that accounts for 1% of IMSCTs [48]. The lesions are rare with approximately only 70 cases reported in literature [71]. On MRI, gangliogliomas appear as a well circumscribed mass that is hypointense on T1 and hyperintense on T2 with tumoral cysts as a common finding. GTR is the primary treatment. Adjuvant radiotherapy is contraindicated because it may induce malignant transformation in recurrent gangliogliomas. Chemotherapy is indicated in anaplastic gangliogliomas.

4 Primary Bone Tumors

Primary bone tumors are rare accounting for less than 0.2% of newly diagnosed tumors [72]. Among all primary bone tumors, only 5% occur in the spine. Primary bone tumors of the spine are far less common than metastatic spinal lesions and only account for less than 5% of all spinal tumors [73]. The aggressiveness of primary bone tumors varies with age. 80% of primary bone tumors are malignant in adults in contrast to 40% malignancy in children [72].

There are two staging systems used to classify primary bone tumors: Enneking [74] and Weinstein–Boriani–Biagini (WBB) [75]. The Enneking system is one of the main staging systems used in classifying tumors of the musculoskeletal system. Enneking was used to classify tumors of the appendicular skeleton, but it has since been adapted to lesions of the spine. The Enneking system divides primary bone tumors of the spine into two groups: benign and malignant [74]. Radiographic attributes of the tumor margin further classify benign primary bone tumors into three distinct stages. Stage 1 is characterized by latent lesions with well-demarcated borders [76]. Stage 2, which is characterized by thinning borders, is indicative of active lesions contained by a thin capsule [73, 76]. Stage 3 lesions are aggressive, rapidly growing tumors with indistinct borders that may spread to neighboring regions.

Staging for malignant tumors considers multiple factors such as anatomic location, grade, and whether there is metastasis [74–76]. Malignant primary bone tumors are divided into three stages. Stage 3 consists of lesions with distant metastasis. Stage 1 and stage 2 are grouped by their grade and are further divided into categories, A and B, based on the local extent of the tumor.

Patients with primary bone tumors of the spine can have a varied clinical presentation with symptoms that may not be directly linked to the current disease [2]. The most common presenting symptom is chronic back pain with an insidious onset that worsens over time, and radicular pain is frequently present. Neurological symptoms are seen in more than 50% of patients with malignant primary bone tumors of the spine and are a poor prognostic indicator [73].

Plain radiographs are the first line imaging modality for the initial characterization of primary bone tumors of the

spine [2]. However, CT and/or MRI are often necessary. The tumors are then further characterized by their location on the spinal column, presence of calcification or ossification, and the age of the patient during diagnosis [77]. The main advantage of CT is for the detection of matrix mineralization [2]. MRI is useful for determining the involvement of bone marrow and the spinal cord along with the relationship between the tumor and neurovascular structures.

Benign, well demarcated primary tumors displaying no active growth typically require no treatment [73]. For instance, vertebral hemangiomas are usually asymptomatic and are found incidentally [78]. However, treatment for vertebral hemangiomas is recommended when neurological symptoms such as intractable pain are present from neural compression or vertebral fracture [78]. Although there is no consensus treatment for vertebral hemangiomas multiple studies show that a multidisciplinary approach involving preoperative embolization, intralesional resection, and percutaneous vertebroplasty under fluoroscopic guidance can maximize the extent of resection while minimizing the risk for recurrence [79, 80].

Benign primary bone with aggressive growth such as osteoblastoma, aneurysmal bone cyst (ABC) and giant cell tumor (GCT) are treated with intralesional resection [81]. However incomplete resection of benign stage 3 tumors carries an increased risk in local recurrence. Boriani et al. examined the differential treatment outcomes using the Enneking staging system patients with osteoblastoma of the mobile spine [82]. In patients with no prior treatment the intralesional group experienced a recurrence rate of 23% 13 months after surgery in comparison to no recurrences in the en bloc resection group. The investigators concluded that en bloc resection with wide margins is recommended as the primary treatment option for stage 3 osteoblastoma. Similarly, studies show that en bloc resection of spinal GCT results in increased disease-free survival and a lower recurrence rate when compared to intralesional resection [83]. Conversely, en bloc resection carries an increased risk for postoperative complications [83]. Surgical planning entails balancing the risk of local recurrence against preservation of neurological function.

In addition to surgical resection, benign primary tumors can also be treated with pharmacological intervention. Denosumab, a monoclonal antibody that inhibits receptor activator of nuclear kappa-B ligand (RANKL), is shown to be an effective form in treatment for GCT. In 2013, The FDA approved the use of denosumab for patients with unresectable GCT or in cases where surgery would result in an increased chance of postoperative complications [84]. In a recent clinical trial, Bukata et al. studied the safety profile and efficacy of denosumab in the treatment of spinal GTC [85]. The investigators found that 83% of the patients experienced clinical benefit as a result of denosumab therapy (pain reduction from baseline, increased neurological function, and improved mobility). 93% of patients with unresectable GCT experienced no progression or recurrence after treatment.

Recent literature has reported the use of MISS for the treatment of benign primary bone tumors of the spine, especially for osteoid osteomas [86]. Pipola et al. conducted a retrospective analysis comparing the long-term outcomes for patients with spinal osteoid osteoma treated with intralesional excision versus radiofrequency ablation [87]. Patients treated with radiofrequency ablation experienced a recurrence rate of 12.5% in comparison to 1.7% in the intralesional excision group. The authors recommended radiofrequency ablation as an adjuvant to surgery in treating spinal osteoid osteoma in cases where surgical excision would damage nearby neurological structures leading to the need for spinal stabilization and reconstruction.

Complete surgical resection is the preferred modality for treating malignant primary bone tumors of the spine. However, there is a 21% failure rate in achieving Enneking appropriate margins with en bloc resection [81]. Radiation is a form of adjuvant therapy used in addition with surgery to increase local control. The radiation protocol will vary depending on the radiosensitivity of the tumor. For instance, chordomas and chondrosarcomas are shown to be relatively radioresistant with the need for dosages higher than 60 Gy to achieve local control with conventional radiotherapy [88]. Proton therapy is a method to deliver high doses of radiation to chordomas and chondrosarcomas while sparing healthy surrounding tissue.

Various chemotherapeutic regimens are used in the treatment of malignant primary bone tumors of the spine. Although chemotherapy is the first-line treatment for Ewing sarcoma, there is no consensus for the initial treatment for spinal Ewing sarcoma. In a recent retrospective study, Zhang et al. analyzed the neurological function and survival outcomes of patients with spinal Ewing sarcoma treated with chemotherapy versus surgery as a first line of treatment [89]. The patients undergoing initial chemotherapy had higher rates for event-free survival (EFS) and OS in comparison to the surgical group. Initial chemotherapy also demonstrated comparable results with surgery in the preservation of neurological function.

5 Metastasis

The survival rate of cancer patients is increasing as treatments continue to improve [90]. However, as the life expectancy of these patients increases, the incidence of metastasis also increases. Metastasis to the bone is the 3rd most common site for metastasis following the liver and lung [91]. The spine is the most common site of metastasis to the

bone with more than 20,000 new cases in the United States reported each year [90, 91]. The highest incidence occurs around 40–65 years of age which coincides with the period of increased cancer risk [92]. Men have a slightly higher incidence of spinal metastasis than women. The most common site on the spine for metastasis is the thoracic spine (60–80%), followed by the lumbar spine (15–30%), and least commonly the cervical spine (less than 10%) [93]. Spinal metastasis is classified based on anatomical location with most cases occurring extradurally [92]. Intradural extramedullary metastasis is rare, but may occur from a cerebral metastasis. Intramedullary metastasis is also rare, but usually appears in the cervical spine.

The treatment of choice for patients with spinal metastasis is radiotherapy [94, 95]. Indications for radiotherapy include pain control and durable local control to prevent neurological complications [94]. Depending on the radiosensitivity of the tumor, radiotherapy can be administered through either conventional external beam radiation (cEBRT) or stereotactic radiosurgery (SRS). Radiosensitive tumors with any degree of epidural spinal cord compression (ESCC) are treated with cEBRT [95]. The total dosage of cEBRT can vary depending on the size and type of the primary tumor with typical dosages of 25–40 Gy divided into 8–20 fractions [96]. The standard of care for pain relief in noncomplicated spine metastasis is a single-fraction radiotherapy with a dose of 8 Gy [97–99]. Single-fraction regimens are cost effective and practical when radiation treatment facilities are limited [99]. However, the benefits of single-fraction radiation need to be weighed with an increased chance of retreatment compared to a multifraction regimen [94]. Rich et al. reported an increased frequency in retreatment in the single-fraction cohort with 20% receiving additional treatment at the same site versus 8% in the multifraction cohort [100].

Radioresistant tumors have been shown to respond poorly to cEBRT [95]. On the other hand, SRS demonstrates greater than a 90% response rate to radioresistant tumors with minimal ESCC. SRS delivers high doses of concentrated radiation to the tumor while sparing adjacent healthy tissue [94]. The effective dose of SRS is three times higher than cEBRT allowing for greater local control. Previous studies have reported a local control rate of approximately 80–90% [101, 102]. Other advantages SRS has over cEBRT include shorter treatment times, longer pain relief, and treatment of previously irradiated tumors [98]. There is currently no optimal treatment protocol for SRS dose fractionation [98, 103]. However, most studies report a dosage 10–24 Gy in 1–5 fractions achieving desirable local control and symptomatic relief [98].

Although radiation is the primary choice of treatment for spine metastasis, surgery can be indicated in patients with spinal instability, intractable pain caused by a radioresistant tumor, and neurological deficits from ESCC refractory to radiosurgery [96]. While not considered an oncological solution, surgery has been reported to provide prolonged ambulation and quality of life in comparison to radiotherapy [104–106]. The primary goal of surgery in the treatment of spinal metastasis is stabilization and reconstruction of the spine as well as nerve decompression [94–96]. The surgical technique will vary depending on characteristics of the lesion such as localization, extent, spinal instability, and ESCC [96]. Decompression has been traditionally performed with a posterior approach through a laminectomy. However, spinal metastasis usually occurs ventrally causing spinal instability. The development of costotransversectomy, transpedicular, and lateral extracavitary approaches has allowed for safer entry to the anterior column from a posterior incision [103]. The surgical outcome will depend on the functional status and favorable primary tumor histology with respect to radiation [95, 103].

With the advancement of surgical techniques, minimally invasive spine surgery (MISS) has become a viable treatment option over traditional open surgery [107]. Seperation surgeon has been widely successful in our hands. The benefits of MISS over surgical decompression include shortened operation time, ability to start postoperative radiation and chemotherapy earlier, reduced blood loss, and decreased surgical complications leading to lower morbidity in patients [95, 108, 109]. The techniques for MISS include percutaneous kyphoplasty, cryoablation, percutaneous vertebroplasty, transarterial embolization, and radiofrequency ablation [95].

One of the most debilitating factors in patients with metastatic spine disease is cancer-induced bone pain. Cancer-induced bone pain is a complex process involving multiple mechanisms including the various interactions between bone cells, tumor cells, inflammatory cells, and bone-innervating neurons [110]. For this reason, treatment involves both anticancer, which comprises radiation, surgery, and systemic treatments, and analgesic therapy. Common drugs used for pain management in spinal metastasis include bisphosphonates, denosumab, and corticosteroids. Bisphosphonates are a drug class that suppresses bone resorption through the inactivation of osteoclasts [95]. Zolendronate, the most commonly used bisphosphonate in treating spinal metastasis, has been shown to decrease bone pain, skeletal-related events, and malignancy-related hypercalcemia becoming an important component of treatment for bone loss associated with breast cancer and multiple myeloma [111]. Denosumab, is a monoclonal antibody that binds to RANKL, preventing the proliferation and maturation of osteoclasts [110]. Studies comparing denosumab versus zoledronate in the treatment multiple myeloma and solid tumors with spine metastasis show that denosumab is superior in delaying first and subsequent skeletal-related events while having a lower incidence of renal toxicity and acute phase reactions in comparison to zoledronate [112]. However, denosumab is associated with

an increased risk of osteonecrosis of the jaw. Further large-scale trials are warranted to compare denosumab as an alternative to zoledronate in the treatment of spinal metastasis.

Corticosteroids are indicated for pain management in spinal metastasis in the setting of symptomatic spinal cord compression [95]. Dexamethasone is the most used corticosteroid due to its long half-life and lack of mineralocorticoid activity leading to decreased fluid retention [110]. The optimal dosage of dexamethasone is a source of controversy. In the earlier studies in treating metastatic epidural spinal cord compression (MESCC), Sorensen et al. demonstrated that patients given a high dose of dexamethasone, which included 96 mg intravenously followed by 96 mg orally for 3 days and then a 10 day taper, had improved ambulation in comparison to the control group [113]. However, other studies show that high dose dexamethasone resulted in no significant difference in gait function compared to low dose dexamethasone [114–116]. Instead, high dose dexamethasone was associated with a higher rate of adverse effects such as GI bleeding with perforation, wound infections, pneumonia, and persistent hyperglycemia. On the basis of available evidence, current guidelines suggest an initial 10 mg bolus of dexamethasone followed by 16 mg orally divided into 4 doses which provides a balance between efficacy and side effects [117].

The goal of treatment for metastatic spinal tumors is pain control and maximizing quality of life. Physicians need to consider multiple patient-specific variables such as the extent of dissemination of the tumor, pain, neurological status, and prognosis before knowing if the patient is a good candidate for treatment [118]. The development of an optimal scoring system that serves as decision-making tools to predict treatment outcomes has been a point of ongoing research. The most widely used scoring system for evaluating prognosis preoperatively in patients with spinal metastasis is the revised Tokuhashi system [118, 119]. The scoring system evaluated six parameters: bone metastases outside the spine, metastases to the vertebrae, metastases to internal organs, location of the primary tumor, degree of palsy (Table 2). The total score, which scaled to 15 points, was shown to predict the survival rate with greater than 75% consistency.

There are other scoring systems/classification methods that depend on neurological symptoms. The Harrington classification divides patients with spinal metastasis into 5 distinct groups based on vertebral instability and neurological compromise (Table 3) [120]. The authors recommended chemotherapy or hormonal manipulation with the addition of irradiation in recurrent disease for patients in Class I–II. Radiotherapy is recommended as the primary treatment for patients in Class III. Surgical intervention is indicated in patients in Class IV–V. One limitation of the Harrington classification is its lack of objectivity [121]. The degree of neurological deficit is not accounted for. Symptoms such as radicular pain and paraplegia are classified together making it difficult to accurately predict functional or survival outcomes using this classification method. The Spinal Instability Neoplastic Score (SINS) provides a method to evaluate the degree of instability of the vertebrae in an objective manner [122]. The system evaluates the six parameters: mechanical pain, quality of the bone lesion, location, radiographic spinal alignment, degree of vertebral body collapse (Table 4). Mechanical pain has been shown to have a strong correlation with preoperative disability and postoperative patient-reported outcomes [123].

The newer generation of scoring systems has focused on providing a more comprehensive analysis of the patient's disease state [124]. As the therapeutic options for treating spinal metastasis continue to advance, future scoring systems should incorporate multidisciplinary approaches to adapt to the increasing diversity of treatments.

6 Discussion

6.1 Cancer Pathophysiology

Cancer is a genetic disease described by uncontrollable cell growth in local tissue and spread to other parts of the body through metastasis. Cancer can be provoked through a myriad of causes such as epigenetic modifications, inactivation of tumor suppressor genes, activation of oncogenes, and mutagenesis caused by external stimuli [125]. Oncogenes play a key role in the development of cancer. Gene addition, deletion, insertion, duplication, chromosomal translocation, or rearrangement have the potential to alter the function of proto-oncogenes converting them into oncogenes [126]. The oncogenes overexpress certain proteins which can potentially lead to a tumor. Tumor suppressors also play a key role in the development of cancer by inhibiting abnormal cell proliferation. Tumor suppressor genes produce certain proteins that have important functions that regulate the cell cycle, promote apoptosis, inhibit cellular growth and proliferation, and engage in DNA repair [126]. Inactivation of tumor suppressor genes eliminates negative feedback over cellular proliferation leading to abnormal cell growth and the formation of a tumor. Spinal cancer presents a complex set of diseases involving the interaction of multiple pathways, genes, and enzymes. Malignant and metastatic spinal tumors can become resistant to the current methods of treatment. Advances in understanding the biology of spinal tumors, has led to the adoption of novel therapeutics that show promise in treatment resistant spinal tumors. The current researched strategies include molecular targeting, immunotherapy, and stem cell therapy.

Table 2 Revised Tokuhashi scoring system [32]

Characteristics	Score
General condition (PS: performance status)	
Poor (PS 10%–40%)	0
Moderate (PS 50%–70%)	1
Good (PS 80%–100%)	2
No. of extraspinal bone metastasis foci	
≥ 3	0
1–2	1
0	2
No. of metastasis in the vertebrae	
≥ 3	0
2	1
1	2
Metastasis to the major internal organs	
Unremovable	0
Removable	1
No metastasis	2
Primary site of the cancer	
Lung, osteosarcoma, stomach, bladder, esophagus, pancreas	0
Liver, gallbladder, unidentified	1
Others	2
Kidney, uterus	3
Rectum	4
Thyroid, breast, carcinoid tumor, prostate	5
Palsy	
Complete (Frankel A, B)	0
Incomplete (Frankel C, D)	1
None (Frankel E)	2
Total	Prognosis (months)
0–8	< 6
9–11	6–12
12–15	≥ 12

Table 3 Harrington classification for spinal metastasis [33]

Class I	Neurological involvement not significant
Class II	Bone involvement without instability or collapse
Class III	Major neurological involvement without bone involvement
Class IV	Vertebral instability or collapse with pain without significant neurological compromise
Class V	Vertebral instability or collapse and significant neurological compromise

6.2 Ongoing Research and Novel Treatment

The genetic aberrations that distinguish cancerous cells from normal cells can be used as molecular targets to develop targeted cancer therapy [127]. Key enzymes involved in signal transduction that have been studied as potential molecular targets include receptor and cytoplasmic tyrosine kinases, farnesyl transferases, and mTor [128]. Other important molecular targets include growth factors, cell-cycle enzymes, and molecules that promote angiogenesis [127].

Targeting molecular pathways has found clinical application in the treatment of advanced spinal chordomas. The first successful medical monotherapy for treatment resistant chordoma was imatinib mesylate, a receptor tyrosinase inhibitor that targets platelet-derived growth

Table 4 Spine instability neoplastic score [35]

Prognostic factor	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semi-rigid (T3-T10)	1
Rigid (S2-S5)	0
Pain onset with movement/loading the spine and/or relief with recumbency	
Yes	3
No (occasional pain but not mechanical)	1
Pain-free lesion	0
Quality bone lesion	
Lytic	2
Mixed (lytic or blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation or translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
> 50% collapse	3
< 50% collapse	2
No collapse with > 50% body involvement	1
None of the above	0
Posterolateral involvement of the spinal elements (facet, pedicle or CV joint fracture or replacement with tumor	
Bilateral	3
Unilateral	1
None of the above	0
Total	Spine stability
0–6	Stable
7–12	Pending Instability
13–18	Instability

factor receptor-α (PDGFA), platelet-derived growth factor receptor-β (PDGFB), KIT, and BCR-ABL [129]. Imatinib was found to have antitumor effects in patients with chordoma potentially mediated by inactivation of PDGFRB. The preliminary findings were followed up in a phase II trial exploring the effect of imatinib in PDGFB-positive advanced chordoma [130]. Using the response evaluation criteria in solid tumors (RECIST) assessment, the authors reported a median PFS and OS of 9.2 and 34.9 months, respectively. Although imatinib was shown to display antitumor activity in advanced chordoma, adverse events were reported with 25% of patients experiencing edema. A newer, PDGFB inhibitor, nilotinib, given with radiation, is currently being investigated in a phase 1 trial for the treatment of advanced chordoma (ClinicalTrials.gov identifier: NCT01407198).

In addition to inhibiting PDGFR, there are other active clinical trials studying therapies that target pathways including programmed cell death-1 (PD-1), mammalian target of rapamycin (mTOR), EGFR, VEGFR, PDGF and brachyury [131]. In a recent systematic review containing 270 patients from 11 clinical trials, Akinduro et al., accessed the role of multimodal targeted therapy in treating recurrent chordomas [131]. The investigators reported a PFS range from 10.2 to 14 months in the multimodule therapy group in comparison to 2.5–9.2 months in the monotherapy group. Concurrent radiotherapy was shown to increase PFS to 58.2 months.

Immunotherapy is a form of cancer treatment that works by detecting and attacking tumor cells curbing the growth of cancer and preventing remission of cancer. This form of treatment has created extensive interest with drugs being approved to treat a variety of different cancers. In terms of the CNS, the success of immunotherapy serves as a catalyst to study its potential in treating gliomas. However, there are

obstacles that need to be overcome to develop immunotherapy drugs to treat CNS tumors. The CNS has been traditionally thought to be "immune-privileged" because of the selectivity of the blood brain barrier to immune cells and its lack of lymphatic vessels [132, 133]. For gliomas in particular, a variety of studies have investigated its immunosuppressive properties. Macrophages associated with gliomas secrete transforming growth factor β (TGF-β) and interleukin (IL)-10 which downregulate the immune response (Fig. 1) [133]. Gliomas can also secrete immunosuppressive agents such as indoleamine 2,3-dioxygenase (IDO) and programmed cell 1 ligand (PD-L1) which decrease antigen presentation. Furthermore, gliomas secrete cytokines that increase regulatory T cells (T_{reg}) which downregulate cytotoxic T cells [132, 133]. Despite these obstacles, immunotherapy in the treatment of gliomas is being looked at in both preclinical and clinical studies. The current major strategies in immunotherapy treatment for glioma are checkpoint inhibitors, cancer vaccines, and chimeric antigen receptor T cells (CAR-T cells).

Immune checkpoints are inhibitory molecules that dampen the T-cell mediated immune response to allow for self-tolerance and prevent autoimmune reactions [61]. Tumors such as gliomas can weaken immune checkpoints to decrease the T-cell mediated response. The major immune checkpoint molecules associated with gliomas include PD-1, CTLA-4, TIM-3, and LAG-3 [134]. Preclinical murine studies of both single and combined checkpoint blockade show an increase in long term tumor-free survival for glioblastoma [135, 136]. However, the results

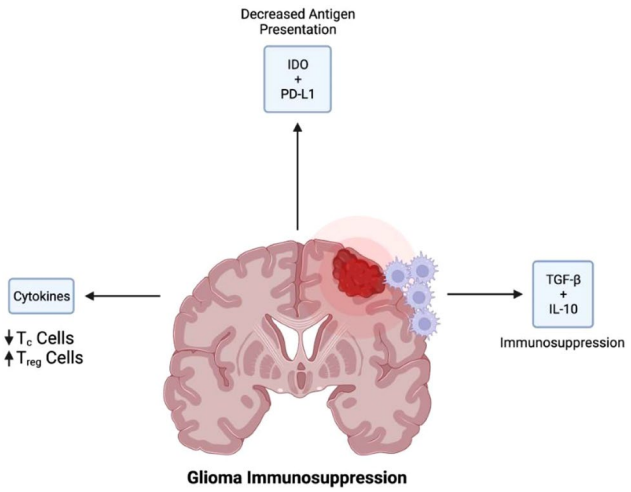

Fig. 1 The immunosuppressive properties of gliomas. Gliomas can suppress the immune response through a variety of mechanisms. The tumors indirectly increase the expression of IL-10 and TGF- β, secrete IDO and PD-L1 decreasing antigen presentation, and activate T_{reg} cells which suppress cytotoxic T cells. Created with BioRender.com

for clinical studies have been unsatisfactory. In a phase III clinical trial, 369 patients with recurrent glioblastoma were treated with either Nivolumab, an anti PD-1 monoclonal antibody, or bevacizumab, an anti-VEGF antibody [137]. The OS for patients treated with nivolumab was 9.8 months in contrast to 10 months for those treated with bevacizumab. The main challenges that need to be overcome to translate the preclinical outcomes to clinical trials include the need for computational characterization of the ability of each glioma subtype to respond to a particular checkpoint blockade and the identification of the optimal sequence and combination for combined blockade [138].

Another emerging immunotherapy approach is CAR-T cell therapy. CAR-T cells are allogenic or autologous T cells that are modified in vitro to express CAR molecules on their membrane [139]. They are then readministered to the patient's body to lyse the tumor cells that carry the target antigen. CAR-T therapy has shown promising preliminary results in the treatment of glioblastomas when specific antigens are targeted such as IL-13 receptor α2 (IL13Rα2) [140], epidermal growth factor receptor variant III (EGFRvIII) [141], and human epidermal growth factor receptor 2 (HER2) [142] (Fig. 2). In 2017, the FDA approved two CAR-T treatments that targeted the antigen CD19 in diffuse large B-cell lymphoma and acute lymphoblastic leukemia [133]. Since then, there have been over 20 clinical trials examining CAR-T therapy in treating glioma targeting mostly EGFR, HER2, and IL13Rα2 as well as novel targets such as MUC1, EphA2, CD147, and GD2 [133].

Also growing in interest is the use of cancer vaccines to treat gliomas. Cancer vaccines are made of antigens that are expressed almost exclusively from a certain type of cancer cell [61]. The antigens activate the immune response for selective elimination of that particular tumor. Currently there are five categories of antitumor vaccine therapies with the two broadest strategies being peptide and dendritic cell vaccines [133, 143]. Peptide vaccines used for glioma therapy are 8–30 amino acids in length and are derived from tumor-associated antigens such as IL13Rα2 or tumor-specific vaccines such as isocitrate dehydrogenase (IDH)-1(R321H) and EGFRvIII [132, 133]. Since the EGFRvIII has a mutated deletion in approximately 20–30% of tumors, it is the most intensely investigated TSA for gliomas [132]. The peptide vaccine rindopepimut shows the greatest promise in targeting EGFRvIII in glioblastoma patients (Fig. 3) [144]. Rindopepimut has been reported to increase PFS and OS in Phase I and II clinical trials [144]. However, in a large Phase III trial, Weller et al., reported that rindopepimut in combination with temozolomide failed to show a survival benefit in EGFRvIII-positive glioblastoma patients [145]. The median OS in the treatment group was 20.1 months in comparison to 20 months in the control group [145]. Additional Phase

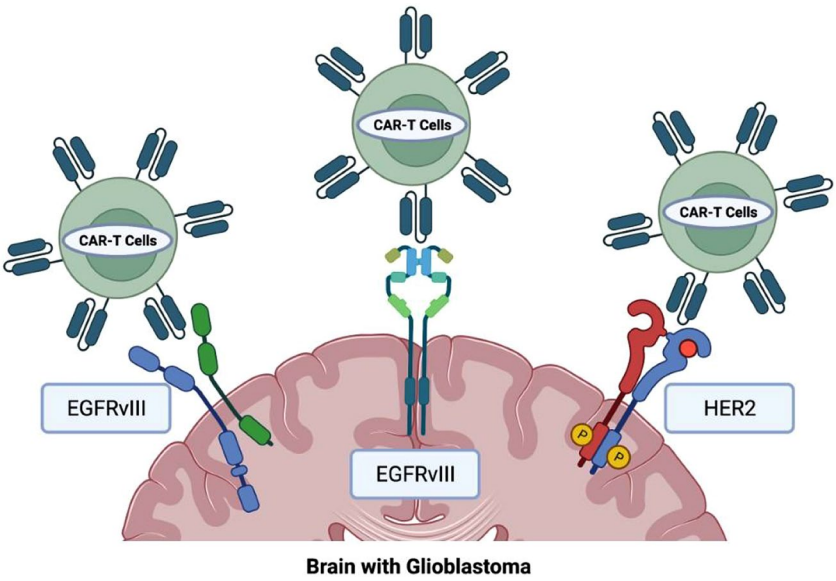

Fig. 2 CAR-T cell therapy in the treatment of glioblastoma. CAR-T cells are autologous immune cells that bind to tumor specific antigens and lyse the tumor cells. Created with BioRender.com

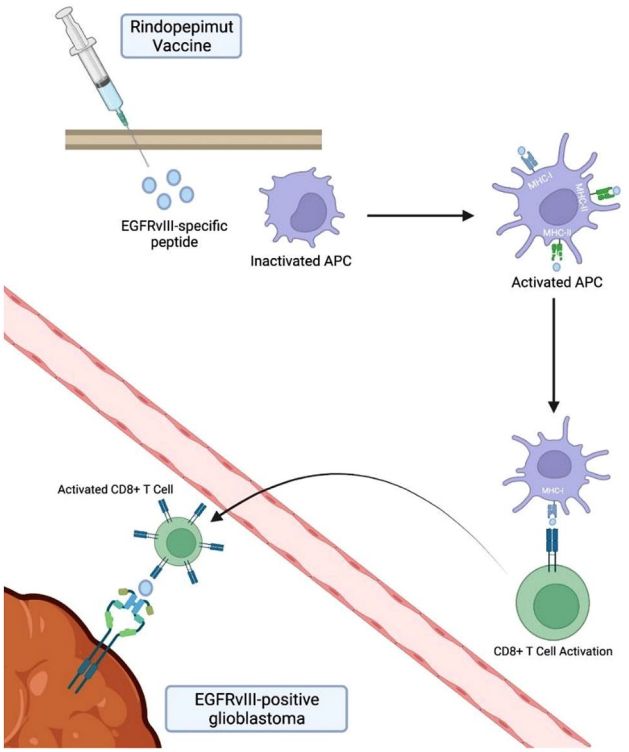

Fig. 3 Treatment of glioblastoma with the Rindopepimut vaccine. Rindopepimut is a peptide vaccine that binds EGFRvIII on glioblastoma cells. The binding of rindopepimut activates the immune response for selective elimination of the tumor. Created with BioRender.com

III trials are needed to determine the role of Rindopepimut in the treatment of glioblastomas.

In contrast to peptide vaccines, autologous dendritic vaccines are cultured ex-vivo using CD14 monocytes stimulated by IL-4 and granulocyte–macrophage colony-stimulating factor (GM-CSF) [117]. The dendritic vaccines are then activated with tumor specific antigens before being transplanted back into the patient. There are multiple small phase I and II trials that demonstrate both the safety and efficacy of DC vaccination for the treatment of high-grade gliomas [146–148]. Currently the most advanced DC vaccination evaluated clinically is the ICT-107 vaccine [145]. The ICT-107 vaccine is generated from priming autologous DC cells with peptides containing HER2, interferon-inducible protein AIM2, glycoprotein 100 (gp100), IL13Rα2, melanoma-associated antigen 1 (MAGEA1), and tyrosinase related protein-2 (trp2) which are proteins believed to be correlated with glioma stem cell signature [145]. In a phase I trial, Phuphanich et al., studied the therapeutic response and safety of ICT-107 in patients with newly diagnosed glioblastoma (ND-GBM) [149]. The investigators reported that on survival analysis PFS and median OS were 16.9 and 38.4 months respectively which shows that the treatment may correlate with a clinically relevant response. In a later randomized double-blind controlled phase II trial investigators evaluated the safety, efficacy, and quality of life for patients with ND-GBM treated with ICT-107 [150]. Although the vaccine was well tolerated, the median OS in the intention to treat group was not statistically significant compared to the control. However, there was a statistically significant improvement of PFS while quality of life was maintained. The study was limited by its small sample size. There is an ongoing randomized-controlled phase III trial for ICT-107 therapy following radiation and temozolomide administration in ND-GBM HLA-A2 + patients (ClinicalTrials.gov identifier: NCT02546102).

Another promising approach in the treatment of gliomas is stem cell-based therapy. There is an increasing amount

of research over the tropism property of neural progenitors towards tumors in the CNS [151]. Currently many different strategies are being studied preclinically with a few advancing to clinical trials for the treatment of malignant gliomas. The strategies include the secretion of anticancer agents, conversion of prodrugs, and delivery of oncolytic virus.

Stem cells can function as vehicles to produce and secrete anticancer agents. One of the most widely studied secreted anticancer therapeutics is Tumor-necrosis factor related apoptosis inducing ligand (TRAIL) [152]. TRAIL functions by binding to the cell death receptors TRAIL-R1 (DR4) and TRAIL-R2 (DR5) leading to the downstream activation of p53-mediated apoptosis. Prior preclinical studies show that soluble TRAIL (s-TRAIL) can be used in conjugation with temozolomide to induce cell death by upregulating proapoptotic proteins in glioma cells [153]. Combining s-TRAIL with the proteasome inhibitor bortezomib has shown to increase its sensitivity to glioma xenografts in mice [154]. Although the preclinical studies for TRAIL in the treatment of malignant glioma have been promising, the results have been unremarkable in clinical trials. Current strategies seek to overcome glioma resistance to TRAIL by modulating the levels of c-FLIP, caspase eight, DR4, DR5, and death-inducing signaling complex (DISC) [155].

An alternative strategy to cell-based therapy for treating malignant gliomas is the delivery of prodrugs to the tumor time. The initial studies in enzyme/prodrug therapy demonstrate that neural stem cells (NSCs) can be made to express cytosine deaminase, an enzyme that converts the prodrug 5-FC to the chemotherapeutic drug 5-fluorouracil [156]. NSCs were shown to effectively deliver the toxic form of the prodrug in glioblastoma rodent models and reduce the volume of the tumor through the bystander effect. Further studies explore a dual-gene approach to stem cell delivery. NSCs were engineered to express cytosine deaminase and thymidine kinase, an enzyme that converts the prodrug ganciclovir to the oncolytic agent ganciclovir triphosphate [157]. The dual gene approach appeared to display a synergistic antitumor response with increased overall survival in cervical rat glioblastoma models in comparison to treatment with only cytosine deaminase. There is an ongoing phase I trial exploring the efficacy of the dual drug approach for high grade glioma by having NSC express carboxylesterase with the addition of intravenous irinotecan hydrochloride (ClinicalTrials.gov identifier: NCT02192359).

Stem cell-mediated oncolytic viral therapy is another strategy for treating malignant gliomas. Oncolytic viruses show the ability to selectively replicate in tumor cells [158]. The viral progeny lyses the cells then goes on to infect surrounding tumor cells continuing the cycle with the potential to eradicate the tumor. Various viral strains have been studied in both preclinical and clinical trials showing the ability of NSCs to effectively deliver the virus to the tumor site while evading the immune system [159–161]. Future approaches in clinical trials include determining route and timing of administration for the delivery of the oncolytic viruses [158].

7 Conclusion

Although spinal tumors are rare relative to lesions of the CNS, they represent a complex pathology that is difficult to treat. Resection is the primary treatment for most spinal tumors. Radiation and chemotherapy can be indicated in recurrent or malignant tumors. With the advent of the molecular biology of spinal cancer, ongoing research is being developed for targeted therapy for these tumors. The preclinical and early clinical results show promise for future advances in survival outcomes and quality of life for patients with this disease.

Acknowledgements BioRender.com for figures.

Authors' Contribution E.A.—Primary manuscript preparation (lead author), manuscript editing. E.P. Primary manuscript preparation (supporting author), manuscript editing, figure preparation. B.L.-W.—Supervision and idea curation, primary manuscript preparation (supporting author), manuscript editing.

Funding No funding was used in the creation of this manuscript.

Declarations

Conflict of interest The authors have no conflicts of interest regarding the published work.

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