ADDIS ABABA UNIVERSITY COLLEGE OF HEALTH SCIENCES DEPARTMENT OF PEDIATRICS AND CHILD HEALTH

Clinico Pathological Patterns and Treatment Outcomes of Pediatric Germ Cell Tumors Treated at Tikur Anbessa Hospital: A 10-Year Single Tertiary Hospital Experience

A Research Paper to be submitted to the Department of Pediatrics and Child Health, College of Health Sciences, Addis Ababa University in Partial Fulfillment of the Requirements for the Specialty Certificate in Pediatrics and Child Health

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April, 2024 GC

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The full title of the research project	Clinico Pathological Patterns and Treatment Outcomes of Pediatric Germ Cell Tumors Treated at Tikur Anbessa Hospital: A 10-Year Single Tertiary Hospital Experience
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DECLARATION

Clinico Pathological Patterns and Treatment Outcomes of Pediatric Germ Cell Tumors Treated at Tikur Anbessa Hospital: A 10-Year Single Tertiary Hospital Experience

Name of the Principal Investigator: Mihret Gebrehiwot

A. Declaration by the Student

I do hereby declare that this research paper is submitted for the partial fulfillment of the requirements for the Specialty Certificate in Paediatrics and Child Health. This is my original work and has not previously been submitted elsewhere. Also, I do declare that a complete list of references is provided indicating all the sources of information quoted or cited.

Name and signature of student Mihret Gebrehiwot _____

Authority to submit the thesis

Name of Advisor: Gashaw Arega (MD, MPH)

In my capacity as an advisor, I do hereby authorize the student to submit this thesis Signature of the Advisor: _____

April, 2024 GC

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Finally, I would like to thank my family and friends for their emotional support throughout this research journey. Their encouragement and belief in me have been a constant source of strength.

Acronyms/Abbreviations

AA…….Addiss ababa

AFP……Alpha-fetoprotein

BHCG ……Bhuman chorionic gonadotropin

CNS……Central nervous system

DFS…….Disease-free survival

ETB…….Ethiopian birr

EVF……..……...Event free survival

GCT……Germ cell tumor

OS……..Overall survival

PI……Principal investigator

RT……..Radiotherapy

SPSS……...Statistical Package for Social Sciences

TASH……Tikur Anbessa Specialized Hospital

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Abstract

Background

Pediatric Germ Cell Tumors (GCTs) are rare heterogeneous neoplasms with a peak incidence in children younger than 4 years old and during adolescence. The clinical presentation and treatment outcomes of GCTs are not well-studied in developing countries. The main aim of this study was to assess the clinic-pathological patterns and treatment outcomes of Pediatric Germ Cell Tumor (GCT) patients treated at Tikur Anbessa Specialized Hospital.

Methods: A retrospective, cross-sectional study was conducted at Tikur Anbessa Specialized Hospital on Pediatric Germ Cell tumor patients treated from January 1, 2014, to December 31, 2023. The collected data were analyzed using a statistical package for social sciences (SPSS) version 25. The Kaplan–Meier Survival estimate was used to assess the Overall Survival (OS) and Event-Free Survival (EFS).

Results: A total of ninety-one patients were included in the study. The median age at diagnosis was 4 years with a female-to-male ratio of 2.3:1. Most patients were under five years of age; constituting 61.6% (n=56). The duration of the illness from the onset of symptoms to the oncologic treatment center ranged from 2 days to 12 months with a mean duration of four months. Sacrococcygeal swelling was the commonest presenting symptom accounting for 38.2% (n=34) followed by abdominal mass (36%). Most of the patients had extracranial GCTs constituting 93.4% (n=85). Mature teratoma was the most common histology of GCTs constituting 52.6% followed by dysgerminomas (17.1%, n=13). About 42% of patients received a combination of chemotherapy and local control measures either surgery or radiotherapy. The Kaplan-Meier survival estimates showed the first and five-year OS was 95.7% and 85%, respectively. The first and five-year EFS was 95% and 84 % respectively.

Conclusion:

Our study showed the mean duration of the illness from the onset of symptoms to the oncologic treatment center was 4 months. Mature teratoma was the commonest histology. The 1-year and 5-year OS probabilities were better than other studies in similar settings.

Keywords; *Germ cell tumors, Pediatric, Histology, Chemotherapy, treatment outcome, Ethiopia*

1. Introduction

1.1 Background

Pediatric Germ Cell Tumors (GCTs) are rare heterogenous neoplasms arising from germ-line cells in children under eighteen years old with a peak incidence in children younger than 4 years old and during adolescence. These germ cell tumors can be gonadal, extragonadal; occurring in midline structures such as the sacroccocyx, mediastinum, and retroperitoneum.[1,2,3]

Genetic and environmental factors; the presence of genetic basis, sporadic mutations, and concomitant environmental factors have been implicated in the etiopathogenesis of pediatric germ cell tumors. The diagnosis and management of GCTs is based on the risk stratification assessment including the age of the child, location of the tumor, histopathology of the tumor, surgical resection of the tumor, and serum or cerebrospinal oncoproteins such as alpha-fetoprotein (AFP) and other biochemical markers.[,3,45,6,14,15,16,17]

Low and Middle-Income Countries (LMICs), mainly Southeast Asia and Sub-Saharan African countries carry the high burden of childhood cancers including pediatric germ cell tumors; where 90% of children with cancer live. Ethiopia has the 12th largest population in the world with a population of over 120 million and the median age is 19.5 years. More than 40 % of the population is under 15 years old and this will fall largely in the risk age group for germ cell tumors making the condition more significant than in other developed and less populous countries.[7,8,9,10,13]

The prevalence of germ cell tumors was 3 % in the general population according to the statistics from the American Cancer Society, though the prevalence in infancy and during adolescence varies.[9,10] Benign mature teratoma was the most common histology and the pathological incidence of malignant germ cell tumors varies based on age, sex, and anatomic site of involvement. [11]

The 5-year survival rate was reported to be 98% and 80% for early-stage and malignant germ cell tumor patients; the stage, the histology, and the site of the tumor affect survival hugely.[12]

Being the most common solid tumor in adolescent males and young adults, testicular tumors were more studied, and histologically they can be seminomatous and non-seminomatous including yolk sac, embryonal carcinoma, choriocarcinoma, and mixed. [16,17,18]

Whereas the other pathologies in gonadal and extragonadal germ cell tumors are composed of dysgerminomas, yolk sac tumors, teratocarcinoma, non-gestational choriocarcinoma, and mixed types. [19,20,21,22,23]

Serum and Cerebrospinal fluid oncoprotein markers such as Alpha-fetoprotein (AFP), and Beta-Human chorionic gonadotropin (B-HCG) help to diagnose and predict the histology of the germ cell tumors; Yolk Sac tumors and Choriocarcinomas are usually associated with an elevation of AFP and B-HCG respectively. [24] Cytogenetic studies of germ cell tumors also help to predict the precise correlation between histologic subtypes, serum tumor markers, and prognosis; i (12p) is a highly nonrandom chromosomal marker seen in about 80% of male germ cell tumors.[25]

A study in Egypt showed that the median age of diagnosis of germ cell tumors was 23 months; females accounted for 72.7% and the median survival was 16 months. Patients with yolk Sac tumor histology, extra-gonadal germ cell tumors, and a high AFP level at diagnosis had the worst prognosis and lower survival rate; whereas a combination of surgery, chemotherapy, and radiotherapy for intracranial germ cell tumors led to better survival. [25,26,27,28,29]

The magnitude, the burden of the diseases, and the treatment outcomes of pediatric germ cell tumors need to be studied and emphasis has to be given to most populous countries, including Ethiopia,

1.2 Statement of the problem

The current population of Ethiopia is 123,417,921 based on worldometer elaboration of the latest United Nations data giving her the rank of 12th largest populations in the world and the median age in Ethiopia is 19.5 years.[7] The largest percentage of this significant number of population is made up by a younger age group. As significant as 40% of the total population is under 15 years old.[8] This will fall largely in the at risk age group for germ cell tumor making the condition significant.

Even though germ cell tumors can be apparent in all age groups, it is epidemiologically rare with its prevalence accounting for less than 5% specifically about 3% from the general population according to the American cancer society [9], the prevalence in certain age groups as infancy and in adolescents is high is high accounting for 13.9% of all cancers among those aged 15 to 19 years.[10]

This information requires proper investigation and research in order to address the specific presentations clinical pattern and tailored treatment as well as follow up.

The gravity of the burden created by germ cell tumor is understudied. Reported data suggests an estimated incidence of 11.6 and 6.7 among boys and girls respectively while benign mature teratomas represent the most common histology with the incidence of the malignant germ cell tumors varying based on sex, age, and location.[11]

In the rare papers published in developing countries, the 5 year survival rate was found to be 98% and 80% for early stage and malignant germ cell tumor patients respectively. [12] The second most populous country in the Africa.

1.3. Significance of this study

The incidence and the burden of Germ cell Tumors are high in Low and Middle-Income Countries (LMICs), mainly in Southeast Asia and Sub-Saharan African countries; where 90% of children with cancer live. Ethiopia has the 12th largest population in the world with a population of over 120 million and the median age is 19.5 years. More than 40 % of the population is under 15 years old and this will fall largely in the at-risk age group for germ cell tumors making the condition more significant than in other developed and less populous countries.

This study aimed to fill this huge gap of data in children with germ cell tumors and generated local data for Ethiopia and other developing countries in sub-Saharan African Countries.

This study creates a better input in tailoring treatment options as well as identifying the diagnosis delay, assessing the common clinical presentation, describing the common pathologies, and estimating the treatment outcomes in children with germ cell tumors using Kaplan Meier survival estimates.

2 Literature review

2.1 Overview of GCT

Germ cell tumors are a heterogeneous group of rare neoplasms that present in different anatomical sites and across a wide spectrum of patient ages from birth through adulthood historically classified according to the site of origin as gonadal and extra gonadal. [2]

The first description of sacral teratomas was found in a list of 62 fetal malformations probably already used by Egyptian fetoscopists around 2500 BC. According to their magic concept, a third foot in the middle meant great prosperity for the land. [14]

From a historical perspective germ, cell tumor were first clearly and fully described in a paper written in 1911 by James Ewing explaining the seven most popular theories of origin of testicular and related tumors which we now classify as germ cell tumors. The theories were summarized as the theory of metaplasia, theory of fetal inclusions, theory of partial hermaphroditism, theory of fertilization of the polar body, theory of isolated blastomeric theory of Wolffian and Mullerian duct origin and adrenal rest theory. [15]

Germ-cell tumors arise from molecular defects in early germ line progenitors known as primordial germ cells. The broad range of possible germ-cell tumor histology is attributed to the totipotent nature of primordial germ cell. The hypothetical model of tumor genesis proposed by Teilum postulates that germinomas (seminomas in testicular sites and dysgerminomas in ovarian sites) arise directly from undifferentiated primordial germ cells and therefore retains their pluripotency. Embryonal carcinomas display early embryonic differentiation and can further differentiate into tumors containing all three germ layers (endoderm, ectoderm, and mesoderm), thereby producing teratomas. [16]

Therefore, regarding the origin of germ cell tumors, a hypothesis forwarded suggested that the anatomical distribution of extra gonadal GCTs is as a result of the migration of primordial germ cells from the yolk sac meaning the proximal epiblast, along the hindgut and its mesentery to the bilateral genital ridges. Other mouse models of teratomas favored Embryonal stem (ES) cells – named Embryonal carcinoma (EC) cells in the neoplasms – as the cells of origin of teratomas. [17]

Relatively testicular germ cell tumors are more studied due to the tumor being the most common solid tumor in adolescent males and young adults. (16) According to a paper published regarding recent advances in testicular germ cell tumors the histologically classified as seminomatous and non seminomatous including yolk sac, Embryonal carcinoma, and choriocarcinoma and mixed. [18]

Whereas the malignant ovarian germ cell tumors constitute of approximately 1-2 percent of malignant ovarian tumors and composed mainly of dysgerminomas, yolk sac tumors, teratocarcinomas, non-gestational choriocarcinoma and mixed types as well. [19]

2.2 clinico pathologic pattern

According to an published regarding the pattern of clinical presentation in GCT patients is varied and it depends on the specific type. For instance malignant ovarian germ cell tumors present as acute or subacute pelvic pain, menstrual disturbance and pelvic or abdominal mass. Commonest presenting symptom is combined abdominal pain with palpable pelvic or abdominal mass in 85% of patients and the rest around 10% present with acute symptoms due to ovarian torsionhemorhage or rupture. [20]

gonadal germ cell tumours that occurs in the ovaries in girls can be difficult to detect because symtoms discussed above like abdominal pain often do not present until the tumour is advanced but those occuring in boys in the testis often are visible and present with pain at an early age [21] which has a diagnostic and prognostic implication.

Sacrococcygeal teratomas may be diagnosed antenatally as an incidental finding on ultrasonography; they may occur in an infant who is large for age, is premature, or has fetal hydrops. Fetal hydrops is an ominous sign, typically due to high flow through the tumor with high-output cardiac failure and placentomegaly. [22]

Also histological confirmation of tumour presence and demarcation of the tumour area on haematoxylin and eosin (H&E) slides is fundamental for downstream nucleic acid extraction. Tumour cell content, stromal proportion and necrosis extent should be assessed on histological slides before pursuing expensive downstream molecular studies. [23]

Tumor markers help to predict tumor histology. YST is characteristically associated with elevation of AFP, but low AFP levels (<100 mg/l) can be seen in immature teratomas possibly due to occult

or microscopic foci of YST within the tumor putting in to consideration that AFP is also normally synthesized by fetal liver, yolk sac and gastrointestinal tract in the neonatal period, [24] interpretation of AFP levels needs to be done cautiously, correlating it with age-related norms.

Cytogenetic studies of germ cell tumors in prospective clinical treatment trials are warranted to define more precisely the relationship between histologic subtype, serum tumor marker production, and prognosis. i(12p) is a highly nonrandom chromosomal marker seen in about 80% of male germ cell tumors with evaluable cytogenetic abnormalities. The presence of this isochromosome has diagnostic and possibly prognostic importance for patients with these tumors. [25]

2.3 Treatment, outcome and prognosis of GCT

In a recent Egyptian resesrch that studied forty four patients consisted of 32 girls (72.7%) and 12 boys (27.3%). Their median age was 23 months. In follow-up 31 (77.5%) patients were in complete remission, 9 (22.5%) had died, and 4 cases did not appear to follow-up visits. The median survival was 16 months. The highest mortality rate was found in patients with yolk sac tumors (8 of 13 cases). The patients with extra-gonadal GCT and a high AFP level have the worst prognosis and lower survival rate. Combination of surgery and chemotherapy can lead to a better prognosis. [26]

Regarding the surgical part of management it is suggested that the initial surgical approach to malignant GCTs at all sites should be complete resection when possible; the morbidity of extensive surgical resection should be weighed carefully against the good tumor control with chemotherapy. Surgical staging does not preclude preservation of fertility, which should always be considered in this young age.[27]

2.4 Factors affecting survival rates in GCT patients

The five year survival of testicular cancer over the past decades has improved significantly from 83 percent to 95 percent in the years between 1975-77 and 2012-18 respectively. [28]

A study done in kagoshima university, twenty-six patients (20 boys, 6 girls) with a mean age of 11.5 ± 4.9 years were included .Patient tumor types included germinomas, immature teratomas , yolk sac tumor, choriocarcinoma, Embryonal carcinoma. The median follow-up period was 96.5 months. Surgical procedures included stereotactic biopsy, endoscopic third ventriculostomy and biopsy and tumor decompression. All patients with germ cell tumors underwent adjuvant

chemotherapy and radiation therapy; patients with germinoma or immature teratoma were still alive, while patients with embryonal carcinoma, yolk sac tumor, or choriocarcinoma had poor prognosis with a median survival of 16 months. The study Patients with germinoma had a relatively good prognosis, while patients with embryonal carcinoma, yolk sac tumor, or choriocarcinoma had a poor prognosis. [29]

Objectives

3.1. General objective

- To assess the clinic-pathological pattern and treatment outcome of children with germ cell tumors Treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

3.2. Specific Objectives

- To describe the demographic and Clinico pathologic pattern of GCT patients
- To determine the event-free and overall survival of GCT patients
- To assess the treatment outcome of GCT patient

4. Methodology

4.1. Study setting

The study was conducted at the Department of Pediatrics and Child Health, Haemato-Oncology Unit, Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. Tikur Anbessa Specialized Hospital is the largest tertiary hospital in the country established in 1974, and administered by Addis Ababa University. Tikur Anbessa Specialized Hospital is the largest tertiary hospital in the country and was used as the only pediatric haemato-oncology treatment center in the county until recently. Tikur Anbessa Specialized Hospital is one of the largest pediatric haemato-oncology treatment centers in the county, and a separate unit for children with cancer began in March 2013. The pediatric haemato-oncology wards have 42 inpatient beds dedicated to pediatric cancer patients and the unit gives both inpatient and outpatient services for more than 800 patients every month.

4.2 Study period

All pathologically confirmed Pediatric germ Cell tumors in children under the age of 14 years from January 1, 2014, to December 30, 2023, were included. A total of ninety-one (n=91) patients met the inclusion criteria and were included in our study.

4.3 Study design

A hospital-based cross-sectional descriptive-analytical study design was carried out. Data were collected from September 1, 2023, to January 1, 2024.

4.4. Source population

All pediatric Cancer patients Treated at the Hematology-Oncology Centre of TASH

4.5. Study population

All pediatric patients with germ cell tumors treated at the Pediatric Hematology-Oncology Unit at TASH during the study period

4.6. Sampling

All pathologically confirmed Pediatric germ Cell tumors in children under the age of 14 years from January 1, 2014, to December 30, 2023, were included. A total of ninety-one (n=91) patients who fulfilled the inclusion criteria were included in our study.

4.7. Inclusion and exclusion criteria

4.7.1 Inclusion Criteria

- Children with histologically/ radiologically, serum, CSF oncoproteins confirmed diagnosis of GCTS
- Children with solid tumors (age 14 or younger without lower age limit) who started treatment at Tikur Anbessa Specialized Hospital

4.7.2. Exclusion criteria

- Children diagnosed with other solid cancer
- Children with incomplete data records (>20% of the data)

4.8. Operational definition

Event-free survival (EFS): denotes the length of time after primary treatment for a GCT ends that the patient remains free of a certain set of complications or events that the treatment was intended to prevent or delay, including pathologic fracture, distant metastasis, laboratory derangements

(Events: include treatment abandonment, induction failure, relapse, and death after completion of treatment)

Overall survival (OS): represents the time from the date of first diagnosis to the date of last follow-up or death from any cause.

Overall survival rate: the percentage of children with GCTS who are alive after their diagnosis or the start of treatment.

4.9. Study variables

4.9.1. Dependent variables

- Histology subtypes
- Overall survival rates
- Event-free survival rates

4.9.2. Independent variables

- Demographic characteristics
- Residence
- Duration of symptoms
- Presenting symptom
- Laboratory profile
- Site of the tumor (Intracranial or extracranial)
- Type of therapy (single or combination of therapy)
- Type of chemotherapy

4.9.3. Data Collection and Data Analysis

Data were collected by the principal investigator and trained General Practitioners using structured questionnaires. The study questionnaires had four parts: Part I was about the socio-demographic characteristics of the study participants, Part II was about the clinical profile of patients at

presentation, Part III was about the diagnosis and diagnostic investigations, and Part IV was about the treatment profiles and outcomes of Pediatric Germ Cell Tumors in children treated at Tikur Anbessa Specialized Hospital.

After selecting the study cases, the data was collected from the registration log book, the patient card, and the follow-up chart by the data collectors. The administered questionnaire encompasses the socio-demography profile, clinical profile, and outcome. ODK version 2022.3.3 software was used to collect the data along with the Kobo Toolbox server to store the collected data. Data was entered into Epi data version 3.1 and exported to SPSS version 25 for analysis. P-value <0.05 was considered to be statistically significant. The Kaplan Meier survival was used to estimate the first, and fifth year overall and event-free survival analysis.

4.10. Data Quality control and management

To ensure data quality, the structured questionnaire checklists were tested on 5% of the sample. Problems highlighted during the pre-test were corrected before the start of the data collection. Each question was properly coded; the principal investigator did continuous cross-checking during the pre-test and data collection period. The collected data were checked for completeness and consistency on each day of data collection.

4.11. Conceptual frame work

Depicted below is the conceptual frame work of this study designed by the principal investigator after extensive background research on related topics.

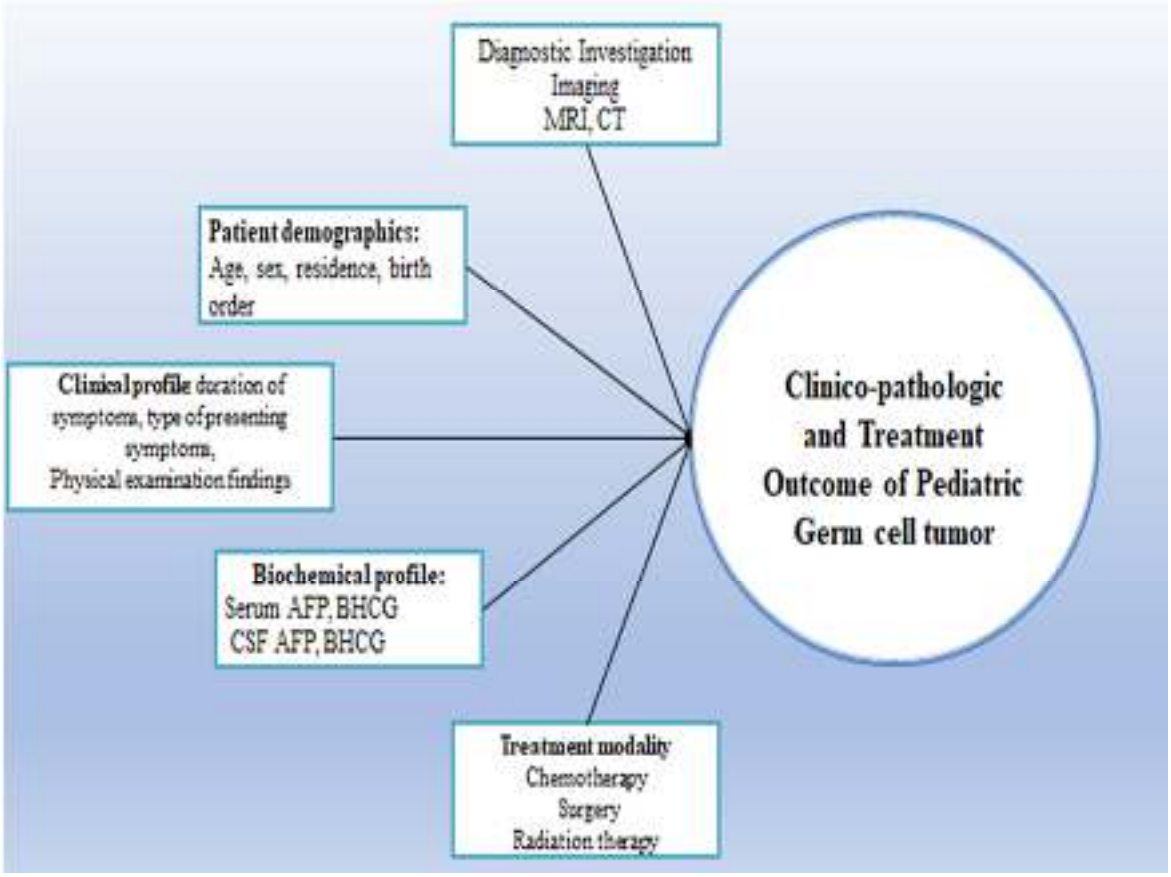

Figure 1. Conceptual framework for overall and event-free survival of pediatric germ cell tumor patients treated at pediatric hematology-oncology unit, Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

4.12. Ethical considerations

Ethical approval was obtained from the Pediatrics and Child Health Department's Research and Publications Committee of the School of Medicine, College of Health Sciences, and Addis Ababa University. Confidentiality was fully maintained during the data collection and analysis. Participants were kept be anonymous which will continue during the dissemination and publication of results.

4.13 Dissemination of Findings

The result of the study will be presented on the research defense day and a formal report will be submitted to the Department of Pediatrics and Child Health. The research output will also be published in local or international peer-reviewed scientific journals and will be shared with the

hospital, and governmental agencies to allow for improvements and to provide essential care and support for children with pediatric germ cell tumors.

5. Results

5.1 Socio-demographic characteristics

A total of ninety-one patients were included in the research fulfilling the inclusion criteria. The median age at diagnosis was 4 years with a range of 1 – 14 years with a female-to-male ratio of 2.3 :1. Most of the children were under five years of age; constituting 61.6% (n=56) followed by 6-12 years of age; 34.1% (n=34.1). Most of the children came from out of Addis Ababa, the capital city of Ethiopia, accounting for 91.2% (n=83) of children with germ cell tumors. From the identifiable sources of referral, the majority of the children; 51.6% (n=17) were referred from tertiary referral hospitals, and 10% (n=8) were referred from private health facilities as shown in Table 1.

Table 1. Distribution by socio-demographic characteristics of pediatric germ cell tumor patients treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014–2023 (n=91)

Variable	Frequency	Percent (%)
Age category		
0-1 years	17	18.7
1-5 years	39	42.9
6-12 years	31	34.1
≥12 years	4	4.3
Sex		
Male	27	29.7
Female	64	70.3
Residence		
Out of Addis Ababa	83	91.2
Addis Ababa	8	8.8
Source of referral identified (n=33)		
Health center	1	3.0

General Hospital	7	21.2
Private health facility	8	24.2
Tertiary referral hospital	17	51.6

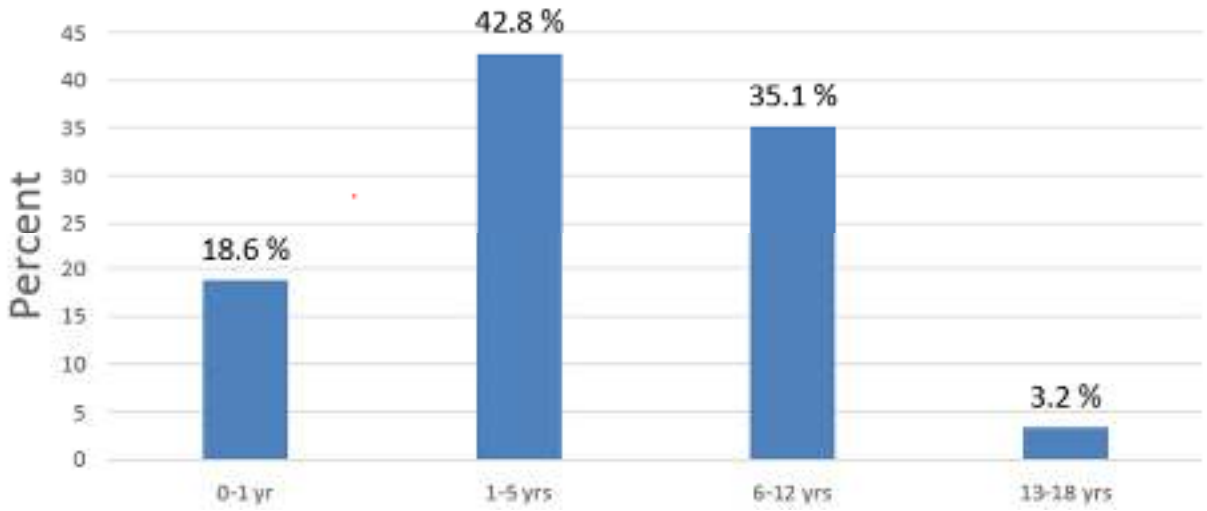

Figure 2: frequency distribution of age in GCT patients

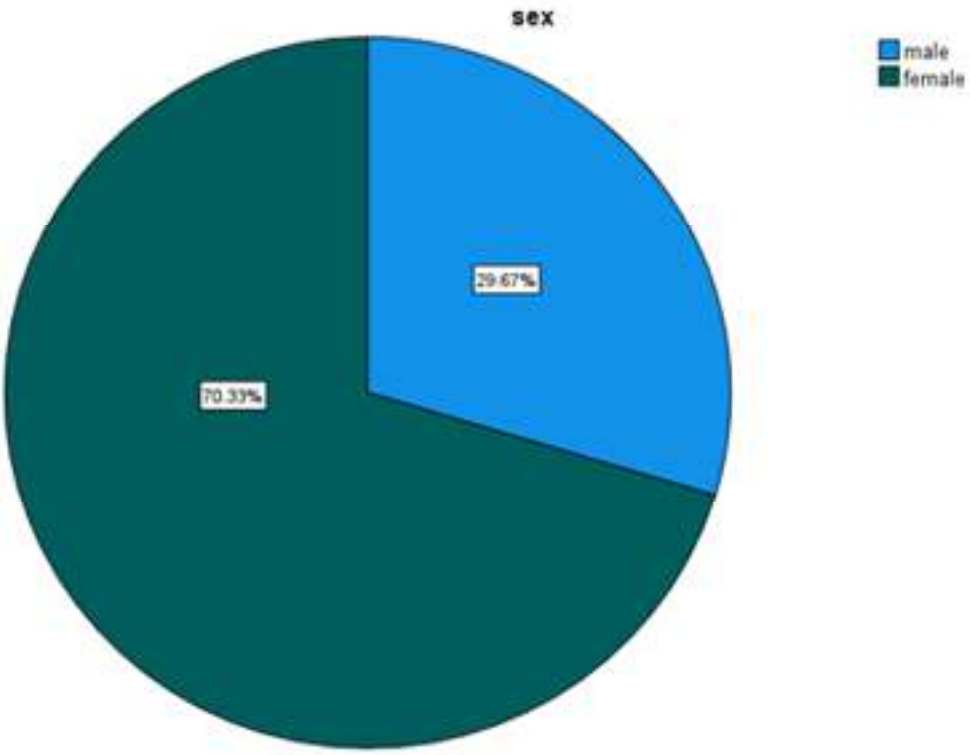

Figure 3: frequency distribution of sex in pediatric GCT patients

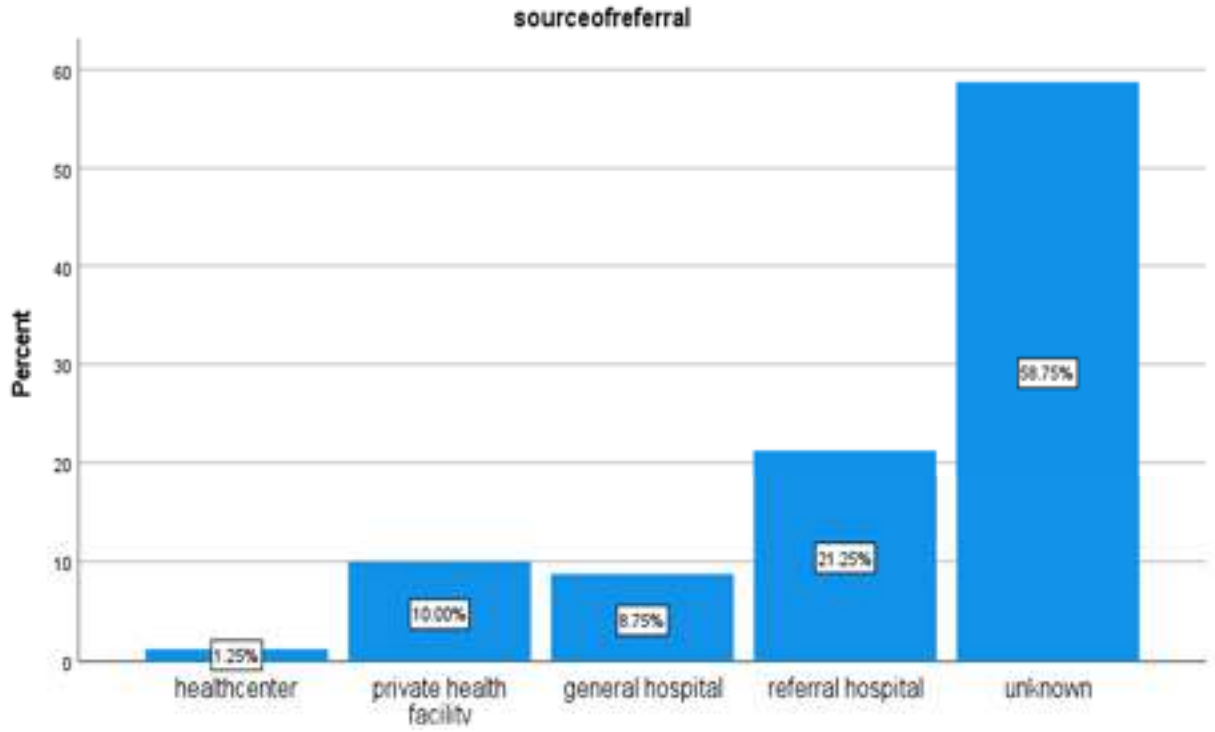

Figure 4: Frequency distribution od source of referral in pediateric GCT patients

5.2 Clinical characteristics of pediatric GCT patients

The median duration of symptoms in children with pediatric germ cell tumors was 4 months with a range of 2 days to 12 months. The commonest presenting symptom in this study was found to be sacrococcygeal swelling constituting 35.2% (n=32), followed by abdominal swelling; 31.9%, n=29), scrotal swelling; 8.8%, n=8), and headache or change in mentation; (4.4%, n=4). On physical examination, the majority of the patients had sacrococcygeal mass; 38.2% (n=34) followed by abdominal mass (36%, n=32), scrotal mass; 6.7%, (=6), and neurologic deficit; 4.5% (n=4) respectively. Most of the patients had extracranial tumors constituting 93.4% (n=85) and intracranial germ cell tumors accounted for 6% of pediatric germ cell tumors.

(**Table 2**)

Table 2. Clinical characteristics of pediatric germ cell tumor patients treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014–2023 (n=91)

Variable (n=91)	Frequency	Percent (%)
Presenting symptoms		
Sacrococcygeal swelling	32	35.2
Abdominal swelling	29	31.9
Scrotal swelling	8	88
Abdominal pain	4	4.4
Neck swelling	1	1.1
Cough/Shortness of breath	2	2.2
Headache/vomiting/change in mentation	3	3.3
Others	11	12.1
Physical findings		
Sacrococcygeal mass	34	38.2
Abdominal mass	32	36.0
Scrotal mass	6	6.7
Neurologic deficit	4	4.5
Others	13	14.6
Metastasis		
Localized	85	93.4
Metastasis	6	6.6
Location		
Extracranial	85	93.4
Intracranial	6	6.6
Duration of symptoms in days (median+ IQR)	120	2–365

IQR: interquartile range

5.3 Biochemical and Histologic characteristics of Pediatric Germ cell Tumor patients

Serum or Cerebrospinal fluid oncoproteins were determined in more than half of the patients (58.2%, n=53) and were elevated for more than one-fourth of the patients (27.4%). About 83.5% (n=76) of the patients had histologic confirmation as the diagnostic modality. The most common histology of GCTs was found to be mature teratoma; 52.6% (n=40) followed by dysgerminomas (17.1%, n=13), choriocarcinoma (13.2%, n=10), immature teratoma (7.9%, n=6) seminoma (6.6%, n=5) and yolk sac tumor (2.6%, n=2) as shown in **Table 3**.

Table 3. Biochemical characteristics of pediatric germ cell tumor patients treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014–2023 (n=91)

Variable	Frequency	Percent (%)
Oncoproteins (AFP, B-HCG)	53	58.2
GCT diagnosed with elevated oncoproteins	25	27.5
Histology confirmed	76	83.5
Histologic subtype		
Mature teratoma	40	52.6
Dysgerminomas	13	17.1
Choriocarcinoma	10	13.2
Immature teratoma	6	7.9
seminoma	5	6.6
yolk sac tumor	2	2.6

AFP: alpha-fetoprotein, BHCG: beta human chorion-gonadotropic hormone, GCT: Germ Cell Tumour

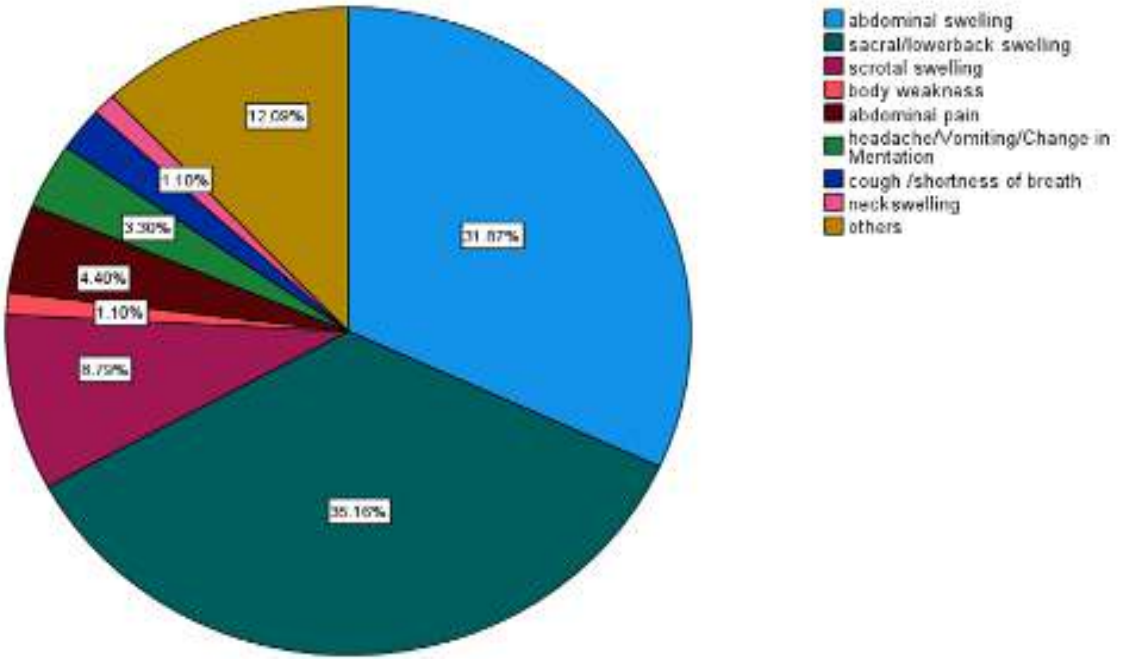

Figure 5: Frequency distribution of presenting symptoms in pediatric GCT patienrs

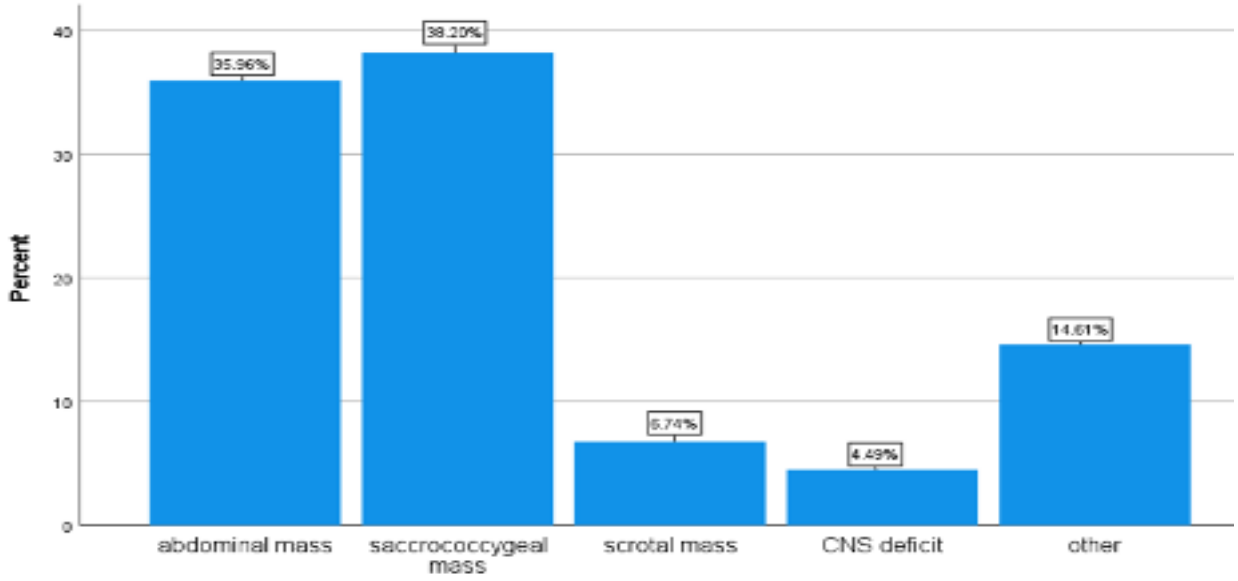

Figure 6: Frequency distribution of physical findings in pediatric GCT patients

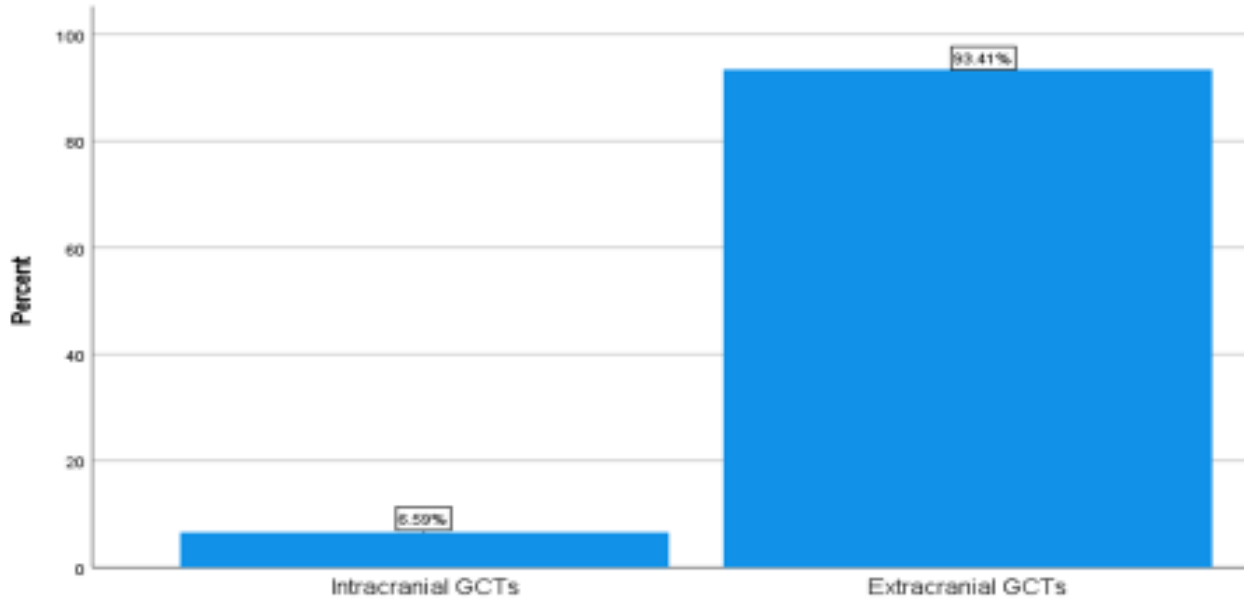

Figure 7: Frequency distribution of location of tumor in pediatric GCT patients

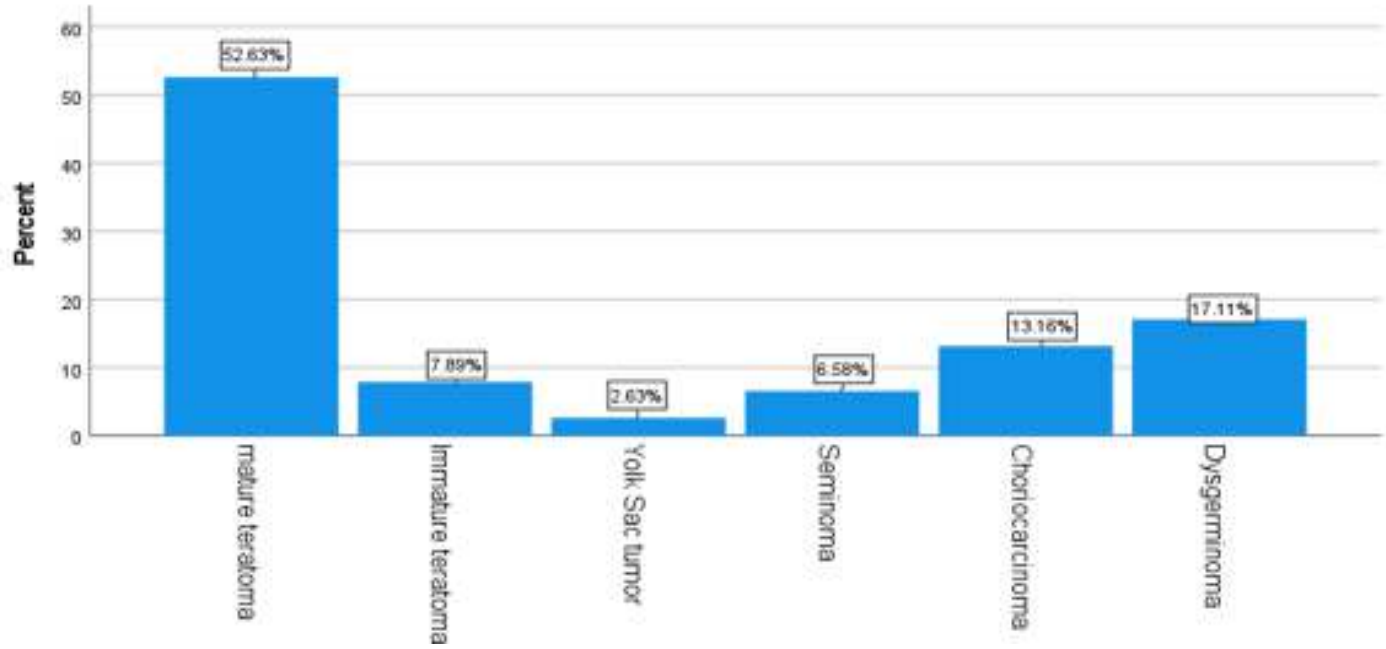

Figure 8: Frequency distribution of histological patteren in pediatric GCT patients

5.4 Management Profile of Pediatric Germ Cell Tumors

About 87.9% of pediatric GCT patients started on at least one of the treatment modalities for GCTs. From this 47.5% of patients (n=38) were given chemotherapy and 65% of them underwent surgery

(n=52). About 42% of patients received a combination of chemotherapy and local control either surgery or radiotherapy (**Table 4**)

Table 4: Management-related characteristics of pediatric germ cell tumor patients treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014–2023 (n=91)

Variable	Frequency	Percent (%)
Treatment initiated		
Yes	80	87.9
No	11	12.1
Treatment Modality		
Surgery	52	65
Chemotherapy	38	47.5
Order of treatment		
Surgery only	32	43.2
Chemotherapy only	11	14.8
Surgery + chemotherapy	27	36.5
Chemotherapy +radiotherapy	3	4.1
Surgery +chemotherapy + RT	1	1.4

RT: radiotherapy

5.5 Survival outcomes of Pediatric Germ cell Tumors (GCT) Treated at Tikur Anbessa Specialized Hospital

The Kaplan-Meier survival estimates showed the first and five-year overall survival (OS) was 92.7% and 85% respectively, and the median overall survival time for all pediatric Germ cell tumor patients was found to be 39 months (CI: 24.8-53.1). The Kaplan-Meier survival estimates showed the first and five-year Event-Free Survival (EFS) wasand the median event-free survival time was found to be 36 months (95% CI: 26.1– 45.8)

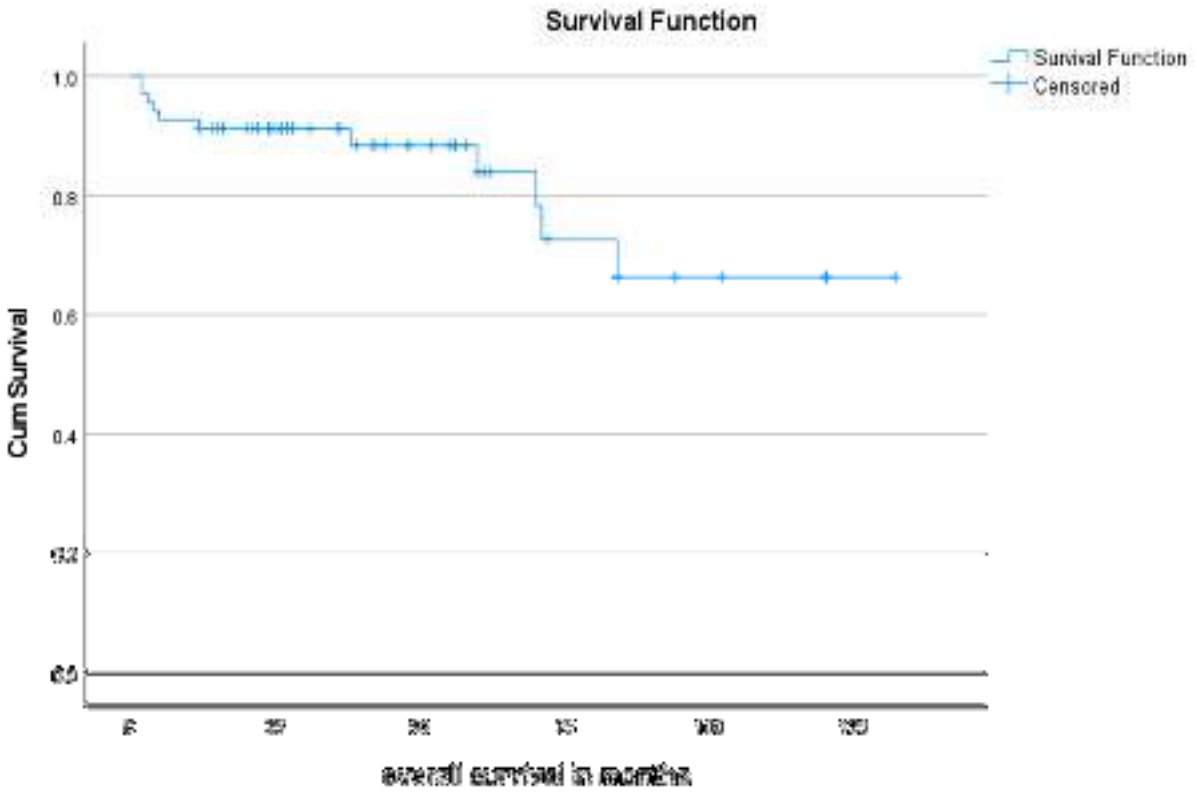

Figure 9: Overall survival estimates of pediatric GCT patients treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014–2023

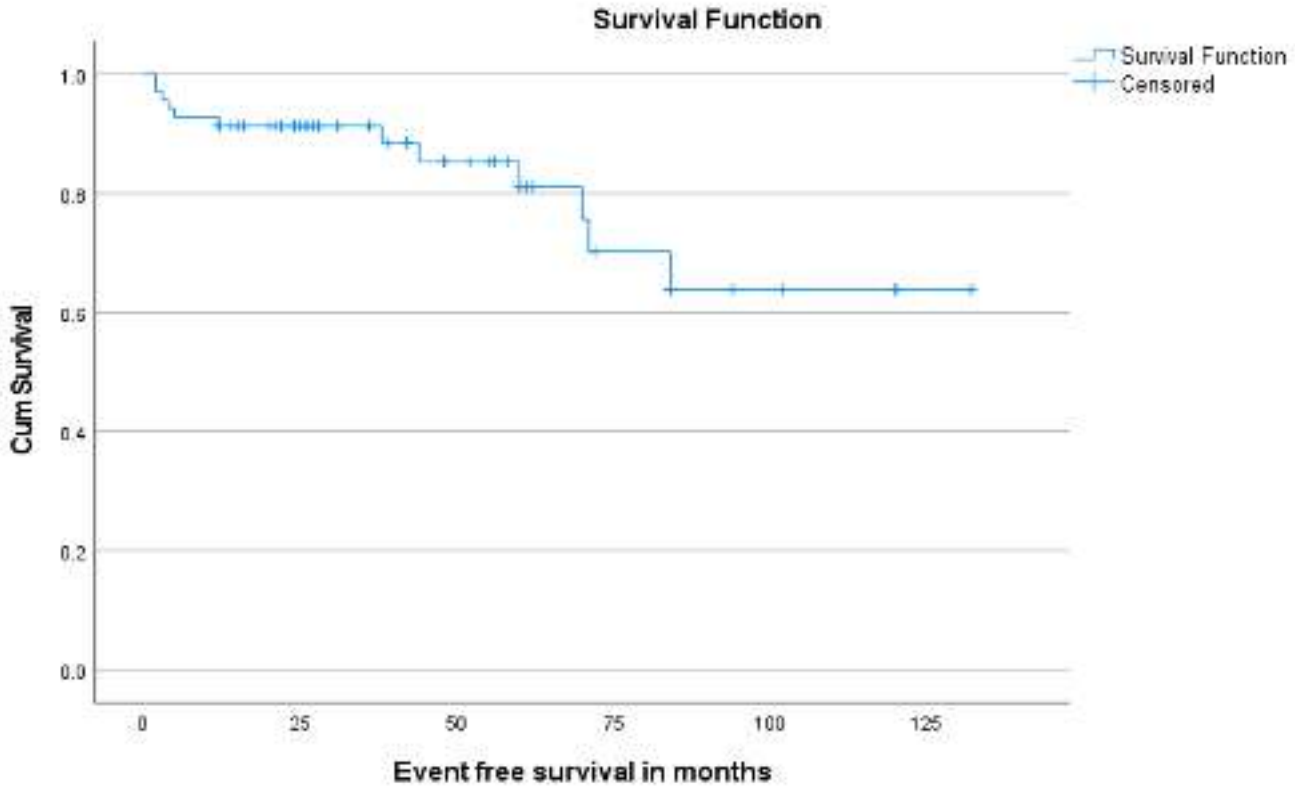

Figure 10: Event-free survival of pediatric GCT patients treated at Tikur anbessa spaecialized hospital, Addis Ababa, Ethiopia, 2014 - 2023

The most common documented event was death, occurring in 83.3% (n=10) followed by progressive disease and relapse occurred in16.6% of patients (n=2)

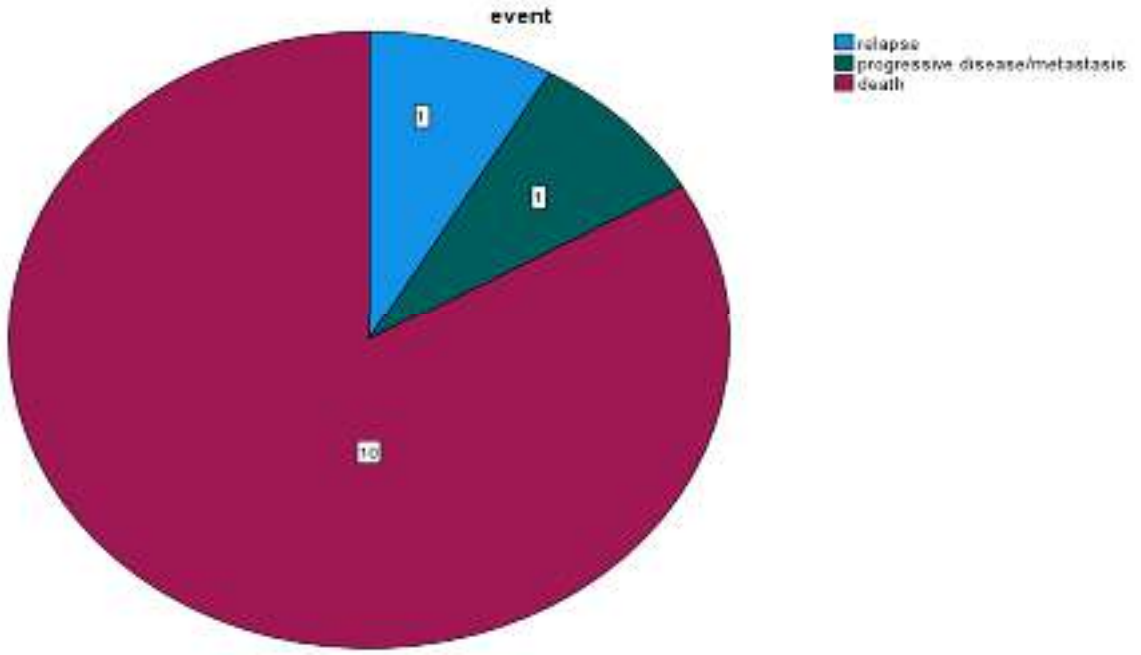

Figure 11 : Events among pediatric Germ cell tumor patients at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2013–2023

5.6 Factors associated with survival outcomes

In this research, tumor location of whether intracranial or extracranial was found to be associated with survival outcome of germ cell tumor patients. In addition to that the age of patients. In which extracranial tumours had higher median survival than those with intracranial tumors.

The metastatic stage of the tumour was another statistically significant factor associated with survival outcome. Metastatic tumours showed lower median survival rated than those of localized tumors.

The age of the patients that presented with germcell tumor was another assiated factor analyzed to show an outcome strongly associated with survival outcome due to the observation that patients above the age of five showed lower median rates of survival as compared to those with age less than or equal to five.

Inaddition to that, the administration of chemotherapy also was found to have statistically significant association with survival outcome. Results demonstrated that the patients who received chemotherapy as mainstay of management showed lower survivsl outcomes than those patients who were treated with other modalities of treatment.

Table 5: Factors associated with survival outcome in pediatric GCT patients treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014–2023 (n=91

Variable	**Eventfree survival**		**Overall survival**	
	CHR	**P value(log rank)**	**AHR**	**Pvalue(log rank)**	**CI**
Age category					
≤ 5years	0.162		4.80	0.86	0.8- 28.8
>5years	-		-	-	-
location					
intracranial	0.011		<0.001	0.007	0 - 0.119
extracranial	-		-	-	-
Was chemotherapy given					
yes	0.21		0.71	0.545	0.27-9.966
no	-		-	-	-
Stage					
localized	0.001		<0.001	230	16.3-3255.2
metastatic	-		-	-	-
Oncoproteins					
Elevated	2.134				
Normal range	-				

6. Discussion

Our study aimed to identify the clinicopathological patterns and treatment outcomes of pediatric germ cell tumors treated at Tikur Anbessa Specialized Hospital, the largest tertiary referral hospital in Ethiopia. According to the findings of this research , results showed that the median age at diagnosis was 4 years with an interquartile range of 1 – 14 years.

The study demonstated a female predominance since the female sex was found to be more frequent reaching up to 70.3% (n=64) of the total study population, with a male: female ratio of 1:2.3. In a similar study in Egypt, the females accounted for 72.7%.

Most of the children were under five years of age; constituting 61.6% (n=56). This was similar to other studies in which the first peak GCTs were in children less than 4 years old.[9,10,25] In contrary a study in Egypt showed that the median age of diagnosis of germ cell tumors was 23 months.

The median duration of symptoms in children with pediatric germ cell tumors was 4 months with a range of 2 days to 12 months. The commonest presenting symptom in this study was found to be sacrococcygeal swelling constituting 35.2%. The median duration of symptoms in children with pediatric germ cell tumors was 4 months with a range of 2 days to 12 months.

The commonest presenting symptom in this study was found to be sacrococcygeal swelling constituting 35.2 % followed by abdominal swelling in 31%. In a similar kenyan study, the Commonest presenting symptom is combined abdominal pain with palpable pelvic or abdominal mass in 85% of patients.

Most of the patients had extracranial tumors constituting 93.4% (n=85) and intracranial germ cell tumors accounted for 6% of GCTs. These findings are similar to other studies.[25,30.31]and the median survival was 16 months.

The most common histology of GCTs was found to be mature teratoma; 52.6% (n=40) followed by dysgerminomas (17.1%, n=13) and yolk sac tumor was the least common histology in the study area. In contrast in a research in bangladesh ,The most frequent GCT histopathology was yolk sac tumor (34.1%) [12]

About 42% of patients got a combination of chemotherapy and local control either surgery or radiotherapy.

The Kaplan-Meier survival estimates showed the first and five-year overall survival (OS) were 95.7% and 85% respectively, and the first and five-year Event-Free Survival 95% and 84% respectively and the median event-free survival time was found to be 36 months. Death, progression of Disease, and relapse were the documented events.

In the Egyptian study mentioned above, patients with yolk Sac tumor histology, extra-gonadal germ cell tumors, and a high AFP level at diagnosis had the worst prognosis and lower survival rate; whereas a combination of surgery, chemotherapy, and radiotherapy for intracranial germ cell tumors led to better survival.

The factors that were associated with survival outcome in pediatric germ cell tumor patient were found to be the stage of the tumor, the location of the tumor, the age of the patient and the use of chemotherapy as a treatment of modality. In comparison, a sudy done in Egypt patients with yolk Sac tumor histology, extra-gonadal germ cell tumors, and a high AFP level at diagnosis had the worst prognosis and lower survival rate; whereas a combination of surgery, chemotherapy, and radiotherapy for intracranial germ cell tumors led to better survival.[25,30]

7. Strength and Limitations

7.1 Strength

- This study is one of a kind in Ethiopia as there are no researches done in the area that aimed to report clinicopathologic patterns and treatment outcomes in children with germ cell tumors.

7.2 Limitations

- The study was retrospective, and most of the patients' data was obtained from their medical charts, which were occasionally compromised by missing or torn pages, or illegible handwriting.
- There is a censoring issue, which can potentially affect the survival estimates. A few patients left censored due to late presentations and right censored due to treatment dropouts and loss of follow-up.

8. Conclusion

- As a summary the research finding depicts the good outcomes of pediatric patients that have been treated surgically and medically at TASH as shown in the survival analysis results. This outcome is similar to research done in other parts of the world.

9. Recommendation

Based on the study findings, the following recommendations are forwarded.

For health professionals

Doctors and other health care professionals who are involved directly or indirectly in the management of patients with germ cell tumors should try to minimize any form of delay during diagnosis and initiation of treatment delay. The treatment should be multidisciplinary with clear communication between different departments as most of the patients need multimodal therapy.

For caregivers,

Caregivers must seek modern medical attention as early as possible, as late disease presentation observed in this study can lead to limited management options, decreased complete remission, and survival outcomes.

For policymakers/ government executives

The local policymakers and other stakeholders should avail pediatric oncologic services in the peripheral regions of the country as more than 90 percent of the patients came out of Addis Ababa They should also avail of up-to-date diagnostic modalities.

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11. Annex I: Information sheet and questionnaire

Addis Ababa University

College of Health Sciences

My name is Dr. Mihret Gebrehiwot and I am a postgraduate student in the Department of Pediatrics and Child Health of the College of Health Sciences, Addis Ababa University.This governmental hospital was selected to conduct the proposed study Clinico Pathological Pattern and Treatment Outcome of Children with Germ Cell Tumor at Tertiary Hospitals in Addis Ababa, Ethiopia: A 10 - Year Retrospective Study, 2023GC.

The purpose of this study is to assess Clinico Pathological Patterns and Treatment Outcomes of Children with Germ cell Tumor at Tertiary Hospitals in Addis Ababa, Ethiopia. The study is designed to be a record review retrospective study of individuals with GCT attending Pediatric Hematology-Oncology at the hospital. All information gathered from the log book and patient medical records will be kept confidential. Any of the patient's personal information will not be registered. The records of this study will be kept private. In any sort of public report, the author will not include any information that will make it possible to identify the patient. Research records will be kept in a locked file; only the researcher will have access to the records

Contact Address of the Principal Investigator

Name**:** Mihret Gebrehiwot Mobile Phone**:** 0920416765

Date_____ number_____

Patient Demographics

1. Age _____(in yrs)
2. Sex Male Female
3. MRN _____
4. Phone number _____
5. Maternal Age _____(in yrs)
6. Maternal Education Status

   None (Illitertate) ____ Read and Write ____ Grade 1-8 ____

   Grade 9-12 ____ College And Above ____
7. Paternal Age _____(in yrs)
8. Paternal Education Status

None (Illitertate) ____ Read and Write ____ Grade 1-8 ____

Grade 9-12 ____ College And Above ____

9. Religion

Orthodox ____ Protestant ____ Muslim ____

Catholic ____ Others____

10. Region

Amhara ____ Oromo____ Tigray ____ Benshangul____

Afar ____ Harar ____ Diredawa ____ Addis Ababa ____

11. Number of children_____

12. Birth Order _____

13. Monthly Income _____birr

Clinico Pathologic Pattern

14. Duration of illness_____ days

15. Referring health facility _____

16. Presented as oncologic emergency yes no

17. If yes, specify_____

18. Presenting Symptoms

A. Abdominal Swelling _____

B. Sacral/Lower Back swelling _____

C. Scrotal Swelling _____

D. Body Weakness_____

E. Abdominal Pain _____

F. headache_____

G. failure to pass urine_____

Physical Finding

19. Anthropometry weight ___ height ____ BMI____

20. Are there any syndromic associations? Yes no

21. If yes, What was the syndrome?_____

22. Palpable abdominal mass yes ____ no ____

23. Sacrococcygeal mass yes ____ no ____

24. CNS deficit? yes ____ no ____

Diagnostic investigations

25. Does the patient have imaging?

Yes ____ no ____

26. If yes, what imaging modality was done?

Ultrasound _____ Ct scans _____ MRI_____

27. Major imaging finding

A. Intra-abdominal mass _____
B. sacrococcygeal mass _____
C. Hydrocephalus/ IC _____
D. Mediastinal mass_____
E. Retropritoneal mass_____

28. Was the initial AFP normal range _____ elevated _____

BHCG normal range _____ elevated_____

29. Subsequent AFP _____ BHCG _____

30. biopsy histologic subtype

A. Seminoma _____
B. dysgerminoma _____
C. germinoma _____
D. Yolk sac tumor _____
E. choriocarcinoma _____
F. embryonal carcinoma _____
G. Gonadoblastoma _____
H. mixed GCT _____

31. stage I II III IV

32. Complete diagnosis _____

Treatment modalities

33. Date of enrollement _____

34. Was surgery done? yes _____ no_____

35. What procedure was done? _____

36. Was chemotherapy given? yes _____ no_____

37. Date of treatment intiation_____

38. Time to definitive diagnosis_____

39. Order of treatment

    A. Surgery
    B. chemotherapy
    C. Surgery ->> chemotherapy
    D. chemotherapy ->> Surgery ->>chemotherapy
    E. Chemotherapy ->>surgery ->> radiotherapy

40. What type of chemo was given?

    Adjuvant chemotherapy _____ Neoadjuvant chemotherapy _____

41. Total cycles of chemotherapy before surgery _____

42. What was the intent of chemotherapy?

    Curative intent _____ palliative intent _____

43. How long was chemo given for? _____

Outcome of treatment

44. Outcome/current status of patients treated with chemotherapy only?

    At 6 months Alive dead relapse _____
    At 1 years Alive dead relapse _____
    At 3 years Alive dead relapse _____
    At 5 years Alive dead relapse _____

45. Outcome/current status of patients treated with surgery and then chemotherapy?

    At 6 months Alive dead relapse _____
    At 1 years Alive dead relapse _____
    At 3 years Alive dead relapse _____
    At 5 years Alive dead relapse _____

46. Outcome/current status of patients treated with surgery, chemotherapy, and then radiation?

    At 6 months Alive dead relapse _____
    At 1 years Alive dead relapse _____
    At 3 years Alive dead relapse _____

At 5 years Alive dead relapse _____

47. If relapse, what is the duration of time between completion of treatment and relapse? _____