



Review Article

EAU-ESPU pediatric urology guidelines on testicular tumors in prepubertal boys

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Summary**Background**

Testicular tumors in prepubertal boys account for 1–2% of all solid pediatric tumors. They have a lower incidence, a different histologic distribution and are more often benign compared to testicular tumors in the adolescent and adult group. This fundamental difference should also lead to a different approach and treatment.

Objective

To provide a guideline for diagnosis and treatment options in prepubertal boys with a testicular mass.

Method

A structured literature search and review for testicular tumors in prepubertal boys was performed. All English abstracts up to the end of 2019

Introduction

In the past 30 years, it has clearly been shown, that there is a fundamental difference between testicular tumors in childhood and those in adolescence and adulthood - not only in terms of the difference in incidence [1] but also in terms of histology [2]. Most intratesticular tumors in prepubertal boys are benign, whereas post puberty, the tumors are most likely malignant. Up to 60–75% of the testicular tumors are benign [3–10] in childhood. Intratubular neoplasia (TIN) is practically non-existent in children [2,11–13]. Testicular tumors can generally be classified as germ cell or stromal tumors. One specific tumor type is the gonadoblastoma, which contains germ cell and stromal cell tumor types and will occur almost exclusively in the setting of differences of sexual differentiation [14].

These differences should also lead to a different treatment approach as compared to

were screened, and relevant papers were obtained to create the guideline.

Results

A painless scrotal mass is the most common clinical presentation. For evaluation, high resolution ultrasound has a detection rate of almost 100%, alpha-fetoprotein is a tumor marker, however, is age dependent. Human chorionic gonadotropin (HCG) was not a tumor marker for testis tumors in prepubertal boys.

Conclusion

Based on a summary of the literature on prepubertal testis tumors, the 2021 EAU guidelines on Pediatric Urology recommend a partial orchiectomy as the primary approach in tumors with a favorable preoperative ultrasound diagnosis.

the adult patients. Based upon recent knowledge on prepubertal testicular tumors, the EAU guideline panel on Pediatric Urology aimed to create a specific guideline for diagnostic and surgical treatment options in prepubertal boys with a testicular mass.

Materials and methods

A literature search was performed using the Medline, Embase and the Cochrane databases. The terms testicular cancer/testis tumor/testicular neoplasms and prepubertal boys/infants/neonate/newborn/child/children or derivatives thereof were used. A total of 1391 English language abstracts were screened for their relevance by RS and JQ and 98 full texts were obtained for appraisal. Relevant publications were used to create the guideline. A summary of the current evidence and recommendations is presented here.

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Results

Clinical presentation

The clinical presentation of a prepubertal testis tumor is a painless scrotal mass in more than 90% of patients, detected by one of the parents, caregivers, physician or the patient himself. A history of trauma, pain or hernia is rare. A hydrocele can be found in 15–50% [5,15]. In boys with a testicular mass and early onset of puberty (e.g. early penile and pubic hair growth) along with high testosterone and low gonadotropin levels, a Leydig cell tumor is most likely [16].

In patients presenting with a scrotal mass, a paratesticular tumor should also be taken into account as a differential diagnosis. However, these are even less common compared to intratesticular tumors. The spectrum of paratesticular tumors includes benign tumors such as leiomyoma, fibroma, lipoma, haemangioma, cystic lymphangioma and lipoblastoma as well as malignant tumors such as the paratesticular rhabdomyosarcoma and the rare melanotic neuroectodermal tumor of infancy [17–20].

Evaluation

To confirm the diagnosis and in order to make decisions regarding the further approach, a high-resolution ultrasound (7.5–12.5 MHz), preferably doppler ultrasound, is required. The sensitivity is almost 100% [21,22]. With high-resolution ultrasound, microlithiasis - small hyperdense areas without sound shadows - is increasingly seen in prepubertal boys. A recent meta-analysis showed that 4 out of 296 boys (<19 years of age) with microlithiasis developed a testicular tumor on the ipsi- or contralateral side [23]. If microlithiasis is detected in patients with additional risk factors for testicular tumor, the caregivers/patients should be informed about the increased risk and encouraged to carry out regular self-examinations - similar to patients treated for undescended testis [24]. There is no evidence, that regular sonographic follow-up is useful [23]. The risk for infertility may be higher in patients with microlithiasis and if these patients have any sign of infertility later, the risk of developing a tumor seems to be higher compared to patients without microlithiasis and infertility [25]. Due to the low incidence of a contralateral tumor, even in cases of testicular microlithiasis, there is no indication for contralateral testicular biopsy in prepubertal boys.

Alpha-fetoprotein (AFP) is the only useful tumor marker for testicular tumors in prepubertal boys. AFP is increased in newborns and thus clearly has limited sensitivity and specificity in the first few months of life [15]. It may take up to 12 months before the serum concentration reaches known standard values (<10 ng/mL) [8,26]. AFP is produced by >90% of yolk sac tumors. Teratomas can also produce AFP, albeit to a lesser extent than yolk sac tumors [27]. AFP should be measured before any therapeutic intervention (tumor enucleation/orchiectomy) and ideally should be available at the time of the procedure. AFP has a serum

biological half-life of 5 days. In case the AFP is elevated preoperatively, it should be measured again 5 and 10 days after tumor resection/orchiectomy to evaluate appropriate decrease in levels.

Human chorionic gonadotropin (β -HCG) is derived from choriocarcinoma, embryonal carcinoma or seminoma. However, these tumors are extremely rare in prepubertal boys and therefore β -HCG is not useful in the diagnostic work-up of prepubertal boys with a testicular tumor [15].

There is no urgent need for preoperative staging, as this has no consequence before definitive histology is available.

Treatment/management

It is not necessary to do this as an emergency procedure. However, in order to confirm the diagnosis and to avoid anxiety, the operation should be scheduled as soon as possible, preferably within a few days of diagnosis.

Organ-preserving surgery should be performed whenever possible. A recently published review article showed only 2 recurrences in 227 patients following organ-sparing surgery (one in a patient with an epidermoid cyst and one in a patient with a mature teratoma) [28–30]. Orchiectomy should be considered only if normal testicular parenchyma is no longer detectable on the preoperatively high-resolution ultrasound and/or the AFP is > 100 ng/mL in a boy older than 12-months, as this is highly suspicious of a yolk sac tumor.

For surgical technique, the guideline panel is in favor of an inguinal approach. Furthermore, clamping of the vessels has the advantage of providing a better view, when organ sparing surgery is performed. However, there is no evidence in the literature, that tumor-spread is prevented by clamping the vessels. Whenever possible, frozen sections should be performed during testis-sparing surgery to confirm the diagnosis (benign vs malignant tumor) and to confirm that a microscopically margin-negative resection has been achieved, in which no gross or microscopic tumor remains in the primary tumor bed (R0 resection). In case of an R0 resection, the tunica is closed and the testis is repositioned in the scrotum. In case of R1 resection (removal of all macroscopic disease, but microscopic margins are positive for tumor) confirmed by frozen section in a malignant or potentially malignant tumor, the guideline panel is in favor of performing an orchiectomy during the primary surgery. If the final pathology later demonstrates an R1 resection in a malignant tumor despite intraoperative negative margins on frozen section, a secondary inguinal orchiectomy can safely be performed.

In patients with a malignant tumor (yolk sac tumor, immature teratoma) staging should be performed, including an MRI of the abdomen and a CT-scan of the chest. If there is any suspicion of a non-organ confined tumor, the patient should be referred to a pediatric oncologist. In patients with the rare diagnosis of a Granulosa cell tumor, imaging of the abdomen to exclude enlarged lymph nodes is reasonable as this may potentially be a malignant tumor. In

those with a Sertoli or a Leydig cell tumor, an MRI is recommended, as 10% are malignant and the metastases do not respond very well to chemotherapy or radiation in the adult literature [31,32]. The TNM classification from 2015 for adult testicular tumors can be used in patients with a malignant tumor [33]. In benign tumors (mature teratoma, epidermoid cysts) no further staging is required.

Tumor entities in prepubertal boys

Germ cell tumors

Teratomas are usually benign in prepubertal children and represent the greatest proportion of intratesticular tumors (around 40%) [3,34]. They present at a median age of 13 months (0–18 months). Only in adolescents and adults, should these be considered as malignant tumors. Histologically they can consist of a combination of the three primitive embryological germ-cell layers (ectoderm, mesoderm and endoderm). Most of these elements show microscopically mature elements [35], however, some immature teratomas in this age group have also been reported [9]. To exclude any malignant potential, like focal areas of a yolk-sac tumor, the entire specimen should be investigated. After organ-sparing surgery only one recurrence was reported in the literature [30].

Epidermoid cysts are of ectodermal origin and seem to be related to well differentiated teratomas; they are always benign [35]. Keratin-producing epithelium is responsible for the keratinized-squamous-epithelial deposits, which appear hyperechogenic on ultrasound [36]. Organ-sparing surgery should be performed and if confirmed by histology, there is no need for surveillance, despite the fact that one “recurrence” was has been reported 13 years after primary diagnosis [29].

Yolk sac tumors are the predominant prepubertal malignant germ cell tumors and may represent around 15% of the prepubertal tumors in boys [3]. They are histologically mostly solid, yellow-grey tumors. These usually occur within the first two years of life [37]. Up to 80–85% of the tumors are organ-confined (stage I) [38]. The tumor usually spreads hematogenously (chest). Those with stage I disease may develop visible metastases in 20% within the next 2 years. In a German study, 14 out of 91 patients with Stage I had a recurrence after observation – all were cured by chemotherapy alone. Four out of 5 with metastatic disease initially, were cured by chemotherapy after radical orchiectomy [39]. In a recent published series from China, 21 of 90 pediatric patients with a stage I yolk sac tumor received primary chemotherapy. One of the 21 had a recurrence, whereas 29 out of 69 who underwent surveillance after initial orchiectomy alone had a recurrence. The overall 4-year survival rate was 97.8% [37]. Almost the same recurrence rate was reported by the American oncology groups [40]. Therefore, in patients with stage I disease (no metastatic disease on MRI-abdomen and CT scan of the chest as well as normal age-adapted AFP-values) close follow-up together with the pediatric oncologists including AFP every 2–3 months and MRI of the abdomen is

recommended, at least for the first 2–3 years [15], this is particularly true in those with invasion of the lymphatic vessels, as this has been shown to be a negative prognostic factor in a recent series [37]. In case of recurrence, chemotherapy should be prescribed by pediatric oncologists according to the national study protocols.

Stromal cell tumors

Juvenile granulosa cell tumors usually occurs in the first year of life, typically within the first 6 months [41]. They are well circumscribed and have a typical yellow-tan appearance; 2/3 have cystic elements and 1/3 are solid [41]. The stroma can be fibrous or fibromyxoid. So far, no recurrence has been reported after organ-sparing surgery [41–43].

Leydig cell tumors arising from the testosterone producing Leydig cells should be suspected in boys with early onset of puberty with high testosterone and low gonadotropin levels [16]. Patients are usually between 5 and 10 years of age; the tumors are well circumscribed with yellow-brown nodules. In children there are no reports of malignant Leydig cell tumors and after organ sparing surgery, there have been no recurrences so far [44]. In the adult literature, there is a reported malignancy rate of 10% and primary retroperitoneal lymphadenectomy should be discussed in cases with enlarged lymph nodes as these metastases do not respond very well to chemotherapy or radiation [45].

Around 1/5 of *Sertoli-cell tumors* occur in children; usually within the first year of life [46]. In the pediatric age group, large-cell calcifying Sertoli cell tumors (LCCSCT) are the most common tumor variant [47]. Except one case report with the histological diagnosis of a malignant LCCSCT [47], all other reported tumors have been benign, therefore organ-sparing surgery should be performed.

Follow-up

Regular ultrasound examination is recommended in the follow-up period to detect any recurrence and/or other abnormalities. As there are only few studies with recurrence after testicular sparing surgery or orchiectomy, no clear recommendation can be made concerning the interval and the duration of follow-up. However, performing an ultrasound examination every 3–6 months within the first year seems to be reasonable, as few recurrences have been detected at this time and the rate of atrophy is extremely low after organ-sparing surgery [28]. Continued follow up beyond the first year after surgery only seems advisable in patients with a malignant tumor (see above). The follow-up in patients with Leydig cell tumors should include endocrinological examinations.

Using the SEER (Surveillance, Epidemiology and End Results) data base, the 5-year relative survival for testicular malignancies for patients less than 14 years of age diagnosed with localized testicular cancer was 97.4%, and for those with distant disease was 72.6% [48].

Summary of evidence	LE	Strength rating
Testicular tumors in prepubertal boys have a lower incidence and a different histologic distribution compared to the adolescent and adult patients	2a	Strong
In prepubertal boys up to 60–75% of testicular tumors are benign	3	Strong
Recommendations	LE	Strength rating
High-resolution ultrasound (7.5–12.5 MHz), preferably doppler ultrasound, should be performed to confirm the diagnosis	3	Strong
Alpha-fetoprotein (AFP) should be determined in prepubertal boys with a testicular tumor before surgery	2b	Strong
Surgical exploration should be done with the option of frozen section; an emergency surgical setting is not necessary	3	Strong
Organ-preserving surgery should be performed in all benign tumors.	3	Strong
Staging (MRI abdomen/CT chest) should only be performed in patients with a malignant tumor to exclude metastases	3	Strong
MRI should only be performed in patients with the potential malignant Leydig or Sertoli-cell-tumors to rule out lymph node enlargement	4	Weak
Patients with a non-organ-confined tumor should be referred to pediatric oncologists postoperatively.	4	Weak

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