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Malignant Peripheral Nerve Sheath Tumor (MPNST): An overview with emphasis on pathology, imaging and management strategies

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Malignant peripheral nerve sheath tumors (MPNST)

An overview with emphasis on pathology, imaging and management strategies.

Timothy Beer
Jefferson Medical College
OVERVIEW

DEFINITION

- Any sarcoma with one of the following features:
  - arising from a peripheral nerve
  - arising from a pre-existing benign nerve sheath tumor
  - demonstrating Schwann cell differentiation on histologic examination
- Any malignant spindled tumor in a patient with neurofibromatosis 1 (NF-1), unless proven otherwise

EPIDEMIOLOGY

- Accounts for 5-10% of all soft tissue sarcomas
- Incidence of 0.001% in the general population
- Up to 50% occur in patients with NF-1, 10% are radiation-induced, 40% are sporadic
  - NF-1 associated MPNST
    - develops from existing plexiform neurofibromas, NOT superficial neurofibromas
    - lifetime risk of MPNST in NF-1 patients has been reported between 5-10%
    - tend to present earlier in life and with larger tumors than sporadic MPNSTs
  - Radiation-induced MPNST
    - mean latency between irradiation and MPNST presentation may be around 15.5 years (range: 2-26)

CLINICAL FEATURES

- Most commonly presents as an enlarging mass +/- pain, paresthesias or neurologic deficits
- Most commonly occurs in or near a nerve trunk (e.g. brachial plexus, sacral plexus, sciatic nerve)
- Tend to recur locally and spread hematogenously, with lungs being the most common site of metastasis by far
Model for the pathogenesis of plexiform neurofibroma development and subsequent malignant transformation to malignant peripheral nerve sheath tumor (MPNST). The NF-1 gene encodes for the protein neurofibromin, which has been demonstrated to have tumor suppressor function. Absence of the second functional NF-1 gene results in loss of neurofibromin function, leading to deregulation of several intracellular signaling cascades, including the Ras → Raf, MEK, ERK pathway, the cAMP → Protein kinase A pathway and calcium signaling pathways, all of which favor increased proliferative activity. Likewise, EGF receptor (EGFR) accumulates because its expression is no longer inhibited by neurofibromin. These pro-growth alterations, together with substantial increases in secretion of the factors Kit ligand (Kit-L) and transforming growth factor beta (TGFβ1) are thought to contribute to the development of neurofibromas. Several additional molecular and genetic aberrations occur in those plexiform neurofibromas that undergo malignant transformation to MPNST. One such aberration is the substantially decreased or absent expression of the key tumor suppressor proteins p53, p16INK4A, p19ARF and Rb (although p53 has actually been found to accumulate in the nuclei of cells in some MPNSTs). Another aberration is further increased expression of several growth factors and their ligands, including EGFR, ErbB2, c-KIT, c-MET, HGF and PDGF.
GROSS PATHOLOGY

FEATURES

- Shape is globoid or fusiform (wide in the middle and tapers at both ends)
- Mean size in most series is 10-15 cm in greatest dimension and infrequently less than 5 cm
- Consistency is fleshy and firm to hard
- Color is typically tan-gray on cut section, but may include a wide variety of colors
- Necrosis is typically present, either focally or extensively
- Areas of cyst formation are commonly present
- May or may not be covered by a fibrous pseudocapsule
- Gross invasion into surrounding soft tissues is a common finding
- Entering and exiting nerve segments may be thickened due to spread along the epineurium and perineurium
- May be surrounded by portions of plexiform neurofibroma which have not yet undergone malignant transformation

EXAMPLES

Retroperitoneal MPNST. Tan-gray with areas of necrosis and cyst formation. A thin pseudocapsule can be seen surrounding this tumor (arrow).

MPNST adherent to psoas muscle. Tan-yellow with some areas of hemorrhage. Adherent vessel (arrowheads) and portion of psoas muscle (arrow) can also be seen.

MPNST of the right arm. This image illustrates the typical “fusiform” (central enlargement with distal tapering) shape these tumors impart as they expand the involved nerve.
**MICROSCOPIC PATHOLOGY**

**FEATURES**

- “Marbled” pattern of hypercellular fascicles of spindle cells interrupted by hypocellular myxoid areas
- The spindle cells are relatively large, with long, hyperchromatic, wavy or “serpentine” nuclei
- Perivascular hypercellularity, with indentation of cells into vascular lumens, is characteristic
- High-grade tumors tend to have high mitotic activity and necrosis, while low-grade MPNSTs often lack these features
- Minority of MPNSTs have variable differentiation (e.g. rhabdomyoblastic, epithelioid, glandular)
- No specific immunohistochemical markers, although several are used to help differentiate from BPNST and melanoma
  - S100+ in 50-60% (but usually only focally), Leu-7+ in 50%, myelin basic protein+ in 50%, HMB45-, cytokeratin-

**EXAMPLES**

*Perivascular accentuation.* Large spindle cells with irregular nuclei (arrows) encroach into vascular lumens, a histologic hallmark of MPNST.

*“Marbled” appearance.* Fascicles or bundles of tightly packed spindle cells alternate with relatively hypocellular myxoid zones, imparting a marbleized architecture.

*S-100 staining.* (left) MPNST stains S-100 positive only focally, whereas (right) benign neurofibroma stains S-100 positive strongly and diffusely.
MRI (with and without contrast)

- Imaging modality of choice for peripheral nerve sheath tumors
- Cannot provide definitive diagnosis, but helps differentiate MPNST from benign plexiform neurofibromas (see table)
- Fat suppression sequences may allow for better visualization of the nerve(s) involved
- Magnetic resonance neurography (MRN) offers superior visualization and delineation of peripheral nerves from surrounding soft tissue and may be superior to MRI for evaluating MPNSTs, where the technology is available

### MRI CHARACTERISTICS OF BENIGN AND MALIGNANT PERIPHERAL NERVE SHEATH TUMORS

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>BPNST</th>
<th>MPNST</th>
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<tbody>
<tr>
<td>Fusiform shape with tapered ends</td>
<td>Present</td>
<td>Present</td>
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<tr>
<td>Oriented longitudinally along direction of peripheral nerve</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Fascicular sign: multiple ring-like structures with peripheral hyperintensity on T2 weighted MR</td>
<td>Present</td>
<td>Absent</td>
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<tr>
<td>Target sign: hyperintense periphery surrounding a hypointense center on T2 weighted MR</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Split-fat sign: rim of fat surrounding the neurovascular bundle (and lesion) on T1 weighted MR</td>
<td>Present</td>
<td>Absent</td>
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</table>

**Fascicular sign.** (T2-MR) A hypointense ring (arrows) within an otherwise hyperintense benign plexiform neurofibroma.

**Target sign.** (T2-MR) A hypointense center with a hyperintense periphery in a benign plexiform neurofibroma of the tibial nerve.

**Split-fat sign.** (T1 MR) A rim of fat (arrow heads) surrounds the neurovascular bundle in which a benign Schwannoma (large arrow) has formed.
IMAGING

CT
• Test of choice for detection of metastases following diagnosis of primary MPNST
• All patients with MPNSTs should receive CT of the chest to assess for pulmonary metastases

FDG-PET & PET-CT
• Shown in several series to be sensitive (89%) and specific (95%) for differentiating MPNST from benign neurofibroma in NF-1 patients. Average SUV of plexiform neurofibromas reportedly 1.54-2.49, average for MPNSTs reportedly 5.4-7.63.
• SUV\textsubscript{max} does not appear to correlate well with tumor grade
• Some recommend using regular interval PET-CT to monitor NF-1 patients for malignant transformation of plexiform neurofibromas (specific intervals not yet defined)

GALLIUM-67 SCINTIGRAPHY
• Rarely used, but increased gallium-67 uptake has been shown to be associated with malignant transformation to MPNST

CT spine with reconstruction algorithm. Destructive MPNST at L2 involving most of the anterior vertebral body, both pedicles, and the right lamina while adjacent disc spaces appear normal.

Whole-body FDG-PET. Mild FDG uptake in several benign neurofibromas (black arrows), but intense uptake in an MPNST along the right sciatic nerve (white arrow).

Fused FDG PET-CT. Increased uptake of FDG (SUV = 4.2) in an MPNST within the left iliopsoas muscle (arrow).
PROGNOSTIC FACTORS

FAVORABLE PROGNOSTIC FACTORS IDENTIFIED IN 11 REVIEWS OF MPNST

<table>
<thead>
<tr>
<th>PUBLICATION</th>
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<th>SIGNIFICANT RELATIVELY FAVORABLE POSTOPERATIVE PROGNOSTIC FACTORS*</th>
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<tbody>
<tr>
<td>Anghileri (2006)</td>
<td>205</td>
<td>smaller tumor size, lack of local recurrence, extremity location</td>
</tr>
<tr>
<td>Stucky (2012)</td>
<td>175</td>
<td>tumor size &lt; 5 cm, lack of local recurrence, low histologic grade, extremity location</td>
</tr>
<tr>
<td>Zou (2009)</td>
<td>140</td>
<td>tumor size &lt; 10 cm, low intensity p53 staining, positive S-100 staining</td>
</tr>
<tr>
<td>Wong (1999)</td>
<td>134</td>
<td>smaller tumor size, low histologic grade, perineural histologic subtype</td>
</tr>
<tr>
<td>Brekke (2009)</td>
<td>64</td>
<td>tumor size &lt; 8 cm, complete surgical resection, lower intensity p53 staining</td>
</tr>
<tr>
<td>Okada (2006)</td>
<td>56</td>
<td>tumor size &lt; 7 cm</td>
</tr>
<tr>
<td>Baehring (2003)</td>
<td>54</td>
<td>complete surgical resection, young age, radiation therapy, lack of chemotherapy</td>
</tr>
<tr>
<td>Gousias** (2010)</td>
<td>43</td>
<td>gross total resection</td>
</tr>
<tr>
<td>Kar (2006)</td>
<td>25</td>
<td>lower histologic grade, greater cellular differentiation</td>
</tr>
<tr>
<td>Romanathan (1999)</td>
<td>23</td>
<td>tumor size &lt; 10 cm, low histologic grade</td>
</tr>
<tr>
<td>Zhu** (2012)</td>
<td>16</td>
<td>low histologic grade</td>
</tr>
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</table>

* For studies that performed both univariate and multivariate analyses, only those risk factors found to be significant on multivariate analysis are included here. Metastasis at time of presentation is a uniformly poor prognostic factor and therefore was not evaluated in most studies.

** Zhu series included only spinal tumors and Gousias series included only intracranial tumors.

SUMMARY

* Evidence overwhelmingly supports tumor size and local recurrence as important postoperative prognostic factors. By extension, because lack of local recurrence by definition requires complete surgical resection, complete surgical resection is likely also an important prognostic factor. This conclusion is also asserted in most of the included series.

* Evidence is suggestive, but not conclusive, that tumor location (extremity vs. trunk, head and neck) and histologic grade are also important prognostic factors.

* Further analysis is needed to determine whether factors such as p53 expression, radiation therapy, histologic subtype and S-100 staining are significant prognostic factors.
Complete surgical excision is required for cure

SURGICAL RESECTION
• Often requires en-bloc resection of major nerves and acceptance of potentially significant functional loss
• Complete resectability rates are determined primarily by neuroanatomic location
  • Reported to be around 95% for extremity lesions and 20% for paraspinal lesions
• Most cases of extremity MPNST can be completely resected without amputation

RADIOThERAPY (ADJUVANT OR NEOADJUVANT)
• Found to improve local control and reduce local recurrence rates in many series
• However, most series have found no benefit with respect to overall survival

CHEMOTHERAPy (ADJUVANT)
• Has NOT been shown in any large studies to significantly improve survival
• Often considered for patients with large tumor size (> 5 cm in most series), unresectability or metastatic disease
• Difficult to assess efficacy of agents and schedules because of the rarity of MPNST
• Most often involves ifosfamide and doxorubicin-based regimens (but no guidelines exist)
• In one series, 2 patients with MPNST lung metastases, who had been unresponsive to ifosfamide-doxorubicin, were given carboplatin-etoposide. This put them into partial remission, allowing for the complete resection of their lung metastases. Both patients remained disease free for 20 and 28 months, respectively, at the time of publication

FOLLOW-UP
• Follow-up guidelines have NOT been defined and vary widely
• Lee et al (2010) reported successful management of several local recurrences using MRI imaging every 3 months
MANAGEMENT BY SITE

SPINAL

GENERAL

- Paraspinal MPNSTs have a relatively dismal prognosis, largely due to their low rate of complete resectability, reported in some series to be as low as 20%.
- Most authors agree that paraspinal MPNSTs should be completely resected to achieve gross total resection, even if this requires an aggressive approach that destabilizes the spine and even in patients who have received prior radiation.

EXAMPLE McLaughlin et al. (Children's Hospital of Philadelphia, 2011)

- **Patient:** 14 year old female with left paraspinal MPNST extending to involve the intercostal muscles, aorta and neural foramina of T4-T10; previous surgeries, radiation and chemotherapy had failed.
- **Intervention:** performed gross total resection (GTR) using a costotransversectomy and multiple hemilaminotomies, then stabilized the patient using T1–12 pedicle screw fusion.
- **Outcome:** at time of publication, patient was 5 years post-op without any evidence of disease.

UPDATE

She went on to be homecoming queen and as of June 2012, is finishing up as a cancer free premed undergrad!

*Intraoperative “before” photo shows exposed spinal cord (yellow arrow), aorta (white arrow), pericardium (white star), and non-ventilated left lung (blue arrow).*

*Intraoperative “after” photo shows methyl methacrylate reconstruction and instrumented fusion. Due to prior thoracotomies, muscle flap was not possible.*
GENERAL

• Over 40 cases of intracranial MPNST have been published and total gross resection has been shown to be essential for the achievement of extended survival

• Adjuvant radiotherapy has been shown to be helpful in some cases but not others. Recently, a case report was published in which the use of adjuvant stereotactically-guided radiotherapy was associated with favorable outcome

EXAMPLE Gousias et al. (University Hospital of Bonn, 2010)

• Patient: 64 year old male with 3 weeks of progressive headache, vertigo, nausea and ataxia. He had a 30 year history of left-sided hearing loss. At the time of presentation, a 3.0 cm and contrast enhancing tumor at the left cerebellopontine angle had been detected.

• Intervention: gross total tumor resection (using neuromonitoring of motor tract and facial nerve function) followed 4 weeks later by stereotactic and image guided single isocenter dose delivery

• Outcome: follow-up clinical exam and MRI at 12 months showed no signs of tumor recurrence

UPDATE

Patient remained recurrence-free for at least 30 months, after which he was lost to follow-up
GENERAL

- Radical excision with wide margins (≥ 2 cm), histologic control of resection borders and adjuvant radiotherapy has been proposed as a standard of care therapy for scalp MPNST.
- In cases where tumor is found to have involvement of important intracranial structures or blood vessels, partial resection in combination with radiotherapy has been recommended.

EXAMPLE Ge et al. (Jilin University, 2010)

- **Patient:** 52 year old male with NF-1 with 22 x 18 cm multilobular, painless, non-mobile scalp mass with intracranial extension. The mass had been present for approximately 8.5 years, but progressively increased from the size of an egg over the past 2 years.
- **Intervention:** total excision of entire scalp mass and intracranial extension using repeated intra-operative margin assessment, followed by scalp repair using a skin flap isolated from the lateral aspect of the left thigh.
- **Outcome:** no sign of tumor recurrence or metastasis at 6-month follow up.

Pre-operative appearance. 22 × 18 cm diffuse multilobular scalp MPNST with focal areas of surface ulceration.

Pre-operative T1 MRI. Large heterogeneous hypointense lesion partially destructing the right parietal cranium.

Post-operative appearance. Scalp repaired with a skin flap isolated from the lateral aspect of the left thigh.
GENERAL

- General consensus favors aggressive gross total resection, sacrificing as much of the brachial plexus, arm and shoulder as necessary
- Neoadjuvant or adjuvant radiation are commonly employed for the purpose of decreasing local recurrence
- Recently, there have been reports of successful brachial plexus reconstruction following MPNST excision

EXAMPLE Spiliopoulos K, Williams Z. (Massachusetts General Hospital, 2010)

- **Patient:** 22 year old female with NF-1 with a rapidly enlarging, non-tender neck mass in the right supraclavicular fossa, encasing the upper trunk of the right brachial plexus. The mass had been biopsied 3 years prior and diagnosed as a benign plexiform neurofibroma, but it had since undergone malignant transformation to MPNST
- **Intervention:** neoadjuvant external beam radiation followed by complete surgical excision of the tumor with negative margins, with subsequent reconstruction of the brachial plexus
- **Outcome:** 19 months after excision of the tumor, no evidence of disease could be detected and the patient had regained function of all of the muscles in her right upper extremity, with some minor residual shoulder weakness

UPDATE

Patient is without recurrence and doing well as of June 2012

**T2 weighted MRI.** 6 cm lesion of heterogeneous intensity encases upper trunk of the brachial plexus

**Intraoperative photo.** Fusiform tumor arising from the upper trunk of the brachial plexus
BREAST

GENERAL
- MPNST of the breast is exceedingly rare (less than 10 total case reports published to date)
- One case of MPNST of the male breast has been reported
- Mastectomy (simple, radical or modified radical) ± radiation has been the treatment approach in all accounts
- No long-term outcome data for breast MPNST has been reported

EXAMPLE Woo et al. (Korea University Hospital, 2007)
- Patient: 56 year old female with breast mass, first noticed over 10 years ago, that had grown to 30 x 27 x 26 cm with extensive necrosis and hemorrhage
- Intervention: modified radical mastectomy and axillary lymph node dissection with right anterior chest wall reconstruction using a pedicled latissimus dorsi muscle flap and a split thickness skin graft from the right thigh
- Outcome: at time of publication was 6 months post-op without evidence of local recurrence or metastasis

Presenting appearance. Massive tumor of the right breast with extensive necrosis and inflammation.
Axial CT. Heterogeneous soft tissue mass with invasion of the right anterior chest wall and substantial necrosis.
Mastectomy specimen. Heterogeneous solid mass has necrosis and hemorrhage with fleshy tan periphery.
There have been very few reported cases of MPNST of the vulva. Among the three case reports published, two were treated with surgical excision and were free of disease at 9 and 16 months, respectively. In the third case report, the patient had recurrent vulvar MPNST and was treated with neoadjuvant radiation, followed by margin-free excision and chemotherapy. She was disease free at 18 months.

**Example** Lambrou et al. (University of Miami Hospital, 2001)

- **Patient**: 34 year old female with NF-1 had a rapidly enlarging recurrent pelvic MPNST (20 x 20 cm at presentation), pain, and difficulty ambulating. Only 6 weeks prior, she had undergone surgical removal of a 6 cm MPNST of the mons pelvis.
- **Intervention**: neoadjuvant external-beam radiation to shrink the mass, followed by anterior pelvic exenteration with intraoperative confirmation of negative margins and pelvic reconstruction and finally adjuvant chemotherapy.
- **Outcome**: No evidence of disease at 18 months after diagnosis.

**Images**
- **MPNST of vulva**: Labeled are vaginal introitus (white arrow), urethral meatus (black arrow) and scar from previous incision (asterisk).
- **En bloc resection of vulvar mass and adjacent structures**: Labeled are vulvar tumor (A), 50% as large as it was prior to radiation therapy, bladder (B), uterus and adnexae (C).
- **Post-operative appearance**: Reconstructed pelvis with rectus femoris myocutaneous flaps.
• Due to the rarity of MPNST, there have been no controlled trials, well designed cohort or case-control studies evaluating treatment. The body of evidence consists primarily of case reports, case series and literature reviews.

<table>
<thead>
<tr>
<th>Article</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Ferner et al. (2002)</td>
<td>All MPNST: postoperative radiotherapy as a uniform treatment policy</td>
</tr>
<tr>
<td>Kar et al. (2006)</td>
<td>All MPNST: radical surgical resection as treatment of choice</td>
</tr>
<tr>
<td>Kar et al. (2006)</td>
<td>All MPNST: postoperative radiotherapy has a definite role in both disease free and overall survival</td>
</tr>
<tr>
<td>Ducatman et al. (1986)</td>
<td>All MPNST: radical tumor excision with as wide of a margin of normal tissue as is feasible and the removal of all but the most vital structures, with amputation if necessary</td>
</tr>
<tr>
<td>Pengfei et al. (2010)</td>
<td>Scalp MPNST: intraoperative assessment of margins to ensure total tumor excision</td>
</tr>
<tr>
<td>Kumar et al. (2007)</td>
<td>Scalp MPNST: partial resection in combination with radiotherapy for cases with involvement of important intracranial structures or blood vessels</td>
</tr>
<tr>
<td>Voth et al. (2011)</td>
<td>Scalp MPNST: radical excision with wide margins (≥ 2 cm), histologic control of resection borders and adjuvant radiotherapy</td>
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<tr>
<td>Woo et al. (2007)</td>
<td>Breast MPNST: modified radical mastectomy and axillary lymph node dissection for massive cases</td>
</tr>
<tr>
<td>Zhu et al. (2012)</td>
<td>Spinal MPNSTs: en bloc surgical resection if at all possible</td>
</tr>
<tr>
<td>Gousias et al. (2010)</td>
<td>Spinal MPNST: maximal surgical resection feasible with preservation of neurological function, followed by adjuvant stereotactically guided radiotherapy</td>
</tr>
<tr>
<td>Lambrou et al. (2001)</td>
<td>Vulva MPNST: complete surgical resection with adjuvant radiation +/- chemotherapy</td>
</tr>
<tr>
<td>Spiliopoulos et al. (2011)</td>
<td>Brachial plexus MPNST: reconstruction as an adjunct to surgical excision in patients in whom surgical morbidity is a necessary outcome of achieving gross total resection</td>
</tr>
<tr>
<td>Minovi et al. (2006)</td>
<td>Head and neck MPNST: complete tumor excision plus adjuvant radiotherapy</td>
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<tr>
<td>Chen et al. (2007)</td>
<td>Intracranial MPNST: complete surgical resection with radiotherapy for local control</td>
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<th>Type</th>
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• MPNSTs are rare malignancies that are classically associated with pre-existing plexiform neurofibromas in neurofibromatosis type 1 (NF-1) patients, but also occur in association with radiation as well as sporadically in patients with no known risk factors.

• The typical presentation of sporadic MPNST is a new painless enlarging mass. The typical presentation of MPNST in an NF-1 patient is rapid enlargement or new onset of pain associated with a pre-existing plexiform neurofibroma.

• Although both MPNST and benign neurofibromas share in common the absence of neurofibromin function due to loss of both NF-1 alleles, malignant transformation to MPNST requires several additional aberrations, most notably constituent activity of the proliferative Ras-GTPase pathway, increased expression of growth factor receptors such as EGFR and decreased activity in additional tumor suppressors such as p53, p16\(^{INK4A}\) and p19\(^{ARF}\).

• Grossly, MPNSTs typically appear "fusiform" (wide in the middle with tapering at both ends), larger than 5 cm and tan-gray on cut section. Necrosis, cyst formation and a "pseudocapsule" are frequently, but not always, present features. They may or may not be surrounded by portions of a pre-existing neurofibroma which have not undergone malignant transformation.

• The histologic features of MPNSTs show considerable variation and they overlap greatly with benign neurofibromas. However, several features argue in favor of MPNST, including perivascular hypercellularity, hyperchromatic wavy nuclei, high mitotic activity, necrosis and only focal or no areas of S-100 positivity.

• MRI is the imaging modality of choice for evaluating MPNSTs. It can be useful for differentiating MPNST from benign neurofibroma based on the absence of the fascicular sign, target sign and split-fat sign. CT is most useful for detecting metastases and chest CT should be ordered for all newly diagnosed patients due to the high incidence of pulmonary metastases. PET-CT has an evolving role, especially with regards to differentiating neurofibroma from MPNST based on SUV.

• Prognostic factors for MPNST include tumor size, local recurrence and completeness of surgical resection. There is some evidence to suggest that tumor location (extremity vs. trunk, head and neck), histologic grade, p53 expression, S-100 expression, radiation therapy and histologic subtype may also be important prognostic factors.

• Complete surgical removal of an MPNST provides the only hope for cure. There are some cases where neoadjuvant radiation and/or chemotherapy have allowed for complete surgical removal and thereby enabled cure. There is considerable evidence to suggest that adjuvant radiation, but not adjuvant chemotherapy, is helpful in preventing local recurrence of MPNST.

• Postoperative follow-up strategies for MPNST varies greatly across practitioners. No formal guidelines for follow-up have been proposed, however one author has demonstrated that regular, frequent re-evaluation with MRI can allow for timely excision of local recurrences, thereby prolonging overall survival and extending the potential for cure.
REFERENCES

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