Introduction:

Most neural neoplasms differentiate towards (or are derived from) peripheral nerves, or their neurocutaneous end organs. Three principle cell types comprise peripheral nerve sheaths: perineurial cells, Schwann cells, and fibroblasts. Perineurial cells differ from Schwann cells by having no basement membrane. Schwann cells give rise to three common cutaneous neural neoplasms: neuromas, schwannomas (neurilemmomas), and neurofibromas, which differ from one another in the proportion and arrangement of Schwann cells, axons, fibrocytes and supporting stroma. Schwann cells are viewed as neuroectodermal cells and are derived from the neural crest, as are perineurial cells and (most likely) Merkel cells. Other neural lesions (nasal gliomas, cutaneous meningiomas) represent herniations and heterotopias of glial and meningeal cells.

Because neural neoplasms recapitulate or consist of varying proportions and arrangements of peripheral nerve components, familiarity with the histology of peripheral nerves illuminates the current classification.

I. Normal Histology
   A. Nerve Fiber
      1. Axon (neurite)
      2. Schwann cells
   B. Nerve fascicle
      1. Endoneurium (nerve fibers, fibrocytes, capillaries and mast cells)
      2. Perineurium (perineurial cells in continuity with the pia-arachnoidal lining of the CNS)
   C. Peripheral nerve
      1. Nerve fascicles
      2. Epineurium (fibrocytes, collagen, adipose tissue, blood vessels)

II. Classification of neural neoplasms
   A. Nerve sheath tumors
      1. Neuromas
         a. Traumatic, amputation (rudimentary polydactyly), solitary and associated with multiple endocrine neoplasia syndrome type 2b
      2. Neurofibroma
         a. Superficial, deep, diffuse, pigmented, plexiform, others
      3. Perineurioma
      4. Schwannoma
a. Common, ancient, cellular, plexiform, others
5. Nerve sheath myxoma
   a. Neurothekeoma, cellular neurothekeoma (historically)
6. Granular cell tumor
B. Malignant neoplasms
   1. Malignant peripheral nerve sheath tumor
   2. Primary cutaneous neuroendocrine (Merkel cell) carcinoma
C. Neural heterotopias
   1. Cutaneous meningioma, meningocele, rudimentary meningocele
   2. Nasal glioma
   3. Metastatic neuroblastoma
   4. Primary primitive neuroectodermal tumor (PNET)
   5. Ganglioneuroma

A. NERVE SHEATH TUMORS
   1. NEUROMAS
      a. TRAUMATIC NEUROMA

Clinical features:
- Firm oval nodules, often painful

Histopathology:
- Irregular nerve fascicles imbedded in fibrous tissue

b. AMPUTATION NEUROMA (RUDIMENTARY POLYDACTYLY)

Clinical features:
- Small nodular tumor along ulnar border of base of fifth finger

Histopathology:
- Dome shaped nodule with numerous nerve bundles throughout the upper dermis in haphazard arrangement

c. PALISADED ENCAPSULATED NEUROMA/ SOLITARY CIRCUMSCRIBED NEUROMA

Clinical features:
- Slow growing painless nodules on head and neck or upper trunk of middle aged individuals

Histopathology:
- Single to multinodular (occasionally plexiform) dermal spindle cell proliferation
- Numerous fascicles with clefts separating the fascicles
- Vague suggestion of nuclear palisading without well formed Verocay bodies
- Delicate spindled nuclei uniform in appearance
- Bodian stain positive; S-100 positive
d. NEUROMAS AND THE MULTIPLE ENDOCRINE NEOPLASIA SYNDROME TYPE 2b

Clinical features:
- Rare autosomal dominant condition
- Medullary carcinoma of the thyroid
- Pheochromocytoma
- Somatic abnormalities
- Mucosal neuromas

Histopathology:
- Two distinct patterns 1): mucosal neuromas resembling solitary neuromas-haphazardly arranged bundles of nerve fascicles; 2): tortuous hyperplastic nerves with a thickened perineurium

2. NEUROFIBROMA

Clinical features:
- Papular, nodular, or pedunculated nodules
- Soft, tend to invaginate ("buttonhole" sign)
- Neurofibromatosis: neurofibromas, café-au-lait macules, pigmented hamartomas of the iris (Lisch nodules), macrocephali, mental retardation, kyphoscoliosis

Histopathology:
- Non-encapsulated spindle cell proliferation in dermis and subcutaneous fat
- Delicate fascicles
- Mucin and mast cells
- Multiple variations, diffuse, plexiform

3. PERINEURIOMA

Clinical features:
- Rare neoplasm composed of perineurial cells involving dermis, subcutaneous fat or deep soft tissue

Histologic features:
- Circumscribed non-encapsulated neoplasm
- Spindle cells with bipolar cytoplasmic processes
- Resemble neurofibromas
- Concentric whorls collections of fascicles ("onion bulbs")
- Fibromyxoid stroma
- EMA and vimentin positive
- S-100 protein, CD34, chromogranin, and NSE negative

4. SCHWANNOMA (NEURILEMMOMA)
Clinical features:
- Uncommon, usually solitary neoplasms
- Extremities of adults
- Painful, tender
- Two to four centimeters in diameter
- Multiple, localized (agminate)
- Neurofibromatosis (schwannomatosis)

Histologic features:
- Circumscribed encapsulated neoplasms
- Located in subcutaneous fat
- Two tissue types: Antoni type A- spindle shaped Schwann cells arranged in fascicles; nuclei aligned in rows or palisades (Verocay bodies); Antoni B-myxedematous stroma, less cellular, dilated vessels with thick hyaline walls
- S-100 protein, vimentin, and myelin basic protein positive

5. NERVE SHEATH MYXOMA/ NEUROTHEKEOMA

Clinical features:
- Face and upper extremities
- No association with neurofibromatosis
- Female predominance

Histologic features:
- Multilobulated and not encapsulated
- Multiple lobules throughout the reticular dermis
- Spindled nuclei arranged in concentric whorls with myxoid stroma
- Mild nuclear hyperchromasia
- Variable mitoses

6. GRANULAR CELL TUMOR (GRANULAR CELL MYOBLASTOMA)

Clinical features:
- Oral cavity, tongue, skin
- Female predominance
- Solitary skin colored nodules
- Multiple granular cell tumors associated with neurofibromatosis
- Malignant granular cell tumor exceedingly rare

Histologic features:
- Schwann cell origin favored
- Non-encapsulated sheets of large cells
- Small central nucleus with coarsely granular eosinophilic cytoplasm
• Pseudoepitheliomatous hyperplasia
• S-100 protein, NSE, NKI-C3 positive
• Myoglobin and glial fibrillary acidic protein negative

B. MALIGNANT NEOPLASMS

1. MALIGNANT PERIPHERAL NERVE SHEATH TUMOR
(NEUROFIBROMASARCOMA-MALIGNANT SCHWANNOMA)

Clinical Features:
• Extremely rare
• Most often associated with von Recklinghausen's disease
• Usually a neoplasm of deep soft tissues
• Proximal extremities in young to middle aged adults
• Cutaneous involvement usually by extension from deeper tissues

Histologic Features:
• Asymmetric densely cellular spindle cell neoplasm
• Vesicular pattern
• Myxomatous foci
• Numerous mitoses, hyperchromatic and pleomorphic nuclei
• Plexiform and epithelioid variants
• S-100 protein positive

2. PRIMARY CUTANEOUS NEUROENDOCRINE (MERKEL CELL) CARCINOMA

Clinical Features:
• Merkel cells are derived from neural crest tissue and may have some association with primary cutaneous neuroendocrine carcinoma.
• Head and neck of older adults
• Rapidly growing solitary nodule

Histologic Features:
• Small round blue cell neoplasm
• Irregularly sized collections, occasionally trabecular pattern
• Numerous mitoses and frequent necrotic cells and pyknotic nuclei
• Intraepidermal involvement and squamous differentiation rare

Differential Diagnosis:
• Metastatic neuroendocrine (small cell) carcinoma of the lung and other organs
• Lymphoma and leukemia
• Small cell melanoma
• Cytokeratin 20, chromogranin, synaptophysin positive
• Cytokeratin 7, thyroid transcription factor 1, S-100 protein negative

C. NEURAL HETEROTOPIAS

1. CUTANEOUS MENINGIOMA

Clinical Features:
- Scalp along cranial closure lines
- Skin colored papules and nodules
- Alopecia or abnormal hair growth
- Composed of arachnoid lining cells misplaced during embryogenesis; or developing along the course of cranial nerves; or representing cutaneous metastasis or direct extension of primary meningiomas of the arachnoid lining (worst prognosis)

**Histologic Features:**
- Ill-defined pseudovascular spaces within dense collagen
- Spaces lined by elongated meningoendothelial cells
- Eosinophilic cytoplasm and round to oval nuclei
- No cytologic or nuclear atypia
- Focal calcification and psammoma bodies
- EMA and vimentin positive

2. **NASAL GLIOMA/ HETEROTOPIC NEUROGLIAL TISSUE**

**Clinical Features:**
- Dome shaped skin colored to pink nodules
- One to five centimeters in diameter
- Sixty percent extranasal
- Forty percent intranasal or both locations
- Twenty percent with intracranial connection
- Present at birth or early infancy
- Rarely present on scalp with ring of dark long hair encircling them ("hair collar sign")

**Histologic Features:**
- Ill-defined unencapsulated dermal and subcutaneous mass of neuropil-like tissue
- Pale staining finely vacuolated glial tissue within which astrocytes may be present
- Normal astrocytes, fibrillary astrocytes and gemistocytic astrocytes
- Mature neurons with triangular cell bodies, large open eccentric nuclei, Nissle granules, and dendritic and axonal processes
- Glial fibrillary acidic protein (GFAP) stains positive glial tissue; neuron specific enolase stain positive neurons; antibodies to neurofilament stain positive axons.

**MUSCLE NEOPLASMS**

**Smooth Muscle**
- arrector pili muscles
- blood vessel walls
- scrotum (dartos muscle)
- vulva
- nipple (areolar smooth muscle)
- spindled nuclei, blunt ends (“cigar-shaped”)
- perinuclear cytoplasmic vacuoles
- trichrome (muscle= red), smooth muscle actin; muscle specific actin, desmin, caldesmon

1. PILAR LEIOMYOMA
   Clinical features:
   - Trunk and extensor extremities, 2nd, 3rd decade
   - Multiple, skin colored
   - Zosteriform rare
   - Familial (auto. dom.)
   - Associated with uterine leiomyomas and renal cell cancer or Reed’s syndrome; 1q 42.2-43 encodes fumarate hydratase (tumor suppressor).

2. SMOOTH MUSCLE HAMARTOMA
   Clinical features:
   - Rare, congenital
   - Plaque (up to 10 cm)
   - Hypertrichosis, hyperpigmentation
   
   Histologic features:
   - Similar to pilar leiomyoma

3. ANGIOLEIOMYOMA
   Clinical features:
   - Solitary, painful
   - Extremities (leg)
   - Female preponderance
   
   Histologic features:
   - Well circumscribed
   - Interlacing smooth muscle bundles
   - Small numerous vessels

4. LEIOMYOSARCOMA
   Clinical features:
   - Rare, painful or tender
   - Dermal or subcutaneous
   - Extensor extremities, scalp, trunk
   - Male preponderance
   
   Histologic features:
   - Irregular, jagged periphery
   - Similar interlacing bundles
   - Hyperchromatic, pleomorphic nuclei
   - Mitoses including abnormal forms
Striated Muscle

- Perioral and periocular
- Neoplasms (striated muscle hamartoma, rhabdomyoma, rhabdomyosarcoma) are exceedingly rare.