MALIGNANT PERIPHERAL NERVE SHEATH TUMORS (MPNST)

An ESUN Article

By David S. Geller, MD
Fellow, Orthopaedic Oncology
Combined Harvard Orthopaedic Surgery Program

and Mark Gebhardt, MD
Frederick W. and Jane M. Ilfeld Professor of Orthopedic Surgery
Harvard Medical School - Children's Hospital, Boston
Chief of the Department of Orthopedic Surgery, Orthopaedic Surgeon-in-Chief
Beth Israel Deaconess Medical Center

INTRODUCTION

Malignant peripheral nerve sheath tumors (MPNSTs) are sarcomas which originate from peripheral nerves or from cells associated with the nerve sheath, such as Schwann cells, perineurial cells, or fibroblasts. Because MPNSTs can arise from multiple cell types, the overall appearance can vary greatly from one case to the next. This can make diagnosis and classification somewhat difficult. In general, a sarcoma arising from a peripheral nerve or a neurofibroma is considered to be a MPNST. The term MPNST replaces a number of previously used names including malignant schwannoma, neurofibrosarcoma, and neurogenic sarcoma.38

A sarcoma is defined as a MPNST when at least one of the following criteria is met:

1. It arises from a peripheral nerve
2. It arises from a preexisting benign nerve sheath tumor (neurofibroma)
3. It demonstrates Schwann cell differentiation on histologic examination

The peripheral nervous system is the part of the nervous system that consists of the nerves and neurons that reside or extend outside the central nervous system and, for example, serve the limbs and organs.

EPIDEMIOLOGY

MPNSTs comprise approximately 5-10% of all soft tissue sarcomas. They can occur either spontaneously or in association with neurofibromatosis-1 (NF1).

Neurofibromatosis I, also known as "von Recklinghausen disease," is an autosomal dominant condition which is clinically characterized in part by pigmented skin lesions known as café-au-lait spots, benign cutaneous and subcutaneous tumors known as neurofibromas, distinctive bone lesions, and focal malformations of the iris. It is the most common single gene disorder in humans and results from the defective protein neurofibromin, which is thought to act as a tumor suppressor. Neurofibromatosis 2, is characterized by tumors involving the cranial nerves, spinal nerves, and lesions of the brain and spinal cord. The defining feature of NF2 is bilateral acoustic neuromas, which are tumors affecting the auditory nerves, in turn causing hearing loss. The defective gene product in NF2 is known as merlin.

The etiology is unknown but there is a higher incidence in patients with a history of radiation exposure.1, 2, 11, 26 Up to 50% of MPNSTs occur in patients with NF1,9, 22 demonstrating the tendency for this tumor to arise from a preexisting neurofibroma. Cross sectional studies have
previously demonstrated a 1-2% prevalence of MPNST among NF1 patients\textsuperscript{20} although a recent study showed these patients have a 10% lifetime risk of ultimately developing an MPNST.\textsuperscript{13}

The development of plexiform neurofibromas has been linked to the loss of NF1 gene expression in a mouse model, while the development of MPNST has been related to other genetic insults, such as those involving p53 and p16.\textsuperscript{8,32,34} While NF1 gene activity does not independently cause MPNSTs, it may in fact predispose these patients to such an event.

MPNSTs generally occur in adulthood, typically between the ages of 20 and 50 years of age. Approximately 10-20% of cases have been reported to occur in the first 2 decade of life,\textsuperscript{10} with occasional cases involving infants as young as 11 months of age.\textsuperscript{12}

**Clinical Features**

MPNSTs usually present as an enlarging palpable mass. Pain is a variable complaint. Rapid enlargement occurs more often in the setting of NF1 and should raise concern for malignant degeneration of a neurofibroma. MPNSTs arising from peripheral nerves may result in a variety of clinical patterns, including radicular pain, paresthesias, and motor weakness. Most MPNSTs occur in conjunction with large peripheral nerves such as the sciatic nerve, the brachial plexus and the sacral plexus (see Figures 1 and 2).

They are usually deep-seated and often involve the proximal upper and lower extremities as well as the trunk. Dermal or flat plexiform neurofibromas, commonly encountered in cases of NF-1, have not been shown to undergo malignant transformation and do not usually require close monitoring. On the other hand, larger nodular tumors associated with large peripheral nerves and deep extensive plexiform neurofibromas do have the potential to undergo malignant transformation and should be observed more diligently.\textsuperscript{14} In rare instances, multiple MPNSTs can arise in the setting of NF1. Most of these tumors are considered high-grade sarcomas with the potential to recur as well as to metastasize.
The importance of referring a patient to a tertiary care center with a formal multidisciplinary sarcoma service cannot be emphasized enough. A multidisciplinary sarcoma service will typically review patient information and formulate a treatment plan within the setting of a formal sarcoma conference. Representatives from all involved disciplines will typically attend and participate actively. This allows for optimal dialogue and efficient coordination of care.

**IMAGING**

Magnetic resonance imaging (MRI) is the imaging modality of choice. To some extent, MPNSTs share basic imaging characteristics with their benign counterparts such as neurofibromas and schwannomas. These include a fusiform shape and a longitudinal orientation in the direction of the nerve. However, some distinctions are noteworthy. Large tumors (> 5 cm), invasion of fat planes, heterogeneity, ill-defined margins, and edema surrounding the lesion are more suggestive of MPNSTs (see Figures 3, 4, & 5).

**Figure 3 (left):** Proton Density axial MRI image demonstrating a large soft tissue mass within the right posterior pelvis.
**Figure 4 (center):** T1-weighted post-contrast axial MRI image showing heterogeneous enhancement of the MPNST.
**Figure 5 (right):** STIR axial MRI image from a different patient demonstrating a large heterogeneous mass (A) within the sciatic notch of the right pelvis. The dark area (B) is artifact from a metal prosthesis in the right hip.

Imaging studies of the chest are an important part of any initial sarcoma evaluation. MPNSTs are most likely to metastasize to the lungs, followed by the bone and finally the pleura. For this reason, a Computed Tomography of the chest is the preferred imaging study to screen for distant disease. A bone scan should also be obtained to help identify metastatic bone disease.

FDG PET is a dynamic imaging modality which evaluates metabolic activity by quantitatively assessing intracellular glucose use. It has been shown to reliably identify areas of increased metabolic activity such as those seen in malignancies (see Figure 6).

While FDG PET has proven useful in detecting metastatic or recurrent disease, its value in differentiating malignant nerve sheath tumors from benign ones remains unclear. More recently, it has been suggested that 18FDG PET technology has prognostic relevance. In a review of 16 NF1 patients with MPNSTs, SUV (standardized uptake values) values were found to predict long-term survival with an accuracy of 94%. Kaplan-Meier survival analysis demonstrated a mean survival time of 13 months in patients with SUV values above 3, in contrast to a mean survival time of 52 months in patients with SUV values below 3. As experience with FDG PET technology grows, clarification of its diagnostic and prognostic implication is expected.
Staging describes the most pertinent tumor characteristics and in turn permits for adequate planning and appropriate treatment. In addition, staging offers prognostic information and allows for comparison in the context of a clinical trial. In general, staging systems are designed to describe either existing metastases or the likelihood of developing metastases. With regard to soft tissue sarcomas, staging is dependent upon histologic grade, tumor size, tumor depth, and the presence or absence of metastases. In the absence of detectable metastases, histologic grade, tumor size, and tumor depth are the strongest predictors of eventual metastases. The stage is based upon imaging studies, which demonstrate the local and distant extent of the disease, and upon the histologic grade, which describes the histological characteristics of individual tumor cells.

A number of staging systems have been described. The most commonly employed staging system is the American Joint Committee on Cancer Staging System for Soft Tissue Sarcomas (see Table 1). Stage I essentially describes any low-grade small soft tissue sarcoma without evidence of metastasis. Stage II describes small high-grade tumors and large but superficial high-grade tumors without evidence of metastasis. Stage III describes high-grade large tumors which are deep. Stage IV includes any tumors with evidence of metastasis. One limitation of this staging system is that it does not reflect the tumor’s anatomic location. This has been demonstrated to be relevant, especially in the setting of local recurrence.33

A biopsy is an integral part of the staging system. It offers both a histologic tissue diagnosis and the ability to determine the grade of the lesion. This information, in turn, permits adequate planning and adjuvant treatment such as radiation or chemotherapy. In addition, this information is incorporated into the tumor staging process which provides prognostic information with regard to the disease and treatment generalizations.

Fine needle aspirations or FNAs is a biopsy method employed to obtain individual cells for cytologic review. It can be done with a very small needle which is more easily tolerated by the patient and is often useful to establish the presence of malignant cells. However, it is not large enough to demonstrate the architectural pattern within a tumor and for this reason is not often
used to make an initial diagnosis. In cases of established diagnoses, such as after surgical resection of a tumor, FNA can often be successfully used to sample tissue which is suspected to be recurrent disease.

**Table 1: The American Joint Committee on Cancer (AJCC) Staging System for Soft Tissue Sarcoma, 6th Edition**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Size</th>
<th>Depth</th>
<th>Grade</th>
<th>Metastases</th>
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<tr>
<td>I</td>
<td>Any</td>
<td>Any</td>
<td>Low</td>
<td>No</td>
</tr>
<tr>
<td>II</td>
<td>&lt; 5cm, any depth OR &gt; 5cm</td>
<td>Superficial</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td>III</td>
<td>&gt; 5cm</td>
<td>Deep</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td>IV</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
</tr>
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*Depth is termed superficial (above the deep fascia) or deep (deep to the deep fascia). Retroperitoneal tumors are considered deep.*

A second type of biopsy is a core needle or tru-cut needle biopsy, which uses a larger hollow-bored needle gauge to obtain a more substantial tissue sample. This type of sample offers inspection of both individual cells as well as the architectural arrangement of those cells within a given part of the tumor mass. This information is often important in establishing a histopathologic diagnosis. In many tertiary care cancer centers, core needle biopsies are often performed with either CT or ultrasound image guidance (see Figure 7). This is an outpatient procedure and it allows for adequate tissue sampling while minimizing bleeding and minimizing contamination or seeding of surround tissue with tumor cells. In addition, it often avoids the need for general anesthesia. In some cases a formal open biopsy is required. This can either be an incisional biopsy, where a small piece of tissue is removed from the larger tumor mass, or an excisional biopsy, in which case the entire tumor is removed. In general, an incisional biopsy is recommended when a sarcoma is suspected.

**Figure 7:**
Axial image from a CT-guided biopsy demonstrating proper placement of the needle within the tumor. The needle tract avoids neurovascular structures and takes a direct course traversing as few tissues as possible, demonstrating a basic tenet of surgical oncology.
Errors, complications, and changes in outcome were demonstrated to greatly increase when the biopsy is performed in a referring institution as opposed to a sarcoma treatment center. This again underscores the importance of referral to a tertiary care center with a multidisciplinary sarcoma team.

A needle biopsy is typically an outpatient procedure, which means the patient does not have to stay in the hospital overnight. It is usually done by an interventional radiologist and it is usually guided by either an ultrasound or a CT scan to ensure proper placement of the needle. Usually local anesthetic or mild sedation is provided to minimize the patient's discomfort. Once the sample is obtained the pathologists can review the specimen under the microscope. A complete review of the biopsy may take a few days or even a few weeks, depending upon the technical limitation such as the use of special stains.

**Histopathology**

The general appearance of MPNSTs is one of dense cellular fascicles which alternate with myxoid regions. This swirling arrangement of intermixed dense and myxoid areas has been described as a marbleized pattern (see Figure 8). The cells may be spindle shaped with very irregular contours. Alternatively, cells may be rounded or fusiform in shape (see Figure 9). Nuclear palisading has also been shown but in less than 10% of cases and even then, only focally. Malignancy is suggested by features such as invasion of surrounding tissues, invasion of vascular structures, nuclear pleomorphism, necrosis, and mitotic activity.

![Figure 8](left): Hypocellular area (lower right corner) is seen adjacent to a more densely cellular area (upper left).

![Figure 9](right): Higher power demonstrating small rounded cells with intermixed spindle or fusiform cells

Approximately 80-85% of MPNSTs are spindle cell tumors with fasciculating patterns that contain histologic features similar to those of a fibrosarcoma. They are often high-grade, demonstrating 4 or more mitotic figures per high powered field. The remaining 15% of MPNSTs is composed of tumors that exhibit variable differentiation, allowing them to be subclassified as distinct entities. A MPNST with rhabdomyoblastic differentiation is characterized by both neural and skeletal muscle differentiation. Within this category is the malignant triton tumor, which refers specifically to a MPNST occurring in association with rhabdomyosarcoma. Other examples of MPNSTs with differentiation include glandular malignant schwannoma, epithelioid malignant schwannoma, and superficial epithelioid MPNST.
S-100 has been identified in approximately 50 – 90% of MPNSTs, however the staining pattern has been noted to be both focal and limited to few cells. Leu-7 and myelin basic protein are noted in 50% and 40% of cases respectively. In general, a combination of antigens is used to help exclude other spindle cell lesions and to confirm the diagnosis of MPNST.

**SURGICAL TREATMENT**

The mainstay of treatment is surgical resection. The goal of the operation is to achieve complete surgical excision of the tumor with negative (wide) margins. This offers the best outcome with respect to both local recurrence and distant metastases.

**RADIATION THERAPY**

Radiation therapy has become an integral part of local disease control in most soft tissue sarcomas and likewise can be employed in pre-operative, intraoperative, and post-operative settings for MPNST. Together with wide surgical excision, radiation therapy offers local and overall survival rates which are similar to those following amputation, and the combined modality treatment often allows patients the option to undergo successful limb-salvage surgery. Treatment of soft-tissue sarcomas with adjuvant radiation therapy has yielded a statistically significant reduction in the rates of local disease recurrence. It has not, however, had a meaningful reduction in either rates of distant metastases or overall survival.

Preoperative external beam radiation therapy is administered before surgical resection. This approach offers a number of potential benefits including accurate radiation planning and tumor localization, smaller treatment volumes, and smaller dose requirements. Pre-operative treatment also offers the theoretical advantages of the "oxygen-enhancement effect" which argues that radiation treatment is more effective in the setting of well-oxygenated tissue. Finally, radiation therapy may result in substantial tumor necrosis, making tumor spill less likely and in some instances making successful limb salvage technically easier. These benefits come at a cost of delayed wound healing, surgical delay following radiation treatments, and less tissue from which to obtain a diagnosis. In such cases a postoperative boost dose of irradiation is administered for positive margins.

Post-operative radiation therapy is administered following surgical resection. Post-operative radiation therapy offers the patient immediate surgical excision, fewer wound healing complications, and a larger specimen from which to make a tissue diagnosis. Its disadvantages, however, are larger treatment volumes, higher dose requirements, and the risk of seeding the surgical scar and bed with viable tumor.

When it is anticipated that a close or microscopically positive margin will occur at the time of resection, intraoperative radiation therapy may be administered in the operating room immediately following surgical resection. Similarly, radiation administered via catheters (plastic tubes) which, are implanted in the surgical bed at the time of resection and loaded with radioactive material in the peri-operative period is another option that may be considered to help with a close or positive margin. This type of radiation is referred to as brachytherapy. Both methods offer focal concentrated treatment, limited collateral damage to surrounding tissue, smaller overall doses, and minimal to no delay in treatment following resection. However, these treatment methods are employed without knowing final pathology margin results. They may also result in wound healing problems.

**CHEMOTHERAPY**

Chemotherapy is intended for systemic disease which is either too small to detect or too diffuse, rendering local treatment techniques ineffective. The use of chemotherapy is only employed in high-grade disease, in which metastatic disease is likely. The benefits of chemotherapy must be weighed against its side-effects, some of which are irreversible. For this reason, the decision to
treat with chemotherapy is somewhat tailored to an individual patient and his or her individual disease.

Chemotherapy can be administered in the pre-operative and post-operative settings. Benefits of pre-operative chemotherapy include immediate treatment of micrometastatic disease and the potential for tumor shrinkage in certain chemotherapy-sensitive tumor types. It has also been shown to radiosensitize some tumors, making a combined protocol of radiation therapy and chemotherapy synergistic. In these ways, it may aid in limb-salvage surgery by making the surgical resection technically easier. Finally, tumor response to chemotherapy may be quantified following tumor resection, which in theory allows for adjustment of adjuvant treatment protocols.

Chemotherapy is typically not administered in the case of smaller lesions, defined as less than 5 to 8 cm in maximum dimension. It is often avoided in cases which are confined to local cutaneous or subcutaneous locations. Significant medical comorbidities or significant cardiac disease often precludes chemotherapy treatment. Lastly, the decision to forgo chemotherapy is sometimes made in the case of extensive terminal disease, in order to avoid a worsened quality of life.

In general, chemotherapy candidates are patients under the age of 65 with good cardiac function and limited medical comorbidities. Large, deep, high grade tumors and tumors which demonstrate metastases or metastatic potential are typical indications for chemotherapy treatment.

**PROGNOSIS**

Recurrence can be discussed in terms of local disease and distant or metastatic disease. The local recurrence rate for MPNSTs has historically been reported to range from 40-65% and the distant recurrence rate has similarly been reported to range from 40-68%.\(^\text{18, 23, 39}\) Five-year survival has been reported to range from 16-52%. Longer survival has been correlated with complete surgical excision, small tumor size (<5 cm), and the presence of a low grade component.\(^\text{18, 23}\) One recent study showed a survival rate overall of 84% in patients treated at a sarcoma center.\(^\text{7}\) This has been largely attributed to improved imaging leading to early diagnosis and aggressive treatment, employing adjuvant and neoadjuvant treatment modalities such as chemotherapy and radiation. In this study, patients with metastatic disease at presentation fared worse (33% survival) as would be expected.

While patients with NF1 were previously thought to have a worse prognosis than did patients with sporadic MPNSTs,\(^\text{9, 31}\) recent reports fail to support this contention.\(^\text{7, 23}\)

The efficacy of chemotherapy in the specific setting of MPNSTs is difficult to measure. In large part this is because these sarcomas are relatively rare. Furthermore, treatment algorithms often vary depending upon institutional experience, physician preference, and patient or case restrictions. In the past, studies of treatment of metastatic MPNSTs with chemotherapy did not show significantly improved survival rates.\(^\text{3, 6, 36}\) More recently, limited success using adjuvant chemotherapy has been demonstrated. The Italian and German soft-tissue sarcoma cooperative group reported an overall pediatric response rate of 45%, which included complete, partial, and minimal responders. The highest response rate (65%) was notably within the ifosfamide group.\(^\text{5}\) In addition, isolated case reports have demonstrated limited success as well.\(^\text{21, 24, 28}\)
**FUTURE ISSUES**

Malignant peripheral nerve sheath tumors have historically been difficult tumors to treat. This in large part resulted from their inherently aggressive nature; however, limitations in both diagnostic and therapeutic methods played an important role as well.

To date, advances in imaging methods, such as MRI and PET have realized earlier disease detection and characterization. Advances in immunohistochemistry have in turn, allowed for more accurate disease identification and classification. Experience with both chemotherapy and radiation therapy has broadened considerably and the multi-disciplinary team approach to sarcoma patient care has become well established.

Future gains will likely stem from a better understanding of the genetics and the molecular biology of soft tissue sarcomas. For example, genetic profiling of MPNST has recently suggested that NF1 related MPNSTs and sporadic MPNSTs are in fact distinct unique entities. Defining characteristics on a molecular level might allow for more precise screening tests, earlier disease detection, and perhaps more reliable prognostic information. Clinical relevance may also be realized through a molecularly engineered medication, specifically targeted to promote or interfere with a particular receptor or pathway. Glivec, for example, is a receptor tyrosine kinase inhibitor which was developed to specifically target KIT receptors and has shown marked improvement in patients with gastrointestinal stromal tumors previously unresponsive to treatment. Similar therapies will hopefully be designed and developed for malignant peripheral nerve sheath tumors in the future.

**REFERENCES**


