Testicular Cancer

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Neoplasms of the Testis

- Neoplasms of the testis comprise a morphologically and clinically diverse group of tumors, more than 95% of which are germ cell tumors (GCTs).
- GCTs are broadly categorized as seminoma and nonseminoma (NSGCT).
- GCT is a relatively rare malignancy, accounting for 1-2% of cancers among adult males.
- 95% of GCTs arise in the testis, and 5% are extragondal in origin
- long-term survival for men with metastatic GCT is 80-90%

Neoplasms of the Testis

- Non-GCT tumors of the testis are rare and include sex cord-stromal tumors, lymphoid and hematopoietic tumors, tumors of the collecting duct and rete testis, and tumors of the testicular adnexa.

I) **Germ Cell Tumors (GCT):**

- Testis tumors are most common between the ages of 15-55.
- peaking at ages 25 to 35, bilateral GCT is approximately 2%.
- The majority of bilateral GCTs are metachronous and occur over an average interval of 5 years (with 30-50% different histology)

Germ Cell Tumors (GCT)

- **Risk Factors: There are five well-established risk factors for testis cancer:**
- **(1) white race, (2) cryptorchidism, (3) family history of testis cancer, (4) a personal history of testis cancer, and (5) germ cell neoplasia in situ (GCNIS), also referred to as intratubular germ cell neoplasia (ITGCN).**
- Infertile and subfertile men also have a higher incidence.
- Cryptorchidism increase risk 4-6 times in the affected gonad, but the relative risk falls to 2-3 if orchidopexy is performed before puberty

Germ Cell Tumors (GCT)

- The contralateral descended testis is also at increased risk
- Most GCTs arise from a precursor lesion called GCNIS.
- GCNIS is present in adjacent testicular parenchyma in 80-90% cases of invasive GCT.
- GCNIS is associated with a 50% risk of GCT within 5 years and 70% within 7 years.
- 5-9% of patients with GCT have GCNIS within the unaffected contralateral testis

Germ Cell Tumors (GCT)

- GCTs are divided into seminoma (52-56%) and NSGCT (44-48%)
- NSGCTs include embryonal carcinoma (EC), yolk sac tumor, teratoma, and choriocarcinoma subtypes.
- I) Seminoma is **the most common type** of GCT.
- Seminomas occur at an older average age than NSGCT, with most cases diagnosed in the 4^{th}-5^{th} decade of life.
- Syncytiotrophoblasts, which stain positive for human chorionic gonadotropin (HCG), can be identified in about 15% of cases but are of no clear prognostic significance

Germ Cell Tumors (GCT)/ Seminoma

- Lymphocytic infiltrates and granulomatous reactions are often seen, and seminomas appear to be associated with an increased incidence of *sarcoidosis*.
- Grossly, seminoma is a soft tan to white diffuse or multinodular mass. Necrosis is not as prominent as other GCTs.
- **Spermatocytic Tumor**: previously referred to as spermatocytic seminoma. Now is considered a distinct entity. Rare & does not arise from GCNIS, is not associated with a history of cryptorchidism or bilaterality, peak incidence is the sixth decade.

➔ A benign tumor and is **almost always** cured with orchiectomy

NSGCT/ Embryonal Carcinoma (EC)

- Consists of undifferentiated malignant cells resembling primitive epithelial cells from early stage embryos with crowded pleomorphic nuclei.
- Grossly, EC is a tan to yellow and exhibits large areas of hemorrhage and necrosis.
- Aggressive tumor associated with a high rate of metastasis, often in the context of normal serum tumor markers
- **The most undifferentiated** cell type, with totipotential capacity to differentiate to other NSGCT cell types (including teratoma) within the primary tumor or at metastatic sites.

NSGCT/ Choriocarcinoma

- A rare and aggressive tumor that typically is seen with extremely highly elevated serum HCG levels and disseminated disease.
- Commonly spreads by hematogenous routes, and common sites of metastases include lungs, liver, and brain.
- Microscopically, the tumor is composed of syncytiotrophoblasts and cytotrophoblasts.
- Areas of hemorrhage and necrosis are prominent.
- Associated with hormonal disturbances, most likely because of highly elevated serum HCG

NSGCT/ Choriocarcinoma

- Stimulation of receptors for thyroid stimulating hormone and luteinizing hormone (LH) by HCG (which shares an identical alpha-subunit) can result in ***hyperthyroidism*** and elevated ***androgen*** production.
- ***Hyperprolactinemia*** has also been reported.

NSGCT/Yolk Sac Tumor

- Sometimes called endodermal sinus tumors.
- More common in mediastinal and pediatric GCTs.
- Mixed GCTs often include elements of yolk sac tumor.
- A characteristic feature is the *Schiller-Duval body*, which resembles endodermal sinuses, and is seen in roughly half of cases
- Yolk sac tumors almost always produce AFP but not HCG.

NSGCT/Teratoma

- Tumors that contain well or incompletely differentiated elements of at least two of the three germ cell layers: endoderm, mesoderm, and ectoderm.
- Well-differentiated tumors are labeled **mature teratomas**, whereas those that are incompletely differentiated are **called immature teratomas**.
- Mature teratomas may include elements of mature bone, cartilage, teeth, hair, and squamous epithelium.
- Generally associated with normal serum tumor markers, but they **may cause** mildly elevated serum AFP levels.

NSGCT/Teratoma

- Approximately 47% of adult mixed GCTs contain teratoma, but pure teratomas are uncommon.
- Have a histologically benign appearance but are **frequently found at metastatic sites** in patients with advanced NSGCT.
- Teratoma is resistant to chemotherapy, that's why patients with residual masses after chemotherapy require surgical resection.
- May grow uncontrollably, invade surrounding structures, and become unresectable.
- May transform into a somatic malignancy: rhabdomyosarcoma, adenocarcinoma, or primitive neuroectodermal tumor.

Presentations: Signs & Symptoms

- **The most common** presentation of testis cancer is a painless testis mass.
- **Acute testicular pain** is less common and is caused by rapid expansion of the testis resulting from intra-tumor hemorrhage or infarction caused by rapid tumor growth.
- Pain is more commonly associated with NSGCT; these tumors tend to be more vascular and exhibit more rapid growth compared with seminomas.
- Patients may also complain of vague scrotal discomfort or heaviness.

Presentations: Signs & Symptoms

- Symptoms related to metastatic disease are the presenting complaint in 10-20% of patients. (**Regional or distant metastasis at diagnosis is present in approximately two-thirds of NSGCTs and 15% of pure seminomas).**
- Bulky retroperitoneal metastasis may cause a palpable mass, abdominal pain, flank pain resulting from ureteral obstruction, back pain because of involvement of the psoas muscle or nerve roots, lower extremity swelling resulting from compression of the inferior vena cava, or gastrointestinal (GI) symptoms.
- Pulmonary metastasis may present with dyspnea, chest pain, cough, or hemoptysis.

Presentations: Signs & Symptoms

- Metastasis to supraclavicular lymph nodes resulting **neck mass**.
- **Gynecomastia**, resulting from either elevated serum HCG levels, decreased androgen production, or increased estrogen levels.
- **Infertility**: two-thirds of men with GCT have diminished fertility, but it is an uncommon initial presentation.
- **Physical Examination:**
- Any firm area within the testis should be considered suspicious for malignancy
- Hydrocele may accompany a testis cancer

Presentations: Physical Examination

- The patient should also be examined for any evidence of palpable abdominal mass or pain,
- inguinal lymphadenopathy (particularly if he has had prior inguinal or scrotal surgery),
- gynecomastia, and supraclavicular lymphadenopathy, and auscultation of the chest for intrathoracic disease
- **A firm intratesticular mass should be considered cancer until proven otherwise and should be evaluated further with a scrotal ultrasound.**

Diagnostic Work Up

- Scrotal ultrasonography should be considered an extension of the physical examination because it widely available, inexpensive, and noninvasive.
- In men with advanced GCT and a normal testicular examination, scrotal ultrasonography should be performed to rule out the presence of a small, impalpable scar or calcification, indicating a "burned-out" primary testis tumor.
- GCTs are one of the most common neoplasms to undergo **spontaneous regression**; *seminoma* is **the most frequent subtype**.

Diagnostic Work Up

- Radical orchiectomy should be performed in those patients with sonographic evidence of intratesticular lesions (discrete nodule, stellate scar, coarse calcification) because GCNIS and residual teratoma are frequently encountered.
- Serum Tumor Markers:
- Serum tumor marker levels should be obtained at diagnosis, after orchiectomy, to monitor for response to chemotherapy, and to monitor for relapse in patients on surveillance and after completion of therapy.

Diagnostic Work Up: Tumor Markers

1. Alpha Fetoprotein (AFP):

- EC and yolk sac tumors secrete AFP.
- Choriocarcinomas and pure seminoma do not produce AFP.
- Patients with pure seminoma in the primary tumor with an elevated serum AFP are considered to have NSGCT.
- AFP also is raised in patients with: hepatocellular carcinoma, cancers of the stomach, pancreas, biliary tract and lung, nonmalignant liver disease (infectious, drug-induced, alcohol-induced, autoimmune), ataxic telangiectasia, and hereditary tyrosinemia.

Diagnostic Work Up: Tumor Markers

2. HCG: Approximately 15% of *seminomas* secrete HCG.

- HCG is also secreted by *choriocarcinoma* and *EC*.
- HCG levels may be elevated in cancers of the liver, biliary tract, pancreas, stomach, lung, breast, kidney, and bladder.
- false-positive HCG: hypogonadism & Marijuana use.

3. LDH: a nonspecific marker for GCT, its main use is in the prognostic assessment of GCT at diagnosis.

- The magnitude of LDH elevation correlates with the bulk of disease.

Radical Inguinal Orchiectomy

- Patients suspected of having a testicular neoplasm should undergo a **radical inguinal orchiectomy** with removal of the tumor-bearing testicle and spermatic cord to the level of the internal inguinal ring.
- A trans-scrotal orchiectomy or biopsy is **contraindicated** because it leaves the inguinal portion of the spermatic cord intact and may alter the lymphatic drainage of the testis, increasing the risk of local recurrence and pelvic or inguinal lymph node metastasis.
- It establishes the histologic diagnosis and primary T stage, and is curative in most of low stage cancers.

TNM

pTx	Primary tumor cannot be assessed
pT0	No evidence of primary tumor (e.g., histologic scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumor limited to testis and epididymis without vascular/lymphatic invasion; tumor may invade into tunica albuginea but not tunica vaginalis
pT2	Tumor limited to testis and epididymis with vascular/lymphatic invasion or tumor extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumor invades spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades scrotum with or without vascular/lymphatic invasion

TNM

	REGIONAL LYMPH NODES (N)
NX	Regional lymph nodes cannot be assessed
No	No regional lymph node metastasis
N1	Metastasis with lymph node mass ≤2 cm in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with lymph node mass, >2 cm, but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass >2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with lymph node mass >5 cm in greatest dimension

TNM

DISTANT METASTASIS (M)		SERUM TUMOR MARKERS (S)	
MX	Distant metastasis cannot be assessed	SX	Marker studies unavailable or not performed
M0	No distant metastasis	S0	Marker study levels within normal limits
M1	Distant metastasis	S1	LDH <1.5 × N (upper normal) and HCG (MIU/mL) <5000 and AFP (ng/mL) <1000
M1a	Nonregional nodal or pulmonary metastasis	S2	LDH 1.5-10 × N or HCG (MIU/mL) 5000–50,000 or AFP (ng/mL) 1000–10,000
M1b	Distant metastasis at site other than nonregional lymph nodes or lung	S3	LDH >10 × N or HCG (MIU/mL) >50,000 or AFP (ng/mL) >10,000

Staging

- With the exception of choriocarcinoma, the most common route of disease dissemination is via lymphatic channels from the primary tumor to the retroperitoneal lymph nodes and subsequently to distant sites.
- For **right testis** tumors, the primary drainage site is **the inter-aortocaval lymph nodes** inferior to the renal vessels, followed by the paracaval and para-aortic (PA) nodes.
- The primary "landing zone" for **left testis** tumors is the **PA lymph nodes**, followed by the interaortocaval nodes
- The pattern of lymph drainage in the retroperitoneum is from right to left.

Staging

- All patients with GCT should undergo staging imaging studies of the abdomen and pelvis.
- Computed tomography (CT) imaging with oral and intravenous contrast is the most effective, noninvasive means of staging the retroperitoneum and pelvis.
- RPLND (Retroperitoneal lymph node dissection): also can be done either open or laparoscopic for staging purposis.
- Chest Imaging (CXR): All patients with GCT should undergo chest imaging before management decisions.

Staging

- Serum Tumor Markers: Post-orchiectomy AFP, HCG, and LDH levels are important for staging, prognosis, and treatment selection.
- all patients should have serum tumor markers drawn after orchiectomy to assess for appropriate decline.
- The presence of newly elevated and/or rising serum tumor marker levels after orchiectomy indicates the presence of metastatic disease, and these patients should receive induction chemotherapy.

risk classification for advanced GCT

NONSEMINOMA	SEMINOMA
GOOD PROGNOSIS (5-year survival 92%)	**GOOD PROGNOSIS (5-year survival 86%)**
Testicular/retroperitoneal primary & No nonpulmonary visceral metastases & S1 markers	Any primary site & No nonpulmonary visceral metastases & Normal AFP, any HCG, any LDH.
INTERMEDIATE PROGNOSIS (80%)	**INTERMEDIATE PROGNOSIS (72%)**
Testicular/retroperitoneal primary & No nonpulmonary visceral metastases & S2 markers.	Any primary site & Nonpulmonary visceral metastases & Normal AFP, any HCG, any LDH.
POOR PROGNOSIS (48%)	**POOR PROGNOSIS (-)**
Mediastinal primary or Nonpulmonary visceral metastases or S3	No poor prognosis Seminomas

Treatment: Seminoma

- **For low stage seminomas (Radiosensitive):** Radiotherapy.
- Primary radiotherapy to the retroperitoneum and ipsilateral pelvis.
- **For low Stage NSGCT (Chemo-sensitive):**
- Either induction Chemotherapy then RPLND,
- Or RPLND +/- adjuvant Chemotherapy.
- **For High stage tumors** (both Seminoma & NSGCT):
- Chemotherapy then RPLND for residual masses.

Thank You