

## ORIGINAL PAPER

# Beyond germ cell tumors: Focus on Leydig cell neoplasms from a single-center experience

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**Summary** *Introduction: Leydig cell tumors (LCTs) are rare testicular neoplasms that account for a small proportion of testicular tumors and are often diagnosed incidentally or on investigation of infertility or hormonal symptoms. Despite their generally benign behaviour, a small percentage may have malignant potential, which poses a diagnostic and therapeutic challenge due to the lack of standardized guidelines.*

*Materials and methods: We retrospectively analysed four cases of histologically confirmed LCTs diagnosed and treated at a single institution between 2000 and 2024. Clinical, biochemical, radiologic, surgical, and pathologic data were collected and analysed.*

*Results: Patients presented with a variety of clinical histories, including testicular swelling, infertility, or incidental findings. Tumor size ranged from 1.8 to 3.5 cm. All patients underwent radical inguinal orchiectomy, and histology confirmed benign LCTs without high-risk features such as necrosis, mitotic activity, or vascular invasion. Hormonal profiles and imaging were key to the diagnostic process, although findings sometimes mimicked germ cell tumours. Adjuvant therapy was not required, and all patients remained disease-free at follow-up.*

*Conclusions: This case series highlights the heterogeneity of LCT presentations and emphasizes the importance of accurate diagnosis, individualized treatment, and multidisciplinary management. Standardized protocols, greater awareness and timely imaging are essential to avoid overtreatment and improve outcomes in LCT patients.*

**KEY WORDS:** Testis; Leydig cells neoplasm; Leydig cell tumors; Testicular cancer; Orchiectomy; Testis-sparing surgery.

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## INTRODUCTION

Testicular tumours account for only 1-2% of all cancer diagnoses in men worldwide, with the highest incidence between the ages of 15 and 44 (1, 2).

These neoplasms can originate from any cell in the testes, but are mainly divided into two categories: germ cell tumours (which account for about 95% of cases), and sex

cord stromal tumours, (which account for the remaining 5% in adults), with *Leydig cell tumours* (LCTs) being the most prevalent among the latter (3). Extra testicular localizations are even rarer (4).

LCTs originate from the cells of the same name, which are located between the seminiferous tubules and are responsible for testosterone production when stimulated by the luteinizing hormone. Most cases are benign neoplasms, but a proportion of 5 to 10% show malignant behaviour, with the incidence being highest in prepubertal age and between 30 and 60 years (4-6).

In post-pubertal men, elevated circulating androgen levels caused by these tumours may be clinically unremarkable. Gynecomastia is the most common hormonal manifestation, although decreased libido, erectile dysfunction, azoospermia, primary infertility, and less commonly, Cushing's syndrome may also occur (7, 8).

Ultrasound is essential for the evaluation of testicular masses. However, the sonographic appearance of LCTs can mimic germ cell tumours, often leading to radical inguinal orchiectomy. *Testis-sparing surgery* (TSS) may be considered for small (< 2.5 cm), histologically characterized lesions (9).

Metastatic spread, although rare, primarily involves retroperitoneal lymph nodes, lungs, and liver (10, 11). Radio- and chemotherapies are not very effective in these cases and have limited impact on survival (12). Considering all these aspects, *retroperitoneal lymph node dissection* (RPLND) has been proposed in selected high-risk cases.

Identified risk criteria for the possible performance of RPLND include: tumor dimension above 5 cm, presence of necrosis, moderate or severe nuclear atypia, angioinvasion, positive resection margins, more than 5 mitoses per high-power field (13).

Due to the rarity of LCTs and the absence of standardized guidelines, management often relies on multidisciplinary evaluation and individual clinical judgment.

This study presents the clinical cases of LCTs that were referred to our institution between 2000 and 2024 and discusses diagnostic and therapeutic considerations considering current literature.

**MATERIALS AND METHODS**

All patients diagnosed with LCTs between January 2000 and December 2024 at a single institution were retrospectively selected. The study was conducted following the principles of the Declaration of Helsinki. Informed consent was obtained from all patients enrolled in the study. Patient data were obtained from the institution's electronic medical records and clinical prospectively collected databases. Inclusion criteria were a histologically confirmed diagnosis of LCT, either after orchiectomy or TSS. Exclusion criteria included patients with incomplete medical records or follow-up data.

Clinical variables included age at diagnosis, presenting symptoms, serum hormone levels (testosterone, estradiol, LH, FSH), tumour markers (AFP,  $\beta$ -hCG, LDH), imaging findings (ultrasound, CT or MRI), tumour laterality, and tumour size. Histopathologic features such as necrosis, nuclear atypia, angioinvasion, mitotic index, and resection margins were documented.

Treatment modalities were recorded, including the type of surgical procedure (radical inguinal orchiectomy or TSS), the use of RPLND, and any adjuvant therapies. Follow-up data included recurrence, metastasis, and overall survival. Descriptive statistics were used to summarize clinical and pathological characteristics. The results were analysed concerning known prognostic factors based on the current literature.

**RESULTS**

The results of the case series are reported in Table 1.

**Case 1**

The patient was a 22-year-old male, with a history of blunt testicular trauma in 2001 and in 2014. On both

occasions, he was clinically assessed in the emergency department, and apart from symptomatic pain relief, no further investigations or treatment were undertaken.

In January 2023, the patient underwent a urological examination due to persistent testicular swelling and pain. As part of the diagnostic work-up, tumour markers including beta-HCG, *alpha-fetoprotein* (AFP) and *lactate dehydrogenase* (LDH), an ultrasound (Figure 1) and a *magnetic resonance imaging* (MRI) of the testicles were performed and were determined.

A right testicular nodule was detected on the MRI. The

**Figure 1.**

Scrotal ultrasound image showing a hypoechoic area within the testicular parenchyma, suggestive of a testicular mass.



**Table 1.**

Summary of clinical and pathological features of four cases of Leydig cell tumour.

Variable	Case 1	Case 2	Case 3	Case 4
Age	22 years	59 years	46 years	31 years
Clinical presentation	Persistent testis swelling and pain	Suspected testicular mass	Left testicular mass on ultrasound	Right testicular lesion found during infertility work-up
Tumor markers	$\beta$ -HCG, AFP, LDH: assessed (values not given)	Not specified	LDH 226, $\beta$ -HCG 0, AFP 3.4	LDH 301, $\beta$ -HCG 0.1, AFP 3.2, CEA 0.5
Imaging	MRI: right testicular nodule	Not specified	Ultrasound: left testicular mass	Ultrasound: 22 mm lesion (right testis)
Surgical procedure	Right radical inguinal orchiectomy	Radical inguinal orchiectomy	Left radical inguinal orchiectomy	Right radical inguinal orchiectomy
Macroscopic description	3.5 cm hemorrhagic nodule in 6×4×3 cm testis	1.8 cm brownish lesion	Two fragments: 1.3×0.6 cm and 0.7×0.5 cm	2 cm lesion at lower pole of testis
Microscopic description	Monomorphic cells, eosinophilic cytoplasm, no mitoses or necrosis	Low mitotic activity, no necrosis	Polygonal eosinophilic cells, necrobiosis, vascular stroma	Typical Leydig cell features, no mitoses
Immunohistochemistry	Inhibin+, AR+, S-100-, OCT4-, CD117-, CD30-, PANCK-, SALL4-	Inhibin+, Melan-A+, AR+, OCT4-, CD117-, PLAP-, CD30-	Not detailed	Not detailed
Ki-67 Index	2%	Not specified	Not specified	0/10 HPF
Margins/Spermatic cord	Free of disease	Free of disease	Not specified	Not specified
Post-op Imaging/Follow-up	Not reported	Not reported	CT: small lymph nodes, liver calcification	CT (2010): no recurrence
Final diagnosis	Leydig cell tumor	Leydig cell tumor	Leydig cell tumor	Leydig cell tumor

patient underwent an intraoperative confirmatory biopsy, revealing a stromal testicular neoplasm, and subsequent surgical removal of the right testicle in March 2023.

The macroscopic pathological examination of the surgical specimen described a testis and epididymis measuring 6 × 4 × 3 cm, in continuity with a 6.5 cm spermatic cord. On dissection, a haemorrhagic area up to 3.5 cm in diameter was noted at the site of intraoperative sampling.

Microscopic analysis revealed a diffuse proliferation of monomorphic cells confined to the testicular tissue. These cells were characterized by a granular eosinophilic cytoplasm, round nuclei and a central nucleolus. There were no signs of mitotic activity or necrosis.

The immunohistochemical profile was as follows: positive for alpha-inhibin and androgen receptors; negative for S-100, OCT4, CD117, CD30, *pancytokeratin* (PANCK) and SALL4. The proliferation index determined by Ki-67 staining was 2%.

These findings were consistent with a sex cord stromal tumour that had the morphologic and immunohistochemical features of a benign LCT. The epididymis, spermatic cord, and surgical margin of the cord were all free of disease.

### Case 2

A 59-year-old male underwent orchiectomy due to a suspected testicular mass in 2023.

Macroscopic examination revealed a testis and epididymis measuring 5.4 × 4 × 3.3 cm connected to a 5 cm long spermatic cord. A brownish tumour with regular margins and a diameter of 1.8 cm was noted. The lesion appeared macroscopically well contained within the testicular parenchyma.

Histological analysis confirmed the diagnosis of a testicular neoplasm in the region of the spermatic cord, which had the characteristics of an LCT. The tumour was confined exclusively to the testis, with no evidence of lymphatic invasion or necrosis. Mitotic activity was low, quantified as 1 mitosis per 10 high-power fields.

The immunohistochemical profile showed positivity for inhibin, melan A, and androgen receptors. The tumour was negative for OCT4, CD117, *placental alkaline phosphatase* (PLAP), and CD30.

Both the spermatic cord and the surgical resection margins were found to be free of neoplastic involvement.

### Case 3

In September 2013, a 46-year-old male underwent an ultrasound examination, which revealed a left testicular mass.

The tumour marker analysis revealed the following values: LDH at 226 U/L, beta-HCG at 0.00 mIU/mL, and AFP at 3.4 ng/mL.

The patient was submitted to left radical inguinal orchiectomy (Figure 2).

A *frozen section examination* (FSE) during surgery was performed, identifying a Leydig cell tumour. A left radical inguinal orchiectomy was completed.

The final histological examination highlighted that two tissue fragments measuring 1.3 × 0.6 cm and 0.7 × 0.5 cm were analysed. The findings indicated a testicular stromal tumour with morphological features of a LCT.

### Figure 2.

Left testicle externalized from the scrotal sac and including the spermatic cord up to the internal inguinal orifice.



Microscopically, the lesion appeared as an unencapsulated solid neoplasm consisting of a thin fibrous and abundantly vascularized stroma. The growth pattern was trabecular or diffuse and consisted of partially contiguous polygonal cells of medium to large size with well-defined cell borders. The cytoplasm of these cells was granular and eosinophilic, sometimes vacuolated, and occasionally contained lipofuscin granules.

The nuclei of the neoplastic cells were round or ovoid and para-centrally arranged, with some cells having multiple nuclei. Areas of course, hyalinized fibrovascular septa were observed within the lesion, along with haemorrhagic foci and microfoci of necrobiosis.

The surrounding testicular parenchyma showed poorly differentiated spherical structures with varying degrees of intertubular oedema, confluent haemorrhagic lacunae, interstitial fibrosis, and testicular tubules with irregular profiles.

A CT scan of the chest and abdomen was performed after surgery. The scan revealed a 4 mm punctate parenchymal calcification in the left lobe of the liver. In addition, some lymph nodes were observed in the para-aortic region, mesenteric compartment, bilateral external iliac and bilateral inguinal regions, which showed non-specific features with a maximum diameter of 13 mm.

#### Case 4

In 2004, a 31-year-old male, during a testicular ultrasound examination for infertility, was diagnosed with a 22 mm lesion occupying a large part of the right testis and a grade III varicocele on the left side.

Subsequent laboratory tests revealed the following values: LDH at 301 U/L, *carcinoembryonic antigen* (CEA) at 0.5 ng/ml, alpha-1-fetoprotein (alpha 1 FP) at 3.2 ng/ml and beta-HCG at 0.10 mIU/ml.

In November 2004, the patient underwent a right radical inguinal orchiectomy.

Histologic examination of the surgical specimen revealed an intraparenchymal neoplasm with a diameter of approximately 2 cm located at the lower pole of the right testis. The histopathological diagnosis confirmed a LCT with a mitotic index of 0 per 10 *high-power fields* (HPF).

In April 2010, a further CT scan of the brain, chest, abdomen, and pelvis was performed, which was negative and showed no evidence of disease recurrence or metastasis.

#### DISCUSSION

The four clinical cases described in this study reflect a spectrum of different presentations, diagnostic challenges, and treatment approaches associated with LCTs, a rare subtype of testicular neoplasms that arise from the interstitial cells of the gonads. Although generally considered benign, LCTs have a documented, albeit low, potential for malignancy, making their early detection and appropriate clinical management essential.

Histologically, all four lesions were compatible with benign LCTs based on morphology and immunohistochemistry. None of them showed high-risk features such as marked atypia, necrosis or vascular invasion (13).

In the first case, there was a discrepancy between the intraoperative biopsy suggestive of a stromal tumor, and the final histologic result.

The absence of a malignant tumour illustrates the importance (and limitations) of preoperative diagnostics. As *Suardi et al.* emphasize, TSS with a FSE can be a sensible alternative in selected cases to avoid overtreatment (9).

*Testis-sparing surgery* (TSS) can be a valuable option for managing small, well-circumscribed Leydig cell tumors with imaging and intraoperative findings suggestive of benignity. When carefully selected, TSS allows preservation of hormonal and reproductive function without compromising oncologic safety (9).

This raises a fundamental clinical question: is a testicular biopsy always warranted, or could it be avoided in selected cases to prevent overtreatment or unnecessary surgery? This dilemma reflects the general uncertainty that often surrounds the diagnostic and therapeutic approach to rare tumours, where guidelines are lacking and clinical decisions may rely heavily on individual judgment.

Equally important is the initial diagnostic phase, where ultrasonography – the first imaging procedure in scrotal pathology – is not always systematically performed. In some of our cases, the lack of an early ultrasound may have delayed the diagnostic process. Given its non-invasive nature, its high sensitivity for testicular lesions, and its usefulness in characterizing intratesticular masses,

scrotal ultrasound should be considered an essential extension of the physical examination, especially in patients presenting with testicular discomfort, swelling, or a history of trauma (3).

The heterogeneity we observed in the anatomic-pathologic reports is another critical issue. Despite the central role of histopathology in making the diagnosis and determining the prognosis, the main prognostic indicators – such as mitotic index, necrosis, lymphatic vessel invasion, and margin status were not consistently reported in all reports. These elements are essential for assessing the risk of malignant behaviour (14, 15) and for deciding on further surgical interventions such as RPLND. The lack of standardization in reporting may reflect the variability of institutional protocols or the varying degree of familiarity of pathologists with this rare tumour entity.

As *Fankhauser et al.* emphasized in their analysis of 1375 LCTs, comprehensive pathology is essential to inform decisions about further treatment (13).

As regards follow-up, analysing over 1300 cases, *Fankhauser et al.* (13) showed that approximately 7% of patients with available follow-up developed metastases, with a median time to recurrence of 12 months. Age > 40 years, tumour size > 4 cm, and the presence of at least two histologic risk factors (e.g., necrosis, vascular invasion, atypia, mitotic rate > 3/HPF) significantly increased the likelihood of malignancy and, thus, the risk of metastatic progression. These results support the use of prognostic scoring systems to stratify patients and adjust the extent of surgical intervention and surveillance protocols (13).

In addition, their analysis revealed that for malignant LCTs, the efficacy of chemotherapy and radiotherapy is low, and most metastatic patients are treated surgically or observed. Therefore, RPLND remains crucial not only for staging but potentially also for curative intent in patients with resectable disease. This is consistent with previous findings by *Mosharafa et al.* (12), who reported long-term disease control with surgery alone in selected metastatic cases.

Clinicians must also consider clinical and endocrine signs that may be overlooked in routine practice, such as gynecomastia, infertility, decreased libido, or other symptoms related to hormonal imbalance. Serum hormone levels, including testosterone, estradiol, *luteinizing hormone* (LH) and *follicle stimulating hormone* (FSH), should be part of the initial workup, as LCTs are often hormonally active.

As *Papadimitris et al.* noted, hormonal dysfunction may be the only symptom in some LCTs (7).

In our series, all four patients are currently alive and free of disease. They are undergoing regular clinical and hormonal monitoring. Only one patient required long-term testosterone replacement therapy, emphasizing the need for close monitoring of endocrine function after orchiectomy, especially in younger patients or those with bilateral disease or pre-existing hypogonadism.

Our report highlights a broader problem in the management of rare testicular tumours: the lack of codified diagnostic pathways often leads to highly variable clinical decisions, especially in the early stages of treatment.

Delays in diagnosis, whether due to underestimated

symptoms or incomplete investigations, can harm outcomes.

In our experience, a multidisciplinary approach – including urologists, radiologists, pathologists, endocrinologists, and oncologists – ensures optimal care. As Zeuschner *et al.* (8) and others have reported, hormonal signs such as gynecomastia can precede testicular findings by months or years.

Based on these findings, it is imperative to raise awareness among primary care physicians and emergency physicians of the importance of timely and thorough diagnostic examination of testicular masses. LCTs are more frequent than generally believed (16). Accurate preoperative diagnosis is essential, especially in young males with suspected scrotal pathology, to avoid unnecessary radical surgery for benign lesions. Early use of imaging and hormonal evaluation, combined with multidisciplinary assessment, can guide more conservative and individualized treatment decisions. Ultrasonography of the testis should be routinely performed as part of the physical examination in any patient with testicular symptoms (17). Moreover, MRI can also be considered in the diagnostic workup. LCTs have distinctive contrast-enhanced MRI features that allow the differential diagnosis of incidental testicular lesions (rapid and marked wash-in). (18). In this context, synchronous bilateral testicular lesions, though extremely rare, should not be overlooked. Their management follows the same principles as unilateral disease, with radical orchiectomy as the standard; however, in selected cases, testis-sparing surgery combined with onco-testicular sperm extraction (TESE) offers a promising fertility-preserving alternative (19).

Some limitations of this study should be mentioned. First, its retrospective design inherently carries the risk of selection and information bias. Second, the generalizability of the results to broader populations may be limited since the study was conducted at a single institution. The results should be validated in future, robust, high-quality comparative studies with other types of testicular tumours. In addition, the relatively small sample size reflects the rarity of LCTs and limits the statistical power to draw definitive conclusions. Finally, the lack of standardized treatment protocols during the long study period may have led to variations in the treatment of patients.

## DECLARATIONS

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## CONCLUSIONS

Despite their rarity, LCTs require a structured, evidence-based approach to ensure optimal patient outcomes. Our case series illustrates the challenges posed by diagnostic uncertainty, inconsistent pathology reports, and the need for coordinated, interdisciplinary treatment. Improved education, standardization of guidelines, and early referral to specialized centers are key strategies to improve the management of these complex cases.

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