



Testis-sparing Surgery for Pediatric Leydig Cell Tumors: Evidence of Favorable Outcomes Irrespective of Surgical Margins

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OBJECTIVE	To review our single institution experience, exploring the role of testis-sparing surgical resection in a cohort of children with Testicular Leydig cell tumors (LCTs).
MATERIALS AND METHODS	We reviewed all consecutive children presenting with testicular tumors between 2003 and 2017 (n = 66), excluding patients with alternative pathologies (n = 57). Subsequently data were collected on age at surgery, laterality, type of surgery, operative time, presenting symptoms, serum markers, imaging findings, frozen section, final pathology, and follow-up.
RESULTS	During the study period, a total of 9 (9/66; 14%) children were treated for LCT of the testis. Age at surgery was 8.4 ± 1.7 years and the majority (7/9; 77%) had unilateral disease. Most presented with a testicular mass, and 3 (33%) complained of testicular pain. None of the patients had elevated tumor markers. The primary method of management was ultrasound-guided testis-sparing surgery, with an operative time of 98.5 ± 58.7 minutes. Mean tumor size was 15 ± 10.8 mm (range 5-40 mm). In 2 of 6 patients with positive margins radical orchidectomy was performed without residual disease encountered. At a mean follow-up of 31.8 ± 26.3 months (range 2-87) none of the patients demonstrated disease recurrence.
CONCLUSION	Our data suggest that LCT in children is associated with a good prognosis, and that TSS is a reasonable surgical approach without detrimental perioperative morbidity or negative long-term outcomes. Moreover, positive margins should not prompt a reflex decision for completion of orchidectomy. UROLOGY 134: 203–208, 2019. © 2019 Elsevier Inc.

Leydig cell tumors (LCTs) account for 0.8%-3% of all testicular neoplasms,¹ occurring most frequently in men between the third and sixth decades of life.² In the adult population, these tumors have been reported to carry a small malignancy risk, supporting the time-honored approach of radical resection.³ Nevertheless, with better understanding of the disease's natural history, in recent years testis-sparing surgery (TSS) has gained popularity, particularly for those with small, incidentally detected lesions.^{4,5}

LCTs are diagnosed in 4%-9% of testis tumors in prepubertal boys.⁶ While their etiology is not fully elucidated, it has been hypothesized that dysregulation of the hypothalamic-pituitary-testicular axis may lead to hormone-mediated stimulation and proliferation of Leydig cells.⁷ This

may explain why LCTs are often associated with an excess of sex steroid production, although clinical symptoms of endocrine disturbance are not always observed.⁷

The natural history of LCT in children is unclear. Studies from the adult literature support a benign course of the disease in most patients² while others report a highly variable rate of metastatic progression.^{1,8,9} Therefore, optimal surgical management of LCT remains controversial, with radical orchidectomy and TSS offering competing options.^{2,10} In order to explore the role of TSS in pediatric patients, with LCT, herein we report a single-institution case series on the management of a cohort of children with these neoplasms. We hypothesized that LCTs in children behave in a benign fashion and hence, similar to other prepubertal tumors, are amenable to TSS.

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MATERIALS AND METHODS

After obtaining institutional ethics approval (REB#1000055097), we retrospectively reviewed medical records and imaging studies of all children presenting with testicular lesions between 2003 and 2017. We excluded patients with additional pathologies that may have impacted proper analysis. We subsequently collected data on

the following variables: age at surgery, laterality of the disease, type of surgery, operative time, presenting symptoms, serum tumor markers (β -human chorionic gonadotropin, α -fetoprotein, and lactate dehydrogenase), hormonal profile (luteinizing hormone, follicle stimulating hormone, and serum testosterone), imaging findings, frozen section results, final pathology, margin status, and follow-up time.

Based on previous data from our institution, we favor TSS for confined neoplasms with negative tumor markers.¹¹ In those cases in particular, any metastatic evaluation such as retroperitoneal imaging is deferred and is only done if tissue shows malignancy.

The surgical procedure is carried through an inguinal incision, with early control of the spermatic cord, prior to delivering the testis. After opening the tunica vaginalis, the gonad is inspected by palpation and/or intraoperative ultrasound. Intraoperative ultrasound is favored for lesions that are nonpalpable, multifocal or deep in the parenchyma of the testis. It is also performed to document absence of other unexpected lesions. At our institution, this is customarily performed by the urologist with subsequent review by a staff radiologist as deemed necessary by the surgeon.

The tunica albuginea is generously incised over the tumor. The neoplasm is then enucleated along with a small rim of adherent seminiferous tubules. In selected cases, the tumor bed is sampled to ensure negative margin status. After closure of the tunica, the testis is reperfused while awaiting pathologic confirmation (Fig. 1).

All patients were followed routinely with physical examination, scrotal ultrasonography, and selective measurement of tumor markers and hormone levels. Follow-up intervals ranged between every 4 and 6 months for the first 2 years, and once a year thereafter.

Data were summarized as means \pm standard deviation, range: minimum-maximum, counts, and percentages. Statistical analyses were completed with SPSS version 22.0 (IBM SPSS software, IBM corp., Armonk, NY).

RESULTS

During the study period, a total of 9 children were treated for LCT of the testis (including 2 bilateral cases), undergoing 11 procedures, resulting in 11 specimens in total. Age at surgery was 8.4 ± 1.7 years, and the majority ($n = 7$) presented with unilateral disease; 4 boys with left-sided mass. One of the patients (case #5 in Table 1) who presented with bilateral disease had multifocal tumors on one side (5×3 mm, 6×6 mm, and 2×2 mm). Most patients presented with a testicular mass detected on physical examination or ultrasound; 3 boys (33%) presented with testicular pain. Precocious puberty symptoms—such as acne, increase in penile size, and pubic hair growth—were present in 5 (55%) boys. None of the patients were found to have gynecomastia. α -fetoprotein and β -human chorionic gonadotropin levels were found to be within the normal reference levels in all cases. Mean lactate dehydrogenase level was 587 ± 132 IU/L. Hormonal profile was obtained preoperatively in 6 patients, and the majority (66%) of those had elevated serum testosterone. Bone age was advanced in 2 of the patients presented with precocious puberty (case #5/6). Scrotal ultrasonography was the initial diagnostic modality, and the tumor was typically described as a heterogeneous mass with a peripheral hyperechoic and central hypoechoic nature with increased vascularity. The preferred method of management for all patients was ultrasound-guided TSS, as described in the methods section. Mean operative time

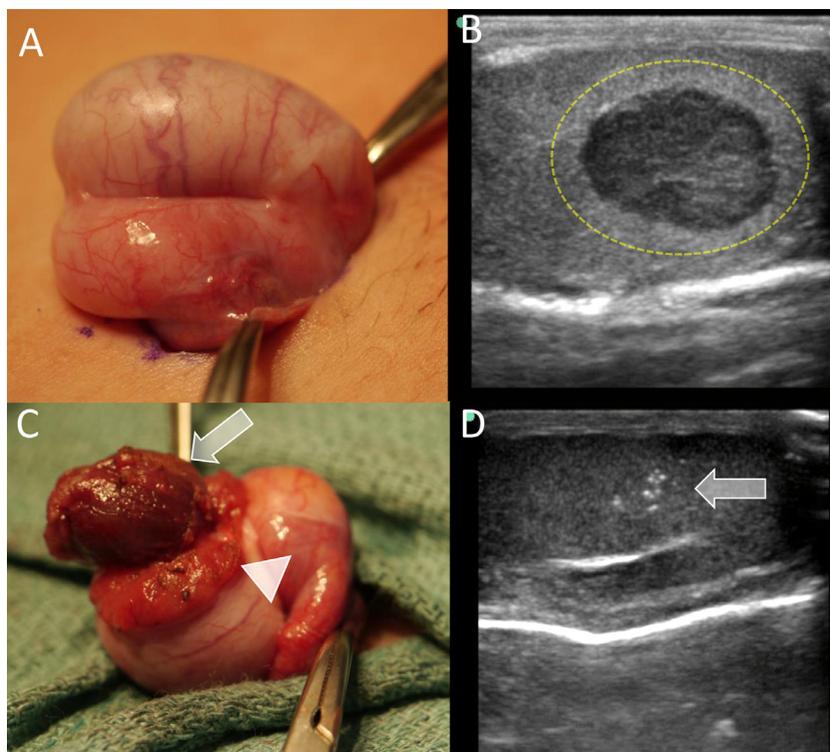


Figure 1. The testicle is delivered through an inguinal incision (A). The location of the tumor is confirmed with intraoperative US (B; tumor inside dotted ellipse). The tunica albuginea is opened and the lesion (arrow) is enucleated from the surrounding normal parenchyma (arrowhead) (C). Intraoperative ultrasound confirms removal of the tumor in its entirety (D). (Color version available online.)

Table 1. Clinical, surgical, pathologic, and oncological outcomes of patients

Age (years)	Side	Disease Focality	βHCG	AFP	LDH	FSH	LH	Testosterone	Precocious Puberty			Frozen Section	Tumor Size (mm)	Perioperative Complications (Clavien-Dindo)	Histologic Diagnosis	Margins	Follow-up (Months)	Post-op Testosterone	Orchiectomy Completion
									Gynecomastia	Surgery	Puberty								
7.7	Rt	S	<3	1	498	N	N	N	-	-	TSS	+	32	1	LCT	+	87	NA	+
9.5	Rt	S	<1	2	478	NA	NA	N	+	-	TSS	+	40	1	LCT	-	39	NA	+
9.5	Bit	S	<1	3	459	NA	NA	NA	+	-	TSS	+	Rt=17; Lt=10	1	LCT	Rt: -; Lt: +	2	NA	+
9.6	Lt	S	<1	1	586	NA	NA	NA	-	-	TSS	-	5	0	LCT	-	43	NA	-
5.5	Bit	M	<1	3	571	UD	UD	↑	+	-	TSS	+	Rt=10; Lt=8	0	LCT	+	48	↑	-
5.6	Rt	S	0	2	582	N	N	↑	+	-	TSS	+	8	0	LCT	+	5	N	-
10.4	Lt	S	<1	2	532	NA	NA	↑	-	-	TSS	+	11	0	LCT	-	22	NA	-
9.2	Lt	S	<1	2	659	NA	NA	NA	-	-	TSS	+	5	0	LCT	-	28	NA	-
9.2	Rt	S	<1	1	924	UD	UD	↑	+	-	TSS	-	18	0	LCT	+	13	NA	-

AFP, α-fetoprotein; βHCG, β-human chorionic gonadotropin; Bit, Bilateral; FSH, follicle stimulating hormone; LCT, Leydig cell tumor; LDH, lactate dehydrogenase; LH, luteinizing hormone; Lt, left; Rt, right; M, multifocal; N, normal; NA, not available; S, solitary; TSS, testis-sparing surgery; UD, undetectable; Elevated (↑).
* Left-sided orchiectomy.

was 98.5 ± 58.7 minutes. Inguinal or retroperitoneal lymphadenectomy was not performed in any case. No intra- or postoperative complications were encountered. Mean tumor size was 15 ± 10.8 mm (range 5-40 mm). In the majority of cases (88%), a frozen section examination (FSE) was requested during the procedure; in the remainder the tumor was deemed to be too small. In 6 of 9 patients, positive surgical margins were reported on permanent section analysis. None of the aforementioned patients had evidence of an infiltrative pattern, or an ill-defined margin between tumor and normal surrounding parenchyma. In review of all pathology reports, all the positive surgical margins were microscopic and small. Based on individual surgeon recommendation, and parental preference due to the possibility of local recurrence or malignant behaviour, 2 boys underwent a subsequent radical orchidectomy (time interval to procedure 1.4 and 3.74 months, respectively) without residual disease encountered. In the remaining 4 patients, who were followed conservatively (mean 23.5 months; range: 5-48 months), there was no evidence of tumor recurrence at the resection site during monitoring.

On review of final pathology reports, the yield of accurate FSE was 85%, with the remainder demonstrating benign histology with active spermatogenesis (highly suggestive of LCT). At a mean follow-up of 31.8 ± 26.3 months, none of the patients experienced disease recurrence on physical examination, hormonal surveillance, or sonographic monitoring (Table 1). Hormonal profile data were available for only 2 patients: One patient (case #6), his testosterone levels normalized after surgery and in the other patient, he developed central precocious puberty (case #5) characterized by elevated luteinizing hormone and gonadotropin-releasing hormone despite absence of a testicular mass, and he was treated with gonadotropin-releasing hormone agonist with subsequent clinical and laboratory regression. None of the patients in the present series had testicular atrophy on follow-up. On postoperative ultrasound monitoring, the affected testicle had a mean volume on 6.92 mL (range: 1.09-15.4 mL), compared with the contralateral gonad (10.38 mL; range: 0.9-26.1 mL), excluding patients who underwent orchidectomy or had multifocal disease. This represents a mean volume difference of 21.1%. None of the cases were diagnosed genetic abnormalities (such as DICER1 syndrome and/or congenital adrenal hyperplasia).

DISCUSSION

TSS has recently been reported to be a safe surgical option in selected patients with testicular tumors, including some cases where the neoplasm is suspected to be malignant.¹² This trend supports the idea of offering this approach to tumors which are typically benign. In pediatric patients, these include teratomas, dermoid tumors, and LCTs. Because of the limited number of small pediatric retrospective case series,¹³⁻¹⁵ the current knowledge of oncologic outcomes for children with LCT undergoing radical orchidectomy or TSS is limited. In the present series, we have shown that LCTs can be safely approached with TSS, particularly when preoperative tumor markers are negative and the procedure is performed with strict adherence to sound operative principles. In contrast to our practice, a recent multicenter retrospective review by Luckie et al¹⁶ of 12 children with LCT of which 9 had radical orchidectomy performed and 3 patients were treated

with enucleation. All patients were alive at last follow-up without evidence of local recurrence or metastasis.

Owing to its rarity, some of the natural history of pediatric LCT has been extrapolated from the adult literature. Two salient examples of this are the risk of malignancy and implications of a positive surgical margin. Even though LCTs are typically benign, it is often stated that up to 10% of cases can exhibit a malignant behavior. It is challenging to distinguish between them, as metastasis is the only reliable criterion of malignancy.¹⁷ To our knowledge, all cases of malignant LCTs have been reported in adults, mostly in patients with large tumors (>5 cm.), extensive local invasion, and age over 40 years old.¹⁰ Although there is no single histologic criterion to define malignant LCT's, these also tend to show nuclear atypia, increased mitotic figures, infiltrative margins, angiolymphatic invasion, necrosis, DNA aneuploidy, and increased MIB-1 proliferative activity.⁹ Reassuringly none of our patients had those features on final pathology. In addition, the clinical implications of positive surgical margins remain unclear but concerning mostly due to implications in cases with malignant potential. In the present cases, the rate of positive surgical margins appears to be high. On a retrospective review, it is very difficult to pinpoint the reasons for this finding, yet irrespective of the reason, the presence of such a rate of surgical margins becomes an opportunity to critically examine their impact on patient outcomes. Thus, we provide evidence that outcomes are satisfactory with partial orchiectomy despite having positive surgical margins, without evidence of local recurrence or distant disease.¹⁸

Anecdotal evidence from the adult literature would indicate that recurrence following enucleation can occur even in the setting of clear margins.¹⁰ In contrast to postpubertal/adult testicular tumors, prepubertal testicular masses are largely benign, and should be managed as such.¹⁸ Taken together, these points allow us to draw parallels with current management trends with prepubertal testicular teratomas.¹¹ Teratoma carries the risk of malignant behavior in postpubertal patients—particularly in the setting of a mixed germ cell tumor—whereas in a pediatric patient a pure teratoma carries a negligible risk.

TSS has important theoretical long-term advantages. Although most LCTs are unilateral (77% in our series), multifocality and bilateral disease is sometimes encountered. In these cases, radical surgery would render the child an orchid. Even in the setting of unilateral disease, there is potential for metachronous lesions (either LCT¹⁹ or other pathologies), as well as trauma. Total orchiectomy for unilateral tumors adversely impacts the amount of testicular parenchyma the child will have for life, and future insults would carry a higher risk of problems with hormone production and fertility. In addition, LCTs are usually small (in our study, ranged between 0.5 cm and 4 cm in diameter), thus, associated with a large amount of otherwise normal parenchyma. Removal would therefore waste a large volume of tissue with normal functional potential.

Due to the possibility of rare neoplasms in pediatric patients, intraoperative FSE is considered an integral part of management. Reassuringly, we found these to be predictive of LCT on final pathology. This is consistent with other reports in the literature.²⁰⁻²² For example, in a large retrospective series by Elert et al, FSE correctly identified malignant and benign lesions which included a myriad of primary testicular tumors (seminomas, nonseminomatous germ cell tumors, epidermoid cysts, LCTs, cystadenomas, cysts, and hemangiomas).²¹ Similarly, Matei et al reported a high sensitivity and specificity of FSE for benign and malignant lesions, with an acceptable concordance rate between FSE and final pathology.²² Thus, in a prepubertal child with negative tumor markers (particularly α -fetoprotein), FSE can provide intraoperative reassurance that parenchyma sparing is a safe approach.

It is estimated that approximately 30% of patients with LCT have endocrine symptoms secondary to dysregulated hormone production, most notably androgens and estrogens.⁷ In our study, 55% presented with symptoms of precocious puberty, including one boy who presented with behavioral changes, assumed to be caused by high testosterone levels. Even though none of our patients presented with gynecomastia, this finding should remain a strong indication for testicular sonography, as small subclinical masses may predate abnormalities by palpation by months or years.^{23,24}

As with other tumors, neoplasms in children (particular multifocal ones), raise suspicion for a genetic component. Even though LCTs have not been associated with a specific syndrome, recent reports have raised a potential relationship between DICER1 mutations and Sertoli-LCTs in females.²⁵ A distinctive DICER1 syndrome is now recognized, which carries an important risk for multiple neoplasms, such as pleuropulmonary blastoma, cystic nephroma, and embryonal rhabdomyosarcoma.²⁶ This is in stark contrast with other testicular neoplasms in childhood, most notably Sertoli cell tumors, which can also present with virilization. In addition, these can often be associated with specific syndromes such as Peutz-Jeghers and Carney complex. Malignant behavior is rarely seen in children, thus partial or radical orchiectomy can be considered potential management options.¹³ These rare neoplasms do not exhibit elevated tumor markers but can have worrisome features on frozen section areas as well as areas of increase echogenicity on ultrasound (particularly in large cell calcifying Sertoli cell tumor). On ultrasonographic examination, LCTs are usually small, homogeneous, hypoechoic masses with occasional cystic areas (due to hemorrhage and necrosis) and blood flow on Doppler (Fig. 2).²⁷

Previous series reporting TSS for Leydig cell-related pathologies in children have included cases of Leydig cell hyperplasia (LCH),¹³ condition that should be distinguished and analyzed separately from LCTs.²⁸ On a histologic level, LCH shows intertubular expansion with entrapment of seminiferous tubules by Leydig cells. In contrast, LCTs are isolated nodules often within a well-

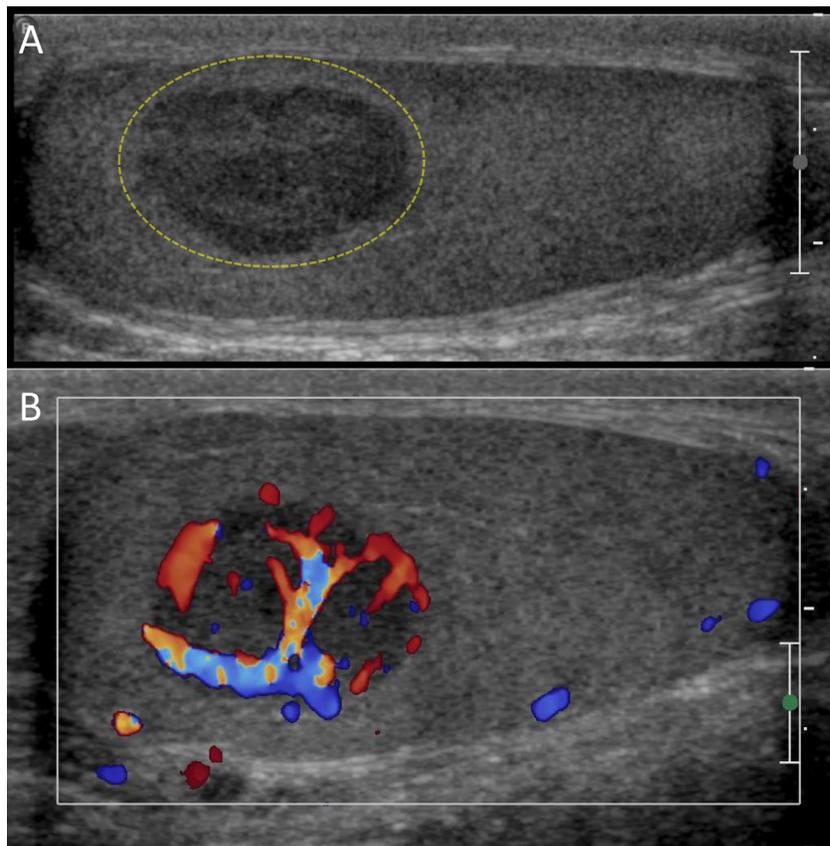


Figure 2. Ultrasound characteristics of Leydig cell tumor: Note well-defined hypoechoic mass (A; tumor inside dotted ellipse) with blood flow detected on Doppler interrogation (B). (Color version available online.)

defined fibrous capsule, and without tubular entrapment. Moreover, there is evidence of differences in their genetic fingerprint, with differential expression of some immunohistochemistry markers, particularly Insulin-3²⁹. Our series focuses exclusively on patients with pathologic diagnosis of a LCT, and findings should be extrapolated with caution to cases of LCH. Risk of recurrence and resolution of endocrinological features may be different between these 2 pathologies.

There are important limitations in our study that should be acknowledged. Even though it represents one of the largest single-center experiences with this pathology, the numbers are admittedly small, a reflection of the rarity of the disease. Retrospective data capture and analysis also introduce important biases. In addition, the procedures were done by different surgeons with unavoidable minor variations in technique. We also lack long-term data, situation that is worsened by the lack of information after transition to an adult facility. Despite these limitations, we believe there is value the present study. Our data add compelling evidence for TSS in pediatric patients. Even though case series have reported a benign course for pediatric stromal cell tumors, radical excision rates are persistently high.³⁰ There are compelling reasons to consider TSS, such as development of pathologically concordant or discordant

metachronous lesions, as well as future damage to the solitary gonad. The risk of hypogonadism and infertility should be contrasted with risk of recurrence or malignant behavior, which appears to be quite low. In a pre-pubertal child with negative tumor markers, the possibility of a LCT should be raised, and TSS appears a reasonable option (even in the setting of other diagnoses, such as teratoma, granulosa cell tumor, and Sertoli cell tumor). In the setting of a positive, microscopic margin, the need for completion orchiectomy should be questioned if the tumor has minimal malignant potential.

CONCLUSION

To our knowledge, this is the largest single-institution-reported series of pediatric LCT.

Children with LCT experienced a good prognosis after TSS without detrimental effects in perioperative morbidity or postoperative outcomes. Our data suggest that positive surgical margins on final pathology should not lead a reflex decision for completion of orchidectomy. As we better understand the natural history of LCT in children, surgeons will be better equipped to discuss prognosis and present the TSS as a viable option.

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