TESTICULAR TUMORS IN PEDIATRIC POPULATION: SINGLE CENTER EXPERIENCE

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TESTICULAR TUMORS IN PEDIATRIC POPULATION: SINGLE CENTER EXPERIENCE (Abstract): Our study **aims** to provide valuable contributions to the understanding and management of this rare condition, with a particular focus on our single-center experience and analysis of cases in light of limited worldwide reports. **Materials and methods:** This study analyzed 18 patients between 2003 and 2023. We categorized patients into two age groups: prepubertal (ages 0-11 yrs.) and postpubertal (ages 12- 18 yrs.), based on the typical onset of puberty in males, in order to compare distinct tumor characteristics. We assessed clinical data, staging imaging, pre-operative serum tumor marker values, surgical approaches, chemotherapy protocols, and clinical outcomes. **Results:** There was no significant difference in the prevalence of the different types of clinical presentations between groups. The overall survival (OS) rate was 94.4%, while the progression free survival (PFS) was 77.8%. The postpubertal age group had a significantly lower PFS period compared to patients in the prepubertal age group. **Conclusions:** This research highlights the importance of precisely performing physical, imaging, and biological tests for the early detection of testicular cancer. It emphasizes the significance of ongoing research and collaborative efforts to enhance testicular cancer management. **Keywords:** TESTICULAR, TUMORS, PREPUBERTAL, POSTPUBERTAL, CHILDREN, ADOLESCENTS.

Testicular tumors (TT) are uncommon across the pediatric population, with an annual incidence of between 1.6 and 2 cases per 100,000 children (1, 2). Based on age, TT in boys exhibits a bimodal distribution, occurring between 2 and 4 years or during infancy (prepubertal group) and after 12 years (postpubertal group) (3). Clinical considerations during these age periods are essential for choosing appropriate and distinct treatment strategies. Given the scarcity of cases and the limited literature available globally on this topic, our goals are to underline the clinical, pathological, and outcome data from single-center cases to enhance understanding and inform future clinical practice.

MATERIALS AND METHODS

This study analyzed only the children with TT who were admitted to our institution between January 2003 and January 2023. We retrospectively selected patients using the ICD-10 coding system and re-

viewed medical chart records for epidemiological and clinical data, staging imaging, pre-operative serum tumor marker levels (STM), surgical procedures, medical oncology therapy(s), clinical outcomes, and the histological subtype. We categorized patients into two age groups: prepubertal (0- 11 years) and postpubertal (12- 18 years), based on the typical onset of puberty in males, approximately at 12 years of age.

Data from the study were analyzed using IBM *SPSS Statistics versions 20 & 25* and illustrated using Microsoft Office Excel/Word 2013. Quantitative variables were tested for normal distribution using the Shapiro-Wilk Test and expressed as averages with standard deviations or medians with interquartile ranges. Kaplan-Meier curves were used to illustrate and calculate overall survival time (OS) and progression-free survival time (PFS) in the analyzed groups. Tarone-Ware tests were used to compare OS and PFS between age groups.

RESULTS

We have identified 18 children with TT, 10 cases in the prepubertal group and 8 cases in the postpubertal group (tab. I). Detailed family histories were limited in the study. One 7-year-old patient had a history of multicystic renal dysplasia. Incidental palpable testicular mass was most common in the 12-18 age group (8/8), but there was no significant difference compared to the 0-11 age group (9/10) (p-value = 0.387). In our study, right-side tumors were more common (10/18), and no patients had bilateral tumors. Testicular pain was more prevalent in postpubertal patients (5/8) compared with prepubertal patients (1/10). Only one child from the postpubertal cohort presented with respiratory distress syndrome because of pulmonary metastasis.

TABLE I.

Comparison of diagnostic age according to age groups

Age	Average ± SD	Median (IQR)	Mean rank
Prepubertal	1.46 ± 2.01	0.91 (0.64-1.25)	5.50
Postpubertal	15.87 ± 1.8	17 (15-17)	14.50

Ultrasound was performed on all symptomatic and diagnosed patients, and only 7 required additional imaging. Computed tomography (CT) was used in 5 out of 18 patients, while magnetic resonance imaging (MRI) of the abdomen and pelvis was used in 2 out of 18 cases. The decision to conduct additional imaging studies was made based on clinical judgment and specific indications. These indications primarily included symptoms suggestive of advanced disease or findings on initial ultrasound examinations warranting further evaluation for accurate staging and treatment planning. In our study cohort, only a subset of patients met these criteria and thus required additional imaging studies. CT scans were exclusively performed on post-pubertal patients (n = 5), and only two results revealed significant findings related to disease spread (p-value = 0.016).

Positron emission tomography (PET-CT) was performed on three postpubertal patients. In the first case, the patient follows the chemotherapy protocol with favorable clinical progress. We conducted imaging one year

after diagnosis, which revealed certain lung abnormalities on CT scans; subsequently, a PET-CT scan was performed, which identified a probability of secondary pulmonary dissemination and hypermetabolism at the mediastino-pulmonary and bilateral axillary levels. While complete exclusion of dissemination was not possible, suspicion of pulmonary and nodal metastasis was high, leading to the initiation of a second-line chemotherapy protocol. In the second case, the patient presented with metastases upon admission and underwent initial chemotherapy for six months; subsequently, a PET-CT was deemed necessary, revealing metabolically active tumor remnants. In the last case, it was performed two months after finishing chemotherapy regimens, prompted by the parents' insistence on obtaining this exam and no detectable malignant FDG-hyper captured lesions were observed.

Histologic subtypes included 7 (38.88%) mixed germ cell tumors (mixed GCTs), 4 (22.21%) immature teratomas, 3 (16.66%) Yolk Sac Tumors (YSTs), 2 (11.1%) PT-RMS, 1 (5.55%) embryonal carcinoma (EC), and 1 (5.55%) cystic dysplasia of the testis (tab. II). Even though PT-RMS is not a TC, we included these 2 patients in our study due to the paratesticular mass. Immunohistochemistry diagnostic procedures were performed on a limited sample, comprising three patients (16.67% of the cohort). These evaluations were specifically focused on 2 PT-RMS (11.1%) and, regarding non-GCNIS derived tumors, were exclusively performed on an 8-month-old patient diagnosed with mixed GCT.

TABLE II.

Patient distributions according to age and histologic subtypes

Tumor subtype	0 - 11 yrs.	12 - 18 yrs.	p-value
Germ cell tumors derived from germ cell neoplasia in situ			0.002
-Mixed Germ Cell Tumors	1	6	
-Nonseminomatous germ cell tumors: Embryonal carcinoma	-	1	
Germ cell tumors unrelated to germ cell neoplasia in situ			
-Teratoma, prepubertal type (immature)	4	-	
-Yolk sac tumor, prepubertal type	3		
Paratesticular tumors (PT-RMS)	1	1	
-Cystic dysplasia of testis (benign)	1	-	

STM values were available for all cases, and measurements were performed preoperatively (tab. III). Alpha-fetoprotein (AFP) levels (normal value <34.8 ng/mL) ranged from 39 ng/mL to 5321 ng/mL (median 2255 ng/mL) in malignant cases. Patients from the postpubertal group had human chorionic gonadotropin (hCG) levels (normal value <1.2 mIU/mL) ranging from 150 mIU/mL to 45654 mIU/mL in malignant cases. The highest hCG value was observed in the patient with mixed GCTTs who had metastases at the time of the presentation. hCG and lactate dehydrogenase (LDH) levels were within the normal range in the prepubertal group. Elevated levels of both AFP and hCG were observed in six postpubertal patients. Among them, five patients were diagnosed with mixed GCTs, while one patient had EC.

TABLE III.
STM distribution according to age groups and histological subtype

Age group (No)/ STM	5 - 11 yrs.	12 - 18 yrs.	p-value
AFP elevated	3	7	0.038
- histological subtype	YST- 2 IT- 1	Mixed GCTTs- 5 EC- 1 PT-RMS- 1	
- highest value (ng/mL)	1800	5321	
hCG elevated	-	6	0.036
- histological subtype	-	Mixed GCTTs- 5 EC- 1	
- highest value (mIU/mL)		45654	
LDH elevated	-	6	0.001
- histological type	-	Mixed GCTTs- 6	
- highest value (U/L)		1200	

All patients within the age range of 12 to 18 years underwent radical inguinal orchidectomy (RO). Testicular sparing surgery (TSS) was deemed appropriate for three patients in the prepubertal age group; Initially, in two patients, the strategy involved performing a total excision of the tumor while preserving the seemingly unaffected testicular parenchyma. However, after a few days, a RO was decided upon following the pathological examination, which revealed a mixed GCT/ YST. In the last case of TSS, a surgical procedure was performed through a trans scrotal approach. Additionally, the right testicle showed enlargement attributed to the presence of a multicystic, septated tumor that was composed of serous citrine fluid. A biopsy was performed on the cystic mass and the testicle, with an extemporaneous evaluation ruling out malignancy. A 1-year-old patient, previously diagnosed with YST and who underwent trans scrotal orchidectomy at another medical facility, presented to our department with a local recurrence in the left hemiscrotum. As a result, a second surgery was performed to remove the recurrent area.

In the prepubertal group, seven patients received platinum-based chemotherapy (CHT) protocol and the SIOP MMT 95.3 protocol was used for patient with PT-RMS. In the postpubertal group, six children underwent platinum base CHT protocol, and patient diagnosed with PT-RMS was initially treated with vincristine, dactinomycin, and cyclophosphamide (VAC Protocol), but due to metastasis spreading to the lungs and lymph nodes, a second regimen with temozolamide and irinotecan was required.

Among the study participants, metastatic spread was observed in two postpubertal cases at initial presentation in our institute. One patient with mixed GCT and another case involved a patient with EC. After initial diagnosis, subsequent metastasis developed in one prepubertal patient after 14 months, and in three patients from the postpubertal group at 8, 12, and 18 months, respectively. The most frequently affected sites were the lung and retroperitoneal lymph nodes, followed by the brain and bones.

To obtain details concerning survival and mortality, an official request was sent

to the National Register of Persons (No. 19315-2022) for the public disclosure of relevant data. Due to the low frequencies of deaths (1 case- 5.6%) and disease events (4 cases- 22.2%), medians with interquartile ranges could not be computed for the OS and PFS periods. As such, the overall survival rate was 94.4%, while the PFS was 77.8%. According to the Tarone-Ware tests, the PFS period was significantly different (**p= 0.047)**. Patients in the postpubertal age group had a significantly lower PFS period (mean = 14, 95% C.I.: 8.15- 19.84 months) in comparison to patients in the prepubertal age group (mean = 187.33, 95% C.I.: 147.29- 227.37 months) (fig. 1).

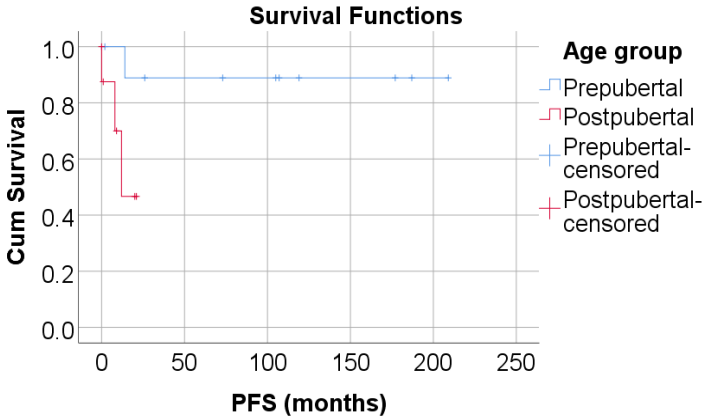

Fig. 1. Comparison of PFS period according to the age groups

DISCUSSION

In this article, we present our experience from a single center focusing on the pediatric population up to 18 years of age. Our hospital serves as a primary referral center for pediatric oncology in Eastern Romania, covering a significant region where the majority of pediatric tumors are treated. The risk of TC is 2-5 times higher in individuals with a history of cryptorchidism (the normal incidence is 1 in 400 men) (4). In contrast to documented risk factors, data on the risk associated with testicular microlithiasis (TM) are contradictory (5). In our study, none of the patients had a known history of cryptorchidism, and only one patient with cystic dysplasia of the testis had a personal history of multicystic renal dysplasia. The majority of TGCTs (85%-90%) manifest as asymptomatic testicular masses, which can be discovered by the patient, parent, or physician (6,7). Scrotal pain, with or without a mass, has been attributed to intratumorally hemorrhage or infarction in up to 50% of TC cases. In our study, beyond a testicular mass, pain was reported only in 5 postpubertal patients, and only 3 of them had the presence of tumoral necrosis or infarction on the histological report.

The connection between age at diagnosis and histologic characteristics, etiology, treatment strategies, and prognosis has been determined to be substantial (8). The age of 12 is commonly used as a proxy for the onset of puberty. Our cohort precisely matched the described bimodal distribution of disease, with peaks of incidence in both

the first year of life and the seventeenth year. Notably, among prepubertal malignant tumors, only a small proportion (5%) of prepubertal YSTs exhibited dissemination at the time of diagnosis, contrasting with postpubertal GCTs, where the percentage of cases with metastasis at presentation ranges from 20% to 30%. Additionally, nearly 90% of prepubertal children are stage 1 at the first presentation, compared to only 35% of postpubertal cases with testicular-limited cancer. This further demonstrates the highly aggressive and distinct nature of TGCTs in adolescents (9).

Increased AFP values were identified in more than half of the patients included in the study, which contrasts with findings by Kashyap, who observed that among 66 children with abnormally high AFP levels (>20 ng/mL), only 18 (27.3%) showed signs of malignancy (10). Preoperative serum AFP levels ranged from 39 ng/mL to 5321 ng/mL (median 2255 ng/mL) in malignant cases. In prepubertal patients, the AFP value was increased in two YSTs and in one case with an immature teratoma. Based on a meta-analysis, AFP was found to be very useful in distinguishing YSTs in prepubertal age cohorts (median 90%). These values were typically >100 ng/mL, which proved very useful for distinguishing teratomas, as they do not always produce elevated AFP values (11). Elevated hCG values were identified in 6 postpubertal patients included in the study. Regarding the type of tumor, we observed the highest value of hCG (45654 mIU/mL) in the patient with mixed GCT who had metastases at the time of presentation. In the literature, choriocarcinomas had the highest incidence of elevated levels, followed by seminomas (15 to 20%) and EC. It has been shown to be considerably higher in just two boys with mixed GCT in a study involving 34 male patients, leading some published research to conclude that testing for it in prepubertal disease age cohorts is minimally useful (11). Significant increases in LDH, have been linked to high tumor burden and may indicate recurrence (12). Elevated LDH values were identified in six postpubertal patients included in the study.

Imaging plays a significant role in the clinical staging and subsequent restaging of patients with GCTs (13,14). US has been used for all diagnosed patients, with only 7 requiring additional imaging studies. Recently, 18F-FDG PET has been used alongside CT to monitor patients for metastasis or recurrence (15). In our series, PET-CT was performed on 3 postpubertal patients. Considering the findings of some researchers, who reported a high incidence of false-negative PET scans within two weeks of chemotherapy, it is imperative that the examination be performed prior to chemotherapy (16). In our series, we provided a rational use for elucidating its diagnostic significance beyond seminoma.

Pohl *et al*. reported that 74% of the testicular masses identified in the prepubertal group in their research were determined to be benign (17). However, in our study, only one prepubertal patient was diagnosed with a benign lesion, which does not align with findings in existing literature. Previously, it was believed that YSTs were the predominant pathology in prepubescent males. Other research has acknowledged that there may have been selection bias in their report due to the absence of benign mature teratoma lesions among participants (18). In our sample population, we had 4 testicular teratoma with immature tissue and only 3 cases with YST.

A meta-analysis combining studies from IGCCCG and COG revealed excellent 6-year event-free survival (EFS) and overall survival (OS), with EFS of 78.5% and OS of 100% for stage 1, 100% for stage 2, 94.1% for stage 3, and 90.6% for stage 4 (19). In our study, the average OS rate was 94.4%, while the overall progression-free survival rate was 77.8%. Patients in the postpubertal age group had a significantly lower PFS period compared to those in the prepubertal age group. Several investigations in the literature have examined the genetic foundation of male infertility following cancer. These studies shed light on the genetic vulnerability associated with different cancer treatments and explore the possibility of men recovering reproductive function at the end of cancer treatment (20, 21).

Our study has a few limitations. These include the relatively small number of patients, the long-time span (20 years), the retrospective nature of the study, and possible selective bias because our institution is not used as a national referral medical center for TT.

CONCLUSIONS

Testicular tumors form a heterogeneous group that varies considerably in clinical presentation, location, histology, and biology. There is a great necessity to include patients in international partnerships, data exchange, and clinical trials at all stages and risk categories for understanding these uncommon tumors and, most critically, to improve outcomes. This study represents the largest pediatric testicular case series in eastern Romania, emphasizing the significance of ongoing research and collaborative efforts to enhance TC management. Achieving this necessitates further investigation through targeted studies and involvement in clinical trials, particularly given the limited number of worldwide reports.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest and they received no funding.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of "Sf. Maria" Emergency Children Hospital's (No. 29289/12.10.2022) and the "Grigore T. Popa" University of Medicine and Pharmacy of Iasi Ethics Committee (No. 247/15.12.2022) both approved the publication of this report.

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