Original article

Treatment outcome of prepubertal gonadal tumors: The **Children's Hospital** Lahore Pakistan experience

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ABSTRACT

Background: Prepubertal gonadal terms are rare with an incidence of 0.5-2 per 100,000 populations. Due to their rare occurrence, their presentation and management have not been established. This study aims to highlight the clinical and histopathological features of prepubertal gonadal tumors along with treatment outcome at a tertiary care specialist hospital in Central Punjab.

Patients and methods: Records of 105 prepubertal children who were treated for gonadal tumors at the Children's Hospital Lahore Pakistan from January 2011 to December 2017 were retrospectively reviewed. Histopathological features, risk stratification, clinical stages, and their outcomes were analyzed. Demographic details, histopathological features, risk stratification (high risk with serum alpha protein (AFP) more than 10,000ng/ml, thoracic tumor and stage IV at presentation), clinical stages at presentation using TNM clinical and post-surgical classification and Children's Oncology Group staging system (COG), and their treatment outcomes were analyzed. The United Kingdom Children's Cancer Study Group (UKCCSG) protocol consisting of Carboplatin, Etoposide and Bleomycin (JEB) chemotherapy was used for treatment.

Results: Out of 105 patients, 69% were females and 41% were less than 5 years of age. Only 6% tumors were benign whereas 94% were malignant. Among them 92 (88%) patients had tumor size more than 5cm. Among total 70% were categorized as high-risk. On histopathology, 49% were yolk sac tumors, 12% were mixed malignant germ cell tumor, 12% dysgerminoma, 8% teratomas, 5% juvenile granulose cell tumor, 2% Sertoli and Leydig cell tumors and rest were unspecified. Out of 105 patients, 16% had stage II, 40% stage III and 44% stage IV at presentation. Orchidectomies and Oosalpingectomies were undertaken in 80% cases. Multidisciplinary team management (MDT) was utilized in 67% cases. Among them 72% completed treatment and were well while 8% abandoned treatment. There were overall 18% deaths, 79% due to disease progression and advanced stage of the disease with delayed treatment and 21% due to infection. Febrile neutropenia was the commonest event during treatment observed in 29% patients followed by obstructive uropathy in 13% patients. Tumor local recurrence following surgery was noted in 10% cases.

Conclusions: Majority of the prepubertal gonadal tumors was malignant, commonest histopathological sub-type being Yolk Sac tumor followed by dysgerminoma. High mortality and treatment abandonment can be reduced by timely diagnosis and efficient multidisciplinary team management to achieve cure rates being obtained in developed countries.

Keywords:
Prepubertal, Gonadal tumors, Resource limited, Low income countries.

INTRODUCTION

As compared to post pubertal tumors, testicular tumors in children are rare making 1 to 2% of all solid tumors of children. For boys with age less than 15 years, the incidence is 1.6 (0.5-2) per 100,000 annually.[1] The clinical course, histopathology as well as management of pediatric testicular tumors is different from those in adults. In adult testicular tumors, mixed type or seminoma is common while teratomas and yolk sac predominate in children.[2] Recent studies have shown that the frequency of teratomas is more as compared to yolk sac tumors. To evaluate these different results, some studies came out with the conclusion that this uneven distribution is due to some genetic or environmental factors while others concluded that it was just reporting bias.[3]

In younger girls when it comes to gynecological malignancies, ovarian tumors are rare. Ovarian tumors account for 8% of abdominal tumors and only 1% of all malignancies in childhood annually with an incidence of 2.6 cases per 100,000 girls.[4] Sex-cord stromal tumors and epithelial tumors are found to be less frequent than germ cell tumors (GCT) histologically and their etiology is not completely understood.[5]

It has been shown that 60% of cases in pediatric GCTs were extragonadal while the sites which are

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gonadal like ovaries and testis have reportedly 40% of cases.[2,3] In adolescents and children, GCTs are reported to be the most frequent gonadal tumors.[4] The exact incidence of gonadal tumors in children is not known.[6] In children most cases of gonadal GCTs are curable when diagnosed at an early stage and managed appropriately by a multidisciplinary team. If this is not done a high morbidity and mortality is seen.[7]

The aim of this study was to look at clinical and histopathological features and treatment outcome of prepubertal gonadal tumors in a government hospital in Central Punjab region of Pakistan. The objective was to determine the challenges faced and identify risk factors to be addressed in the future to improve survival.

PATIENTS AND METHODS

This retrospective observational study was carried at the Haematology/Oncology department after approval from the Institutional Review Board of the Children's Hospital Lahore. Total 105 patients with ages less than 13 years were diagnosed with primary gonadal tumors from January 2011 to December 2017. Data of all these patients was analyzed for age, sex, clinical manifestations, size, clinical staging at presentation (the Children's Oncology Group Staging[7]), risk stratification, histopathology, treatment protocol used and complications, multidisciplinary team working and outcome, abandonment of treatment and causes of death were also reviewed. A pre-designed questionnaire of details of all patients were evaluated by reviewing the medical records of patients, including clinical history and diagnostic information (imaging, tissue biopsy and tumor markers), histopathology and staging reports, treatment received, and outcome of management. All the data was analyzed using SPSS 20. The p-value was calculated for clinical characteristics and histopathology and age distribution comparing with sex distribution as well as outcome.

RESULTS

Total 105 patients were reported during the study period, 33 (31%) were male and 72 (69%) female with a male to female ratio of 1:2.2. Age range was from 1 month to 13 years with 41% less than 5 years old. The girls predominantly presented with abdominal pain and abdominal/pelvic mass and boys with painless scrotal swelling. The diagnostic workup included tissue biopsy, imaging (abdominal ultrasound/CT scan/MRI), tumor markers (AFP, BHCG) along with staging workup (CT scan, bone scan, bilateral bone marrow aspirate).

Table 1. Clinical characteristic of patients with prepubertal gonadal tumors

Characteristics	Male	Female	p-value for gender and outcome
Stages			
Stage II	10	7	0.026/0.04
Stage III	12	30	
Stage IV	11	35	
Risk stratification			
High Risk	14	59	0.000/0.009
Intermediate Risk	19	13	
Size			
>5cm	20	72	0.000/0.274
<5cm	13	0	
Management			
Surgery done	31/33	53/72	0.05/0.004
MDT done	26/33	45/72	0.09/0.000

Serum Alpha Fetoprotein was high in yolk sac tumors (YST), mixed malignant germ cell tumors (MMGCT) and immature teratomas. The tumor staging was done according to the Children's Oncology Group (COG) staging guidelines.[7] Majority had advanced stage and large tumors and was of high risk at presentation (Table 1). The histological diagnosis is summarized in Table 2 with statistical significant p-values for gender but not for outcome 0.414. A p-value was statistically significant when staging and risk stratification compared with gender and outcome as shown in Table 1 and also statistically significant p-value where surgery was performed and multidisciplinary team management done comparing with overall outcome with p-value of 0.004 and <0.001 respectively. A p-value of 0.414.and 0.952 was not statistically significant when histopathology and age distribution compared with outcome in Table 2 and 3 respectively. Surgery was done in the form of Salpingo-Oophorectomy and Orchidectomy in 83 (79%) cases, while unilateral ovarian-sparing tumorectomy was done only in one girl with bilateral ovarian tumor. These children were treated with UKCCSG protocol with 4-6 courses of JEB- composed of Etoposide, Carboplatin and Bleomycin every 21 days, no patient received radiotherapy. As far as events during management is

Table 2. Histopathological findings

Histopathology	Male	Female	p-value for gender and outcome
Yolk sac tumor	24	27	0.000/0.414
MMGCT	0	13	
Dysgerminoma	0	13	
Mature teratoma	4	1	
Immature teratoma	0	3	
GCT	4	9	
Stromal/Juvenile granulose cell tumor	1	5	
Leydig-Sertoli cell tumor	0	1	

Table 3. Age-wise distribution of gonadal tumors

Age	YST	DG	MMGCT	Teratomas	SCST/JGCTO/ Sertoli-Leydig	p-value for gender/outcome
<5 years	31	0	2	3	2	0.003/0.952
5-10 years	9	5	6	4	4	
10-13 years	11	8	5	1	1	

YST: Yolk sac tumor; DG: Dysgerminoma, MMGCT: Mixed malignant GCT, SCST: Sex cord stromal tumor, JGCTO: Juvenile granulose cell tumors

concerned, 30 children had febrile neutropenia/ sepsis requiring hospital admission,14 presented with obstructive uropathy, 14 required blood products and 11 cases had recurrent growth after surgery due to lack of MDT affecting overall outcome significantly (p-value=0.000). Outcome of patients is summarized in Figure 1, showing 72% completed treatment 8% abandoned and 18% deaths and among 4 relapsed 2 expired due to refractory disease.

DISCUSSION

In this study, 6% of all the prepubertal gonadal tumors were benign, mature teratoma being the most common in both males and females and all the remaining 94% were malignant. On the contrary a study was done in India showed 35% of cases were malignant in nature with immature teratoma being the most common malignant ovarian neoplasm, while 65% cases were benign.[8] In another study only 10-30% of all the operated cases of ovarian neoplasms in prepubertal girls were malignant.[9] A study done in Taiwan on prepubertal testicular GCT showed similar results to our study. Their study revealed that 15% cases were of mature teratoma and benign while 85% of cases were Yolk sac tumors and malignant in nature.[10]

In this study, among 98 (93%) germ cell tumors, the commonest histology among all tumors was YST which accounted for 49% along with MMGCT and dysgerminoma which showed low percentage of 12.5% each. Major percentage belonged to GCT that was 93%. Out of total germ cell tumor cases, 17% were among male patients while 83% cases were female patients. A previous study showed that about 60-85% of all the neoplasms of ovarian type that belong to pediatric age group were mainly of germ cell type.[11] Another study revealed that only 38% of cases of neoplasm were of germ cell type and 66% among the malignant neoplasms were malignant GCT variety with Dysgerminoma being most common.[12] Dysgerminoma was also the most common diagnosis in patients with median age of 18 years and had overall survival of 88% in stage 1 and 26% in stage IV in a local study on MMGCT.[13] Another study in paediatric population on GCT presented from same centre showed 43% had YST, 19% were of mixed GCT and 16% Dysgerminoma and 80% were of gonadal origin. Authors had OS of 64% and 26% lost to follow up with expected OS of 45%.[14]

In present research majority of these patients had advanced disease at presentation (stage III and IV-84%), high risk stratification and with >5cm larger size tumors. All these factors affected the overall management outcome both in boys and girls. In a study from Taiwan, only 10% of the cases were advanced, with 5-year survival of 96.5% for yolk sac tumors and 100% for teratomas.[10] Similarly one study from Netherlands showed only 11% cases presenting with stage III or IV requiring only salpingoophorectomy/ Oophorectomy in 83% of the cases and chemotherapy along with surgery in 15 % and radiotherapy was used only for one patient resulting in excellent prognosis with only 3% mortality and recurrence rate of 4.5%.[15] The rate of survival increases to the percentage of 90% in localized forms of gonadal malignant GCTs. The gonadal tumors respond better as compared to mediastinal germ cell tumors (MGCT) which are extragonadal. Ever since the platinum-based regimens were introduced, the outcomes of malignant forms have improved.[16]

In this study 8% left the treatment against medical advice. Treatment abandonment is a major cause of

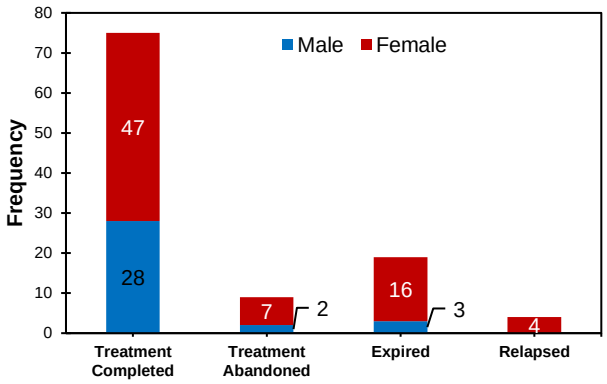

Figure 1. Treatment outcome of patient reported with prepubertal gonadal tumors

failure of treatment in childhood cancer in low-income countries (LIC).[17] In LIC main factors leading to abandonment are social/economic factors, low parents education, long distance from primary treatment centers, belief that cancer is not curable, alternative therapies, religious beliefs, worries for painful tests and treatment , malnutrition, younger age and female gender.[17,18] A study done in Karachi showed 22% children abandoned therapy and half of them left even before start of treatment despite offer of free treatment proving treatment abandonment is one of the most arduous challenges faced in LIC.[19]

This study showed 18% of patients expired due to infections, toxicity of treatment and advanced disease at presentation and progressive disease. Many studies have shown a low rate of morbidity and mortality. A study done in Cape Town, South Africa using the same CCLG protocol with JEB chemotherapy and minimum blood products usage, there was no death due to infection or toxicity. In this study the advanced disease rate was very high 89.5% and there were 2 deaths reported due to refractory disease.[20] In our current study the rate of overall survival (OS) was almost 72% while that of event free survival (EFS) was 68%. The results of this study were compared with another study that was done in children suffering with gonadal GCT of stage I and II showing 93-96% of survival at 6 years.[21] Another study comparing children with adolescents and adults diagnosed with testicular malignant GCTs, the 5-year OS was 100% and EFS 87.2%, 84.8% and 59.9% in children, adolescents and adults respectively.[22] Another study done in Shaukat Khanum Cancer Hospital Lahore on testicular tumors in children over 15 years of age showing survival of 96% and 90% with histopathology of seminomas and non-seminomatous GCTs.[23,24]

CONCLUSION

Most of the malignant germ cell tumors can be cured with chemotherapy. Ninety-four percent patients in this study had malignancy because most benign tumors are probably diagnosed can be treated locally. Public awareness about these curable tumors should be done, to enable early presentation and diagnosis. All patients should be discussed in a multidisciplinary team consisting of pathologists, radiologists, oncologists and surgeons so that the appropriate surgical and chemotherapy approach can be planned at an early stage.

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