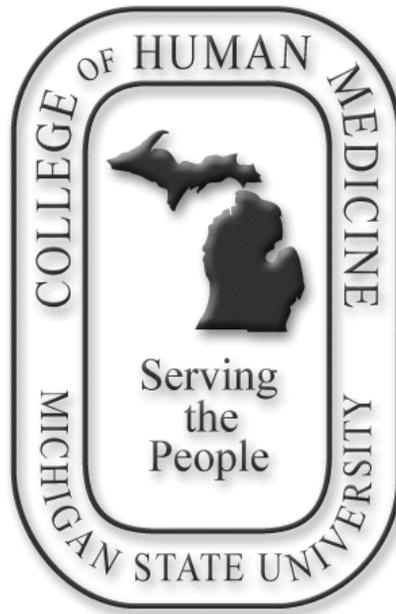


CNS NEOPLASMS MODULE



Objectives:

1. Contrast neoplasms of the nervous system in children and adults:
 - A. type
 - B. location
 - C. primary or metastatic in nature
2. Discuss general symptoms of nervous system neoplasms and the diagnostic studies used most frequently. List signs and symptoms secondary to space-occupying effects of supratentorial and infratentorial tumors and discuss pathogenesis of these clinical signs.
3. Describe remote effects of neoplasms on the nervous system (paraneoplastic syndromes) and give examples.
4. For the 3 primary central nervous system neoplasms found in children (pilocytic astrocytoma, ependymoma, medulloblastoma):
 - A. list sites where found
 - B. list signs and symptoms
 - C. describe gross and microscopic lesions, and potential for spread in CSF
 - D. list cell of origin
 - E. classify as benign or malignant, and understand prognosis

For retinoblastoma and neuroblastoma, describe locations and general features.

5. For the more common primary central nervous system neoplasms in adults (gliomas, meningioma):
 - A. list sites where found
 - B. describe signs and symptoms
 - C. describe gross and microscopic lesions
 - D. list cell of origin
 - E. list relative frequency
 - F. classify as benign or malignant
6. List cell of origin, site, and clinical signs for pituitary adenoma, acoustic Schwannoma, primary CNS lymphoma, germ cell tumors and pineal parenchymal tumors.
7. Discuss the neurocutaneous syndromes (phakomatoses) in terms of associated lesions and genetic defect.
8. Discuss metastasis of tumors to CNS from primary sites outside of the CNS, including morphology (gross and microscopic), and describe most frequent locations in CNS.
9. Discuss spinal cord tumors; list intramedullary and extramedullary tumor types

10. Discuss toxic effects of radiation treatment.

I. Introductory Concepts

A. Tumor Classification

1. Tumors may be primary, originating in cells found in the brain and its coverings, or secondary, that is, metastatic from sites outside the CNS, or developmental, arising from displaced midline epithelium or germ cells.

2. Tumors may be classified as intra-axial, within the brain parenchyma, or extra-axial tumors originating in skull, meninges, cranial nerves and brain appendages such as pituitary gland.

3. Neoplasms may be benign or malignant. The distinction between benign and malignant tumors is less evident in the CNS than in other organs. E.g. histologically benign tumors may infiltrate large regions of the brain or may have high morbidity and mortality because of their location in the nervous system. The ability to resect CNS tumors depends on location, and may be limited.

4. Tumors can be classified by their cell of origin. The cell of origin of CNS primary tumors lies within the brain, spinal cord, or their coverings. A common classification scheme includes the following major types:

- gliomas
- neuronal tumors
- poorly differentiated neoplasms
- meningiomas

5. CNS tumors do not metastasize to other organs. However, some tumors may spread through the subarachnoid space to other locations in the CNS

Direct vs. Remote (paraneoplastic) Effects of Tumors

Signs and symptoms of nervous system tumors are generally caused by their localized neuronal destruction and/or space-occupying effects with consequent brain compression or displacement -- these are DIRECT effects. REMOTE or paraneoplastic effects of tumors refer to changes in the peripheral or central nervous system caused by a primary tumor elsewhere in the body. This section will first describe paraneoplastic effects (or syndromes), and then discuss the many types of direct effects of a tumor within the skull.

A. Paraneoplastic Syndromes (Remote Effects)

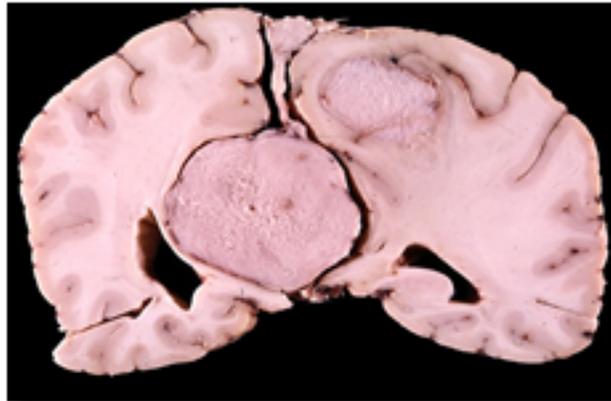
Remote effects of a neoplasm involve changes in the peripheral or central nervous system caused by a primary tumor elsewhere in the body, sometimes before clinical recognition of the primary neoplasm. Paraneoplastic syndromes are more common with certain primary neoplasms - the most common tumor causing paraneoplastic syndromes is small cell carcinoma of the lung. Peripheral nerves, muscle, dorsal root ganglia or CNS structures may be involved. CNS syndromes that have been recognized include paraneoplastic cerebellar degeneration, limbic encephalitis, and subacute sensory neuropathy. Most or all paraneoplastic neurologic disorders are immune-mediated. (Darnell & Posner, NEJM, 349:16, 2003) One mechanism involves production of autoantibodies associated with the tumor, which cross-react with antigens in the nervous system to produce different clinical syndromes.

B. Direct Effects

1. Space-occupying effects with increased intracranial pressure

a. Causes of increased intracranial pressure:

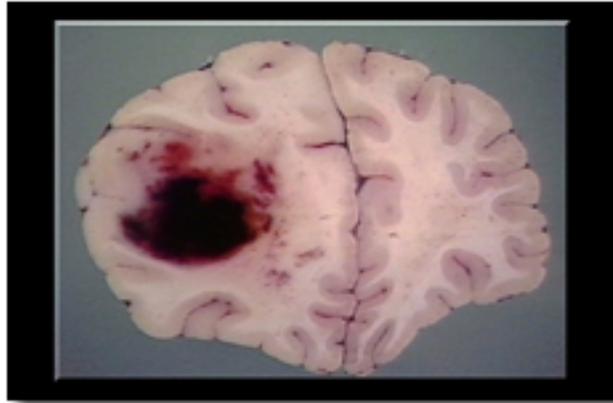
- Direct compression of brain tissue by tumor mass



NEO 01

Large tumor compressing adjacent brain tissue

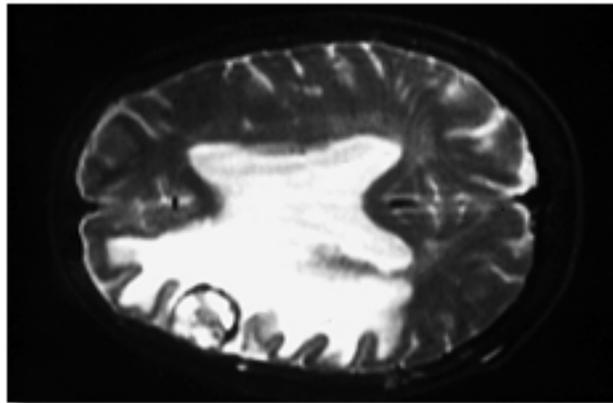
- Hemorrhage within the tumor;



NEO 02

Hemorrhage into a neoplasm causing mass effect and increased intracranial pressure

- Edema - surrounding tumor or widespread throughout brain;



NEO 03

Bright areas show edema surrounding tumor (CSF in ventricles is also bright)

- Impairment of CSF flow, resulting in non-communicating hydrocephalus

b. Results:

- Focal neurological signs
- Generalized signs of increased intracranial pressure (e.g. headache, lethargy, nausea)
- Herniation

2. Loss of Neuronal Function: due to destruction in specific areas

- a. Causes include tumor infiltration, compressive effects, alteration in vascular supply
- b. Resulting focal neurological symptoms depend on the specific area involved

3. Seizure production by initiation of abnormal neuronal activity; seizures may be generalized, focal or psychomotor (complex partial seizures).

4. Endocrine abnormalities -- e.g. may cause changes in growth, metabolism or sexual function; less common than the mechanisms above.

Clinical Presentation and Diagnosis

Signs and Symptoms

Symptoms depend on the location and size of the mass. Common presenting symptoms include headache, seizures, personality or behavioral changes, dizziness and focal signs (e.g. motor, sensory or visual). Usually symptoms of benign or low grade tumors have gradual onset and are slowly progressive (i.e., weeks to months). Higher grade lesions are more likely to present with rapidly progressive headache and focal neurologic signs. Headache occurs in about half of all patients with intracranial tumors. Typically the headache is diffuse, but may be located in one hemisphere. Generally the headache is more noticeable on awakening in the morning and dissipates within a few hours.

The occurrence of seizures varies with the tumor type. Typically, the seizures are focal, but may become generalized. Other focal symptoms typically have a subacute onset and are progressive. The exception is a visual field deficit that may develop progressively but that often goes unnoticed by the patient until it contributes to an injury or automobile accident. Many, but not all, patients with an intracranial tumor and increased intracranial pressure have papilledema (illustrated in the image). Characteristics seen on funduscopic exams include blurring of the disc margins, congestion of retinal veins, and hemorrhages.

Diagnostic Studies

The major diagnostic study needed for a suspected brain tumor is cranial MRI. If a brain tumor is a diagnostic consideration, MRI with gadolinium enhancement is the test of choice; a normal contrast-enhanced MRI scan essentially rules out the possibility of a brain tumor.



NEO 04

Papilledema may be a clinical indication of a brain tumor.

Molecular Genetics

Genetic alterations are correlated with the occurrence or progression of some tumor types. Examples of alterations are inactivation of p53, overexpression of PDGF-A and its receptor, disruption of tumor suppressor genes, amplification of the epidermal growth factor receptor (EGFR) gene, and chromosomal variations. Understanding the role of such changes may eventually lead to more specific and effective therapies.

II. Primary Neoplasms in Children

A. General Characteristics

- Nervous system tumors are the second most common neoplasm in children (leukemia is first) and are usually primary.
- Brain tumors are usually infratentorial, most often in the cerebellum in children.
- The three most common are: pilocytic astrocytoma, medulloblastoma, ependymoma.
- Signs and symptoms are generally those of posterior fossa space-occupying lesions, including: headache, especially on waking, nausea, vomiting, papilledema, signs of cerebellar dysfunction

Pilocytic Astrocytoma

- **Location:** most often in cerebellum, often cerebellar hemispheres; sometimes in brain stem
- **Signs and symptoms:** if in cerebellar hemispheres, symptoms are ipsilateral, including limb ataxia and falling to one side
- **Gross characteristics:** cystic lesion with mural nodule of tumor. Cyst wall is glial tissue and not neoplastic
- **Microscopic characteristics:** astrocytes often have very dense fibers; micro- and macrocysts may be present

- **Prognosis:** The good prognosis associated with cerebellar astrocytomas is not altered by a variation in histological cell types. Survival is generally more than 10 years.



NEO 05

Cerebellar astrocytoma - illustration of large cyst and mural nodule of tumor (at top of cyst)

Medulloblastoma

- **Origin:** incompletely differentiated fetal cells; probably arises from external germinal layer or cell rests in cerebellum; classified as a poorly differentiated neoplasm
- **Location:** cerebellum, often midline in nodulus; may project into ventricle or progress into brainstem
- **Signs and symptoms:** symptoms of midline cerebellar dysfunction (truncal ataxia), plus increased intracranial pressure in posterior fossa and hydrocephalus due to fourth ventricle occlusion (headache, nausea, vomiting, papilledema)
- **Gross pathology:** solid, soft to granular tumor, sometimes with seeding throughout subarachnoid space
- **Microscopic pathology:** cells are lymphocyte or granule cell-like, closely packed in sheets, mitotically active
- **Prognosis:** gloomy, but some success attained with surgical removal, radiation of entire neuraxis and chemotherapy; this tumor is very radiosensitive
- **Molecular Genetics:** The most common genetic alteration is loss of material from the short arm of chromosome 17. Other alterations include one in the Sonic hedgehog/patched pathway (involved in control of normal proliferation of cerebellar granule cells).

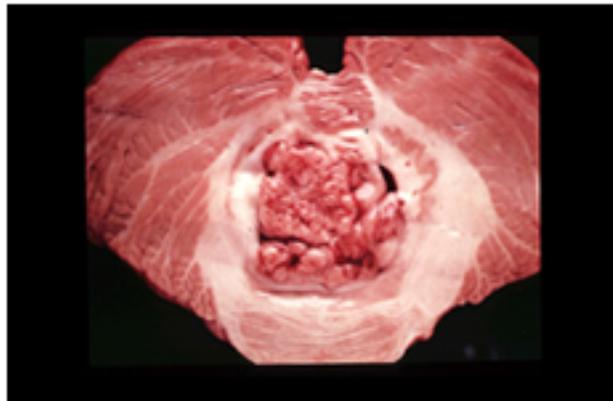


NEO 06

medulloblastoma in the cerebellum, with seeding in the subarachnoid space producing opaque appearance on the right side of the image

Ependymoma

- **Origin:** ependymal cells
- **Location:** fourth ventricle usually; may extend out foramen of Luschka into "cerebellopontine angle"
- **Signs and symptoms:** due to increased intracranial pressure (headache, nausea, vomiting, papilledema)
- **Gross pathology:** friable and granular solid cut surface
- **Microscopic pathology:** cuboidal, well circumscribed cells arranged in patterns with true ependymal rosettes as well as perivascular pseudorosettes
- **Prognosis:** poor, tend to recur because location limits chance of complete resection.



NEO 07

This image shows a solid ependymoma tumor in fourth ventricle. The pons is located below the tumor, the cerebellum surrounds the tumor.

Other Types (less common)

1. Retinoblastoma

- Location: eye, sometimes bilateral, may extend along optic nerve
- Prognosis: good if diagnosis is made when tumor is small

2. Neuroblastoma (70% in children under age 4)

- Origin: neuroblast rests
- Location: peripheral nervous system, often in adrenal gland
- Prognosis: poor, unless child is very young (<1 yr. old)

III. Primary Neoplasms in Adults

General Characteristics

In the adult, about 50% of neoplasms are primary and 50% are metastatic (the numbers depend somewhat on the type of study performed). About half the primary neoplasms are gliomas, (astrocytomas, oligodendrogliomas, ependymomas) and 50% of these gliomas are the most malignant variety, glioblastoma. Of the nonglial primary tumors, meningiomas are the most common.

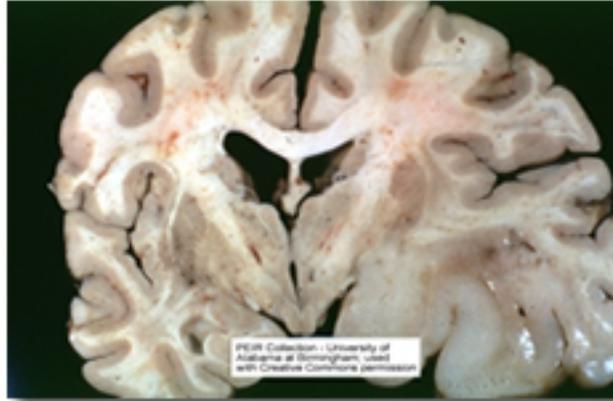
Gliomas

Gliomas (gliomas are the most common primary intracranial neoplasm in adults, and glioblastoma is the most common type of glioma)

1. Fibrillary Astrocytoma, Anaplastic Astrocytoma and Glioblastoma (these tumors arise from astrocytes) -- this is a series of tumor grades, with well-differentiated fibrillary astrocytoma considered benign (by histologic criteria), and glioblastoma considered the most malignant.

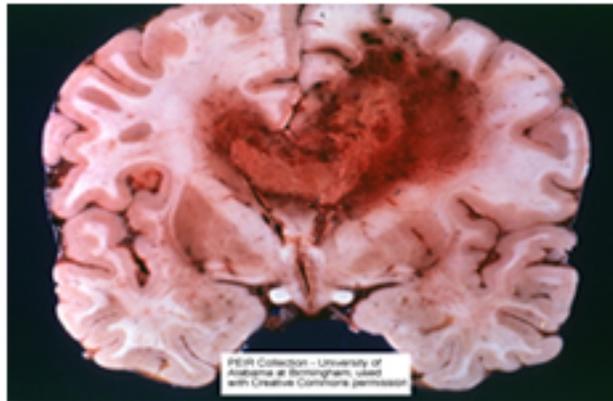
- **Location:** more often in cerebral hemispheres, but may occur anywhere
- **Signs and symptoms:** related to location of tumor plus displacement effects
- **Incidence:** for glioblastoma, increases with patient age; rare before age 30; more males affected
- **Prognosis:** Survival is inversely related to grade and age of the patient. Low grade neoplasms usually progress to high grade neoplasms with time. For glioblastoma, most patients survive less than 1 year after diagnosis.
- **Molecular Genetics:** Genetic alterations have been observed to be correlated with the progression of astrocytic tumors from low to high grade. Alterations commonly found in low-grade astrocytomas include inactivation of p53 and overexpression of PDGF-A and its receptor. The transition to higher grade is associated with

disruption of additional genes. Some glioblastomas arise without a pre-existing low-grade tumor; these primary glioblastomas are characterized by amplification of the epidermal growth factor receptor (EGFR) gene.



NEO 08

Fibrillary astrocytoma in right temporal lobe. Note that there is no obvious demarcation between the tumor and the normal brain parenchyma.



NEO 09

Glioblastoma with hemorrhagic regions crossing the corpus callosum. Note that there appears to be a border between normal parenchymal tissue and the tumor.

- **Gross pathology:** varies with degree of malignancy. There are two images available (click to enlarge the image shown) that compare some gross characteristics of well-differentiated astrocytomas and glioblastoma.
 - Lower grades (1-2) are firm, usually white (not hemorrhagic), APPEAR poorly circumscribed.
 - Grades 3-4 (anaplastic astrocytoma and glioblastoma) look well circumscribed, but infiltrate widely. The cut surface has many colors and consistencies produced by areas of hemorrhage, necrosis and cysts. Marked edema is characteristic and may involve the entire hemisphere.

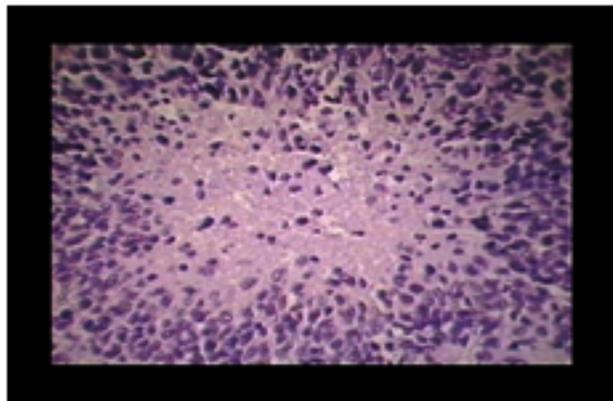
- Microscopic pathology: varies with degree of malignancy
----- Fibrillary astrocytoma (well-differentiated) -- astrocytes are easily recognizable with large, pleomorphic nuclei, prominent fibers; negligible mitotic activity.

-----**Glioblastoma** -- nuclear pleomorphism; mitoses; glomeruloid endothelial proliferation; necrosis, perinecrotic palisading of tumor cells. Click on the image at right to see examples of these characteristics.



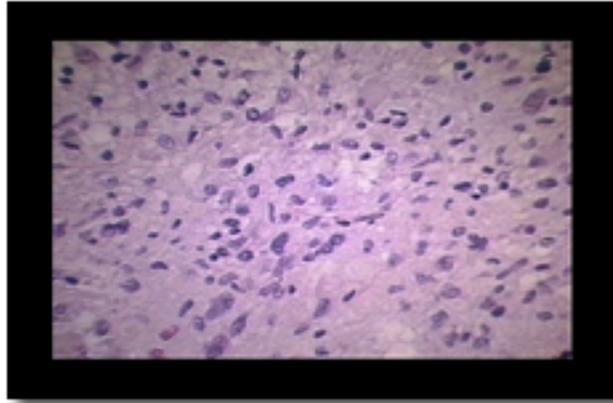
NEO 10

Coronal section showing glioblastoma in cerebral hemisphere. The tumor has infiltrated most of the tissue on the right side of the image. Note the variation in color, compression of the ventricle, and cingulate gyrus herniation.



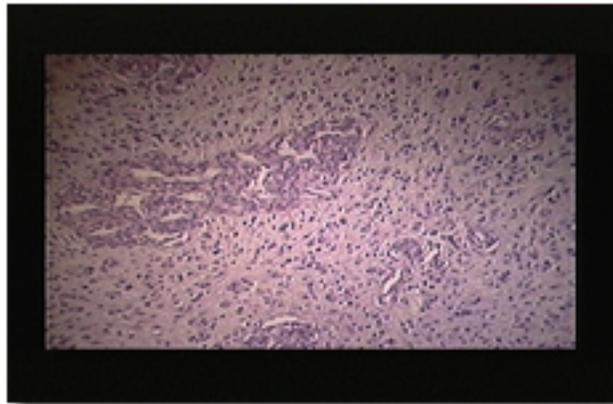
NEO 11

Glioblastoma microscopic pathology - perinecrotic palisading of tumor cells; the cells in the center have undergone necrosis due to outgrowing the blood supply.



NEO 12

Glioblastoma microscopic pathology – pleomorphism

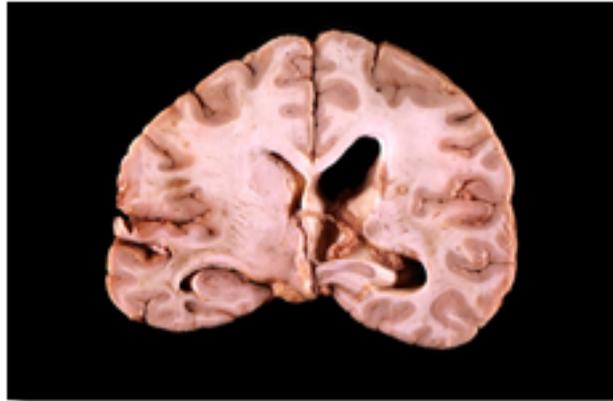


NEO 13

Glioblastoma microscopic pathology - glomeruloid endothelial proliferation

2. Oligodendroglioma (arises from oligodendrocytes)

- **Location:** often located in cerebral hemispheres
- **Signs and symptoms:** depends on location
- **Gross pathology:** calcification is common, and can be seen on radiology studies
- **Microscopic pathology:** central nuclei and halo of clear cytoplasm ("fried-egg appearance"); divided into two categories, low grade and high grade (anaplastic), which are of prognostic and therapeutic use; calcification may be seen microscopically
- **Incidence:** peak between 30 and 50 years
- **Prognosis:** This is a slow-growing tumor and patients may do well for many years, but rapid progression may occur; sensitive to chemotherapy



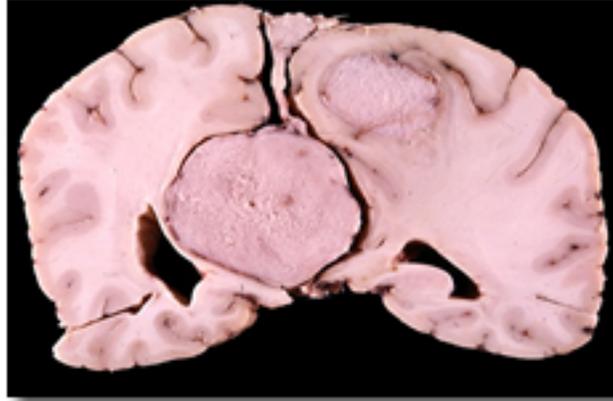
NEO 14

Coronal section showing oligodendroglioma, infiltrating most of the hemisphere on the left side of the image. Pathologically, the calcification is only seen on microscopic exam.

Other Primary Neoplasms

1. Meningioma (arises mainly from arachnoid cells; histologically benign)

- **Location:** often parasagittal; attached to dura
- **Signs and symptoms:** often focal, related to location
- **Gross pathology:** irregular, lobulated, well-circumscribed mass; does not invade adjacent brain tissue
- **Microscopic pathology:** several patterns, including whorls or sheets of meningothelial cells, psammoma bodies (concentrically laminated structures produced by mineral deposition in whorls of cells)
- **Incidence:** women more often affected
- **Prognosis:** depends on location and accessibility for surgery; after surgery, prognosis is related to completeness of removal
- **Molecular Genetics:** The most common cytogenetic abnormality is loss of chromosome 22, including the region that contains the NF2 gene.



NEO 15

Example of two lobes of a single meningioma. Both regions of the tumor are attached to the meninges, and are very well-circumscribed. It is more common to see only a single lobe of the tumor, Click to enlarge and also see a MRI of a meningioma in the posterior fossa, a less common location.

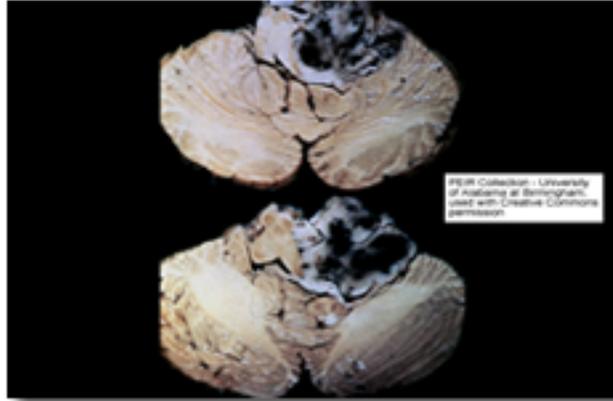


NEO 16

MRI showing well-circumscribed meningioma in the posterior fossa in a 27-year-old woman.

2. Peripheral Nerve Sheath Tumors- e.g. Schwannoma/Neurilemoma

- **Origin:** Schwann cells in peripheral nerves
- **Location:** may occur on any peripheral nerve, but the most common site is the eighth nerve at the cerebello-pontine angle
- **Signs and symptoms:** for acoustic Schwannoma (acoustic neuroma), clinical signs include tinnitus, hearing loss and vertigo
- **Prognosis:** good, since this is a slow growing, benign tumor, usually amenable to resection

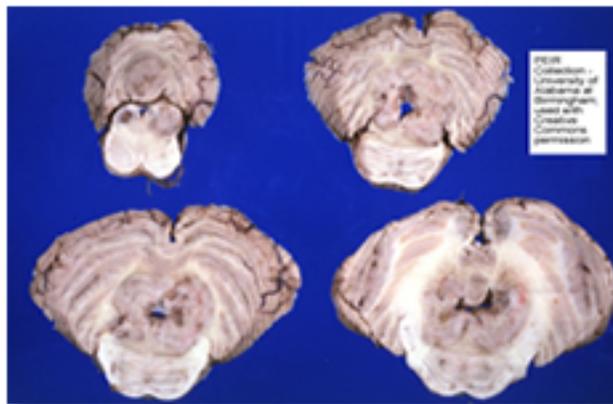


NEO 17

Vestibulo-acoustic Schwannoma at the cerebellopontine angle. The tumor mass is compressing the cerebellum, pons and medulla. the tumor originated on Cranial Nerve VII and grew to compress adjacent cranial nerves.

3. Primary brain lymphoma

- **Origin:** arises from B lymphocytes in the CNS
- **Location:** deep in the cerebral hemispheres
- **Signs and symptoms:** nonspecific, headaches, seizures
- **Gross pathology:** soft, often multiple separate nodules (multifocal)
- **Microscopic pathology:** perivascular cuffing of tumor cells and diffuse infiltration of surrounding neural tissue by cells with scant cytoplasm and large pale nuclei; diagnosis is usually established by stereotactic biopsy.
- **Incidence:** Occurs in immunocompromised patients (AIDS patients, organ transplant recipients); this is the most common CNS tumor in immuno-suppressed patients
- **Prognosis:** Initially responds to steroids, radiotherapy (1-2 yrs) then rapidly progressive.



NEO 18

Primary cerebral lymphoma in multiple locations in brainstem and cerebellum.

4. Tumors of the Sellar (Pituitary) Region

Tumors in the region of the pituitary gland may occur at any age. They may cause endocrine disturbances with either hypofunction or hyperfunction of the anterior pituitary, and/or diabetes insipidus. It is common for pituitary tumors to exert compressive effects on the optic chiasm, causing bitemporal hemianopsia. There may also be compression of optic nerves, optic tracts, or hypothalamus. Children usually come to clinical attention because of endocrine deficiencies such as growth retardation, whereas adults usually present with visual disturbances.

- Pituitary adenomas of the anterior pituitary are the most common. These are usually benign, slow growing and circumscribed.
- Craniopharyngioma is a suprasellar epithelial tumor

5. Germ Cell Tumors

- Origin: ectopic germ cells
- Location: midline, most commonly pineal and suprasellar region
- Prognosis: very sensitive to chemotherapy and radiotherapy, good prognosis for pure germinoma

6. Pineal parenchymal tumors

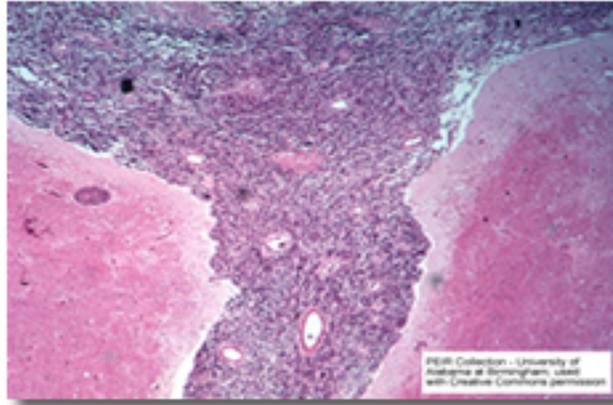
The pineal gland lies between the superior colliculi at the base of the brain. Clinical effects of compression by pineal tumors (pinealomas) commonly include visual disturbances and headache.

IV. Metastatic Neoplasms

A. Incidence: adults (about half of CNS tumors in adults are metastatic); incidence varies with primary tumor

B. Origin: hematogenous spread from neoplasms in the body, especially from lung and breast tumors and malignant melanomas

C. Location: multiple sites are common, but there may be a single focus of a metastatic neoplasm; junction between cortex and underlying white matter most common, but metastases may occur anywhere in the brain. Also, diffuse meningeal infiltration (carcinomatous meningitis) may occur (see image at right).



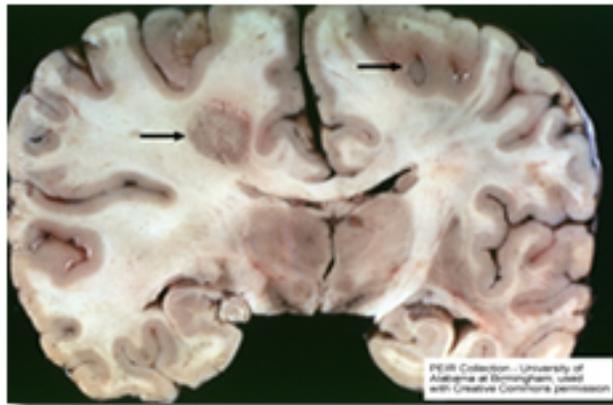
NEO 19

Carcinomatous meningitis - tumor cells filling space between arachnoid and pia

D. Gross Pathology: Usually well-demarcated, but finger-like extensions are seen microscopically; central necrosis; hemorrhage common; widespread edema may be produced;

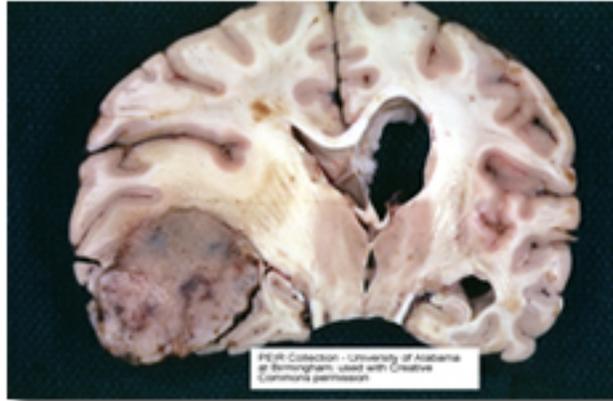
E. Microscopic Pathology: Microscopically, the tumor recapitulates the structure of the primary lesion

F. Prognosis: poor (survival of months); multiple sites usually preclude resection



NEO 20

Multiple metastatic carcinoma lesions. Two of the tumor foci in this coronal section are indicated by arrows.



NEO 21

Single large metastatic carcinoma focus in the temporal lobe on the left side. Note the extensive mass effect compressing the lateral ventricle and causing midline shift.

V. Familial Tumor Syndromes

This group of inherited diseases is characterized by the development of hamartomas (proliferations of normal cellular elements without progressive growth) and tumors throughout the body with particular involvement of the nervous system. Seizure disorders or mental retardation may be associated. The pattern of inheritance is variable. Many of the disorders are autosomal dominant and have been linked to tumor suppressor genes.

A. Neurofibromatosis Type 1 (NF1)

This autosomal dominant disorder is one of the more common genetic disorders. Characteristic nervous system lesions include neurofibromas and gliomas of the optic nerve. The gene, which encodes a protein termed neurofibromin, is a tumor suppressor gene.

B. Neurofibromatosis Type 2 (NF2)

In this autosomal dominant disorder, patients develop a range of tumors, including bilateral acoustic schwannomas and multiple meningiomas. The NF2 gene encodes a protein called merlin.

C. Tuberous sclerosis

Tuberous sclerosis is an autosomal dominant syndrome characterized by the development of hamartomas and benign neoplasms involving the brain and other tissues. Several distinct genetic loci have been identified at which mutations can cause tuberous sclerosis.

VI. Tumors of the Spinal Cord: arise from all cellular elements, uncommon.

A. Location:

1. Intramedullary (within the spinal cord): ependymomas (most common)

2. Extramedullary

a. Intradural: neurofibroma, meningioma

b. Extradural: metastatic carcinoma, lymphoma, neuroblastoma

B. Mode of Action: Compression, invasion or replacement of spinal cord, nerve roots and/or vascular supply

VII. Toxic Effects of Radiation Treatment

In some patients, delayed effects of radiation can be a complication of treatment for CNS tumors. This reaction is called radiation encephalopathy (or radiation myelopathy if it occurs in the spinal cord). Characteristics include a latent interval of months, local or generalized seizures, stupor and coma. Morphologically, white matter lesions are characteristic and may vary from cystic necrosis to discrete demyelinated areas to a single zone surrounding the tumor. There may also be vascular damage following radiation. A long-term complication is the development of radiation-induced meningiomas, sarcomas and gliomas.