**Testis- Sparing Surgery for Testicular Tumors in Children: A 20 Year Single Center Experience And Systematic Review Of The Literature**

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Abbreviations:

 TT: testicular tumors

 TSS: testicular sparing surgery

 GSCCT: Giant Sertoli Cell Calcifying Tumor

**Abstract**

Purpose: Although surgical therapy for testicular tumors (TT) is often radical orchidectomy, tumor resection with preservation of healthy testicular parenchyma has been proposed. This study herein reports a 20 year single center experience applying testicular sparing surgery (TSS) as a primary operative strategy in pediatric patients. A systematic literature review summarizes the utility and outcomes of TSS in appropriately selected patients. Methods: Pediatric patients with TT who underwent TSS between 1997 - 2018 were studied. TSS was indicated if patients presented evidence of adequately spared healthy testicular parenchyma on preoperative ultrasound and negative serum tumor markers. Results: 12 cases met full inclusion criteria with 10 of 12 subjects in the prepubertal age group. Follow-up was 73 months (range:18-278 months). Only a single male patient (GSCCT) presented with early recurrence and orchidectomy was then performed. No cases of postoperative testicular atrophy were identified. Sexual maturation (Tanner stage) expected for age in each patient was documented. Review of the literature identified 34 published studies including 269 patients (94% prepubertal). Pathologic lesions here were mainly mature teratoma(s)- (62%) with a follow up period of 4 yrs. Recurrent tumors were observed in only 3 patients (1.1%) notably 2 Leydig Cell Tumors and 1 Teratoma. Testicular atrophy reportedly occurred in only 1 single case (0.37%). Discussion: TSS is a feasible alternative to radical orchidectomy in pediatric male patients with localized TT and negative tumor markers. Long term follow up is essential to monitor testicular growth, puberty with sexual development and psychological male health.

**Introduction**

Testicular tumors (TT) occur with a low frequency in pediatric subjects. These tumours account for 1%- 2% of all solid neoplasms in children, and some 75% following resection are reported to have benign pathology [1]. The traditional or standardized treatment strategy for a suspected testicular mass involves surgical exploration with an inguinal incision and exteriorization of the affected testicle. If surgical findings are consistent with TT, a unilateral orchiectomy is performed with high ligation of the spermatic cord. [2] The management of testicular tumors in childhood has however varied in the last decade or so. There has been a growing opinion with pediatric oncology surgeons that radical operations are now unnecessary and efforts to preserve the native testis where possible should be undertaken with organ sparing surgery.[3] This is linked to pathology analysis of many pediatric testicular tumors after orchidectomy showing a high percentage of benign lesions.[3,4]

Most malignant testicular tumors are of germ cell origin, and serum tumor markers have been widely used for diagnosis. Elevated levels of AFP are consistently found in yolk sac tumors, which is the most frequent malignant testicular tumor in prepubertal males. Elevated hCG levels are consistent with choriocarcinoma, this tumor type being more frequent in older patients. Especially in the case of AFP, elevated serum levels are not wholly specific of testicular germ cell tumors, as AFP may also be abnormal in liver tumors, ataxia-telangiectasia, and in otherwise normal healthy infants [2, 5]. These conditions associated with elevated tumor markers can be easily ruled out, so in the context of a pediatric patient presenting with a TT and positive tumor markers, a malignant tumor should be suspected and orchidectomy considered the procedure of choice.

On the contrary, prepubertal patients with TT and negative tumor markers can be presumed to have a benign lesion thus avoiding need of orchidectomy. Tumor resection using a testis-sparing surgical (TSS) strategy in patients with negative tumor markers is thus increasingly favoured by pediatric surgeons and urologists.[6,7-8]. TSS should be considered more cautiously in postpubertal patients, as the incidence of malignant tumors with negative tumor markers (most frequently seminoma) is higher in this age group. Nevertheless TSS has also been proposed in cases of TT affecting less than 30% of the total testicular volume. [4] Organ sparing operations for testicular neoplasms have been established at our pediatric surgical center now for more than 2 decades with good interim outcome(s).[5]

Although TSS is more widely performed, there are few studies (if any) that address the long term outcomes of such patients into their teenage and young adult years.

The aim of this present study outlines a 20 year experience defining management of pediatric testicular tumors with testicular sparing surgery (TSS) as a primary therapy strategy in a cohort of selected index cases. A systematic literature review critically addresses published outcome metrics from other worldwide centers.

**Methods**

1. *Patients And Methods*

A retrospective cohort study was undertaken. Patient information was analyzed with personal data anonymization for confidentiality. Data were obtained from institutional electronic records. The study was carried out in accordance with current national and international regulations: the Declaration of Helsinki and the Standards of Good Clinical Practice ICH E6. This research protocol was reviewed and approved by the Institutional Ethics Committee under Law Number: 5042.

Patient selection:

Patients younger than 18 years of age with an index diagnosis of a testicular tumor (TT) who underwent a Testis-Sparing Surgery (TSS) between July 1997 - August 2018 were studied. TSS was indicated if male patients met the following criteria: (1) evidence of a localized solid or solid- cystic mass with spared testicular parenchyma (non- involved by tumor) on preoperative ultrasound (Fig. 1), and (2) negative serum tumor markers. Tumor markers analysed in every patient preoperatively included alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG).

TSS Surgical Technique:

An inguinal incision is performed and the spermatic cord identified. The involved testicle is delivered into the wound field with atraumatic clamping of the exteriorized spermatic cord. The tunica vaginalis is opened and the tumor visualized and palpated. If tumor cannot be localized by surgeon palpation intraoperative ultrasound examination is undertaken to exclude multifocal lesion(s). The tunica albuginea is then opened with a scalpel to minimize damage of healthy testicular parenchyma. Upon ready identification of tumor enucleation of the lesion is performed (Fig. 2). If this is not feasible tumor resection with a clear macroscopic margin of healthy testicular parenchyma is undertaken. Hemostasis of the resection site is achieved with bipolar cautery. The testis capsule is then carefully repaired with a running absorbable monofilament suture (PDS, polydioxanone- EthiconⓇ).[12] In the early years of the study and with only a small accrued number of patients frozen section tissue biopsy of adjacent healthy normal testicular parenchyma was performed though with growing confidence with TSS this practice has been abandoned.

Tumor pathology, surgical morbidity - notably need for re-intervention , postoperative residual testicular volume(s) as measured by ultrasound and sexual maturation scoring with Tanner staging were analyzed.

Postoperative patient follow-up comprised a clinical physical examination, measurement of serum tumor markers with testicular ultrasound every 6 months until 2 years from operation and then annually thereafter.

1. *Systematic literature review*

In order to compare our study findings with varied published cohorts a systematic review of the literature was performed with screening PubMed, Cochrane Library and Embase. databases. Criteria for selection of eligible studies were ( i ) language of publication (Spanish/English), ( ii ) availability of full manuscript texts and study population(s) matching inclusion criteria and ( iii ) relevance of studies to our cohort analysis.

Articles considered not relevant for inclusion, ie ‘excluded‘ non eligible reports, were: (a) studies in which TSS was performed for another indication other than primary testicular neoplasms (b) studies in which an identifiable and / or comparable series of pediatric patients was not presented or (c) articles in which important key information relating to any of the analyzed variables we studied were not explicitly reported.

The following variables for each selected eligible published study were recorded notably (1) age at surgery, (2) tumor histology, (3) postoperative follow-up, (4) recurrence rate, (5) asymmetry or testicular atrophy, (6) pubertal stage at last follow-up visit, (7) frozen section biopsy.

Selection criteria and flowchart used for the illustration of the systematic literature review were based on the guidelines proposed by the PRISMA group. [61]

1. *Setting:*

The study was carried out within the Pediatric Surgery and Urology Division in a large University-affiliated general hospital.

1. *Statistical Analysis:*

Continuous variables are expressed with their mean value(s) with related standard deviation; median as well as interquartile range are provided according to the distribution of data. Categorical variables are expressed in proportions. Confidence intervals are reported where appropriate. Statistical analysis was performed using STATA v13 software. (StataCorp LLC 4905 Lakeway Drive, College Station, Texas 77845-4512, USA)

**Results**

Hospital case records showed a total of 76 males with an index diagnosis of testicular tumor(s) during the whole study period. Orchidectomy was performed here in 64 cases, 52 had positive tumor markers; 12 remaining patients were not eligible for TSS because the testicular parenchyma was completely replaced by tumor on US preoperative evaluation. A germ cell tumor was confirmed by pathology in 100% of patients with positive tumor markers. Among orchidectomy specimens from patients with preoperative tumor marker studies, final diagnosis included seminoma (25%), vascular malformations (25%) and paratesticular rhabdomyosarcoma (50%).

Eligibility criteria for TSS surgery were identified in 12 males. The median patient age was 10.5 years (range 3 months - 17 years). Physical examination showed prepubertal status in 10 of 12 patients at primary diagnosis. The left testicle was more frequently affected (n=7, 58.3%). Involvement of the epididymis was observed in a single patient. (Table 1)

Preoperative findings at ultrasound were varied: In all cases, more than 50 % of normal appearing testicular parenchyma was identified adjacent to the tumor. (Fig. 2) A mean of 22.5% of the testicular volume was replaced by tumor, ranging from 4 to 40%. Most of the tumours were focal and discrete lesions and 25% (n=3) were centrally located. There were no cases of bilateral or multiple tumors.

All surgical procedures were uncomplicated with a mean operative time of 78.7 minutes (range 40-104 mins). Tumor enucleation was performed in 7 cases and partial orchidectomy in 4; in the remaining case the tumor was fragmented during enucleation. No intraoperative complications were registered. Surgery was performed as an ambulatory day care procedure in all males. A resident or fellow was the primary surgeon in all operations supervised by the attending pediatric urologist or surgical oncologist.

Tumor pathology were as follows: dermoid cyst (n=5); mature teratoma (n=3); stromal tumors (n=3), Giant Sertoli Cell Calcifying Tumor [GSCCT] (n= 1), juvenile type Granulosa Cells Tumor (n= 1), Leydig Cell Tumor (n= 1), and a fibrous nodule in the epididymis (n= 1). (Table 1) This last case was a 13 years old boy with a 2.3 c.c. solid nodule in the superior pole of the epididymis. Enucleation was performed and a fibrous nodule reported. Eight focal enucleated tumors were considered to have macroscopic disease clearance. Histologically free margins were reported in all other tumor cases requiring partial orchidectomy.

Mean patient follow-up in the study was 73 months (range: 18 - 278 months). No postoperative morbidity was documented. An early tumor recurrence was found in a single boy with a GSCCT who was under close surveillance in view of pathology findings; a radical orchiectomy was later performed at 3 months postoperatively with no complications; pathology here confirmed tumor recurrence. No further disease recurrence(s) were noted during follow up of all other cases. A mean testicular volume variation of 20.14% (range 56% +/- 25%) of the preserved native testis compared to the contralateral non-involved healthy testis was noted at last clinic ultrasound follow- up assessment. Significant testicular volume loss reduction was recorded in 3 testes also confirmed by clinical examination. Serum tumor markers were within normal parameters in all TSS patients in the study. Physical exams showed an age-appropriate sexual maturation according to Tanner staging in 11 of the 12 patients years after surgery (no information update was available for the other single remaining patient). Prepubertal staging was as follows- [Tanner Stage 1, n=2], midpubertal [Tanner Stage 2–3, n=3] or postpubertal [Tanner Stage 4–5, n=6]).

*Systematic Literature Review:*

Database searching showed a total of 132 publications. After discarding duplicates and those not suitable based on language criteria, not available full texts, or those considered non-relevant, 34 eligible papers were included for final analysis. All of the articles here reported clinical cohort studies and / or small case series. (Fig. 3)

A summary of data from the reviewed articles is shown in Table(s) 2a & 2b. Mean age of patients was 5.5 years (ranging 2 months - 13 years). Analyzed studies included 269 male patients 94% (n=253) having pre-pubertal status. Of note 2.6% (n= 7) cases presented with para-testicular tumors; testicular tumour involvement alone was observed in all the other patients. The most frequent type of tumor encountered was mature teratoma, responsible for 62% of all resected lesions (n=166). Cystic tumors were less frequent n= 40 (14.8%). Tumors arising from the testicular stroma included: Leydig Cell Tumor (n= 29, 10,8%); Granulosa Cell Tumor (n=8, 3%) and Sertoli Cell Tumor (n= 5, 1,8%), of which 3 of 5 had a histological sub-type variant notably Giant Sertoli Cell Calcifying Tumor (GSCCT). Carney´s syndrome was diagnosed in one of these latter patient cases.

Mean duration of follow-up in published studies was 4 years (range 5 months - 8 years), however five reports did not fully provide complete information regarding patient surveillance and follow up.

 A single paper reported tumor recurrence after TSS: Hisamatsu E. [8] here published a recurrent mature teratoma that was later resected by orchidectomy 10 months after TSS; histology analysis of the further resected specimen also confirmed a mature teratoma. Conversely, Zu'bi [7] had 9 cases of Leydig Cell Tumor; 6 patients here presented with positive microscopic surgical margins. After surgeon counseling and parental choice, 2 patients underwent subsequent radical orchiectomy due to the possibility of malignant biology. No residual disease(s) were encountered. No recurrences were documented among the other published studies reviewed.

Regarding residual volume(s) of the testicular organ parenchyma, this was reported as showing viable healthy testes in all cases except for a single male patient. Tröbs et al [9] recorded testicular atrophy after a tumor enucleation operation for a centrally located Leydig Cell Tumor in a 10 year old boy.

Only 5 studies adequately reported data on male puberty with sexual maturation. [9,10,45-47] Delayed puberty was not recorded in these published reports.

Regarding the utility of frozen section testicular biopsy, all but 3 study authors recommended this practice. [20, 24, 37]. Data about frozen section was not recorded in 2 published studies, [20, 24] and a third report stated that it had been abandoned in their surgical practice practice. [20]

**Discussion**

Testicular tumors are rare in children with a reported incidence of *6* new index cases per 100,000 male children *[3].* Age at presentation displays 2 incidence peaks- the 1st at 3 years of age and a second spike around 15 years of age *[2*]. When malignant testicular biology is suspected the recommended surgical management plan requires radical orchidectomy. [1,4-6,9].

Although a number of publications addressing the concept(s) of testis-sparing surgery for resection of testicular tumors are available, this ‘organ sparing’ approach has not been universally or widely adopted by many pediatric surgeons. [10,60]From the outset of our clinical programme TSS with fertility preserving operations were apparent to the multidisciplinary health care team [5]. Twelve of 76 patients were eligible and thereafter scheduled for TSS. All other male patients with testicular tumors (as indicated earlier above) had orchidectomy, showing malignant histology in the majority of cases or diffuse testicular whole organ replacement from benign pathology. Study authors who have published their clinical outcomes with TSS have deployed very similar patient selection criteria as we have done here in our present study notably including tumor lesions limited to the gonad with adjacent healthy testicular parenchyma and serum tumor markers within normal values. [2-4]

Of interest in the present study 2 older male patients were amenable for TSS, despite having postpubertal status. Ultrasound testes findings included one boy with a cystic tumour lesion and the other patient had a focal epididymal nodule. Systematic literature review showed some 6% of all males studied were in a postpubertal age group. All underwent TSS having benign histology. Taskinen et al from Finland recorded that 68% of prepubertal males will have benign tumors. While after puberty the percentage of benign tumors falls to below 38%, and here testicular germ cell tumors (including teratomas) have been associated with intratubular germ cell neoplasia within the adjacent testicular tissue. [5,6] Kay et al have postulated that some 98% of prepubertal malignant testicular germ cell tumors will have yolk sac biology. The distribution of metastatic disease burden here highlights clear difference(s) between prepubertal testis tumors and those encountered post puberty. [4,57] It should be noted that malignant TT in the postpubertal male may not harbour elevated tumor markers. Here malignant teratoma and mixed germ cell tumors can be linked with significant patient morbidity including distant metastasis and lethality. For these very reasons, TSS is generally only strongly recommended in prepubertal patients.

Most patients in this present study were of prepubertal age at time of primary diagnosis. All the TSS cases analysed had normal serum tumor markers. Reassuringly, published data demonstrates that the likelihood of finding a malignant germ cell tumor in a patient with negative serum tumor markers is highly unlikely in the prepubertal male. [3,5] On the other hand, encountering a benign testicular tumor in a patient with preoperative positive elevated tumor markers is distinctly uncommon. Although tumor markers are not wholly specific to testicular tumors, we know that other conditions associated with abnormal elevation of AFP or HCG can be readily confirmed and excluded before scheduling testis operations. [5] In our study cohort population all males that had preoperative positively elevated markers had a malignant germ cell tumor confirmed in the orchidectomy pathology specimen. Metcalfe et al reported 3 males with elevated serum AFP that had benign histology from a total of 13 study patients. In spite of such findings, the study authors firmly recommend avoiding TSS in patients with elevated AFP [14]. In a cohort study published by Romo Muñoz et al., 2 AFP positive patients presented with a final diagnosis of granulosa cell tumor(s). Interestingly, both males were under 1 year of age, so elevated AFP can be attributed to the normal physiological elevation(s) seen in infancy. [28,55] Other study authors report deployment of TSS in AFP positive males under 1 year of age. [10, 54] It has been collectively proposed therefore that TSS can be performed safely in this particular age group with the caveat that AFP serum levels are recorded below 100ng/ml [26, 8]. Normal preoperative serum tumor markers are considered by most pediatric oncology surgeons a mandatory key prerequisite before embarking on TSS, with the special exception we have already mentioned where it can be safely undertaken in the infant under one year of age with serum AFP less than 100 ng/ml. [12, 13, 28] These observations and criteria are consistent with the present study report where all our cases encountered with positive tumor markers proved to have malignant lesions while those with negative tumor markers had benign pathology with the exception of testis stromal tumors, where benign biology could be subject to varied debate and discussion.[7,22,26]

It is really important to emphasize that high quality ultrasound examination allows imaging evaluation of the tumor as well as surrounding testicular parenchyma thereby identifying cases that may therefore benefit from TSS. ‘Benign‘ ultrasound criteria features notably include - (I) unilocular lesions with anechoic content, (II) well defined tumors and (III) those with avascularity; however it should be noted that hypervascularization is not a wholly specific sign for malignancy. Additionally, testicular imaging studies showing a hyper-echogenic cystic area in a solid matrix have been reported as characteristic hallmarks of mature teratoma. [5,12]

In our study cohort, clamping of the exteriorized spermatic cord during TTS was performed as described by Steiner et al [12]. Frozen section tissue biopsy of adjacent healthy testicular parenchyma was performed in the early years of our study, with negative margins documented in all cases. Over time this practice has been abandoned by the surgical team because of testis viability concern(s) with regard duration of spermatic cord clamping, while awaiting pathology confirmation. Detailed information with regard to spermatic cord clamping time(s) was not found in the published literature we reviewed. We believe this is an important topic to share with oncology surgeons and will be likely subject to future ongoing studies.

Histopathology findings in the present study cohort are consistent with published literature showing a broad predominance of benign neoplasms with mature teratoma and cystic lesions being the most frequent biology encountered. [5,17,19] Mature teratomas are therefore by far the most frequent pathology encountered compared to other benign cystic lesions in many published studies. By contrast we found benign cystic testicular lesions were the most frequent tumor type reported here in our study. It is interesting to speculate that this may well be attributable to chance alone due to small study sample size. No single case of a malignant germ cell tumor was encountered. Such patients as mentioned before will often harbor positively elevated serum tumor markers mandating orchidectomy and should not be offered TSS. All germ cell tumors with negative tumor markers were mature benign teratomas confirming the safety in the patient selection criteria for TSS. [28; 33] There remains however a small group of testicular stromal tumors which can be so classified as ‘intermediate‘ lesions with the reported potential for local recurrence(s). [7,22,26]

Although we have found that the reported follow-up time periods were variable between individual published series we examined several comments can be drawn from our present study report. Tumor recurrence rate(s) following TSS were very low, with only 3 out of 4 cases affecting males with lesions arising from testicular stroma notably two boys with Leydig Cell biology and a single patient with GSCCT pathology [43]. Only a single reported published case of a mature teratoma was noted to recur with no multifocal neoplasms so far [26]. Remarkably no disease progression to a malignant germ cell tumour(s) was reported in the published literature we surveyed for this study report.

With regard to ‘disease- free’ status- 2 males had orchidectomy due to positive disease margins (reported by Zubi et al [7]) and also here one of our own study patients with GSCCT pathology, presented with an early recurrence. We speculate here that a microscopic residue was left behind after the primary operation as this was the only single case with tumor fragmentation during enucleation.

Some patients had postoperative testicular volume loss in our present study, not widely reported elsewhere except for a single published case which documented testicular postoperative atrophy [9]. Metcalfe et al. showed such similar findings with ultrasound surveillance imaging with residual testicular mean volume losses of some 85% compared to the native contralateral healthy testis. [14] However despite such sonographic findings reported not a single case of delayed puberty or sexual development was demonstrated. These results were consistently further reported in five published studies we analysed. [42,44-47]

Semen analysis was not performed in our present study though most of the male patients had reassuringly completed Tanner stage(s) of pubertal development confirmed at clinical examination with their outpatient clinic visits. Half of the patients in our study cohort here were postpubertal stage (Tanner Stage 4-5), with three other males in the mid pubertal stage(s) (Tanner stage 2-3). It is noteworthy that pubertal development has not been fully or accurately reported in any of the published studies we have analyzed. We therefore advise long term follow-up should be undertaken in all boys having TSS to accurately document male sexual development, psychological well-being, quality of life and reproductive health. [11,12,17,25,43,58]

We fully acknowledge the present study has its inherent limitations from retrospective design and the data reporting. In closing, we wish to further highlight and promote the concept(s) and feasibility of testicular sparing surgery in the carefully selected male patient(s) showing that there is a crucial role for health care teams to provide after care with long term follow up.

**Annex:**

SEARCH QUERY

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(('testis sparing surgery'/exp OR 'partial orchiectomy':ti,ad OR 'parenchymal surgery':ti,ab) AND ('testis tumor'/exp OR 'testicular tumor':ti,ab)) AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [preschool]/lim OR [school]/lim)

**Declarations:**

## Conflict of Interest: The authors declare that they have no conflict of interest.

## Ethics approval: This retrospective study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) approved this study.

## Consent to publish: participants have consented to the submission of the study series to the journal.

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