# Peripheral nerve sheath tumors: an update and review of diagnostic challenges

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## Abstract

Peripheral nerve sheath tumors (PNSTs) are one of the more common soft tissue neoplasms encountered in the daily surgical pathology practice, most of which have classic histologic features. There are, however, some common diagnostic challenges encountered by surgical pathologists and neuropathologists, as well as controversies regarding classification and grading of PNSTs. As molecular studies advance and novel targeted therapies are developed, it has become imperative that we become familiar with the diagnostic criteria for these common neoplasms and their potential mimics.

**Keywords** hybrid nerve sheath tumors; malignant peripheral nerve sheath tumor; neurofibroma; perineurioma; peripheral nerve; schwannoma

## Introduction

Peripheral nerve sheath tumors (PNSTs) represent the large majority of tumors of the peripheral nerve system, ranging from the most common neoplasm of benign schwannian cells, schwannoma, through to malignant peripheral nerve sheath tumor (MPNST), a rare but high grade malignancy that is difficult to treat and does not respond well to conventional therapy.[1] Unlike the majority of soft tissue tumors, PNSTs arise from distinct compartments of the peripheral nerve, namely: the myelin sheath surrounding axons, formed by Schwann cells comprising the myelin barrier; the endoneurium, composed of capillaries, fibroblasts, macrophages and mast cells; the perineurium, a specialized epithelial-like layer encompassing the endoneurium; and the epineurium, an external layer composed predominately of fibroadipose tissue. While tumors can originate from each of these components, the majority of lesions are composed of Schwann cells. Neuroectodermal in origin, Schwann cells arise from the neural crest and display a great deal of plasticity, producing myelin and collagen, but also capable of divergent differentiation, including rhabdomyoblastic, chondroblastic and epithelial cell types. Given the heterogeneous composition of cell types comprising PNSTs as a whole, with the most common cell type exhibiting metaplastic capabilities, it is not surprising that PNSTs comprise a morphologically diverse and heterogeneous group of neoplasms. We present the most common PNSTs encountered in surgical pathology practice, as well as discuss selected variants, addressing some of the challenges in the differential diagnoses of these lesions.

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## Challenges addressed in this review

- Diagnostic criteria for the most common subtypes of PNST: schwannoma, neurofibroma and perineurioma
- Review of diagnostically challenging, uncommon variants such as cellular, plexiform and melanotic schwannomas
- Classification of composite, "hybrid" tumors
- Grading of malignant peripheral nerve sheath tumors

## Schwannoma

Schwannoma (a.k.a. neurilemmoma) is a benign peripheral nerve sheath tumor composed of a pure population of Schwann cells. Peak incidence is in the 4th–6th decade and there is no predilection for male or female sex. Schwannomas can occur at numerous body sites, of which the skin and subcutaneous tissues, especially the head and neck and flexor surfaces of the extremities, are the most common locations. In addition to the skin/subcutaneous tissues, peripheral schwannomas are also frequently encountered in the gastrointestinal tract. Schwannomas involving the central nervous system are less common than those of the peripheral nervous system, and may be either intracranial or intraspinal, comprising approximately 30% of all spinal nerve root tumors.[2] Intracranial tumors most commonly involve the vestibular branch of the eighth cranial nerve; the cerebellopontine angle (CPA) is the most commonly localized anatomic site. Involvement of cranial nerves other than the eighth cranial nerve is rare. Intraspinal tumors involve the sensory (dorsal) nerve roots with sparing of the motor (ventral) nerve roots. The clinical presentation varies depending on the site of the lesion. Tumors involving the peripheral nerves are usually asymptomatic, while tumors involving spinal nerve roots present with radicular pain and nerve compression syndromes. Tumors localized to the CPA present with hearing-related symptoms including tinnitus and sensorineural hearing loss. Of note, while most sporadic peripheral nerve schwannomas are asymptomatic, the lesions of schwannomatosis are often painful.

Unlike neurofibromas, which arise within the central portion of the nerve fiber and are consequently composed of an intimate admixture of Schwann cells and nerve axons, schwannomas arise from the periphery of the nerve and are composed of a pure population of Schwann cells.[3] For this reason, nerve fibers are not usually appreciated either grossly or microscopically in the resection specimen. From a surgical point of view this is significant, as schwannomas can often be removed without associated nerve deficit, as the nerve axons are not disrupted in the course of the procedure.[4]

**Pathologic features:** schwannomas are usually relatively small (<5 cm). The gross appearance is that of an encapsulated mass with a soft tan-white appearance with or without focal areas of




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cystic degenerative change. On low power, schwannomas have a fibrous capsule and may have an associated rim of lymphoid cells ("pericapsular lymphoid cuff"). The main lesion displays alternating hypercellular (Antoni A) and hypocellular (Antoni B) areas (Figure 1A). Antoni A areas are composed of spindled cells arranged in compact whorls and fascicles. Focally, the spindle cells form columns of palisaded cells surrounded by extracellular pink neurofibrillary material (Verocay bodies). The cells in the Antoni B areas are similar to those in the Antoni A areas, however architecturally the cells are spaced further apart and have a looser, more myxoid matrix. The cells in both the hypercellular and hypocellular regions exhibit spindled nuclear contours with pointed (tapered) ends, as opposed to the blunt ends observed in smooth muscle tumors. The cytoplasm is eosinophilic and cell borders are not readily appreciated. The nuclear chromatin is homogenous with absent nucleoli. Mitotic activity (up to 5–10 mitoses per 10 high power fields in cellular variants) can be observed and does not confer a worse prognosis. A helpful diagnostic feature is the presence of hyalinized, thick-walled vessels that have a tendency to bleed, resulting in areas of hemosiderin deposition (Figure 1B). Degenerative changes are common and include cystic degeneration, hemorrhage with hemosiderin deposition, calcification and nuclear atypia. The cells with degenerative nuclear atypia can become markedly enlarged with irregular nuclear contours and hyperchromasia of a smudgy, non-granular character ("bizarre nuclei"). Variable degenerative changes exist and lesions with significant nuclear atypia can be diagnosed as "ancient schwannoma". These atypical cells should show a low proliferation index with immunohistochemistry for Ki-67 (MIB-1).

Immunohistochemically, schwannomas exhibit strong and diffuse nuclear immunoreactivity for S-100 (as opposed to more variable staining seen in neurofibroma) (Figure 1C). Basement membrane markers collagen IV and laminin stain individual Schwann cells in a membranous pattern ("pericellular pattern"). Neurofilament is negative, or may highlight peripherally displaced nerve fibers separate from the main mass lesion. Epithelial membrane antigen (EMA) is negative in Schwann cells but may be positive in entrapped perineurial cells in the capsule. Glial fibrillary acidic protein (GFAP) is positive in a minority of cases. CD34 is negative in lesional cells. SOX-10, a newer immunohistochemical marker used in the diagnosis of melanoma, has been shown to have increased specificity for tumors of neural crest origin when compared to S-100 and is positive in schwannian and melanocytic tumors.[5,6]

Schwannomas are benign and do not recur given adequate primary excision. Transformation to MPNST is extremely rare. The risk for malignant transformation is not increased in syndromic cases, and is also not increased in most of the variants of schwannoma such as cellular schwannoma and plexiform schwannoma. When occurring in the central nervous system, non-melanotic schwannoma and its variants correspond to a WHO grade I tumor. It is important to note that melanotic schwannoma is specifically excluded from the definition of a WHO grade I schwannoma; a specific grade for melanotic schwannoma is not currently assigned.[2]

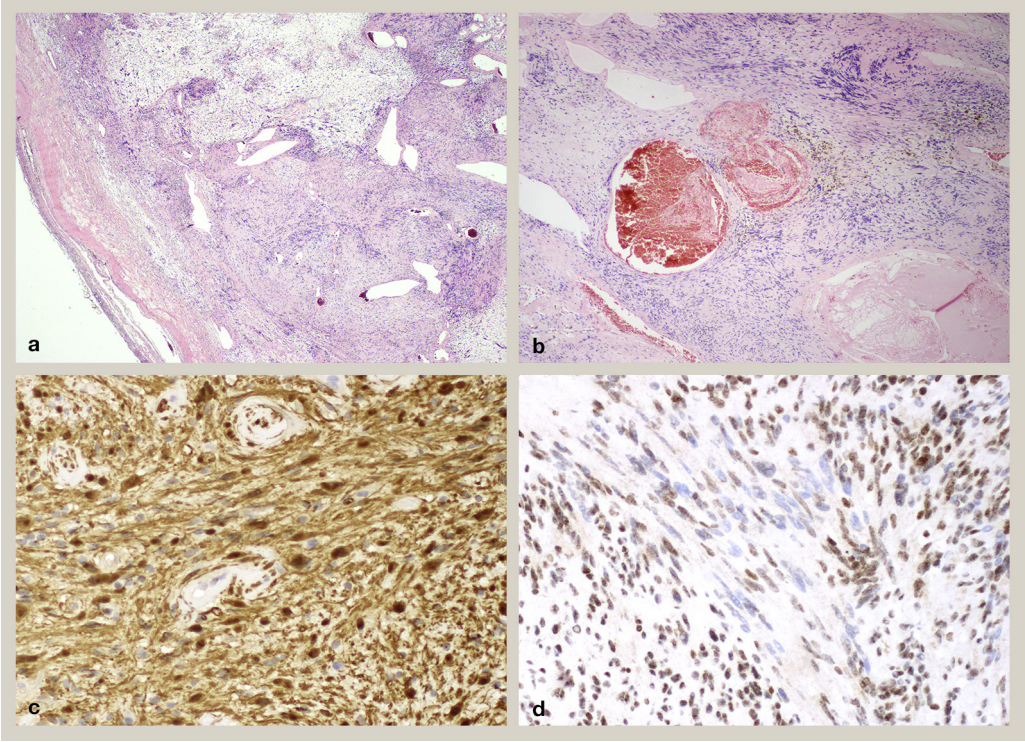


**Figure 1** Schwannoma: (**a**) Well-encapsulated lesion displaying alternating hypercellular (Antoni A) and hypocellular (Antoni B) areas; (**b**) Hyalinized, thick-walled blood vessels with associated hemorrhage and hemosiderin deposition; (**c**) Spindle cells exhibit strong and diffuse nuclear staining for S-100; (**d**) "mosaic" pattern of nuclear staining for INI-1 that can be seen in cases of NF2 and schwannomatosis.




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