

Pineal Region Tumors

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Pineal gland region has greatest variety of tumor types among CNS!

- pineal gland is **neuroendocrine transducer** that **synchronizes hormonal release** (LH, FSH) with **light-dark cycle** by means of its sympathetic input from retina.
- **PINEALOCYTE** - pineal parenchymal cell (specialized neuron).

EPIDEMIOLOGY

- 0.4-1.0% of intracranial tumors in **adults** (3.0-8.0% in **children**); **GERM CELL TUMORS** are endemic in Japan (unexplained).

ETIOLOGY

- A) displaced embryonic tissue
- B) transformation of pinealocytes
- C) transformation of pineal astroglia.

- no specific *genetic mutations* have been associated.

CLASSIFICATION, PATHOLOGY

1. Germ cell tumors (40-65%)
2. Pineal parenchymal tumors (17%)
3. Astrocytomas (15-25%)

1. **GERM CELL TUMORS** (40-65%) – from residual primordial tissue derived from ectoderm, mesoderm, or endoderm. see also p. 2626 (germ cell tumors in ovaries) >>
see also p. 2611 (germ cell tumors in testicles) >>

- most common in 2nd decade (peak 10-14 yrs); male-to-female ratio 2-9 : 1
Boys in childhood or adolescence

- found primarily in midline:
 pineal region (55%)
most prevalent neoplasms of pineal region in children!
 suprasellar cistern (32%)
 pineal & suprasellar (7%)
 3rd ventricle (3%)
 basal ganglia/thalamus (3%)
 spinal canal

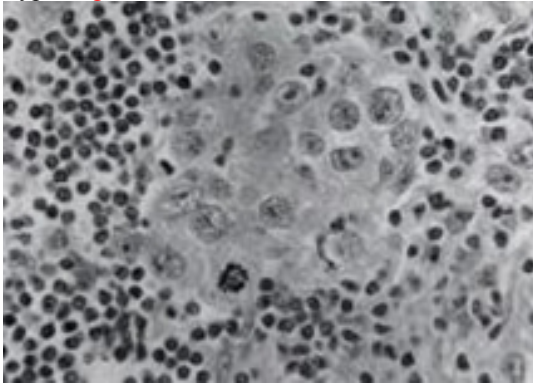
- histologically indistinguishable from those found *extracranially* (incl. mediastinum and gonads).
- often multifocal.

- A. **GERMINOMA (s. INTRACRANIAL SEMINOMA)** (commonest histology - 33-50% of pineal tumors; 60-70% of all germ cell tumors) - intermediate degree of malignancy; arise from **primordial germ cells** - large round cells interspersed with **lymphocytes** (!!!) and septae of fibrous tissue (virtually pathognomonic *"two-cell" appearance* - contrast between smaller, darkly staining lymphocytes and larger, pale staining cytoplasm of neoplastic cells);
 - tumor cell cytoplasm is glycogen-rich (PAS-positive).
 - characteristic **cellular junctions** (simplified desmosomes) and focal **microvilli** within intercellular lumina (microvilli is histologic characteristic that distinguishes intracranial lesion from its extracranial correlate).
 - infiltrating germinomas can elicit **atypical gliosis** (may be confused with malignant glioma).
 - **noncaseating granulomatous inflammation** (with multinucleated giant cells) can be found in biopsy taken from periphery of some germinomas.
 - occur in gonads, in midline CNS (pineal or suprasellar region), midline body (mediastinum or sacrococcygeal region).
 - although histologically identical in all sites, germinomas in **testes** are called **SEMINOMAS**, in **ovaries** **DYSGERMINOMAS**, and in **CNS** **GERMINOMAS** (previously called **ATYPICAL TERATOMAS**).

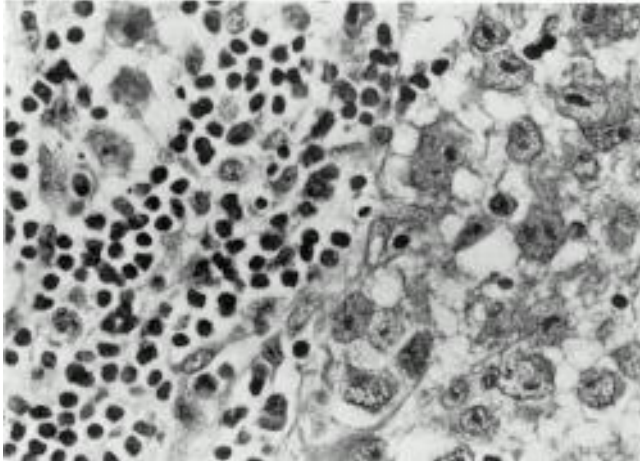
- B. **NONGERMINOMATOUS germ cell tumors** - derived from **totipotent germ cells** that aberrantly migrated to cranial midline during embryogenesis:
 - 1) **EMBRYONAL CELL CARCINOMA*** (5%) - least differentiated tumor.
 - 2) **TERATOMA** (18%) - result from maturation along **embryonic** cell lines;
 - mature teratoma** - well encapsulated, noninvasive mixture of tissues derived from all 3 germinal layers, with varying degrees of differentiation.
vs. DERMOID – only ectoderm & mesoderm; EPIDERMOID – only ectoderm
 - immature teratoma (s. teratoid)** - composed of primitive cells derived from 1 of 3 germinal layers (small round cells resemble hypercellularity of **MEDULLOBLASTOMA**).
 - rhabdoid tumor** - atypical teratoid tumor; universal presence of rhabdoid (rod-shaped) cells; characteristic monosomy 22; occurs in infancy and early childhood; clinically aggressive.
 - 3) **YOLK SAC TUMOR (s. endodermal sinus tumor)*** (7%) - result from maturation along **extraembryonic** cell lines *towards yolk sac*; contains endodermal sinuses or **Schiller-Duval bodies** (pathognomonic glomeruloid structure - tumor cell-lined space with invaginated vascular pedicle covered by single layer of tumor cells).
 - 4) **CHORIOCARCINOMA*** (5%) - result from maturation along **extraembryonic** cell lines *towards trophoblast*; intratumoral hemorrhage is common!
 - 5) **MIXED** germ cell tumor (e.g. **TERATOCARCINOMA** - embryonal carcinoma containing elements of immature teratoma).

*highly malignant

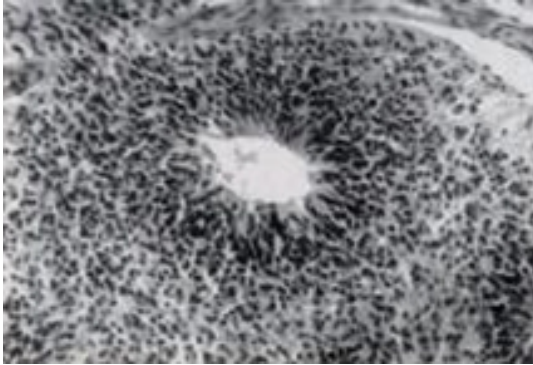
Typical **germinoma**:



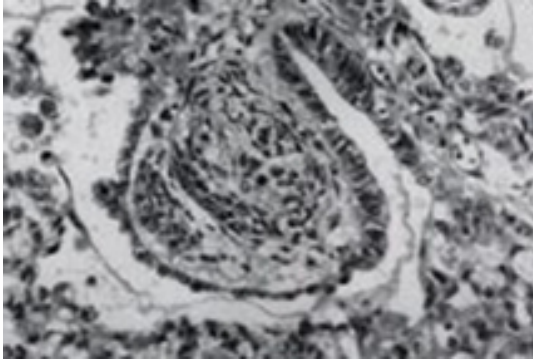
Germinoma - large cells with large nucleoli + focus of lymphocytes:



Immature teratoma - highly cellular primitive elements resembling fetal neural tube structure:

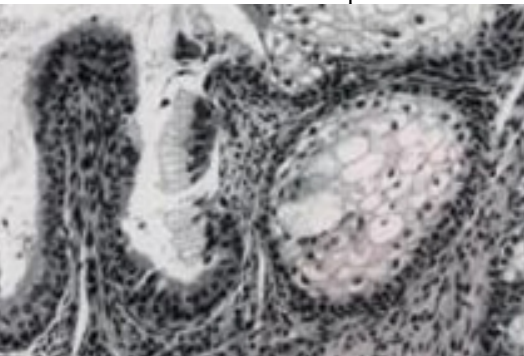


Endodermal sinus tumor - Schiller-Duval body:

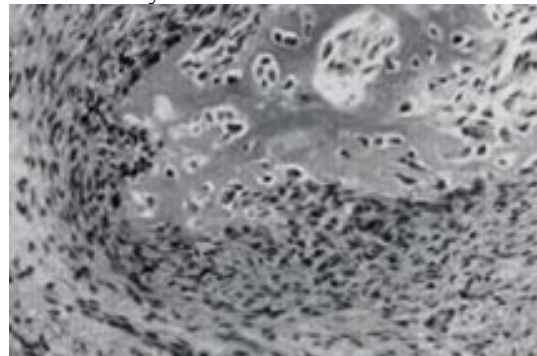


Mature teratoma (well-differentiated tissue from all 3 germinal layers):

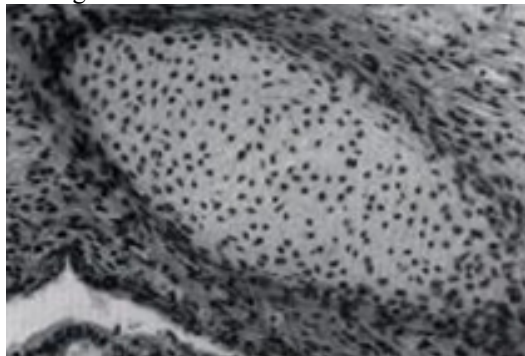
nonkeratinizing squamous epithelium alternating with areas of ciliated columnar epithelium:



osteoid bone with surrounding periosteal tissue and mesenchymal stroma:



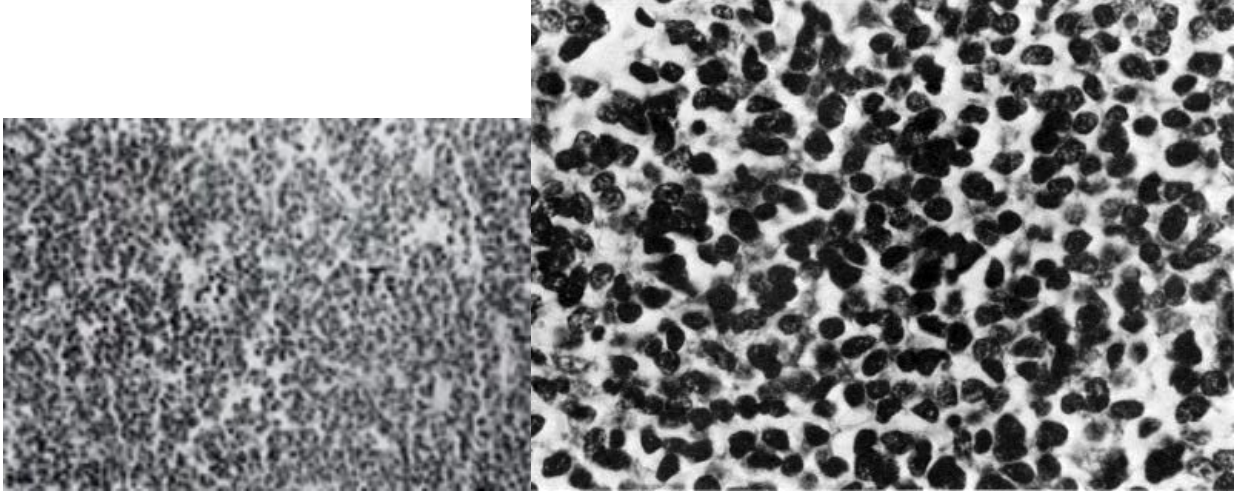
cartilaginous tissue:



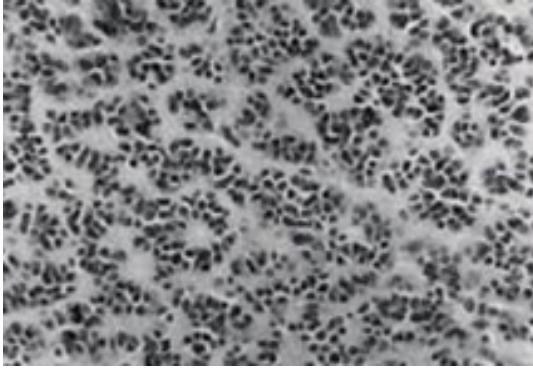
2. **NON-GERM CELL TUMORS:**

- a) **PINEAL PARENCHYMA tumors (PINEALOMAS)** (≈ 17%) - from pinealocytes; males = females; most frequent in 1st decade:
 - 1) **pineoblastoma** (high grade) (50%) – undifferentiated aggressive tumor more common in younger patients; dense populations of small primitive cells* that can form neuroblastic rosettes or **Homer-Wright rosettes** - histologically resembles *MEDULLOBLASTOMA*; less common are **Flexner-Wintersteiner rosettes** (differentiation toward *RETINOBLASTOMA* - ciliary 9 + 0 configuration similar to that of retinal photoreceptor); **propensity to seed subarachnoid space**; pineoblastoma with retinoblastic features is found in some cases of familial bilateral retinoblastoma (“*TRILATERAL RETINOBLASTOMA*”).
 - *some consider *PINEOBLASTOMA* as PNET arising in pineal region
 - 2) **pineocytoma** (low grade) – more common in adults; cells are generally larger; true rosettes are rare.
 - 3) **mixed** (intermediate grade).
- b) **gliomas, esp. astrocytomas** (second most frequent histology ≈ 15-25% of pineal region tumors) – from pineal gland stroma or surrounding tissue.
- c) **meningiomas** – from tentorium.
- d) **hemangioblastomas** – from endothelial cells.
- e) **chemodectomas** – from sympathetic nerve cells.

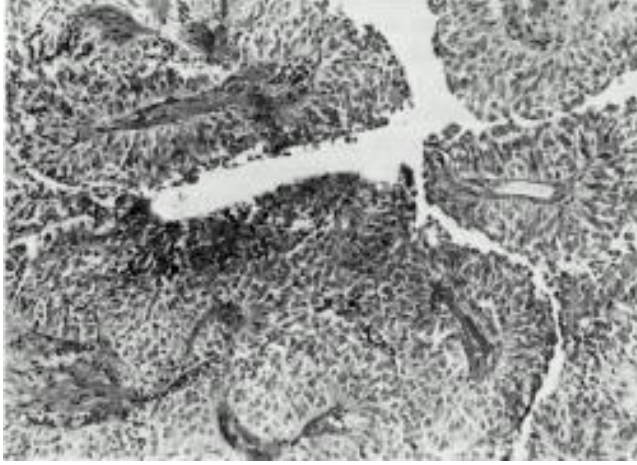
Pineoblastoma - highly cellular, poorly differentiated cells that form patternless sheets:



Pineocytoma - benign well-differentiated cells forming rosettes:



Pineocytoma - prominent perivascular growth of neoplastic cells; note papillary pattern:



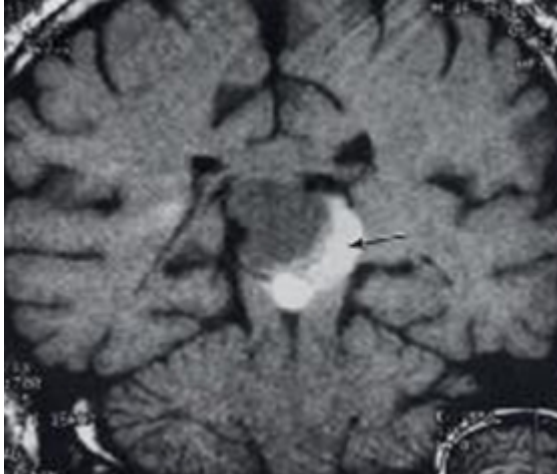
CLINICAL FEATURES

- Anatomic compression** of adjacent structures:
 - dorsally** - splenium of corpus callosum and tela choroidea;
 - ventrally** - quadrigeminal plate and midbrain tectum → **Parinaud syndrome**;
 - rostrally** - posterior aspect of 3rd ventricle; one of most common presentations is **aqueductal compression** → **obstructive hydrocephalus** (distended proximal aqueduct causes other disorders of ocular motility: convergence-retraction nystagmus, lid retraction (*Collier sign*), paralysis of downgaze, ptosis).
 - caudally** - cerebellar vermis → **ataxia, dysmetria**, etc.
- Neuroendocrine dysfunction** due to:
 - specific factors secreted by tumor (e.g. β-hCG [properties of LH] in germ cell tumors → **pseudoprecocious puberty** in boys).
 - suprasellar extension or hydrocephalus (e.g. **diabetes insipidus**, secondary **amenorrhea, growth arrest**).

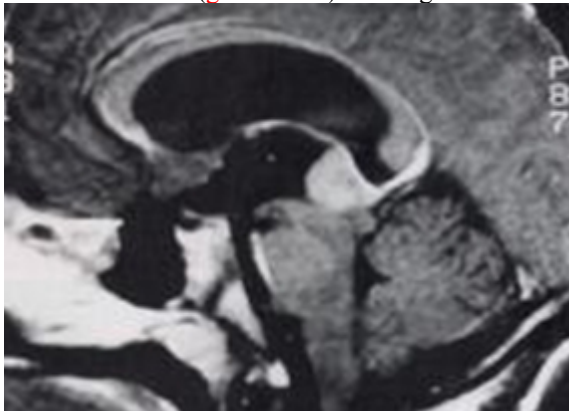
DIAGNOSIS

- High-resolution contrast **MRI**
 - PINEALOCYTE TUMORS** demonstrate homogenous enhancement (vs. **ASTROCYTOMAS** - variable enhancement patterns); intratumoral **calcium** may be present in either **PINEALOCYTE TUMORS** or **ASTROCYTOMAS**.
N.B. **pineal calcification in child < 7 yrs** is suggestive of neoplasm (normal pineal gland does not calcify at this age)
 - PINEOBLASTOMAS** - irregular shape and large size (some > 4.0 cm), strong enhancement, can have **calcification**.
 - GERMINOMAS** - strong homogenous enhancement; only rarely have **calcification** (surrounds pineal gland as germinoma grows).
 - TERATOMAS** can contain tissue from all 3 germinal layers → well-circumscribed benign tumor with multilocular markedly heterogenous MRI signals (fat* and **calcification** are typical; can demonstrate ring enhancement).
*areas of low attenuation (adipose tissue) help to distinguish it from other pineal region tumors.
 - MRI of spine** - for drop metastasis of pineal or germ cell tumors (perform before and after surgery). see p. Onc3 >>

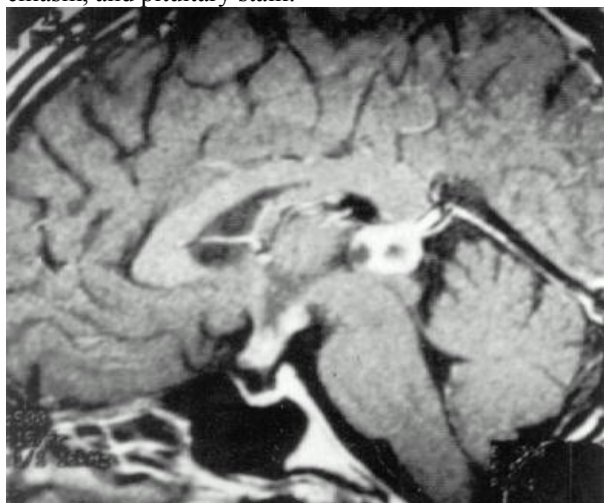
Noncontrast MRI of **pineocytoma**; acute hemorrhage (*arrow*):



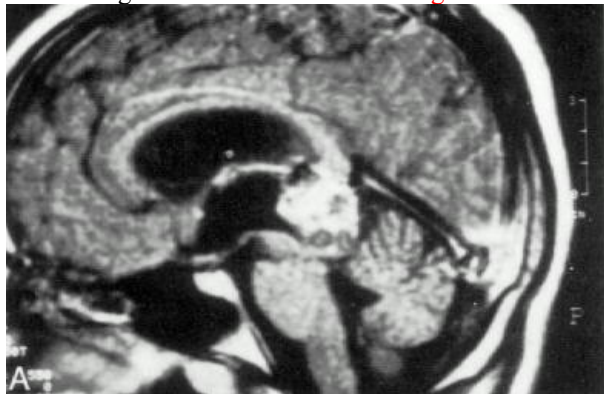
Contrast T1-MRI (**germinoma**) - homogenous enhancement:



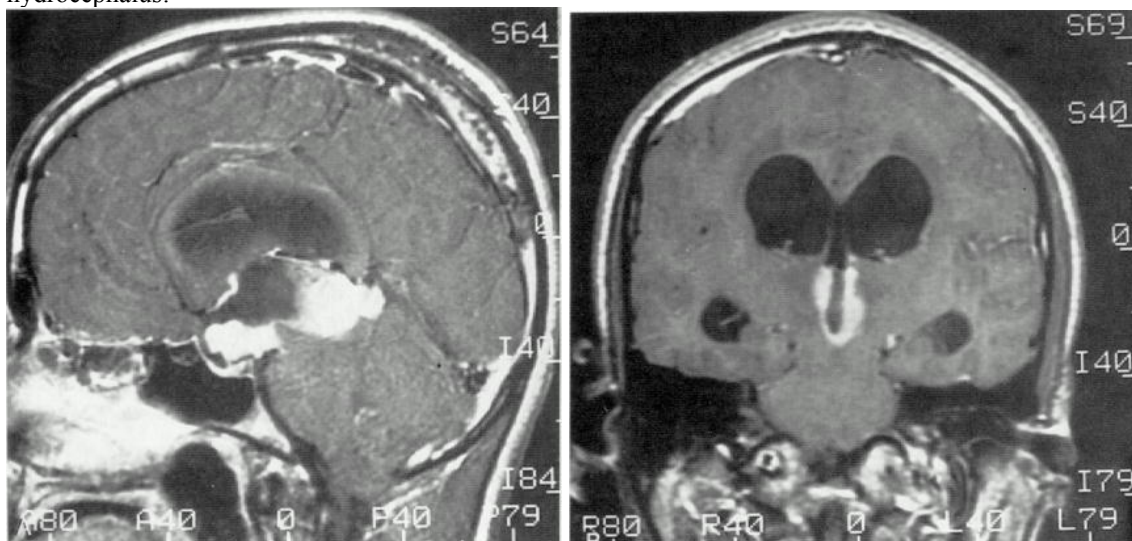
MRI with gadolinium - multicentric **germinoma** involving pineal region, infiltrating mammillary bodies, optic chiasm, and pituitary stalk:



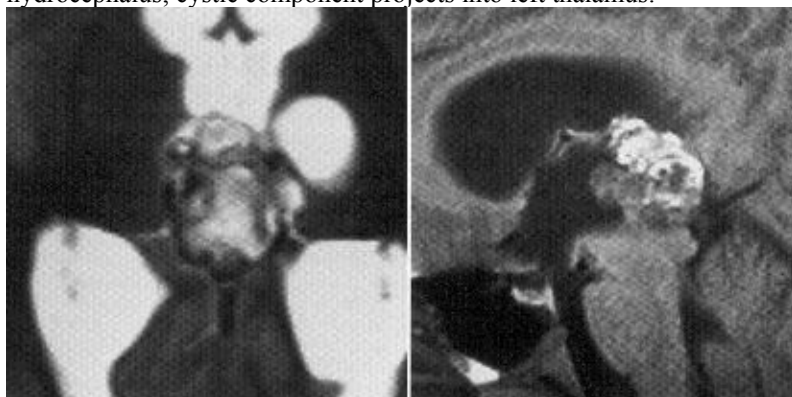
MRI with gadolinium - **mixed dermoid/germinoma**:



Contrast MRI - pineal and suprasellar **germinoma**, with spread along walls of 3rd ventricle; obstructive hydrocephalus:



Pineal **teratoma** (T2- and T1-MRI) - large, mixed signal intensity tumor infiltrates midbrain and causes hydrocephalus; cystic component projects into left thalamus:



2. Serum and CSF **tumor markers** (extremely important prior to surgical resection - provides reference point for follow-up); CSF should be compared with serum levels; see p. 1707a >>

Germ cell tumors:

Absence of AFP or β -hCG does not rule out mixed germ cell tumor!

N.B. AFP and β -hCG may also be elevated in other conditions! see p. 1707a >>

- 1) **alpha-fetoprotein (AFP)** – *ENDODERMAL SINUS TUMORS, EMBRYONAL CELL CARCINOMAS, IMMATURE TERATOMAS* (*MATURE TERATOMAS* do not secrete AFP)
- 2) **β -hCG** – *CHORIOCARCINOMAS, EMBRYONAL CELL CARCINOMAS, MIXED GERMINOMAS* with syncytiotrophoblastic giant cells (*PURE GERMINOMAS* are nonsecretory).

Tumor	AFP	β -hCG
endodermal sinus tumors	+	
choriocarcinomas		+
embryonal cell carcinomas	+	+
immature teratomas	\pm	
mature teratomas		
mixed germinomas with syncytiotrophoblastic giant cells		+

- *GERMINOMAS* also secrete **lactic dehydrogenase (LDH)** isoenzyme and **placental alkaline phosphatase**.

Pineal parenchymal cell tumors (markers are less well characterized; not valuable in diagnosis):

- 1) **melatonin**
- 2) **S antigen**.

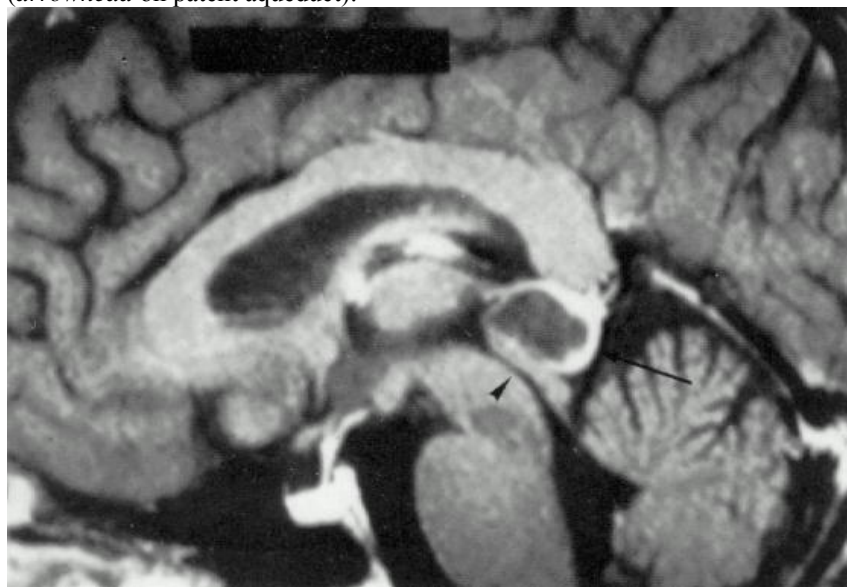
3. **CSF cytology** (if available).

4. **Biopsy** is recommended whenever possible! (concern that stereotactic biopsies may injure adjacent deep veins).

DIFFERENTIAL DIAGNOSIS

- 1) **vascular anomalies** (e.g. vein of Galen aneurysm)
- 2) **metastatic tumor**
- 3) **benign cysts** of pineal gland - normal variants of pineal gland anatomy; found in 4% normal people; can exhibit rim enhancement following IV gadolinium; ensure with MRI that lesion is not growing or causing hydrocephalus (if so → surgical resection).

T₁-MRI with gadolinium (**pineal cyst**): rim enhancement (*arrow*); rarely cause compression of sylvian aqueduct (*arrowhead* on patent aqueduct):



TREATMENT

Therapy is based on tumor pathology;

e.g. markedly elevated AFP and β -hCG (pathognomonic for *GERM CELL TUMORS*) → trial chemotherapy or radiotherapy without tissue biopsy (initial surgical intervention may become obsolete for *GERMINOMAS*)

PINEOCYTOMA, MATURE TERATOMA – surgery.

PINEOBLASTOMA – surgery → radiation ± chemotherapy.

NONGERMINOMATOUS GERM CELL TUMORS – chemotherapy → radiation.

GERMINOMAS – radiation.

SURGERY

Treat hydrocephalus prior to biopsy or resection! (third ventriculostomy or ventriculoperitoneal shunt)

N.B. peritoneal seeding is rare, but well-documented, complication!

Except for well-encapsulated teratomas, *few pineal region tumors are amenable to complete resection!*

A. Supratentorial approach - best for tumors extending supratentorially or laterally into trigone of lateral ventricle; wide exposure can be obtained; difficult removal of tumor that lies below convergence of deep venous system.

- parietal-interhemispheric-transcallosal approach** (described by Dandy 1936) - paramedian trajectory between falx and right parietal lobe, with partial resection of corpus callosum; excellent access to tumors that may have expanded into third ventricle; perform in *sitting slouch position*.
- occipital-transtentorial approach** (originally described by Horrax, later modified by Poppen) - requires retraction of occipital lobe and division of tentorium for adequate exposure; perform in *three-quarter prone lateral position*.

B. Infratentorial approach - direct *midline approach* (originally described by Krause and popularized by Stein); trajectory between tentorium and cerebellum; tumor is encountered below deep venous system.

- perform in *sitting slouch position* - cerebellum falls away, exposing pineal region while minimizing pooling of venous blood in operative field.
- limited access to tumors that extend above deep venous complex and anteriorly into 3rd ventricle; lateral exposure is also restricted.

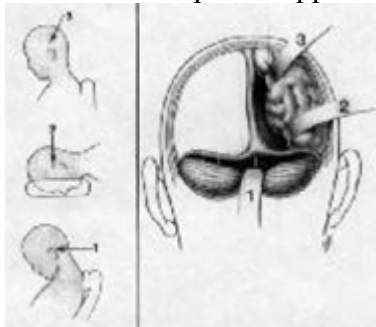
C. Combined supratentorial-infratentorial approach - for large pineal region tumors.

- in *semiprone position*.
- advantage - wide exposure laterally, superiorly (to posterior 3rd ventricle), and inferiorly (to superior medullary velum), safe visualization of venous structures and minimal retraction of cerebellum and occipital lobe.
- disadvantage - very extensive operation, including sacrifice of nondominant transverse sinus (only suitable for exceptional cases).

Patient positions:

- sitting slouch position* (for infratentorial-supracerebellar and transcallosal-interhemispheric approaches); main complications - subdural / epidural hematoma (secondary to ventricular and cortical collapse), pneumocephalus, air embolus.
- three-quarter prone lateral position* (for occipital-transtentorial approach) and avoids many of complications associated with sitting slouch position.
- prone position* - elevation of shoulders and head tilted to right - combined advantages of sitting slouch and three-quarter prone lateral positions.
- Concorde position* - more comfortable for surgeon and reduces risk of air embolism; desirable for preadolescent patients; more cumbersome in larger patients.

- 1 - supracerebellar-infratentorial approach.
- 2 - occipital-transtentorial approach.
- 3 - parietal-interhemispheric approach.



Postoperative cranial & spinal MRI! see p. Onc3 >>

COMPLICATIONS

Overall MORTALITY of pineal region surgery is 0-8% and MORBIDITY 0-12% (vs. 90% mortality in early part of 20th century).

Most common complications - *extraocular movement dysfunction**, *ataxia**, *altered mental status*.

*may be present preoperatively and become transiently worse postoperatively before significantly improving or resolving completely.

Most devastating complications:

- 1) **pineal apoplexy** (bleeding into vascular-rich subtotally resected tumor bed); may be delayed for several days.
- 2) **venous infarction** (with or without hemorrhage).

RADIOTHERAPY

- depends upon tumor histology:

- low-grade pineocytomas, mature teratomas* – cured with surgery alone → no adjuvant radiation (follow with serial MRIs).
- malignant **pineal cell tumors**: 40 Gy whole brain radiation → 15 Gy to pineal region (in 1.8 Gy daily fractions).
- malignant **germ cell tumors**:

GERMINOMAS: 26 Gy to tumor with 1.5-2 cm margin → 24 Gy to ventricular field (*GERMINOMAS* tend to spread along ventricular walls).

N.B. *GERMINOMAS* are among most radiosensitive tumors (vs. nongerminomatous malignant germ cell tumors)

NONGERMINOMATOUS MALIGNANT GERM CELL TUMORS (whether localized or disseminated) → chemotherapy → restaging:

localized tumors → 54-60 Gy to tumor → 24 Gy to ventricular field.

disseminated tumors → craniospinal irradiation (54-60 Gy to tumor, 45 Gy to ventricular system, 35 Gy to spinal cord, 45 Gy to any localized spinal cord lesions).

- prophylactic spinal irradiation** is controversial (reasonable approach is to administer spinal irradiation *only for documented seeding*); rate of drop metastases is highest for *PINEOBLASTOMAS* and *ENDODERMAL SINUS TUMORS*.

CHEMOTHERAPY

- means of minimizing amount of radiation for children.

Germ cell tumors are more sensitive than **pineal cell tumors** (although pineal area is outside BBB)

Although systemic germ cell tumors are very chemosensitive, CNS germ cell tumors are less responsive!

- *NONGERMINOMATOUS germ cell tumors* - chemotherapy prior to radiation!
- *GERMINOMAS* are so radiosensitive that chemotherapy is not required (platinum-based chemotherapy first-line treatment only in very young children in order to avoid radiation).
- *PINEOBLASTOMAS* - high-dose **CYCLOPHOSPHAMIDE** as single-agent.

PROGNOSIS

Can recur locally / distally as late as 5 yrs after diagnosis! – regular follow-up:

- MRI**
- tumor marker*** follow-up: q 1-2 months for 1 year → q 3 months for 1 year → less frequently.

*even if markers were not abnormal at diagnosis

Prognosis:

MATURE TERATOMAS > *GERMINOMAS* (excellent prognosis; > 90% 5-yr survival) > *PINEAL CELL TUMORS* > *NONGERMINOMATOUS GERM CELL TUMORS* (patients rarely survive beyond 2 years)

BIBLIOGRAPHY for ch. “Neuro-Oncology” → follow this [LINK >>](#)