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Current state of spinal nerve sheath tumor management and future advances

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Abstract

Nerve sheath tumors are the most common tumors of the spine after meningiomas. They include schwannomas, neurofibroma, and malignant peripheral nerve sheath tumors. These can arise sporadically or in association with tumor predisposition syndromes, including neurofibromatosis type 1, neurofibromatosis type 2, and schwannomatosis. Though surgery is the traditional mainstay of treatment for these tumors, the discovery of the genetic and molecular basis of these diseases in recent decades has prompted investigation into targeted therapies. Here, we give a clinical overview of spinal nerve sheath tumors, their imaging features, current management practices, and explore ongoing advances in systemic therapies.

Keywords

malignant peripheral nerve sheath tumor | neurofibroma | neurofibromatosis | schwannoma | spinal nerve sheath tumor

Nerve sheath tumors are the second most common primary neoplasm in the spine, making up 24%–31% of spinal tumors.[1,2] They encompass benign schwannomas and neurofibromas as well as malignant peripheral nerve sheath tumors (MPNSTs). The initial insights into nerve sheath tumor biology came from observations of a family of genetic conditions that predisposed individuals to develop innumerable nerve sheath tumors. In 1882, Friedrich von Recklinghausen comprehensively described a syndrome that resulted in multiple tumors of the skin, peripheral and central nervous system.[3] It was not until a century later, in 1982, that Riccardi clearly differentiated between neurofibromatosis type 1 (NF-1), neurofibromatosis type 2 (NF-2), and neurofibromatosis type 3 (later renamed Schwannomatosis).[4] Further observations identified neurofibromas and MPNSTs as the most common tumors in NF-1, while schwannomas and meningiomas were the most common tumors in NF-2 and Schwannomatosis. The clinical subclassification of this family of tumor predisposition syndromes was an important catalyst to our understanding of the underlying biology of nerve sheath tumors.

In this review, we discuss the clinical features, imaging characteristics, and management options of spinal nerve sheath tumors. The molecular basis of these neoplasms and the subsequent development of novel targeted therapies are then explored.

Schwannomas

Approximately 95% of schwannomas arise spontaneously and are solitary. In contrast, multiple schwannomas are usually associated with neurofibromatosis type 2 or Schwannomatosis.[5,6] These tumors can occur at any age, but peak incidence is in the 4th to 6 decades of life.[2] Spinal schwannomas typically occur along a dorsal (sensory) spinal nerve root. The most common presenting symptoms are radicular pain and sensory symptoms in the distribution of the involved nerve, followed by motor weakness and sphincter dysfunction.[6–11] If large enough, schwannomas with an intradural component can compress the spinal cord and cause symptoms of myelopathy as well. Rarely, schwannomas can occur within the spinal cord, most commonly in the cervical region.[8] The pathophysiology of these intramedullary schwannomas remains unclear, given the absence of Schwann cells in the spinal cord. Like their intradural

extramedullary counterparts, sensory disturbances are the most common presenting symptom, and sphincter dysfunction is a late sign.[8] Schwannomas can but very rarely transform into malignant tumors.[12]

Neurofibromas

Neurofibromas may be spontaneous, solitary lesions, or multiple and associated with NF-1.[13,14] They can be categorized into cutaneous neurofibromas, peripheral nerve fibromas, and plexiform neurofibromas. Plexiform neurofibromas involve multiple nerve fascicles and are pathognomonic for NF-1, occurring in 40%–60% of NF-1 patients. Most importantly, these tumors, while benign, have the potential to transform into MPNSTs.[3,4,15,16] Within the spine, neurofibromas have a predilection for the cervical region and tend to be intraforaminal with extension into the extradural space.[13] MRI studies of NF-1 patients have revealed that while many have spinal tumors, about one-third of patients are asymptomatic.[14,17] In one series of 66 surgical cases, most patients presented with radicular pain (84%), 25% complained of sphincter dysfunction, and 30% had motor symptoms.[18] As with plexiform neurofibromas that develop elsewhere, the development of pain, new neurological symptoms, or growth in the setting of a known spinal plexiform neurofibroma may be an indication of malignant transformation into an MPNST.[6,19–21]

Malignant Peripheral Nerve Sheath Tumors

MPNSTs are aggressive nerve sheath tumors that can develop de novo or from malignant transformation of neurofibromas.[21] They are rare soft tissue sarcomas, occurring in only about 0.001% of the general population, and of these, only 2%–3% occur in the spine. MPNSTs are more common in NF-1 population, with 5%–10% developing an MPNST in their lifetime.[14,17] About 50% occur in patients with NF-1, and 10% are associated with prior radiation. Prognosis of MPNSTs overall is poor, with 5-year survival ranging from 34% to 44% despite aggressive treatment.[22–25] Spinal MPNSTs are poor and thought to be worse than extraspinal MPNSTs, likely related to the difficulty in achieving complete resection with wide margins, a critical prognostic factor for recurrence-free and overall survival.[22,26–28] Distant metastases are associated with NF-1 status and positive surgical margins, occurring in 40% of MPNST patients within 5 years despite aggressive treatment.[28] Prognosis after the development of metastasis is grim, with progression-free survival (PFS) and overall survival (OS) of 1.77 and 8.9 months, respectively.[22,29]

New to the 2021 WHO classification of CNS tumors is a subtype of neurofibroma entitled atypical neurofibromatous neoplasm of unknown biological potential (ANNUBP).[30] These are neurofibromas with some features of malignant transformation and likely represent an intermediary stage in the evolution from neurofibroma to MPNST.[30] As discussed later, ANNUBP should be considered malignant MPNST precursors and treated aggressively.

Imaging Features

MRI is the imaging modality of choice to characterize nerve sheath tumors of the spine.[31–33] [NO_PRINTED_FORM] Schwannomas are typically well-circumscribed lesions that extend along a dorsal spinal nerve root (Figure 1). They are hypointense to isotense on T1, hyperintense on T2, and enhanced with gadolinium contrast.[20] They may exhibit some heterogeneity due to cystic degeneration, and areas of T1 hyperintensity may be present due to hemorrhage.[20]

Like schwannomas, neurofibromas are usually well-demarcated and demonstrate T1 isointensity, T2 hyperintensity, and intense, homogenous enhancement.[20] Plexiform neurofibromas involve multiple nerve fascicles and are described as having a "bag of worms" appearance. Bilateral neurofibromas at the same spinal level can occur in NF-1 and spinal neurofibromatosis, a related clinical entity of predominantly spinal neurofibromas with few other NF-1 features.[16] These are described as "kissing" or mirror-image tumors.[14,20] Cervical "kissing" neurofibromas, lumbar spinal neurofibromas, and intradural neurofibromas are associated with neurologic impairment and have been incorporated in a scoring system that predicts risk for neurologic morbidity.[14] A described "target sign" on T2 sequences may also be seen in neurofibromas, where an area of low intensity corresponding to fibrocollagenous tissue is surrounded by a high-intensity ring of myxomatous tissue.[34] It is nonspecific sign, however, and can be seen in schwannomas and MPNSTs as well.[20,35]

The differentiation of MPNSTs from neurofibromas on MRI is challenging and generally unreliable, but some associated features have been described.[33] MPNSTs are often larger in size, have increased peripheral enhancement, more perilesional edema, poorly defined margins, poor contiguity with a single nerve, and more intratumoral cystic changes.[34,36] The target sign, although sometimes present in MPNST, is more predictive of neurofibromas.[34] On ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) imaging, MPNST are also more likely to demonstrate FDG uptake compared to benign nerve sheath tumors, with one study describing an overall sensitivity of 0.89 and specificity of 0.95, and a sensitivity of 1.0 for high-grade MPNSTs.[37] DWI sequences may also be helpful in identifying MPNSTs, which have a higher apparent diffusion coefficient.[38] A machine learning approach was recently developed with only post-gadolinium T1 sequences and outperformed human experts who had access to all available sequences. With further optimization and validation, such artificial intelligence tools may be useful adjuncts to help differentiate MPNSTs from benign lesions.[39]

Management

Benign Nerve Sheath Tumors

Schwannomas and neurofibromas causing intolerable radicular symptoms, spinal cord compression, and myelopathy, or those demonstrating growth on imaging warrant consideration of surgical resection. Gross total

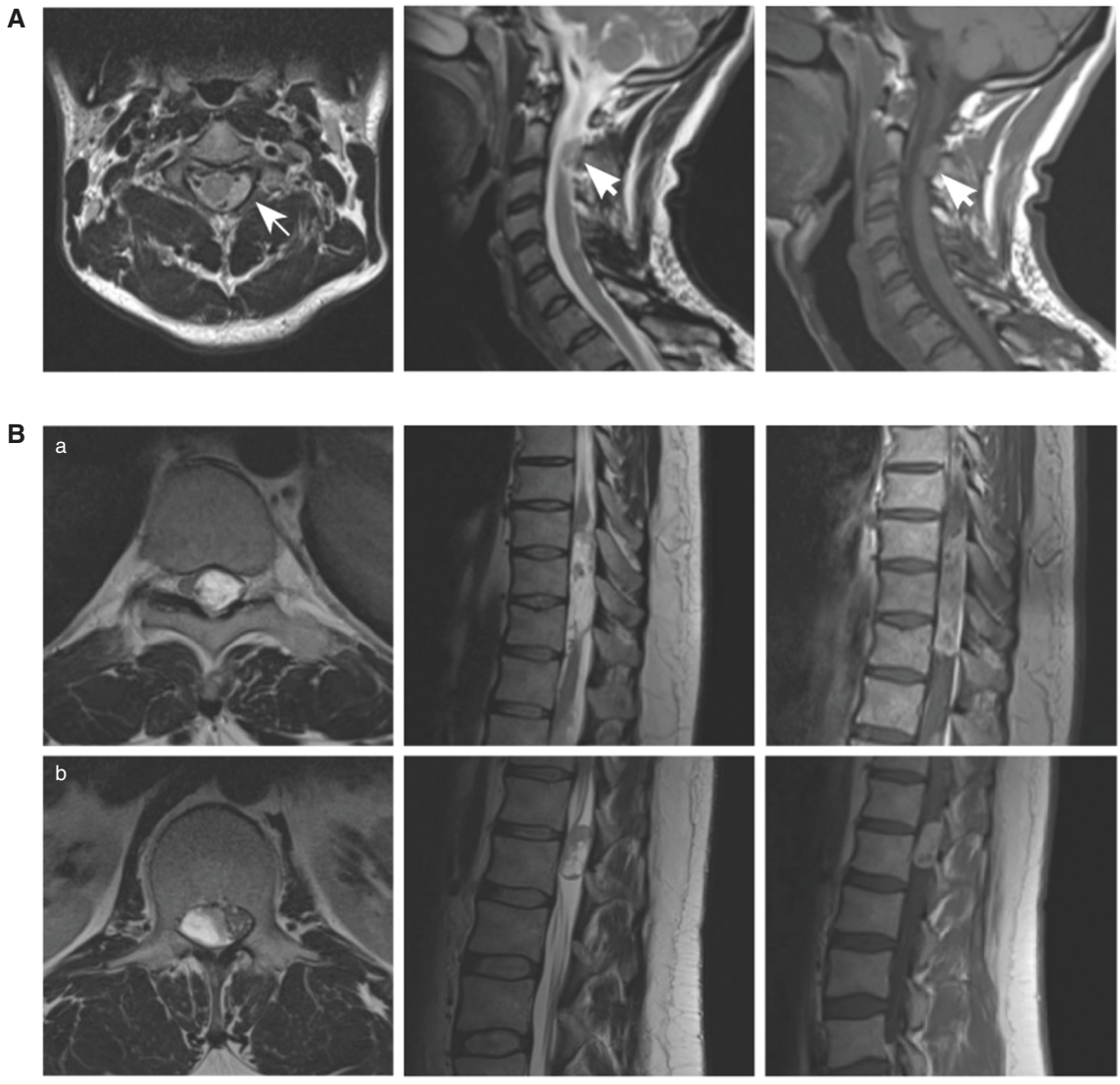

Figure 1. MRIs of spinal schwannomas. **(A)** Sporadic cervical spine schwannoma at C2. **(B)** Multiple spinal schwannomas in an individual with genetically confirmed SMARCB1-related Schwannomatosis. (a-c) Left-sided T9-11 thoracic lesion compressing the spinal cord and (d-f) right-sided lesion compressing the conus and cauda equina to the left at T12/L1. Both are partially cystic and enhancing.

resection without causing new deficits is the goal, and as schwannomas and neurofibromas are generally non-infiltrative lesions, complete resection is usually achievable and prevents recurrence.[10,11] Intraoperative neurophysiologic monitoring should be incorporated to identify and avoid sacrificing functional nerves.[11] Surgical series report postoperative improvement or complete recovery in 69%–78% of[5,7,8,13,40] patients, with the best chance of improvement in lumbosacral tumors (81.53% vs. 72/73% in cervical/thoracic in one study).[5,7,8,13,40] Postoperatively, MRI is again the ideal imaging modality within 2–3 months to confirm the extent of resection.[10,11,41] Longer-term radiologic follow-up is surgeon- and institution-specific depending on the extent of resection, post-operative symptoms, and NF-1 status.[10,11,41] In uncomplicated patients with gross total resection, follow-up of 1–5 years has been reported. Recurrence is uncommon (3%–9%) and usually occurs within 4 years of surgery.[10,11,42] If residual tumor is present, regular repeat imaging should be performed to rule out interval growth that may prompt further treatment. The frequency should take the patient's individual risk factors into account, with sooner imaging if new symptoms or interval radiographic changes occur.

Surveillance with clinical examination and serial MRI is reasonable for asymptomatic or incidental lesions.[43,44] Natural-history studies of schwannomas suggest that most remain stable or grow slowly and may never require intervention, but a subset of faster-growing tumors warrant closer monitoring. One study reported 27.5% of 109 spinal schwannomas demonstrated 84%/year volume increase versus moderate- (26%/year) and slow-growing (7.3%/year) tumors. Another study of 42 spinal schwannomas reported an average volume increase of 5.45% annually, and their analysis suggested that tumors with more than 2.5% annual

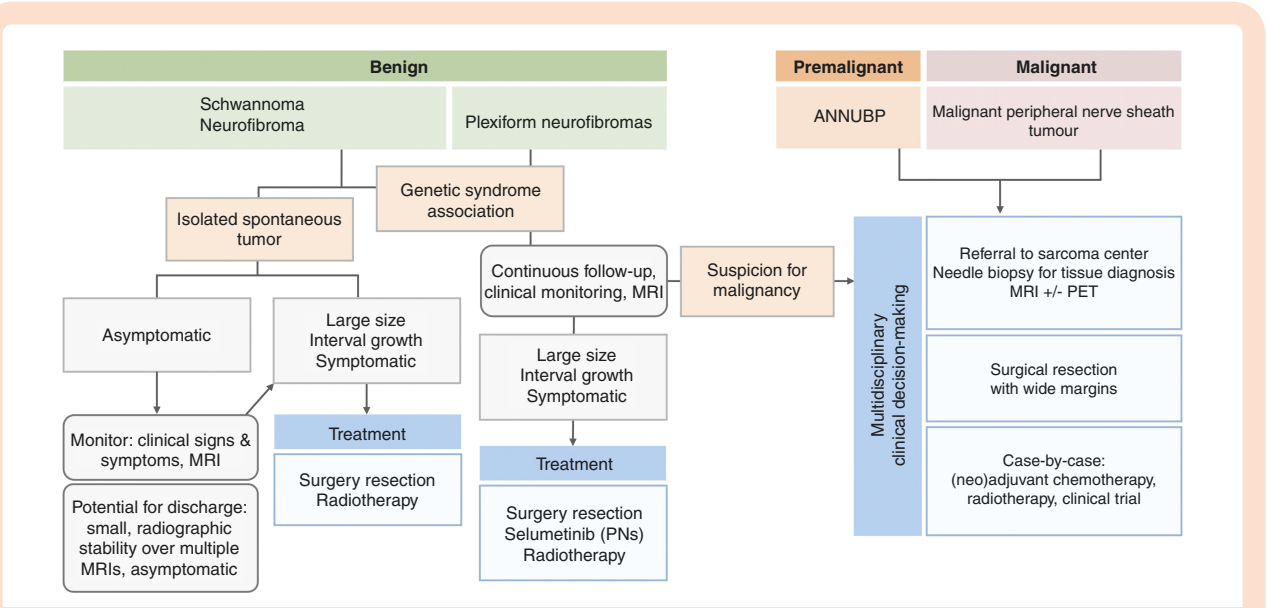

Figure 2. Schematic of clinical management pathways of spinal nerve sheath tumors. PNs, plexiform neurofibromas; atypical neurofibromatous neoplasm of unknown biological potential, Atypical neurofibromatous neoplasm with unknown biological potential.

growth, termed "growing" as opposed to "stable" tumors with slower growth, warranted close follow-up.[45,46] There are no consensus guidelines for the frequency or duration of imaging in isolated findings of asymptomatic benign spinal nerve sheath tumors, but at least 2 follow-up scans to assess growth rate have been suggested as a minimum.[46] Tumors associated with genetic syndromes may behave more aggressively and should be followed with regular repeat imaging according to their individual risk factors.

Plexiform neurofibromas, which are exclusive to NF-1 patients, are associated with malignancy risk. European consensus guidelines for management of NF-1 patients have recommended a whole-body MRI during adolescence to assess for tumor burden and risk of MPNST development.[19] Frequency of repeat imaging should be tailored to the individual's risk and managed by a multidisciplinary team.[19] In patients with an existing plexiform neurofibroma, new rapid growth, development of new neurological symptoms, worsening pain, or change in consistency of the lesion raises the possibility of transformation, and the tumor should be further investigated.[19] Surgical resection is the mainstay of treatment and is strongly considered for symptomatic plexiform neurofibromas.[19,26] Selumetinib, a MEK inhibitor that has demonstrated partial efficacy in symptomatic inoperable pediatric plexiform neurofibromas, was recently approved as the only systemic therapy for plexiform neurofibromas.[47,48]

Radiotherapy for benign spinal nerve sheath tumors is less established than that for intracranial lesions. Stereotactic body radiotherapy (SBRT) regimens remain physician- and institution-specific, with no specific guidelines. Indications and considerations described include residual or recurrent tumors after surgery, patient comorbidities, patient age, patient/clinician preference, and anatomic relationship to the spinal cord.[49–52] SBRT has been reported in retrospective series to be effective for pain relief (42%–73%) and tumor control in post-surgical residual tumors, recurrent tumors, and as an alternative to surgery in select patients.[9,51,52] It is also viable strategy for multiple spinal nerve sheath tumors in the setting of neurofibromatosis or Schwannomatosis.[52] Tumor regression in 2 of the largest series of SBRT on schwannomas ($n = 47$, $n = 47$) occurred in about half of lesions (47%–55%) with a local control maintained in 91%–95% over median follow-up periods of 43 and 29 months, respectively.[49,53] The effectiveness of SBRT on neurofibromas appears to be lower, with 20%–33% of patients experiencing worsening symptoms or radiographic progression despite treatment.[49–51] The ideal dose is currently uncertain, and this has been previously reviewed.[51] Longer-term studies, especially those assessing SBRT on neurofibroma and patients with neurofibromatosis, need to be conducted to understand characteristics associated with radiation response and to develop clearer patient selection criteria and treatment regimens.

Malignant Peripheral Nerve Sheath Tumors

The aggressive nature of MPNSTs demands accurate and timely tissue diagnosis if there is suspicion of malignancy.[19] As previously discussed, MRI should be performed to characterize suspicious lesions, and [18]FDG-PET can be useful in assessing potential malignancy. If ANNUBP or MPNST is suspected, imaged-guided needle biopsy is performed for histopathological diagnosis and guidance of the next steps.[19,31,32] Unplanned incomplete resection of a sarcoma where malignancy is only realized upon the reporting of pathology results is associated with increased morbidity and mortality.[54–56] This should be avoided with prompt referral to a sarcoma specialist center upon suspicious of a possible malignancy, and the referral should not await completion of imaging or biopsy.[31,57] Indeed, some surgical reports of MPNSTs specifically have

noted that radiographic misdiagnoses as benign entities are common, with 63.5% (5/8 patients) misdiagnosed on imaging in a series of craniospinal MPNSTs.[56,58] A multidisciplinary team at a sarcoma center should guide management decisions, including surgical management and whether there is a role for radiotherapy, chemotherapy, or experimental treatments.[31,54] En-bloc surgical resection with negative margins is the mainstay of treatment for ANNUBP and MPNSTs when possible, though this is often limited by surrounding anatomy.[12,19,21–23,58] An MRI with gadolinium performed within 24 hours of surgery before the development of post-surgical radiographic changes is ideal for an accurate baseline assessment, though international consensus guidelines developed from a surgical perspective suggest a baseline at 2–3 months is acceptable as well.[59,60] Subsequent imaging should be tailored to the patient's individual management. Though rare, schwannomas can also undergo malignant transformation into MPNSTs, and those with aggressive radiologic or clinical features should be similarly investigated.[12]

There is currently minimal evidence surrounding radiation and systemic therapies for MPNSTs.[21,22,61] In clinical trials, MPNSTs are often only present in small numbers and grouped with other biologically heterogeneous sarcomas, making it difficult to generalize trial findings to MPNSTs specifically. Retrospective series on MPNSTs have shown that adjuvant radiotherapy improves local control of the disease and recurrence-free survival.[22–24,60,61] Adjuvant radiotherapy has therefore been recommended for intermediate- and high-grade tumors when possible to delay recurrence, and low-grade tumors with subtotal resection should be considered as well.[60]The vast majority of these series, however, have not observed any overall survival benefit.[22–24,60,61]

The role of systemic treatment for MPNST similarly remains controversial, and chemotherapy is usually reserved for unresectable, progressive, or metastatic disease.[60,62] Clinical trials on adjuvant chemotherapy for sarcomas have produced conflicting results. Two large randomized control trials comparing adjuvant chemotherapy to control, European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) 62771 trial testing a cyclophosphamide/vincristine/doxorubicin/dacarbazine combination ("CYVADIC") and EORTC-STBSG 62931 testing a doxorubicin/ifosfamide combination, failed to show survival benefit with adjuvant chemotherapy.[63,64] The CYVADIC regimen improved local control only in a subgroup of head, neck, and trunk lesions, whereas the doxorubicin/ifosfamide did not delay local recurrence. Pooled analysis of both trials, however, showed adjuvant chemotherapy improved PFS but not OS,[27] and a post hoc analysis of the 62931 trial showed that a subgroup of high-risk patients (defined as predicted OS < 60% by the Sarculator nomogram[65]) had improved PFS and OS with adjuvant doxorubicin and ifosfamide.[66] A pooled analysis of only MPNST patients from 12 EORTC-STBSG trials later suggested that adjuvant chemotherapy improved PFS and that doxorubicin/ifosfamide was more effective than either agent alone.[67] Interestingly, this analysis also demonstrated that MPNSTs had similar responses to therapy compared to other sarcomas, with similar response rates, PFS, and OS.[67] In current practice, first-line chemotherapy for unresectable or metastatic MPNSTs is typically a combination of doxorubicin and ifosfamide.[62] Notably, chemotherapy-related toxicities are more common with combinatory therapy compared to treatment with ifosfamide alone but without added OS benefit, and this needs to be considered on an individual patient basis.[68] Multidisciplinary discussion regarding adjuvant therapy should include the identification of high-risk patients that may have increased benefit,[66] consideration of performance status and ability to tolerate chemotherapy,[67,68] the extent of disease,[68,69] and the degree of surgical resection.[27,69] Systemic therapy trials for MPNSTs are detailed in Table 3.

Table 1. Table of Clinical Trials for Schwannomas Since 2015

NCT number	Study title	Phase	Tumor	Drug	Mechanism	Start date	Completion date	Study status
NCT04374305	Innovative Trial for understanding the impact of targeted therapies in NF2-related schwannomatosis (INTUITT-NF2)	2	NF2-related tumors	Brigatinib Neratinib	Brigatinib: multi-target tyrosine kinase inhibitor Neratinib: EGFR, HER2, and HER4 tyrosine kinase inhibitor	June 20, 2020		Recruiting
NCT03095248	Trial of selumetinib in patients with neurofibromatosis type II related tumors	2	NF2-related tumors	Selumetinib (AZD6244)	MEK inhibitor	May 08, 2017		Recruiting
NCT05684692	Screening trial for pain relief in schwannomatosis (STARFISH)	2	Schwannoma	Siltuximab	Interleukin-6 antagonist antibody	August 31, 2023		Recruiting
NCT04163419	Phase 2 study of tanezumab in subjects with moderate to severe pain due to schwannomatosis	2	Schwannoma	Tanezumab	Anti-nerve growth factor antibody	April 30, 2020		Active, not recruiting

Table 2. Table of Clinical Trials for Neurofibromas Since 2015

NCT number	Study title	Phase	Tumor	Drug	Mechanism	Start date	Completion date	Study status
NCT02839720	Selumetinib in treating patients with neurofibromatosis type 1 and cutaneous neurofibroma	2	Neurofibroma	Selumetinib (AZD6244)	MEK inhibitor	August 26, 2017		Active, not recruiting
NCT05107037	A clinical trial to evaluate the tolerability and pharmacokinetics of TQ-B3234 in patients with type I neurofibromatosis	1	Neurofibroma, MPNST	TQ-B3234	MEK inhibitor	November 2021		Not yet recruiting
NCT05011019	A clinical trial to evaluate the safety and efficacy of AL2846 capsules in Chinese patients with type I neurofibromatosis	1/2	Neurofibroma, MPNST	AL2846	Multi-target receptor tyrosine kinase inhibitor, c-Met inhibitor	September 07, 2021		Recruiting
NCT03326388	Intermittent dosing Of selumetinib in childhood-associated tumors	1/2	NF1-related tumors	Selumetinib (AZD6244)	MEK inhibitor	September 26, 2019		Recruiting
NCT04495127	Selumetinib pediatric NF1 Japan Study	1	Plexiform neurofibroma	Selumetinib (AZD6244)	MEK inhibitor	August 31, 2020	March 24, 2023	Completed
NCT03962543	MEK inhibitor mirdametinib (PD-0325901) in patients with neurofibromatosis type 1 associated plexiform neurofibromas	2	Plexiform neurofibroma	Mirdametinib (PD-0325901)	MEK inhibitor	September 29, 2019		Active, not recruiting
NCT03741101	Treatment of NF1-related plexiform neurofibroma with trametinib	2	Plexiform neurofibroma	Trametinib	MEK inhibitor	June 10, 2019		Active, not recruiting
NCT03363217	Trametinib for pediatric neuro-oncology patients with refractory tumors and activation of the MAPK/ERK pathway.	2	Plexiform neurofibroma	Trametinib	MEK inhibitor	August 16, 2018		Active, not recruiting
NCT03231306	Phase II study of binimetinib in children and adults with NF1 plexiform neurofibromas	2	Plexiform neurofibroma	Binimetinib	MEK inhibitor	November 28, 2017		Active, not recruiting
NCT02407405	MEK 1/2 inhibitor selumetinib (AZD6244 hydrogen sulfate) in adults with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas	2	Plexiform neurofibroma	Selumetinib (AZD6244)	MEK inhibitor	January 07, 2016		Active, not recruiting
NCT02390752	Phase I trial of turalio(R; pexidartinib, PLX3397) in children and young adults with refractory leukemias and refractory solid tumors including neurofibromatosis type 1 (NF1) associated plexiform neurofibromas (PN)	1	Plexiform neurofibroma	Pexidartinib (PLX3397)	CSF1R tyrosine kinase inhibitor	April 29, 2015		Recruiting
NCT02124772	Study to investigate safety, pharmacokinetic (PK), pharmacodynamic (PD), and clinical activity of trametinib in subjects with cancer or plexiform neurofibromas and trametinib in combination with dabrafenib in subjects with cancers harboring V600 mutations	1/2	Plexiform neurofibroma	Trametinib Dabrafenib	Trametinib: MEK inhibitor Dabrafenib: BRAF inhibitor	January 15, 2015	December 29, 2020	Completed

Bench to Bedside: Advances in Targeted Therapy

[34]In the early 1990s, the *NF1* gene was identified as a tumor suppressor gene, sequenced and mapped to chromosome 17q11.2.[70–73] Around the same time, the *NF2* gene was discovered and also characterized as a tumor suppressor gene on chromosome 22q.[74–76] However, uncovering the genetic drivers for Schwannomatosis was a bigger challenge, with the *SMARCB1* gene implicated in 2007 and the *LZTR1* gene implicated in 2014. Notably, Schwannomatosis

Table 3. Table of Clinical Trials for MPNSTs Since 2015

NCT number	Study title	Phase	Tumor	Drug	Mechanism	Start date	Completion date	Study status
NCT04917042	Tazemetostat in malignant peripheral nerve sheath tumors	2	MPNST	Tazemetostat	EZH2 inhibitor	August 24, 2021		Recruiting
NCT04465643	Neoadjuvant nivolumab plus ipilimumab for newly diagnosed malignant peripheral nerve sheath tumor	1	MPNST	Nivolumab Ipilimumab	Nivolumab: PD-1 inhibitor Ipilimumab: CTLA-4 inhibitor	June 08, 2021		Recruiting
NCT04872543	A Study of ASTX727 in people with malignant peripheral nerve sheath tumors (MPNST)	2	MPNST	Cedazuridine/ decitabine (ASTX727)	Cedazuridine: cytidine deaminase inhibitor Decitabine: cytosine analogue	April 29, 2021		Recruiting
NCT03433183	SARC031: MEK inhibitor selumetinib (AZD6244) in combination with the mTOR inhibitor sirolimus for patients with malignant peripheral nerve sheath tumors	2	MPNST	Selumetinib (AZD6244) Sirolimus	Selumetinib: MEK inhibitor Sirolimus: mTOR inhibitor	October 02, 2019		Active, not recruiting
NCT02691026	A study of pembrolizumab in patients with malignant peripheral nerve sheath tumor (MPNST), not eligible for curative surgery	2	MPNST	Pembrolizumab	PD-1 inhibitor	June 2016	December 2020	Terminated
NCT05253131	Trial of selumetinib and bromodomain inhibitor with durvalumab for sarcomas	2	MPNST and other sarcomas	Selumetinib Bromodomain inhibitor Durvalumab	Selumetinib: MEK inhibitor Bromodomain inhibitor Durvalumab: PD-L1 inhibitor	January 15, 2024		Not yet recruiting
NCT04811196	A study of different dosing schedules of selinexor in sarcoma patients	1	MPNST & other sarcomas	Selinexor	Inhibitor of XPO-1 (nuclear export protein)	March 29, 2021		Recruiting
NCT04420975	Nivolumab and BO-112 before surgery for the treatment of resectable soft tissue sarcoma	1	MPNST and other sarcomas	Nivolumab	PD-1 inhibitor	October 29, 2020		Active, not recruiting
NCT03009201	Ribociclib and doxorubicin in treating patients with metastatic or advanced soft tissue sarcomas that cannot be removed by surgery	1	MPNST and other sarcomas	Ribociclib Doxorubicin	Ribociclib: CDK4/6 inhibitor Doxorubicin: DNA interacalator, topoisomerase II inhibition	March 10, 2017	June 30, 2023	Completed
NCT02584309	Doxorubicin with upfront dexrazoxane for the treatment of advanced or metastatic soft tissue sarcoma	2	MPNST and other sarcomas	Doxorubicin	DNA interacalator, topoisomerase II inhibition	February 22, 2016	July 17, 2022	Completed
NCT02601209	Sapanisertib or pazopanib hydrochloride in treating patients with locally advanced or metastatic sarcoma	1/2	MPNST and other sarcomas	Sapanistertib (MLN0128) Pazopanib	Sapanistertib: mTOR inhibitor Pazopanib: multi-target tyrosine kinase inhibitor (VEGFR, PDGFR, c-KIT)	November 30, 2015	July 11, 2022	Terminated
NCT02584647	PLX3397 plus sirolimus in unresectable sarcoma and malignant peripheral nerve sheath tumors	1/2	MPNST and other sarcomas	Sirolimus	mTOR inhibitor	November 04, 2015		Recruiting

patients do not harbor germline *NF2* gene mutations. However, genetic studies on resected schwannomas in this patient population showed inactivating somatic mutations in the NF2 gene, in addition to either *SMARCB1* or *LZTR1* germline mutations.[77,78] The initial work characterizing the neurofibromatosis family of genetic conditions therefore identified the key genetic drivers of oncogenesis in nerve sheath tumors.

From the work done on neurofibromatosis syndrome, it was clear that *NF1* gene mutations were important in the development of neurofibromas and MPNSTs, while the *NF2* gene mutations were important in the development of schwannomas. Further studies have demonstrated that *NF1* and *NF2* are important in inhibiting and regulating the Ras pathway.[3,79] Recently, large-scale tumor sequencing projects have identified additional targetable molecular alterations in nerve sheath tumors. Agnihotri et al. performed DNA and RNA sequencing on 125 schwannomas and identified a recurrent in-frame *SH3PXD2A-HTRA1* gene fusion in approximately 10% of schwannomas and demonstrated that the fusion resulted in elevated MEK-ERK signaling.[80] Most importantly, the study showed that MEK inhibitors were effective in treating schwannomas with gene fusion. Similarly, in NF-1 mouse models, MEK inhibitors caused shrinkage of neurofibromas.[48,81] MEK1 and MEK2 proteins play an important role in Ras signaling, which supports the role of MEK inhibitors as a targeted therapy in nerve sheath tumors. In clinical trials of pediatric NF-1 patients with symptomatic but inoperable plexiform neurofibromas, the MEK inhibitor selumetinib demonstrated tumor shrinkage, with a median 28-31% tumor volume reduction occurring in 71%–74% of patients. In contrast, tumor progression (20% or more volume increase) was observed in 78% of age-matched patients in a previous natural history study (NCT00924196).[48,81] A phase 2 trial focusing on the clinical benefit of selumetinib found that at 12 months of treatment, most patients or parents also reported improvement in tumor-related symptoms.[48] There was a significant reduction in pain intensity in 74% of patients with pain, and 50% of parents (38% of patients) reported significantly reduced pain interference in daily function. Strength, range of motion, and mobility were improved in 56%, 38%, and 54% of patients with baseline motor dysfunction.[48] Overall, 58% of patients and 72% of parents reported that "tumor-related problems other than pain" were "much improved" or "very much improved."[48] Clinical improvement did not correspond to the degree of tumor shrinkage, likely due to the heterogeneous symptoms and impact nerve sheath tumors have depending on their location. As a result, selumetinib has become the first targeted therapy to be approved for the treatment of inoperable plexiform neurofibromas.[47] A 5-year follow-up study demonstrated durable pain reduction to 48 cycles (1 cycle every 28 days), and a median progressive-free survival of 7 years compared to 1.3 years in patients from a natural-history study.[48,82] There are several ongoing clinical trials looking at various MEK inhibitors for treatment of neurofibromas and schwannomas (Tables 1 and 2).

Another major area of basic science and clinical research is understanding the drivers of malignant transformation from a neurofibroma into an MPNST. *CDKN2A* gene deletions are a common observation in MPNSTs, with heterozygous and homozygous deletions seen in over 70% of malignant tumors.[83] More notably, mutations in the PRC2 complex (including *EZH2* and *SUZ12*) were found in over 80% of tumors.[83–85] The PRC2 complex is important in establishing and maintaining repressive gene expression patterns that govern cell fates. Specifically, PRC2 methylates histone H3 on K27. The PRC2 gene mutations in MPNSTs result in loss of H3K27me3 leading to epigenetic dysregulation.[86–88] These studies have led to several epigenetic-based therapeutic strategies to be explored in clinical trials (Table 3). Recently, molecular studies have identified 2 distinct methylation and transcriptome-based MPNST subgroups, with a subtype driven by SHH pathway activation and another driven by WNT pathway activation.[89] Future clinical studies should delineate the 2 subgroups of MPNSTs and create separate arms for each subgroup to ensure that we appropriately evaluate the efficacy of targeted therapies on each MPNST subgroup.

Conclusion

Over the past decade, there have been many advances in our understanding of the molecular drivers of neurofibromas, schwannomas, and MPNSTs. Molecular insights enable the discovery of specific genetic and epigenetic markers that can aid in early diagnosis, prognosis, and personalized treatment strategies (Figure 2). Moreover, the delineation of molecular landscapes provides a foundation for the development of targeted therapies, offering more effective and less invasive options for patients. The development of MEK inhibitors as a treatment option for inoperable plexiform neurofibromas has been a large step forward and will lead to more emphasis on developing targeted therapies for these challenging nerve sheath tumors. As we improve our understanding of the molecular drivers of nerve sheath tumors, the integration of genetic and molecular findings into clinical practice holds promise for advancing precision medicine and improving outcomes for individuals with neurofibromas, schwannomas, and MPNSTs.

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All authors wrote, critically reviewed, and edited the manuscript.

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