Chapter

Intramedullary Spinal Tumors

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Abstract

Intramedullary spinal tumors are uncommon intra-axial lesions, which can be either primary or metastatic. Primary tumors arise from cell of spinal cord and account for 2–4% of all intrinsic tumors of the central nervous system, being much less common of brain tumors. They are slow-growing tumors, so symptoms precede diagnosis by an average of 2 years. Metastatic lesions usually originate from lung and breast tumors and are usually diagnosed within 1 month from symptom onset. Pain and weakness are the most common presenting symptoms. Magnetic resonance imaging represents the gold standard technique to study the spinal cord tumors, and first-line treatment is surgical resection, but it is not always curative. In selected situations, watchful waiting can be considered. Chemotherapy and radiation are considered, but controversy exists. Novel treatment options must be developed to supplement partial resection and recurrence.

Keywords: neurosurgery, spinal surgery, spinal cord, neurological outcome, neurological deficit, intramedullary tumors, ependymoma, astrocytoma, hemangioblastoma, vascular malformation

1. Introduction

Intramedullary tumors (ITs) refer to a group of heterogeneous neoplastic lesions, which arise from the cells of spinal cord, accounting approximately 2–4% of primary intra-axial tumors of the central nervous system (CNS) [1, 2], or from metastatic cells of extra-neural tumor. Primary tumors are most often derived of neuroepithelial cell origin, with ependymoma being the most common in adults, and astrocytoma the most common in children and adolescents. Metastatic lesions usually originate from lung and breast tumors.

ITs differ from the tumors of the adjacent structures of spinal canal as nerve roots and meninges, and they are so distributed [3]:

Children and adolescents, 65% ITs (36.3% neuroepithelial, 19.6% ependymal tumors), 17.2% nerve sheath tumors, 17.8 tumors of meninges.

Adults, 30.1% ITs (4.7% neuroepithelial tumors, 17% ependymal tumors), 30.4% nerve sheath tumors, 30.5% tumors of meninges.

We can classify the ITs related to the cell of origin:

Neuroepithelial (90–95% of all ITs)

- **Ependymal tumors** 60%, e.g., ependymoma, myxopapillary ependymoma.

- **Astrocytic tumors** 33%, e.g., pilocytic astrocytoma, diffuse astrocytoma, glioblastoma.

- Neuronal 1%, e.g., **ganglioglioma**.

- Embryonal tumors, e.g., primitive neuroectodermal tumors (PNET), atypical teratoid/rhabdoid tumor (AT/RT)

Non-neuroepithelial

- Mesenchymal tumors, e.g., **hemangioblastoma**

- Lymphocytic tumors, e.g., **primary lymphoma**

- Melanocytic tumors, e.g., **melanocytoma**

- **Metastatic tumors**

Intramedullary benign masses as vascular malformation or congenital/developmental lesions can be encountered, and they should be considered in differential diagnosis. They can be ectodermal inclusion as epidermoid and dermoid cyst, mesodermal inclusion as lipoma, and endodermal inclusion as neurenteric cyst.

Genetic factors correlate with ITs. The syndromes associated with these tumors are neurofibromatosis 1 (NF1, 19% of patients), 2 (NF2, 33–53% of patients), and Von Hippel Lindau disease (VHL) [4, 5]. These patients develop mostly astrocytoma in case of NF1, ependymoma in NF2, and hemangioblastoma in VHL.

Approximately 70% of intramedullary tumors are associated with cysts [6]. Two types of cysts are recognized: the *tumoral cyst* and the *reactive cyst/syringomyelia* (non-tumoral). The *tumoral cyst* contained within the tumor itself typically demonstrates peripheral enhancement and may result from necrosis, fluid secretion, or degeneration of the neoplasm. It normally needs to be resected along with the solid portion of the tumor because there is a high likelihood of neoplastic cells within the wall. It occurs in association with the following tumors: 46% for ganglioglioma, 22% for ependymoma, 21% for astrocytoma, and 2–4% for spinal hemangioblastoma [7–9].

The *reactive cyst or syringomyelia* (**Figure 1**) generally occurs rostral or caudal to the solid portion of the tumor. It is a cystic collection of the central canal, it does not enhance, and it is present in 25–58% of all ITs, most frequently associated with hemangioblastomas [6]. It may resolve once the neoplasm is resected.

1.1 Clinical presentation

The clinical features of ITs depends on their location, grow rate, and longitudinal extension. They can potentially lead to severe neurologic deterioration, decreased function, and poor quality of life. Diagnosis is often delayed, as symptoms are slowly progressive and nonspecific. An exception is intramedullary metastases, which are diagnosed within 1 month from symptom onset in up to 75% of cases [8].

The most common presenting symptom includes back or neck axial pain. It can be associated with irradiated radicular pain, weakness, sensory disturbance, spasticity, gait disturbance, and bowel or bladder dysfunction. The neurological symptoms do

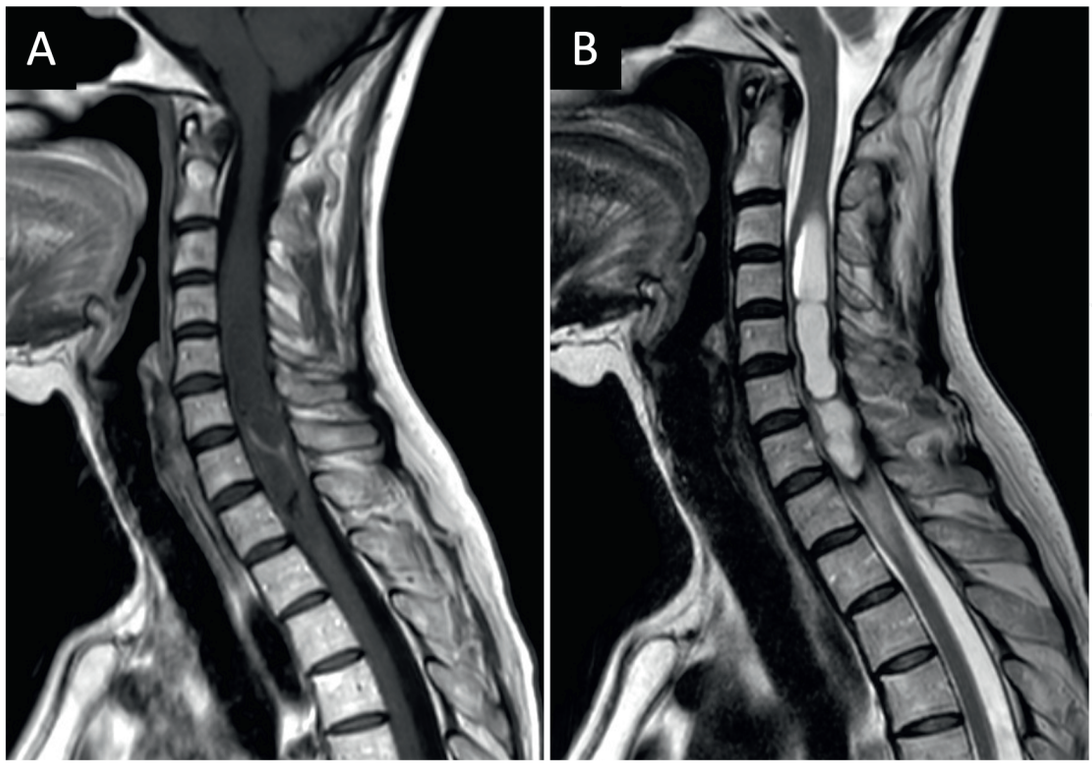

Figure 1.
Cervical ependymoma. Contrast-enhanced sagittal T1-weighted image (A) shows an enlarged spinal cord with an intramedullary lesion. It is a cervical ependymoma with light heterogeneous enhancement. Syringomyelia and caudal spinal cord edema are evident in sagittal T2-weighted image (B).

not involve head and face. Incomplete spinal cord syndrome as central, anterior, or Brown-Sequard may occur.

In children, progressive scoliosis may be seen in one-third of patients [10]. Motor regression and frequent falls may be the presenting features in young children [11].

1.2 Radiographic features

Radiographic evaluation can determine the location and extension of tumor. On plain radiograph and computerized tomography (CT), widening of the interpedicular distance, bony erosions, or scoliosis may be seen.

Myelography has been used in the past to evaluate the cord shape, but it is supplanted by MRI.

MRI is the preferred modality and helps to differentiate between lesions. General characteristics and T-1 and T-2 pattern of ITs are usually recognized, even if accurate diagnosis may be challenging. Focal spinal cord expansion and at least light contrast enhancement are seen. In contrast to intracranial neoplasms, even low-grade intramedullary tumors enhance to some degree.

Spinal angiography is mandatory to differentiate vascular lesions and for confirmed suspected diagnosis of hemangioblastoma.

Ependymomas are centrally located within the cord and display symmetric expansion with diffuse heterogeneous enhancement. Astrocytomas can be eccentrically positioned and non-enhancing. Hemangioblastomas are richly vascularized tumors with significant surrounding edema. Embolization can be useful in cases of hemangioblastoma. Metastatic lesions are well encapsulated, with no cystic change or hemorrhage. They are associated with cancer history.

1.3 Treatment and prognosis

The standard of care for most ITs is the surgical resection, which has improved with the modern operating microsurgery and intraoperative neuromonitoring.

Radiotherapy and chemotherapy are often reserved for high grade and infiltrative tumors and for recurrence. They are limited by adverse effects and blood-spinal cord barrier.

The best predictive factors of outcome are preoperative neurological status and tumor histology [12].

1.4 Differential diagnosis

Various expansile lesions non-neoplastic may mimic ITs. The differential diagnosis includes inflammatory disease, congenital-developmental lesions, and vascular malformation.

The inflammatory lesions can be:

- demyelination (e.g., multiple sclerosis), which usually presents no spinal cord enlargement, but diffuse plaque enhancement in brain and spinal cord correlated with acute lesion activity.

- transverse myelitis, which shows acute clinical course and typically occupy greater than two-thirds of the cross-sectional area of the cord.

- spinal cord abscess, with rim enhancement and restricted diffusion.

Among vascular lesion we find:

- Cavernous malformation, a low flow capillary malformation, which appears as rounded region of heterogeneous hyperintensity at T1 and T2-weighted images and peripheral hypointensity due to blood products of varying ages and hemosiderin deposition ("popcorn appearance").

- Glomus arteriovenous malformation (AVM), a high-flow compact intramedullary nidus with AV shunting characterized by flow voids at spin-echo MRI.

- Spinal cord infarction appears hyperintense on T2-weighted images and DWI, without enhancement after contrast.

Congenital-developmental (ecto, meso, endoderm) no-enhancing lesions are:

- Epidermoid and dermoid cysts lined by squamous epithelium and skin appendages, whose signal at CT and MRI appear like cerebrospinal fluid (CSF), excepted for restricted diffusion and DWI.

- Lipoma, mature adipose tissue, characterized by homogeneous fat attenuation at CT and MRI.

- Neuroenteric cyst, usually ventral, which can manifest with varying signal intensity at T1 and T2-weighted imaging due to mucin content.

Spinal cord contusion is usually associated with other spinal injuries (osseous, ligament), and it is correlated with specific medical history (trauma, acute symptoms onset).

2. Spinal ependymoma

2.1 Epidemiology

Ependymomas are uncommon neuroepithelial tumors and represent 1.8% of all primary CNS tumors and 50–60% of all ITs. The annual incidence is reported between 0.14 and 0.21 per 100.000 person [13, 14]. They are classified in the WHO 2021 CNS tumor classification by anatomic site, (supratentorial, posterior fossa, spinal), histology (ependymoma, subependymoma, myxopapillary ependymoma), and molecular alterations.

Spinal ependymomas are now classified according to amplification status of MYCN, which regulates genes involved in cell growth. Spinal ependymomas are more common in adults than children, with a peak of incidence between the third and the fifth decade. They showed a slight male preponderance (male:female = 1.6:1), except for spinal subependymoma (SSE). Gender and age distribution showed slight variation according to different molecular types, while distribution along the spinal cord is extremely variable. SSE is predominantly in the cervical segment, followed by the thoracic. Conversely, spinal myxopapillary ependymomas (SMPEs) arise in the distal spinal cord (**Figure 2**) [15].

Extra-neural metastases from ependymomas are possible but uncommon.

2.2 Histopathology

Ependymomas are tumors of neuroectodermal origin. They are well-circumscribed lesions of ependymal differentiated cells and typically present eosinophilic cells with round nuclei and scant cytoplasm, organized in *rosette* around a central vessel.

Historically, they were supposed to origin from periventricular ependymal layer. Recent gene expression analysis suggested to origin from embryonic radial glial cells (RGCs) in the subventricular zone. RGCs in the supratentorial, infratentorial, and spinal canal have different chromosomal abnormalities and gene expression and consequently, morphologically similar ependymomas have different molecular profile [16].

Emerging evidence showed that despite histologic similarities, ependymomas arising in different localization widely differ for prognosis, molecular and genetic alteration.

The WHO 2021 CNS tumors classification introduced the anatomical and molecular pattern in the tumors type definition. The new classification defined 10 different CNS ependymal tumors. Types are defined based on the localization in one of the three neuroanatomical compartments, supratentorial, infratentorial and spinal cord, the molecular pattern, and the immunohistochemical analysis. Subependymoma and myxopapillary ependymoma are the only two types not restricted to a specific localization and may occur in the three different compartments.

Discordance between histological grade and clinical behavior cause controversy about grading system. Moreover, grading system showed to have high interobserver variability. For these reasons, treatment should not be based only on the histopathological grading system.

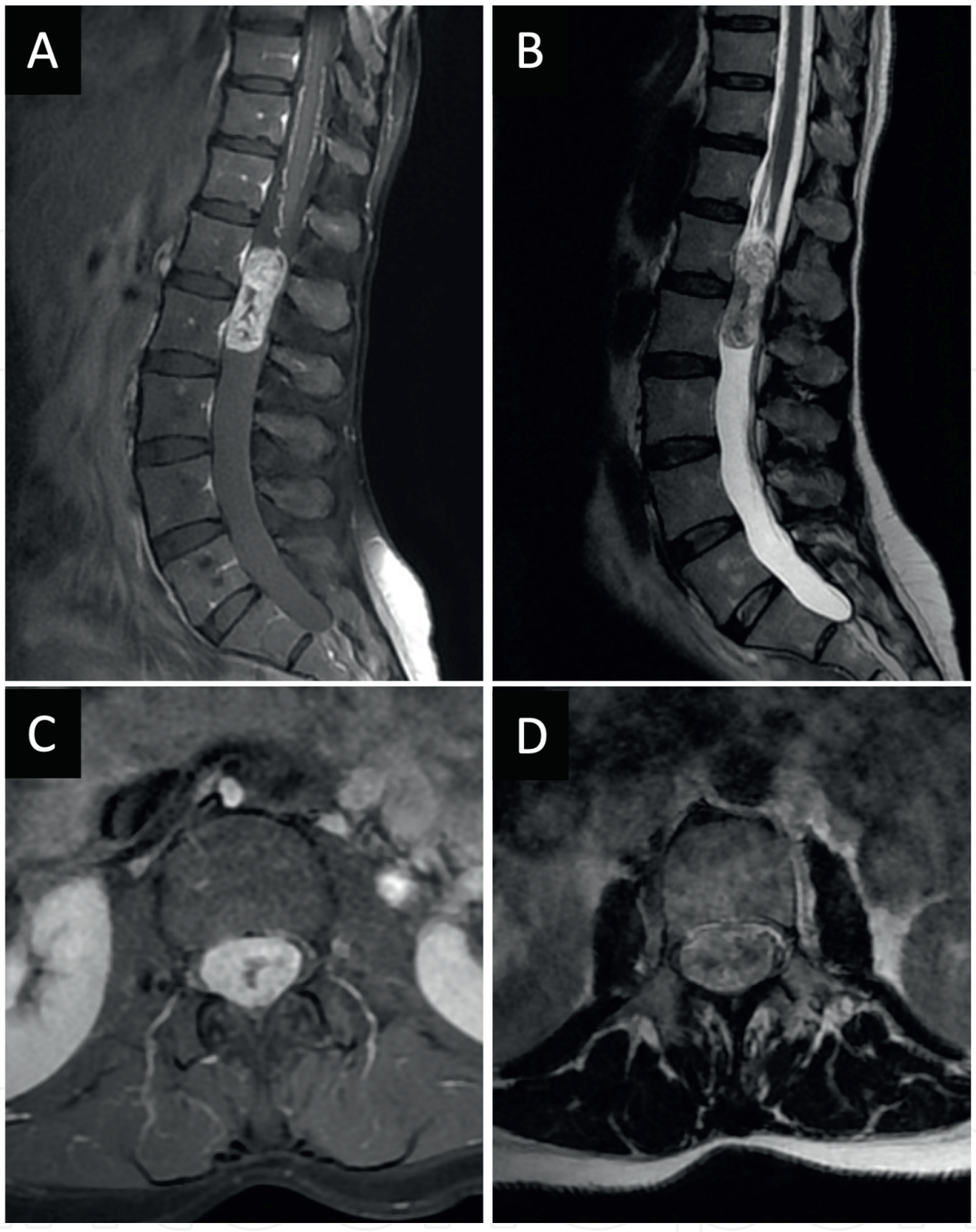

Figure 2.
Spinal myxopapillary ependymoma. Contrast-enhanced sagittal T1-weighted image (A) and non-enhanced sagittal T2-weighted image (B) show intradural lesion at distal part of spinal cord (lumbar region). The lesion presents heterogeneous contrast enhancement (A, C). In the axial plane (C, D), the myxopapillary ependymoma occupies the entire spinal canal, displacing and compressing cauda equina nerve roots.

Four different ependymomas types may involve the spinal cord: spinal ependymoma w/o MYCN amplification (SP-EPN), spinal ependymoma with MYNC amplification (SP-MYCN), SSE, and SMPE. Except for the spinal ependymoma with MYNC amplification, which shows aggressive characteristics, all of them are mostly benign.

SP-EPN is an ependymoma occurring in the spine without the morphological characteristics of SSE and SMPE. Most SP-EPNs have chromosome 22q losses that harbor the NF2 gene. The role of NF2 loss in ependymomas is still unclear, but SP-EPN is observed in 33–53% of NF2 patients [17]. Histologically, it shows a solid

and circumscribed mass, composed of regular cells organized in perivascular pseudorosette and papillary organization. SP-EPN is classified as grade 2 or 3 according to general WHO grading system for CNS tumor.

SP-MYCN is a spinal ependymoma with MYNC amplification, and only a few cases have been described. This tumor occurs as large lesion with early leptomeningeal dissemination, high recurrence rate, rapid progression following recurrence, and poor responses to medical treatment. Aggressive histopathological features such as microvascular proliferation, high mitotic rate, and necrosis are described.

SSE arises in all neuroanatomical compartments. It is circumscribed glioma composed of cluster of cells with low mitotic rate and no nuclear atypia, embedded in a fibrillary matrix with microcystic changes and dystrophic calcification. It was classified as CNS WHO tumor grade I.

SMPE is characterized by myxoid changes, occurring along the neuroaxis but predominantly in the conus medullaris. It is mostly benign, but intradural dissemination and recurrence may occur. Histologically, the papillary organization around a fibrovascular core with perivascular myxoid changes and GFAP immunoreactivity are pathognomonic of this tumor. It was graded II in the WHO 2021 tumor classification.

2.3 Clinical presentation

Spinal ependymomas are centrally located lesion presenting with progressive signs and symptoms of spinal cord lesion. They depend on tumor size, location, and syrinx extension. Axial pain is primary initial symptom, predominant in supine position, and probably caused by dural distension. Radicular pain is uncommon. Then progressive neurological symptoms appear. Due to the not specific onset, diagnosis is often delayed, and symptoms last for 3–4 years before diagnosis.

Dysesthesia and paresthesia are common. Dissociated sensory loss with sacral sparing for somatotopic distribution of spinothalamic tract and bowel and bladder dysfunction occur early.

Posterior cord signs such as ataxia and giant instability occur later.

Para or tetraparesis appears with progressive growth, depending on the tumor site. Motor pattern is spastic in 50% of cases and frequently associated with muscle atrophy.

Pyramidal signs, irritations as hyper-reflexia, Babinski, Hoffman signs, clonus of the ankles are usually seen.

SMPE is predominant in the conus medullaris and presents with conus syndrome: autonomous bladder, fecal incontinence, impotence, saddle hypo or anesthesia, and distal legs weakness without pyramidal sings.

Preoperative paraclinical evaluation includes motor-evoked potentials (MEPs) and sensory evoked potentials (SEPs). They may identify subclinical deficit and show to have a functional prognostic value [18]. Urodynamic exam is routinely performed to explore bladder function.

2.4 Radiographic features

MRI with contrast enhancement is the gold standard for radiologic evaluation. Plain radiography and CT scan may identify nonspecific signs of bony remodeling (see above general overview) from intracanal lesions. Bony anomalies occurred tardively when neurological symptoms already justify an MRI evaluation.

Classic MRI appearance is well circumscribed, centered, enhancing masses causing spinal cord widening. Signal can be heterogeneous, especially for the SMPE type,

for the presence of cysts (65% of case) and hemorrhagic components. But commonly, spinal ependymomas are described as hypointense to isointense from spinal cord signal at T1-weighted images and isointense to hyperintense at T2-weighted images.

More aggressive lesions with increased cellularity show lower signal.

The hemosiderin cap sign (hypointense T2) at rostral and caudal extremities is reported in up to one-third of cases and is highly suggestive.

Perilesional edema and syringomyelia are seen in more than 50% of cases.

SSE has different MRI features. It usually appears as expansile lobulated masses with hyperintense T2-weighted signal, without significant enhancement. Moreover, they are more eccentric compared to classic one and the steep spinal cord swelling causes a fusiform dilatation known as "bamboo leaf sign" [17].

Because of the risk of CSF dissemination, full craniospinal MRI is recommended especially for patients with NF2 at risk of multiple spinal ependymomas and schwannomas [19].

2.5 Treatment and prognosis

Complete microsurgical resection is the gold standard of treatment for these unencapsulated, well-circumscribed lesions. *En bloc* gross total resection (GTR) is preferred to avoid perioperative CSF dissemination, and it is now possible with good functional outcome in most of cases thanks to advances in modern microsurgery.

Since small tumor size and good preoperative status are associated with good functional outcome, early treatment is recommended. Due to the rarity of these lesions, referral center is preferred to improve GTR and functional outcome.

Intraoperative MEPs and SEPs are recommended. MEPs decline of 50% or more seem to be predictive of postoperative motor deficit [20]. An epidural electrode, the D-wave, may be placed on the caudal spinal cord to directly record the impulse on the corticospinal tract avoiding peripheric nerve conductance. The D-wave is considered the most specific monitoring for the corticospinal tract and is consequently the strongest predictor of postoperative motor deficit [21]. SEPs decrease or disappear following midline myelotomy, which is less predictive for functional outcome.

Standard posterior midline approach with multilevel facet sparing laminectomy is usually performed. Laminectomy should include one level above and below the lesion extension. Multilevel laminectomies at the cervical and cervico-thoracic junction level are associated with long-term kyphotic deformity. Arthrodesis is suggested if more than three-level laminectomy is performed. Alternatively, laminoplasty or transtubular approaches may be used [22].

Intraoperative ultrasound may be used to identify the tumors' boundaries before dural opening.

Midline durotomy and dural suspension are performed. The arachnoid is opened separately. A standard midline myelotomy through the posterior medial septum is performed. Spinal ependymomas have a smooth, reddish gray glistening tumor surface. Operative microscope allows to easily identify and develop the dissection plane. Tumoral cysts must be distinguished from reactive/non-tumoral cysts and removed accurately, especially in case of SMPE.

At the end, the arachnoid is grossly closed to avoid spinal cord tethering at the surgical site. A tight water suture of dura is mandatory to avoid postoperative CSF fistula. Postoperative bed rest of 36–48 hours is suggested to minimize CSF pressure and prevent fistula. A symptomatic CSF fistula with CSF leak is at risk of meningitis

and should be treated aggressively with revision surgery. Small asymptomatic pseudo meningocele may be treated nonoperatively with close observation.

The second most frequent complication is surgical site hematoma and should be evacuated whenever is compressive.

Majority of patients experience sensory deterioration immediately after surgery as the results of the posterior myelotomy and posterior cord manipulation. Slight motor deterioration may also occur because of intraoperative manipulation. Corticoids are frequently used to reduce postoperative edema.

Long-term functional outcome is related to preoperative status. Patients with major chronic neurological impairment rarely recovered significantly. On the other hand, minor and recent deficit frequently improves. Preservation rather than restoration of the functional outcome should be the goal.

In SP-EPN GTR increases overall survival (OS) and progression-free survival (PFS). Reported OS at 5 years following GTR is between 90 and 100% [23]. Whereas GTR resection is not achievable, radiotherapy increases PFS from 48 to 96 months. In lesions showing histopathologic signs of aggressivity and classified as CNS WHO tumor grade III postoperative, radiotherapy is recommended independently of the extent of resection. The suggested recommended dose is 45–54 Gy.

SP-MYNCs are more aggressive, with a recurrence rate of 75–100% and a median OS and PFS of 87 and 17 months, respectively, Radiotherapy is generally used for these rare and aggressive ependymomas [24].

SSEs are benign lesions with excellent prognosis, recurrence is extremely rare, even in case of subtotal resection (STR).

SMPEs are recognized to be at high risk of local recurrence and intradural spreading. The reported 10-year OS is of 92.4% and the PFS of 69.5 and 61.2% at 5 and 10 years, respectively. Local recurrence, increased by capsular violation, occurs in 84% of cases while CSF spreading is reported in 9.3% of patients. The irregular shape, the adherence to the cauda equine, and the myxoid matrix make GTR challenging. Postoperative radiotherapy increases PFS from 40–70% in patients with STR. While adjuvant postoperative radiotherapy following GTR showed increased local control compared to GTR alone in a small series. Larger prospective studies are needed to confirm these results.

A few data are available regarding chemotherapy, the topoisomerase-2 inhibitor showed partial responses in 20% of cases with good tolerance in recurrent tumors. Bevacizumab can provide clinical benefits, but no extensive data are available.

Because of the risk of CSF spreading, lumbar puncture for CSF cytology is recommended 3 weeks after surgery. Immediate postoperative MRI should be performed to evaluate the grade of resection and repeated regularly to identify relapse.

In case of relapse, reoperation should be considered.

3. Spinal astrocytoma

3.1 Epidemiology

Gliomas are primary tumors of the CNS of neuroepithelial origins. Spinal astrocytomas (SAs) correspond to 3% of CNS gliomas. They represent approximately 30% of all ITs, with an incidence of 0.07–0.1 per 100.000 person per year. They are the most common ITs in children representing the 60% of all tumors and 90% of tumors in patients younger than 10 years. SAs are rarely observed in patients older than 60 years

old. Up to 60% of SAs occur in the cervical and cervicothoracic region. A slight male predilection is reported. SAs may be associated with NF1.

3.2 Histopathology

SAs are classified according to the 2021 WHO CNS classification and grading system, ranging from 1 to 4. Genetic markers have been incorporated to histopathological characteristics into the WHO grading system.

Histopathologic features are equivalent to the corresponding intracranial astrocytoma.

The new 2021 WHO CNS classification distinguishes the adult and pediatric gliomas. The pediatric subgroups include low-grade pilocytic astrocytoma and diffuse astrocytoma while adult type includes astrocytoma IDH-mutant (possible grade 2, 3, and 4) and astrocytoma IDH-wild type (glioblastoma-like tumor).

Pilocytic astrocytoma is characterized by biphasic cell population, Rosenthal fibers, and eosinophilic granular bodies. Distinction with a grade II astrocytoma may be not easy on morphological criteria. Molecular findings, as BRAF fusion is usually reported in pilocytic astrocytoma.

Astrocytoma (grade 2, 3, 4) is an infiltrating tumor. WHO grading is based on the presence of histological signs of malignity. They appear as hypercellular areas with tumor cells mixed with normal cellular elements. Tumor cells have elongated nuclei and eosinophilic fibrillary cytoplasm. Tumor cells clustering around the vessels are frequently founded. Necrosis and microvascular proliferation are observed in grade 4. Nuclear atypia, pleomorphism, increased mitotic count, and Ki-67/MIB-1 proliferative index increase with tumor grade. Moreover, the presence of CDK2A/B homozygous deletion in IDH-mutant astrocytoma is a negative prognostic factor, classifying tumor as grade 4, independently from necrosis and microvascular proliferation. Astrocytoma IDH-wild type with intermediate behavior is very rare, so it is now classified as glioblastoma IDH-wild type, independently from the histopathologic grade [25].

Diffuse and pilocytic astrocytomas are the most frequent ITs and account for 75% of all intramedullary SAs. Pilocytic astrocytoma is more common in the pediatric population while high-grade (grade 3 and 4) astrocytoma occurs mostly in adults.

3.3 Clinical presentation

Clinical presentation is like the other ITs (see above section “Spinal Ependymoma”). Axial pain is still the most frequent symptom. Slow progressive signs of spinal cord injury vary on form depending on the spinal location and tumoral extension. SAs tend to occur more eccentrically with signs and symptoms of unilateral spinal cord sufferance or incomplete Brown-Sequard syndrome (ipsilateral upper motor neuron paralysis and loss of proprioception, as well as contralateral loss of pain and temperature sensation). A zone of partial preservation or segmental ipsilateral lower motor neuron weakness and analgesia may be noted. Symptoms often appear from distal to proximal at the unilateral extremities before affecting the opposite site. Upper cervical lesion may involve lower cranial nerve [2].

3.4 Radiographic features

SAs appear as intramedullary fusiform multilevel intramedullary lesions on spinal cord MRI. Compared to spinal ependymomas, they are eccentric, and exophytic

component can be observed. Moreover, they tend to be less defined and separate from normal spinal cord. Syringomyelia is less frequent compared to the other ITs and occurs in 20% of cases. SAs are hypo to iso-intense on T1-weighted images and hyper-intense on T2-weighted images. Contrast enhancement may be uniform, minimal, or patchy. In high-grade lesion, it is usually heterogeneous for necrosis and cysts. Peritumoral edema is observed in up to 40% of cases. Intra-tumoral and reactive (perilesional/non-tumoral) cysts occur in 20 and 15% of cases, respectively, while hemorrhage is rare [2, 26].

Diffuse tensor imaging (DTI) tractography, which shows white matter tracts, has been proposed as a diagnostic tool. It may help to distinguish tumor lesion, which displaces or destroys fibers of spinal cord, from acute inflammatory lesions, which are crossed by [27]. DTI can predict the presence of a dissecting plane between tumor and lesion or identify a "safe" entry zone [28].

Pilocytic astrocytomas are well circumscribed showing displacement of the spinal cord lesion and contrast enhancement. Cystic and syringomyelia are more frequent compared to other SAs.

Grade II SAs are infiltrating tumors, with no clear boundaries and dissection plane. Contrast enhancement varies from absent, heterogeneous, or homogeneous.

Glioblastomas show constant enhancement. Necrotic areas can be seen at MRI. Perilesional edema is more frequent due to the infiltrative and aggressive pattern [2, 26].

Plain RX and CT scan may be useful in case of extended bony erosion.

3.5 Treatment and prognosis

Treatment modalities for SAs are derived from brain glioma experience. Specific guidelines are still lacking, especially for diffuse and extensive cases. Surgical resection is generally proposed in patients experiencing neurological deficits, while it is still debated for asymptomatic patients.

The surgical management of SA should achieve the maximal degree of resection without major neurological deterioration. The surgeon should balance the functional and oncological outcomes. Finally, the extent of resection depends on histopathological diagnosis, clinical presentation, tumor extension, and modifications at intraoperative monitoring.

Resection of well-circumscribed lesions with benign behavior results in good functional and oncological outcome. Aggressive GTR without severe neurological deterioration can be achieved in these cases.

For high-grade infiltrative tumors, multimodal treatment is preferred. Biopsy or partial resection followed by adjuvant therapy as radiotherapy and chemotherapy is suggested. In these patients, GTR is usually unachievable without severe functional impairment and a high risk of recurrence is still present.

Standard midline approach as described above is performed. Midline myelotomy is usually performed, the dorsal root entry zone may be used for more lateralized lesions. Operating microscope is used to identify lesion borders whenever is possible. The lesion is resected alternating debulking and dissection from normal spinal cord to obtain vascular deafferentation. Debulking allows dynamic retraction and lesion mobilization, limiting spinal cord traction.

Intraoperative neuromonitoring is mandatory. PEM registration has a high sensitivity (84%) and specificity (83%) in detecting motor impairment, but it has a delay of several seconds from the injury to recognition. It is also influenced by heart rate, blood pressure, and anesthetic drugs. Conversely, the D-wave shows immediate

changes and increased reliability. In highly infiltrative lesions, resection should be stopped if significant PEM and PES amplitude reduction are observed.

Watertight dural closure and hemostasis are crucial to avoid postoperative complications. Perioperative biopsy may be performed. Partial removal should be considered if malignancy is detected in extemporaneous examination of samples.

Early postoperative enhanced MRI is recommended to evaluate the extent of resection.

As for spinal ependymomas, patients usually experience a transient worsening of preoperative status, caused by posterior myelotomy and manipulation of the spinal cord. An improvement of the preoperative status is rare.

In a recent meta-analysis, surgical resection and low histopathologic grade show to improve local control and survival [29]. GTR increases 10-year OS from 45–71% and mean OS from 50 to 67 months for low-grade SAs. The 5-year OS results of 100% in WHO grade II lesions, and 67–83% in mixed series. The range PFS in all SAs is 7–138.8 months.

Radiotherapy and chemotherapy are used in high-grade lesions or in case of progression following surgical resection. There are no randomized trials to guide recommendations for adjuvant treatment, so institutional practice varies. Some authors suggest fractionated radiotherapy for low-grade tumors partial resected and for all high-grade.

Radiotherapy improves OS in high-grade SAs, but no benefits are reported for low-grade lesions.

The potential benefits of radiotherapy should be balanced with the high risk of radiotoxicity. The spinal cord has a limited radiosensitivity, and these lesions occur mostly in children, who are at higher risk of adverse effect.

Limited data are available for chemotherapy too. It is reserved for high-grade SAs, which progress following resection and radiotherapy. It is also proposed to children younger than 3 years old, in whom radiotherapy is not performed. Chemotherapy regimens are based on the Stupp protocol for brain glioblastomas and Temozolomide is mostly used. Some small series reported promising results for recurrent or unresectable lesion, but controversies still exist [30].

4. Spinal hemangioblastoma

4.1 Epidemiology

The spinal hemangioblastoma (SH) is a benign lesion of mesenchymal origin, arising from the vascular system. It is the third most frequent intramedullary lesion and accounts for 3–4%. The annual incidence is approximately 0.01 per 100.000 persons. 30% of patients with SH present VHL syndrome, which is characterized by mutation of VHL gene causing increased expression of the vascular endothelial growth factor (VEGF), responsible for the development of these vascular tumors. Patients affected by VHL syndrome usually present multiples CNS hemangioblastomas and concomitant retinal hemangioblastomas, pheochromocytoma, renal cell carcinoma, and pancreatic cysts [31].

SH occurs more commonly in men and during the fourth decade, but they may remain asymptomatic for years. In half of the cases, they are located in the cervical spinal cord while thoracic and lumbar spines are involved in 37 and 12% of cases, respectively [32].

4.2 Histopathology

SH is a highly vascularized lesion, well demarcated but not capsulated. It usually has a pial attachment and arises from the dorsal or dorsolateral region of spinal cord. A solid nodule is normally found, and it is frequently associated with cysts. The liquid cysts are similar to blood plasma, and it is probably a vascular exudate of the hypervascularized nodule.

SH is composed of a rich vascular network of capillary containing endothelial cells, pericytes, and lipid-laden stromal cells. The cell of origin is unknown but genetic analysis of sporadic and syndromic hemangioblastomas suggests VEGF-secreting undifferentiated mesenchymal cell. The most common staining proteins are S100 and vimentin.

According to histopathological morphology, two forms of SH exist. The reticular form, composed of irregular nuclei and prominent vessels, and the cellular form, which has minor vascular component and increasing stromal cells. The latter one may be histologically similar to astrocytomas.

The two forms are classified as WHO tumor grade I [32].

4.3 Clinical presentation

Medical history is like the other intramedullary lesion, with a combination of axial-radicular pain and spinal cord compression signs. Posterior cord signs and symptoms may be predominant while motor impairment is more delayed because of the posterior location [32]. Unilateral spinal cord compression with dissociate sensory impairment may occur.

Despite the high vascularity, hemorrhage is rare. The hemorrhage is subarachnoid in 73% of cases and intramedullary in 27%. Subarachnoid hemorrhage generally manifests with acute headache and/or axial pain. Intramedullary bleeding causes acute neurological signs.

4.4 Radiographic features

SH is a well-circumscribed lesion typically founded in the posterior and posterolateral spinal cord.

MRI allows differentiation from other ITs in most of the cases. SH appears as hypervascular highly enhancing nodule arising from the pial surface (**Figure 3**). In T1-weighted images, the nodule is usually iso to hypointense compared to spinal cord and identification is difficult. T2-weighted images show an iso- to hyperintense nodule associated with flow voids, vascular anomalies, and vasogenic edema. Cysts formation is observed in 50–70% of cases and syrinx in more than 50% of cases. Spinal cord widening is commonly observed and is mainly related to vascular congestion and consequent edema.

Spinal angiography is usually performed preoperatively, and it clearly identifies the main arterial feeders and draining veins. It allows a better comprehension of the vascular anatomy to confirm diagnosis and aiding surgical planning. Embolization may be performed in selected cases [33].

4.5 Treatment and prognosis

Surgery is recommended for all symptomatic SHs, otherwise observation is recommended for asymptomatic lesions. Surgical resection is extremely favorable

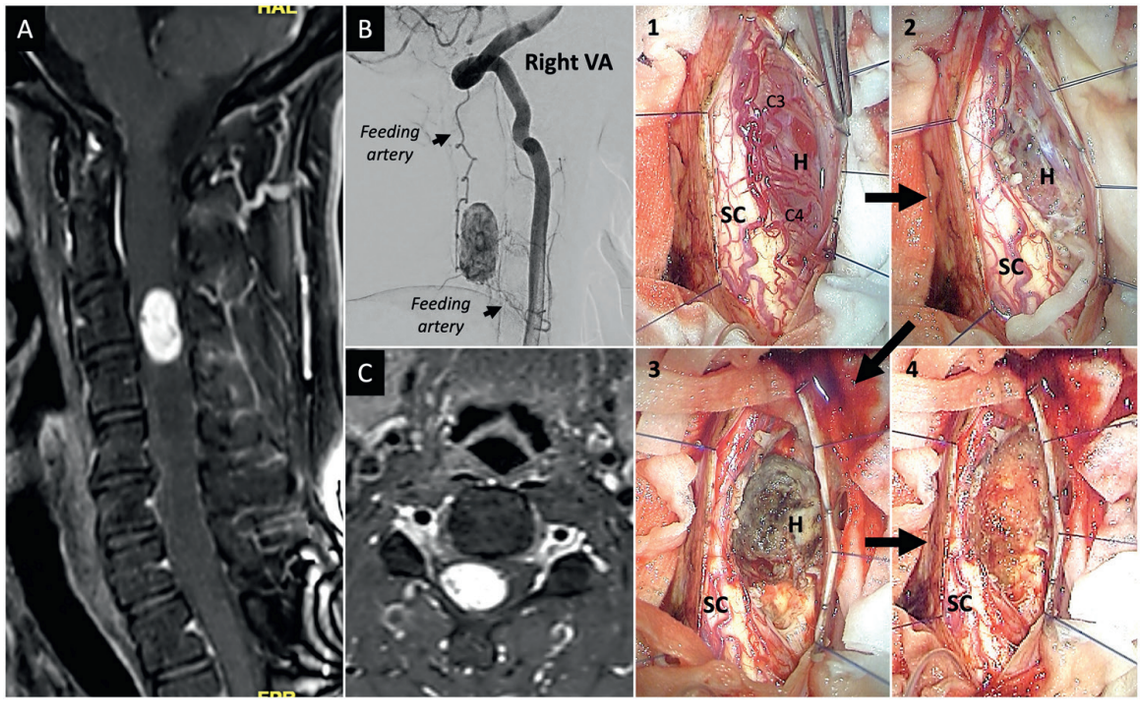

Figure 3.
Spinal hemangioblastoma. Preoperative MRI (A, C) shows a highly enhancing lesion. Angiography (B) confirms the hypervascularity with multiple feeders from the right vertebral artery. Intraoperative sequences are reported: exposition [1], partial deafferentation [2, 3], and complete resection [4] of the hemangioblastoma. VA vertebral artery, SC spinal cord, H hemangioblastoma, C3-C4 third and fourth cervical nerve root.

due to the posterior localization, the limited size, and the well-demarcated margins. Commonly more than 95% of patients are addressed for surgical resection, and GTR is obtained in approximately 83.5% of cases [32]. Preoperative spinal angiography allows an extensive comprehension of the vascular anatomy. It may help to distinguish the arterial feeder and the draining veins from the normal vasculature. The understanding of the vascular anatomy simplifies the surgical resection decreasing the risk of erroneous artery sacrifice and spinal cord ischemia.

Preoperative embolization significantly reduces the risk of intraoperative bleeding. It is technically challenging and can be performed in selected cases. It is reported in around 8% of cases [32]. The superselective catheterization of the small tortuous feeders is frequently not possible. A more proximal embolization is at risk of spinal cord ischemia and may develop collateral revascularization of the tumor. A subtotal embolization is usually preferred to avoid vascular rupture and ischemia.

Surgical approach depends on localization of the lesion. Most of the SHs are posterior and surgical resection is then performed through a standard posterior midline approach. More lateral lesions may be exposed thanks to dentate ligament opening, mobilization, and gentle spinal cord rotation. Transtubular resection is possible depending on nodule size. Anterior approach is described for anterior locate lesions. Intraoperative monitoring is mandatory with PEM and PES registration. Epidural D-was is preferable.

After durotomy, SH is usually easily identified. It appears as a well-delimitated bright red lesion with pial attachment associated with adjacent vascular anomalies. The feeding arteries should be rapidly identified and coagulated, to obtain a complete devascularization. The draining veins should be coagulated at the final stage to avoid vascular surcharge and rupture. Sometimes it is not easy to discriminate the arterial feeders from the vessels supplying the normal spinal cord. The Indocyanine green

video-angiography (ICG-VA) is a useful tool to distinguish arterial feeders and draining veins intraoperatively. Temporary clipping of the arterial feeders associated with intraoperative neuromonitoring may provide additional information to avoid spinal cord injury [34, 35]. Operative microscope is used to identify and dissect the tumors' margins from the pia. Complete *en bloc* resection is preferable. There is no evidence that syrinx or cysts opening may improve functional outcome, and they usually disappear following the resection of SH [36].

The most common postoperative complication is CSF leak, up to 30%, followed by surgical site hematoma and infection, reported in 20 and 16.6% of cases, respectively.

The outcome is generally good with a mortality rate lower than 2%. Compared to neuroepithelial lesions (ependymomas and astrocytoma), functional recovery is observed in most cases, because of the superficial and non-infiltrative features. Sensory symptoms and pain have shown to improve in 72 and 90% of cases in a recent systematic review [32].

Early postoperative enhanced spinal MRI to verify the extent of resection is usually performed. Follow-up is conducted with repeated MRI. The frequency depends on the estimated risk of recurrence.

Recurrence is reported in 8% of sporadic SH and in 22% of patients affected by VHL syndrome and is more frequent following STR.

Radiotherapy is reserved for recurrent or inoperable lesions. The advancement in radiosurgery improved the accuracy, reducing spinal cord irradiation.

5. Other intramedullary tumors

5.1 Spinal gangliogliomas

Gangliogliomas are benign tumors (WHO grade I and II) of neuronal and glial origins. Intramedullary gangliogliomas occur mostly in the pediatric populations. They are composed of ganglions and glial cells. The glial cells are at risk of malignant transformation. Two histologic subtypes are described: the classic ganglioglioma, which is reported in 59% of cases, and the pilocytic-like ganglioglioma (41% of cases) where ganglion cells are combined with histological features of pilocytic astrocytoma. Ganglioglioma is typically associated with scoliosis and at MRI, it is not easily differentiated from neuroepithelial spinal cord tumors.

Among treatment, surgery is the first option, with GTR generally obtained in about 80% of cases. Radiotherapy is reported for recurrence. The oncological outcome is favorable with a 10-year survival rate of 83% [37, 38].

5.2 Spinal lymphoma

Lymphoma in spinal cord is usually secondary. Primary intramedullary lymphoma accounts for 1% of all primary CNS lymphomas. Primary lymphoma is usually non-Hodgkin diffuse B-cell lymphoma. It occurs mostly in adults or elderly [2] and appears as a heterogeneously enhancing, diffuse lesion with hyperintensity in T2-weighted and ADC signal. It may be misdiagnosed with demyelinating lesions [26]. Chemotherapy is the recommended therapy. Treatment regimen is based on methotrexate and temozolomide. Surgery and radiotherapy are not suitable for the systemic nature and diffuse localization. Outcome is generally poor, and recurrence occurs in 2 months despite treatment [38].

5.3 Spinal melanoma

Primary intramedullary melanomas arise from the melanocytes normally present in the two inner meningeal layers (leptomeninges), the arachnoid and the pia. They are pigmented tumors of the spinal cord, without any evidence of systemic melanoma and account for 1% of all melanomas. They present a rapid growth and consequently symptoms of spinal cord compression progress promptly compared to other primary lesion of the spinal cord [2, 38]. At MRI they appear as lesion with homogeneous contrast enhancement. The presence of melanin gives hyperintense signal on T1-weighted images and causes susceptibility artifact in gradient recalled echo T2-weighted.

The protocol of treatment is based on anecdotal evidence in individual cases. Surgical resection seems to be the best treatment option, but GTR is rarely obtained, and radiotherapy is usually performed postoperatively. Intrathecal chemotherapy has been reported to improve OS and PFS [38].

5.4 Spinal metastases

Spinal metastases represent the 1–3% of ITs. They occur in 0.4% of patients with cancer and usually originate from lung and breast tumors [2]. Spinal metastases appear as circumscribed enhancing lesions with peripheric edema. They present typically two signs, which help to differentiate from primary spinal lesion, the rim, and the flame signs. The rim sign is a more intense peripheric enhancement compared to the central portion. The flame sign is a flame-shaped enhancement at the cranial and/or caudal portion [26]. Due to the rarity, few reports are available about treatment options. The outcome is poor, with a mean survival time of 4 months. Surgical resection may be attempted, but GTR is limited by the absence of clear margins. Long-course multifractionated radiotherapy is rarely an option for these patients with poor functional and oncological outcome. Chemotherapy shows controversial results [38].

6. Conclusions

ITs are rare tumors of CNS, potentially devastating. They represent a clinical and surgical challenge, although advances in the management were made. It is imperative to reduce delay in diagnosis and to develop novel treatments for aggressive and infiltrating type.

Clinical and radiological manifestations are quite homogeneous and preoperative diagnosis is rarely conclusive. Surgical resection is the primary treatment option in most cases and can be curative in benign lesions. Conversely, total resection avoiding major neurological impairment is demanding. Radiotherapy and chemotherapy are generally used for incomplete resection, recurrence, or inoperable lesions. No definitive guidelines exist for adjuvant treatments due to the rarity of these lesions. Functional improvement is rarely obtained, and neurological stability should be considered the goal. Oncological outcome is variable and depends on the histological grade.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

ITs	intramedullary tumors
GTR	gross total resection
CNS	central nervous system
PNET	primitive neuroectodermal tumors
AT/RT	atypical teratoid/rhabdoid tumor
NF1	neurofibromatosis 1
NF2	neurofibromatosis
VHL	Von Hippel Lindau disease
AVM	arteriovenous malformation
CSF	cerebrospinal fluid
RGCs	radial glial cells
SP-EPN	spinal ependymoma
SP-MYCN	spinal ependymoma with MYNC amplification
SSE	subependymoma
SMPE	spinal myxopapillary ependymoma
MEPs	motor evoked potentials
SEPs	sensory evoked potentials
GTR	gross total resection
STR	subtotal resection
WHO	world health organization
SAs	spinal astrocytomas
DTI	diffuse tensor imaging
SH	spinal hemangioblastoma
VEGF	vascular endothelial growth factor
ICG-VA	Indocyanine green video-angiography.

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