Ref: Ro J Neurol. 2024;23(1)
DOI: 10.37897/RJN.2024.1.18

Spinal Schwannoma: A review of the literature

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ABSTRACT

Spinal Schwannomas are rare, benign tumors originating from Schwann cells around peripheral nerves in the spinal canal, with significant clinical implications due to their potential to cause life-threatening neurological impairments. This comprehensive literature review integrates insights from pathology, anatomy, genetics, physiology, and radiology to offer a holistic understanding of spinal schwannomas, covering their clinical characteristics, diagnosis, management, and recent research developments. The aim is to enhance understanding, facilitate accurate diagnosis, develop targeted therapies, and improve clinical management, thereby contributing to better patient care and expanding knowledge on spinal schwannomas.

Keywords: Spinal Schwannoma, pathology, diagnosis, surgical resection, clinical management

INTRODUCTION

Spinal schwannomas are rare benign tumors that originate from Schwann cells, which form the sheath around peripheral nerves in the spinal canal [1]. Although rare, spinal schwannomas have a significant clinical impact due to their ability to cause potentially life-threatening neurological impairment. In-depth knowledge of the pathogenesis, clinical presentation, diagnosis and management of spinal schwannomas is important to guide appropriate clinical practice and maximize patient outcomes [2].

Although there has been significant research on spinal schwannomas, the literature covering various aspects of the disease is still not fully integrated. Therefore, in this article, we conduct a thorough review of the available literature to present a holistic understanding of spinal schwannomas. This review integrates information from various disciplines, including pathology, anatomy, genetics, physiology, and radiology, to provide a comprehensive overview of the clinical characteristics, diagnosis, management, and recent developments in spinal schwannoma research. Our goal is to gain a better understanding of spinal schwannoma, facilitating accurate diagnosis, the development of targeted therapies, and improvements in the clinical management of patients with this condition. As such, this article is expected to make a valuable contribution in improving patient care and expanding knowledge of spinal schwannoma as a whole.

EPIDEMIOLOGY

Spinal schwannomas are benign tumors that originate from Schwann cells, which form the sheath around peripheral nerves. These tumors are generally slow-growing and are most commonly found in the intradural extramedullary compartment of the spine [3,4]. Spinal schwannoma is a benign nerve sheath tumor within the spinal canal, usually arising from the spinal nerve roots and is the most common spinal nerve sheath tumor. It is one of the two most common intradural extramedullary spinal tumors, representing 15-50% of such lesions [5,6]. Spinal schwannomas are relatively rare, accounting for only a small proportion of spinal tumors. The disease is more common in adults, with a peak incidence in middle age, and shows no significant gender predilection [7].

Spinal schwannomas are relatively rare tumors, constituting only a small percentage of spinal tumors. Schwannomas, one of the most common intradural extramedullary tumors of the spine, show an annual incidence ranging from 0.3 to 0.5 per 100,000 people [8]. Typically, the disease appears in individuals during

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Article History:
Received: 28 February 2024
Accepted: 30 March 2024

their fourth and fifth decades of life, with a higher frequency occurring in adults than children or the elderly [9]. Interestingly, gender does not seem to affect the incidence of spinal schwannoma significantly, as the incidence is almost equal between men and women [10]. There are rare cases where schwannoma tumors arise within the spinal cord, which only occurs in about 1.1% of all spinal schwannoma cases. Usually, if these tumors occur in the spinal cord, they tend to appear in the neck of the spinal cord in 63% of the cases. Intramedullary schwannomas are more common in men at a ratio of 3 to 1 compared to women, and usually appear at around 40 years of age [11].

Although most schwannomas arise sporadically, the disease can also be associated with genetic conditions such as Neurofibromatosis Type 2 (NF2) and, more rarely, schwannomatosis, which has some clinical similarities with NF2 [12]. These tumors are predominantly localized in the cervical and lumbar regions of the spine, often presenting as intradural extramedullary growths [13], spinal schwannoma is relatively rare, mainly affecting adults showing a significant gender preference in its incidence.

MORPHOLOGICAL FEATURES

Schwannomas are encapsulated tumors composed primarily of Schwann cells. Embryologically, these tumors arise from neural crest cells and form a thin barrier around extracranial nerve fibers. These tumors can be single or multiple, and the latter is often seen in neurofibromatosis 2 (NF2). Morphologically, schwannomas are characterized by smooth, globoid masses attached to the nerve, and usually do not enlarge the nerve. Visibly, schwannomas can appear solid or rubbery, and sometimes contain melanin bodies or psammoma [14].

Microscopically, spinal schwannomas are circumscribed but incompletely encased. They contain spindle and epithelioid cells arranged in interlaced fascia, often with spin and sometimes nuclear palisades. Histologically, they consist of compact, interwoven collections of long spindle-shaped Schwann cells (Antoni tissue type A) and areas of more polymorphic Schwann cells embedded in a loose matrix (Antoni tissue type B) [15].

The first pattern, now called Antoni A, consists of cells that are more densely packed and arranged in fascicles, often in alternating rows forming a palisade of nuclei. The other pattern, now called Antoni B, contains more loosely arranged cells with variable lipidization. These differences in cellular populations may have a correlation with neuroimaging images, where heterogeneous signal intensity on MRI is often seen in regions with more Antoni B tissue. In contrast, regions with denser Antoni A tissue seem to correlate with slightly increased brightness on CT compared to regions dominated by Antoni B tissue. If the nuclear palisade within the schwannoma is prominent enough, then the structure forms what are now known as Verocay bodies. These two observations, both the palisade and Verocay bodies, together form the classic histopathological picture of a schwannoma [11].

There are several forms of schwannoma variations, including cellular schwannoma, plexiform schwannoma, and ancient schwannoma. Cellular schwannomas are characterized by an increased number of cells (usually consisting of Antoni A areas) compared to conventional schwannomas, and often occur in the paravertebral region. Plexiform schwannomas show a plexiform or multinodular growth pattern and tend to occur in the skin and subcutaneous tissues, rarely involving the spinal axis. Rarely, if nuclear pleomorphism (especially with cytoplasmic inclusions) and mitotic features are present, the tumor may be referred to as an ancient schwannoma. Recurrence is more common in cellular and plexiform schwannomas, and there are rare reports of transformation into malignant tumors [11].

There are several clinico-pathologic variants of schwannoma, including cellular schwannoma, plexiform schwannoma, epithelioid schwannoma, and melanotic schwannoma. Cellular schwannomas have a histologic appearance that resembles malignant neoplasms but have a favorable prognosis [16]. Spinal schwannomas are most commonly found in intradural-extramedullary locations. They may extend extraforaminally as a dumbbell mass or be purely extradural. Some schwannomas can be cystic, hemorrhagic, or fat-containing, and can be associated with degenerative changes [17]. On CT and MRI scans, schwannomas show varying density and intensity. They may show isodense or heterogeneous features on CT, while MRI shows isointense or slightly hyperintense characteristics on T2-weighted imaging. Schwannomas may also show hyperintense cystic areas and heterogeneous enhancement [18].

PATOPHYSIOLOGY

Schwannomas arise from the nerve sheath and are usually single lesions. The disease can be associated with genetic conditions such as Neurofibromatosis Type 2, but is often sporadic. The growth can cause compression of surrounding neural structures, leading to clinical symptoms. Schwannomas, also known as neurilemmomas, are benign tumors that arise from Schwann cells, which form the nerve sheath. Schwannomas originate from Schwann cells, which sheath peripheral nerves and are responsible for the myelinization of nerve fibers in the peripheral nervous system [19].

Although most schwannomas occur sporadically, the disease can also be associated with genetic condi-

tions such as Neurofibromatosis Type 2 (NF2), which is characterized by mutations in the NF2 gene encoding merlin or schwannomin, a tumor suppressor protein. Loss of function of this gene contributes to tumor progression [20]. Despite their sporadic nature, schwannomas, when growing, can compress surrounding neural structures, resulting in a variety of clinical symptoms including pain, sensory changes, and weakness, thus highlighting the importance of the compression effect on schwannoma symptoms [21].

HIPPO SIGNALING PATHWAY

The Hippo signaling pathway is an intracellular signaling pathway involved in the regulation of various physiological processes, including cell growth, proliferation, differentiation, and tissue formation. The pathway is named after the *Drosophila melanogaster* gene, Hippo, which was first identified as a regulator of cell growth and division in fruit flies.

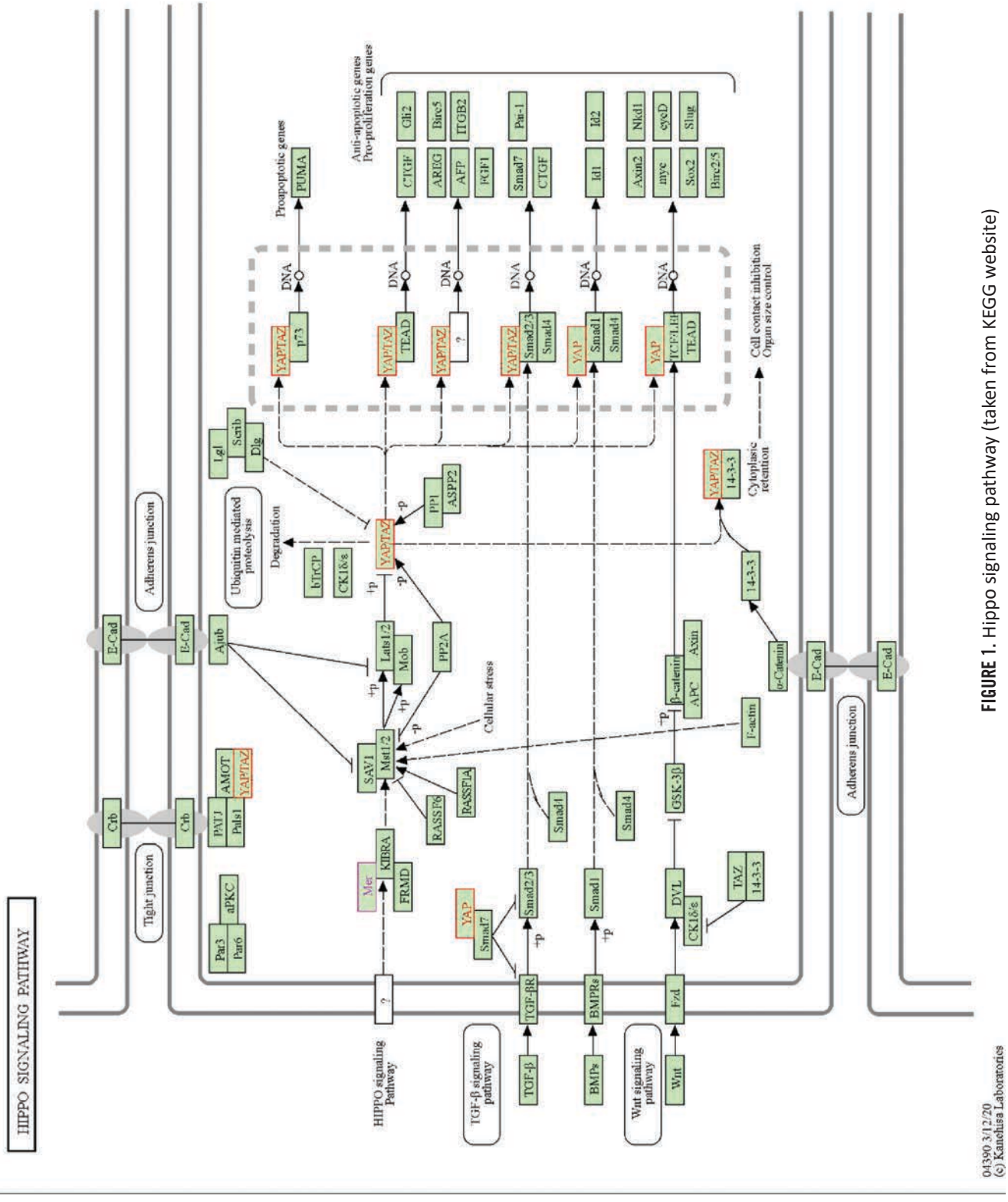

FIGURE 1. Hippo signaling pathway (taken from KEGG website)

1. Essential components: The Hippo signaling pathway involves a number of proteins and signaling molecules that work together to control cell growth. Some of the key components in this pathway include Hippo kinases (MST1/2), WW domain-containing scaffolding proteins (Salvador), and Yorkie-like transcription factors (YAP/TAZ) [22].

2. Regulation of cell growth: Activation of the Hippo signaling pathway results in phosphorylation and inactivation of Yorkie transcription factors (YAP/TAZ). YAP/TAZ normally functions as transcriptional coactivators that trigger the expression of genes that promote cell proliferation and growth. Thus, the Hippo signaling pathway plays a role in inhibiting cell growth by inhibiting the activity of YAP/TAZ [23].

3. Role in organ and tissue size regulation: The Hippo signaling pathway is also important in the regulation of organ and tissue size. Regulation of this pathway can affect cell division, cell size and the coordination of balanced tissue growth [23,25].

4. Response to mechanotransduction: The Hippo signaling pathway also responds to mechanical and mechanotransduction signals from the cellular environment. External factors such as extracellular matrix stiffness can affect the activity of these pathways, which in turn can affect cell morphology and other cellular responses [26]. Although the Hippo signaling pathway was initially identified in the context of organismal growth and development, the understanding of its role has expanded to involve many aspects of cellular biology, including cancer and tissue regeneration. Further research into the Hippo signaling pathway may provide new insights into disease mechanisms and potential new therapeutic targets.

Spinal schwannomas usually arise in or around the spinal cord. They can arise inside the spinal cord (intramedullary), outside the spinal cord (extramedul-

TABLE 1. Types of schwannomas

A. Intramedullary schwannomas			
Author & year	**Study type**	**Location**	**Suggestion**
Ho T et al., 2006 [27]	Case report	C5-6	tumor is in continuity with a thickened and enhancing spinal nerve root
Colosimo et al., 2003 [28]	Case report	C2-7, T-8	MRI findings of spinal cord intramedular tumor with edema and contrast enhancement should be considered as schwannoma, especially if there is enlargement of the spinal nerve root with contrast enhancement.
Solomon, R., et al. 1987 [29]	Case report	C1-5	Intramedullary schwannoma is a benign tumor with a distinct plane between the normal spinal cord and neoplastic tissue
Karatay, M et al., 2017 [30]	Case report	T12	Due to the high risk of postoperative complications, surgical management for these tumors should be planned according to intraoperative findings such as tumor attachment to neural tissue and frozen section examination.
B. Extramedullary schwannomas			
Author & year	**Study type**	**Location**	**Suggestion**
Ryu, K., et al 2011 [31]	Case report	T6 and T7	Surgery of intramedullary schwannomas that are accompanied by the same pathology as extramedullary beads in the thoracic spine. Complete surgical excision is the treatment of choice for spinal schwannomas, including intramedullary ones.
Kim, S. B., et al. 2010	Case report	L2-3	Spine surgeons should pay attention to the possibility of mobility and prevent additional laminectomy or secondary surgery with consideration of intraoperative myelography before the dural incision, as well as utilizing ultrasound or MRI to detect hidden or displaced tumors
Gorman, P., et al., 1989 [32]	Case report	C4-5	The use of MRI with gadolinium contrast post-operatively is helpful in determining the extent of the tumor and differentiating it from spinal cord edema. Intramedular schwannoma actually originates at or near the point of the dorsal nerve root penetrating the pia-arachnoid, an intraspinal "dumbbell" neurilemmoma with both intramedular and extramedular components.
C. Intradural-extramedullary schwannomas			
Author & year	**Study type**	**Location**	**Suggestion**
Friedman, D. P et al., 1992 [33]			Recognition of the MRI features of these types of neural tumors is essential for differentiating spinal lesions. Peripheral contrast enhancement in intradural extramedullary tumors specifically signals the diagnosis of schwannoma.
Koeller, K., & Shih, R. Y. 2019 [11]			Schwannomas associated with NF2, more commonly involving the dorsal spinal nerve roots, and causing radicular pain and other sensory symptoms.

lary), or between the spinal cord and the dura mater (intradural-extramedullary).

Spinal schwannomas are benign tumors of the peripheral nerve sheath, commonly found at intradural-extramedullary locations. Surgery is the primary treatment for these tumors, and radiation therapy is limited to managing residual or recurrent lesions that are not suitable for surgery [34]. Schwannomas can also appear in various types, including single and multiple forms, and can be cystic, hemorrhagic, melanotic, malignant, or even intraosseous. Its typical location is usually intradural and extramedullary, but some can be found intramedullary, extradullary, or intra-/extradullary [17].

CLINICAL PRESENTATION

1. General symptoms – Pain: local or radiating according to the tumor site, can be the first sign - Weakness: decreased muscle strength in the affected area - Sensory disturbances: tingling, numbness, or loss of sensation in the affected area

2. Location-dependent symptoms – Radicular symptoms: pain radiating to one or both extremities, corresponding to the nerves involved - Medular symptoms: sensory or motor deficits below the level of the affected spinal nerve, may result in impaired motor or sensory function in the lower body

3. Specific clinical manifestations – cervical schwannoma: symptoms in the neck, arms, and shoulders, sometimes accompanied by neurologic symptoms of the lower neck or symptoms of dysphagia - Thoracic Schwannoma: pain in the chest or upper back, sensory or motor disturbances along the thorax - Lumbar Schwannoma: pain or weakness in the lower back, hips, or lower legs, may be accompanied by symptoms of urinary incontinence or fecal incontinence if the cauda nerve is affected.

4. Course of disease – Symptoms may develop gradually over time, depending on the size and location of the tumor - Symptoms may increase progressively as the tumor grows or if the tumor begins to compress important nerve structures

5. Presentation variants – Clinical presentation may vary depending on the nature of the tumor, such as size, growth, and location - Smaller or slow-growing tumors may be asymptomatic or have mild symptoms, while larger or fast-growing tumors are more likely to cause noticeable symptoms.

Patients with spinal schwannomas often present with complaints of pain, which can be localized or radicular. Other symptoms may include sensory disturbances, weakness, or bowel/bladder dysfunction, depending on the location and size of the tumor. Patients with spinal schwannoma often present with a range of symptoms that vary based on the location and size of the tumor. Patients with spinal schwannomas typically experience a variety of symptoms that significantly impact their quality of life. Pain is a common complaint, often local or radicular in nature and associated with nerve roots affected by tumor growth. Despite surgical and medical interventions, chronic pain may persist, posing challenges in its management [35]. Sensory disturbances, including abnormal sensations such as dysesthesia, numbness, and tingling, often accompany the presence of schwannomas, stemming from tumor pressure on the spinal nerves [36]. Muscle weakness, especially in the limbs, may also occur if the schwannoma compresses the spinal cord or nerve roots, leading to mobility difficulties and hampering daily activities [37].

In addition, when the tumor is located near critical areas such as the conus medullaris or cauda equina, patients may experience bladder and bowel dysfunction due to nerve compression affecting these functions [38]. Although rare, acute neurological damage can occur, especially in cases of abrupt tumor changes such as torsion or infarction, highlighting the potential severity of spinal schwannomas [39]. So it can be said that the clinical picture of spinal schwannoma can include pain, sensory disturbances, weakness, and bladder/bowel dysfunction, reflecting the impact of the tumor on various nerve structures in the spine.

DIAGNOSIS

Diagnosis is primarily done through imaging, with MRI as the modality of choice. Schwannomas usually present as well-demarcated, contrast-enhancing lesions. Postoperative histopathologic examination confirms the diagnosis. On MRI examination, spinal schwannoma is usually shown as a nodular mass appearing within the dural sheath (intradural), with a higher signal than the surrounding tissue on T1 images and a distinct signal on T2 images. These masses usually have clear borders. Contrast enhancement on MRI is also often seen, indicating the presence of blood vessels associated with the tumor. This schwannoma most commonly arises from the dorsal sensory nerve root in the lower lumbar region [11].

Schwannomas show distinct imaging images on MRI, usually appearing as well-demarcated lesions with contrast enhancement. On T1-weighted images, they often display a low-intensity or iso signal, whereas on T2-weighted images, they appear as a high-intensity signal. This characteristic plays an important role in distinguishing them from other spinal tumors, such as meningiomas [40]. Histopathologic examination after surgery is essential to confirm the diagnosis of schwannoma. Features such as Antoni A area, Verocay bodies, and positive S-100 staining are typical indicators of schwannoma and help in establishing a definitive diagnosis. [41]. Despite their typical MRI images, schwannomas sometimes present with variations, such as hy-

pointensity on T2-weighted imaging, which may pose diagnostic challenges [42]. Although MRI remains the primary diagnostic tool, other imaging modalities such as CT scans may be used in certain cases to assess bony involvement or provide additional anatomical details that complement MRI findings [43], MRI plays an important role in the initial diagnosis of spinal schwannoma, providing detailed information about the characteristics of the lesion. Postoperative histopathology analysis is essential to confirm the diagnosis. The variability of MRI features and the use of complementary imaging techniques can aid accurate diagnosis and treatment planning.

MRI characteristics of spinal schwannomas, compared to neurofibromas, can be distinguished by certain features:

1. T1 signal intensity: About 75% of schwannomas are isointense, while 25% are hypointense on T1-weighted MRI images. This characteristic helps differentiate schwannomas from other spinal tumors [44].

2. T2 signal intensity: More than 95% of schwannomas appear hyperintense on T2-weighted images, often displaying mixed signal intensities. This feature is crucial for differentiating schwannomas from neurofibromas, which may have different T2 characteristics [45].

3. Enhancement with contrast: Almost all schwannomas are enhanced with contrast on T1-weighted images. This almost universal enhancement is a key diagnostic feature that distinguishes them from other similar tumors [46].

4. A unique case of melanotic schwannoma: Melanotic schwannomas are an exception to the general MRI characteristics of typical schwannomas. They are hyperintense on T1 and hypointense on T2-weighted images, which is opposite to the signal characteristics of typical schwannomas [42]. These MRI characteristics are critical for accurate diagnosis and differentiation of spinal schwannomas from neurofibromas and other similar spinal tumors..

TREATMENT

The primary treatment is surgical resection, which is often curative. The approach and extent of surgery depends on the size and location of the tumor. If surgery is not possible, radiotherapy or routine monitoring may be an alternative. The primary treatment for spinal schwannomas often involves surgical resection, which aims for total removal while preserving neurovascular structures. Surgical approaches and techniques have undergone significant advances, with a focus on maintaining neurological function alongside tumor removal. Total resection is usually curative for sporadic tumors, emphasizing the importance of this measure in achieving long-term outcomes [10].

In cases where surgery is not possible or for malignant or recurrent tumors, radiotherapy is an appropriate alternative. Fractionated stereotactic radiotherapy has shown good effectiveness and tolerance, particularly for cranial nonacoustic schwannomas, with excellent tumor control rates [47]. However, in situations where surgery is a high risk or the tumor is asymptomatic, regular monitoring may be recommended, and treatment initiated, if necessary, based on behavioral changes or tumor symptoms.

Preservation of neurologic function, especially cranial nerve function, is crucial in medicine. Advances in neurophysiologic monitoring techniques have played an important role in improving the safety and efficacy of surgery, reducing the incidence of postoperative neurologic deficits[48], the choice between surgical resection, radiotherapy, or monitoring of spinal schwannomas depends on a variety of factors, including tumor size, location, and overall patient health. Surgical resection remains the primary modality, but advances in radiotherapy provide an effective alternative for non-surgical cases. The ultimate goal is to achieve tumor control while preserving neurological function.

PROGNOSIS

The prognosis of patients with spinal schwannoma is generally good, especially with complete surgical resection. Recurrence is rare, but long-term follow-up is recommended. After complete surgical resection, conventional spinal schwannomas show a recurrence rate of approximately 5%, with local recurrence often occurring several years after surgery, thus underscoring the need for long-term follow-up [49].

Postoperative neurological outcomes, including functional recovery within 12 months, tended to be good, and utilization of intraoperative monitoring served as a significant predictor of positive functional outcomes [50]. Total resection of spinal schwannomas with preservation of neurovascular structures is the current treatment approach, aiming for neurologic and radiologic recovery with minimal perioperative and postoperative complications. The application of the proposed tumor classification system can facilitate preoperative planning and assist in choosing the appropriate surgical approach, thus avoiding unnecessary procedures [10].

Factors affecting recurrence and survival include tumor size and extent of surgical resection, with larger tumors and intralesional resection posing a greater risk of local recurrence. Overall patient survival in cases of spinal schwannoma is closely related to factors such as recurrence, tumor location, grade of pathology, as well as additional factors such as Ki67 labeling index and P53 expression [51].

It can thus be concluded that the prognosis for patients with spinal schwannoma following complete

surgical resection is generally good, with low recurrence rates and positive neurological outcomes. Long-term follow-up is recommended due to the potential for late recurrence. Factors such as tumor size, surgical technique, and degree of pathology have a significant impact on prognosis.

MINIMALLY INVASIVE SURGERY

Recent advances in minimally invasive surgery (MIS) and intraoperative monitoring have significantly improved outcomes and reduced complications in the treatment of spinal schwannomas. Minimally invasive surgical techniques have revolutionized the resection of intradural extramedullary schwannomas, with approaches such as muscle splitting and unilateral hemilaminectomy demonstrating efficacy in reducing operative time, blood loss and hospitalization compared to traditional total laminectomy methods [52].

Endoscopic-assisted microsurgery has emerged as a useful approach, particularly for vestibular schwannomas, providing better results in nerve preservation and reducing postoperative complications. The superior visualization produced by endoscopic techniques plays an important role in preserving vital structures in the operative field [53]. In addition, the integration of robotic systems such as the da Vinci robot with traditional approaches has been explored for the removal of large whole spinal schwannomas, especially those with intrathoracic extension, showing promising results and expanding the armamentarium of surgical options [54].

Intraoperative neurophysiologic monitoring has become standard practice in spinal schwannoma surgery, contributing significantly to decreasing the rate of postoperative neurologic deficits and improving overall surgical safety [48], the integration of MIS, endoscopic techniques and robotic systems, as well as improved neurophysiological monitoring, has greatly improved the surgical management of spinal schwannomas, resulting in better patient outcomes and reduced complication rates.

CONCLUSION

Spinal schwannomas are rare tumors that originate from Schwann cells, which line the peripheral nerves. Although rare, these tumors can cause a variety of neurological symptoms, depending on their location and size. Diagnosis usually relies on careful clinical evaluation, followed by the use of imaging techniques such as MRI to get a clearer picture. In some cases, a biopsy may be required for histological confirmation.

The primary treatment for spinal schwannoma is surgical resection, which aims to remove the tumor in its entirety while minimizing damage to healthy nerve tissue. The use of minimally invasive surgical techniques and intraoperative monitoring has evolved, providing improvements in patient outcomes with reduced risk of complications. Prognosis is generally good, with many patients achieving full or substantial neurological recovery after surgery. However, long-term follow-up is required to detect and appropriately manage possible tumor recurrence.

Conflicts of interest: none declared
Financial support: none declared

REFERENCES

1. Suárez C, López F, Rodrigo JP, Mendenhall WM, de Bree R, Mäkitie AA, et al. Benign Peripheral Non-cranial Nerve Sheath Tumors of the Neck. *Adv Ther.* 2022 Aug;39(8):3449-3471. doi: 10.1007/s12325-022-02191-5.
2. Lubelski D, Pennington Z, Ochuba A, Azad TD, Mansouri A, Blakeley J, Belzberg AJ. Natural History of Brachial Plexus, Peripheral Nerve, and Spinal Schwannomas. *Neurosurgery*. 2022 Dec 1;91(6):883-891. doi: 10.1227/neu.0000000000002118. Epub 2022 Sep 7. PMID: 36069570.
3. Qi X, Shan FY, Feng D, Huang And JH. Surgical Treatment of Benign Spinal Cord Tumors,. In: Arnouk H (Ed). Cancer Immunotherapy and Biological Cancer Treatments. IntechOpen, 2019. doi: 10.5772/intechopen.86580.
4. Mueller KB, Voyadzis JM. Resection of a Large Thoracic Schwannoma: 2-Dimensional Operative Video. *Oper Neurosurg* (Hagerstown). 2021 Mar 15;20(4):E297. doi: 10.1093/ons/opaa381.
5. Chung JY, Kim SS, Kim SK. Spindle cell type malignant peripheral nerve sheath tumor arising in benign schwannoma with multiple intraosseous spinal metastasis: A case report. *J Back Musculoskelet Rehabil.* 2017 Sep 22;30(5):1129-1135. doi: 10.3233/BMR-169590.
6. Landeiro JA, Ribeiro CH, Galdino AC, Taubman E, Guarisch AJ. Cellular schwannoma: a rare spinal benign nerve-sheath tumor with a pseudosarcomatous appearance: case report. *Arq Neuropsiquiatr.* 2003 Dec;61(4):1035-8. doi: 10.1590/s0004-282x2003000600029.
7. Kshettry VR, Hsieh JK, Ostrom QT, Kruchko C, Barnholtz-Sloan JS. Incidence of vestibular schwannomas in the United States. *J Neurooncol.* 2015 Sep;124(2):223-8. doi: 10.1007/s11060-015-1827-9. Epub 2015 May 30. PMID: 26024654.
8. Zamorano J, et al. Risk Factors for Local Recurrence after Surgical Resection of Spine Schwannomas: Retrospective Analysis of 169 Patients from a Multicenter International Database. *Glob Spine J.* 2015 May; 5(1_suppl):s-0035-1554109-s-0035-1554109. doi: 10.1055/s-0035-1554109.
9. Pfeifle R, Baur DA, Paulino A, Helman J. Schwannoma of the tongue: report of 2 cases. *J Oral Maxillofac Surg.* 2001 Jul;59(7):802-4. doi: 10.1053/joms.2001.24298.
10. Sun I, Pamir MN. Non-Syndromic Spinal Schwannomas: A Novel Classification. *Front Neurol.* 2017 Jul 17;8:318. doi: 10.3389/fneur.2017.00318.
11. Koeller KK, Shih RY. Intradural Extramedullary Spinal Neoplasms: Radiologic-Pathologic Correlation. *Radiographics*. 2019 Mar-Apr;39(2): 468-490. doi: 10.1148/rg.2019180200.
12. Evans DG, Bowers NL, Tobi S, Hartley C, Wallace AJ, King AT, et al. Schwannomatosis: a genetic and epidemiological study. *J Neurol Neurosurg Psychiatry.* 2018 Nov;89(11):1215-19. doi: 10.1136/jnnp-2018-318538.
13. Shah KA, Shah AC. Paraspinal Schwannoma of dorsal ramus nerve: A case report. *J Clin Orthop Trauma*. 2018 Jun;9(Suppl 2):S1-S4. doi: 10.1016/j.jcot.2018.04.012.
14. Carney JA. Psammomatous melanotic schwannoma. A distinctive, heritable tumor with special associations, including cardiac myxoma and

the Cushing syndrome. *Am J Surg Pathol.* 1990 Mar;14(3):206-22. doi: 10.1097/00000478-199003000-00002.
15. Kalra RR, Gottfried ON, Schmidt MH. Spinal Schwannomas: An Updated Review of Surgical Approaches. *Contemp Neurosurg.* 2015 Jul; 37(15):1–8. doi: 10.1097/01.CNE.0000475612.02065.01.
16. Seppälä MT, Haltia MJ. Spinal malignant nerve-sheath tumor or cellular schwannoma? A striking difference in prognosis. *J Neurosurg*. 1993 Oct;79(4):528-32. doi: 10.3171/jns.1993.79.4.0528.
17. George B, Bruneau M. Schwannomas of the Cervical Spine. In: Van De Kelft E (Ed). Surgery of the Spine and Spinal Cord. Cham: Springer International Publishing, 2016, p. 679–690. doi: 10.1007/978-3-319-27613-7_42.
18. Zhang E, Zhang J, Lang N, Yuan H. Spinal cellular schwannoma: An analysis of imaging manifestation and clinicopathological findings. *Eur J Radiol.* 2018 Aug;105:81-86. doi: 10.1016/j.ejrad.2018.05.025.
19. MacCollin M, Woodfin W, Kronn D, Short MP. Schwannomatosis: a clinical and pathologic study. *Neurology*. 1996 Apr;46(4):1072-9. doi: 10.1212/wnl.46.4.1072.
20. Twist EC, Ruttledge MH, Rousseau M, Sanson M, Papi L, Merel P, et al. The neurofibromatosis type 2 gene is inactivated in schwannomas. *Hum Mol Genet.* 1994 Jan;3(1):147-51. doi: 10.1093/hmg/3.1.147.
21. Skolnik AD, Loevner LA, Sampathu DM, Newman JG, Lee JY, Bagley LJ, Learned KO. Cranial Nerve Schwannomas: Diagnostic Imaging Approach. *Radiographics*. 2016 Sep-Oct;36(5):1463-77. doi: 10.1148/rg.2016150199.
22. Nishioka N, Inoue K, Adachi K, Kiyonari H, Ota M, Ralston A, et al. The Hippo signaling pathway components Lats and Yap pattern Tead4 activity to distinguish mouse trophectoderm from inner cell mass. *Dev Cell.* 2009 Mar;16(3):398-410. doi: 10.1016/j.devcel.2009.02.003.
23. Watt KI, Harvey KF, Gregorevic P. Regulation of Tissue Growth by the Mammalian Hippo Signaling Pathway. *Front Physiol.* 2017 Nov 24;8:942. doi: 10.3389/fphys.2017.00942.
24. Bhavnagari H, Raval A, Shah F. Deciphering Potential Role of Hippo Signaling Pathway in Breast Cancer: A Comprehensive Review. *Curr Pharm Des.* 2023;29(44):3505-3518. doi: 10.2174/0113816128274418231215054210.
25. Masliantsev K, Karayan-Tapon L, Guichet PO. Hippo Signaling Pathway in Gliomas. *Cells*. 2021 Jan 18;10(1):184. doi: 10.3390/cells10010184.
26. Barzegari A, Gueguen V, Omidi Y, Ostadrahimi A, Nouri M, Pavon-Djavid G. The role of Hippo signaling pathway and mechanotransduction in tuning embryoid body formation and differentiation. *J Cell Physiol*. 2020 Jun;235(6):5072-83. doi: 10.1002/jcp.29455.
27. Ho T, Tai KS, Fan YW, Leong LL. Intramedullary spinal schwannoma: case report and review of preoperative magnetic resonance imaging features. *Asian J Surg.* 2006 Oct;29(4):306-8. doi: 10.1016/S1015-9584(09)60108-1.
28. Colosimo C, Cerase A, Denaro L, Maira G, Greco R. Magnetic resonance imaging of intramedullary spinal cord schwannomas. Report of two cases and review of the literature. *J Neurosurg.* 2003 Jul;99(1 Suppl):114-7. doi: 10.3171/spi.2003.99.1.0114.
29. Solomon RA, Handler MS, Sedelli RV, Stein BM. Intramedullary melanotic schwannoma of the cervicomedullary junction. *Neurosurgery*. 1987 Jan;20(1):36-8. doi: 10.1227/00006123-198701000-00010.
30. Karatay M, Koktekir E, Erdem Y, Celik H, Sertbas I, Bayar MA. Intramedullary schwannoma of conus medullaris with syringomyelia. *Asian J Surg*. 2017 May;40(3):240-42. doi: 10.1016/j.asjsur.2014.04.004.
31. Ryu KS, Lee KY, Lee HJ, Park CK. Thoracic intramedullary schwannoma accompanying by extramedullary beads-like daughter schwanommas. *J Korean Neurosurg Soc.* 2011 May;49(5):302-4. doi: 10.3340/jkns.2011.49.5.302.
32. Gorman PH, Rigamonti D, Joslyn JN. Intramedullary and extramedullary schwannoma of the cervical spinal cord--case report. *Surg Neurol.* 1989 Dec;32(6):459-62. doi: 10.1016/0090-3019(89)90012-8.
33. Friedman DP, Tartaglino LM, Flanders AE. Intradural schwannomas of the spine: MR findings with emphasis on contrast-enhancement characteristics. *AJR Am J Roentgenol.* 1992 Jun;158(6):1347-50. doi: 10.2214/ajr.158.6.1590138.
34. Sohail A, Tariq A, Virani QU, Aziz HF, Shamim MS. Spinal Schwannomas; Classification, Management And Outcomes. *J Pak Med Assoc.* 2023 Oct;73(10):2118-2120. doi: 10.47391/JPMA.23-75.
35. Merker VL, Esparza S, Smith MJ, Stemmer-Rachamimov A, Plotkin SR. Clinical features of schwannomatosis: a retrospective analysis of 87 patients. *Oncologist*. 2012;17(10):1317-22. doi: 10.1634/theoncologist.2012-0162.
36. Morita H, Ito K, Miyazaki D, Fukushima K, Iwaya M, Hongo K, Ikeda S. Giant cauda equina schwannoma. *Neurol Clin Neurosci.* 2013 Jan;1(1): 42–43. doi: 10.1002/ncn3.1.
37. Sarikaya C, Varol E, Çakici YE, Naderİ S. Acute Neurologic Deterioration in Mobile Spinal Schwannoma. *World Neurosurg.* 2021 Feb;146:270-273. doi: 10.1016/j.wneu.2020.10.142.
38. Yang KS, Ho CS, Tai PA, Kung WM. Intraspinal schwannoma and neurogenic bladder. *Ann R Coll Surg Engl.* 2018 Apr;100(4):e69-e72. doi: 10.1308/rcsann.2018.0002.
39. Choy W, Khanna R, Ortmeier TC, Tapia-Zegarra GG, Lindley TE, Smith ZA, Dahdaleh NS. Acute Presentation of Lumbar Spinal Schwannoma Due to Torsion: A Case Report. *Cureus*. 2016 Apr 25;8(4):e586. doi: 10.7759/cureus.586.
40. Naruo S, Nakamura T, Ikeda T, Kikuchi T, Takagi K. Differential Diagnosis of Spinal Schwannoma and Meningioma with MRI. *Orthop Traumatol.* 2000;49(1):256–260. doi: 10.5035/nishiseisai.49.256.
41. Saha N. The attitudes and practice of Muslim patients using guttae medication during Ramadan. *Eye* (Lond). 2007 Jun;21(6):878-9. doi: 10.1038/sj.eye.6702753.
42. Kons ZA, Regenhardt RW, Dmytriw AA, Vranic JE, Huynh A, Frosch MP, et al. T2 Hypointense Schwannoma Masquerading As A Vascular Lesion: A Case Report. *Neurohospitalist*. 2022 Oct;12(4):659-663. doi: 10.1177/19418744221112539.
43. Liu WC, Choi G, Lee SH, Han H, Lee JY, Jeon YH, et al. Radiological findings of spinal schwannomas and meningiomas: focus on discrimination of two disease entities. *Eur Radiol.* 2009 Nov;19(11):2707-15. doi: 10.1007/s00330-009-1466-7. Epub 2009 Jun 6. PMID: 19504105.
44. Loke TK, Ma HT, Ward SC, Chan CS, Metreweli C. MRI of intraspinal nerve sheath tumours presenting with sciatica. *Australas Radiol.* 1995 Aug;39(3):228-32. doi: 10.1111/j.1440-1673.1995.tb00281.x.
45. Gouliamos AD, Kontogiannis DS, Androulidakis J, Kalovidouris AE, Vlahos LJ, Papavasiliou CG. Spinal neurilemmomas and neurofibromas: central dot sign in postgadolinium MRI. *J Comput Assist Tomogr*. 1993 May-Jun;17(3):446-8. doi: 10.1097/00004728-199305000-00021.
46. Mautner VF, Lindenau M, Baser ME, Hazim W, Tatagiba M, Haase W, et al. The neuroimaging and clinical spectrum of neurofibromatosis 2. *Neurosurgery*. 1996 May;38(5):880-5; discussion 885-6. doi: 10.1097/00006123-199605000-00004.
47. Zabel A, Debus J, Thilmann C, Schlegel W, Wannenmacher M. Management of benign cranial nonacoustic schwannomas by fractionated stereotactic radiotherapy. *Int J Cancer.* 2001 Dec 20;96(6):356-62. doi: 10.1002/ijc.1036.
48. Lenzi J, Anichini G, Landi A, Piciocchi A, Passacantilli E, Pedace F, et al. Spinal Nerves Schwannomas: Experience on 367 Cases-Historic Overview on How Clinical, Radiological, and Surgical Practices Have Changed over a Course of 60 Years. *Neurol Res Int*. 2017;2017:3568359. doi: 10.1155/2017/3568359.
49. Fehlings MG, Nater A, Zamorano JJ, Tetreault LA, Varga PP, Gokaslan ZL, et al. Risk Factors for Recurrence of Surgically Treated Conventional Spinal Schwannomas: Analysis of 169 Patients From a Multicenter International Database. *Spine* (Phila Pa 1976). 2016 Mar;41(5):390-8. doi: 10.1097/BRS.0000000000001232.
50. Hohenberger C, Hinterleitner J, Schmidt NO, Doenitz C, Zeman F, Schebesch KM. Neurological outcome after resection of spinal schwannoma. *Clin Neurol Neurosurg.* 2020 Nov;198:106127. doi: 10.1016/j.clineuro.2020.106127.
51. Li B, Li J, Miao W, Zhao Y, Jiao J, Wu Z, et al. Prognostic Analysis of Clinical and Immunohistochemical Factors for Patients with Spinal Schwannoma. *World Neurosurg.* 2018 Dec;120:e617-e627. doi: 10.1016/j.wneu.2018.08.135.
52. Lee JY, Lee SW, Nasir NH, How S, Tan CS, Wong CP. Diabetes telemonitoring reduces the risk of hypoglycaemia during Ramadan: a pilot randomized controlled study. *Diabet Med*. 2015 Dec;32(12):1658-61. doi: 10.1111/dme.12836.
53. Chovanec M, Zvěřina E, Profant O, Skřivan J, Cakrt O, Lisý J, Betka J. Impact of video-endoscopy on the results of retrosigmoid-transmeatal microsurgery of vestibular schwannoma: prospective study. *Eur Arch Otorhinolaryngol.* 2013 Mar;270(4):1277-84. doi: 10.1007/s00405-012-2112-6.
54. Perez-Cruet MJ, Welsh RJ, Hussain NS, Begun EM, Lin J, Park P. Use of the da Vinci minimally invasive robotic system for resection of a complicated paraspinal schwannoma with thoracic extension: case report. *Neurosurgery*. 2012 Sep;71(1 Suppl Operative):209-14. doi: 10.1227/NEU.0b013e31826112d8.