Review Article

Molecular foundations of primary spinal tumors—implications for surgical management

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Abstract: Primary spinal tumors are rare lesions that require careful clinical management due to their intimate relationship with critical neurovascular structures and the significant associated risk of morbidity. While the advent of molecular and genomic profiling is beginning to impact the management of the cranial counterparts, translation for spinal tumors has lagged behind. Maximal safe surgical resection remains the mainstay of patients with primary spinal tumors, with extent of resection and histology the only consistently identified independent predictors of survival. Adjuvant therapy has had limited impact. To develop targeted neoadjuvant and adjuvant therapies, improve prognostication, and enhance patient selection in spinal oncology, a thorough understanding of the current molecular and genomic landscape of spinal tumors is required. In this review, we detail the epidemiology, current standard-of-care, and molecular features of the most commonly encountered intramedullary spinal cord tumors (IMSCT), intradural extramedullary (IDEM) tumors, and primary spinal column malignancies (PSCM). We further discuss current efforts and future opportunities for integrating molecular advances in spinal oncology with clinical management.

Keywords: Intramedullary spinal cord tumor (IMSCT); meningioma; schwannoma; chordoma; genomics

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Introduction

Surgical management of primary spinal tumors can be guided by both anatomic location and histology. Anatomically, lesions within the thecal sac are either (I) within the parenchyma of the spinal cord [intramedullary spinal cord tumors (IMSCT)], or (II) not within the parenchyma but still within the thecal sac [intradural, extramedullary (IDEM) tumors]. Tumors external to the thecal sac are simply termed extradural tumors. Of the extradural tumors, primary lesions arising from the bony structures of the spine, such as the vertebral bodies, are termed primary spinal column malignancies (PSCM). Histologically, many primary spinal tumors have cranial counterparts, and management of these tumors often draws on the principles applied to primary brain tumors (1). With the advent of genetic and genomic profiling, key molecular differences between cranial and spinal tumors of shared histology have emerged. Furthermore, targeted therapies may complement the current standard-of-care by providing patient-specific neoadjuvant and adjuvant therapies.

In this review, we will detail the current landscape of molecular alterations in primary spinal tumors, focusing on the most commonly encountered IMSCTs (astrocytoma, ependymoma, and hemangioblastoma), IDEM tumors (meningioma and schwannoma), and PSCMs (chordoma). We will also discuss current efforts at genotype-directed therapy for patients with these lesions and the implications

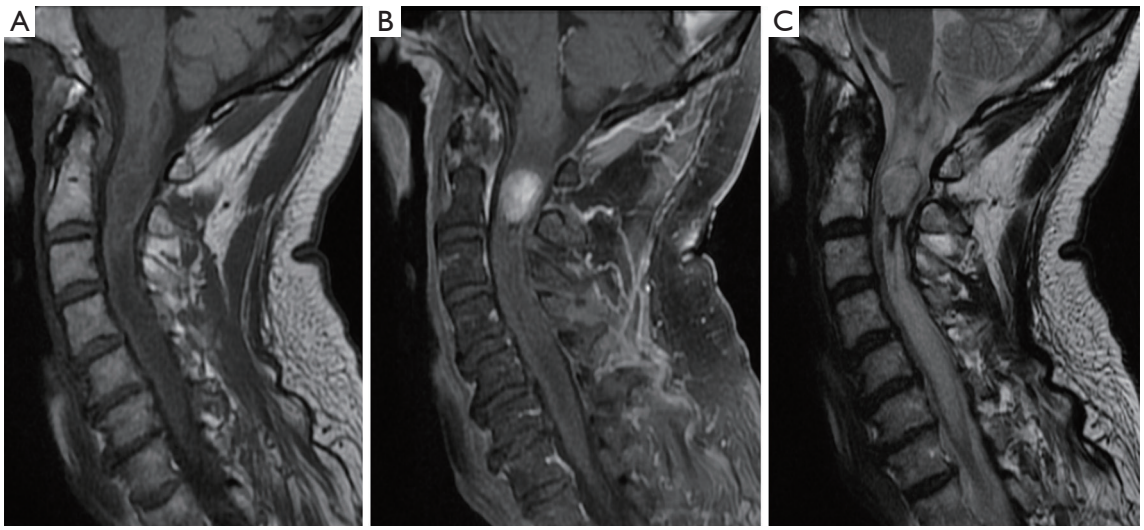

Figure 1 Spinal cord ependymoma. Preoperative sagittal T1-weighted, fat-saturated pre-gadolinium (A) and post-gadolinium (B) MRI demonstrates a discrete, enhancing C2 intramedullary mass. Sagittal T2-weighted MRI (C) reveals characteristic T2 hyperintensity. Associated hemorrhage may lead to a hypointense hemosiderin rim on T2 images.

of these results for surgical decision-making.

IMSCT

In adults, IMSCTs comprise 5–10% of all spinal tumors and are the most common spinal tumor in children (2). The most commonly encountered IMSCTs are ependymomas, astrocytomas, and hemangioblastomas. Collectively, spinal ependymomas and astrocytomas account for 80–90% of IMSCTs, with ependymomas occurring roughly twice as frequently as astrocytomas (3).

Ependymoma

Ependymomas are the most common IMSCT in adults, occurring equally often in men and women (*Figure 1*) (4). Spinal ependymomas are associated with neurofibromatosis type 2 (NF2) (5). These neuroepithelial lesions occur most commonly in the cervical or cervicothoracic spine. The myxopapillary variant occurs almost exclusively in the conus medullaris or filum terminale and tends to present earlier in life (*Figure 2*). Spinal ependymomas are histopathologically classified by the World Health Organization (WHO) as grade I (subependymoma or myxopapillary), grade II (classic), or grade III (anaplastic). Recently, a molecularly defined entity, RELA fusion-positive ependymoma, has been introduced into the WHO classification of ependymoma. To date, RELA fusion-positive ependymoma have only been reported as lesions occurring supratentorially in children and young adults (6).

Standard of care

Management of spinal ependymoma is influenced by extent of spinal cord compression and symptomatic presentation. Asymptomatic patients with low concern for cord compromise may be managed with serial surveillance imaging. For patients with symptomatic ependymoma, surgical resection with the goal of achieving gross total resection (GTR) is standard-of-care. Single-institution series, population-level studies, and meta-analyses have demonstrated a survival benefit for surgical resection, particularly if GTR is achieved (7-11). GTR is achievable in the majority of cases, as a surgical plane can often be identified between the tumor and cord parenchyma (11). For myxopapillary ependymoma, *en bloc* resection should be attempted, as capsular violation during resection is strongly associated with local recurrence (12).

Adjuvant radiotherapy for spinal ependymoma continues to be debated and is generally reserved for high grade, difficult-to-access, and partially resected tumors (13,14). Oh *et al.* conducted a literature review (adjuvant radiotherapy, n=47) and found that adjuvant radiotherapy prolonged progression-free survival (PFS) among spinal ependymoma patients undergoing subtotal resection (STR), while Lee *et al.*, used data from the Korea Spinal Oncology Research Group database (adjuvant radiotherapy, n=20), did not

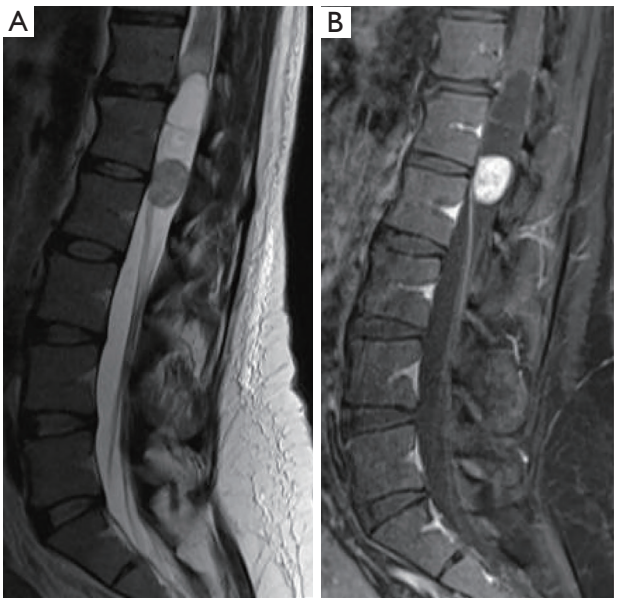

Figure 2 Spinal myxopapillary ependymoma. Preoperative sagittal T2-weighted (A) and T1-weighted, fat-saturated, post-gadolinium (B) MRI reveals 5.9 cm mixed cystic and solid intradural lesion with enhancing mural nodule arising from the conus medullaris at the T12-L2 levels. Associated pathologic T2 hyperintensity within the conus medullaris is observed superior to the lesion.

observe this benefit (15,16). Studies of conventional chemotherapy for spinal ependymoma are rare. A small study on recurrent spinal ependymoma (n=10) found oral etoposide is well tolerated and may benefit some patients (17), but these results have not been further validated.

Molecular characterization

Classically, spinal ependymomas are thought to arise from ependymal cells in the central canal. However, there is increasing evidence that genes regulating radial glial cell differentiation play a role in molecular pathogenesis. Compared to supratentorial and posterior fossa ependymomas, spinal ependymomas overexpressed homeobox (*HOX*) family genes and insulin like growth factor 1 (*IGF1*). Distinct malignant transformations in regional radial glial cells also can give rise to anatomically and molecularly distinct ependymomas (18). These findings underscore the notion that cranial and spinal ependymomas should be considered separately, for both clinical management and biological investigation.

Pajtler *et al.* extended these findings by performing DNA methylation profiling on 500 ependymal tumors (19). The authors discovered nine discrete subgroups, including three subgroups of spinal ependymoma: subependymoma (SP-SE, WHO grade I), myxopapillary ependymoma (SP-MPE, WHO grade I), and (anaplastic) ependymoma (SP-EPN, WHO grade II/III). SP-SE harbored 6q deletions, while SP-MPE and SP-EPN demonstrated chromosomal instability. Moreover, most SP-EPN tumors had loss of the 22q locus, which harbors the neurofibromin (*NF2*) gene. In another study, whole exome sequencing of eight spinal cord ependymomas revealed loss of heterozygosity (LOH) of chromosome 22 in all eight tumors and somatic alterations in *NF2* in 4/8 tumors (20). *NF2* was then sequenced in an independent validation cohort of 32 intracranial ependymoma and 11 spinal ependymoma; alterations in *NF2* were found in 9 of 19 spinal ependymomas (47%) and in 0 of 40 intracranial ependymomas (20). A recent study by Witt *et al.* sought to validate the ependymoma DNA methylation-based subtypes and correlate molecular subtypes with histologic subtypes (21). While all tumors were assigned to a previously defined molecular subtype, there was marked reassignment of spinal ependymomas, suggesting that molecular subtyping may enable more accurate risk assessment and precise clinical trial design (21).

Microarray studies, measuring mRNA expression, have also identified molecular differences between intracranial and extracranial ependymoma (22-24). Korshunov *et al.* profiled 39 central nervous system ependymomas (spinal, n=10) and reported increased expression of homeobox B5 (*HOXB5*), phospholipase A2 group 5 (*PLA2G5*), inter-αtrypsin inhibitor heavy chain 2 (*ITIH2*), and cyclin-dependent kinase inhibitor 2A (CDKN2A) in spinal ependymoma (24) (*Table 1*).

Genotype-directed therapy and targeted agents

Achieving GTR in spinal ependymoma offers a durable treatment option with excellent survival outcomes. However, for patients in whom GTR is not technically feasible or for patients with higher grade tumors, other therapeutic options are necessary. Taken together, the rarity of spinal ependymomas and the dearth of recurrently aberrant targets have limited efforts to develop targeted therapies. One case report describes treatment with imatinib, a PDGF-receptor-targeted agent in a patient with recurrent spinal ependymoma expressing PDGF (25). Additionally, molecularly-guided therapies include mammalian target of rapamycin (mTOR) inhibitors and bevacizumab. Merlin, the protein encoded by *NF2*,

Table 1 Mutations associated with intramedullary spinal cord tumors (IMSCTs)

Tumor	Gene	Locus	Grade	Molecular finding
Ependymoma	*HOXB5*	17q21.3	I–II	Increased expression in spinal versus intracranial ependymoma
	PLA2G5	1p35	I–II	
	ITIH2	10p15	I–II	
	CDKN2A	–	I–II	
	NF2	22q12	II–III	Characteristic of spinal ependymoma; absent intracranial ependymoma
	–	6q	I	Associated with spinal subependymoma
Astrocytoma	*BRAF*	7q34	I–II	BRAF-KIAA1549 fusion and other somatic mutations identified in low-grade spinal astrocytoma
	CDKN2A	9q21	I	Deletions in 2/10 spinal pilocytic astrocytoma
	H3F3A	17q25	III–IV	Mutation that discriminates grade III–IV spinal astrocytoma from grade I–II tumors
Hemangioblastomas	*VHL*	3p25.3	–	Recent WES studies find VHL mutations in sporadic, as well as familial, spinal hemangioblastomas

WES, whole exome sequencing; VHL, von Hippel-Landau.

has been shown to interact with rapamycin, thus forming the basis of mTOR inhibitors in the management of *NF2*-mutated ependymoma. A phase II trial evaluating the efficacy of everolimus, an mTOR inhibitor, in children with recurrent ependymoma (NCT02155920) was scheduled to end in July 2018 though no formal results have been published. Morris *et al.* recently described a retrospective review of 32 NF2 patients treated with bevacizumab who had spinal ependymomas. They observed clinical improvement in seven patients, all of whom had cystic spinal ependymomas. However, no assessment of survival benefit was reported (26). A recent multi-center retrospective review attempted to compare surgical management of NF2-associated spinal ependymomas with bevacizumab (27). Despite confounding variables inherent to the study design, the authors concluded that while resection may prevent neurological deterioration, bevacizumab may be beneficial for patients with significant tumor burden that is not amenable to resection (27).

Astrocytoma

Astrocytomas are the second most commonly observed IMSCT in adults but represent the most common pediatric IMSCT (*Figure 3*) (28,29). The incidence of spinal astrocytomas is slightly higher among males. Spinal astrocytomas are rarely observed caudal to the thoracic spine and appear on magnetic resonance imaging (MRI) as heterogeneously enhancing lesions within the parenchyma of the spinal cord.

Standard of care

Maximal, safe surgical resection is standard-of-care for patients with symptomatic spinal astrocytomas. In contrast to ependymomas, astrocytomas tend to be diffuse and infiltrative, lacking a good plane of dissection. Thus, achieving GTR must be balanced against iatrogenic neurological damage. Current evidence suggests that higher grade spinal astrocytomas are more infiltrative, further limiting the ability to achieve GTR (30). While the benefit of extent of resection is well-established in intracranial astrocytoma, the survival benefit of more aggressive resection in spinal astrocytoma is less evident (31-35). A recent multi-institutional study suggested that GTR is associated with longer PFS and overall survival (OS) (36). The authors observed higher post-operative McCormick scores, suggesting potential iatrogenic harm; however, a subgroup analysis of the change in McCormick score by extent of resection revealed no significant difference among groups (36).

Adjuvant radiotherapy for spinal astrocytomas remains controversial and is generally reserved for patients in whom GTR cannot be achieved. Single-series studies have generally concluded non-significance for adjuvant

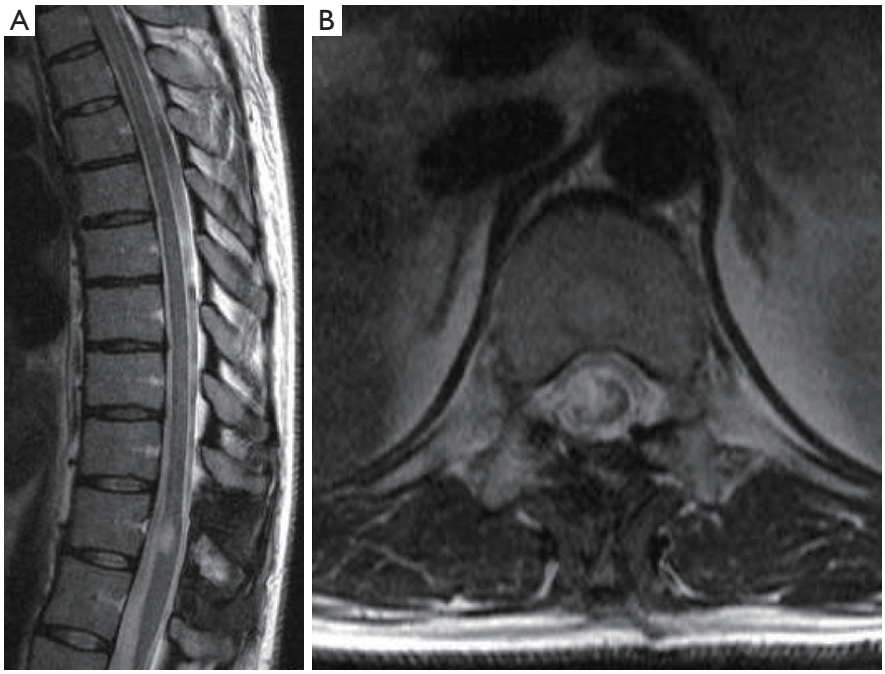

Figure 3 Spinal cord astrocytoma. Preoperative sagittal (A) MRI demonstrates T2 hyperintensity within the cord at T11, measuring 1.3 cm × 0.6 cm in craniocaudal and AP dimensions. Axial (B) image reveals the lesion expanding the cord, measuring 9 mm in transverse dimension.

radiotherapy, whereas a multi-institutional study by Zou *et al.* found that radiotherapy may improve survival outcomes when adjusting for tumor grade (36). In contrast to intracranial astrocytoma, the benefit of temozolomide for spinal astrocytoma has been limited for both low-grade spinal astrocytoma and spinal glioblastoma (37-40). Bevacizumab has also been trialed in small series of patients with recurrent spinal glioblastoma with mixed results (38,41).

Molecular characterization

Large-scale sequencing studies of supratentorial gliomas have revealed distinct genomic alterations capable of discriminating pilocytic astrocytomas, WHO grade II and III diffuse gliomas, and WHO grade IV glioblastoma, with important differences observed between adult and pediatric tumors (42-47). While these discoveries have been used to enhance WHO classification of astrocytoma (48,49), the implications for spinal astrocytoma remain unclear.

Genomic studies of spinal astrocytoma are limited due to the rarity of these lesions. Mutations in the isocitrate dehydrogenase 1 (*IDH1*) gene are observed in 12% of intracranial glioblastoma and 50–80% of lower grade intracranial astrocytomas (47,50,51). However, in a series of spinal cord astrocytomas (n=9), the *IDH1* R132H mutation was not observed (52). Shankar *et al.* performed targeted sequencing of adult and pediatric spinal cord astrocytomas (n=17) and observed *IDH1* or *IDH2* alterations in four patients. However, none represented recurrent *IDH1* or *IDH2* mutations previously described in adult glioma (53). It remains unknown if *IDH* mutations in spinal astrocytoma confer survival benefits.

Alterations in the proto-oncogene *BRAF* do appear to have correlates between intracranial and spinal astrocytoma. The majority (50–70%) of intracranial pilocytic astrocytoma harbor *BRAF-KIAA1549* fusion genes (54-57). Shankar *et al.* report this fusion in 3/10 grade I spinal astrocytomas and also detected amplifications in *BRAF* in 5/10 specimens (53). Another recurrent alteration in intracranial astrocytoma is the *BRAF V600E* missense mutation, which occurs in 10–20% of pediatric pilocytic astrocytomas and is associated with poor outcome (58,59). The importance of this mutation in spinal astrocytoma remains unclear, with Shankar *et al.* reporting 0/17 spinal astrocytomas harboring this alteration (53). Deletion of *CDKN2A* may be another recurrent alteration in spinal pilocytic astrocytoma.

Horbinski *et al.* (59) reported LOH at the 9p21 locus (which includes *CDKN2A)* in nearly one-third of pilocytic astrocytomas of the midbrain, brainstem, and spinal cord (spinal cord, n=9). Shankar *et al.* observed deletions of *CDKN2A* in 2/10 pilocytic astrocytomas (53).

In higher grade spinal astrocytomas (grade III and IV), histone 3 variant H3.3 (H3F3A) K27M mutations have been reported. Shankar *et al.* report the presence of *H3F3A* K27M in 6/7 grade III and IV and absence in grade I and II (0/15) (53). This mutation was initially reported in 2012 and found to be recurrently mutated in pediatric midline gliomas (44,60). Tumor suppressor protein 53 (*TP53*) has also been shown to be frequently altered in spinal cord glioblastomas (80–90%) (61).

Genotype-directed therapy and targeted agents

The *BRAF* alterations identified in WHO grade I and II spinal astrocytomas suggests that these tumors may be amenable to BRAF-MEK inhibitors. In keeping with this concept, the recent VE-BASKET study found evidence of durable antitumor activity of selective $BRAF^{V600}$ inhibition in some patients with $BRAF^{V600}$-mutant gliomas, though further investigation is needed to determine which patients are most likely to benefit (62). Patients with the *H3F3A* K27M spinal cord astrocytoma currently have exceedingly poor outcomes. Ongoing investigations of diffuse intrinsic pontine glioma (DIPG), which also harbors this mutation, suggest that inhibition of histone deacetylase and histone demethylase may be promising therapeutic avenues (63).

Hemangioblastoma

Spinal cord hemangioblastomas are vascular lesions which constitute 8–15% of IMSCTs and occur with equal frequency in men and women (64). Hemangioblastomas can be sporadic or familial, with familial hemangioblastomas associated with von Hippel-Landau (VHL) disease. VHL-associated hemangioblastomas account for 20–40% of presenting cases (65), with 20% of these lesions presenting in the spinal cord (65,66).

Standard of care

Patients with asymptomatic spinal cord hemangioblastomas can be managed with serial MRI and clinical evaluation. Given the relatively high incidence of spinal cord hemangioblastomas in patients with VHL disease, regular MRI screening is recommended (67). Though these vascular lesions arise from the pia, and are thus considered juxtamedullary, they may possess an intramedullary component. If a spinal cord hemangioblastoma hemorrhages, space-occupying hematomas can develop and lead to neurological deficits. Therefore, surgical resection is appropriate for patients with symptomatic spinal cord hemangioblastoma (68,69). Preoperative spinal angiography may be performed for surgical planning, but embolization is rarely indicated (1). Advances in microsurgical resection have improved the ability to achieve GTR of the lesion and associated mural nodule, while limiting post-operative complications (68). Stereotactic radiosurgery (SRS) for symptomatic spinal cord hemangioblastoma has delivered promising results, though results of long-term follow up remain limited (70,71).

Molecular characterization

VHL disease is characterized by an autosomal dominant pattern of inheritance, has 90% penetrance, and is caused by germline alterations in the eponymous tumor suppressor gene, *VHL* (72). This gene encodes an E3 ubiquitin ligase which has been shown to degrade hypoxia-inducible factor 1a (HIF-α), a well-described effector of vascular proliferation. Alterations in *VHL* limit a cell's ability to ubiquitinate and degrade HIF-α, leading to increased angiogenesis (73). The pathogenesis of VHL disease is hypothesized to occur via a "two-hit" mechanism, where patients have a germline mutation in *VHL* and later develop a second somatic mutation, resulting in biallelic inactivation of *VHL* (74,75).

Glasker *et al.* reported that 94% of VHL-associated hemangioblastomas (n=29; spinal, n=4) express germline mutations in *VHL*, with 62% of these tumors harboring LOH at the *VHL* locus (3p25-56) (75). Interrogating sporadic hemangioblastomas (n=13; spinal, n=2), the authors found that 23% of these tumors possessed somatic mutations in *VHL*. Takayanagi *et al.* profiled a series of sporadic (n=21; spinal, n=2) and VHL-related (n=11; spinal, n=0) CNS hemangioblastomas, identifying *VHL* alterations in 100% of VHL-associated tumors and 62% of sporadic lesions (74). Moreover, the authors observed alterations specific to sporadic hemangioblastomas, namely *VHL* promoter hypermethylation (33% of sporadic tumors) and LOH of chromosome 6 or 10 (43% of sporadic tumors) (74). Shankar *et al.* performed whole-exome sequencing of 32 sporadic hemangioblastomas (spinal, n=9) and detected *VHL*-inactivating events in the majority of cases (78%). The recent studies by Takayanagi *et al.* and Shankar *et al.*, using modern molecular profiling techniques,

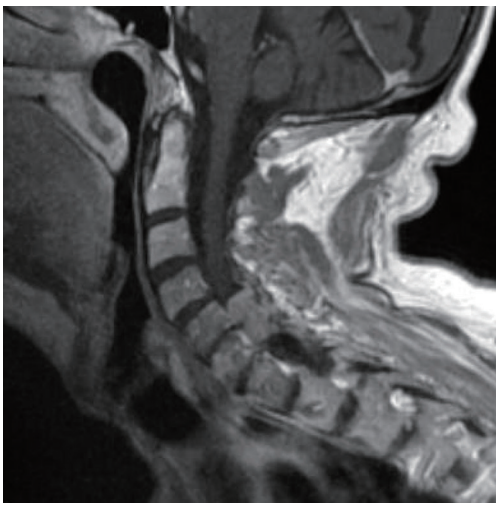

Figure 4 Spinal meningioma. T1-weighted MRI of the cervical spine reveals an extra-axial intraspinal soft tissue mass lesion with dural tail occupying the spinal canal at the C5–C6 level. The mass homogeneously enhances and exerts mass effect on the cord.

suggest that both *VHL*-inactivation is a key pathogenic mechanism in both VHL-associated and sporadic hemangioblastoma.

Genotype-directed therapy and targeted agents

Microsurgical resection and SRS are likely to continue to be mainstays in the management of spinal hemangioblastomas. However, genotype-informed therapies may play a role in surgically-challenging lesions and for patients with VHL-associated disease. To this end, bevacizumab has been used effectively in case reports of patients with unresectable spinal hemangioblastoma (76,77). Thalidomide, which demonstrates anti-angiogenic effects, has also been used in the management of a patient with progressive, multifocal spinal hemangioblastomas (78). Pazopanib, a tyrosine kinase inhibitor (TKI) which blocks the VEGF and PDGF pathways, was recently shown in a single-arm phase II trial (n=31) to achieve objective responses in 42% of patients with VHL disease. There were 49 CNS hemangioblastomas, only two of which demonstrated a response (79). Case reports of VHL patients with multiple CNS hemangioblastomas treated with pazopanib have shown varying results (80,81).

Intradural extramedullary (IDEM) spinal tumors

IDEM tumors include meningiomas, schwannomas, and neurofibromas. The majority of these tumors are benign, generally becoming symptomatic due to mass effect, and are managed with surgical resection. Presentation of multiple IDEM is often characteristic of underlying a genetic syndrome.

Meningioma

Meningiomas of the spine are IDEM tumors arising from meningothelial cells of the leptomeninges of the spinal cord and are the most common primary spinal tumor in adults (2) Spinal meningiomas occur most frequently in the thoracic spine and arise more commonly in females (*Figure 4*) (82). WHO classification of meningiomas consists of grade I (benign), grade II (atypical), and grade III (malignant). Meningiomas can be subtyped histologically, with psammomatous, meningothelial, and transitional subtypes most commonly observed in spinal meningiomas (83,84).

Current standard of care

Although spinal meningiomas are typically benign, they can result in mass effect and spinal cord compression. Therefore, surgical resection is standard-of-care and can be performed with limited rates of iatrogenic injury and low recurrence rates (1–4%) (84). The completeness of meningioma resection is evaluated by Simpson grading. Grade I is defined as complete removal of the tumor, including resection of underlying bone and associated dura. Grade II resection requires complete removal and coagulation of dural attachment. Grade III is defined as complete removal without dural resection or coagulation. Grade IV is STR and grade V is only surgical decompression. When possible, Simpson grade I resection, complete removal of the tumor and involved dura, should be the surgical goal. Nakamura *et al.* reported their experience with spinal meningiomas (n=62) in whom complete resection was achieved (Simpson grades I and II) and long-term follow up was available. Six patients of these patients (9.7%) recurred, all of whom had received Simpson grade II resection (85). However, extensive resection must be balanced with concern for operative morbidity. Kim *et al.* reported their experience with spinal meningiomas (Simpson grade I, n=21; Simpson grade II, n=20) and observed lower recurrence in the Simpson grade I group but a slightly increased rate of complications, described as neurological deterioration by the authors (86). Recently, Chin *et al.* reported long-term results of benign spinal tumors (meningioma, n=39) treated with SRS, observing 5-year and

Table 2 Mutations associated with intradural extramedullary (IDEM) tumors

Tumor	Gene	Locus	Grade	Molecular finding
Meningioma	–	22	I–III	Most consistently reported finding of spinal meningioma
	MMP9	20q11.2	I–III	Overexpressed in spinal meningiomas via IHC
	SMARCE1	17q21.2	I–III	Familial spinal meningiomas in patients without NF2; all clear-cell histology
Schwannoma	*NF2*	22q12	–	Germline inactivating mutations
	SMARCB1	22q11	–	Germline alteration in ~50% of familial and ~10% of sporadic schwannomatosis cases
	LZTR1	22q11	–	Germline LoF in majority of schwannomatosis cases lacking mutations in SMARCB1, but with loss of chromosome 22q in tumors
	ARID1A	1p36.11	–	Recurrent somatic mutations in sporadic schwannomas, identified by WES
	ARID1B	6q25.3	–	
	DDR1	6p21.33	–	
	SH3PXD2A-HTRA1	–	–	Recurrent fusion in 10% of sporadic schwannoma

IHC, immunohistochemistry; LoF, loss-of-function; WES, whole-exome sequencing.

10-year local failure rates of 2% and 8%, respectively (87). No SRS-related secondary malignancies were observed.

The use of adjuvant radiation for spinal meningiomas is controversial and generally limited to higher grade meningiomas or cases where complete resection cannot be achieved. Sun *et al.* investigated outcomes following surgical management of WHO grade II meningiomas (n=18) and found Simpson grade I–III resection without adjuvant radiation therapy could achieve symptomatic resolution and low recurrence (88).

Molecular characterization

Complete or partial loss of chromosome 22 is the most consistently reported genetic hallmark of spinal meningiomas, compared to intracranial meningiomas (89,90). Other cytogenetic abnormalities include loss of 1p, 9q, and 10q and gains of 5p and 17q (90). Notably, these cytogenetic abnormalities appear to be more frequently observed in atypical and anaplastic spinal meningiomas, compared to benign lesions. Barresi *et al.* used immunohistochemistry to assess hormone receptor and matrix metalloproteinase (MMP) immunoexpression in spinal meningiomas (n=58), observing that progesterone receptor immunoexpression in 86% of cases and elevated MMP-9 immunoexpression in 46% of cases (91).

Presentation with multiple meningiomas is often associated with NF2. However, Smith *et al.* identified cases of familial spinal meningiomas without *NF2* mutations and performed whole-exome sequencing to identify germline mutations in a chromatin-remodeling gene, switch/sucrose, nonfermentable related, matrix associated, actin dependent regulator of chromatin, subfamily E, member 1 (*SMARCE1*) (92). Importantly, the tumors from patients with germline *SMARCE1* mutations were all of clear-cell histology and had loss of SMARCE1 protein, supporting a tumor suppressor mechanism (92).

Large-scale sequencing studies of spinal meningiomas lag behind intracranial meningiomas, where potentially actionable mutations have been identified. Somatic mutations in cranial meningiomas have been identified in Smoothened (*SMO*), *AKT1*, Krüppel-like factor 4 (KLF4), TNF receptor associated factor 7 (TRAF7), and POLR2A (93-96), potentially forming the basis of targeted therapeutics. Recently, Juratli *et al.* identified deletions in *DMD* of patients with WHO grade II–III cranial meningiomas that appear to be associated with poor survival outcomes (97). However, the relevance of these findings to spinal meningiomas remains to be elucidated (*Table 2*).

Genotype-directed therapy and targeted agents

While the discovery of somatic mutations in intracranial meningiomas is fostering investigation into targeted

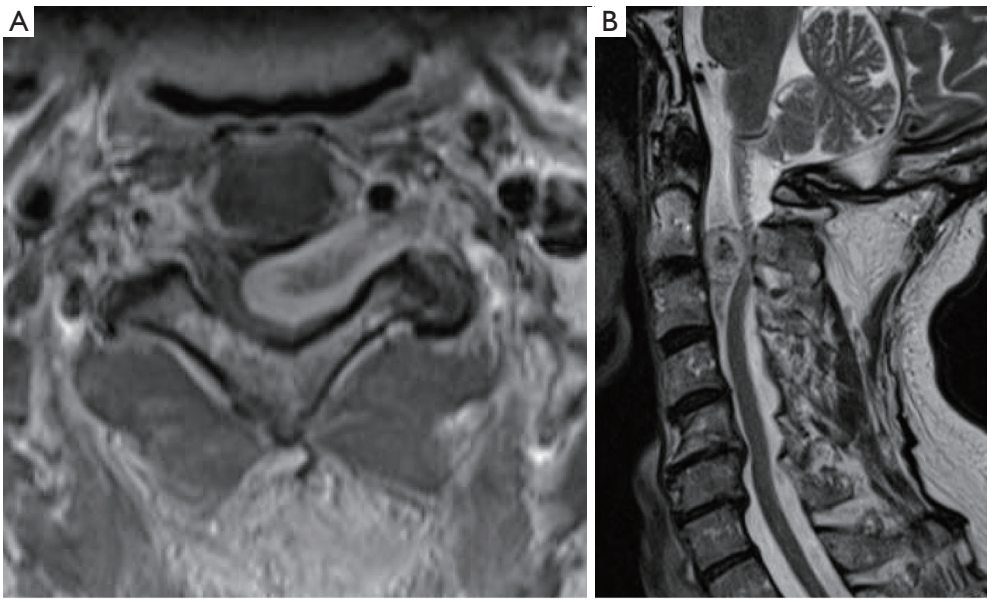

Figure 5 Spinal schwannoma. Preoperative axial (A) and sagittal (B) post-gadolinium MRI demonstrates a heterogeneously enhancing mass centered in the left C2–C3 neural foramen with intraspinal canal extension resulting in marked compression of cord.

therapies (98), genotype-directed therapy of spinal meningiomas remains limited. Further studies interrogating the molecular features of spinal meningioma are likely necessary before effective neoadjuvant or adjuvant treatment strategies can be devised.

Schwannoma

Schwannomas arise from the transformation of Schwann cells, the myelin-producing cells of the peripheral nervous system and can develop in association with both cranial and spinal nerves. Neoplastic Schwann cells form two patterns: (I) compact, elongated cells with occasional nuclear palisading (Antoni A pattern) or (II) less cellular, loosely textured cells with indistinct processes (Antoni B) (99). Spinal schwannomas are most commonly sporadic and solitary (90%) but can also be familial in origin (*Figure 5*) (100). Multiple schwannomas increase suspicion for an underlying syndromic disorder, typically NF2 (and schwannomatosis (101). The vast majority of schwannomas are benign though malignant schwannomas have been observed and are characterized with markedly poor outcome (102).

Current standard of care

Maximal safe surgical resection is the standard-of-care for most cases of spinal schwannoma (103). Safaee *et al.* report their experience with spinal nerve sheath tumors (schwannoma, n=163), observing that GTR was achieved in 83% of patients and lower recurrence rate (4% versus 19%). Notably, GTR was less readily achieved in NF2-associated spinal schwannoma (104). SRS has also been used as first-line management of spinal schwannoma, with multiple case series demonstrating high rates of symptomatic improvement and local control with limited radiation-related adverse events (105-107). Adjuvant radiation can be considered in cases of STR, though the benefit of this therapy remains undetermined (104,108).

Molecular characterization

Patients with NF2-associated spinal schwannomas likely harbor germline inactivating mutations of *NF2* and later accumulate a second alteration resulting in biallelic *NF2* inactivation, providing a basis for transformation of Schwann cells into schwannomas. Familial schwannomatosis clinically presents with multiple schwannomas throughout the body, though generally sparing the vestibular nerve. This disorder is associated with constitutional alterations of *SMARCB1*, a tumor-suppressor gene also located also on chromosome 22 (109). *SMARCB1* has been shown to be altered in roughly 50% of familial and nearly 10% of sporadic schwannomatosis cases (110). In schwannomatosis

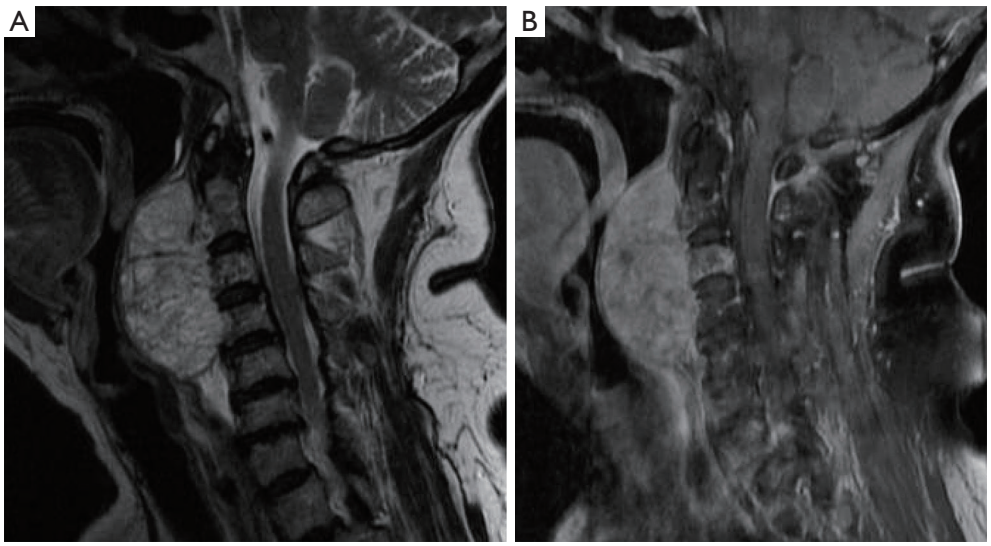

Figure 6 Spinal chordoma. Preoperative T2-weighted (A) and T1-weighted, fat-saturated, post-gadolinium (B) MRI reveals a large prevertebral mass extending from C2–C5, characterized by abnormal signal and enhancement in the C3 vertebral body.

cases lacking mutations in SMARCB1, but with loss of chromosome 22q in tumors, germline loss-of-function mutations in LZTR1 were identified in 80% of cases (111).

To better characterize sporadic schwannomas, Agnihotri *et al.* performed DNA and RNA sequencing on 26 schwannomas (spinal, n=13) and targeted sequencing and methylation profiling of 125 schwannomas (spinal, n=61) (112). As expected loss of 22q was identified in 56% of spinal schwannomas by methylation profiling and found two methylation-based clusters, which almost uniformly segregated vestibular and spinal schwannomas. They identified recurrent somatic mutations in *ARID1A*, *ARID1B* and *DDR1*. RNA sequencing identified a recurrent in-frame *SH3PXD2A-HTRA1* fusion in 10% (vestibular, n=7; spinal, n=5) of cases and demonstrated the fusion resulted from a balanced 19-Mb chromosomal inversion on chromosome 10q (112).

Genotype-directed therapy and targeted agents

Agnihotri *et al*. further observed that expression of the *SH3PXD2A-HTRA1* fusion resulted in elevated phosphorylated ERK, leading to increased cellular proliferation, invasion, and *in vivo* tumorigenesis (112). The authors provided *in vitro* evidence that targeting the MEK-ERK pathway with a MEK inhibitor, trametinib, may be an effective therapeutic strategy (112). While data on NF2-associated spinal schwannomas is lacking, bevacizumab is being actively investigated in the management of NF2-associated vestibular schwannomas and is beginning to be explored in the management of patients with schwannomatosis (113-115).

PSCM

PSCM are a rare group of lesions which include chordoma, chondrosarcoma, osteosarcoma, and Ewing's sarcoma. Chordoma and chondrosarcoma are indolent but locally invasive, while Ewing's sarcoma and osteosarcoma are more aggressive and associated with higher rates of tumor progression and recurrence (116-118).

Chordoma

Chordomas are locally aggressive notochord-derived lesions of the axial skeleton and comprise 1–4% of all primary bone tumors (*Figure 6*) (119). They affect men more commonly than women and often present in the fifth and sixth decades of life (120). An analysis of the SEER database (n=400) revealed a median survival of 6.3 years with 10-year survival of 39.9% (120). Chordomas arise in the skull base (32%), mobile spine (32.8%), and sacrum (29.2%) (120).

Current standard of care

Despite chordoma's indolent course, these lesions are locally aggressive and may present with large size at diagnosis,

complicating management. Standard-of-care for spinal column chordomas is wide margin, *en bloc* surgical resection. Fuchs *et al.* demonstrated that patients with sacral chordoma who underwent radical resection had markedly longer time to local recurrence compared to those who underwent STR (2.3 years *vs.* 8 months, respectively) (121). These results have been confirmed in other series and in chordomas of the mobile spine (122,123). Among patients in the study by Fuchs *et al.* in whom a wide margin was achieved, 5-year local control rate was 100% (121). While *en bloc* resection has been consistently shown to have superior local control, this management approach introduces morbidity due to the critical neurovascular structures involved. *En bloc* resection can be achieved in roughly 50% of sacral chordomas with markedly lower rates of total resection in chordomas of the mobile spine (124). Adjuvant radiation therapy is appropriate and may have benefit when true oncologic margins have not been achieved (125). Definitive radiation therapy using high-dose photons or protons continues to be actively investigated, with recent results demonstrating 5-year local control rates of 85.4% (126). Conventional chemotherapy has shown little efficacy in the management of chordoma (124).

Molecular characterization

In 2009, Yang *et al.* identified unique duplications of 6q27 in four families with multiple members who had developed chordoma. The duplicated genomic region contains the transcription factor T (*brachyury*) gene, further providing evidence of the notochordal origin of chordoma (127). Pillay *et al.* conducted a genetic association study and identified a common nonsynonymous SNP, rs2305089, with a highly significant association with chordoma risk (allelic odds ratio =6.1) (128). This finding was confirmed in an independent study by Kelley *et al.*, in both familial and sporadic chordoma. These authors identified another common variant, rs1056048, strongly associated with chordoma in families and an additional common variant, rs3816300, in sporadic cases significantly associated with risk when jointly analyzed with rs2305089 (129).

Recently, Tarpey *et al.* investigated the somatic mutational landscape of sporadic chordoma (n=104). They identified somatic duplications of *brachyury* in up to 27% of cases, PI3K signaling mutations in 16% of cases, and recurrent inactivation mutations in *LYST* in 10% of cases (130). An additional feature of chordomas is expression and activation of tyrosine kinase receptors and downstream signaling molecules, a finding which has been confirmed in multiple studies (131-134).

MicroRNA (miRNA) has also been explored in defining the molecular landscape of chordomas (135). miRNA is a 20–30 nucleotides, non-coding, single-stranded ribonucleic acid (RNA) molecule which can play oncogenic or tumor suppression roles by modulating gene regulation and transcription. Recently, Chen *et al.* profiled miRNA in chordomas, compared to fetal nucleus pulposus tissue, and found expression of hsa-miR-21-3p, hsa-miR-150-5p, hsa-miR-1290 and hsa-miR-623 to be upregulated (135). Further work is necessary to determine the mechanistic, prognostic, and therapeutic roles of miRNA in chordoma.

Genotype-directed therapy and targeted agents

The somatic mutations in PI3K signaling genes may form the basis of targeted agents for chordoma patients with these alterations. Further characterization of *LYST* mutations may also provide a basis for targeted chordoma therapies. Drawing on studies identifying activation of tyrosine kinase receptors in chordoma, a phase II study of imatinib in patients with advanced chordoma (n=50) found a 64% clinical benefit rate (136). Another promising targeted agent is afatinib, a TKI, as a recent *in vitro* study demonstrated this agent degraded both EGFR and *brachyury* (137). Other targeted agents that have been explored in larger studies of chordoma include lapatinib and sorafenib (138,139).

Recently, our group sought to determine the prognostic significance of the rs2305089 SNP. We genotyped this locus in 109 patients with spinal chordomas and found 102 patients (93.6%) harbored the A variant at this position. We observed that these patients had significantly improved OS compared with those lacking the variant but did not appreciate any association between SNP status and local recurrence-free survival (140). An additional molecular prognostic biomarker in spinal chordoma appears to be mutations in the *hTERT* promoter. Our group recently performed genotyping of 92 spinal chordomas and found that eight patients (8.7%) harbored mutations in the *hTERT* promoter region. Notably, all patients with *hTERT* mutations were alive at 10-year follow up, significantly better than patients lacking these mutations (141) (*Table 3*).

Conclusions

Primary spinal tumors are rare and diverse lesions that present unique clinical challenges due to their intimate relationship with the spinal cord and nerve roots. The current standard-of-care for spinal tumors involves

Table 3 Mutations associated with primary spinal column malignancies (PSCM)

Tumor	Gene	Locus	Grade	Molecular finding
Chordoma	*T*	6q27	–	Multiple germline SNPs associated with development of familial and sporadic chordoma; rs2305089 shown to be prognostic for OS
	LYST	1q42.1-q42.2	–	Recurrent inactivating somatic mutations in sporadic chordomas
	TERT	5p15.33	–	Mutations in *TERT* promoter shown to have prognostic implications

OS, overall survival; SNP, single nucleotide polymorphism.

maximal safe resection with adjuvant therapy for cases of residual tumor or recurrent disease. Dissection of molecular mechanisms and identification of genetic biomarkers has begun to influence the management of the cranial counterparts of spinal tumors by enhancing patient selection, improving prognostication, and forming the basis of targeted therapies. However, application of these discoveries to spinal tumors must proceed cautiously with rigorous validation—important differences have been identified between many cranial and spinal tumors of shared histology. Surgical resection will likely remain the mainstay of spinal tumors, but further interrogation of the molecular underpinnings of these lesions is necessary to identify improved neoadjuvant and adjuvant treatment and to better inform patient stratification and risk assessment.

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Footnote

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