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CLINICOPATHOLOGICAL ASSESSMENT OF TESTICULAR MALIGNANT TUMORS IN A SAMPLE OF IRAQI PATIENTS

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ABSTRACT

Background: Although most testicular tumors are primarily germ cell tumors, which include seminomas and non-seminomas, pathologists need to study their clinical behaviors, biomarkers, and possibly other variables just to classify these tumors into different histologic subtypes. **Aim of the study:** Study the clinicopathological parameter (Age, size, site of tumors, gross finding, tumor type, tumor subtype, serum markers, margin involvement, invasion, pathological stage) of testicular malignant tumors in a sample of Iraqi patients. **Materials and method:** This was a retrospective analysis conducted over the period from January 2024 to December 2024, enrolling 75 samples of testicular malignant tumors was received between 2017 to 2023 from different pathology centers around Iraq. Histopathological reports and slides were reviewed, and clinical parameters were recorded from patient records. Inclusion criteria were patients with orchiectomy for testicular malignancy, while recurrent tumors, benign testicular tumor, and non-testicular tumors and Cases without available slides or blocks were excluded. Procedures included collecting and reviewing histopathological data and using microscopes for slide examination. **Result:** All the enrolled patients were over six years, with a mean age of 32.1± 12.1 years. Most tumors were germ cell types (93.2%), often well-circumscribed and solid, with the right side being slightly more affected. Seminoma was the predominant subtype at 56.9%, followed by mixed tumors at 24.3%. High rates of free surgical margins (96.0%) were observed, with tumor stages T1b and T2 being the most common. Statistical analysis highlighted significant associations with tumor subtypes and serum marker levels. **Conclusions:** The mean age of patients in the study aligned with other regional studies (common over 30 years). Most testicular tumors in this study were germ cell tumors, specifically seminomas, which aligned with global trends. Elevated tumor markers usually in non-seminomas highlighted their diagnostic and prognostic significance, in addition, larger tumors and those detected at later stages (more common in seminomas) suggested the need for early detection and intervention.

KEYWORDS: Histopathological reports and slides were reviewed, and clinical parameters were recorded from patient records.

1.1. INTRODUCTION

Testicular cancer is a relatively uncommon malignancy primerly affecting young men with a peak incidence between 25 and 29 years of age. The disease remains highly curable with 5-year survival for all stages being 95%, although survival rates drop to 73% for distant disease, thereby highlighting the importance of early detection.[1]

The vast majority 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 different types of germ cell tumors remains of prime clinical importance.[2]

The main factors thought to predispose to testicular germ cell tumors are testis cryptorchidism, disorders of sex development, family history, testicular microliths in subfertility, and prior germ cell tumor.[3] Hereditary forms are described, but almost all are related to low penetrance autosomal recessive susceptibility genes. Specifically, the AZFc region (gr/gr microdeletion) of

chromosome Y, 12q22 (KITLG), and 5q31 (RAS-ERK-MAPK pathway) are proposed as susceptibility loci, in some cases possibly due to interactions with c- KIT.[4] It is also suggested that PTEN hamartoma tumor syndrome, Li–Fraumeni syndrome, and neurofibromatosis type 1 may rarely be associated with germ cell tumors.[5]

A painless testicular mass is highly suggestive of a testicular tumor; however, most patients present with diffuse testicular swelling, induration, hardness, pain, or some combination of these findings. For patients who are present with scrotal or testicular pain. Scrotal ultrasonography (specificity of 89% to 90% and sensitivity of 98% to 99%). Levels of biologic tumor markers (human chorionic gonadotropin [hCG], α-fetoprotein [AFP], and Lactate dehydrogenase [LDH]) should also be determined before and after orchiectomy. The relation between stages of tumor and serum markers represented by the following: Sx:serum tumor markers not available, S0:markers within normal limits, S1: LDH < 1.5 x upper limit of normal, hCG < 5,000 mIU/mL and AFP < 1000 ng/mL. S2: LDH 1.5 - 10 x upper limit of normal or hCG 5,000 - 50,000 mIU/mL or AFP 1,000 - 10,000 ng/mL. S3: LDH > 10 x upper limit of normal or hCG > 50,000 mIU/mL or AFP > 10,000 ng/mL.[6]

Since e the last World Health Organization (WHO) Classification scheme for tumors of the urinary tract and male genital organs, there have been a number of advances in the understanding, classification, immunohistochemistry, and genetics of testicular germ cell tumors.[7]

This 2022 WHO classification has been adapted to the new format of the fifth edition of the classification. The testis tumor classification follows the definitions of "category", "family", then "type", and then "subtype" with a possibility of different patterns that do not fit neatly, especially in the diversity of germ cell tumors. The term "variants" is reserved for genomic variants and is no longer used as a histologic descriptor.[8]

With current treatment protocols, testicular germ cell tumors represent the most curable solid cancer in men, even when metastatic spread is present. For stage I tumors, whether seminoma or non-seminoma, cure rates are close to 100%. With metastatic spread, cure rates remain high, but vary with prognostic groups as defined by the International Germ Cell Cancer Collaborative Group classification.[9] Even in this metastatic group, overall cure rates are over 80%, and salvage therapy may cure over half of the patients with initial treatment failures. Later relapses (defined as >2 years after initial treatment with complete remission) are less common, but may occur and portend an adverse prognosis, particularly when associated with secondary somatic malignancy.[5]

1.2. Aim of the study

The aim of this study is to assess the histopathological diagnosis of testicular malignant tumors in a sample of Iraqi patients in relation to various clinicopathological parameters (Age, size, site of tumors, gross finding, tumor type, tumor subtype, serum markers, margin involvement, invasion, pathological stage).

REVIEW OF LITERATURE

2.1. Normal anatomy of testis

The testicles are sex glands that have both an exocrine secretory function in the production of sperm and an endocrinological function as part of the hypothalamic-pituitary-gonadal axis in men through the production of androgens. The normal anatomy of the testicles is that of an oval shape located in the scrotum, further separated by the scrotal septum. The length of the testis is between 3 cm to 5 cm, whereas the width is between 2 cm to 3 cm.[10]

The consistency of normal testicles on palpation is smooth and soft. The testes are suspended superiorly by the spermatic cord and inferior to the scrotum by the scrotal ligament. During embryological development, the scrotal ligament is also known as the gubernaculum.[11]

The tunica vaginalis is a double-layered structure that covers all the testes apart from the posterior and superior borders, which represent the attachment of the epididymis and spermatic cord. The posterior lateral testis has a small space between the body of the epididymis and the testis. This small space is known as the sinus of the epididymis. The tunica albuginea is found deep in the tunica vaginalis. It is a thick fibrous sheath that covers the testes.[12]

2.2. Normal histology of testis

The testicular parenchyma is mostly occupied by multiple lobules of seminiferous tubules with their components of various germ cells and Sertoli cells. The interstitium contains Leydig cells, blood and lymphatic vessels, fibroblasts, myoid cells, and occasional lymphocytes, plasma cells, and macrophages.[13]

The seminiferous tubules converge to empty into the rete testis at the testicular hilum, and these, in turn, anastomose with the efferent ductules that, external to the testis, coil to form the head of the epididymis. At the hilum, the rete tubules are supported by a fibrous tissue stroma, and together, these structures comprise the testicular mediastinum. In this area, the tunica albuginea and vaginalis are absent. The epididymis is applied to much of the posterior surface of the testis and gives rise to the ductus (vas) deferens, which empties into the distal seminal vesicle.[2]

2.3. WHO classification of testicular malignant tumors

There have been numerous previous classifications of testicular tumors from a variety of panels and resources. For many years the British Testicular Tumor panel was widely used in many countries. The WHO publications in the 21st century have helped to unify this field.[7] This

especially pertains to the schism which had developed between those using different nomenclatures for the pre-neoplastic lesion of testicular germ cell tumors (previously 'carcinoma in situ', 'intratubular germ cell neoplasia, unclassified' and 'testicular intra-epithelial neoplasia'), that undoubtedly has caused confusion. The resolution of this rift and now near-universal use of germ cell neoplasia in-situ (GCNIS) as the nomenclature has united many and has healed large divisions.[14]

The fifth edition of the WHO classification of urogenital tumors include.[8]

1. Germ cell tumors derived from germ cell neoplasia in situ

- Noninvasive germ cell neoplasia
  - Germ cell neoplasia in situ
  - Specific forms of intratubular germ cell neoplasia
    - Intratubular seminoma
    - Intratubular embryonal carcinoma
    - Intratubular trophoblast
    - Intratubular yolk sac tumor
    - Intratubular teratoma
  - Gonadoblastoma
- The germinoma family of tumors
  - Seminoma
    - Seminoma with syncytiotrophoblast cells
- Nonseminomatous germ cell tumors
  - Embryonal carcinoma
  - Yolk sac tumor, postpubertal type
  - Choriocarcinoma
  - Placental site trophoblastic tumor
  - Epithelioid trophoblastic tumor
  - Cystic trophoblastic tumor
  - Teratoma, postpubertal type
  - Teratoma with somatic type malignancy
- Mixed germ cell tumors
  - Mixed germ cell tumors
    - Polyembryoma
    - Diffuse embryoma
- Germ cell tumors of unknown type
  - Regressed germ cell tumors

2. Germ cell tumors unrelated to germ cell neoplasia in situ

- Spermatocytic tumor
  - Spermatocytic tumor with sarcomatous differentiation
  - Teratoma, prepubertal type
  - Dermoid cyst
  - Epidermoid cyst
- Yolk sac tumor, prepubertal type
- Testicular neuroendocrine tumor, prepubertal type (well differentiated neuroendocrine tumor [monodermal teratoma])
- Mixed teratoma and yolk sac tumor, prepubertal type

3. Sex cord stromal tumors of the testis

- Leydig cell tumor
  - Leydig cell tumor
  - Malignant Leydig cell tumor
- Sertoli cell tumor (Sertoli cell tumors)
  - Sertoli cell tumor
  - Malignant Sertoli cell tumor
  - Large cell calcifying Sertoli cell tumor
- Granulosa cell tumors
  - Adult granulosa cell tumor
  - Juvenile granulosa cell tumor
- Tumors in the fibroma thecoma group (the fibroma thecoma family of tumors)
  - Thecoma
  - Fibroma
- Mixed and other sex cord stromal tumors
  - Mixed sex cord stromal tumor
  - Signet ring stromal tumor
  - Myoid gonadal stromal tumor
  - Sex cord stromal tumor, NOS

4. Metastatic tumors

Tumors of the testicular adnexa

1. Ovarian type tumors of the collecting ducts and rete testis

- Serous cystadenoma (serous cystadenoma, NOS)
- Serous tumor of borderline malignancy (serous borderline tumor, NOS)
- Serous cystadenocarcinoma
- Mucinous cystadenoma
- Mucinous borderline tumor
- Mucinous cystadenocarcinoma
- Endometrioid tumor, borderline
- Endometrioid adenocarcinoma
- Clear cell adenocarcinoma
- Brenner tumor

2. Tumors of the collecting duct and rete testis

- Adenoma of the collecting ducts and rete testis (adenoma)
- Adenocarcinoma of the collecting ducts and rete testis (adenocarcinoma)

3. Paratesticular mesothelial tumors

- Adenomatoid tumor
- Well differentiated papillary mesothelial tumor
- Mesothelioma
  - Epithelioid mesothelioma
  - Sarcomatoid mesothelioma
  - Biphasic mesothelioma

4. Tumors of the epididymis

- Cystadenoma of the epididymis
- Papillary cystadenoma
- Adenocarcinoma of the epididymis
- Squamous cell carcinoma
- Melanotic neuroectodermal tumor

2.4. Germ cell tumors of the testis

More than 90% of testicular neoplasms originate from germ cells the most common tumors in adolescent and young men and germ cell tumors (TGCTs) account for most of all testicular cancers. Increasing incidence of

TGCTs among males provides strong motivation to understand their biological and genetic basis. Gains of chromosome arm 12p and aneuploidy are nearly universal in TGCTs, but TGCTs have low point mutation rate.[15]

It is thought that TGCTs develop from premalignant intratubular germ cell neoplasia that is believed to arise from the failure of normal maturation of gonocytes during fetal or postnatal development. Progression toward invasive TGCTs (seminoma and nonseminoma) then occurs after puberty. Both inherited genetic factors and environmental risk factors emerge as important contributors to TGCT susceptibility. Genome-wide association studies have so far identified more than 30 risk loci for TGCTs suggesting that a polygenic model fits better with the genetic landscape of the disease.[16]

2.4.1. Molecular markers

The most consistent abnormality in adolescent and adult males with testicular GCTs is the presence of an isochromosome of the short arm of chromosome 12 (i12p) and approximately 80 percent of NSGCTs and 50 percent of pure seminomas possess at least one i12p.[17] Most tumors in adolescent and adult males with GCTS that do not have an i12p have other chromosomal abnormalities in this region that result in overrepresentation of chromosome 12p material.[18] Identification of an i12p may be useful in establishing the diagnosis of a GCT in atypical cases, particularly for tumors arising in the mediastinum. In contrast, prepubertal yolk sac tumors and teratomas are not associated with isochromosome.[19]

2.4.2. Staging system

GCTs are staged using the eighth (2017) Tumor, Node, Metastasis (TNM) staging system developed jointly by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). In previous versions of the AJCC staging system, tumors were pT1 if confined to the testisand tunical albuginea, pT2 if they demonstrated vascular invasion or extension beyond the tunica vaginalis, pT3 they involved the spermatic cord and pT4 direct secrotal invasion. In the eighth edition of the AJCC staging system, the pT2 category includes tumors that demonstrated vascular invasion, extension beyond the tunica vaginalis, invasion of hilar soft tissue, and/or involvement the epididymis. Additionally, for pure seminomas only, the pT1 category is subdivided into pT1a and pT1b for tumors that are <3 cm and ≥3 cm, respectively.[20]

2.4.3. Noninvasive germ cell neoplasia

2.4.3.1. Germ cell neoplasia in situ

Germ cell neoplasia in situ (GCNIS) is a noninvasive germ cell neoplasia that is defined by the presence of clearly malignant GCT elements within seminiferous tubules; these can include intratubular seminoma or, less commonly, intratubular embryonal carcinoma.[21] However, a clear distinction of the intratubular component subtype is not always possible, and therefore, these are simply classified as GCNIS. GCNIS was previously classified as "intratubular germ cell neoplasia," a term which is no longer used.[22]

Morphologically, the in situ neoplasia often replaces all other germ cell elements within the seminiferous tubules **(Figure 2.1)**. Occasionally, tumor cells may demonstrate pagetoid spread from within the tubules into the rete testis. Intratubular neoplastic cells resemble their invasive counterparts cytomorphologically and immunophenotypically.[23]

The clinical significance of GCNIS is not entirely clear. GCNIS has been associated with GCTs of all types in adolescents and adults, except for spermatocytic tumor. However, prepubertal-type testicular tumors, which are not associated with GCNIS, have been reported in postpubertal males.[19]

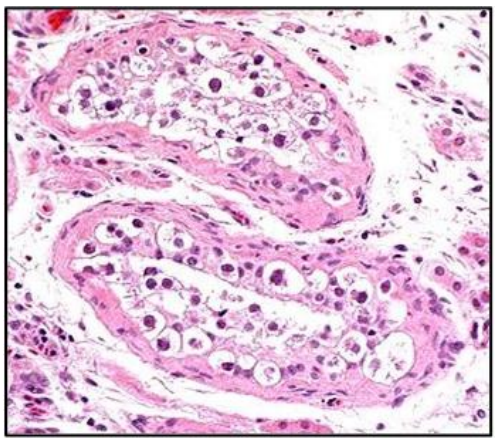


Figure (2.1): Light micrograph of germ cell neoplasia in situ (GCNIS). The seminoma- like cells of GCNIS are seen in two seminferous tubules. These cells have a "fried egg" appearance with clear cytoplasm surrounding a round, dark nucleus.[24]

2.4.3.2. Gonadoblastoma

Gonadoblastomas is a noninvasive germ cell neoplasia that contains both neoplastic germ cells and sex cord-stromal cells. Gonadoblastoma can be a precursor to more invasive tumors such as dysgerminoma or seminoma.[25]

Gonadoblastomas consist of seminoma-like cells interspersed among cells resembling immature Sertoli cells that are arranged in a characteristic pattern. The Sertoli-like cells are arrayed in a palisading fashion around small collections of eosinophilic basement membrane material. Focal calcification is a prominent feature in most cases **(Figure 2.2)**. Occasionally, Leydig-like cells are also present. Each of the cell types has the expected immunohistochemical phenotype. It is believed that gonadoblastoma is a premalignant lesion with the potential for the development of GCTs, especially seminoma, and gonadoblastoma can coexist with such a malignancy.[26]

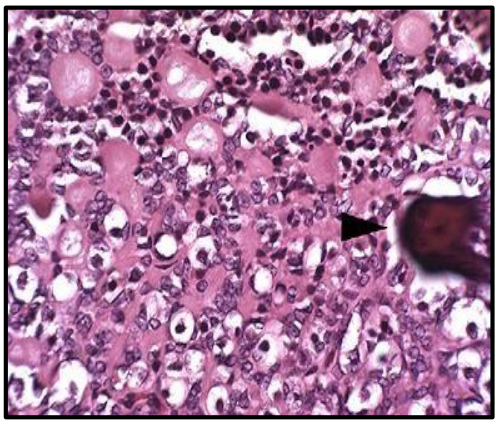


Figure (2.2): Light micrograph of an ovarian gonadoblastoma. Cells with small round, dark nuclei resemble immature Sertoli cells and are arrayed around spherical collections of eosinophilic material. Larger seminoma-like cells with clear cytoplasm are scattered about in the lower half of the field. The arrowhead points to a calcification that is typical of this neoplasm.[24]

Most gonadoblastomas arise within dysgenetic gonads. Mixed gonadal dysgenesis, cryptorchidism, and abnormalities of the external genitalia, such as ambiguous genitalia or hypospadias, are common. In some cases, female external and/or internal genitalia can be seen. Although 80 percent of cases occur in phenotypic females, most have a 46 XY karyotype with the remainder exhibiting 45, X/46, XY mosaicism. Presentation is usually in childhood or adolescence in patients with male external genitalia.[27]

Phenotypic females may show some virilization, usually manifested by clitoral hypertrophy.[27] Endocrine manifestations are rare in phenotypic males, although gynecomastia may be present.[27]

Other unclassified tumors consisting of a mixture of cells with the appearances of germ cells and sex cord-stromal cells are quite rare and appear to be confined to adults. Further characterization has been hampered by their scarcity.[28]

2.4.4. Seminomatous germ cell tumors

Seminoma is subclassified under the "germinoma" family of tumors.[8] Pure seminomas account for approximately 50 percent of all testicular GCTs, and a seminomatous component is present in approximately 20 percent of mixed GCTs.[29] The average age at presentation for pure seminoma is approximately 40 years old (approximately 10 years older than for testicular NSGCTs). A seminomatous component is uncommon in GCTs in prepubertal males. Aside from age, there are no other reliable clinical correlates. In the ovary, a tumor nearly identical to seminoma is termed dysgerminoma.[30]

2.4.4.1. Seminoma

Histologic characteristics of classic seminoma include a clonal proliferation of neoplastic germ cells that demonstrates well-defined cytoplasmic borders, central to marginally located nuclei with prominent nucleoli, angled ("squared-off") nuclear membranes, and clear cytoplasm secondary to intracytoplasmic glycogen (**Figure 2.3**).[31] This overall pattern at low power is often described as having a "fried-egg" appearance. The neoplastic cells of seminoma tend to be less cohesive than in embryonal carcinoma, yolk sac tumor, or choriocarcinoma, all of which are epithelial tumors. Additionally, clusters of lymphocytes are almost invariably seen in intimate association with the tumor cells.[32]

The differential diagnosis for seminoma includes lymphoma (especially with retroperitoneal tumors) and other GCTs, especially embryonal carcinoma. The latter distinction is most problematic when a seminoma demonstrates cytologic atypia or is poorly preserved during processing.[26] Of note, the term anaplastic seminoma is no longer recognized by the WHO and should not be used. Instead, cases that were previously classified as anaplastic are included with the typical/classical seminomas.[33] This change in terminology is based upon the observation that the previously so-called "anaplastic seminomas" have similar outcomes when compared with classic seminomas of comparable stage with modern treatment. It should be recognized, however, that some seminomas have increased cytologic atypia and a higher number of mitotic figures.[34]

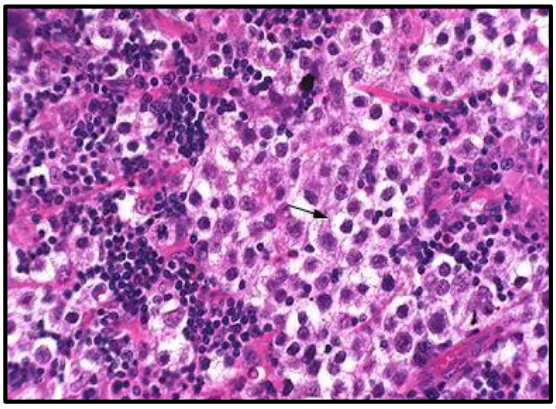


Figure (2.3): Light micrograph of a testicular seminoma. Many of the seminoma cells have clear cytoplasm and a "fried egg" appearance (black arrow). Intermixed clusters of smaller lymphocytes are typical.[24]

2.4.4.2. Immunohistochemistry for seminomas

Immunohistochemistry for seminomas is straightforward and helpful in difficult cases. Seminoma is immunoreactive with OCT3/4, KIT (CD117), NANOG, and D2-40; however, OCT3/4 and NANOG do not distinguish seminoma from embryonal carcinoma as both are positive for this marker. By contrast, yolk sac tumor

and choriocarcinomas are negative for all four of these seminoma biomarkers.[35] Traditionally, the use of cytokeratin and CD30 immunostains have been helpful in distinguishing seminoma from embryonal carcinoma, as only the latter should be positive for these biomarkers. However, it is not infrequent for embryonal carcinoma to show only patchy, weak, or focal staining for cytokeratins and CD30, which in theory still raises the possibility of a mixed GCT instead of one that contains a pure component. Additionally, seminoma may express weak, focal (aberrant) CD30 expression, especially near areas of necrosis.[36]

Table (2.1): Immunohistochemistry markers in diagnoses and subtyping of testicular germ cell tumors[36-38]

Immunomarker	Description
OCT3/4 and NANOG	Very sensitive and specific markers that stain both embryonal carcinoma and seminoma but are negative in yolk sac tumor
Sox-2	Stains embryonal carcinoma, while being negative in both seminoma and yolk sac tumor
KIT (CD117)	Present in seminoma but is negative in both embryonal carcinoma and yolk sac tumor. (Up to approximately 20 percent may be KIT (CD117) negative.)
AFP	AFP immunostaining has low sensitively and variable specificity for yolk sac tumor
SALL4	A stem cell marker that has been shown to stain all subtypes of GCT and can be used when a GCT is in the differential diagnosis of a metastatic tumor of unknown primary. Of note, testicular sex cord-stromal tumors (SCSTs) are negative for SALL4, and a small subset of non-GCTs are focally and weakly positive for SALL4. Examples of the latter include rare SALL4 positive gastric, esophageal, and colonic carcinomas
Glypican-3	Glypican-3 is another sensitive immunomarker for yolk sac tumor. However, studies demonstrate that it stains fewer tumor cells (ie, decreased sensitivity) when compared with SALL4
βHCG	Staining for hCG is usually supportive of a component of choriocarcinoma. However, it is not uncommon to find isolated, scattered hCG-positive syncytiotrophoblastic giant cells in any (non-choriocarcinomatous) GCT, and their presence tends to correlate with a modestly elevated serum hCG concentration.
GATA3	For diagnostic purposes, GATA3 is typically used as a biomarker of breast and urothelial carcinomas[43]; however, other studies have shown GATA3 immunoreactivity in choriocarcinoma (diffuse, strong intensity), yolk sac tumor (focal to patchy, weak to moderate intensity), and within syncytiotrophoblast (in the absence of choriocarcinoma). Seminoma and embryonal carcinoma are negative for GATA3

2.4.5. Non-seminomatous germ cell tumors

2.4.5.1. Embryonal carcinoma

Pure embryonal carcinoma accounts for approximately 2 percent of all testicular GCTs, but it is a histologic component of approximately 85 percent of all mixed GCTs. The average age at presentation is approximately 30 years, similar to other NSGCTs. Embryonal carcinoma is rare in prepubertal males.[39]

Pure embryonal carcinomas usually do not produce AFP. A more than modest elevation (ie, >60 ng/mL) in the serum AFP concentration should prompt a suspicion that a concomitant element of yolk sac tumor is present. As with seminoma, syncytiotrophoblastic giant cells within embryonal carcinomas may cause a modest elevation in the serum beta-hCG concentration.[40] Microscopically, embryonal carcinoma shows epithelial differentiation with cohesive clusters and sheets of cells that show marked cytologic atypia, and this is often helpful in distinguishing them from yolk sac tumors, which generally exhibit blander cytomorphology **(Figure 2.4)**. Several architectural patterns exist, including glandular, papillary, and solid. None of these distinctions is of any clinical significance. Syncytiotrophoblastic giant cells may be present.[41]

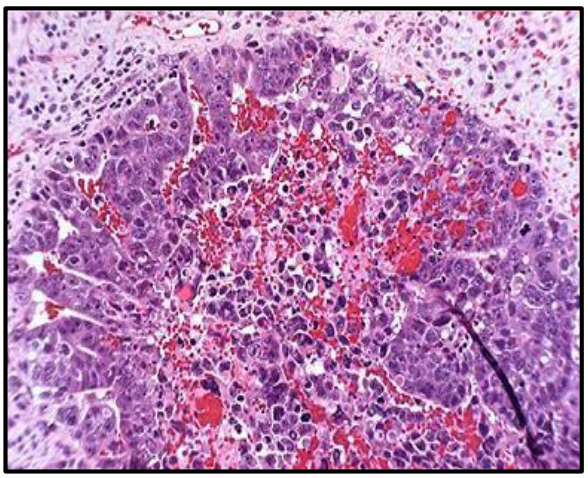


Figure (2.4): Light micrograph of a testicular embryonal carcinoma. Focus of embryonal carcinoma with central necrosis. Marked nuclear atypia characterizes the cells of embryonal carcinoma.[24]

The differential diagnosis is primarily with yolk sac tumor, which is often intimately associated with embryonal carcinoma, and with seminoma. Immunohistochemical staining can be helpful with this, as well as in the broader differential diagnosis that may

arise in metastatic deposits where non-GCTs are considered in the differential diagnosis.[40] CD30 is the traditional marker used for embryonal carcinoma; however, the use of the transcription factors/stem cell markers, OCT3/4, NANOG, Sox-2, and SALL4 are the most sensitive and specific immunomarkers for embryonal carcinoma. However, one must be aware that both OCT3/4 and NANOG also stain seminoma, and that SALL4 stains all subtypes of GCT.[36] Keratins are typically negative to weakly positive in well- stained embryonal carcinomas, and this can be useful to distinguish from yolk sac tumors, which are nearly always strongly and diffusely positive for keratin, such as AE1/AE3.[42]

2.4.5.2. Yolk sac tumor

The terms "yolk sac tumor" and "endodermal sinus tumor" are synonymous; however, the latter is not used in diagnostic reports. Pure yolk sac tumor is the most common malignant testicular GCT in prepubertal children, although (benign) teratomas are actually more prevalent in this age group. Pure yolk sac tumor is rarely seen in the adult, whereas a component of yolk sac tumor occurs in approximately 40 percent of mixed GCTs in adults.[43]

Nearly all yolk sac tumors are accompanied by increased serum AFP, usually >100 ng/mL. Furthermore, the AFP level correlates with disease extent, with concentrations >1000 ng/mL often indicating the presence of extensive tumor. Yolk sac tumor does not produce hCG.[44]

Microscopically, yolk sac tumors are the most morphologically variable of all GCTs **(Figure 2.5)**. Although a wide variety of patterns are recognized (eg, microcystic, reticular, papillary, glandular, solid, hepatoid), their only significance is the degree to which they can make the recognition of yolk sac tumor difficult.[45] Hyaline-type globules and Schiller-Duval bodies are most characteristic of yolk sac tumor, but they are only present in a subset of cases. Typically, but not invariably, yolk sac tumors have lower nuclear grade, and may be associated with edematous to myxoid stroma. Following chemotherapy, yolk sac tumors may recur with sarcomatoid and/or glandular differentiation.[46,47]

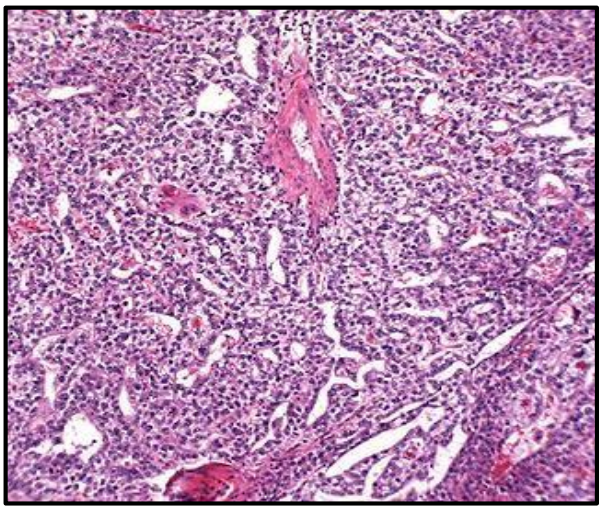


Figure (2.5): Light micrograph of a testicular yolk sac tumor showing one of its many histologic patterns. The cells show less atypia than do those of embryonal carcinoma.[24]

The most common entity in the microscopic differential diagnosis is embryonal carcinoma, with which yolk sac tumor often merges. Occasionally, difficulty may also be experienced in differentiating yolk sac tumor from teratoma as both can form gland-like structures.[48] Immunohistochemical staining for AFP can be helpful when present, and is generally positive, focally, in yolk sac tumor. The absence of AFP staining does not preclude the diagnosis of a yolk sac tumor as sensitivity is low. Additionally, background staining for AFP is often high and can be positive in a few scattered cells, at most, in embryonal carcinoma.[44] The most specific staining profile for yolk sac tumor is the presence of SALL4, strong and diffuse AE1/AE3, and AFP, and an absence of OC3/4, c-kit, NANOG, and Sox-2. The presence of Glypican3 and GATA3, at least focally or multifocally, is also supportive of a yolk sac tumor diagnosis.[36]

2.4.5.3. Choriocarcinoma

The most aggressive and least common type of GCT is choriocarcinoma. Widespread hematogenous dissemination occurs early, and many patients present with metastatic disease. Choriocarcinoma is present as an element of approximately 10 percent of testicular mixed GCTs, but is rare in its pure form at this site, and the average age at presentation is somewhat younger than for other NSGCTs but is rare or nonexistent in the prepubertal male.[49]

The serum beta-hCG concentration is often greater than 1000 international units/L and may even be much higher. Choriocarcinomas do not produce AFP.[50]

Choriocarcinomas are characterized by areas of hemorrhage and necrosis, both grossly and microscopically. As such, the treatment of choriocarcinomas with chemotherapy is sometimes complicated by hemorrhagic emergencies.[51] The most

important diagnostic characteristic is the coexistence and intimate association of both syncytiotrophoblast and cytotrophoblast cells, which distinguishes this tumor from other GCTs with only scattered syncytiotrophoblast **(Figure 2.6)**. Recapitulating their normal embryonic function, the syncytiotrophoblastic giant cells and cytotrophoblastic cells often display extensive vascular invasion. This characteristic is presumed to account for the propensity for early hematogenous dissemination.[52]

Immunohistochemical staining for hCG is of limited utility in choriocarcinomas, as the antibody is not very reliable due to significant background staining and differential staining patterns. While the syncytiotrophoblast is essentially always strongly hCG positive, this is diagnostically insufficient. Staining for hCG generally does not help to identify the crucial cytotrophoblastic elements, which are less conspicuous on H&E-stained material, and at most are only weakly beta- hCG-positive.[50]

GATA3 has been shown to be a sensitive immunomarker for choriocarcinoma. Choriocarcinomas are negative for OCT3/4, NANOG, Sox-2, and c-kit, but SALL4 may be expressed in the neoplastic cytotrophoblast (syncytiotrophoblast are negative). Nevertheless, extensive sampling of GCTs and careful microscopic examination is the best way to detect this most aggressive tumor.[53]

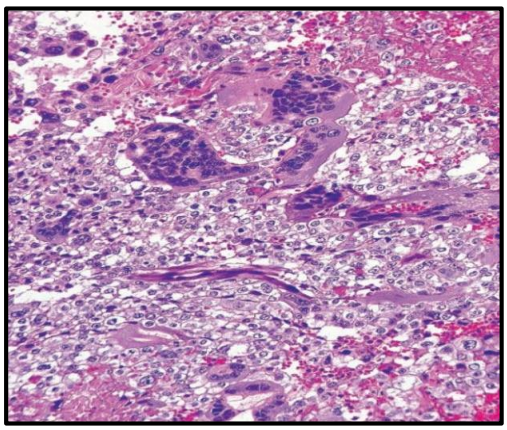


Figure (2.6): Light micrograph of a testicular choriocarcinoma. Characteristic mixture of syncytiotrophoblast cells and mononucleated trophoblast cells in choriocarcinoma.

The background is hemorrhagic.[24]

2.4.5.4. Germ cell tumors unrelated to germ cell neoplasia in situ

2.4.5.4.1. Spermatocytic tumor

Spermatocytic tumor is the recognized name for the group of tumors previously known as "spermatocytic seminoma." These tumors are classified under GCTs unrelated to germ cell neoplasia in situ, in the 2022 WHO classification system for testicular tumors.[8]

Despite being previously classified as a variant of seminoma, it has been well recognized and accepted that spermatocytic tumor differs from classic seminoma in essentially all histologic, immunohistochemical, molecular, and clinical characteristics.[46] This distinct clinicopathologic entity accounts for 1 percent of GCTs and can occur in males of any age; but is most frequently seen in older males.[54]

Histologically, spermatocytic tumors have a characteristic admixture of three cytologically distinct populations of neoplastic germ cells of varying size (small, medium, and large) and nuclear features.[55] SALL4 has been shown to be immunoreactive in spermatocytic tumors and cannot be used to distinguish from (classic) seminoma. Immunohistochemical staining for placental-like alkaline phosphatase (PLAP) and OCT3/4 is negative, in contrast to seminoma, whereas KIT has shown to be reactive in a subset of spermatocytic tumors.[56]

It has been shown that a novel SSX antibody directed against a conserved C- terminal region of SSX1, SSX2, and SSX4 (SSX CT) can be used to distinguish spermatocytic tumor and seminoma. Spermatocytic tumor is nearly always strongly and diffusely positive for SSX, whereas seminoma is typical negative or only focally positive for SSX.[57]

Unlike classic seminomas, spermatocytic tumors do not occur as part of mixed GCTs, do not contain an isochromosome 12p, and are not associated with germ cell neoplasia in situ (GCNIS; formally called intratubular germ cell neoplasia of unclassified type) or a significant lymphocytic infiltrate.[58]

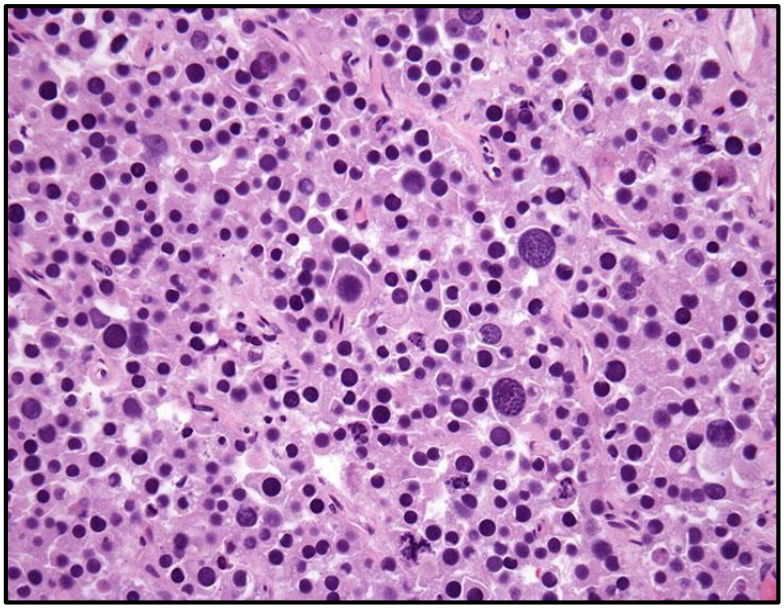


Figure (2.7): Spermatocytic tumors. Note the tumor cells of three distinct sizes in the lesion: small tumor cells that resemble the size of a lymphocyte, medium size tumor cells, and large tumor cells with spireme (speckled) nuclear features.[24]

2.4.5.4.2. Teratoma, prepubertal and postpubertal types

A tumor usually seen in the prepubertal testis (but it encompasses all age groups) composed of tissue derived from one or more of different germinal layers. Teratomas are, after YST, the second most frequent (14–20%) GCT in infancy. This tumor occurs before puberty, while when occurring in older patients they may have been diagnosed postpubertal and exhibit malignant potential, associated with chromosome12p ampilification, always occur with previous GCNIS. Prepubertal teratoma occur before the age of 6 years, while the latter the oldest patient being 59 years.[59] No documented cases have exhibited malignant behavior.[19] The exception is carcinoid tumor that has a metastatic potential. Like postpubertal-type teratoma, it can resemble morphologically mature and differentiated tissues (mature areas) or immature tissues. "Mature" areas contain cysts lined with squamous, ciliated, respiratory-type, or, less frequently, intestinal-type epithelium mixed with stromal mesenchyme (smooth-muscle, cartilage, bone, etc.). Immature areas are less frequently present containing neuroepithelium and blastema. In the peripheral parenchyma, there is no GCNIS and there should be no tubular atrophy, parenchymal scars, tubular microlithiasis, necrosis, or impaired spermatogenesis, in contrast to the postpubertal teratoma Virtually all elements lack significant atypia.[59] postpubertal teratoma grossly cystic and multiloculated, microscopically, the most common being neural tissue, cartlage, and various type of epithelium, havecomponents of primitive neuroepithelial or peripheral neuroectodermal tumors (PNET).[5]

2.4.5.4.3. Mixed germ cell tumors

Approximately one-third of all testicular GCTs are mixed, with two or more GCT types present within a single mass. Many possible combinations of seminoma, teratoma, embryonal carcinoma, yolk sac tumor, and choriocarcinoma can be seen. A teratomatous component is identified in approximately one-third of all mixed GCTs, and the term teratocarcinoma has, in the past, been applied to cases in which teratoma coexists with embryonal carcinoma. However, this term has largely been abandoned, and these tumors are referred to as a malignant mixed GCT, with a description of the specific GCT elements present.[60]

In adults, the epidemiologic and clinical features of mixed GCTs are similar to those of NSGCTs. The average age at diagnosis is approximately 30 years, and they are rare in prepubertal males. Elevations in serum AFP and beta-hCG reflect some of the components that are present within the tumor.[61]

2.4.5.4.4. Polyembryoma and diffuse embryoma:

Polyembryoma, is a separately categorized, rare form of mixed germ cell tumor composed predominantly of embryoid bodies, is considered by some as a unique germ cell tumor and is listed under one histologic type. However, the individual components consisting of embryonal carcinoma, yolk sac tumor, syncytiotrophoblastic cells and teratoma, suggest that these should be regarded as mixed germ cell tumors with a unique growth pattern. It is perhaps the most photogenic of all gonadal germ cell tumors and is also intriguing because of its distinctive, organized arrangement of yolk sac tumor and embryonal carcinoma elements and recapitulation of very early embryonic development, even to the extent of having in its fundamental unit, the embryoid body, a miniature yolk sac, and amniotic cavity.[62] Diffuse embryoma is a very rare, distinct form of mixed germ cell tumor (MGCT) that

is often separately categorized because of its unique histologic features. Histologically, it is characterized by a diffuse, orderly arrangement of embryonal carcinoma (EC) and yolk sac tumor (YST) with scattered trophoblastic elements. To the best of my knowledge, only 5 cases of diffuse embryoma of the testis have been reported in the English Medical literature.[63]

2.5. Sex cord-stromal tumors

Testicular sex cord-stromal tumors (SCSTs) show differentiation towards Leydig cells, Sertoli cells, and/or other types of sex cord-stromal cells (eg, granulosa cells). In contrast to testicular germ cell tumors (GCTs), assessing the potential for malignant behavior is often difficult for SCSTs. Nevertheless, the likelihood for a given tumor to display malignant or metastatic behavior increases in the presence of local vascular invasion, large size (ie, greater than 5 cm), large numbers of mitotic figures, cytologic atypia, and necrosis.[64]

2.5.1. Leydig cell tumors

Leydig cell tumors are the most common type of testicular SCSTs. Up to 20 percent of Leydig cell tumors in adults are classified as malignant, based predominantly upon large size >5 cm, infiltrative growth, vascular invasion, increased mitotic activity >3/10HPF and necrosis. Malignant behavior has not been documented in children. However, in some cases, Leydig cell tumors with aggressive behavior are associated with fumarate hydratase inactivation, Wnt pathway activation, and copy number changes without recurrent mutations.[65]

Microscopically, Leydig cell tumors consist of monomorphic sheets or nests of large cells with round, usually regular nuclei with a prominent nucleolus, and abundant eosinophilic cytoplasm. Occasional tumors may have spindle-shaped cells, or vacuolated cytoplasm. Eosinophilic crystals of Reinke may be seen in the cytoplasm in approximately one-third of cases, although they may be quite sparse and inconspicuous. These crystals, which also have a characteristic appearance by electron microscopy, are characteristic of Leydig cells, but not diagnostic of neoplasia.[66]

The differential diagnosis for a Leydig cell tumor includes Leydig cell hyperplasia and other neoplasms, such as lymphoma, plasmacytoma, and, occasionally, a Sertoli cell or GCT (especially the hepatoid variant of yolk sac tumor). Immunohistochemical staining with inhibin (inhibin-A) can be helpful for the distinction from most GCTs and somatic tumors, but not from Sertoli cell tumors as these can also be immunoreactive with inhibin.[67] Additionally, SF1, calretinin, and WT-1 immunostaining can be helpful; however, calretinin is more frequently present in Leydig cell tumors, whereas WT-1 is more frequently positive in Sertoli cell tumors. SALL4, a stem call marker that has been used to distinguish GCTs from other carcinomas and sarcomas, is negative in SCSTs, including Leydig cell tumors.[68]

2.5.2. Sertoli cell tumors

The general function of Sertoli cells is to facilitate spermatogenesis, and they are normally found scattered among germ cells within the seminiferous tubules. The secretory products of Sertoli cells include a variety of proteins.

A. Sertoli cell tumors, NOS: Sertoli cell tumors, NOS, which are the most common, have a greater range of histologic appearances, making recognition of this group of neoplasms challenging.[69] The cells exhibit a variety of cytomorphologic appearances, including small polygonal cells with scant cytoplasm, fusiform cells, and cells with abundant eosinophilic cytoplasm, which may mimic those of Leydig cell tumors. Furthermore, the architecture may also vary widely, with cells arranged in sheets, pseudorosettes, tubules, slit-like spaces, nests, or cords. Sertoli cell tumors with dense fibrous stroma surrounding scattered small tubules, cords of cells, and individual cells with small nuclei and scant cytoplasm (previously referred to as "sclerosing Sertoli cell tumor") are included in this diagnostic category; mention of the sclerosed stroma can be mentioned in the pathology report if so desired.[70]

B. Large cell calcifying Sertoli cell tumors: Large cell calcifying Sertoli cell tumor has very distinctive histologic features. The cells can be arranged in a variety of patterns, sometimes with tubule formation, and generally have abundant, eosinophilic cytoplasm, as the name implies. Varying degrees of myxoid change or fibrosis can be seen in the surrounding stroma, and areas of calcification are usually a prominent feature. Neoplastic Sertoli cells are often present in the surrounding seminiferous tubules.[71] Large cell calcifying Sertoli cell tumors can be sporadic or associated with the Carney complex; the latter are associated with a *PRKAR1A* gene mutation in approximately two-thirds of cases. PRKAR1A immunohistochemistry can be used to support the diagnosis of a large cell calcifying Sertoli cell tumor; loss of staining is both sensitive and specific.[72]

C. Intratubular large cell hyalinizing Sertoli cell neoplasia: Intratubular large cell hyalinizing Sertoli cell neoplasms are frequently seen in patients with Peutz-Jeghers syndrome and are associated with gynecomastia. The WHO also classifies this neoplasm as a genetic tumor syndrome because of its association with Peutz-Jeghers syndrome.[8] The lesion consists of an intratubular Sertoli cell proliferation that is accompanied by prominent basement membrane deposits. Lesions may be multifocal and microscopic. Secretion of aromatase by the tumor, which is then converted to androgens and estrogens, is the cause of the gynecomastia.[73]

2.5.3. Granulosa cell tumors

Granulosa cell tumors are rare neoplasms that morphologically resemble their ovarian counterparts, although studies suggest they may be molecularly distinct.[74] Granulosa cell tumors of the testis are divided

into adult and juvenile types, like in the ovary. In the testis, the juvenile type is almost exclusively seen in children under the age of two years. These tumors can be difficult to classify, since their histologic and immunophenotypic (eg, inhibin positive) features can overlap with other SCSTs. Granulosa cell tumors may be hormonally active or inactive.[75]

2.6. Other tumors

Brenner tumors (transitional cell carcinomas), papillary cystadenoma, desmoplastic small round cell tumor, lymphomas, leukemias, plasmacytomas, fibromas, vascular tumors, and sarcomas (eg, rhabdomyosarcoma) have all been rarely described in the testis or paratesticular tissues. Metastatic deposits of cancers originating in a wide variety of organs, particularly the prostate and lung, have also been observed.[76]

2.6.1. Testicular lymphoma

Primary testicular lymphoma is a unique and aggressive extranodal non-Hodgkin lymphoma with a high incidence of bilateral involvement, and a propensity for extranodal spread to the skin, subcutaneous tissue, bone marrow, central nervous system, and lung. In males over 60 years old, malignant lymphoma is the most common cause of a testicular mass. Large cell diffuse B-cell types account for the majority of cases.[77]

2.6.2. Leukemia and plasmacytoma

In 5 percent of boys with acute lymphoblastic leukemia, the testis is involved either at presentation or as a site of relapse following initial successful induction therapy. Less commonly, adults with acute promyelocytic leukemia may have isolated testicular relapse. Primary testicular plasmacytoma is an extremely rare tumor.[78]

MATERIALS AND METHODS

3.1. Study design and setting

This was a retrospective analysis conducted over the period from January 2024 to December 2024, enrolling 75 samples of testicular malignant tumors was received between 2017 to 2023 from different pathology centers around Iraq (Teaching Laboratory of Al-Imamain Al-Kadhimain Medical City, Pathology Departments of Ghazi Al- Harreri Surgical Specialties Teaching Hospital, Educational laboratories and Oncology Hospital in Medical City, and Oncology Center in Marjan Medical City in Babylon).

3.2. Ethical consideration

The scientific committee of the iraqi board of medical specialization approved the study(approval number: Patho 4, approval date 21 st february 2024.

3.3. Data sources

For each case the histopathological reports were collected, and slide review was carried out for each case. In addition, the clinical parameters such as (age, size of tumors, side, tumor site, gross finding, tumor types, tumors subtypes, surgical margin status, histopathological stage and serum tumor markers) were taken from patients' admission case sheets and pathology reports.

3.4. Inclusion criteria

All patients with orchiectomy operation for testicular malignant tumor.

3.5. Exclusion criteria

1. Recurrent testicular tumor.
2. Benign testicular tumor.
3. Tumor of testicular adnexa.
4. Cases without available slides or blocks

3.6. Procedures

1. Collection of 75 histopathological reports, and slides from orchiectomy specimens.
2. In the Pathology Department at College of Medicine/Al-Nahrain University, H&E-stained slides were inspected and re-evaluated by the study's supervising pathologist for revision of the histological diagnosis.

3.7. Image capture

Each H&E-stained slide was initially examined using a light microscope (Leica, Germany) at 4x,10x and 40x magnifications to look for histopathological features indicative of the disease, and then microscopic sections photomicrograph were taken with a I phone 11 pro max (12 MP wide angle camera, f/1.8 aperture).

3.8. Statistical analysis

For this study, the collected data were analyzed using the appropriate statistical techniques (SPSS) version 23. So that, the data were plotted as bar chart to get better insight on the data distribution. Additionally, the analysis included contingency tables where the Chi-squared test was hypothesized to test whether the investigated variables are significantly correlated or not with p value less than 0.05 was regarded as statistically significant.

RESULTS

4.1. Demographic data

Mean age ± SD is (32.1±12.1) years, with a wide range spanning from 1.6 to 66 years. Specifically, 63 cases (84.0%) of patients are over 20 years old, while the remaining 10 cases (13.3%) are between 11-20 years. This indicates a slightly higher prevalence in the older age group within the studied population. Only two cases was less than 10 years old. As shown in **(Table 4.1)**.

Table (4.1): The distribution of age in the studied patients.

Variables		Mean ± SD	Range
Age (years)		32.1 ± 12.1	1.6 – 66
		Number	**%**
Age categories	0-10 y	2	2.7
	11-20 y	10	13.3
	>20 y	63	84.0
Total		**75**	**100%**

4.2. Clinicopathological features of testicular malignant tumors Most tumors were grossly homogenous, well-circumscribed, solid, and fleshy 47 cases (62.7%), with the right side being slightly more affected 40 cases (53.3%) than the left 34 cases (45.3%). Most tumors were in the 4-9 cm size range 43 cases (57.3%), and a significant portion of patients 51 cases (68%) showed no lymho-vascular invasion. Germ cell tumors dominated the types identified in 70 cases (93.3%), and over half of the patients had normal serum markers (S0) at 43 cases (57.3%), These are the common characteristics and patterns in testicular malignant tumors in the studied group. As shown in **(Table 4.2)**.

Table (4.2): The distribution of clinicopathological features of testicular malignant tumors in the studied patients.

Variables		Number	%
Gross finding	Homogenous, well circumscribed, solid, fleshy	47	62.7
	Heterogenous, cystic and solid	23	30.7
	Ill define, variegated, hemorrhage and necrosis	4	5.3
	Nodular or lobulated, smooth, homogeneous	1	1.3
Tumor site	Bilateral	1	1.3
	Left	34	45.3
	Right	40	53.3
Tumor size	1-3 cm	23	30.7
	4-9 cm	43	57.3
	10-13 cm	9	12.0
Lympho-vascular invasion	No	51	68
	Yes	24	32
Tumor type	Germ cell tumor	70	93.3
	Malignant lymphoma	1	1.3
	Sex cord stromal tumor	4	5.4
Serum marker	S0	43	57.3
	S1	24	32.0
	S2	8	10.7
Total		75	100

4.3. Subtypes of testicular malignant tumors
Seminoma was the most common subtype 43 cases at (56.9%). Mixed germ cell tumors comprised 18 cases at (24.3%), followed by embryonal carcinoma 4 cases at (5.4%). Less common subtypes included teratoma two cases at (2.7%) and Leydig cell tumor 4 cases at (5.4%), and yolk sac tumor two cases at (2.7%), malignant lymphomawas diffuse large B cell lymphoma, spermatocytic tumor, which represented (2.6%) of the cases collectively. As shown in **(Table 4.3)**.

Table (4.3): The distribution of testicular malignant tumors subtypes in the studied patients.

Tumor subtypes	Number	%
Seminoma	43	56.9
Mixed germ cell tumors	18	24.3
Embryonal carcinoma	4	5.4
Malignant Leydig cell tumor	4	5.4
Teratoma	2	2.7
Yolk sac tumor	2	2.7
Spermatocytic tumor with sarcomatous differentiation	1	1.3
Malignant lymphoma(DLBCL)	1	1.3
Total	**75**	**100%**

Among the 18 cases of mixed testicular malignant tumors, 12 cases had teratoma with a mean percent of 42.92%, 11 cases had yolk sac tumor with a mean percent of 42.73%, 9 cases had seminoma with a mean percent of 26.11%, and 9 cases had embryonal carcinoma with a mean percent of 42.22%. As shown in (**Figure 4.1**). While the most frequent combination of mixed germ cell tumor in this study is seminoma with teratoma, followed by semionam with yolk sac and then embryonal carcinoma with yolk sac as amixed germ cell tumor.

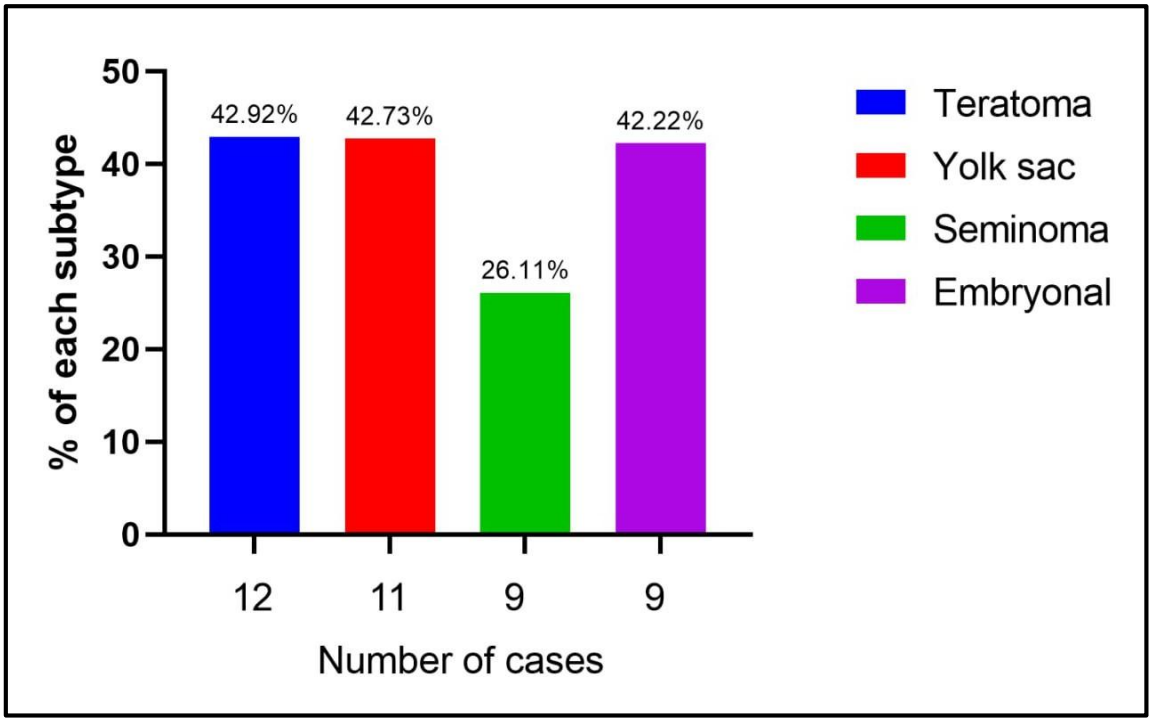


Figure (4.1): Percentage of germ cell tumors subtypes existence in mixed germ cell tumors.

4.4. Tumor margin and stage

There were 72 cases (96.0%) tumors with free margins, while only three cases (4.0%) had positive margin. The staging of the tumors reveals that T1b was the most frequant stage 24 cases at 32.0%, followed by T2 was 20 cases (26.6%), T1 was 18 cases at 24.0%. Other stages included T1a was 9 cases (12.0%), and T3 was 4 cases (5.3%). As shown in **(Table 4.4)**.

Table (4.4): The distribution of testicular malignant tumors margin and stages in the studied patients.

Variables		No. [total=75]	Percent %
Tumor margin	Free margin	72	96.0
	Involved margin	3	4.0
		75	**100**
Tumor stage	T1	18	24.0
	T1a	9	12.0
	T1b	24	32.0
	T2	20	26.6
	T3	4	5.3
Total		**75**	**100**

4.5. Association between seminoma/ other tumors with age

The relationship between tumor subtype and age group shows that seminoma is more common in patients over 20 years old 40 cases (93.0%), while other tumors are also more frequent in old patients over 20 years was 23 cases at (71.8%). This age-dependent distribution indicates that seminoma and other tumors incombination tends to present later in life. **P-value=0.442 insignificant value** As shown in **(Table 4.5)**.

Table (4.5): The association between testicular tumors subtype and age groups.

Age groups	Other tumors		Seminoma		P-value*
	n.	%	*n.*	%	
0-10 years	1	3.2	1	2.3	0.442
11-20 years	8	25.0	2	4.7	
>20 years	23	71.8	40	93.0	
Total	32	100	43	100	

*** Chi square test.**

4.6. Association between seminoma/ other tumors with tumor site The seminoma more in right side was 23 cases at (53.5%) and other tumors was 17 cases at (53.1)% also more in the right side . One case of bilateral involvement was observed in a seminoma (SALL4+OCT3/4 strong positive) patient. **P-value=0.884**. As shown in **(Table 4.6)**.

Table (4.6): The association between testicular tumors subtype and tumor site.

Tumor site	other tumors		Seminoma		P-value*
	n.	%	*n.*	%	
Bilateral	0	0.0	1	2.3	0.884
Left	15	46.8	19	44.2	
Right	17	53.1	23	53.5	
Total	32	100	43	100	

*** Chi square test**

4.7. Association between seminoma/ other tumors with tumor size

In **(Table 4.7)**, larger tumors (4-9 cm) were more frequently seminoma was 29 cases at (67.4%) compared to other tumors was 14 cases at (43.7%) the percentage are approximately close across the size. **P-value=0.092 insignificant** As shown in **(Table 4.7)**.

Table (4.7): The association between testicular tumors subtype and tumor size.

Tumor size	other tumors		Seminoma		P-value*
	n.	%	*n.*	%	
1-3 cm	13	40.7	10	23.2	0.092
4-9 cm	14	43.7	29	67.4	
10-13 cm	5	15.6	4	9.3	
Total	32	100	43	100	

*** Chi square test.**

4.8. Association between seminoma/ other tumors with lymphovascular invasion

Table 4.8 Shows that lymphovascular invasion in other tumors was 14 cases at (43.7%) compared to seminoma was 10 cases at (23.3%), **P-value=0.458 insignificant,** .As shown in **(Table 4.8)**.

Table (4.8): The association between testicular tumor subtype and lymphovascular invasion.

Lymphovascular invasion	other tumors		Seminoma		P-value*
	n.	%	*n.*	%	
Absent	18	56.3	33	76.7	0.458
Present	14	43.7	10	23.3	
Total	32	100	43	100	

*** Chi square test.**

4.9. Association between seminoma/ other tumors with serum markers

There is a significant association between tumor subtype and serum marker levels. Seminoma patients predominantly have normal serum markers was 36 cases (83.7% in S0), while other tumors patients tend to have elevated markers, especially in S1 was 17 cases at (53.1%) and S2 was 8 cases at (25%) categories **P-value=0.001** significant association in this study. As shown in **(Table 4.9)**.

Table (4.9): The association between testicular tumor subtype and Serum marker.

Serum marker	Other tumors		Seminoma		P-value*
	n.	%	*n.*	%	
S0	7	21.8	36	83.7	**0.001**
S1	17	53.1	7	16.3	
S2	8	25	0	0.0	
Total	32	100	43	100	

*** Chi square test.**

4.10. Association between seminoma/ other tumors with tumor margin

Both seminoma and other tumors showed high rates of free margins following orchiectomy, with 42 cases at (97.7%) in seminomas and 30 caese at (93.7%) in other tumors. **P-value=0.751**.As shown in **(Table 4.10)**.

Table (4.10): The association between testicular tumor subtype and tumor margin.

Tumor margin	Other tumors		Seminoma		P-value*
	n.	%	*n.*	%	
Free margin	30	93.7	42	97.7	0.751
Involved margin	2	6.3	1	2.3	
Total	32	100	43	100	

*** Chi square test.**

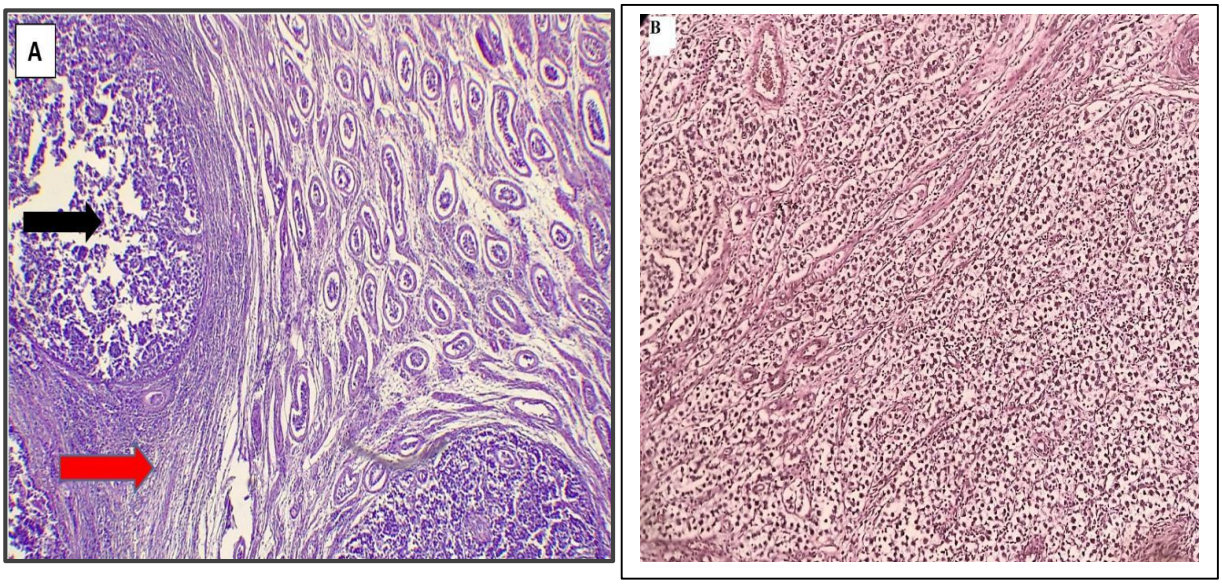
4.11. Association between seminoma/other tumors with tumor stage

Tumor staging varies significantly between subtypes, with seminomas more likely to be detected in (T1b and T2) was 24 cases and 10 cases at (55.8% and 23.3%) respectively , compared to other tumors, which are often found in stages (T1) was 18 cases at (56.2%),and T2 was (10) cases **P-value=0.001** significant association in this study. As shown in **(Table 4.11)**.

Table (4.11): The association between testicular tumor subtype and tumor stage.

Tumor stage	Other tumors		Seminoma		P-value*
	n.	%	*n.*	%	
T1	18	56.2	0	0.0	**0.001**
T1a	0	0.0	9	20.9	
T1b	0	0.0	24	55.8	
T2	10	31.3	10	23.3	
T3	4	12.5	0	0.0	
Total	32	100	43	100	

*** Chi square test.**



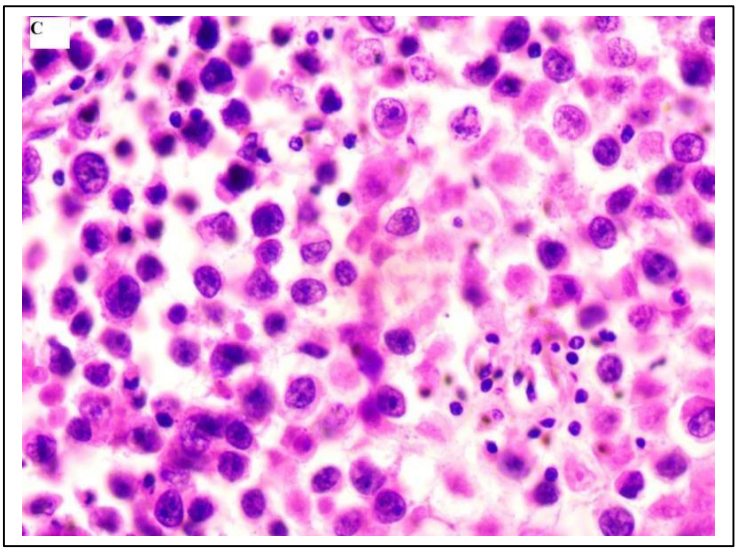


Figure (4.2): Aphotomicrograph of Testicular seminoma. A: showing a lobular pattern of growth form sheet of cell (black arrow) with fibrous septae (red arrow) and ajecent to the seminiferous tubules. (H&E stain; 4x). B: showing large pale cells with clear cytoplasm, distinct borders, squared off nuclei and prominent nucleoli admixed with lymphocytes. (H&E stain; 10x).C:showing large cells with clear cytoplasm, with lymphocytic infiltration in the fibrous septae. (H&E stain; 40x).

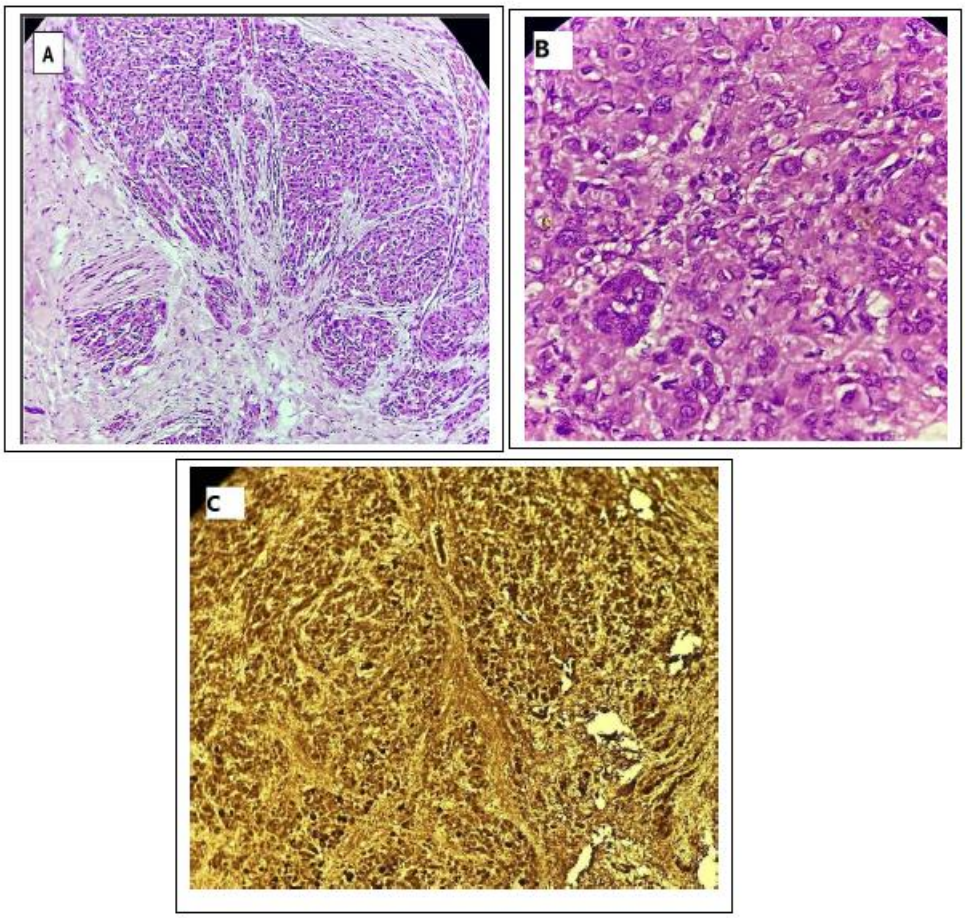


Figure (4.3): Aphotomicrograph of Leydig cell tumor. A: Low power view showing nodular pattern of growth with fibrous bands and sheets of polygonal cells with eosinophilic cytoplasm.(H&E stain; 10x). B: High power view of leydig cell tumor showing cells with abundant eosinophilic granular cytoplasm, round nuclei and prominent nucleoli at (H&E stain; 40x).C:strong nuclaer and cytoplasmic staining of calretinin. (H&E stain; 10x).

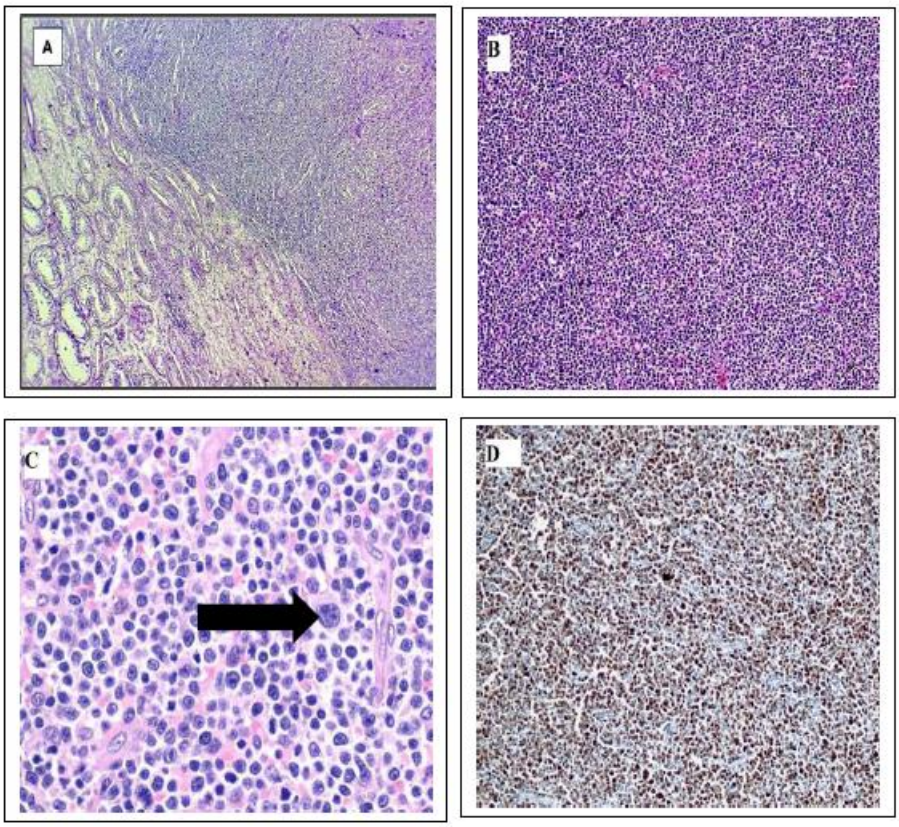


Figure (4.4): Aphotomicrograph of Testicular lymphoma (diffuse large B cell lymphoma), was strong positive for CD20, PAX5, BCL2 and negative for CD5,CD10,Cyclin D1 Ki67 >80%. A: showing atypical lymphoid tissue on the right side arranged as sheets of cells replacing normal testicular parenchyma (seminferous tubules) on the left side of the picture. (H&E stain; 4x), B: showing a sheet of non-cohesive lymphoid cells. (H&E stain; 4x) C: a large irregular cells with centroblastic (black arrow). (H& Estain; 10x).D: Immunohistchemistery stain Ki67 positive in >80%.(H&E stain; 4x).

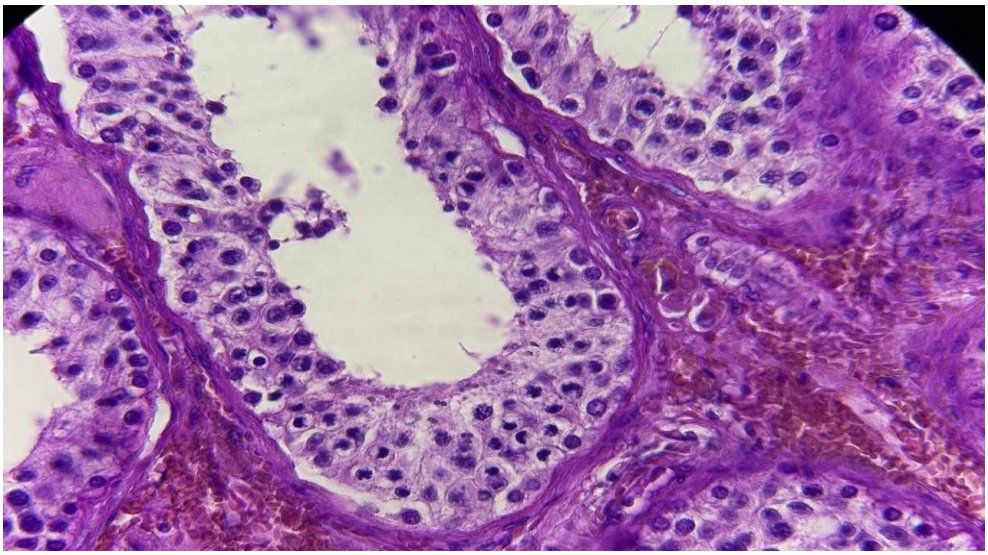


Figure (4.5): Aphotomicrograph of Germ cell neoplasia in situ (GCNIS) showing focal involvement of seminiferous tubules and the later was replaced by tumor cell with clear cytoplasm, enlarge vesicular nuclei and prominent nucleoli with absent of spermatogenesis. (H&E stain; 10x).

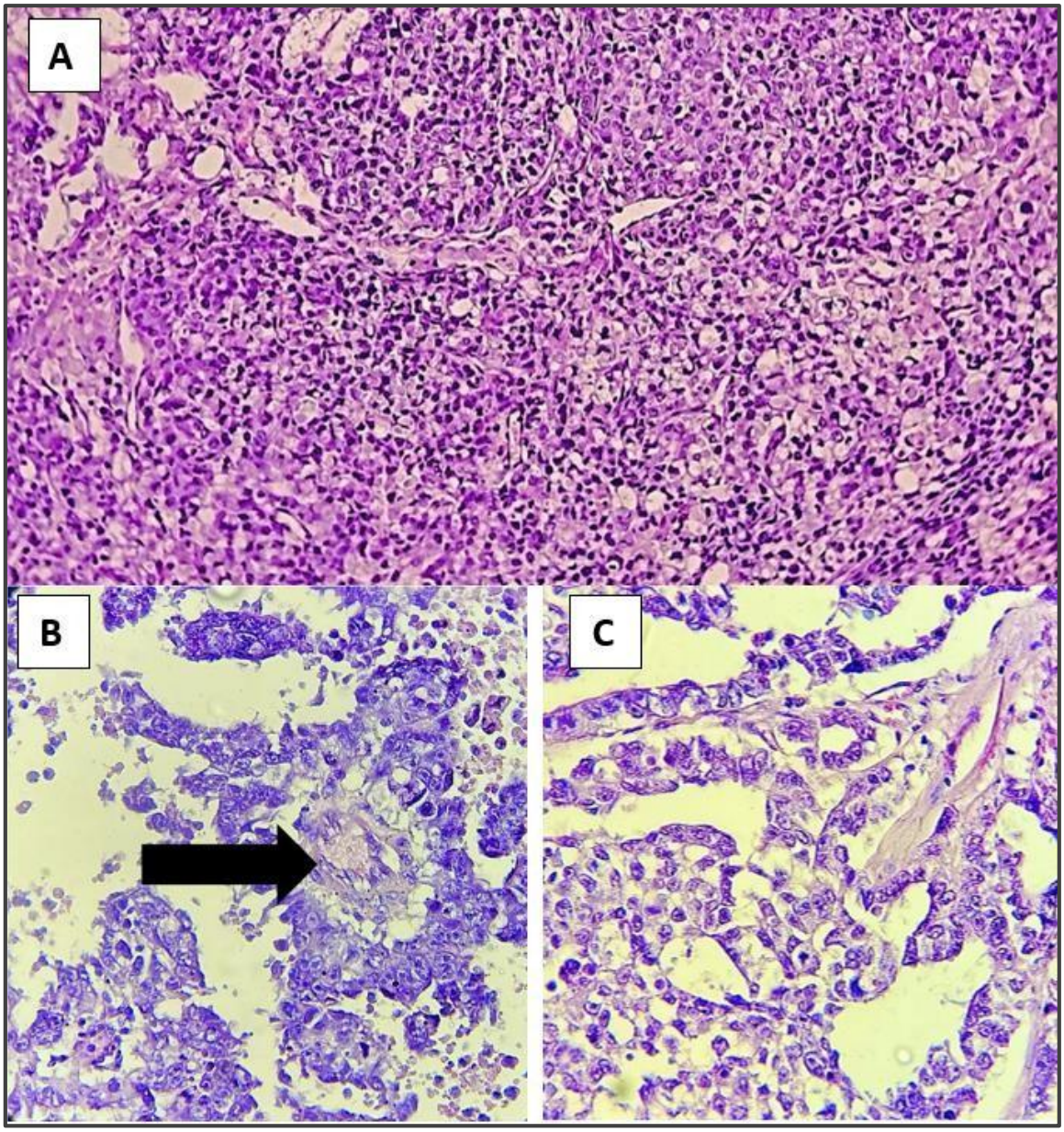


Figure (4.6): Aphotomicrograph of Yolk sac tumor. A: microcystic, reticular pattern of growth of flattened cells forming a honeycomb/ spider web meshwork space enclosing mucoid basophilic material. (H&E stain; 10x). B: Schiller-Duval body; papillary structures characteristic but not pathognomonic (black arrow) (H&E stain; 40x). C: Cytological atypia of glandular patterns within cystic spaces, lined by cuboidal to columnar cells. (H&E stain; 40x).

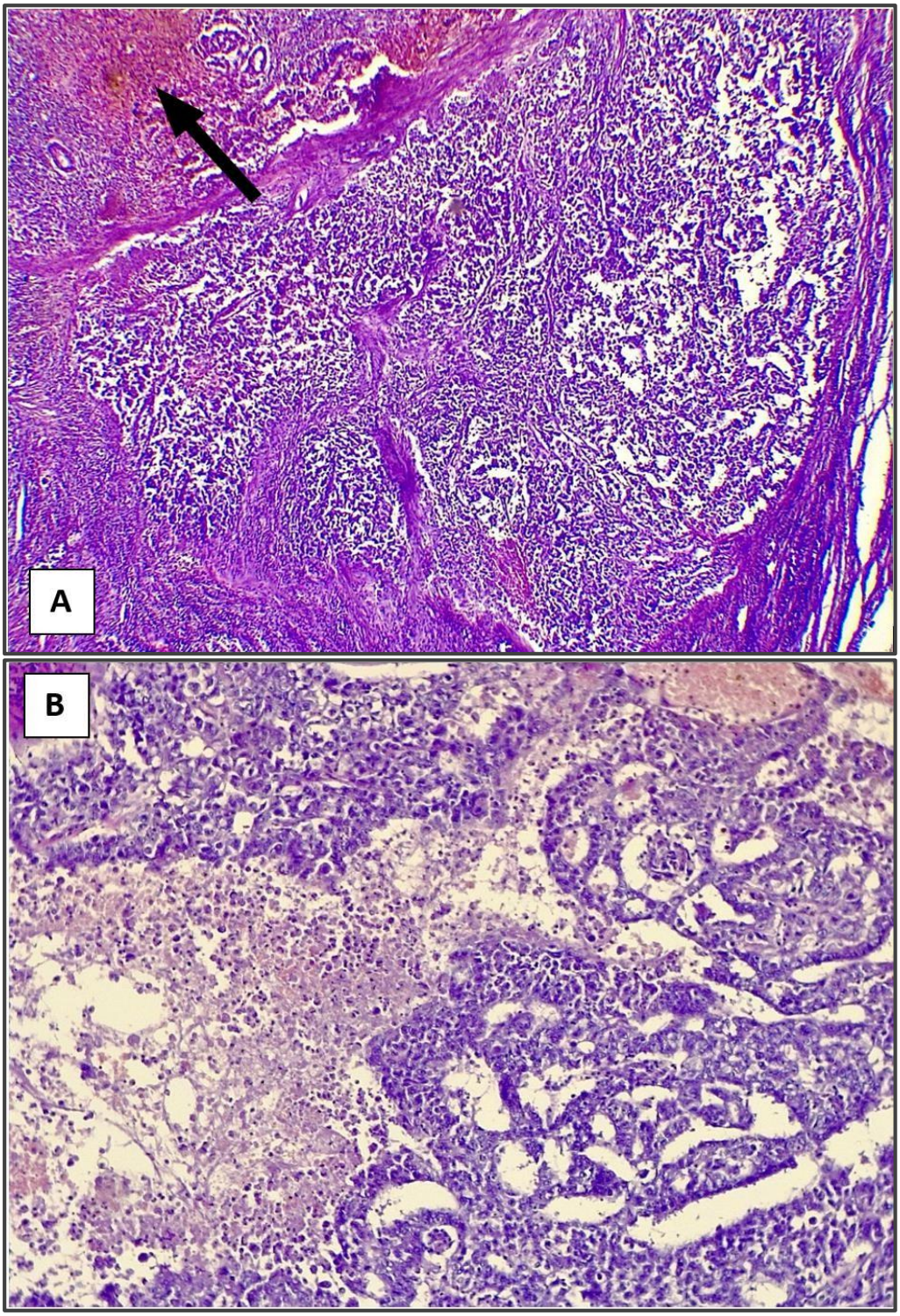


Figure (4.7): Aphotomicrograph of Embryonal carcinoma. A: solid pattern of growth of diffuse sheets of atypical cell, with area of coagulative necrosis (black arrow). (H&E stain; 4x). B: crowded and overlapping cells, large nuclei, prominent nucleoli, abundant necrosis. (H&E stain; 10x).

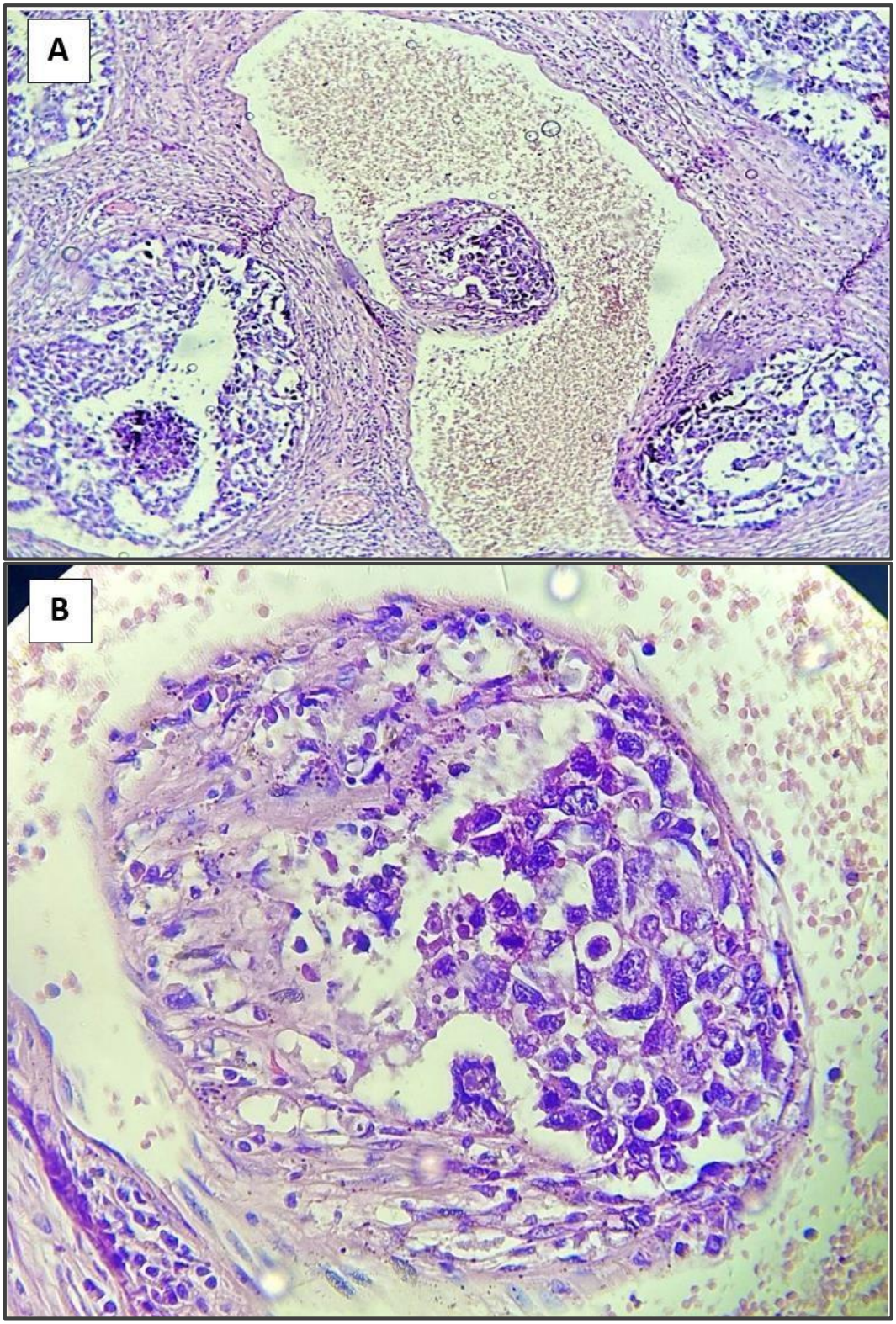


Figure (4.8): Aphotomicrograph of Vascular invasion by highly atypical irregular cell and nuclear membrane high N\C ratio with hyperchromatic nuclei cells of embryonal carcinoma. A: (H&E stain; 10x). B: (H&E stain; 40x)

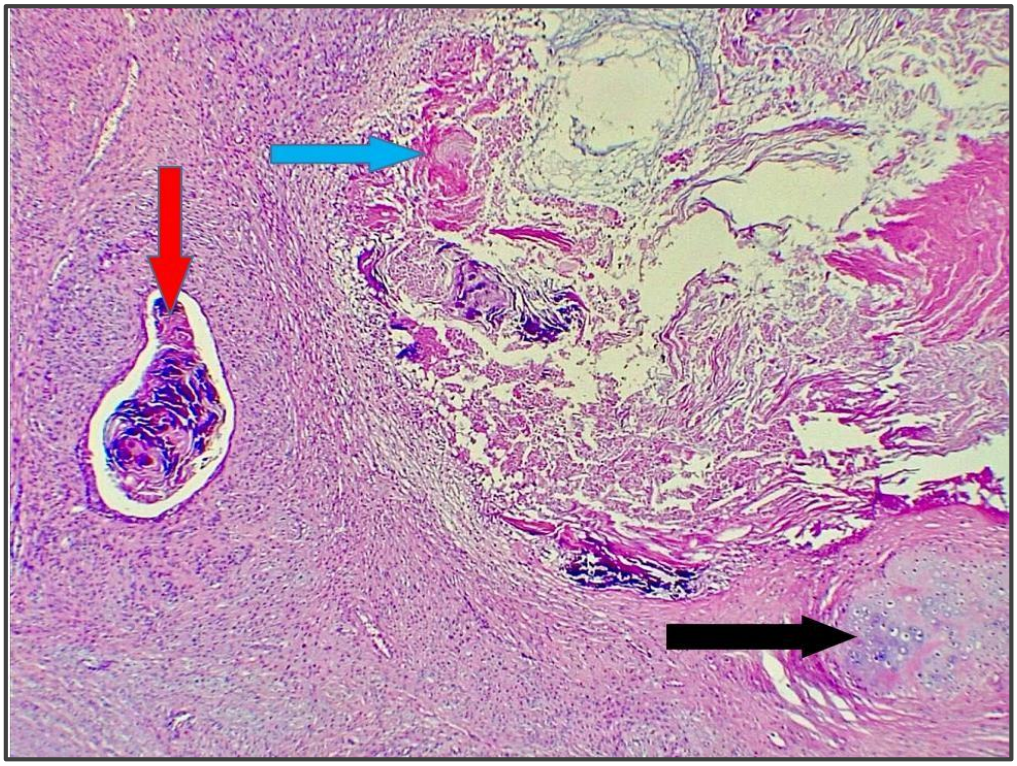


Figure (4.9): Aphotomicrograph of Testicular postpubertal teratoma showing the epithelial component (blue arrow), and immature cartilage (black arrow) within mesenchymal tissue. (H&E stain;10x).

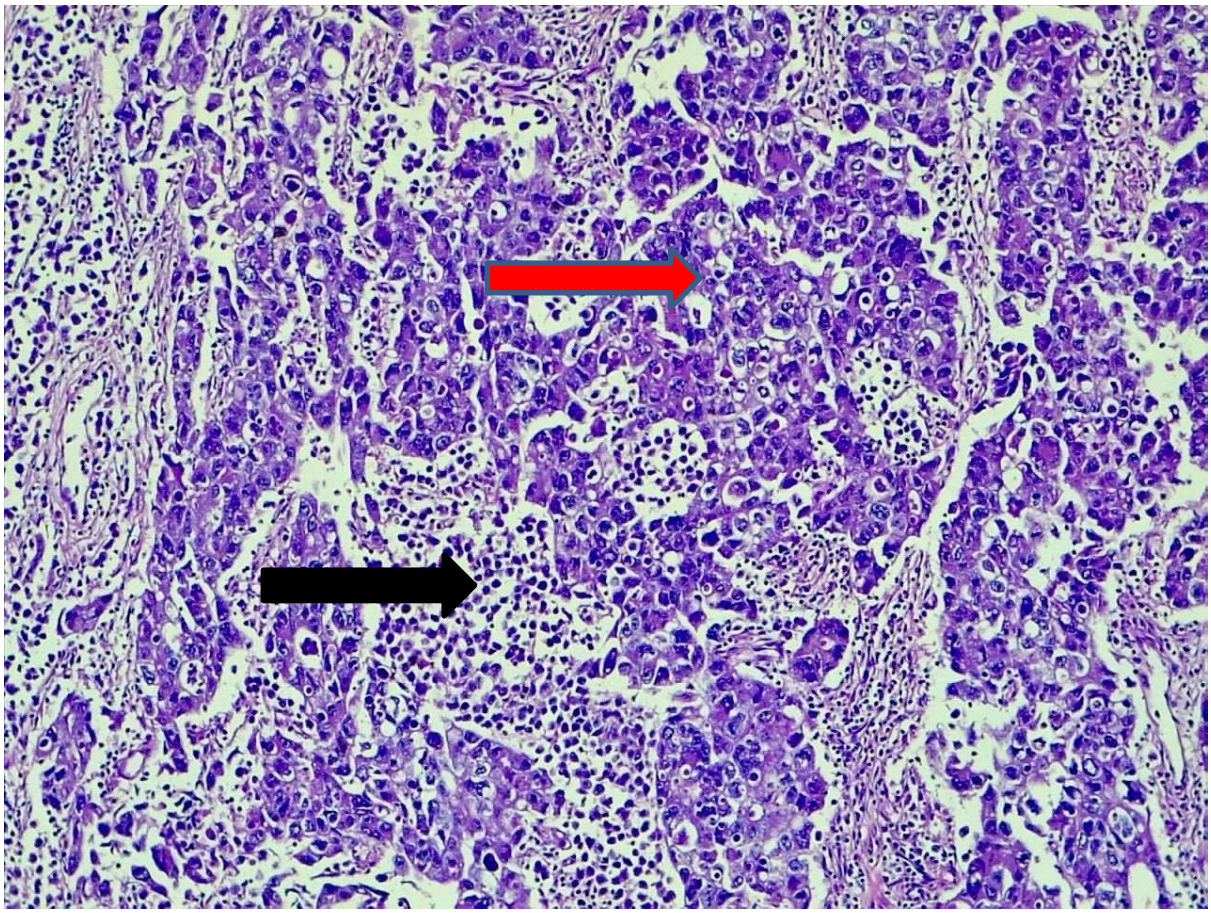


Figure (4.10): Aphotomicrograph of Mixed germ cell tumor show two components of tumor, seminoma (black arrow) and embryonal carcinoma (red arrow). (H&E stain; 10x).

DISCUSSION

Testicular cancer is expected to have killed 410 people and caused 8850 new cases in 2017.[78] Testicular neoplasms, despite they account for just around 1 percent of all solid tumors in men, are the most common solid malignancy to affect men between the ages of 15 and 35. GCTs and SCSTs are the two main types of testicular neoplasms. Seminomas and nonseminomatous tumors comprise the subgroups of GCT. The most frequent malignant tumors of the testicles in the world are seminomas.[79] The total number of testicular cancer cases in Iraq in 2022 was 258, with 15 of these cases resulting in death. The overall incidence rate was 1.58 per 100,000 population, while the mortality rate stood at 0.26 per 100,000 population.[95]

The average age of testicular tumors in this study is thirty-two years old. In particular, Specifically, sixty three cases of patients are over twenty years old, while ten cases are between eleven and twenty years and only two cases under ten years old. This indicates a slightly higher frequancy in the older age group within the studied population. The average age of testicular tumors was 32 years old in a study in Lebanon conducted by **Assi et al. (2015)**[80] A research conducted in Pakistan in 2021 by **Murtaza et al (2021)** found that the mean age was 35.1 years.[81] **Beigh et al (2017)** found a mean age of (35 years).[82] this similarity may suggest shared regional, biological and environmental factors which warrents further investigation and the seminoma was the most frequent in the study.

In this study, 53.3% of patients had tumors on their right side and 45.3% had on their left side. In **Assi et al. study (2015)**[80], the right testis (55%) was more commonly impacted than the left testis (44%). The right testis also had the highest frequency (59.3%) of tumors in **Murtaza et al. (2021)** study.[81] While **Beigh et al (2017)** reported 70.3%.[82] The fact that cryptorchidism is more common in the right testis and is linked to a 2-4 fold greater risk of testicular cancer helps to explain the predominance of the right side.[80]

Ninety-four percent of testicular tumors in this study were germ cell tumors (93.3%) followed by sex cord stromal tumors (5.4%) and lymphomas (1.3%). Seminoma at (56.9%) is the most frequant subtype of germ cell tumors followed by mixed germ cell tumors (24.3%). The most frequant histology observed in (31.2%) of the cases was mixed germ cell tumors, followed by seminoma (25%) in the **Murtaza et al. (2021)** Study.[81] According to **Beigh et al. (2017)**, germ cell tumors accounted for 89.2%) of all tumors, with lymphomas coming in second at(8.1%).[82] The most frequant form accounting for (90–95%) of cases, was germ cell tumors according to a research by **Park et al (2018).**[83] According to **Chakrabarti et al (2016)** from Central India, germ cell tumor (77.1%) was the most frequant tumor, followed by lymphoma (17.1%).[84] The slight differences in tumor subtype across these studies could be attributed to study type, sample size, the age of patients included in each study and genetic factors variation.

Elevated tumor markers have prognostic significance in addition to being crucial for diagnosis. It is impossible to overstate their significance for these patients' ongoing care.[81] The current investigation showed that serum markers (HCG, LDH, and AFP) in over half of the patients had normal serum markers at S0 (57.3%) were raised in (32%) S1 and 10.7% in S2. In addition, Seminoma patients predominantly have normal serum markers (83.7% in S0), while non- seminoma patients tend to have elevated markers, especially in S1(53.%) and S2 (25%) categories (p value = 0.001) was significant association. In **Murtaza et al (2021)** study, non-seminomatous germ cell tumors (60%) had elevated AFP and (53.3%) had elevated β HCG out of all testicular cancers, with 12.5% of seminomas having an elevated β-HCG level. LDH was only 15.6% higher.[81] **Beigh et al. (2017)** indicated that increased levels of AFP and β-human chorionic gonadotrophin were seen in preoperative assays of tumor markers in (8.10%) and (43.24%), respectively.[82] That explain Seminomas are associated with normal AFP levels because they do not produce it, and HCG is only mildly elevated in some cases with syncytiotrophoblastic cells, In contrast, non-seminomas produce AFP and/or HCG in other GCT (yolk sac tumor and choriocarcinoma) due to their differentiation into tissues that naturally secrete these markers, leading to elevated levels.[96]

The study found that among the cases of mixed testicular malignant tumors, had teratoma had 42.92%, yolk sac had 42.73%, seminoma had 26.11%, embryonal carcinoma had 42.22% and choriocarcinoma 0% case. It is crucial to determine the component and percentage of each component in mixed germ cell tumors because it has prognostic value, embryonal carcinoma germ cell tumors tend to be more aggressive and more likely to have lymphovascular invasion. the most frequent combination of mixed germ cell tumor in this study is seminoma with teratoma, followed by semionam with yolk sac and then embryonal carcinoma with yolk sac as amixed germ cell tumor[85] The most frequent combination of germ cell tumors in the **Beigh et al** study was teratoma with yolk sac which accounted for (60%) and was followed by (20%) of seminoma with teratoma and (20%) of yolk sac tumor with embryonal carcinoma.[82] While **Stang et al (2019)** reported that 80.4% of mixed germ cell tumors histology were embryonal carcinoma followed by 59% for teratoma, 46.9% for seminoma and 33.4% for yolk sac tumor.[86] In this study the teratoma was the most common among mixed germ cell tumors unlike to **Stang et al** study that result to histopathological diagnostic discrepancy in determine the percentage of each subtypes, in addition to data collection and reporting. while embyronal carcinoma globally most common among mixed germ cell tumor due to it is pluripotent nature, which allows it

to differentiate into various subtype.[97]

Stage is a crucial component in determining treatment options and prognosis evaluation. It also plays a major role in directing surgery, chemotherapy, and follow-up care plans for the best possible patient care.[12] In this study reveals that T1b was the most frequant stage at (32.0%), with lymphovascular invasion was absent in 68% of the cases. According to a retrospective investigation by **Abd et al (2023)**[87], stage I is the most frequant stage in testicular malignancies, occurring in 71.1% of cases. According to **Bal and Hasbay (2018)**, pT1 is the most common stage of testicular cancers in 94% of patients; it is followed by pT2 (89%), and pT3 (80%).[88] We found T1b was 32% in seminoma. The non- seminomas tumors which were frequently discovered in late stage, while seminomas were more likely to be discovered in stages (T1b) p value = 0.001. in comparison to **Bumbasirevic et al (2022)** studies, Seminomas are most frequently found in stage I, although around 15% of patients in this stage have subclinical metastasis[89], and it was also the most common stage in non- seminomas (53.3%) according to **Rothermundt et al. (2018)**[90] while according to **Berghen et al (2019)** about 75% of seminomas manifest at Stage I, but non- seminomatous germ cell tumors usually exhibit a greater percentage of advanced stages, such as Stage II and III.[91] The study's stage distribution of seminomas and other tumors differs due to most common nonseminomtous combination in mixed germ cell tumor was yolk sac and teratoma in this study while most aggressive tumor such as choriocarcinoma and embryonal carcinoma was few cases present as a mixed germ cell tumor that reflected why the stage T1 most common in nonseminoma combonent of mixed germ cell tumor, also the small sample size affected the result.[98]

Regarding the size of testicular tumors, the prognosis and stage of a tumor are significantly influenced by its size, which also distinguishes benign from malignant lesions. For instance, **Dieckmann et al. (2022)** reported that 50% of cases with tumors <1cm were benign, 3cm for seminoma and 3.5 cm for non- seminoma.[92] According to an additional investigation by **Kilinc et al. (2023)**, the size of the tumor, particularly over 3 cm, increased the rates of lymphatic/vascular invasion and rete testis invasion.[93] The majority of the tumors in this study (57.3%) had sizes between (4-9 cm), since there were more malignant tumors than benign tumors. The testicular tumors in the study which was carried out in Turkey by **Bal N. and Hasbay B. (2018)**, had an average size of about 3.9 cm.[88] This study also revealed that Seminomas accounted for (67.4%) at (4–9 cm) and non-seminomas (43.7%) at the same size. Statistically insignificant,but the most common stage in this study (T1b) that show the large size of tumors at presentation due to most tumor was seminoma more than 3 cm that aligns to the finding as well as lake of awareness, delayed medical consultation.[98]

The most common gross feature in this research was a homogenous, well- circumscribed, solid, fleshy tumor (62.7%), followed by the finding of a heterogeneous, cystic, and solid tumor (30.7%). According to **Ulbright et al**.**(2009)** found 40-50% of testicular tumors are seminomas, which tend to have a more uniform appearance, while 50-60% are non-seminomatous tumors, often showing more heterogeneous features. This result reasonable because seminomas were the most common tumor in this study in that they usually appear grossly as well-demarcated, homogeneous, soild tumors. Mixed tumors were the second in line in this study, and they do appear grossly as heterogeneous, cystic, and solid tumors.[94]

There were (96.0%) tumors with free margins, while only (4.0%) had positive margin in comparison to the study of **Anderson et al.(2020)** reported that approximately 2.4% (1 out of 42) of the cases had positive surgical margins.[99] **Harari et al.(2017)** study found initial diagnosis indicating positive margins were 35% and changes to 9% positive after review.[100] This highlights the importance of slide review, selecting the appropriate urological surgical approach for tumor removal from the testicle, and utilizing frozen section analysis during the procedure.

Regarding free margin in this study was 72 case was free margin and there are three cases with involved margins, and the margin was the spermatic cord there they were seminoma and postpubertal teratoma metastasis to the mediastinum, and pure embryonal carcinoma metastasis to the supraclavicular lymph node. Research on surgical margins in testicular cancer treatment, particularly concerning positive or involved margins post-orchiectomy, is limited however **Maurer T, et al (2022)**, compared partial orchiectomy and radical orchiectomy outcomes. The findings indicated that patients undergoing partial orchiectomy had a higher likelihood of positive surgical margins compared to those undergoing radical orchiectomy, regardless of clinical stage, partial orchiectomy was 95% positive margin.[101] **Gupta S, et al (2021)** study evaluated the subinguinal orchiectomy approach for testicular masses. Out of 42 orchiectomies performed via this method, three patients had involvement of the spermatic cord, with one patient having a positive surgical margin due to venous invasion.[102] most of cases was positive free margin in due to anatomical nature of testicle surround by tunica albuginea which facilitates complete tumor resection without breaching the surgical border ,most tumor confirm with in testicule allowing surgons to remove them entirely, surgical approach such as (radical orchiectomy), and testicular tumor characteristics such as seminoma tend to remain confined with in testicle for long term befor invading adjacent tissues.

CONCLUSIONS AND RECOMMENDATIONS

6.1. Conclusions

1. The mean age of patients in the study aligned with

other regional studies, emphasizing a higher frequancy in patients over 30 years.
2. Most testicular tumors in this study were germ cell tumors, specifically seminomas.
3. The presence of elevated tumor markers in non-seminomas highlighted their diagnostic and prognostic significance.
4. Larger tumors and those detected at later stages (more common in seminomas) suggested the need for early detection and intervention.

6.2. Recommendations

1) A prospective approach should be adopted, including more samples and better-equipped centers to obtain more accurate information about the association between clinical, histopathological, and gross features of the tumor.
2) Immunohistochemistry study with various immunostainings and their correlation with clinical and pathological characteristics malignant testicular tumors.
3) Molecular and genetic studies of the tumors, especially the presence of chromosome 12p gains and isochromosome i(12p), should be performed to detect those at risk.
4) A more vigilant follow-up system should be used to study the different serum markers (HCG, AFP, LDH) at the time in which they are most significant.
5) It is recommended to focus on the presence of germ cell neoplasia in situ (GCNIS) adjacent to the diagnosed testicular tumor, as it is crucial for determining whether the tumor is related to it in the classification of testicular tumors.

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