Testicular Tumors: What's New, True, Important

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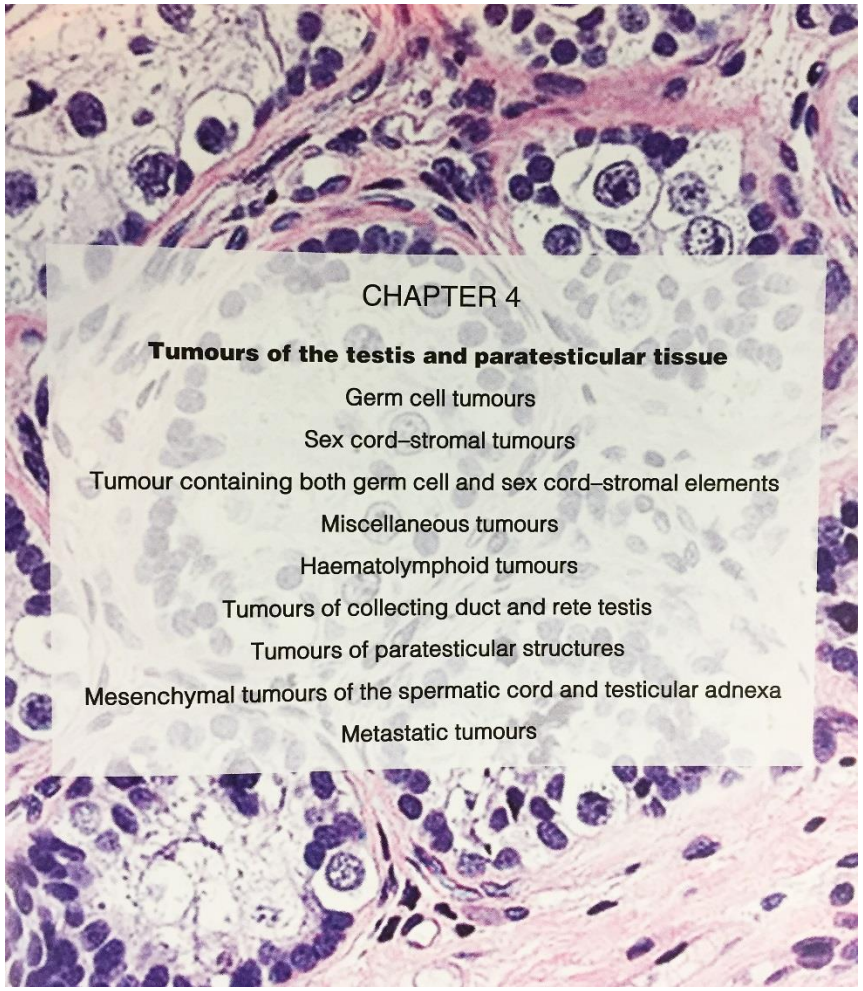
Testicular Cancer

- Uncommon (~1% cancer in male)
- 90-95% germ cell origin
- Most common cancer in white males age 20-35
- Incidence has ↑ in the last half century and is variable in different regions

Risk factors for Germ Cell Tumors (GCTs)

- Cryptorchidism
- Prior testicular GCT
- Family history of GCT (brother > sons > fathers)
- Disorders of sex development (gonadal dysgenesis)
- *(Infertility, Marijuana use)*

WHO 2016: Tumors of the Testis



- Updated pathogenetic model for GCTs
- Restructuring of classification
- New entities
  - Germ cell tumors
  - Sex cord stromal tumors

Preinvasive lesion to malignant testicular germ cell tumors (GCTs): evolution of nomenclature

CIS

- Skakkebaek, Lancet 1972
- CIS had characteristics of primordial germ cells

IGCNU

IGCN

GCNI

GCNIS

GCNIS

IGCNU

- Scully, Rosai, Mostofi, Kurman, et al, 1980
- WHO classification 2004

Germ Cell Neoplasia In Situ

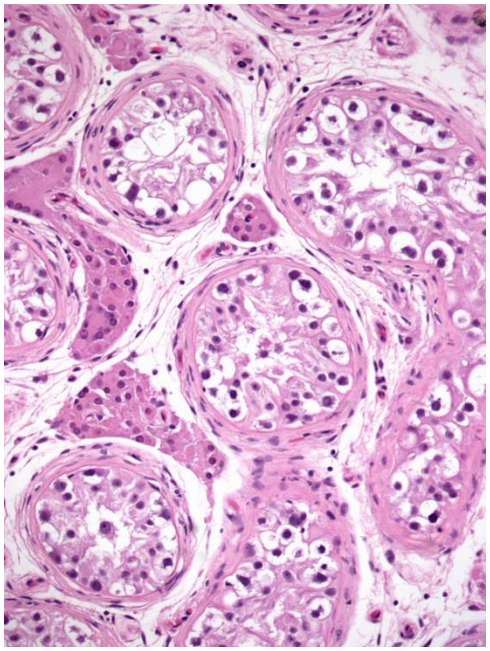
2016 WHO classification

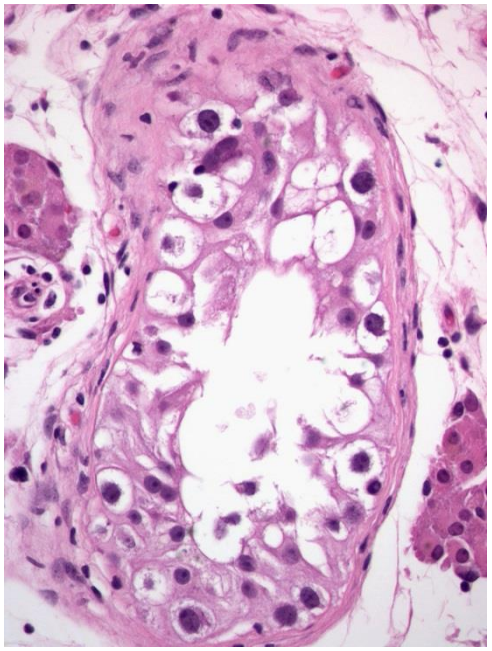
Germ Cell Neoplasia In situ (GCNIS)

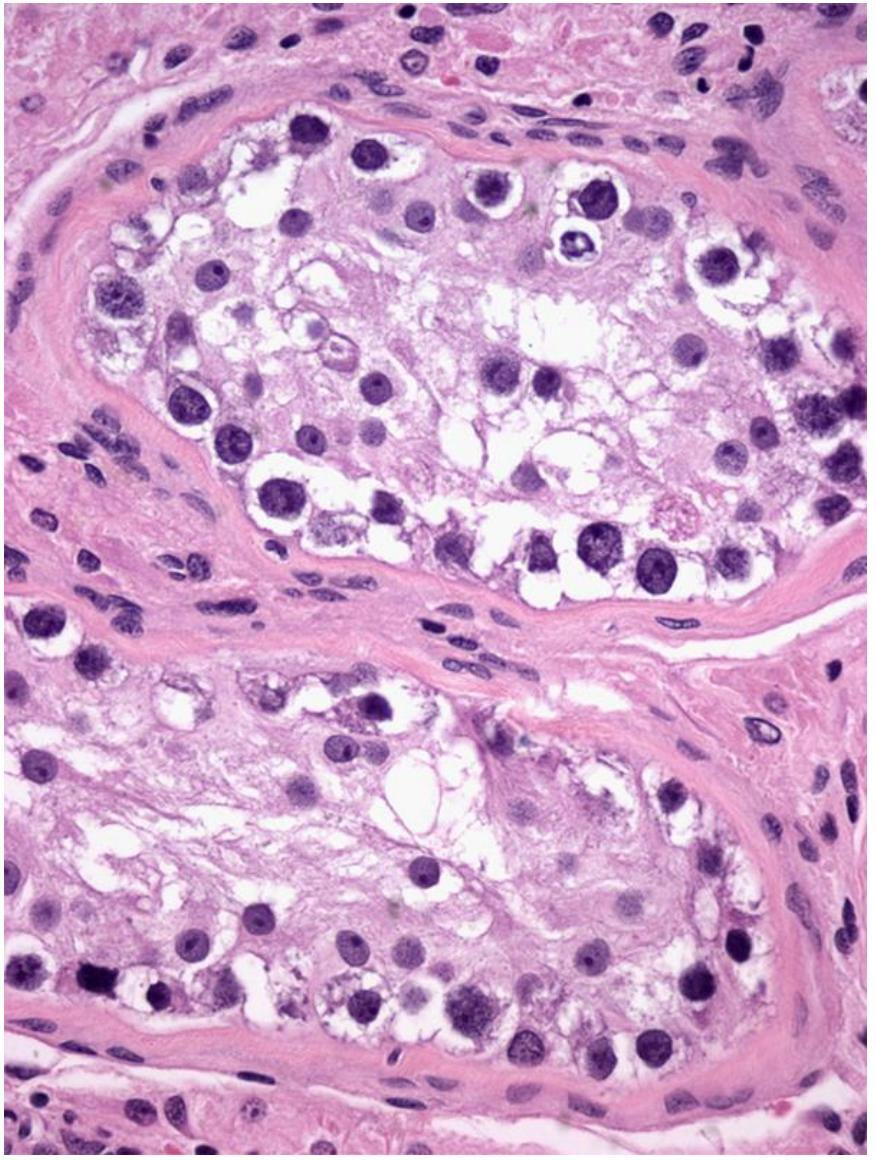
- Malignant germ cells in ”spermatogonial niche”
- Increased incidence in sex development disorders, up to 70%
  - Cryptorchidism
  - Gonadal dysgenesis
  - Androgen insensitivity syndrome
- 1-4% in subfertile/infertile men
- Seen in most seminomas and non-seminomas; 2-6% of testes contralateral to unilateral GCT
  - GCNIS supports a diagnosis of GCT
- 50% of men with GCNIS develop invasive GCT within 5 years

Germ Cell Neoplasia In situ (GCNIS)

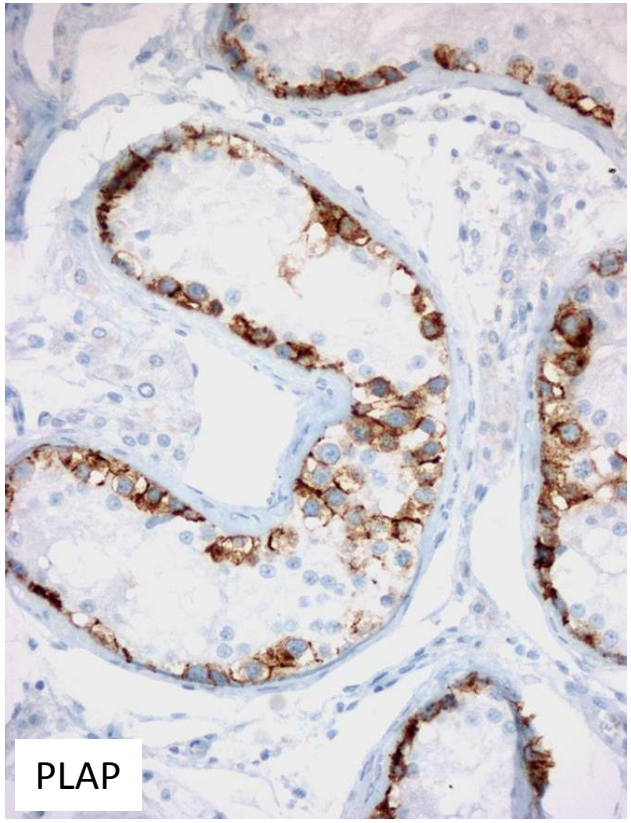
- Gonocyte-like germ cells
- Single layer in basilar location
- Decreased or absent spermatogenesis

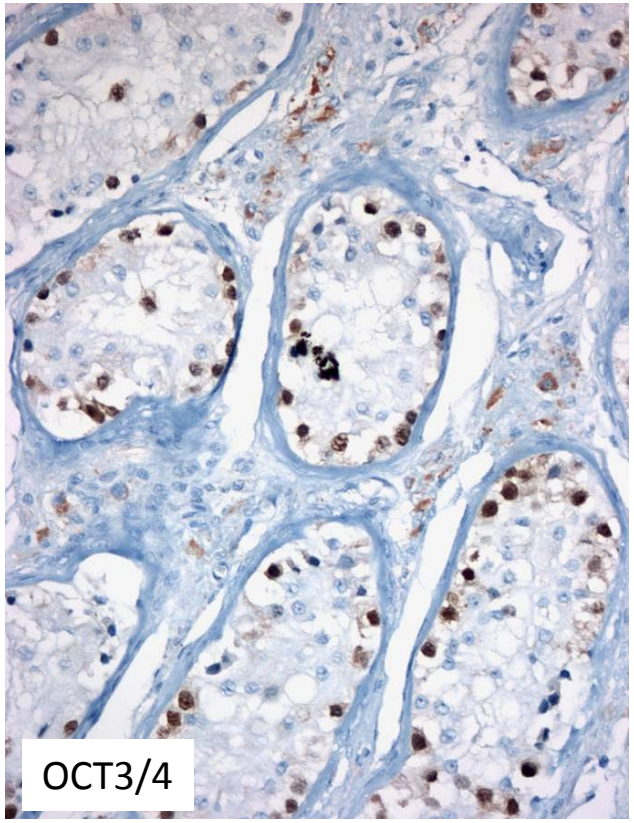


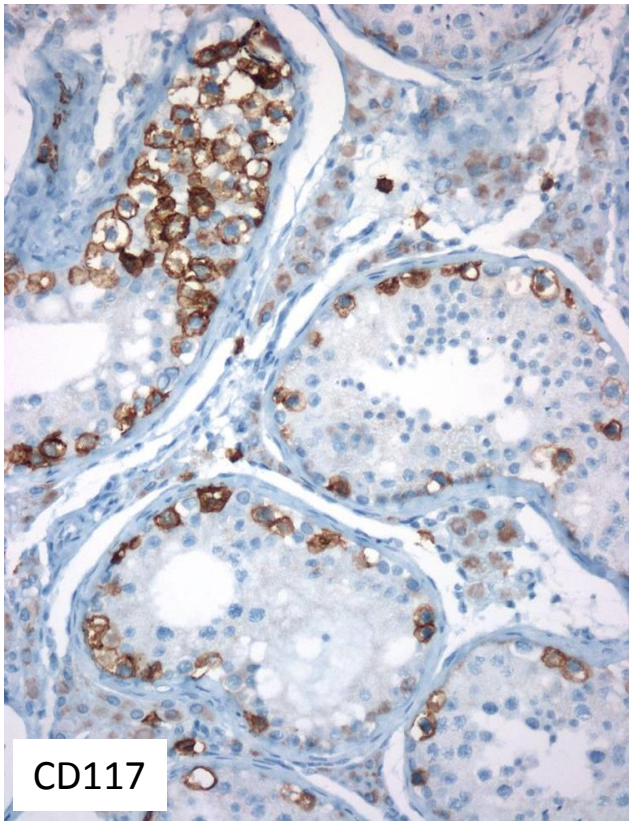




Germ Cell Neoplasia In situ (GCNIS)



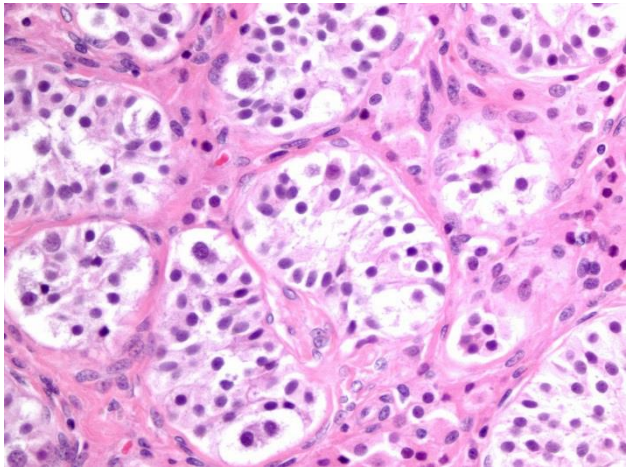




Differential Diagnosis of GCNIS

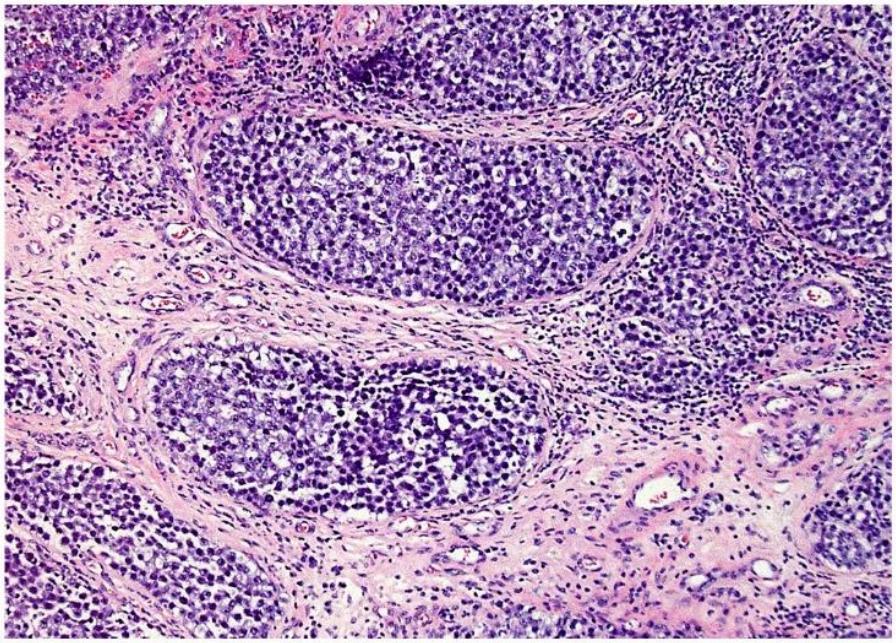
- Delayed maturation of gonocytes in prepubertal patients with sex development disorder (beyond 6 mo)
  - OCT3/4+, PLAP+; central tubular location

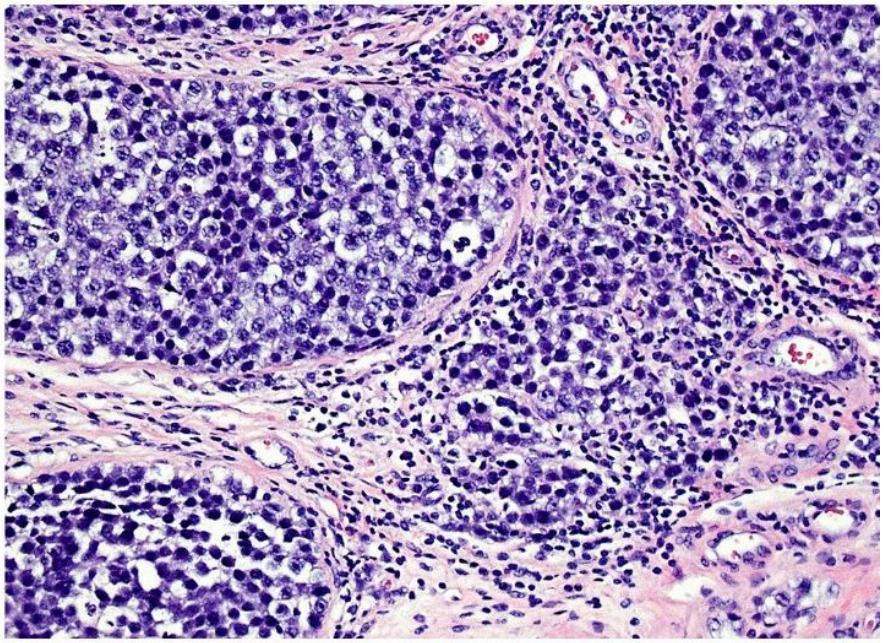
- Atypical germ cells due to perturbation of spermatogenesis (cryptorchidism, infertility)
  - Binucleation, OCT3/4-



- Specific forms of intratubular neoplasia
  - Intratubular seminoma
  - Intratubular non-seminoma (embryonal carcinoma, YST, teratoma)

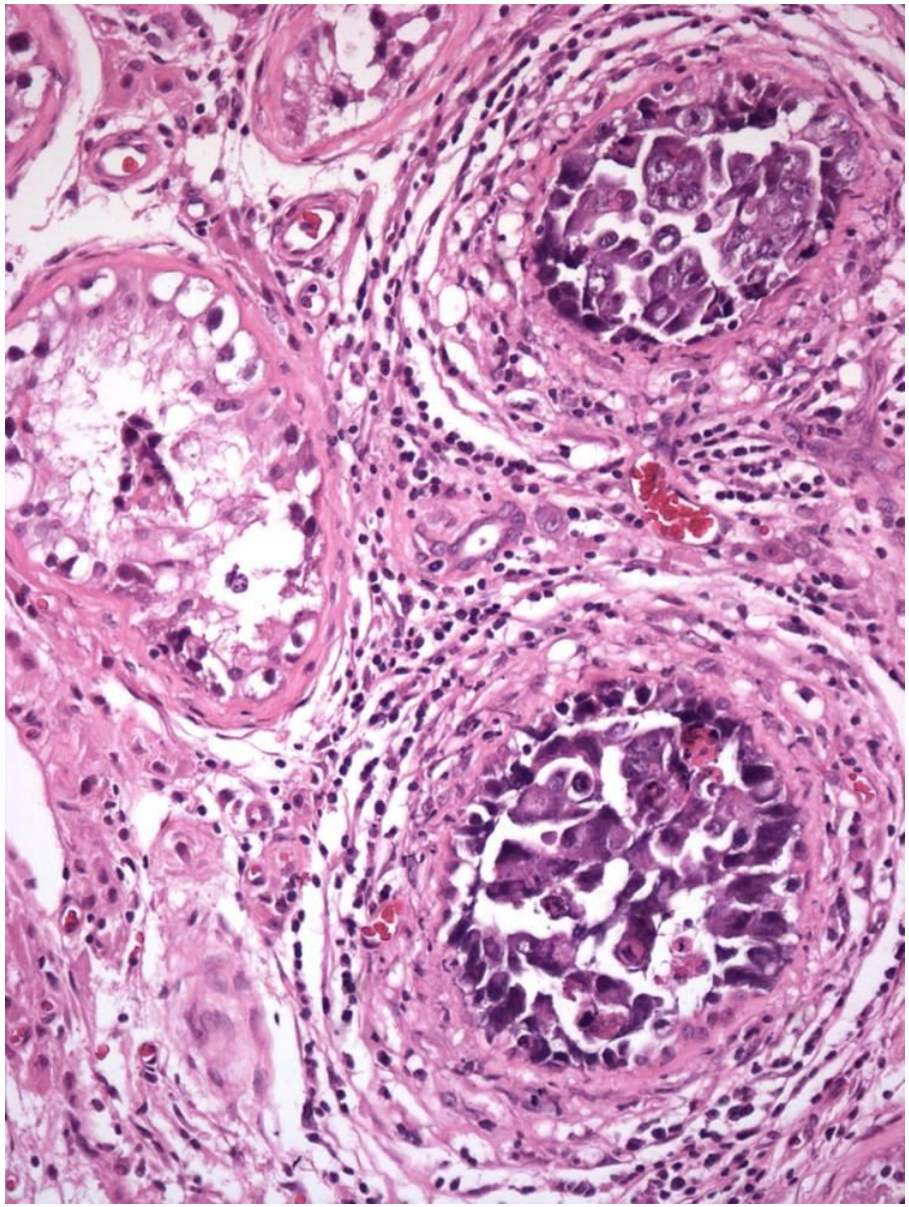
Intratubular Seminoma

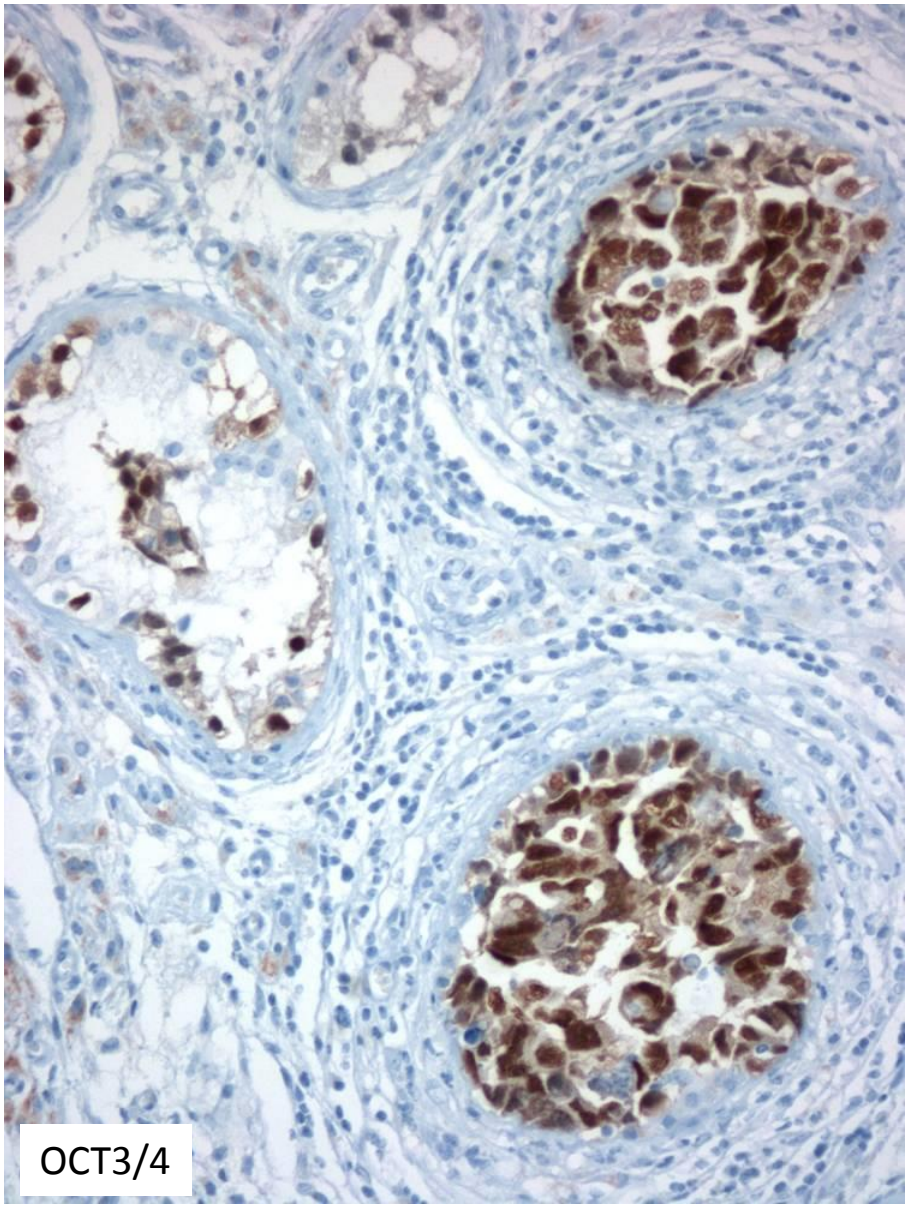




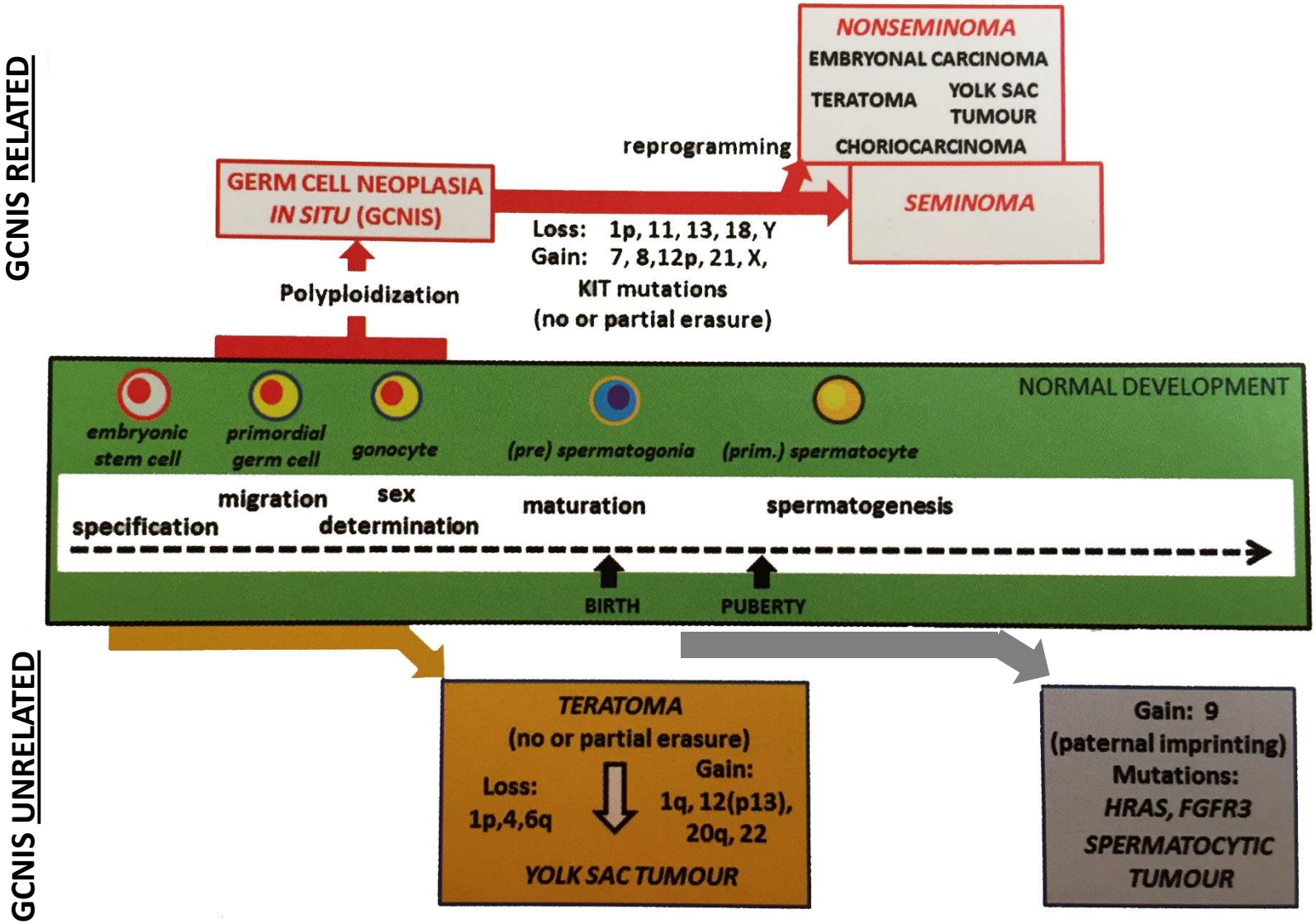
- Expanded tubules, no residual Sertoli cells
- Tubules often contain lymphocytes
- IHC identical to seminoma

Intratubular Embryonal Carcinoma

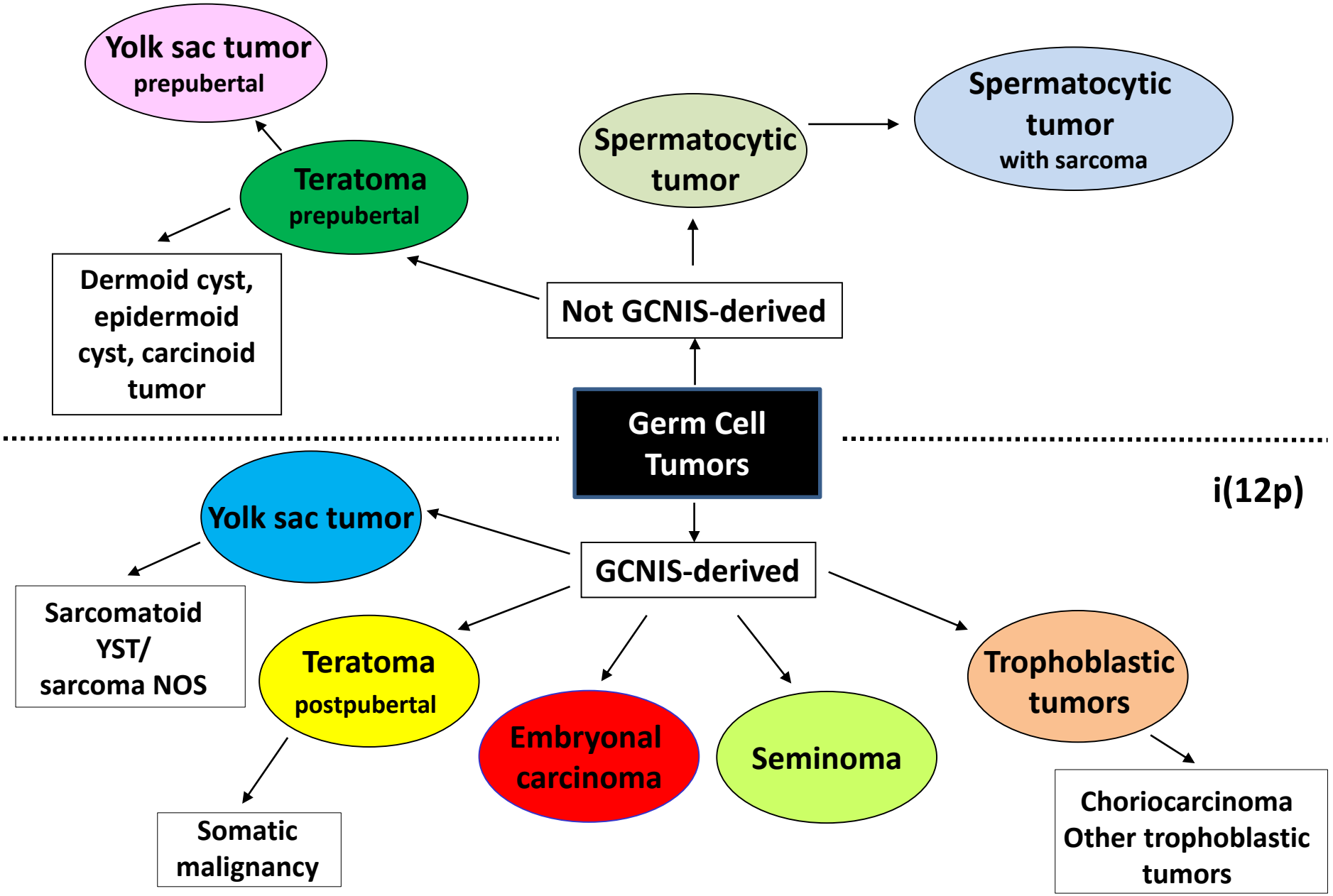




Pathogenetic Model for Germ Cell Tumors



2016 WHO Germ Cell Tumor Classification



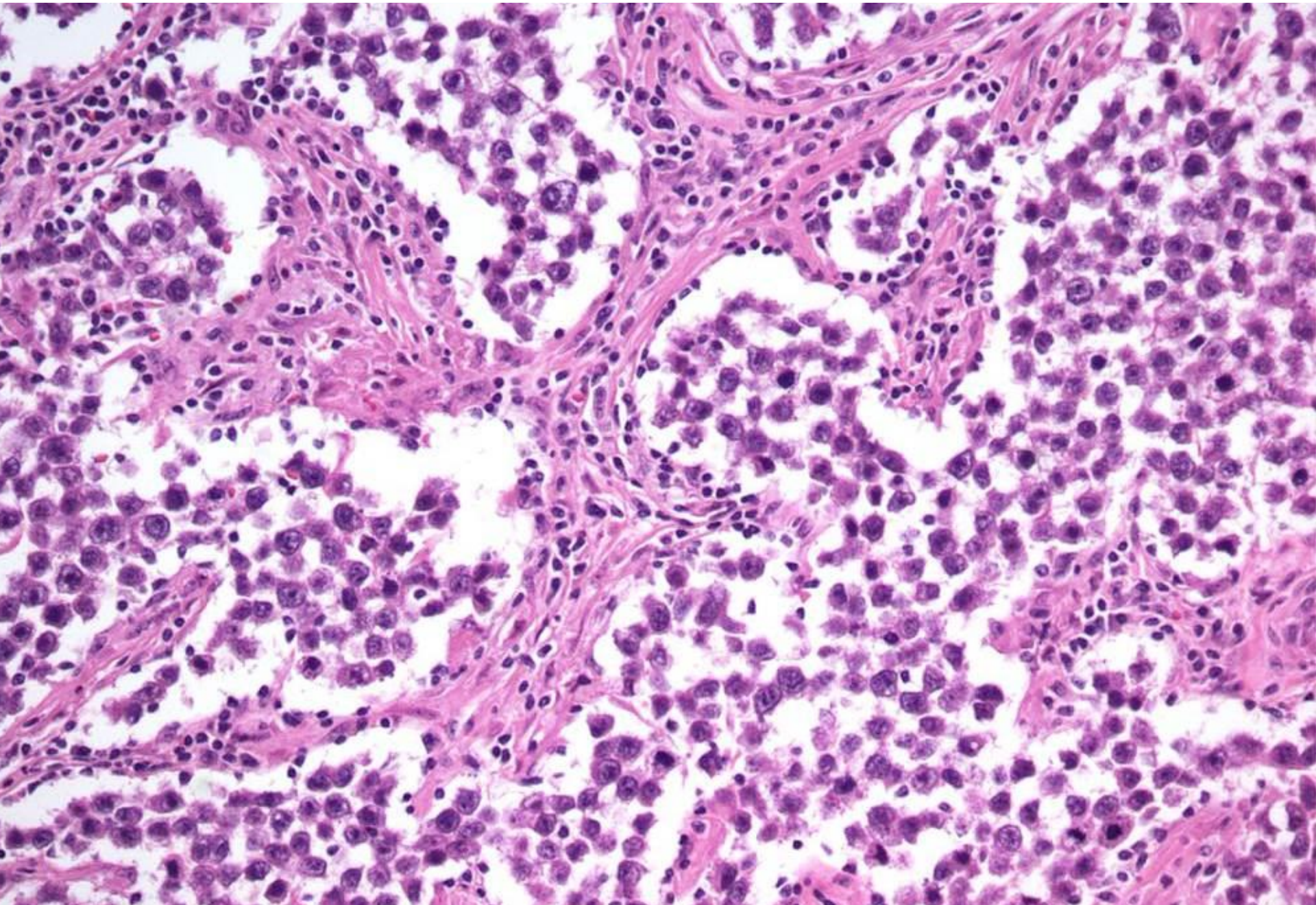
Seminoma

- Most common type of testicular GCT (up to 50%)
- Average age = 40.5 years (decade later than others GCT)
- Usually presents with testicular mass
- Pain or dull aching sensation
- A few present with metastatic disease
  - 75% limited to testis
  - 20% retroperitoneal involvement
  - 5% distant metastases
  - may have mild elevated βHCG, AFP normal

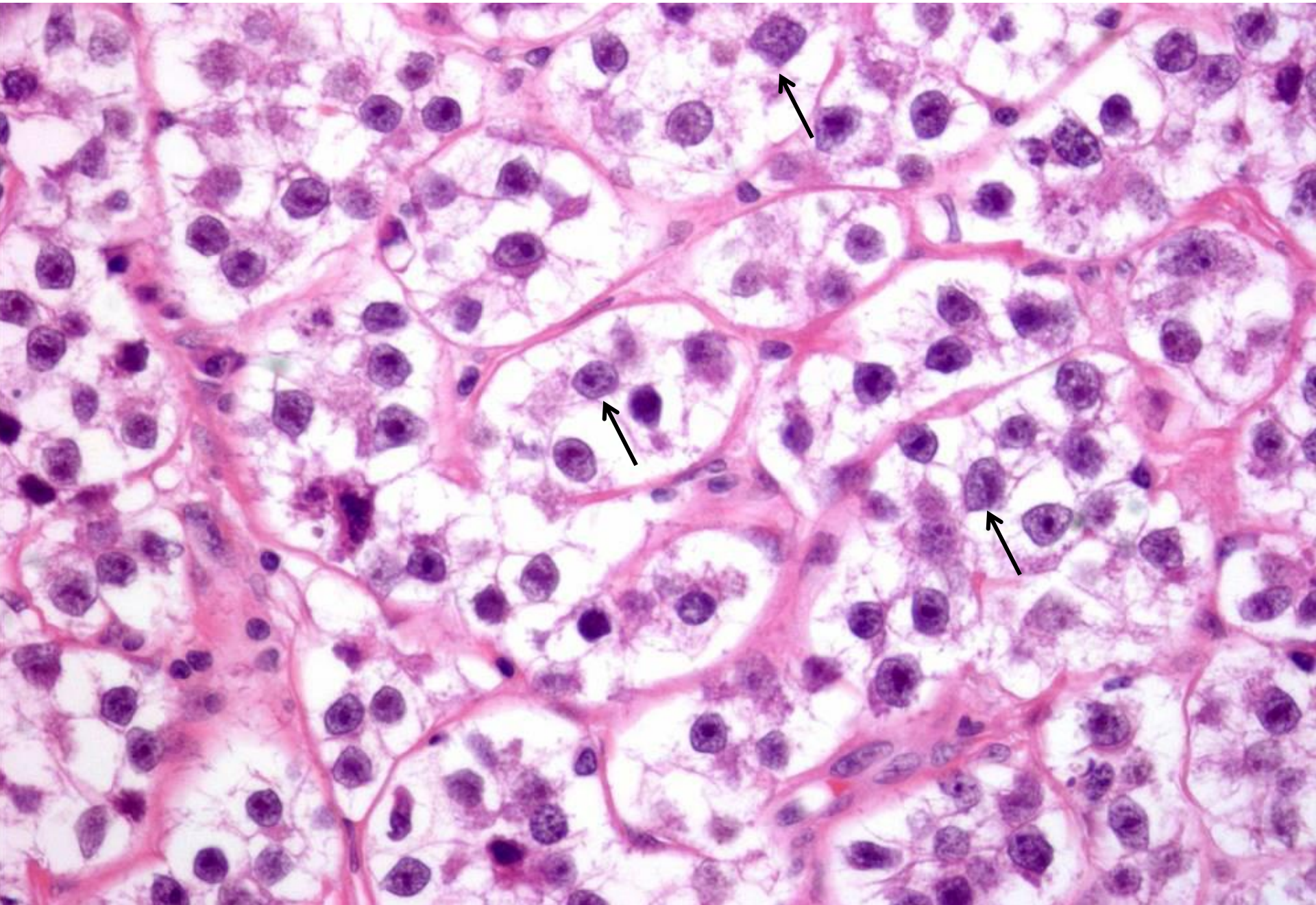
Seminoma

- Homogeneous light-tan nodular fleshy mass
- Hemorrhage & necrosis

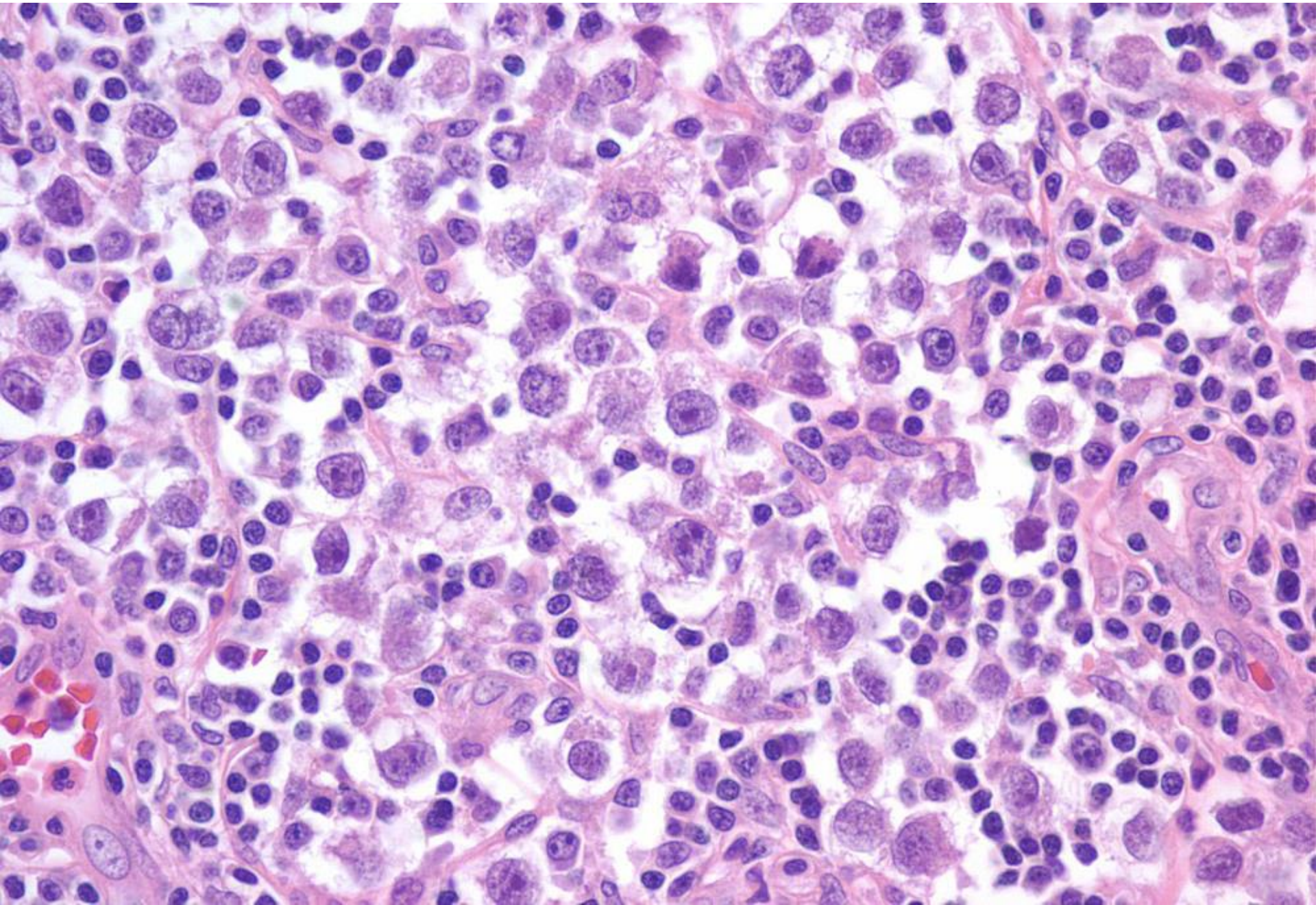
Seminoma



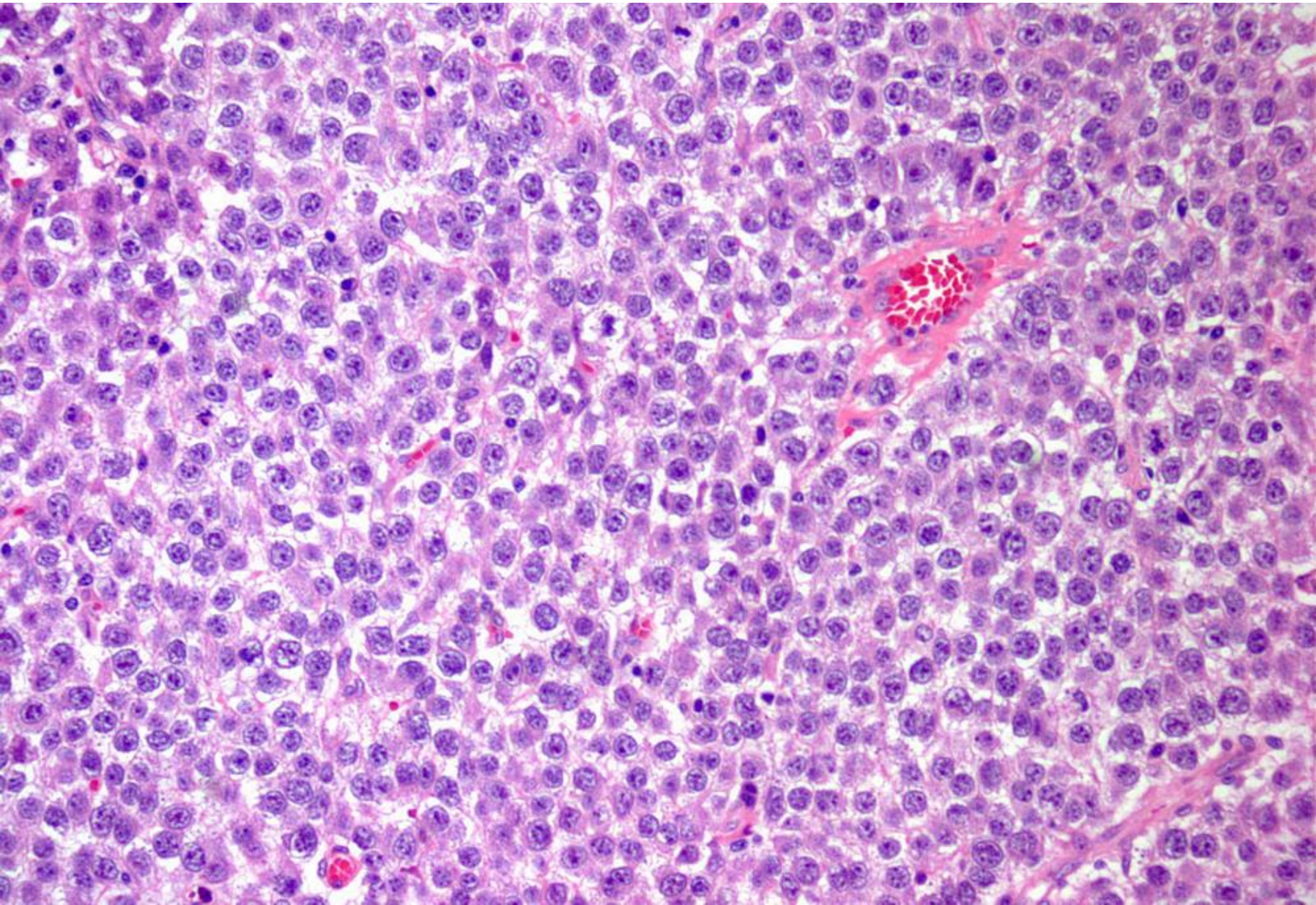
Seminoma



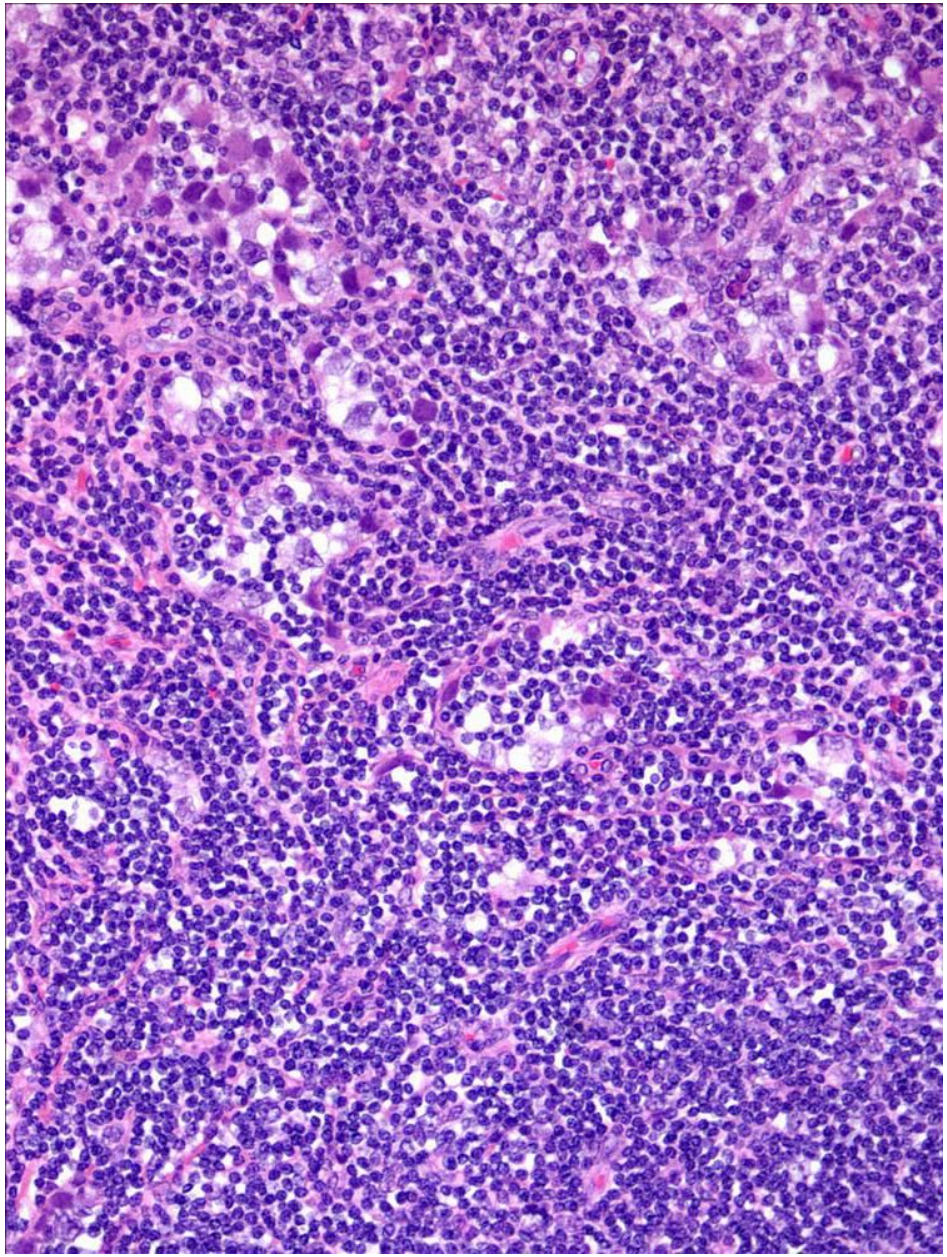
Seminoma

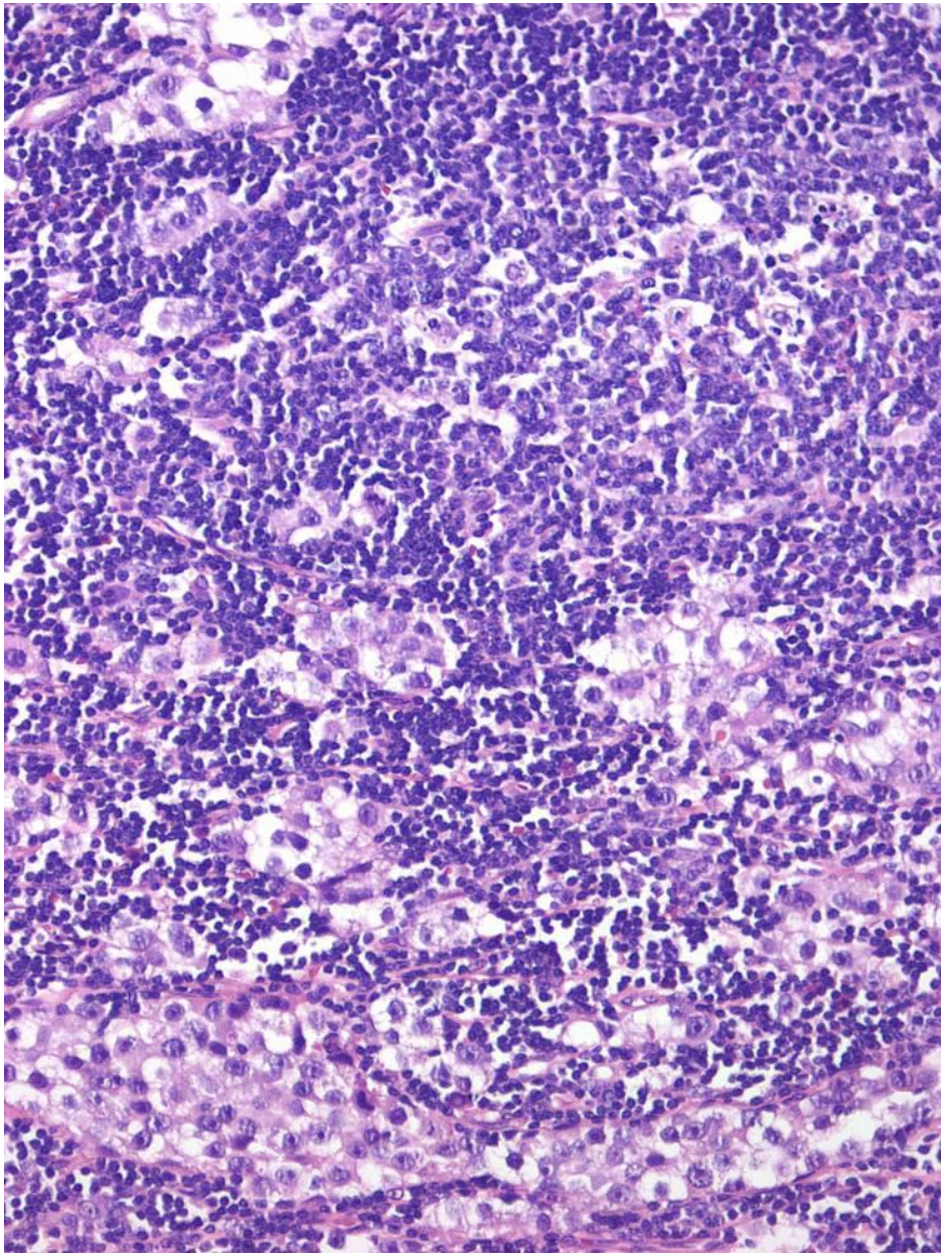


Seminoma

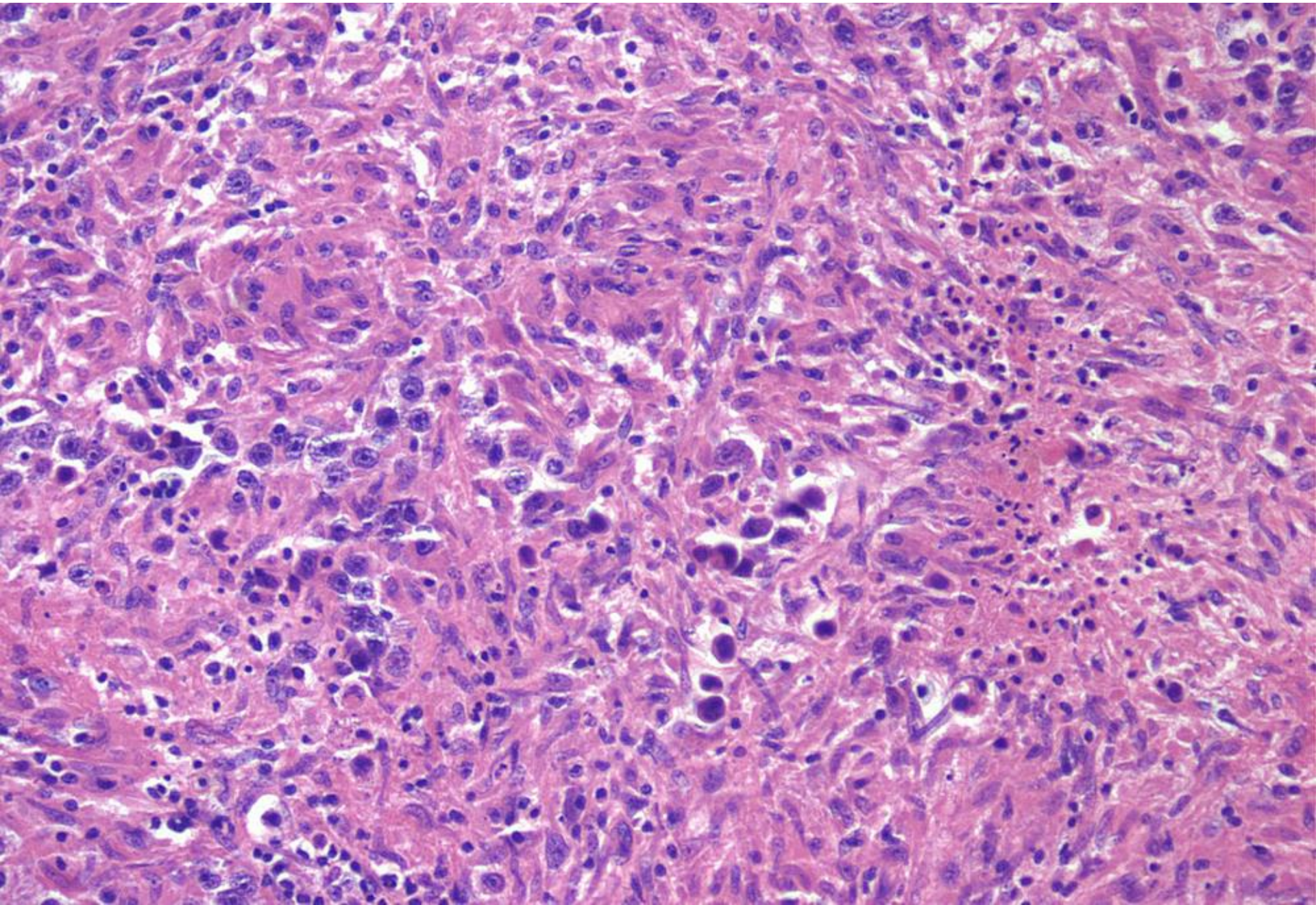


Seminoma with marked inflammatory infiltrate

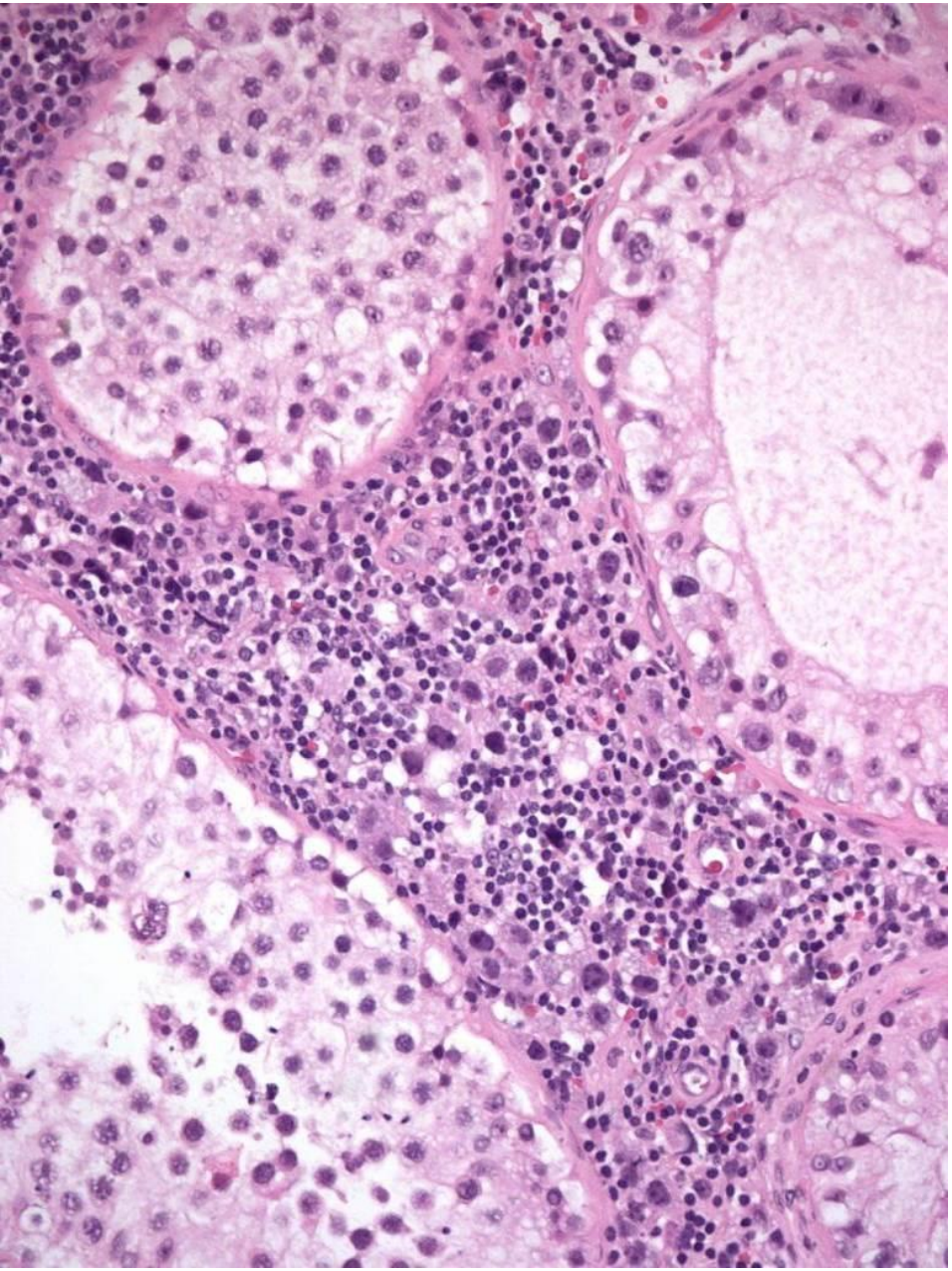


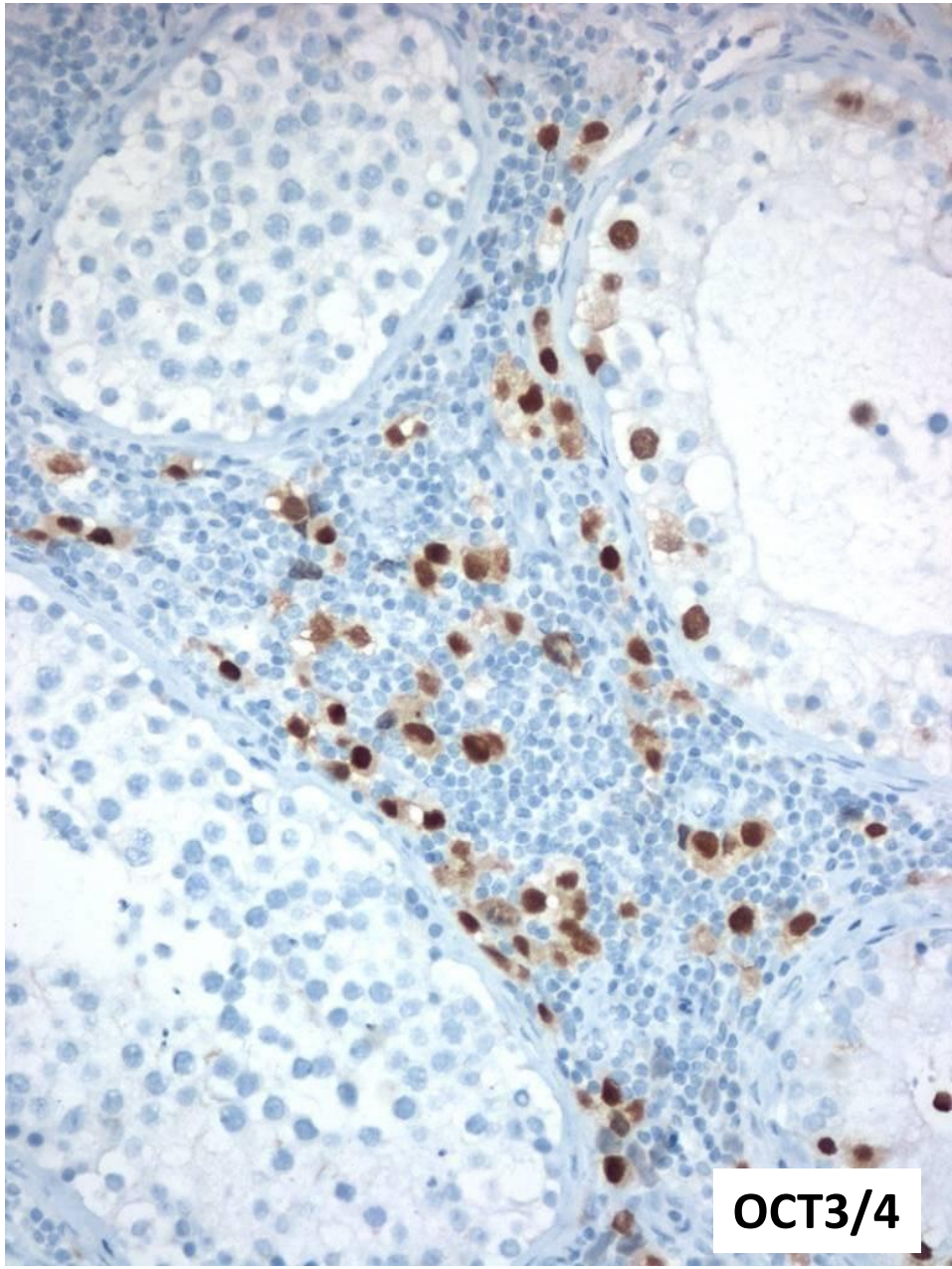


Seminoma with granulomatous inflammation



Seminoma: intertubular pattern of spread





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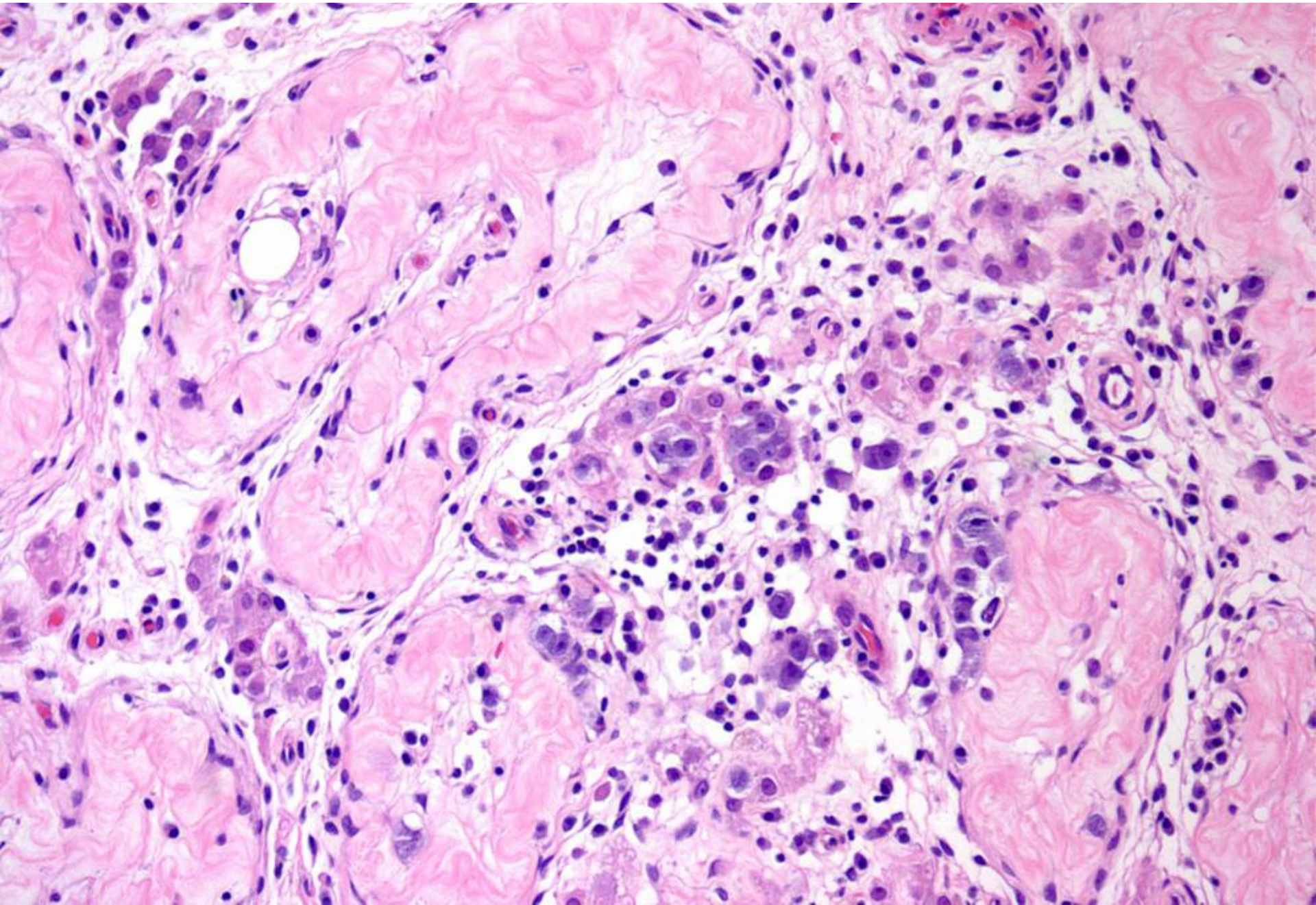
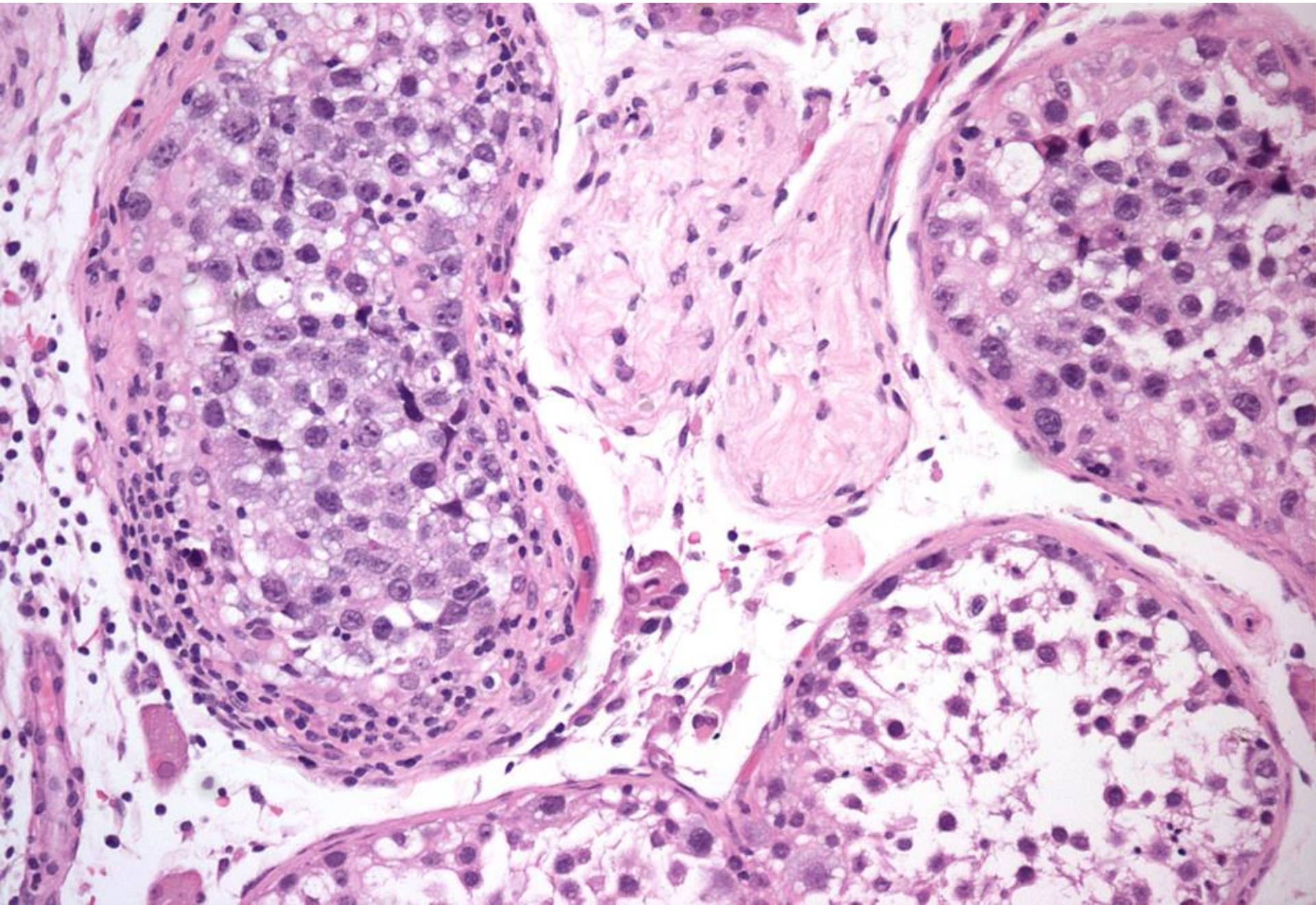
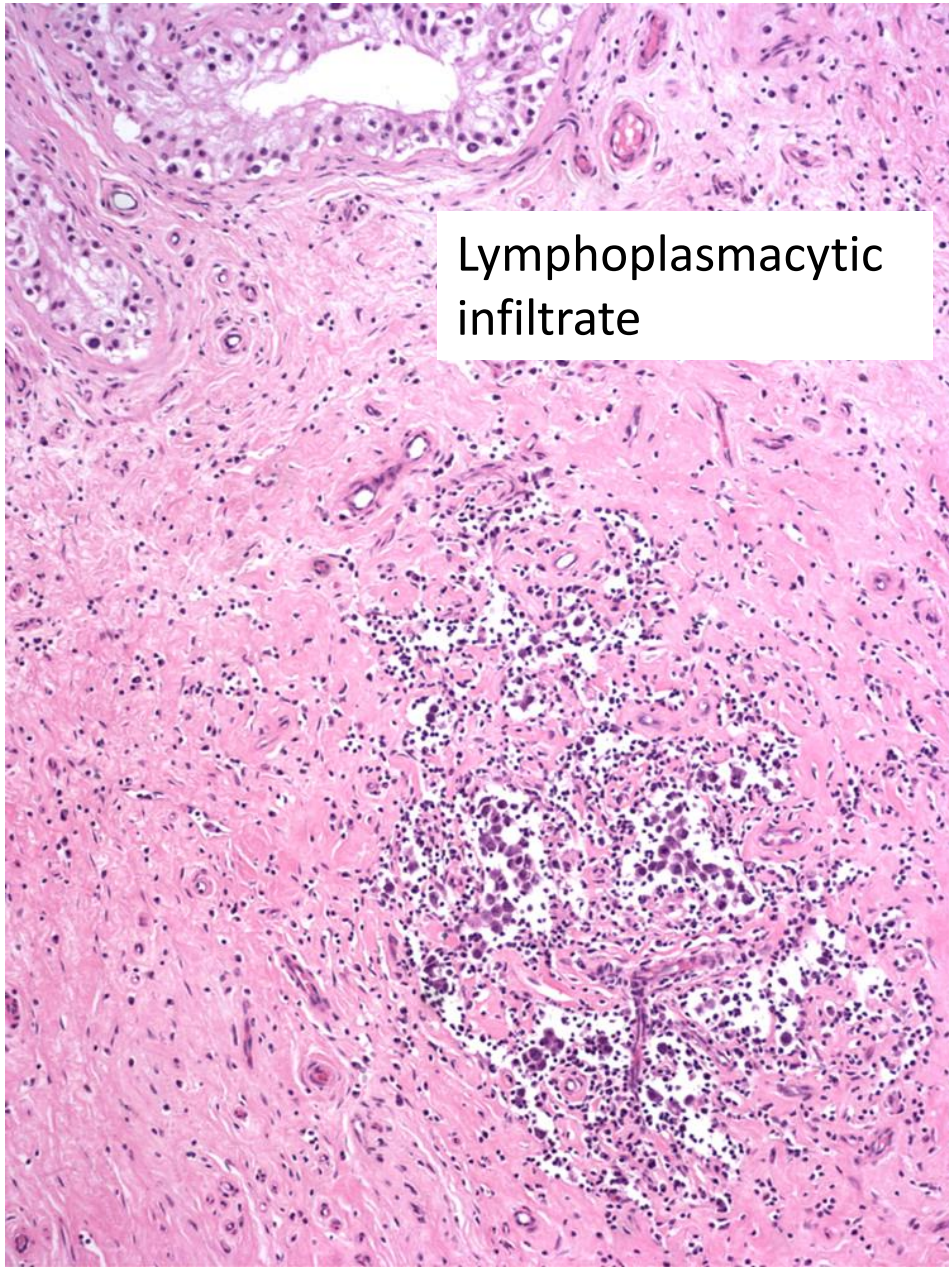


Intratubular Seminoma



‘Burnt-out’ germ cell tumor



Spontaneous regression of gonadal GCT [so-called – 'burnt-out' germ cell tumor]

- No identifiable invasive neoplasm
- Dense, hyaline scarring, sometimes with GCNIS in adjacent tubules
- Intratubular calcifications
- Lymphoplasmacytic infiltrate
- Hemosiderin-containing macrophages
- Testicular atrophy

Seminoma: differential diagnosis

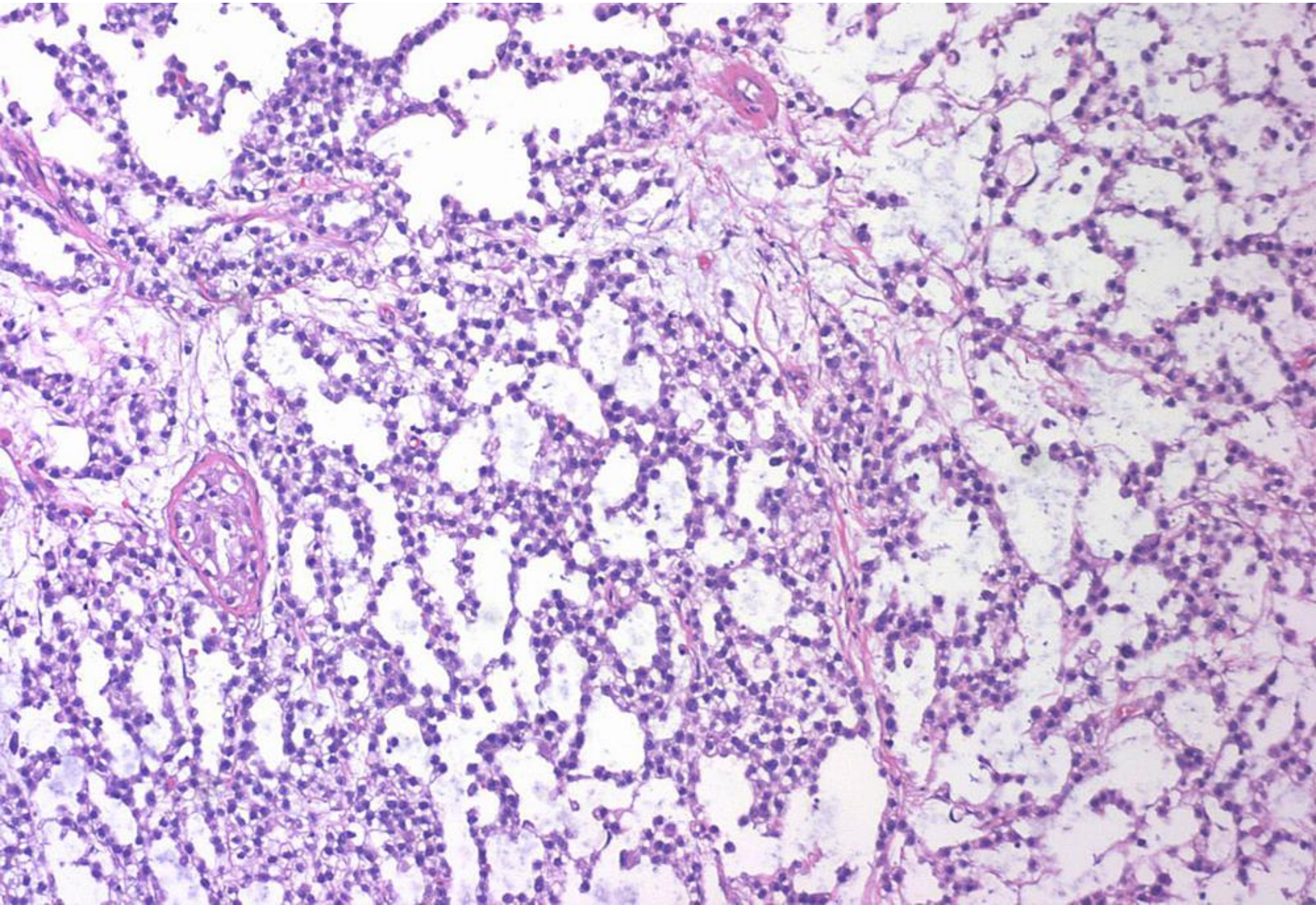
	PLAP	OCT3/4	AE1/3	CD30	CD117	SALL4	CD45	AFP
Seminoma	+	+	focal	–	+	+	–	–

- **Embryonal carcinoma (solid pattern)**
  - Indistinct cell border and overlapping nuclei
  - Glandular structure only seen in EC
  - AE1/3 and CD30 +
  - OCT3/4 +
- **Yolk sac tumor (solid pattern)**
  - No fibrous septae
  - Solid YST is usually associated with other types
  - Edema in seminoma may resemble reticular YST
  - AE1/3+, Glypican 3, AFP +/-; OCT3/4 –, CD117 –

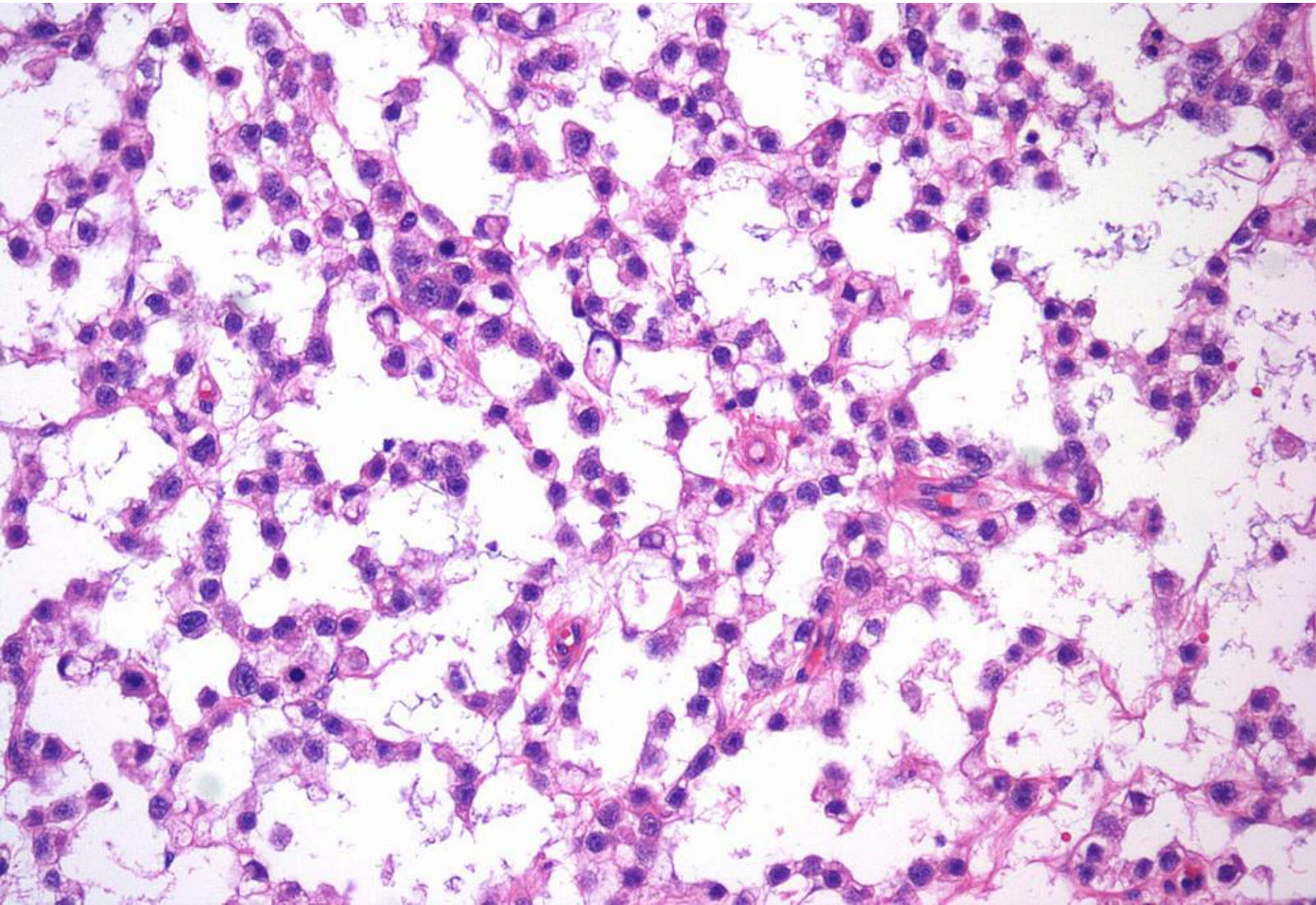
Seminoma: differential diagnosis

- **Sertoli cell tumor**
  - Tubular pattern may be confused with Sertoli cell tumor
  - Lipid (not glycogen) is responsible for clear cytoplasm
  - PLAP –, OCT3/4 –, inhibin +
- **Lymphoma**
  - No fibrous septae
  - Older patients
  - CD45 +
  - Bilateral involvement more likely
- **Choriocarcinoma (CC)**
  - No biphasic pattern is seen in seminoma
  - HCG is markedly elevated in CC; modestly in seminoma
  - AE1/3+, EMA +; OCT3/4 –

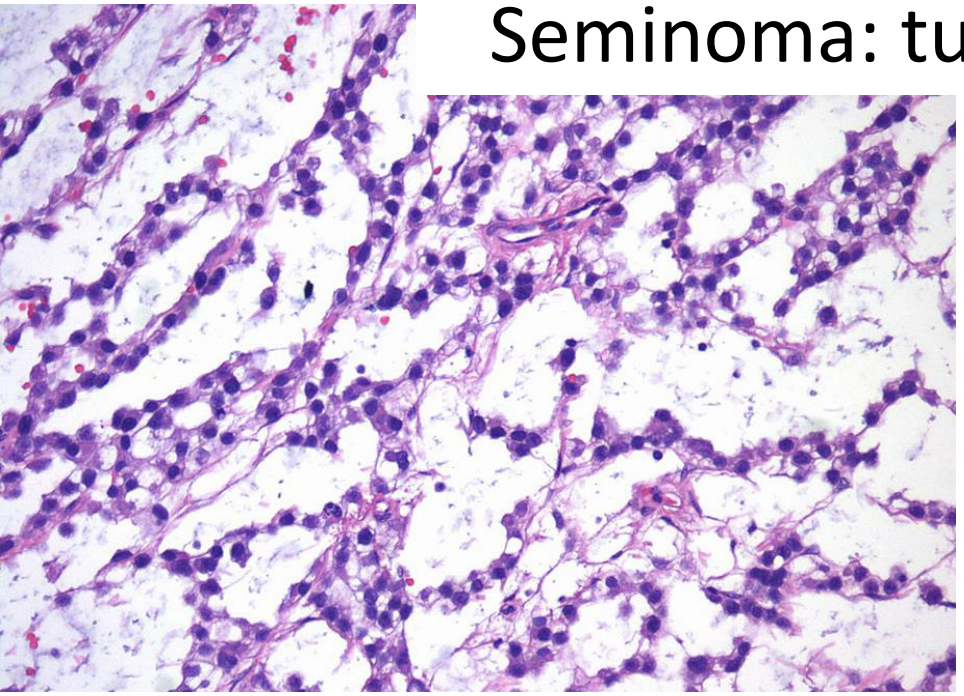
Seminoma: tubular pattern

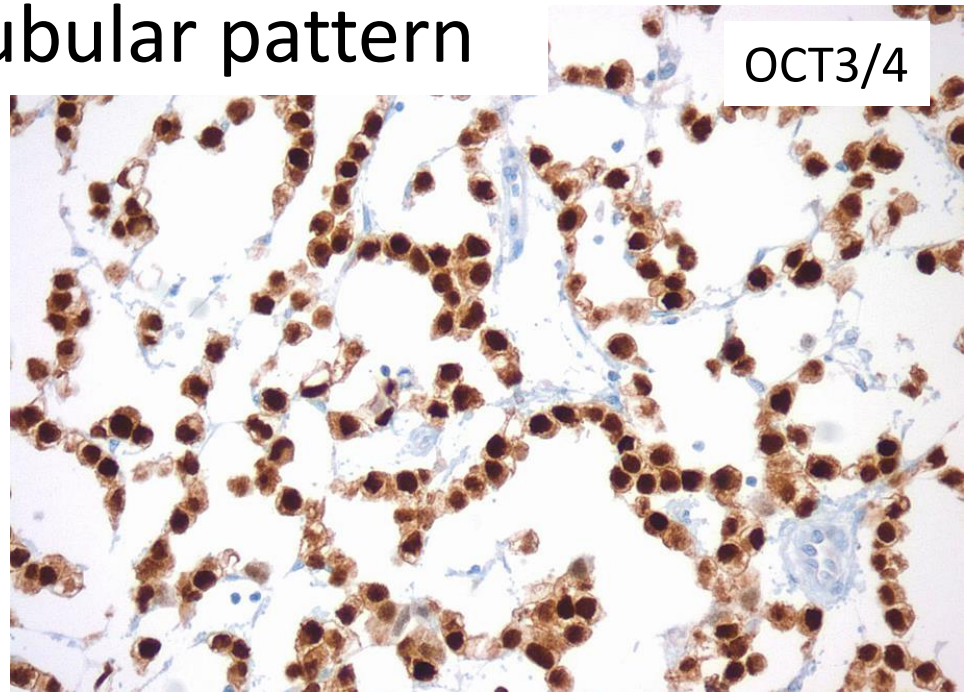


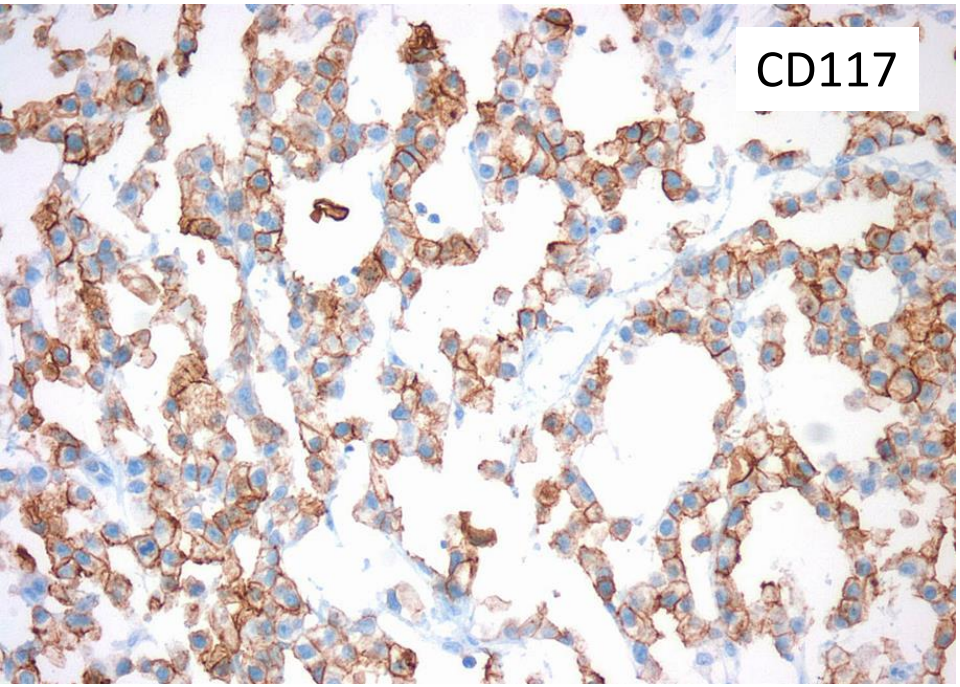
Seminoma: tubular pattern

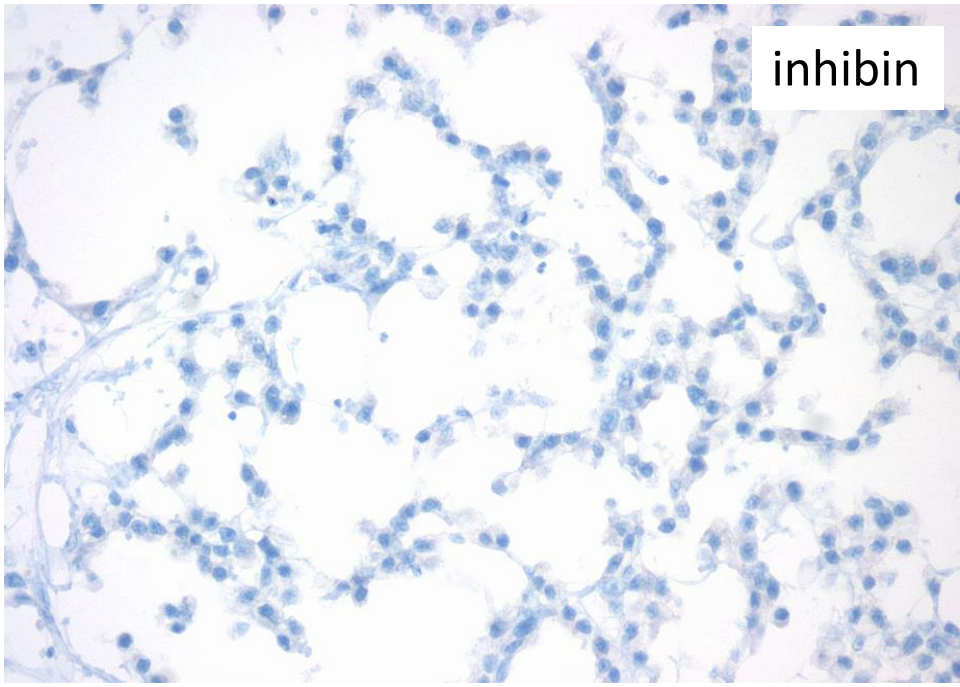


Seminoma: tubular pattern



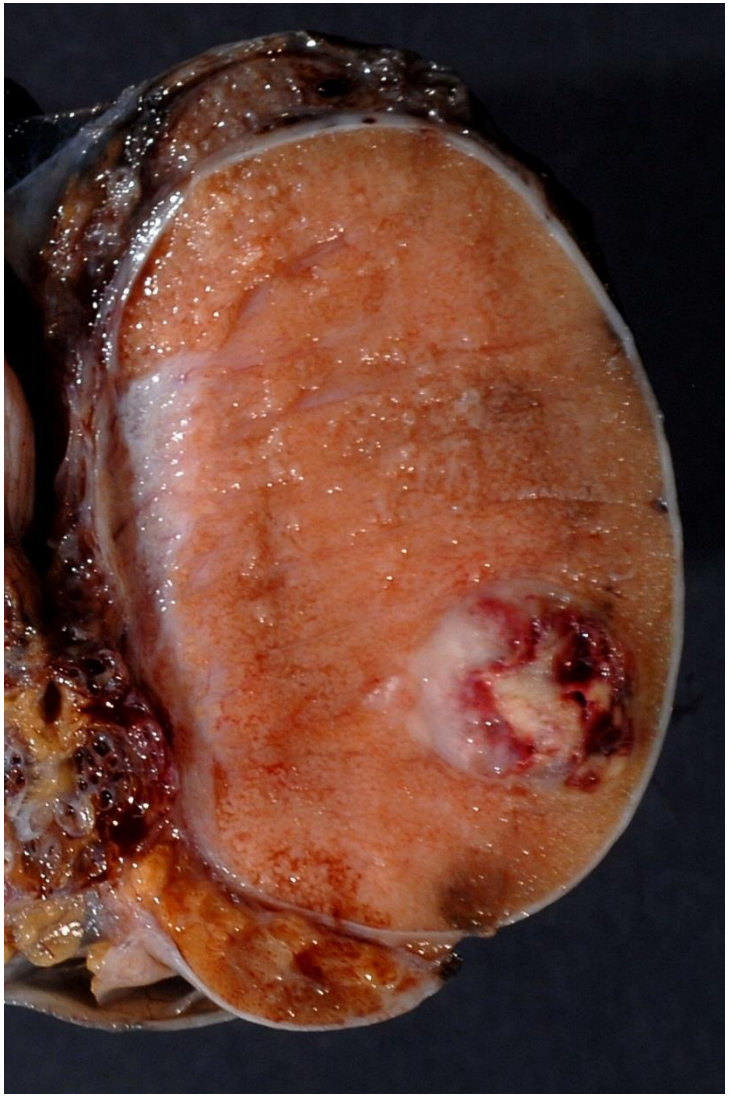




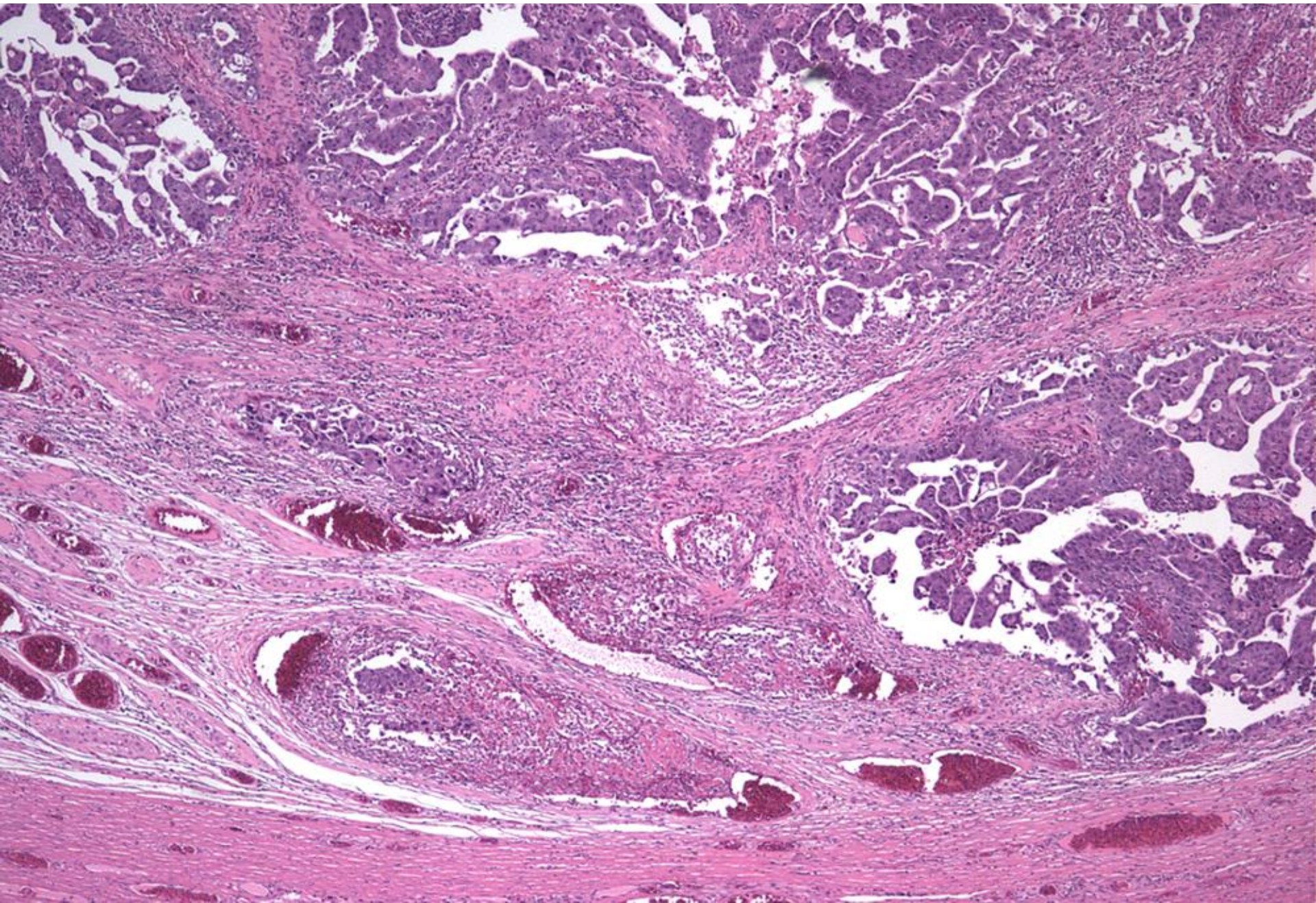


Embryonal Carcinoma

- Pure is rare (10%)
- Seen in 40% of TGCTs
- Mean age = 32
- Only 40% have disease limited to testis at presentation
- 2/3 have metastatic disease upon staging
- Hemorrhage/necrosis common
- Not as well circumscribed as seminoma



Embryonal Carcinoma



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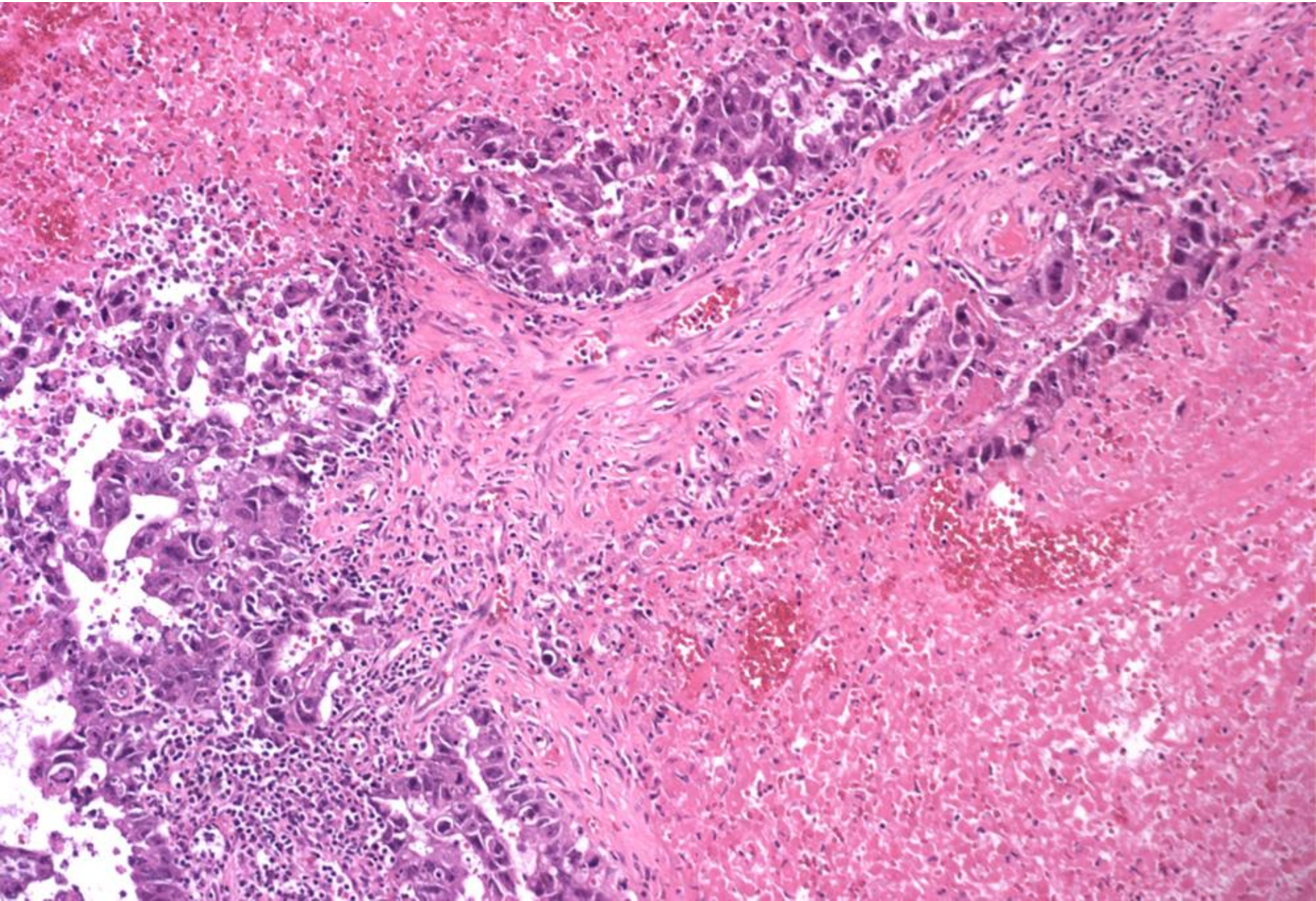
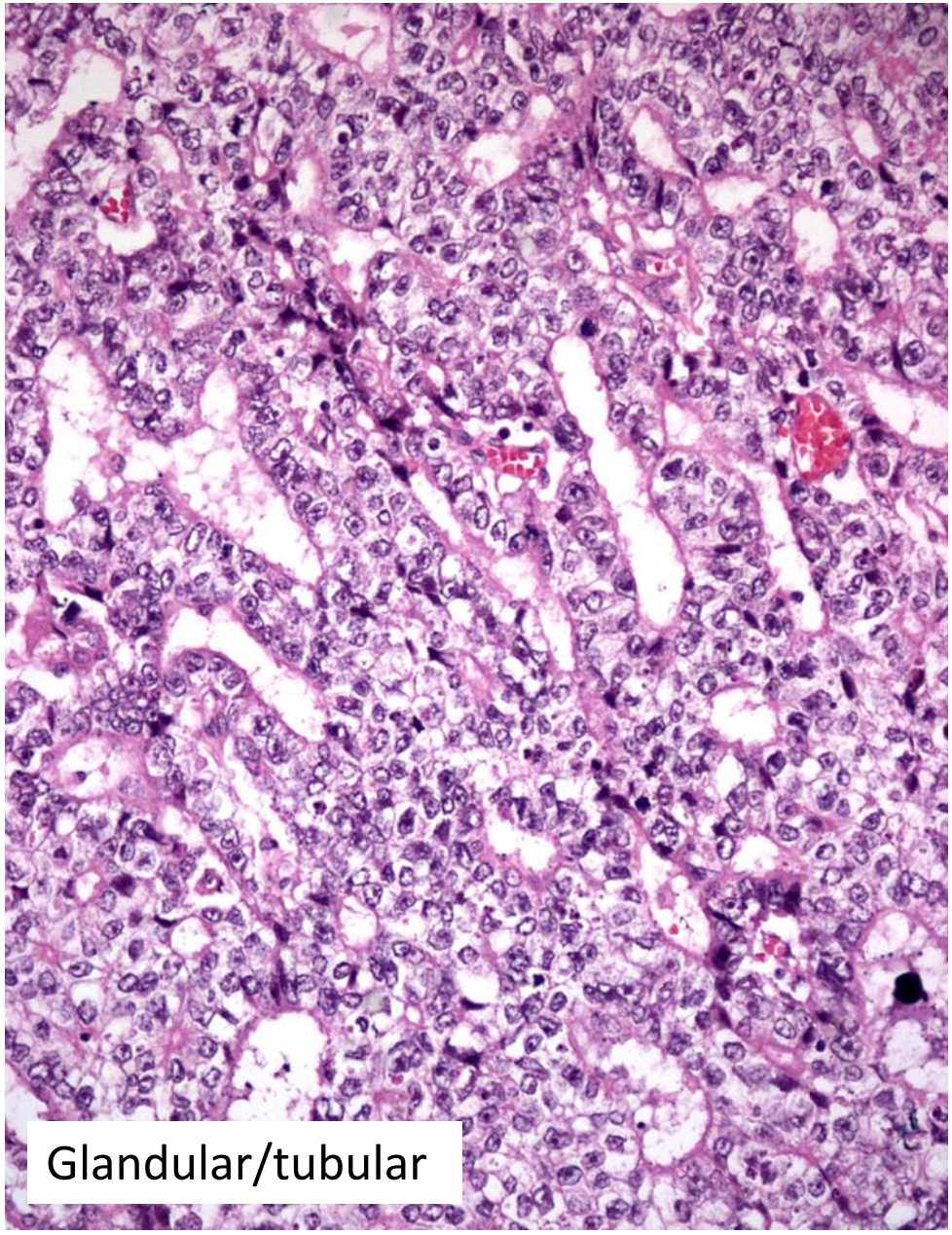
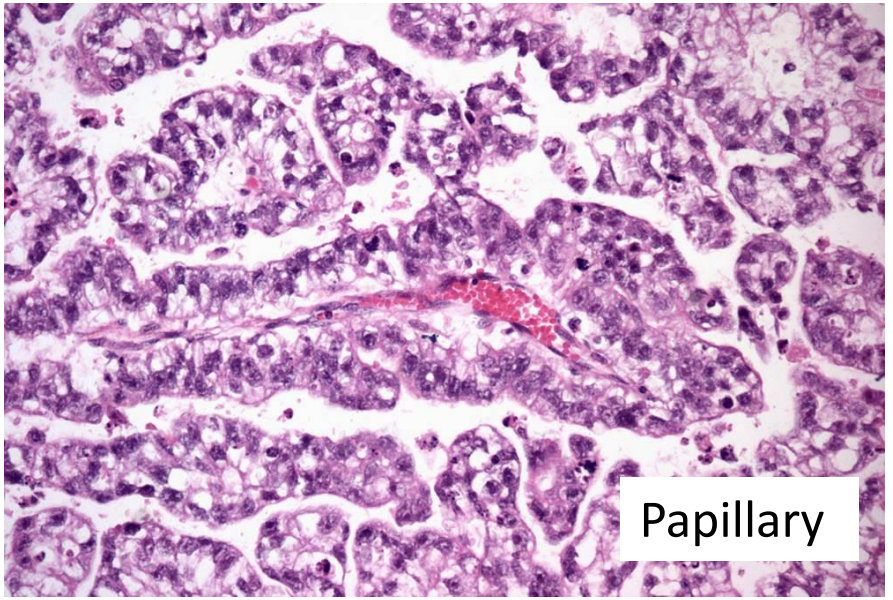
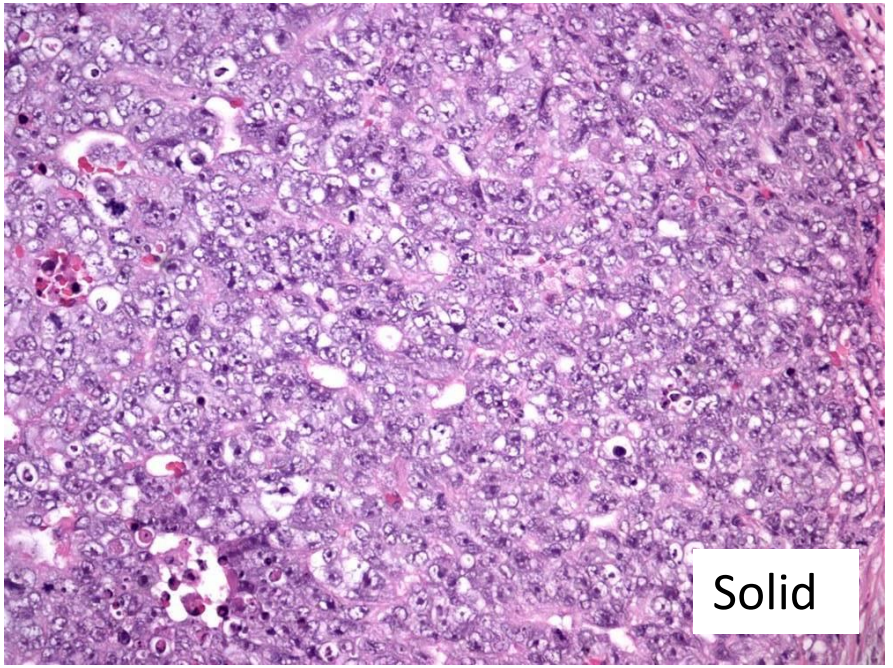


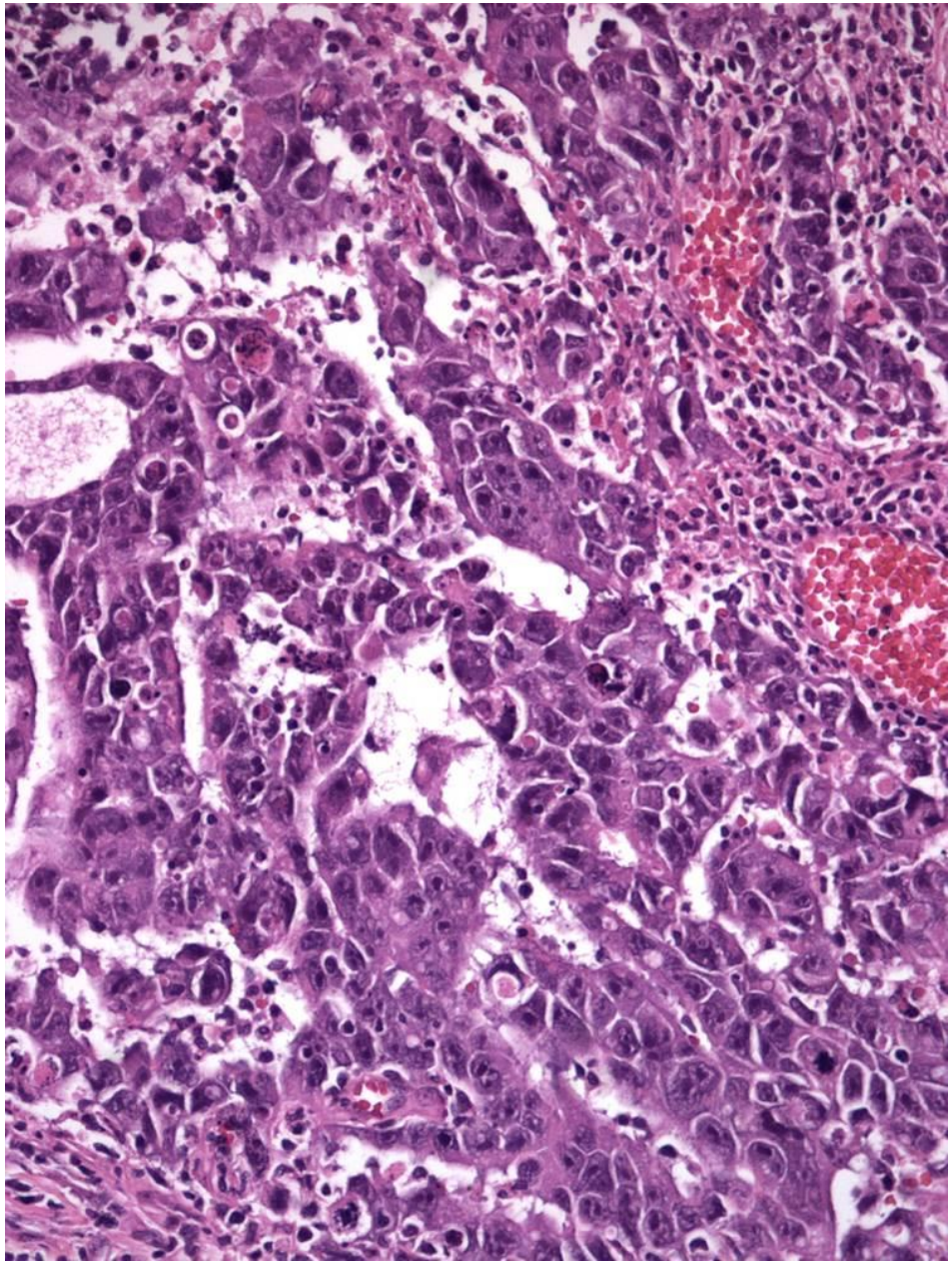
Embryonal Carcinoma: growth pattern

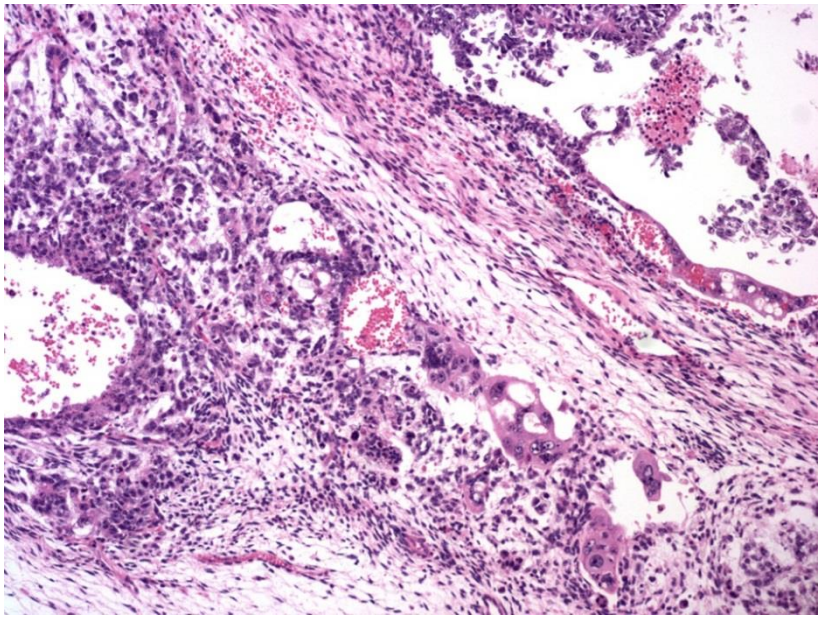


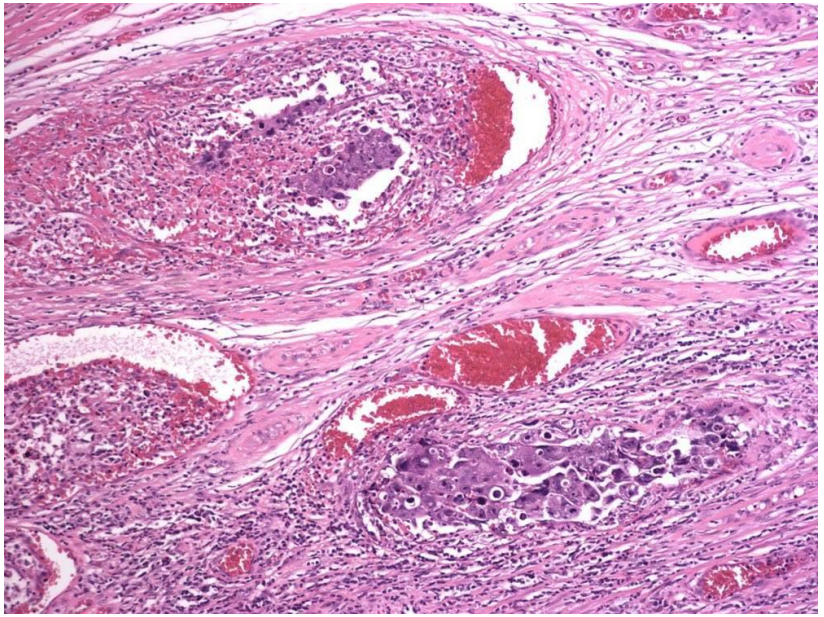




Embryonal Carcinoma







EC: differential diagnosis

	PLAP	OCT3/4	AE1/3	CD30	CD117	SALL4	EMA	CEA	AFP
EC	focal	+	+	+	_	+	_	_	focal

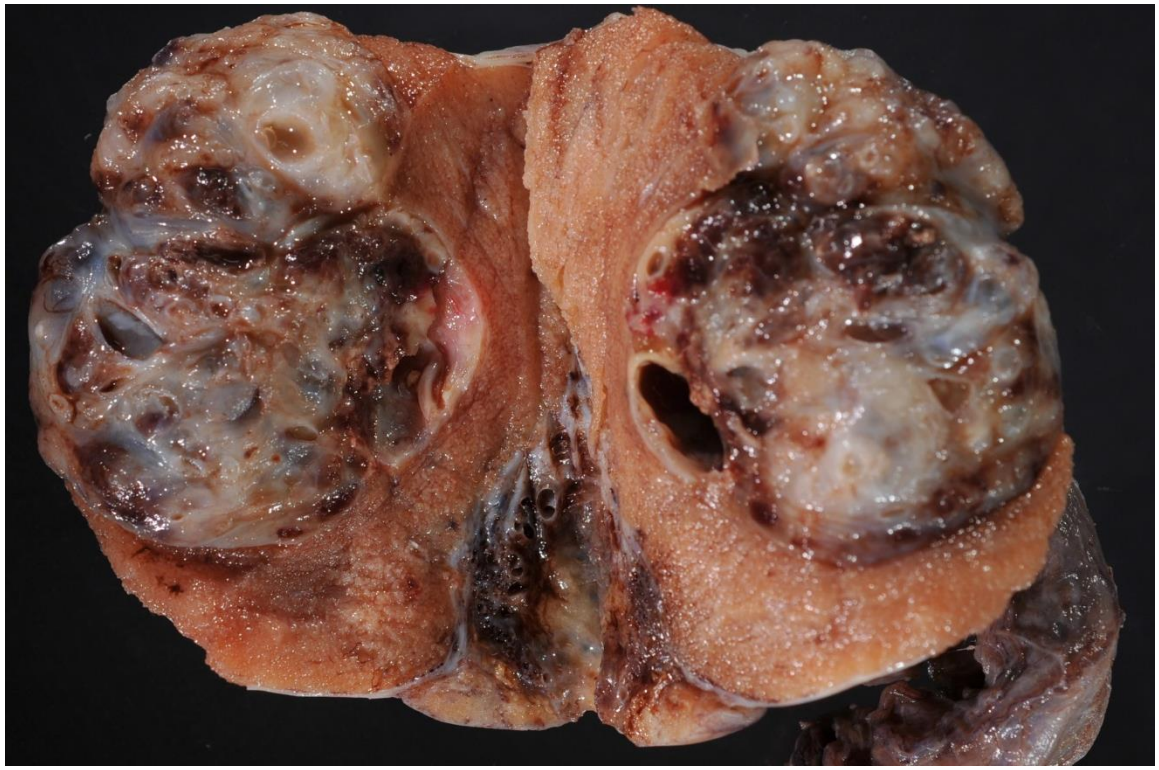
- **Seminoma**
  - Previously discussed
- **Yolk sac tumor**
  - Cells are smaller and less pleomorphic
  - Hyaline globules are present
  - AFP is diffusely +
  - CD30 and OCT3/4 –
- **Choriocarcinoma**
  - Syncytiotrophoblast cells are mixed with cytotrophoblast cell (biphasic pattern)

Yolk sac tumor (YST)

- Most common testicular neoplasm in children: 80% of pure YSTs occur in the first 2 years of life
- Pure YST is uncommon in adults (1.5% of GCTs); however YST is a component of ~40% of mixed GCT
- In adults present as a painless mass
- Serum alpha fetoprotein (AFP) levels are elevated in 90% of cases
- Patterns resemble portions of rat placenta

YST: gross appearance

- Typically solid and soft, white-gray, light yellow with cystic degeneration
- Large tumors may show necrosis and hemorrhage

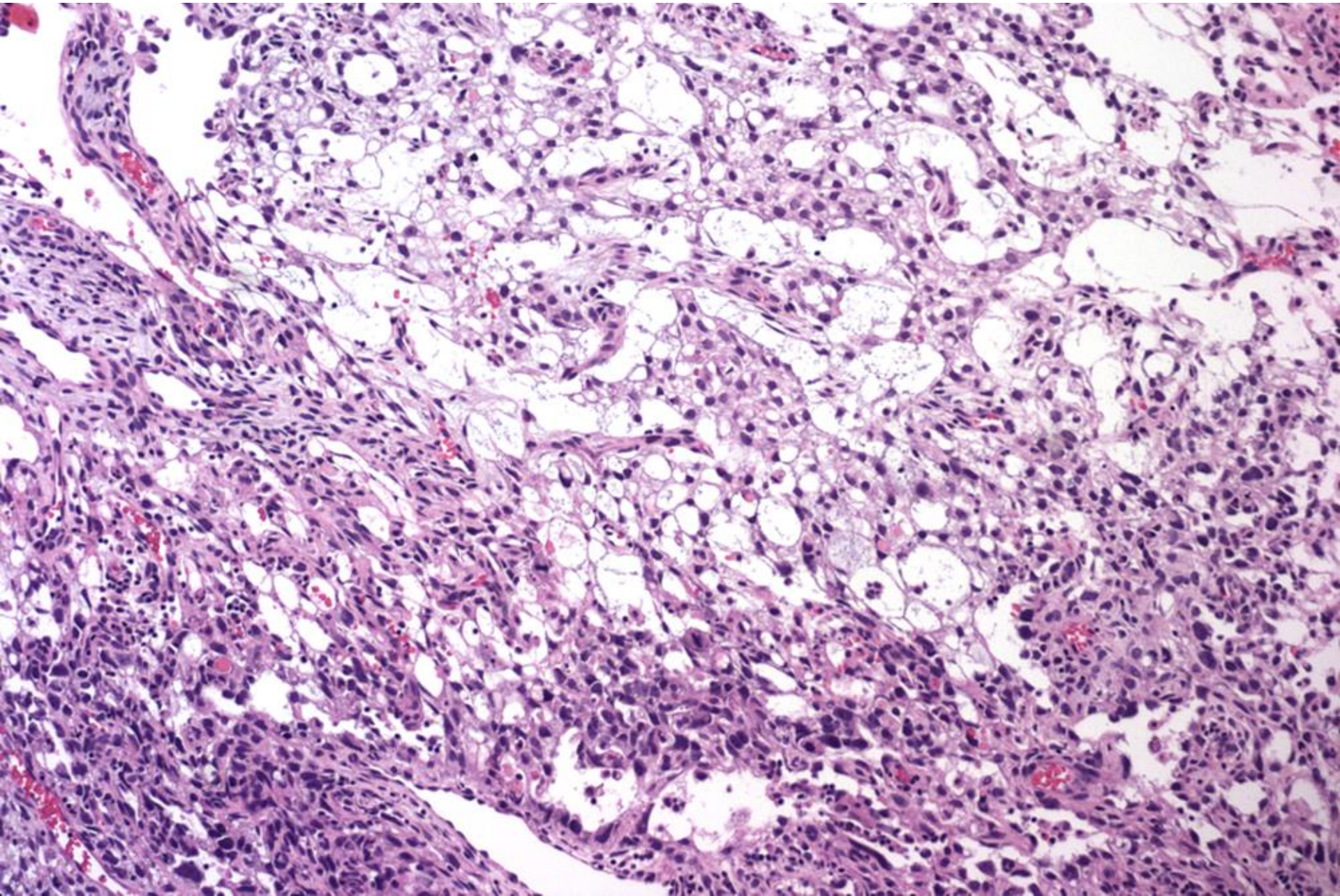


Yolk sac tumor (YST)

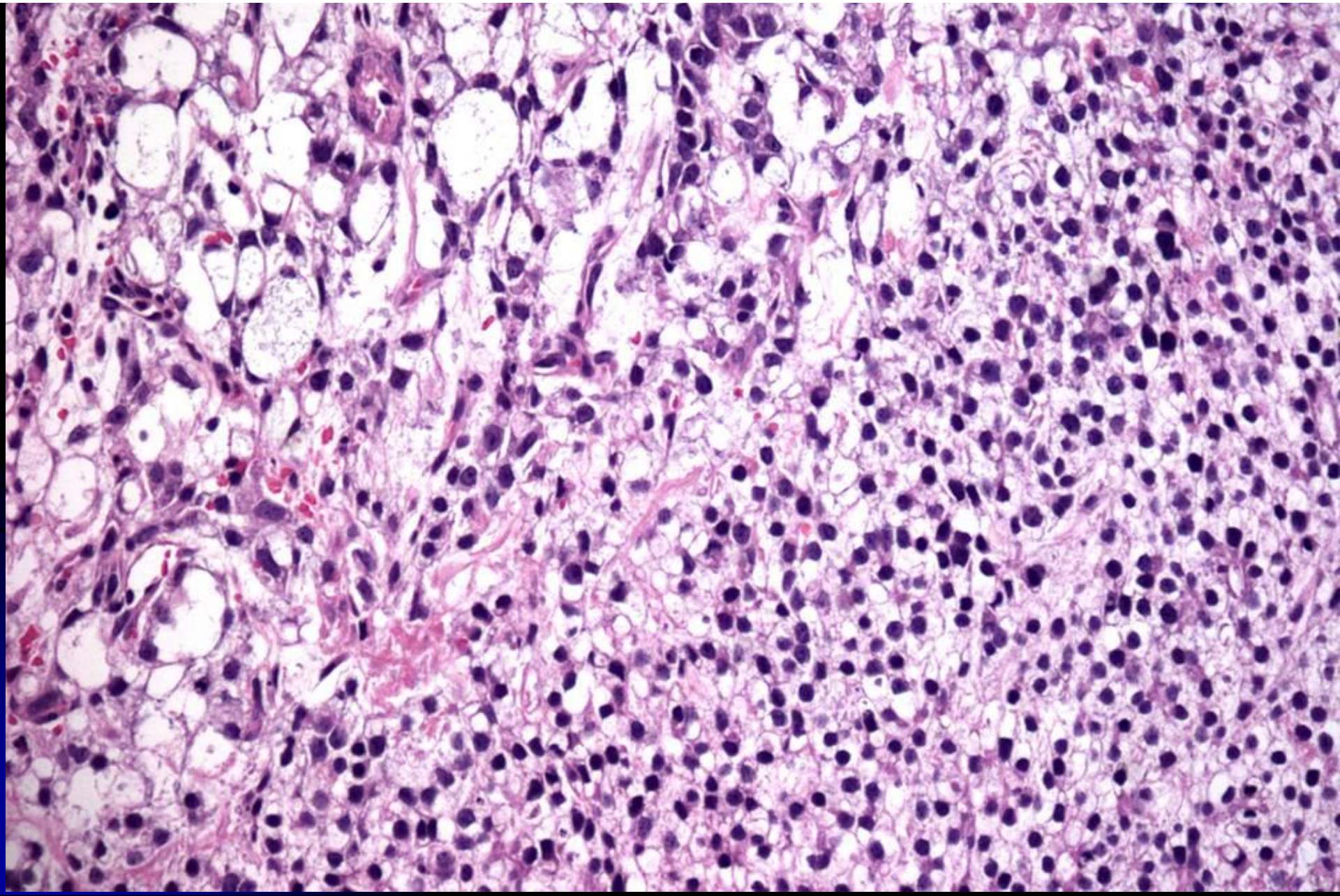
Histologic patterns

- Microcystic (reticular)
- Macrocystic
- Myxoid
- Endodermal sinus (festoon)
- Solid
- Polyvesicular vitelline
- Hepatoid
- Spindle cells (in post-chemotherapy tumors)
- Parietal (AFP -)
- Glandular (clear cells)

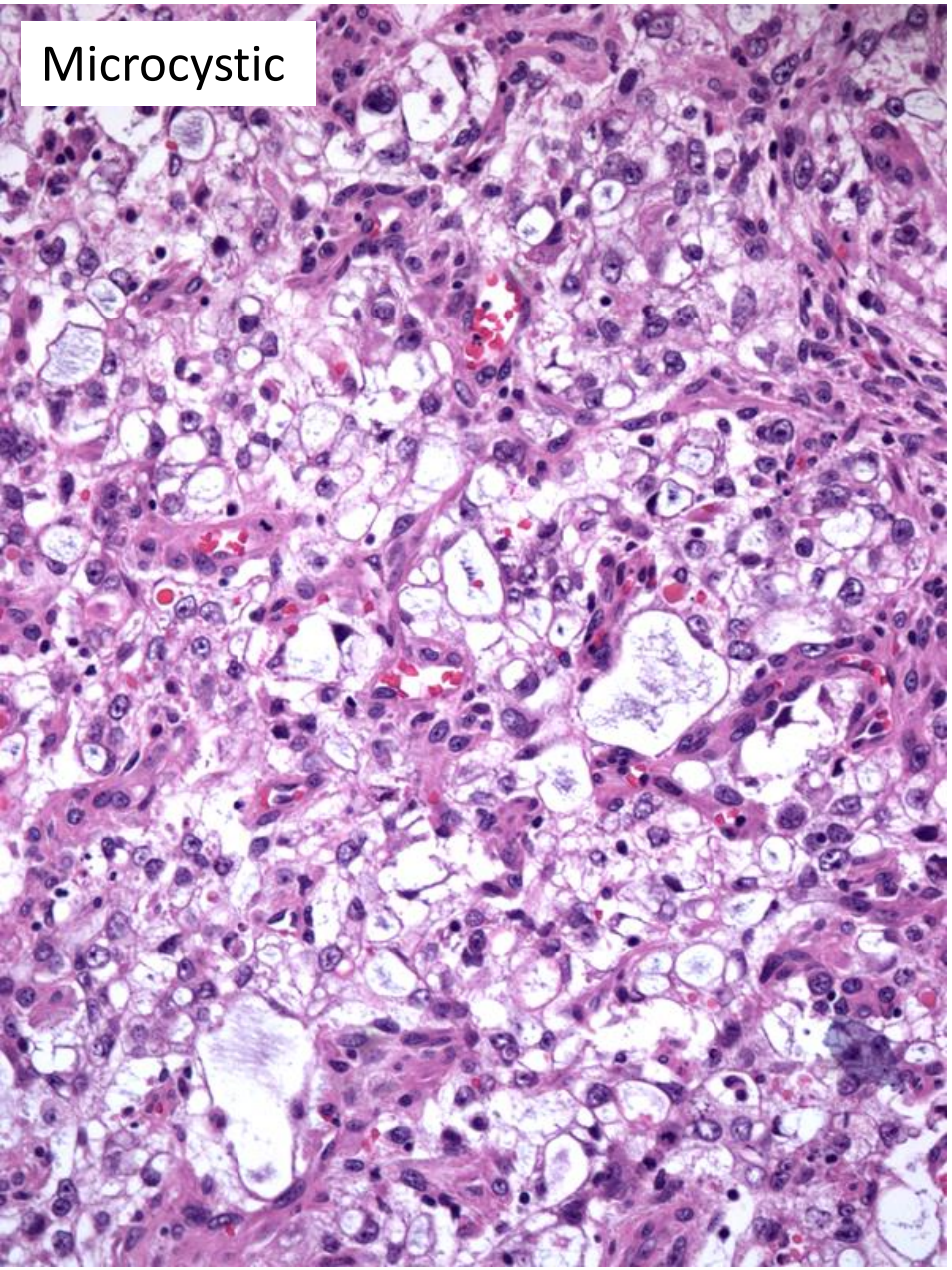
YST: microcystic variant

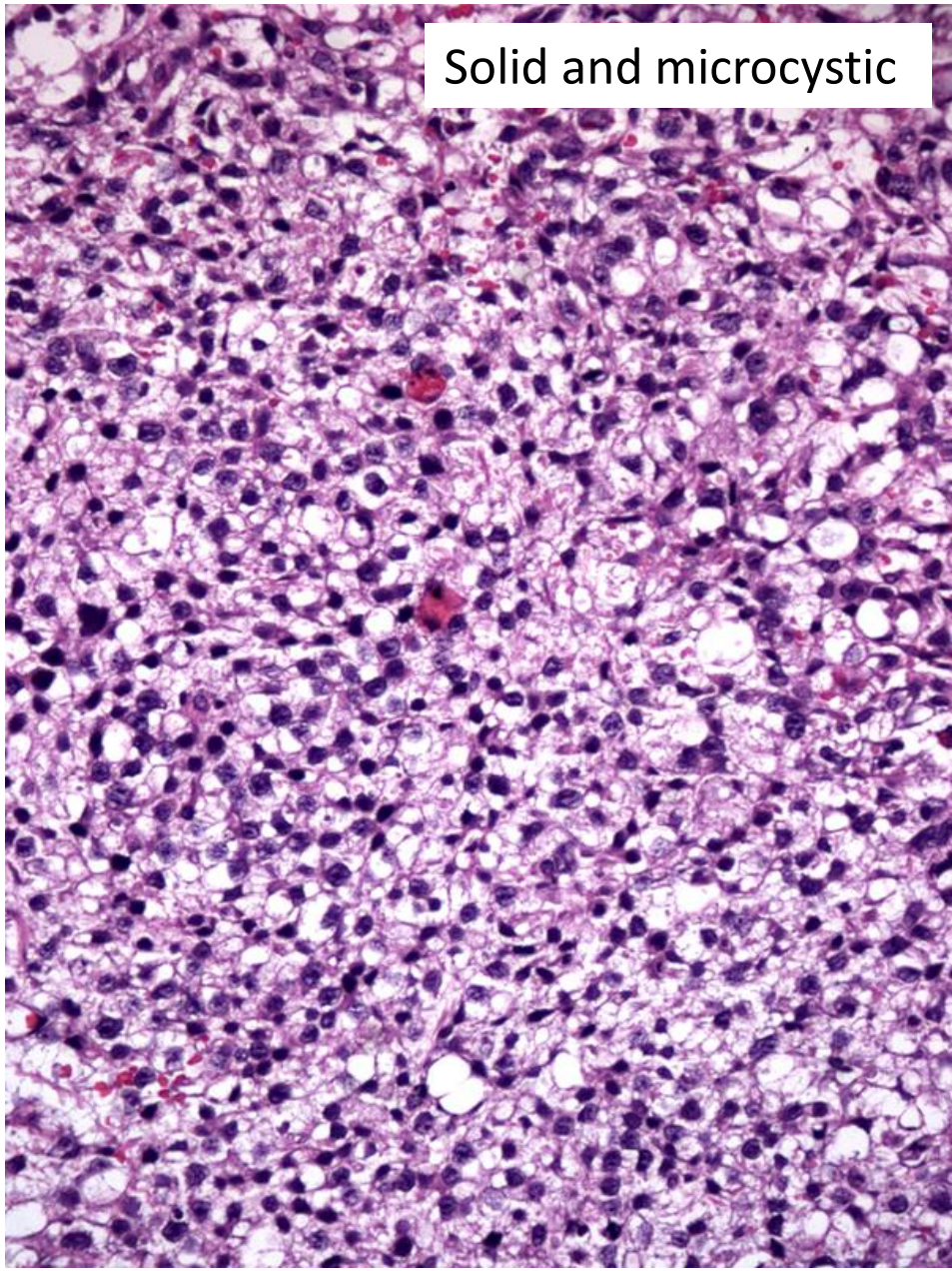


YST: microcystic and solid variant

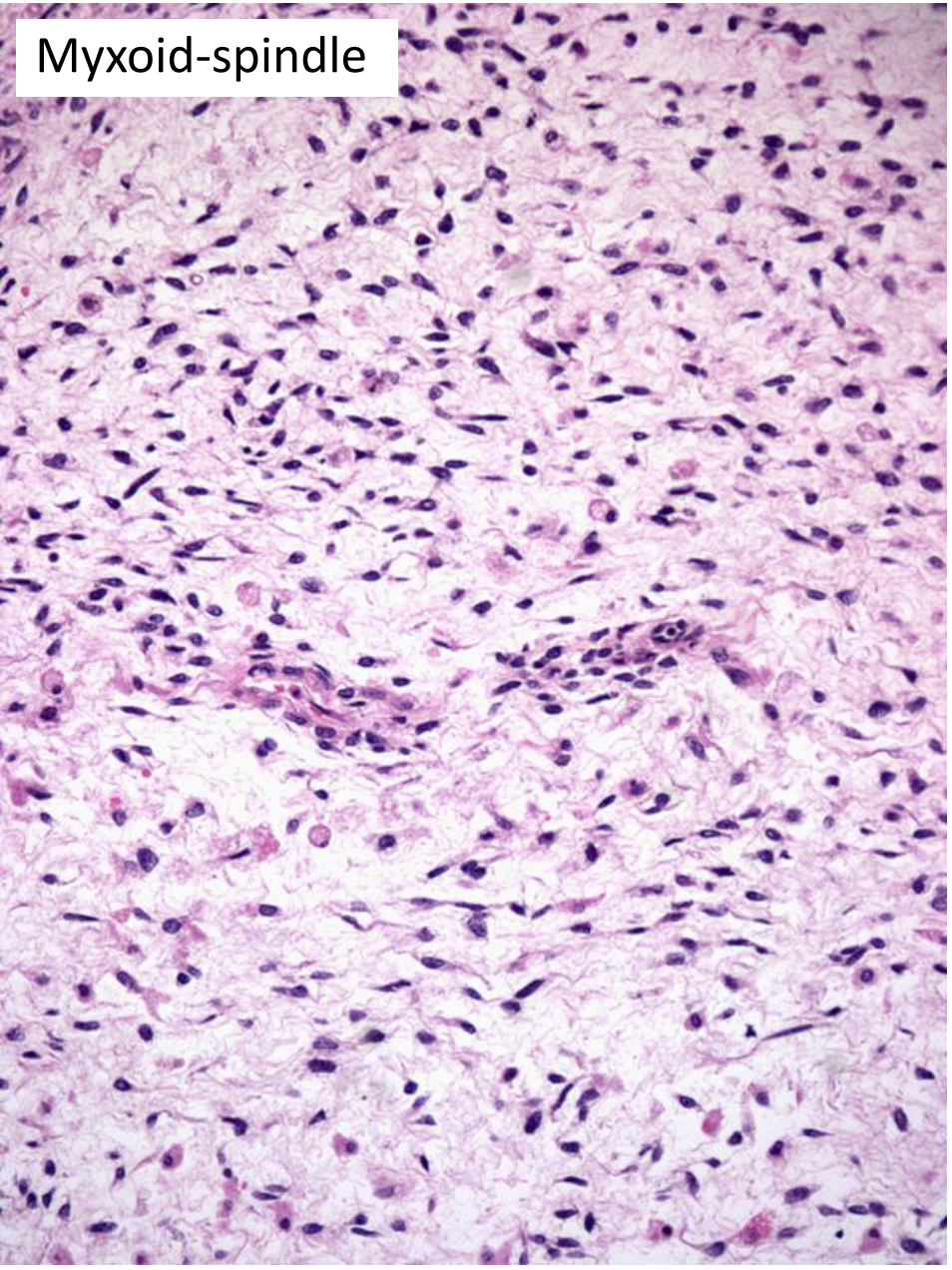


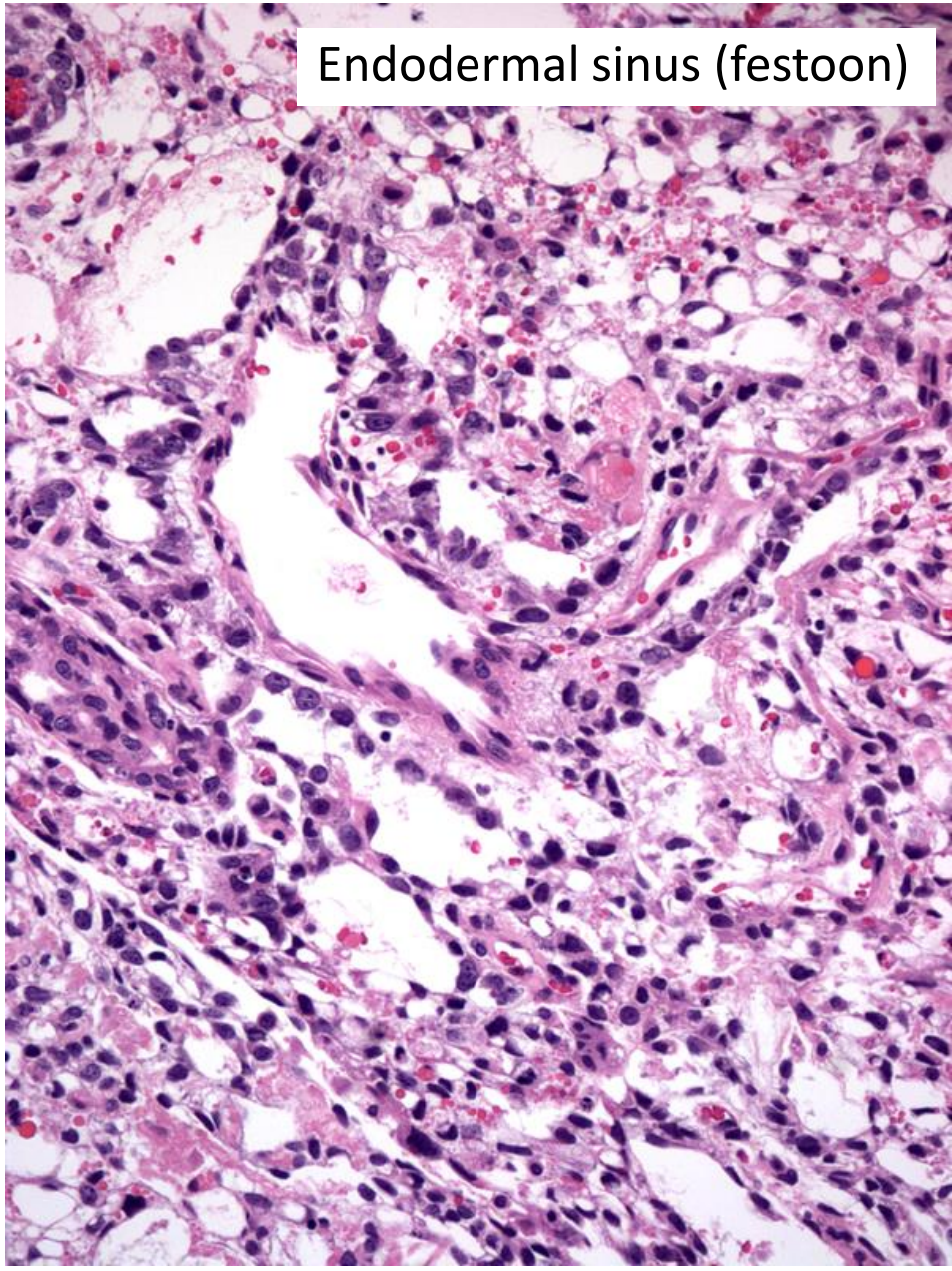
YST: histologic patterns



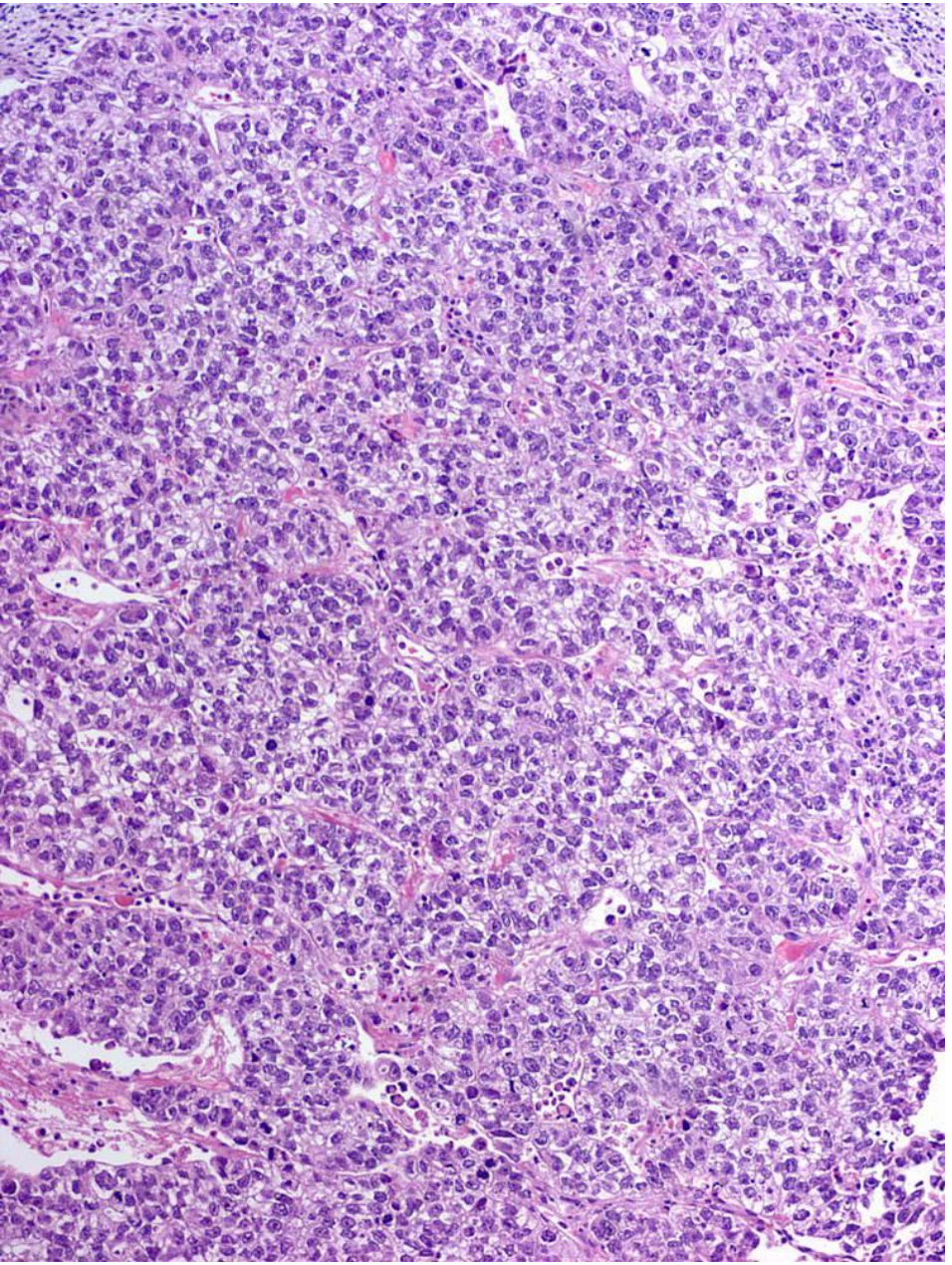


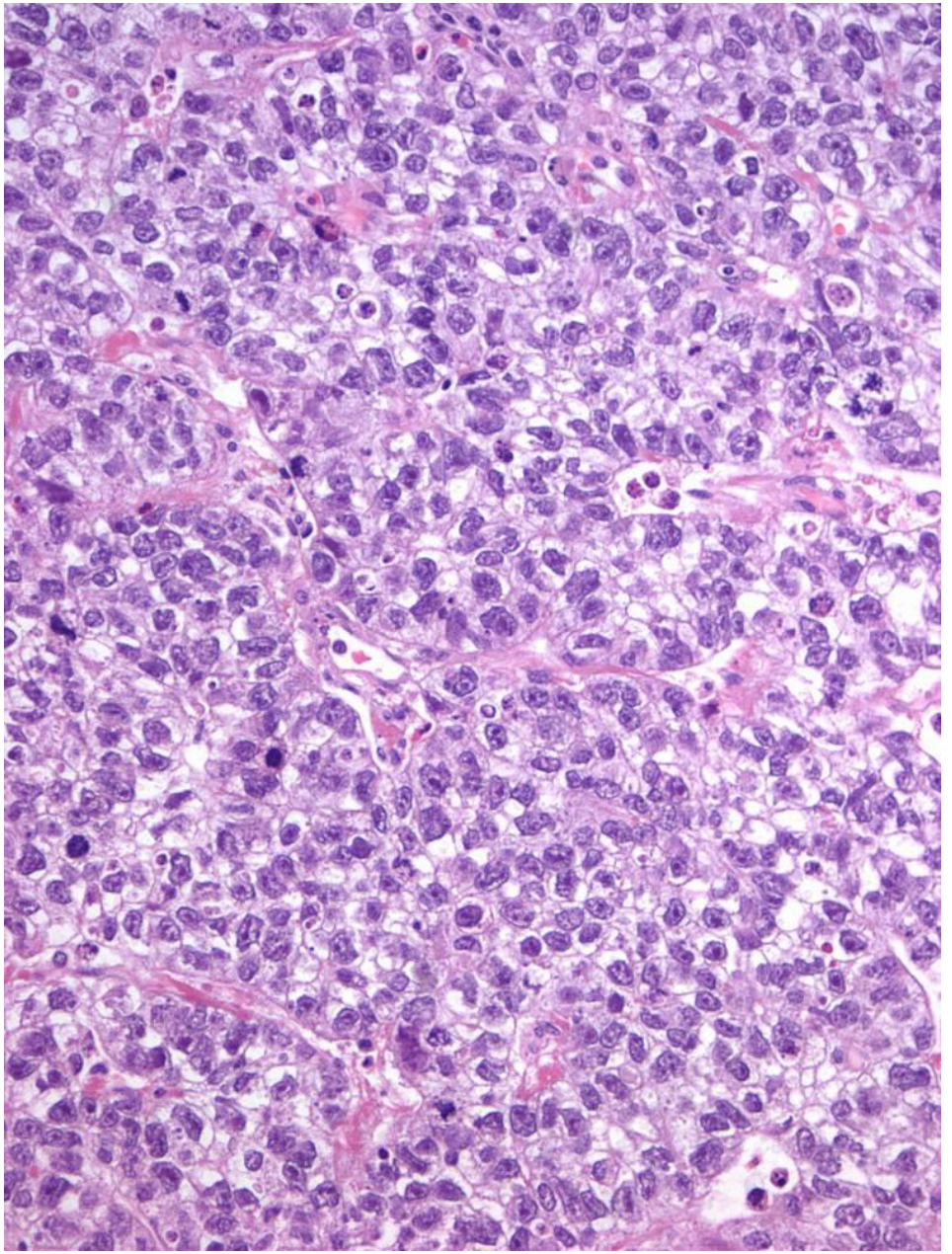
YST: histologic patterns



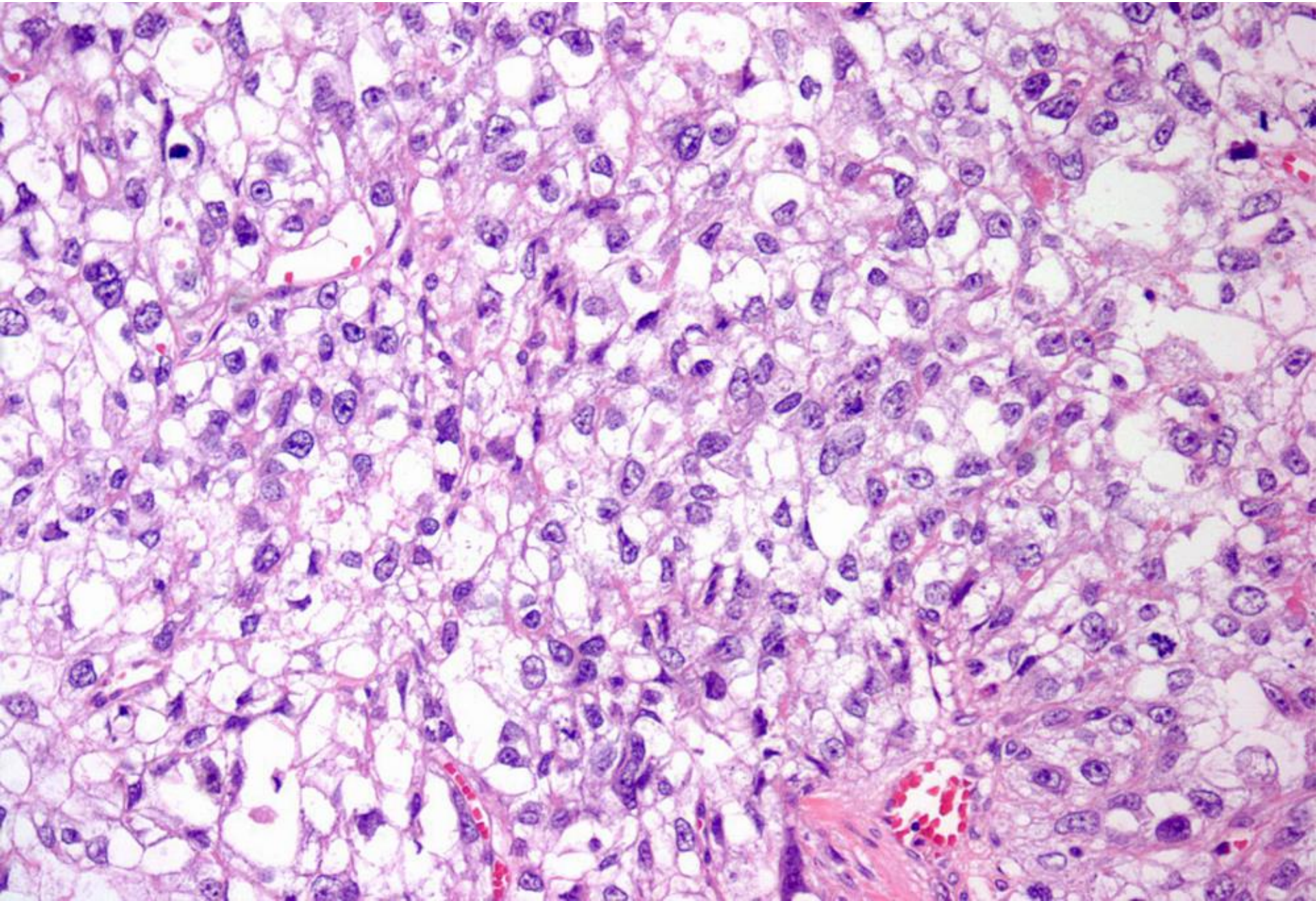


YST: solid variant





YST: solid variant



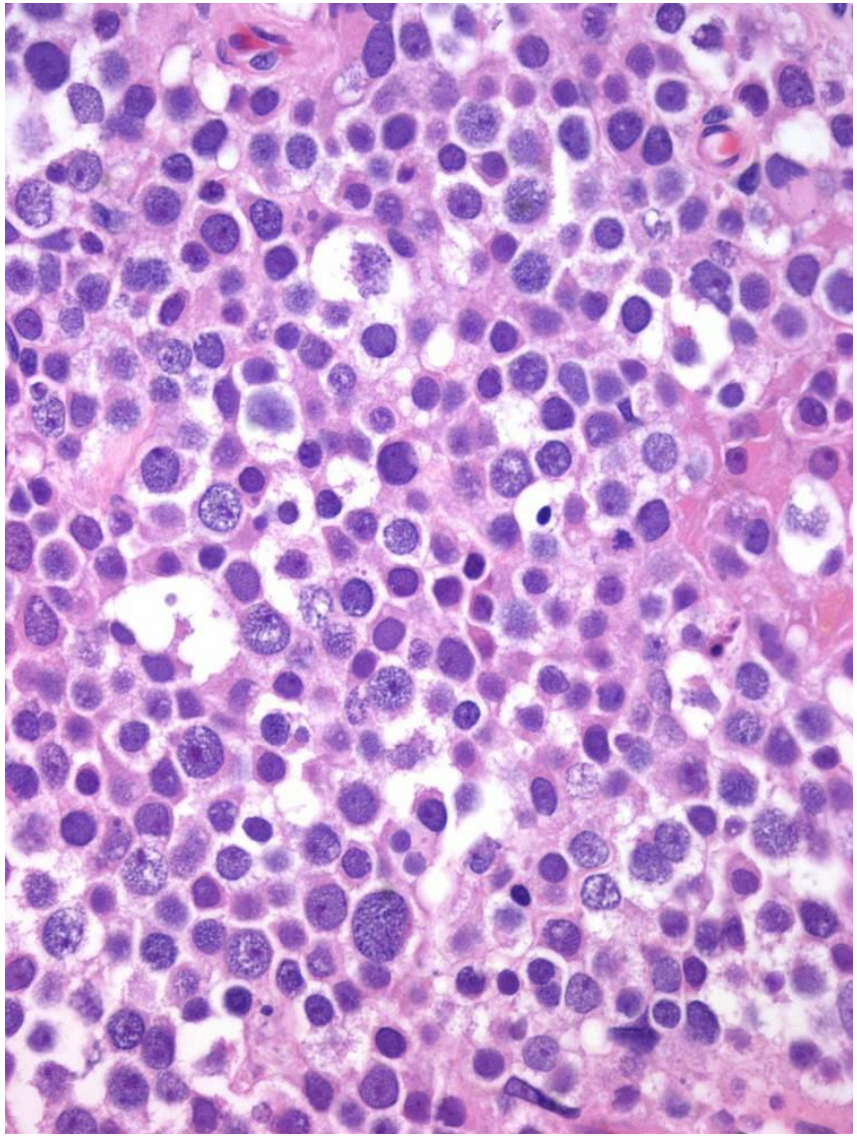
YST: differential diagnosis

	PLAP	OCT3/4	AE1/3	CD30	Glypican-3	SALL4	EMA	CEA	AFP
YST	+/-	–	+	–	+	+	–	+	+

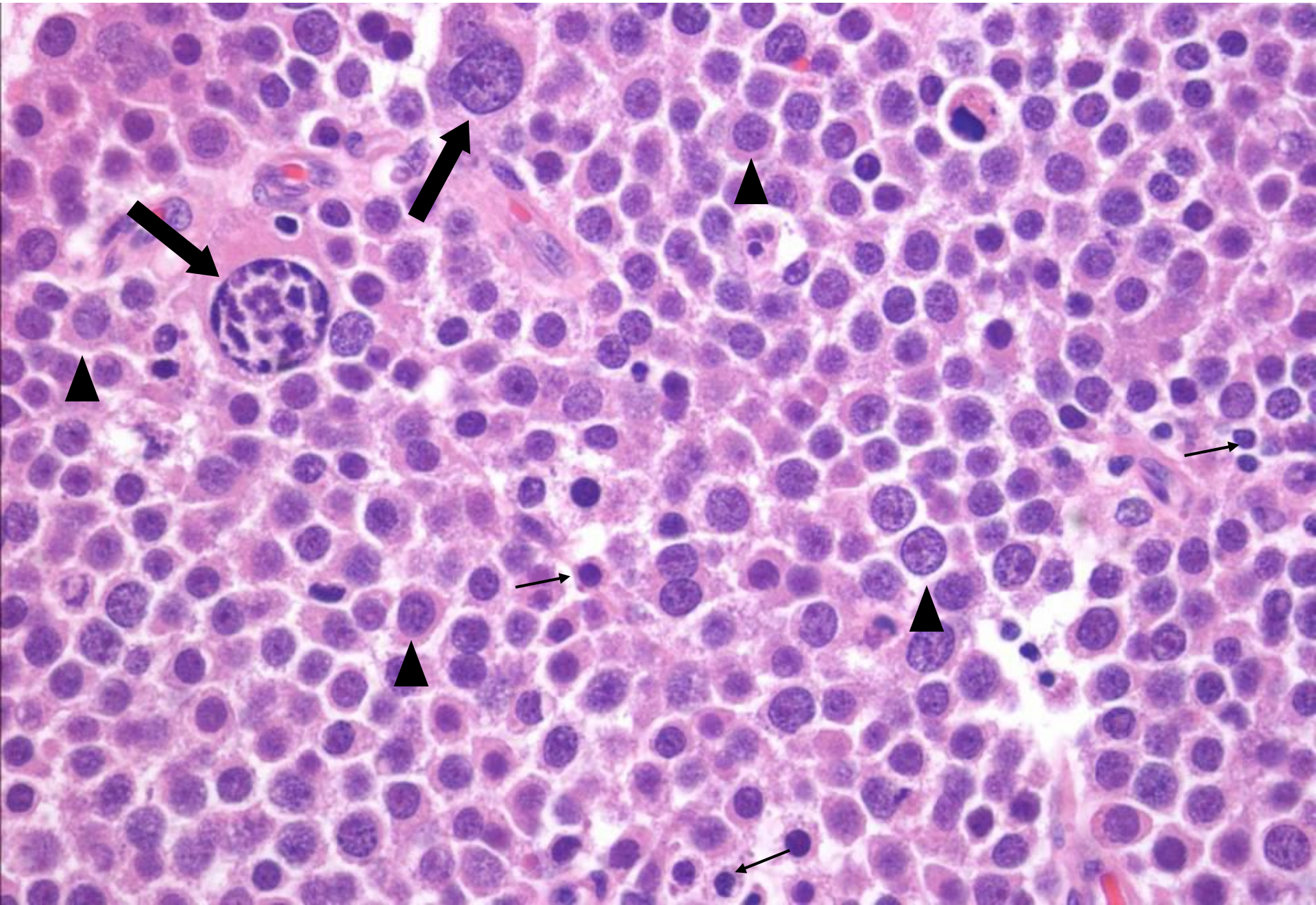
- **Seminoma (vs. solid YST)**
  - No hyaline globules seen
  - Glypican 3 –, AFP –, OCT3/4 +
- **Embryonal carcinoma**
  - Marked nuclear crowding not seen in YST
  - CK +, focally AFP + (similar to YST)
  - CD30 and OCT3/4 +
- **Teratoma (vs. glandular YST)**
  - AFP –

Spermatocytic ~~Seminoma~~ Tumor

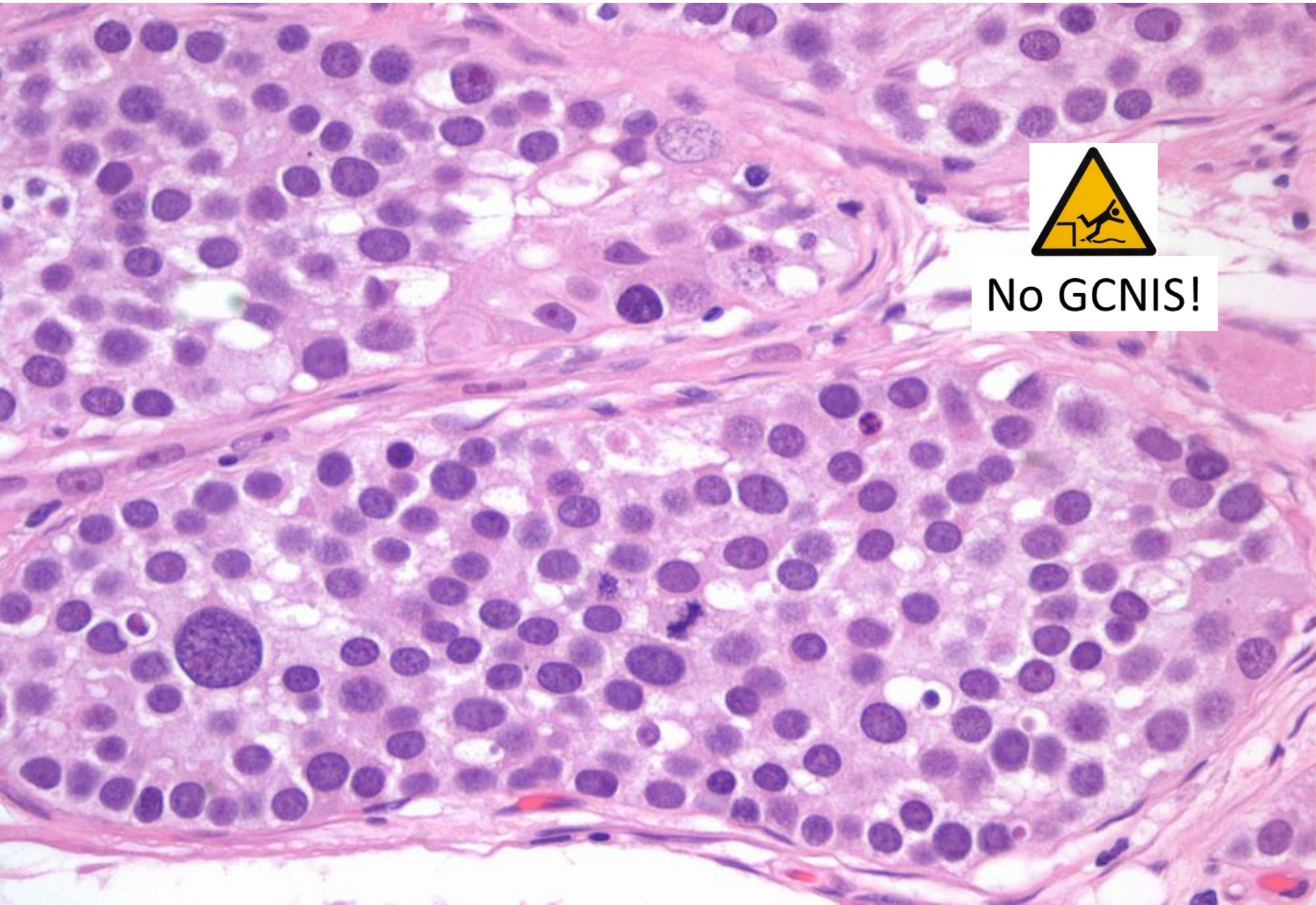
- Derived from postpubertal-type germ cells
- No relationship with seminoma
- 50-60 years old patients
- More frequently bilateral than other CGTs (9%)
- Never described in any site other than testis
- No association with cryptorchidism; no racial predisposition
- Amplification of chr. 9 (*DMRT1*) is most consistent genetic abnormality



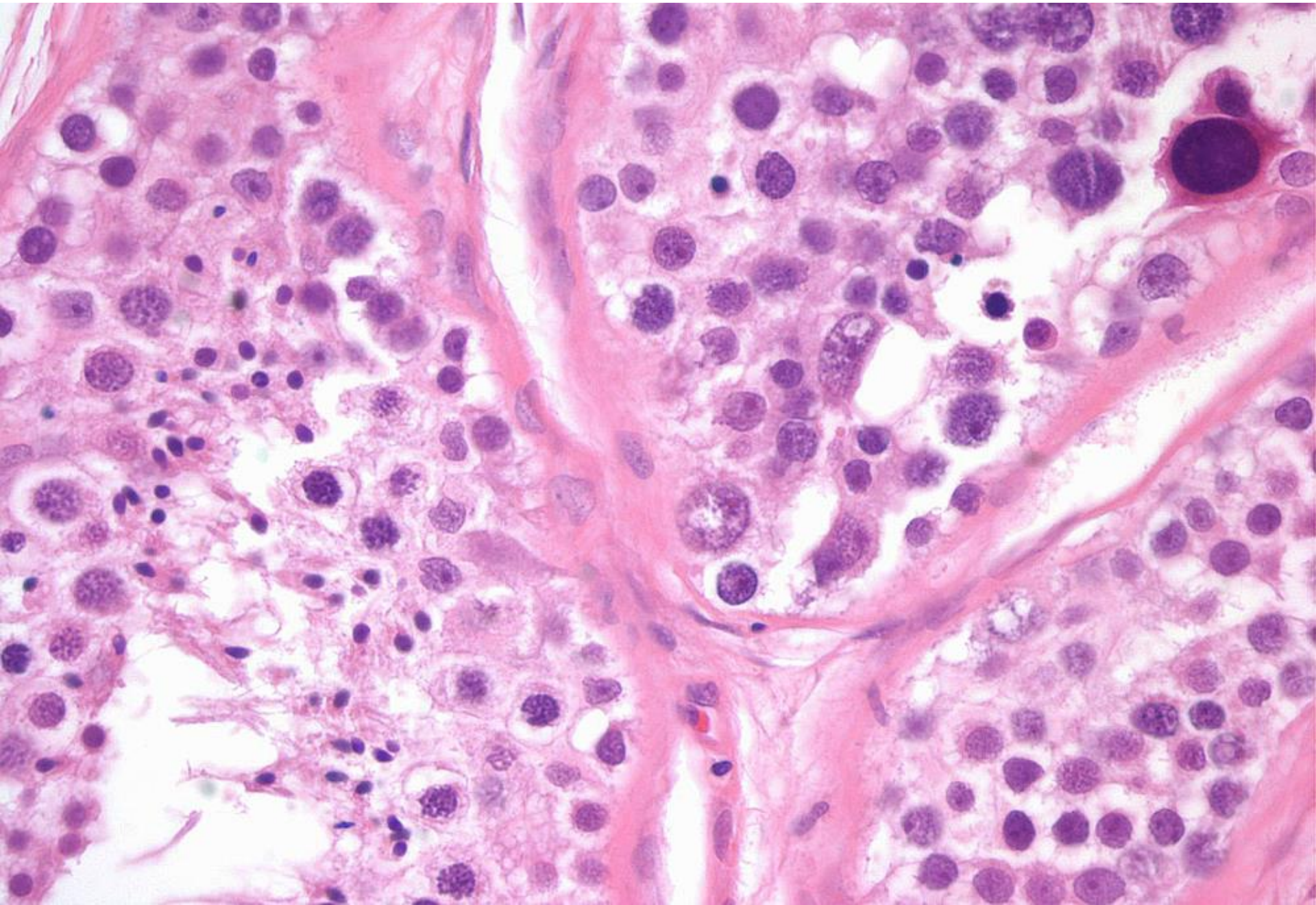
Spermatocytic Tumor



Intratubular Spermatocytic Tumor



Spermatocytic Tumor: Intratubular Growth



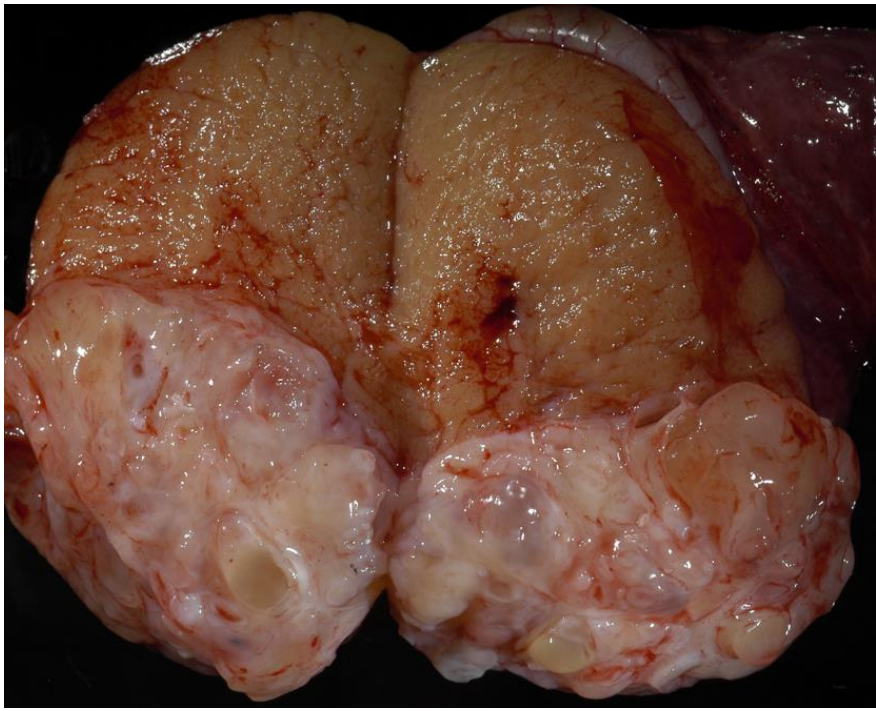
Spermatocytic Tumor

- It metastasizes only exceedingly rarely (2 cases)
- Treatment: orchiectomy without adjuvant treatment
- Sarcomatous transformation is a rare complication: ~50% of patients develop metastatic disease and die of it
- Differential diagnosis:
  - Classic seminoma
  - Embryonal carcinoma
  - Lymphoma

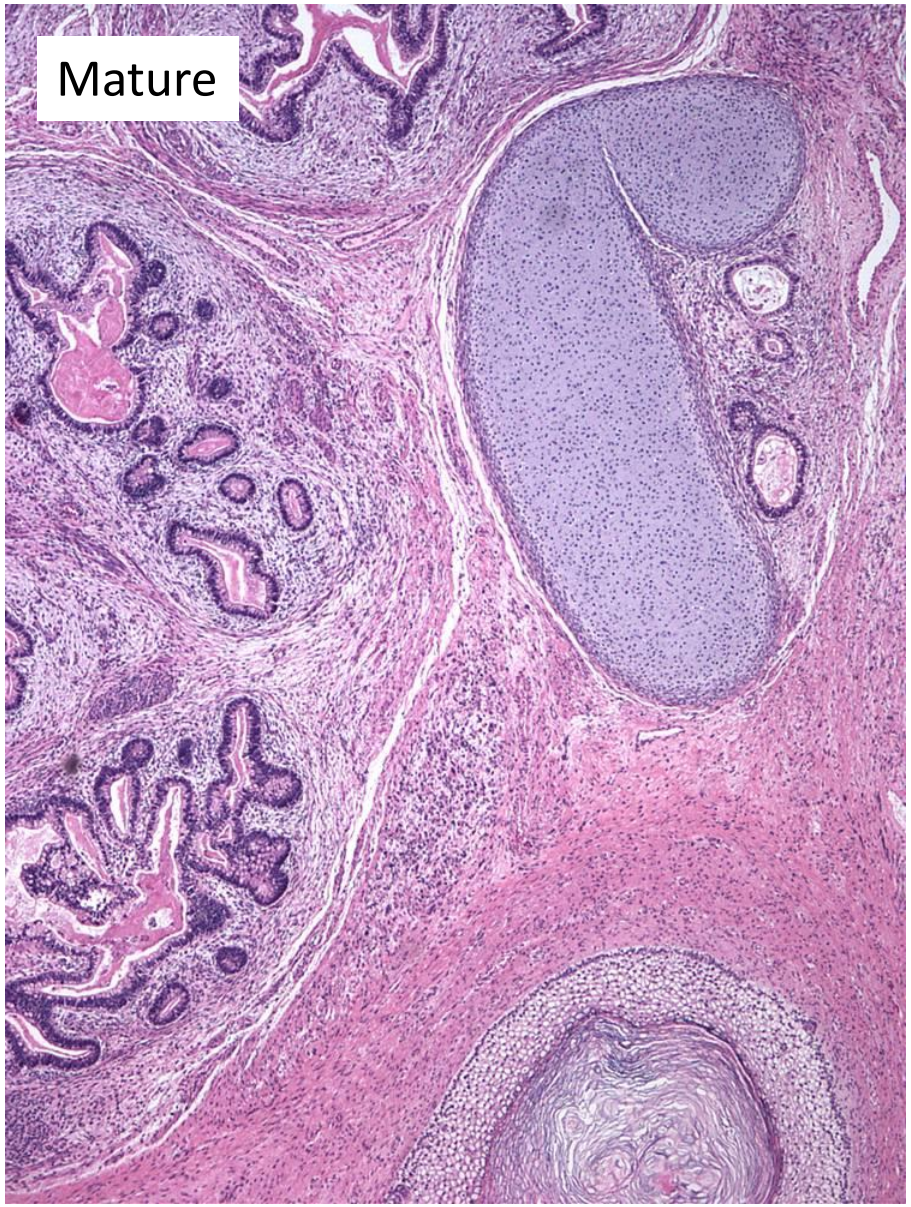
	PLAP	OCT3/4	AE1/3	CD30	CD117	SALL4	CD45
Spermatocytic Tumor	–	–	–	–	+	+	–

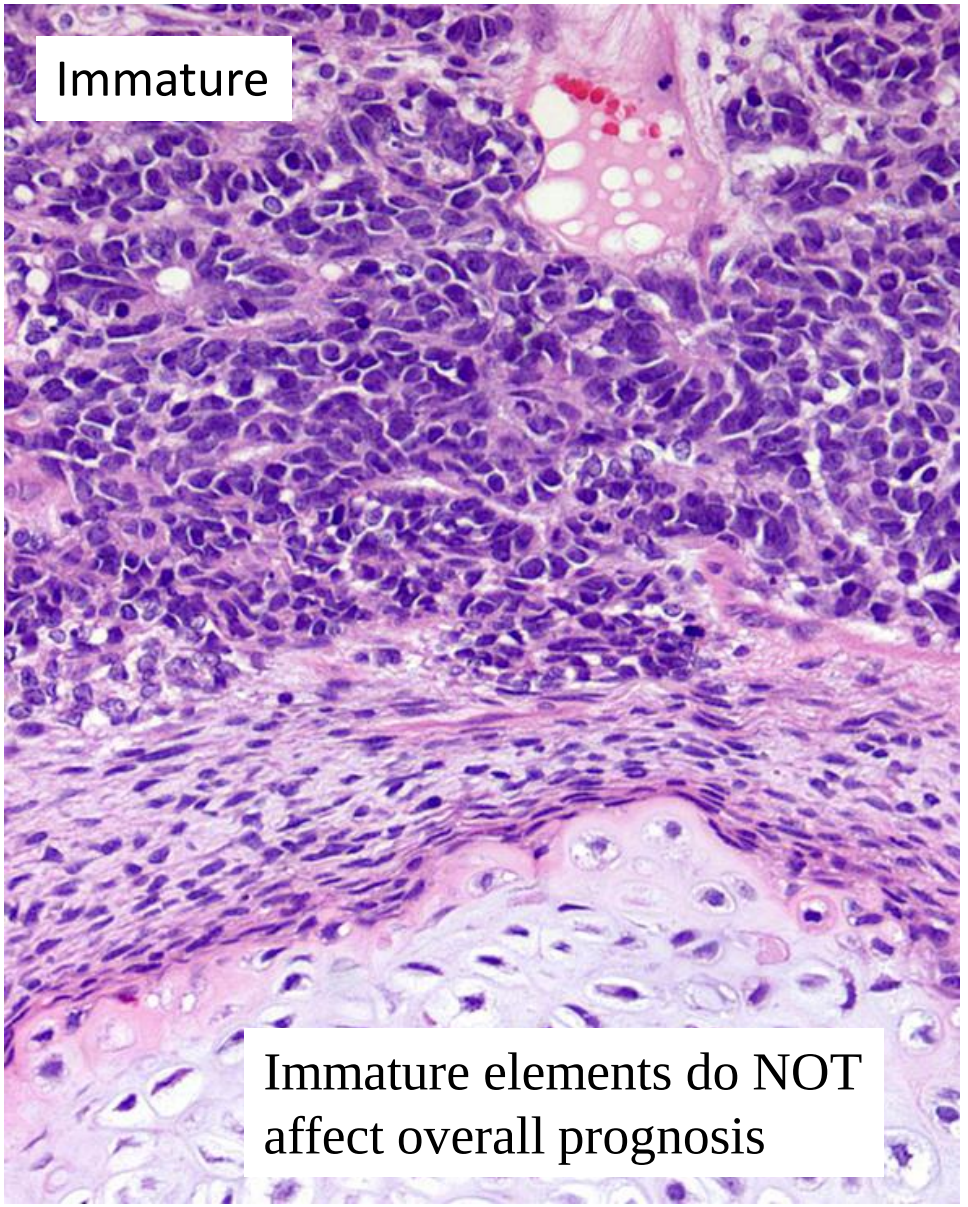
Teratoma: Post-Pubertal Type

- Most are mixed with other GCT elements; 4% are pure
- Capable of metastasis despite lack of malignant appearance
- May displays differentiation toward mature or immature somatic tissue
- Even patients with pure teratoma may develop metastases containing other GCT types

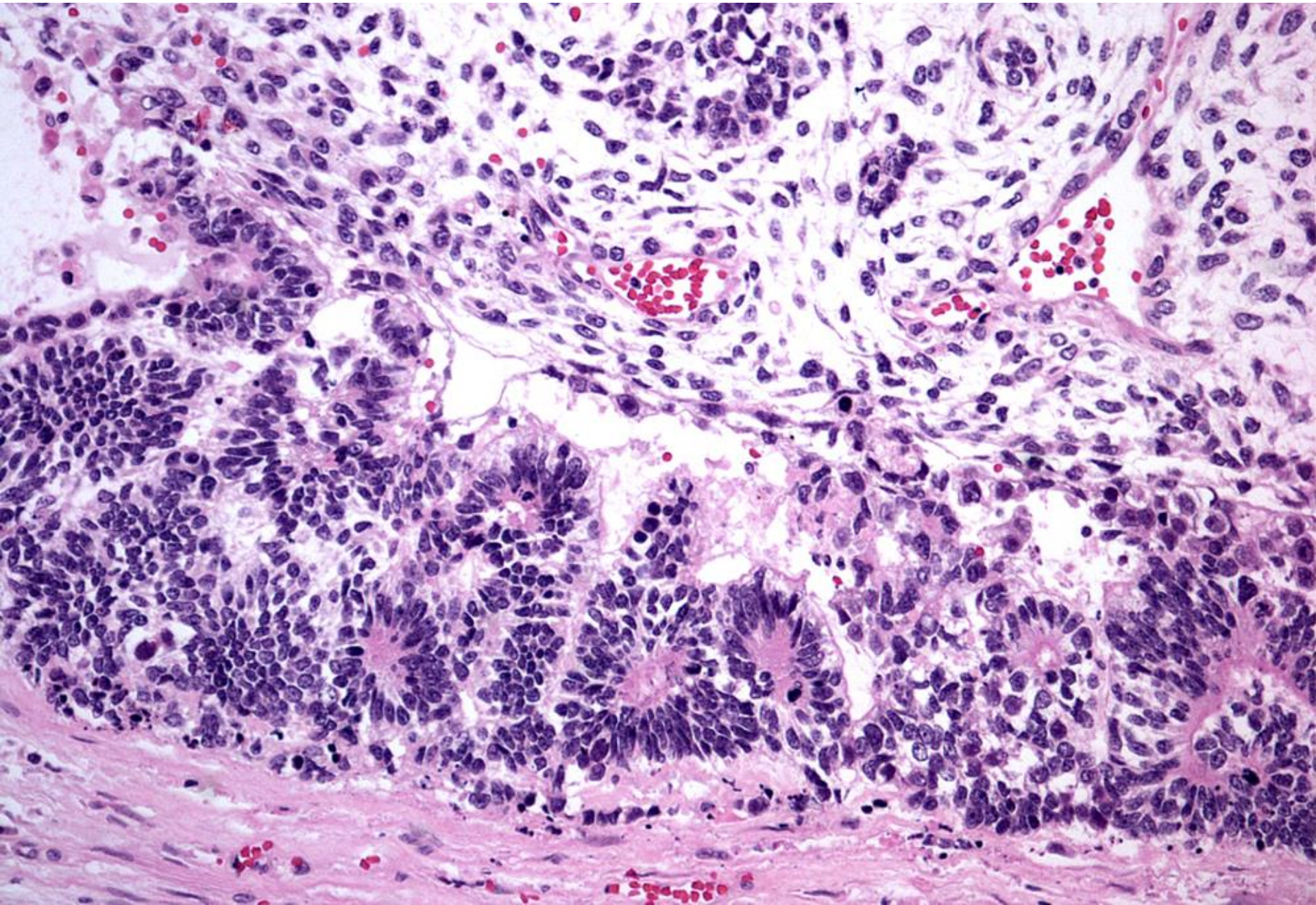


Teratoma


Mature


Immature
Immature elements do NOT affect overall prognosis

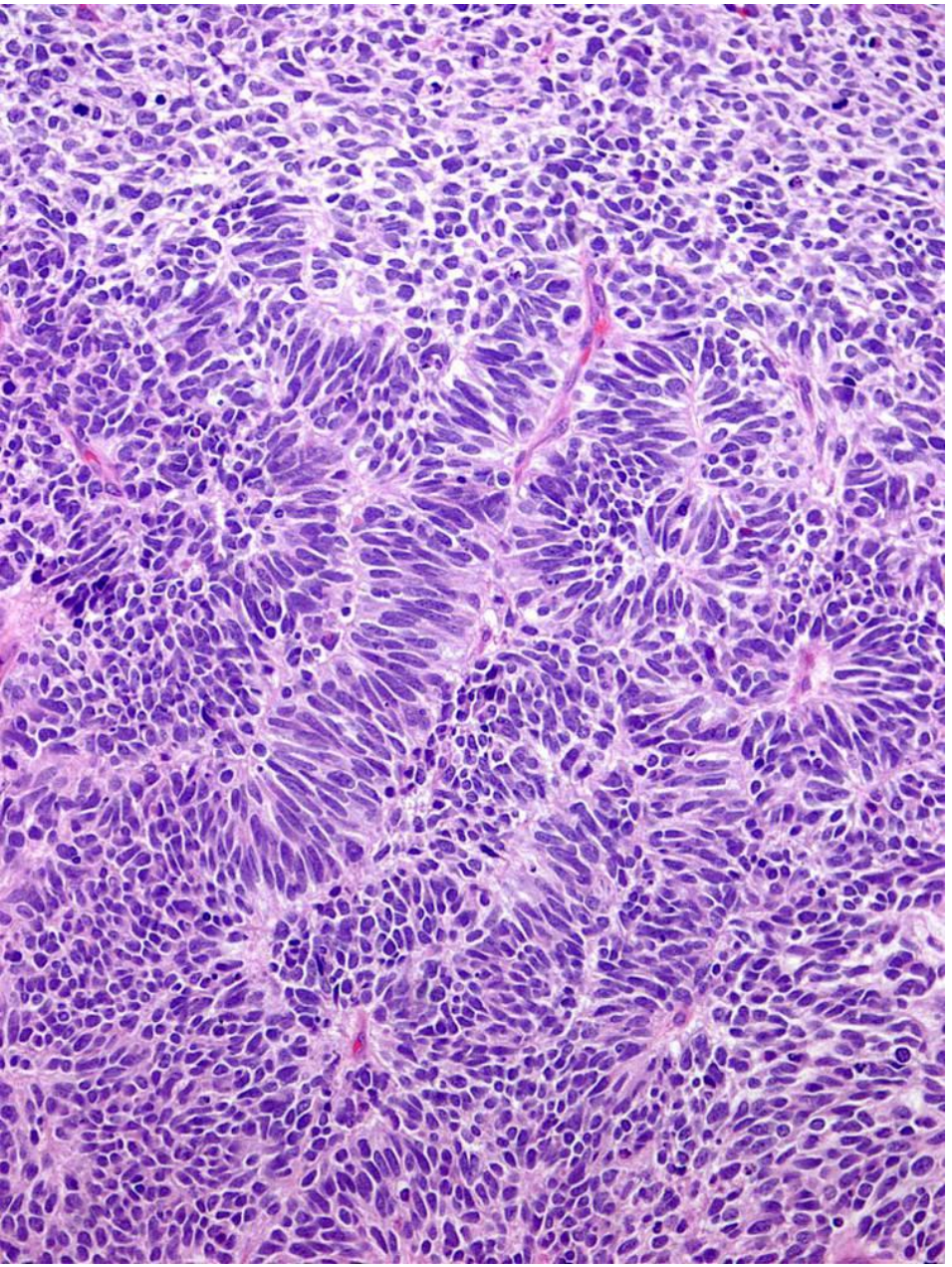
Teratoma: immature elements

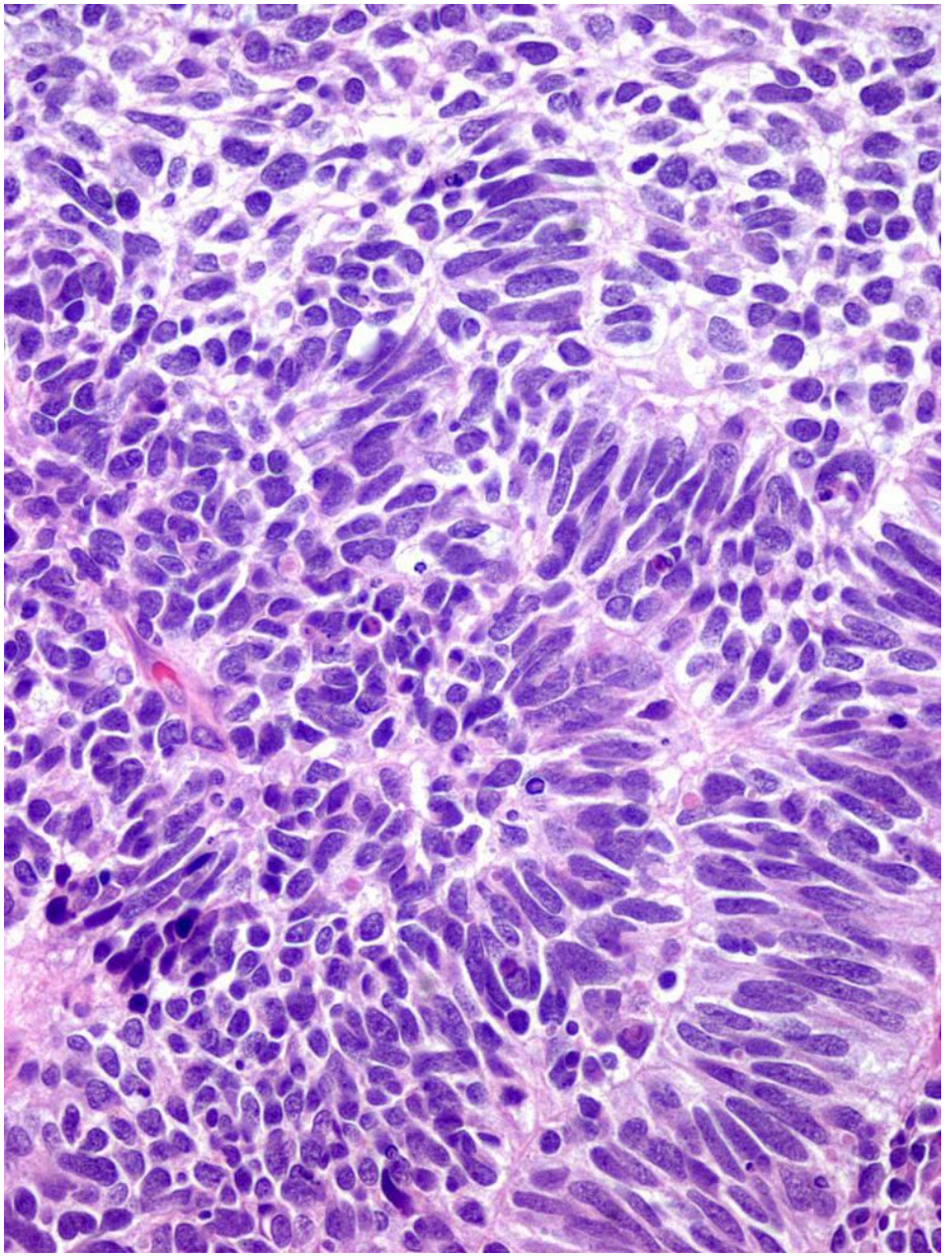


Teratoma: Malignant Transformation

- Carcinomatous transformation requires an overtly invasive growth pattern
- Somatic-type malignancy requires overgrowth of malignant-appearing mesenchymal or embryonic tissues to exclude other elements (at least a 4X low power field)
- Overgrowth of primitive neuroectodermal tissue should be recognized as primitive neuroectodermal tumor (PNET):
  - Limited to testis: most men are cured of the disease
  - In metastases: surgical resection is mainstay of therapy; outcome is generally poor

Teratoma: overgrowth of PNET





Teratoma: Prepubertal Type

- GCT usually seen in pre-pubertal testis
- Composed of elements resembling somatic tissues derived from one of more germinal layers
- NOT associated with:
  - GCNIS or atypia
  - Dysgenetic changes
  - Scarring
  - Chr. 12p amplification
- Conservative treatment

Changes in Trophoblastic Tumor

WHO 2004

Trophoblastic Tumors

- Choriocarcinoma
- Trophoblastic neoplasms other than choriocarcinoma
  - Monophasic choriocarcinoma
  - Placental site trophoblastic tumor

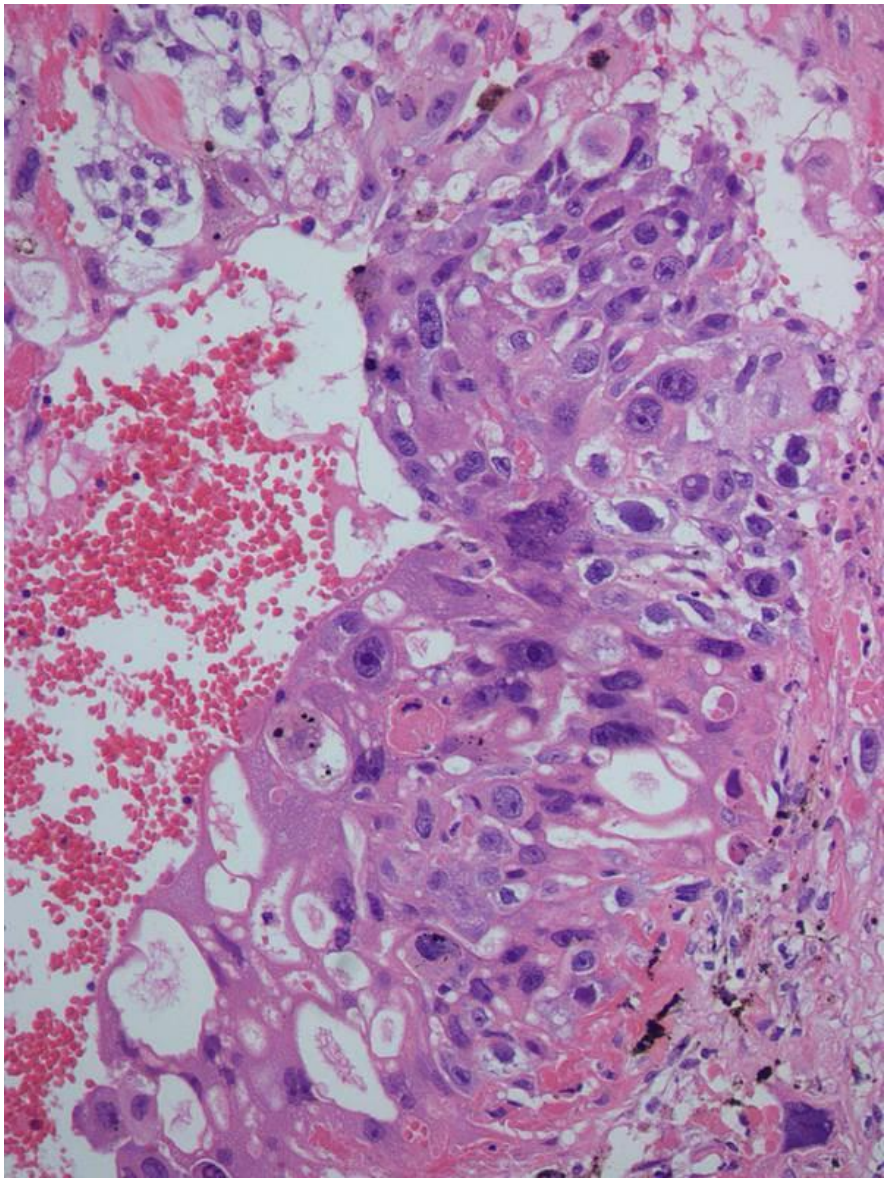
WHO 2016

Trophoblastic Tumors

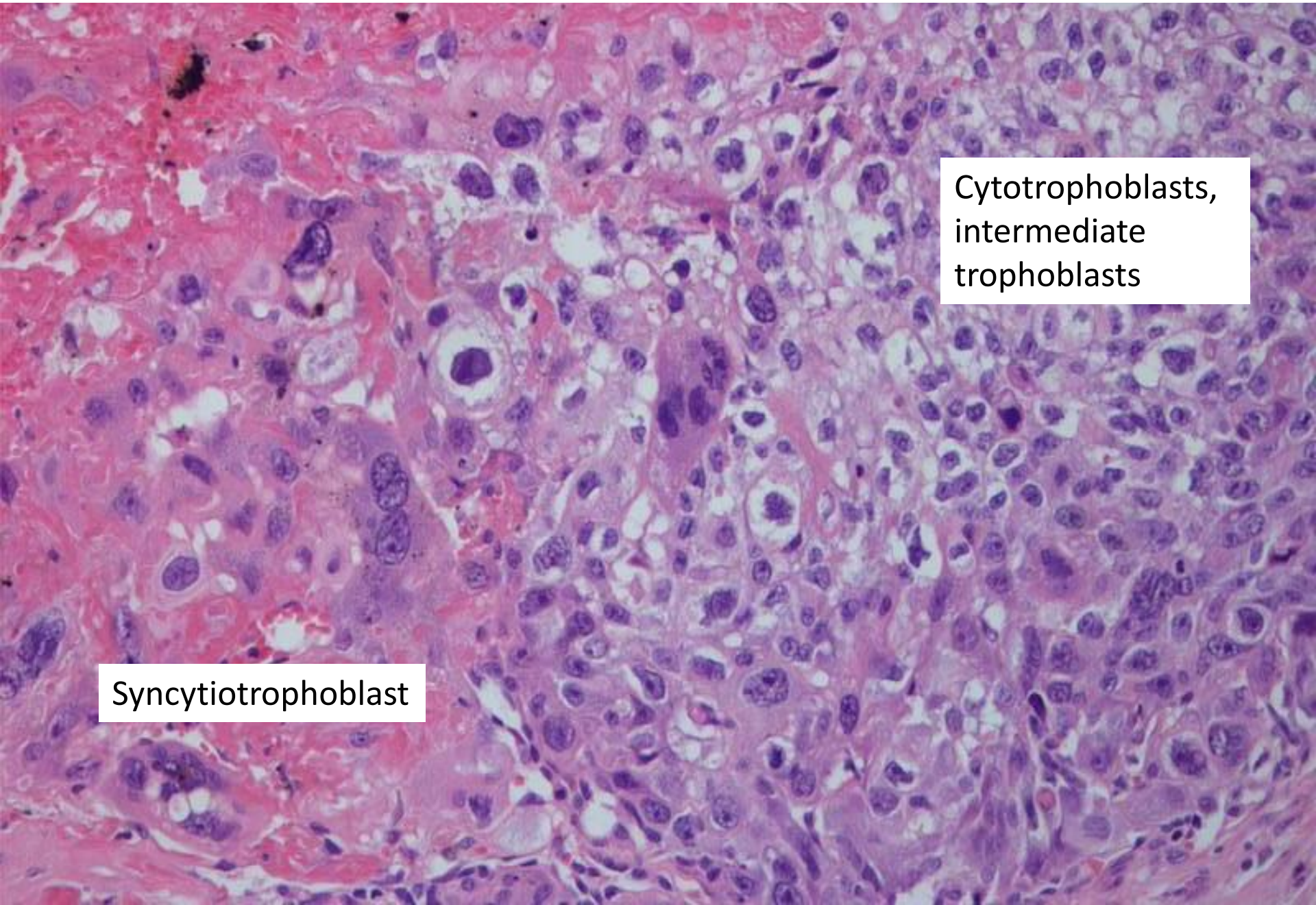
- Choriocarcinoma
  - Monophasic choriocarcinoma
- Non-choriocarcinomatous trophoblastic tumors
  - Placental site trophoblastic tumor (PSTT)
  - Epithelioid trophoblastic tumor (ETT)
  - **Cystic trophoblastic tumor**

Choriocarcinoma

- Pure is quite rare (<1%); uncommon in mixed GCT (15%)
- Young patients (mean age 25-30 years)
- Symptoms related to metastatic disease (lungs, brain, GI tract)
- Serum HCG is typically elevated (> 55,000 IU/L)
- Prognosis is worse than for other GCT



Choriocarcinoma



Choriocarcinoma: Differential Diagnosis

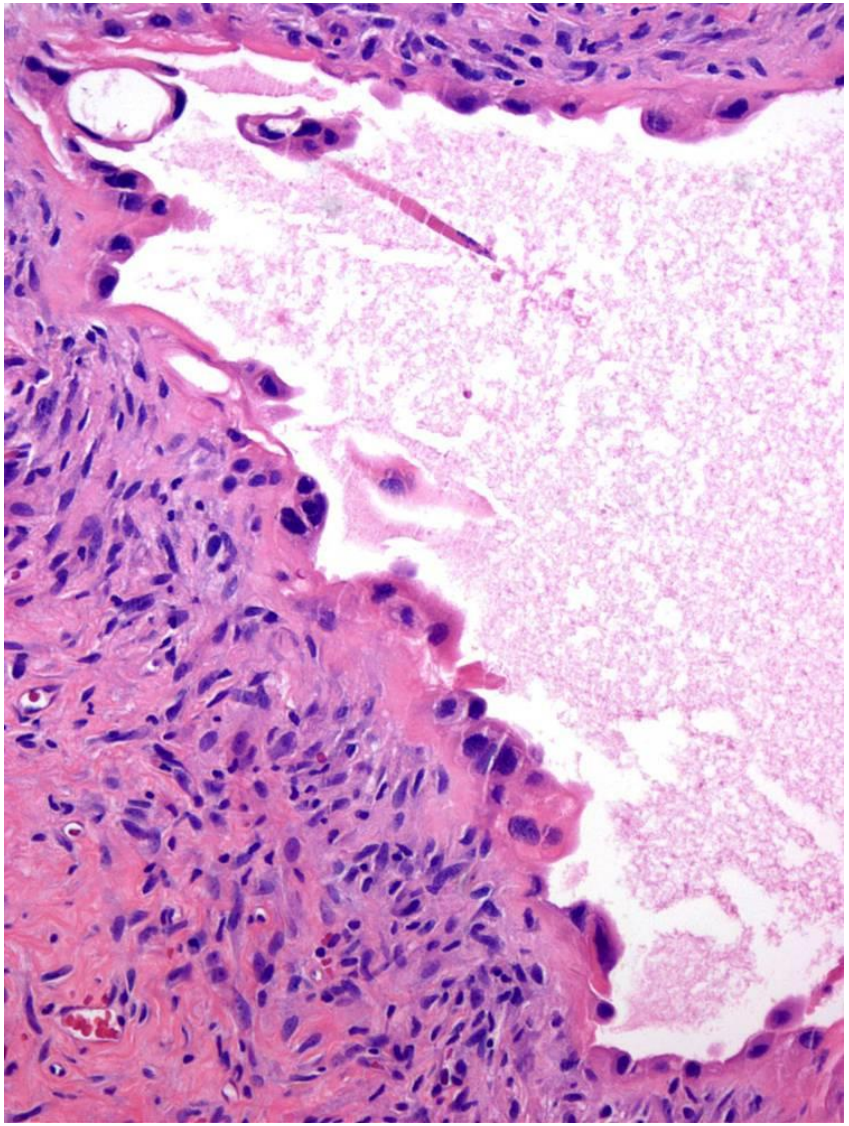
- Other GCT may contain trophoblast cells, but they are scattered individual cells and lack biphasic pattern
- EC may show degenerate cells with a poorly defined syncytiotrophoblastic component: lack of hemorrhage, hCG+ and OCT3/4+ distinguish EC from chorio
- Monophasic chorio should be distinguished from seminoma and solid pattern YST:
  - diffuse hCG +, AFP -, OCT3/4 –
  - greater pleomorphism than in seminoma

	PLAP	OCT3/4	CK	CD30	Inhibin	GATA3	EMA	hCG	AFP
Chorio	+/-	_	+	_	+	+	+/-	+	_

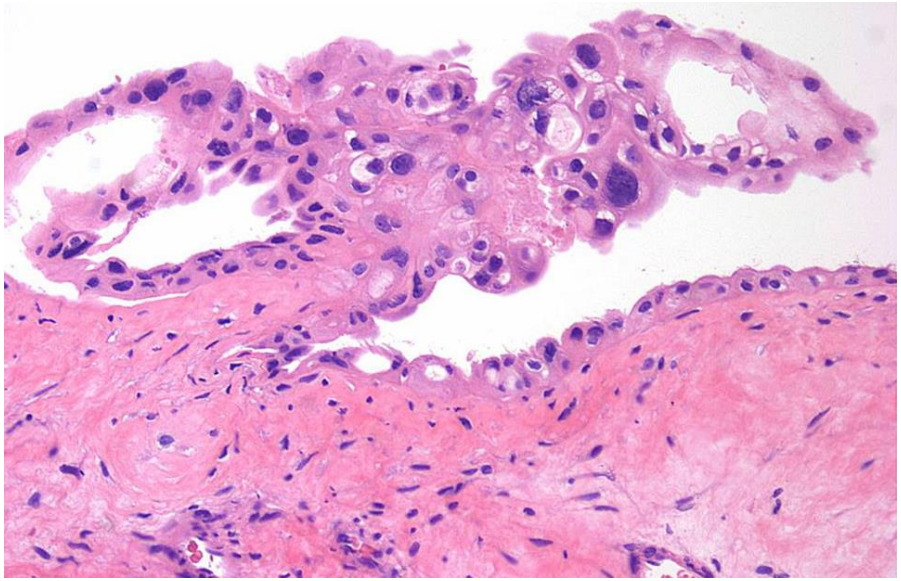
Non-choriocarcinomatous trophoblastic tumors:

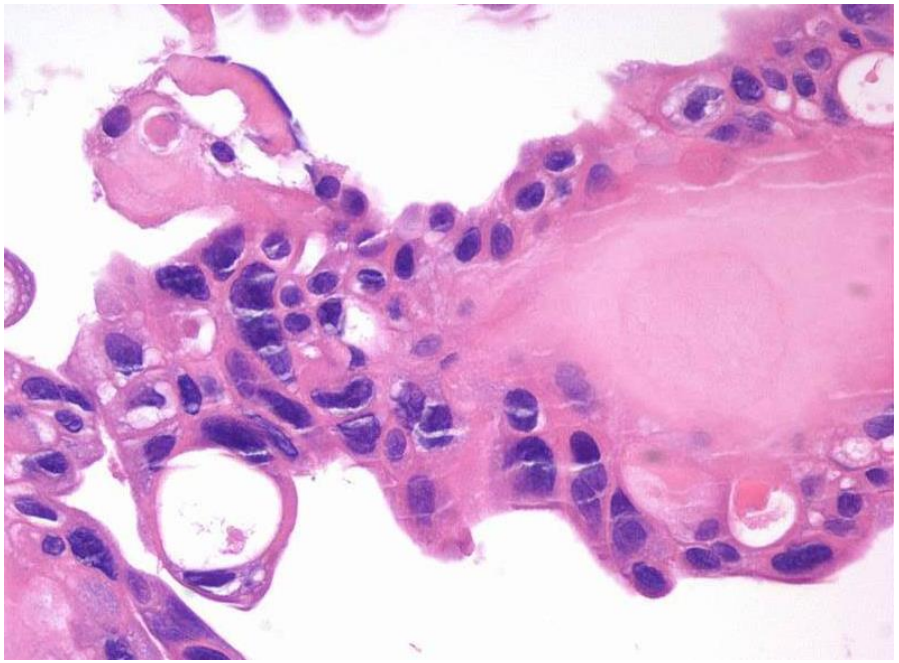
Cystic Trophoblastic Tumors

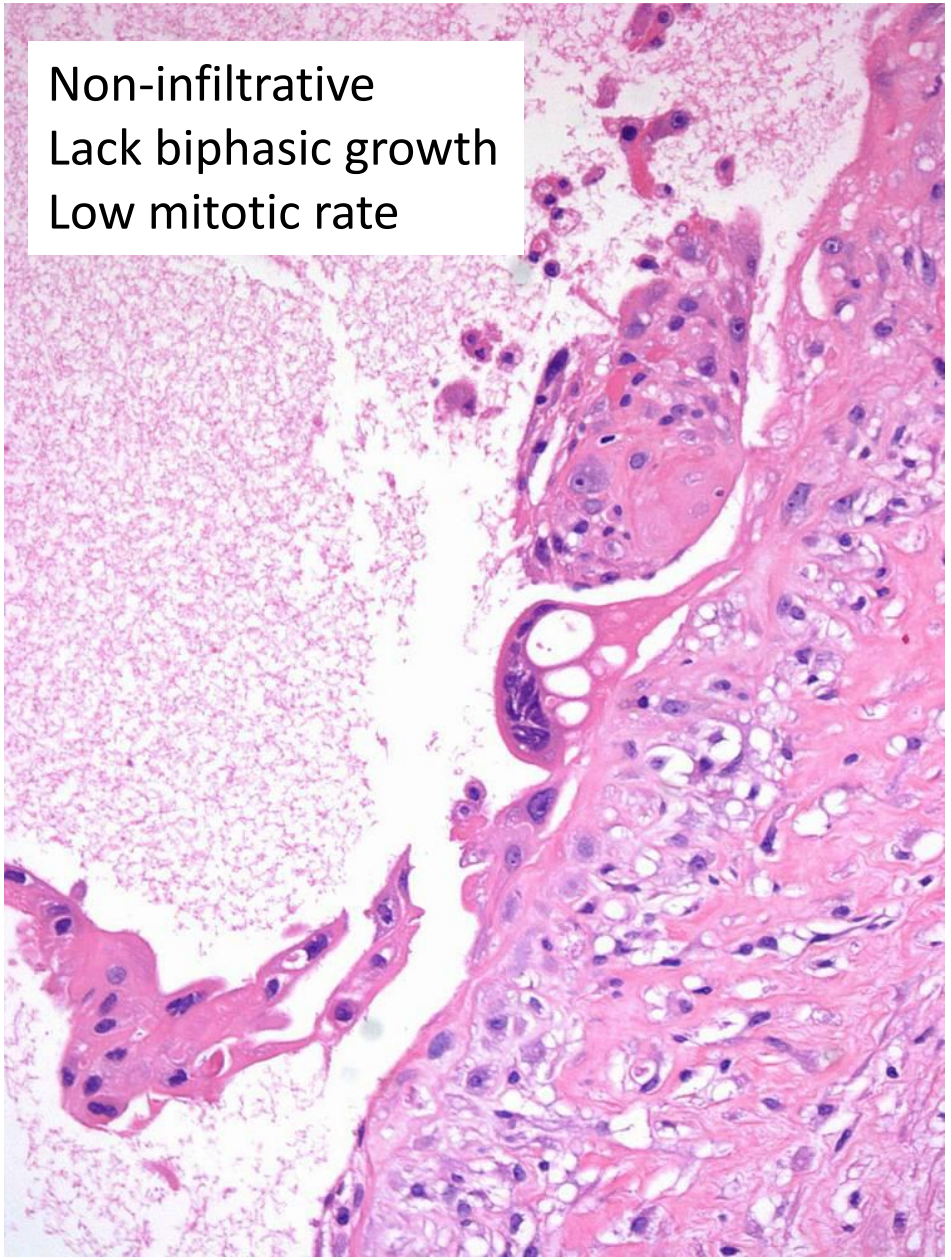
- May evolve from choriocarcinoma with regression of highly proliferative elements
- Occur mostly in metastatic sites after chemotherapy
- Rare *de novo* tumors in testis
- Normal/slightly elevated hCG
- Clinical significance similar to residual teratoma
- Treat as post-chemo teratoma (surgical resection; no additional chemo)



Cystic Trophoblastic Tumors



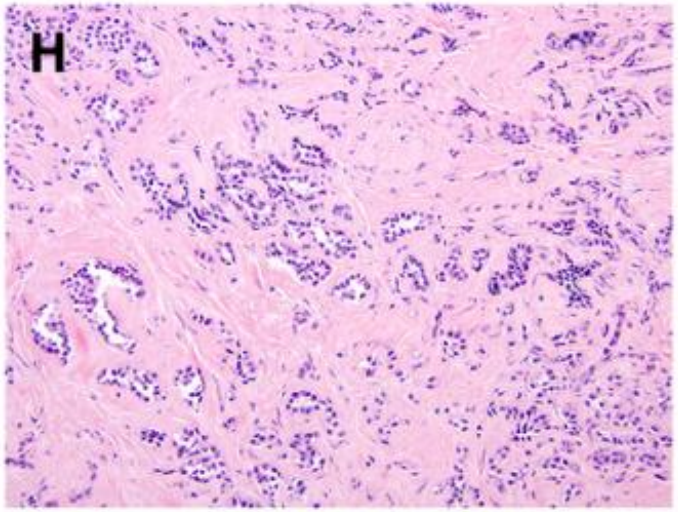




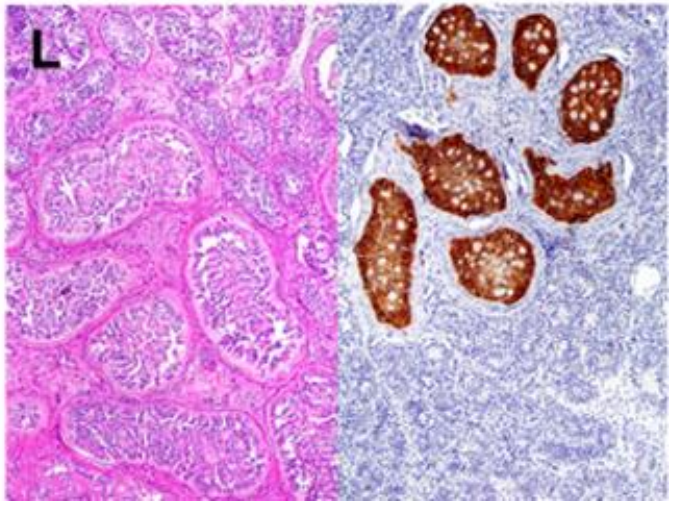
Non-infiltrative
Lack biphasic growth
Low mitotic rate

Changes in Sex Cord-Stromal Tumor

- Sclerosing Sertoli cell tumor
  - Variant of Sertoli cell tumor NOS
  - Similar *CTNNB1* gene mutation and nuclear ß-catenin

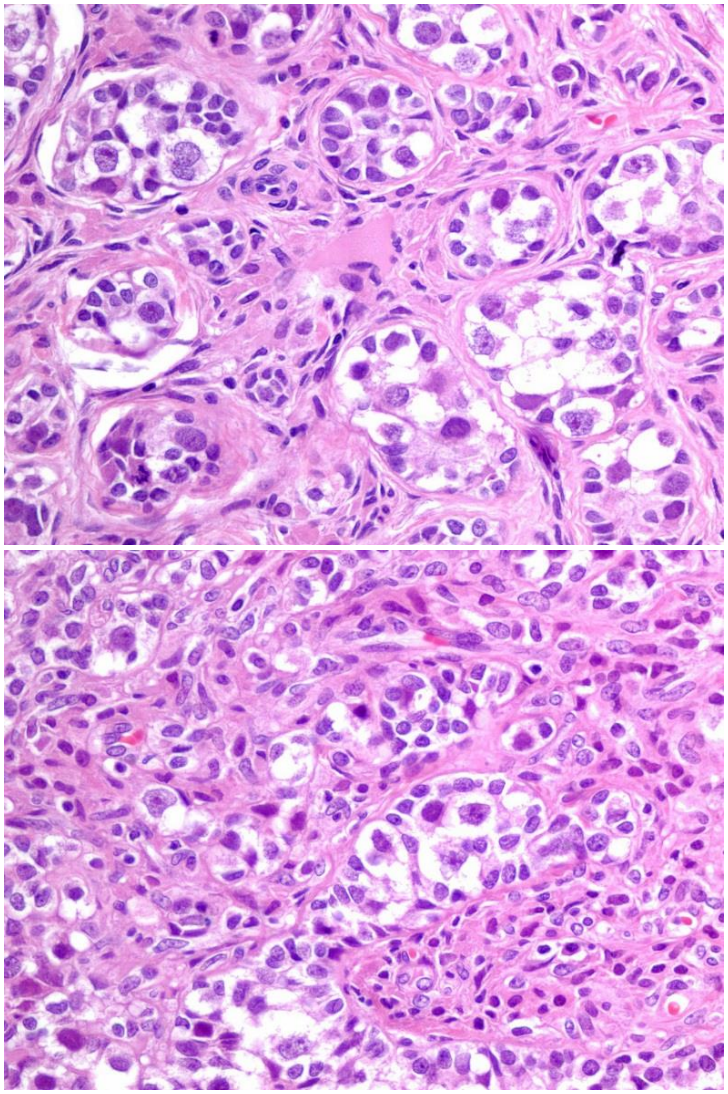


- Intratubular large cell hyalinizing Sertoli cell tumor
  - Distinct entity associated with Peutz-Jeghers syndrome
  - *STK11* gene mutation



Changes in Mixed Germ Cell Sex Cord-Stromal Tumors

- Gonadoblastoma (only entity)
  - Germ cells, similar to GCNIS
  - Sex cord cells resembling immature granulosa cells
- Rare, but seen in 50% of sex development disorders
- 70% diagnosed in neonatal period due to ambiguous genitalia
- May occur in dysgenetic testis: 40% bilateral
- If untreated, progresses to invasive GCT

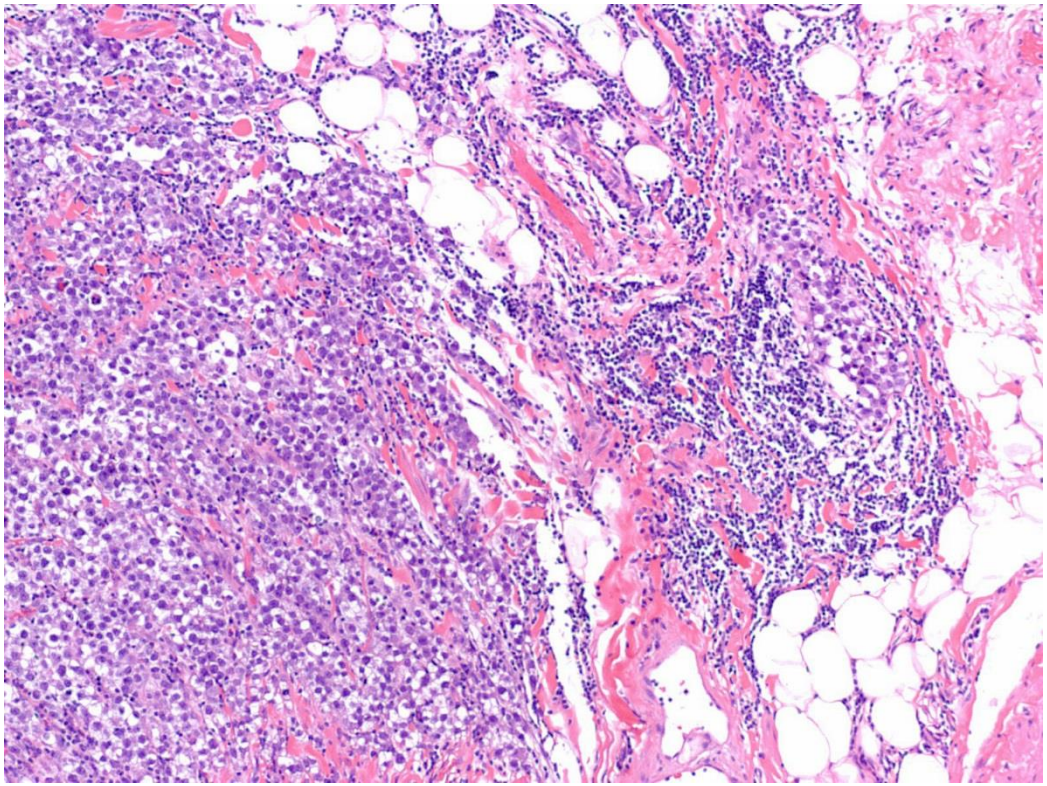


8th AJCC/TNM Staging of Testicular Tumors

- In **seminoma**, T1 is subclassified to T1a and T1b according to size, using a 3 cm cutoff
- Size is independent predictor of disease recurrence

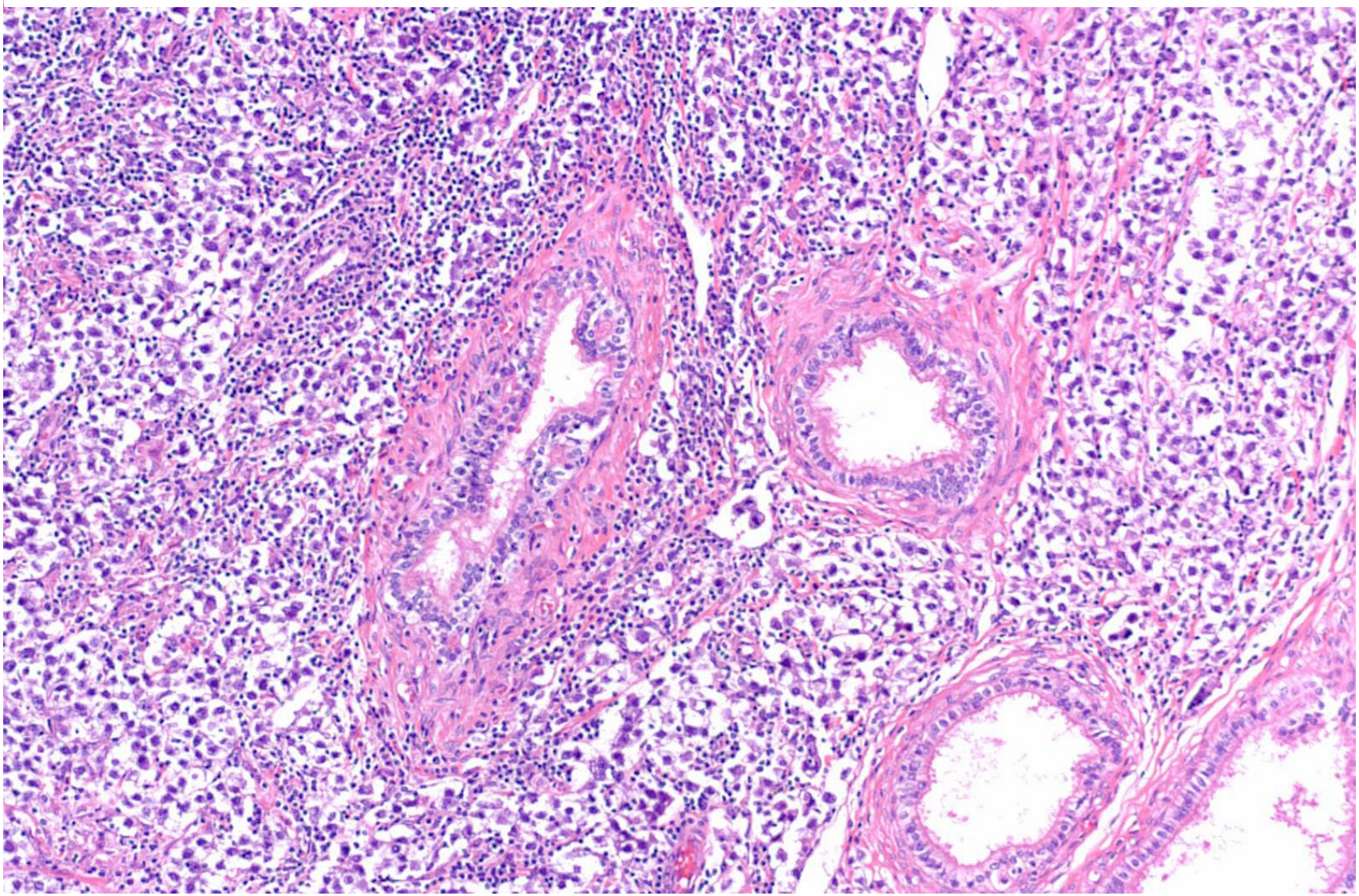
8th AJCC/TNM Staging of Testicular Tumors

- Hilar soft tissue invasion is T2



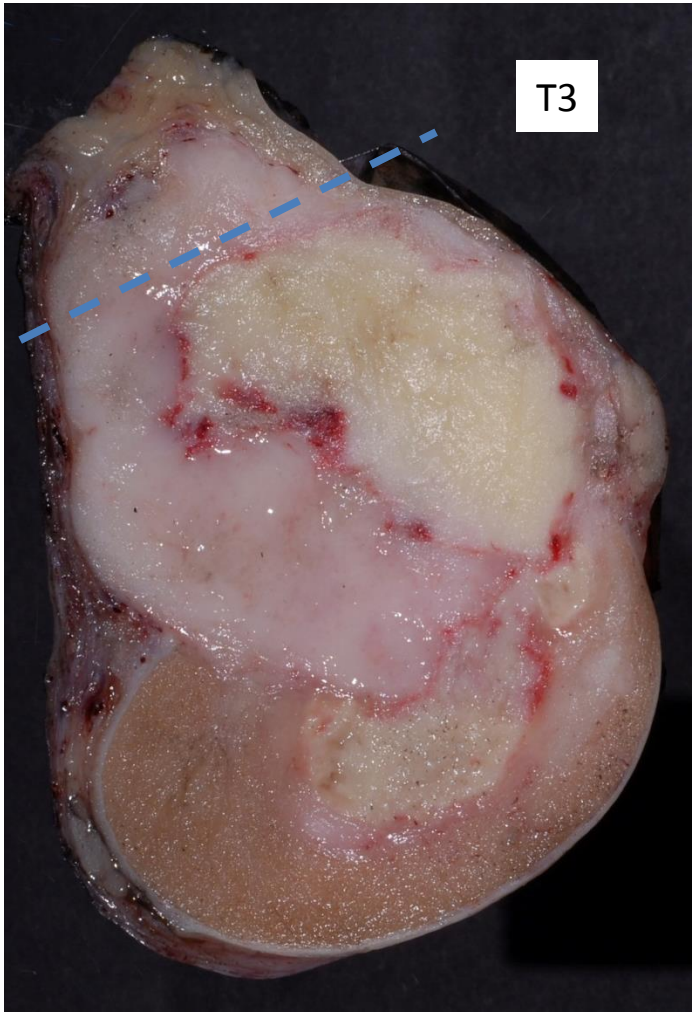
8th AJCC/TNM Staging of Testicular Tumors

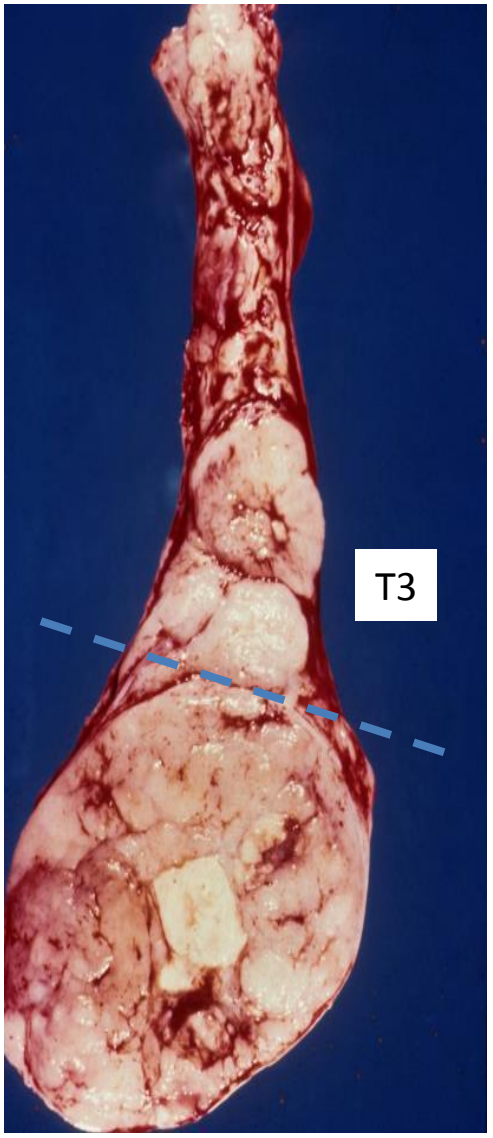
- Epididymal invasion is T2 rather than T1



8th AJCC/TNM Staging: Spermatic Cord Invasion

- Vascular invasion in spermatic cord without stromal invasion: T2
- Cord involvement continuous with primary tumor: T3
- Cord involvement discontinuous with primary tumor: M1





Take Home Message

- Updated pathogenetic model for GCTs
- Restructuring of classification
  - GCNIS related
  - GCNIS unrelated
- New entities
- Changes in testicular tumor staging

Thank you!

Cleveland Clinic

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