Surgical management of malignant peripheral nerve sheath tumors

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Object. The aim of this study was to describe the presentation of patients harboring soft tissue sarcomas involving the nerves, most of which were malignant peripheral nerve sheath tumors (MPNSTs), and provide an algorithm for their treatment.

Methods. The authors retrospectively analyzed data on 43 surgically treated soft tissue sarcomas involving the nerves, 34 (79%) of which were MPNSTs. Tumor classifications are presented, together with patient numbers, locations of MPNSTs, surgical techniques, and adjunctive treatments.

Results. The 34 MPNSTs were surgically treated during a period of 40 years. Most of these lesions (19 MPNSTs [56%]) were located in the brachial plexus, whereas the rest were located on other major nerves. Neurofibromatosis Type 1–associated tumors (12 lesions) represented 35% of the total number of MPNSTs. Although the main goal of surgery was complete excision, it was successful in only 16 patients (47%). Of the available records, 18 patients (53%) died due to disease progression.

Conclusions. Malignant peripheral nerve sheath tumors are rare. Surgical removal with margins when possible coupled by adjuvant radiotherapy offers the best chance of survival. The role of chemotherapy is still being defined.

KEY WORDS • brachial plexus • malignant peripheral nerve sheath tumor • pelvic plexus • peripheral nerve • soft tissue sarcoma

MALIGNANT PNSTs have been classified as soft tissue sarcomas, in part due to their rarity, as they comprise only 3 to 10% of all soft tissue sarcomas.^{1,2,10} Other terminology used for these tumors includes “malignant schwannoma,” “malignant neurilemmoma,” and “neurofibrosarcoma.”^{6,8,12} The World Health Organization coined the term “MPNST” to replace these confusing terms and to indicate that the lesions are malignant lesions of neurogenic origin with similar biological behavior.¹⁰ Such malignancies are more common in patients with NF1: 4% of patients with NF1 also have an MPNST, compared with an incidence of 0.001% in the general population.^{1–3,7} Recent data have shown that the incidence of neurogenic sarcomas in patients with NF1 is 3 to 5%,¹ whereas other findings have indicated that the rate varies from 5 to 42% of patients with NF1.^{8,10}

Malignant PNSTs can also occur without a background of NF1, and such sporadic presentations are actually more common than NF1-associated lesions. Neurogenic sarcomas associated with NF1 tend to occur in patients with a

younger age, although there is no sex difference in their incidence. Malignant PNSTs can arise either de novo or from a sarcomatous degeneration within a preexisting plexiform neurofibroma.¹ They have also been shown to arise within a field of previous irradiation.^{3,7,8} A review of the literature has shown that 4 to 11% of MPNSTs are thought to arise from previously irradiated areas.¹² The latency for tumor formation after irradiation has been varied as well, ranging anywhere between 10 and 15 years.

A palpable mass with or without progressive loss of function is the most common presenting symptom.⁵ Most frequently, painful paresthesias along the distribution of the affected nerve increases gradually, prompting a medical and an eventual surgical examination. In addition, some patients notice a lump that is painful when palpated. There is a subset of patients who present with initial mild functional loss that progresses relatively rapidly, resulting in severe functional loss and pain. Such a finding suggests a malignant neural sheath tumor. Generally, a rapid increase in lesion size is also indicative of malignancy. Such tumors tend to be firmer and more fixed to adjacent structures than their benign counterparts. As with benign lesions, these malignant nerve sheath tumors can sometimes be moved side to side but not up and down. Percussion or deep palpation over them causes pain radiating distally and sometimes proximally in the distribution of

Abbreviations used in this paper: CT = computed tomography; LSUHSC = Louisiana State University Health Sciences Center; MPNST = malignant peripheral nerve sheath tumor; MR = magnetic resonance; NF1 = neurofibromatosis Type 1.

the nerve or element of origin. A definitive diagnosis, however, requires excision of a biopsy tissue specimen when the tumor is removed.

Excision represents the mainstay of treatment and is the most important prognostic factor, whereas the roles of chemotherapy and radiotherapy are still being defined.^{2,6,11,12} Note, however, that the malignant nature of these tumors, coupled with limitations in the extent of resection, results in a poor overall survival rate.

Clinical Methods and Materials

We retrospectively evaluated the charts of patients who had been surgically treated at LSUHSC between 1969 and 2006 for 34 malignant neural sheath tumors of the brachial and pelvic plexuses and major peripheral nerves. Each patient's family history and physical and neurological examination findings of NF1 had been documented. Tumor size, location, and mobility; localized tenderness on palpation; and the presence or absence of a Tinel sign had been assessed, and neurological deficits had been determined using the muscle strength and sensory grading systems used at LSUHSC. Chest x-ray films were evaluated for their depiction of lower plexal tumors, and plain x-ray films of the cervical spine were reviewed to find evidence of intervertebral foraminal enlargement or vertebral erosion. Computerized tomography and/or MR imaging had been performed to document tumor location, margins, and relationship to adjacent structures (Figs. 1 and 2). For MPNSTs, the metastatic evaluation had included lung and abdominal CT scans and liver, spleen, and bone technetium scans. In some cases, angiography had been used to document the extent of vascularity and to delineate feeding vessels to the tumor. Myelographic results were included when lesions involved the spinal canal. Electromyography was performed in each patient in this series. Histological diagnoses based on light microscopy studies (and, at times, electron microscopy studies for difficult-to-diagnose cases) were reviewed. The types of surgical and adjunctive treatments for MPNSTs and the status of the surgical margins were also assessed.

Immunohistological Methods

Immunohistological methods were used in the series of neural sheath tumors to differentiate Schwann and perineurial cells and endoneurial fibroblasts. Included were S100 protein, which appears to be less intense and less uniform in neurofibromas than in schwannomas, Leu-7, epithelial membrane antigen, vimentin, collagen, and neurofilament protein. Glial fibrillary acidic protein was useful in approximately one third of the cases. These tests were used to decide whether a tumor had its origin in the neural sheath.

Pathological examinations included the use of H & E stains supplemented by immunohistochemistry as well as electron microscopy (Figs. 3–5).

Malignant PNSTs are highly cellular, showing a fascicular pattern with spindle-shaped nuclei and scant cytoplasm. These tumors are placed into one of three grades, depending on the degree of cellularity, nuclear pleomorphism, anaplasia, mitotic rate, microvascular proliferation, and degree of necrosis and invasion.³

Diagnosis of gross fusiform tumors in relation to nerves included the microscopic features of spindle cells with a fascicular pattern and positive immunostaining for S100 protein and neuron-specific enolase. Additional studies involving actin, cytokeratin, smooth-muscle actins, desmin, and vimentin are used to differentiate MPNSTs from other spindle-cell sarcomas.¹⁰ These additional tests are often required, given the difficulty in differentiating these tumors from other sarcomas arising from fibroblasts or smooth-muscle cells.

Ultrastructural features include wavy, buckled, or comma-shaped nuclei arranged in sweeping fascicles with extensive perineurial and intraneural spread of the tumor and often its proliferation in the subendothelial zones of vessels so that neoplastic cells appear to herniate into the lumen.¹ This subendothelial proliferation is characteristic of MPNSTs.¹⁰ Myofibrillar structures can also be assessed using electron microscopy.

Surgery for MPNSTs

Malignant PNSTs are rapidly growing, firm, fixed lesions initially causing either progressive loss of function or severe pain. An open biopsy was performed in patients presenting with such symptoms; if an MPNST was confirmed, an evaluation for metastatic disease was conducted. Resection was then performed in the following manner.

Brachial Plexus MPNSTs. Resection of a malignant brachial plexus tumor varied depending on its origin and location. Although total resection was the goal, it was often impossible without producing severe vascular and functional loss; some of this loss was the result of the necessary sacrifice of the element of origin. Nonetheless, simple biopsy sampling of such a lesion alone, without removal or substantial decompression, was usually not indicated. Amputation was seldom indicated at the time of the initial operation, because it was necessary to obtain permanent specimen sections from multiple sites to confirm the diagnosis of malignancy and to assess its invasion of adjacent structures.

Proximal Limb MPNSTs. For MPNSTs involving a proximal limb, wide resection would involve the removal of vessels necessary for the preservation of the limb or adjacent nerves. Therefore, amputation of the limb proximal to the lesion could occasionally be performed but only after results of a frozen-section analysis had verified that the lesion was malignant and the metastatic workup had shown no evidence of distant spread of the disease. When the diagnosis of malignancy was less certain because of less definitive pre- and intraoperative findings and frozen-section results, or because of very proximal paraspinous extension or origin on the tumor, only total lesion removal was attempted. Additional surgery then depended on the histological findings on permanent sections and on patient and family wishes.

Distal Limb MPNSTs. For MPNSTs of the distal limb, depending on the extent of metastatic disease, a wide local resection was performed. This procedure included removal of the nerve, adjacent soft tissues (whether adherent or not), and a several-centimeter margin of the entering and exiting nerve, all proving to be free of tumor on frozen and permanent tissue sections. By definition, such

FIG. 1. Sagittal T1-weighted MR image demonstrating sciatic nerve MPNST. Thick, shorter black arrow indicates the proximal nerve; thin, longer black arrow, the lesion; white arrow, the distal portion of the nerve.

a procedure led to neural deficit. Depending on the morphological characteristics of the tumor, further options included intraoperative placement of radioactive seeds in rods and postoperative external radiotherapy or chemotherapy alone or in combination. In patients who refused surgery that went beyond an attempt to remove the lesion or in those with metastatic disease, radiation was applied to the limb with or without adjuvant chemothera-

FIG. 2. Axial CT scan of sciatic nerve lesion, featuring posterior displacement of the gluteus muscles and a plane of separation between the lesion and musculature.

py. In recent years, an attempt at limb-sparing surgery has been favored whenever possible for sarcomas involving the extremities, but sometimes amputation or forequarter amputation is still performed. In our earlier experience, amputations were done only after the final pathological results were available. It is not recommended to perform amputations based on frozen sections, because it is not uncommon to have disparities in the histopathological results of frozen sections compared with final permanent sections (Figs. 6–8).

Results

Incidence of MPNSTs

Of 43 soft tissue sarcomas of the brachial and pelvic

TABLE 1
Malignant neural sheath tumors treated between 1969 and 2006*

Tumor Type & Location	Sporadic Cases	NF1-Associated Cases	Treatment						Average FU (mos)	Deaths†	
			LR	LRM	RT	Rods	Amputation	Forequarter Amputation			
neurogenic sarcoma											
brachial plexus	12	7	12	7	8	0	1	6	52	14 (25)	
ulnar nerve	2	0	0	2	1	1	0	0	52	1 (37)	
lumbar plexus	2	0	2	0	2	0	0	0	0	0	
sciatic nerve	4	2	3	3	2	1	0	3	32	2 (16)	
femoral nerve	1	1	0	2	1	1	1	0	46	1 (16)	
peroneal nerve	1	1	0	2	2	0	0	0	48	0	
tibial nerve	0	1	1	0	1	0	1	0	50	0	
other sarcoma‡											
brachial plexus	3	1	4	0	4	0	0	0	47	2 (40)	
sciatic nerve	3	0	2	0	1	0	0	0	27	1 (12)	
femoral nerve	1	0	0	1	1	0	0	1	18	1 (18)	
peroneal nerve	1	0	0	1	0	1	0	0	28	0	
total	30	13	24	18	23	4	3	10	46	22 (25)	

* Values represent the number of cases. Abbreviations: FU = follow-up; LR = local resection; LRM = local resection with margin; RT = radiotherapy.
† Includes fibrosarcomas and spindle-cell, synovial, and perineurial sarcomas.
‡ Values in parentheses represent the average postoperative survival in months among patients for whom the data were available.

FIG. 3. Photomicrograph of MPNST specimen revealing intraneural spread of the tumor. The malignant bundles are hypercellular and hyperchromatic in comparison with normal nerve tissue. H & E, original magnification $\times 20$.

FIG. 4. Photomicrograph of MPNST specimen depicting a highly cellular tumor with large hyperchromatic nuclei. H & E, original magnification $\times 200$.

plexuses and the major peripheral nerves, 34 (79%) were neurogenic sarcomas and nine (21%) were other sarcoma types such as fibrosarcoma and spindle cell, synovial, and perineurial sarcomas (Table 1). Of the 34 neurogenic sarcomas, 22 (65%) were solitary tumors in patients without NF1 and 12 (35%) were found in patients with NF1.

Locations of MPNSTs

In this MPNST series, the brachial plexus was the location in which the majority of sarcomas (19 lesions [44.2%]) were found. Of 23 brachial plexus MPNSTs and other sarcomas, eight (19%) were associated with NF1 and 15 (35%) were not.

Preoperative and Intraoperative Characteristics and Outcomes

Pain, which was sometimes but not always progressive, and/or progressive loss of function and paresthesias in the distribution of the involved nerve were the most common presenting symptoms in patients with MPNSTs. Some patients noticed a lump that was painful when it was palpated or bumped. In other cases, an initial mild loss of function rapidly became severe. It was rare for these patients to present initially with metastasis to the lung, bone, liver, and/or spleen. Despite some differentiating features on physical examination, the majority of MPNSTs were not suspected of being malignant until the biopsy procedure or attempted removal. Either procedure in relatively inexperienced hands can lead to a neural loss, just as occurs with more benign PNSTs. Neural loss is more likely with malignant than with benign tumors, not only because of their more intrinsic nature in relation to the nerve or element of origin, but also because of their adherence to adjacent neural structures and other soft tissues such as vessels, muscle, and even bone. Twenty-four (56%) of 43 patients with neurogenic and other sarcomas underwent local resection of the lesion. Eighteen (42%) of 43 underwent a local resection with margins. Data were unavail-

able in one patient. In 10 patients (23%) forequarter amputations of the shoulder and arm or hip disarticulation were performed, and in three patients (7%) amputations of the extremities were performed.

Adjunctive Treatment and Survival

Seventeen (50%) of 34 patients with MPNSTs received radiotherapy, and in three patients (9%) radioactive seeds in rods were placed. Note that some patients elected to forego radiotherapy. Eighteen (53%) of the 34 patients died, although they had survived an average of 25 months before succumbing to the disease. Most of the deaths were attributable to pulmonary metastasis.

Discussion

Patient Presentation

As with other nerve tumors, patients harboring MPNSTs present with signs of nerve irritation as well as neurological loss. The most frequent initial symptom or sign is a painless mass.^{1,3,6} Subsequent rapid growth of these lesions and the onset of pain usually trigger a medical evaluation. Other presentations include neurological deficits as well as neuropathic pain. Patients with NF1 tend to present at a younger age. In their series, Angelov and colleagues¹ found that the mean age at presentation was 47.4 years (range 16–82 years); patients with NF1 presented at a mean age of 36.8 years. Kar and associates¹⁰ found that the most common presenting symptom was a mass (96%), followed by pain (71%); only one person presented with a neurological deficit. The duration of symptoms is variable. Long histories of symptoms were particularly notable among patients with NF1.⁸ These patients pose a diagnostic dilemma, especially in the setting of existing neurofibroma, which requires the clinician to have a high suspicion of malignant transformation.

Areas of lesion involvement include spinal roots, peripheral nerves, brachial plexus, lumbosacral plexus, and

FIG. 5. Photomicrograph demonstrating numerous mitotic figures in an MPNST. H & E, original magnification $\times 400$.

cranial nerves. The most common origin in other studies has been the sciatic nerve, followed by the brachial plexus; spinal nerve roots; the vagus, femoral, sacral plexus, popliteal, obturator, posterior tibial, and ulnar nerves; and the vulva, posterior mediastinum, or retroperitoneal locations.¹³ There are cases in which the nerve of origin cannot be identified, however. Such tumors are thought to arise from terminal fibers within soft tissues, intestine, lung, or bone.^{3,10} The nerve of origin is identified in up to 70% of patients.⁵

Before embarking on treatment plans, an adequate metastatic workup is indicated, including chest x-ray films, CT scans of the chest and abdomen, and bone scans.

In some patients referred to us, the disease had been diagnosed using needle biopsy procedures. The role of such a procedure in the diagnosis of PNSTs remains controversial, however. Patients have been referred to us after either core-needle or fine-needle biopsy procedures for PNSTs have resulted in deficits. We do not generally advocate the use of needle biopsy procedures in the diagnosis of PNSTs because of the potential for introducing a neural deficit, which would be especially unfortunate in the treatment of a benign tumor. Moreover, tumors can be heterogeneous, with certain sections being representative of less malignant histological characteristics and other parts having more obvious malignant features. The sampling error from such needle biopsy procedures can thus lead to unfavorable decision making in the management of PNSTs. Not uncommonly, needle biopsies are nondiagnostic; therefore, over the years we have favored open resection of suspected PNSTs, during which we attempt to resect the lesion while preserving neurological functioning.

Magnetic resonance imaging is the most useful, noninvasive diagnostic tool. It allows assessment of the nerve of origin and the tumor's relationship to adjacent structures.¹⁰ Magnetic resonance imaging findings suggestive of neurogenic sarcoma include nonhomogeneous enhancement indicating intratumoral necrosis or hemorrhage, but these findings are nonspecific.¹ Imaging facilitates both assessment of the extent of disease and surgical planning. A target lesion on T2-weighted MR imaging supports but does

FIG. 6. Intraoperative photograph showing a dissected *in situ* MPNST. The white arrow is proximal, at the level of the sciatic notch; the black arrow points to the distal portion of the tumor.

not definitively prove the presence of a low-grade or benign lesion, whereas a heterogeneous lesion due to necrosis and hemorrhage and patchy contrast enhancement supports a diagnosis of MPNST.¹⁰ Loss of the target sign can be an indication of malignant degeneration.¹⁴

Computed tomography is useful in the staging process, especially in the assessment of pulmonary and sometimes osseous metastasis, of the spine in particular.

Electromyography and nerve conduction studies can be helpful in localizing small tumors as well as in differentiating them from noncancerous pathophysiology such as radiation-induced plexopathy. Radiation plexopathy is often suggested by myokymia on electromyography. Such findings do not exclude concomitant malignant tumor in or about the plexus or nerve in question.

As previously mentioned, MR imaging remains the modality of choice in the workup of malignancies involving the peripheral nerve. Differentiating between malignancy and radiation plexopathy on the basis of imaging remains difficult, especially given that both can show enhancement with Gd. The clinical features—including the history, myokymia on electromyography, and the usual delayed occurrence of radiation plexopathy—can be useful in distinguishing between the two pathological entities. Although we have not had extensive experience with positron emission tomography, it can be a useful imaging adjunct in distinguishing between radiation plexopathy and tumor, and thus its role in this regard should be further evaluated.

Systemic spread, especially pulmonary metastasis, remains the major problem and is the ultimate cause of death in cases of neurogenic or other soft tissue sarcomas.

Surgical Approach

Resectability and outcome are strongly related to the anatomical location of these tumors. Proximal structures such as the root or plexus as opposed to distal structures such as the nerves or terminal nerve branches determine resectability and outcome.³ Survival is dependent on wide resection. Resectability ranges from 20% for paraspinal MPNSTs to 95% for tumors of the extremity.³ A curative

FIG. 7. Photograph revealing the resection cavity. The white arrow points to the sciatic notch.

FIG. 8. Photograph displaying the resected tumor. The white arrow points to the sciatic nerve leading to and from the tumor.

local resection involves total removal with tumor-free margins of at least 2 cm in all directions.¹ Thus, a major determinant of outcome in patients with soft tissue sarcomas is the adequacy of the primary tumor resection.¹⁵ Adequate removal is not always possible, however, because of anatomical constraints as well as significant perineural spread of the tumor at diagnosis.

Treatment usually includes local resection followed by amputation more proximal to the level of involvement, which in turn may be followed by radiotherapy or chemotherapy or both. After the lesion has been identified, we try to accomplish as wide a resection of the tumor and surrounding tissues as possible. This approach is more workable for distal neural sheath tumors than for proximal ones, for which wide resection involves the removal of vessels vital to preservation of the limb or adjacent nerves and may lead to severe paralysis. Amputation of the limb proximal to the lesion is recommended, but only after the lesion has been pathologically verified as malignant and provided that there is no evidence of metastasis according to radiography and CT scanning of lungs, liver, and spleen, as well as bone scans. Amputations are indicated when wide excision is not feasible and in patients with severely compromised limb function.¹⁰ For proximal thigh lesions involving the sciatic nerve or distal femoral nerves, amputation can mean hip disarticulation. For a distal brachial plexus lesion involving cords of the plexus or their proximal outflows, a forequarter amputation is performed with removal of the scapula, clavicle, and shoulder, as is transection and ligation of subclavian vessels and division of plexus elements at a spinal nerve level.

Historically, the indication for amputation after sciatic nerve lesion excision was the belief that the motor and sensory loss expected with adequate margins would mean intolerable functional deficits. This circumstance would then favor the development of pressure sores and thus high rates of secondary amputations.⁴ However, most of these concerns have not materialized because femoral nerve-innervated muscles flex and extend the thigh and a kick-up foot brace provides a fairly good substitute for the loss of foot function. Limb-sparing resection should be considered and adjuvant radiotherapy initiated as necessary. The functional outcomes are good and correlate with

the level of the sciatic nerve sectioning, with more distal resections having a better outcome.⁴

As mentioned previously, tumors tend to disseminate along perineural planes, often precluding one's ability to achieve tumor-free margins. If a major nerve is involved, nerve sacrifice should be undertaken at the initial operation. Nerve grafting should not be attempted for three reasons. First, more proximal nerves are not amenable to reinnervation with grafting. Second, the natural history of the disease in some patients is too short for effective reinnervation.¹ Third, postoperative irradiation of the tumor and thus the graft site invariably kills the graft.

Limb salvage programs have also been initiated, usually including wide local resection of the tumor and adjacent tissues and leaving a good margin of soft tissue free of tumor. This procedure is then followed by local soft tissue irradiation with implanted rods, which can be supplemented with external radiation treatment. More recent experience has revealed that en bloc resections in conjunction with neoadjuvant and/or adjuvant irradiation achieve the same goals as the more radical approach of amputation without requiring limb sacrifice.^{1,15} Current literature reveals that for all soft tissue sarcomas, limb-sparing procedures allow an 85 to 90% local disease-free survival rate; therefore, limb sacrifice occurs in only 5 to 10% of patients.⁹

The major options are discussed with the patient and his or her family, and a joint decision is made favoring one approach over another. In the past several decades, our experience with limb sparing, which included wide local resection followed by rod irradiation, has been favorable. To date, at a plexus level, forequarter amputation has offered the longest survival. Lesions located more proximally and arising from the plexus have had to be treated by as thorough a resection as possible and not wide local resection because the latter would have resulted in a flail and devascularized arm. Such a resection was followed by radiotherapy as well as chemotherapy in several cases.

Radiation Therapy

Adjuvant or neoadjuvant radiotherapy decreases the hazard of death.³ Currently, postoperative radiotherapy is

recommended by oncological consensus groups as part of a uniform treatment policy for MPNSTs, much like other high-grade soft tissue sarcomas, even though clear surgical margins are obtained.¹⁰ Radiation has been shown to reduce local recurrence, and hence early initiation of radiotherapy is advocated.⁶

Chemotherapy for MPNSTs

Malignant PNSTs are considered to be poorly responsive to chemotherapy. Therefore, chemotherapy remains of unproven benefit, having no well-defined role in patients without metastasis in whom gross-total resection is performed.³ The role of chemotherapy as an adjuvant treatment is still largely unclear.⁶ If systemic spread occurs, chemotherapy is usually advocated in the management of both soft tissue and neurogenic sarcomas as a palliative measure.¹ In one study involving children, all patients with metastatic disease received chemotherapy consisting of dactinomycin, doxorubicin, and cyclophosphamide, but all showed progressive disease.⁶ In another trial of adjuvant chemotherapy for soft tissue sarcomas in adults, results showed that a cure was difficult to achieve, with 60% of the patients experiencing a relapse and succumbing to the sarcoma.⁹

Prognostic Factors

Tumor Size. A tumor size greater than 5 cm has been correlated with a worse prognosis.^{1,6,10} Patients with larger tumors on presentation tend to have more pronounced neurological deficits. Larger tumors also represent a challenge with regard to an ability to achieve local tumor-free margins. Almost all tumors in the present series were greater than 5 cm in diameter. This size favors local recurrence as well as distant metastasis, both of which are negative prognostic factors.² Last, tumor size has been shown to correlate with pathological grade, which is an important predictor of survival as well as of systemic spread.¹

Tumor Grade. A high tumor grade is also a significant negative prognostic factor.^{1,6,10} Not surprisingly, patients with higher-grade tumors have a shorter median survival time than those with more favorable histological characteristics. Cellular differentiation has been shown to be a significant prognostic factor for disease-free survival on both univariate and multivariate analyses.¹⁰ Patients with high-grade tumors show a higher incidence of distant metastasis with an increased risk of death from the disease.²

Tumor-Free Margins. The ability to achieve tumor-free margins is also an important prognostic factor.⁵ As stated previously, this factor is intimately related to tumor size as well as tumor grade. A larger lesion, especially in a more proximal location, often presents a challenge in achieving tumor-free margins while preserving at least some function in the extremity. In our view, the nerve or elements of origin should always be excised more proximal and distal to the lesion. In addition, larger tumors tend to correlate with a poor histological grade and more tumor spread on presentation, which again limits the ability to achieve surgical margins. Anghileri and colleagues² have shown that patients with positive resection margins bore a 2.4-fold risk of local recurrence and a 1.8-fold risk of death due to

the disease. It is therefore not surprising that positive resection margins are correlated with a significantly heightened risk for local recurrence as well as metastatic disease and poorer disease-specific survival.¹⁵ This trend is also seen in children, with authors of one report citing a 10-year survival rate of 80% in patients with total tumor resection, as opposed to only 14% in those with partial tumor removal.⁶

Tumor Location. More proximal tumors present a challenge in achieving adequate surgical margins without incurring prohibitive surgical morbidity. It is therefore not surprising that such tumors have poor local control. Patients with tumors of the extremities have more favorable outcomes compared with those harboring tumors of the trunk and the head and neck.^{2,7}

Malignant PNSTs in NF1. Although patients with NF1 tend to present at a younger age and with larger tumors, these factors have not been shown to result in a less favorable survival compared with patients without NF1.² The average age at presentation in patients with NF1 tends to be younger, 28.7 years compared with 39.7 years in patients with the sporadic form of MPNST.⁸ There are also indications that in patients with NF1, MPNSTs have a greater likelihood of resulting from malignant degeneration of a preexisting neurofibroma. The incidence of malignant transformation varies and can be between 2 and 29%.¹³ Findings supporting such a transformation include localization of the sarcoma within a neurofibroma, atypical neurofibromatous components, and a long history of a mass lesion. Patients with such features also tend to present with larger tumors at diagnosis.^{2,8} These lesions tend to be more poorly differentiated, recur locally, and spread. Survival in patients with such lesions thus tends to be shorter than in those with non-NF1-associated MPNSTs.^{7,8} Despite these findings, however, there is also evidence that there are no differences in survival with regard to NF1.²

Patient Survival. The disease-specific mortality rate at 10 years after definitive surgery can be up to 43%, but the probability of achieving a cure was no greater than 40%.² Patients presenting with local recurrence have worse outcomes than those presenting with primary disease.² A review of an orthopedic database has shown the overall survival rate to be approximately 84%; note that the duration of the follow-up was highly variable, from a few months to several years.⁷ However, reported death rates have ranged from 10 to more than 65%.

Management Algorithm. The following steps comprise the MPNST management algorithm. Neurogenic sarcoma is suspected. Perform imaging studies and electrodiagnostics. Refer the patient to a tertiary care center. Perform a surgical diagnosis via a limited biopsy procedure or a wide local resection with tumor-free margins if possible. During the latter procedure, the nerve or plexus element of origin must be completely resected. If malignancy is suspected from a prior biopsy procedure, a workup for metastatic disease should precede either wide local excision or amputation. Conduct a tumor grading and metastatic survey. Administer neoadjuvant or adjuvant chemotherapy and/or radiotherapy rather than amputation. Administer physiotherapy and occupational therapy for tumor- and surgery-induced morbidity. Closely monitor the patient

for relapses. If systemic relapse occurs, administer palliative chemotherapy.

Conclusions

Complete surgical removal of a tumor and the nerve or element of origin remains the most effective treatment for an MPNST. A favorable outcome also seems possible with gross-total resection followed by adjuvant treatment, including radiotherapy and chemotherapy. Note, however, that the role of chemotherapy is still evolving, with no clear indication of its utility in the management of MPNSTs.

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