

Malignant Peripheral Nerve Sheath Tumor



Aaron W. James, MD^a, Elizabeth Shurell, MD^b, Arun Singh, MD^c, Sarah M. Dry, MD^d, Fritz C. Eilber, MD^{e,*}

KEYWORDS

- Neurofibroma • Atypical neurofibroma • Malignant peripheral nerve sheath tumor
- Neurofibromatosis • NF1

KEY POINTS

- Malignant peripheral nerve sheath tumor (MPNST) is the sixth most common soft tissue sarcoma, often arises from a neurofibroma, and in half of cases occurs in a patient with neurofibromatosis type I.
- The most accurate radiographic evaluation of MPNST uses a combination of PET along with CT or MRI.
- The pathologic diagnoses of peripheral nerve sheath tumors with atypia represent a histologic continuum, and include neurofibroma with atypical features, low-grade MPNST, and high-grade MPNST.
- Management and prognosis significantly differ between low-grade MPNST and high-grade MPNST.

INTRODUCTION TO MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

MPNST is the sixth most common type of soft-tissue sarcoma, accounting for approximately 5% to 10% of cases.^{1–3} Although its exact cellular origins remain unclear, most MPNSTs arise in association with a peripheral nerve and are hypothesized to be of neural crest origin.⁴ Approximately 50% of all MPNST cases arise sporadically, whereas the other 50% of cases are observed in patients with neurofibromatosis

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^a Department of Pathology, Johns Hopkins University, 600 North Wolfe Street, Baltimore, MD 21287-6417, USA; ^b Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA; ^c Sarcoma Service, Division of Hematology/Oncology, University of California, Los Angeles, 2825 Santa Monica Boulevard, Suite 213 TORL, Santa Monica, CA 90404, USA; ^d Department of Pathology & Laboratory Medicine, University of California, Los Angeles, Box 951732, 13-145D CHS, Los Angeles, CA 90095-1732, USA; ^e Division of Surgical Oncology, University of California, Los Angeles, 10833 LeConte Avenue, Room 54-140 CHS, Los Angeles, CA 90095-1782, USA

* Corresponding author.

E-mail address: fceilber@mednet.ucla.edu

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type 1 (NF1).^{5,6} NF1 (also termed von Recklinghausen disease) is an autosomal-dominant genetic disorder with high penetrance that is characterized by mutations in the *Neurofibromin 1* gene, in which patients develop both superficial and deep neurofibromas, among other tumor types.^{7,8} Guidelines for the diagnosis of NF1 are summarized in **Box 1**. NF1 patients carry an estimated 8% to 13% lifetime risk of developing MPNST, and 30% of NF1-associated MPNSTs progress from a deeply situated neurofibroma.^{8,9} The incidence of MPNST among NF1 patients is 1:3,500, in comparison to the incidence among the general population of 1:100,000.⁶ NF1 patients are also predisposed to developing astrocytic brain tumors, pheochromocytoma, and myeloid leukemia, among a diverse array of other benign and malignant tumors.^{10,11} Another main risk factor for the development of MPNST is radiation exposure. An estimated 3% to 10% of all MPNST patients have a clinical history of prior radiation exposure.⁵ The latency period for radiation-associated MPNST is typically more than 15 years.¹² The median age at diagnosis among sporadic MPNST patients is 41 years of age, whereas NF1-associated MPNST patients are generally younger (mean age of 28 years).¹³ Although infrequent, NF1-associated MPNSTs in childhood do occur.¹⁴ The incidence of sporadic MPNST is approximately equal among men and women,¹⁵ whereas NF1-associated MPNST is somewhat more common in men.⁵

In general, the clinical presentation of MPNST is typical of a soft tissue sarcoma. MPNST presents as an enlarging mass for several months. The location is most commonly near nerve roots and bundles of the extremities and the pelvis, including the sciatic nerve, brachial plexus, and sacral plexus.¹⁵ Therefore, a majority of MPNST occur in the proximal portions of the upper and lower extremities. Symptoms include pain, paresthesia, and neurologic deficits.¹⁶ New-onset pain in an existing neurofibroma, especially in an NF1 patient, should prompt evaluation for MPNST. Currently, the clinical standard of care for localized high-grade MPNST is surgical resection and adjuvant radiation. An estimated 40% to 65% of MPNST patients experience local recurrence and 30% to 60% develop metastasis, with the most common site primarily located in the lungs.^{17–20} Although chemotherapy is administered to systemically manage metastatic MPNST, survival rates remain low.^{21,22} In general, a diagnosis of MPNST carries a poor prognosis. For all patients with high-grade MPNST, overall 5-year survival rate ranges from 20% to 50% and a mortality rate of up to 75%.^{1,4} Although it was previously believed that patients with NF1-associated tumors have a worse prognosis,⁹ this has been disproved across multiple studies.

Box 1

Diagnostic criteria for neurofibromatosis type 1

Two or more of the following signs or factors

Six or more café au lait macules

Two or more neurofibromas or one plexiform neurofibroma

Axillary or inguinal region freckling

Optic glioma

Two or more iris hamartomas (Lisch nodules)

First-degree relative with NF1

Adapted from NIH consensus development conference statement of neurofibromatosis. Bethesda (MD): US Department of Health and Human Services; 1987.

MOLECULAR PATHOGENESIS OF MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

MPNSTs exhibit many different genetic aberrations that lead to the dysregulation of crucial signaling pathways that modulate cellular proliferation, growth, and apoptosis. Specifically, proteins that have been implicated in MPNST pathogenesis include neurofibromin 1, phosphatase and tensin homolog (PTEN), insulinlike growth factor 1 receptor (IGF1R), epidermal growth factor receptor (EGFR), and mitogen-activated protein kinases (MAPKs). As such, targeting these signal transduction pathways is an active area of research.

Neurofibromin 1

Mutations in the neurofibromin 1 tumor suppressor gene responsible for NF1 have been examined in research into the molecular pathogenesis of MPNST. In 1 study, Cichowski and Jacks¹¹ found that the neurofibromin 1 gene is closely linked to the tumor suppressor gene *p53* on chromosome 11 in mice. Specifically, mice carrying null mutations of both genes developed MPNST at high frequencies, indicating that concomitant loss of these tumor suppressors enables tumor cells to avoid growth arrest and apoptosis.²³

Phosphatase and Tensin Homolog

The tumor suppressor PTEN is a central negative regulator of the PI3K/AKT/mTOR signaling cascade, which controls cell growth, proliferation, and survival.²⁴ PTEN is the most commonly altered component of the PI3K pathway in human malignancies, including MPNST.²⁴ Specifically, the reduction or deletion of PTEN is associated with the malignant transformation of neurofibroma to MPNST in humans and animal models.^{6,25,26}

For example, Keng and colleagues²⁶ created transgenic mice lacking both the *Pten* and *Nf1* in Schwann cells and their precursors to elucidate the role of these 2 tumor suppressor genes in vivo. When coupled with *Nf1* loss, both the decrease and loss of *Pten* resulted in MPNST development from neurofibromas and seemed to accelerate the progression from low-grade to high-grade MPNST.²⁶ Additionally, genetic analysis of human MPNST exhibited down-regulation of *PTEN* expression, suggesting that *PTEN*-regulated pathways play key roles as tumor suppressors to inhibit the progression of benign neurofibroma to MPNST.²⁶

Likewise, Gregorian and colleagues²⁵ found that concomitant activation of the *K-ras* oncogene along with single allelic deletion of *Pten* led to 100% development of NF1 lesions and subsequent progression to MPNST in mice.²⁵ In the same study, they observed loss of PTEN expression in human NF1-associated MPNST lesions, because less than 20% of the tumor cells were PTEN positive.

In a similar study, Bradtmoller and colleagues⁶ discovered significantly reduced PTEN expression in human MPNST samples (5%) compared with benign neurofibromas (30%). Furthermore, a significantly higher methylation frequency in MPNST was observed compared with benign peripheral nerve sheath tumor (PNST), including neurofibroma.⁶ These findings indicated that the methylation of CpG island 3' as one mechanism that down-regulates PTEN in MPNST.⁶

In summary, deletion of the tumor suppressor PTEN in the cell-cycle regulatory PI3K/AKT/mTOR pathway plays a critical role in the malignant transformation of neurofibroma to MPNST. For a more detailed review on the role of PTEN in neoplastic growth, please refer to the article by Chow and Baker.²⁴

Insulinlike Growth Factor 1 Receptor and Epidermal Growth Factor Receptor

Genetic alterations of the IGF1R pathway have been correlated to MPNST progression. For example, Yang and colleagues²⁷ observed *IGF1R* amplification and

increased IGF1R protein expression, respectively, in 24% and 82% of human MPNST samples. Higher IGF1R protein expression correlated with worse tumor-free survival and increased risk of tumor progression.²⁷ Moreover, activation of IGF1R induces MPNST cell proliferation, migration, and invasion via up-regulation of the PI3K/AKT/mTOR pathway.²⁷ Specifically, inhibition of IGF1R in ST88 to 14 MPNST cells via small interfering RNA or the IGF1R inhibitor MK-0646 significantly decreased cell proliferation, invasion, and migration due to attenuation of the PI3K/AKT/mTOR pathway.²⁷

Likewise, up-regulation of EGFR has also been implicated in the progression of MPNST. DeClue and colleagues²⁸ found significantly increased EGFR expression in the Schwann cells of MPNST compared with benign neurofibromas. Additionally, proliferation of cultured primary cells from human MPNST was inhibited by the EGFR antagonists mAb225, A-25, and AG-1478.²⁸

Mitogen-Activated Protein Kinase

MAPK has also been found overexpressed in MPNST.^{16,29,30} This signaling cascade, which includes rapidly accelerated fibrosarcoma (RAF), extracellular signal-regulated kinase (ERK), and MAPK/ERK kinase [MEK]), is responsible for cell-cycle progression from the G1 phase to the S phase.¹⁶ Thus, dysregulation of the MAPK pathway leads to uncontrolled growth in cancer. For example, Zou and colleagues³⁰ observed that 91% of MPNST samples stained positive for phosphorylated MEK compared with only 21% of benign neurofibromas. See [Table 1](#) for a brief summary of main molecular pathways dysregulated in MPNST.

RADIOGRAPHIC DIAGNOSIS OF MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

The detection of MPNST and its differentiation from benign neurofibromas remains a clinical challenge, because the symptomology of these 2 conditions, including tumor size, pain, and neurologic deficits, exhibits considerable overlap. Currently, the imaging modalities that are used to evaluate and diagnose MPNST include CT, MRI, and PET. Each is discussed.

Both CT and MRI are used to define the anatomic tumor size and local invasiveness of PNST. For example, Benz and colleagues³¹ used CT imaging and observed that MPNSTs are larger than their benign counterparts. Specifically, the mean tumor size for malignant and benign PSNT were 7.4 cm ± 4.1 cm and mean 4.8 cm ± 2.7 cm, respectively.³¹ Due to the clear overlap between the size ranges of benign and

Table 1
Dysregulation of molecular pathways in malignant peripheral nerve sheath tumor

Molecular Pathway	Normal Role	Change in Malignant Peripheral Nerve Sheath Tumor
NF1	Tumor suppressor	Down-regulation
PTEN	Tumor suppressor Negative regulator of PI3K/AKT/mTOR signaling cascade	Down-regulation
IGF1R	Positive regulator of PI3K/AKT/mTOR signaling cascade	Up-regulation
EGFR	Positive regulator of PI3K/AKT/mTOR signaling cascade	Up-regulation
MAPK	Phosphorylation of RAF/MEK/ERK signaling cascade	Up-regulation

malignant PNST, however, CT-based evaluation of tumor size is limited when used as the sole imaging modality to diagnose MPNST.

Several studies have established diagnostic criteria for distinguishing benign PNST and MPNST using MRI (Table 2). Mautner and colleagues,³² however, evaluated the efficacy of MRI in the diagnosis of MPNST and concluded that MRI when used alone can likewise not reliably distinguish between malignant and benign PNST, especially when tumors are inhomogeneous. Overall, the central limitation of both CT and MRI is that they cannot effectively confirm malignant transformation of lesions.^{31,33,34}

To improve on anatomic imaging, various studies have used quantitative fludeoxyglucose F 18 (FDG) PET imaging to distinguish between benign PNST and MPNST based on a tumor's metabolic activity.^{31,33,34} In these studies, the maximum standardized uptake value (SUVmax) is used to measure tumor glucose utilization; in summary, lower tumor FDG uptake is correlated with benign peripheral nerve sheath tumors, whereas higher tumor FDG uptake is correlated with MPNST.^{31,33,34}

Benz and colleagues³¹ determined that the mean SUVmax for MPNSTs (12.0 g/mL \pm 7.1 g/mL) was significantly higher than that of benign peripheral nerve sheath tumors (3.4 g/mL \pm 1.8 g/mL). In addition, they determined that the optimum threshold for separating MPNSTs from their benign counterparts was an SUVmax of 6.1 g/mL, with sensitivity and specificity of 94% and 91%, respectively.³¹ In a similarly conducted study, Ferner and colleagues⁴⁰ determined that lesions in NF1 patients with an SUVmax of 3.5 g/mL should be resected to prevent progression towards MPNST, with sensitivity and specificity of 89% and 95%, respectively.

In summary, the definitive radiographic distinction of benign PNST and MPNST is a challenge. Currently, quantitative FDG-PET imaging used in conjunction with CT or MRI offers the best ability to distinguish benign PNST from MPNST. The authors think that these data should be combined with the clinical assessment of patients to identify patients undergoing and who have undergone malignant transformation. Radiographic imaging and clinical features of PNST/MPNST have not supplanted histopathologic examination as the gold standard for the diagnosis of MPNST.

HISTOPATHOLOGIC DIAGNOSIS OF MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

The diagnosis of MPNST may be suspected prior to biopsy, based on a variety of factors, including known diagnosis of NF1, changes in the tempo of clinical symptoms, relationship to a peripheral nerve, relationship to preexisting neurofibroma, or imaging characteristics, including rapidly growing tumors and highly FDG-avid lesions. The typical histology of MPNST is that of a proliferation of spindle cells showing a

Parameter	Malignant Peripheral Nerve Sheath Tumor	Benign Peripheral Nerve Sheath Tumor
Tumor size (mm)	74–100	43–69
Intratumoral lobulation (%)	50–63	12–17
Intratumoral heterogeneity (%)	51–90	30–52
Irregular or peripheral contrast enhancement (%)	34–75	5–33
Intratumoral cystic changes (%)	21–39	10–17
Peritumoral edema (%)	29–66	0–23

Data from Refs.^{35–39}

fascicular growth pattern, often with a branching hemangiopericytoma-like vascular pattern, as well as alternating hypercellular and hypocellular areas. The histologic appearance of MPNST may vary significantly — from tumors appearing similar to neurofibroma ranging to those more resembling a fibrosarcoma. From a biological perspective, this variation in appearance may reflect different elements within the native peripheral nerve sheath, including Schwann cells, perineural cells, and fibroblasts. Given this spectrum of findings and the lack of definitive markers for MPNST, it is important to recognize that there is still a lack of widely accepted diagnostic criteria for MPNST.

Typical cytologic features of MPNST include nuclei that are wavy, buckled or comma-shaped.⁴¹ Other less common histologic features of MPNST that may be present include epithelioid or pleomorphic cytomorphology, heterologous elements, glandular differentiation, and melanin pigment. Heterologous elements are more common in MPNST compared with other tumor types and most commonly include mature islands of cartilage and bone (seen in up to 15% of MPNST).⁴² Glandular differentiation is rare⁴³ and most commonly brings up the diagnostic alternative of biphasic synovial sarcoma.⁴¹ Epithelioid MPNST constitutes less than 5% of MPNST and is distinctive for diffuse S100 immunoreactivity in a majority of tumors⁴⁴ as well as loss of INI1 in approximately half of cases.⁴⁵ A more comprehensive discussion of the histopathologic variation with MPNST can be found within the following reference.⁴¹

Immunohistochemistry (IHC) is of some help in the diagnosis of MPNST, including the exclusion of competing diagnostic possibilities. All IHC markers, however, have limited sensitivity or specificity, so a single diagnostic marker for MPNST is not currently available. S100 protein expression is the most commonly used in the evaluation of MPNST. When present (estimated at anywhere from 50% to 90% frequency^{46,47}), S100 immunostaining is usually focal. Diffuse S100 expression is more consistent with a cellular schwannoma, melanoma, or clear cell sarcoma. The exception to this is epithelioid MPNST, which often shows diffuse S100 immunostaining.⁴⁴ SOX10 may show improved sensitivity and specificity over S100 protein for MPNST.⁴⁸ Melanocytic markers are negative, whereas keratins may be positive (either in epithelioid MPNST or glandular MPNST). TLE1 expression is usually focal and weak in MPNST, rather than strong and diffuse, as seen in synovial sarcoma.⁴⁹

Two diagnostic dilemmas that may face pathologists when considering the diagnosis of MPNST are discussed briefly. The first is distinguishing low-grade MPNST from neurofibroma and neurofibroma with atypical features. When neural differentiation is clearly identified, the next step is histopathologic subcategorization. The differentiation of atypical neurofibroma from low-grade MPNST is challenging and not entirely agreed on by experts in the field, because these lesions likely represent a histologic continuum.⁴¹ For example, some investigators maintain that both hypercellularity and nuclear atypia, with or without mitoses, are consistent with low-grade MPNST.^{50–52} Other experts add that if mitotic activity is not present, low-grade MPNST may be diagnosed if the cellularity and atypia are marked and the architectural pattern is fascicular.⁴¹ Other experts accept any mitotic activity in a cellular or atypical neurofibroma, particularly in a patient with NF1, as evidence for malignant transformation.⁵³ In contrast, the current World Health Organization classification maintains that “hypercellularity of otherwise unremarkable neurofibroma cells, atypical tumour cells with hyperchromatic smudgy nuclei, or mitotic activity, alone or together, do not indicate malignant change.”⁵⁴ This debate over the hematoxylin-eosin diagnosis is compounded by the fact that current molecular or immunohistochemical assays do not distinguish between these diagnostic categories. Current guidelines that the authors

use in practice for the light microscopic diagnosis of neurofibroma are shown in **Box 2**, adapted from Goldblum and colleagues.⁴¹

The second potential diagnostic dilemma is distinguishing high-grade MPNST from other high-grade malignancies. Based on the hematoxylin-eosin appearance, high-grade MPNST has overlapping appearance with a diverse array of high-grade sarcomas and other malignancies. Other sarcomas with overlapping spindle cell morphology include monophasic synovial sarcoma, fibrosarcoma, leiomyosarcoma, malignant solitary fibrous tumor, dedifferentiated liposarcoma, dedifferentiated dermatofibrosarcoma protuberans, and high-grade spindle cell sarcoma not otherwise specified. In the case of a pleomorphic/anaplastic MPNST, other sarcomas with pleomorphic features must be considered, including, for example, high-grade myxofibrosarcoma, pleomorphic leiomyosarcoma, or high-grade pleomorphic sarcoma not otherwise specified. In the case of suspected anaplastic MPNST, a careful search for more typical areas of high-grade MPNST should be undertaken. As well, melanoma, in particular desmoplastic melanoma, must always be excluded; as discussed previously, IHC stains for S100, SOX-10, and melanoma-specific markers (such as HMB45 or MART-1) are helpful in this regard. Finally, poorly differentiated or sarcomatoid carcinomas may also mimic MPNST histologically. A careful hunt for distinguishing cytologic features as well as initial panel of immunohistochemical stains aid in the diagnosis. A potential list of immunohistochemical stains for the evaluation of suspected high-grade MPNST is in **Box 3**.

SURGICAL MANAGEMENT OF MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

Complete surgical resection with wide negative margins is the current standard of care for localized high-grade MPNST and is a strong predictor of survival.^{5,7,55} Specifically, it is recommended that tumors should be excised with wide margins.⁷

The location of MPNST affects tumor accessibility and consequently affects the rate at which negative surgical margins are successfully achieved. For example, Wong and

Box 2

Histologic criteria for distinguishing neurofibroma from low-grade malignant peripheral nerve sheath tumor

Neurofibroma

- Nuclear atypia (may be focal or diffuse)
- No diffuse cellularity
- No mitotic activity

Neurofibroma with atypical features

A combination of nuclear atypia, cellularity, and/or mitotic activity that falls short of the criteria for low-grade MPNST

Low-grade MPNST

All of the following 3 attributes must be present (In the absence of mitotic activity, atypia and cellularity must be marked):

- Generalized nuclear atypia
- Diffuse cellularity
- Low levels of mitotic activity

Adapted from Goldblum JR, Folpe AL, Weiss SW, et al. Enzinger and Weiss's soft tissue tumors. 6th edition. Philadelphia: Saunders/Elsevier; 2014. p. xiv, 1155.

Box 3**Potential immunohistochemical stains in the evaluation of high-grade malignant peripheral nerve sheath tumor**

Pan cytokeratin
 High-molecular-weight cytokeratin
 S100
 SOX10
 HMB45/MelanA/MART1
 CD34
 SMA
 Desmin
 TLE1
 STAT6

colleagues¹⁸ observed large differences in the frequency of positive surgical margins dependent on anatomic site (reproduced in **Table 3**).

Various studies have indicated that the surgical margin status is a significant prognostic factor for high-grade MPNST.^{18,56,57} Wong and colleagues¹⁸ observed that MPNST patients with positive margins exhibited 3-year and 5-year overall survival rates of 47% and 22%, respectively, whereas those with negative margins exhibited higher rates of 74% and 67% respectively. Likewise, Porter and colleagues⁵⁷ found that only 6% of MPNST patients with negative surgical margins experienced local recurrence compared with 30% of patient with positive surgical margins. Additionally, the rate of 10-year distant metastases is higher for MPNST patients with positive margins (27%–31%) compared with those with negative margins (21%–27%).^{15,58} Moreover, MPNST patients with positive resection margins exhibited a 1.8-fold risk of disease-specific mortality.¹⁵ Follow-up guidelines regarding the management of MPNST after surgical resection have not been definitively established.

Importantly, the surgical management of low-grade MPNST versus high-grade MPNST may be different. Bernthal and colleagues⁵⁹ determined that surgical margins did not have a significant effect on the clinical outcome of patients with low-grade MPNST or atypical neurofibroma. Of the 23 patients studied, 78% exhibited positive surgical margins; strikingly, these patients also demonstrated a 0% occurrence of

Table 3

Frequency of positive margins in malignant peripheral nerve sheath tumor based on anatomic site

Anatomic Site	Frequency of Positive Margins in Malignant Peripheral Nerve Sheath Tumor (%)
Pelvis	42
Chest	32
Abdomen	27
Head/neck	22
Extremities	6

pulmonary metastasis and a 100% rate of disease-specific survival at 4 years.⁵⁹ Although local recurrence of disease occurred in 16.7% of patients with positive surgical margins, none of them developed metastatic disease or died of the disease itself. Therefore, this study suggests that obtaining wide resections with negative surgical margins in low-grade MPNST or atypical neurofibroma patients is not as critical compared with high-grade MPNST. The absolute requirement and timing for resection in low-grade MPNST with positive margins is not yet clear.

RADIATION THERAPY AND MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

Both neoadjuvant and postoperative adjuvant radiation therapy have been used to locally control MPNST. For example, Kahn and colleagues⁶⁰ examined the clinical outcomes of adjuvant radiation therapy in both sporadic and NF1-associated MPNST patients. Tumors were located in the extremities (58%), trunk (36%), and the head/neck region (6%).⁶⁰ The various modalities of administered radiation therapy included external beam radiation, brachytherapy, proton therapy, and a combination of external beam radiation and brachytherapy.⁶⁰ The median total doses of sporadic and NF1-associated tumors were 58.5 Gy and 59.4 Gy, respectively.⁵⁵ Additionally, the local control rate at 5 years for NF1-associated tumors was 51%, and the rates of pulmonary metastasis in sporadic and NF1-associated tumors were 47% and 28%, respectively.⁵⁵ The median survival of all patients was 46.5 months, with a 43.7% overall 5-year survival.⁶⁰ Strikingly, the median overall survival of NF1-associated MPNST patients treated with radiation was 33.1 months, whereas the median survival among those not treated with radiation was 17.4 months.⁶⁰ Thus, Kahn and colleagues⁶⁰ determined that adjuvant radiation therapy is effective in achieving local control and improving overall survival among patients with MPNST.

Various other studies have also recommended the use of intraoperative or postoperative adjuvant radiation therapy to treat MPNST.^{55,61} For example, Wong and colleagues¹⁸ found that the 3-year and 5-year overall survival rates for patients receiving either brachytherapy or intraoperative electron irradiation were 84% and 72%, respectively, compared with 61% and 50% among patients who did not receive the treatment.

Similarly, Kar and colleagues⁵⁵ concluded that postoperative adjuvant radiotherapy increased both 5-year disease-free and overall survival of MPNST patients. Adjuvant radiotherapy ranging in dosage from 54 Gy to 62 Gy was administered to patients who exhibited deep-seated, high-grade tumors that were larger than 5 cm.⁵⁵ Specifically, the 5-year disease-free survival rates among patients who did and did not receive postoperative radiotherapy were 42% and 0% respectively.⁵⁵ Likewise, the 5-year overall survival rates for patients who did and did not receive radiotherapy were 65% and 38%, respectively.⁵⁵

Additionally, a group of clinicians and scientists specializing in MPNST reached an international consensus that recommended the use of postoperative radiation therapy to combat local recurrence of disease.⁷ Moreover, Stucky and colleagues⁶¹ recommended the use of postoperative therapy for tumors with the following characteristics: greater than or equal to 5 cm, high grade, and R1 (microscopically positive; closest margin within 2 mm of inked surface) or R2 (macroscopically positive) margin status.

SYSTEMIC THERAPY AND MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

In contrast to surgical resection and radiation therapy, chemotherapy is usually limited to the management of metastatic MPNST or in patients with unresectable tumors.^{7,21}

Treatment regimens typically consist of either single-agent doxorubicin or a combination of doxorubicin and ifosfamide.^{7,21} In one study, Kroep and colleagues²¹ observed a response rate, progression-free survival, and median overall survival of 21%, 17 weeks, and 48 weeks, respectively, among MPNST patients who underwent chemotherapy. The combination of ifosfamide and doxorubicin has a higher response rate than single-agent doxorubicin in MPNST and in most soft tissue sarcomas. In the recently completed EORTC 62012 trial, however, although the combination improves progression-free survival, it was not associated with improved overall survival in locally advanced/metastatic soft tissue sarcomas.⁶²

At the authors' institution, neoadjuvant chemotherapy/radiation therapy is used in selected cases of MPNST in an effort to downstage borderline unresectable tumors and to determine the *in vivo* chemosensitivity of patients who have a high risk of disseminated disease. In these cases, doxorubicin plus ifosfamide is used due to the higher response rate. Furthermore, tumors with greater than 90% necrosis have been shown to have improved disease-specific survival.³³ This retrospective observation needs to be tested in prospective randomized trials.

CURRENT AND COMPLETED CLINICAL TRIALS OF TARGETED AGENTS

Recent advances in therapy have focused on targeting the various molecular pathways implicated in MPNST, such as the Ras-MAPK, PI3K/AKT/mTOR, Hsp90, and EGFR signaling cascades.^{16,29} Although anecdotal reports have implicated the targeting of driving mutations, for the most part, a common driving genetic event has not been targeted in this disease. A summary of recently completed trials was reviewed by Farid and colleagues.²⁹ Information regarding recent clinical trials involving MPNST patients is in [Table 4](#).

OUTCOMES OF MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

A majority of MPNST are high-grade sarcomas, with a high probability of local recurrence and distant metastasis. As discussed previously, 40% to 65% of MPNST patients experience local recurrence and 30% to 60% develop metastasis.^{15,17–20,30,63} Factors that predict local recurrence among high-grade MPNST include anatomic site, tumor size (greater than 10 cm), and positive margins.^{15,30,63} Factors that predict metastasis include tumor size greater than 10 cm or tumors that are American Joint Committee on Cancer stage III.^{15,30,63} Although it was previously believed that patients with NF1-associated tumors have a worse prognosis, this has later been disproved across multiple studies. Approximately 65% of metastases are to the lungs, whereas other sites of disease spread include the liver, brain, bone, and adrenal gland.⁴¹ Regional lymph node involvement is uncommon, and for this reason lymph node dissection should not be routinely performed.

Table 4

Recent clinical trials offered to malignant peripheral nerve sheath tumor patients

Study Number	Clinical Trial Phase	Interventional Drug Under Investigation	Mechanism	Status
NCT02584647	I/II	PLX3397/sirolimus	mTOR inhibitor	Recruiting
NCT02008877	I/II	Ganetespib/sirolimus	mTOR inhibitor	Recruiting
NCT01661283	II	Everolimus/bevacizumab	mTOR inhibitor	Ongoing
NCT00068367	II	Erlotinib hydrochloride	EGFR inhibitor	Completed

SUMMARY

In summary, MPNST is a common high-grade soft tissue sarcoma. Its diagnosis and management is complex – and a team approach in an experienced sarcoma center is best for patients. Team members should include surgical oncologists, radiation oncologists, and medical oncologists as well as radiologists and pathologists with specialization in sarcoma. From a diagnostic perspective, there are many histologic mimics of MPNST and re-review of all outside slides is a critical step in the management of patients. From a therapeutic perspective, it is important to recognize the differences in management between low-grade MPNST and high-grade MPNST. Potential differences include the need for adjuvant radiation therapy and the prognostic importance of positive margins.

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