

Testicular sparing surgery in the pediatric population: Multi-center review of practice with review of the literature

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Abstract:

Pediatric testicular tumors have predominantly favorable histology, which may permit testicular sparing surgery (TSS). Limited guidance exists for TSS in adults and is absent in pediatric practice.

The international survey and retrospective case series evaluated the current use of TSS in pediatric testicular tumors. Alongside the complementary literature review the aim of this work was to provide evidence that could be used to produce a guideline document.

Published evidence advocates small mass size as an indicator for TSS, this was not supported in the pediatric literature. Frozen section examination at TSS was not always performed by surgeons and yet the literature reports close to 100 % specificity. Tumor markers and ultrasound findings are also used as indicators for TSS, a finding reflected in our survey results.

Multiple case series are reported but no large data series exists, which will require international collaboration rather than a drive to publish the results of individual centers.

Common indicators for TSS use; such as tumor markers and imaging are known but further work needs to evaluate the role of on-table histology and the risks of this not being available.

Keywords: Testicular-sparing surgery, guidelines, biopsy, consensus, pediatric

Introduction

Testicular tumors are uncommon in the pediatric population representing 1-2 % of all children's tumors. Post-pubertal testicular tumors are likely to be germ cell in origin (GCT), however in pre-pubertal males non-GCT are more common [1]. A similar pathological separation exists in ovarian tumors and recently there has been a move to perform ovarian-sparing surgery raising the possibility, in selected male patients with favorable pathology, of testicular sparing surgery [2].

Some guidance exists on use of testicular sparing surgery (TSS) in adult men with a tumor size <2cm and a single testis or bilateral tumors comprise the most indications [3–5]. For the pediatric population some literature is available, however, there is no consensus [6,7]. The aim of this international survey and retrospective case series was to try and evaluate the current use of the TSS approach in the management of pediatric testicular tumors and what factors determine individual decision-making in specific cases. A literature review was also performed to evaluate the current use of testicular sparing surgery and rationale in the pediatric population.

Materials & Methods

The Survey Monkey platform was used to create a ten-question survey. The respective link was disseminated amongst the members of the ESPU YPUC, the BAPU and the French Association of Junior Pediatric Surgeons (ACPF). Questions were designed to identify

indications for choosing TSS and the use of intraoperative frozen section to aid diagnosis.

Further questions were directed at redo-procedures.

An online form for patient data collection was created by the JotForm Website

(www.jotform.com) and this form was sent to respondents of the first survey willing to supply patient data (n=31). The platform used a SSL (secure socket layer) transmission of 256bit encrypted data and before data analysis, data decryption was performed.

A comprehensive electronic English-language literature search of PUBMED was conducted with the keywords "*testicular sparing surgery*", "*testis sparing surgery*", "*gonad sparing surgery*", "*human*", "*paediatric*", "*pediatric*", "*child*", "*infant*" and "*adolescent*". Age, imaging modalities, serum tumor markers, indication for testicular-sparing surgery, and description of the surgical approach, histopathology findings, postoperative treatment methods, complications, and long-term outcomes were collected.

Results

Thirty-eight surgeons responded to the primary survey request from 10 countries and 4 continents. Thirty-five (92.1 %) had adopted a testicular-sparing approach in some cases. The majority of surgeons (86.84 %) had performed between 1-10 cases and 5.26 % had been involved in 11-20, none had performed > 20. Tumor markers were the most important factor when deciding to perform TSS 35/38 (92.1 %). Ultrasound was also considered an important guide, with 32/38 (84.21 %) stating that this may change their approach. Age of the patient was a minor consideration, with 36.84 % never using this as an indication for

TSS. Only 23/38 (60.53 %) surgeons used intra-operative histology as part of the decision-making process with only 5.26 % (n=2) stating that this was because it was no available. In terms of outcomes the final histology did not change management. However adverse histology resulted in redo-procedures for 5/38 (13.2 %) surgeons and a further 6/38 (15.8 %) reported anecdotal cases.

The case series, although limited by the number of responses has highlighted some important issues which both confirm some of the findings from the survey and raise other important areas of variation in practice. 81.58% (31/38) of survey respondents offered to contribute to a multi-center case series. The aim of which was to produce the basis for a consensus statement for the use of TSS in managing pediatric testicular masses. 17 cases were provided by respondents. However, since the dissemination of the survey four case series have been published by individual centers and the major findings are summarized in our literature review [8–11]. The 17 cases sent to our encrypted database were provided by 8 surgeons, from 5 different centers in 3 different countries. Patient mean age was 72.5 months (\pm 89.9) with a right-sided predominance 64.7 % (11/17). A painless testicular mass was the most common presenting symptom 88.2 % (15/17). Tumor markers were performed in 15/17 (88.2 %), ultrasound in 16/17 (94.1 %) again demonstrating both ultrasound and tumor markers as being the favored investigations. An inguinal approach was performed in 13/17 (76.5 %) with the remaining cases being performed via the scrotum. Frozen section histopathology on-table was only performed in 52.9 % (9/17) of the cases; none of the cases have required redo-surgery after a mean of 34.1 months follow-up (\pm 34.9). The on-table histology and final histology were comparable in 6/9 cases (66.7 %) with the two of the three discrepancies being differentiating between epidermoid cyst and

mature cystic teratoma. The final anomaly was in a DSD case presenting with an acute inguinal mass whereby on table histology suggested the tissue to be ovarian and final histology finding mixed gonadal dysgenesis (table 1).

A total of 152 articles were selected during the first review. Ninety-five did not meet the inclusion criteria (3 editorials, 6 including only adult patients, 7 reviews, 15 non-English articles and 64 non relevant). Thirty-two case reports and ten small series (N < 5) were also excluded. Fifteen studies eventually met the criteria (table 2) including 466 pediatric patients of whom 227 (48.7%) had undergone testicular-sparing surgery [8, 9,12–24] with a mean follow-up of 69.8 months (14-138). Table 2 summarizes the main findings of this review. The time period covered by this review is from 1990 to 2018 with inclusion time between 1970 and 2015. The first article about the feasibility of TSS in a large series was published by Rushton *et al.* in 1990 with 5 cases of prepubertal tumors (testicular teratoma) [24] and the largest series comes from a multicentric and collaborative study from the French Society of Pediatric Surgery published in 2001 [21]. The most common clinical presentation was a painless scrotal mass or swelling between 53 and 100% of the cases at a mean age of 48.9 months (2 – 210). Indications of TSS in all articles included: prepubertal male patients with benign lesions on US and negative serum tumor marker (AFP, B-hCG and sometimes LDH). TSS was performed in 16.8 to 100% of the cases depending of the design of the studies. Histopathology finding reported teratoma (mature and immature), epidermoid cyst, sex-cord cell tumor (Leydig cell tumor, Sertoli cell tumor, and juvenile granulosa cell tumor), and benign tumors (simple cyst, hemangioma, lipoma, fibroma, hamartoma, splenogonadal lesion, testicular adrenal rest tumors). Two recurrences (0.88%)

have been reported for one epidermoid cyst and for one mature teratoma [13,18].

Orchiectomy was eventually performed. No case of testicular atrophy has been reported in the literature.

Discussion

The survey demonstrated that the vast majority of responding surgeons were adopting a TSS in some cases. There is a risk of response bias inherent in all surveys and this may be a cause for the high rate of TSS uptake in our population. The individual surgeons' low case numbers, beneath reflecting the rarity of these tumors, might suggest that respondents were either early in their careers or this is an approach that is being slowly adopted.

The importance of adopting an organ sparing strategy clearly lies in the prevention of loss of testicular tissue. In adult populations it has been shown convincingly that the preservation of testicular tissue is important concerning the long-term outcomes of these patients [25,26]. More importantly it has to be an integrative discussion to each treatment decision in children and adolescents, especially regarding the potential histology of their tumors [1].

The most valued investigations leading to a surgeon choosing a TSS approach were normal tumor markers (92.1 %) and only two of the 17 reported cases did not have tumor markers performed (11.8 %). Tumor markers were frequently combined with USS findings of a simple/epidermoid-type cyst (84.2 %) and again in the 17 cases reported to us only 1/17 (5.9 %) did not have an USS performed. Both tumor markers and ultrasound, which has been shown to be particularly reliable in pediatric populations, are accepted as instrumental in the work-up for any testicular mass and therefore these results were not particularly surprising [16].

One of the controversial aspects highlighted by this work was the choice of a scrotal approach over an inguinal approach in some cases. The oncological theory behind the inguinal approach is so that there is optimum control over the venous and lymphatic drainage of the potentially malignant lesion to prevent inadvertent spread. The reason why a scrotal approach was used in 4 cases reported to us is not known. Relevant, available literature, reviewed in this manuscript only supports an inguinal approach as a safe technique.

A further unexpected finding was that 23/37 (60.53 %) of the survey respondents reported using TSS with no histological diagnosis available at the time of operating. Within the survey setting 11/37 (29.7 %) of respondents either personally or anecdotally had performed secondary operations to complete treatment in light of the final histology. In the case series a similar percentage of surgeons (52.9 %) were not using on table histology but none reported a requirement for redo procedures. Whether this is again a form of response bias i.e. those who had needed to re-operate did not contribute to the case series, is unknown but is a possible factor in this discrepancy. Of those that did perform on-table histology there was not a clinically significant difference in the final histology demonstrating consistency between the two methods as reported in literature. From the experience in adult testicular tumors, however, it is absolutely clear, that frozen section evaluation is a key component of effective organ sparing surgery.

The first series about TSS was published in 1990 by Rushton et al. [24] who reported 5 cases of teratoma without any recurrence. Since then, fourteen articles about TSS in the pediatric population with a good reporting of methodology (indication, surgical approach) and complete outcomes (age, histopathology, follow-up, recurrence) have been published [8, 9,12–23]. All of them concluded that in case of selective indications (prepubertal male patients, benign lesion on US, negative serum tumor marker), TSS through an inguinal approach is a safe procedure. Two (0.88%) cases of recurrence have been reported in the literature without any mortality [13,18]. This is the reason why several reviews of the literature advocate for the use of TSS in cases of benign lesions in children [7,27–31].

Most of the prepubertal lesions are benign and the most common pathological finding is mature teratoma. Testis-sparing surgery should be performed for these tumors. However, a preoperative assessment is mandatory. Serum tumor markers (AFP, hCG and sometimes LDH) must be negative according to the age of the child. US is an helpful tool to differentiate malignant and benign tumors[16,32]. Scrotal US is highly sensitive for the detection of childhood primary intratesticular tumors and, when combined with clinical data, highly reliable for differential diagnosis [16,32]. Initial US findings suggestive of a benign lesion included a homogeneous or mainly cystic morphology, moderate to good demarcation, sometimes with an echogenic rim, normal to increased echogenicity and reduced or normal perfusion when compared to the healthy testicular parenchyma. A malignant histology was suspected when US showed a rather inhomogeneous, hypoechoic, not well-circumscribed lesion, often with increased perfusion and also with diffuse infiltration of the testis, hardly leaving any residual normal parenchyma [16]. However, ultrasonography might underestimate the amount of normal residual parenchyma because this tissue is

compressed against the capsule into a thin rim and therefore should not be used as a factor when deciding whether a testis sparing procedure might be appropriate [19].

The size of the tumor is often discussed to perform a TSS. Size does not matter according to Caldwell et al. [8]: they reported 22 TSS to assess for correlation between the tumor size and final pathology diagnoses. A 2-cm size cutoff did not accurately predict pathology for this cohort, or for just pubertal and post-pubertal patients ($p = 0.132$, $p = 0.154$, respectively). The present data refute the finding in adults that a 2-cm cutoff accurately predicts pathology in pediatric patients with an intratesticular mass and normal STMs.

Most of the articles highlight the help of frozen section examinations [8,12,16,18,21,30]. The specificity of a negative frozen section examination is close to 100%. There were no contradictions between the definitive histopathological examination and frozen section [21]. Frozen section analysis did not miss a TSS inappropriate pathology [8,33]. These data suggest that FSE is a valid tool to discriminate between benign and malignant neoplastic testicular tumors. However, some authors concluded that it is not necessary: Patel *et al.* reported seven cases of TTS where frozen section was not performed because preoperative laboratory and ultrasonography findings were so characteristic of benign lesions [19].

Limitations of this study include the relatively low number of respondents; however, considering the rare incidence of this pathology, the data at hand seem to provide a valid overview over current practice.

Conclusions

Testicular-sparing surgery is being increasingly used in the management of testicular tumors in the pediatric population. Currently there are no guidelines or best practice available. Multiple case series exist highlighting success, but no central repository or large data series exists, which will require international collaboration rather than a drive to publish the results of individual centers. There are some common aspects being used such as tumor markers and imaging, but further work needs to be performed to evaluate the use of on table histology and the risks of this not being available.

Key points:

- Testicular-sparing surgery is becoming an increasingly used approach for managing pediatric testicular masses in selected cases
- Negative tumor markers and favorable ultrasound findings are the most important pre-operative investigation
- On table frozen section histology provides a reliable indication of the final histology and therefore where available allows TSS to be performed safely.
- Without on table histology there is an unacceptable risk of a child requiring a further operation.
- Central repository of testicular masses in children required to allow meaningful consensus and guidelines to be produced

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Table 1: Summary of the multi-center case series performed by the authors

| Indication | Operative Approach | Frozen section histology | Final histopathology |
|-------------------|---------------------------|---------------------------------|-----------------------------|
| PTM | Scrotal | NS | Mullerian residues |
| PTM | Scrotal | LCT or benign lesion | LCT |
| PTM | Inguinal | NS | MCT |
| PTM | Inguinal | Benign lesion | Fibrous lesion |
| PTM | Inguinal | Not sent | EC |
| PTM | Inguinal | EC | MCT |
| PTM | Inguinal | EC | MCT |
| PTM | Inguinal | LCT | LCT |
| PTM | Inguinal | Testicular parenchyma | Testicular parenchyma |
| PTM | Inguinal | NS | MCT |
| PTM | Inguinal | NS | EC |
| DSD + PTM | Scrotal | NS | Testicular parenchyma |
| PTM | Inguinal | NS | Lymphoma |
| PTM | Inguinal | NS | Lipoblastoma |
| PTM | Inguinal | MCT | MCT |
| PTM | Inguinal | EC | EC |
| DSD + AIM | Scrotal | Ovarian tissue | Mixed gonadal tissue |

PTM = painless testicular mass

AIM = acute inguinal mass

DSD = disorders of sex development

NS = not sent

MTC = Mature cystic teratoma

LCT = Leydig cell tumor

EC = Epidermoid cyst

Table 1: Summary of the multi-centre case series performed by the authors (original)

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| PTM | Inguinal | Not sent | EC |
| PTM | Inguinal | EC | MCT |
| PTM | Inguinal | EC | MCT |
| PTM | Inguinal | LCT | LCT |
| PTM | Inguinal | Testicular parenchyma | Testicular parenchyma |
| PTM | Inguinal | NS | MCT |
| PTM | Inguinal | NS | EC |
| DSD + PTM | Scrotal | NS | Testicular parenchyma |
| PTM | Inguinal | NS | Lymphoma |
| PTM | Inguinal | NS | Lipoblastoma |
| PTM | Inguinal | MCT | MCT |
| PTM | Inguinal | EC | EC |
| DSD + AIM | Scrotal | Ovarian tissue | Mixed gonadal tissue |

Legend: PTM = painless testicular mass, AIM = acute inguinal mass, DSD = disorders of sex development, NS = not sent, MCT= Mature cystic teratoma, LCT = Leydig cell tumor, EC = Epidermoid cyst

Table 2: Review of the literature between 1990-2019, reporting any series with > 5 patients

| Date | Study period | Author | n= | n= (TSS) | % TSS | Age (months) | Follow-up (months) | Painless scrotal mass | Pathology of TSS specimen | Recurrence | Testicular atrophy |
|------|--------------|-----------|----|----------|-------|----------------|--------------------|-----------------------|-----------------------------------------------------------------------------------------------------------------------|----------------------------|--------------------|
| 2019 | 2003 -2015 | Caldwell | 24 | 22 | 91.7 | 128 (1-210) | 138 | NS | NS | NS | NS |
| 2018 | 2005- 2015 | Wu | 67 | 30 | 44.8 | 18 (3-168) | 32 | 100 % | 63.3 % Teratoma 26.7 % EC 3.3 % Leydig cell tumor 3.3 % Hemangioma 3.3 % Fibrosarcoma | 0 | 0 |
| 2017 | 2001- 2015 | Ye | 47 | 16 | 34 | 38 (3-141) | 56 | NS | NS | 0 | NS |
| 2016 | 2008- 2015 | Friend | 12 | 7 | 58.3 | 48 (2.4 - 150) | NS | NS | NS | 1 EC (14.2 %) | NS |
| 2015 | NS | Kao | 6 | 6 | 100 | NS | 35 | NS | 100 % JGCT | 0 | NS |
| 2012 | 1997- 2008 | Wang | 40 | 15 | 37.5 | 11 (1-144) | 50 | 95.2 % | NS | 0 | 0 |
| 2011 | 1991- 2007 | Tallen | 5 | 5 | 100 | 74 (6-185) | NS | 75 % | 40 % Mature Teratoma 40 % Leydig cell tumor 20 % EC | NS | NS |
| 2011 | 1984- 2008 | Bujons | 15 | 11 | 73 | 96 (36-156) | 67 | 100 % | 36.3 % EC 18.2 % Teratoma 9 % JGCT 9 % Hemangioma 9 % Lipoma 9 % Hamartoma 9 % Splenogonadal fusion | 0 | 0 |
| 2010 | 1987- 2008 | Hisamatsu | 40 | 8 | 20 | 14 (0.2-128) | 68 | 80 % | 63 % Teratoma 37 % EC | 1 Mature Teratoma (12.5 %) | NS |
| 2007 | 2000- 2006 | Patel | 7 | 7 | 100 | 68 (10-188) | 14 | NS | 57 % Cystic Teratoma 29 % EC 14 % Simple cyst | 0 | 0 |
| 2004 | 1976 -2002 | Shukla | 77 | 13 | 16.8 | 34 (4-120) | 72 | NS | 62 % Mature Teratoma 38 % EC | 0 | 0 |
| 2001 | 1985 -2000 | Valla | 83 | 56 | 67 | NS | 58 | 53 % | 29 % Teratoma 25 % Cyst 23 % EC 9 % Sertoli cell tumor 7% Leydig cell tumor 7% Miscellaneous | 0 | 0 |
| 2001 | 1970- 1999 | Ciftci | 5 | 5 | 100 | NS | 89 | NS | 60% Teratoma 40% EC | 0 | NS |
| 1999 | 1967 -1996 | Sugita | 33 | 21 | 63.6 | 31 (2 - 168) | 127 | 83.8 % | 81 % Teratoma 9 % Leydig cell tumor 5 % Sertoli cell tumor 5 % Fibroma | 0 | 0 |
| 1990 | NS | Rushton | 5 | 5 | 100 | (14 - 78) | 96 | 100 % | 80 % Mature Teratoma 20 % Immature Teratoma | 0 | 0 |

Legend: n = number TSS = testicular-sparing surgery, NS = not specified, EC = epidermoid cyst, JGCT = juvenile granulose cell tumor