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

Stein, Raimund; Quaedackers, Josine; Bhat, Nikita R.; Dogan, Hasan S.; Nijman, Rien J. M.; Rawashdeh, Yazan F.; Silay, Mesrur S.; 't Hoen, Lisette A.; Tekgul, Serdar; Radmayr, Christian

Published in:
Journal of Pediatric Urology

DOI:
10.1016/j.jpurol.2021.06.006

Publication date:
2021

Journal of Pediatric Urology (2021) 17, 529–533

Review Article

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

Raimund Stein [a,*], Josine Quaedackers [b], Nikita R. Bhat [c], Hasan S. Dogan [d], Rien J.M. Nijman [b], Yazan F. Rawashdeh [e], Mesrur S. Silay [f], Lisette A. 't Hoen [g], Serdar Tekgul [d], Christian Radmayr [h], Guy Bogaert [i]

[a]Center for Pediatric, Adolescent and Reconstructive Urology, Medical Faculty Mannheim, University of Medical Center Mannheim, Heidelberg University, Mannheim, Germany

[b]Department of Urology and Pediatric Urology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

[c]Department of Urology, Norfolk and Norwich University Hospital, Norwich, United Kingdom

[d]Department of Urology, Division of Pediatric Urology, Hacettepe University, Ankara, Turkey

[e]Department of Urology, Aarhus, Denmark

[f]Division of Pediatric Urology, Department of Urology, Istanbul Medeniyet University, Istanbul, Turkey

[g]Department of Pediatric Urology, Erasmus Medical Center, Rotterdam, the Netherlands

[h]Department of Urology, Medical University of Innsbruck, Innsbruck, Austria

[i]Department of Urology, University of Leuven, Leuven, Belgium

* Correspondence to: Raimund Stein, Center for Pediatric, Adolescent and reconstructive Urology, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany, Theodor-Kutzer Ufer 1 – 3, Mannheim, D 68167, Germany, Telefon: +49 (0) 621 383 1137, Telefax: +49 (0) 621 383 1504 raimundstein01@gmail.com (R. Stein)

Keywords
Testicular cancer; Prepubertal boys; Diagnostics; Organ sparing surgery; Guidelines; Pediatrics

Received 10 January 2021
Revised 3 May 2021
Accepted 4 June 2021
Available online 9 June 2021

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 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.

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 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.

https://doi.org/10.1016/j.jpurol.2021.06.006

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
Testicular tumors in prepubertal boys have a lower incidence and a different histologic distribution compared to the adolescent and adult patients	2a
In prepubertal boys up to 60–75% of testicular tumors are benign	3

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

References

[1] Kusler KA, Poynter JN. International testicular cancer incidence rates in children, adolescents and young adults. Cancer Epidemiology 2018;56:106–11.

[2] Hawkins E, Heifetz SA, Giller R, Cushing B. The prepubertal testis (prenatal and postnatal): its relationship to intratubular germ cell neoplasia: a combined Pediatric Oncology Group and Children's Cancer Study Group. Hum Pathol 1997; 28(4):404–10.

[3] Pohl HG, Shukla AR, Metcalf PD, Cilento BG, Retik AB, Bagli DJ, et al. Prepubertal testis tumors: actual prevalence rate of histological types. J Urol 2004;172(6 Pt 1):2370–2.

[4] Taskinen S, Fagerholm R, Aronniemi J, Rintala R, Taskinen M. Testicular tumors in children and adolescents. J Pediatr Urol 2008;4(2):134–7.

[5] Metcalfe PD, Farivar-Mohseni H, Farhat W, McLorie G, Khoury A, Bagli DJ. Pediatric testicular tumors: contemporary incidence and efficacy of testicular preserving surgery. J Urol 2003;170(6 Pt 1):2412–5. discussion 5-6.

[6] Shukla AR, Woodard C, Carr MC, Huff DS, Canning DA, Zderic SA, et al. Experience with testis sparing surgery for testicular teratoma. J Urol 2004;171(1):161–3.

[7] Nerli RB, Ajay G, Shivangouda P, Pravin P, Reddy M, Pujar VC. Prepubertal testicular tumors: our 10 years experience. Indian J Canc 2010;47(3):292–5.

[8] Wu D, Shen N, Lin X, Chen X. Prepubertal testicular tumors in China: a 10-year experience with 67 cases. Pediatr Surg Int 2018;34(12):1339–43.

[9] Li Z, Zhang W, Song H, Sun N. Testis-preserving tumor enucleation is applicable in children with immature testicular teratoma. Urol Int 2020:1–4.

[10] Woo LL, Ross JH. Partial orchiectomy vs. radical orchiectomy for pediatric testis tumors. Transl Androl Urol 2020; 9(5):2400–7.

[11] Manivel JC, Reinberg Y, Niehans GA, Fraley EE. Intratubular germ cell neoplasia in testicular teratomas and epidermoid cysts. Correlation with prognosis and possible biologic significance. Cancer 1989;64(3):715–20.

[12] Renedo DE, Trainer TD. Intratubular germ cell neoplasia (ITGCN) with p53 and PCNA expression and adjacent mature teratoma in an infant testis. An immunohistochemical and morphologic study with a review of the literature. Am J Surg Pathol 1994;18(9):947–52.

[13] Rushton HG, Belman AB, Sesterhenn I, Patterson K, Mostofi FK. Testicular sparing surgery for prepubertal teratoma of the testis: a clinical and pathological study. J Urol 1990;144(3):726–30.

[14] Roth LM, Cheng L. Gonadoblastoma: origin and outcome. Hum Pathol 2020;100:47–53. https://doi.org/10.1016/j.humpath.2019.11.005.

[15] Ahmed HU, Arya M, Muneer A, Mushtaq I, Sebire NJ. Testicular and paratesticular tumours in the prepubertal population. Lancet Oncol 2010;11(5):476–83.

[16] Henderson CG, Ahmed AA, Sesterhenn I, Belman AB, Rushton HG. Enucleation for prepubertal leydig cell tumor. J Urol 2006;176(2):703–5.

[17] Soles BS, Wilson A, Lucas DR, Heider A. Melanotic neuroectodermal tumor of infancy. Arch Pathol Lab Med 2018; 142(11):1358–63.

[18] Yada K, Ishibashi H, Mori H, Shimada M. Intrascrotal lipoblastoma: report of a case and the review of literature. Surg Case Rep 2016;2(1):34.

[19] Marulaiah M, Gilhotra A, Moore L, Boucaut H, Goh DW. Testicular and paratesticular pathology in children: a 12-year histopathological review. World J Surg 2010:1–6.

[20] Walterhouse DO, Barkauskas DA, Hall D, Ferrari A, De Salvo GL, Koscielniak E, et al. Demographic and treatment variables influencing outcome for localized paratesticular rhabdomyosarcoma: results from a pooled analysis of north American and European cooperative groups. J Clin Oncol 2018:JCO2018789388.
[21] Lock G. [Contrast-enhanced ultrasonography of testicular tumours]. Urologe 2019;58(12):1410—7.
[22] Esen B, Yaman MO, Baltaci S. Should we rely on Doppler ultrasound for evaluation of testicular solid lesions? World J Urol 2018;36(8):1263—6.
[23] Yu CJ, Lu JD, Zhao J, Wei Y, Zhao TX, Lin T, et al. Incidence characteristics of testicular microlithiasis and its association with risk of primary testicular tumors in children: a systematic review and meta-analysis. World J Pediatr 2019.
[24] Ludwikowski B, Becker K, Stein R, Rösch W, Albers N, Reschke F. S2kHodenhochstand — maldescensus testis. 2016. https://www.awmf.org/uploads/tx_szleitlinien/006-022l_S2k_Hodenhochstand_Maldescensus-testis_2018-08.pdf.
[25] Barbonetti A, Martorella A, Minaldi E, D'Andrea S, Bardhi D, Castellini C, et al. Testicular cancer in infertile men with and without testicular microlithiasis: a systematic review and meta-analysis of case-control studies. Front Endocrinol 2019;10:164.
[26] Schneider DT, Calaminus G, Gobel U. Diagnostic value of alpha 1-fetoprotein and beta-human chorionic gonadotropin in infancy and childhood. Pediatr Hematol Oncol 2001;18(1):11—26.
[27] Ross JH, Rybicki L, Kay R. Clinical behavior and a contemporary management algorithm for prepubertal testis tumors: a summary of the Prepubertal Testis Tumor Registry. J Urol 2002;168(4 Pt 2):1675—8. discussion 8-9.
[28] Radford A, Peycelon M, Haid B, Powis M, Lakshminarayanan B. Testicular-sparing surgery in the pediatric population: multicenter review of practice with review of the literature. Curr Opin Urol 2019;29(5):481—6.
[29] Friend J, Barker A, Khosa J, Samnakay N. Benign scrotal masses in children - some new lessons learned. J Pediatr Surg 2016;51(10):1737—42.
[30] Hisamatsu E, Takagi S, Nakagawa Y, Sugita Y, Yoshino K, Ueoka K, et al. Prepubertal testicular tumors: a 20-year experience with 40 cases. Int J Urol 2010;17(11):956—9.
[31] Fankhauser CD, Grogg JB, Hayoz S, Wettstein MS, Dieckmann KP, Sulser T, et al. Risk factors and treatment outcomes of 1,375 patients with testicular leydig cell tumors: analysis of published case series data. J Urol 2020;203(5):949—56.
[32] Grogg J, Schneider K, Bode PK, Kranzbuhler B, Eberli D, Sulser T, et al. Sertoli cell tumors of the testes: systematic literature review and meta-analysis of outcomes in 435 patients. Oncol 2020.
[33] Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Fizazi K, et al. Guidelines on testicular cancer: 2015 update. Eur Urol 2015;68(6):1054—68.
[34] Little T, Lala S, Upadhyay V. Paediatric testicular tumours in a New Zealand centre. N Z Med J 2017;130(1467):68—72.
[35] Williamson SR, Delahunt B, Magi-Galluzzi C, Algaba F, Egevad L, Ulbright TM, et al. The world health organization 2016 classification of testicular germ cell tumours: a review and update from the international society of urological pathology testis consultation panel. Histopathology 2017;70(3):335—46.
[36] Chang MY, Shin HJ, Kim HG, Kim MJ, Lee MJ. Prepubertal testicular teratomas and epidermoid cysts: comparison of clinical and sonographic features. J Ultrasound Med : official journal of the American Institute of Ultrasound in Medicine 2015;34(10):1745—51.
[37] Ye YL, Zheng FF, Chen D, Zhang J, Liu ZW, Qin ZK, et al. Relapse in children with clinical stage I testicular yolk sac tumors after initial orchiectomy. Pediatr Surg Int 2018.
[38] Grady RW. Current management of prepubertal yolk sac tumors of the testis. Urol Clin 2000;27(3):503—8 [ix].
[39] Haas RJ, Schmidt P, Gobel U, Harms D. Testicular germ cell tumors, an update. Results of the German cooperative studies 1982-1997. Klin Pädiatr 1999;211(4):300—4.
[40] Rogers PC, Olson TA, Cullen JW, Billmire DF, Marina N, Rescorla F, et al. Treatment of children and adolescents with stage II testicular and stages I and II ovarian malignant germ cell tumors: a Pediatric Intergroup Study-Pediatric Oncology Group 9048 and Children's Cancer Group 8891. J Clin Oncol 2004;22(17):3563—9.
[41] Kao CS, Cornejo KM, Ulbright TM, Young RH. Juvenile granulosa cell tumors of the testis: a clinicopathologic study of 70 cases with emphasis on its wide morphologic spectrum. Am J Surg Pathol 2015;39(9):1159—69.
[42] Shukla AR, Huff DS, Canning DA, Filmer RB, Snyder 3rd HM, Carpintieri D, et al. Juvenile granulosa cell tumor of the testis:: contemporary clinical management and pathological diagnosis. J Urol 2004;171(5):1900—2.
[43] Grogg JB, Schneider K, Bode P-K, Kranzbühler B, Eberli D, Sulser T, et al. Risk factors and treatment outcomes of 239 patients with testicular granulosa cell tumors: a systematic review of published case series data. J Canc Res Clin Oncol 2020;146(11):2829—41.
[44] Luckie TM, Danzig M, Zhou S, Wu H, Cost NG, Karaviti L, et al. A multicenter retrospective review of pediatric leydig cell tumor of the testis. Journal of Pediatric Hematology/Oncology. 2019;41(1):74—6.
[45] Geminiani JJ, Marshall SD, Ho TS, Brandes SB. Testicular leydig cell tumor with metachronous lesions: outcomes after metastasis resection and cryoablation. Case reports in urology 2015;2015:748495.
[46] Talon I, Moog R, Kauffmann I, Grandadam S, Becmeur F. Sertoli cell tumor of the testis in children: reevaluation of a rarely encountered tumor. J Pediatr Hematol Oncol 2005;27(9):491—4.
[47] Li G, Lee MS, Kraft KH, Heider A. Prepubertal malignant large cell calcifying Sertoli cell tumor of the testis. Urology 2018;117:145—9.
[48] Alanee S, Shukla A. Paediatric testicular cancer: an updated review of incidence and conditional survival from the Surveillance, Epidemiology and End Results database. BJU Int 2009;104(9):1280—3.