Pathology And Work UP of Testicular Tumors

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- Testicular pathology is a nosologically complex subject because of the
 - spectrum of histologic subtypes and
 - variable clinical behavior, particularly among GCTs.
- Testicular neoplasms span an amazing gamut of anatomic types
 - subdivided into two major categories.
- Approximately
 - 94–96 % of testicular tumors are of germ cell origin
 - Remaining 3% to 4% are sex cord–stromal tumors, and most are benign
 - the remaining are lymphomas

- The germ cell tumors are
 - Rare
 - Approximately 1% of all tumors in men
 - Classified histologically into seminomas and non-seminomas
 - More than 50% consist of more than one cell type
- Nonseminomas include
 - Embryonal carcinoma
 - Yolk sac (endodermal sinus tumour)
 - Teratoma
 - Choriocarcinoma, and
 - Mixed germ cell tumors

- Seminomatous tumors are composed of
 - cells that resemble primordial germ cell or early gonocytes
- The non seminomatous tumors may be composed of
 - undifferentiated cells that resemble embryonic stem cells,
 - as in the case of embryonal carcinoma,
 - but the malignant cells may also differentiate along other lineages,
 - Generating yolk sac tumors, choriocarcinoma and teratomas.

Classification - 2004

1:Intra tubular germ-cell neoplasia(IGCN)

2:GERM CELL TUMORS 95%

Seminoma 40%

Classic type anaplastic Spermatocytic type

Non seminomatous germ-cell tumors 60%

- Embryonal carcinoma 20-25%
- Teratoma 25-35%
- Yolk sac (endodermal sinus) tumor
- Choriocarcinoma 1%
- Mixed germ-cell tumor

3:Classification of Sex-Cord Stromal Tumors of the Testis 2-3%

- Leydig cell tumor
- Sertoli cell tumor
- Granulosa cell tumor
- Fibroma-thecoma stromal tumor
- Gonadoblastoma
- Sex cord-stromal tumor unclassified type

4: others 5%

- Iymphoma
- rabdomyosarcoma
- melanoma

Introduction

- The updated 2016 draft classification
 - discussed at an International Society of Urological Pathology Consultation on Testicular and Penile Cancer.
 - addresses the main updates to germ cell tumour classification
- Advances in the understanding, classification, immunohistochemistry and genetics of testicular germ cell tumors

Major changes include

• a pathogenetically derived classification using germ cell neoplasia in situ (GCNIS) as a new name for the precursor lesion,

Distinction of

- prepubertal tumours (non-GCNISderived) from
- postpubertal-type tumours (GCNIS derived),
- acknowledging the existence of rare benign prepubertal-type teratomas in the postpubertal testis.

- Spermatocytic tumour is adopted as a replacement for spermatocytic seminoma
 - to avoid potential confusion with the unrelated usual seminoma.
- The spectrum of trophoblastic tumours arising in the setting of testicular germ cell tumour continues to expand
 - to include epithelioid and placental site trophoblastic tumours analogous to those of the gynaecological tract

- Currently, reporting of anaplasia (seminoma or spermatocytic tumour) or immaturity (teratoma)
 - is not required, as these do not have demonstrable prognostic importance.
- In contrast, overgrowth of a teratomatous component (somatic-type malignancy) and sarcomatous change in spermatocytic tumour
 - indicate more aggressive behaviour, and should be reported

Classification of the tumors of testes

Germ cell tumors derived from Germ cell neoplasia in situ

- Germcell neoplasia insitu
- Seminoma(40%)
- Classic type
- Anaplastic type
- Spermatocytic type
- Spermatocytic seminoma with sarcoma
- Seminoma with syncytiotrophoblast cells

- Non seminomatous germ cell tumors(60%)
- Embryonal carcinoma
- Yolk sac tumor, postpubertal type
- Teratoma(postpubertal type)
- Teratoma with somatic type malignancy
- Trophoblastic tumors(choriocarcinoma)
- Mixed germ cell tumors
- Regressed germ cell tumors.

Germ cell tumors unrelated to GCNIS

Spermatocytic tumor

- Yolk sac tumor, prepubertal type
- Teratoma, prepubertal type
- Dermoid cyst, monodermal teratoma,
- Teratoma with somatic type malignancies.
- Mixed teratoma and yolk sac tumor, prepubertal type
- Sex cord stromal tumors(2-3%)
- Leydig cell tumor
- Sertoli cell tumor
- Granulosa cell tumor
- Tumors in the fibroma- thecoma group
- Mixed sex cord stromal tumor
- Unclassified sex cord stromal group
- Gonadoblastoma

2016 edition of the World Health Organization classification of germ cell tumor



Miscellaneous tumors of the testis

- Ovarian epithelial type tumors
- Serous cystadenoma
- Serous tumor of borderline malignancy
- Serous cystadenocarcinoma
- Mucinous cystadenoma
- Mucinous borderline tumor
- Mucinous cystadenocarcinoma
- Endometrioid adenocarcinoma
- Clear cell adenocarcinoma
- Brenner tumor
- Juvenile xanthogranuloma
- Hemangioma

Hematolymphoid tumors

- Diffuse large B cell lymphoma
- Follicular lymphoma, NOS
- Extranodal NK / T cell lymphoma, nasal type
- Plasmacytoma
- Myeloid sarcoma
- Rosai-Dorfman disease

Restructuring of classification

- A major change to the structure of the WHO classification system for testicular germ cell tumors is the division into two main groups
 - (i) tumors not derived from GCNIS (predominantly but not exclusively) occurring in prepubertal patients, and
 - (ii) tumors derived from GCNIS.
- This change reflects the different behaviour, pathogenesis and tumour biology of similar histological patterns occurring in different contexts.

Precursor lesions

GERM CELL NEOPLASIA INSITU (GCNIS)

- The lesion that is most widely accepted as the precursor of adult malignant testicular germ cell tumors
- is composed of seminoma-like cells with
- enlarged hyperchromatic nuclei,
- clumped chromatin, and
- often prominent nucleoli,
- aligned along the basement membrane of seminiferous tubules (within the spermatogonial niche)

- This lesion was officially regarded as intratubular germ cell neoplasia, unclassified type (IGCNU) in the 2004 WHO system
- GCNIS was accepted as an abbreviated but precise replacement for these terms in the 2016 WHO system,
 - as it combines elements from the two most widely used terms, IGCNU and carcinoma in situ
- These cells are uniformly positive for the embryonic stem cell marker OCT3/4 (POU5F1)
 - similarly to what is seen in seminoma and embryonal carcinoma

Germ cell neoplasia in situ typically shows



an absence of maturing spermatogenesis



a conspicuous layer of atypical cells resembling seminoma cells aligned along the basement membrane [the spermatogonial niche]

Pathogenesis

- ~90% of germ-cell tumors associated with adjacent GCNIS.
- GCNIS carries a 50% risk of testicular cancer within 5 years.
- The invasive potential of GCNIS not attained until after hormonal changes occur during puberty.

Pathogenesis

- Most testicular germ cell tumors
 - originate from a precursor lesion called germ cell neoplasia in situ (GCNIS).
- The exception to this rule are
 - pediatric yolk sac tumors and teratomas and adult spermatocytic seminomas,
 - all of which are of uncertain origin.
- GCNIS is believed to
 - arise in utero and
 - stay dormant until puberty
 - after which it may progress to seminoma or non seminomatous tumors.
- The lesion consists of atypical primordial germ cells with large nuclei and clear cytoplasm, which are about twice the size of normal germ cells.

- GCNIS is characterized by
 - seminiferous tubules showing decreased spermatogenesis
 - the normal constituents of the tubules are replaced by abnormal germ cells
 - with the appearance of seminoma cells
- These cells stain strongly for placental alkaline phosphatase (PLAP)
 - whereas normal germ cells are negative
- IGCN has a 50% risk of developing
 - into an invasive germ cell tumor within 5 years

- These cells
 - retain the expression of the transcription factors OCT3/4 and NANOG,
 - which are important in maintenance of pluripotent stem cells.
- GCNIS shares some of the genetic alterations that are found in germ cell tumors.
- One that is particularly important is the
 - reduplication of the short arm of chromosome 12 (12p) in the form of an isochromosome I (12p),
 - a cytogenetic alteration that is invariably found in invasive germ cell tumors regardless of histological type.
- Activating mutations in the gene encoding the KIT receptor tyrosine kinase, which may be present in seminomas, are also frequently present in GCNIS.

- About 50% of individuals with GCNIS develop invasive germ cell tumors within 5 years after diagnosis
- And it may be that all patients with GCNIS will eventually develop invasive tumors.



- It is hypothesized that
 - the cells originate from primordial germ cells
 - Early during embryogenesis,
 - possibly owing to an excess of estrogens
- They likely
 - remain within the seminiferous tubules
 - in a dormant stage
 - until puberty when replication begins,
 - possibly as a consequence of raised sex hormone levels
- Transition to an invasive germ cell tumor then occurs



- Seminomas transformed germ cells that resemble the gonocyte but are blocked in their differentiation.
- Embryonal carcinoma cells resemble undifferentiated stem cells, and their patterns of gene expression are similar to those of stem cells and GCNIS.
- Choriocarcinomas and yolk-sac tumors have extraembryonic differentiation.
- Teratomas have somatic differentiation.

Predisposing factors

- Cryptorchidism
- Klinefelter syndrome
- Positive family history for testicular germ cell tumor
- Intratubular germ cell neoplasia
- Trauma
- Viral infection
- Hormonal factors

Seminomas

- Seminomas are the most common type of germ cell tumor
- Constitute around 50% of these tumors.
- One of the most treatable and curable cancers with a survival rate of around 95%
- The peak incidence is the third decade and
- They almost never occur in infants'
- Testicular seminoma originates in the germinal epithelium of the seminiferous tubules.

Morphology

- Seminomas produce bulky masses, upto ten times the size of normal testis.
- Grossly it is a
 - soft tan-colored diffuse multinodular mass
- The typical seminoma has a
 - homogenous, grey white, lobulated, cut surface usually devoid of hemorrhage and necrosis.
- Generally the tunica albuginea is not penetrated,

- Microscopically, typical seminoma consists of
 - sheets of uniform cells, divided into poorly demarcated lobules by delicate fibrous septa containing a lymphocytic infiltrate.
- The classic seminoma cell is
 - large and round to polyhedral and
 - has a distinct cell membrane; clear or watery-appearing cytoplasm;
 - a large, central nucleus with one or two prominent nucleoli.
 - Mitoses vary in frequency.
 - The cytoplasm contains varying amounts of glycogen.

Immunohistochemistry

- More than 90% of seminomas will stain positive for PLAP.
- Negative for CD30, AFP and epithelial membrane antigen
- Negative or weak/ focal positive for cytokeratin.

- Seminomas contain isochromosome 12p and express OCT3/4 and NANOG.
- Approximately 25% of these tumors have KIT activating mutations.
- KIT amplification and KIT overexpression through other unknown mechanisms have also been reported.

- Serum alpha-fetoprotein (AFP) is not elevated in pure seminoma.
- Serum level of human chorionic gonadotropin (HCG) is elevated in 15% to 30% of men at presentation
 - related to the presence of syncytiotrophoblastic cells.
- When especially prominent, their presence may lead to potential diagnostic confusion with choriocarcinoma

- By Immunohistochemistry, seminoma cells stain positively for
 - KIT, (regardless of KIT mutation status),
 - OCT4, and
 - placental alkaline phosphatase (PLAP).
- A few scattered keratin-positive cells may also be present.
- Approximately 15% of seminomas contain syncytiotrophoblasts.
- Seminomas may also be accompanied by an ill-defined granulomatous reaction

• Histologic variations of seminoma such as "anaplastic" or "atypical" seminoma are of no known clinical relevance.

- Spermatocytic seminoma, however, is the one variant of seminoma that has a different natural history and is even of uncertain relation to other germ cell tumors.
- It usually occurs in older individuals and has low metastatic potential.
- Orchiectomy is the only treatment required.
- Unlike all other germ cell tumors, spermatocytic seminoma is not associated with ITGCN.

Non seminomatous GCTs

- Variety of morphological and histological features with common origin from the stem germ cells
 - differentiate to various embryonal or extra-embryonal elements during oncogenesis
 - explains the significant overlap between different histologies and the frequent discovery of mixed NSGCTs in the same patient
Embryonal carcinoma

- Neoplastic transformation during the fetal phase of blastocele
- Most frequent in the 2nd and 3rd decade of life
- Often located in extragonadal places (ie mediastinum)
 - worse prognosis compared to gonadal counterparts
- Potential for distal metastasis.
- Less radiosensitive than seminoma but very sensitive to chemotherapy

Embryonal carcinoma is

- the most common component in mixed tumors
- AFP- positive cells are present in 33%
- HCG-positive cells are present in 20%

- These tumors are more aggressive than seminomas.
- share some markers with seminomas
 - such as OCT 3/4 and PLAP,
- but differ by
 - being positive for cytokeratin, CD 30 and
 - negative for KIT.

- The neoplastic cells have
 - an epithelial appearance,
 - are large and anaplastic, and
 - have hyperchromatic nuclei with prominent nucleoli.
- The cell borders are usually indistinct and there is
 - considerable variation in cell and nuclear size and shape.
- Mitotic figures and tumor giant cells are frequently seen.

Embryonal Carcinoma



Embryonal carcinoma characterized by highly atypical cells with scant cytoplasm and numerous mitoses Left: solid pattern Right: glandular or microcystic pattern

Yolk sac tumors

- Neoplastic transformation of the germ cell of the endodermal duct in the phase of blastomeride
- α -FP production
- Pure form: Infants and children up to 2 years
- Have excellent prognosis
- Mixed form: as a component of a mixed NSGCT,
- worse prognosis
- α -FP very useful for disease staging, monitoring of response to treatment and early detection of recurrence .

Also known as Endodermal sinus tumor

Morphology

- Nonencapsulated and have a homogenous, yellow-white, mucinous appearance.
- Composed of a lacelike (reticular) network of medium-sized cuboidal or flattened cells.
- In addition, papillary structures, solid cords of cells, and a multitude of other less common patterns may be found.

- SCHILLER-DUVAL BODIES (structures resembling endodermal sinuses)
 - seen in approximately 50% of tumors.
 - These consist of mesodermal core with a central capillary and a visceral and parietal layer of cells resembling primitive glomeruli.
 - Eosinophilic, hyaline-like globules are present within and outside the cytoplasm
- Alpha-fetoprotein and alpha1-antitrypsin can be demarcated by immunocytochemical staining.
- The presence of AFP in the tumor cells is highly characteristic, and undergoes resemblance to yolk sac cells.

Schiller-Duval Bodies



Schiller-Duval body

Choriocarcinoma

- Choriocarcinoma is highly malignant form of testicular tumor
- Most frequent in young men 20-30 years of age
- Choriocarcinoma in it's pure form

is rare,

constitutes less than 1% of all germ cell tumors

• Aggressive biological behaviour but very chemosensitive

Choriocarcinoma

- Neoplastic transformation in the stage of syncytiotrophoblasts of the chorionic villi
- production of β -hCG
 - gynecomastia, testicular atrophy, azoospermia

 Potential to invade vessels and promote angiogenesis¹ early hematogenous metastases (lungs, hemoptysis)

 β-hCG very useful for disease staging, monitoring of response to treatment and early detection of recurrence

Morphology

- Choriocarcinomas often cause no testicular enlargement and are detected only as a small palpable nodule.
- Typically, these tumors are small, rarely larger than 5 cm in diameter.
 - Hemorrhage and necrosis are extremely common.
- Histologically the tumors contain two cell types, syncytiotrophloblasts and cytotrophoblasts.

Choriocarcinoma is

- The least common type of pure NSGCT
- Present in about 4% of mixed tumors
- It is particularly aggressive
- Almost always metastatic at diagnosis
- Associated with high levels of HCG





Teratoma

- Neoplastic transformation of germ-cells that have been differentiated to the level of embryonal elements
- Possible co-existence of tissues originating from all three embryonal layers
 - ectoderm, mesoderm, endoderm
 - (i.e. cartilage, neuronal tissue, epithelia)
- Possible co-existence with other NSGCTs, (i.e. embryonal carcinoma)

- Teratoma is
 - Not associated with elevated AFP or HCG
- Both mature and immature teratomas are
 - considered malignant with
 - ability to metastasize.

- They may occur at any age from infancy to adult life.
- Pure forms of teratoma are fairly common in infants and children, second in frequency only to yolk sac tumors.
- In adults, pure teratomas are rare, constituting 2% to 3% of germ cell tumors
- However, the frequency of teratomas mixed with other germ cell tumors is approximately 45%.

Morphology

- Grossly teratomas are
 - usually large, ranging from 5-10 cm in diameter.
- They are composed of various tissues
- the gross appearance is
 - heterogenous with solid, sometimes cartilagenous, and cystic areas.
- Hemorrhage and necrosis usually indicate
 - admixture with embryonal carcinoma, choriocarcinoma or both.

Teratomas are composed of heterogenous, Helter-Skelter collection of differentiated cells or organoid structures such as

- neural tissue,
- muscle bundles,
- islands of cartilage,
- clusters of squamous epithelium,
- structures reminiscent of thyroid gland,
- bronchial or bronchiolar epithelium, and
- bits of intestinal wall and
- brain substance,
- all embedded in a fibrous or myxoid stroma

Elements may be

- mature (resembling various adult tissues) or
- immature (sharing histologic features with fetal or embryonal tissue)
- "Teratoma with malignant transformation"
 - Rarely malignant non-germ cell tumors arise in teratomas.
- Transformation into
 - squamous cell carcinoma,
 - mucin-secreting adenocarcinoma,
 - sarcoma, or other cancers.
- A non-germ cell malignancy arising in a teratoma
 - chemo resistant;
 - the only hope for cure resides in the resectability of the tumor.

• These non germ cell malignancies retain isochromosome 12p, proving a clonal relationship to a preceding teratoma.

- In the child, differentiated mature teratomas usually follow a benign course.
- In the post pubertal male, all tumors are regarded malignant, capable of metastatic behaviour, whether the elements are mature or immature.
- Consequently it is not critical to detect immaturity in a testicular teratoma of a post pubertal male.



Trophoblastic tumours

- Testicular trophoblastic tumors other than the most widely recognized choriocarcinoma
- Important
 - Cystic trophoblastic tumour
 - Refers to a unique lesion
 - non-aggressive behaviour, and
 - is composed of cystic spaces lined by trophoblastic cells with smudged nuclei, often containning luminal fibrin

Cystic trophoblastic tumour is often associated with teratoma, composed of cystic spaces lined by trophoblastic cells with enlarged, hyperchromatic or smudged nuclei (B) and fibrinoid luminal contents.

Despite the trophoblastic differentiation of this lesion, it appears to have similar behaviour to teratoma





- other trophoblastic tumours increasingly recognized
 - epithelioid trophoblastic tumour,
 - placental site trophoblastic tumour,
 - regressing choriocarcinoma, and
 - rare unclassified and
 - hybrid trophoblastic tumours

Other forms of trophoblastic tumors such as epithelioid trophoblastic tumour have been rarely reported to arise in a primary testicular germ cell tumour





- Despite the trophoblastic appearance of these cells and occasional reactivity for beta-hCG,
 - the lesions are not infiltrative,
 - lack the biphasic growth pattern of choriocarcinoma, and
 - have low mitotic activity.
 - Patients typically have only modest, if any, elevation of serum beta-hCG

- GATA3 has emerged as a useful immunohistochemical marker of these various trophoblastic cell lineages
- other trophoblastic lineage markers such as
 - human placental lactogen (HPL),
 - beta-hCG,
 - placental alkaline phosphatase, and
 - inhibin,
- may be helpful both in confirming a trophoblastic lineage

Epithelioid trophoblastic tumours

- diffuse immunoreactivity for p63 and
- negative for HPL

Placental site trophoblastic tumour shows the opposite pattern

- Non-choriocarcinomatous trophoblastic tumours
 - appear to be rare in the testis
 - Have to be distinguished from choriocarcinoma
 - because of their less aggressive behaviour.

Teratoma, postpubertal type

- One of the key changes in the 2016 WHO classification system
 - the discrimination of postpubertal type teratoma from prepubertal-type teratoma
- Post pubertal Teratoma is regarded as
 - differentiation from other germ cell tumour types
- Therefore, patients with apparently pure testicular teratomas
 - often have GCNIS in the testis, and
 - may develop metastases consisting of teratoma or other germ cell tumours,
 - the vast majority are still regarded as malignant germ cell tumours.

SOMATIC-TYPE MALIGNANCY ARISING FROM TERATOMA

- A variety of malignancies have been reported to occur as secondary, somatictype neoplasms arising from germ cell tumours, including:
 - Sarcoma (commonly embryonal rhabdomyosarcoma, more often than leiomyosarcoma or angiosarcoma),
 - PNET,
 - Carcinoma,
 - Glial and
 - Meningeal neoplasms,
 - Haematological neoplasms, and
 - Nephroblastoma-like (Wilms) tumour
- Thought to arise via overgrowth of a particular component of teratoma

• Prepubertal-type tumors (including dermoid and epidermoid cyst)

Teratomas occurring in prepubertal patients

- lack association with GCNIS
- have a more organoid architecture,
- lack significant cytological atypia, and
- largely lack 12p amplification,
- have not been reported to metastasize

Prepubertal-type yolk sac tumour

- Biologically & pathogenetically diff from postpubertal-type yolk sac tumour
- In children, yolk sac tumour occurs primarily in pure form
 - rather than as a component of a mixed germ cell tumour
- Associations with GCNIS and cryptorchidism are lacking,
- Low incidence of extratesticular involvement (non-clinical stage I)
- In cases of advanced disease, chemotherapy is very effective,
- Indicating less aggressiveness as well

Regression of germ cell tumor

- Also known as 'burnt-out' germ cell tumour
- represent metastases from an occult or regressed testicular primary tumour.
- Findings in the testes of such patients typically include a scar, reduced spermatogenesis, and microlithiasis.

Spermatocytic tumour

- Spermatocytic seminoma reclassified as spermatocytic tumour
- This entity labelled as a tumour rather than as an unequivocal malignancy emphasizes that
 - The behaviour is non-aggressive,
 - metastases very rare examples of
 - Treatment with orchiectomy is typically curative,
 - Surveillance is enough
WORK UP of TESTICULAR TUMORS

General

History (document cryptorchidism and previous inguinal or scrotal surgery) Physical examination

Laboratory Studies Complete blood count Biochemistry profile (including lactate dehydrogenase) Serum assays α-Fetoprotein (AFP) β-Human chorionic gonadotropin (β-HCG) Surgery Radical inguinal orchiectomy Diagnostic Radiology Chest x-ray films, posterior/anterior and lateral views Computed tomography (CT) scan of abdomen and pelvis CT scan of chest for nonseminomas and stage II seminomas Ultrasound of contralateral testis Special Study

Semen analysis

WORKUP

PRIMARY TREATMENT^a



Suspicious testicular mass

- History and Physical
- Serum Tumor Markers
- Chemistry profile
- Testicular ultrasound
- Discuss sperm banking if clinically indicated

Presenting symptoms

- Painless swelling in the scrotum
 - usual presentation of a testicular tumor
- Pain, heaviness, and tenderness
 - not uncommon
- Back pain or abdominal swelling
 - disease in the lymph nodes of the retroperitoneum

- Systemic symptoms
 - Widely disseminated parenchymal disease in lungs, liver, bone, or brain
- Gynecomastia
 - a rare presentation of embryonal carcinoma
 - may be seen in association with the very uncommon sex cord-stromal tumors
- Occasionally, patients present with metastatic germ cell malignancies
 - diagnosed by biopsy or elevated levels of serum tumor markers
 - without evidence of a palpable mass in the testis
- Occult primary disease in the testis is
 - often detected by testicular ultrasound
- Diagnosis of extratesticular germ cell tumor
 - usually mediastinal, retroperitoneal, or pineal
 - If there is no evidence of a primary tumor in the testis

- A complete history
 - previous inguinal or scrotal surgery
 - cryptorchidism
 - retractile testes, and
 - orchidopexy
- The physical examination
 - Possible sites of lymph node metastases
 - The contralateral testis should be examined clinically.
 - The presence or absence of gynecomastia is an important observation.
- If testicular tumor is suspected,
 - testicular ultrasound should be performed.
 - a solid mass within the testis, often with associated testicular microlithiasis.
- Radical orchiectomy through an inguinal incision is diagnostic and removes the primary tumor.

- If testicular tumor is suspected,
- A trans scrotal ultrasound with Doppler should performed
- Testicular ultrasound
 - Confirms the presence of a testicular mass
 - Determines whether the mass is intra or extra testicular
 - Explores the contralateral testis
- Testicular GCTs are typically heterogeneous, hypoechoic and vascular

Tumor Markers

- β-subunit of Human Chorionic Gonadotropin (β-HCG)
- Serum Alpha Fetoprotein (AFP)
- The metabolic half-life of
- AFP is approximately 5 days and
- β-HCG is approximately 18 to 24 hours
- β-HCG may be modestly elevated in 15% to 30% of patients with pure seminomas
- Any elevation of AFP connotes nonseminomatous disease
- NSGCTs of the testes are uniquely associated with reliable serum tumor markers:
- In disseminated nonseminomatous disease
- One or both of these serum markers are elevated in 80% to 85% of patients

- Serum lactate dehydrogenase (LDH), although nonspecific,
 - is elevated in 80% of patients with advanced testicular cancer.

- Serum tumor markers may be elevated in other circumstances or conditions, such as
 - laboratory error,
 - cross-reactivity with luteinizing hormone,
 - marijuana use,
 - hepatitis, or
 - development of antibodies to the glycoproteins

For patients in whom treatment is likely to compromise fertility.

• Semen analysis and banking of sperm should be considered

With newer technologies, it is possible to retrieve and bank sperm

• even with poorer-quality sperm.

- Investigations should routinely include
 - Chest x-ray films for all patients

- Computed tomography (CT) of the thorax
 - for any patient with NSGCTs of the testis

- CT scans of the abdomen and pelvis should be performed
 - to evaluate the retroperitoneal nodal areas
 - assess the liver
- CT of abdomen and pelvis
 - relies on nodal size to assess the retroperitoneal nodes
 - with a sensitivity of 40% and a specificity of 95%
- Magnetic resonance imaging (MRI) appears equivalent to CT in
 - determining the size and location of retroperitoneal adenopathy.

- Fluorodeoxyglucose positron emission tomography (FDG-PET) scan
 - slightly higher sensitivity (66%) than CT
 - comparable specificity (98%).
 - It has little role in initial disease staging
 - but may have a role where CT is questionable.
- Cannot detect lesions
 - <5 mm in size or
 - teratomas of any size owing to their very low metabolic activity
- It also has an important role in evaluating residual retroperitoneal disease following chemotherapy

• Baseline ultrasonography of the remaining testis should be performed.

- If the contralateral testis is atrophic and the patient is <30 years age,
 - then there is a 30% risk of IGCN.
- Biopsy of the contralateral testis may be considered in this setting

Role of tumour markers

- Marker elevation seen in 80 to 85% of Testicular tumors.
- Diagnosis markers give clue to the diagnosis and histology of tumor
- Help infer clinical behavior, monitor therapy, detect residual or recurrent disease.
- Levels of marker elevation appears to be directly proportional to tumor burden

Tumour markers

Marker	seminoma	Non seminoma
Alpha fetoprotein	Never raised	40%
B HCG	15-20%	40%
LDH	40-60%	40-60%

Use	s of markers
	Diagnosis
	Prognosis
	Treatment response assessment
	Monitoring

Othe causes of raised markers HCG- neuroendocrine, bladder kidney lung and rarely other cancers. Marijuana, hypogonadism AFP- Hepatocellular Ca, gastric ca, alcohol, other liver disease, hereditary

- Post orchiectomy elevated marker levels denotes residual disease/or higher stage disease.
- Markers are detected earlier than radiological studies.
- Detection of an elevated AFP in Seminoma denotes presence of Non-Seminomatous elements.



Radical orchiectomy

- In this involved testis is removed enbloc with the spermatic cord enclosed by tunica layers
- performed through an inguinal incision
- This minimizes the chance of tumor spillage.
- Scrotal violation (transscrotal orchiectomy, FNAC, open testicular biopsy) should be avoided
 - increases local/ regional recurrence (2.9% vs 0.4%) and
 - compromises prognosis

- Diagnostic as well as a therapeutic modality
 - Removes primary tumor,
 - Confirms histopathological diagnosis.
 - Guides about prognostic factors- tumor size/rete testis/cord invasion/ LVI.

AJCC 8th edition Staging

American Joint Committee on Cancer (AJCC) TNM Staging Classification for Testis Cancer 8th ed., 2017

Table 1. Definitions for T, N, M

- Clinical T Primary Tumor
- cTX Primary tumor cannot be assessed
- cT0 No evidence of primary tumor
- cTis Germ cell neoplasia in situ
- cT4 Tumor invades scrotum with or without vascular/lymphatic invasion

Note: Except for Tis confirmed by biopsy and T4, the extent of the primary tumor is classified by radical orchiectomy. TX may be used for other categories for clinical staging.

Pathological T	Primary Tumor
рТХ	Primary tumor cannot be assessed
рТ0	No evidence of primary tumor
pTis	Germ cell neoplasia <i>in situ</i>
pT1	Tumor limited to testis (including rete testis invasion) without lymphovascular invasion
pT1a*	Tumor smaller than 3 cm in size
pT1b*	Tumor 3 cm or larger in size
рТ2	Tumor limited to testis (including rete testis invasion) with lymphovascular invasion OR Tumor invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer covering the external surface of tunica albuginea with or without lymphovascular invasion
рТЗ	Tumor directly invades spermatic cord soft tissue with or without lymphovascular invasion
pT4	Tumor invades scrotum with or without lymphovascular invasion

*Subclassification of pT1 applies to only pure seminoma.

Clinical N	Regional Lymph Nodes
cNX	Regional lymph nodes cannot be assessed
cN0	No regional lymph node metastasis
cN1	Metastasis with a lymph node mass 2 cm or smaller in greatest dimension OR Multiple lymph nodes, none larger than 2 cm in greatest dimension
cN2	Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension OR Multiple lymph nodes, any one mass larger than 2 cm but not larger than 5 cm in greatest dimension
cN3	Metastasis with a lymph node mass larger than 5 cm in greatest dimension

Pathological N Regional Lymph Nodes

- pNX Regional lymph nodes cannot be assessed
- pN0 No regional lymph node metastasis
- **pN1** Metastasis with a lymph node mass 2 cm or smaller in greatest dimension and less than or equal to five nodes positive, none larger than 2 cm in greatest dimension
- **pN2** Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension; or more than five nodes positive, none larger than 5 cm; or evidence of extranodal extension of tumor
- pN3 Metastasis with a lymph node mass larger than 5 cm in greatest dimension

M Distant Metastasis

- M0 No distant metastases
- M1 Distant metastases
 - M1a Non-retroperitoneal nodal or pulmonary metastases
 - M1b Non-pulmonary visceral metastases

S Serum Markers

- SX Marker studies not available or not performed
- S0 Marker study levels within normal limits
- S1 LDH <1.5 x N* and hCG (mIU/mL) <5,000 and AFP (ng/mL) <1,000</p>
- S2 LDH 1.5–10 x N* or hCG (mIU/mL) 5,000–50,000 or AFP (ng/mL) 1,000–10,000
- S3 LDH >10 x N* or hCG (mIU/mL) >50,000 or AFP (ng/mL) >10,000

Serum Tumor Markers (S)

•

- + SX: Serum marker studies not available or performed
- + SO: Serum marker study levels within normal limits

	LDH		HCG (mIU/mL	.)	AFP (ng/mL)
• + S1:	<1.5 X N#	and	<5,000	and	<1,000
• + S2:	1.5-10 X N	or	5,000-50,000	or	1,000-10,000
• + S3:	>10 X 10	or	>50,000	or	>10,000

Table 2. AJCC Prognostic Stage Groups

	т	N	м	S
Stage 0	pTis	N0	MO	S 0
Stage I	pT1-T4	N0	MO	SX
Stage IA	pT1	N0	MO	S 0
Stage IB	pT2	N0	MO	S 0
	рТЗ	N0	MO	S 0
	pT4	N0	MO	S 0
Stage IS	Any pT/TX	N0	MO	S1-3
Stage II	Any pT/TX	N1-3	MO	SX
Stage IIA	Any pT/TX	N1	MO	S 0
	Any pT/TX	N1	MO	S1
Stage IIB	Any pT/TX	N2	MO	S 0
	Any pT/TX	N2	MO	S1
Stage IIC	Any pT/TX	N3	MO	S 0
	Any pT/TX	N3	MO	S1
Stage III	Any pT/TX	Any N	M1	SX
Stage IIIA	Any pT/TX	Any N	M1a	S 0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-3	MO	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-3	MO	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

Table 1

IGCCCG Classification of Metastatic Disease

Classification	Seminoma	Nonseminoma
Good risk	Any primary site and No nonpulmonary visceral metastases and Normal AFP, any HCG, any LDH	Gonadal or retroperitoneal primary tumor No pulmonary or visceral metastases Good tumor markers (all): AFP <1,000 ng/mL, HCG <5,000 IU/L, LDH <1.5 × ULN
Intermediate risk	Any primary site and Nonpulmonary visceral metastases and Normal AFP, any HCG, any LDH	Gonadal or retroperitoneal primary tumor No pulmonary visceral metastases Intermediate tumor markers (any): AFP 1,000-10,000 ng/mL, HCG 5,000-50,000 IU/L, LDH 1.5 × ULN
Poor risk	NA	Mediastinal primary tumor <i>or</i> Nonpulmonary visceral metastases <i>or</i> Poor tumor markers (any): AFP >10,000 ng/mL, HCG >50,000 IU/L, LDH >10 × ULN

AFP: alpha-fetoprotein; HCG: human chorionic gonadotropin; IGCCCG: International Germ Cell Cancer Collaborative Group; LDH: lactic dehydrogenase; NA: not applicable; ULN: upper limit of normal. Source: Reference 11.

- The factors most strongly associated with a poor prognosis were
 - mediastinal primary,
 - nonpulmonary visceral metastases,
 - grossly elevated tumor markers
 - AFP >10,000 ng/mL
 - HCG >50,000 IU/L
 - LDH >10 times normal

- Patients with NSGCT were divided into three prognostic groups
 - Good,
 - Intermediate,
 - Poor prognosis
- Patients with seminomas into two prognostic groups
 - Good or
 - Intermediate

- The good prognosis group comprised
 - >50% of all patients with metastatic NSGCTs and
 - 90% of seminomas and
 - a 5-year survival >90%.
- The intermediate prognosis group comprised
 - 25% to 30% of patients and
 - 5-year survival of 80%.
- The poor prognosis group comprised
 - 15% to 20% of patients with NSGCT and
 - 5-year survival of approximately 50%

THANK YOU