Male genital system - 1

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SLO

- Classify testicular tumours
- Describe testicular tumours with respect to –

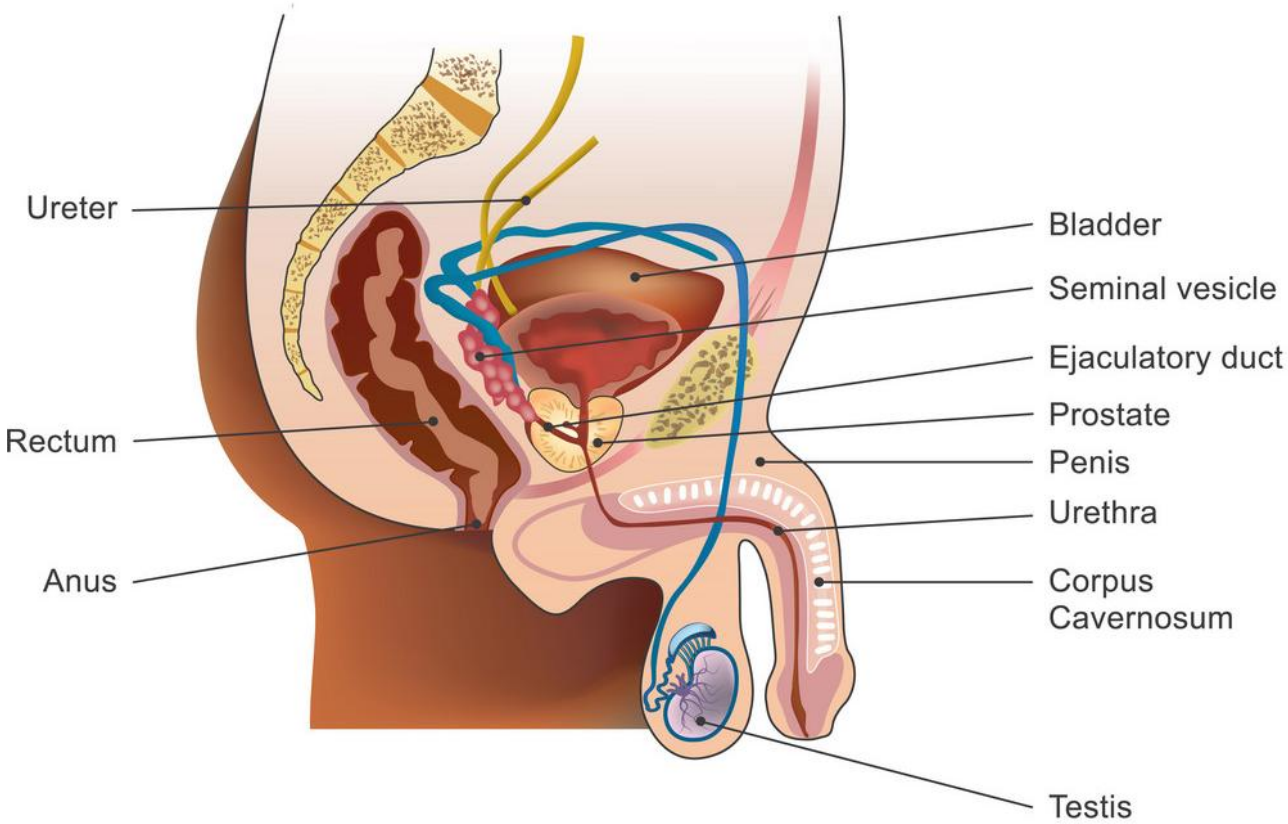
Pathogenesis

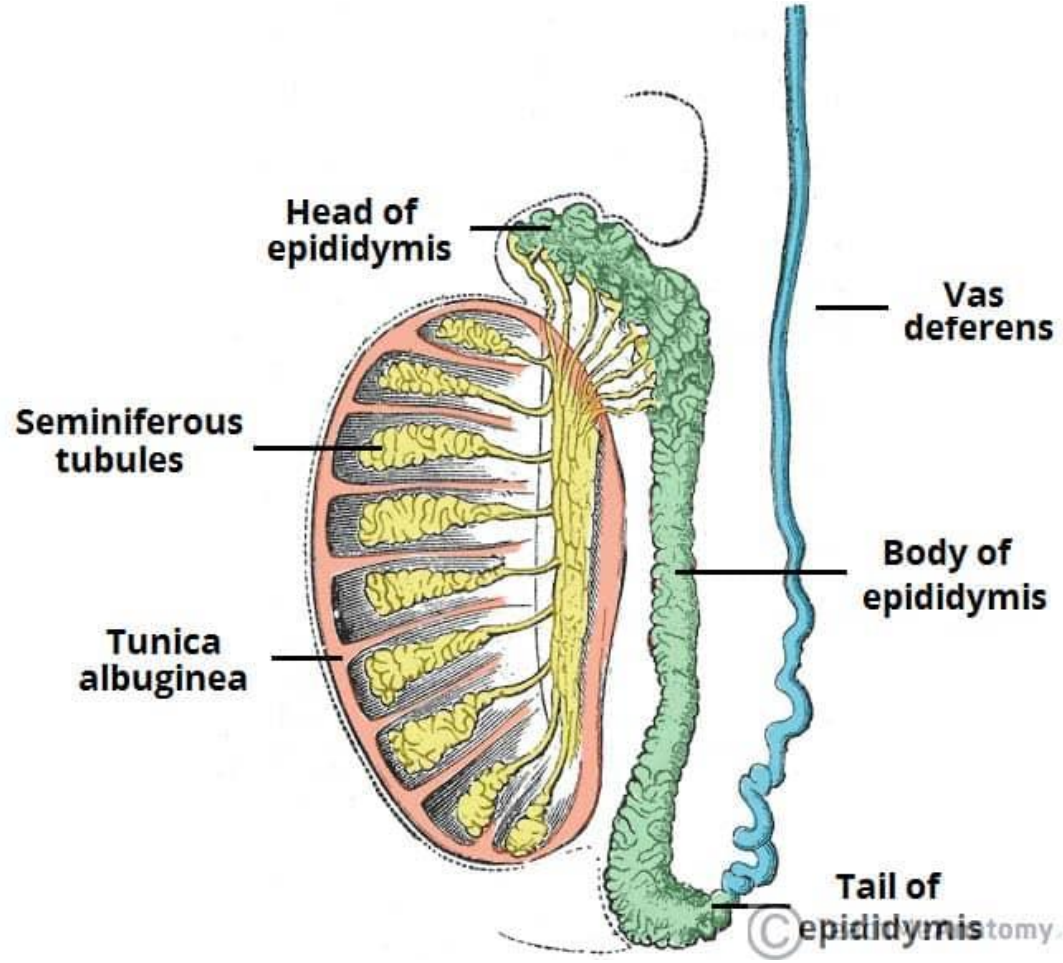
Pathology

Presenting and distinguishing features

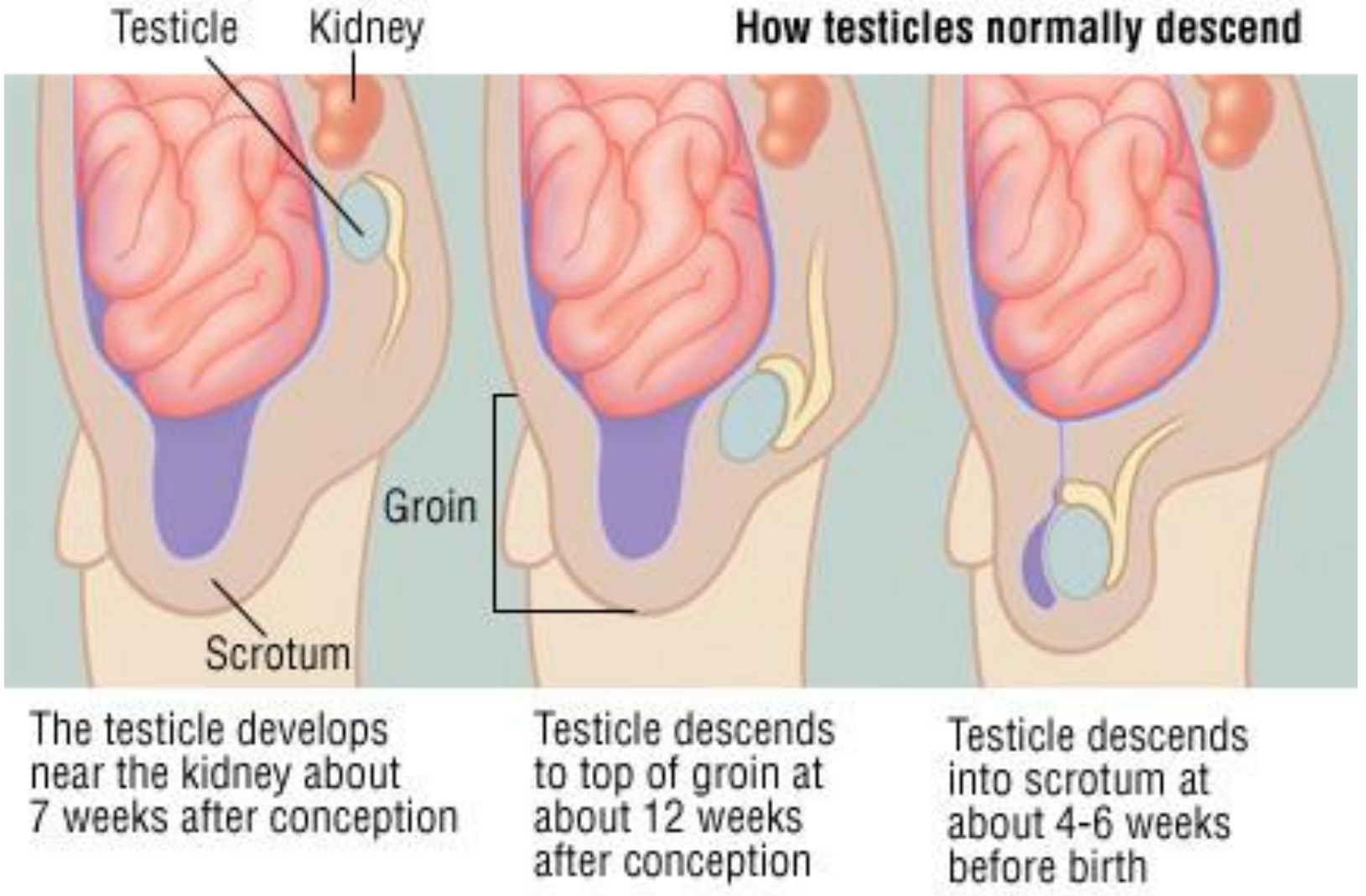
Diagnostic tests

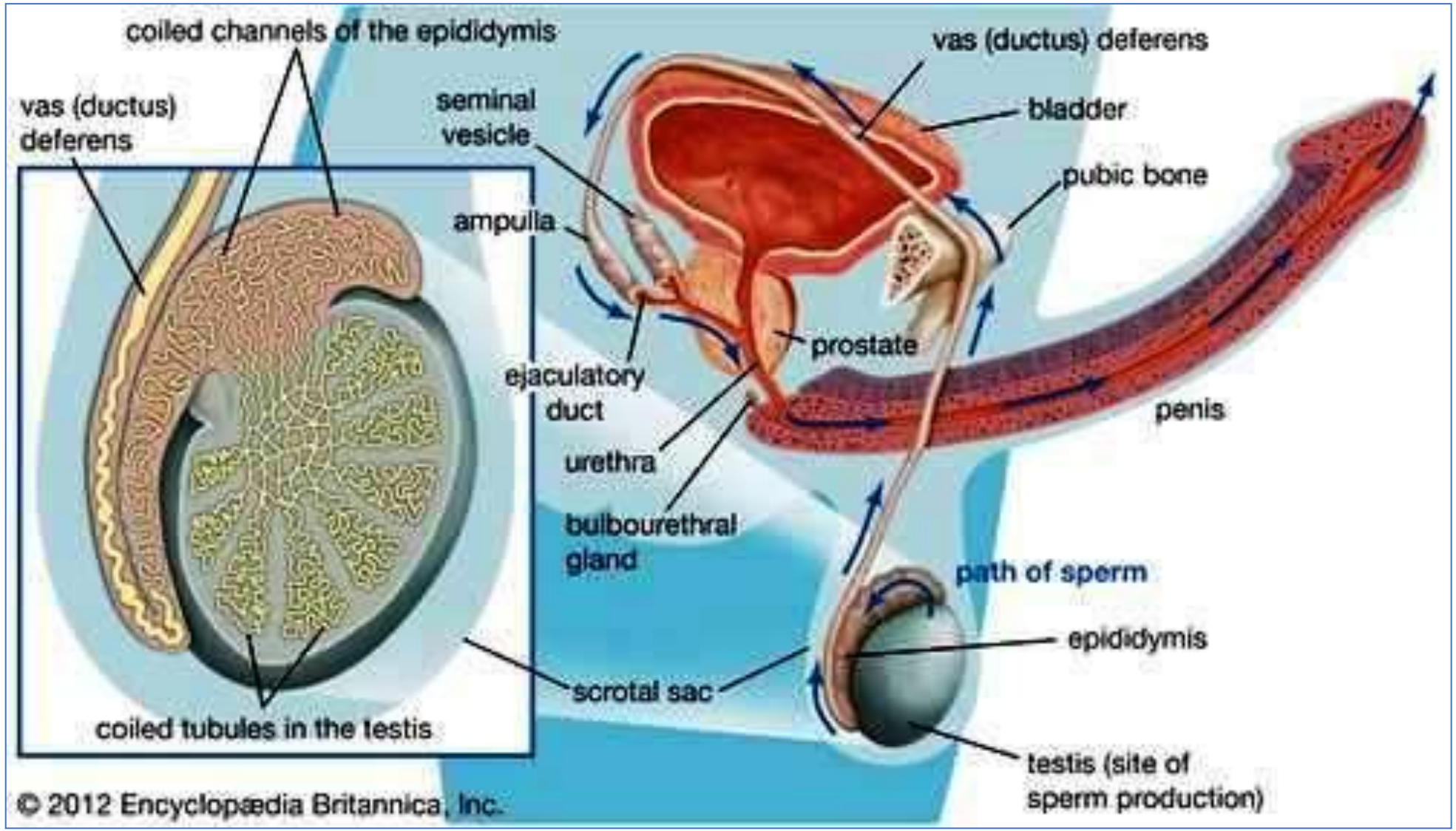
Progression and spread


Ureter
Rectum
Anus
Bladder
Seminal vesicle
Ejaculatory duct
Prostate
Penis
Urethra
Corpus Cavernosum
Testis


Head of epididymis
Vas deferens
Seminiferous tubules
Body of epididymis
Tunica albuginea
Tail of epididymis

Testis And Epididymis




coiled channels of the epididymis
vas (ductus) deferens
seminal vesicle
ampulla
ejaculatory duct
urethra
bulbourethral gland
coiled tubules in the testis
vas (ductus) deferens
bladder
pubic bone
prostate
penis
path of sperm
epididymis
scrotal sac
testis (site of sperm production)
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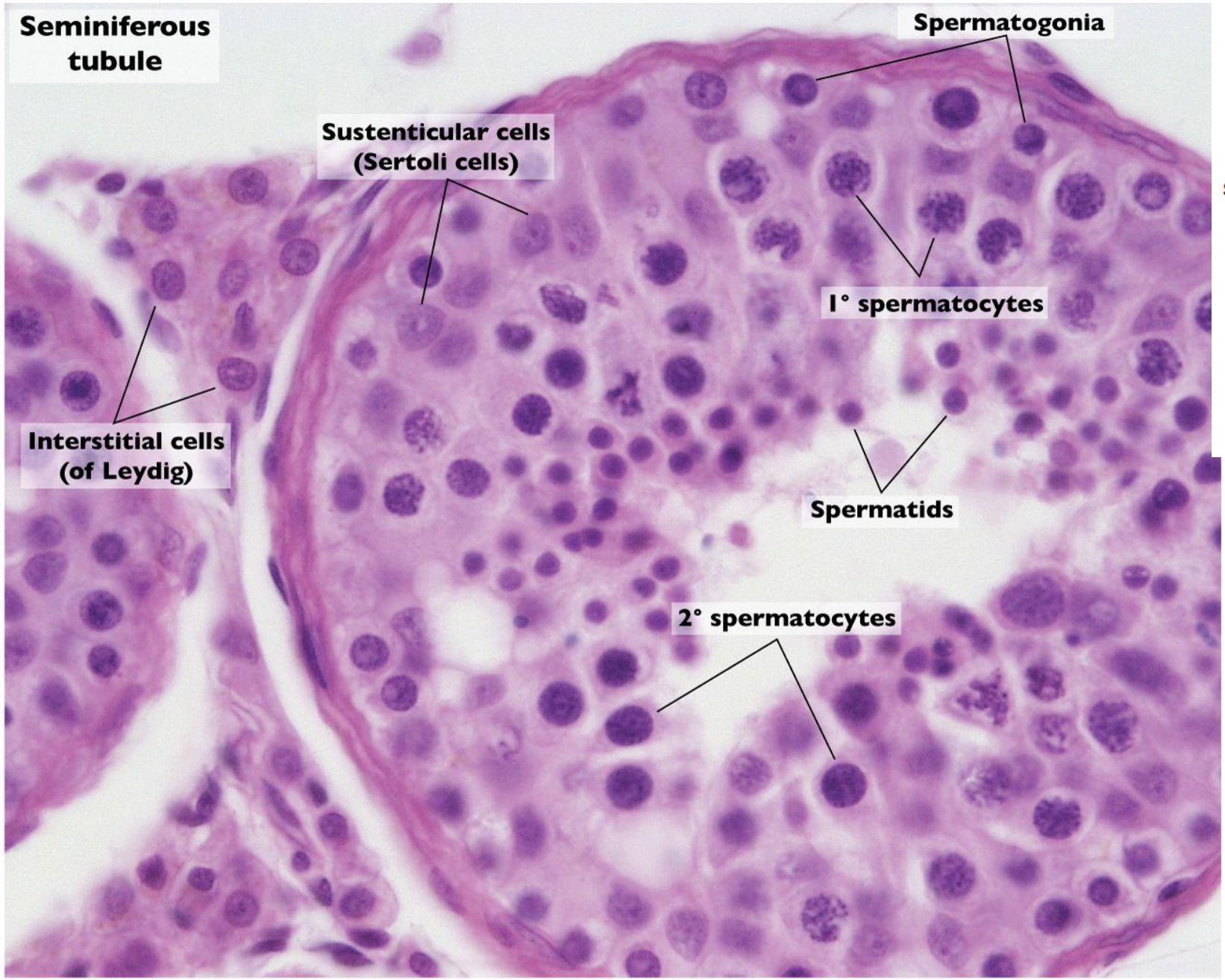
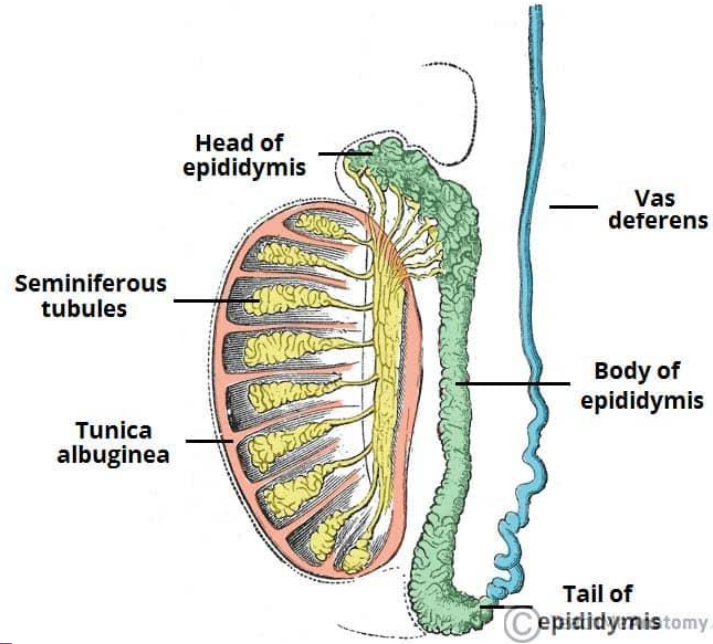
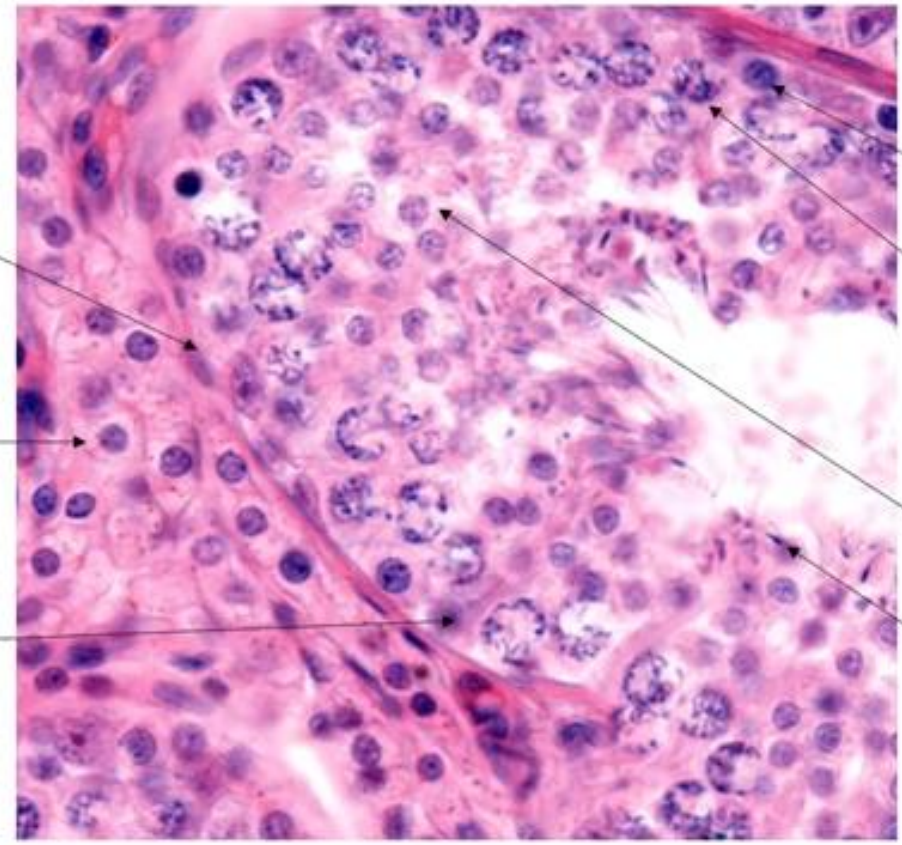

Seminiferous tubule
Spermatogonia
Sustenticular cells (Sertoli cells)
1° spermatocytes
Interstitial cells (of Leydig)
Spermatids
2° spermatocytes


Head of epididymis
Vas deferens
Seminiferous tubules
Body of epididymis
Tunica albuginea
Tail of epididymis

SEX CORD STROMAL CELLS

GERM CELLS



Myoid cells

Leydig cells

Sertoli cells

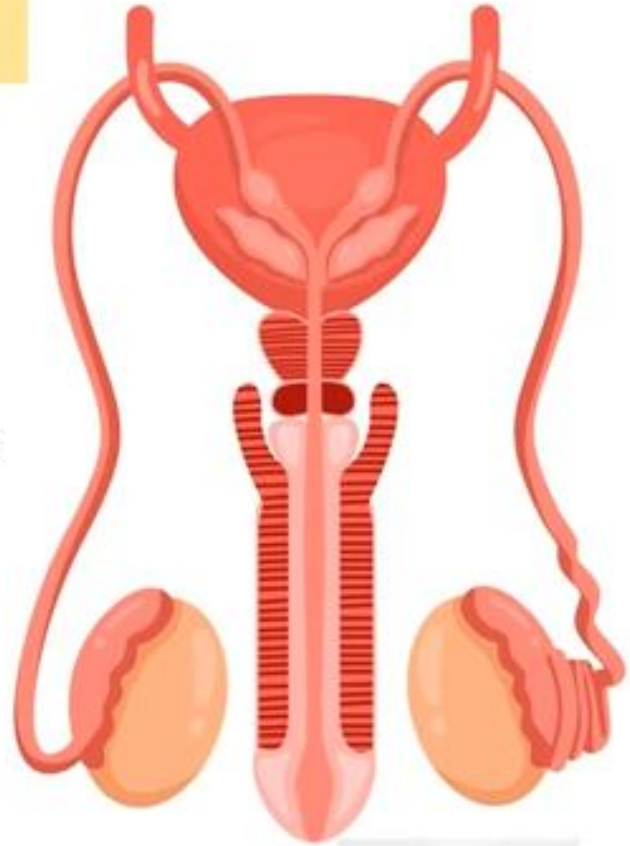
Spermatogonia

spermatocyte

Spermatids

Spermatozoa

Testis



Functions

Spermatogenesis

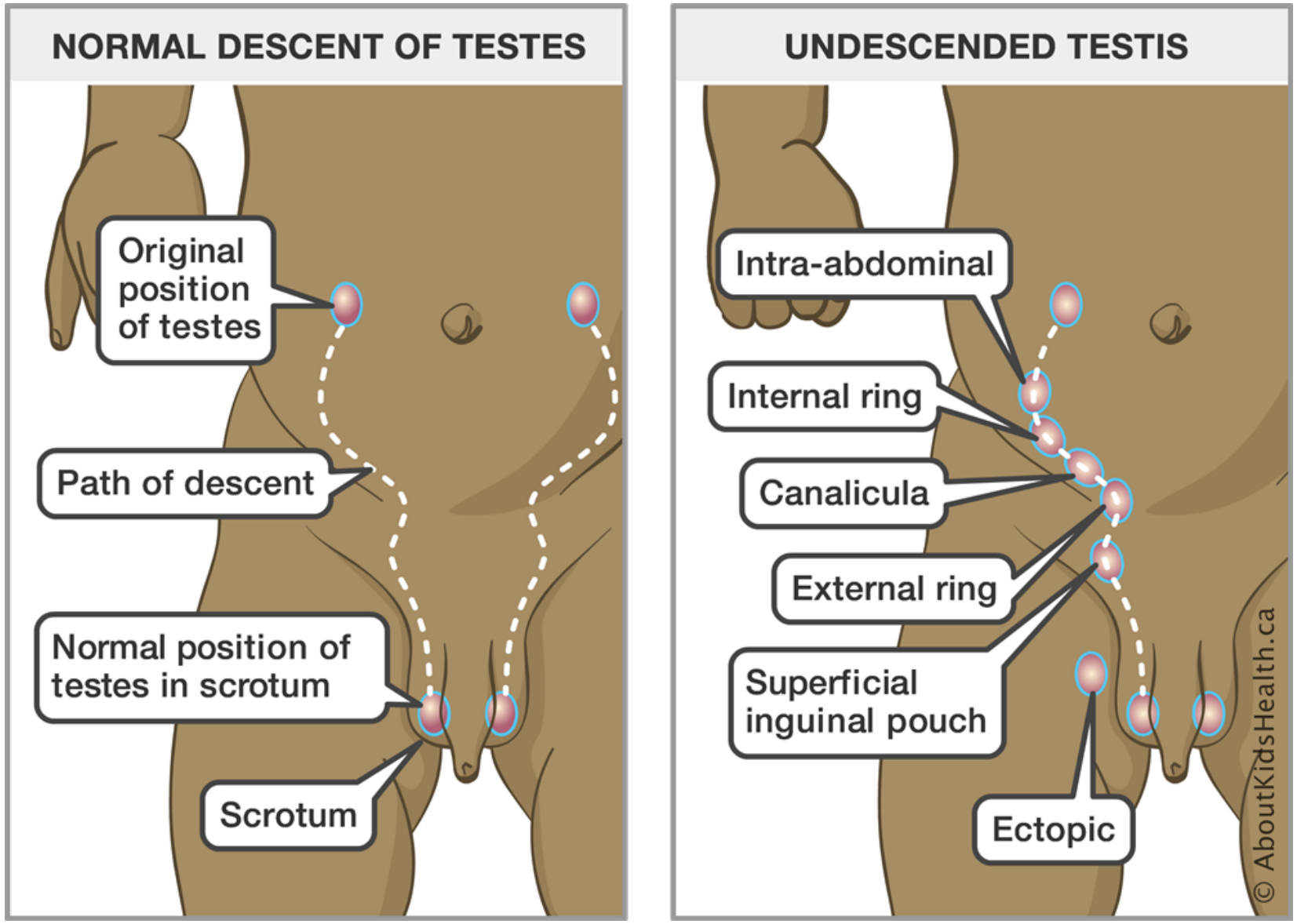
Production of male gametes or spermatozoa. This occurs in the seminiferous tubules

Endocrine Function

Testosterone Production – by Leydig cells
Responsible for secondary sexual characteristics
Crucial for libido, spermatogenesis, and overall reproductive health

Inhibin Production – by Sertoli cells
Regulates spermatogenesis by providing negative feedback to the anterior pituitary to suppress FSH secretion.

Cryptorchidism



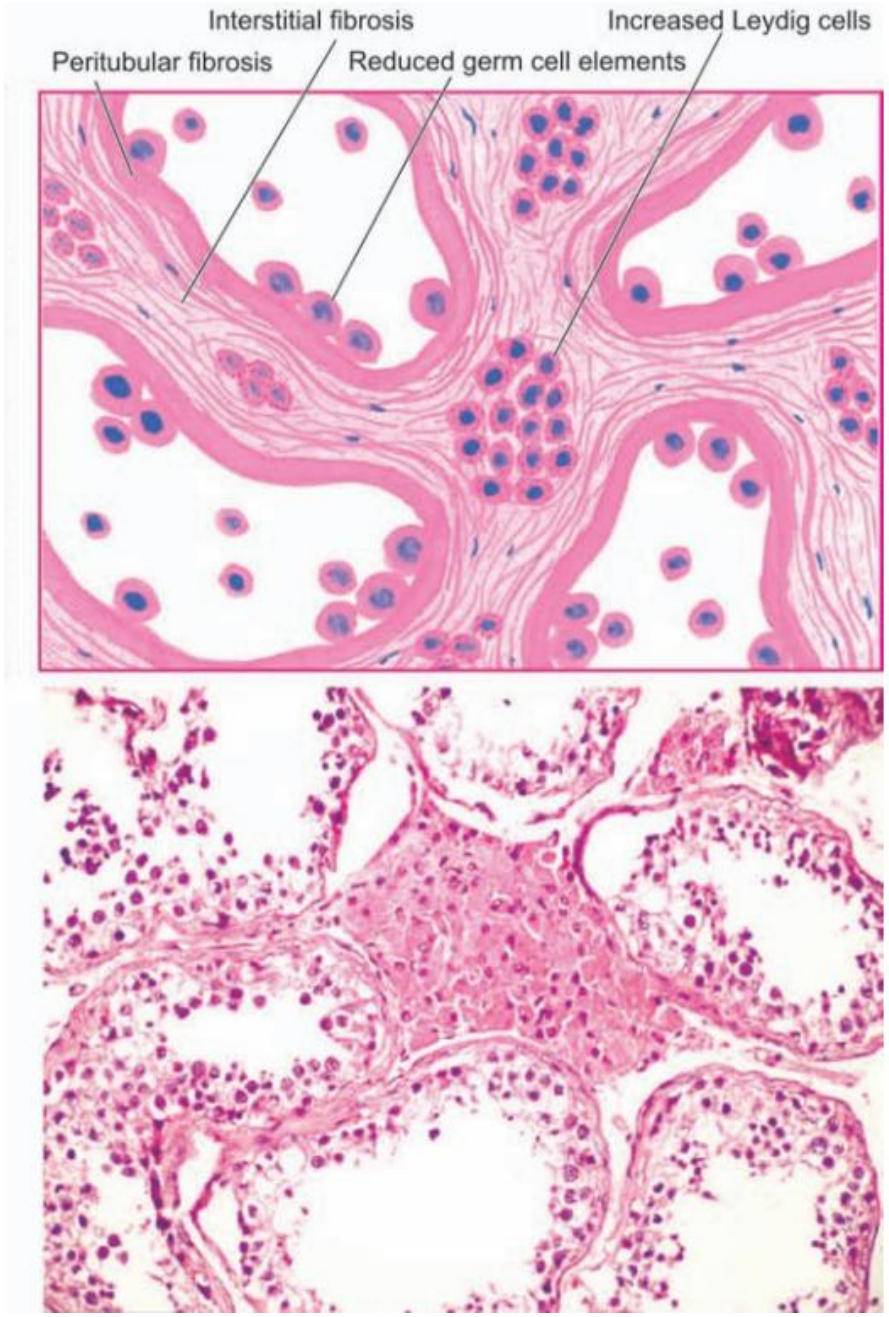
Cryptorchidism = Undescended testis

Etiological factors :

1. Mechanical factors e.g. short spermatic cord, narrow inguinal canal, adhesions to the peritoneum.
2. Genetic factors e.g. trisomy 13, maldevelopment of the scrotum or cremaster muscles.
3. Hormonal factors e.g. deficient androgenic secretions.

Gross :

Small, firm and fibrotic


Interstitial fibrosis
Increased Leydig cells
Peritubular fibrosis
Reduced germ cell elements

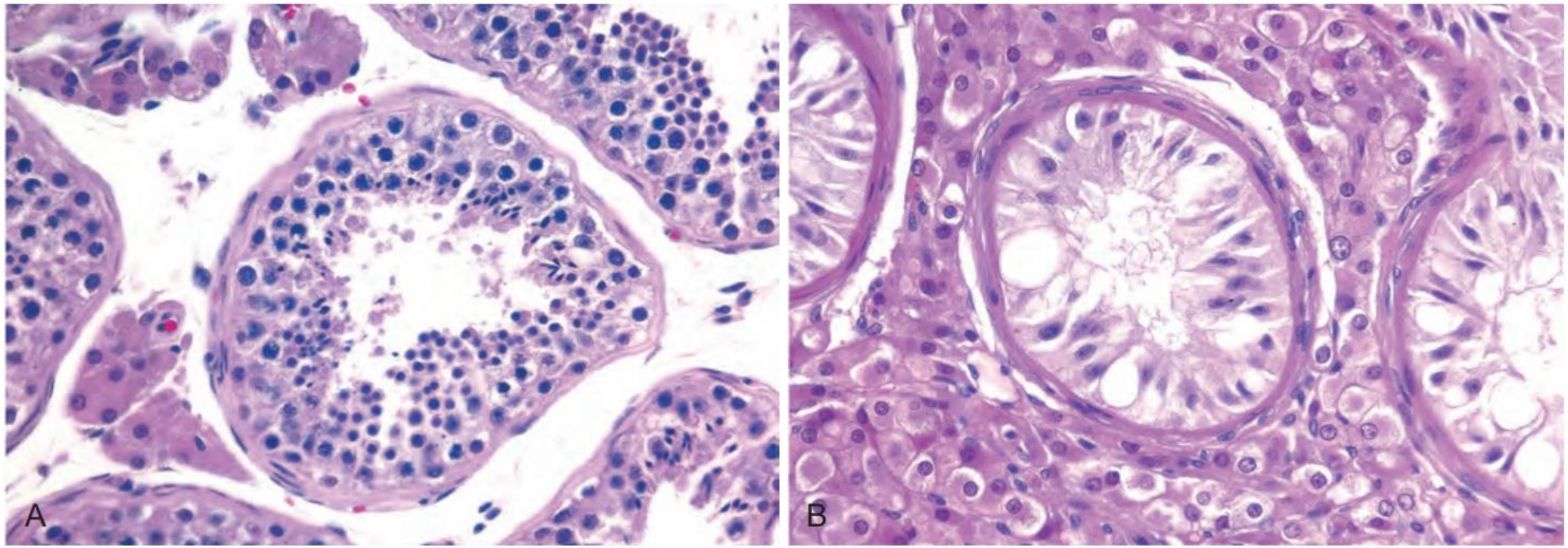


Figure 21.15 Cryptorchidism. (A) Normal testis shows tubules with active spermatogenesis. (B) Testicular atrophy in cryptorchidism. The tubules show Sertoli cells but no spermatogenesis. There is thickening of basement membranes and an apparent increase in interstitial Leydig cells.

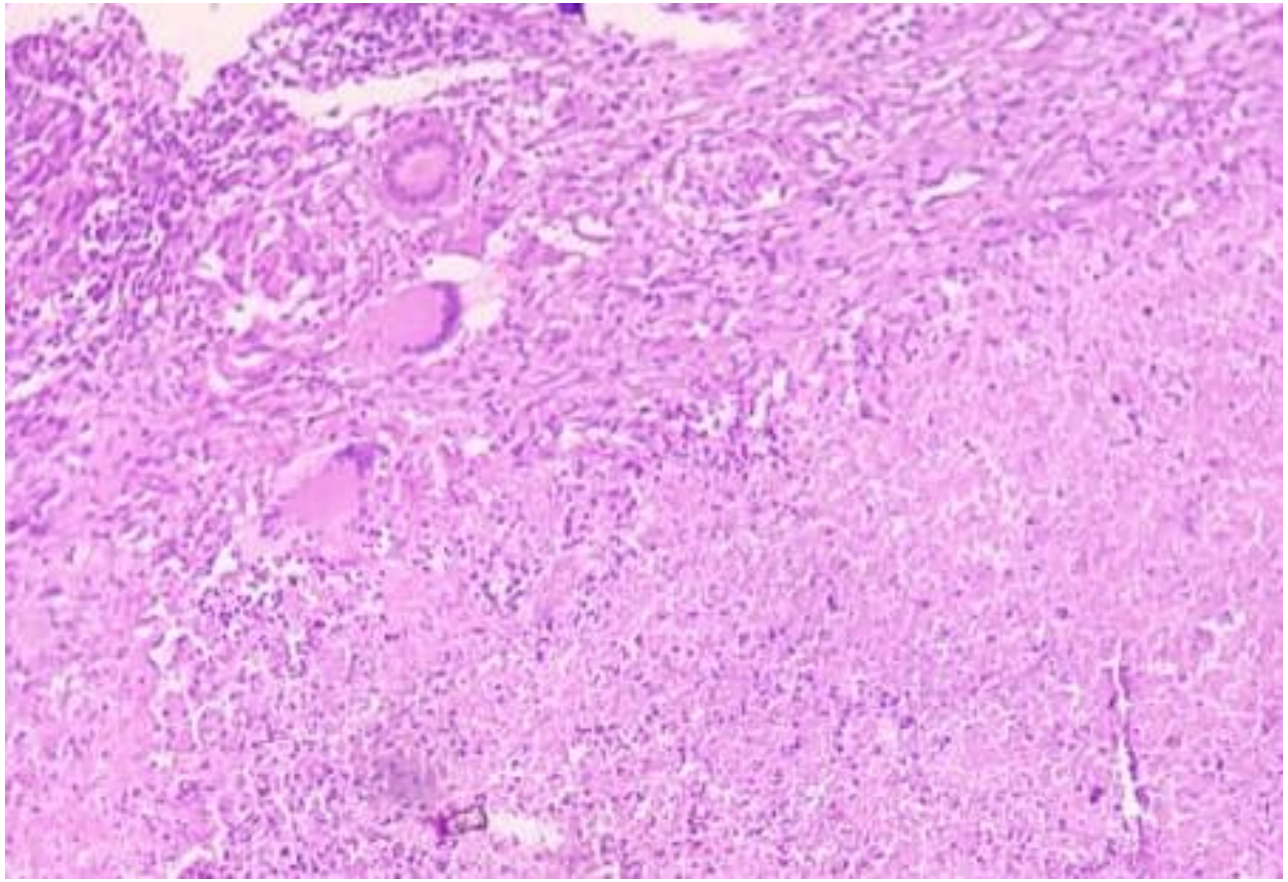
Clinical consequence

1. Infertility
2. Increased risk of testicular malignancy

Epididymitis and orchitis

- **Nonspecific Epididymitis and Orchitis** - C. trachomatis, Neisseria gonorrhoeae, E. coli and Pseudomonas
- **Granulomatous (Autoimmune) Orchitis** - Moderately tender testicular mass of sudden onset, sometimes associated with fever. Histologically non-caseating granulomas
- **Tuberculous Epididymo-orchitis** – Caseating granulomas

Tuberculous Epididymo-orchitis



Torsion of testis

Twisting of the spermatic cord leads to sudden cessation of venous drainage and arterial supply to the testis – Haemorrhagic infarction and coagulative necrosis of testis

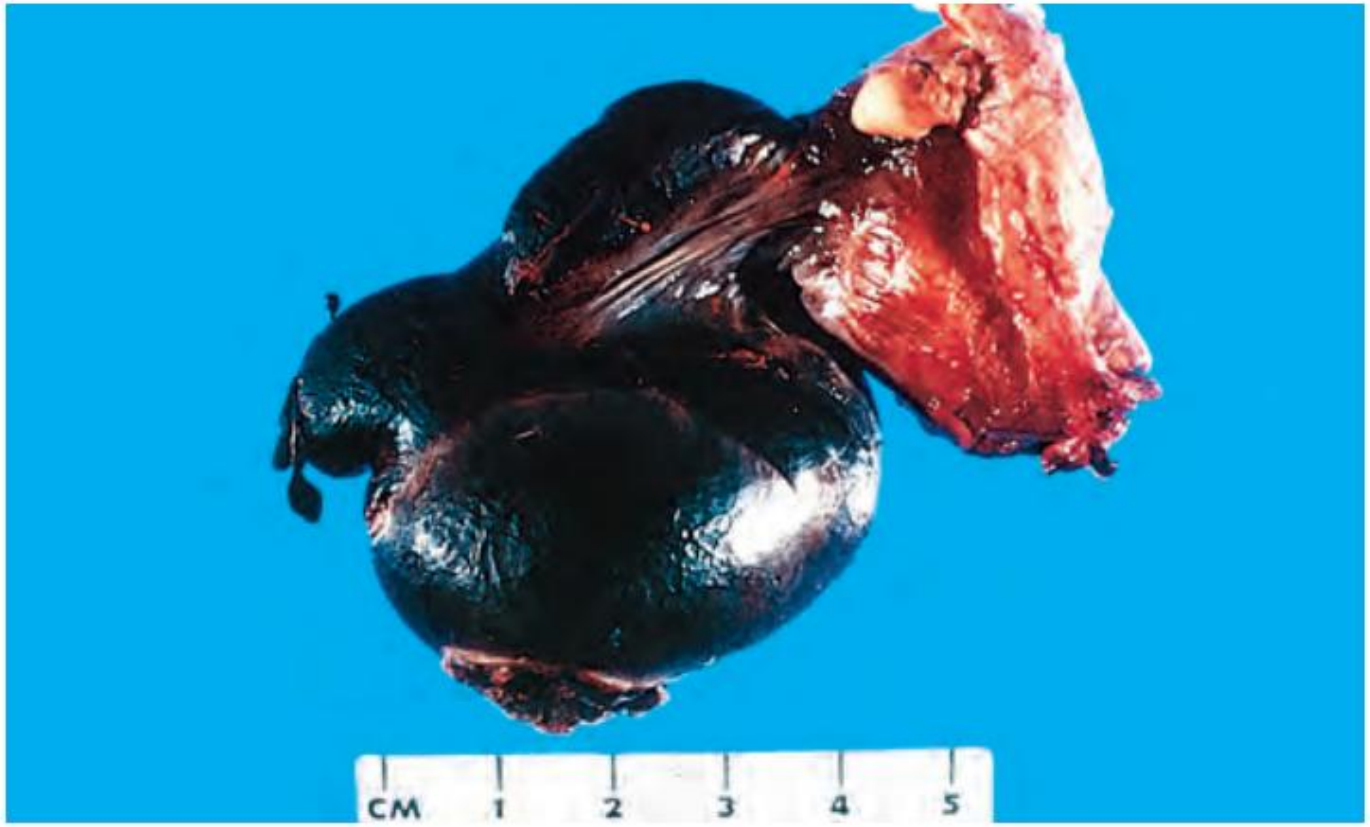
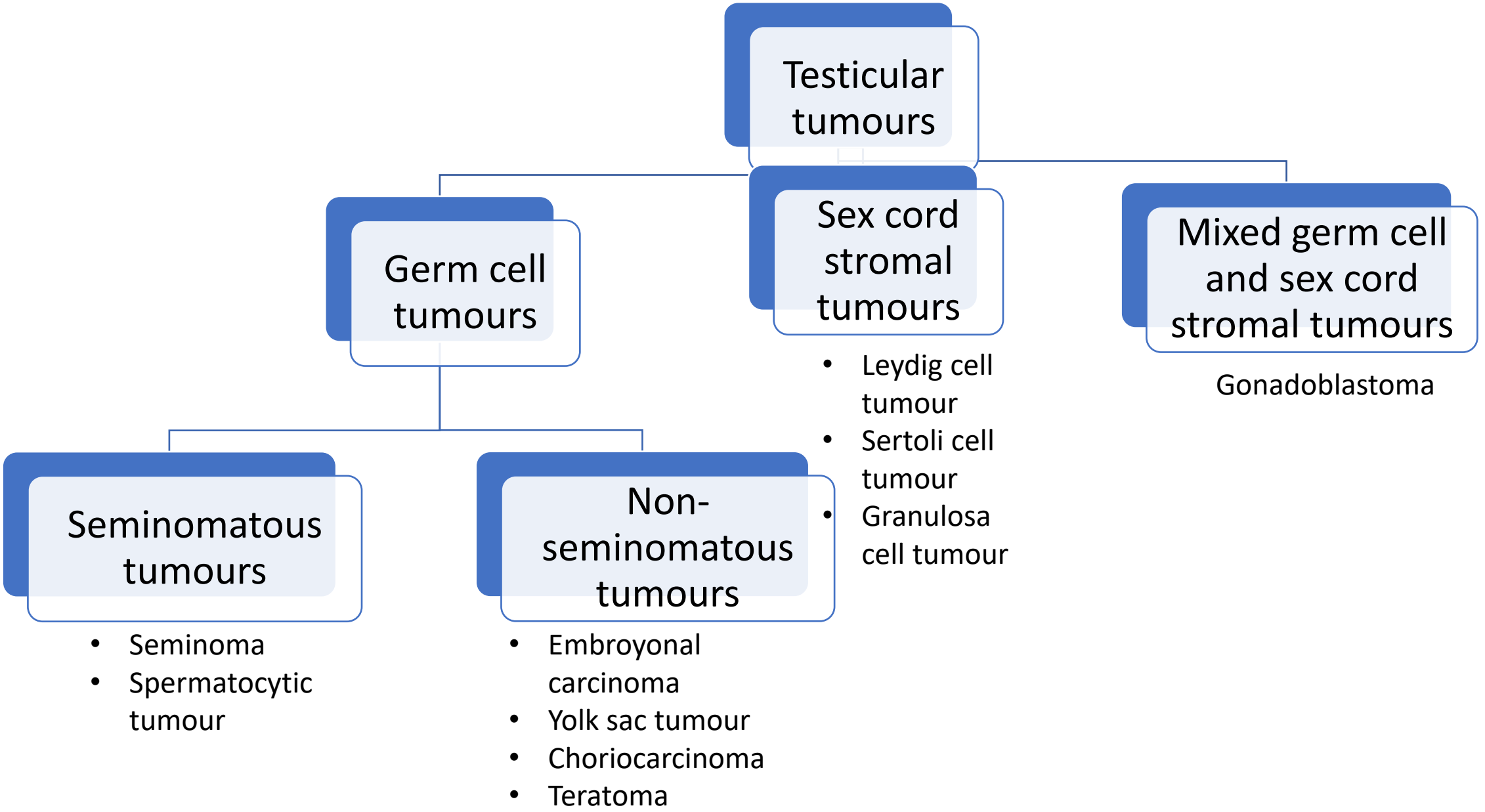
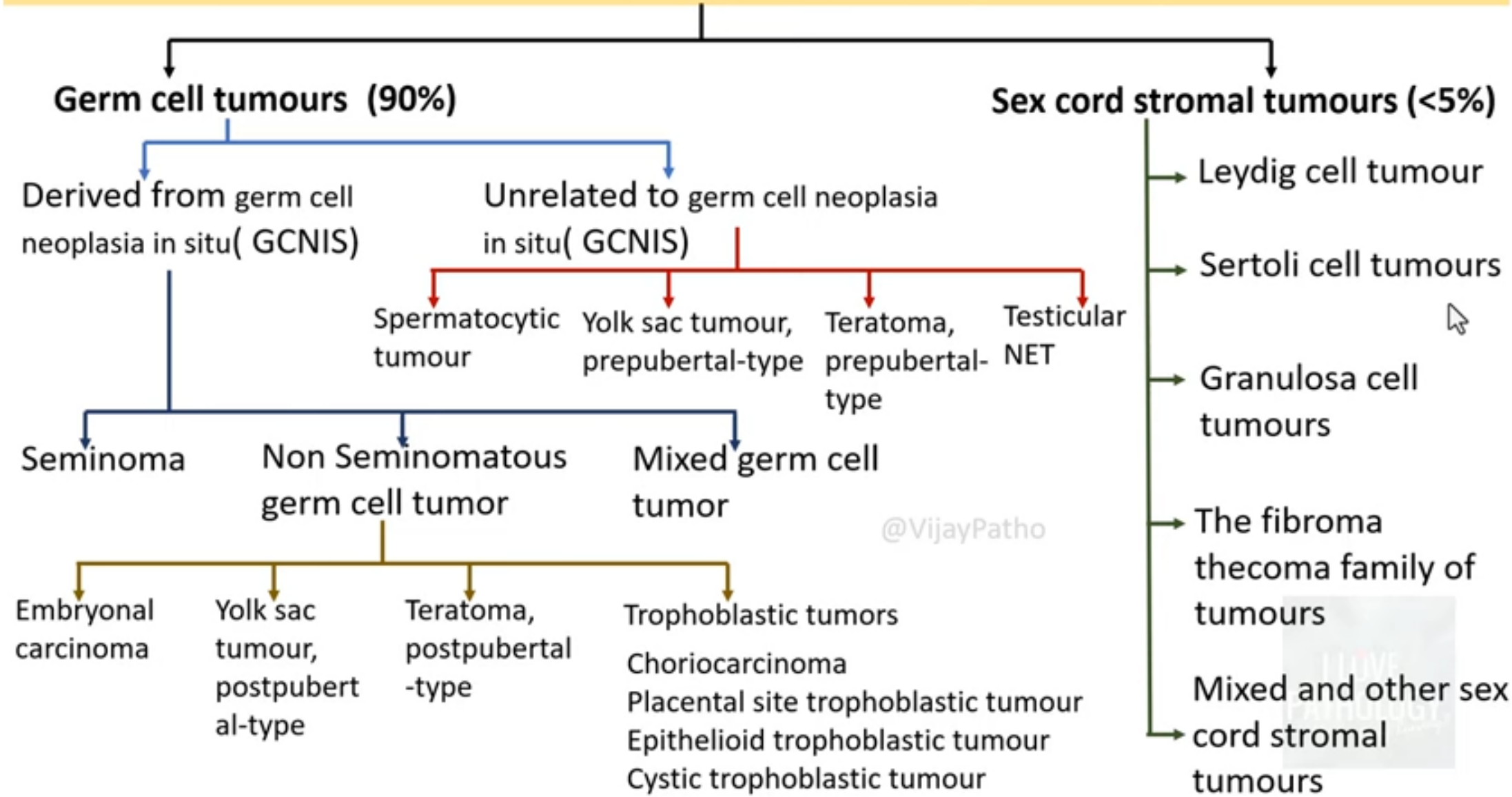


Figure 21.17 Torsion of testis. The dark discoloration is the result of hemorrhage and infarction.

Testicular tumours


Testicular tumours
Germ cell tumours
Sex cord stromal tumours
Mixed germ cell and sex cord stromal tumours
Seminomatous tumours
Non-seminomatous tumours
• Leydig cell tumour
• Sertoli cell tumour
• Granulosa cell tumour
Gonadoblastoma
• Seminoma
• Spermatocytic tumour
• Embroyonal carcinoma
• Yolk sac tumour
• Choriocarcinoma
• Teratoma

TUMORS OF TESTIS – CLASSIFICATION [WHO-2022]



YESPCT

TABLE 23.1: Classification of Testicular Tumours.

I. GERM CELL TUMOURS

1. Seminoma
2. Spermatocytic seminoma
3. Embryonal carcinoma
4. Yolk sac tumour (*Syn.* endodermal sinus tumour, orchioblastoma, infantile type embryonal carcinoma)
5. Polyembryoma
6. Choriocarcinoma
7. Teratomas
   - (i) Mature
   - (ii) Immature
   - (iii) With malignant transformation
8. Mixed germ cell tumours

II. SEX CORD-STROMAL TUMOURS

1. Leydig cell tumour
2. Sertoli cell tumour (Androblastoma)
3. Granulosa cell tumour
4. Mixed forms

III. COMBINED GERM CELL-SEX CORD-STROMAL TUMOURS

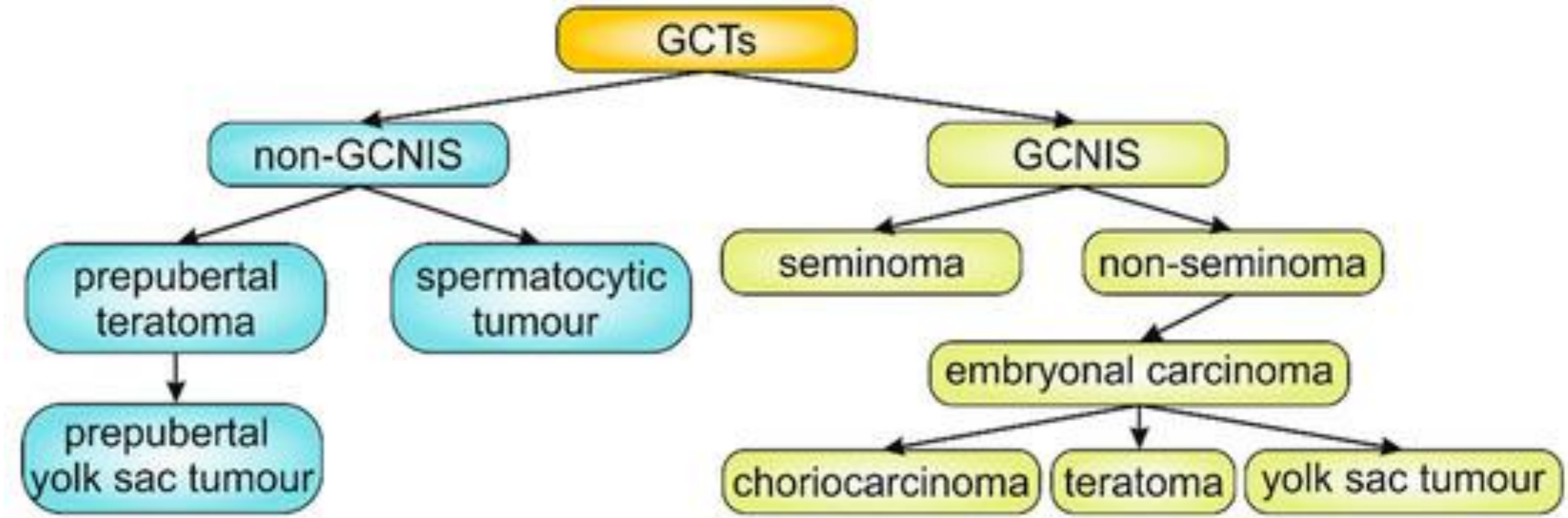
Gonadoblastoma

IV. OTHER TUMOURS

1. Malignant lymphoma (5%)
2. Rare tumours

Intratubular Germ Cell Neoplasia (ITGCN)

- It is used to describe the preinvasive stage of germ cell tumours, notably intratubular seminoma and intratubular embryonal carcinoma.
- Others have used **carcinoma in situ (CIS)** stage of germ cell tumours as synonymous term.
- Histologically, the malignant atypical tumour cells are **restricted to the seminiferous tubules without evident invasion into the interstitium.**


GCTs
non-GCNIS
GCNIS
prepubertal teratoma
spermatocytic tumour
seminoma
non-seminoma
prepubertal yolk sac tumour
embryonal carcinoma
choriocarcinoma
teratoma
yolk sac tumour

Etiological factors

- **Cryptorchidism**
- Dysgenetic gonads associated with endocrine abnormalities such as **androgen insensitivity syndrome**
- **Genetic factors** - high incidence in first-degree family members, twins and in white male
- **Orchitis**
- **Trauma**
- **Carcinogens** - LSD, hormonal therapy for sterility, copper, zinc
- **Exposure to radiation**
- **Endocrine abnormalities**

Molecular genetics factors

i) Hyperdiploidy

ii) isochromosome of short arm of chromosome 12, abbreviated as i(12p), is found.

iii) deletion of long arm of chromosome 12 abbreviated as del(12q), is present.

iv) Telomerase activity is present in all germ cell tumours of

the testis.

v) Other mutations include p53, cyclin E and FAS gene.

PATHOGENESIS

Environmental factors

In utero exposures to pesticides and nonsteroidal estrogens

Associated with testicular dysgenesis syndrome

Cryptorchidism, hypospadias, and poor Sperm quality.

cryptorchidism, associated with appr 10% of testicular GCTs

Genetic factors

Four times higher than normal in fathers and sons of affected patients

8 to 10 times higher in brothers

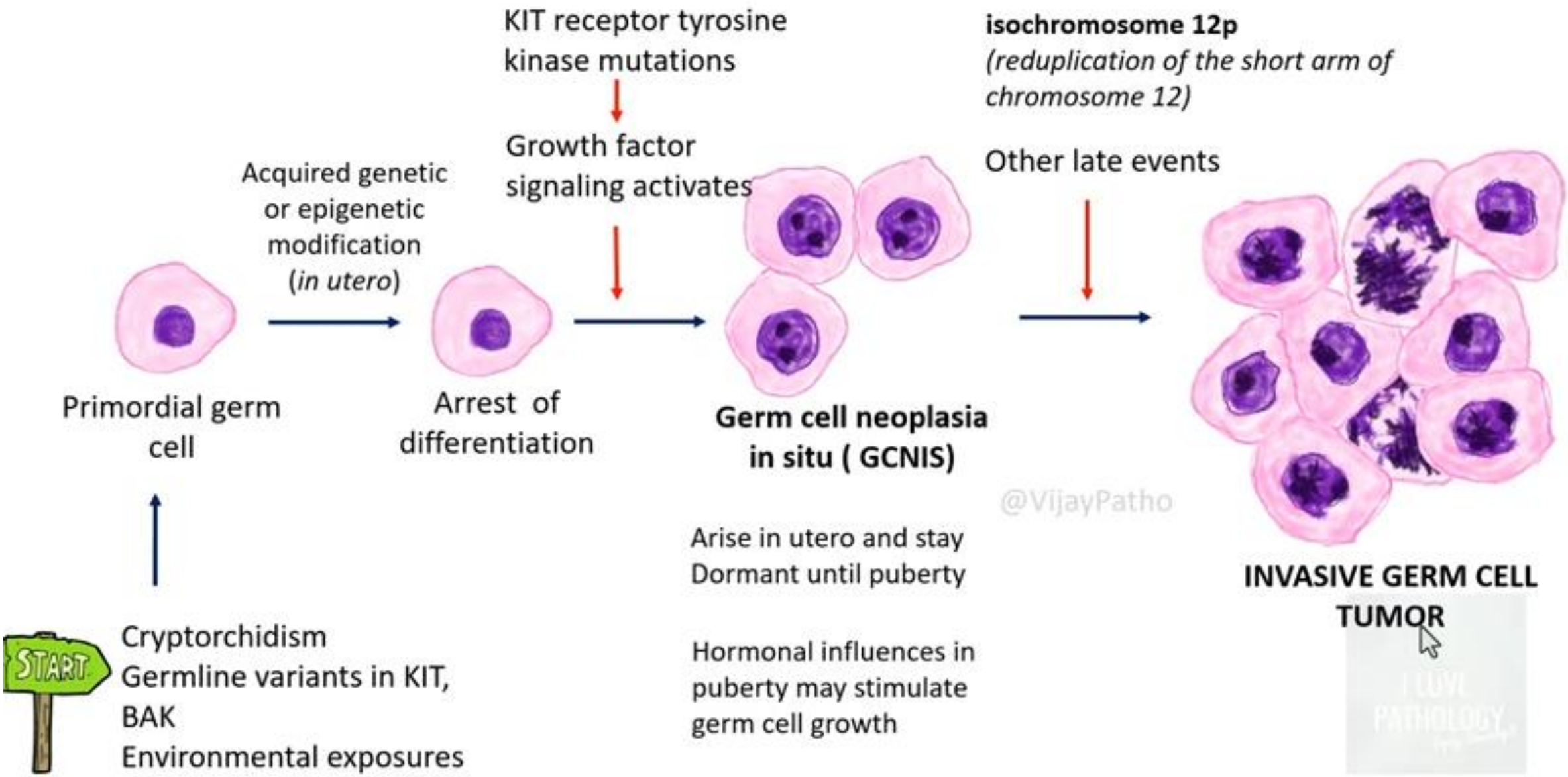
Genetic Variations:

KIT ligand: Linked to familial GCT risk.

BAK gene: A key player in apoptosis (cell death).

Both genes are crucial for proper gonadal development.

PATHOGENESIS OF TESTICULAR GERM CELL TUMORS



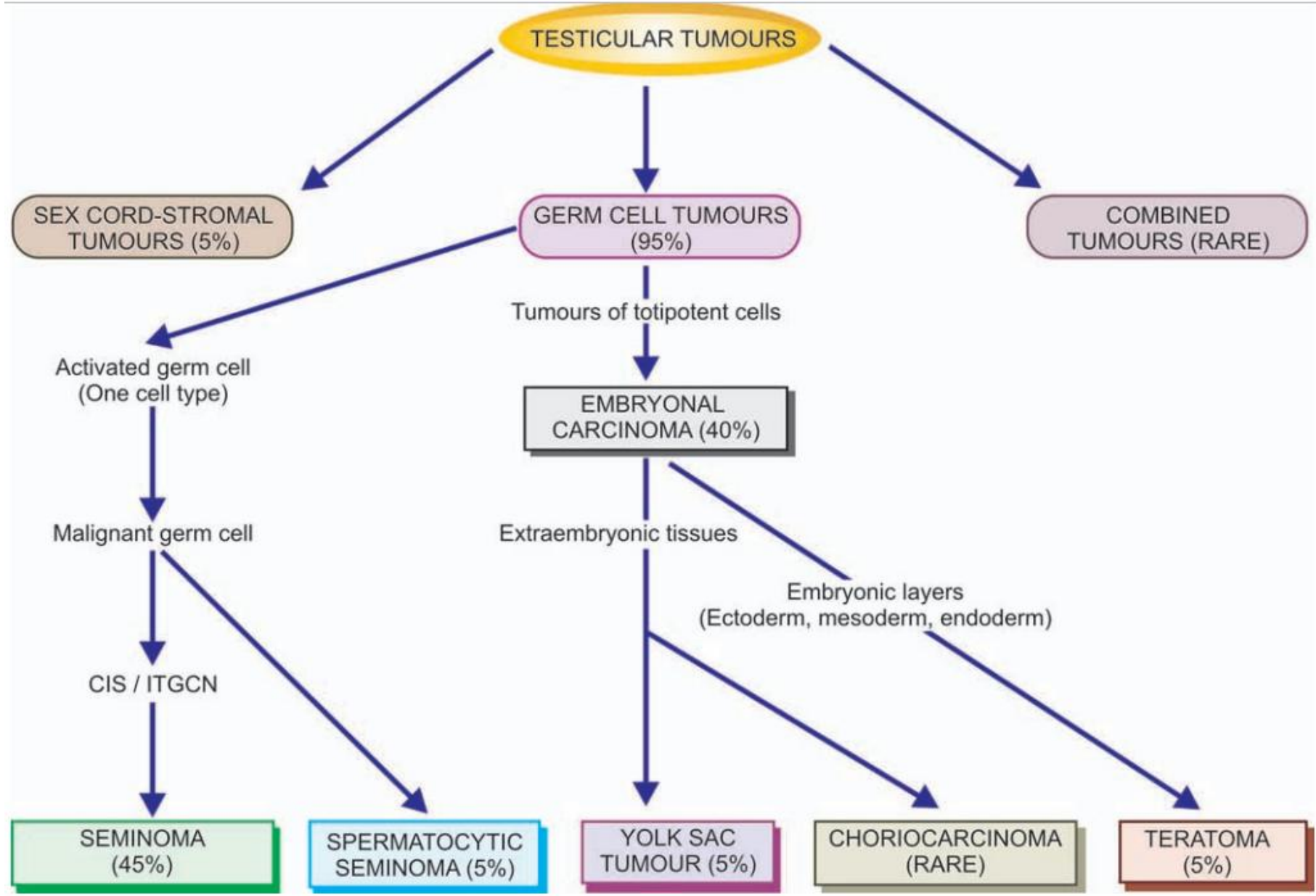


Figure 23.4 Schematic diagram showing histogenesis of testicular tumours.

Classic Seminoma

- Commonest malignant tumour of the testis
- Peak incidence in the 4th decade of life and is **rare before puberty**

Pathogenesis

Delayed maturation of primordial germ cells / gonocytes

↓

Polyploidization

↓

Transformed germ cell

↓

Germ cell neoplasia in situ

↓

Invasive seminoma

Investigations

- Testicular ultrasound - Uniform, well delineated and hypoechoic mass on ultrasound
- Serum LDH and PLAP may be elevated
- hCG : Modest elevation in up to 20% of cases
- AFP should not be increased, if elevated think liver disease or nonseminoma component

Gross :

Enlarged up to 10 times its normal size

Tends to maintain its normal contour

Rarely invades the tunica.

Cut section :

homogeneous, grey-white, lobulated.

Necrosis and haemorrhage in the tumour are rare.

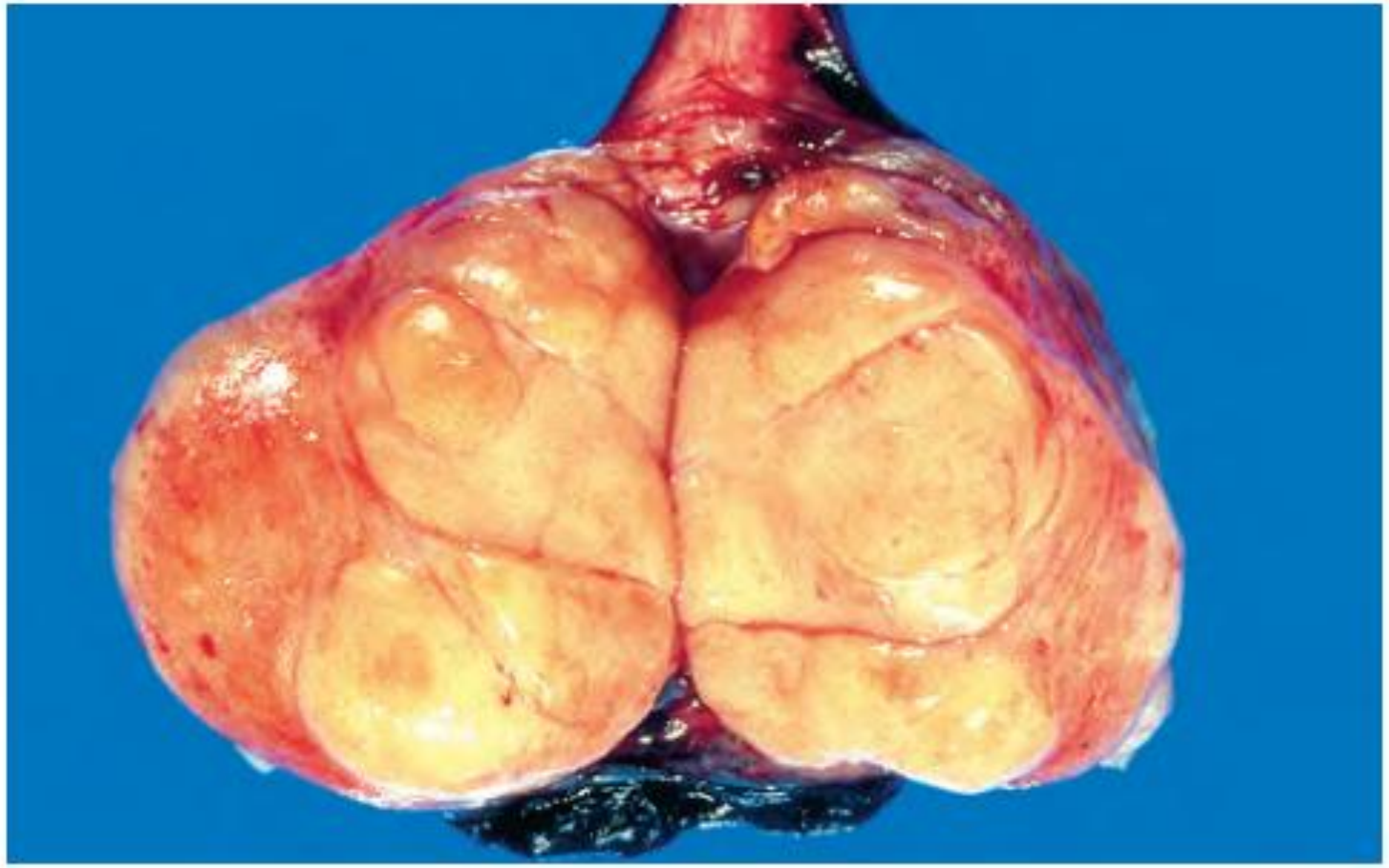


Figure 21.19 Seminoma of the testis, appearing as a well-circumscribed, pale, fleshy, homogeneous mass on cut surface.

Microscopy

1. Tumor cells:

- In cords, sheets or columns forming lobules.
- uniform size; well-defined cell borders.
- The cytoplasm : Clear with variable amount of glycogen that stains positively with PAS reaction.
- Nuclei : centrally located, large, hyperchromatic and usually contain 1-2 prominent nucleoli.
- Tumour giant cells may be present.

2. Stroma :

- Delicate fibrous tissue which divides the tumour into lobules.
- characteristic lymphocytic infiltration, indicative of immunologic response of the host to the tumour.
- About 20% of the tumours show granulomatous reaction in the stroma.

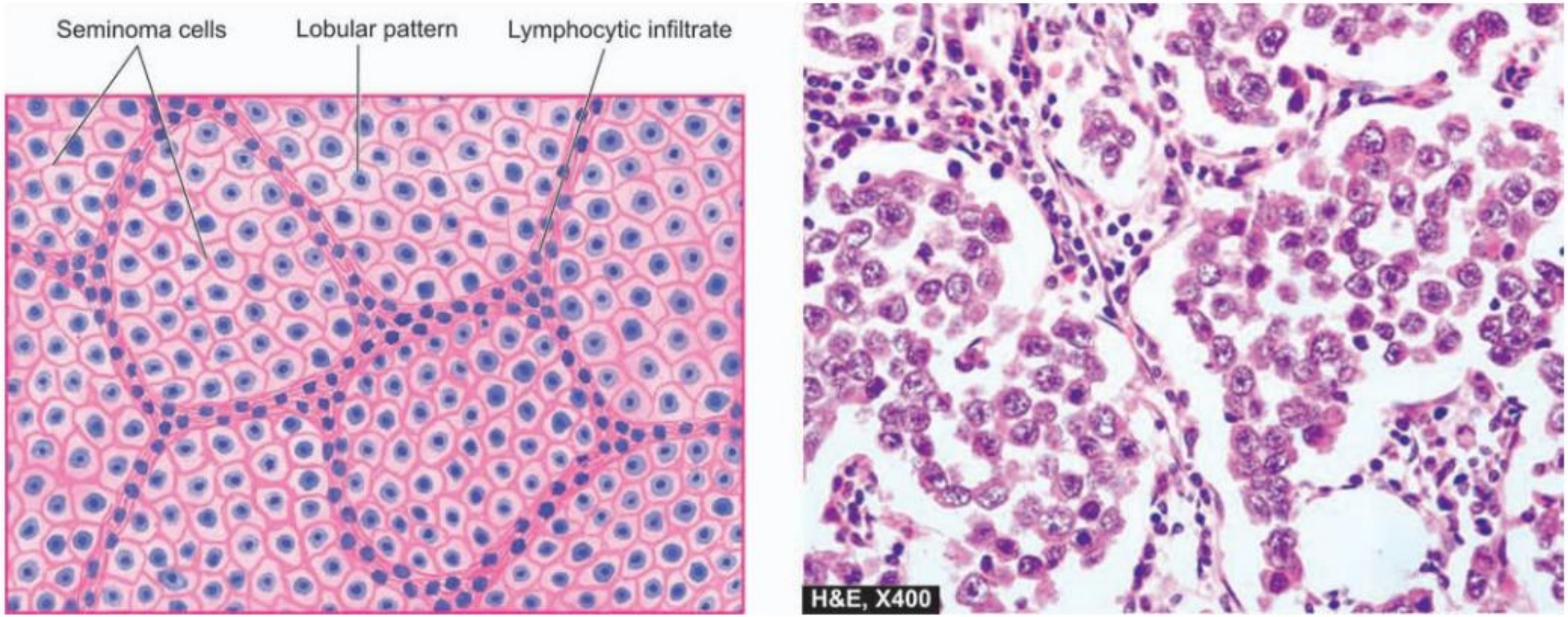
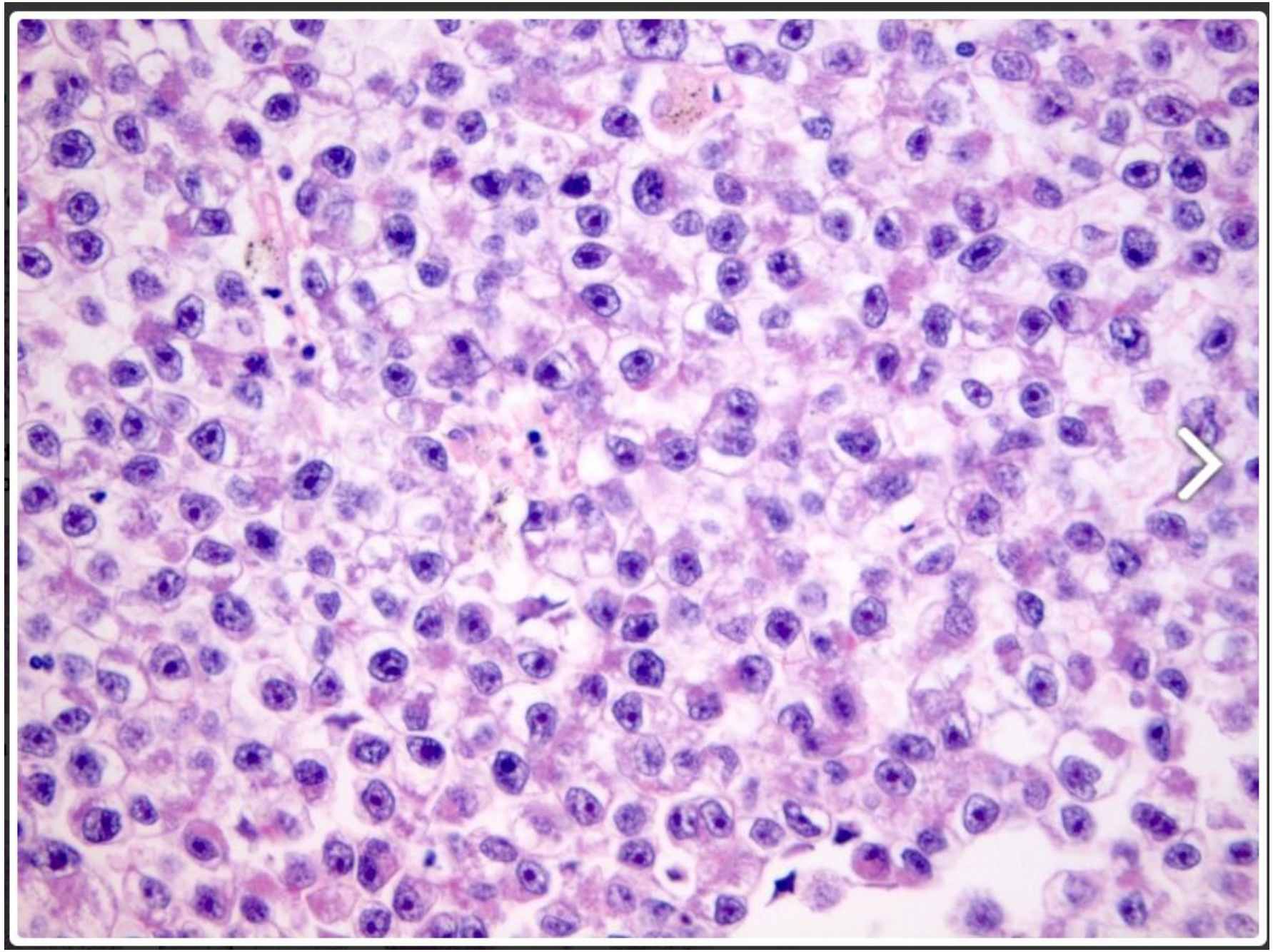
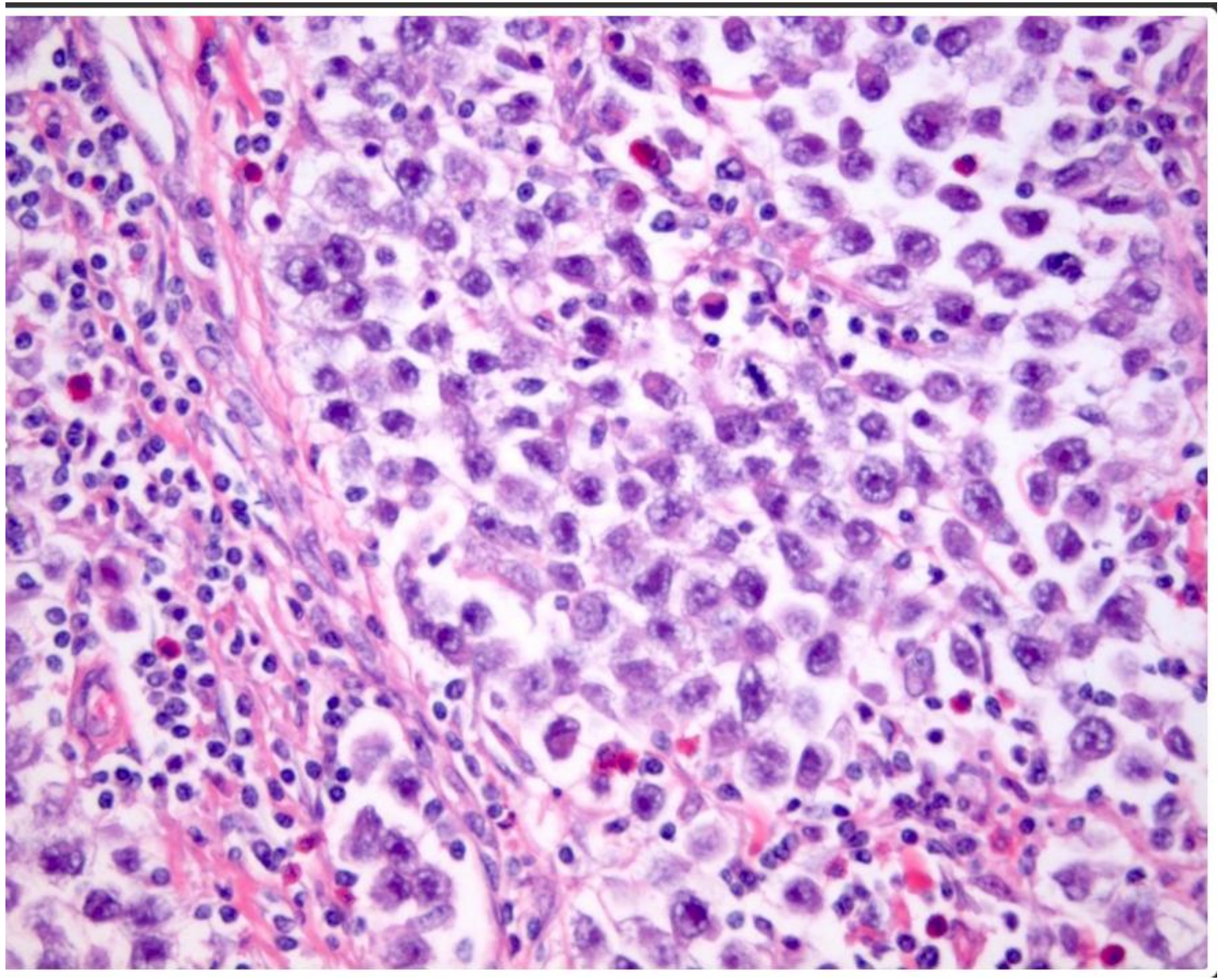


Figure 23.6 Seminoma testis. Microscopy of the tumour shows lobules of monomorphic seminoma cells separated by delicate fibrous stroma containing lymphocytic infiltration.





Special stains/ IHC Markers

- **Positive stains**

OCT 3/4, **CD117**, **D2-40**, **PLAP**, **SALL4**, **SOX17, PAS**

- **Negative stains**

CD30, **AFP**, **glypican 3**, **hCG** (syncytiotrophoblasts may be positive)

EMA, **AE1 / AE3** stains cytoplasm of occasional cells in < 30% of cases, **CK7**

Inhibin, **p63**, **PAX8**, **GATA3**

Treatment

- Prognosis is better than non-seminomatous tumours
- **Highly radiosensitive**

Spermatocytic ~~Seminoma~~ Tumour

- Clinically and morphologically a distinctive tumour from classic seminoma
- 5% of all germ cell tumours
- 6th decade of life.
- bilateral in 10% of patients.

- Gross :

homogeneous, larger, softer and more yellowish and gelatinous than the classic seminoma.

Pathogenesis

Postpubertal type germ cells (spermatogonium / spermatocyte)

Chromosomal abnormalities (amplification of chromosome 9)

Spermatocytic seminoma

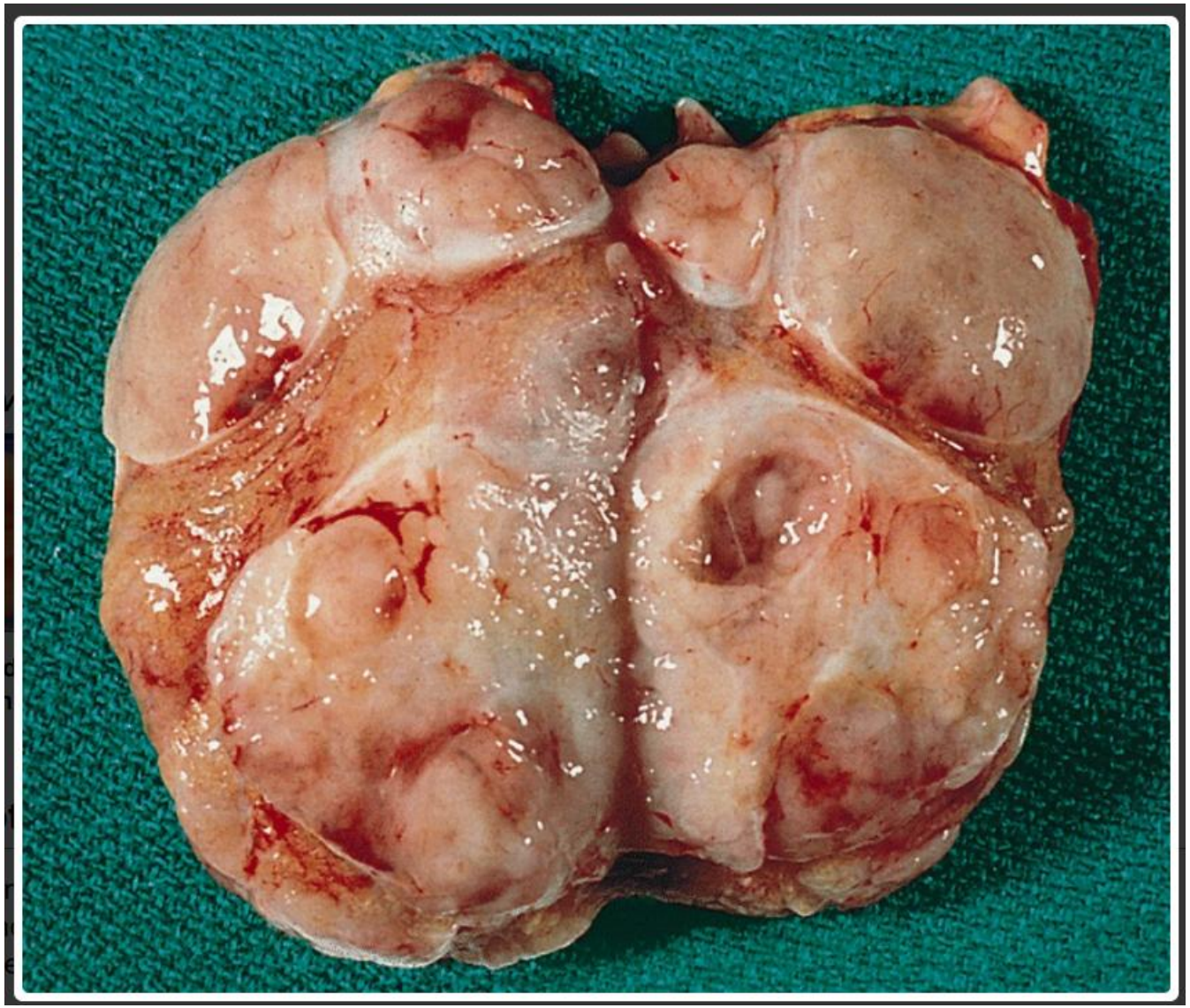
No Germ cell in situ neoplasia

Labs

- LDH, AFP, beta hCG: Not elevated

- Gross :

Homogeneous, larger, softer and more yellowish and gelatinous than the classic seminoma.

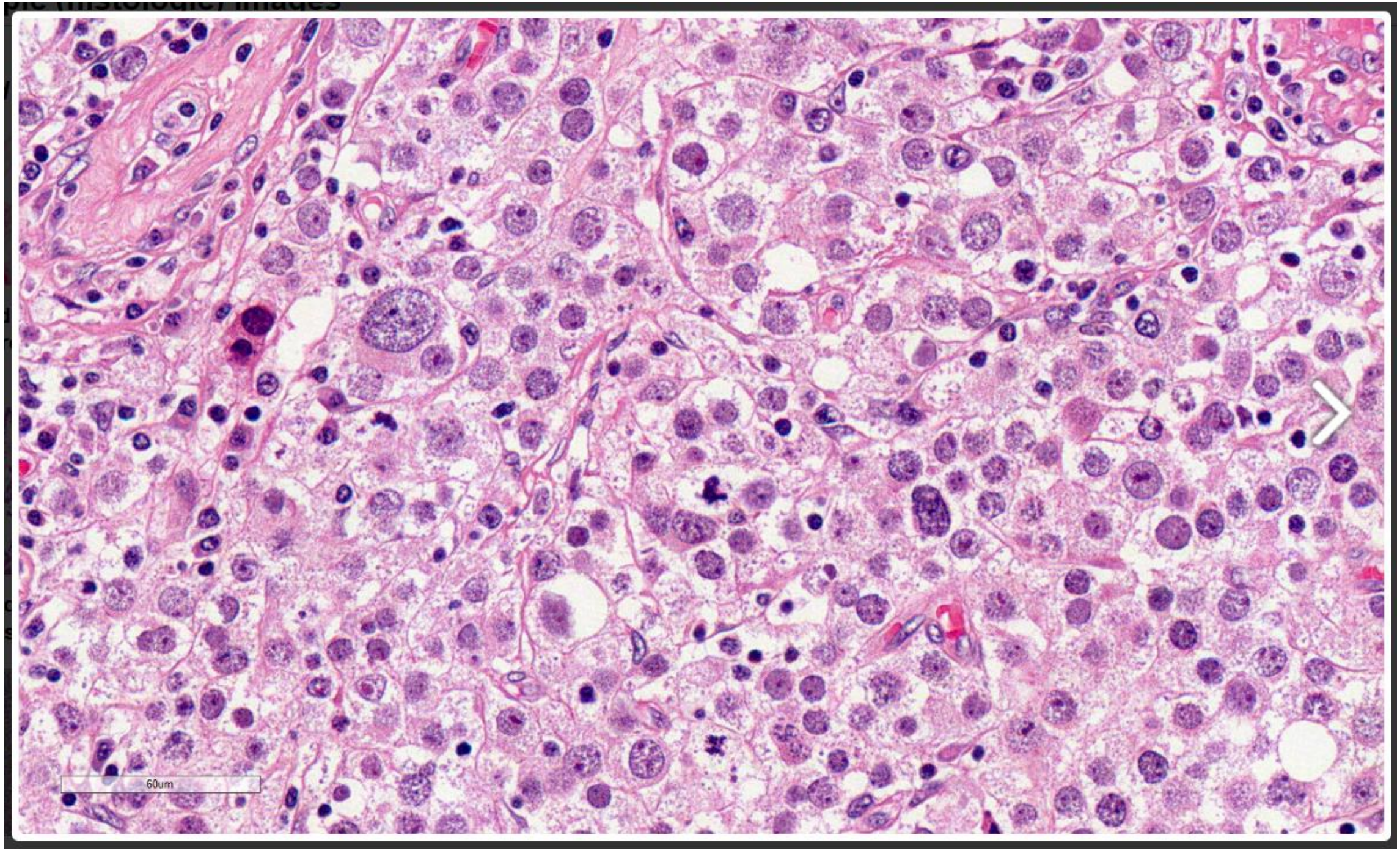


Microscopy :

1. Tumour cells.

- Vary considerably in size from lymphocyte-like to huge mononucleate or multinucleate giant cells. **Three types of cells**.
- Majority of the tumour cells are of intermediate size.
- Eosinophilic cytoplasm devoid of glycogen
- The nuclei of intermediate and large cells have filamentous pattern.
- Mitoses are often frequent.

2. Stroma. The stroma lacks lymphocytic and granulomatous reaction seen in classic seminoma.

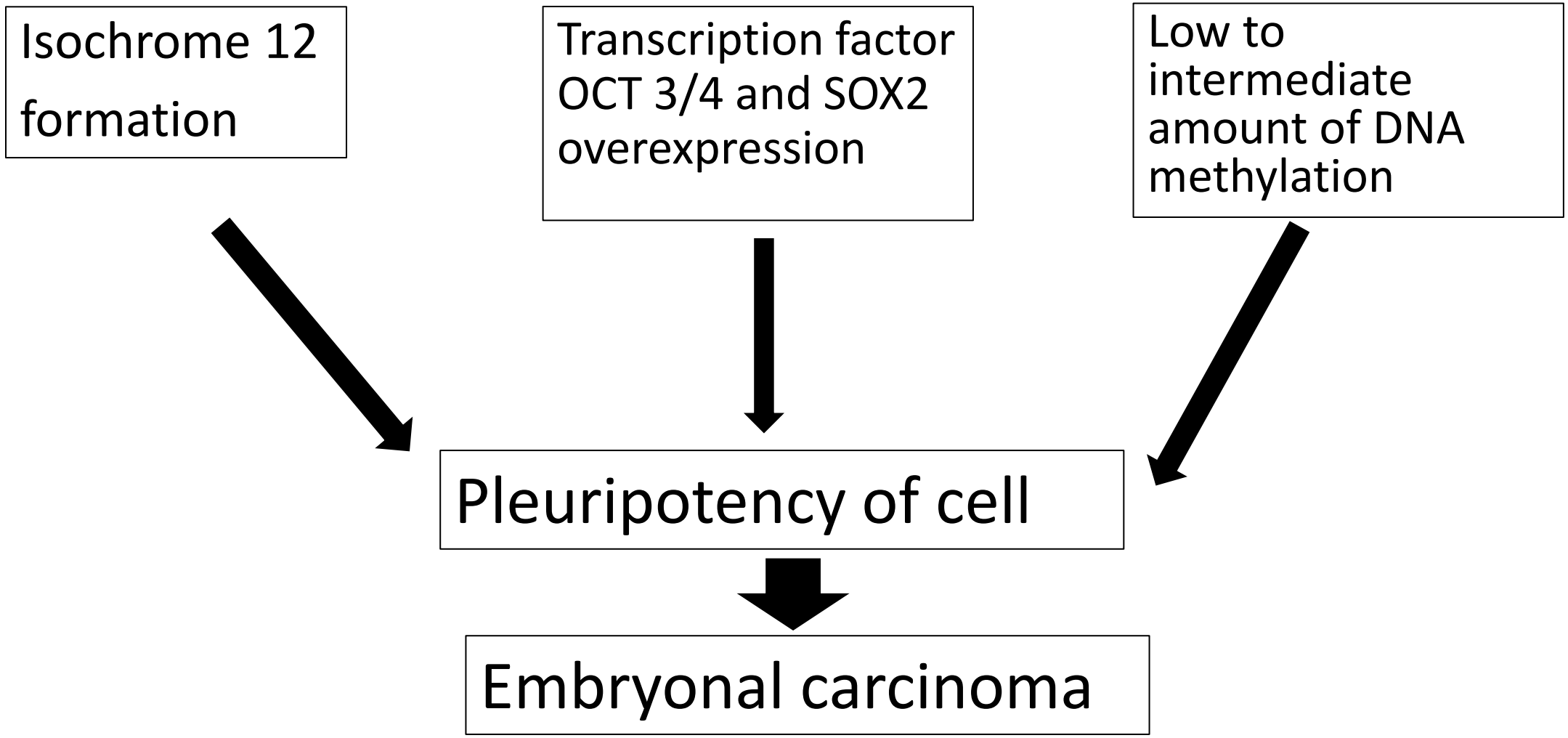

60um

- Slow growing
- Rarely metastasizes
- Radiosensitive
- Good prognosis

Embryonal Carcinoma

- 2nd to 3rd decades of life
- Can be pure or as a component of germ cell tumour
- 90% cases are associated with elevation of AFP or hCG or both

Pathogenesis



Lab

- Serum tumor markers should not be used as a screening tool
- Elevated serum human chorionic gonadotropin (hCG),
- alpha fetoprotein (AFP) and
- lactate dehydrogenase (LDH) may be present
- Current guidelines recommend measuring hCG, AFP and LDH before and after initial treatment –Serum tumor markers can be used to monitor for recurrence

Gross :
A small tumour in the testis

Frequently invades the tunica and the epididymis

Cut surface - variegated appearance due to the presence of foci of hemorrhage or necrosis

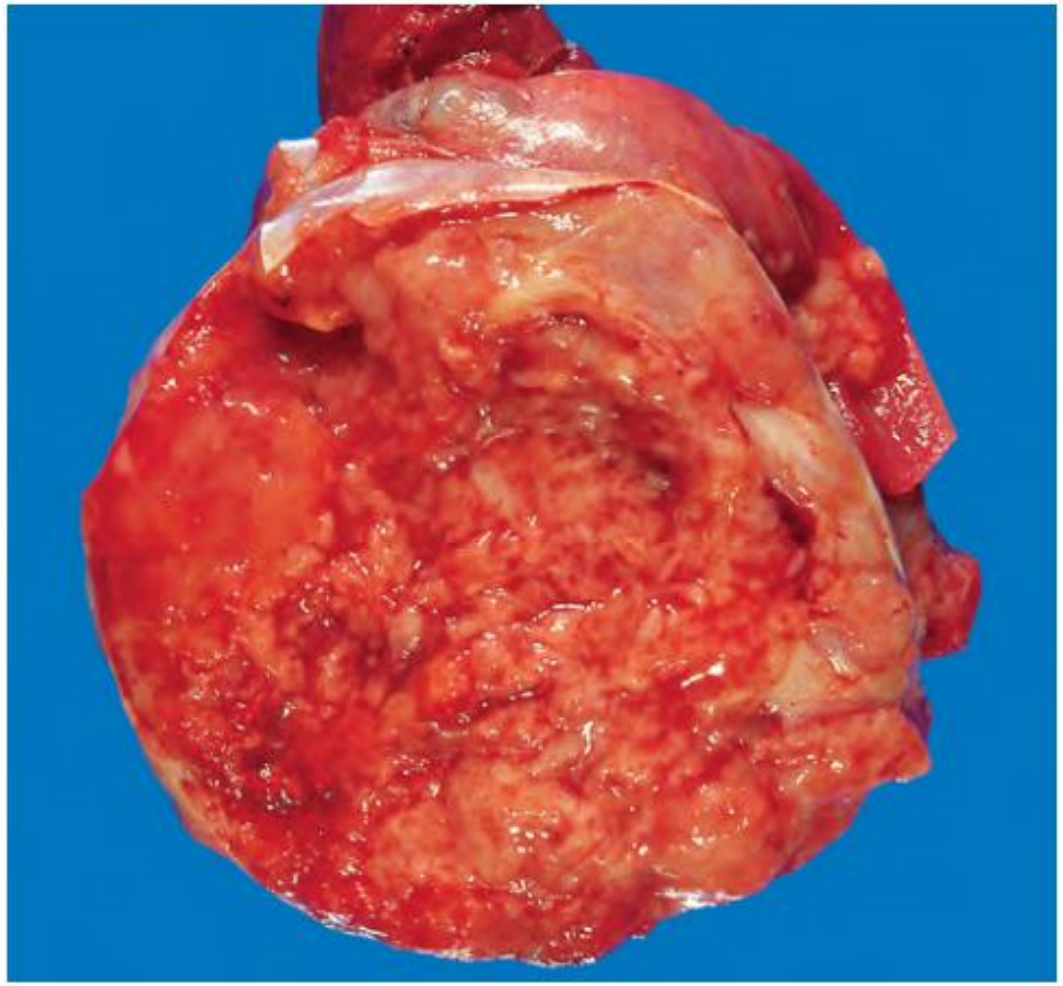


Figure 21.21 Embryonal carcinoma. In contrast to the seminoma illustrated in Fig. 21.19, as shown here, embryonal carcinoma often produces a hemorrhagic mass.

Microscopy :

1. The tumour cells are arranged in a variety of patterns— glandular, tubular, papillary and solid.
2. The tumour cells –
   highly anaplastic carcinomatous cells
   large size,
   indistinct cell borders,
   amphophilic cytoplasm
   prominent hyperchromatic nuclei

showing considerable variation in nuclear size

   Mitotic figures and tumour giant cells

3. Haemorrhage and necrosis are common.
4. Stroma - contain variable amount of primitive mesenchyme.

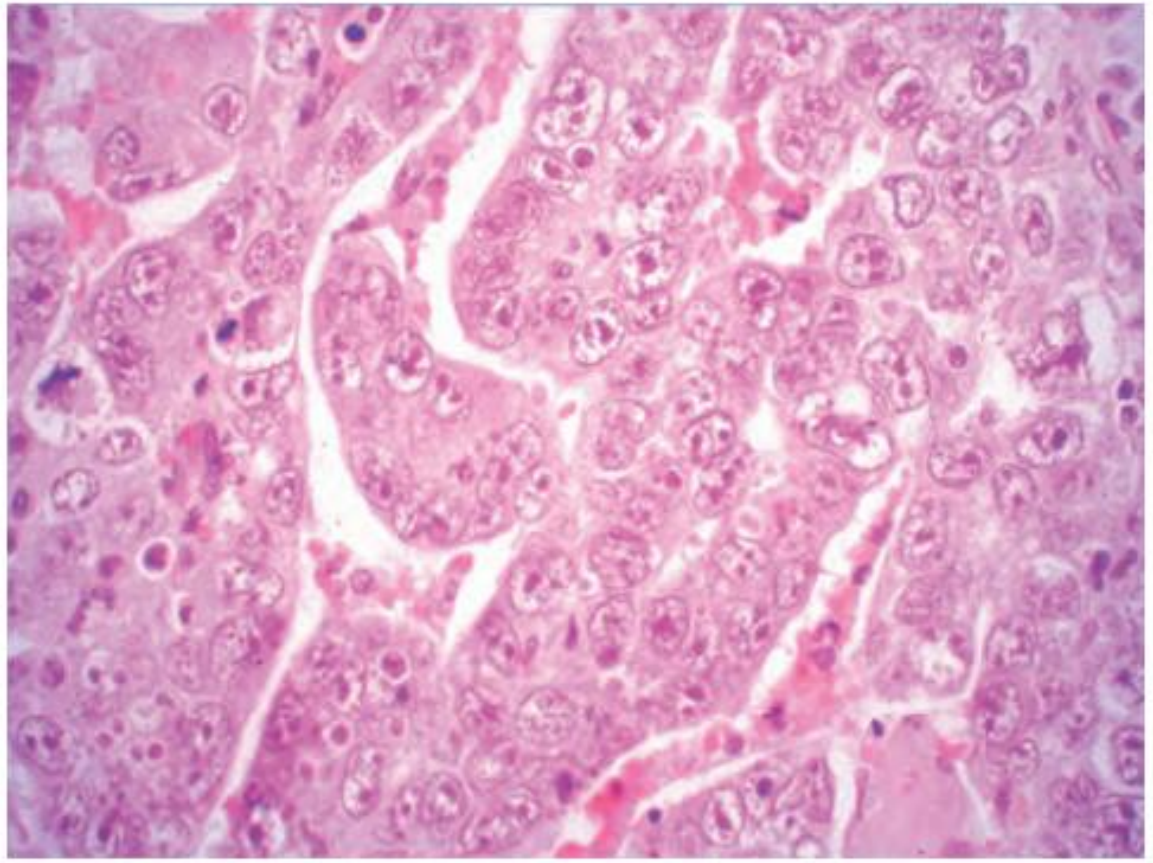


Figure 21.22 Embryonal carcinoma composed of cells with large, hyperchromatic nuclei arranged in sheets and poorly formed glands.

IHC Markers

- **Positive stains**
- **OCT 3/4** (nuclear and cytoplasmic) , **CD30** , **PLAP**: heterogenous, **SOX2** , **AE1 / AE3** , **SALL4**
- **Negative stains**
- **CD117 / KIT**: patchy, weak; **D2-40 / podoplanin**: patchy, weak, nonmembranous; **Glypican 3**: weak, focal; **AFP**: 21% positive; **CK7**: 52% weak; **Inhibin**; **p63**; **GATA3**; **Calretinin**; **SOX17**
- **Beta hCG**: caveat that tumors containing choriocarcinoma can have expression that diffuses into all GCT types, requiring careful interpretation and use of more specific markers

Treatment

- More aggressive than seminoma
- Less radiosensitive than seminoma.
- Chemotherapy is more effective

Yolk Sac Tumor

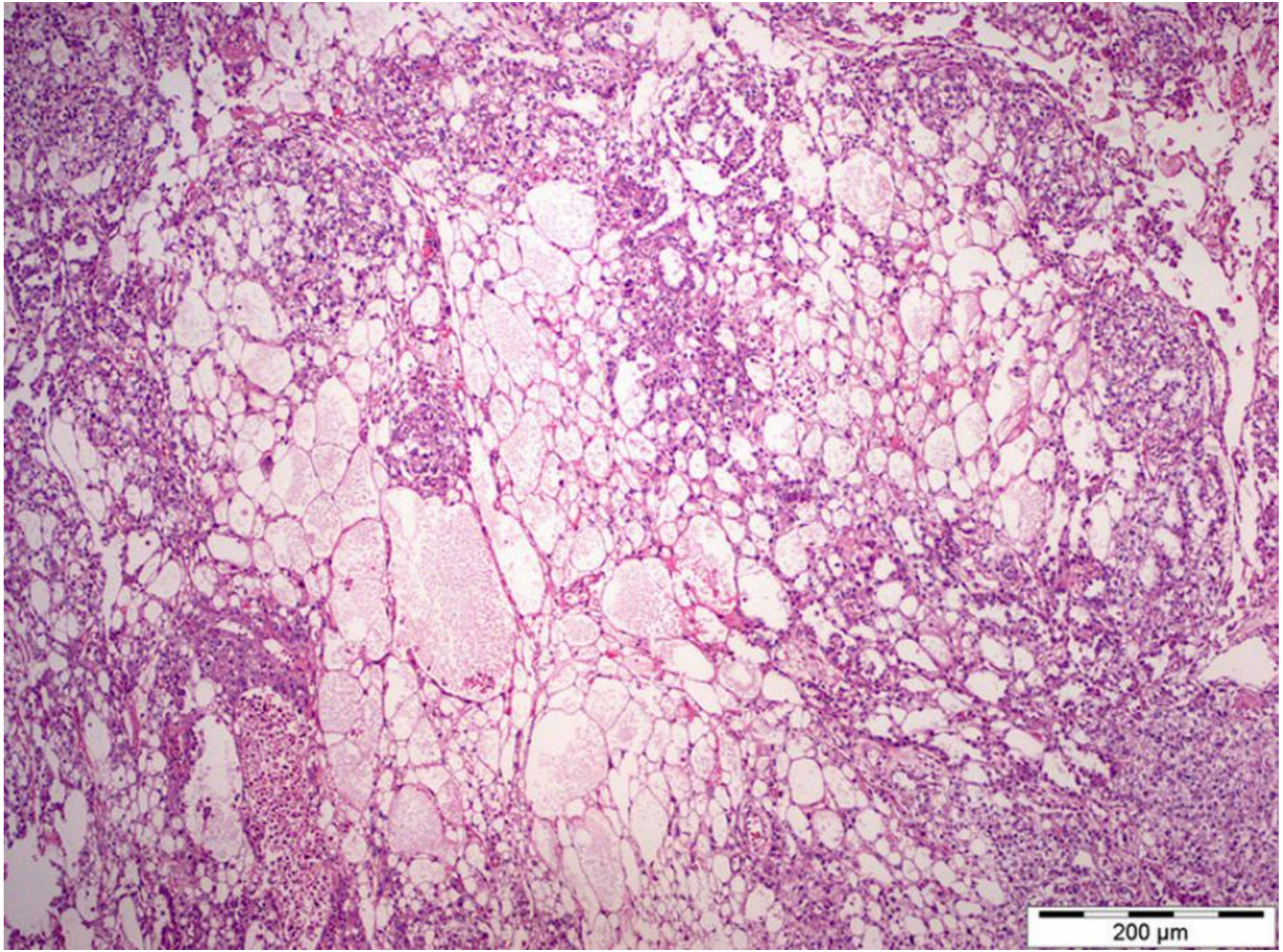
- Synonyms: Endodermal Sinus Tumour, Orchioblastoma, Infantile Embryonal Carcinoma
- Most common testicular tumour of infants and young children upto the age of 4 years
- In adults – **As a component of mixed germ cell tumour**
- AFP elevated.
- Germ cell neoplasm composed of cells / structures reminiscent of embryonic / fetal yolk sac, allantois and extraembryonal mesenchyme

Gross:

- Soft, yellow-white, mucoid with areas of necrosis and haemorrhages.

Microscopy,

1. The tumour cells arrangement : Variety of patterns—loose reticular network, papillary, tubular and solid arrangement.
2. The tumour cells : flattened to cuboid epithelial cells with clear vacuolated cytoplasm.
3. Distinctive perivascular structures resembling the yolk sac or endodermal sinuses of the rat placenta called **Schiller-Duval bodies.**



Microcystic pattern

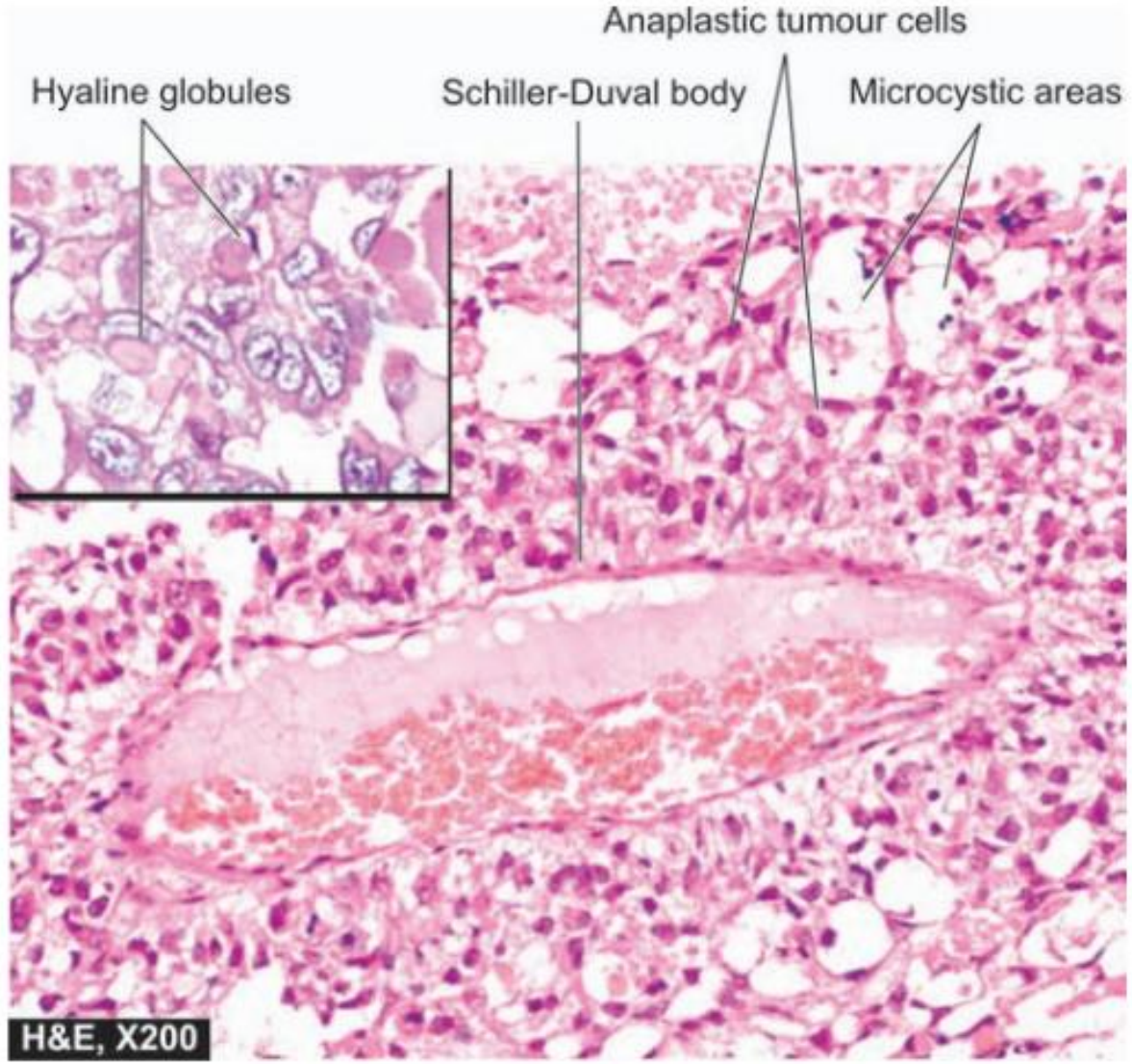
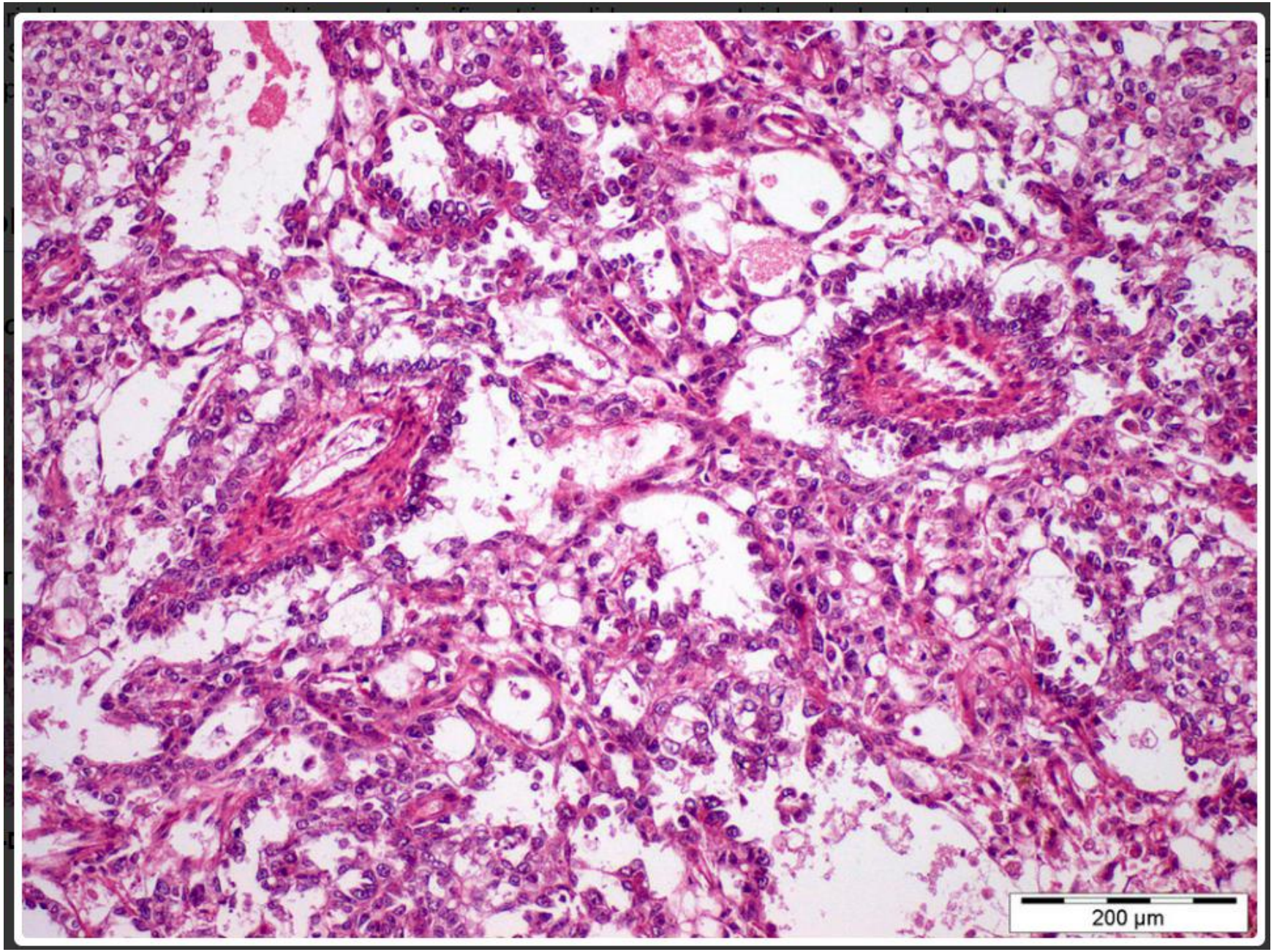


Figure 23.7 Yolk sac tumour testis. The tumour has microcystic pattern and has highly anaplastic tumour cells. Several characteristic Schiller-Duval bodies are present. Inset shows intra- and extracellular hyaline globules.


200 µm

IHC markers

Positive stains

- **Alpha fetoprotein** (more specific but less sensitive: variable, often focal, in many cases entirely absent)
- **Glypican 3** (more sensitive, staining almost all cases but less specific)
- **SALL4** (sensitive and specific for most germ cell tumor types including yolk sac tumor)
- **Pancytokeratin** (uniformly positive)
- **Villin** (usually positive)
- **CK7** (84%)

Negative stains

- **OCT 3/4**

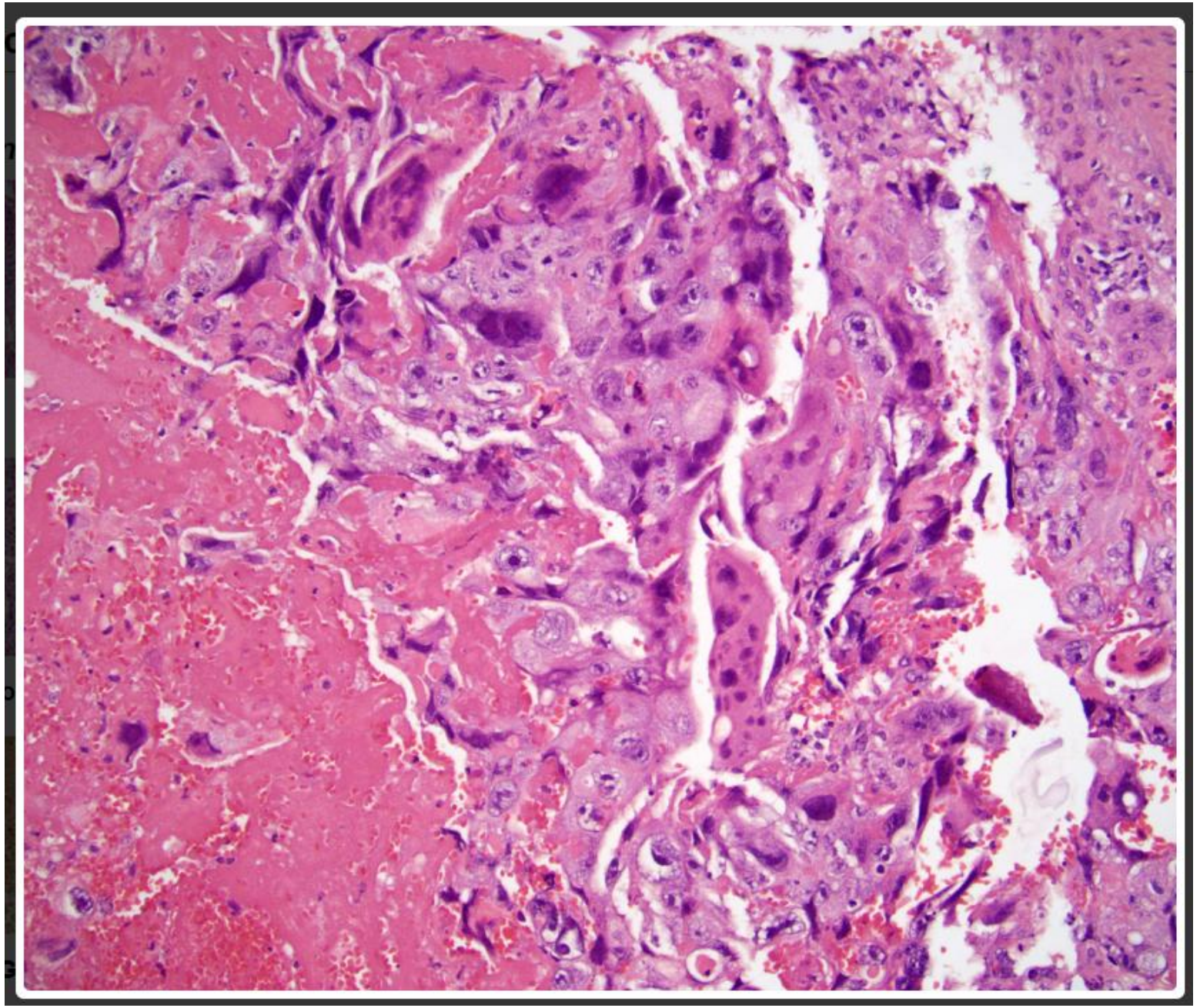
Choriocarcinoma

- Pure form is extremely rare
- 2nd decade of life
- The serum and urinary levels of hCG : greatly elevated
- Choriocarcinoma is a **malignant nonseminomatous germ cell tumor (GCT) composed of trophoblastic cells with associated hemorrhage**

- Gross:

Small, soft, haemorrhagic and necrotic mass.

- Microscopically,
  - Syncytiotrophoblast and cytotrophoblast
  - No formation of definite placental-type villi.
  - Syncytiotrophoblastic cells – large, irregular and bizarre nuclei, abundant eosinophilic vacuolated cytoplasm, positively for hCG.
  - Cytotrophoblastic cells - polyhedral cells, regular, clear or eosinophilic cytoplasm, hyperchromatic nuclei.



IHC Markers

- **Positive stains**
- **AE1 / AE3**
- **hCG**: 96% (caveat that tumors containing choriocarcinoma can have expression that diffuses into all GCT types, requiring careful interpretation and use of more specific markers)
- **GATA3**: 100% (syncytiotrophoblasts, mononucleated trophoblasts)
- **Glypican 3**: 30 - 100% (strong in syncytiotrophoblasts, mononucleated trophoblasts)
- Syncytiotrophoblasts:
  - **CK7**: 100%
  - **Inhibin**: 89%
  - **HPL**: 100%

  Mononucleated trophoblasts:
  - **SALL4**: 100%, but variable percentage of cells
  - **p63** (cytotrophoblasts): 85 - 100%

- **Negative stains**
- **OCT 3/4**: 0%
- **CD30**: 0%
- **CD117 / KIT**: 0%
- **HNF-1B**: 13%
- **CDX2**: 25%
- **AFP**: 25%

Teratoma

- Composed of tissues derived from more than one of the three germ cell layers— endoderm, mesoderm and ectoderm
- Found in combination with other germ cell tumors

Pathophysiology

- Post pubertal type associated with germ cell neoplasia in situ (GCNIS) and chromosome 12p amplification

  Thought to arise from GCNIS
- Prepubertal is not associated with GCNIS or chromosome 12p amplification

  Prepubertal type significantly less likely to metastasize or recur

Gross :

large, grey-white masses

Cut surface : variegated appearance— grey-white solid areas, cystic and honey-combed areas, and foci of cartilage and bone

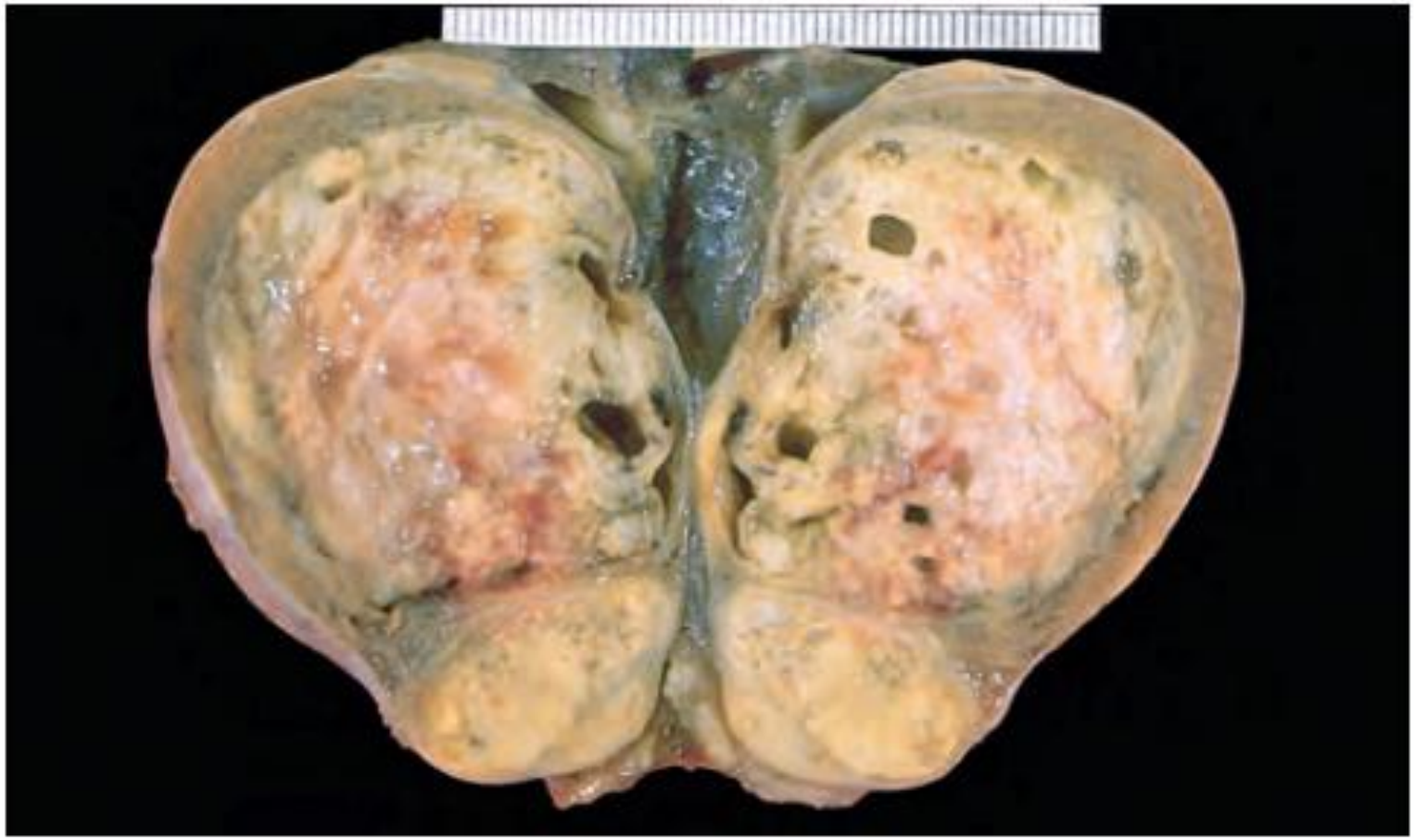


Figure 21.24 Teratoma of testis. The variegated cut surface with cysts reflects the presence of multiple tissue types.

Microscopy

- Mature teratoma : mixture of a variety of well differentiated structures

➢cartilage,

➢smooth muscle,

➢intestinal and respiratory epithelium,

➢mucus glands,

➢cysts lined by squamous and transitional epithelium,

➢neural tissue,

➢fat

➢bone

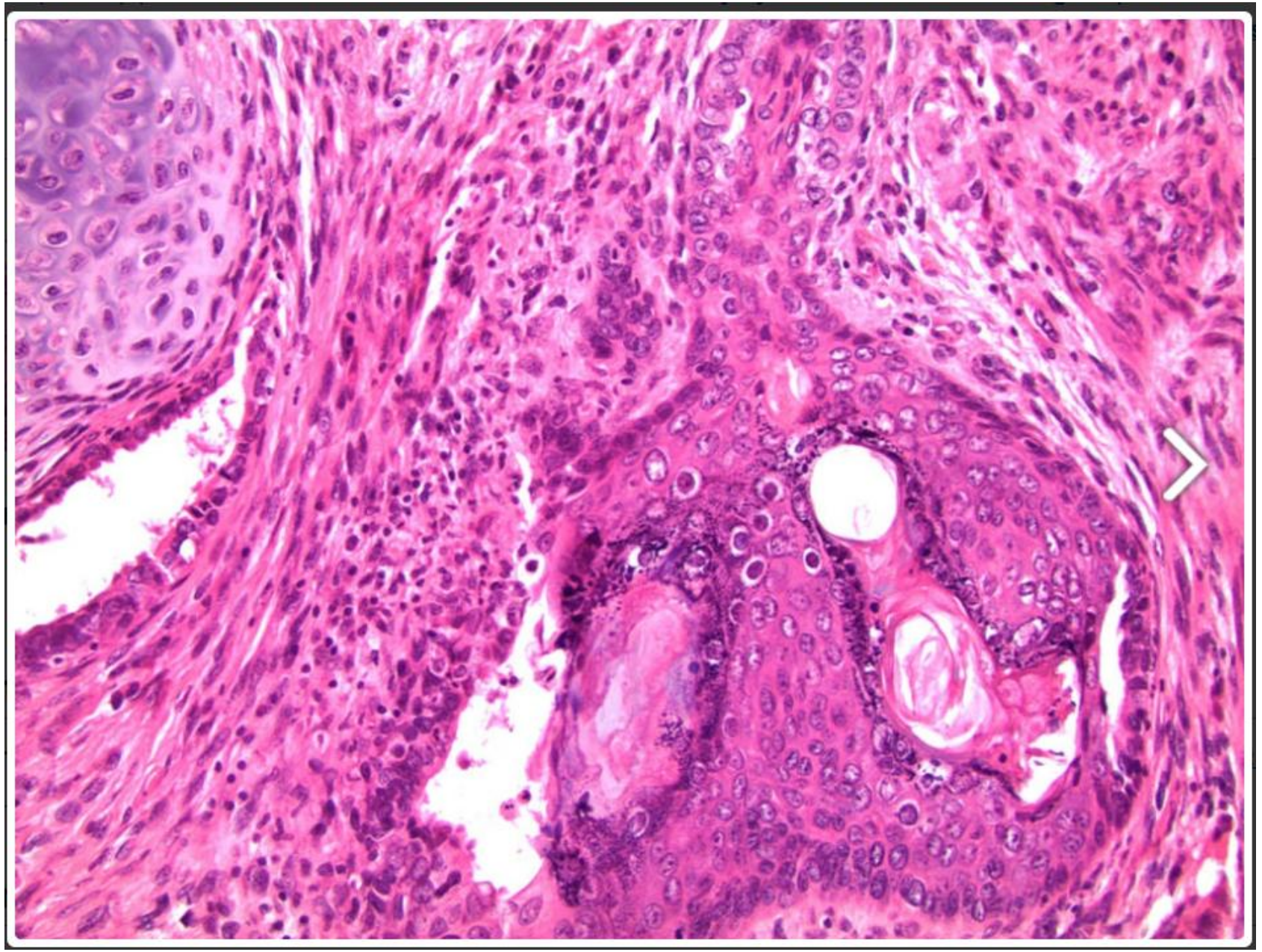
Immature teratoma :

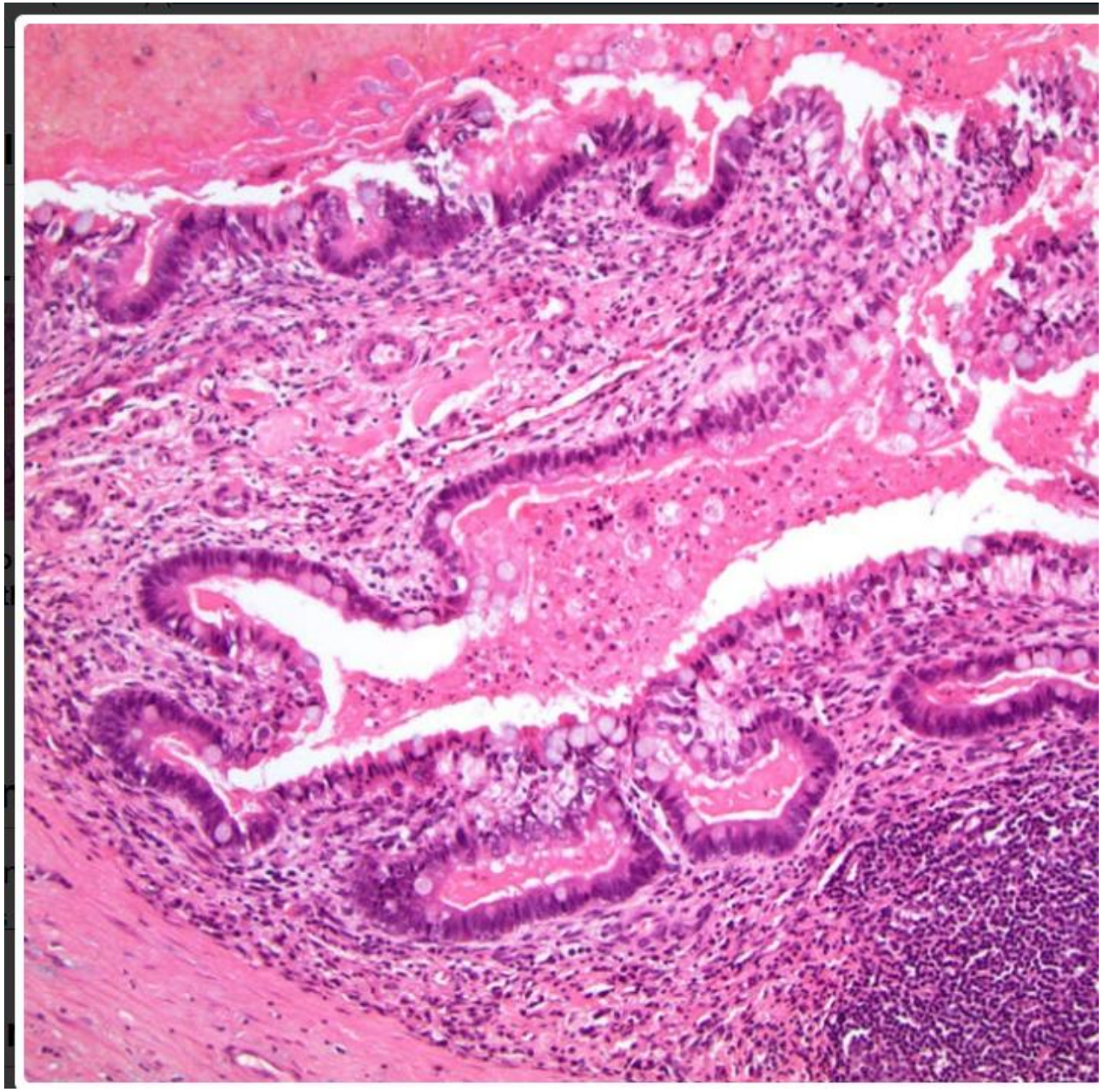
Primitive or embryonic tissue commonly present are poorly-formed-

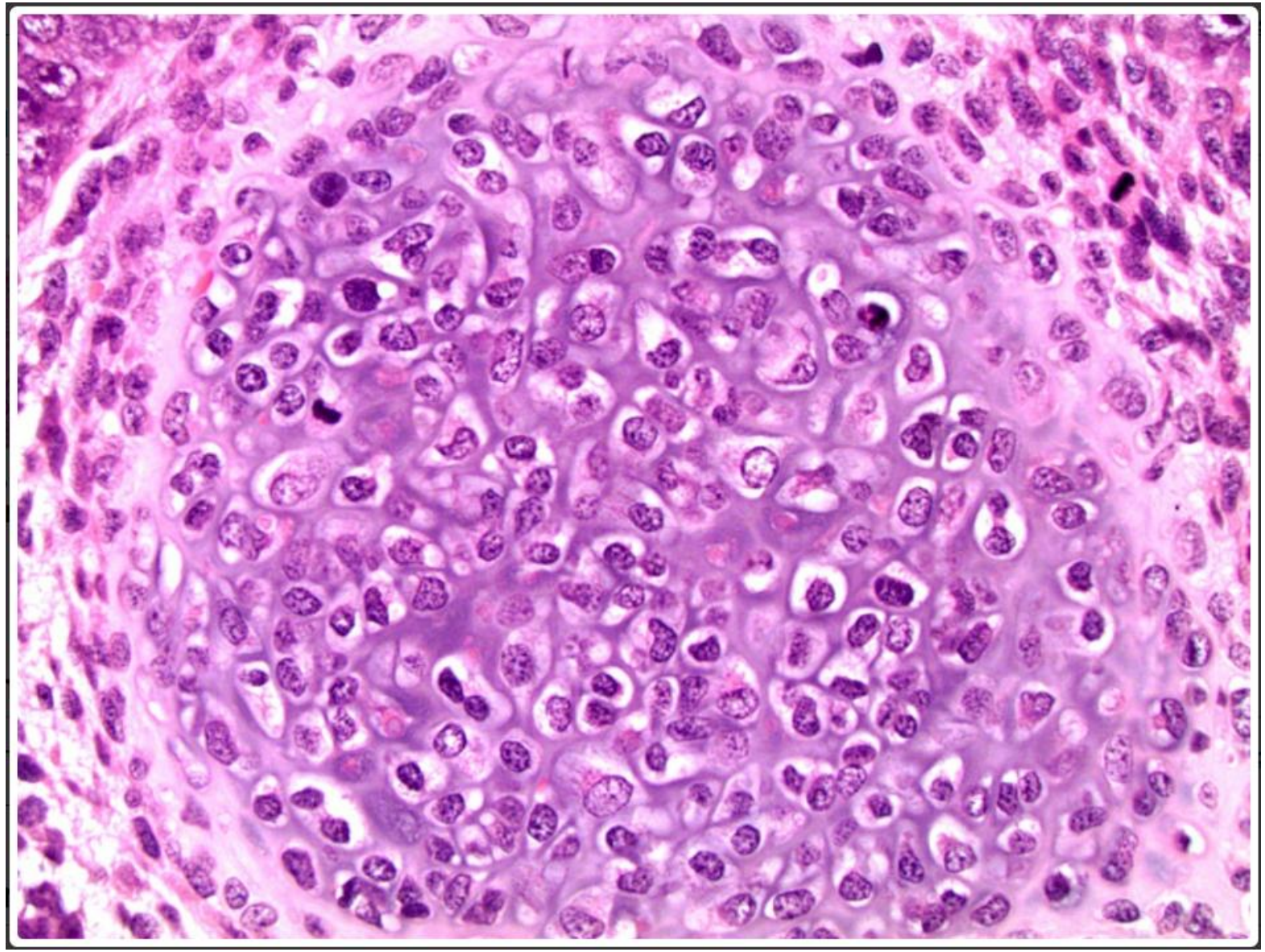
- Poorly-formed cartilage,
- Poorly-formed mesenchyme,
- Poorly-formed neural tissues,
- Abortive eye,
- Intestinal and respiratory tissue elements
- Mitoses are usually frequent.

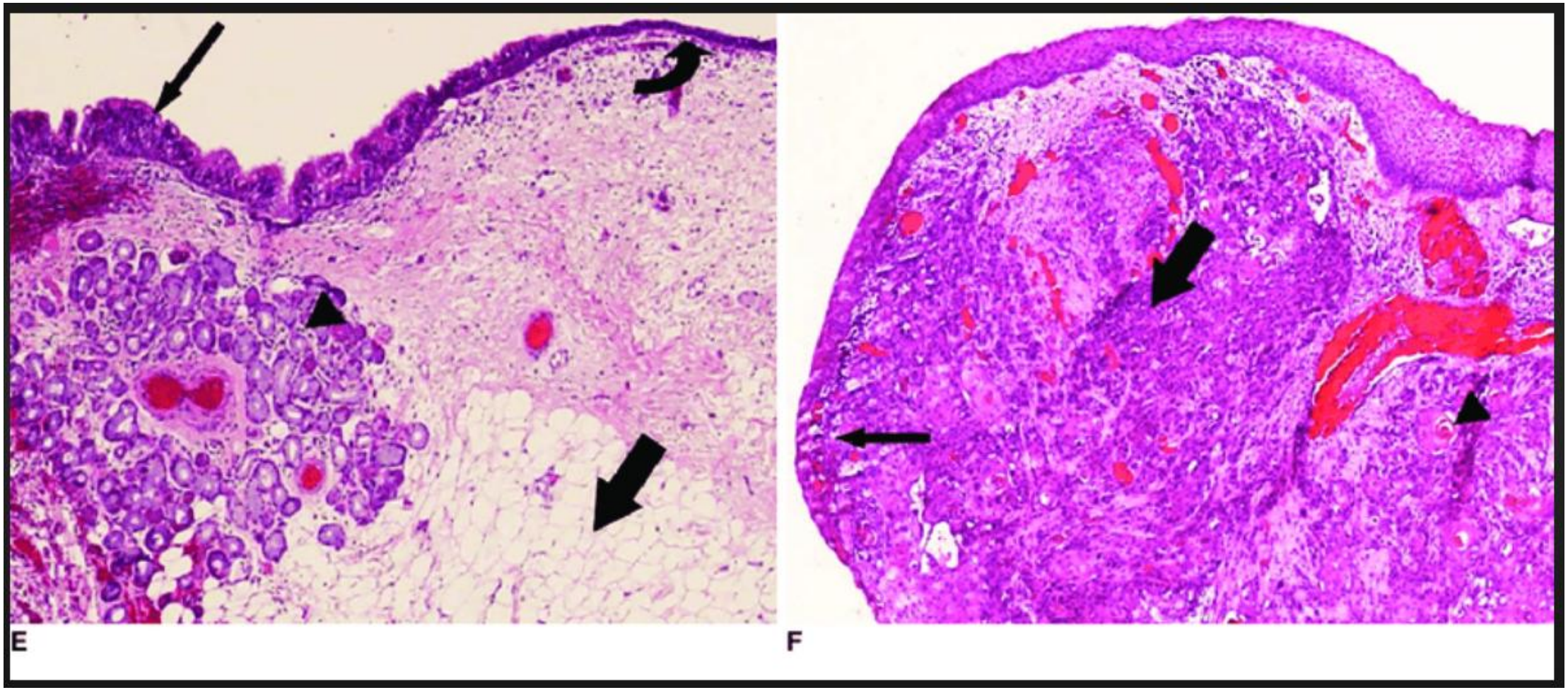
Teratoma with malignant transformation

- This is an extremely rare form of teratoma
- one or more of the tissue elements show malignant transformation.
- Eg - rhabdomyosarcoma, squamous cell carcinoma and adenocarcinoma.








E
F

Pre-pubertal teratoma –

- In infants and children
- Not associated with Germ cell in situ neoplasia or i12
- Benign course
- Good prognosis

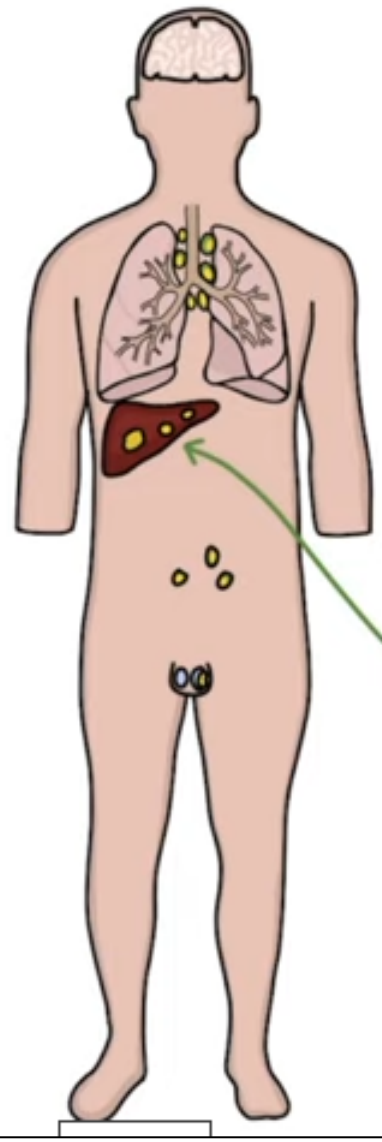
Post-pubertal teratoma -

- In adults
- Associated with Germ cell in situ neoplasia or i12
- Malignant course
- Worse prognosis

Spread of germ cell tumours

- Lymphatic spread – Para-aortic and retroperitoneal lymph nodes
- Hematogenous spread – Most commonly to lung.

Other organs – Liver, brain, bone



ROYAL MARSDEN STAGING SYSTEM

STAGE 1 → ISOLATED TO THE TESTICLE

STAGE 2 → RETROPERITONEAL LYMPH NODES

STAGE 3 → LYMPH NODES ABOVE THE DIAPHRAGM

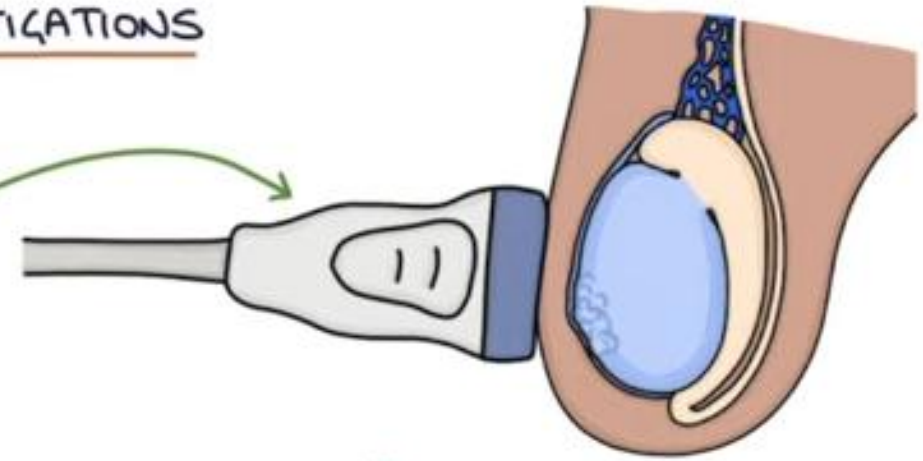
STAGE 4 → METASTASISED TO OTHER ORGANS

Germ cell tumors – IHC markers

Tumour	SALL 4	Oct 3/4	PLAP	C-Kit/ CD117	D2-40	DMRT1, NUT, OCT2, SSX2	CD30	SOX2	AE1/AE3	AFP	Glypican 3	hCG	GATA3
Seminoma	+	+	+	+	+								
Spermatocytic tumour	+					+							
Embryonal carcinoma	+	+	+				+	+	+				
Yolk sac tumour	+								+	+	+		
Choriocarcinoma	+											+	+

INVESTIGATIONS

→ SCROTAL ULTRASOUND



→ TUMOUR MARKERS

- ↳ ALPHA-FETOPROTEIN → TERATOMAS (NOT SEMINOMAS)
- ↳ BETA-HCG → TERATOMAS
  - → SEMINOMAS
- ↳ LACTATE DEHYDROGENASE (LDH)
  - ↳ NON-SPECIFIC

→ STAGING CT SCAN → LOOK FOR SPREAD

→ STAGE

FEATURE	SGCT	NSGCT
Primary tumour	Larger, confined to testis; testicular contour retained	Smaller, testicular contour may be distorted
Metastasis	Regional lymph nodes	Haematogenous spread early
Response to radiation	Radiosensitive	Radioresistant
Serum markers	OCT -4,KIT,PLAP → high hCG, AFP → generally low levels	hCG, AFP, or both → high levels
Prognosis	Better	Poor

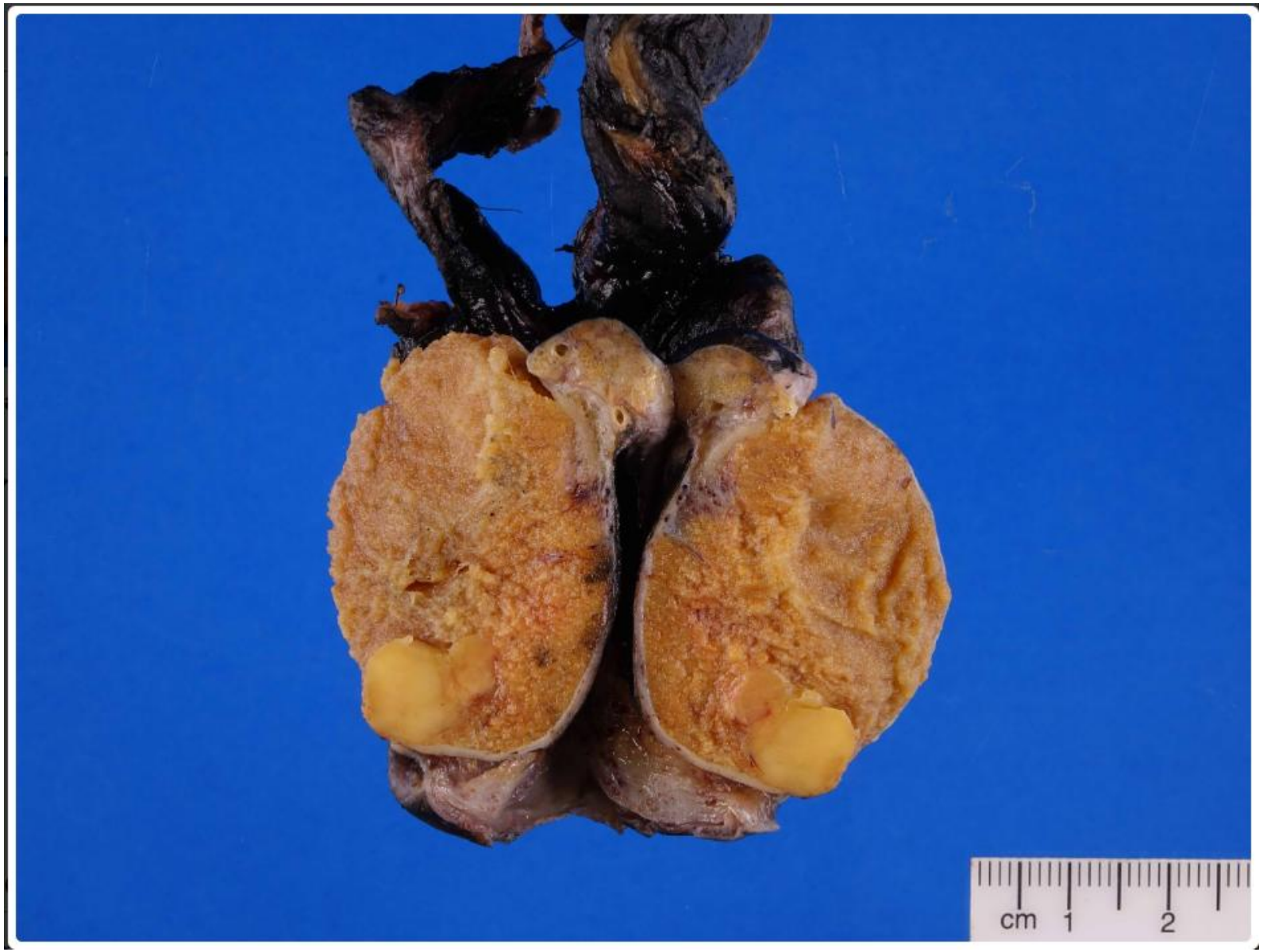
Sex cord stromal tumours

Leydig (Interstitial) Cell Tumour

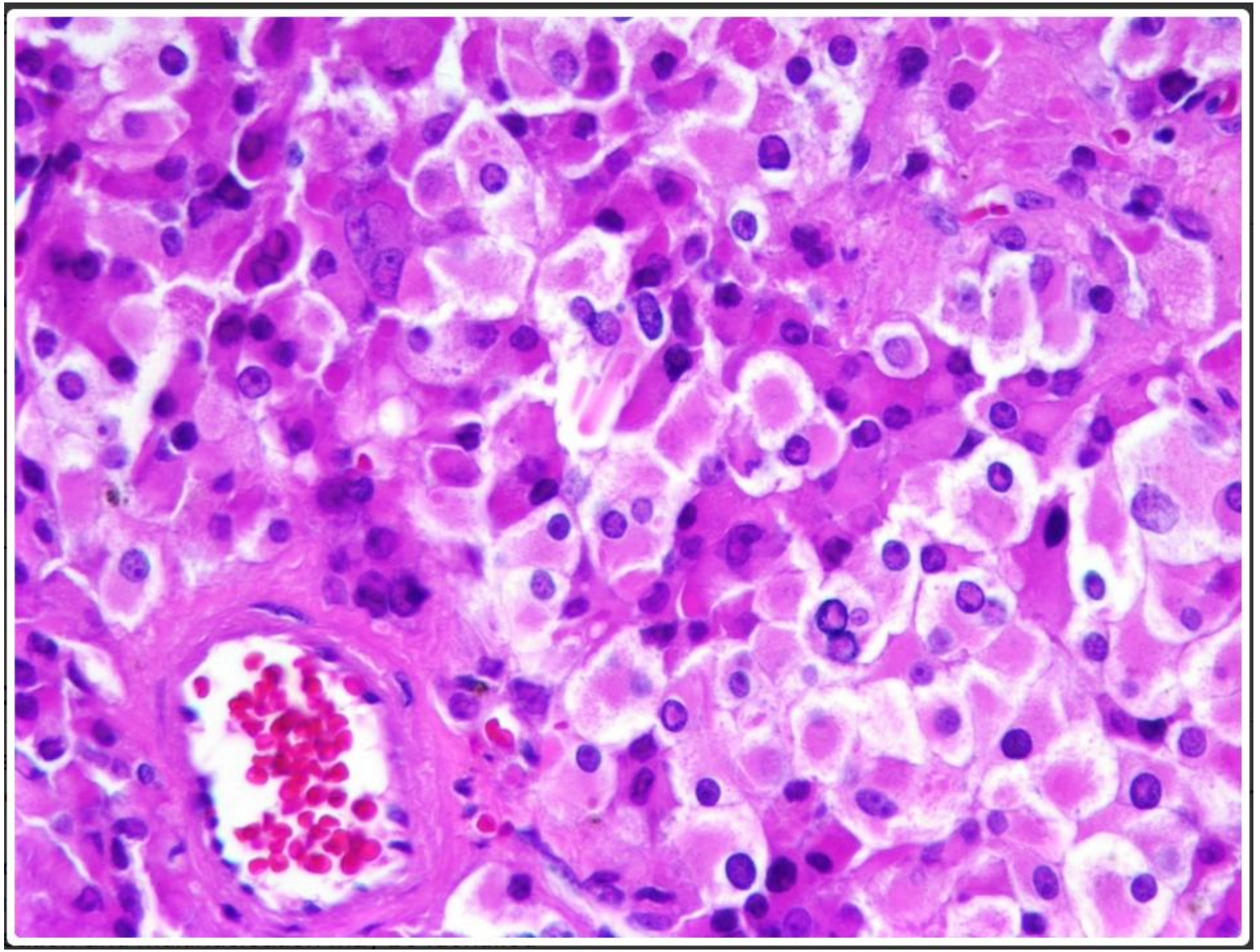
- Age group of 20 to 50 years.
- secrete androgen or both androgen and oestrogen, and rarely corticosteroids

Gross:
Small, well-demarcated and lobulated nodule.

Cut surface : homogeneously yellowish or brown.



Microscopy :
Sheets and cords of normal-looking Leydig cells.
Contain abundant eosinophilic cytoplasm and Reinke’s crystals and a small central nucleus.



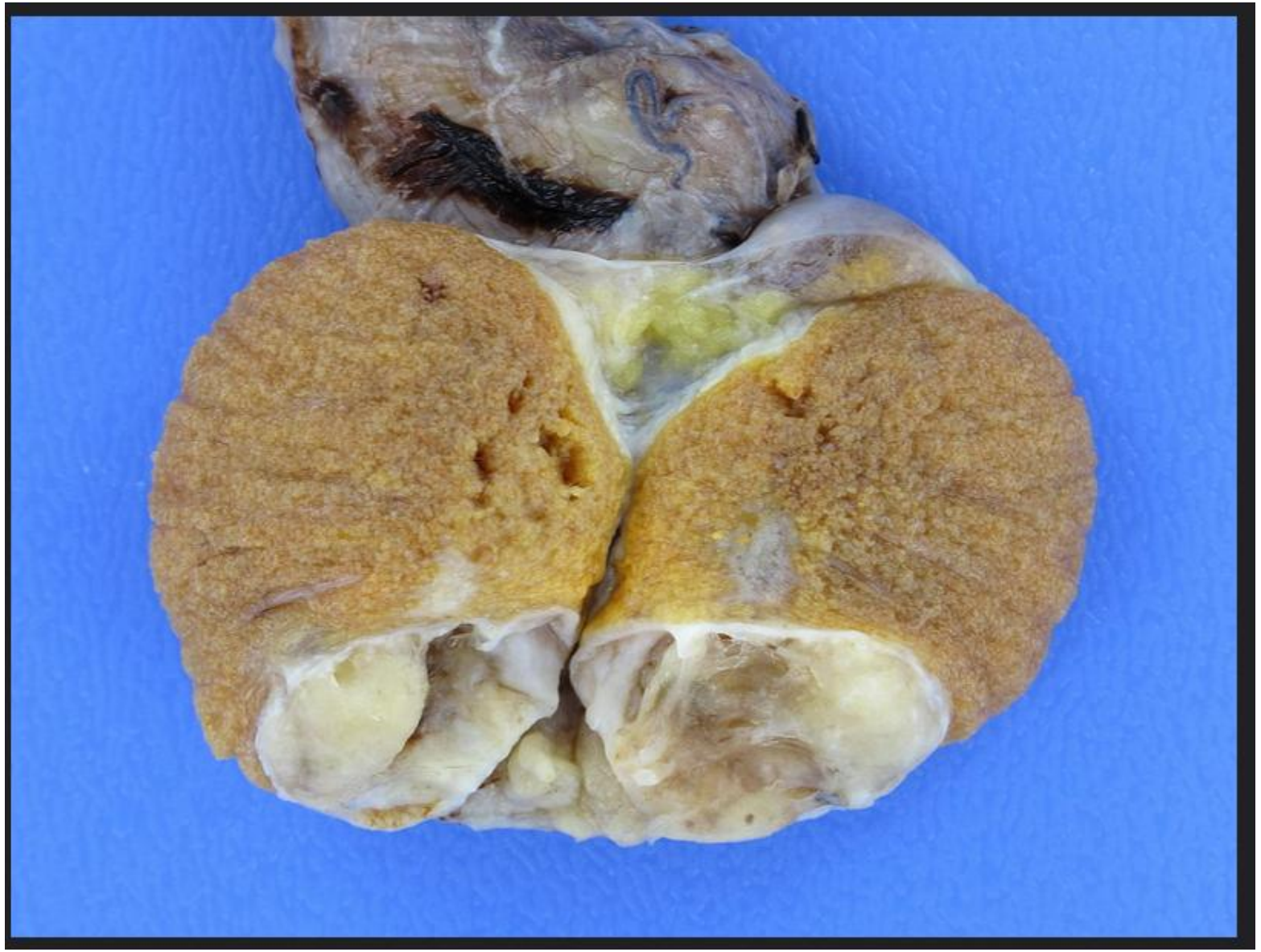
- Benign
- About 10% may invade and metastasize

Sertoli Cell Tumours (Androblastoma)

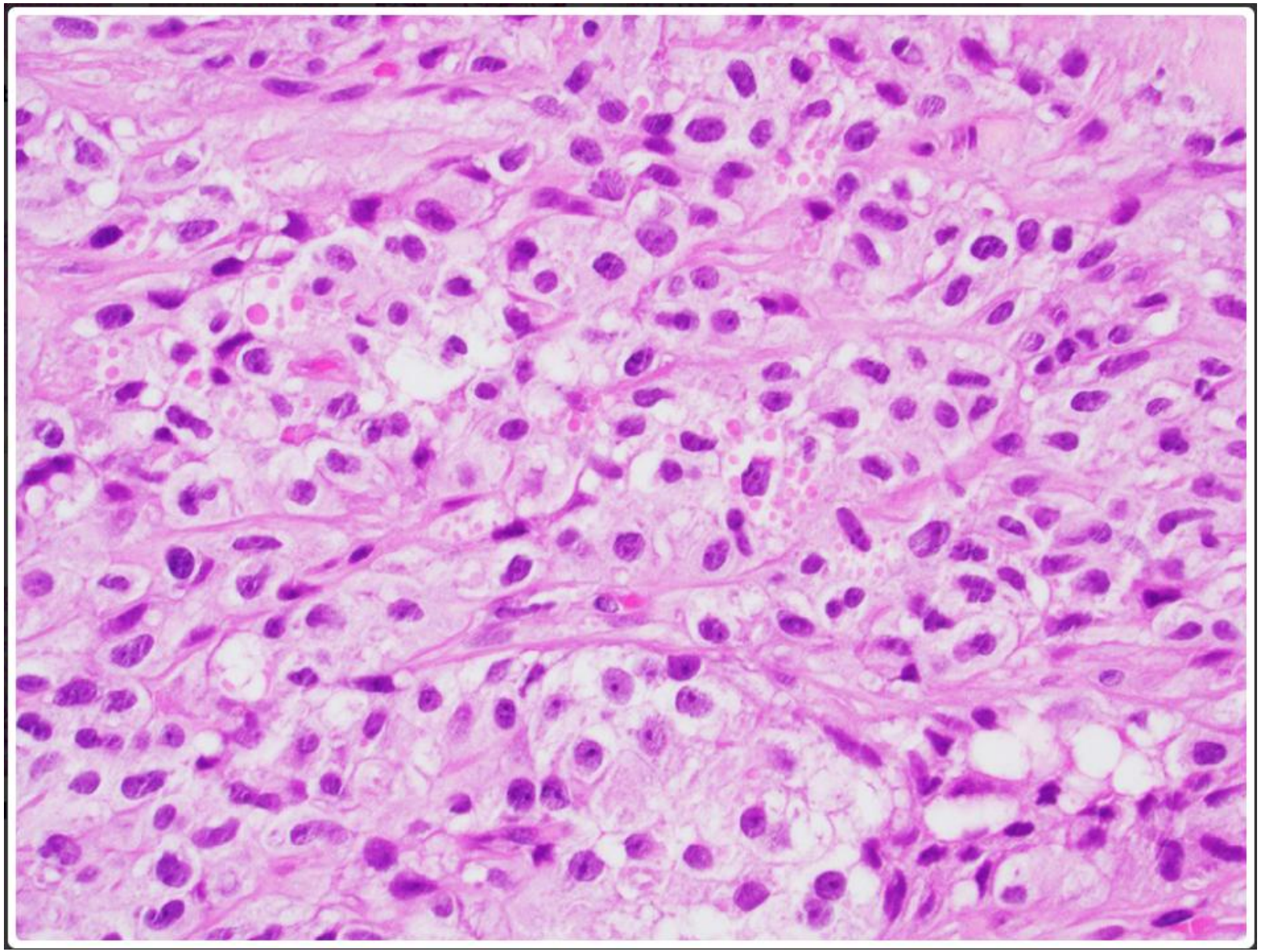
- Corresponds to arrhenoblastoma of the ovary
- More frequent in infants and children.
- Elaborate oestrogen or androgen - may account for gynaecomastia in an adult, or precocious sexual development in a child.

Gross
large, firm, round, and well circumscribed.

Cut surface : yellowish or yellow-grey.



Microscopy : composed of benign Sertoli cells arranged in well-defined tubules.



- Majority are benign
- About 10% may metastasize to regional lymph nodes.

Overview of lab investigations

Raised serum levels of –

- LDH – Seminoma
- hCG – Embryonal carcinoma, seminoma with syncytiotrophoblast
- AFP – Yolk sac tumour
- Androgens – Leydig cell tumour/ Sertoli cell tumor

Immunohistochemistry in testicular germ cell tumors

Tumor Type	SALL4	OCT4	CD30	GPC3	AFP	Keratin	c-kit	D2-40	Sox2	hCG	GATA3
Classic/typical seminoma	+	+	–	–[c]	–	–	+	+	–	–[c]	–[c]
Spermatocytic tumor[a]	+	–	–	–	–	–	–/+	–	–	–	–
Embryonal carcinoma	+	+	+	–/+[c]	–	–/+	–	–	+	–[c]	–[c]
Yolk-sac tumor	+	–	–	+	+	+	–/+	–	–	–	+/–
Teratoma[b]	+/–	–/+	–	–	–	+	–	–	+/–	–	–/+
Choriocarcinoma	+/–	–	–	+	–/+	+	–	–/+	–	+	+

–, negative; +, positive.

[a] Previously called "spermatocytic seminoma."

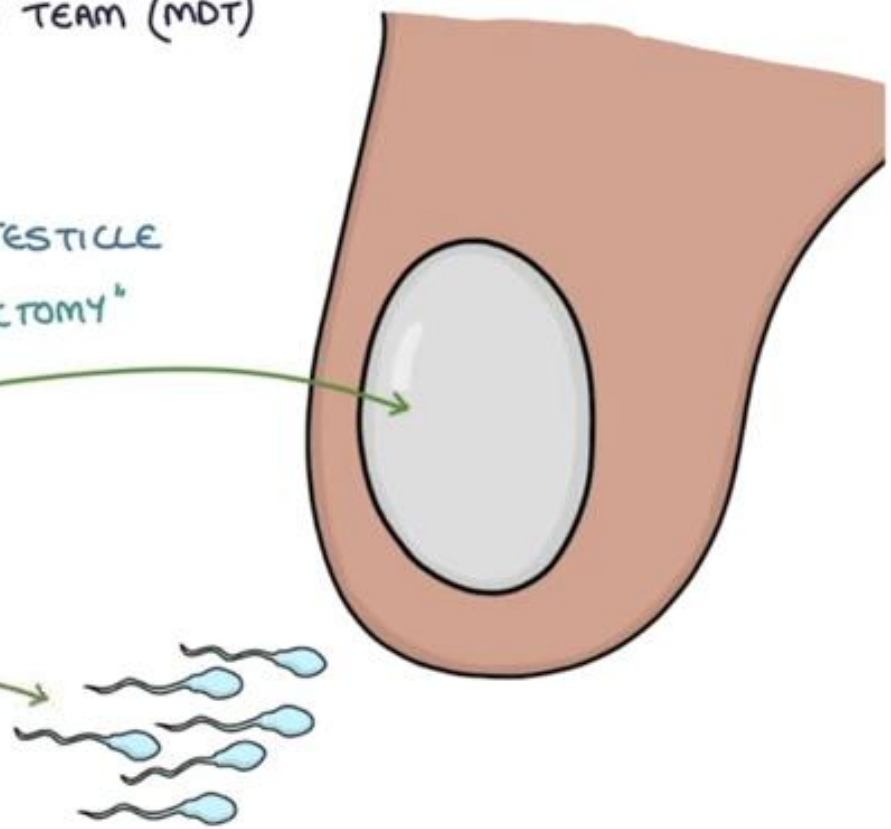
[b] Staining patterns depend on the teratomatous elements present.

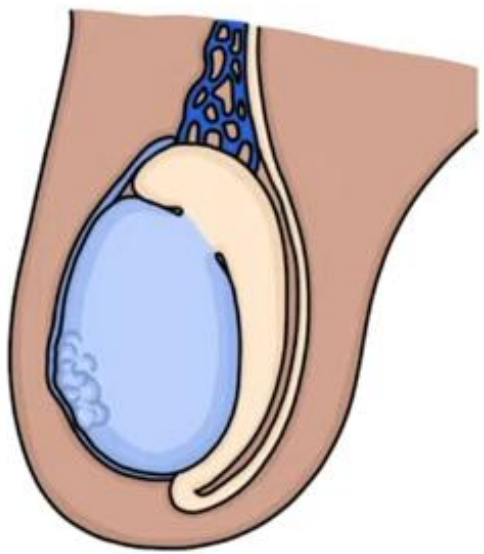
MANAGEMENT

ANY CANCER → MULTIDISCIPLINARY TEAM (MDT)

DEPENDING ON STAGE AND GRADE

- ↳ SURGERY TO REMOVE TESTICLE
  - ↳ "RADICAL ORCHIDECTOMY"
  - ↳ PROSTHESIS
- ↳ CHEMOTHERAPY
- ↳ RADIOTHERAPY
- ↳ SPERM BANKING





PROGNOSIS

EARLY TESTICULAR CANCER

↓

GOOD

>90% CURE

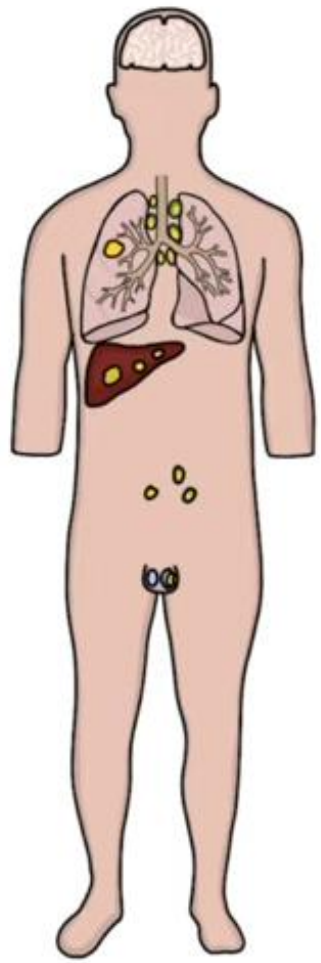
METASTATIC DISEASE

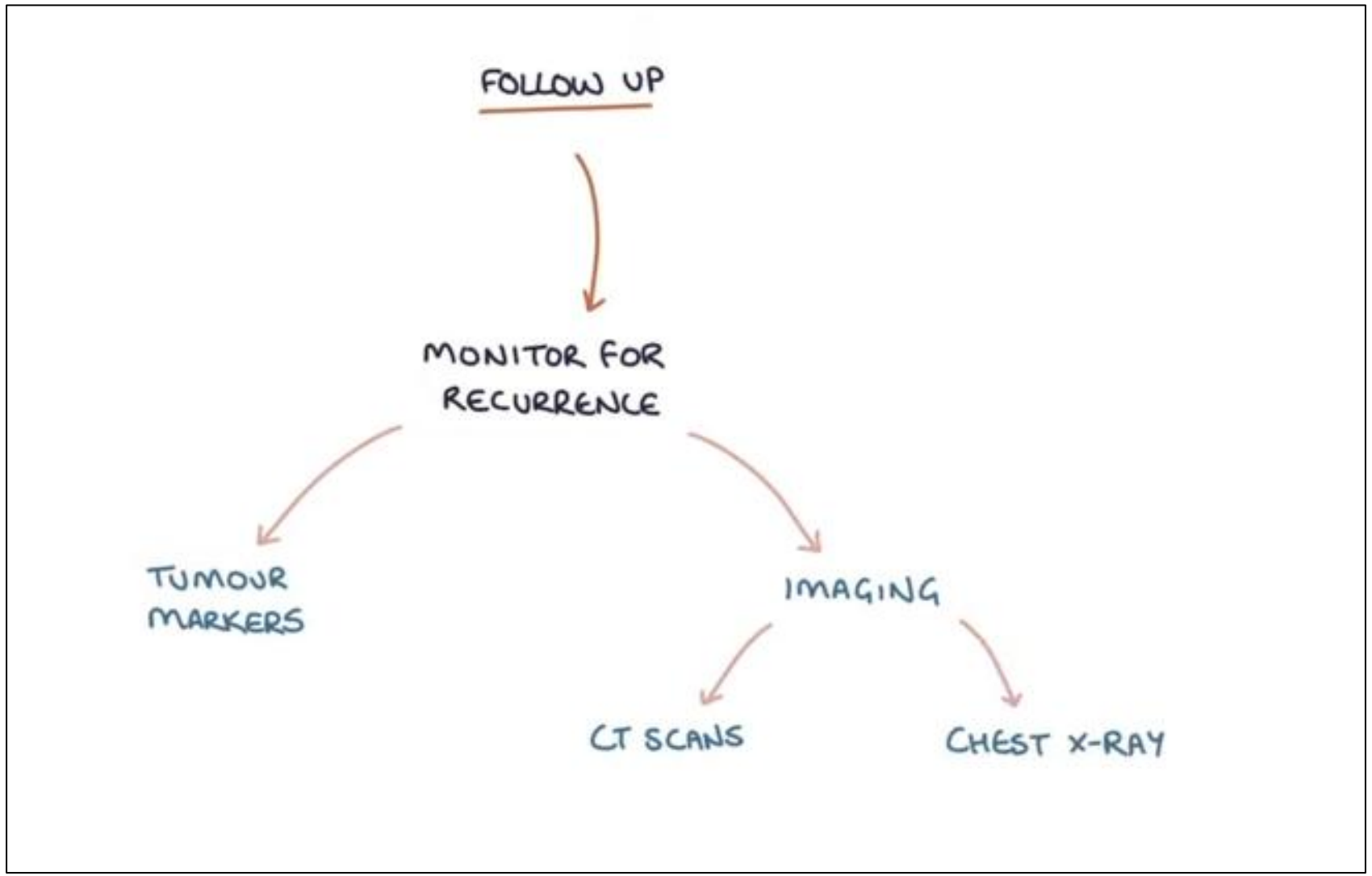
↓

OFTEN CURABLE

SEMINOMA ← NON-SEMINOMAS

BETTER PROGNOSIS




FOLLOW UP
MONITOR FOR RECURRENCE
TUMOUR MARKERS
IMAGING
CT SCANS
CHEST X-RAY

Thank you