Testicular Tumors

Germ Cell Tumors

3 main subtypes depending on age and if they are derived from germ cell neoplasia in situ (GCNIS).

Most common: Germ cell tumors derived from GCNIS (Post-pubertal type) (Type 2, below)**, which is often sub-grouped into seminoma and non-seminoma germ cell tumors**
Although only 1% of all male cancers, they are **the most common cancers among young men between puberty and 40s.**

Risk factors: Family history, **cryptorchidism,** subfertility, pesticides, marijuana, microlithiasis.

Although can be aggressive tumors, with current treatments can **often be cured as very responsive to chemoradiation.**

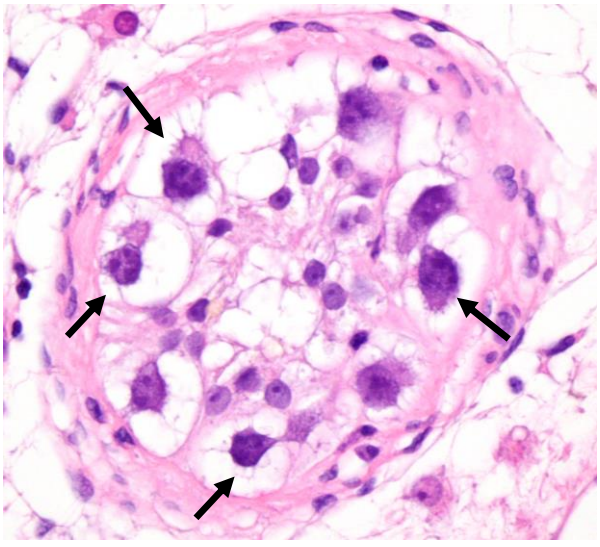
Type	Tumors	Age	Derived from GCNIS	Genotype	Behavior
1	Teratoma (prepubertal) Yolk sac tumor (prepubertal) Dermoid cyst	Usually < 6 yrs	No	Diploid or aneuploid. No i12p gains	Very good. Mostly benign.
2	Seminoma Embryonal carcinoma Choriocarcinoma Yolk sac tumor Mixed Germ cell tumor	Post-pubertal Usually 20s-30s	**Yes**	Aneuploid Frequent gains and losses. Overexpression of **isochrome 12p**	Malignant, but responsive to therapy
3	Spermatocytic Tumor	Usually > 50 yrs	No	Aneuploid No i12p gains	Excellent

Germ Cell Neoplasia In situ ("GCNIS")

Proliferation of atypical germ cells *within* seminiferous tubules
Large, angulated nuclei with coarse chromatin
(resemble seminoma cells)
Often located at base of tubules with prominent halos
Often present in nearby parenchyma adjacent to most associated germ cell tumors.
Often absent spermatogenesis.

Identical IHC profile to seminoma: OCT3/4, cKit (+)

Precursor lesion: ~50% progresses to overt Germ Cell Tumor within 5yrs.



Intermediate stages between GCNIS and invasion:
Intratubular seminoma→ complete filling of expanded seminiferous tubule by neoplastic cells with obliteration of normal components.

Intratubular non-seminoma→ Same concept, but almost exclusively embryonal carcinoma. Thought to be reprogrammed GCNIS cells.

Seminoma

Think: Clear/White color

Most common germ cell tumor (~50%).
Present with mass. Usually unilateral.
Grossly solid, fleshy, lobulated, cream-colored.

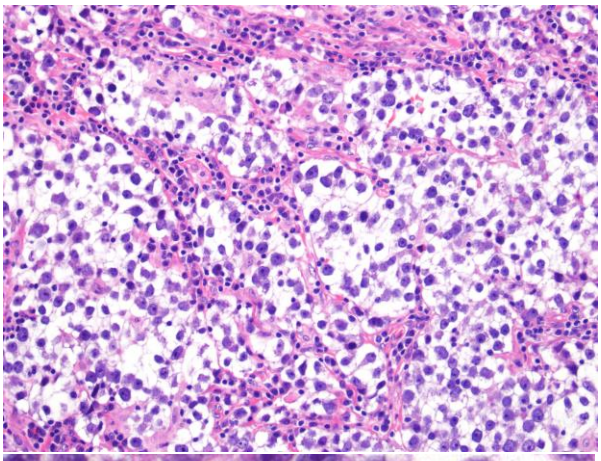
Large polygonal cells with clear to eosinophilic cytoplasm (full of glycogen), distinct cell membranes, vesicular chromatin, and prominent nucleoli
Fibrous septae and **nested architecture**
Lymphocytic infiltrate; Sometimes granulomas.
GCNIS usually in residual tubules. Rare syncytiotrophoblasts.

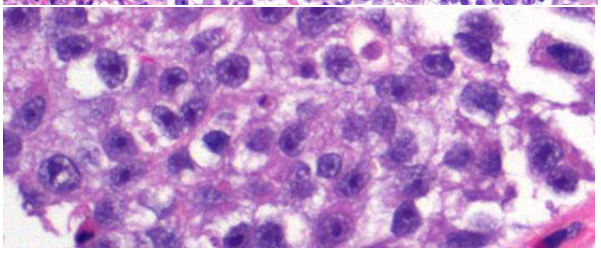
IHC: (+) OCT3/4, CD117, D2-40, SALL4

Elevated serum LDH, rarely hCG.
First site of metastases often retroperitoneal lymph nodes.

Molecular: majority have **isochrome 12p**; ckit mutations in many.

Prognosis: **Good if treated.**





Embryonal Carcinoma

Think: Purple color

Second-most common testicular GCT.
Usually part of a mixed GCT

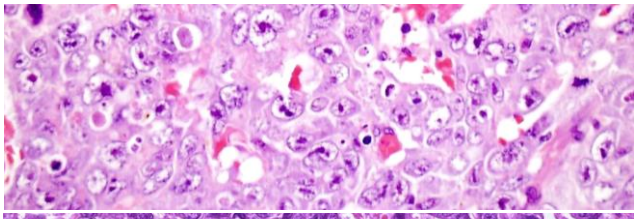
Rudimentary epithelial differentiation

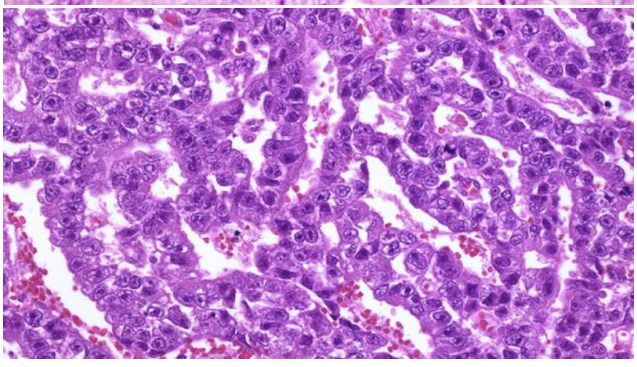
Large, crowded, "Primitive" pleomorphic cells
Vesicular nuclei with prominent nucleoli.
Coarse, basophilic chromatin. **Amphophilic cytoplasm.**
Variable architecture (nests, sheets, papillae, glands)
Prominent mitoses and apoptotic bodies.

IHC: (+)CD30, OCT3/4, AE1/AE3, SALL4

Molecular: Isochrome 12p amplification

Aggressive, but often responds to chemotherapy





Choriocarcinoma

Think: Red color

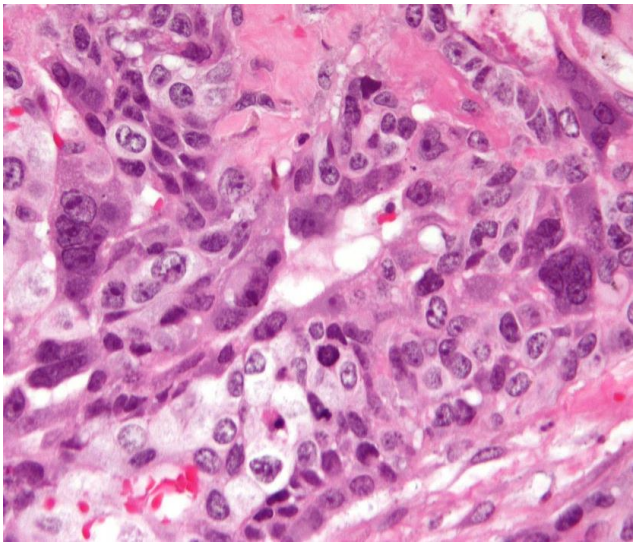
Usually part of a mixed GCT.

Malignant cytotrophoblasts and trophoblasts (mononuclear with light cytoplasm**)** ***and*** **syncytiotrophoblasts (multinucleated** with deeply eosinophilic cytoplasm**). Abundant Hemorrhage**

IHC: (+) hCG. Syncytiotrophoblasts: (+) inhibin, glypican-3.
Cytotrophoblasts: (+) SALL4, p63, GATA3

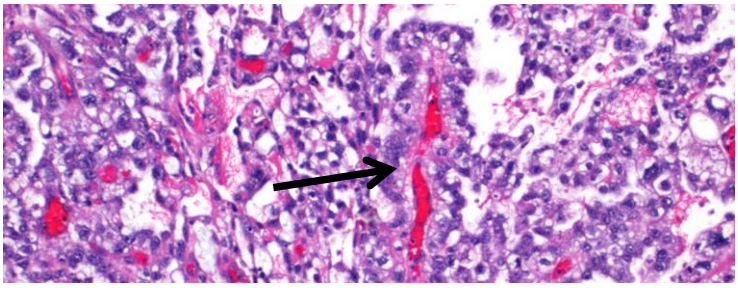
Very elevated Serum hCG → (similar to LH and TSH)→ gynecomastia, thyrotoxicosis

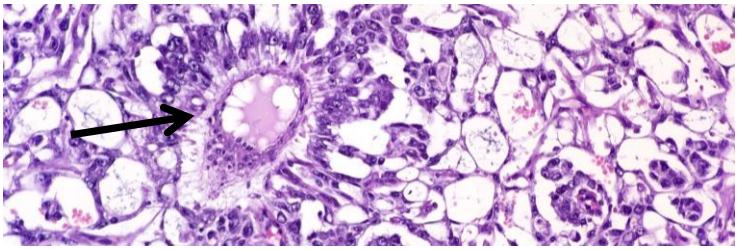
Most aggressive GCT. Frequent hemorrhagic metastases.
Less responsive to treatment.

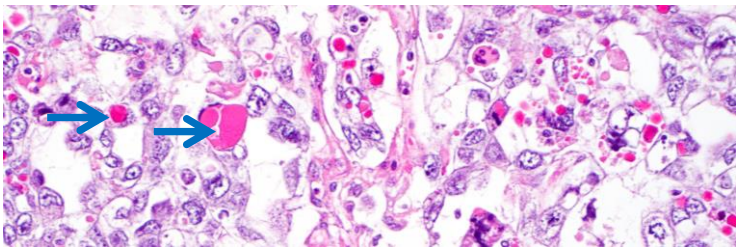


Yolk Sac Tumor, Postpubertal-type

Think: Pink color







aka: “Endodermal Sinus Tumor” or “YST”

Almost always a component of mixed GCT

Many patterns/architecture (often combined)
- Most common = reticular/microcystic (Honeycomb meshwork)
- Can also be solid, papillary, glandular, etc…

Often hypocellular myxoid areas

Schiller-Duval Bodies (endodermal sinus)(→)

Refractile eosinophilic **hyaline globules** (→)
Band-like intercellular basement membrane material

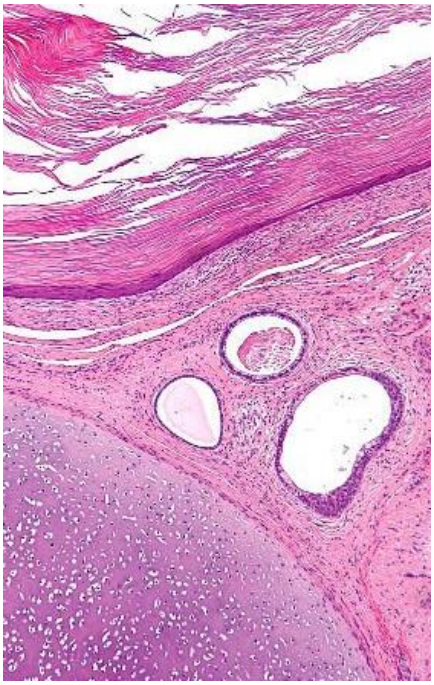
Can have “hepatoid” areas resembling liver that stains with liver markers.

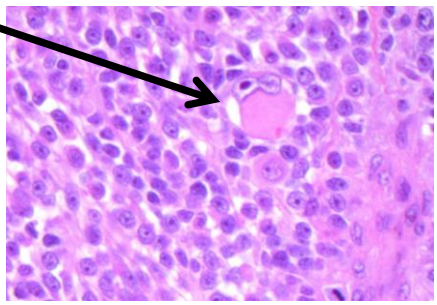
IHC: (+)AFP, Glypican-3, SALL4, AE1/AE3,

Elevated Serum AFP

Post-chemo can get sarcomatoid YST

Teratoma, Postpubertal-type





Composed of tissues from one or more germinal layers.
May be composed of **differentiated mature tissue *or* immature, embryonic-type tissue**. Often part of a mixed GCT.

In contrast to ovary, pretty much all teratomas in postpubertal testis are *malignant*!

Can see **virtually all tissue types** including epithelial and mesenchymal.
Often multiple cysts lined by glandular or squamous epithelium.
Frequent immature neuroectodermal structures.

IHC: Differentiated elements express profile of that tissue type.

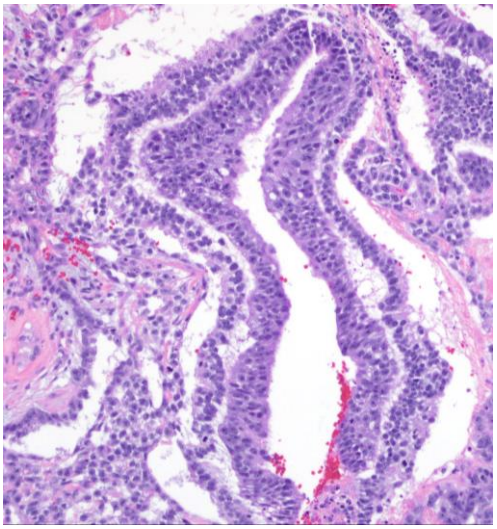
Often areas of cytologic atypia, including primitive mitotically active stroma cuffing glands.

If a dysplastic component forms a nodule that is larger than a 4X field (5 mm)→ **somatic-type malignancy** arising in a teratoma. Usually a sarcoma, most commonly rhabdomyosarcoma.

Most common component in a treated GCT.

Rare situation where can be benign teratoma in an adult: Dermoid cysts, or, organoid morphology with prominent components of ciliated epithelium and smooth muscle and no GCNIS, isochrome 12p, or testicular scarring.

Mixed Germ Cell Tumor



Malignant tumors with more than one germ cell tumor component. Clinically regarded as "non-seminoma" (even if seminoma present).

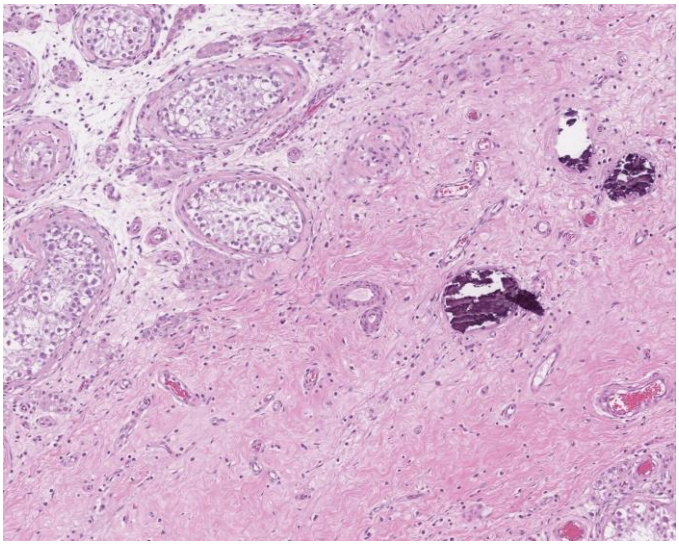
Majority of all non-seminomatous GCT are mixed.
Must report approximate % of each component.

Note: Syncytiotrophoblasts ≠ choriocarcinoma (can see in other tumors, like seminoma)

Special subtypes:
Polyembryoma→ combination of embryonal carcinoma and YST resembling an embryo

Diffuse embryoma→ orderly combination of embryonal carcinoma and YST in parallel flat layers (pictured→).

Regressed Germ Cell Tumors



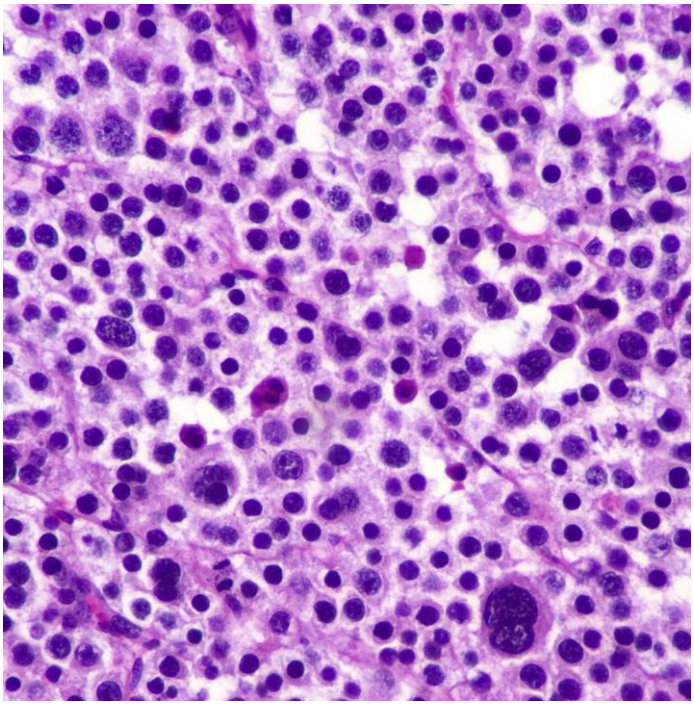
Germ cell tumors that have **undergone either partial or complete regression** ("burnt-out"), leaving behind a **well-delineated nodular focus of scaring fibrosis in the testis.**

Can present with metastatic disease, but primary has completely regressed. Can be seminoma or Non-seminoma.

Scar findings: **Well-demarcated scar, Coarse calcifications within tubules**, chronic inflammation, hyalinized tubular ghosts.

Nearby findings: **GCNIS**, tubular atrophy, microliths

Spermatocytic tumor



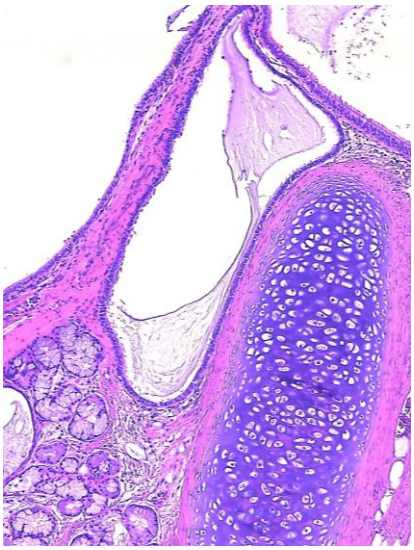
Relatively rare. Generally **excellent prognosis**.
***NOT* associated with GCNIS** or cryptorchidism
***NOT* a component of mixed GCT**
Usually occurs in **OLD**er men (>50yo)

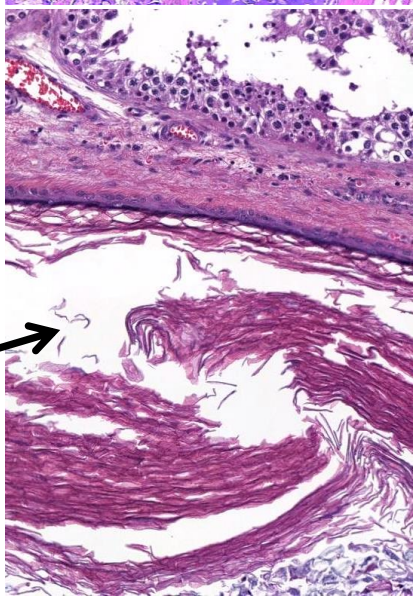
Polymorphous cell population (**3 cell types**: small, medium, and large)
Poorly-defined cell membranes. **Dense cytoplasm**.
Round nuclei with dense to granular chromatin.
Diffuse to multinodular pattern of growth.
Frequent cystic change/**edema**.
No significant inflammation/granulomas

IHC: Negative for usual seminoma markers (e.g., OCT3/4). (+) cKit and SALL4

Can undergo sarcomatous transformation.

Teratoma, Prepubertal-type





Composed of elements resembling **somatic tissues from one or more germ cell layers.**

Primarily occurs in **<u>prepubertal</u>** males <6 years old
(but can see in older)

In contrast with Postpubertal-type:
<u>Benign</u> behavior. Do not recur or metastasize.
***NO* association with GCNIS or isochrome 12p amplification.**
***NO* cytologic atypia. *NO* association with mixed GCT.**
As such, they are most akin to the mature cystic teratomas seen in the ovary.

Frequently include skin structures, ciliated epithelium, fat, cartilage, bone, and muscle in organoid structures. No significant cytologic atypia.

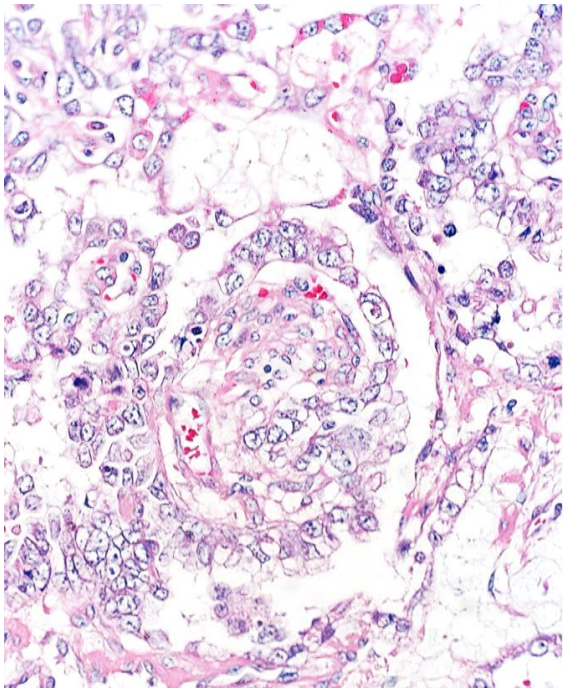
Normal surrounding testicle: *<u>No</u>* GCNIS, tubular atrophy, scars, microlithiasis, necrosis, or impaired spermatogenesis (which might suggest a GCNIS-derived GCT)

Specialized variants:
<u>Dermoid Cyst</u>: replicate skin in an organoid arrangement. Squamous epithelium *<u>with</u>* adnexal structures. Cured by excision.

<u>Epidermoid Cyst</u>: Unilocular cyst with squamous lining and keratinaceous debris. No adnexal structures or other elements. Cured by excision.

<u>Well-differentiated Neuroendocrine Tumor</u>: Similar morphology to elsewhere. Often pure. Usually good behavior. Only variant that can behave aggressively.

Yolk Sac Tumor, Prepubertal-type

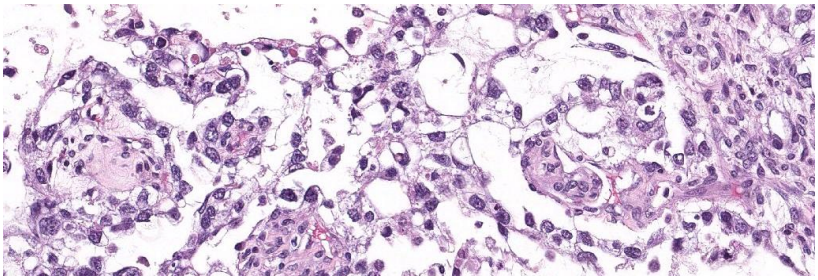


Rare. Usually in **young boys <6 years old**

Identical morphology and IHC profile to postpubertal-type.
Secretes AFP

However, <u>unlike</u> postpubertal YST:
NOT associated with GCNIS. NO isochrome 12p amplification.
<u>Excellent survival</u>, even with advanced stage.

Usually pure, but can see in combination: Mixed teratoma and yolk sac tumor, prepubertal-type



Immunohistochemistry of Germ Cell Tumors

	GCNIS	Seminoma	Embryonal Carcinoma	Yolk Sac Tumor	Choriocarcinoma	Teratoma	Spermatocytic Tumor	Metastatic Carcinoma	Other Tumors
AE1/AE3	-	±	+	+	+	+	-	+	Many!
OCT3/4	+	+	+	-	-	-	-	-	Rare NSCLC and RCC and large cell lymphoma
CD30	-	-	+	-	-	-	-	±	Lymphomas, melanoma, nasopharyngeal carcinoma, mesenchymal tumors
Glypcian-3	-	-	-	+	+	±		±	HCC, gastric cancers, syncytiotrophoblasts
D2-40	+	+	±	-	-	±	-	±	Gliomas, meningiomas, mesothelial tumors, lymphatic tumors,
PLAP	+	+	+	±	+	-	-	±	Numerous adenocarcinomas (colon, endometrium, etc..)
SALL4	+	+	+	+	±	±	+	±	Hematologic malignancies, rhabdoid tumors, Wilms tumor, lots of GI adenocarcinomas among others
βhCG	-	-	-	-	+	-	-	±	Other trophoblastic tumors, syncytiotrophoblasts
cKIT (CD117)	+	+	-	±	-	-	±	±	Lots of tumors
AFP	-	-	±	+	-	±	-	±	Hepatocellular tumors, etc..
CK7	±	±	+	-	+	+		±	Many carcinomas

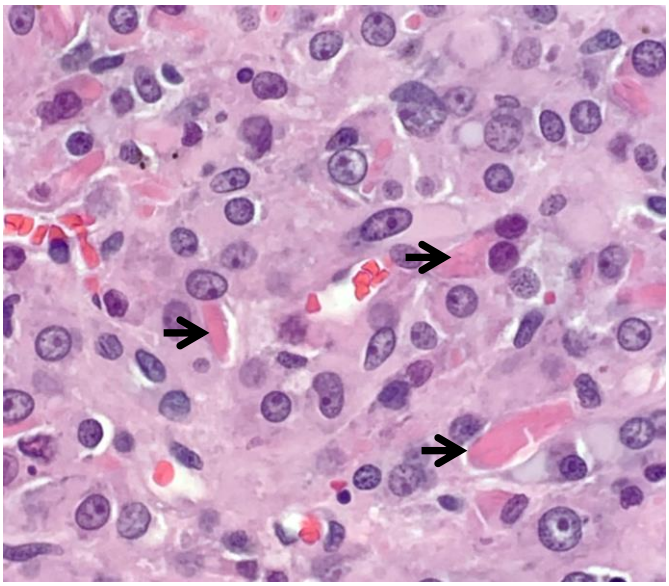
Modified from: WHO classification of Tumors of the Urinary System and Male Genital Organs. 4th ed.

Sex Cord-Stromal

Rare. More common in kids. Vast majority are benign.

A little variable, but often stain with some combination of: **Inhibin, calretinin, SF-1**, **FOXL2, Melan A**

Leydig Cell Tumor



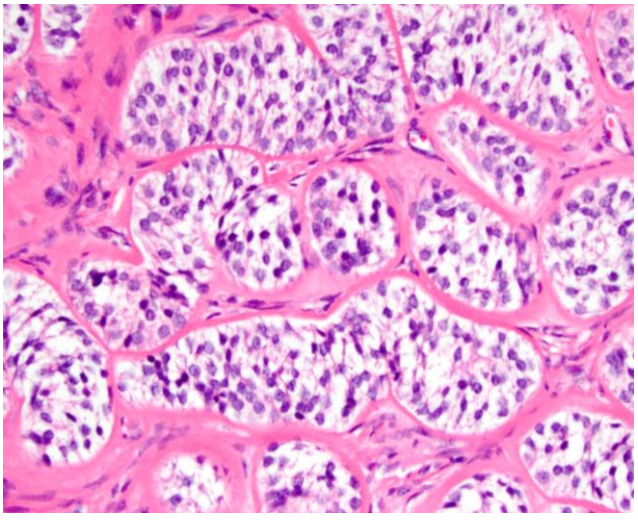
Abundant, eosinophilic granular cytoplasm.
Diffuse growth. Uniform round cells.
Round, central nuclei with prominent nucleoli.
Frequent **Reinke crystals** (→)

Usually **asymptomatic**, but children can present with precocious puberty as the tumor can secrete steroid hormones (e.g., testosterone).

Most common testicular sex cord-stromal tumor.

Vast majority are benign.

Sertoli Cell Tumor

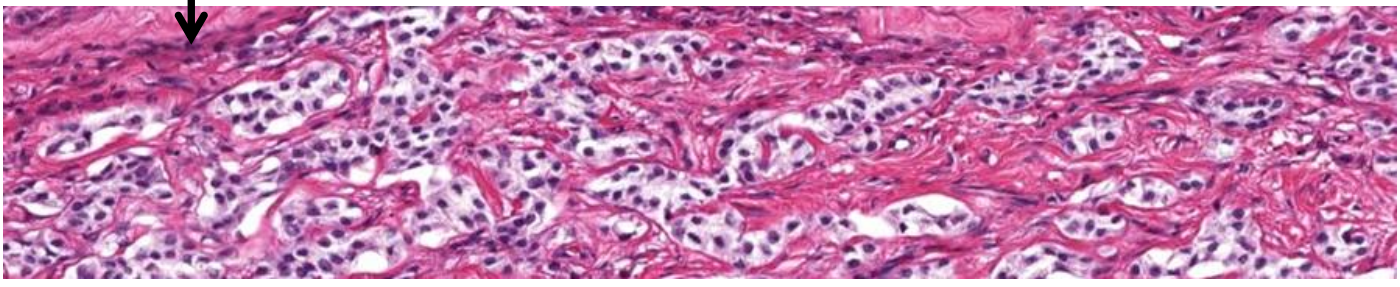


Often shows at least focal **tubular differentiation**.
Usually moderate pale cytoplasm.
Rarely diffuse growth.

Unique IHC: Frequent **nuclear β-catenin**, WT-1, CK AE1/AE3, and neuroendocrine markers.

Vast majority are benign.

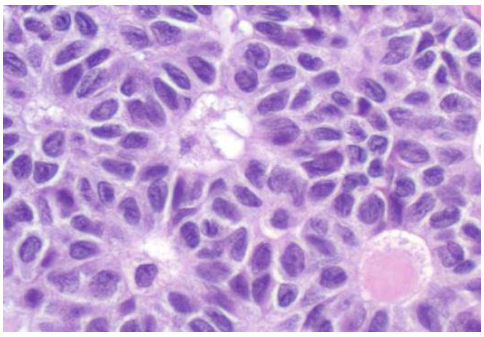
Variant:
Sclerosing Sertoli Cell Tumor—extensively hyalinized stroma with cells arranged in tight cords and clusters



Factors associated with *Malignant* behavior in Sex Cord-Stromal Tumors:
Cytologic Atypia, Abundant Mitoses, Large size, Vascular Invasion, Necrosis, Infiltrative growth

(Pretty common-sense bad findings ;-)

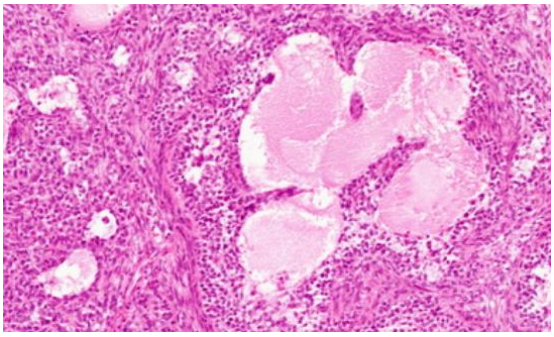
Granulosa Cell Tumors



Similar to the more common ovarian counterpart

Adult Granulosa Cell Tumors →

Rare.
Often asymptomatic, but can secrete estrogen
Cells: Scant pale architecture with **grooved nuclei**
Varied architecture: Sheet-like, trabecular, ribbon-like, microfolicular (with "**Call-Exner bodies**" filled with pink secretions).



Molecular: Frequent **FOXL2 point mutations**

Juvenile Granulosa Cell Tumors →

Rare. Almost all in first decade, often before 6 months old.
Usually presents as a mass.
Macrofollicles with mucinous secretions
Round nuclei with **NO GROOVES**

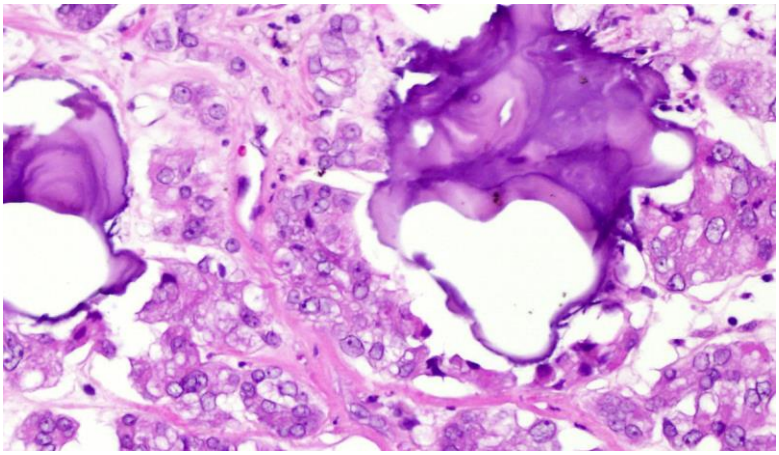
Large Cell Calcifying Sertoli Cell Tumor

Large Sertoli cells with abundant granular eosinophilic cytoplasm

Calcifications (focal, psammomatous to large, plaque-like)
Often prominent neutrophilic infiltrate.

NO nuclear β-catenin

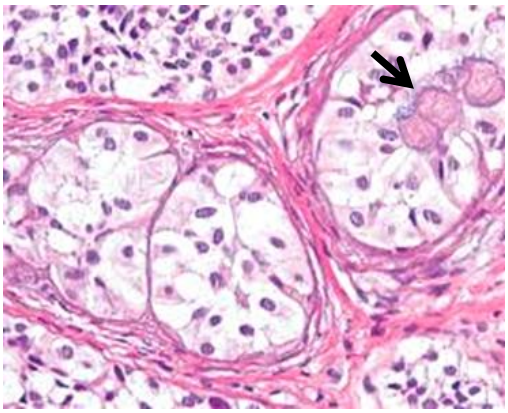
Frequently associated with **Carney complex**
Frequent PRKAR1A mutations



Other Tumors

Intratubular Large Cell Hyalinizing Sertoli Cell Neoplasia:

Expanded seminiferous tubules with large Sertoli cells with pale cytoplasm accompanied by prominent basement membrane deposits around and within tubules (→).
Almost exclusively in Peutz-Jegher's syndrome (*think: like SCTATs!*).
Often present as prepubertal males with gynecomastia (aromatases made by tumor convert androgens→ estrogen).
Always benign.

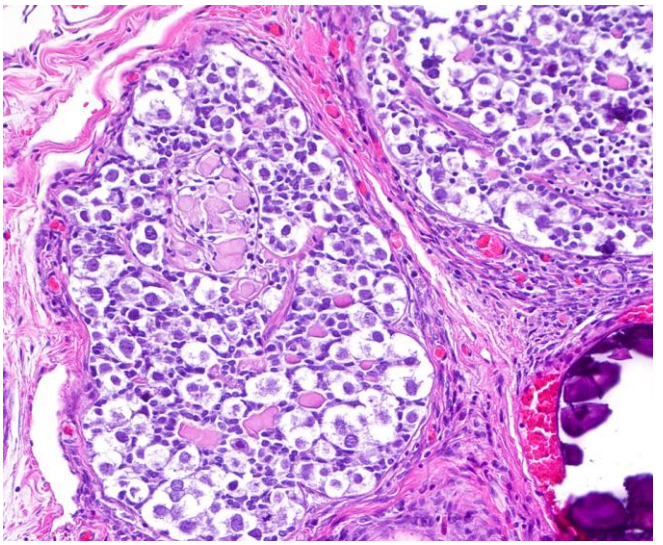


Fibroma/Thecoma:

Resemble ovarian counterparts. Benign. Rare.
Unencapsulated proliferation of spindled cells with scant eosinophilic cytoplasm.

Miscellaneous Tumors

Gonadoblastoma

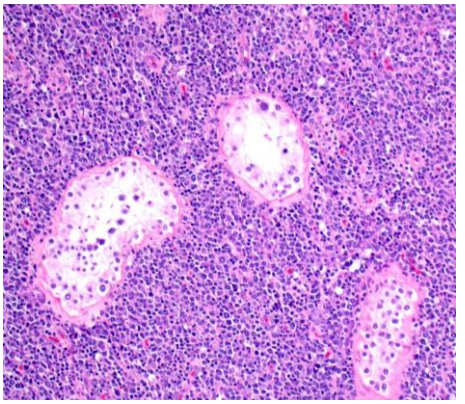


Germ cells resembling GCNIS cells and spermatogonium
Sex cord cells resembling immature granulosa cells
Arranged in round nests with round deposits of eosinophilic basement membrane
Frequent calcifications

Develop in individuals with **gonadal dysgenesis**.

Can progress to a germ cell tumor, often seminoma.

Hematolymphoid Tumors



Most common testicular tumor in men over 50 years old.
Can be primary or part of systemic involvement.

Often obliterate the seminiferous tubules centrally with **peripheral *intertubular* spread.**

Diffuse Large B-Cell Lymphoma comprises ~90% of primary testicular lymphomas.

Same stains as elsewhere.

Other Tumors

Ovarian-type Epithelial Tumors:
Resemble entire spectrum of ovarian type epithelial tumors. Most commonly Serous and Mucinous, with most being Serous Borderline Tumors, which do not recur or metastasize.

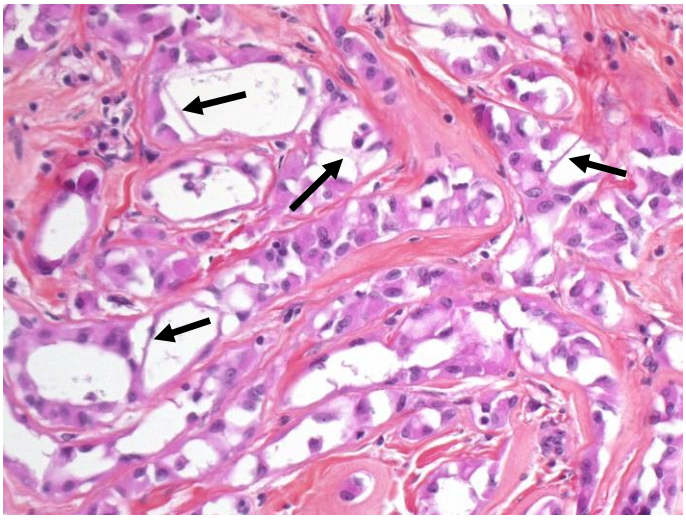
Rete Testis Adenoma:
Very rare. Benign tumor of rete epithelium that spans the spectrum from packed tubules (adenoma) to tumors with a cystic component (cystadenoma), papillary architecture (papillary cystadenoma), or glands with prominent fibrous tissue (adenofibroma).

Rete Testis Adenocarcinoma:
Very Rare. Malignant. Diagnosis of exclusion. Malignant gland forming tumor of rete epithelium. Must be centered in hilum of testis, patient must have no other similar primary, and other Dx's (e.g., mesothelioma), must be excluded. Poor prognosis.

Myoid Gonadal Stromal Tumor:
Spindle cell tumor near rete testis with features of gonadal stroma and smooth muscle. Circumscribed with densely packed spindled cells arranged in short fascicles. IHC: (+)SF1, FOXL2, SMA, S100.

Paratesticular Tumors

Adenomatoid Tumor



Benign Mesothelial tumor.
Most common neoplasm of paratesticular region
Often based in the epididymis and < 2cm.

Irregularly shaped gland-like microcystic spaces composed of flattened or cuboidal cells with associated fibrous stroma and lymphoid aggregates.
Bland cytologic features.

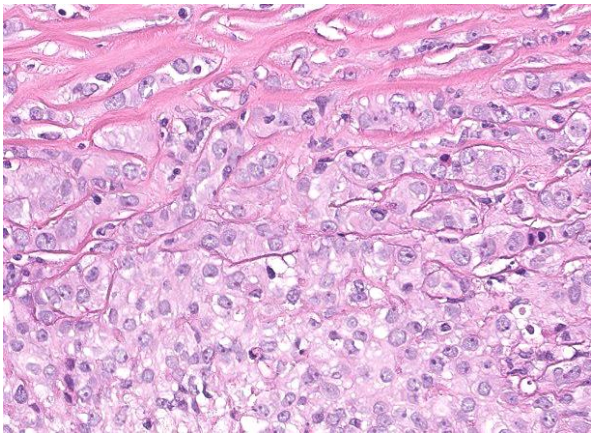
***Helpful feature*: "thread-like bridging strands"** (→)

Sometimes signet ring-like vacuolated cells.

Solitary, localized.

IHC: Mesothelial markers: D2-40, Calretinin, WT-1, CK5/6 , CK AE1/AE3.

Mesothelioma



Rare. **Malignant** proliferation of **mesothelial cells** arising from tunica vaginalis.

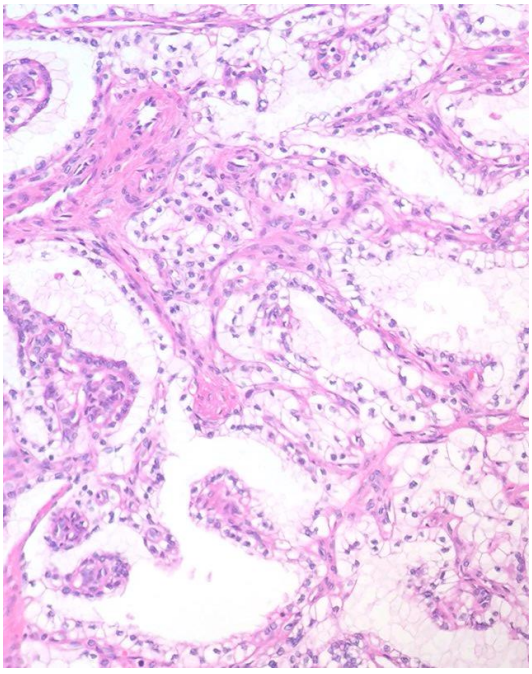
Mass **envelops testicle**, often invading it.

Like in the pleura, **variable appearance. Often epithelioid** with papillary or tubulopapillary architecture.

Less associated with asbestos.

IHC: Usual mesothelial markers (see above)

Papillary Cystadenoma of the Epididymis



Rare. **Benign** Tumor of Epididymal ducts.

Associated with **von Hippel-Lindau syndrome** (but is more often sporadic)

Cystic structures that are focally papillary.
Clear columnar/cuboidal cells with abundant clear cytoplasm.
Frequent reverse nuclear polarity.
Colloid-like secretions.

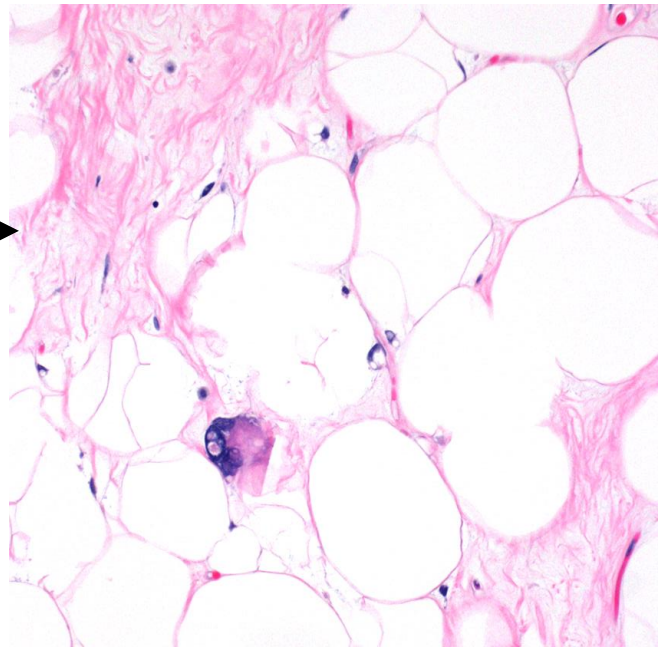
Morphologically (and immunophenotypically) resembles papillary clear cell RCC (see separate Kidney guide)

Adipocytic Tumors

Lipoma:
Benign. Most common mesenchymal tumor of region.
Consist of entirely mature adipocytes.

Well-differentiated Liposarcoma: →
Common paratesticular sarcoma. Recur, but won't metastasize unless dedifferentiate.
Varying proportion of adipocytes, fibrous bands with enlarged, hyperchromatic stromal cells, and occasional lipoblasts. Can see inflammation/myxoid change.
Giant marker and/or ring chromosomes→ MDM2 amplification.

If large or questionable atypia→ consider getting FISH to help differentiate.

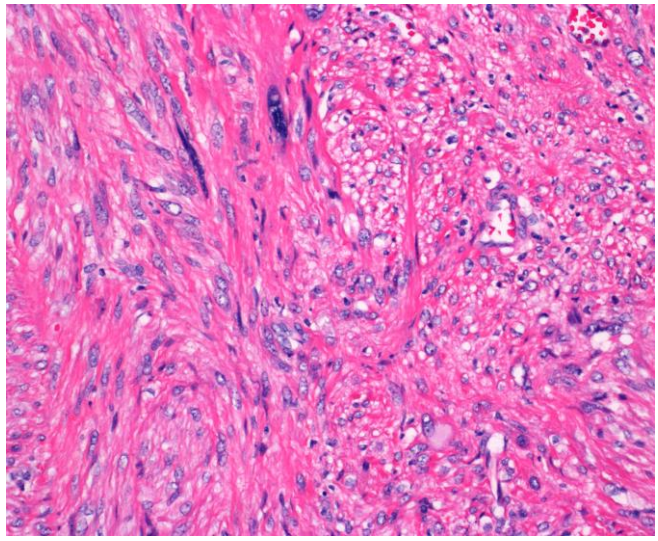


Smooth Muscle Tumors

Leiomyoma:
Benign. Somewhat common.
Consist of entirely bland smooth muscle (like in other locations).

Leiomyosarcoma: →
Common paratesticular sarcoma.
Fascicles of spindled cells with brightly eosinophilic cytoplasm and "cigar-like" blunt nuclei.
Significant atypia, mitoses, and/or tumor necrosis.

IHC: Desmin, SMA, H-Caldesmon, Calponin

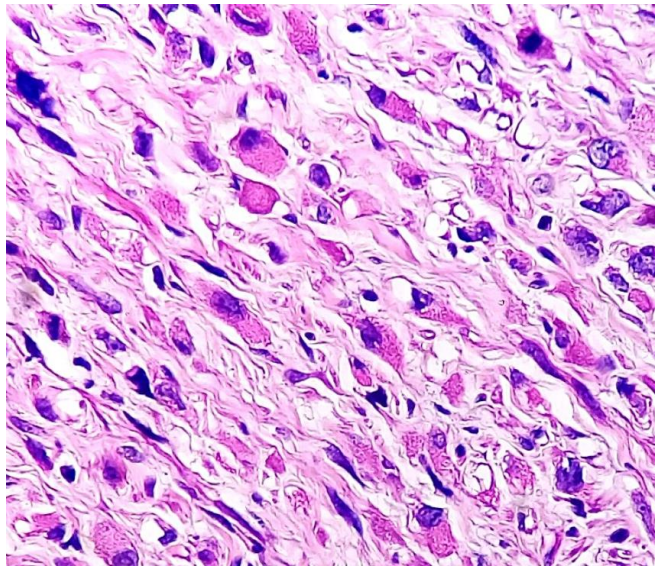


Skeletal Muscle Tumors

Rhabdomyoma:
Benign. Very rare. Most often adolescents.

Rhabdomyosarcoma: →
Often in children or young adults and Embryonal subtype with primitive round or spindled cells and variable eosinophilic rhabdomyoblasts with abundant eccentric cytoplasm. Often good prognosis.

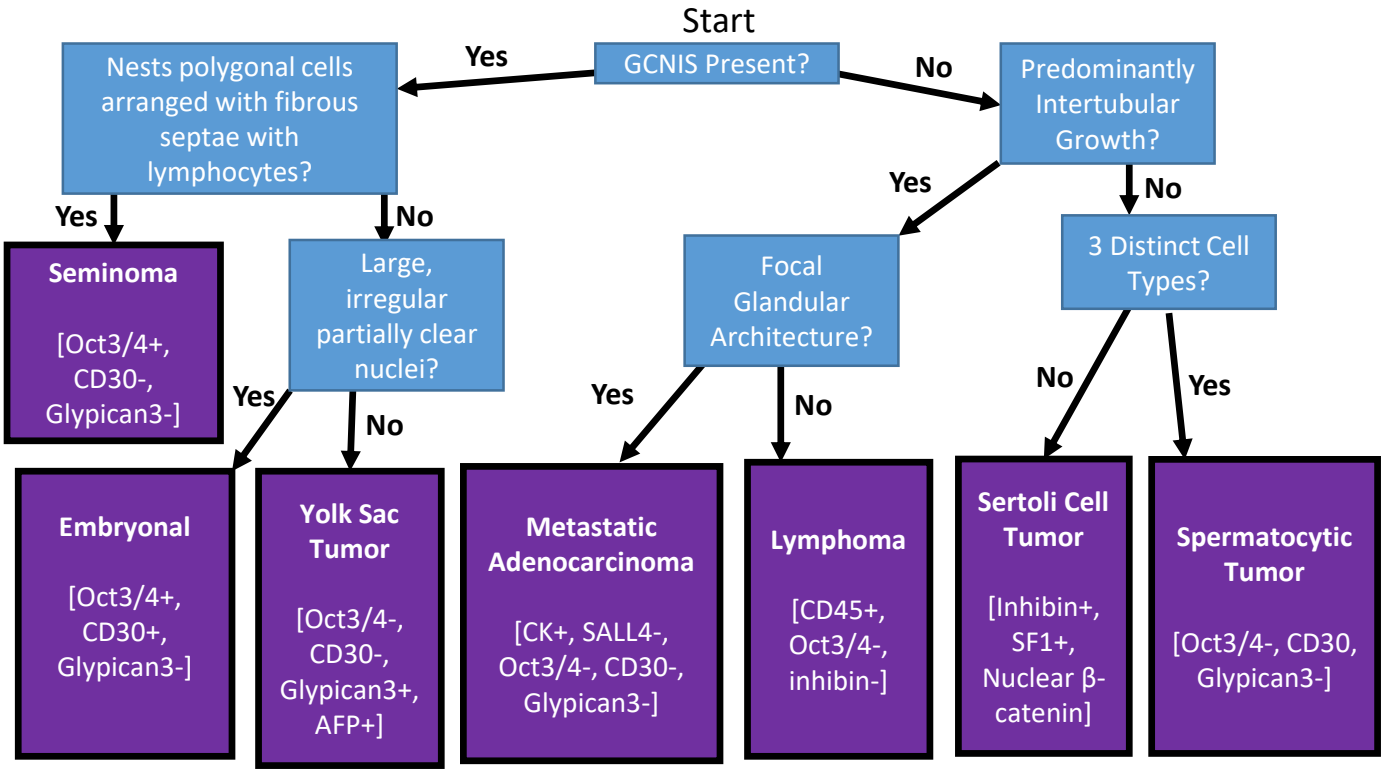
IHC: MyoD1, Myogenin, Desmin.



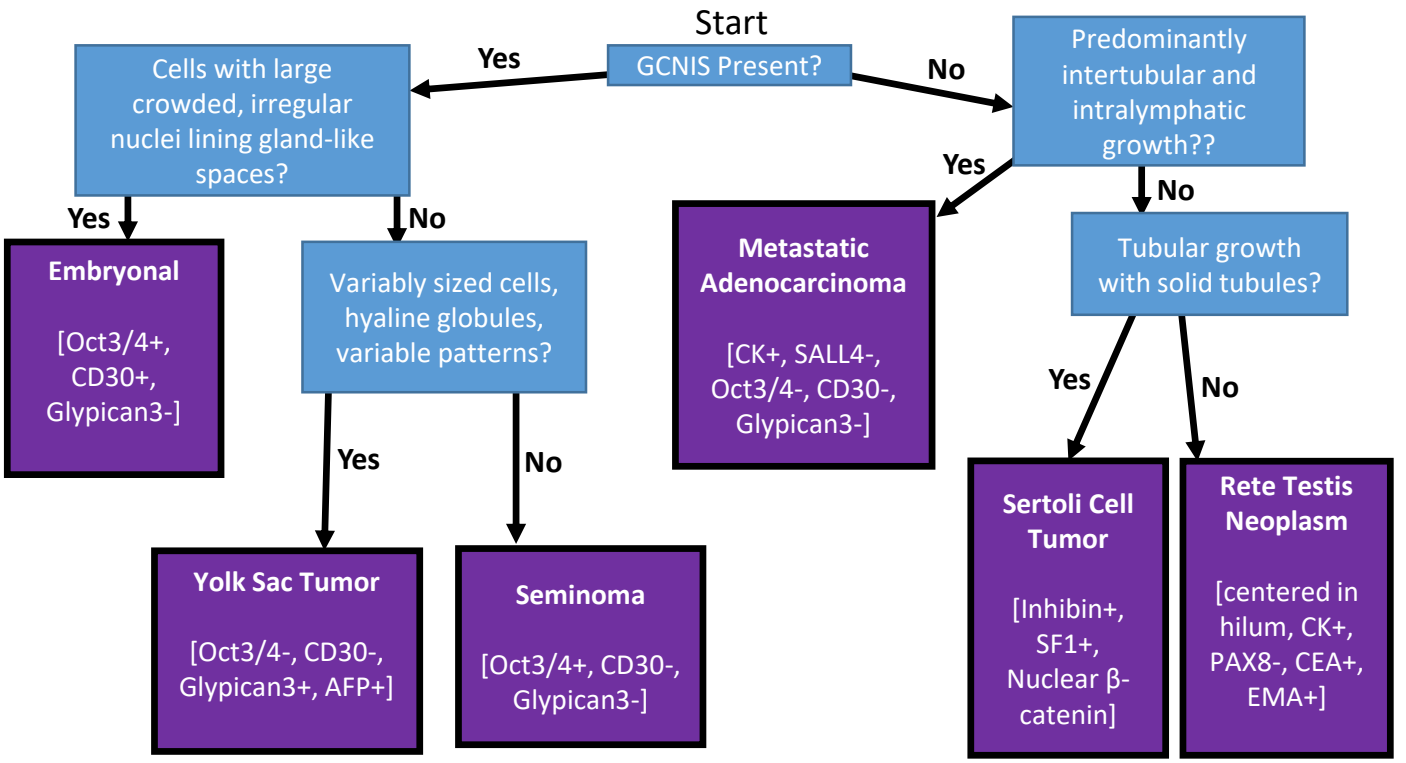
Algorithmic Diagnosis of Testicular Tumors

Algorithms modified from: Urologic Surgical Pathology. Liang Chen et al. 2020.

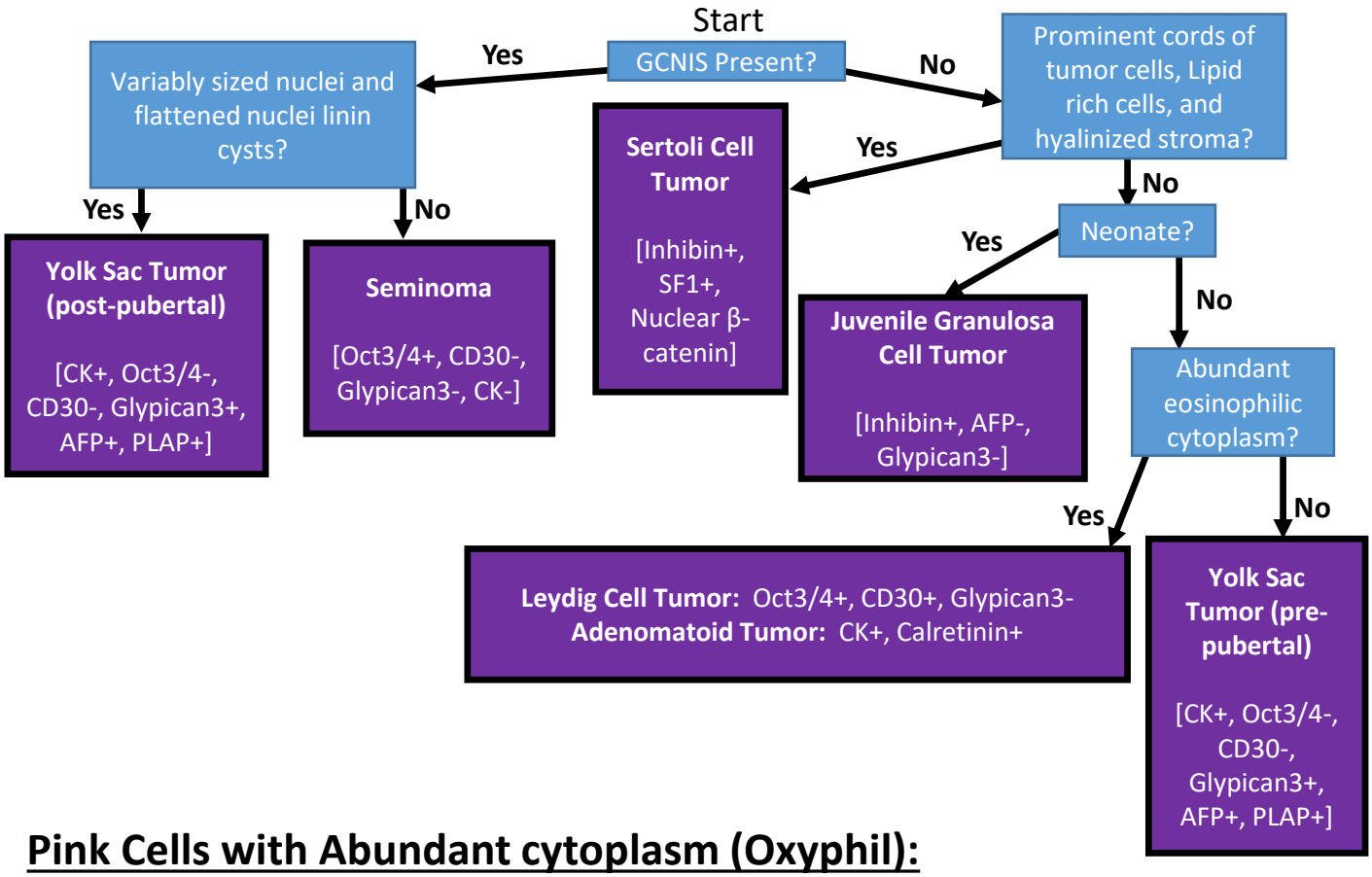
Clear Cytoplasm:



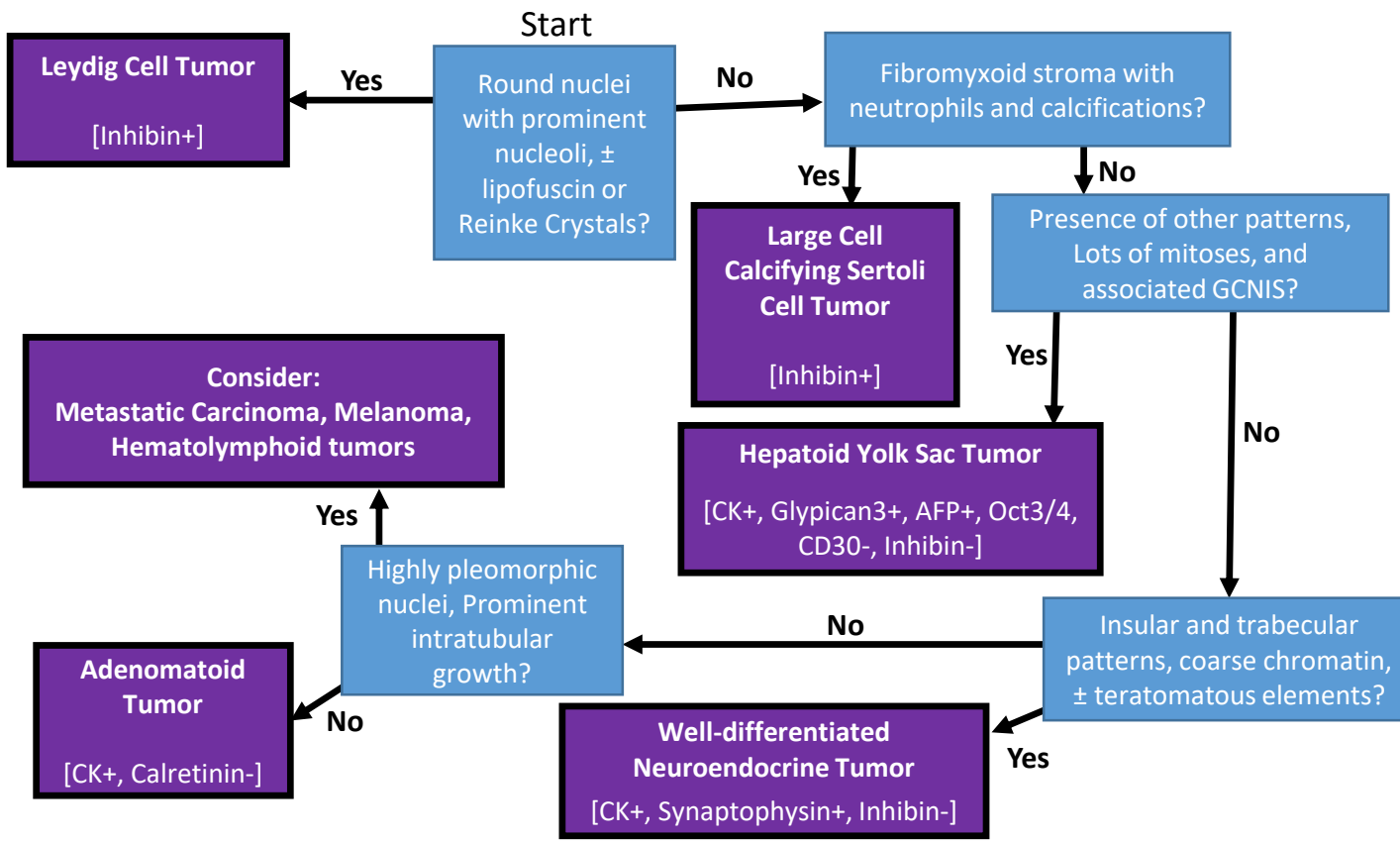
Glandular and/or Tubular growth:



Microcystic:



Pink Cells with Abundant cytoplasm (Oxyphil):



Spindle Cells: