Original Article

Clinical Profile and Survival Outcomes in Pediatric Germ Cell Tumors: Single Centre Experience

Ayesha Latif*, Tariq Ghafoor, Benish Hira, Abdul Wahab Siddique, Rabiha Manzoor, Shaista Naz

Department of Pediatric Oncology, Combined Military Hospital, Rawalpindi, Pakistan

Article Info

Corresponding Author
Ayesha Latif
Department of Pediatric Oncology, Combined Military Hospital, Rawalpindi, Pakistan
Email: ayeshalatif088@gmail.com

Date Received:
12th October, 2024
Date Revised:
14th December, 2024
Date Accepted:
19th December,2024

This article may be cited as:
Latif A, Ghafoor T, Hira B, Siddique AW, Manzoor R, Naz S. Clinical profile and survival outcomes in pediatric germ cell tumors: single centre experience. J Postgrad Med Inst. 2024;38(4):247-53. http://doi.org/10.54079/jpmi.38.4.3511

Abstract

Objective: This study was designed to assess the clinical features and survival outcomes of pediatric Germ cell tumors (GCTs) in our center.

Methodology: All newly diagnosed cases of GCTs in the Pediatric Oncology Department, Combined Military Hospital, Rawalpindi, between 1st January 2012 and 31st December 2023 were evaluated prospectively.

Results: During the study period, 100 cases were treated for Germ Cell tumors. The cases with central nervous system GCTs, those who relapsed after receiving initial treatment at another institute, and those who lost to follow-up were excluded from this study The data of the remaining 86 cases was analyzed. The median age of the patients at presentation was 24 months (IQR: 15 to 66). The male-to-female ratio was 1.5:1. The most common symptom at presentation in males was scrotal swelling (68.4%), while in females, it was abdominal pain (55.1%). The most common anatomic site at presentation was gonadal n=57 (66.3% with 46.5% cases in the testis and 19.8% in the ovaries). Yolk sac tumor was the commonest type in 51(59.3%), followed by teratoma in 17(19.8%). The disease was metastatic in 29(33.7%) cases, and the most frequent site of metastasis was pulmonary 44.8%. The most common stage at presentation according to COG staging is stage 1(39.5%), followed by stage 4 (32.6%), and upon applying MaGIC risk group classification, Standard Risk 1 was the most common type, followed by Low-Risk type in 60.5% and 36% cases respectively. Serum Tumor Markers (STMs), α FP, and β HCG were measured in all cases, and α FP value was raised in 77 (89.5%) cases, whereas β HCG was high in 5 cases (5.81%). The Overall Survival (OS) and Disease-Free Survival (DFS) in our study was 90.7%.

Conclusion: The clinical profile of GCTs in our study population is similar to those reported in other Asian and European studies. Our analysis points out age as the most critical determinant in the prognosis of pediatric GCT. Although Factors like serum AFP greater than 10,000 ng/ml and metastatic disease were associated with poor prognosis, we could not prove statistical significance due to the limited size of our study population. Therefore, multicentre prospective collaborative research is needed to ensure early diagnosis and adapt more effective treatment strategies for advanced cases.

Keywords: Alpha fetoprotein, Chemotherapy, Germ cell tumor, Malignant, Pediatrics, Teratoma

Introduction

Germ Cell tumors (GCTs) are a rare and heterogeneous group of malignancies originating from Primordial Germ Cells (PGCs). These tumors develop following disturbances in the maturation of germ cells during embryonic development.[1,2] GCTs are mainly found in the gonads. However, they can arise anywhere along the migratory path of PGCs, in which case they are categorized as extragonadal.[3,4] GCTs are classified into benign and malignant variants.[5] As a group, these constitute 3.5% of pediatric malignancies diagnosed before the age of 15 years.[6] The most common type of GCT is the yolk sac tumor(YST), followed by mixed GCTs, dysgerminomas, and teratomas.[7] The prognosis of GCTs primarily depends on the case's age, the tumor site, and the stage at diagnosis.[8]

The main manifestations of GCT are palpable mass at the tumor site, abdominal pain, and distension.[9] Serum Tumor markers, Alpha-Fetoprotein (α FP), and Beta Human Chorionic Gonadotrophin (β HCG) have a role in the initial diagnosis and risk grouping along with having prognostic implications on pediatric GCTs.[10] In developed countries, survival rates of pediatric GCTs have significantly improved over the past three decades due to advancements in histopathological diagnosis, platinum-based chemotherapies, aggressive surgical staging, and interventions. However, in low-income settings, limited access to healthcare resources often leads to delayed diagnosis and treatment, resulting in poor outcomes for pediatric GCTs.[11] Moreover, the lack of comprehensive studies involving a larger cohort also poses challenges in fully understanding treatment outcomes for these cases.

There is a notable scarcity of published research regarding the treatment outcomes for pediatric GCTs in developing countries, particularly Pakistan. Despite the significance of risk stratification for GCTs and its crucial impact on prognostic outcomes, researchers have overlooked this important aspect in their discussions. This study aims to analyze the clinical characteristics and treatment outcomes of pediatric GCTs in low-income settings. By examining various factors such as demographics, tumor type, treatment modalities, and survival rates, we intend to identify specific features that may correlate with poor outcomes. The insights obtained from this research will serve as a valuable resource for clinicians, enabling them to understand better the challenges faced in treating GCTs in resource-limited environments and to improve patient management practices to enhance survival rates.

Methodology

Data collection:

This Prospective cohort study was conducted in the Pediatric Oncology Department, Combined Military Hospital, Rawalpindi. All newly diagnosed patients with Germ Cell Tumors (GCT) aged 1 to 18 years who were registered for treatment between January 1, 2012, and December 31, 2023, were included in the study. The cases with central nervous system GCTs, those who relapsed after receiving initial treatment at another institute, and those who lost to follow-up were excluded from the study. The last follow-up for the study (either on the phone or in person) was performed on June 30, 2024. Approval was obtained from the Institutional Review Board (serial number 544) and informed consent from the parents or guardians.

Data on epidemiological characteristics, history, examination findings, histological diagnosis, biochemical markers, stage, risk grouping, primary and adjuvant treatment modality, chemotherapy plan, treatment complications, and outcomes were analyzed. The mixed type of GCT was defined by the presence of more than one histological subtype regardless of the proportion. The TNM staging system for testicular tumors [12] and The International Federation of Gynaecology and Obstetrics (FIGO) system for ovarian tumors [13] were both applied, but the final analysis and associations were checked based on location using Children Oncology Group (COG) for gonadal as well as extragonadal tumors [14]. Risk stratification was done using MaGIC revised criteria. (web). https://magiccon-sortium.com/. All cases were treated by "Protocol for the treatment of extracranial germ cell tumors in children and adolescents (GC III) (GC 2005 04)".

Statistical analysis:

In the descriptive analysis, we calculated frequencies and percentages for categorical variables and the median (IQR) for continuous variables. In univariate analysis, the chi-square test was used to associate age with characteristics of GCT. In survival analysis, Overall survival (OS) and Disease-Free Survival (DFS) were both evaluated by the Kaplan-Meier test. The DFS was calculated from the start of treatment until the first event, identified as relapse, progression, or death. OS was measured from the date of diagnosis to the date of death. The log-rank test was used to assess the relationship between GCT characteristics and OS and DFS, accompanied by 95% confidence intervals (CIs). A P-value of less than 0.05 was considered significant. The statistical analysis was conducted using SPSS Statistics for Windows, version 25.0.

Results

During the study period, 100 cases were treated for GCT. The cases with central nervous system GCTs, those initially treated at another setup and subsequently relapsed, and those who lost to follow-up were excluded from the study. The data of the remaining 86 cases, including 57 (66.3%) males and 29 (33.7%) females was analyzed (male-to-female ratio of 1.5:1). The median age at presentation was 24 months (IQR: 15 to 66); 64

(74.41%) cases fell in 0-5 years age group, 18 (20.93%) in 6-10 years and 4 (4.65%) in more than 10 years. The most common presentation in males was scrotal swelling in 39(68.4%), while the most common presentation in females was abdominal pain in 16(55.1%) cases. The presenting complaints of GCT are summarized in Figure 1. The predominant site was gonadal overall, with 57 cases (66.27%), within which testicular tumors were present in 40 (46.51%) while ovarian in 17(19.76%), and the remaining 29 cases of extragonadal type (33.72%). Sacrococcygeal was the predominant type in terms of location in 21 (24.41%), followed by abdominal in 6 (6.97%) and mediastinal in 2(2.32%). The most common histological subtype was YST in 51 (59.30%), followed by teratoma in 17 (19.76%). Tumour was metastatic in 29 cases (33.72%), and the most common sites of metastasis are shown in Table 1.

Based on the COG staging system, 34(39.5%) cases were in stage I, 4(4.7%) in stage II, 20 (23.3%) in stage III and 28 (32.6%) in stage IV. Seventeen cases of ovarian tumors were categorized by FIGO staging (Table 2). On applying MaGIC Risk stratification, the majority of the cases fell in Standard Risk 1 with 52 (60.5%), Low Risk type in 31 (36.0%), Standard Risk 2 in 2 (2.3%), and Poor Risk in 1 (1.2%), respectively. αFP and HCG were measured in all cases; αFP value was raised in 77 (89.5%) cases, whereas β-HCG was high in 5 cases (5.8%) where Serum αFP was considered elevated if >15 ng/ml and HCG when >10miu/ml. Forty-nine (63.6%) cases with elevated αFP had YST, 9 (11.6%) had teratoma as their primary pathological type, while mixed tumors comprised the remaining. In 30 (38.9%) cases, αFP levels were more than 10,000, while 38(49.3%) cases had moderately raised levels of >300. Out of the 8 cases that expired, 6(75.0%) had an elevated value of αFP >10,000 ng /ml, and 4(80.0%) out of these 5 cases with elevated HCG had their primary tumor in ovaries. Febrile Neutropenia was the most common complication in 30% of cases, while anemia was seen in only one case. A total of 78 (90.6%) underwent some form of surgery; 40 (46.5%) cases had orchidectomy, while 38(44.1%) had resection of mass, either partial or complete. A wait-and-watch strategy with serial tumor marker monitoring and without any chemotherapy for stage 1 tumors that underwent complete resection was employed. In our study, 23 (26.7%) cases with Stage I tumors were maintained on follow-up without any chemotherapy while the remainder 63 (73.2%) cases received chemotherapy. All the cases received 4 or 6 cycles of JEB chemotherapy comprising Carboplatin, Etoposide, and Bleomycin, depending upon individual risk stratification.

Age was significantly associated with the tumor's site, histopathology, MaGIC risk stratification, and COG classification (Table 3).

After a median follow-up of 12.4 ± 0.42 years, the DFS and OS were 90.7%. (Figure 2 & 3). Out of the 8 cases who died, 7 (87.5%) had Relapsed /Refractory disease, while one (12.5%) died from treatment-related mortality. All the instances who relapsed were subsequently treated with second-line chemotherapy consisting of a combination of Vinblastine, Ifosfamide, and Cisplatin (VIC).

In univariate analysis, the OS was 93.0% in males and 86.2% in females (p=0.27). When we compared the OS after categorizing values of αFP into mild (>15 to <300ng/ml), moderate (>300 to <10,000 ng/ml), and marked categories (>10,000 ng/ml), OS was 100% in cases with mild elevation of αFP, 97.4% with moderate elevation and 80.0% in cases with markedly raised αFP levels (p=0.10). The OS in cases without metastasis was 93% and decreased to 86.25% in cases with metastasis (p=0.27). There was no statistically significant relationship between OS and DFS concerning tumor site(p=0.43), histopathology(p=0.30), and COG stage(p=0.34).

Discussion

GCTs are a diverse group of malignancies that include both benign and malignant varieties. Since they are rare, we conducted a prospective comprehensive study regarding GCTs in pediatrics to guide future management decisions.

The male-to-female ratio of 1.5:1 in our setup is in congruence with literature quoting figures of 2:1 by

Table 1. Common sites of metastasis (n=29)

Location of Metastasis	N	%
Pulmonary	13	44.8
Abdomen	2	6.8
Hepatic	4	13.7
Brain	1	3.4
Bones	2	6.8
Mediastinum	1	3.4
Multiple sites	6	20.6

Table 2. FIGO Classification of Ovarian Tumor

FIGO stage	N	%
IA	3	17.6
IB	3	17.6
IC2	1	5.9
IC3	2	11.8
II	1	5.9
III	4	23.5
IIIA	1	5.9
IVB	2	11.8
Total	17	100

Table 3. Association of age with the characteristics of GCT

Characteristics		Total cases	< 5 years	5 to 10 years	>10 years	
		n (%)	n (%)	n (%)	n (%)	P-value
Site of the tumour	Testicular	40 (46.5)	39 (60.90)	1(5.60)	0(0.00)	0.0001
	Ovary	17(19.7)	0(.00)	13(72.20)	4(100)	
	Extragonadal	29 (33.7)	25(39.10)	4(22.20)	0(0.00)	
Histopathology	Yolk Sac tumor	51(59.3)	44(68.80)	6(33.30)	1(25.00)	0.0001
	Teratoma	17 (19.7)	14(21.90)	3(16.70)	0(0.00)	
	Dysgerminoma	8 (9.3)	0(0.00)	6(33.30)	2(50.00)	
	Mixed GCT	9 (10.4)	6(9.40)	3(16.70)	0(0.00)	
	Choriocarcinoma	1(1.1)	0(0.00)	0(0.00)	1(25.00)	
Metastatic Disease	No Mets	57 (66.2)	38(59.40)	16(88.90)	3(75.00)	0.06
	Yes	29 (33.7)	26(40.60)	2(11.10)	1(25.00)	
Magic Risk Stratification	Low Risk	31(36.0)	25(39.1)	5(27.8)	1(25.0)	0.0001
	Standard Risk 1	52 (60.4)	39(60.9)	13(72.2)	0(0.0)	
	Standard Risk 2	2 (2.3)	0(0.0)	0(0.00)	2(50.0)	
	Poor Risk	1 (1.1)	0(0.0)	0(0.00)	1(25.0)	
COG Classification	I	34 (39.5)	27(42.2)	6(33.3)	1(25.0)	0.0001
	II	4 (4.6)	2(3.1)	1(5.6)	1(25.0)	
	III	20 (23.2)	10(15.6)	9(50.0)	1(25.0)	
	IV	28 (32.5)	25(39.1)	2(11.1)	1(25.0)	

another study.[15] The median age in our study is 24 months, which is comparable to the reported median age of 23 months reported by the survey conducted in Iran.[5] The age distribution in our study is identical to the study conducted by Incesoy-ozdemir et al with 74 % of cases younger than 5 years and 4% older than 10 years.[16] In terms of symptoms at presentation, scrotal swelling being the predominant symptom in testicular GCTs followed by abdominal pain in ovarian and extragonadal tumors was supported by the work of Lin et

J Postgrad Med Inst 2024;38(4):247-53.
http://doi.org/10.54079/jpmi.38.4.3511

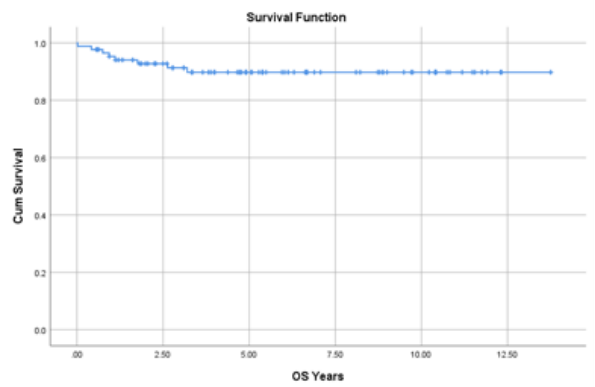

Figure 2 Overall survival

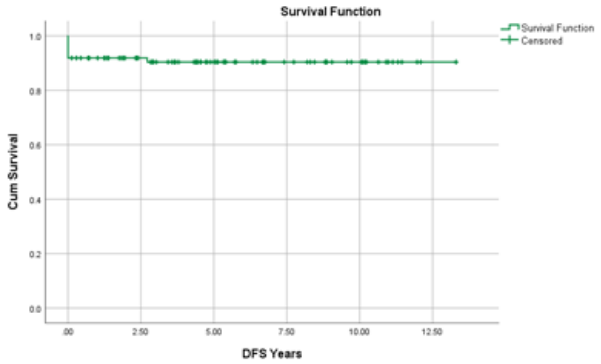

Figure 3 :Disease Free Survival

al.[17] The Gonadal tumors being the predominant site in our study was consolidated by a survey conducted at another center in Pakistan and Italy.[7,18] When we compared the sites in the extragonadal variety, Sacrococcygeal tumors were the predominant type, supported by work done in China and Turkey.[19,20] Yolk Sac Tumours, the most common histopathological subtype, were supported by a second germ cell tumor study, Children's Cancer Study Group.[21]

When we compared the predominant stage at presentation, our findings and the work of Terenziani et al. yielded similar results, with the maximum number of cases as stage I followed by stage IV in the case of testicular tumors.[22] The small number of ovarian tumors limited the significance of staging interpretation per FIGO classification. The Malignant Germ Cell Tumour International Collaborative (MaGIC) was established to lay the groundwork for future international trials. It aims to develop an updated risk classification for pediatric extracranial germ cell tumors by integrating data from the Children's Oncology Group (COG) and the Children's Cancer and Leukaemia Group (CCLG).[23] Although in our study, the Standard Risk 1 category is the predominant type, other studies categorizing the paediatric tumours based on MaGIC were limited, which is a potential area for future studies in GCTs.

Alpha-fetoprotein (αFP) is secreted by malignant germ cell tumors (MGCTs) of the following histologies: YSTs, immature teratomas, and embryonal carcinomas. The study by Frasier et al. clearly illustrates the importance of αFP as a prognostic factor.[24] The IGCCC classification categorizes cases into three risk groups based on the initial αFP (alpha-fetoprotein) levels: those with a good prognosis have αFP levels less than 1000 ng/ml, intermediate prognosis falls between 1000 ng/ml and 10,000 ng/ml, and poor prognosis is indicated by αFP levels greater than 10,000 ng/ml. In our study, 6 out of 8 cases that expired had αFP values greater than 10,000 ng/ml.

Regarding metastatic disease at presentation, our study yielded results similar to that of COG, with the lung as the predominant site and the impact of metastatic disease on OS.[25]

Research indicates that stage I gonadal germ cell tumors (GCTs) can often be effectively managed with surgery and monitoring. Many patients don't need additional treatment, and in cases of relapse, chemotherapy typically results in successful recovery.[26,27] For stage I testicular tumors, total tumor resection through inguinal orchiectomy with high cord ligation, followed by the normalization of serum tumor markers, is considered adequate [28, 29]. In stage I tumors of ovarian origin, the treatment is regarded as complete with salpingo-oophorectomy of the involved side. Cases with stage II to IV are treated with adjuvant chemotherapy. In our study, 23 cases (26.74%) out of 27 cases with stage I were treated with this approach.

Regimens Chemotherapy that uses platinum-based compounds is effective for children with extracranial MGCT. [30]. The OS and DFS in our study were in the same range as that of the previous work done in Turkey on GCTs [31]. Research groups have concluded that the OS and DFS for stage I and II cases are approximately 95%. In contrast, the OS and DFS rates for stage III-IV cases range between 70% and 85%.[26,32,33]

Our study assessed various factors that could influence prognosis, including histological type, location, disease stage, gender, and age, and found no significant differences in survival rates. This may be because GCTs are a very heterogeneous group, and we have limited cases enrolled in our study. Our research showed variations in how age, stage, tumor location, and survival are related. Still, we could not establish statistical significance because of the limited size of our study group.

Conclusion

The clinical profile of GCTs in our study population is similar to those reported in other Asian and European studies. Our analysis concludes that age is the most critical determinant in the prognosis of pediatric GCT. Although Factors like serum AFP greater than 10,000 ng/ml and metastatic disease were associated with poor prognosis, statistical significance could not be

proved due to the limited size of our study population. Therefore, multicentre prospective collaborative research is needed to ensure early diagnosis and adapt more effective treatment strategies for advanced cases.

References

1. Van Leeuwen MT, Gurney H, Turner JJ, Turner SL, Pearson SA, Laaksonen MA, et al. Patterns and trends in the incidence of pediatric and adult germ cell tumors in Australia, 1982–2011. Cancer Epidemiol 2016;43:15-21.
2. De Felici M, Klinger FG, Campolo F, Balistreri CR, Barchi M, Dolci S. To be or not to be a germ cell: the extragonadal germ cell tumor paradigm. Int J Mol Sci 2021;22(11).
3. Oosterhuis JW, Looijenga LH. Testicular germ-cell tumours in a broader perspective. Nat Rev Cancer 2005;5(3):210-22.
4. Oosterhuis JW, Looijenga LH. Human germ cell tumors from a developmental perspective. Nat Rev Cancer 2019;19(9):522-37.
5. Khaleghnejad-Tabari A, Mirshemirani A, Rouzrokh M, Mohajerzadeh L, Khaleghnejad-Tabari N, Hasas-Yeganeh S. Pediatric germ cell tumors; A 10-year experience. Iran J Pediatr 2014;24(4):441-4.
6. Fonseca A, Frazier AL, Shaikh F. Germ cell tumors in adolescents and young adults. J Oncol Pract 2019;15(8):433-41.
7. Nasir IU, Ashraf MI, Ahmed N, Shah MF, Pirzada MT, Syed AA, et al. Clinical profile, treatment and survival outcomes of pediatric germ cell tumors: a Pakistani perspective. Liver 2016;6:25.
8. Rusner C, Trabert B, Katalinic A, Kieschke J, Emrich K, Stang A, et al. Incidence patterns and trends of malignant gonadal and extragonadal germ cell tumors in Germany, 1998–2008. Cancer Epidemiol 2013;37(4):370-3.
9. Reniarti L, Febri A, Sari NM. Clinical characteristics of pediatric with germ cell tumor: Experience in a developing country. Althea Med J 2021;8(1):28-34.
10. Jezierska M, Gawrychowska A, Stefanowicz J. Diagnostic, prognostic and predictive markers in pediatric germ cell tumors—past, present and future. Diagnostics 2022;12(2):278.
11. Mosbech CH, Rechnitzer C, Brok JS, Rajpert-De Meyts E, Hoei-Hansen CE. Recent advances in understanding the etiology and pathogenesis of pediatric germ cell tumors. J Pediatr Hematol Oncol 2014;36(4):263-70.
12. Wittekind C, Bertolini J. TNM system 2010: Amendments in the new 7th edition of the TNM classification of malignant tumors. Der Onkol 2010;16:175-80.
13. Prat J, FIGO Committee on Gynecologic Oncology.. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet 2014;124(1):1-5.
14. Niramis R, Anuntkosol M, Buranakitjaroen V, Tongsin A, Mahatharadol V, Poocharoen W, et al. Long term outcomes of sacrococcygeal germ cell tumors in infancy and childhood. Surg Res Pract 2015;2015(1).
15. Hulsker CC, Schulpen M, Mavinkurve-Groothuis AM, Visser O, Zsiros J, Wijnen MH, et al. Malignant extracranial germ cell tumors in the Netherlands between 1990 and 2018: Stable incidence and improved survival. EJC Pediatr Oncol 2024;3.
16. Incesoy Ozdemir SO, Ertem SO, Sahin G, Bozkurt C, Yüksek N, Oren A, et al. Clinical and epidemiological characteristics of children with germ cell tumors: A single center experience in a developing country. Turk J Pediatr 2017;59(4).
17. Lin X, Wu D, Zheng N, Xia Q, Han Y. Gonadal germ cell tumors in children: A retrospective review of a 10-year single-center experience. Medicine 2017;96(26):e7386.
18. Curto ML, Lumia F, Alaggio R, Cecchetto G, Almasio P, Indolfi P,. Malignant germ cell tumors in childhood: Results of the first Italian cooperative study "TCG 91." Med Pediatr Oncol 2003;41(5):417-25.
19. Zhao Q, Wang X, Jin M, Zhang D, Su Y, Zhao W, et al. A summary of single center diagnosis and treatment experience of extracranial malignant germ cell tumor in children. Chin J Appl Clin Pediatr 2020;996-9.
20. Drozynska E, Połczynska K, Popadiuk S, Niedzwiecki M, Wiśniewski J, Balcerska A, et al. Characteristics of extracranial malignant germ cell tumors in two age groups of children (0-10 and 10-18 years). Multicentre experiences. Med Wieku Rozwojowego 2011;15(1):16-24.
21. Mann JR, Raafat F, Robinson K, Imeson J, Gornall P, Sokal M, et al. The United Kingdom Children's Cancer Study Group's second germ cell tumor study: Carboplatin, etoposide, and bleomycin are effective treatments for children with malignant extracranial germ cell tumors with acceptable toxicity. J Clin Oncol 2000;18(22):3809-18.
22. Terenziani M, De Pasquale MD, Bisogno G, Biasoni D, Boldrini R, Collini P, et al. Malignant testicular germ cell tumors in children and adolescents: The AIEOP protocol. Urol Oncol 2018;36(11): 502.e7-502.e13.
23. Frazier AL, Hale JP, Rodriguez-Galindo C, Dang H, Olson T, Murray MJ, et al. Revised risk classification for pediatric extracranial germ cell tumors. J Clin Oncol 2015;33(2):195-201.
24. Frazier AL, Rumcheva P, Olson T, Giller R, Cushing B, Cullen J, et al. Application of the adult international germ cell classification system to pediatric malignant non-seminomatous germ cell tumors. Pediatr Blood Cancer 2008;50(4):746-751.
25. Malogolowkin MH, London WB, Cushing B, Giller R, Davis M, Cullen J, et al. The site of metastases does not influence the clinical outcome of children with metastatic germ cell tumors. J Clin Oncol 2006;24(18_suppl):9002.
26. Rescorla FJ, Ross JH, Billmire DF, Dicken BJ, Villaluna D, Davis MM, et al. Surveillance after initial surgery for Stage I pediatric and adolescent boys with malignant testicular germ cell tumors. J Pediatr Surg 2015;50(6):1000-3.
27. Billmire DF, Cullen JW, Rescorla FJ, Davis M, Schlatter MG, Olson TA, et al. Surveillance after initial surgery for pediatric and adolescent girls with stage I ovarian germ cell tumors. J Clin Oncol 2014;32(5):465-70.
28. Wood L, Kollmannsberger C, Jewett M, Chung P, Hotte

S, O'Malley M, et al. Canadian consensus guidelines for the management of testicular germ cell cancer. Can Urol Assoc J 2010;4(2):e19.

29. Green DM. Chemotherapy for the treatment of children and adolescents with malignant germ cell tumors. J Clin Oncol 2008;26(20):3297-8.
30. Einhorn LH, Donohue J. Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Intern Med 1977;87(3):293-8.
31. Kupesiz FT, Tuysuz G, Akınel AN, Tekneci A, Sivrice AÇ, Melikoğlu M, et al. Clinical characteristics and treatment outcomes of cases with malignant extracranial germ cell tumors: A 20-year single-center experience. J Curr Pediatr 2021;19(2):176-184.
32. Rescorla FJ, Sawin RS, Coran AG, Dillon PW, Azizkhan RG et al. Long-term outcome for infants and children with sacrococcygeal teratoma. J Pediatr Surg 1998;33(2):171-6.
33. Gobel U, Schneider DT, Calaminus G, Haas RJ, Schmidt P, Harms D, et al. Germ-cell tumors in childhood and adolescence. Ann Oncol 2000;11(3):263-72.

Authors' Contribution Statement

AL contributed to the conception, design, acquisition, analysis, and interpretation of data, and drafting the manuscript. TG contributed to the conception, design, and analysis of data, and critically reviewed the manuscript. BH and AWS contributed to the design and analysis of data, and were involved in drafting the manuscript. RM and SN contributed to the design and analysis of data, and approved and reviewed the manuscript. All authors are accountable for their work and ensure the accuracy and integrity of the study.

Confilct of Interest

Authors declared no conflict on interest

Grant Suppport and Financial Disclosure

None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.