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Research Article

Leydig Cell Tumour of Testis and Scrotal Contents: A Review and Update

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Abstract

It has been iterated that even though testicular cancers are relatively uncommon, and they account for only 1% to 2% of global male cancer diagnoses, it is the commonest malignancy in men who are aged between 15 years and 44 years. It has also been iterated that testicular tumours may originate from any of the cell types that are present within the testes and the on the whole fall into the two competing categories of germ cell tumours, of which approximately 95% of testicular cancer is comprised of, and sex cord-stromal tumours which constitute the remaining 5% of testis tumours in in adults. Out of the 5% of sex cord-stromal tumours, Leydig cell tumours are regarded to be commonest tumour which is derived from the same Leydig cells which normally reside within the interstitium of testis and secrete testosterone in the presence of luteinizing hormone. Leydig cell tumours of the testis are generally known to be benign tumours and only 5% to 10% being of Leydig Cell Tumours of the testis are considered to be malignant or portend malignant features. Leydig Cell Tumours of the testis have a bimodal distribution with peaks in the prepubertal age group and between the ages of 30 to 60. Apart from this Leydig Cell Tumours of the testis, had been reported in all age groups of males including young males and the over 90-yearl old male individuals sporadically. Due to Leydig cells' hormonally active properties, Leydig Cell Tumours might manifest with precocious puberty, breast tenderness, or gynecomastia, as well as infertility problems. Leydig cell tumours are derived from Leydig cells, which are histologically packed between the seminiferous tubules of the testis and they are physiologically responsible for testosterone secretion in response to luteinizing hormone. Apart from Leydig cell tumour afflicting the testis or rare occasions, Leydig Cell Tumour may also on very rare occasions afflict the epididymis. Leydig Cell Tumour of testis may manifest in different ways including: painless mass in the testis or intra-scrotal mass, precocious puberty, including early development of pubic hair as well as penile and musculoskeletal growth beyond that expected for the child's age. Diagnosis of Leydig Cell Tumour of Testis whether benign or malignant is made based upon the histopathology examination and immunohistochemistry staining features of the tumour. Traditionally, Leydig cell tumours of the testis had been treated by the undertaking of radical orchidectomy based upon the provisional diagnosis of a malignant tumour only to find that the pathology examination of the orchidectomy specimen has confirmed features of Leydig Cell tumour of the testis which most often is benign. Radical orchidectomy alone has generally been curative for clinically benign Leydig cell tumours of testis. Testis-sparing surgery could be considered if the clinical suspicion of Leydig cell tumour is high, and pre-operative testicular serum tumour marker levels are within normal limits, and the size of the tumour is less than 2.5 cm. An intra-operative frozen section should always be undertaken to confirm benign Leydig Cell tumour of the tests, and a radical orchiectomy undertaken if the tumour is reported to be malignant. Leydig cell tumours of testis, do depict malignancy by metastasizing. About 10% of Leydig cell tumours in adults exhibit malignant biological behaviour. The only treatment for malignant Leydig cell tumour of testis is retroperitoneal lymph node dissection, in addition to the undertaking of radical orchidectomy due to the fact that they are known to be resistant to chemotherapy and radiotherapy. Because of the possibility of local recurrence of Leydig Cell Tumour of Testis, it is important for clinicians to ensure their patients undergo regular clinical and radiology imaging follow-up assessments for a long time.

Keywords: leydig cell tumour; testis; benign; malignant; diagnosis; histopathology; immunohistochemistry; electron microscopy; biopsy; radiology imaging; orchidectomy; frozen section biopsy; follow-up; lymph node dissection; tumour markers

Introduction

Leydig cell tumours are rare tumours of the testis of the gonadal interstitium which may be hormonally active and which may lead to feminizing or virilising syndromes. Leydig cell tumours do comprise about 4% of adult testicular tumours [1] [2] and 3% of testicular tumours in infants and children. These Leydig Cell Tumours of testis could be pure tumours or they could be mixed tumours with other sex cord–stromal or germ cell tumours. Leydig cell tumours usually have a local manifestation; metastases of Leydig Cell Tumours had been stated to occur in about 2.5% of cases. [1] [2] The commonest sites for metastases are lymph nodes, lung, liver, and bones. [1,3] It has been pointed out that as with germ cell tumours, the route of spread of Leydig cell tumour of testis is via hematogenous and lymphatic spread to the retroperitoneal lymph nodes. Unlike germ cell tumours; nevertheless, it has been pointed out that Leydig cell tumours of testis and scrotal contents do portend a relative lack of sensitivity to radiotherapy and chemotherapy agents. [1,4]

Clinical presentations of Leydig cell tumour of testis include the following: [1]

- A nontender palpable testicular mass or nodule;
- Precocious puberty in prepubertal boys who have androgen-secreting tumours;
- Feminizing symptoms in boys who have oestrogen-secreting tumours
- Adults who have androgen-secreting tumours generally tend to be asymptomatic.
- Manifestations in adults who have oestrogen-secreting tumours do include the ensuing: [1]
    - Loss of libido
    - Erectile dysfunction
    - Infertility
    - Gynecomastia
    - Feminine hair distribution
    - Gonadal-genital atrophy
    - Leydig cell tumours may be an incidental finding of a testicular mass upon scrotal ultrasound scan undertaken for other reasons.

Diagnosis of Leydig cell tumour of testis is confirmed by the histopathology and immunohistochemistry staining study features of the testis tumour. In cases of Leydig Cell Tumour of testis, Serum testosterone levels usually tend to raised; nevertheless, serum oestradiol levels might also be increased, especially when feminization is evident in the tumour. The results of the ensuing laboratory studies tend to be normal in patients who have pure Leydig cell tumours of testis: [1]

- Serum alpha-fetoprotein
- Serum Beta human chorionic gonadotropin
- Serum Lactate dehydrogenase
- Urine ketosteroids
- Plasma cortisol
- Adrenocorticotropic hormone stimulation test
- Dexamethasone suppression test

Ultrasound scan of scrotal contents and testis is stated to be a radiology imaging option which confirms the diagnosis, especially when clinical examination findings of patients are equivocal [1,5,6] Magnetic resonance imaging (MRI) scan could demonstrate small nonpalpable Leydig cell tumours which are not visible upon ultrasound scan. Computed tomography (CT0 scanning of the abdomen and chest radiography is stated to be indicated when malignancy is suspected. Radical orchidectomy was previously the primary treatment for Leydig cell tumours of testis, and radical orchidectomy remains in use for malignant cases. Nevertheless; the prognosis is poor for metastatic Leydig Cell tumour of testis and there are no standard treatment recommendations. Even though complete or partial remission following chemotherapy had been reported, it has been found ineffective in the majority of cases. [1,3] Testis-sparing surgery with the undertaking of enucleation of the mass is stated to be increasingly reported in the scenario of benign cases of Leydig cell tumour of testis, in both the adult and paediatric populations. [1,7,8] [9]

It has been pointed out that when Leydig cell tumours of testis are diagnosed and treated early, testicle-sparing surgery had proven to be feasible and safe and could be regarded as first-line option of treatment. Nevertheless, because of the rarity of Leydig cell Tumour of testis, and non-availability of frozen section pathology examination facilities in many hospitals in the world, it would be envisaged that many cases of Leydig Cell tumours of the testis would continue to be diagnosed pursuant to the undertaking of radical orchidectomy based upon a provisional clinical diagnosis of malignant tumour of the testis. A high index of suspicion is required to establish a pre-operative diagnosis of Leydig Cell tumour of Testis. The ensuing article on Leydig Cell Tumour of testis and Scrotal contents has been divided into two parts: (A) Overview which has discussed general miscellaneous aspects of Leydig Cell Tumour and (B) Miscellaneous Narrations and Discussions from Some Case Reports, Case Series, And Some Studies related to Benign and Malignant Leydig Cell Tumours of Testis and Epididymis.

Aims

To review and update the literature on Leydig Cell Tumour of Testis and Epididymis.

Methods

Internet data bases were searched. The search words that were used included: Leydig cell tumour of testis; Testicular Leydig cell tumour; Leydig cell tumour of testes; Intra-scrotal Leydig cell tumour; Leydig cell tumour of epididymis; and epididymal Leydig cell tumour. Seventy-one (71) references were identified which were used to write the article which has been divided into two parts: (A) Overview which has discussed miscellaneous general aspects of Leydig Cell Tumour and (B) Miscellaneous Narrations and Discussions from some case reports, case series and some studies related to Leydig tumour of testis and epididymis in human beings.

Definition / General Statements Related to Leydig Cell Tumour of Testis

The ensuing generation statements had been made related to Leydig Cell Tumour of testis: [10]

- Leydig cell tumour of testis is the commonest sex cord stromal tumour of the testis and Leydig Cell Tumour of Testis is comprised of cells simulate non-neoplastic Leydig cells.
- It has been iterated that a small minority, comprising of less than (<) 10% of cases of Leydig Cell Tumours of testis are clinically malignant. [11,12]

Essential features

The essential features of Leydig Cell Tumour of testis had been summated as follows: [10]

- Leydig cell tumour of testis is the commonest sex cord stromal tumour of the testis.
- Histology examination of specimens of Leydig Cell Tumour of testis does demonstrate the following: diffuse / nodular growth of polygonal cells with abundant eosinophilic cytoplasm, uniform round nuclei and prominent central nucleoli; Reinke crystals may be found to be present within the tumour.
- Immunohistochemistry staining studies of Leydig Cell Tumour of testis does demonstrate the following: The tumour upon immunohistochemistry staining studies exhibit positive staining for the ensuing tumour markers as follows:
    - inhibin A+,
    - calretinin+,
    - MelanA+,
    - SF1+,
    - AR+
- Features of Leydig Cell Tumour of testis that are associated with malignant potential include the following:
    - Size of tumour greater than (>) 5 cm,
    - Infiltrative borders of the tumour,
    - Evidence of cytological atypia upon pathology examination of the tumour.
    - Presence of frequent mitoses within the tumour greater than (>) 3 mitoses within (/) 10 high power fields
    - Vascular invasion of the tumour,
    - Necrosis within the tumour
- Treatment:
    - Surgical resection of the testicular tumour is regarded as the standard treatment of Leydig Cell Tumour of testis and surgical resection of Leydig cell tumour of testis is regarded as curative for non-metastasizing Leydig cell tumours of testis.
- Prognosis of Leydig Cell Tumour of Testis:
    - It has been iterated that the overall 5-year survival following the undertaking of orchidectomy for Leydig Cell Tumour of testis is higher than (>) 90%

Terminology

- Another term that is utilized for Leydig cell tumour of testis is interstitial cell tumour of testis; but this name is iterated to be an obsolete terminology [10]

Epidemiology

The epidemiology of Leydig Cell Tumour of testis has been summated as follows: [10]

- It has been documented that Leydig cell tumour of testis does constitute 1% to 2% of testicular tumours in adults and 3% to 6% of testicular tumours in prepubertal males [13,14]
- Leydig Cell Tumour of testis is mostly sporadic found or reported, and Leydig Cell Tumour is rarely associated with hereditary leiomyomatous and renal cell carcinoma syndrome [15]
- Leydig cell tumour of testis does tend to occurs at any age with 2 peaks that are reported in the 5 years to 10 years group and in the 30 years to 60 years group of patients. [13]

Sites

The sites within the testis that tend to be afflicted by Leydig Cell Tumour of testis include the following: [10]

- The parenchyma of the testis.
- On rare occasions, Leydig cell tumour tends to be found within ectopic rests of Leydig cells in the epididymis. [16]

Pathophysiology

The pathophysiology of Leydig Cell Tumour of testis has been summated as follows: [10]

- Leydig cell tumour of testis produces androgen, mainly testosterone and this production of androgen can cause symptoms related to the androgen.
- It has been stated that Leydig Cell Tumour of Testis can also produce oestrogen by either direct production of oestradiol or by peripheral aromatization of testosterone [17]

Aetiology

The ensuing iterations had been made regarding the aetiology of Leydig Cell Tumour of Testis. [10]

- Little is known about the aetiology of Leydig Cell Tumour of Testis.
- There is a rare association of Leydig Cell Tumour of Testis with germline fumarate hydratase mutations in patients with hereditary leiomyomatosis and renal cell carcinoma syndrome and activating mutations of the luteinizing hormone receptor [18]

Clinical features

The clinical manifestations of Leydig Cell Tumour of testis had been summated as follows: [10]

- Higher than (>) 90% of Leydig Cell Tumours of testis are benign tumours.
- Leydig Cell Tumour of Testis is usually a unilateral tumour, and on rare occasions, Leydig Cell Tumour of Testis is a bilateral tumour.
- Leydig Cell Tumour of testis manifests as a painless testicular enlargement
- Children
    - In children Leydig Cell Tumour of Testis in children may manifest with precocious puberty which has been caused by the production of androgen by the tumour.
    - Leydig Cell Tumour of Testis in children may manifest with gynecomastia and breast tenderness related to the production of oestrogen by the tumour. [17]
- Adults

- In adults, Leydig Cell Tumour of testis may manifest with gynecomastia.
- In adults, Leydig Cell Tumour of Testis, may manifest with infertility, with the presentation of loss of libido and erectile dysfunction [19]
- In adults, Leydig Cell Tumour of testis may on rare occasions manifest with Cushing syndrome. [20]

- Malignant Leydig Cell Tumours of Testis:
  - Malignant Leydig Cell Tumours of Testis may rarely manifest with metastases, usually related to the retroperitoneal lymph nodes that are enlarged or pulmonary metastases. [21,22]

Diagnosis [10]

- The diagnosis of Leydig Cell Tumour of Testis is made and confirmed by histopathology examination and immunohistochemistry staining study features of the tumour.

Laboratory tests

- Routine Haematology and biochemistry blood tests as well as Germ Cell Tumour Marker level Tests including Serum Beta-Human Chorionic Gonadotrophin (BHCG), Alpha Fetoprotein (AFP), and LDH, tend to be done in the general assessment of patients who have Leydig Cell Tumours of Testis as part of their general assessment but generally, the results would tend to be normal. Sex Hormone Level testing also tends to be undertaken upon the finding of Leydig Cell Syndrome or for the evaluation of gynaecomastia and precocious puberty features.
- Urinalysis, Urine microscopy and urine culture and sensitivity tend to be undertaken in the general assessment of patients who have Leydig Cell Tumour of Testis, and the results would usually be normal unless the patient has a urinary tract infection which is not directly related to the testicular tumour.
- In cases of Leydig Tumour of Testis, Serum testosterone and oestrogen levels may be found to be raised above the normal range.
- Patients who have Leydig Cell Tumour of Testis, may have lower sperm concentration, lower total sperm count and motility. [19]

Radiology Imaging

- Ultrasound Scan: Ultrasound scan of testes and scrotal contents, abdomen, pelvis and groin tend to be undertaken in the initial assessment of patients who have Leydig Cell Tumour of Testis, and the scan would enable the radiologist and clinician ascertain the site, the size and sonography features of the tumour. Since Majority of Leydig Cell Tumour of the testis, are benign tumours, there would be no ultrasound scan evidence of tumour within the abdomen and retroperitoneum including the lymph nodes.
- Computed Tomography (CT) Scan: CT scan of testes and scrotal contents, abdomen, pelvis and groin could also be undertaken in the initial assessment of patients who have Leydig Cell Tumour of Testis, and the scan would enable the radiologist and clinician ascertain the site, the size and CT Scan features of the tumour. Since Majority of Leydig Cell Tumour of the testis, are benign tumours, there would be no CT scan evidence of tumour within the abdomen and retroperitoneum including the lymph nodes.
- Magnetic Resonance Imaging (MRI) Scan: MRI scan of testes and scrotal contents, abdomen, pelvis and groin could also be undertaken in the initial assessment of patients who have Leydig Cell Tumour of Testis, and the scan would enable the radiologist and clinician ascertain the site, the size and MRI Scan features of the tumour. Since Majority of Leydig Cell Tumour of the testis, are benign tumours, there would be no MRI scan evidence of tumour within the abdomen and retroperitoneum including the lymph nodes.
- The radiology imaging scan assessment features of the testicular lesion in Leydig Cell Tumour of the testis tends to be non-specific findings.
- Upon ultrasound scan, the tumours are found to be generally well defined, homogeneous hypoechoic, small solid masses with hypervascularity. [17]
- The radiology imaging assessment of Leydig Cell Tumour of the testis may demonstrate cystic areas within the testis.

Prognostic factors

The prognostic factors of Leydig Cell Tumours of the testis had been summated as follows: [10]

- Benign Leydig Cell Tumours: The prognosis of Benign Leydig Cell Tumours of testis is excellent, and its treatment by the undertaking of surgical removal of the tumour is curative.
- Malignant Leydig Cell tumours: The prognosis of Malignant Leydig Cell Tumours of testis is poor survival, and most patients with develop metastatic disease leading to death. [22]

Treatment

The treatment of Leydig Cell Tumour of the testis has been summarized as follows: [10]

- Benign Leydig Cell Tumours
  - Orchidectomy has tended to be the treatment for Benign Leydig Cell Tumour of Testis.
  - The undertaking of testis sparing surgery in small Leydig Cell Tumours of Testis tumours is a safe alternative treatment option. [11,19,11]

- Malignant Leydig Cell Tumours
  - Orchiectomy with retroperitoneal lymph node dissection can be curative in cases of Malignant Leydig Tumours of Testis.
  - It has been pointed out that in cases of Malignant Leydig Cell Tumours of Testis, there tends to be no significant response to radiotherapy or chemotherapy [11,23]

Gross macroscopy Examination Features.

The macroscopy examination features of Leydig Cell Tumour of the Testis, had been summated as follows: [10]

- Macroscopy examination of a Leydig Cell Tumour of Testis does demonstrate a well- circumscribed, solid homogeneous mass within the testis.
- Gross examination of a specimen of Leydig Cell Tumour of Testis does tend to demonstrate a tumour that measures usually less than (<)5 cm in size.
- Gross examination of a specimen of Leydig Cell Tumour of Testis does tend to demonstrate a tumour that has a golden brown or brownish green cut surface.
- Gross examination of a specimen of Leydig Cell Tumour of Testis does tend to demonstrate a tumour may have hyalinization and calcification present within the tumour.
- Gross features upon macroscopy examination of a Leydig Cell Tumour of Testis that is indicative of malignancy include the following: [17]
  - A Large size of the tumour: A tumour that measures higher than (> 5) cm.

- A Leydig Cell Tumour of Testis that has infiltrative margins.
- Haemorrhage and necrosis
- Extra-testicular extension of the tumour

Frozen section description of Leydig Cell Tumour of Testis

The frozen section examination features of Leydig Cell Tumour of Testis had been summarized as follows: [10]

- Frozen section examination of specimens of Leydig Cell Tumour of Testis does demonstrate diffuse sheets of uniform polygonal cells with round nuclei, central nucleoli, abundant granular, eosinophilic cytoplasm and rectangular to club shaped Reinke crystals [24]
- Frozen section examination of specimens of Leydig Cell Tumour of Testis does demonstrate that touch imprint and scrape smear preparations are better to highlight Reinke crystals [25]

Microscopy (histopathology) examination features of Leydig Cell Tumours of Testis description

The microscopy (histopathology) examination features of Leydig Cell Tumours of Testis had been summarized as follows: [10]

- Architecture:
  Microscopy histopathology examination of Leydig Cell Tumour of Testis does demonstrate the ensuing patterns:
  - Diffuse or nodular with fibrous bands within the tumour
  - Uncommon patterns including the following patterns:
    - Insular pattern,
    - Trabecular pattern,
    - Pseudo-tubular pattern,
    - Ribbon-like pattern,
    - Trabecular pattern,
    - Spindled and microcystic pattern [26]
- Cytology examination Features
  Cytology examination features of Leydig Cell Tumour of the Testis had been summarized as follows: [10]
  - Polygonal cells associated with abundant eosinophilic granular cytoplasm, uniform round nuclei and prominent central nucleoli; rarely, nuclei might have a ground glass appearance.
  - Uncommon cell types can also be seen and some of these include the following:
    - Scant cytoplasm,
    - Foamy cytoplasm
    - And spindling [27]
  - Lipofuscin pigment might be present: golden yellow on H&E stain, red-purple granular appearance upon PAS stain.
  - Binucleated and multinucleated cells may be present within the tumour.
  - Reinke crystals which are pathognomonic of Leydig Tumour of Testis and these tend to be identified in only up to 30% (degradation / dissolution by formalin fixation); intracytoplasmic, rarely extracellular
  - Mitosis: rare
  - Mild nuclear atypia permissible
  - Occasionally, psammoma bodies, calcification, osseous and adipocytic metaplasia may be identified [27]
- Microscopic features that are indicative of malignancy (taking note of the fact that majority of malignant tumours will have more than 2 of these features): [21]
  - Tumour measuring 5 cm.
  - Tumour with infiltrative borders
  - Evidence of cytological atypia
  - Finding of frequent mitoses (> 3/10 high power fields)
  - Evidence of vascular invasion of the tumour
  - Evidence of necrosis within the tumour.

Cytology description

The cytopathology examination features of Leydig tumour of the testis had been summarized as follows: [10]

- Fine needle aspiration is rarely undertaken unless within a metastatic lymph node.
- Cellular smears with dis-cohesive cells that have eccentric round nuclei, that are evenly distributed chromatin, evidence of prominent nucleoli and abundant eosinophilic granular cytoplasm.
- Naked nuclei tend to be common.
- Cytoplasm in Leydig Cell Tumour of Testis may be vacuolated due to lipid accumulation.
- Presence of nuclear grooves, binucleation and multinucleation might be identified.
- Nuclear pseudo-inclusions and Reinke crystals could be visualized.
- There are no cytological features to differentiate Leydig cell tumours of testis from nodular Leydig cell hyperplasia of testis [28]

Positive Immunohistochemistry stains

It has been iterated that Leydig Cell Tumours of the Testis Cells do exhibit positive immunohistochemistry staining for the following markers: **[10]**

- Inhibin A.
- Calretinin
- Melan A
- Androgen receptor (AR)
- And Steroidogenic factor 1 (SF1)
- Insulin-like 3 (INSL3) are variably reported to be positive
- CD99 (MIC2) membranous staining [29]

Negative Immunohistochemistry stains

It has been iterated that Leydig Cell Tumours of the Testis Cells do exhibit positive immunohistochemistry staining for the following markers: [10]

- SALL4.
- OCT4, and
- Beta catenin. [30]
- Cytokeratin
- Chromogranin
- Synaptophysin
- S100, and
- PLAP (rarely focally positive)

Electron microscopy description

The electron microscopy examination features of Leydig Cell Tumour of Testis had been summarized as follows: [10]

- Reinke crystals are diagnostic of Leydig Cell Tumour of Testis.

- The electron microscopy appearance of the tumour depends upon the plane of sectioning: prismatics, hexagonal lattices or hexagonal microtubules with parallel lines.
- Located within the cytoplasm but could be visualized within the nucleus or interstitium

- Abundant smooth endoplasmic reticulum, mitochondria with tubulovesicular cristae, numerous lipid droplets and lipofuscin granules [31**]**

Molecular / cytogenetics description

The molecular and cytogenetics examination features of Leydig Cell Tumour of Testis had been summarized as follows: [10]

- DNA aneuploidy is associated with malignant Leydig cell tumours, benign Leydig cell tumours are diploid.
- Gain of chromosome X, 19 or 19p and loss on chromosome: 8 and 16 are the most frequent findings [32]
- Somatic GNAS (guanine nucleotide binding protein, alpha stimulating activity polypeptide 1)
    - Activating mutation (R201S) has been reported [33]

Differential diagnosis

The differential diagnoses of Leydig Cell Tumour of Testis had been summated as follows: [10]

Testicular tumour of adrenogenital syndrome or testicular adrenal rest tumours:

- These arise in males who have congenital adrenal hyperplasia.
- Hormonal profile with high 17-hydroxyprogesterone and adrenal androgen levels and frequent regression following the undergoing of dexamethasone treatment.
- These are usually bilateral, dark brown nodules.
- Spotty cytological atypia, abundant cytoplasmic lipofuscin pigment but no Reinke crystals, broad bands of hyalinized collagenous stroma
- **Androgen receptor** and **INSL3** negative.
- More frequently positive for neuroendocrine markers (synaptophysin) and CD 56 [34]

Leydig cell hyperplasia:

- Interstitial growth pattern with small nodules < 0.5 cm; usually bilateral and multifocal
- Diffuse positivity for **INSL3**
    - Reference: [35]

Granular cell tumour.:

- Abundant granular cytoplasm, no Reinke crystals
- Positive for S100, CD68 and PASD and negative for Inhibin A, SF1, and Melan-A.

Large cell calcifying Sertoli Cell Tumour. [10]

- Large cell calcifying Sertoli Cell tumour is stated to be associated with Carney complex
- Large cell calcifying Sertoli Cell Tumour is stated to contain Sertoli cells that contain abundant eosinophilic cytoplasm and extensive calcification, variable tubular or intratubular growth, stroma more myxoid and neutrophil rich, no Reinke crystals.
- It has been documented that Large Cell Calcifying Sertoli Cell Tumour cells do exhibit positive immunohistochemistry staining for SMA and for desmin as well as more diffuse positive staining for S100**.** [36]

Malakoplakia: [10]

- It has been iterated that Malakoplakia of testis involves tubules and interstitium with xanthogranulomatous inflammation and Michaelis-Gutmann bodies.

Seminoma: [10]

- It has been iterated that Seminoma of testis is in the differential diagnosis of Leydig cell tumour of testis with clear cytoplasm.
- It has been stated that Seminoma of testis is associated with **germ cell neoplasia in situ** which contains, fibrous septae, lymphocytic infiltrate and granulomas.
- It has been iterated that Seminoma of testis tumour cells do exhibit positive immunohistochemistry staining for SALL4 as well as for OCT4.
- It has been iterated that Seminoma of testis tumour cells do exhibit negative immunohistochemistry staining for Inhibin A, Melan A as well as for SF1.

[B] Miscellaneous Narrations and Discussions from Some Scase Reports, Case Series, And Studies Related to Leydig Cell Tumours of Testis.

Ruf et al. [11] stated that Leydig-cell tumours (LCT) of the testis are poorly understood clinically. Ruf et al. [11] analysed the clinical characteristics of LCT in a large patient sample and compared their findings with corresponding data of germ-cell tumours (GCT). Ruf et al. [11] reported that in a sample of 208 patients who had been treated during between 1995 and 2017 in 33 institutions, the following characteristics were registered: age, manifesting symptoms, primary tumour size, testis-sparing surgery (TSS) or orchidectomy, malignancy, laterality, medical history, and outcome. Ruf et al. [11] reported that their data analysis included descriptive statistical methods and logistic regression analysis. Ruf et al. [11] summarized the results as follows:

- The ratio LCT:GCT was 1:23 (4.4%).
- The findings were as follows: median age 41 years, undescended testis 8%, bilateral LCTs 3%, malignant LCT 2.5%, contralateral GCT 2.5%, incidental detection 28%, scrotal symptoms 43%, infertility 18%, elevated oestradiol levels 29%.
- TSS was undertaken in 56% with no local relapse.
- Out of the patients who had malignant LCT, one was cured through surgery.

Ruf et al. [11] made the ensuing conclusions:

- LCT is rare, with a relative frequency (relative to GCT) of 1:23.
- Malignancy was found in 2.5%. LCT and GCT shared a number of clinical features, for example: bilaterality, history of undescended testis, and manifesting age.
- TSS is safe in benign LCT.
- Surgery is the treatment of choice in malignant LCT.

Pozza et al. [19] undertook a study in order to understand their question regarding when should 'not so rare' Leydig cell tumours (LCTs) of the testis be suspected, diagnosed, and treated? Pozza et al. [19] iterated the ensuing summations related to their study:

- LCTs are more frequent than it has been generally believed, and LCTs are associated with male infertility, cryptorchidism and gynecomastia, and LCTs should be treated conservatively (in compliant patients) with active surveillance, which does appear to be a safe alternative to surgical enucleation of the testicular tumour.
- With regards to, what had been known already pertaining to Leydig Cell tumour of testis, increasing referrals for testicular radiology-imaging had led to an increase in findings of LCTs.
- The features and natural history of these tumours of the testis do remain largely unknown, as the available studies had been small and heterogeneous.
- LCTs were previously treated aggressively, and follow-up data were lacking.

With regards to the Study design, size, and duration, Pozza et al. [19] reported that a case-cohort study of consecutive patients who were diagnosed with LCTs over a 10-year period was prospectively enrolled from 2009 to 2018 and they were compared to matched cohorts of patients with seminomas or no testicular lesions that were screened in the same timeframe. Relating to the participants/materials, setting, methods, Pozza et al. [19] reported the following:

- Out of the 9949 inpatients and outpatients who were referred for scrotal ultrasound, a total of 83 men who had LCTs had been included in the study.
- Enrolled subjects had undergone medical history taking and clinical examination and they were asked to undergo routine laboratory blood tests, hormone investigations (FSH, LH, total testosterone, oestradiol, inhibin B, sex hormone-binding globulin (SHBG), prolactin), and semen analysis.
- The Patients who consented also underwent contrast-enhanced ultrasound, elastography, gadolinium-enhanced scrotal magnetic resonance imaging, and HCG stimulation test (5000 IU i.m.) with serum total testosterone and oestradiol measured at 0, 24, 48, and 72 hours.

Pozza et al. [19] summated the main results of their study and the role of chance as follows**:**

- In total, 83 patients who were diagnosed as having LCTs were compared against 90 patients who had been diagnosed as having seminoma and 2683 patients without testicular lesions (NoL).
- LCTs were diagnosed based upon pathology examination of testis tumour specimen that were obtained by enucleation that amounted to 48.2% the cases, orchidectomy which accounted for 13.3% of the patients, or clinical surveillance which amounted to 38.5% of the patients.
- Testicular volume, sperm concentration, and morphology were lower ($P = 0.001$, $P = 0.001$, and $P < 0.001$, respectively) in patients who had LCTs in comparison with in the NoL group.
- FSH, LH, and SHBG were higher, and the testosterone/LH ratio was lower in LCTs in comparison with in the NoL group ($P < 0.001$).
- The LCT group demonstrated higher SHBG ($P = 0.018$), lower sperm concentration ($P = 0.029$), and lower motility ($P = 0.049$) than the seminoma group.
- Risk factors for the development of LCTs included cryptorchidism ($\chi2 = 28.27$, $P < 0.001$), gynecomastia ($\chi2 = 54.22$, $P < 0.001$), and low testicular volume ($\chi2 = 11.13$, $P = 0.001$).
- Five cases were recurrences or bilateral lesions; none of the LCT patients had developed metastases during follow-up over a median follow-up period of 66 months.

Pozza et al [19] also stated the ensuing:

- With regards to the limitations, and reasons to exercise caution, their study had some limitations. Firstly, Serum Beta Human Chorionic Gonadotrophin, (HCG) and second-line diagnostic investigations were not available for all-of the tumour patients. Secondly, their department, was a referral centre for infertility, thus a selection bias might have altered the baseline features of the LCT population. Nevertheless, given that the comparison cohorts were also from the same centre and had been managed with a similar protocol, they did not expect a significant effect.
- Regarding the wider implications of their findings, LCTs were strongly associated with male infertility, cryptorchidism, and gynecomastia, supporting the postulate that testicular dysgenesis syndrome does play a role in their development.
- Patients who have LCTs are at a greater risk for the development of endocrine and spermatogenesis abnormalities even when the tumour has been resected, and hence does require long-term follow-up and prompt efforts to preserve fertility after the diagnosis of LCTs.
- LCTs have a good oncological prognosis when they are diagnosed early, as tissue-sparing enucleation is curative and should replace the undertaking of orchidectomy.
- Conservative surgery and, in compliant patients, active surveillance via the process of clinical and radiology imaging follow-up are safe options; nevertheless, they do the monitoring of testicular failure and recurrence.

Abe et al. [37] reported a 33-year-old man who was referred to their hospital for male infertility with painless swelling of his left scrotal content. He underwent a left high orchidectomy was based upon a diagnosis of left testicular tumour. Histologically, the testicular mass was a Leydig cell tumour.

Shiraishi et al. [38] stated the following:

- A Leydig cell tumour is an uncommon disease entity which does afflict the testis.
- On rare occasions, Leydig Cell Tumour, had been regarded to be related to male infertility.

Shiraishi et al. [38] reported a case study of a Leydig cell tumour in a single testis manifesting as male infertility. Shiraishi et al. [38] reported A 38-year-old male who was referred to their hospital because of a tumour within his right testis. He had undergone left orchidectomy when he was one year old because of a testicular tumour. During an examination related to his infertility, he had ultrasound scan which had demonstrated a 1 cm tumour. His serum tumour markers were all within normal ranges. The results of his hormonal examination showed that the results of his serum luteinizing hormone (LH) 30.3 mIU/ml (1.5-12.4) and follicle stimulating hormone (FSH) 11.9 mIU/ml (1.7-8.6) were higher than the normal limits, but his serum total testosterone (total T) and oestradiol (E2) were within normal ranges. He underwent firstly, testicular tumour enucleation, and then testicular sperm extraction (TESE) was undertaken from a macroscopically normal site of the testis. Histopathology examination diagnosis of the testis tumour as a benign Leydig cell tumour encompassed by Leydig cell hyperplasia. For 12 months following his operation there had not been any recurrence of his testis tumour. Even

though his high serum LH and FSH had persisted, his serum total T and E2 were within normal ranges.

Komai et al. [39] reported a case of Leydig cell tumour of the post-pubertal cryptorchid testis with the main manifestation of male infertility. Komai et al. [39] reported a 36-year-old man who had consulted another clinic and his semen analysis had demonstrated oligospermia. A solid mass was found palpable within his right inguinal undescended testis. He was referred to the hospital of Komai et al. [39] for treatment of the testicular tumour. He underwent a right inguinal orchidectomy and pathology examination diagnosis was Leydig cell tumour with no malignant findings. After the surgery improvement was seen in his semen analysis. There was no evidence of recurrence of his tumour 9 months after surgery.

Medina Pérez et al. [40] reported a case of Leydig cell tumour in a cryptorchid testis. Medina Pérez et al. [40] reported a 55-year-old man who had presented with no specific scrotal symptoms. A cryptorchid testis was found upon his clinical examination and the patient underwent orchidectomy. During his operation, a solid, well-circumscribed, round nodule of 0.8 cm in diameter was found in an atrophic testis. Histopathology examination of the tumour showed a Leydig cell tumour with crystals of Reinke and immunostaining with vimentin.

Efthimiou et al. [41] 72-year -old man who had manifested with a 2-month history of painless left testicular enlargement. In the past, he had had undergone orchidopexy of the contralateral testis for cryptorchidism. His clinical examination demonstrated an irregular hard swollen left testis and a small right one. He did not have any gynecomastia. The results of his serum tumour markers (Alpha-fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase) were negative for malignancy. He had ultrasound scan of testes which demonstrated an 11 cm × 6-cm nonhomogeneous testicular mass with multiple hypoechoic nodules. Metastases were not evident in the staging investigations. He underwent a left radical orchidectomy. Histopathology of the specimen demonstrated malignant LCT. Immunohistochemistry was positive for inhibin A, and Ki-67, and immunohistochemistry staining studies of the tumour had shown that the tumour was negative for pancytokeratin, cytokeratins AE1/AE3, cytokeratins 8/18, epithelial membrane antigen, carcinoembryonic antigen, alpha-fetoprotein, human chorionic gonadotropin, vimentin, CD30, and actin. His post-operative hormone profile demonstrated hyper-gonadotropic hypogonadism. The patient was placed on testosterone substitution treatment and retroperitoneal lymph node dissection was suggested, but he refused to undergo any further operation.

Michalec et al. [42] stated the following:

- Leydig cell tumours arising from the gonadal stroma represent one per cent of all testicular tumours.
- They may occur at any age.
- Ten per cent of cases are malignant.
- There is no evidence that confirms that they are prone to develop in undescended testis.

Michalec et al. [42] reported the rare case of leydigioma in 71-year-old man with unilateral cryptorchidism. Michalec et al. [42] stated that only a few cases had been reported as arising from undescended testis.

Taguchi et al. [43] reported an 85-year-old man who had visited their hospital with a complaint of painless swelling of his right testis. He underwent a right high orchiectomy under the diagnosis of right testicular tumour. Histopathology examination of the right testicular tumour specimen confirmed the diagnosis of Leydig cell tumour. Taguchi et al. [43] stated that they had reviewed 86 cases of this tumour that had been previously reported in Japan and to their knowledge, their patient is the oldest one who had been treated in Japan.

Harada et al. [44] reported a 63-year-old man who had visited their hospital with a symptom of painless swelling of his left scrotum. He underwent left trans-inguinal high orchidectomy since he had ultrasound scan which had suggested a testicular tumour. Histologically, the testicular mass was a Leydig cell tumour of testis.

Sugimoto et al. [45] reported a 40-year-old man who was referred to their hospital with gynecomastia and painless swelling of his right scrotum. He had ultrasound scan which demonstrated 15 mm x 10 mm mass with low echogenicity within his right testis. He underwent right high orchidectomy. Histologically, Reinke's crystals and capsular invasion by tumour cells were found. The final diagnosis, the tumour was a malignant Leydig cell tumour of the testis.

Bertola et al. [46] stated that Leydig cell tumours (LTC) are uncommon neoplasms that arise from gonadal stroma which account for 1% to 3% of all testicular tumours. Bertola et al. [46] reported a case of LCT in a 36-year-old man who had been suffering from painful bilateral gynecomastia for one year. The results of his endocrine function tests showed decreased gonadotropin concentrations, and reduction of testosterone/oestradiol ratio. He had ultrasound scan which revealed a 10 mm to 12 mm hypoechoic area within his right testis, which was not evident upon his clinical examination. He underwent right orchidectomy and histological examination of the orchidectomy specimen confirmed the supposed existence of an LCT. After surgery, the gynecomastia had completely disappeared, and his hormonal alterations had returned to normal.

Dounis et al. [47] reported a man had manifested with left painful breast enlargement and impotence as his main complaints of a right cryptorchid young man. He underwent ultrasound scan which demonstrated a hypoechoic mass which was found in his right testis. He underwent right orchidectomy and post-operatively the increased level of his serum oestrogens and the decreased levels of testosterone were normalized 6 months following his orchidectomy, his gynecomastia had subsided considerably, and his impotence had improved quite satisfactorily.

De Jong et al. [48] reported one case of a bilateral testicular Leydig cell tumour in a man of 29 years old. They stated that there are few cases of such tumours which had been reported in the literature and that Gynecomastia forced the patient to consult his doctor. His hormonal profile was found to be practically normal; nevertheless, his serum oestradiol level was at the limit superior of normal range, and his serum testosterone level was at the limit inferior (lower range). His testicular palpation was normal. He had scrotal ultrasound scan which confirmed the diagnosis of testicular tumour. They recommended that scrotal ultrasound scan should be performed in every patient who has unexplained gynecomastia. There was no metastasis in the reported patient. Before the treatment, the patient's sperm conservation was performed (his sperm was normal). The reported surgical treatment sequence for the patient who did not have a child was the next one as follows: 1. inguinal orchidectomy was undertaken at the side of bigger tumour. Histological diagnosis was the benign Leydig cell tumour; 2. one month later, an inguinal orchidotomy at the other side was undertaken and the palpable tumour of 9 mm was removed. The extemporaneous biopsy confirmed the same diagnosis as at the other side; 3. one year later, there is no evidence metastasis, and the woman of the reported patient became pregnant.

Carmignani et al. [9] undertook a long-term evaluation of conservative surgical treatment of benign Leydig cell tumour. Carmignani et al. [9] performed a multi-centre retrospective clinical study at 6 European centres. They examined case files of all patients who were diagnosed as having Leydig cell tumour and treated with conservative surgery. Patients underwent clinical examination, hormone and tumour marker assays, scrotal and abdominal ultrasound, chest x-ray, and an endocrinological examination. Carmignani et al. [9] summarized the results as follows:

From 1987 to 2006, 22 patients who had Leydig cell tumour had undergone conservative surgery. The mean patient age of the patients was

35 years and the ages of the patients had ranged between 5 years and 61 years. The mean follow-up of the patients was 47 months and the follow-up of the patients had ranged between 1 month and 230 months. No local recurrence or metastasis was found. The patients presented with symptoms as follows: a palpable testicular nodule in 3 patients, that amounted to 13.7% of the patients or a nodule which was diagnosed by ultrasound scan on 15 patients, that amounted to 68.2% of the patients, gynecomastia by 2 patients, which amounted to 9.1% of the patients, precocious pseudo-puberty by 1 patient, which amounted to 4.5% of the patients, or scrotal pain by 1 patient, which amounted to 4.5% of the patients. Three patients were monorchid after their undergoing of contralateral orchidectomy for inguinal hernia repair (1 patient, 28 years before surgery) and nonseminomatous germ cell tumour (2 patients, 1 month and 6 years before surgery). The diagnosis after frozen section biopsy examination of the testis specimen was Leydig cell tumour in 20 of 22 cases that amounted to 91.0% of the cases. The mean histological size of the nodule was 1.11 cm, and this had ranged from 0.5 cm to 2.5 cm. Preoperative serum FSH and LH levels were high in 4 patients. Serum tumour marker levels were normal before and after surgery. Follow-up was undertaken for all patients every 3 to 6 months with clinical examination, tumour marker levels assessments, scrotal and abdominal ultrasound scan, chest x-ray. Six patients which amounted to 27.3% of the patients underwent abdominal computerized tomography. Carmignani et al. [9] made the following conclusions:

- When diagnosed early Leydig cell tumours do present a favourable follow-up.
- In select cases with motivated patients, conservative surgery had proven to be a feasible and safe choice.

Giannarini et al. [49] stated that even though majority of Leydig cell tumours are benign, radical orchidectomy at the time of publication of their article in 2007 was considered the standard therapy. Giannarini et al. [49] retrospectively analysed the long-term follow-up of a series of patients who had Leydig cell tumours who were electively treated with testis sparing surgery. Giannarini et al. [49] reported that between November 1990 and December 2005, 17 consecutive patients with Leydig cell tumours had undergone testis sparing surgery on an elective basis. The pre-operative evaluation of the patients included clinical examination, serum markers for germ cell tumours, scrotal ultrasound, abdominal computerized tomography, chest x-ray and hormonal profile if clinically required. Testis sparing surgery was undertaken through an inguinal approach with spermatic cord clamping. Frozen section examination was undertaken in all cases, which had revealed Leydig cell tumours. Follow-up of the patients consisted of clinical examination, scrotal ultrasound scan, abdominal computerized tomography and chest x-ray every 6 months for the first 2 years, then annually. Tumour recurrence and survival were evaluated. Giannarini et al. [49] summarized the results as follows:

- The mean patient age was 41.6 years and the age of the patients had ranged between 28 years and 55 years.
- Medical referral was prompted by symptoms/signs including infertility, gynecomastia or self-palpation of scrotal mass in 11 patients which amounted to 64.7% of the patients, while in the remaining 6 patients which amounted to 35.3% of the lesions were incidentally diagnosed. Hormonal profile was performed in 9 patients, showing abnormalities in all. The mean tumour diameter was 13.4 mm and the diameter of the tumour had ranged between 5 mm and 31 mm. Definitive pathological examination confirmed benign Leydig cell tumour in all cases. After a mean follow-up of 91 months and a follow-up which had ranged between 12 months to 192 months, neither local recurrence nor distant metastases had been identified and all patients are alive without evidence of disease.

Giannarini et al. [49] concluded that in patients with Leydig cell tumours testis sparing surgery with frozen section examination does provide an excellent long-term oncological outcome.

Vergho et al. [50] compared retrospectively the outcome of testis-sparing surgery (TSS) to radical orchiectomy (RO) in patients who had Leydig cell tumour (LCT). About the methods of their study, Vergho et al. [50] reported that between 1992 and 2008, 16 patients with LCT of the testis were identified. All but 1 tumour could be identified by ultrasonography. Alpha-fetoprotein and beta-human chorionic gonadotropin levels were normal in all patients. Eight patients had undergone RO and their mean age during their surgical operation was 42 years and their ages at the time of their surgery had ranged between 27 years and 61 years; the median tumour size was 12.9 mm and the tumour size had ranged between 10 mm and 25 mm. and the remaining 8 patients underwent TSS and their mean age at surgery was 34 years and their ages had ranged between 18 years and 49 years; the median tumour size was 8.6 mm and the tumour size had ranged between 4 mm 23 mm. Staging (abdominal computed tomography and chest x-ray or thoracic computed tomography) was negative in all patients. , Vergho et al. [50] summarized the results as follows:

- The median follow-up was 77 months and the follow-up had ranged between 17 months and 186 months after RO and 42 months (1-86 months) after TSS.
- There was no local recurrence or metastasis in patients following RO.
- A metachronous LCT was removed from the spermatic cord 29 months following TSS of the ipsilateral testis in 1 patient.
- Another patient underwent surgical exploration of the testis 31 months after ipsilateral TSS because of a suspicious lesion identified in ultrasonography; a tumour excluded by histopathology.

Vergho et al. [50] concluded that in the medium term, TSS is a safe procedure in patients with LCT that measure less than 25 mm.

Laclergerie et al. [51] compared the oncological outcomes of testicle-sparing surgery (TSS) and radical orchiectomy (RO) in patients who had Leydig cell tumour (LCT) of the testis. Laclergerie et al. [51] undertook a multi-centre retrospective clinical study within 12 centres in France. All the patients who had histologically proven LCT were included and analysed according to treatment (organ-sparing surgery or radical orchiectomy). The patients had undergone preoperative clinical, biological and imaging assessment. Demographic, clinical, and pathological variables were collected at baseline and compared between the groups according to surgical treatment. Follow-up was calculated utilizing the reverse Kaplan-Meier estimation and was updated at the end of 2015. Laclergerie et al. [51] summarized the results as follows:

- Between 1986 and 2014, 56 patients who had manifested with LCT were identified and included in the study.
- Twenty-one patients which amounted to 37.5% of the patients underwent TSS and 35 patients that amounted to 62.5% of the patients underwent RO.
- Demographics and tumour characteristics were not significantly different between the groups.
- The median follow-up was 62 months after TSS, but only 35 months after RO.
- Two patients which amounted to 9.5% of the patients had developed local recurrence 15 and 34 months after TSS and they underwent secondary RO.

- No local recurrence or metastasis was identified after complementary treatment.
- No recurrence was identified after RO.
- Disease-free survival did not differ between the groups which was 95.2% in TSS versus 77.1% in the RO group, p = 0.23).
- None of the patients died in the TSS group, but three patients that amounted to 8.6% in the RO group died from other diseases without evidence of relapse.
- One patient that amounted to 4.8% in the TSS group versus five that amounted to 14.3% in the RO group were lost to follow-up.

Laclergerie et al. [51] concluded that long-term follow-up had indicated that testicle-sparing surgery does not compromise relapse-free survival in the treatment of Leydig cell tumour of the testis.

Loeser et al. [52] compared retrospectively the outcome of testis-sparing surgery (TSS) to radical orchiectomy (RO) in patients who had Leydig cell tumour (LCT). Loeser et al. [52] reported that between 1992 and 2008, 16 patients who had LCT of the testis were identified. All but 1 tumour could be detected by ultrasound scan of scrotum and scrotal contents. Alpha-fetoprotein and beta-human chorionic gonadotropin levels were normal in all patients. Eight patients underwent RO and their mean age at surgery was 42 years and their ages had ranged between 27 years and 61 years; the median tumour size was 12.9 mm and the tumour size had ranged between 10 mm and 25 mm and the remaining 8 underwent TSS and their mean age at surgery 34 years as well as their ages had ranged between 18 years and 49 years; the median tumour size was 8.6 mm and the size of the tumour had ranged between 4 mm and 23 mm. Staging (abdominal computed tomography and chest x-ray or thoracic computed tomography) was negative in all patients. Loeser et al. [52] summarized the results as follows:

- The median follow-up was 77 months and the follow-up had ranged between 17 months and 186 months pursuant to RO and 42 months (1-86 months) pursuant to TSS.
- There was no local recurrence or metastasis in patients pursuant to RO.
- A metachronous LCT was removed from the spermatic cord 29 months after TSS of the ipsilateral testis in 1 patient.
- Another patient had undergone surgical exploration of the testis 31 months pursuant to ipsilateral TSS because of a suspicious lesion identified in ultrasonography; a tumour was excluded by histopathology.

Canda et al. [53] reported their experience in performing testis sparing surgery (TSS) to treat sequential bilateral testicular tumours. Canda et al. [53] undertook TSS on two patients with bilateral sequential testicular tumours. Canda et al. [53] summarized the results as follows: A 43-year-old patient (Case 1) and a 33-year-old patient (Case 2) had previous inguinal orchidectomy for seminoma. The patients were diagnosed as having secondary testicular tumours within the contralateral testes on follow up. They were treated by means of TSS after frozen section analysis of the peritumoral testicular tissue. Pathology examination of the excised tumours demonstrated immature teratoma and Leydig cell tumour. Both patients were disease free without local recurrence and did not have erectile dysfunction, and thus did not require androgen replacement therapy after a follow up of 6 months and 44 months, respectively. Canda et al. [53] concluded that TSS after frozen section analysis appears to be a safe and feasible procedure that, in carefully selected cases, offers adequate cancer control, preserves sexual function, and provides psychological benefits.

Bozzini et al. [54] iterated that the gold standard treatment for Leydig cell tumours (LCTs) is still considered to be radical orchidectomy, but testis sparing surgery (TSS) in conjunction with intraoperative frozen section (FSE) had been recently attempted with promising results. Bozzini et al. [54] identified studies by searching electronic databases. A bibliographic search covering the period from January 1980 to December 2012 was conducted utilizing PubMed/MEDLINE and EMBASE database. Bozzini et al. [54] excluded studies if they were single case reports, meeting abstracts and conference proceedings. Bozzini et al. [54] stated that their analysis was based upon a total of 13 studies which had fulfilled the predefined inclusion criteria. A total of 247 participants were included in the 13 studies examined in their systematic review. 145 cases were treated with radical orchiectomy and 102 with TSS. In the radical surgery group, the follow-up had varied from 6 months to 249 months. In the TSS group, the follow-up had varied from 6 months to 192 months. Frozen section was undertaken in a total of 96 patients. Sensitivity was 87.5%. None of the patients treated with TSS had manifested a metastatic recurrence, while in patients treated with radical orchiectomy three patients had manifested with metastatic recurrence. Bozzini et al. [54] stated that in selected cases radical surgery appeared excessive and the potential for a shift to TSS as the standard management is gathering momentum. Bozzini et al. [54] made the following conclusions:

- The results had confirmed the favourable course of LCT treated with TSS.
- The results obtained are encouraging and the concept is attractive to become the standard therapy in all patients and not only in people affected by (sub)fertility or with solitary testis.

Kong et al. [55] stated the following:

- Testicular tumours do represent 1% to 1.5% of all tumours in men.
- Testicular tumours that are derived from Leydig cells are rare and account for 1% of testicular tumours.
- Leydig tumour cells can produce steroid hormones such as oestrogen, progesterone and testosterone.
- The amount and type of hormones that are secreted by these tumours might produce complicated clinical characteristics in these patients.

Kong et al. [55] reported a patient with azoospermia, a testicular Leydig cell tumour (LCT), and elevated plasma testosterone levels. Kong et al. [55] described the diagnostic and therapeutic experience of this case, and their follow-up of the patient's clinical indicators and fertility status. Kong et al. [55] reported that the patient was diagnosed with azoospermia and a testicular LCT. The patient underwent testicular tumour excision and long-term follow-up. After 4 months of follow-up, the patient's semen examination index had significantly- improved and his wife became naturally pregnant. At 4 months of gestation, the foetus was delivered because of a ruptured amniotic cavity. Twenty-six months after tumour removal, the patient's sex hormone levels had completely returned to normal and spermatogenic function had partially recovered, but there was no natural pregnancy with his partner. Kong et al. [55] made the ensuing conclusions:

- For LCTs, testis sparing surgery might provide a safe and feasible option to restore spermatogenic function, even though longer-term follow-up is required.
- Drug assistance might be required in order to maintain spermatogenic function and achieve fertility, and further research is required.

Luckie et al. [14] stated the following:

- Leydig cell tumours (LCTs) are uncommon tumours which arise from testosterone-producing Leydig cells.
- Even though LCTs are usually benign, malignancy had been reported in 10% of cases in adults, and local recurrence or metachronous tumours of the contralateral testis had been described.
- Radical orchiectomy was the current standard of care of LCTS at the time of publication of their article.

Luckie et al. [14] reported on 12 children with LCT within 3 institutions between 2000 and 2016. Luckie et al. [14] reported that the manifesting symptoms of LCT included precocious puberty, palpable testicular mass, and scrotal swelling. Radical orchidectomy was undertaken in 9 patients. Three patients were treated with enucleation. All patients were alive at their last follow-ups without evidence of local recurrence or metastasis.

Carvajal-Carmona et al. [15] stated the following:

- Leydig cell tumours (LCTs) are the commonest non-germ-cell neoplasms of the testis.
- LCTs are often hormonally active and could result in precocious virilization or in adult feminization.
- They had identified an LCT in an affected individual from a-kindred, with hereditary leiomyomatosis and renal cell cancer (HLRCC) and a germline fumarate hydratase (FH) mutation (N64T).

Carvajal-Carmona et al. [15] investigated the role of FH mutations in predisposition to LCTs. Carvajal-Carmona et al. [15] tested for pathogenic effects of the N64T mutation and screened an additional 29 unselected adult LCTs for FH alterations. Carvajal-Carmona et al. [15] also tested these LCTs for mutations in two genes, the LH/choriogonadotropin receptor (LHCGR) and the guanine nucleotide-binding protein alpha (GNAS) that had been implicated in LCT tumorigenesis. Carvajal-Carmona et al. [15] summarized the results as follows:

- No mutations were found in GNAS, and one tumour had a LHCGR somatic substitution.
- In addition to the HLRCC case with the N64T germline FH mutation, Carvajal-Carmona et al. [15] identified one other LCT with a previously unreported FH mutation (M411I).
- Both LCTs from these patients had shown loss of the wild-type FH allele.
- Immunohistochemistry staining studies and in situ hybridization analyses had demonstrated activation of the hypoxia/angiogenesis pathway not only within the tumours that belonged to the FH mutation carriers but also in several other mutation-negative LCTs.

Carvajal-Carmona et al. [15] concluded that their study had shown that some LCTs are caused by FH mutations and represented one of the first reports of germline mutations within any type of adult testicular tumour.

Huang et al. [16] stated the following:

- Leydig cell tumour (LCT) is a rare tumour which typically occurs within the testis.
- Primary epididymal LCT is extremely rare.
- To the best of their knowledge, only two cases had been reported in the world literature.

Huang et al. [16] reported a case of primary epididymal LCT in a 41-year-old Chinese man. The patient manifested with right epididymal swelling for 3 months without endocrine manifestations, including gynaecomastia and decreased libido. He had ultrasound scan of his scrotal contents which demonstrated a mass that measured about 1.5 cm in diameter entirely within the cephalic region of his right epididymis. No abnormality was found within his bilateral testes. The patient underwent total mass resection without any post-operative treatment. Histological examination of the excised mass had demonstrated that the well-circumscribed tumour was separated by conspicuous hyalinised fibrous stroma; the tumour cells were noted to be large and polygonal with round nuclei and abundant eosinophilic cytoplasm. Immunohistochemistry staining studies of the tumour demonstrated that phenotypically, the tumour cells had expressed four markers of sex cord differentiation which included: calretinin, melanA, CD99 and inhibin. There was no recurrence at his 2-year follow-up. Huang et al. [16] also stated the ensuing:

- Their observation once again had confirmed that LCT could primarily occur within the epididymis, and that they supposed that the LCT probably originated from the ectopic Leydig cells.
- As little is known about the pathogenesis and prognosis for such a rare disease, accumulation of more pathological and clinical data could help to better interpret this tumour.

Al-Agha and Axiotis [17] stated the following:

- Leydig cell tumour (LCT) is an uncommon tumour of the male testicular interstitium.
- Their article had provided an overview of the major pathological presentations of LCT of the testis; patient characteristics; clinical, radiologic, and laboratory features; prognosis; and management. LCTs of the testis are frequently hormonally active, leading to either feminizing or virilizing syndromes.
- The tumour is usually benign, but malignant variants of the tumour could occur.
- The pathological diagnosis of LCT is usually made based upon morphological characteristics of the tumour cells.
- The significance of Reinke crystals in the diagnosis of LCT both cytologically and histologically has been underscored.
- Pathologists need to be familiar with the diagnostic histopathology examination features, immunohistochemical panel of this tumour, and its principal differential diagnoses in order to prevent tumour misdiagnosis.

Rossato et al. [56] made the ensuing iterations:

- Insulin-like 3 (INSL3) is a novel peptidic hormone member of the relaxin-insulin-like family of peptide factors.
- INSL3 is almost exclusively produced by Leydig cells within the testis and does participate to the complex mechanisms leading to physiological testicular descent during embryonic development.

Rossato et al. [56] undertook a retrospective study evaluating the clinical and histopathological characteristics of 13 patients who were surgically treated for testicular tumour and diagnosed to be afflicted by Leydig cell tumour (LCT). Rossato et al. [56] stated that it was possible to retrieve the archived paraffin embedded tumour together with neighbouring healthy testicular tissue of all subjects who were affected by LCT (12 benign and 1 malignant form), that were analysed for INSL-3 expression. Immunohistochemistry staining studies of the tumour sections of the 13 patients affected by LCT had demonstrated constitutive expression of INSL3 protein within all LCT, irrespective of the histological pattern of each LCT and with no significant differences of staining intensity between all tumours. Particularly, no gross differences were observed

between the staining for INSL3 in the 12 benign LCTs and the only one showing malignant clinical behaviour. Rossato et al. [56] made the ensuing discussing iterations:

- Their reported study had shown that LCTs, a very rare form of testicular tumour with no proven specific serum and histological markers, express a novel member of the relaxin-insulin-like family of peptide factors previously identified as a secretory product of Leydig cells and named INSL3.
- Hence, there could be the possibility to evaluate the expression and secretion of this novel hormone as a marker of this rare testicular tumour.

Pozza et al. [19] undertook a study which was aimed to answer when should 'not so rare' Leydig cell tumours (LCTs) of the testis be suspected, diagnosed, and treated. Pozza et al. [19] stated the following:

- LCTs are more frequent than generally believed, and LCTs are associated with male infertility, cryptorchidism and gynecomastia, and should be treated conservatively (in compliant patients) with active surveillance, which appears to be a safe alternative to surgical enucleation.
- Increasing referrals for testicular radiology-imaging had led to an increase in findings of LCTs.
- The features and natural history of these tumours have remained largely unknown, as the available studies are small and heterogeneous.
- LCTs were previously treated aggressively and follow-up data on LCTs are lacking.

Pozza et al. [19] reported a case-cohort study of consecutive patients who were diagnosed with LCTs over a 10-year period who were prospectively enrolled from 2009 to 2018 and compared to matched cohorts of patients with seminomas or no testicular lesions screened in the same timeframe. Pozza et al. [19] reported that out of the 9949 inpatients and outpatients who had been referred for scrotal ultrasound scans, a total of 83 men with LCTs were included. Pozza et al. [19] reported that the enrolled subjects had undergone medical history and clinical examination and they were asked to undergo routine blood tests, hormone investigations (FSH, LH, total testosterone, oestradiol, inhibin B, sex hormone-binding globulin (SHBG), prolactin), and semen analysis. Patients who consented also underwent contrast-enhanced ultrasound, elastography, gadolinium-enhanced scrotal magnetic resonance imaging, and hCG stimulation test (5000 IU i.m.) with serum total testosterone and oestradiol measured at 0, 24, 48, and 72 hours. Pozza et al. [19] summarized the results as follows:

- In total, 83 patients who were diagnosed as having LCTs were compared against 90 patients who were diagnosed as seminoma and 2683 patients without testicular lesions (NoL).
- LCTs were diagnosed by means of enucleation (48.2%), orchiectomy (13.3%), or clinical surveillance (38.5%).
- Testicular volume, sperm concentration, and morphology were lower ($P = 0.001$, $P = 0.001$, and $P < 0.001$, respectively) in patients with LCTs than in the NoL group.
- FSH, LH, and SHBG were higher and the testosterone/LH ratio was lower in LCTs than in the NoL group ($P < 0.001$).
- The LCT group did show higher SHBG ($P = 0.018$), lower sperm concentration ($P = 0.029$), and lower motility ($P = 0.049$) than the seminoma group. Risk factors for LCTs were cryptorchidism ($\chi2 = 28.27$, $P < 0.001$), gynecomastia ($\chi2 = 54.22$, $P < 0.001$), and low testicular volume ($\chi2 = 11.13$, $P = 0.001$).
- Five cases were recurrences or bilateral lesions; none had developed metastases during follow-up over a median follow-up time of 66 months.
- Their study had some limitations including: Firstly, hCG and second-line diagnostic investigations were not available for all tumour patients. Secondly, their institution was a referral centre for infertility, thus a selection bias might have altered the baseline features of the LCT population. Nevertheless, given that the comparison cohorts were also from the same centre and had been managed with a similar protocol, they did not expect a significant effect.
- LCTs are strongly associated with male infertility, cryptorchidism, and gynecomastia, supporting the postulate that testicular dysgenesis syndrome does play a role in their development.
- Patients who have LCTs are at a greater risk for the development of endocrine and spermatogenesis abnormalities even when the tumour is resected, and thus require long-term follow-up and prompt efforts to preserve fertility after diagnosis.
- LCTs have a good oncological prognosis when they are diagnosed early, as tissue-sparing enucleation is curative and should replace orchiectomy.
- Conservative surgery and, in compliant patients, active surveillance through clinical and radiology-image follow-ups are safe options, but they require monitoring of testicular failure and recurrence.

Kim et al. [21] analysed the clinical and pathological features of 40 Leydig cell tumours of the testis. The ages of the patients had ranged from 2 years to 90 with an average age of 46.5 years of age. The commonest initial presentation of the patients was testicular swelling, which was at times associated with gynecomastia; 15% of the patients had manifested because they had gynecomastia and they were found to have palpable testicular tumours. All three children were brought to the physician because of the finding that they had isosexual pseudo-precocity. The tumours, one of which was asynchronously bilateral, had ranged from 0.5 cm to 10.0 cm (with an average size of 3 cm) in greatest diameter. They were usually well circumscribed, however, in seven of them the margin with the adjacent testis was noted to be ill-defined. Upon microscopy examination the commonest pattern was that of diffuse sheets of neoplastic cells, but insular, trabecular, pseudo-tubular, and ribbon-like patterns were also found. The neoplastic cells were noted to be most often large and polygonal with abundant eosinophilic, slightly granular cytoplasm; occasionally the cytoplasm was found to be abundantly vacuolated. In eight of the tumours some of the cells were found to be spindle-shaped, and in six of the tumours some had scanty cytoplasm. Crystalloids of Reinke were found in 35% of the tumours. Conspicuous nuclear atypicality was present in 12 tumours and the mitotic rate had ranged from less than 1 to 32 per 10 high-power fields. Blood vessel invasion, lymphatic invasion, or both were noted in four tumours. Follow-up information of 2 months to 22 years, with an average follow-up of 4 years was available for 30 patients. Five of the patients died as a result of spread of their tumour. A comparison of the clinically malignant tumours with those that were associated with survival for 2 years or longer than 2-years post-operatively had revealed that the former occurred in older patients and they were accompanied by symptoms of shorter duration and an absence of endocrine presentations. The malignant tumours were larger, often they had an infiltrative margin and they had spread beyond the confines of the testis, they frequently exhibited blood vessel or lymphatic invasion, and had a greater degree of cellular atypia and necrosis and a higher mitotic rate than the benign tumours.

Fankhauser et al. [22] stated the following:

- Leydig cell tumours are uncommon but they are the most common non-germ cell testicular tumours.
- Only limited evidence exists for reliably distinguishing between benign and malignant Leydig cell tumours and for optimally managing the different types and stages of this uncommon disease.
- They had in their reported review synthesized the available evidence on the clinical manifestation and clinicopathological characteristics associated with Leydig cell tumour malignancy and management.

Fankhauser et al. **[**22**]** analysed published case series data on Leydig cell tumours. They assessed the association between clinicopathological variables and the presence of metastatic disease was assessed using regression analyses. Fankhauser et al. **[**22] summarized the results as follows

- They had included 357 reports, with reviewing available data from 1,375 patients whose median age was 34 years.
- Testis sparing surgery was undertaken in 463 patients.
- Local recurrence after testis sparing surgery occurred in 8 of 121 patients which had amounted to 7% of the patients who had available follow-up information.
- Metastases were identified in 101 patients and they were most often located within the retroperitoneal lymph nodes in 60% of cases, the lungs in 38% of cases and/or liver in 29% of cases.
- The multivariable models with or without multiple imputation predicting metastatic disease had included older age, larger tumour size, presence of any adverse factor including: larger tumour diameter, necrosis, angiolymphatic invasion, pleomorphism, high mitotic index, atypia, and any protective factor including Reinke crystals, lipofuscin pigments, gynecomastia with model AUCs of 0.93.
- Durable remission following resection of metastases or utilization of platinum-based chemotherapy was rarely seen.

Fankhauser et al. [22] made the ensuing conclusions:

- Their risk tables utilizing clinicopathological parameters could help identify patients who have malignant tumours.
- These patients should undergo disease staging and they should be followed-up or receive further treatment.
- In some patients with metastatic disease surgical and systemic treatment might result in the control of the disease.

Mukhopadhyay et al. [57] reported A 6-year-old boy presented with precocious puberty (see figure 1). He had isotope scan, which had demonstrated that his bone age was greater than (>) 12 years and less than (<) 14 years. He had ultrasound scan which demonstrated a heterogeneous echogenic space-occupying lesions which had involved the whole of his left testis with many micro- and macrocalcification and increased vascularity. The volume of his left testis was 12 cc. He had hormonal assay which showed his serum luteinizing hormone (LH) levels was <0.07 U; normal human chorionic gonadotropin level <1 mIU/ml; alpha-fetoprotein (AFP) level 0.97 IU/ml; serum testosterone 17.9 nmol/L; and serum cortisol, adrenocorticotropic hormone, and 17 OH progesterone level were 8.86 μ/dl, 37.9 pg/ml, and 31.56 ng/ml, respectively. All the levels of his hormonal studies were within normal limits except his serum testosterone levels that were raised. He had computed tomography (CT) scan of abdomen which was normal. The patient underwent orchidectomy. Grossly, the testis with scrotum measured 5.5 cm × 3.5 cm × 2.5 cm, testis was 4 cm × 3 cm × 2 cm, and the attached spermatic cord was 5.5 cm in length. Cut section had shown lobulated, yellow well-circumscribed mass (see figure 2). Upon microscopy pathology examination, the sections showed polygonal cells with abundant eosinophilic cytoplasm and prominent nucleoli which were arranged in sheets and nodular pattern (see figure 3). Pleomorphism was noted to be present in some places. Immunohistochemical staining of the tumour with calretinin was undertaken and this showed positive staining of the tumour (see figure 4). Diagnosis of benign LCT was made based upon his clinical, hormonal, pathological, and immunohistochemical study findings.

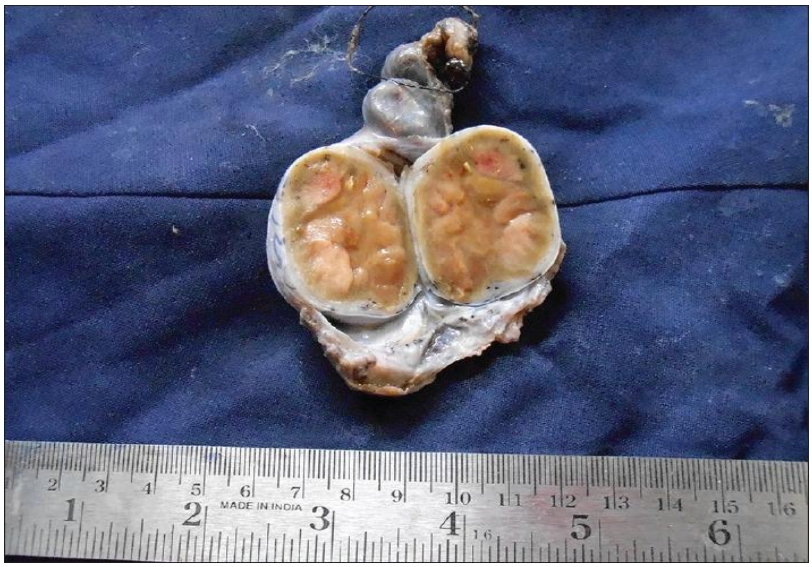

Figure 1: Gross picture of lobulated yellow well-circumscribed mass. Reproduced from: Reproduced from: [57] under Copyright: © 2017 Journal of Indian Association of Pediatric Surgeons. This is an open access article distributed under the terms of the Creative Commons Attribution-Non-Commercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

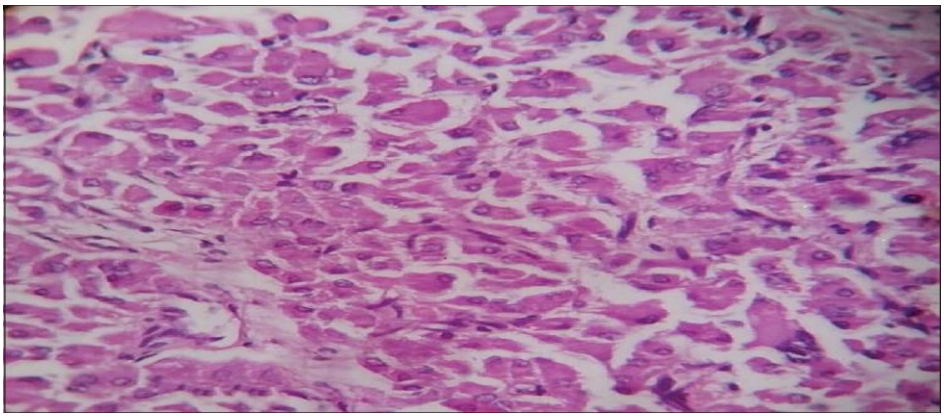

Figure 2: Polygonal cells with abundant eosinophilic cytoplasm, prominent nucleoli (x 400). Reproduced from: [57] under Copyright: © 2017 Journal of Indian Association of Pediatric Surgeons. This is an open access article distributed under the terms of the Creative Commons Attribution-Non-Commercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

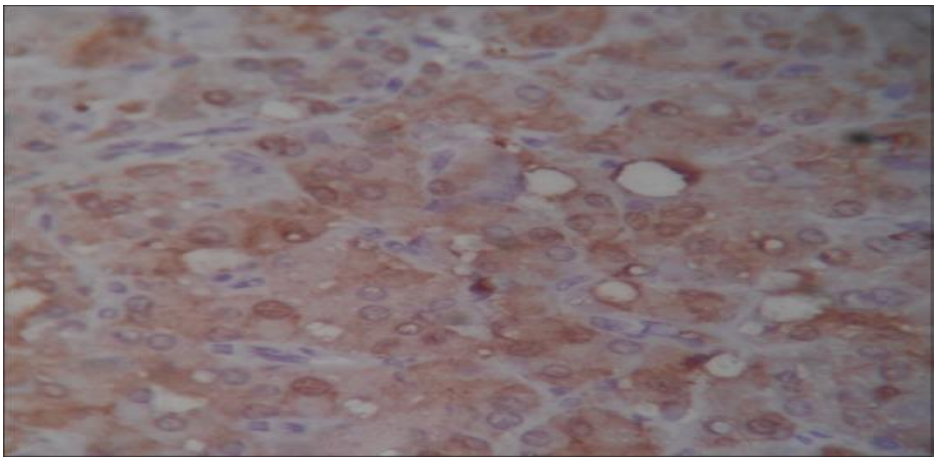

Figure 3: Immunohistochemistry positivity for calretinin (x 400). Reproduced from: [57] under Copyright: © 2017 Journal of Indian Association of Pediatric Surgeons. This is an open access article distributed under the terms of the Creative Commons Attribution-Non-Commercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

Zeuschner et al. [58] stated that Gynecomastia is a common incidental finding in males which can be caused by a variety of benign or malignant diseases and that in rare cases, it results from Leydig cell tumours, which is an uncommon clinical entity that accounts for 3% of all testicular tumours. Zeuschner et al. [58] also iterated that some of them are hormonally active but they rarely cause symptomatic endocrine disturbance. Zeuschner et al. [58] reported a 32-year-old man who had presented with gynecomastia which he had already been suffering from for the preceding two years. Even though he had been seen by three other specialists, including a urologist, none of them had identified the small mass in the upper pole of his right testis. Zeuschner et al. [58] decided to undertake testis-sparing surgery which confirmed the diagnosis of a hormonally active Leydig cell tumour. During follow-up, his hormonal status normalized, and his gynecomastia began to resolve.

Genov et al. [59] reported that in April 2019, a 45-year-old man was admitted to their Urology department with a large painless mass within his right testis of 1 year duration. The patient stated that one month preceding his admission, the lesion had commenced to grow. On his clinical examination, his right testis was found to measure 6.5 cm × 3.0 cm in size, with a palpable tumoral mass of about 3.5 cm × 2.0 cm in size, also the patient had a regular pulse of 78beats/min, a temperature of 36.9 °C, as well as a respiratory rate of 18-breaths per minute. No other signs were found, including gynecomastia or swelling of superficial lymph nodes. His penis and pubic hair were normally developed. The results of the patient's laboratory blood tests such as complete blood cell count, renal function tests, liver function tests, and urinalysis were within normal ranges. The results of his serum tumour markers including: alpha-fetoprotein (AFP), β-human chorionic gonadotropin (β-hCG) and lactate dehydrogenase (LDH) were negative, and his hormonal investigations like serum testosterone, prolactin and follicle stimulating hormone (FSH) were within normal ranges. He underwent ultrasound scan assessment which revealed a mixed echogenic space occupying lesion which had involved half of his right testis with increased vascularity and some cystic areas. The patient underwent trans-inguinal radical high right orchidectomy, based upon a preliminary diagnosis of right testicular tumour and the specimen was submitted for histopathology examination. Postoperative pathology examination of the orchidectomy specimen showed that the tumour had cells in nets and trabeculae with chailinized and oedematous stroma, without haemorrhage and necrosis or vascular invasion. The tumour nuclei were noted to be monomorphic, oval-shaped with passing nucleoli, finely dispersed chromatin and no mitoses were found (see figure 5). The spermatic cord, scrotal skin, and surgical margins were free of any tumour. Immunohistochemistry staining studies of the tumour showed that the tumour cells had exhibited positive staining for inhibin and negative staining for pan-cytokeratin, calretinin and synaptophysin (see figure 6). Based upon the pathology and immunohistochemical examination features of the tumour, the testicular tumour mass was diagnosed as a benign Leydig cell tumour of testis

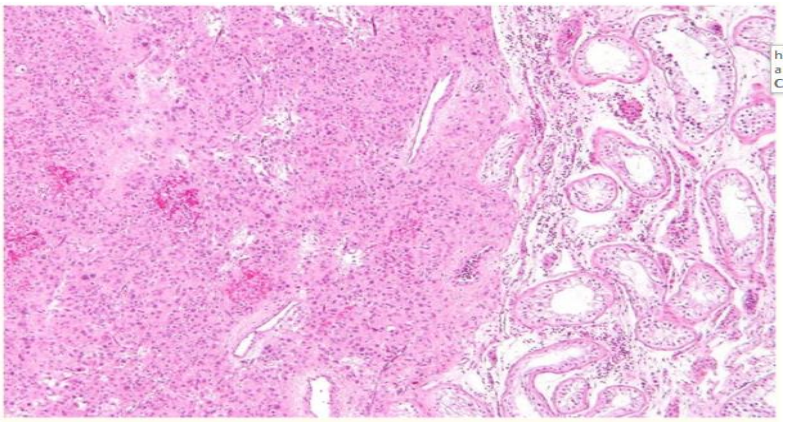

Figure 4: Histology image of Leydig cell tumour. Reproduced from: [59] under Copyright © 2019 The Authors. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

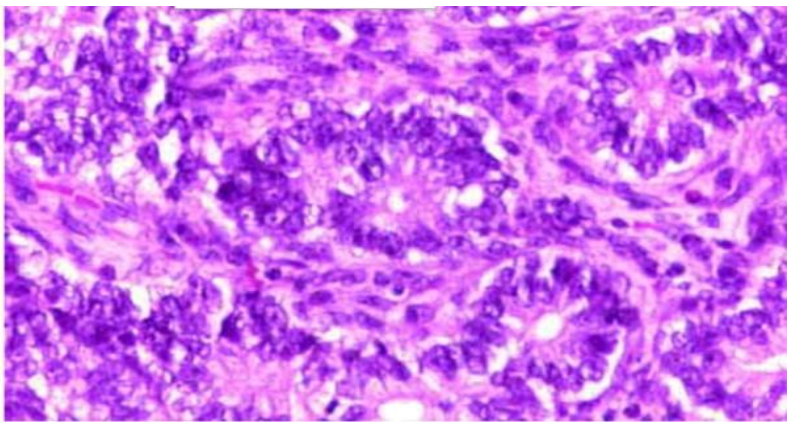

Figure 4: Immunostaining image of Leydig cell tumour. Reproduced from: [59] under Copyright © 2019 The Authors. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Six months pursuant to his surgery, the follow-up CT-scan did not identify any local recurrence and distant metastases and his hormonal investigations had remained within the normal ranges.

Zhu et al. [60] stated the following:

- Testicular Leydig cell tumour (LCT) is an uncommon neoplasm.
- LCT commonly manifests as a painless testicular mass with or without endocrine changes.
- Histological and immunohistochemical examination play important roles in differentiating LCT from testicular germ cell tumours.

Zhu et al. [60] highlighted the radiology-imaging phenotype, as well as the pathological findings of a case of LCT in a 62-year-old man. Zhu et al. [] reported that pre-operative non-contrast CT scan of the patient's abdomen had revealed a 7.0 cm × 6.4 cm × 5.3 cm oval mass that had heterogeneous density, which was located within his right testis. He also had Pelvic non-contrast MRI scan which showed a heterogeneous mass on T1-weighted and T2-weighted images. The solid part of the tumour exhibited high signal on the diffusion-weighted imaging, and an obvious enhancement on the contrast-enhanced MR imaging. He had ultrasound scan examination which demonstrated a large mixed echogenic space occupying lesion which had involved the whole of his right testis with multiple cystic areas and increased vascularity. The patient underwent radical orchiectomy. The pathologic diagnosis was LCT. The patient underwent operative resection of the tumour. Due to the negative resection margins and absence of distant metastases, the patient did not receive additional radiotherapy or chemotherapy. Four months pursuant to his surgery, he had follow-up assessment CT-scan which did not reveal any local recurrence and distant metastases. Zhu et al. [60] made the ensuing additional iterations:

- Their reported case had improved their ability to detect and diagnose LCT by summarizing its radiology imaging characteristics as well as reviewing the literature.
- Additionally, they had described the state-of-the-art management of this rare tumour.

Justo et al. [61] reported a 91 years old man who had manifested with an increase of the volume of his scrotum for about 1 year, with local pain and hyperaemia over the preceding 7 months. He sought medical attention at the time and was treated with antibiotic therapy for epididymo-orchitis. When it was noted that his symptoms had persisted, he was then referred to the Urology outpatient clinic of the Santa Casa de Misericórdia de Ribeirão Preto. During his clinical examination, he was found to have an enlarged scrotum on the left with transillumination showing fluid, without hyperaemia. During the consultation, a scrotal ultrasound scan was requested. Upon his return, he produced an ultrasound scan report of hydrocele with fine debris within the left side, with a nodular, solid, rounded, partially defined, hypoechoic image with increased flow to the Doppler study that measured 2.0 cm x 1.4 cm x 1.1cm. The patient had complained of dysuria and polyuria, and Justo et al. [61] opted for treatment with antibiotic guided by urine culture and surgical treatment afterwards. He had a frontal chest radiography as a first radiology imaging

procedure which demonstrated diffuse osteopenia and ectasia of the aorta. He had Computed tomography (CT) scan which had demonstrated a left renal cyst and infra-centimetric bilateral inguinal lymph nodes. After 3 months, he underwent a trans-inguinal left unilateral orchidectomy, with hydrocele repair. The surgical specimen was sent for histopathology examination. Macroscopic examination of the surgical specimen demonstrated a left testis which measured 5.8 cm x 2.9 cm x 2.7cm, with a smooth outer surface and cut with a yellowish, spongy parenchyma, containing a brown nodule, firm, well delimited and homogeneous, that measured 1.7 cm x 1.5cm, restricted to the parenchyma. Microscopy examination of the surgical specimen demonstrated features of a neoplasm which had consisted of cells with a hypertrophic nucleus, sometimes with evident nucleolus and broad and eosinophilic cytoplasm, all were contained within the testicular parenchyma, with no evidence of infiltration in testicular coating. Absence of invasion of vein and lymphatics. Epididymis and spermatic cord without evidence of neoplastic infiltration. The surgical resection margin of the spermatic cord was free of tumour. The pathology staging of the tumour was: pT1, pNx, pMx. Immunohistochemistry staining studies of the tumour showed that the tumour cells had exhibited positive staining for inhibin, calretinin, melan-A and KI-67. Diagnosis was reported to be consistent with the diagnosis of Leydig cell tumour. The patient returned for follow-up assessment 1 month after his operation, with the presence of hematoma within his scrotum, which was confirmed by ultrasound scan of his scrotum and scrotal contents. sonogram. Just et al. [61] opted for a conservative treatment. Justo et al. [61] made the ensuing educative detailed summating discussions:

- The major representative of the stromal tumours is the Leydig cell tumour.
- Leydig cell tumour of testis It corresponds to 75% to 80% of all cases.
- There is no association with cryptorchidism.
- It does have a bimodal age incidence, with involvement of children and adults between 30 years and 60 years. Children account for 25% of cases. Elderly people tend to have malignant tumours [62].
- The first article that described the ultrastructure of a Leydig's tumour, which had been reported in a 3-year-7-months-old boy, was reported by Cervos-Navarro and associates in 1964 [63].
- Leydig cell tumour of testis is an uncommon tumour with few citations in articles.
- G. Cruceyra Betriu et al. had reported 8 cases of Leydig Cell Tumour of testis in one review, during the period from 1985 to 2000, with a median age of 33.5 years, with a follow-up which had ranged from 8 years to 60 years [64].
- Another review by Luca Carmignani during the period from 1990 to 2004 operated on 24 patients aged 22 years to 61 years at three centres [65].
- There are few cases of this histological type in patients who are older than 80 years of age [43].
- They were reporting a case of a patient who had this histological type and who was aged over 90 years, which had provided evidence of the need to think about differential diagnoses of scrotal masses in the elderly (see table 1).
- Primary lymphoma is an uncommon disease which does constitute only 1% to 9% of testicular tumours. Nevertheless, it is the most common malignancy in men within this age range and 85% of cases are diagnosed in men who are older than 60 years old.

Table 1

Scrotal Masses in elderly men.

Testicular
Primary lymphoma
Stromal tumours
Spermatocitic Seminoma
Metastasis
Epidermoid cyst
Leydig Cell Hyperplasia
Fibroma of gonadal origin
Haemangioma
Paratesticular
Lipomas
Adenomatoid Tumours
Leiomyomas
Testicular Appendage with Torsion
Fibrous Pseudo-tumour
Liposarcoma

Reproduced from: [61]

- Furthermore, about 2% to 3% of these tumours are extra-testicular and they do arise from para-testicular tissue.
- The para-testicular region does comprise of: the spermatic cord, testicular tunics, epididymis, and vestigial remnants. Even though not common, these tumours had been documented as the main urogenital location for sarcomas in the elderly [66].
- About 90% of the testicular masses tend to be benign and only 10% are malignant.
- Features of malignancy include larger tumours that measure larger than 5cm, infiltrative margins, foci of necrosis, angiolymphatic invasion, nuclear atypia, mitotic count of more than 3 mitoses per 10 high power fields, DNA aneuploidy, and increased MIB-1 activity [67].
- Even though the most reliable criterion is the presence of metastasis [68].
- Adults usually manifest with painless testicular masses, orchialgia, gynecomastia, impotence, decreased libido or infertility.
- Children usually tend to be aged between 5 years and 10 years old and they tend to manifest with testicular masses and precocious signs of virilization, including pubic hair, increased penis size and acne due to abnormal amounts of testosterone. In this age group the differential diagnoses that should be made for causes of early puberty should include: congenital adrenal hyperplasia, adrenocortical carcinoma and isosexual precocious puberty [62].
- Ultrasound scan of scrotum is very useful for the confirmation of the diagnosis of testicular tumour; however, it has been pointed out that ultrasound scan of scrotum cannot differentiate between a benign and a malignant tumour [69].

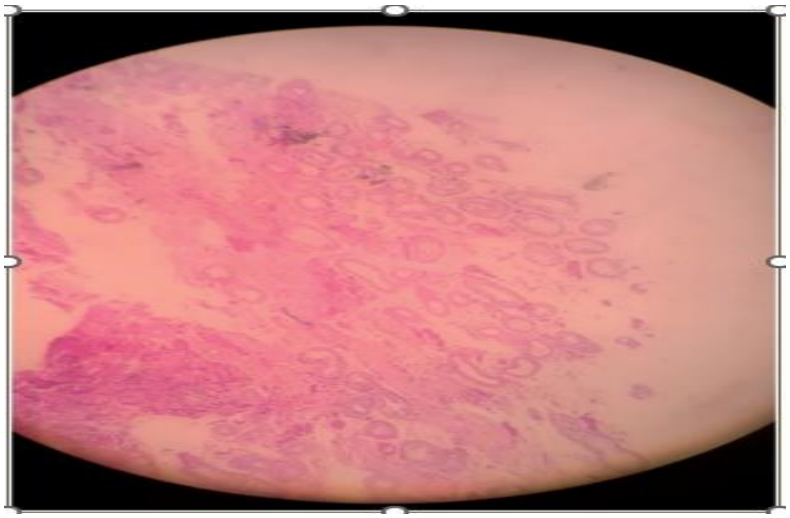

Figure 7: Epididymis (4x). Reproduced from: [61] under Copyright: This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

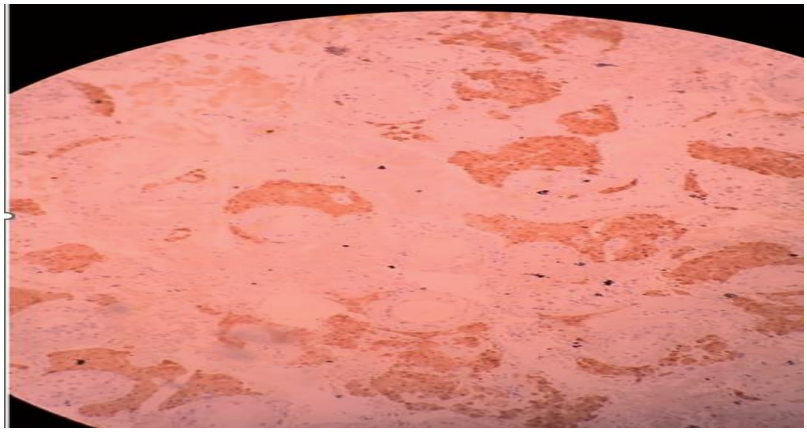

Figure 8: Seminiferous tubules (4x). Reproduced from [61] under Copyright: This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

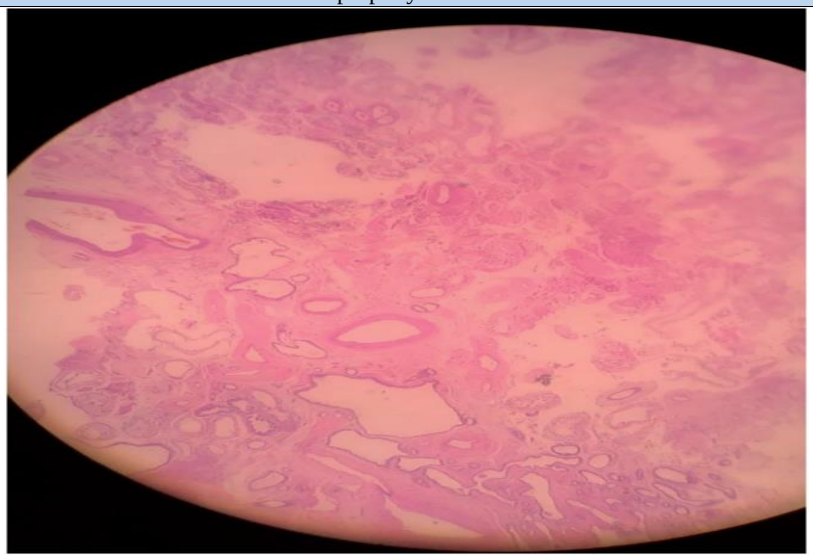

Figure 9: Rete testis and seminiferous tubules. (4x). Reproduced from: [61] under Copyright: This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

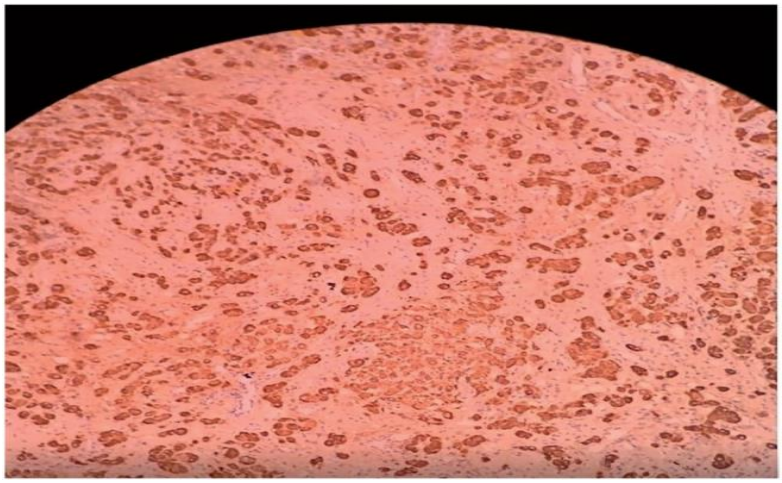

Figure 10: Inhibin antibody (4x). Reproduced from: [61] under Copyright: This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Figure 11: Calretinin antibody (4x). Reproduced from: [61] under Copyright: This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

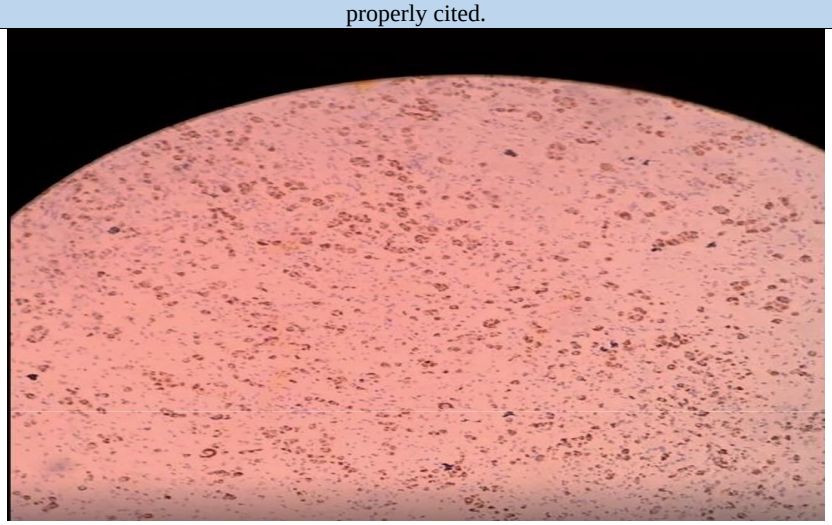

Figure 12: Melan-A antibody (4x). Reproduced from: [61] under Copyright: This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

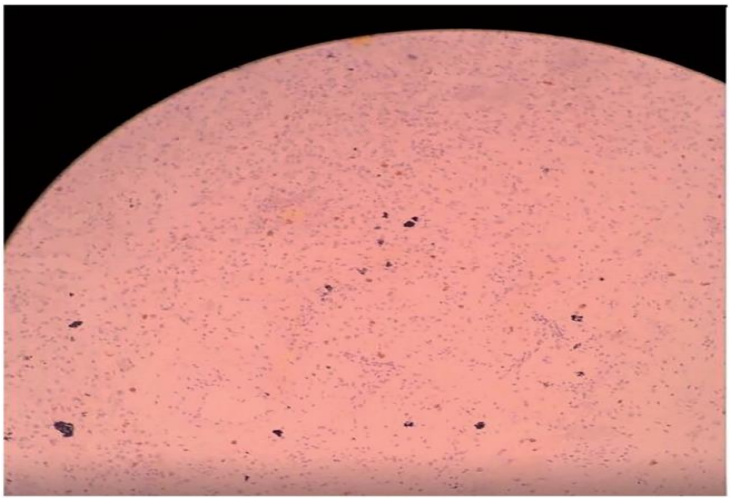

Figure 13: Ki-67 antibody (4x). Reproduced from: [61] under Copyright: This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

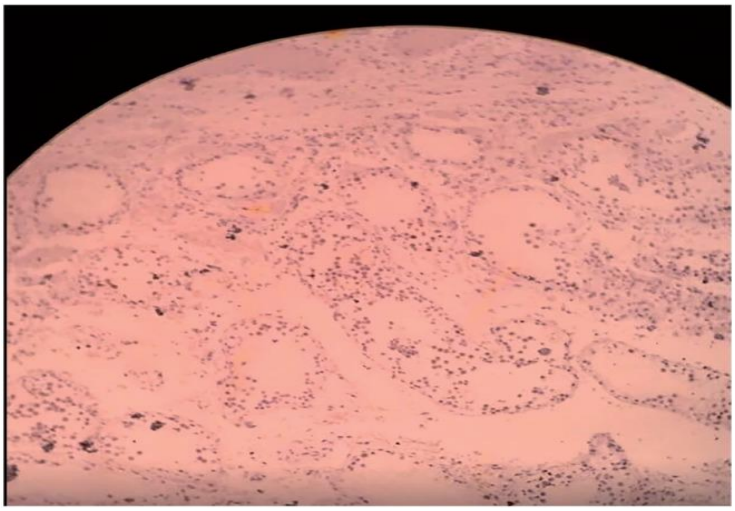

Figure 14: CD 117 antibody (4x), Reproduced from: [61] under Copyright: This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

- It has been pointed out that in the case of infertility, gynecomastia, decreased libido or precocious puberty, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, oestrogen and oestradiol should be dosed [70].
- Leydig cell tumour of testis should be differentiated from Leydig cell hyperplasia, which leads to atrophic testis, adjacent to germ tumours.
- Cell infiltrates seminiferous tubules without displacing or obliterating it. Unlike the tumour, Leydig Cell Hyperplasia of testis tend to be associated with normal values of urinary 17-ketoesteroides.
- Macroscopically, cases of Leydig Cell Hyperplasia of testis do appear as nodules with coloration between brown and yellow, well circumscribed, without areas of necrosis or haemorrhage.
- Histologically, the cells are large and round or polygonal, they contain abundant eosinophilic granular cytoplasm with a central round nucleus.
- About 25% to 40% demonstrate Reinke crystals. Reinke crystals contain lipofuscin pigment and have rounded shape, crystal structure with diameters from 3 μm to 20μm [62].
- Avoiding the undertaking of surgery should be considered if the testis lesions are smaller than 3cm and there is histological confirmation by frozen section pathology examination of biopsy of the specimen.
- Leydig cell dysfunction and hypogonadism might occur pursuant to the undertaking of orchidectomy, and 40% of patients might require testosterone supplementation.
- More than 70% of testicular tumours tend to be diagnosed in the initial phase; the remainder already tend to have metastasized at the time of the initial diagnosis.
- The commonest metastatic sites include: the regional lymph nodes, lung, liver and bones [67]. Hence, retroperitoneal lymph node dissection is acceptable in selected cases of tumours with adverse characteristics, despite high rates of progression observed in positive lymph nodes, which is suggestive of the

fact that the lymph node dissection would only have role in staging of the tumour.

- Metastatic Leydig cell tumours of the testis tend to be resistant to chemotherapy and radiotherapy and they tend to be associated with low survival rates.

Mesa et al. [71] stated the ensuing:

- Reinke crystals (RC) are pathognomonic of Leydig cells (LCs); they are considered to be rare in normal testes and to occur only in approximately one third of LC tumours.
- They had noticed that crystals do present in touch imprint and frozen sections of an LC tumour disappeared after tissue fixation.
- This phenomenon had led them to postulate that their reported low frequency within normal and neoplastic LCs might be secondary to degradation/dissolution of the crystals after formalin fixation.
- Their review of the literature also led them to postulate that RC are better preserved after air-drying and alcohol fixation.

Mesa et al. [71] had collected testicular samples from 21 autopsies including air-dried cytology preparations and tissue samples that had been fixed in alcohol or formalin. Mesa et al. [71] found that RC are common in normal LC but they dissolve rapidly in formalin and slowly and only partially in alcohol. Mesa et al. [71] stated that the composition of RC is unknown; nevertheless, they had been reported to stain specifically for nestin, an intermediate filament expressed mainly in neural and muscle tissue. Mesa et al. [71] also stated that because the crystals had only been described in androgen-producing cells, they had hypothesized that the crystals might represent a crystallized form of androgenic hormones, hormone complexes, or enzymes involved in their synthesis. Mesa et al. [71] performed immunohistochemistry staining for androgens and enzymes that are involved in androgenesis. Mesa et al. [71] also performed nestin immunostaining to confirm the previous study. They reported that the crystals stained specifically with antibodies anti-3β-hydroxysteroid dehydrogenase and they were negative for the remaining androgenic enzymes, androgenic hormones, and nestin.

Ulbright et al. [27] reported 19 Leydig cell tumours (LCTs) of the testis with adipose differentiation (n = 12) and/or spindle cell growth (n = 8) in patients whose ages had ranged between 28 years and 70 years of age. They reported that three tumours with adipose differentiation had shown psammomatous calcifications, two of which also had foci of ossification. Within eight tumours fat-like cells which had apparently been derived from lipid accumulation within neoplastic Leydig cells and which appeared as focal to prominent clusters in a background of vacuolated, neoplastic Leydig cells were noted. The fat-like cells were usually immunoreactive for Leydig cell markers (inhibin-alpha, calretinin, and melan-A) but they were typically strongly positive for the adipose tissue marker, S-100 protein, which had supported a hybrid cell phenotype. Four tumours had fat of stromal derivation. In two of these tumours, there were intermixed mature adipocytes, but in two other tumours only lipoblastic cells were noted to be present. These four tumours were noted to have lacked vacuolated, neoplastic Leydig cells, and the fat cells in the single case studied were negative for inhibin-alpha and melan-A but positive for S-100. Three of the 12 LCTs with adipose differentiation were found to be clinically malignant, and each had several of the established malignant features. Eight tumours that had spindle cells occurred in men who were aged between 34 years and 70 years of age. Two tumours were noted to have ill-defined fascicles of spindle cells, and three of the tumours had shown prominent oedematous to myxoid areas with spindle-shaped tumour cells. Two additional tumours were noted to contain a fibroma-like spindled component which had blended with islands of more plump, polygonal to spindle-shaped Leydig cells. Finally, one tumour was noted to contain foci that simulated an unclassified sarcoma that merged with conventional LCT; the spindle cell component within this case did not react for Leydig cell markers in contrast to the spindle cells in five of the six other cases in which immunohistochemistry staining studies were performed. It was noted that spindle cell differentiation, by itself, did not appear to have prognostic significance. Out of the six patients who had available follow-up data, two had developed metastases, but their tumours had malignant features apart from spindle cells; the remaining four patients were disease free at a mean follow-up assessment of 3.6 years. Ulbright et al. [27] made the ensuing recommendation:

- Awareness of these unusual patterns in LCTs might prevent misinterpretation of fat admixed with neoplastic Leydig cells as evidence of extra-testicular growth (a criterion for malignant LCT) might help avoid misdiagnosis of a LCT as a testicular "tumour" of the adrenogenital syndrome (which may contain fat) and might prevent misdiagnosis of a LCT with spindle cells as a sarcoma or unclassified sex cord-stromal tumour.

Biemer et al. [28] stated the ensuing:

- Leydig cell tumours are rare sex cord-stromal tumours which account for less than 1% of all testicular tumours.
- Less than 10% of these tumours demonstrate metastatic malignant behaviour.

Biemer et al. [28] reported a case of metastatic malignant Leydig cell tumour within an iliac lymph node which was diagnosed upon fine-needle aspiration (FNA) in a 70-year-old man. Biemer et al. [28] iterated that the patient was referred from an outside institution because he had lymphadenopathy and he had a past medical history of lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia as well as a past surgical history of orchidectomy. An iliac lymph node FNA was undertaken and pathology examination of the FNA specimen had demonstrated large dis-cohesive plasmacytoid cells with indistinct cell borders; abundant and finely granular cytoplasm; round, eccentric nuclei with evenly distributed chromatin; and prominent nucleoli. The tumour cells had exhibited positive immunohistochemistry staining for inhibin and negative staining for calretinin and keratin which led to the establishment of the diagnosis of metastatic malignant Leydig cell tumour. Biemer et al. [28] stated that review of the patient's history and of his previous pathology specimen, careful evaluation of the cytomorphology features, and the judicious utilization of immunohistochemistry could enable an accurate diagnosis of metastatic Leydig cell tumour.

Colecchia et al. [29] investigated the morphological and molecular characteristics of Leydig cell tumours (LCTs) of the testis for the identification of cases that may metastasise. Colecchia et al. [] evaluated six parameters for a predictive model of the metastatic risk in 37 benign and 14 malignant LCTs of the testis [LCT Scaled Score (LeSS)]. The tumour size (benign LCTs, mean 13.3 mm; malignant LCTs, mean 44 mm) ($P < 0.001$) and five other parameters (infiltrative margins, necrosis, vascular invasion, mitotic count, and nuclear atypia) did show significant differences (Wilcoxon's test, $P < 0.001$). Eight metastatic LCTs and one benign LCT had infiltrative margins. Foci of coagulative necrosis were noted to have occurred in 10 metastatic LCTs, whereas vascular invasion was identified within nine of 14 metastatic LCTs and none of 37 benign LCTs. Benign LCTs had shown less than 2 mitoses per 10 high-power fields (HPFs), whereas a high mitotic count (with a range of between 3 and 50 mitoses per 10 HPFs, was a feature of malignant LCTs. Colecchia et al. [29] stated the ensuing:

- These parameters were selected by utilization of an inferential analysis based upon univariate logistic regression models to develop a score.

- A LeSS of <4 had correctly identified all histologically and clinically benign LCTs.
- A LeSS of ≥4 had correctly identified all malignant LCTs.
- MDM2 and CDK4 immunohistochemistry staining was applied in all 51 cases: benign LCTs were negative; three of 11 malignant LCTs (27%) had exhibited strong and diffuse immunopositivity and high levels of MDM2 and CDK4 amplification as determined with fluorescence in-situ hybridisation analysis and next-generation sequencing.

Colecchia et al. [29] concluded that they had provided a new tool, the LeSS, for the prediction of malignant behaviour in LCTs.

Zhang et al. [30] stated the following:

- The diagnosis as well as sub-classification of Sertoli cell tumours (SCT) of the testis are often challenging to general surgical pathologists due to the rarity of the tumours.
- Immunohistochemical study up to the time of their article had limited diagnostic value.
- Nuclear localization of β-catenin, which correlated closely with CTNNB1 gene mutation, had been recently reported in SCTs.

Zhang et al. [30] investigated the utility of β-catenin nuclear localization in diagnosing SCTs and differentiating them from other testicular sex cord-stromal tumours. Zhang et al. [30] evaluated immunohistochemical staining for β-catenin in 87 cases of testicular sex cord-stromal tumour: 33 SCTs, not otherwise specified (SCT-NOS) (15 with benign and 18 with malignant features), 10 sclerosing SCTs (SSCT), 5 large-cell calcifying SCTs (LCCSCT), 6 Sertoli-stromal cell tumours, 10 Leydig cell tumours, 7 juvenile granulosa cell tumours, 4 adult granulosa cell tumours, and 12 sex cord-stromal tumours, unclassified. Twenty-one of 33 SCT-NOS that amounted to 64% SCT-NOS, 6 of 10 SSCTs that amounted to 60% SSCTs, and 4 of 6 (67%) Sertoli-stromal cell tumours had exhibited strong, diffuse β-catenin nuclear staining. Nuclear β-catenin positivity was found to be more frequent in SCTs-NOS with benign features than in those with malignant features (93% and 39%, respectively, P=0.13) and, in the Sertoli-stromal cell tumours, occurred only in the Sertoli component. All 5 LCCSCTs and all other types of sex cord-stromal tumour were found to have exhibited negative staining for β-catenin nuclear staining. Zhang et al. [30] made the ensuing conclusions:

- SCT-NOS and SSCT frequently showed β-catenin nuclear localization.
- Positive nuclear staining of β-catenin is specific for SCT-NOS, SSCT, and Sertoli-stromal cell tumour among testicular sex cord-stromal tumours but has limited sensitivity (63%) in this group.
- The similar reactivity of SCT-NOS and SSCT provides additional support that these 2 variants are not distinct entities.

Moreno Muno et al. [31] reported light and electron-microscopic study of a Leydig cell testicular tumour in an 18-year-old male. He was found to have bilateral gynaecomastia and normal hormonal blood levels. Emphasis on the diagnostic value of electron-microscopy was remarked upon, based upon the following ultrastructural characteristics of the cells; (1) Ovoid shaped nuclei with ondulating contours and dispersed and homogeneous chromatin, (2) Rich agranular endoplasmic reticulum with frequent special modifications, such as membranous whorls with a central cytoplasmic mass or lipid droplets, (3) Numerous mitochondria with occasional tubular cristae, (4) Numerous lipid vacuoles. Other structures that were also identified within this tumour included: Reinke crystalloids, cytoplasmic microbodies, myelin figures, gap-type junctional complexes and para-crystalline inclusions of Payer type E, which are less common.

Verdorfer et al. [32] iterated that the following:

- Genetic features of the uncommon Leydig cell tumours (LCT) are largely unknown.
- Consequently, it is of great importance to elucidate the pathogenesis of testicular germ cell tumours by means of cytogenetic as well as by molecular biological investigations.

Verdorfer et al. [32] undertook a study which aimed at the examination of cytogenetical features of these tumours in a large series of LCT. The study comprised of formalin-fixed, paraffin-embedded tissue samples from 25 LCT which were utilized to analyse the chromosomal constitution using comparative genomic hybridization (CGH). In majority of the studied cases, the aberrant cell population was additionally defined by interphase fluorescence in situ hybridization (I-FISH). Verdofer et al. [32] stated that their molecular-cytogenetic study had indicated chromosomal imbalances in the majority of their cases which was found in 21 out of 25 cases that amounted to 84% of the cases. The most frequent findings were gain of chromosome X, 19 or 19p and loss on chromosome 8 and 16

Libé et al. [33] stated the following:

- Leydig cell tumours of the testis are the commonest type of non-germ cell testicular tumours.
- In adult patients, gynecomastia, oligozoospermia, erectile dysfunction, and other signs of feminization could be present, whereas testosterone levels tend to be frequently within the normal range or slightly reduced.

Libé et al. [33] reported a patient with a history of impaired sexual function, as well as progressive enlargement of the left testis, without gynecomastia. His hormonal assessment demonstrated very high testosterone, oestrogen, and pan-alpha-inhibin levels. He had magnetic resonance imaging (MRI) scan which demonstrated the presence of left testicular hypertrophy without evidence of testicular mass. After he had undergone left orchidectomy, histopathology examination of the testis specimen confirmed the diagnosis of Leydig cell tumour, and his steroid hormone levels normalized. A heterozygous missense somatic gsp mutation (R201C) was found within his tumoral tissue, whereas no mutation was found within the encompassing normal tissue or within leukocyte DNA. Libé et al. [33] iterated that:

- Their reported case had provided evidence that somatic activating gsp mutation in Leydig cells might result in tumour development, leading to overexpression of the inhibin alpha subunit and hyperactivity of the testosterone biosynthetic pathway.

Lakis et al. [35] iterated that insulin-like 3 (INSL3) is a hormone which is produced by Leydig cells (LCs) and leads to physiological testicular descent during embryonic development. Lakis et al. [35] investigated the immunohistochemistry expression of INSL3 in normal LCs, in Leydig cell tumour (LCT) (n=17 including 15 testes and 2 ovaries) and in Leydig cell hyperplasia (LCH) (n=10). Lakis et al. [35] reported that normally distributed LCs had shown strong immunostaining within the cytoplasm in all cases. All 10 cases that amounted to 100% of LCH were strongly and diffusely positive within the inter-tubular areas. Six cases of LCH had nodules which had ranged in size from 0.2 cm to 0.9 cm with variable INSL3 staining. Fifteen of 17 LCTs that amounted to 88.2% of LCTs showed marked decrease INSL3 staining, 10 out of 17 that amounted to 58.8% were completely negative, and 5 out of 17 that amounted to 29.4% were only focally positive. Two cases with multifocal LCTs had exhibited strong and diffuse cytoplasmic staining of LCs around seminiferous tubules while the LCTs were negative. Two cases that were diagnosed as LCT had exhibited strongly positive staining for INSL3. Other sex cord stromal tumours that were tested were consistently negative including Sertoli-cell tumour (n=4) of testis, granulosa cell tumour of testis (n=2),

and fibro the coma of testis (n=1). Lakis et al. [35] made the ensuing conclusions:

- Their results had contrasted with those of previously published studies, and had shown that the great majority of LCTs are negative or have decreased expression of INSL3 while its expression is retained in LCH.
- INSL3 negative nodules within LCH might represent early LCTs.
- INSL3 immunostaining could be helpful to highlight LCs in cases where it is difficult to identify them, for example in small testicular biopsies that are undertaken for infertility workup, and in the differential diagnosis between florid LCH and LCT.

Summary and Conclusions

- Leydig cell tumours are rare tumours that tend to afflict the testis and on rarer occasions, Leydig cell tumours afflict the epididymis.
- Leydig cell tumour like other tumours of the testis, most often does manifest as painless intra-scrotal testicular mass.
- In view of the hormonally active nature of Leydig cell tumours of testis, patients who are afflicted by this tumour may manifest with gynaecomastia, tenderness within the breast, precocious puberty, hypogonadism, or erectile dysfunction.
- Leydig cell tumours of the testis could affect all age groups of males including children and adults.
- Majority of Leydig cell tumours of the testis are benign tumours but a small proportion of Leydig cell tumours are malignant tumours that portend an aggressive biological behaviour, and these malignant tumours tend to be associated with poor prognosis.
- The undertaking of radical orchidectomy alone has been generally a curative treatment for benign Leydig cell tumours of testis and benign Leydig cell tumours of the epididymis.
- Testis-sparing surgery or enucleation of the testicular tumour whilst preserving the normal testis could be considered if there is clinical suspicion that the testis tumour is a Leydig cell tumour, and the pre-operative serum testicular tumour marker levels are within normal ranges as well as when the size of the tumour is small and preferably less than 2.5 cm.
- Intra-operative frozen section pathology examination of the testicular tumour should be undertaken to confirm the diagnosis of benign Leydig cell tumour, and if the pathology examination does confirm malignant Leydig cell tumour of testis, radical orchidectomy should be undertaken instead of enucleation of the tumour or testis preserving surgery.
- Leydig cell tumours of the testis that are malignant, do demonstrate malignancy by their metastasizing.
- About ten percent (10%) of Leydig cell tumours do exhibit malignant biological behaviour.
- The treatment of malignant Leydig cell tumour is testis is the undertaking of radical orchidectomy plus retroperitoneal lymph node dissection, considering that it had been demonstrated that generally, malignant Leydig cell tumours of testis had tended to be resistant to radiotherapy and chemotherapy.
- Experience related to the treatment of malignant Leydig cell tumour of testis with utilization of immunotherapy in combination with radical orchidectomy plus chemo-radiation has not been reported.
- Leydig cell tumour affecting the epididymis alone should also be treated like treatment for Leydig cell tumour of testis.

Conflict of interest – none

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References

1. Calvert T, Elsworth P I, Talavera F, Kim E D. Sebanegh Jr, (2023) Leydig Cell Tumors. Medscape.
2. Nicol D (Chair), Beney D, Boormans JL et al; European Association of Urology. EAU Guidelines on Testicular Cancer.
3. David J, Chumbalkar V, Chadha J. An insight into metastatic Leydig cell tumors: A case report. *SAGE Open Med Case Rep*. 2023
4. Farkas LM, Székely JG, Pusztai C, Baki M. (2000) High frequency of metastatic Leydig cell testicular tumours. Oncology. 59(2):118-121.
5. Leonhartsberger N, Ramoner R, Aigner F, Stoehr B, Pichler R, et al. (2011) Increased incidence of Leydig cell tumours of the testis in the era of improved imaging techniques.
6. Lock G, Schmidt C, Helmich F, Stolle E, Dieckmann KP. (2011) Early experience with contrast-enhanced ultrasound in the diagnosis of testicular masses: a feasibility study. *Urology*. 77(5):1049-1053.
7. Henderson CG, Ahmed AA, Sesterhenn I, Belman AB, Rushton HG. (2006) Enucleation for prepubertal leydig cell tumor. J Urol. 176(2):703-705.
8. J.S. Valla for the Group D'Etude en Urologie Pédiatrique. (2001) Testis-sparing surgery for benign testicular tumors in children. *J Urol*. 165(6 Pt 2):2280-2283.
9. Carmignani L, Colombo R, Gadda F, Galasso G, Lania A, et. al., (2007) Conservative surgical therapy for leydig cell tumor. *J Urol*. 178(2):507-511.
10. Chen Z, Aron M. Tretiakova M, Zynger D L. (2021) Testis & para-testis Sex cord stromal tumours Leydig cell tumor.
11. Ruf CG, Sanatgar N, Isbarn H, Ruf B, Simon J, et. al., (2020) Leydig-cell tumour of the testis: retrospective analysis of clinical and therapeutic features in 204 cases. *World J Urol*. 38(11):2857-2862.
12. Heer R, Jackson MJ, El-Sherif A, Thomas DJ. (2010) Twenty-nine Leydig cell tumors: Histological features, outcomes and implications for management. *International journal of urology*. 17(10):886-889.
13. Jou P, Maclennan GT. (2009) Leydig cell tumor of the testis. *J Urol*. 181(5):2299-2300.
14. Luckie TM, Danzig M, Zhou S, Wu H, Cost NG, et. al., (2019) A Multicenter Retrospective Review of Pediatric Leydig Cell Tumor of the Testis. *J Pediatr Hematol Oncol*. 41(1):74-76.

15. Carvajal-Carmona LG, Alam NA, Pollard PJ, Jones AM, Barclay E, et. al., (2006) Adult leydig cell tumors of the testis caused by germline fumarate hydratase mutations. *J Clin Endocrinol Metab*. 91(8):3071-3075.
16. Huang Y, Song J, Xu M, Zan Q. (2013) Primary Leydig cell tumour of epididymis: a rare case report with review of literature. *Andrologia*. 45(6):430-433.
17. Al-Agha OM, Axiotis CA. (2007) An in-depth look at Leydig cell tumor of the testis. Arch Pathol Lab Med. 131(2):311-317.
18. Liu G, Duranteau L, Carel JC, Monroe J, Doyle DA, (1999) Leydig-cell tumors caused by an activating mutation of the gene encoding the luteinizing hormone receptor. *N Engl J Med*. 341(23):1731-1736.
19. Pozza C, Pofi R, Tenuta M, Tarsitano MG, Sbardella E, et al., (2019). Clinical presentation, management and follow-up of 83 patients with Leydig cell tumors of the testis: a prospective case-cohort study. *Hum Reprod*. 34(8):1389-1403.
20. Papadimitris C, Alevizaki M, Pantazopoulos D, Nakopoulou L, Athanassiades P, et al., (2000) Cushing syndrome as the presenting feature of metastatic Leydig cell tumor of the testis. *Urology*. 56(1):153.
21. Kim I, Young RH, Scully RE. (1985) Leydig cell tumors of the testis. A clinicopathological analysis of 40 cases and review of the literature. *Am J Surg Pathol*. 9(3):177-192.
22. Fankhauser CD, Grogg JB, Hayoz S, Wettstein MS, Dieckmann KP, (2020). Risk Factors and Treatment Outcomes of 1,375 Patients with Testicular Leydig Cell Tumors: *Analysis of Published Case Series Data. J Urol*. 203(5):949-956.
23. Cost NG, Maroni P, Flaig TW. (2014) Metastatic relapse after initial clinical stage I testicular Leydig cell tumor. Oncology (Williston Park). 28(3):211-214.
24. Mesa H, Gilles S, Smith S, Dachel S, Larson W, Manivel JC. (2015) The mystery of the vanishing Reinke crystals. *Hum Pathol*. 46(4):600-606.
25. Hribar KP, Warner NE, Sherrod AE. (2005) Cytologic identification of reinke crystalloids in scrapings and imprints of fresh testicular tumors: a simple and rapid technique for intraoperative use. *Arch Pathol Lab Med*. 129(3): e65-66.
26. Mooney KL, Kao CS. (2018) A Contemporary Review of Common Adult Non-germ Cell Tumors of the Testis and Paratestis. *Surg Pathol Clin*. 11(4):739-758.
27. Ulbright TM, Srigley JR, Hatzianastassiou DK, Young RH. (2002) Leydig cell tumors of the testis with unusual features: adipose differentiation, calcification with ossification, and spindle-shaped tumor cells. *Am J Surg Pathol*. 26(11):1424-1433.
28. Biemer J, Pambuccian SE, Barkan GA. (2019) Fine needle aspiration diagnosis of metastatic Leydig cell tumor. Report of a case and review of the literature. *J Am Soc Cytopathol*. 8(4):220-229.
29. Colecchia M, Bertolotti A, Paolini B, Giunchi F, Necchi A, (2021) The Leydig cell tumour Scaled Score (LeSS): a method to distinguish benign from malignant cases, with additional correlation with MDM2 and CDK4 amplification. *Histopathology*. 78(2):290-299.
30. Zhang C, Ulbright TM. (2015) Nuclear Localization of β-Catenin in Sertoli Cell Tumors and Other Sex Cord-Stromal Tumors of the Testis: An Immunohistochemical Study of 87 Cases. *Am J Surg Pathol*. 39(10):1390-1394.
31. Moreno Muro M, Coca Menchero S, Martos Pelegrín JA, Izquierdo Hernández A. (1989) Ultrastructure and light microscopical study of a Leydig cell tumor of the testis associated with bilateral gynaecomastia. *Histol Histopathol*. 4(2):247-250.
32. Verdorfer I, Horst D, Höllrigl A, Susani M, Hartmann A, (2007) Leydig cell tumors of the testis: a molecular-cytogenetic study based on a large series of patients. *Oncol Rep*.17(3):585-589.
33. Libé R, Fratticci A, Lahlou N, Jornayvaz FR, Tissier F, (2012) A rare cause of hypertestosteronemia in a 68-year-old patient: a Leydig cell tumor due to a somatic GNAS (guanine nucleotide-binding protein, alpha-stimulating activity polypeptide 1)-activating mutation. *J Androl*. Jul-Aug;33(4):578-584.
34. Idrees MT, Ulbright TM, Oliva E, Young RH, Montironi R, (2017) Members of the International Society of Urological Pathology Testicular Tumour Panel. The World Health Organization 2016 classification of testicular non-germ cell tumours: a review and update from the International Society of Urological Pathology Testis Consultation Panel. *Histopathology*. 70(4):513-521.
35. Lakis NS, Lombardo KA, Mangray S, Netto GJ, Salles D, Matoso A. (2019) INSL3 Expression in Leydig Cell Hyperplasia and Leydig Cell Tumors. *Appl Immunohistochem Mol Morphol*. 27(3):203-209.
36. Petersson F, Bulimbasic S, Sima R, Michal M, Hora M, et.al., (2010) Large cell calcifying Sertoli cell tumor: a clinicopathologic study of 1 malignant and 3 benign tumors using histomorphology, immunohistochemistry, ultrastructure, comparative genomic hybridization, and polymerase chain reaction analysis of the PRKAR1A gene. *Hum Pathol*. 41(4):552-559.
37. Abe T, Takaha N, Tsujimura A, Nonomura N, Matsumiya K, et.al., (2003) Leydig cell tumor of the testis presenting male infertility: a case report. *Hinyokika Kiyo*. 49(1):39-42. Japanese.
38. Shiraishi Y, Nishiyama H, Okubo K, Iguchi R, Inoue T, et. al., (2009) Testicular Leydig cell tumor presenting as male infertility: a case report. *Hinyokika Kiyo*. 55(12):777-781.
39. Komai Y, Urushibara M, Morimoto S, Sakai K, Kobanawa K. (2004) Male infertility in an adult with unilateral Leydig cell tumor of the undescended testis. *Hinyokika Kiyo*. 50(12):881-883.
40. Medina Pérez M, Valero Puerta J, Sánchez González M. (1999) Tumor de células de Leydig oculto en testículo criptorquídico An occult Leydig-cell tumor in a cryptorchid testis. *Arch Esp Urol*. 52(1):76-78.
41. Efthimiou I, Mamoulakis C, Papageorgiou G, Kazoulis S, Prevedorou D, Kontogiorgos G, Christoulakis I. Unilateral malignant leydig cell tumor of testis in a patient with contralateral cryptorchidism. *Urol J*. 2009 Winter;6(1):60-62.
42. Michalec J, Jardanowski R, Pykało R. (1997) Leydigioma--rzadki nowotwór jadra rozpoznany u dorosłego mezczyzny w jadrze zlokalizowanym w jamie brzusznej Leydigioma--rare testicular tumor diagnosed in an adult male with undescended intraabdominal testis. Wiad Lek. 50(4-6):128-131.
43. Taguchi S, Yamaguchi K, Takahashi S, Iida K, Mizutani T, Tominaga T, Mori M, Homma Y. (2011) Leydig cell tumor of the testis: a case report. Hinyokika Kiyo. 57(9):521-524.
44. Harada Y, Kuroda H, Seguchi T, Higashino M, Senoh H, Tsujimoto M. (1998) Leydig cell tumor of the testis: a case report]. Hinyokika Kiyo. 44(1):61-63.
45. Sugimoto K, Matsumoto S, Nose K, Kurita T, Uemura H, Park YC, Hanai J. (2006) A malignant Leydig cell tumor of the testis. *Int Urol Nephrol*. 38(2):291-292.
46. Bertola G, Giambona S, Balza G, Sironi C, Colombo E, et.al., (2006) Una causa infrequente di ginecomastia: il leydigioma del testicolo. Profilo ormonale prima e dopo l'orchiectomia [An uncommon cause of gynecomastia: testicular Leydig cell tumor. Hormonal profile before and after orchiectomy]. *Recenti Prog Med*. 97(2):85-88.

47. Dounis A, Papacharalampous A. (1997) Clinically occult Leydig cell tumor in a cryptorchid man. Report of a case presenting with unilateral gynecomastia and impotence. *Eur Urol*. 32(3):368-370.
48. De Jong Z, Pontonnier F, Plante P, Bennet A, Escourrou G, et. al., (1988) Tumeur testiculaire bilatérale à cellules de Leydig. Conduite à tenir [Bilateral testicular Leydig cell tumor. Procedure to follow]. *J Urol* (Paris). 94(4):217-221.
49. Giannarini G, Mogorovich A, Menchini Fabris F, Morelli G, De Maria M, et.al., (2007) Long-term followup after elective testis sparing surgery for Leydig cell tumors: a single center experience. J Urol. 178(3 Pt 1):872-876
50. C A, Vergho DC, Katzenberger T, Brix D, Kocot A, (2009) Testis-sparing surgery versus radical orchiectomy in patients with Leydig cell tumors. *Urology.* Aug;74(2):370-372.
51. Laclergerie F, Mouillet G, Frontczak A, Balssa L, Eschwege P, (2018) Testicle-sparing surgery versus radical orchiectomy in the management of Leydig cell tumors: results from a multicenter study. *World J Urol*. 36(3):427-433.
52. Loeser A, Vergho DC, Katzenberger T, Brix D, Kocot A, (2009) Testis-sparing surgery versus radical orchiectomy in patients with Leydig cell tumors. *Urology*. 74(2):370-372.
53. Canda AE, Atmaca AF, Ozdemir AT, Akbulut Z, Balbay MD. (2009) Testis sparing surgery for sequential bilateral testicular tumors. *Can J Urol*. 16(3):4677-4681.
54. Bozzini G, Ratti D, Carmignani L; en representación de Young Academic Urologists (YAU) Men's Health Group. Treatment of leydig cell tumours of the testis: Can testis-sparing surgery replace radical orchidectomy? Results of a systematic review. Actas Urol Esp. 2017 Apr;41(3):146-154.
55. Kong Q, Yu Y, Tian T, Zhang H, Sun M, Liu R, Liu Y. (2020) Leydig cell tumor of a testis with azoospermia: A case report and literature review. Medicine (Baltimore). Sep 4;99(36): e22085.
56. Rossato M, Tavolini IM, Calcagno A, Gardiman M, Dal Moro F, Artibani W. (2011) The novel hormone INSL3 is expressed in human testicular Leydig cell tumors: a clinical and immunohistochemical study. *Urol Oncol*. Jan-Feb;29(1):33-37.
57. Mukhopadhyay M, Das C, Sarkar S, Mukhopadhyay B, Mukhopadhyay B, Patra R. (2017) Leydig Cell Tumor of Testis in a Child: An Uncommon Presentation. J Indian Assoc Pediatr Surg. 22(3):181-183.
58. Zeuschner P, Veith C, Linxweiler J, Stöckle M, Heinzelbecker J. Two Years of Gynecomastia Caused by Leydig Cell Tumor. Case Rep Urol. 2018 Jul 19; 2018:7202560.
59. Genov PP, Georgieva DP, Koleva GV, Kolev NH, Dunev VR, Stoykov BA. Management of Leydig cell tumors of the testis-a case report. Urol Case Rep. 2019 Oct 31; 28:101064.
60. Zhu J, Luan Y, Li H. Management of testicular Leydig cell tumor: A case report. Medicine (Baltimore). 2018 Jun;97(25): e11158.
61. Justo RM, Bernabe E Neto, Ronchini MC, Lucas E Filho, Saber G, da Silva LCZ. Malignant leydig cell tumor in a 91-year-old man: Case report. Int Braz J Urol. 2019 Nov-Dec;45(6):1260-1265.
62. Stephenson AJ, Gilligan JD. Neoplasms of the Testis. In: Wein AJ, Kavoussi LR, Novick LR, Partin AW, Peters CA, editors. Campbell-Walsh urology. 11th ed. Philadelphia: Saunders Elsevier; 2016. pp. 784–814.
63. Cervós-Navarro J, Tonutti E, Bayer JM. Electron microscope study of an androgen-forming Leydig cell tumor. Endokrinologie. 1964; 47:23-51.
64. Cruceyra Betriu G, Tejido Sánchez A, Duarte Ojeda JM, (2002) García De La Torre JP, De La Morena Gallego JM, Martínez Silva V, Leiva Galvis O. Tumor de células de leydig: presentación de ocho casos y revisión de la literatura [Leydig cell tumor: report of 8 cases and review of the literature]. *Actas Urol Esp*. Jan;26(1):36-40.
65. Carmignani L, Salvioni R, Gadda F, Colecchia M, Gazzano G, Torelli T, Rocco F, Colpi GM, Pizzocaro G. Long-term follow-up and clinical characteristics of testicular Leydig cell tumor: experience with 24 cases. *J Urol*. 2006 Nov;176(5):2040-2043
66. Lioe TF, (1993) Biggart JD. Tumours of the spermatic cord and paratesticular tissue. A clinicopathological study. *Br J Urol*. 71(5):600-606.
67. Sengupta S, Chatterjee U, Sarkar K, Chatterjee S, Kundu A. (2010) Leydig cell tumor: a report of two cases with unusual presentation. Indian J Pathol Microbiol. 53:796-798.
68. Unlüer E, Ozcan D, Altin S. (1990) Malignant Leydig cell tumour of the testis: a case report and review of the literature. Int Urol Nephrol.;22(5):455-460.
69. Singh V, Chaudhary H, Srivastava A. (2004) Leydig cell tumor of the testis - a case report. *Indian J Urol*.166:20.
70. Kelalis P, King L., Bellman A. Genitourinary tumors. *Clinical pedriatric urology*. 3rd edition. pp. 1462-1463.
71. Mesa H, Gilles S, Smith S, Dachel S, Larson W, (2015) The mystery of the vanishing Reinke crystals. Hum Pathol. 46(4):600-606.

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