Types of Germ Cell Tumors (GCT) and Non Germ Cell Tumors

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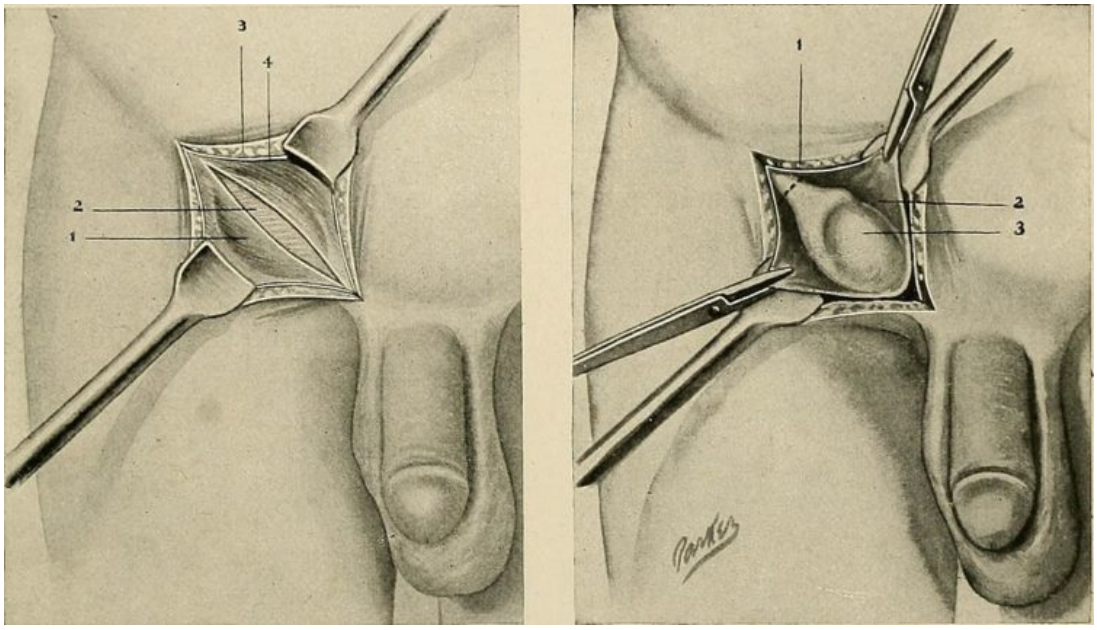
Testicular tumors are common and potentially annihilating to the male population. With a brief prologue to testicular tumors; this article focuses on the significant, relevant types of testicular tumors such as Germ Cell Tumors (GCTs) and Non-Germ Cell Tumors (NGCT).Various clinical, patho-physiological and prognostic aspects of the same have been expatiated.



Testicular Tumor

Though representing only about 1% of all human neoplasms; testicular tumor is the most common cancer in males of reproductive age group. Evidence suggests an approximate incidence of about 23 % of 15–35 years aged males. The tumors are more common in males aged 15–35 years and the incidence increases with age for unknown reasons.

Testicular tumors have been variously classified based on histology and prognostic outcome. The **World Health Organization (WHO)** has standardized the pathologic segregation of testicular malignancies.

The WHO taxonomy for testicular tumors is as follows:

Tumor type	Subsets (if applicable)
Germ cell tumor	
Precursor lesions	Intratubular malignant germ cell tumor (carcinoma in situ)

Pure form tumors (of single histology)	Seminoma (variant: seminoma with syncytiotrophoblastic cells) Spermatocystic seminoma (variant: spermatocystic with sarcoma) Embryonal carcinoma Yolk sac tumor Polyembryoma
Trophoblastic tumors	Choriocarcinoma
Teratoma	Immature teratoma Mature teratoma Dermoid cyst Teratoma with malignant areas
Mixed tumors	
Sex-cord/gonadal stromal tumors	
Pure forms	Sertoli's cell tumor: • Lipid-rich cell • Large cell calcifying
Incompletely differentiated sex cord/gonadal stromal tumors	
Tumors of the thecoma/fibroma group	
Mixed forms	
Miscellaneous tumors	
Unclassified forms	Ovarian epithelial tumors Carcinoid tumors
Granulosa cell tumor	Adult type of granulosa cell tumor Juvenile type of granulose cell tumor
Tumors containing both germ cell and sex cord/gonadal stromal elements	Gonadoblastoma Mixed germ cell-sex cord/gonadal stromal tumors Unclassified
Lymphoid and hematopoietic tumors	Lymphoma Plasmacytoma Leukemia
Tumors of collecting duct and rete testis	Adenoma Carcinoma
Tumors of tunica, epididymis, spermatic cord, supporting structures, and appendices	Adenomatoid tumor Mesothelioma Adenoma Carcinoma Melanotic neuroectodermal tumor
Soft tissue tumors Unclassified tumors Secondary tumors	

Simply put, testicular tumors are either germ cell tumors (GCTs) or non-germ cell tumors (NGCTs). A succinct description of each is as follows:

Germ Cell Tumors (GCTs)

Introduction

GCTs are the most common of all testicular tumors. The nomenclature follows origin from totipotent germ cells. They account for about 95% of all testicular malignancies and are classified into seminomatous and non-seminomatous types with about 60% being of mixed type. Literature suggests that the only known risk factor for the germ cell tumors (GCTs) is Klinefelter syndrome (47XXY), which is associated with mediastinal nonseminomatous germ cell tumors. This is commonly characterized by their location on the midline plane of the human body and thus may appear anywhere from the pineal gland to the coccyx.

Epidemiology

GCTs are the most prevalent solid tumors of males of reproductive age group from 20–34 years and second most common in men age 35–40 years. There is predisposition to GCTs in the Caucasian population.

With equivocal evidence for genetic factors; there is about 2–3% incidence of bilateral tumors.

Frequency

Study in Norway incidence of GCT is at 0.5 per 1,000,000 population per year. This is around 2% of the number of testicular cancers reported.

The incidence of various histologic types of GCTs is as follows:

Type	Incidence
Seminoma	30–60%
Embryonal carcinoma	40% (mixed form); 2–4% pure form
Teratoma	5–10%
Mixed GCT	60%
Pure Choriocarcinoma	1%

Classification

There are 5 basic types of GCTs:

1. Seminoma: This type of tumor generally occurs in men between the ages of 25 and 55.
2. Teratoma
3. Choriocarcinoma
4. Embryonal cell carcinoma
5. Yolk sac tumor

Note: Seminoma may resemble a yolk sac tumor by forming tubular and microcystic growth patterns.

Pathogenesis

GCTs arise from totipotent germ cells which undergo further differentiation into **extraembryonic and intraembryonic** cell types. The origin of the basic types of GCTs can be summarized as follows:

Tumor	Origin
Seminoma Teratoma	Totipotent germ cell
Yolk sac tumors	
Choriocarcinoma	Extraembryonic differentiation of totipotent germ cells
Yolk sac tumor	
Teratoma	Intraembryonic differentiation

Various conditions predispose an individual to developing a GCT. These conditions with potential hypotheses and evidence rationalizing this probable relationship can be summarized as follows:

Predisposing condition	Evidence
Testicular atrophy	While the exact role is not yet defined; there are speculations that nonspecific or mumps-associated atrophy have probable causal effect in testicular cancer.
Trauma	While some call it an incidental finding; or something that brings the scrotal mass to the patient's notice; there is little evidence to suggest otherwise.
Cryptorchidism	About 6–10% of testicular malignancy patients have undescended testes. Evidence attests to about 13 times increased risk of developing cancer in maldescended testis compared to normal. Almost one-fourth patients with bilateral cryptorchidism and history of testicular tumor progress to develop a second GCT.
Hormonal	Male children of mothers exposed to Diethylstilbestrol and oral contraceptives are prone to develop testicular cancer.

Presentation

The most frequent presentation of testicular malignancy is **painless unilateral scrotal swelling**. Other infrequent symptoms can be summarized as follows:

- Infertility
- Dull aching pain
- Difficulty in walking
- Heaviness in scrotum, lower abdomen and perianal region
- Acute pain

About 10% patients present symptoms of metastasis with chronic long-standing; often ignored scrotal swelling. These signs must caution the medical personnel to look for the primary etiology whenever relevant. Despite the name, germ cell tumors occur both within and outside the testis. They can be summarized as follows:

Symptom	Interpretation
Painless neck swelling	Supraclavicular lymph node metastasis
Abdominal discomfort	Retroduodenal metastasis
Lumbar back pain	Psoas muscle involvement
Back pain, bony pains	Skeletal metastasis
Lower extremity edema	Venous obstruction

Diagnosis

Clinical examinations offer few salient features traditionally used to differentiate benign scrotal massed from testicular tumors. Bimanual palpation is the key and the findings can be summarized as follows:

Test	Explanation
Transillumination	Negative
Fluctuation	Negative
Palpate the testes	Firm, hard or fixed mass can occasionally be felt
Getting above the swelling	Possible

Ultrasonography is the most basic preliminary radiological imaging investigation always performed. Hypoechoic region within the tunica albuginea is of crucial relevance. Other advanced radioimaging tests are of ancillary nature. Their findings can be summarized as follows:

Diagnostic Test	Explanation
Abdominal CT	It is most effective in identifying retroperitoneal lymph node involvement. Clear visualization of kidney, ureters, retro-crural space and the para-aortic region is feasible.
MR Imaging	Testicular tumors enhance early on MRI and are T2 hypointense.
PET scan	It is used to detect radiographic aberrations after chemotherapy. It fails to identify microscopic nodal metastatis.
Chest Skiagram	Used to screen the chest in patients with negative abdominal CT findings.
Chest CT	Performed in patients with abnormal abdominal CT findings.

Treatment

The treatment of GCT is heavily dependent on the stage of the disease. The first step towards staging is to perform **orchiectomy** to determine the histologic features. Histology and radiology with tumor markers assessment whenever relevant; help in ascertaining the correct stage of the disease and developing the most definite management protocol. Most patients with germ cell cancer will need to be treated with combination chemotherapy for at least 3 cycles. The chemotherapy regimen most commonly used in germ cell tumors is called PEB (or BEP), and consists of bleomycin, etoposide, a platinum-based antineoplastic (cisplatin)

The **AJCC** staging for GCTs is universally followed. Based on four parameters: **T** for **primary tumor, N** for **lymph node status, M** for **metastasis and S** for **serum markers status**; there are 4 stages defined from stage I for locally contained disease to a progressively increasingly complex grading where stage IV implies distant metastatic illness. AJCC staging details are as follows:

Parameter	Subset
Primary tumor (T)	pTx: primary tumor cannot be assessed pT0: no evidence of primary tumor pTis: intratubular germ cell neoplasia pT1: tumor limited to the testis and epididymis and no vascular or lymphatic invasion pT2: Tumor limited to the testis and epididymis with vascular or lymphatic invasion or tumor extending through the tunica albuginea with involvement of tunica vaginalis. pT3: invasion of the spermatic cord with or without vascular/lymphatic invasion pT4: invasion of the scrotum

Regional lymph nodes (N)	Nx: cannot be assessed No: no regional lymph node metastasis N1: lymph node mass 2 cm or less in greatest dimension N2: lymph node mass more than 2, less than 5 cm N3: lymph node mass more than 5 cm		
Distant metastasis (M)	M0: no evidence of distant metastasis M1: non-regional nodal or pulmonary metastasis M2: nonpulmonary visceral metastasis		
Serum tumor markers (S):	AFP	LDH	HCG
S0:	≤ N	≤ N	≤ N
S1:	< 1,000	< 1.5 times N	< 5,000
S2:	1,000–10,000	1.5–10 times N	5,000–50,000
S3:	> 10,000	> 10 times N	> 50,000

Seminomas tend to spread lymphatically to the para-aortic lymph nodes (versus penile drainage through the inguinal LNs) and nonseminomatous metastasize hematogenously, for example: to the lungs.

Once staged, patient is treated using the following modalities:

- Surgical resection with retroperitoneal lymph node dissection (RPLND)
- Chemotherapy: cisplatin-based chemotherapy
- Radiation: abdominal and pelvic
- Surveillance

The individual tumor types of GCTs can be summarized as follows:

Tumor	Characteristics	Serum marker	Prognosis
Seminoma	Seminoma constitutes 35–70% of GCTs. Only 5–10% of tumors are anaplastic with lethal potential; the rest have a very good outcome. Typical morphological appearance resembles '**Fried-egg'**	Placental ALP (**PLAP**) is present in about 90% of seminomas. About 10% patients stain positive for HCG. HCG is from syncytiotrophoblastic cells and does not behave as choriocarcinoma.	Late metastasis, lymphatics, radiosensitive. Excellent outcome with good response to radiation and carboplatin-based chemotherapy. The female ovarian tumor '**dysgerminoma'** is its counterpart.
Embryonal	Contributing to about 3–6% of GCTs; embryonal carcinoma is seen in males of age 25–35 years.	Embryonal carcinomas stain positive for **CD30, keratin** and infrequently to PLAP. HCG positivity is attributed to syncytiotrophoblasts adjacent to EC cells.	Prognosis is not as favorable as seminoma.
Yolk sac (EST)	Most prevalent testicular malignancy in **pre-pubertal males**, especially boys < 3 yrs of age. Schuller-Duval bodies are characteristically seen.	**ALP** positive in about 90% of these tumors.	Aggressive
Choriocarcinoma	Represent about 1-2% of all GCTs. Trophoblastic cells are appreciated on histology.	**HCG** positivity in more than 90% of patients; some also stain for PLAP.	Aggressive associated with hemorrhagic tendency and hyperthyroidism.
Teratoma	Teratomas comprise of **2 or more embryonic germ cell layers**. They are incriminated in almost 1/3rd of childhood GCTs. Childhood teratomas are benign; while adult teratomas are malignant.	Immature form is aggressive	Prognosis is heterogenous depending on the cell lines involved; less favorable compared to embryonal.

Other NGCTs are relatively very rare and their clinical characteristics can be summarized as follows:

Non-germ cell tumors(NGCTs)	Clinical presentation

Leydig cell tumor	Golden brown color, contains **Reinke crystals** (eosinophilic cytoplasmic inclusions) produces androgens or estrogens: leads to gynaecomastia in males, precocious puberty in boys.
Sertoli cell tumor	**Androblastoma** from sex cord stroma
Testicular lymphoma	**Most common testicular cancer in older men**; not a primary cancer; arises from metastatic lymphoma to testes.

Summary

Testicular tumors can be segregated into eerm cell tumors and non-germ cell tumors based on cell of origin.

Germ cell tumors are divided into seminomatous and non-seminomatous types, whereby seminomatous have very good prognosis and are chemo-radiosensitive.

It is of crucial importance to differentiate between testicular neoplasm and benign scrotal masses.

History, clinical examination and ultrasonography findings often corroborate to form a preliminary diagnosis of testicular neoplasm. Further management depends exclusively on the stage of malignancy; determination of which begins with orchiectomy.

Adjuvant treatment options include radiation, chemotherapy, surgical resection with RPLND and surveillance.

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Notes