

## **Clinicopathological Characteristics of Testicular Tumors**

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### **Review Article**

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### **Abstract**

Testicular tumors constitute one of the most common tumors of men. Of all the testicular tumors, Germ cell tumors (GCT's) comprise 95%. Others include sex-cord stromal tumors, mixed germ cell sex-cord stromal tumors, hematopoietic tumors, miscellaneous tumors and secondary tumors. A number of pre-existing medical conditions have been associated with the development of TGCT (testicular germ cell tumour). Most patients of testicular neoplasms present with progressive painless enlargement of testis, history of trauma and hydrocele. Testicular ultrasonography is used to determine the location of a palpable mass when testicular cancer is suspected. Generally, palpable extra-testicular lesions are benign. On the other hand, intratesticular masses, especially if they are palpable, are likely to be malignant and must be surgically explored. The vast majorities of testicular tumors are of germ cell origin and, like the totipotent germ cells from which they arise, may differentiate along several pathways

**Keywords:** Testicular Tumor; GCNIS (germ cell neoplasia in situ) Seminoma; Non Seminomatous Germ Cell Tumor; Cryptorchidism; Serum Markers

### **Introduction**

Testicular neoplasms span an amazing gamut of anatomic types. They constitute one of the most common tumors of men. The incidence increases shortly after the onset of puberty and reaches maximum in men in late twenties and thirties (15-34 years). It decreases in men in their sixties and older. A distinct peak in incidence of testicular tumors occurs in infants. Testicular tumors comprise approximately 1% of all cancers in men, but only about 0.1% of cancer deaths in males because the majority of these tumors are curable [1-3]. However for unclear reasons, the incidence of testicular tumors has increased progressively in twentieth century.

Of all the testicular tumors, Germ cell tumors (GCT's) comprise 95% others include sex-cord stromal tumors,

mixed germ cell sex-cord stromal tumors, hematopoietic tumors, miscellaneous tumors and secondary tumors. Histologically, germ cell tumors are divided into two major groups i.e. Seminomas and Non-seminomatous germ cell tumors (NSGCT). In WHO classification 2016 germ cell tumours are broadly classified into two categories germ cell tumor derived for germ cell neoplasia in situ and germ cell tumor unrelated to germ cell neoplasia in situ. The former category is further divided into four categories including Non invasive germ cell neoplasia, tumors of single histological type, non seminomatous germ cell tumor of more than one histological type, germ cell tumors of unknown type. Seminoma is commonest tumour of single histological type and accounts for approximately 50% of the testicular

tumors, differentiate along the gonadal cell lines, and resemble primordial germ cells and gonocytes. NSGCT (Non seminomatous germ cell tumors) in turn, have retained pluripotency and include a number of different subgroups. These tumors display various stages of embryonic differentiation; ranging from highly undifferentiated cells resembling embryonic stem cells in the embryonal carcinomas, to the highly differentiated cells of somatic tissue in the teratomas. NSGCT's may also present as extra embryonic tissue, that is, as yolk sac tumors or as choriocarcinomas. NSGCT's comprise 40% of testicular cancers. The remaining 10% of testicular cancers are combined tumors containing both seminomatous and non-seminoma to us elements [1,4-6].

Extragenadal germ cell tumors account for 1-5% of all germ cell tumors. The most widely accepted theory suggests that extragonadal germ cell tumors arise from primordial germ cells misplaced during their migration to gonads. Klinefelter syndrome is the only known predisposing factor. The clinical course is variable, with a potential for aggressive behavior and widespread metastases. Extra-gonadal germ cell tumors are considered as metastases from occult or "burned out" gonadal cancer until proved otherwise. If a primary testicular tumor is detected, the extra-gonadal mass is always considered metastatic. They affect men during third and fourth decade of life.

Testicular pathology is a nosologically complex subject because of the spectrum of histologic subtypes and variable clinical behavior, particular among GCTs. This diversity is best reflected in various systems offered to classify these tumors. Currently the most comprehensive and widely accepted system of classification is the one proposed by the World Health Organization (WHO) [2] in 2004 and the recent revised WHO classification of 2016 [1].

Biologic behavior depends upon the types of tumors present, as well as clinical features, including the age of the patient and primary site (testicular versus retroperitoneal), since histologically identical tumors can behave differently depending upon these clinical parameters. Clinically, NSGCT's have a more aggressive behavior, are less susceptible to radiation, and manifest at an earlier age. Moreover, mature teratoma, in contrast to other tumors, are less sensitive to platinum-based chemotherapy. These differences indicate etiological heterogeneity between the two groups.

High inguinal orchiectomy is the standard initial treatment for suspected testicular carcinoma. This allows accurate staging and histological diagnosis of the tumor,

while ensuring the best local control and minimizing treatment morbidity. However, the tumor is remarkably sensitive to chemotherapy and is a model for a highly curable, advanced cancer. Appropriate integration of surgery, chemotherapy and radiation therapy in treatment has lead to high cure rates. The introduction of Cisplatin-based chemotherapy has revolutionized the management of testicular tumors, with considerable improvement in response rates and excellent outcome reported even in presence of metastatic disease [7].

### **Etiology & Risk Factors**

A number of pre-existing medical conditions have been associated with the development of TGCT (testicular germ cell tumour). These conditions include prior diagnosis of TGCT in the contralateral testicle, cryptorchidism, impaired spermatogenesis, inguinal hernia, hydrocele, disorders of sex development, prior testicular biopsy, atopy and testicular atrophy [8].

Cryptorchidism, or undescended testis, is the antecedent medical condition most closely associated with TGCT. A meta-analysis has estimated the relative risk of TGCT among men with prior cryptorchidism to be 4.8 (95%CI=4.0-5.7) [9]. Nevertheless, only 10% of TGCTs develop in men with prior cryptorchidism. High birth weight has also been associated with TGCT in at least one study [10], the majority of studies have not supported a relationship [8].

In general, studies have found that men with TGCT have higher follicle stimulating hormone (FSH) levels and somewhat lower testosterone levels than do control men. Studies in cryptorchid men have reported a similar hormonal milieu [11]. The associations of reduced body muscle mass and reduced frequency of baldness among men with TGCT have also suggested that testosterone levels in TGCT patients may be in the lower end of the spectrum [12].

Studies have found an increased risk of TGCT among firefighters, metal workers, leather workers, aircraft technicians, agricultural workers, unionized carpenters, paper mill maintenance employees and writers. In general, white collar workers have been found to be at higher risk of TGCT than blue collar workers. Thus occupational associations could be confounded by socioeconomic status [13].

An infectious etiology of testicular cancer has been suggested. Recent support for a viral etiology has been the reports of increased risk of TGCT among men infected with human immunodeficiency virus (HIV) [14].

The majority of risk factor analyses stratified by histologic group appear to support a shared etiopathogenesis [8]. Several studies have reported that cryptorchidism, low birth weight and low birth order are factors predominantly associated with an increased risk of seminoma [8].

In comparison with the general population, the risk of testicular cancer has been reported to be eight-fold higher in brothers and four-fold higher in sons of affected men [15]. Despite the evidence that testicular cancer has a genetic component, it is likely that the risk is largely mediated by environmental exposures.

The onset of testicular cancer is insidious, and there are few symptoms. The diagnosis of testicular cancer is based on histopathologic evaluation of the testis after orchiectomy or rarely, biopsy of a retroperitoneal mass or subclavian lymph node. Such extraprimary/extragenital disease constitutes less than 5% of cases.

Other than genital examinations during routine physical examination, no formal screening algorithm exists for testicular cancer. Routine ultrasound examinations and serologic testing are not cost-effective.

### Clinical Features

**Presenting Complaints:** Patients of testicular tumor present with different complaints. Most patients present with progressive painless enlargement of testis, history of trauma and hydrocele. Tan G.H. et al., reported testicular swelling in 100% of cases while Shirish C. et al., reported scrotal swelling in 96% of cases [16,17]. Testicular pain was observed in 14-24.8% of patients with testicular tumors as reported by various authors. Secondary hydrocele is observed in testicular tumors due to reactionary fluid accumulation between tunica vaginalis and tunica albuginea. In a study done by Mahalik SK, et al. 50% of patients with testicular tumors had associated hydrocele [18-20].

**Age of Patients:** There is good correlation between age and incidence of different types of testicular tumors. The peak is 41.9 years for classic seminoma, 65 years for spermatocytic seminoma, 30.4 years for the different types of NSGCT, and 35.1 years for the combination of seminoma and NSGCT. In prepubertal children, seminomas and combined tumors are rare. Only NSGCT occur with some frequency, notably of the yolk sac tumor and the mature teratoma types [19]. Fischer CG, et al. [20] from Germany reported highest age related incidence in two age groups 25-29 years and 30-35 years. Albrecht W. et al from Vienna Austria (2004) noted

testicular tumors more frequently in 15-34 years of age [21]. Salako AA, et al. in a retrospective study from Nigeria (2010) reported maximum number of cases in 20-39 years of age [22].

### Laterality and Un-Descended Testes

A predilection for the right side is well established although unexplained feature of testicular cancer. Right side preponderance has been reported worldwide in various series by different authors [17]. In various other studies, the incidence of bilateral testicular tumors varies from 0.5-7%. Collins and Pugh (1964) recorded a frequency of 2.3%. Some authors recorded a frequency of 1%. Cryptorchidism (undescended testis) is consistently associated with an increased risk of testicular germ cell tumor. The incidence is about 3-5 fold increased in men with a history of cryptorchidism. The most common type of tumor in cryptorchid testis is seminoma believed to be derived from pleuripotent prenatal germ cells [23].

### Radiological Characteristics

Ultrasonography is the standard imaging technique used to identify testicular carcinoma. It has a high sensitivity, but it must be combined with physical examination to achieve the best specificity. More than 95% of testicular parenchymal abnormalities are identifiable on routine sonograms, but several other lesions commonly mimic testicular cancer (Figure 1A). Ultrasonography is more specific in presence of a palpable mass. Non palpable intratesticular lesions larger than 1 cm are unlikely to be malignant [24,25]. The false-negative rate for ultrasonographic identification of testicular lesions is extremely low.

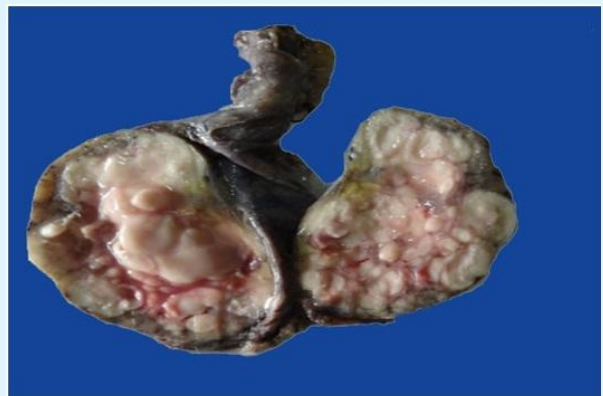


Figure 1A: Gross specimen of testis with Seminoma. Cut section showing well encapsulated growth replacing whole testicular parenchyma. Areas of hemorrhage and necrosis are also seen.

Testicular swelling or pain warrants a scrotal ultrasonography. Ultrasound images of seminoma are more often hypoechoic, homogeneous, and lobulated than those of non-seminoma ( $p < 0.001$ ). Images of non-seminoma are more often heterogeneous and cystic ( $p < 0.001$ ). There is no difference in tumor size, multiplicity, presence of calcium or lesion margination. Testicular microlithiasis is more common in seminoma ( $p < 0.02$ ). These observations were based on a study of 107 patients of testicular cancer by McDonald MW, et al. in 2012 [26].

Testicular ultrasonography is used to determine the location of a palpable mass when testicular cancer is suspected. Generally, palpable extra-testicular lesions are benign. On the other hand, intratesticular masses, especially if they are palpable, are likely to be malignant and must be surgically explored. Therefore, ultrasonography is useful for localizing palpable abnormalities and to triage them for surgical repair when indicated [27].

Testicular cancers are hypoechoic relative to the surrounding parenchyma in about 95% of cases. Published findings suggest that seminomas are often more homogeneously hypoechoic and that nonseminomatous lesions are often more cystic, with interspersed areas of calcification [28].

### Computed Tomography

CT scan imaging is routinely performed as part of the initial staging process, but it is not sensitive or specific enough to be useful in evaluating undiagnosed testicular masses. Chest, abdominal, and pelvic CT scan studies are indicated for the evaluation of retroperitoneal and mediastinal metastases. Both computed tomography (CT) scanning and ultrasonography have been used to search for metastatic retroperitoneal lymphadenopathy, but CT scanning is more commonly used.

### Magnetic Resonance Imaging

Ultrasonographic findings may occasionally be inconclusive in the evaluation of scrotal masses. Magnetic Resonance imaging may provide additional information in these cases, often affecting patient management [29]. Increased signal intensity in the testicle is seen on T2-weighted images of testicular malignancies, but it is not specific.

### Tumor Markers

There are three relatively sensitive and specific serum biomarkers that are being used for diagnosis, prognosis and surveillance of testicular cancer. These serum

markers include alpha feto protein, human chorionic gonadotrophin and lactase dehydrogenase. AFP is a 70kD glycoprotein produced by fetal yolk sac, liver and gastrointestinal tract. Increased levels of AFP are typically found in non seminomatous tumors (embryonal carcinoma and yolk sac (Figure 1B)). AFP levels are typically not elevated in seminomas; however if increased levels of AFP are found in pure seminoma, it must be considered and treated as non seminomatous germ cell tumor. Elevated serum HCG levels are typically present in both seminomas and non seminoma. Increased levels of serum HCG following orchiectomy is an indication of persistent disease, where as recurrence of HCG following chemotherapy-induced complete remission of metastatic disease indicates the presence of relapse. LDH is less specific marker but has an independent prognostic value in men with advanced testicular cancer. It has been reported that LDH reflects the growth rate and tumor burden. Germa-Lluch JR, et al. in study of 1490 cases noted that tumor markers were raised in 21% of seminomas and 79% of Non-seminomatous germ cell tumors [30].



Figure 1B: Gross specimen of testis with Mixed Non Seminomatous germ cell tumor Cut section of growth revealing a cystic cavity (shown by arrow) with adjacent fragile grey white tumor. Testicular parenchyma is reduced to a thin rim at the periphery.

LDH is raised in 40-60% of patients with testicular germ cell tumors [31] with limited sensitivity and specificity for seminomatous component, but LDH levels  $>2000$  ukat/l are more consistent with bulky disease, and rising levels are an accurate indicator of recurrence. In NSGCT's, LDH is directly related to tumor burden [32].

Tumor marker studies in testicular cancer help in diagnosing and planning the treatment of the tumors, however, the diagnosis of testicular cancer cannot be

made based on elevated tumor markers alone, as these markers lack sufficient sensitivity and specificity. Diagnosis instead relies on the histopathologic examination of the orchiectomy specimen.

The degree of tumor marker elevation is directly proportional to tumor burden, and higher serum levels of these tumor markers have been recognized as poor prognostic indicators. According to risk stratification system given by International germ cell cancer collaborative group classification (IGCCCG), seminomas can have good or intermediate prognosis depending upon the degree of tumor marker elevation and presence or absence of non-pulmonary visceral metastasis. Seminomas never have bad prognosis. The degree of tumor marker elevation in patients with NSGCT's has been incorporated with staging criteria to stratify patients into good, intermediate, and poor risk groups according to IGCCCG.

### **Pathology: Gross Examination**

Seminoma has a characteristic gross appearance. It is usually of moderate size solid homogenous and light yellow and may contain sharply circumscribed zones of necrosis. Areas of cystic change and hemorrhage are not seen [19]. Embryonal carcinoma has grossly more variegated appearance than seminoma. It is mainly solid and gray or white with area of haemorrhage and necrosis. Teratoma is predominantly cystic and multiloculated, foci of cartilage are usually evident the presence of bone is infrequent. Teratocarcinomas are multicystic in areas of teratoma and solid with areas of haemorrhage and necrosis in areas of embryonal carcinoma. Choriocarcinomas are often small with no enlargement of testis. They are usually haemorrhagic and partly necrotic. Pure yolk sac tumor of infancy has a soft consistency and a microcystic appearance on cut section. Leydig cell tumor presents as generally small, sharply delimited solid nodule embedded within the testicle. The brown color it exhibits is one of its most distinguishing gross features. Sertoli cell tumors are well circumscribed white or yellow and firm with focal cystic areas. Testicular lymphomas grossly result in a solid homogenous replacement of testicular parenchyma similar to that of seminoma.

### **Microscopic Examination**

The vast majorities of testicular tumors are of germ cell origin and, like the totipotent germ cells from which they arise, may differentiate along several pathways. The distinction of seminoma from the non-seminomatous germ cell tumors remains of critical clinical importance. Tumors of non-germinal origin, although relatively uncommon, are frequent diagnostic problems, both from the standpoint of classification and prognosis. The mesothelium that lines the tunica vaginalis testis may give rise to mesotheliomas, as well as provide the basis, through mullerian metaplasia, for the formation of epithelial tumors more typically identified in the ovary [33].

The overwhelming majority of primary testicular tumors are of germ cell origin. The new World Health Organization (WHO) classification 2016 of testicular tumors is given in Table 1 [1]. Some important changes have been made in the WHO classification of testicular tumours in 2016 compared with that adopted in 2004. These revisions were discussed over the course of several months in 2014 through e-mail communications and were finalized in Zurich, Switzerland, in March 2015. The most significant differences between the newly published classification and the prior version concern the germ cell tumours, but other categories are also affected. The comparison of relative incidence of various histological types in different series is a difficult task. The international histological classification published by WHO (2004) has been an important landmark in bringing unanimity in the study of testicular tumors all over the world. Small differences in the incidence of germ cell tumors in various studies may be due to different sample sizes. Chitale A and Vadera V have noted 142 germ cell tumors of one histological type out of total 154 germ cell tumors (92.20%) [34].

The percentage of seminomas in all testicular tumors in various series ranges from 30.43% to 53.6%. Fischer C.G. et al in a study of 6594 cases with testicular tumors reported 3327 cases of seminoma amounting to 53.6% of the Germ cell tumors [23] where as Shirish C, et al. noted 7 seminomas which constituted 37.78% of 45 Germ cell tumors and 47.22% of 36 Germ cell tumors of one histological type [20].

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| <p><b>Germ cell tumours derived from germ cell neoplasia in situ</b></p> <p style="padding-left: 20px;"><b>Non invasive germ cell neoplasia</b></p> <p style="padding-left: 40px;">Germ cell neoplasia in situ</p> <p style="padding-left: 20px;">Specific forms of intratubular germ cell neoplasia,</p> <p><b>Tumours of a single histological type (pure forms)</b></p> <p style="padding-left: 20px;">Seminoma</p> <p style="padding-left: 40px;">Seminoma with syncytiotrophoblastic cells</p> <p style="padding-left: 20px;">Nonseminomatous germ cell tumor</p> <p style="padding-left: 40px;">Embryonal carcinoma</p> <p style="padding-left: 20px;">Yolk sac tumour postpubertal type</p> <p style="padding-left: 40px;">Trophoblastic tumours</p> <p style="padding-left: 40px;">Choriocarcinoma</p> <p style="padding-left: 20px;">Non choriocarcinomatous trophoblastic tumor</p> <p style="padding-left: 40px;">Placental site trophoblastic tumour</p> <p style="padding-left: 40px;">Epitheloid trophoblastic tumor</p> <p style="padding-left: 40px;">Cystic trophoblastic tumor</p> <p style="padding-left: 40px;">Teratoma, postpubertal type</p> <p style="padding-left: 20px;">Teratoma with somatic type malignancy</p> <p style="padding-left: 40px;">Monodermal teratoma</p> <p style="padding-left: 20px;">Teratoma with somatic type malignancies</p> <p><b>Non seminomatous germ cell tumor of more than one histological type (mixed forms)</b></p> <p style="padding-left: 20px;">Mixed germ cell tumor</p> <p style="padding-left: 20px;">Germ cell tumors of unknown type</p> <p style="padding-left: 20px;">Regressed germ cell tumors</p> <p><b>Germ cell tumors unrelated to germ cell neoplasia in situ</b></p> <p style="padding-left: 20px;">Spermatocytic tumor</p> <p style="padding-left: 20px;">Teratoma prepubertal type</p> <p style="padding-left: 40px;">Dermoid cyst</p> <p style="padding-left: 40px;">Epidermoid cyst</p> <p style="padding-left: 20px;">Well differentiated neuroendocrine tumor (monodermal teratoma)</p> <p style="padding-left: 20px;">Mixed teratoma and yolksac tumor, prepubertal type</p> <p style="padding-left: 20px;">Yolksac tumor, prepubertal type</p> <p style="padding-left: 20px;"><b>Sex cord stromal tumors</b></p> <p style="padding-left: 40px;"><b>Pure tumors</b></p> <p style="padding-left: 60px;">Leydig cell tumour</p> <p style="padding-left: 60px;">Malignant Leydig cell tumour</p> | <p style="padding-left: 20px;">Sertoli cell tumour</p> <p style="padding-left: 40px;">Malignant Sertoli cell tumour</p> <p style="padding-left: 40px;">Large cell calcifying Sertoli cell tumour</p> <p style="padding-left: 20px;">Intratubular large cell hyalinising sertoli cell neoplasia</p> <p style="padding-left: 40px;">Granulosa cell tumour</p> <p style="padding-left: 40px;">Adult type granulosa cell tumour</p> <p style="padding-left: 40px;">Juvenile type granulosa cell tumour</p> <p style="padding-left: 20px;">Tumours in the thecoma/fibroma group</p> <p style="padding-left: 20px;">Mixed and unclassified sex cord stromal tumors</p> <p style="padding-left: 40px;">Mixed Sex cord/stromal tumour:</p> <p style="padding-left: 40px;">Unclassified Sex cord-stromal tumours,</p> <p><b>Tumours containing both germ cell and sex Cord-stromal elements</b></p> <p style="padding-left: 20px;">Gonadoblastoma</p> <p><b>Miscellaneous tumours of the testis</b></p> <p style="padding-left: 20px;">Ovarian epithelial type tumors</p> <p style="padding-left: 40px;">Serouscystadenoma</p> <p style="padding-left: 20px;">Serous tumor of borderline malignancy</p> <p style="padding-left: 20px;">Well differentiated endometrioid carcinoma</p> <p style="padding-left: 40px;">Serouscystadenocarcinoma</p> <p style="padding-left: 40px;">Mucinouscystadenoma</p> <p style="padding-left: 40px;">Mucinous borderline tumor</p> <p style="padding-left: 40px;">Mucinous cystadenocarcinoma</p> <p style="padding-left: 40px;">Endometrioid adenocarcinoma</p> <p style="padding-left: 40px;">Clear cell adenocarcinoma</p> <p style="padding-left: 40px;">Brenner tumor</p> <p style="padding-left: 40px;">Juvenile Xanthogranuloma</p> <p style="padding-left: 40px;">Hemangioma</p> <p><b>Haematolymphoid tumours</b></p> <p style="padding-left: 20px;">Diffuse large B cell lymphoma</p> <p style="padding-left: 20px;">Follicular lymphoma NOS</p> <p style="padding-left: 20px;">Extranodal NNK/T cell lymphoma nasaltype</p> <p style="padding-left: 40px;">Plasmacytoma</p> <p style="padding-left: 40px;">Myeloid sarcoma</p> <p style="padding-left: 40px;">Rosai dorfman disease</p> <p><b>Tumours of collecting ducts and rete testis</b></p> <p style="padding-left: 40px;">Adenoma</p> <p style="padding-left: 40px;">Adenocarcinoma</p> |
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Table 1: Classification of testicular tumors (2016).

Granulomatous inflammation may be associated in 20% of cases [35]. Invasion of epididymis and spermatic cord is noted in 10-15% cases [17,36] Extension beyond capsule to scrotal skin, epididymis and spermatic cord is seen in 8% cases. It has been recognized for several decades that the majority of germ cell tumours arise from progression of an intratubular malignant germ cell that has the morphologic and immunohistochemical features of a seminoma cell. Such cells were usually designated as

either carcinoma in situ (CIS) or intratubular germ cell neoplasia, unclassified (IGCNU) , with those terms receiving preferential use in Europe and North America, respectively. The main objection to CIS was that the malignant germ cells to which it referred were not epithelial (a similar objection applied to testicular intraepithelial neoplasia), whereas IGCNU, be-cause it contained the word unclassified, was felt to falsely convey an element of doubt concerning the nature and clinical

behaviour of the lesion. Germ cell neoplasia in situ (GCNIS) was proposed as an alternative term, retaining the in situ nomenclature that correctly conveys the fact that the lesion is a well-established precursor to an invasive germ cell tumour and simultaneously does away with both the misleading epithelial-based nomenclature and the use of the word unclassified.

GCNIS is now the WHO-recommended term for this precursor lesion, and other forms of intratubular neoplasia should be referred to by their differentiated phenotype with the prefix intratubular. A new emphasis in WHO 2016 is the distinction of GCNIS from maturation-delayed germ cells, which are a relatively common feature in the gonads of patients with disorders of sex development. It is believed that maturation-delayed germ cells likely give rise to GCNIS, but they should be distinguished from the latter because progression is not invariable. Unfortunately, both lesions express the usual markers used for the identification of GCNIS (eg, OCT3/4, placental alkaline phosphatase, AP-2g). The differentiation of the two relies on the more diffuse distribution and central tubular location of maturation-delayed germ cells (as well as the lack of expression of KIT ligand (stem cell factor) in the associated seminiferous tubules, which contrast with the findings in GCNIS.

The prior version of the WHO classification was purely morphologically based and divided the germ cell tumours into those of single or more than one histologic type. In this process, many dissimilar tumours came to be placed under similar diagnostic terms. The new approach recognizes that there are significantly different pathogeneses for testicular germ cell tumours, despite only subtle or even no perceptible morphological differences the germ cell tumours are now broadly separated into two fundamentally different groups: those derived from GCNIS and those unrelated to GCNIS. It is apparent, however, that the latter group is heterogeneous. In contrast, the former group shows a number of basic similarities despite varied morphologies and, to some extent, behaviours. The GCNIS-derived tumours have comparable epidemiologic associations and usually occur in a background of perturbed testicular development that has recognizable morphologic features: impaired spermatogenesis, tubular shrinkage, peritubular Sclerosis, immature Sertoli cells, interstitial widening, hyalinized tubules and microlithiasis. They share the finding of amplification of genetic material from the short arm of chromosome 12, often in the form of isochromosome 12p, and represent progression from GCNIS, often through at least a transient stage of seminoma that may be intratubular. Earlier seminomas were classified into three

main types. Histologic characteristics of anaplastic seminoma include increased mitotic activity ( $\geq 6$  mitoses per high-power field), nuclear pleomorphism, and cellular anaplasia [37]. Differentiating anaplastic from classic seminoma is worthwhile, as up to 30% of patients who die from seminoma have anaplastic morphology. Features suggesting greater aggressiveness of this subtype include increased mitotic activity, higher rate of local invasion, and increased rate of metastatic spread. However, when compared stage to stage, treatment outcomes for patients with classic versus anaplastic seminoma have been similar, suggesting that anaplastic seminoma may have a greater metastatic potential and patients with this subtype may present at an advanced stage [37].

Spermatocytic tumor (spermatocytic seminoma) accounts for 2% to 12% of all seminomas, and approximately half occur in men older than 50 years. Cells usually vary in size and have deeply pigmented cytoplasm and rounded nuclei containing characteristic filamentous chromatin (Figure 2A). These tumors tend to have an extremely low metastatic potential and a favorable prognosis [34]. The frequency of spermatocytic seminoma in germ cell tumors described by various authors varies from 1.1-7.4% [17,19,37,38]. Spermatocytic tumor lacks association with GCNIS and shows a unique amplification at chromosome 9 in contrast to 12 p amplification present in case of seminomas. This is the reason that the term spermatocytic seminoma has been replaced by spermatocytic tumor and is placed in separate category of germ cell tumors unrelated to germ cell neoplasia *in situ*.

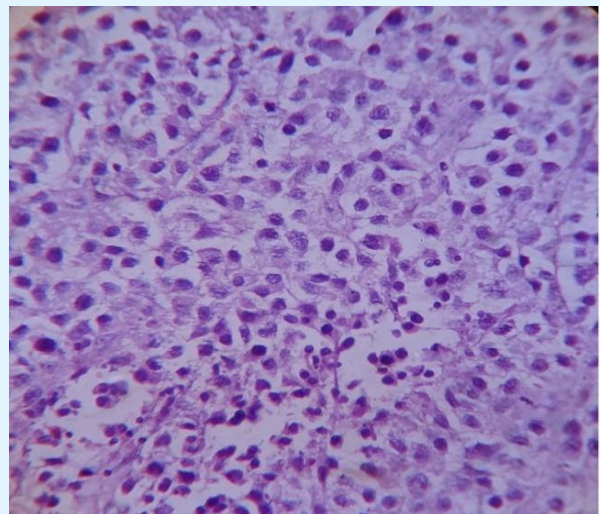


Figure 2A: Photomicrograph showing round cells with a distinct cell membrane. Cells are uniform with abundant cytoplasm showing clearing. Nuclei are centrally located with clumped chromatin (Haematoxylin & Eosin, 400x) - Classical Seminoma.

The frequency of teratoma reported by various authors range from 1.2 to 25.13% [17,34]. Teratomas in children and the dermoid cyst are benign. Agarwal PK and Palmer JS reported 48% cases of teratoma in pre-pubertal males [39]. The well differentiated, mature tissue types consist of keratinizing and non keratinizing squamous epithelium, neural and glandular tissues. Organoid structures are not uncommon, particularly in children such as skin, respiratory, gastrointestinal and genitourinary tract. Thyroid tissue has rarely been observed of the mesodermal components, muscular tissue is the most common. Virtually any other tissue type can be seen. Fetal type tissue may also consist of ectodermal, endodermal and/or mesenchymal tissues (Figure 2B). They can have an organoid arrangement resembling primitive renal or pulmonary tissues. The prepubertal type teratomas have also been categorized as Germ cell tumor unrelated to germ cell neoplasia *in situ* in WHO 2016 Classification as they lack GCNIS and 12p amplification and do not occur in malformed testis.

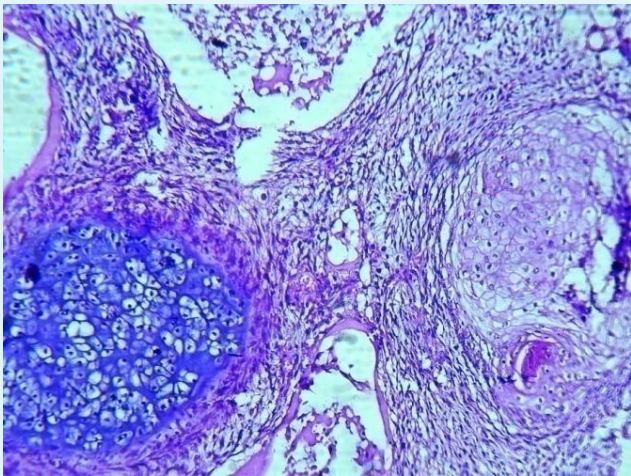


Figure 2B: Photomicrograph showing mature component of Teratoma. Cartilage with mature mesenchymal tissue is seen (Haematoxylin & Eosin, 400x).

Same was found true for yolk sac tumor (prepubertal type) The frequencies of yolk-sac tumor recorded in various studies range from 2.4 – 20% [17,19,39]. Several different patterns are usually admixed, and may be present in equal amounts, although not in frequently one pattern may predominate. Tumors composed entirely of a single histologic pattern are rare. Embryonal carcinoma is a tumour composed of undifferentiated cells of epithelial appearance with abundant clear to granular cytoplasm and a variety of growth patterns. The growth pattern varies from solid and syncytial to papillary with or without stromal fibro vascular cores, forming clefts or gland-like structures. The frequency of embryonal

carcinoma in various series ranged from 4.2 to 37% of germ cell tumors. This is due to different interpretation of this term by different workers and inclusion of yolk-sac tumors in adult embryonal carcinomas. Cases of embryonal carcinoma show areas of hemorrhage and necrosis and infiltration into capsule. The tumor cells are undifferentiated and of epithelial appearance, cytoplasm is abundant, usually finely granular but may also be clear. Cell borders are indistinct and the cells show overlapping [36].

The percentage in various series shows wide range. Shirish C, et al. recorded 20% of cases with Germ cell tumors of more than one histological type [22]. Figures as high as 62% are described by some authors [36]. Embryonal carcinoma and seminoma was the commonest combination reported by Shirish C, et al. (33.33%) while the combination of teratoma and embryonal carcinoma (teratocarcinoma) was the commonest combination noted by Mostofi FK, et al. [36]. Early metastasis with poor prognosis is seen in tumors with embryonal carcinoma element. Presence of seminoma does not alter the prognosis, while as the presence of choriocarcinoma element suggests grave prognosis. The average age of patients of germ cell tumor of more than one histologic type is 33.77 years with age range from 21 years to 43 years [17].

Among the unusual tumors of testis Leydig cell tumors comprise between 1% and 3% of all testicular tumors. about 3% are bilateral either synchronously or metachronously. Microscopically the tumor cells have well defined outlines, deeply acidophilic but occasionally clear cytoplasm and a round or oval nucleus. Some of the cells have plasmacytoid appearance. The frequency of sex-cord stromal tumors in various series is reported as 3 to 4%.

Percentage of lymphoma in various series ranged from 1 to 8% [34]. The gross and microscopic features of lymphoma are same in many studies. On microscopy in various studies DLBCL is the most common primary testicular lymphoma and constitutes about 27-75% of primary testicular lymphomas [40-43].

Miscellaneous group includes very rare tumors which can occur in testis. Extramedullary involvement is frequent in cases of acute lymphoblastic leukemia with particular predilection for CNS, lymphnodes and testis in male patients. 25 out of 35 (65%) ALL cases in boys presented with leukaemic infiltration into the testis in a survey done by H Reid et al in children hospital Royal Manchester. This survey supported the view that



testicular infiltration is an indication of wide spread disease.

Metastasis to testes is rare except for lymphoma and leukemia. These lesions are typically incidental findings at autopsy in about 0.02% to 0.06% of men with malignant tumors. The ratio may be as high as 2.5% if the testis is thinly sliced. Most common primary malignancies metastasizing to testes arise from prostate, followed by the lung, gastrointestinal tract, melanoma and kidneys [44].

### Immuno Histochemical Markers for Testicular Tumors

OCT 4 is the stem cell marker very sensitive and specific for seminoma and embryonal carcinoma. SOX2 is also a stem cell marker expressed in embryonal carcinoma SALL4 is again a stem cell marker and a pan germ cell tumor marker, primary utility being to identify Yolk sac tumor which are negative for OCT4 (Figure 2C).

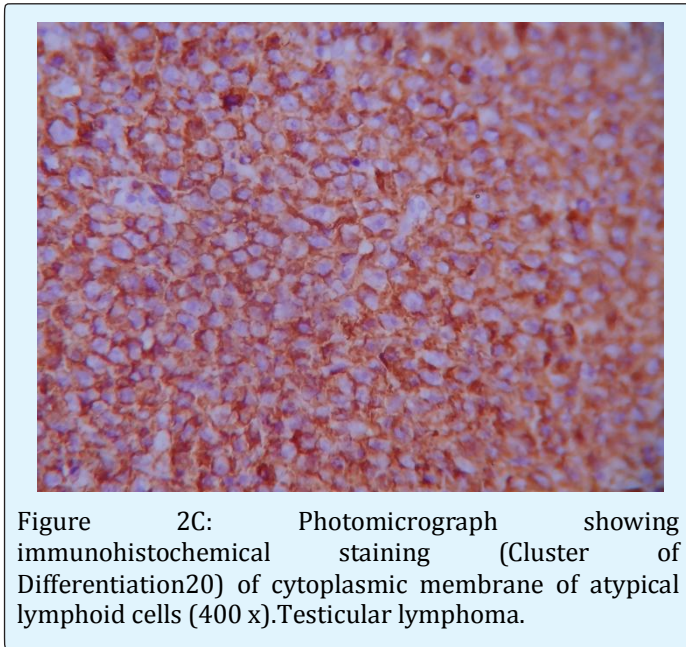


Figure 2C: Photomicrograph showing immunohistochemical staining (Cluster of Differentiation20) of cytoplasmic membrane of atypical lymphoid cells (400 x). Testicular lymphoma.

D2-40 Podoplanin is mesothelial and lymphatic marker which also identifies seminoma and embryonal carcinoma. Epithelial markers like cytokeratins and EMA can also be used. All non seminomatous germ cell tumors are cytokeratin positive but EMA negative while as seminoma is negative for all epithelial markers [45,46].

### Staging

Once a diagnosis of testicular cancer is made (almost always after radical orchiectomy: the removal of the testis and spermatic cord), treatment decisions are primarily

based on clinical staging, which usually consists of computed tomography (CT) imaging of the chest, abdomen, and pelvis. Patterns of metastatic spread in testicular cancer are very predictable, and the reproducibility of expected “landing sites” aids tremendously with staging and treatment decision making. In the simplest form, staging is divided into localized (testis only), retroperitoneal (minimal or bulky), and extralymphatic/extra-retroperitoneal metastatic disease. The staging data are combined with levels of serologic tumor markers to guide management. The prevalence of several different staging schemes, as well as the complexity of the chosen tumor, nodes and metastases (TNM) system, has confounded data acquisition and outcome reporting. The currently recommended staging system for testicular tumors is the American Joint Committee on Cancer (AJCC) tumor- node – metastasis (TNM) classification as given in (Table 2) [33].

| TNM System   | Stage Grouping   |
|--|--|
| TX: Unknown status of testis   | Stage 0: Tis, N0, M0, S0   |
| T0: No apparent primary (includes scars)   | Stage IA: T1, N0, M0, S0   |
| Tis: Intratubular tumor, no invasion   | Stage IB: T2-T4, N0, M0, S0  |
| T1: Testis and epididymis only; no vascular invasion or penetration of tunica albuginea                  | Stage IS: any T, N0, M0, S1-S3<br>Stage IIA: any T, N1, M0, S0-S1  |
| T2: Testis and epididymis with vascular invasion or through tunica albuginea to involve tunica vaginalis | Stage IIB: any T, N2, M0, S0-S1<br>Stage IIC: any T, N3, M0, S0-S1 |
| T3: Spermatic cord   | Stage IIIA: any T, any N, M1a, S0-S1                               |
| T4: Scrotum  | Stage IIIB: any T, any N, M0-M1a, S2                               |
| NX: Unknown nodal status   | Stage IIIC: any T, any N, M0-M1a, S3 any T, any N, M1b, any S      |
| N0: No regional node involvement   |  |
| N1: Node mass or single nodes ≤2 cm; ≤5 nodes involved; no node >2 cm                                    |  |
| N2: Node mass >2 but <5 cm; or >5 nodes involved; none >5 cm; or extranodal tumor                        |  |

|  |                  |     |              |                |
|--|------------------|-----|--------------|----------------|
| N3: Node mass >5 cm  |                  |     |              |                |
| MX: Unknown status of distant metastases   |                  |     |              |                |
| M0: No distant metastases  |                  |     |              |                |
| M1a: Non regional nodal or lung metastases                                       |                  |     |              |                |
| M1b: Distant metastasis other than non regional nodal or lung                    |                  |     |              |                |
| SX: No marker studies available  |                  |     |              |                |
| S0: All marker studies normal  |                  |     |              |                |
|  | LDH <sup>a</sup> |     | hCG (mIU/mL) | AFP (ng/mL)    |
| S1:  | <1.5 × N         | and | <5000        | and <1000      |
| S2:  | 1.5-10 × N       | or  | 5000-50,000  | or 1000-10,000 |
| S3:  | >10 × N          | or  | >50,000      | or >10,000     |
| <sup>a</sup> LDH levels expressed as elevations above upper limit of normal (N). |                  |     |              |                |

Table 2: Classification of tumor- node – metastasis (TNM).

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