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Original Article

Pediatric testicular tumors: 10 years of clinical approach at the Antiguo Hospital Civil de Guadalajara.

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Abstract. - Introduction: In recent decades, the prevalence of testicular cancer has increased. The prevalence of testicular cancer in children under 19 years of age worldwide represents the sixth position in terms of frequency. The estimated prevalence is 0.3-3.1, incidence 0.17-1.4 and mortality 0.02-0.1 per 100,000. Considering the increase in the prevalence of testicular cancer, we conducted this study with the intention of knowing the clinical characteristics, the diagnostic and therapeutic approach, as well as the incidence and mortality in our environment. **Methods:** A case series of pediatric patients attended from January 1, 2013 to January 1, 2023 at the Antiguo Hospital Civil de Guadalajara Fray Antonio Alcalde was carried out. Age, risk factors, clinical presentation, tumor markers (BHCG, AFP, LDH), imaging studies, therapeutic management, tumor size and histopathological study were reviewed. The data was collected by reviewing clinical records; these data were downloaded into the Office Excel program and transferred to SPSS version 25. **Results:** We analyzed the records of 11 pediatric patients who met the inclusion criteria, 4 patients had a testicular tumor and 7 patients had a paratesticular tumor, estimating an incidence of 0.15/100 000. The mean for age at diagnosis was 14 years with a deviation of 8 with respect to the mean, only 2 patients (18.18%) presented cryptorchidism as a risk factor, all patients presented increased testicular size at diagnosis, tumor markers were positive in 41.6% of the cases in which it was measured. Ultrasound was performed in all cases, the mean size of the masses was 3 cm, 1 patient presented benign histology, while 3 patients presented positivity to malignancy. Five orchiectomies were performed, one lumpectomy and five are still under follow-up and surveillance. **Conclusion:** testicular and paratesticular tumors are infrequent in pediatric age, nevertheless, understanding them is of great importance in order to make an early diagnosis and offer an individualized therapeutic approach, considering limiting radical orchiectomy to cases in which malignancy is suspected.

Keywords: Testicular tumor; Paratesticular tumor; Pediatric patient; Tumor markers; Clinical presentation; Diagnosis; Treatment; Risk factor; Histopathology.

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1. Introduction

Testicular masses in prepubertal and post-pubertal pediatric patients are two distinct entities considering their epidemiology, diagnostic approach and treatment[1]. Most prepubertal tumors are usually benign, with patients most often presenting teratomas, whereas postpubertal tumors are similar to those diagnosed in adults and probably associated with greater malignancy[2].

The prevalence of testicular cancer has increased in recent decades, especially in industrialized countries[3]. In patients under 19 years of age, its estimated prevalence is 0.3-3.1, incidence 0.17-1.4 and mortality 0.02-0.1 per 100,000 population[4], in Mexico, according to the same source, a prevalence of 3.5, a mortality of 0.34 and an incidence of 1.3 per 100,000 is reported.

Testicular and paratesticular masses in pediatric patients are not part of the main motives for pediatric consultation at the Antiguo Hospital Civil de Guadalajara Fray Antonio Alcalde, nevertheless, it is important to establish the initial management that patients with testicular masses should receive and to provide an early diagnosis, offering a therapeutic approach according to the clinical characteristics, ultrasonographic and histopathological findings.

In order to approach the diagnosis, we can make use of tools such as imaging studies and tumor markers, and depending on the results, we may or may not be able to offer a preserving surgery[5–7].

Moreover, it is essential to know the main histological strains of testicular and paratesticular tumors that occur in patients under 18 years of age, since depending on age, due to the influence of gonadotropins, patients are more likely to present some histological subtypes, also, in the case of adolescents (post-puberty), the risk of presenting a malignant neoplasm is higher, so it is essential to perform an appropriate approach[5,8].

Establishing an early diagnosis is crucial since the short and long term prognosis of patients treated in early stages of testicular cancer is better. In addition to being useful for the creation of prevention strategies and establishing a starting point for future research that will contribute to generate more knowledge on this topic.

Considering the above, we conducted a case series report with the aim of analyzing and documenting the cases of pediatric testicular and paratesticular tumors (under 18 years of age) treated at the Antiguo Hospital Civil de Guadalajara that occurred during the period from January 1, 2013 to January 1, 2023, in order to determine the incidence, clinical characteristics, diagnostic and therapeutic approach in each one of them, as well as the mortality caused by this pathology.

2. Method

A case series study was performed at the Antiguo Hospital Civil de Guadalajara. The population corresponded to those patients diagnosed with a testicular or paratesticular mass, while the sample was according to patients who met the inclusion criteria.

The inclusion criteria were pediatric patients diagnosed with testicular or paratesticular mass, patients under 18

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years of age at the time of diagnosis, having been treated in the pediatric surgery service at the Antiguo Hospital Civil de Guadalajara Fray Antonio Alcalde, patients with a complete electronic and/or physical clinical record and having been cared for in the period from January 1, 2023 to January 1, 2023.

We excluded pediatric patients treated in other institutions, patients diagnosed with testicular mass over the age of 18 years, incomplete clinical records, and patients who did not have diagnostic support tests prior to definitive treatment.

Data collection was performed by means of clinical records and no data that could identify the patient were considered. Quantitative and qualitative variables were taken into account. Quantitative variables included age, tumor markers such as alpha-fetoprotein beta subunit of human chorionic gonadotropin and lactate dehydrogenase, tumor size and stage. The qualitative variables considered were risk factors, clinical picture, ultrasonographic findings, treatment, and as dichotomous variables, histologic findings and mortality.

The data were imported into Microsoft Excel and transferred to SPSS (Statistical Package Social Science) Version 25. For the statistical analysis of categorical variables, frequency and percentages were used, and for numerical variables, medians and mode were used. The data are represented in bar and sector graphs depending on the type of variable.

3. Results

We conducted a review of 12 records of pediatric patients who met a diagnosis of tumor of uncertain or unknown behavior of the testicle at the Antiguo Hospital Civil de Guadalajara for 10 years from January 1, 2013 to January 1, 2023.

Out of a total of 12 patients, 11 patients met inclusion criteria and 1 patient met exclusion criteria. Of the 11 cases included in the present study, 4 patients had a testicular tumor and 7 patients had paratesticular tumors.

The mean age of diagnosis was 14 years (range, 29 days to 15 years). Of the total cases 45.45% (5 patients) were prepubertal (Tanner pubertal stage I) and 54.55% (6 patients) were pubertal or postpubertal.

Regarding risk factors, it can be seen in Figure 1 that 9 patients were free of risk factors (81.82%), while 2 of the patients presented cryptorchidism (18.18%), one of them being right cryptorchidism and the other left cryptorchidism.

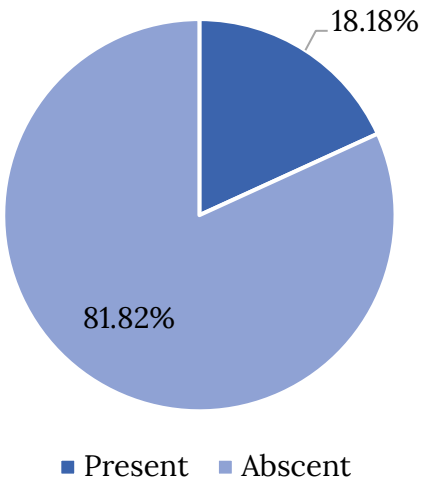

Figure 1. Presence of risk factors for testicular cancer in the evaluated sample.

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The most common form of presentation was testicular enlargement in all cases, and in 6 patients (55.45 %) this was accompanied by pain. Only 2 patients had reactive hydrocele and 1 patient had gynecomastia. As for the transillumination test, in 54.55 % of the cases it was positive and in 45.45 % it was negative. Figure 2 shows that the tumor was unilateral in 90.9% of the cases and only 9.1% presented a bilateral tumor.

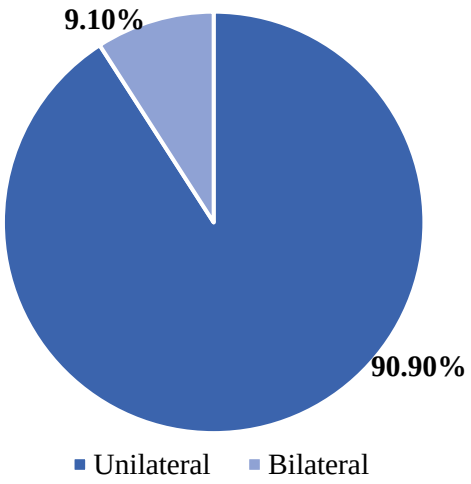

Figure 2. Type of presentation of testicular tumor.

During diagnostic evaluation of tumor markers, the level of human chorionic gonadotropin hormone beta fraction was measured in 8.4% (1 patient), alpha-fetoprotein in 33.3% (4 patients) and lactate dehydrogenase in 41.6% (5 patients). Only 41.6% (5 patients) had positive tumor markers.

As shown in Figure 3, ultrasound was performed in all cases, 3 patients had a solid tumor, 5 patients had an epididymal cyst, 2 patients had microcalcifications and 1 patient had increased intratesticular flow. The mean size of painful masses was 3 cm (2-4) and of non-painful masses 3.98 cm (1-10).

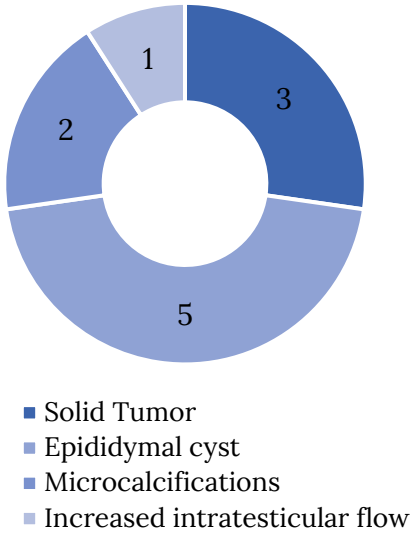

Figure 3. Type of ultrasonographic finding.

A total of 5 radical orchiectomies were performed, of which 80% (4 patients) had a solid testicular tumor and 20% (1 patient) a paratesticular tumor with testicular infiltration. Lumpectomy was performed in only 9.09% of the cases (1 patient). In 5 of the cases, 45.5%, benign pathology was found and did not require intervention and so far they are under follow-up and surveillance.

Figure 4 shows that, out of the 11 patients, 4 had testicular tumors, of which 1 patient had benign histology, while 3 patients had histology positive for malignancy. The distribution of the histology of the testicular tumors was one pure germinal tumor of prepubertal mature teratoma type (benign), one mixed germinal tumor 90% teratoma and 10% embryonal carcinoma, one prepubertal yolk sac

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germinal tumor and the remaining case was negative for malignancy.

The other 7 patients had testicular adnexal tumors, 5 corresponded to epididymal cysts, 1 paratesticular tumor, which was positive for malignancy (embryonal rhabdomyosarcoma) while the remaining case continues to be followed up (probable embryonal rhabdomyosarcoma).

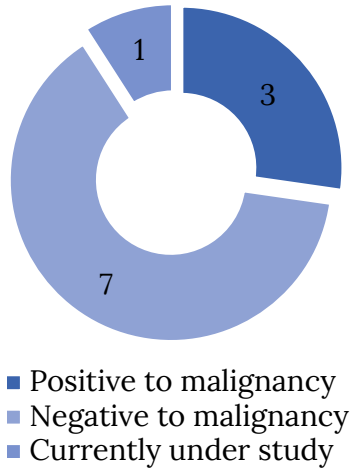

Figure 4. Histology of the presented tumors.

Of the total number of patients with testicular tumors, those that were positive for malignancy, 2 patients were stage I (PTIB) and 1 patient was stage III (PT2). The stage III patient was the only one with retroperitoneal metastases (mass measuring 23.5 x 10.5 x 7.3 cm).

In addition to the initial surgical treatment, 2 patients with testicular tumors received adjuvant chemotherapy, one of them based his scheme on etoposide, bleomycin and carboplatin, while the other patient's cycles consisted of vincristine, actinomycin D and cyclophosphamide.

No cases of death were reported for the patients included in the present study. The tables show the characteristics of each of the patients analyzed with the presence of testicular tumors, and Table 2 shows the patients with paratesticular tumors. It is worth mentioning that so far no deaths were reported in the follow-up.

Table 1 shows the characteristics of each of the patients analyzed with the presence of testicular tumors and paratesticular tumors

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Tabla 1. Resultados de pacientes pediátricos con tumor testicular y paratesticular.

Case	Age	Risk Factors	Presentation	Tumor markers	Ultrasound	Therapeutic management	Tumor size	Histology	Stage
1	1 year	No	Painful mass, transillumination negative.	Positive AFP: 1.4 LDH: 319	Solid tumor with reactive hydrocele	Radical orchiectomy	4 x 2.5 x 2.5 cm	Pure germinal tumor of prepubertal mature teratoma type.	PT1B, Stage I.
2	15 years	No	Non painful mass, transillumination negative.	Positive AFP: 525.5 BHCG: 387. 6 LDH: 209	Solid tumor with characteristics of germ cell tumor + right varicocele grade II	Radical orchiectomy	10 x 7 x 6 cm	Mixed germinal tumor 90% teratoma and 10% embryonal carcinoma	PT2, Stage III.
3	2 meses	No	Painful mass, transillumination negative.	Not reported.	Calcifications and hypoperfusion	Radical orchiectomy	2 x 3 x 2 mm	Negative for malignancy	
4	11 meses	Right cryptorchidism	Palpable, non-painful mass, transillumination negative.	AFP: 4587 LDH: 346	Solid tumor with increased intratesticular flow	Radical orchiectomy	3.5 x 2 x 2cm	Prepubertal yolk sac germinal tumor	PT1B, Stage I.
5	14 years	No.	Painful mass, transillumination positive.	LDH: 227	Epididymal cyst	Under follow-up			
6	9 years	No.	Painful mass, transillumination positive.	Negative	Bilateral epididymal cyst	Under follow-up			
7	14 years	No.	Painful mass, positive transillumination.	Negative	Epididymal cyst	Under follow-up			
8	12 years	No.	Painful mass, positive transillumination.	Negative	Epididymal cyst	Under follow-up			
9	14 years	No.	Non painful mass, positive transillumination.	Negative	Epididymal cyst	Tumorectomy	2 cm diameter	Serous cyst of epididymis	
10	8 years	No.	Non painful mass, negative transillumination.	AFP: 2.27 LDH: 482	Testicle with hyperechogenic lobulated structures, with increased intratesticular flow	Radical orchiectomy	3.4 cm in greatest diameter	Paratesticular embryonal rhabdomyosarcoma, with infiltration of the epididymis and testicular network	
11	29 days	Left cryptorchidism	Painful mass, negative transillumination.	Negative	Heterogeneous mass with microcalcifications, nodal growth in both inguinal canals	Under follow-up (probable embryonal rhabdomyosarcoma).			

AFP = Alphafetoprotein; LDH = Lactate dehydrogenase; BHCG = Human chorionic gonadotropin hormone beta fraction; cm = centimeters.

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4. Discussion.

Testicular tumors currently account for 1-2% of all pediatric tumors[1], with an incidence of 0.05-2 per 100,000 infants[2]. There is a bimodal age distribution, with the first peak occurring during the first 2 years of life and the second around 15 years of age[1-3]. The increased incidence of tumors after 9 years of age could be associated with the high hormonal levels at puberty[9,10]. These tumors usually have a good prognosis, with an approximate benignity of 50% and an overall survival of 99% at five years[1,5]. In our study we found an incidence of 0.15, similar to the overall estimate, with no deaths reported during the follow-up period.

The histology of testicular tumors varies according to the cell line from which they originate. Among prepubertal intratesticular tumors, 90% are germ cell tumors and only 10-15% are epidermoid cysts[10,11]. Benign germ cell tumors are frequent, approximately 40-50% are teratomas[9,13,14]. Epidermoid cysts are always benign. Malignant germ cell tumors are mainly represented by yolk sac tumors 8-30%[9,14,15]. On the other hand, among non-germ cell derived tumors, Leydig cell tumors are usually the most frequent, followed by juvenile stromal granulosa cell tumors[9,14,16].

Regarding prepubertal testicular malignant neoplasms, 5-year survival is 97% in boys with localized tumors, while only 73% in those with distant disease[17,18]. Moreover, in post-pubertal boys most tumors are malignant and mixed germ cell tumors predominate among them[14,19], from the data obtained we found similarity in the presentation of benign and malignant tumors, however, the most frequent histology was that of germ cell tumors.

In post-pubertal adolescents aged 15 to 19 years, the incidence increases and represents 12% of all cancers in adolescents[17,18]. In this population, there is a higher probability of malignancy and includes immature teratomas, mixed non-seminomatous germ cell tumors and embryonal carcinomas[6]. In young adults, 95% of testicular cancers are malignant germ cell tumors and 50% of these correspond to seminomas[17,21].

The malignant potential of germ cell tumors increases rapidly after the age of 9 years, whereas benign tumors tend to be more frequent in young children[17]. The etiology of pediatric testicular tumors is unknown, however, a possible association with prenatal diethylstilbestrol exposure has been postulated[10].

Some risk factors for testicular tumors have been identified, such as cryptorchidism, gonadal dysgenesis, Klinefelter's syndrome, history of testicular cancer in a first-degree relative, presence of contralateral tumor and infertility[20,22]. In addition, bilateral abnormal external genitalia and late descended or uncorrected testes are risk factors for the development of malignancy in cryptorchidism, this being the association found in 2 cases of germinal tumors[17,23].

Tumorogenesis depends on the action of gonadotropins in the testis, since gonadotropin levels follow the same age-adjusted pattern of testicular cancer incidence. Thus, the disease would begin in fetal life, with alterations in the formation of primordial cells, giving rise

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to neoplastic cells in situ that remain quiescent until stimulated by gonadotropin-mediated signals[5,25].

The clinical presentation of testicular tumors is usually as a painless testicular mass (82-90%) and less than 10% as a painful mass secondary to hemorrhage or necrosis. Only a few patients present with hydrocele, scrotal pain or history of trauma. About 10-25% of patients with malignant tumors usually present with hydrocele[23].

Tumor markers are an important diagnostic tool for evaluating pediatric testicular tumors, including alpha-fetoprotein, beta-subunit of human chorionic gonadotropin and lactate dehydrogenase[17,24].

Serum alpha-fetoprotein values are generally higher in children than in adults and are usually reduced to normal levels by 1 year of age (<10 ng/ml). Thus, in children <1 year with testicular tumors, the level of alpha-fetoprotein may be elevated in those with benign tumors, whereas in those >1 year a normal level of alpha-fetoprotein usually indicates a benign tumor[25].

An elevated serum alpha-fetoprotein level is strongly associated with >90% of yolk sac tumors, whereas immature teratomas may have only a slightly elevated serum alpha-fetoprotein level[25]. 25 Alpha-fetoprotein should be measured prior to any therapeutic management and after surgery to assess for adequate lowering of the level[17]. Currently, it is discouraged to base treatment solely on elevated alpha-fetoprotein when its levels are stable and <25 ng/mL[26].

Human chorionic gonadotropin beta subunit is elevated in embryonal carcinomas, choriocarcinomas or seminomas, which are extremely rare in prepubertal children, but can be seen in postpubertal patients. Therefore, it is not useful in the diagnosis of prepubertal boys with a testicular tumor, but is useful in adolescents presenting with a testicular mass[27].

Lactate dehydrogenase may serve as a diagnostic tool, since high serum levels are associated with bulky disease and increasing levels after therapy may signify disease recurrence, however, they are only elevated in 20% of low-stage germ cell tumors[17,26].

Ultrasonography is the imaging modality of choice in the study of testicular tumors, with a sensitivity of 100% and a negative predictive value of almost 100%[23,28,29]. Testicular tumors are predominantly homogeneous hypoechoic, but in some cases may be heterogeneous with solid, cystic or calcified components, in which they reflect the underlying histological features[8]. In the case of Doppler ultrasound, most malignant masses show elevated blood perfusion, whereas benign tumors are usually well demarcated with decreased blood flow[2,30].

Contrast-enhanced ultrasound helps in the discrimination of focal testicular lesions, it can show microvascularization and in case of hyperenhancement it is indicative of a malignant tumor[6,31]. Elastography increases diagnostic accuracy by assessing the stiffness of the lesions. It should be noted that malignant neoplastic lesions are harder due to the

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higher density of tumor cells and vessels than in normal testicular tissue[31,32].

MRI is usually used as a complementary imaging technique in those exceptional cases in which scrotal ultrasound findings are inconclusive or non-diagnostic, in the evaluation of abdominal cryptorchidism and in the extension of a histologically confirmed malignant testicular tumor[23].

Therapeutic management requires clinical suspicion and ultrasonographic confirmation of an intratesticular lesion, determination of serum markers (alpha-fetoprotein and beta subunit of human chorionic gonadotropin, hormone levels (testosterone) and lactate dehydrogenase. Percutaneous testicular biopsy is not usually performed due to the risk of lymphatic tumor seeding[23,33].

The traditional treatment of choice for testicular masses is radical orchiectomy; however, due to the benignity in children, in recent years the medical-surgical approach has been re-evaluated, where lumpectomy (conservative surgery) is considered depending on tumor markers (alpha-fetoproteins or beta subunit of human chorionic gonadotropin), tumor size and histological findings[9].

Testicular sparing surgery is limited in infants in whom normal testicular tissue is seen to be salvageable by ultrasound and tumor markers within normal serum values, i.e. in those where malignancy is not suspected. In some cases intraoperative frozen section examination can be used to confirm a pathological tumor, as well as to justify the choice of conservative surgery[9,19,23]. Cases of malignant testicular tumors are rare and usually occur in older children, so radical orchiectomy with postoperative follow-up is recommended in patients 5 years of age or older[9].

When specific tumor markers are found to be increased, radical inguinal orchiectomy is considered. In addition, adjuvant chemotherapy is required in malignant testicular tumors[9,23]. Some short- and long-term treatment-related complications may occur. Adverse effects include the risk of infertility, hemorrhagic cystitis and the development of a secondary malignancy[10].

After surgical treatment, infants should be monitored with physical examination, scrotal ultrasound and tumor markers[23,34,35]. Especially in the case of malignant testicular tumors, follow-up is performed according to the type of testicular cancer (seminoma, non-seminoma or advanced stages) and is based on evaluating four parameters: physical examination, tumor markers, chest x-ray and abdomino-pelvic computed axial tomography, which, depending on the year of follow-up, are requested more and more frequently. In advanced stages, chest or brain tomography may be requested in particular cases[26].

On the other hand, paratesticular tumors are a heterogeneous group of infrequent tumors. Approximately 70% of paratesticular tumors are benign, among which lipomas, leiomyoma, dermoid cyst and adenomatoid tumors are the most frequent[36,37]. However, malignant tumors represent the other 30% and rhabdomyosarcoma and leiomyosarcoma are common, in some cases malignant mesothelioma and adenocarcinoma of the rete testis and epididymis have been described[36].

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In pediatric patients, rhabdomyosarcoma is the most frequent malignant paratesticular tumor. Its age of distribution is bimodal, with a peak at 3-4 months and another at 16 years of age[38]. It develops from the mesenchymal tissues of the spermatic cord, epididymis and tunica testicularis[39]. The clinical presentation is a large painless mass and metastatic in up to 40% at the time of presentation.

On ultrasound it is seen as a large heterogeneous mass with no other differentiating findings. It can locally infiltrate adjacent tissues and metastasize by hematogenous and lymphatic routes; in 70% of patients it metastasizes regionally and 25% to the lung and bone[2]. The treatment of choice in this type of tumor depends on the age and size of the primary tumor; however, radical orchiectomy with radical retroperitoneal lymphadenectomy is usually performed. In those patients where there is evidence of lymphatic involvement after lymphadenectomy, radiotherapy and chemotherapy with vincristine, actinomycin D and cyclophosphamide is also administered[2].

Survival is greater in prepubertal children than in adolescents, being 90% at 3 years in children aged 3-4 months and only 63% respectively. Age older than 7 years, alveolar histology, unresectable retroperitoneal dissemination or distant metastases should be considered indicators of poor prognosis in this type of tumor[2].

5. Conclusions

Testicular and paratesticular tumors are not so frequent entities in pediatric patients; however, knowledge of these tumors is of great importance for an adequate diagnosis and treatment, considering the clinical, imaging and histological characteristics of each tumor mass.

It is of great relevance to determine the initial management and follow-up that should be given to patients with testicular and paratesticular masses under study, in order to establish an early diagnosis and offer an individualized therapeutic approach, taking into account the clinical manifestations, age, ultrasonographic findings, tumor markers, among other variables. Likewise, by individualizing the treatment, it is possible to offer patients who meet the selection criteria lumpectomies instead of radical orchiectomies, which allows the preservation of healthy testicular tissue in those cases with no risk of malignancy.

It should be considered that the histologic strains of testicular and paratesticular masses are different depending on whether the patients are prepubertal, pubertal or postpubertal due to the influence of gonadotropins on cell differentiation. In addition, the probability of malignancy is higher in pubertal and postpubertal patients, so that timely diagnosis and treatment could improve the prognosis and survival of patients.

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6. Statements

6.1 Conflict of interest

The authors declare no conflict of interest.

6.2 Funding

No funding was required to carry out this research.

6.3 Ethical considerations

The ethical considerations that guarantee the privacy, dignity and well-being of the patient under investigation were respected in the development of this study. This study did not entail any risk for the patient, as it was a research study in which only documents with a retrospective approach were handled, given that no intervention was given.

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