Malignant peripheral nerve sheath tumors

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Malignant peripheral nerve sheath tumors (MPNSTs) are rare soft tissue sarcomas of ectomesenchymal origin. The World Health Organization coined the term MPNST to replace previous heterogeneous and often confusing terminology, such as “malignant schwannoma,” “malignant neurilemmoma,” “neurogenic sarcoma,” and “neurofibrosarcoma.” Malignant peripheral nerve sheath tumors arise from major or minor peripheral nerve branches or sheaths of peripheral nerve fibers, and are derived from Schwann cells or pluripotent cells of neural crest origin.

The Schwann cell is thought to be the major contributor to the formation of benign as well as malignant neoplasms of the nerve sheath. While this fact remains essentially true, the identity of cell of origin of the MPNST remains elusive, and has not yet been conclusively identified. It has been suggested that these tumors may have multiple cell line origins. In this review, the authors discuss the epidemiology, diagnosis, management, and treatment of MPNSTs.

KEY WORDS • malignant tumor • neurofibromatosis • peripheral nerve sheath

MALIGNANT peripheral nerve sheath tumors are rare soft tissue sarcomas of ectomesenchymal origin. The World Health Organization coined the term MPNST to replace previous heterogeneous and often confusing terminology, such as “malignant schwannoma,” “malignant neurilemmoma,” “neurogenic sarcoma,” and “neurofibrosarcoma.” Although the term MPNST is now used to identify any malignant tumor arising from a peripheral nerve or its attendant sheath, it does not, however, refer to tumors arising from the epineurium or the vasculature of peripheral nerves.^{17,58}

Malignant peripheral nerve sheath tumors arise from major or minor peripheral nerve branches¹⁶ or sheaths of peripheral nerve fibers,^{11,28} and are derived from Schwann cells or pluripotent cells of neural crest origin.⁴ Arthur Purdy Stout (1885–1967) played a pivotal role in the development of our current understanding of the pathogenesis of peripheral nerve sheath tumors by identifying the Schwann cell as the major contributor to the formation of benign as well as malignant neoplasms of the nerve sheath.^{48,49,63} While this remains essentially true, the cell of origin of the MPNST is elusive and has not yet been identified conclusively. Some researchers have suggested these tumors may have multiple cell line origins. In the present review, the epidemiology, diagnosis, management, and treatment of MPNSTs are discussed.

Abbreviations used in this paper: CYVADIC = cyclophosphamide, vincristine, adriamycin, dacarbazine; FDG = 18F-labeled fluorodeoxyglucose; MPNST = malignant peripheral nerve sheath tumor; MR = magnetic resonance; NF1 = neurofibromatosis Type 1; PET = positron emission tomography.

EPIDEMIOLOGY AND RISK FACTORS

It is estimated that from 5 to 10% of the 6000 soft tissue sarcomas diagnosed in the United States per year are malignant nerve sheath tumors, with an incidence of 0.001% in the general population.²⁶ These tumors occur with equal frequency in male and female patients, although some series have shown a female preponderance.^{11,16} There is no racial association. Most studies show that the peak incidence of MPNSTs is in the seventh decade of life in the general population, but in the third or fourth decade in people with NF1;^{2,20} however, these tumors can occur at a much younger age in either population.¹⁹

The great majority of MPNSTs occur in patients with NF1 with a cumulative lifetime risk of up to 10%. These tumors are 18 times more likely to arise in individuals with NF1 and internal plexiform neurofibromas than in patients without internal plexiform neurofibromas.⁵⁴ The dermal neurofibromas seen in patients with NF1, while more numerous and a more troubling cosmetic problem, do not undergo malignant transformation. Only rarely do MPNSTs arise from malignant degeneration of a schwannoma, ganglioneuroma, or pheochromocytoma. Ten percent of these tumors occur in patients who have undergone radiation treatments for other disease processes, on average, 15 years after the initial treatments.

The effect of radiation on peripheral nerves was described initially in Bergstrom and Cavanagh's^{6,12} experimental work in animals. The incidence of radiation-induced MPNSTs reported in large series studies ranges from 5.5 to 11% of patients.^{4,19,32,62} There are also several published reports relating to patients with and without NF1 who had undergone radiation treatments.^{15,19,34} Ducatman

et al.¹⁹ described 12 patients with MPNSTs after radiation therapy, seven of whom also had NF1. Two of the seven with NF1 had undergone irradiation for optic gliomas 5 and 17 years previously. More recently, Lore and colleagues³⁴ described two of four patients with NF1 who developed MPNSTs after head and neck irradiation, while Baehring and coworkers⁴ reported the same development in patients after radiation treatment for Wilm tumor and Hodgkin disease. Malignant peripheral nerve sheath tumors of the cauda equina have also been described after radiation therapy for testicular malignancy.¹

Diagnosis

The diagnosis of these tumors remains problematic as it is based primarily on clinical suspicion. As with any patient, a complete history and physical examination is the place to begin assessment for peripheral nerve tumors. In the history, special note should be made of when the mass, if palpable, was first noticed, and/or the onset of symptoms such as pain or motor or sensory deficits. Rapid increase in the size of the mass or a rapid onset of symptoms should immediately alert the surgeon to the possibility of a malignant tumor (Fig. 1). Patients with a known history of NF1, neurofibromatosis Type 2, or schwannomatosis who present with tumors that have shown recent rapid increases in size, or with new or progressive neurological deficits and/or pain, should alert the examiner to the suspected malignant degeneration. The examiner should question and record the location, quality, and radiation of pain, if present, and whether there are “pins and needles” or “electric shock”-type paresthesias. The location and extent of motor weakness, if present, and the location and extent of sensory deficits should be defined and recorded. Any family history of peripheral nerve problems or any other genetic disorders should be closely questioned and a history of previous radiation treatments should be discussed. Systemic diseases or any preexisting conditions, such as diabetes mellitus, that can contribute to peripheral nerve problems should also be investigated. Any recent illnesses, even those as seemingly minor as influenza, should be questioned and recorded. Because many prescription medications can cause peripheral neuropathy, a medication history should also be obtained.

During the physical examination, special attention should be given to examining for the presence of café au lait spots, axillary freckling, inguinal freckling, and Lisch nodules (pigmented iris hamartomas) that can indicate the presence of a genetic disease such as neurofibromatosis. Any spinal scoliosis that may indicate the possibility of intraforaminal tumors distorting the spinal column should also be noted. A complete motor examination should be conducted in all four extremities with standard motor strength grading, as well as a sensory examination. The sensory examination should define deficits in terms of dermatomal distribution as well as specific nerve distribution. Reflexes should be tested and the patient should be examined for the presence of a Tinel sign at the site of the mass or suspected tumor. The distribution and extent of the Tinel sign should also be noted, as it will offer clues as to which nerve is involved. If a mass is palpable, its size, quality, and mobility should be noted. Traditional teaching relates that a nerve tumor is mobile from side to side but

not along the length of the nerve proximally and distally. The likelihood of malignancy is increased with increasing tumor size, a consistency that is hard on palpation, and a mass that is fixed to the surrounding soft tissue.

Imaging

Prior to 1970, imaging of nerve lesions depended primarily on plain radiographs that surveyed for secondary bone changes. At one time, ultrasonography was also utilized to define peripheral nerve tumors. However, with the advent of computed tomography and MR imaging, soft tissue and nerve became visible. The gold standard for imaging of peripheral nerve tumors has become MR imaging. If a solitary palpable mass is encountered clinically in a patient and a peripheral nerve tumor is suspected, then MR imaging of the involved extremity, plain and with contrast enhancement, is indicated. If there are multiple tumors palpable, or any indication of neurofibromatosis or schwannomatosis on examination, then the imaging should be more comprehensive and include a full spine series to define any spinal or foraminal masses. Scans with contrast agent should always be ordered to evaluate the enhancing quality of the mass. Information on the enhancing qualities of the mass, combined with its appearance on T1- and T2-weighted images, can give valuable clues as to its histopathology.

On any contrast-enhanced image of a peripheral nerve tumor, fat suppression sequences should be used to better define the nerve in question. However, the use of conventional MR imaging techniques such as fat suppression can suffer from spatial and contrast resolution limitations as well as motion artifacts, problems that are a frequent complication of longer imaging times. Newer techniques utilizing MR neurography have the potential to offer enhanced visualization and definition of peripheral nerve mass lesions and produce higher resolution images of the nerves with greater separation from the surrounding soft tissue. Proper MR neurography requires special phased array surface coils and radiologists familiar with the short tau inversion recovery sequences necessary to obtain the desired images. Since this equipment and personnel may not be commonly available in most medical centers, the use of standard MR imaging techniques is more common.

Magnetic resonance images can contribute useful preoperative information concerning the suspected pathological entity. Unfortunately, whether a tumor is benign or malignant cannot be discerned definitively from the scan alone (Fig. 2). Areas of hemorrhage or necrosis, heterogeneous enhancement, and cystic areas may suggest a malignancy, but are by no means definitive, and can occasionally be seen in benign tumors.

Careful assessment of the images should include surrounding blood vessels and nearby vital structures and should note whether or not any infiltration of these surrounding structures is present. All images should be reviewed with an experienced radiologist so that as much information as possible concerning anatomic relationships and possible lesion types can be gleaned. There are occasions when the surgeon may be tempted to forego preoperative MR imaging, especially when the mass is obviously palpable. However this can lead to unexpected results in

FIG. 1. Preoperative (A) and intraoperative (B) photographs obtained in a 71-year-old man. This man had previously undergone complete excision of what had been diagnosed histologically as a benign median nerve tumor in the axilla of the left arm. Within 1 year he returned with a recurrent, fixed, and painful mass in the same area. The tumor was resected again and identified histologically as a malignant schwannoma that would require significant adjuvant therapy. This case underscores that a rapidly enlarging or recurring, painful, or immobile mass, should alert the surgeon to the possibility of malignancy.

the operating room such as mistaking a vascular structure or lymph node for a nerve sheath tumor.

Positron emission tomography with the glucose analog FDG is a dynamic imaging technique, which permits the visualization and quantification of glucose metabolism in cells and reflects the increase in metabolism in malignant tumors.^{23,50} A retrospective study of 18 patients with NF1 demonstrated that FDG-PET is a potentially useful, noninvasive method for detecting malignant changes in plexiform neurofibromas.²³ However, the distinction between low-grade MPNSTs and benign plexiform neurofibromas was not clear in all of the cases. The new tracer ¹⁸F-thymidine, which detects DNA turnover, might be helpful in distinguishing low-grade MPNSTs from active, benign plexiform neurofibromas in future PET-based studies.²²

Treatment

Once the diagnosis of MPNST is suspected, surgery is the mainstay of treatment.^{19,22,46} Resectability depends largely on tumor location, and ranges from 20% in paraspinal MPNSTs to 95% in tumors of the extremities.^{4,19,29,32,55,58,62} The ultimate aim of surgery is complete removal of the lesion with tumor-free margins.^{7,19}

There are many different approaches to these tumors, some of which are controversial. Because the resection to clean margins may require sacrifice of vital nerve and soft tissue structures, some surgeons advocate fine needle biopsy prior to definitive surgery. Other surgeons feel that a fine needle biopsy may miss malignant rests and lead to subsequent misdiagnosis or allow for spread of tumorigenic cells. A modification of this approach has an open biopsy performed with a multiple quadrant biopsy of the

tumor. Still others advocate a staged approach in which gross-total resection of the tumor is performed first, with care taken not to violate the tumor capsule. A full pathological examination of the entire tumor ensues, and if malignancy is proven histologically on permanent sections, the patient is returned to surgery in a timely fashion for definitive surgery. The margins around the resected tumor and surrounding tissue are then explored, and sampled tissue sent for frozen sectioning and pathological examination. As this surgery progresses, the definitive operation to clean the tumor margins to at least 2 cm on all sides is performed.

This last approach, in our opinion, allows for a thorough pathological examination of the initial tumor tissue so that nothing is overlooked, a situation that may not be possible if only a small biopsy sample is taken. Furthermore, this approach allows the surgeon to discuss with the patient, in the interval between the two surgeries, more accurately what can be expected and the greater likelihood of postoperative neurological deficits if diseased nerve and soft tissues are removed.

Unfortunately, in neurogenic sarcomas that involve the brachial or pelvic plexus or the proximal portion of the arm, a wide resection to clean margins is not accomplished without paralysis or even limb loss necessitated by vascular supply sacrifice. Thus, wide local resection seems to work better for neurogenic sarcomas involving the more distal portions of the limb. For more proximal lesions, amputation of the limb may be required, and many patients, given the cosmetic deformity and overall poor prognosis of these tumors, often refuse such recommendations (Fig. 3).

The reported local recurrence rate of MPNST following gross total resection is 32 to 65% after median intervals of

FIG. 2. A: Intraoperative image of a benign neurofibroma resected in a 34-year-old woman with NF1 who presented with a painful mass of the right thigh associated with the sciatic nerve. The patient is positioned prone intraoperatively. Although not all painful masses are malignant, given the consequences of a missed malignancy it is better to err on the side of caution with surgical excision of such lesions. B: A T1-weighted, contrast-enhanced, coronal MR image of the patient's thigh. Note that despite a lack of uniform enhancement, this tumor was ultimately shown to be histologically benign. Magnetic resonance imaging may not always predict malignancy accurately.

5 to 32.2 months.^{4,18,19,29,32,55,58,62} Murray Brennan,¹⁰ during his presidential address to the Society of Surgical Oncology, observed that a microscopically non-tumor-free margin may be an indication of a highly aggressive, invasive tumor, rather than a reflection of inadequate surgical technique, assuming that scrupulous attempts to attain microscopically tumor-free margins have been made. Local aggressive resection and control is thought to decrease the risk of systemic metastasis and lead to a better overall prognosis.

Reconstruction of the nerve after surgery for removal of malignant brachial and lumbosacral plexus lesions is not advocated. Because the needed adjuvant radiation and chemotherapy will compromise the ability of the axons to grow down to the target organ, attempts at reconstruction are thought to be a futile exercise. Furthermore, the natural history of MPNSTs is often not long enough for effective reinnervation.⁷ Amputation may be indicated for extensive tumors and for MPNSTs that recur after apparently adequate excision.²² Radiotherapy and chemotherapy are unfortunately of only limited value in these lesions, but are routinely applied as our armamentarium against these tumors is so limited. To date, only complete surgical excision prior to metastasis is likely to result in a good prognosis.^{4,19,25,34,58}

Classification/Pathological Diagnosis and Grading

The *NF1* gene at 17q11.2 was identified by positional cloning, and its protein product, neurofibromin, functions as a tumor suppressor.^{56,57,64} One of the functions of neurofibromin is to reduce cell proliferation by accelerating the inactivation of the protooncogene *p21-ras*, which has a pivotal role in mitogenic intracellular signaling pathways.⁶⁴ Patients with MPNSTs demonstrate aberrations in

17q11.2-22 and a loss of *NF1* gene expression, with resultant increase in *ras* oncogene expression.

A soft tissue sarcoma is thought to be of neurogenic origin if it fulfills any of the following criteria: 1) macro- or microscopic association with a peripheral nerve; 2) malignant transformation of a preexisting neurofibroma; or 3) immunohistochemical or ultrastructural features consistent with peripheral nerve origin.² The classification of MPNSTs (Grade I–III) is based on the system used for the much more common soft tissue sarcomas, and depends on the number of mitotic figures and the degree of nuclear and cellular atypia.²

Tumors are also classified based on gross size. Tumor size at surgery is stratified to be greater than or less than 5 cm. This has been based on previous reports in which soft tissue sarcomas of greater than 5 cm correlated with a worse prognosis.^{2,19,33,41,43,46} Tumor size influences the outcome and choice of treatment in several ways. First, patients with neurogenic sarcomas larger than 5 cm present twice as often with neurological motor or sensory deficits than patients with neurogenic sarcomas of 5 cm or smaller. Second, tumor size correlates with pathological grade, an important predictor of survival and systemic spread. The most aggressive Grade III tumors are found in patients with neurogenic sarcomas larger than 5 cm. Third, the size of the presenting neurogenic sarcoma influences the ability to obtain tumor-free margins in the first en bloc resection. Fourth, as with other sarcomas, the size of the neurogenic sarcoma at presentation seems to influence the survival rate negatively.²

Pathological Characteristics

Gross inspection of MPNSTs reveals a fusiform, fleshy, tannish white mass with areas of degeneration and secondary hemorrhaging. The nerve proximal and distal to the tumor may be thickened due to spread of the tumor

FIG. 3. A: Photograph of a 16-year-old boy with NF1 who originally presented with a painful supraclavicular mass. The lesion was only partially resected as it extended deeply under the sternum, making total resection impossible. On histological examination, the tumor was determined to be benign. B: Photograph of the patient 1-year later. He had been lost to follow-up during that time. On open biopsy sampling, the tumor was determined to have undergone malignant degeneration to an MPNST. After discussion the boy's family agreed to the necessary four quadrant amputation of the limb, which was followed by adjuvant radiation therapy.

along the epineurium and perineurium. The cell of origin is the Schwann cell, although the mature Schwann cell S-100 marker may be absent in about 50% of cases due to dedifferentiation.⁷

The minimum histological examination should comprise sections stained with conventional tinctorial stains, including H & E and reticulin. Malignant peripheral nerve sheath tumors are unencapsulated infiltrating tumors composed of spindle cells arranged in a whorling pattern with irregular nuclei, cyst formation, and nuclear palisading.¹⁴ Mitotic figures are readily visible, with more than one per hpf, and in 50 to 90% of cases the cells are immunoreactive to S-100 protein staining.³⁰ Necrosis, pseudocystic change, or hemorrhage may also be found. The pathological criteria for malignancy include invasion of surrounding tissues by tumor cells, vascular invasion, marked nuclear pleomorphism, necrosis, and the presence of mitoses.⁵⁹

Using the H & E-stained sections, the tumors are graded on a scale of I to III, with a scheme for soft tissue sarcomas based on cellularity, nuclear pleomorphism, anaplasia, mitotic rate (mitotic figures in 10 hpfs), microvascular proliferation, and degree of necrosis and invasion.^{2,16,53,61} In addition, immunohistochemical stains for S-100 protein, the skeletal muscle markers desmin and myogenin, and a proliferation marker (MIB-1) are required.

Other spindle cell tumors may be excluded with appropriate immunohistochemical markers. The diagnosis of a neurogenic sarcoma cannot be made reliably from examination of H & E-stained sections alone, because other soft tissue sarcomas, arising from fibroblasts or smooth muscle cells, may have similar appearances. Three immunohistochemical markers, S-100, Leu-7, and myelin basic protein, although not diagnostic by themselves because of significant false-positive and false-negative

rates, are used to facilitate the diagnosis of neurogenic sarcomas.^{19,27,31,35–37,60}

Mitotic rates are graded as 0, 1, and 2 depending on the numbers per hpf of fewer than five, five to 10, and more than 10, respectively. More than five mitotic rates per 10 hpf has been considered as a high-grade tumor, as a single mitotic figure may be significant in a tumor with hypercellularity and nuclear atypia.²² A greater than 5% cellular staining with MIB-1 proliferation marker has been considered to indicate the presence of a high-grade tumor.^{65,67}

On electron microscopic examination, ultrastructural features suggestive of a neurogenic origin for the tumors recapitulate the features of normal Schwann cells. These features include wavy, buckled, or comma-shaped nuclei arranged in sweeping fascicles with extensive perineural and intraneural spread of the tumor. Also often seen is a proliferation of the tumor in the subendothelial zones of vessels, so much so that neoplastic cells appear to herniate into the lumen.²¹ Also important is the lack or relative lack of ultrastructural features such as myofibrils, which suggest other origins for soft tissue sarcomas.

These tumors often create diagnostic problems because of their cellular origin and histopathological similarities with other spindle cell sarcomas such as monophasic synovial sarcoma, leiomyosarcoma, and fibrosarcoma. Another interesting clinical feature of this tumor is multifocality and the development of second primary tumors of the same histological characteristics.¹⁹ However, it is not always possible to demonstrate the origin from a nerve, especially when it arises from a small peripheral branch. This point was exemplified in a series by Nambisan and colleagues³⁸ in which nerves could not be identified in 61% of cases of MPNST and in the series by Bilgic et al.,⁸ in which nerve origin could be identified in 45 to 56%

cases only. Still, there are several distinct features, such as proliferation of tumor cells in the subendothelial zones of vessels with neoplastic cell herniation into vessel lumina and proliferation of small vessels in the walls of the large vessels, which are characteristic features of MPNSTs.⁵⁹

Radiotherapy

Although radiotherapy provides local control and may delay the onset of recurrence, it has little effect on long-term survival rates. There are reports, however, of routine postoperative radiotherapy and even radiotherapy as a single modality alone for MPNST in the literature.⁵¹ Currently, postoperative radiotherapy is recommended by the Oncology Consensus Group²² as part of a uniform treatment policy for MPNSTs, much like other high-grade soft tissue sarcomas,^{49,58} even if clear surgical margins are obtained. Adjuvant radiotherapy should be administered wherever possible for intermediate- to high-grade lesions and for low-grade tumors after a marginal excision.

The timing of irradiation (either before or after surgery) and the associated pros and cons is actively being studied by a group at the University of Toronto. Postoperative radiotherapy involves irradiation of the entire operative field, with a 5-cm field margin. Preoperative radiotherapy involves radiation doses to the overt tumor tissue alone, again with a 5-cm margin. The typical dose is 6000 to 7000 cGy. Radiation therapy before surgery has been recommended if the location, size, and distribution of the tumor make it more technically difficult to provide optimal radiotherapy after excision; if dissection is anticipated along a major neurovascular bundle (with the possibility of leaving microscopic disease in critical structures); or if remote tissue flaps or skin grafts are required for wound management after resection.^{2,39,40}

Chemotherapy

Like most soft tissue sarcomas, MPNSTs are traditionally chemotherapy insensitive. Chemotherapy for adult soft tissue sarcomas is usually confined to the treatment of metastatic disease. Systemic spread, especially pulmonary metastasis, is the terminal event and despite its limited efficacy, chemotherapy is indicated in this situation.² Due to the rare incidence of MPNSTs, large trials of the effectiveness of chemotherapy in MPNSTs are impossible and most current data are based on case reports, small case series, or regimens proven to be successful for other soft tissue sarcomas.

Few drugs have been shown to be effective, and treatment comprises single-agent doxorubicin or a combination of doxorubicin and ifosfamide,⁴⁴ with a partial response rate of 20 to 25%. With doxorubicin there was little impact on survival. Dacarbazine was later noted to have activity against these tumors and was combined with doxorubicin in the CYVADIC chemotherapy regimen.⁹ In the late 1980s, a number of Phase II trials demonstrated the superiority of ifosfamide to cyclophosphamide in soft tissue sarcomas. The European Organization for Research and Treatment of Cancer reported a Phase III study comparing doxorubicin to doxorubicin plus ifosfamide to CYVADIC, demonstrating an insignificantly increased response rate

with combination therapy, but at a cost of increased toxicity with doxorubicin plus ifosfamide.⁴⁴

Because chemotherapy is not curative, its use is controversial. As shown by a metaanalysis of the literature,³ there is a benefit at 10 years for progression-free survival for both local and distant relapse; however, the magnitude of any overall survival benefit is small (4%, not statistically significant).

Prognosis

Patients with NF1 (or their parents should the patient be a minor) should be made aware of the relatively high risk of MPNST associated with the disease. They should be instructed to contact their physician sooner rather than later should rapid enlargement, pain, or neurological deficit occur.²⁰ Patients with MPNSTs have a poor prognosis, and in most studies, the prognosis appears to be worse in patients with NF1 than in those who do not have NF1.^{18,19} In broad terms, MPNSTs can be considered fatal tumors, with the worst outcomes related consistently to incomplete tumor resection.^{19,62} Sarcomatous cells spread extensively within the fascial planes, resulting in high recurrence rates and ultimate systemic spread.^{2,45}

Patients with MPNSTs have a poor prognosis because metastases to the lung, liver, brain, soft tissue, bone, regional lymph nodes, skin, or retroperitoneum are common.¹⁹ Adverse prognostic factors include large size (> 5 cm), high-grade tumor, advanced histological characteristics, surgical margin with tumor invasion, and NF1.²

Basso-Ricci⁵ demonstrated a 56% disease-free survival rate using surgery in combination with radiation therapy in patients with MPNSTs. These lesions have the highest recurrence rate of any sarcoma,¹³ and adequate initial treatment gives the best chance of survival.²⁴ Even with aggressive therapy, local recurrence is seen in 50% of patients.³⁷ Angelov et al.² recommend that sacrifice of major neural structures such as the sciatic nerve be performed, without exception, to achieve resection with tumor-free margins. Other studies using preoperative radiotherapy or interstitial radiotherapy demonstrated that only a minority of patients with tumor-invaded margins ultimately develop locally recurrent or distant metastatic disease.^{42,52,66} Hematogenous metastatic spread occurs most commonly to the lungs. The 5-year survival rates in large series have been reported to range from 16 to 52%.^{19,32,47,62} The reported 5-year survival rate for patients with MPNSTs without NF1 is as high as 50% and drops to as low as 10% in patients with MPNSTs and NF1.¹⁸

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