CHAPTER

16 Tumors of the Male Genital Organs

PROSTATE CANCER

Anatomy

Mcneal (1972) divided the prostate into 4 zones with distinctly separate groups of glands namely; peripheral, central, periurethral and transitional zones (Fig 16-1). The peripheral zone constitutes 70% of the prostate. It is a posteriorly located horseshoe structure with right and left lobes. The central zone makes up 25% of prostate forming a cone shaped volume surrounding the ejaculatory ducts, with its apex at verumontanum and its base at bladder neck. The periurethral and transitional zones form 5% of normal prostatic volume and are located anteriorly in intimate relation with the anterior fibromusclar stroma.

The zonal anatomy of the prostate is often simplified with a two zone concept, namely; the inner prostate which includes the transitional zone, periurethral zone and the anterior fibromusclar stroma, whereas, the outer prostate includes the central and peripheral zones. The inner prostate is commonly affected by nodular hyperplasia and atypical adenomatous hyperplasia (adenosis). The outer prostate, however, is the site of preference to prostatic intraepithelial neoplasia (PIN) and invasive carcinoma (Fig 16-1). Hence, a transrectal needle biopsy, guided by TRUS, is more accurate than samples taken by TUR in the diagnosis of prostatic carcinoma.

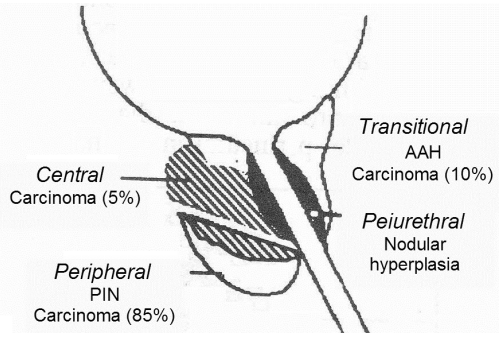


Fig 16-1 *Zonal anatomy and sites of prostatic lesion . AAH atypical adenomatous hyperplasia PIN prostatic intraepithelial hyperplasia*

Normal histology

The prostate is formed of acini, ducts and fibromusclar stroma. The stroma accounts for about 70% of the prostate mass. The epithelial cells lining the prostatic acini and ducts include:
(1) *Luminal cells*: include the functioning terminally differentiated columnar cells (positive for CK8/18 and PSA), intermediate cells (positive for CK19), and neuroendocrine cells (positive for chromogranin) which secrete bioactive molecules to control the functioning cells.
(2) *Basal cells*: rest on basement membrane and include stem cells (positive for C-kit) and progenitor cells (positive for CK 5/14 and p63). Stem cells are undifferentiated cells that can give rise to all other epithelial cells through multilineage differentiation (cell renewal). There are no myoepithelial cells among basal cells, but, contractile smooth muscle cells (positive for actin) are present in prostatic stroma.

Incidence

It is estimated that about 242,000 men will be diagnosed with and 28.000 will die of prostatic cancer in 2012. The median age at diagnosis was 67 years (NCI's SEER Cancer Statistics review, 2011). In Egypt, prostatic cancer formed the majority of male genital cancer (60.7%) at the NCI in the last 10 years. The median age was 72.8 years.

Etiology

Although the specific causes of prostate cancer initiation and progression are not yet known, considerable evidence suggests that both genetics and environment (inflammation and infection) play a role in its origin and evolution. Familial cases contribute about 15% of prostatic cancer.

Molecular oncogenesis

Prostate cancer is unique among solid tumors in that it exists in two clinicopathologic forms (Wein et al, 2012): an occult form (30%) and a clinically manifest form (70%). The molecular relationship between the two is still obscure. The contemporary model of prostatic cancer proposes

4 stages namely: hyperplasia, prostatic intraepithelial neoplasia (PIN), localized cancer and metastatic disease.

Androgens and chronic inflammation play key role in oncogenesis by inducing epithelial hyperplasia. The primary most active androgen of the prostate is dihydrotestosterone (DHT), formed by the action of the enzyme 5α-reductase on testosterone. Androgens induce proliferation of stem cells which is considered an initial step of oncogenesis. Insulin growth factor (IGF) pathway is capable of inducing the activation of the androgen receptor even in the absence of androgen. Inflammatory cells produce reactive oxygen species which cause oxidative DNA damage (mutation). Moreover, COX-2 enzyme induced in response to inflammation leading to overexpression of prostaglandins which causes cell proliferation, inhibit apoptosis and stimulates oncogenesis. Reactive oxygen species are inactivated by a group of protective enzymes (including glutathione-S-transferase), hence deficient or absent expression of these enzymes will promote prostatic oncogenesis.

Molecular genetic changes involved in early phases of oncogenesis include loss of NKX3.1 gene, PTEN, Rb, p27, telomerase expression and quantitative or qualitative alterations in androgen receptors. Molecular genetic changes observed with progression of occult to metastatic disease include: loss of TP53, loss of E-cadherin, overexpression of vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF).

Macroscopy

Grossly, about 85% of invasive carcinomas are located in the peripheral zone, 10% from transitional zone, and 5% from central zone. It appears as multifocal nodules (> 5 mm), yellowish white in color and hard in consistency (P 16-1). Conversely, senile nodular hyperplasia shows large, soft glistening nodules affecting mainly the central lobe (P 16-2).

Precursor lesions

Prostatic intraepithelial neoplasia (PIN), is the only proven preneoplastic conditions with clinical significance. PIN affects large ductules in the peripheral zone, it may be low or high grade. In high grade PIN and small glandular proliferative lesions, the risk of cancer in subsequent biopsy is almost 45%, hence, the need of repeat biopsy regardless of serum PSA level. The risk of cancer is directly related to the number of cores involved by PIN. Conversely, low grade PIN has no clinical relevance and should not be mentioned in the final pathologic diagnosis.

Morphologic variations of PIN include tufting, micropapillary, cribriform and flat/atrophic patterns. Of these, the cribriform pattern is the most difficult to distinguish from invasive carcinoma (Figure 16-2) and (P 16-3). Cytologically, the acini are lined by a layer of pseudostratified cells with cytologic atypia, such as nuclear irregularity, nucleomegaly, hyperchromasia, and prominent nucleoli. PIN glands characteristically contain basal cells around their periphery (P 16-4).

Atypical adenomatous hyperplasia (AAH), is no longer considered a premalignant lesion but rather a benign small glandular proliferation (adenosis) of the transitional zone that simulates acinar adenocarcinoma. It is characterized by a well-defined periphery and a discontinuous basal cell layer.

Histopathology

Primary prostatic tumors are commonly epithelial, however mesenchymal tumors account for about 0.1% of all prostatic tumors. Acinar (conventional) adenocarcinoma forms the majority of epithelial prostatic tumors (90%) (P16-5). Other unusual types constitute 10% of epithelial prostatic tumors (Table 16-1). This classification has practical importance. Thus, the adenocarcinoma, whether acinar or ductal, is the type associated with the rise of PSA and is expected to benefit from hormonal treatment. Conversely, the unusual types are usually not associated with PSA expression and are nonresponsive to hormones.

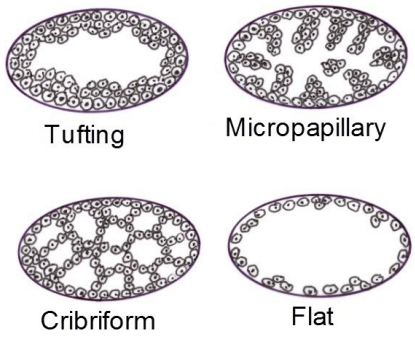


Fig 16-2 *Morphologic variations of high grade PIN. The diagnostic criteria in the presence of prominent nucleoli in all cells lining the gland.*

Table 16-1 Histological Classification of Epithelial Prostatic Tumors and Their Frequency

Conventional adenocarcinoma (acinar)(90%) (P 16-5, 16-6, 16-7, 16-8, 16-9, 16-10)
Unusual types (10%)
Ductal adenocarcinoma (P 16-11)
Urothelial carcinoma (P16-12)
Adenosquamous carcinoma
Squamous cell carcinoma
Basal cell carcinoma (P16-13)
Endocrine differentiation within adenocarcinoma
Carcinoid tumor
Small cell carcinoma (P16-14)

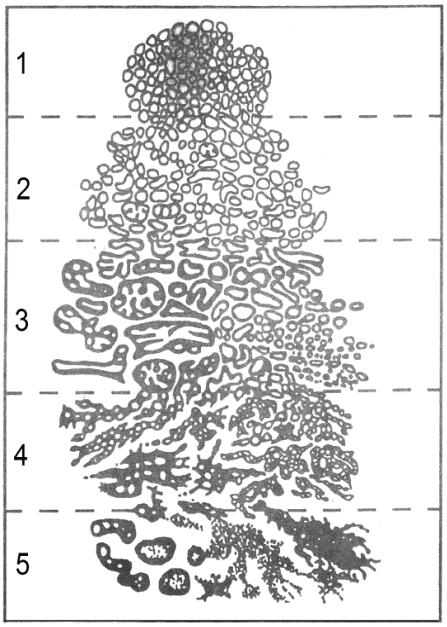
Some morphologic criteria characterize prostatic adenocarcinoma. Thus, malignant cells have large nuclei with prominent nucleoli. A malignant acinus is nonconvoluted and lacks a basal cell layer, hence, negative staining with CK5/14 and p63. Other diagnostic features include, perineural invasion, angioinvasion, collagenous micronodules, crystalloids in lumen and acidic mucin positivity. In metastatic lesions, immunohistochemical reaction to PSA is diagnostic.

Grading

For prostatic carcinoma grading, Gleason grading system (1974) is the most commonly widely accepted. It was modified by the international society of urological pathology in 2005 (Figure 16-3). It is based on the glandular pattern of the tumor. Cytologic features play no role in this system. Both the primary (predominant) and the secondary (second most prevalent) architectural patterns are identified and given a grade from 1 to 5 based on the degree of differentiation. The Gleason score is obtained by the addition of the primary and secondary grades. However, for needle biopsy specimens in which the typical scenario includes tumors with patterns 3, 4, and 5 in various proportions, both the primary and the highest grade should be added to derive the Gleason score. Gleason grading is applicable only in acinar adenocarcinoma. Ductal adenocarcinoma is graded Gleason 4, or 5 according to the absence or presence of necrosis respectively. The AJCC considered Gleason ≤6 grade 1, Gleason 7 as grade 2, and Gleason 8-10 as grade 3.

Differential diagnosis

A useful method for classifying benign mimickers is to consider the major growth patterns adopted in Gleason grading. The 4 major patterns are small glands (Gleason 1,2 ,3), large glands (Gleason 3), fused glands (Gleason 4), and solid pattern (Gleason 5).



Pattern 1: Circumscribed nodule of closely packed, separate, uniform, medium sized acini (P 16-5).

Pattern 2: Fairly circumscribed nodule, may be minimal infiltration at the edge. Glands loosely arranged and variable sized (P 16-6).

Pattern 3: Discrete small glands infiltrating among large non-neoplastic acini (P 16-7).

Pattern 4: Fused microacinar glands, ill-defined with poorly formed lumina, with cribriform and rarely clear cell type (P 16-8).

Pattern 5: Solid sheets, cords, single cells, or comedo necrosis (P 16-9) .

Fig 16-3 *Modified Gleason System (Gleason et al 1974 / Wein et al, 2012)*

1. Small gland pattern

Seminal vesicle tissue may be sampled in needle biopsies. The seminal vesicles are complex branching structures with central lumen and small numerous surrounding glands (adenotic pattern of seminal vesicle). The presence of striking atypia without any mitoses suggests adenotic seminal vesicle rather than acinar adenocarcinoma.

Atrophy of prostatic gland although more common at old age and in the peripheral zone, it can occur at any age and at any prostatic zone. Four main patterns of atrophy are recognized; simple (lobular), sclerotic, cystic, and linear. The important features of distinguishing prostatic atrophy from acinar adenocarcinoma are the low power maintenance of lobular architecture, uniform cytology, absence of prominent nucleoli, the presence of basal cells as highlighted by high molecular weight cytokeratin (P 16-15).

Basal cell hyperplasia is typically seen as part of the spectrum of nodular hyperplasia or in association with atrophy. In the complete form, it presents as nodular expansion of solid nests of dark blue cells. In the incomplete form, it shows uniform round glands with residual lumina lined by secretory cells surrounded by multiple layers of basal cells. The nodular arrangement, association with nodular hyperplasia, cellular uniformity, and lack of prominent nucleoli serve to distinguish it from adenocarcinoma (P 16-16).

2. Large gland pattern

Clear cell cribriform hyperplasia enters the differential diagnosis of both prostatic intra-epithelial neoplasia and cribriform adenocarcinoma. The distinction of cribriform hyperplasia from cribriform carcinoma is based on the low power nodularity, cellular stroma, presence of basal cells and lack of significant cytologic atypia.

3. Fused gland pattern

Xanthogranulomatous prostatitis may be confused with the clear cell pattern of adenocarcinoma (Gleason 4). Immunohistochemical stains for epithelial prostatic cells and histiocytes (CK and CD 68) are useful for differentiating.

4. Solid pattern

Prostatitis (granulomatous or non-granulomatous) may cause diagnostic problems in needle biopsies especially with poor preservation or crushing artifacts. Immunohistochemical stains (CK and LCA) help in the differential diagnosis (P 16-17).

Prostatic infarction associated with squamous metaplasia of ducts: is a common change seen near prostatic infarcts and commonly mistaken for squamous cell carcinoma (P 16-18).

Spread

1. Local spread: A carcinoma arising from the outer prostate is prevented from extending backward by the strong fascia of Denonvilliers, consequently, it tends to grow upwards to involve the seminal vesicles which is infiltrated in 15 % of patients with clinically localized prostatic cancer. Further upward extension may obstruct the lower ends of ureters. The prostatic urethra may also be invaded terminating in anuria. In advanced cases, the base of bladder may be invaded. The rectum may become stenosed by growth infiltrating around it, but direct involvement is very late.

2. Lymphatic spread to internal and external iliac lymph nodes.

3. Hematogenous spread occurs particularly to bones, especially, pelvic bones, lower lumbar vertebrae, femoral head, ribs and skull (Fig 16-4). The frequent proximity of skeletal metastases to the primary growth has been attributed to retrograde venous spread.

Staging

Clinical staging is the assessment of disease extent using pretreatment parameters (digital rectal examination, PSA, needle biopsy findings, and

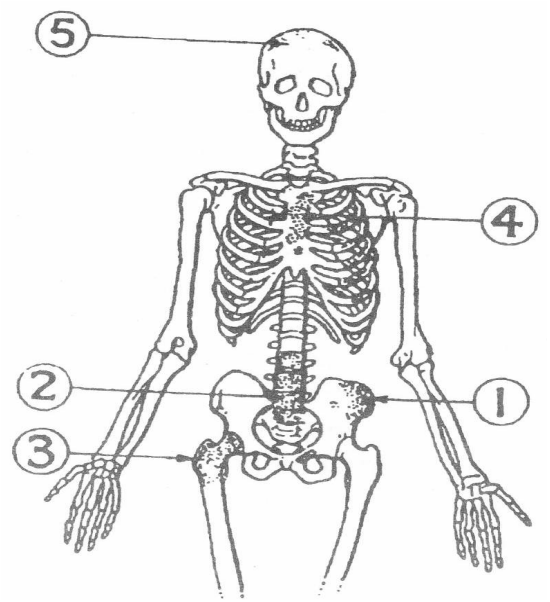


Fig 16-4 *Location of bone metastases from prostatic carcinoma (in order of frequency)*

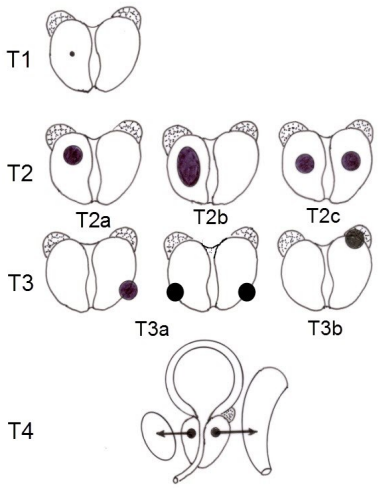


Fig 16-5 *The T category in the clinical staging system*

radiologic imaging), whereas, pathologic stage is determined after prostate removal and involves histologic analysis of the prostate, seminal vesicles, and pelvic lymph nodes. The T category in the clinical staging is illustrated (Fig 16-5) and (Table 16-2). There is a considerable level of clinical understaging (59%) and mild risk of overstaging (5%). Moreover, pathologic staging more accurately estimates disease burden and more useful for outcome prediction.

To minimize this error, combined modality staging is adopted by AJCC (Edge et al, 2010). Accordingly, the combination of Gleason score, serum PSA, and clinical stage, more accurately predicts the final stage, as well as, the prognostic group than any single variable alone (Table 16-3).

Prognostic factors

The three most important prognostic factors are the stage, Gleason score and PSA level. Thus, the 5-year survival for localized and regional stages is nearly 100% and for distant metastases 29% (SEER, 2011). Patients with Gleason score > 6 have unfavorable prognosis (Fig 16-6) and PSA level > 10 points to extraprostatic spread (Table 16-3). Other independent prognostic factors are DNA aneuploidy, microvessel density, and androgen receptors. But, perineural invasion is not a prognostic factor for occurrence of recurrence or survival (Lee et al, 2010).

Table 16-2 TNM Staging System for Prostatic Carcinoma

Non-palpable cancer	
≤ 5 % of TURP	T1a
> 5% of TURP	T1b
Positive needle biopsy	T1c
Palpable but organ- confined	
≤ 1/2 of one lobe	T2a
> 1/2 of one lobe	T2b
Both lobes	T2c
Extracapsular spread	
Unilateral or bilateral	T3a
Seminal vesicle (s)	T3b
Bladder, rectum, levator, pelvic wall	T4
Metastatic	
Regional lymph nodes	N1
Non-regional lymph nodes	M1a
Bone	M1b
Other metastases	M1c

(Edge et al, 2010)

Table 16-3 Correlation of Gleason Score and Serum PSA with the Frequency of Pathologically localized Prostate Cancer

Gleason score	Organ confined disease%	PSA ng/ml	Organ confined disease
2-4	77	0-4	75
5	69	4-10	53
6	57	10-30	26
7	30	30-50	10
8-10	13	>50	0

(Partin et al, 1993)

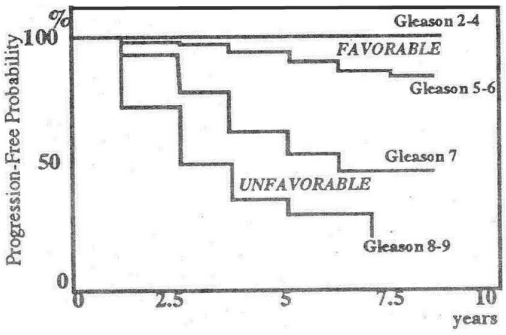


Fig 16-6 *Gleason's score and natural history of prostatic cancer*

Table 16-4 Risk Stratification of Prostatic Carcinoma by the American Urology Association

Risk Level	PSA score	Gleason score	Clinical stage
Low	<10	<6	T1c or T2a
Intermediate	10–20	7	T2b
High	>20	8–10	T2c

(Thompson et al, 2007

Table 16-5 Combined Staging for Prostatic Carcinoma based on Clinical Stage, PSA level and Gleason Score

Group	T	N	M	PSA	Gleason
I	T1a-c	N0	M0	PSA< 10	Gleason ≤ 6
	T2a	N0	M0	PSA< 10	Gleason ≤ 6
IIA	T1a-c	N0	M0	PSA < 20	Gleason 7
	T1a-c	N0	M0	PSA ≥ 10 < 20	Gleason ≤ 6
	T2a	N0	M0	PSA < 20	Gleason ≤ 7
	T2b	N0	M0	PSA < 20	Gleason ≤ 7
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA ≥ 20	Any Gleason
	T1-2	N0	M0	Any PSA	Gleason ≥ 8
III	T3a-b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

(Edge et al, 2010)

Prognosis

In an attempt to better stratify patients according to the risk of recurrence, the American Urology Association combined the 3 prognostic factors to stratify patients with localized disease into 3 risk groups, which serves as a guide to therapeutic decisions and prediction of prognosis (Table 16-4). Also, a vast majority of nomograms are developed by researchers to predict biochemical recurrence and patient-free survival at the individual level. Kattan nomograms are widely used (Eskicorapciet al, 2011).

More recently the American joint committee on cancer (AJCC) has stratified the patients into 4 groups and 13 subgroups (Table 16-5). However, the survival is still under research studies.

Detection

Annual examination of males after the age of 40 years by digital rectal examination, prostatic specific antigen (PSA) and transrectal ultrasono-

graphy (TRUS) is recommended. Biopsy is needed for PSA values above 4 ng/ml. For greater accuracy, the following modifications may be adopted: (1) Volume-based PSA parameters. (2) Prostate-specific antigen velocity. (3) Free prostate - specific antigen. (4) PSA isoforms. For follow-up, patients' course is followed every 3 to 6 months until 5 years after surgery, and then every 6–12 months thereafter. Biochemical recurrence is defined as a PSA value of 0.2 ng/mL or greater. The volume of tumor burden in needle biopsy is related to the occurrence of biochemical recurrence (Tanaka et al, 2012).

Table 16-6 WHO Classification of Testicular Tumors

Testicular tumors
Germ cell tumors
Sex cord/stromal tumors
Tumors of more than one histologic type
Primary hematopoietic tumors
Unusual tumors (Carcinoid, nephroblastoma, tumors of ovarian epithelial types, tumors of collecting ducts and rete)
Paratesticular tumors
Secondary tumors

(Eble et al, 2004)

TESTICULAR CANCER

Normal anatomy

The testes are composed of convoluted seminiferous tubules with a stroma containing functional endocrine interstitial cells. Both are encased in a dense capsule, the tunica albuginea, with fibrous septa extending into the testis and separating them into lobules. The tubules converge and exit at the mediastinum of the testis into the rete testis and efferent ducts, which join a single duct. This duct- the epididymis- coils outside the upper and lower poles of the testicle and then joins the vas deferens, a muscular conduit that accompanies the vessels and lymphatic channels of the spermatic cord.

Incidence

Testicular cancer accounts for about 1 % of human malignancies (Cancer facts and figures, 2010). It is estimated that 8,590 men will be diagnosed with and 360 men will die of cancer of the testis in 2012. The median age at diagnosis for cancer of the testis is 33 years of age (Howlader et al, 2011). But, in young patients between the ages of 20 and 34 years, it accounts for almost 30% of all cancers. The highest incidence is reported from Denmark (9 per 100,000).

Classification

The WHO classification of testicular tumors (Table 16-6) included tumors arising from the testes, those arising from testicular adnexa as well as adjacent structures and metastatic tumors to the testis.

Germ cell tumors

Incidence

Testicular germ cell tumors comprise more than 90% of all testicular malignancies (Cancer facts and figures, 2010).

Etiology

The only risk factors for testicular germ cell tumors are cryptorchidism and gonadal dysgenesis with a risk of malignancy is 5 to 10 times higher in men with undescended testes.

Histogenesis

The primitive germ cells originate in the yolk sac during the fifth week of development, and migrate from the hind gut wall first to the urogenital ridge then to the definitive gonads. The gonads later descend to their normal position according to the sex. Germ cells also have a great capacity to migrate by ameboid movement into ectopic locations. The germ cells are multipotential and they reproduce by either: (1) meiosis to produce gametes (haploid cells) or (2) mitosis or asexual reproduction (parthenogenesis) to produce germ cell tumors (diploid cells). These tumors characteristically arise in abnormal or dysgenetic gonads.

The origin of germ cell tumors is supported by the following argument: (1) germ cell tumors are most common in the gonads, (2) extragonadal germ cell tumors generally occur close to the midline, in keeping with the origin and migration of germ cells in the embryo, (3) germ cell tumors

in distant locations (e.g. pineal) is explained by ectopic migration of germ cells.

Recent cytogenetic studies have further clarified the histogenesis of germ cell tumors. Thus, the presence of both X and Y chromosomes in germ cell tumors of males indicates that malignant transformation affects a premeiotic germ cell which undergoes mitosis instead of reduction division. In addition, hyperdiploidy (triploid or tetraploid) is common in tumors indicating endoreduplication of genetic material. Finally, in germ cell tumors, there is excess of chromosome 12p copy number, increase of isochromosome (i12p) and widespread gene loss, suggesting that a gene on 12p is responsible for malignant transformation of germ cells (Fig 16 -7).

The origin of germ cell tumors differs before and after puberty. Thus most prepubertal germ cell tumors are derived from a benign non-transformed germ cell. On the other hand, the precursor lesion of almost all postpubertal testicular germ cell tumors is intratubular germ cell neoplasia (IGCN) (P 16-18).

Molecular oncogenesis

At the gene level, several genes are involved at each stage of development. In utero, hormonal, environmental and KIT activating mutation induce arrest of embryonic germ cells at the gonocyte stage. Gonocytes have almost completely demethylated genomic DNA, which facilitates accumulation of mutations during cell replication and development of IGCN. IGCN may present as early as before birth. Hormonal stimulation during puberty facilitates proliferation of IGCN. Gain of chromosome 12p is associated with invasion of IGCN through the basement membranes of seminiferous tubules. Individual gene mutations such as TP53, BRAF, CCDN2 and KRAS may determine the development of seminomas and nonseminomas. Within nonseminomas, selected gene expression may determine different directions of differentiation (Sheikine Y et al, 2012).

Classification of testicular germ cell tumors

Germ cells reproduce the process of organogenesis in the embryo, but in a malformed way. Hence, different tumor types are produced according to the different maturation pathways,

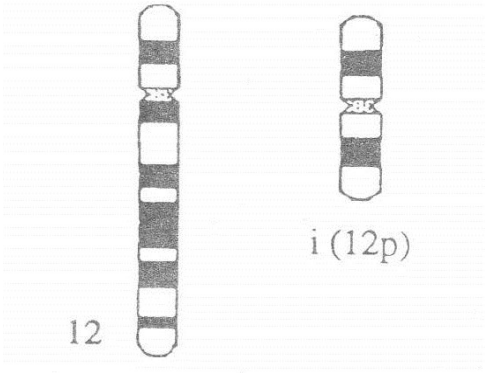


Fig 16-7 *Schematic diagram of isochromosome 12 (i12p). This results from translocation and fusion of two short arms of chromosome 12*

thus, reproduction of a totipotent germ cell without differentiation results in seminoma (classic type or spermatocytic seminoma (SS)), embryonal or somatic differentiation may result in a primitive embryonic epithelium (embryonal carcinoma) or more differentiated embryonic structures representative of the three germ cell layers (teratomas).

Differentiation to extraembryonic structures results in choriocarcinoma and yolk sac tumor. Multiple differentiation may occur, especially in adults, resulting in mixed or combined tumors.

The most common combination is embryonal carcinoma with extraembryonal differentiation. The combination of embryonal carcinoma with teratomas is called teratocarcinoma (Fig 16-8). A modified molecular and histopathologic classification of testicular germ cell tumors based on the WHO 2004 classification is recently introduced. It focuses on the association of the precursor lesion (IGCN) and the chromosomal abnormality with certain germ cell tumors (Table 16-7).

Macroscopy

Seminoma appears grossly as a homogenous light yellow or creamy colored tumor. Whereas, teratomas classically show multilocular cystic structure. The presence of hemorrhage and necrosis in the tumor is suggestive of choriocarcinoma or embryonal carcinoma. Bilateral testicular cancer is reported in 2% of cases, but up to 15% in cases complicating undescended testes.

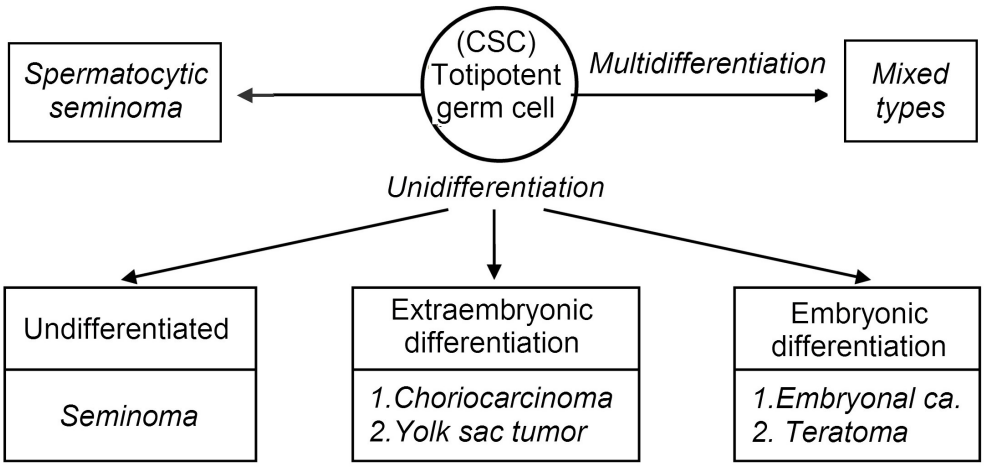


Fig 16-8 *Histogenesis of Germ cell tumor and its differentiation pathways. CSC cancer stem cell*

Table 16-7 Classification of Testicular Germ Cell Tumors Based on Molecular Genetics and Histopathology

Tumors with IGCN as precursor and gain of 12p in invasive tumors (> 90%)
Seminoma
Non–seminomatous germ cell tumor (NSGCT)
NSGCT of one histologic type
Embryonal carcinoma
Yolk sac tumor
Trophoblastic tumors
Teratoma
NSGCT of more than one histologic type (mixed form)
Tumors not associated with IGCN and 12p abnormalities (< 10%)
Spermatocytic seminoma, dermoid cyst, pediatric testicular germ cell tumors

(Sheikine et al, 2012)

Histopathology

The classification of testicular germ cell tumors into seminoma and non-seminomatous germ cell tumor is important both conceptually and practically (Table 16-8). Moreover, it is noteworthy that germ cell tumors exhibit striking variations between pediatric and adult patients, both in the biology and frequency of pathologic types (Table 16-9).

(1) Seminoma (P16-19, P16-20)

It accounts for about 40% of testicular tumors. The median age for classic pure seminoma is 40 years. Histologically, it is composed of large rounded cells arranged in solid nests with fibrous septa rich in lymphocytes. The cytoplasm is clear due to glycogen content and the nucleus contains a prominent elongated nucleolus. Immunohistochemical diagnostic markers include placental alkaline phosphatase (PLAP)+, vimentin+ and cytokeratin ± Syncytiotrophoblasts may be present in 10-20% of pure seminoma, but this does not influence prognosis or treatment as long as cytotrophoblastic elements are absent.

Seminoma variants include spermatocytic seminoma (SS) which constitutes 5% of seminomas, with a median age of 45 years. Contrary to the classic seminoma, it is not associated with carcinoma in situ or i12p. Histologically, 3 cell types are observed in the tumor: small, intermediate and giant cells with dense cytoplasm and filamentous nucleus. PLAP is negative. The metastatic potential is minimal; hence, its prognosis is more favorable than classic seminoma. Anaplastic seminoma (mitosis >3/ HPF) and atypical seminomas are not distinct variants, since they are similar in treatment, response and prognosis to classic seminoma.

(2) Non-seminomatous germ cell tumors (NSGCT)

Embryonal carcinoma (P16-21)

This is the most undifferentiated somatic cell type. It constitutes about 10% of testicular tumors. Histologically, it shows epithelioid pattern, im-

Table 16-8 Comparative Features of Seminoma and NSGCT

	Seminoma	NSGCT
Frequency	40%	60%
Median age	40 years	30 years
Localized (stage I)	70%	40%
Radiotherapy response	Radio-sensitive	Radio-resistant
i 12p	Less common	More common
5-year survival	90%	70%

Table 16-9 GCT Differ with Age

	Pediatric	Adult
Class	Pure	Mixed
Subtypes	Yolk sac tumor 50% Teratoma 50%	Seminoma 40% NSGCT 60%
Mature teratoma	Benign	Malignant
Carcinoma component	--	+
DNA ploidy	Diploid or tetraploid	Aneuploid
Extra-gonadal	Common (50%)	Rare
CIS (IGCN)	--	+
i12p	--	+

mature cells with vesicular nuclei, clumped chromatin, prominent nucleoli and dense ill-defined cytoplasm. The characteristic marker profile is cytokeratin +, CD30+, and AFP-.

Teratoma

It is composed of the 3 germ cell layers. Four subtypes are recognized:

Monodermal teratoma: A tumor that consists of only one of the three germ layers (endo-, ecto- or mesoderm) e.g. dermoid cyst (P16-22) .

Mature teratomas: composed of well differentiated adult-type cells, behaving benign in children and malignant in adults.

Immature teratomas: contains undifferentiated elements especially neuroepithelial and stromal cells (P16-23).

Teratomas with malignant transformation of one of its components into squamous carcinoma, adenocarcinoma, embryonal sarcoma, neuroendocrine tumor or leukemia.

Choriocarcinoma (P 16-24, P 16-25)

It is the most aggressive germ cell tumor due to its widespread hematogenous spread and it does not show the dramatic response to chemotherapy as gestational choriocarcinoma (due to absence of paternal antibodies). By definition, both cytotrophoblast and syncytiotrophobalst must be present to make the diagnosis. Tumor markers include β-HCG in tumor tissue and serum.

Yolk sac tumor (P 16-26, P 16-27)

Also known as endodermal sinus tumor. It constitutes 2.5% of testicular tumors, and 50% of pediatric testicular tumors. Histological patterns include microcystic (reticular), macrocystic, solid, glandular-alveolar, endodermal sinus, papillary, myxomatous, polyvesicular vitelline, enteric, and hepatoid. A glomerulus-like structure of Schiller-Duval bodies, and rarely embryoid bodies are characteristic. Positivity for the AFP is diagnostic.

Sex-cord stromal tumors

These tumors constitute about 4 % of adult testicular tumors and over 30% of testicular tumors in infants and children. About 10% of these tumors, almost always in adults, metastasize. However, it may not be possible on histological grounds to forecast their behavior.

Leydig cell tumor constitutes about 2% of testicular tumors. It is common in adults (80%). The tumor may be hormone active and secretes estrogen or androgen. Histologically, it is composed of polyhedral cells with eosinophilic granular cytoplasm (hepatocyte-like) which may contain Reinke crystals. Some of these tumors occur bilaterally in children in the setting of androgen insensitivity syndrome (AIS) and adrenogenital syndrome (AGS) and should be classified under tumor-like lesions. Such condition is reversible by medical treatment, thus, orchiectomy should be avoided after taking a

proper history and full laboratory studies (P 16-28).

Sertoli cell tumor constitutes 1% of testicular tumors. It may secrete estrogens. The cell pattern is either cords or tubules (P 16-29).

Granulosa cell tumors of the testis are rare and morphologically similar to their ovarian counterparts. Two variants are distinguished: adult and juvenile types.

Tumors of the thecoma/fibroma group resemble their ovarian counterparts. Most intratesticular thecomas that have been reported are actually fibromas of gonadal stromal origin. Fibroma of gonadal stromal origin is a benign tumor, which displays fusiform cells and variable degrees of collagenization.

Sex cord tumor with annular tubules is a rare tumor that may be sporadic or associated with Peutz-Jeghers syndrome.

Mixed testicular tumors

These are classified into 3 main groups:

1. Mixed germ-germ cell tumors (35-50% of germ cell tumors)

Mixed embryonal carcinoma and teratomas (P 16-30, P 16-31)

Mixed teratoma and seminoma

Mixed choricarcinoma and teratoma/ embryonal carcinoma

Polembryoma: a rare variant consisting mainly of embryoid bodies, but may show other germ cell tumor component (P 16-32).

2. Mixed germ –sex cord/gonadal stromal tumors

Gonadoblastoma is most commonly seen in gonadal dysgenesis. The estimated risk of developing gonadoblastoma in this setting is 15-25% (P 16-33).

3. Mixed sex cord-gonadal stromal tumors

Gynandroblastoma: Typically it consists of adult-type granulosa cells and Sertoli cells, but it has been reported with juvenile-type granulosa cells.

Hematopoietic tumors

Primary lymphomas or plasmacytomas of testes or paratesticular tissues arise in the testicles, epididymis or spermatic cord and are neither associated with lymphoma elsewhere nor leukemia. Testicular lymphomas constitute 2% of all testicular neoplasms, 2% of all high grade lymphomas and 5% of all extranodal lymphomas in men. In adult testis, primary diffuse large B- cell lymphoma (DLCL) is the single most frequent lymphoma (70-80%).

Paratesticular tumors

These are classified into 5 main groups:

1. Mesothelial tumors: Adenomatoid tumors are the most common tumors of the testicular adnexa, representing 32% of all tumors in this location and 60% of all benign neoplasms in this area. Other mesothelial tumors include cystic mesothelioma and malignant mesothelioma.

2. Epithelial

Adenocarcinoma of the epididymis

Papillary cystadenoma of the epididymis

3. Melanotic neuroectodermal tumor

4. Desmoplastic small round cell tumor

5. Mesenchymal tumors: Embryonal rhabdomyosarcoma is the most common tumor in children. But, any type can occur e.g. fibromatosis (P16-35)

Metastatic tumors

The most common origin of metastatic testicular tumors is prostate, lung or skin melanomas. The testis may also be involved in patients with NHL/leukemia.

Spread

1. Local: to epididymis, cord and soft tissue.

2. Lymphatic: to retroperitoneal lymph nodes, preaortic, and paraaortic on left side, and pre and paracaval lymph nodes on right side. With bulky disease, retrograde spread occurs to iliac nodes, contralateral side, mediastinum and left supraclavicular lymph nodes. Inguinal lymph nodes may be positive following an intrascrotal surgical procedure or tumor infiltration of the scrotum.

3. Hematogenous spread: to lungs. The histologic type of the metastases may differ from that of the primary tumors, especially after chemotherapy. Blood spread is common with teratoma, but exceedingly rare in seminoma.

Prognosis

The prognosis of testicular cancer depends on stage (Table 16-10), histologic type, and serum markers.

1.The stage: over 95% of the patients with disease clinically limited to the testis (stage I) or to subdiaphragmatic lymph nodes (stage II), can be cured by modern multimodality therapy.

2. Histologic type: seminoma is generally more favorable than NSGCT with overall 5-year

Table 16-10 Stage Grouping of Testicular Cancer

Stage 0	Intratubular germ cell neoplasia (Tis), No nodal (N0) or distant metastases (M0)
Stage I A	Tumor limited to testis and epididymis without vascular or tunica vaginalis invasion, (N0), (M0)
Stage I B	Tumor limited to testis and epididymis with vascular, tunica vaginalis and tunica albuginea invasion (N0), (M0)
Stage II A	Regional lymph node (s) ≤ 2 cm
Stage II B	Regional lymh node 2-5 cm
Stage II C	Regional lymph node > 5cm
Stage III	Distant metastases

N. B. For testicular germ cell tumors serum markers (LDH, AFP, HCG) are additionally considered *(Edge et al, 2010)*

survival of 90% and 70% respectively. Spermatocytic seminoma (SS) is even more favorable than classic seminoma. In NSGCT, choriocarcinoma is the most aggressive. In yolk sac tumors, the prognosis is directly proportional to the age of the patients, being more favorable in children than adults. The prognosis of mature teratoma is also more favorable in children than in adults. In combined seminoma/NSGCT, The prognosis depends on the histologic type and extent of NSGCT component.

3. Serum markers are important in the monitoring of testicular germ cell tumors (e.g. HCG, AFP, and LDH). The rate of markers decrease after chemotherapy is of great prognostic value.

PENILE CANCER

Normal anatomy

The penis is composed of three cylindrical masses of cavernous tissue bound together by fibrous tissue. Two masses are lateral and known as corpora cavernosa. The corpus spongiousum is a median mass and contains the greater part of the urethra. The distal expansion of the corpus spongiousum forms the glans penis. The prepuce (foreskin) is infolding of the distal skin upon itself.

Incidence

Penile cancer constitutes less than 1% of all malignancies in men in the USA and 0.1% of cancer deaths (Morris et al, 2011). In Egypt, it represented about 1% of all male genital malignant tumors at the NCI in the last 10 years. The mean age was 65 years.

Etiology

Lack of neonatal circumcision, HPV infection (types 16, 18, 31, 33) are the most common predisposing factors for the occurrence of penile cancer. HPV-16 appears to be the most frequently detected type in primary carcinoma as well as in metastatic lesions, although, its presence is invariable (31-63%). On the contrary, genital warts (condylomas) which are associated with HPV types 6 and 11, are considered of low oncogenic potential (P 16-36). Chronic inflammation, phimosis and poor hygiene may be important contributing factors.

Molecular oncogenesis

Male circumcision, which is associated with a reduced risk of penile HPV infection has also been associated with decreased penile cancer. HPV contributes to tumorigenesis predominantly through the action of the viral oncoproteins (E6 and E7). The interaction of E7 with the retinoblastoma (Rb) tumor suppressor leads to Rb degradation, E2F activation and overexpression of the cyclin-dependent kinase inhibitor p16INK4A.

Macroscopy

Penile tumors may present anywhere on the penis but occur most commonly on the glans (48%) and prepuce (21%). Four gross patterns are recognized namely; superficial spreading, verruciform, vertical, and multicentric (P 16-37).

Precursor lesions

Squamous cell carcinoma in situ of the penis is known as erythroplasia of Queyrat or Bowen disease according to the site of origin (P 16-38, and P 16-39). Paget disease is a form of intraepidermal adenocarcinoma, primary in the epidermis or spread from an adenocarcinoma.

Histopathology

Squamous cell carcinoma with its variants (basaloid, warty, verrucous, sarcomatoid, papillary, mixed, and adenosquamous) are the most com-

mon penile cancer (P 16-39). WHO grading depends on the degree of differentiation and mitosis and grade 1, 2, or 3 are used. WHO histopathologic classification of the penile malignant tumors are presented in Table (16-11). The second most common malignant neoplasm is Kaposi sarcoma, and is strongly associated with HIV. Vascular tumors constitute the majority of benign penile tumors. A rare but peculiar tumor of borderline malignancy is penile fibromatosis.

Staging

The AJCC staging classification applies only to carcinomas (Table 16-12).

Prognosis

The prognosis is related to following factors:

1. Stage: this is the most important parameter. In carcinoma in situ (stage 0), the 10-year survival rate is 93%. In stage I and II, the 10-year survival rate is 89% and 81% respectively. In stage III, the 9-year survival was 50%. In stage IV, the 2-year survival was 21% (Graafland, 2011).

2. Microscopic type: verrucous carcinoma is associated with a better prognosis, followed by warty carcinoma. Basaloid and sarcomatoid carcinomas are associated with high rate of nodal metastases and poor survival.

Table 16-12 Stage Grouping of Penile carcinoma

Stage 0	Carcinoma in situ (Tis) or non-invasive verrucous carcinoma (Ta) No nodal (N0) or distant metastases (M0)
Stage I	Tumor invades subepithelial connective tissue, no vascular invasion, G1-2 (T1a), N0, M0
Stage II	Tumor invades subepithelial connective tissue with vascular invasion/ G3-4 (T1b), or either corpora (T2), or urethra (T3), N0, M0.
Stage IIIa	Metastasis in a single inguinal lymph node (N1)
Stage IIIb	Metastasis in multiple or bilateral inguinal lymph node (N2)
Stage IV	Adjacent structures invasion (T4), Extranodal extension, pelvic node (s) metastasis (N3), or distant metastasis (M1)

(Edge et al, 2010)

Table 16-11 WHO Histopathologic Classification of Penile Tumors

Primary malignant epithelial tumors
Squamous cell carcinoma and its variants (P 16-39)
Merkel cell carcinoma
Small cell neuroendocrine carcinoma
Sebaceous carcinoma
Clear cell carcinoma
Basal cell carcinoma
Melanocytic tumors
Mesenchymal tumors (Kaposi sarcoma, leiomyosarcoma, …etc)
Hematopoietic tumors
Secondary tumors (direct spread or metastatic) (P 16-40)

(Eble et al, 2004)

3. Microscopic grade: Presence of grade 3 is indicative of poor prognosis.

4. Invasion: Vascular and perineural invasion: are predictors of poor prognosis independent of stage and grade.

5. Gene alteration: p53 is significantly associated with lymph node metastases.

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