University of Free State Faculty of Health Sciences
Department of Paediatrics and Child Health

The incidence, subtypes and demographics of patients with Germ Cell Tumours at Universitas Paediatric Oncology Services from 2000 to 2021

Submitted in partial fulfilment of the requirements for the degree

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Acknowledgements and Dedication

"I am the destroyer of ignorance and the creator of knowledge. Seek me and you shall find the truth." – Shiva Mahapurana

My sincere thanks to my supervisor, Prof J du Plessis, as well as Prof D Stones, whose dedication to paediatric oncology patients over the years have paved the way for this study.

I dedicate this manuscript to my parents and my brother, who have shown me the value of compassion and selflessness.

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Executive Summary

Extracranial Germ Cell Tumours (EGCTs) are a recognised rare oncological entity and most of the information available comes from the developed world. There is a paucity of information regarding these tumours (especially from a Paediatric Oncology standpoint) in South Africa and the world.

This research endeavours to describe the incidence, subtypes and demographics of patients with EGCTs in the Free State and associated drainage areas and see how it compares to available published data on the matter.

To achieve this, a retrospective descriptive study approach was adopted, and data was collected from patients who have attended the Paediatric Oncology Unit at Universitas Academic Hospital in the last 21 years.

The research outputs are firstly to describe the incidence, subtypes, demographics, treatment modalities and mortality of patients with GCTs who have presented to the Universitas Paediatric Oncology Services from 2000 until 2021. Secondly, to compare our findings with other South African studies, studies from other parts of Africa, Asia, and developed regions.

The impact of this study does not lie solely in the information it provides but in the possible questions, it will raise. With the careful and studied analyses of the available data, this research can provide information that can be used as a platform on which to build further research questions to better clinical practice. Without adequate data collection and analyses in the current South African setting, the South African population is incumbent on the use of data collected in dissimilar populations and with different challenges. By filling this niche, we can better direct future research, focus and resources, for the benefit of this studied population.

KEYWORDS
1. Extracranial Germ Cell Tumours
2. Paediatric cancers
3. Age Standardised Rate
4. Incidence
5. Histological subtypes
6. Demographics
7. Treatment
8. Mortality
9. Free State
10. South Africa

Abbreviations

ACCIS	: Automated Childhood Cancer Information System
AFP	: Alpha feto-protein
AFRCN	: African Cancer Registry Network
APC	: Annual Percentage Change
ASR	: Age Standardised Rate
CI5	: Cancer Incidence in Five Continents Volumes V – XI (CI5PLUS)
DOH	: Department of Health
GCNIS	: Germ Cell Neoplasm in Situ
GCT	: Germ Cell Tumour (GCTs – Plural)
GDP	: Gross Domestic Product
HSREC	: Health Science Research Committee
MaGIC	: Malignant Germ Cell Tumour International Consortium
EGCT	: Extracranial Germ Cell Tumour
NORDCAN	: Cancer Database of Nordic countries: Denmark, Finland, Iceland, Norway, Sweden, Faroe Islands and Greenland
NPCR	: National Program of Cancer Registries (USA)
PGC	: Primordial Germ Cell
PGCTs	: Paediatric Germ Cell Tumours
PLAP	: Placental Alkaline Phosphatase
POU	: Paediatric Oncology Unit
SEER	: Surveillance, Epidemiology and End Results
UAH	: Universitas Academic Hospital
UFS	: University of Free State
USA	: United States of America
WHO	: World Health Organisation
β-hCG	: Beta Human Chorionic Gonadotropin

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1. CHAPTER 1

1.1 Background, Literature Review and Research Problem

Introduction:

Neoplasms arising from primordial germline cells in patients less than 18 years, are known collectively as Paediatric Germ Cell Tumours (GCTs). (1) Primordial germ line cells are totipotent, meaning that they have the potential to differentiate into any cell of the organism and indeed, an individual organism as well. Neoplasm refers to an abnormal growth of cells or an inability to initiate appropriate apoptosis. These GCTs are commonly found in extragonadal sites in younger children and gonadal sites in the older age group (2) and this is attributed to the embryonal migration of the primordial cells to the genital ridge. (3)

Embryological development, Types and Classification of Germ Cell Tumours

Arising from the yolk sac endoderm, primordial germ cells migrate around the hindgut to their final destination on the genital ridge on the posterior aspect of the abdominal wall and here becomes part of the developing gonads. Due to this path of migration, GCTs when they arise, can be seen anywhere in these midline sites from the pineal gland area to the ovaries/testes with the most common site being the sacrococcygeal region. (4)

The migratory primordial germ cell undergoes proliferation and if a deviation from the norm arises at this point, then it may result in the formation of teratomas especially those consisting of all cell lines (endoderm, mesoderm, ectoderm). There also may be differentiation into the yolk sac tumour which under normal differentiation and proliferation would have given rise to the extra-embryonic structures. After migrating to the genital ridge, further sex-specific differentiation takes place and in the normal course this will eventually form the mature gametes. In the event of neoplastic change, a precursor known as Germ Cell Neoplasm in Situ (GCNIS) is noted prior to differentiation into malignant types of GCT. These cells have also been found surrounding malignant cells. (1,4)

Characteristics of the tumours are largely variable, as they can be attributed to the development of the tumour as both a reflection of and a deviation from normal embryonal development. This variety lends to the complexity of the classification of this group of tumours.

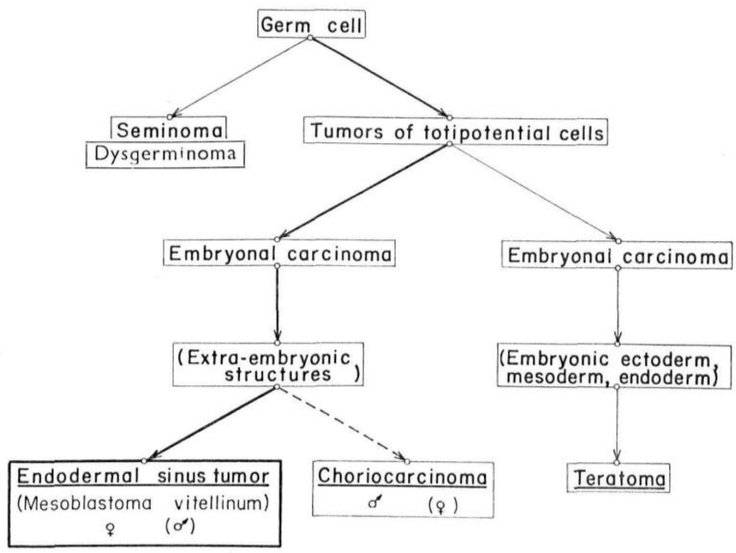

Figure 1: Pathological Classification of Germ Cell Tumours adapted from (5)

Although GCTs were widely known prior, it was only in 1965 that Telium proposed a classification that has been widely accepted as the pathological classification. (5)

This is the schematic from Telium's paper. He used the term Endodermal Sinus Tumour which is currently referred to as Yolk Sac Tumours.

More in keeping with advancements in knowledge, Oosterhuis and Looijenga proposed a classification based on epidemiology, clinical presentation, phenotypic characterization, chromosomal constitution, and genomic imprinting. (3) This distinction was recognized in 2004 by the World Health Organization (WHO) as the preferred classification system for testicular GCTs. Advancements in cytogenetic analysis have led to the identification of isochromosome 12 p (i12p) as a specific abnormality in more than 80% of germ cell tumours in post-pubertal patients. (4)

Treatment orientated studies tend to group the tumours by site. This is largely as extracranial and intracranial tumours as it becomes necessary to make this distinction due to the different treatment modalities employed for these 2 groups. (6–9)In other studies, the authors prefer to classify the tumours as either gonadal or extragonadal and then histologically as Seminomatous or Non-seminomatous. Within these subsets there are further histological subtypes and, in some cases, separate gradings may exist (for e.g. Teratomas). (3,10,11)

Table 1: Adapted from Oosterhuis and Looijenga (3)

Table 1 | **The five types of germ-cell tumour**

Type	Anatomical site	Phenotype	Age	Originating cell	Genomic imprinting	Genotype	Animal model
I	Testis/ovary/ sacral region/ retroperitoneum/ mediastinum/ neck/midline brain/other rare sites	(Immature) teratoma/ yolk-sac tumour	Neonates and children	Early PGC/ gonocyte	Biparental, partially erased	Diploid (teratoma). Aneuploid (yolk-sac tumour): gain of 1q, 12(p13) and 20q, and loss of 1p,4 and 6q	Mouse teratoma
II	Testis	Seminoma/ non-seminoma	>15 years (median age 35 and 25 years)	PGC/gonocyte	Erased	Aneuploid (+/– triploid): gain of X, 7, 8, 12p and 21; and loss of Y, 1p, 11, 13 and 18	Not available
	Ovary	Dysgerminoma/ non-seminoma	>4 years	PGC/gonocyte	Erased	Aneuploid	Not available
	Dysgenetic gonad	Dysgerminoma/ non-seminoma	Congenital	PGC/gonocyte	Erased	Diploid/tetraploid	Not available
	Anterior mediastinum (thymus)	Seminoma/ non-seminoma	Adolescents	PGC/gonocyte	Erased	Diploid/tri-tetraploid	Not available
	Midline brain (pineal gland/ hypothalamus)	Germinoma/ non-seminoma	Children (median age 13 years)	PGC/gonocyte	Erased	Diploid/tri-tetraploid	Not available
III	Testis	Spermatocytic seminoma	>50 years	Spermatogonium/ spermatocyte	Partially complete paternal	Aneuploid: gain of 9	Canine seminoma
IV	Ovary	Dermoid cyst	Children/adults	Oogonia/oocyte	Partially complete maternal	(Near) diploid, diploid/tetraploid, peritriploid (gain of X, 7, 12 and 15)	Mouse gynogenote
V	Placenta/uterus	Hydatidiform mole	Fertile period	Empty ovum/ spermatozoa	Completely paternal	Diploid (XX and XY)	Mouse androgenote

PGC, primordial germ cell.

These developmental, typological and classificational differences hold very important implications in gathering information about GCT, as there is loss of standardization between different texts, making comparison laboured. Although once identified, standardization becomes clearer due to established and recognized staging systems for the different subsets of GCTs, this differentiation has again meant that we may be able to represent the number of each subset and their incidence, severity and complications but cannot then look at the larger group with the same ease. The sites of the tumours have also led to difficulties in gathering information. Urology is responsible for testicular cancers, gynaecology for ovarian, a general surgeon or physician may be the first point of contact for an intra-abdominal mass.

Epidemiology

150 children per million below the age of 15 years are diagnosed with cancer annually. (12) The incidence of GCTs is varied among sources of different geographical origins. In the USA the incidence is quoted as 2.5 per million in white children and 3.0 per million in their African American counterparts, with the overall incidence accounting for 2-3% of all paediatric malignancies under the age of 15. (4) The incidence increases in adolescents and young adults.(1)

Due to the apparent rarity of their incidence, the epidemiological data collected on GCTs is not as extensive or as well represented as other more life-threatening childhood cancers. Notably, the landmark Children's Cancer Survival Study did not include GCTs.

Even in the higher income countries, there has been recognition of the paucity of data and to combat this, there has been a move to establish the Malignant Germ Cell Tumour International Consortium (MaGIC) in 2009 which involves different groups from America, UK, Australia, New Zealand, Japan and one centre in India. They are facilitating many different trials in these countries, that focus on GCTs and their treatment. (1)

Reliable information from low and middle-income countries tends to be from single institutions, if even available, or small registries, and thus is hard to make reliable conclusions.

There are two distinct peaks in incidence: young children from birth to four years and a second peak beginning in puberty. There are important histological and molecular biological differences between childhood and adolescent GCTs, with adolescent GCT behaving more like the adult counterpart. (1) This bimodal differentiation has led to a difficulty in consolidating the available data, as paediatricians are most likely to see and deal with the first peak of incidence and in many South African hospitals only see children until the age of 12. This means that gynaecology, urology, and general surgery see the bulk of the next peak in incidence, even though paediatric GCT are defined as those below the age of 18. American data is represented as those below the age of 15 (at best still an arbitrary cut-off.) Most data that tries to be inclusive of all ages are done in adults and due to unavoidable retrospective data collection problems like the reliability of memory and sourcing very old files, summaries or other documents, further holes are poked in the proverbial bucket of information. (13)

In South Africa the South African Children's Tumour Registry was established in 1987 by the South African Children's Cancer Study Group (SACCSG) and reported an age-standardized ratio of 1.7 per million for GCTs. This number comes from data collected from nine paediatric oncology institutions all over South Africa from 1987 to 2007. The article however does not provide in-depth details about GCTs as the aim of the article was to give an overview of the spread of paediatric oncology in that 20-year span. (14)

Gurney, et. al., published in European Urology in 2019 a summary of international trends in the incidence of testicular cancers that span over 35 years from 1978 to 2012, and cover 41 countries. The data was obtained from Cancer Incidence in Five Continents (CI5) volumes V – XI CI5plus and the NORDCAN databases. There is only one country (Uganda) representing the 54 countries in Africa. (8) In using this method, one sees that the authors have inadvertently introduced a bias that has come from very little available high-quality data. Though a useful resource in a setting where data is scarce, the article clearly shines a light on problems spoken about previously, such as the difficulty in classifications used by different areas and indeed over a long-time span when there have been various iterations of the same classification system.

Similarly, Asia is represented by India, China, Thailand, Philippines and Japan and the Middle East by only Israel and Kuwait. Europe is subdivided into four areas with a total of 24 countries contributing to the data. Some places have more than one registry contributing to the data like from the UK there are 11 registries contributing, Canada there are eight, Australia has five and although places like USA and

Norway only have one registry noted, we know that in the USA the SEER registry actually comprises of many other local registries (but only nine are mentioned in this study) and in countries like Norway, the national registries are kept quite meticulously and are reflective of the entire population due to the nature of the healthcare system. (15)

The following table summarises information obtained from multiple sources and serves to highlight the difficulties in standardizing this data. (13,16–25)

Table 2: Germ Cell Tumour data from different studies and regions							
		Study/ Journal – Type of cancer	Period	Country/ Population/ Registries	Available DATA	Cons	Pros
WORLD	1	Gurney, et al./ European Urology 2019 - Testicular cancers	1978 -2012	Data from 41 countries: CI5*, CI5plus, NORDCAN	ASR Norway (Highest): 11.5/100000 person years ASR Uganda (Lowest): 0.3/100000 person years	As discussed above	
	2	Stiller, et al. / Cancer Treatment Reviews 2007 MEGCTs	1978 - 2003	Data from multiple registries: ACCIS#, SEER and NPCR@, CI5, Cancer in Africa	USA (Age 15 -19, 1993–2003) • Non-Hispanic Blacks: 9.5/1000000 person years (Male) 16.6/1000000 person years (Female) • Non-Hispanic Whites: 42.0/1000000 person years (Male) 13.6/1000000 person years (Female)	Classification systems used are not uniform	Provides more details in some categories like Africa
AFRICA	3	Babatunde, et al./ Paediatrics and International Child Health, 2015 MEGCTs	1991 - 2010	University College Hospital, Ibadan	3.4 % incidence of PGCT, total 625 children diagnosed with malignant tumours. 0.3 M:F Median age 2 years	Total 21 children over 20 years, 5 males and 16 females with PGCT, this suggests the data collection is poor or something has drastically changed in the management and prevention of childhood cancers	Included data from past Ibadan studies: 1960 -1972: 1.6 % (Williams 1975) Total 1326 cases 1973 -1990: 1.4% (Akang 1996) Total 1881 cases

ASIA	4	Suita, et al./ Journal of Paediatric Surgery, 2002 Paediatric Solid Malignant Tumours	1975 - 2000	Committee for Paediatric Solid Malignant Tumours in Kyushu Area	Focuses on treatment outcomes and prognostic factors.	No incidence rates worked out and small number in study	
	5	Joel, et al./ eCancer 2021 Mediastinal GCTs	April 2001 – June 2019	Christian Medical College and Hospital Vellore	Mediastinal tumours common symptoms, therapy.	Focuses only on mediastinal tumours	
Europe/ Australia	6	Pesola, et al./ British Journal of Cancer 2017 GCTs	1971 - 2013	English children and adolescents	Age 0-14 yr. Male: 1989: 0.5 ASR per million, 2009: 0.7 ASR per million, 2029 projection: 0.8 ASR per million Female: 1989: 0.7 ASR per million, 2009: 0.8 ASR per million, 2029 projection: 1.1 ASR per million		APC also included and Adolescent group from 15 -24 years also included
	7	Paapsi, et al. / BMC Cancer 2020 GCTs	1970 - 2016	Estonia	Total cases: 75 (4.6%) Avg annual cases: 2% ASR/ per million: 1970 – 1994: 4.7 1995 – 2016: 8.3 APC 2.5%	Very narrow population group	Also includes survival rates and addresses essentially one country with two different healthcare systems and makes comparisons of the data
	8	Baade, et al./ British Journal of Cancer 2010 GCTs	1983 - 2006	Australian population	Total cases 511 Avg cases per year: 25.1 (4.1%) ASR/million per year: 6.4		Further includes age group incidence, incidence for each sex, APC

	9	Magnanti, et al./ BMC Cancer 2008 GCTs	1968 - 2005	Northern England	Total cases: 534 (14.9 %) ASR/million: 0-14years: Male: 5.2 Fem: 5.5 ASR/million:15-24years Male: 34.8 Fem: 15.4		Further breaks it down as Gonadal and Extra gonadal. Includes APC, and breaks it down into further into 3 time periods

CI5 - Cancer incidence in 5 continents volumes V-XI
Automated Childhood Cancer Information System
@ Surveillance, Epidemiology and End Results and National Program of Cancer Registries (USA)
ASR – Age Standardised Rate
APC – Annual Percentage Change
Avg - average
GCTs- germ cell tumours

Another important source for African Cancer statistics is the Cancer in Sub- Saharan Africa report. (18) Of note, is that Egypt has not contributed data to this report as this only includes sub- Saharan countries, which may have been a valuable country for comparison as it has the second highest GDP on the continent after Nigeria. This data is from the latest volume (Vol. 3) which includes data up to and including 2017. African Cancer Registry Network (AFRCN) required that submitted data included >70% of expected national rates to be registered for the report. (18) One must keep in mind that registries are from specific regions within cities/hospitals and further provide data to the registry only for specific years (where the data has been collected accurately and reliably). The expected rates are worked out from previous reports or comparing to previous reports which inherently introduces bias to the report. Another very important criticism in using this data, is that it has been presented as site specific tumours. Therefore numbers for testicular tumours and ovarian tumours can be ascertained but one cannot be sure which of these account for malignant GCT, not to mention which of the other tumours account for extra-gonadal malignant GCTs. This type of classification is much more pertinent to adult medicine than paediatrics. Also looking at the raw numbers, it becomes evident that the representation of those under 15 is severely deficient. (26)

India interestingly does have a registry of their own, but in 2013 this included only 25 population-based cancer registries and only covered 7.45% of the total population. GCTs were reported from this data as male incidence ASR 1.3-12.9 and female incidence ASR 0.2-1.3 per million, covering the years 2009 to 2011. (27)

The inclusion of these other data sets is important to this comparative analysis as the South African diaspora is one of diverse and mixed ethnicities and economic status.

Diagnosis

As paediatric GCTs can occur in any part of the body, the clinical presentation can vary as such, for example an ovarian dysgerminoma which in the pre pubertal child may present with either abdominal pain or compression of bowel. (28)

Certain markers in the blood may assist in the diagnosis of GCT. Depending on the histopathological type, the tumour may secrete Alpha feto-protein (AFP), beta human chorionic gonadotropin (β-hCG) and/or Placental alkaline phosphatase (PLAP). Yolk Sac tumours exhibit the highest AFP levels with embryonal carcinomas exhibiting intermediate levels, however teratomas of only histological type or pure teratomas usually do not exhibit higher AFP levels and if present may be a prompt for further evaluation. B-hCG levels are often elevated in embryonal carcinomas and choriocarcinomas. Although these markers are useful, they are not specific and so results must always be interpreted with age of the patient and other comorbidities in mind. (4)

The following table from the Manual of Pediatric Hematology and Oncology (5^{th} Edition) details histological identifiers as well as the markers that may be exhibited by the tumour. (4)

Table 3 as adapted from (4)

Histologic Variant	Morphology	Common Sites of Origin	Markers* AFP	β-hCG	PLAP
Germinoma	Cells are round with discrete membranes, abundant clear cytoplasm. Round nucleus with one to several prominent nucleoli. Cells arranged in nests or lobules separated by fibrous stroma. Areas of necrosis with granulomatous reaction Multinucleated giant cells may be present	Ovary: dysgerminoma Testis: Seminoma Anterior mediastinum	−	−	+
Mature teratoma	Mature tissue derived from Ectoderm: squamous epithelium, neuronal tissue Mesoderm: muscle, teeth, cartilage, bone Endoderm: mucous glands, gastrointestinal and respiratory tract lining No mitoses seen	Sacrococcygeal/ presacral Gonads Mediastinum	−	−	−
Immature teratoma	Immature tissue derived from the three germinal layers. Lesions are graded histologically: Grade 1: Some immaturity with neuroepithelium absent or limited to a rare low magnification (×40) field and not more than one such field in any slide Grade 2: Immaturity and neuroepithelium present but does not exceed three low-power microscopic fields in any slide Grade 3: Immaturity and neuroepithelium prominent; occupying four or more low-magnification microscopic fields	Sacrococcygeal/ presacral Gonads Mediastinum	−	−	−
Embryonal carcinoma	Tumor cells polygonal with abundant pink vacuolated cytoplasm with ill-defined cellular membranes. Nucleus irregular and pleomorphic with prominent nucleoli. Cells arranged in solid sheets with scanty stroma or in tubules, acini, or papillary structures. Typical and atypical mitoses present.	Testis (young adult)	−	±	±
Yolk sac tumor (Endodermal sinus)	Five characteristics are seen microscopically: 1. Aggregates of small undifferentiated embryonal cells 2. Areas of stellate mesodermal cells 3. Areas of perivascular formation consisting of a mesodermal core with a capillary in the center lined by columnar cells (Schuller-Duvall body) 4. Cystic structures which form small cavities lined by flat cells continuous with the parietal lining of the endodermal sinuses 5. Intra- and extracellular hyaline globules that are PAS positive and that contain α-fetoprotein, α_1-antitrypsin, albumin, or transferrin as demonstrated by immunohistochemical staining	Testis (Infant) Ovary Presacral	+	−	−
Choriocarcinoma	Presence of 1. Syncytiotrophoblastic cells that have multiple hyperchromatic nuclei and abundant eosinophilic cytoplasm AND 2. Cytotrophoblasts that have a single nucleus with abundant clear cytoplasm and well-defined cell borders. The two cell populations are often arranged in biphasic plexiform pattern	Ovary Mediastinum Pineal region	−	+	−

Treatment modalities

To decide on the most effective treatment modalities for GCT, one must first determine the histological subtype, site of origin and stage of disease. (4) As most GCT are benign surgical resection is the treatment of choice. Low stage malignant tumours may also be treated in this way. Staging is done by subtype and site of origin as these are not standard for all GCTs. (4)
Cisplatin /Carboplatin and Etoposide and Bleomycin, three-weekly for 4 cycles with re-evaluation at week 12, is the first line of chemotherapy if a responsive subtype is identified. Second line chemotherapy may be necessary if there is residual tumor on imaging and raised tumour markers. Radiotherapy is reserved for persistent cases, mixed germ cell tumours and intracranial tumours. (4)

The SACCSG aims to develop a national treatment protocol, which will be investigated prospectively. In preparation of this, retrospective data was collected from 9 paediatric oncology units in SA, anonymized and then pooled. The aim of the study is to standardize care, and demographic, patient and tumour-related data is being prospectively collected to evaluate if any of those factors impact outcomes. (29)

Survival and rates of relapse

Most GCTs have excellent cure rates if found early enough. For example, ovarian dysgerminomas have 95% 5-year survival rate if found in Stage 1 but presentation at Stage 4 reduces that 5-year survival rate to 33%. Location plays an important role in treatment and therefore survival. For example, in mediastinal tumours there may be problems with primary resection regardless of stage due to the proximity to vital structures. Teratomas are highly favourable in the less than 2-month age group as only 7% is malignant in female and 10% is malignant in males in this age group. However, over the age of 2 months the percentage of malignant tumours rise drastically to 48% in females and 67% in males. (4)

1.2 Aim and Objectives

Study aim

The aim of this study is to profile the epidemiological data, especially concerning incidence and subtypes of Malignant Extracranial Germ Cell Tumours (MEGCT) seen at the Paediatric Oncology Unit, Universitas Academic Hospital from 2000 to 2021.

Study objectives

- Firstly, to describe the incidence, subtypes, demographics, tumour stage at presentation, associated morbidity, mortality, and treatment modalities of patients with GCTs who have presented to the Universitas Academic Hospital (UAH) Paediatric Oncology Services from 2000 until 2021.
- Secondly to compare our findings with other South African studies as well as international studies.

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2. Chapter 2

2.1 Publishable Manuscript according to South African Journal of Oncology:

Title: The demographics of patients with Germ Cell Tumours at a South African Hospital from 2000 to 2021

Authors: Dr K Thottekkat (University of Free State Paediatric Registrar, Free State Department of Health,)
Prof J Du Plessis (University of Free State Professor in Paediatric Haematology and Oncology, Head of Clinical Unit at Universitas Academic Hospital)

Abstract:
Background: Paediatric Extracranial Germ Cell Tumours (EGCTs) are a rare type of cancer. Available data comes from mostly high-income countries. **Aim:** To profile the epidemiological data of EGCTs. **Setting:** Universitas Academic Hospital (UAH), Bloemfontein. **Methods:** Retrospective data from the Paediatric Oncology Unit's (POU) database was analysed from January 2000 to December 2021. **Results:** Over the course of 21 years, 111 patients with germ cell tumours presented to the unit. The average incidence of GCT in our population is 6.4 Age Specific Rate (ASR) per million per year from 2000 until 2021. Mature and Immature Teratomas are the most common histological subtypes seen in our demographic. **Conclusion:** This study shows the incidence of EGCTs is higher than that noted in the rest of South Africa (SA), Africa, and other regions of the world. **Contribution:** Dr K Thottekkat (Author of article, data collection) Prof J du Plessis (Supervisor)

Introduction:
Neoplasms arising from primordial germline cells in patients less than 18 years of age, are known collectively as Paediatric Germ Cell Tumours (GCTs). (1) These GCTs are commonly found in extragonadal sites in younger children and gonadal sites in the older age group (2) and this is attributed to the embryonal migration of the primordial cells to the genital ridge. (3)
The migratory primordial germ cell undergoes differentiation until it becomes normal gonadal tissue. However, a deviation from the norm at different important points of differentiation give rise to the multiple histological subtypes of GCTs known. This variety lends to the complexity of the classification of this group of tumours. In 1965 Telium proposed a classification that has been widely accepted as the pathological classification. (5) In 2004, World Health Organisation (WHO) recognised Oosterhuis and Looijenga's classification system for testicular GCTs. (3) Advancements in cytogenetic analysis have led to the identification of isochromosome 12 p (i12p) as a specific abnormality in more than 80% of germ cell tumours in post-pubertal patients. (4) Classificational differences hold very important implications in gathering information about GCTs, as there is loss of standardization between different texts, making comparison laboured.
150 children per million below the age of 15 years are diagnosed with cancer annually.(12) The incidence of GCTs is varied among different geographical regions. In the USA the incidence is quoted as 2.5 per million in white children and 3.0 per million in their African American counterparts, with the overall incidence accounting for 2-3% of all paediatric malignancies under the age of 15. (4)
There has been recognition of the paucity of data. To combat this, there has been a move to establish the Malignant Germ Cell Tumour International Consortium (MaGIC) in 2009 which involves different groups from America, UK, Australia, New Zealand, Japan and one centre in India They are facilitating many different trials in these countries that focus on GCTs and their treatment. Reliable information from low and middle-income countries tends to be from single institutions, if even available, or small registries, and thus is hard to make reliable conclusions. (1)
In South Africa the South African Children's Tumour Registry was established in 1987 by the South African Children's Cancer Study Group (SACCSG) and reported an age-standardized ratio of 1.7 per million for GCTs. This number comes from data collected from 9 paediatric oncology institutions all over South Africa from 1987 to 2007. The article however does not provide in-depth details about GCTs as the aim of the article was to give an overview of the spread of paediatric oncology in that 20-year span. (14)

Gurney, et. al., published in European Urology in 2019 a summary of international trends in the incidence of testicular cancers that span over 35 years from 1978 to 2012, and covers 41 countries. The data was obtained from Cancer Incidence in Five Continents (CI5) volumes V – XI CI5plus and the NORDCAN databases. There is only one country (Uganda) representing the 54 countries in Africa. (16) India, interestingly does have a registry of their own, but in 2013 this included only 25 population-based cancer registries and only covered 7.45% of the total population. (27)

To decide on the most effective treatment modalities for GCT, one must first determine the histological subtype, site of origin and stage of disease. (4) As most GCT are benign surgical resection is the treatment of choice. Low stage malignant tumours may also be treated in this way. Staging is done by subtype and site of origin as these are not standard for all GCTs. (4)

Most germ cell tumours have excellent cure rates if found early enough. For example, ovarian dysgerminomas have 95% 5-year survival rate if found in Stage 1 but presentation at Stage 4 reduces that 5-year survival rate to 33%. Location plays an important role in treatment and therefore survival. For example, in mediastinal tumours there may be problems with primary resection regardless of stage due to the proximity to vital structures. Teratomas are highly favourable in the less than 2-month age group as only 7% is malignant in female and 10% is malignant in males in this age group. However, over the age of 2 months the percentage of malignant tumours rise drastically to 48% in females and 67% in males.(4)

Methods:

The study design used was a descriptive cross-sectional retrospective study from the data available in the existing Paediatric Oncology database. All patients with EGCTs attending the POU at UAH between January 2000 and December 2021, below the age of 15 years at the time of diagnosis with EGCTs and for whom clinical records were available in the existing database, were chosen to participate in this study. Data was collected regarding age at presentation, sex, histological subtype, stage at presentation, anatomical sites at presentation, mode of treatment and outcomes. Ethical approval was obtained from the Health Sciences Research Ethics Committee (HSREC) UFS (ETVOS NR 108/02; UFS-HSD2022/1157) and the Free State department of health (DOH). Patients above the age of 15 years at the time of diagnosis and patients diagnosed with intracranial GCTs were excluded. Data was captured onto the REDCap database. As the data was of a categorical nature, it was quantified using frequencies and percentages.

Results:

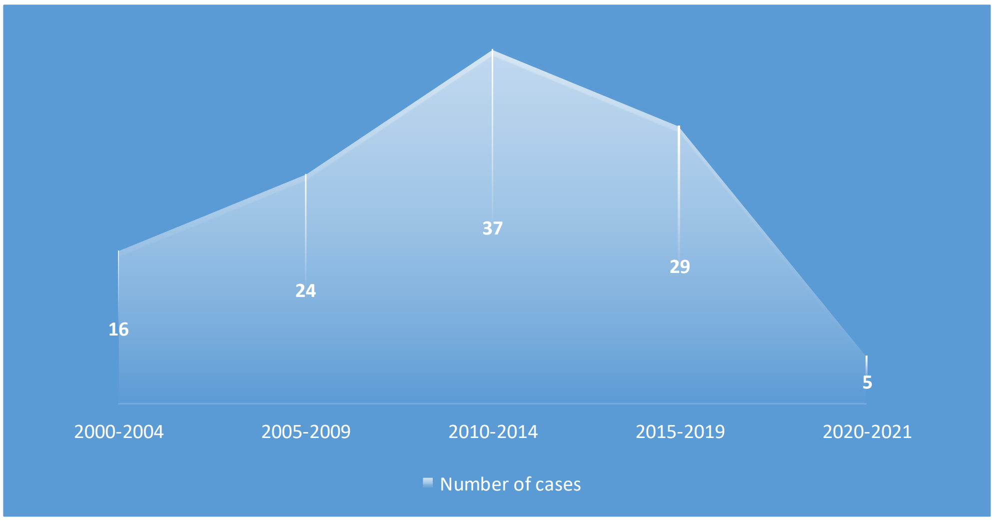

Figure 1: Graph of Incidence of MEGCTs from 2000 to 2021

Over the course of 21 years, 111 patients with germ cell tumours presented to the POU. The incidence of patients presenting with MEGCTs have been increasing over the years, with a peak reached in the 2010-2014

period, but numbers has been declining since 2015.
Using the most recent available census (2011) in the Free state, the average incidence of GCT in our population is 6.4 ASR per million per year from 2000 until 2021. (Appendix F)

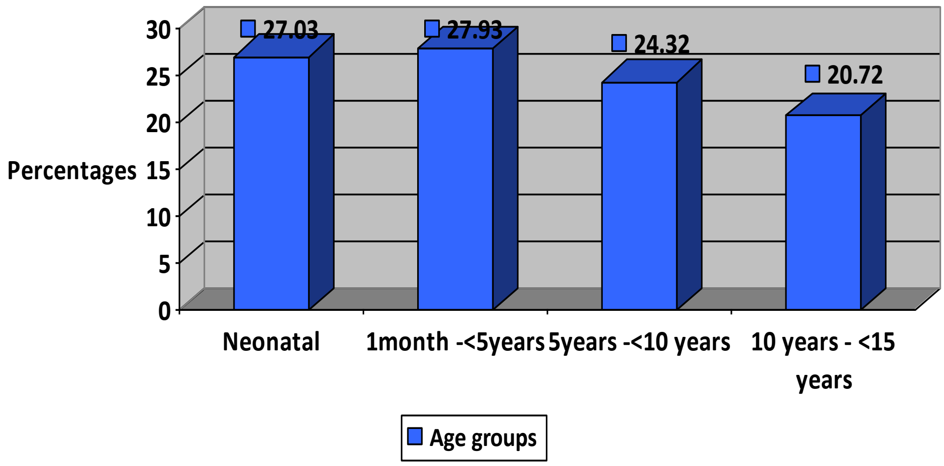

Figure 2: Bar graph of percentage of cases by age groups

As expected, there were a high incidence amongst neonates, but what is important to note is that the graph indicates the age of presentation. As the graph delineates, the ages of presentation are quite evenly distributed within the different age groups.

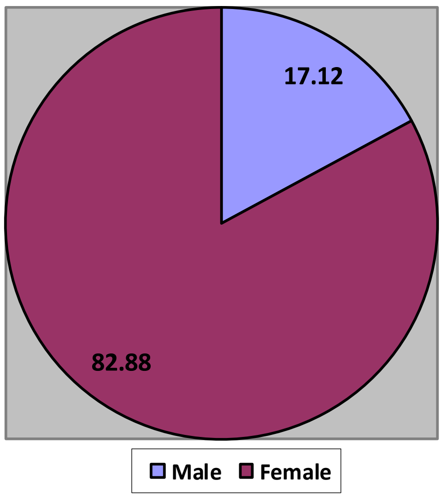

Figure 3: Pie chart of percentage of cases by sex

Figure 3 shows most patients that have presented over the last 21 years are female at 82.88% (n = 92 participants), with a male to female ratio of 1:4.8.

The following bar graph (Figure 4) shows the histological distribution of the tumours seen in the unit over the last 21 years in percentages. Some tumours are undefined as the patients demised prior to tissue diagnosis or the data was not captured on the database.

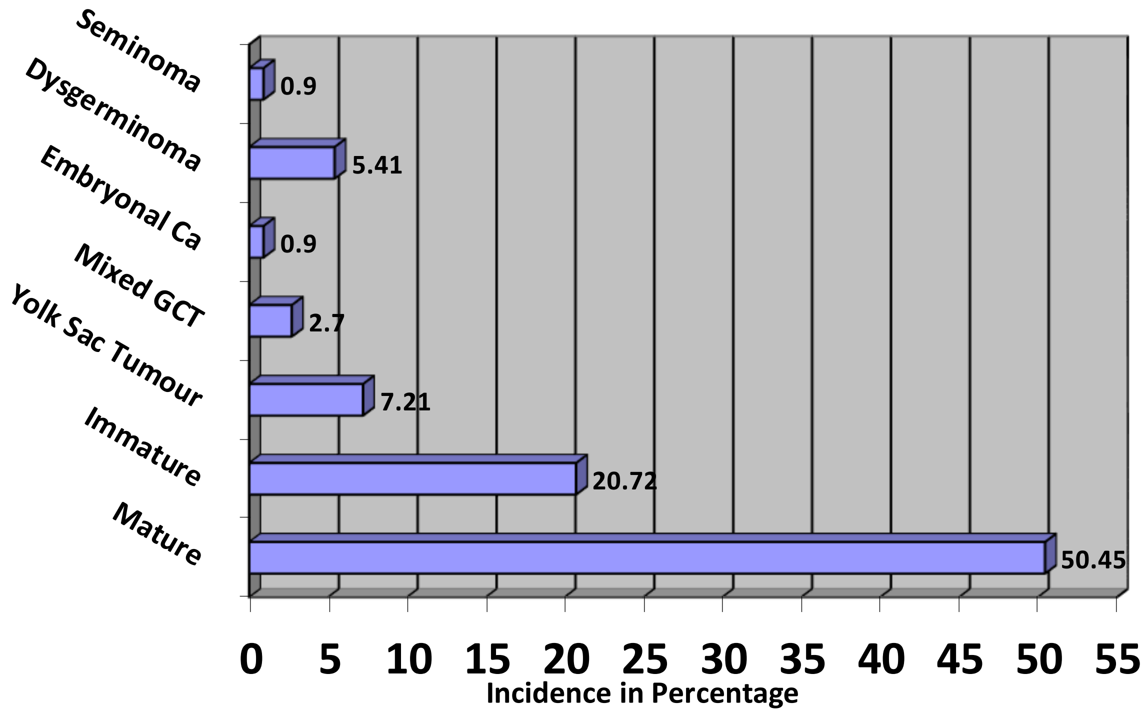

Figure 4: Bar graph of histological distribution of cases

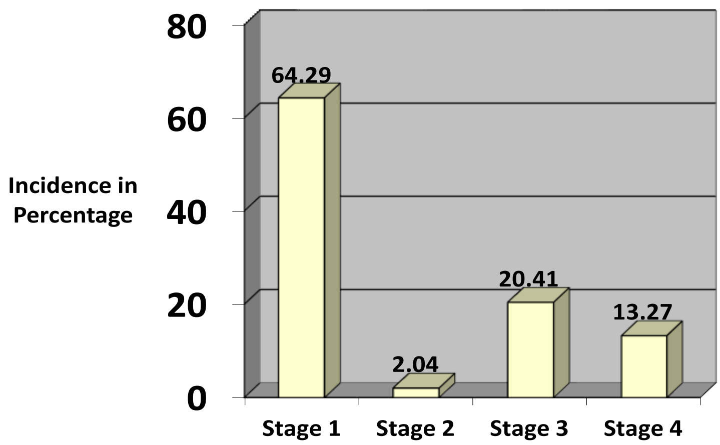

Figure 5: Bar graph of stages at presentation in percentages

The most used staging system is the International Federation of Gynaecology and Obstetrics (FIGO) staging, however there are multiple staging systems used for the different EGCTs. To simplify staging amongst all different histological types, the simpler method of staging solid tumours was used. Stage 1 fully resected, no residua, Stage 2, microscopic residua, Stage 3, macroscopic residua / rupture with positive peritoneal fluid sampling and stage 4 is metastatic disease. This was only applied at data analysis. At the time of diagnosis, staging specific to tumour type was allocated. (30) Thirteen patients presented with stage 4 disease and of these six patients demised. This accounts for 46,2% of patients presenting with metastatic disease. One patient who presented in Stage 4 was successfully treated with chemotherapy but then drowned at home.

The remaining six patients only one relapsed but all were successfully treated. Of the 20 patients who presented with stage 3 disease, only three (15%) demised. The smallest number of patients presented in stage 2 and all were successfully treated. Of the stage 1 group, only four (4%) demised from causes actually related to the tumour, such as compression of the airway by a cervical tumour or facial tumour. One of these 4 patients presented quite late and the other demised due to intraoperative complications. The other stage one patients who demised, were successfully treated and then demised from unrelated causes (see table.)

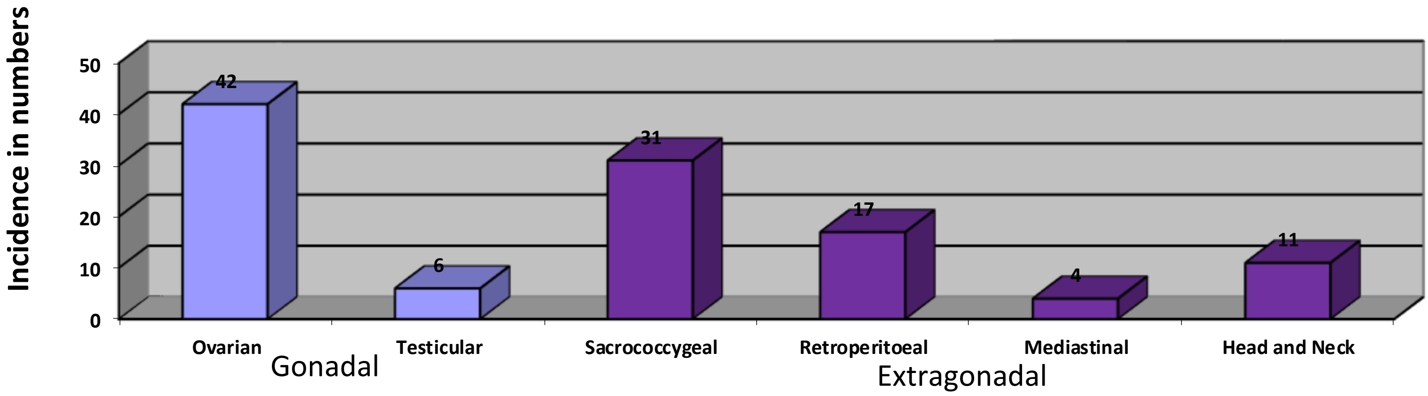

Figure 6: Bar graph of anatomical distribution of tumours at presentation

By far most EGCTs are found in the ovaries and the sacrococcygeal areas. The incidence of Ovarian tumours is explained by the majority of females in the sample size.

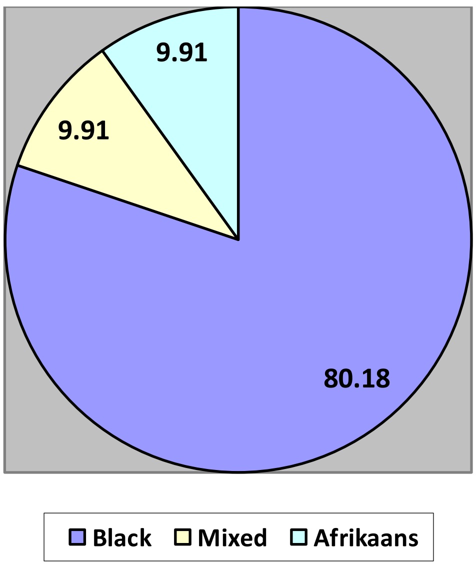

Figure 7: Pie chart of racial distribution of cases

As there are advancements in the field of genetics, it may become relevant to consider the frequency of EGCTs among different subsets of people, but this data is currently not available to us. This pie chart is a reflection of the population we serve.

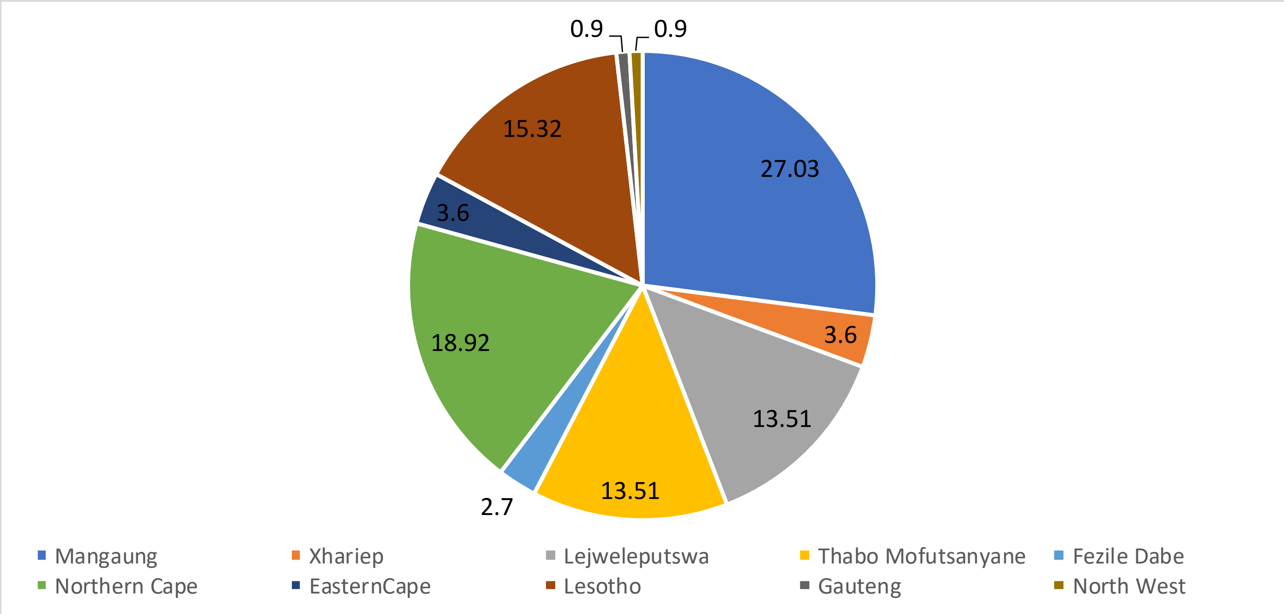

Figure 8: Pie chart of geographical locations from where cases presented

As expected, the largest group of participants is from the Mangaung area, and most of this group are presenting in the neonatal period. The Northern Cape provides the next largest group with 18.92 % (21 participants.) Not surprisingly, the third largest group is from Lesotho, and this is due to the lack of adequate medical expertise in Lesotho, making referral to South Africa pertinent.

The following graph (Figure 9) depicts the treatment choices in our unit in MEGCTs. Of the 99 cases that received surgery, 25 patients received adjuvant chemotherapy and 11 patients received neoadjuvant chemotherapy. The chemotherapy regimens were either bleomycin, etoposide, cisplatinum (BEP), carboplatinum, etopiside and bleomycin (JEb), cisplatinum, etopiside, bleomycin (PEb) or other. Other refers to variations of the above 3 or changes necessitated by drug sensitivities/ organ dysfunctions of the patient. There were 4 patients whose severity of illness at time of the presentation, excluded them from treatment and so were palliated.

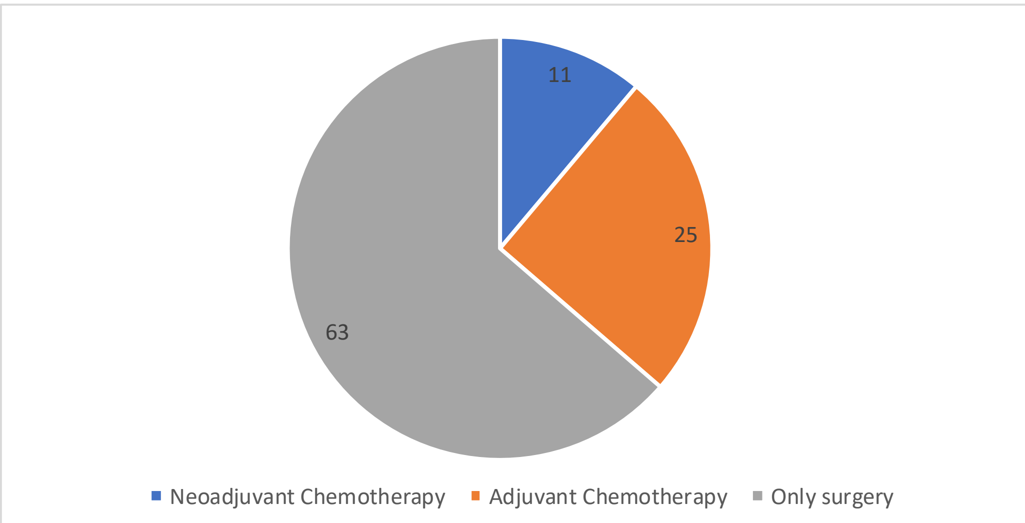

Figure 9: Pie chart showing proportion of patients who received surgery and chemotherapy

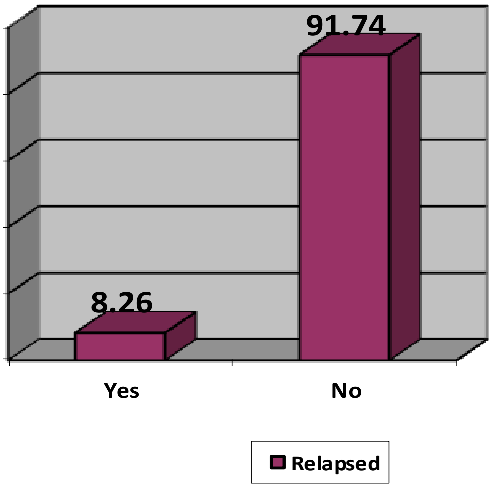

Figure 10: Bar graph depicting percentage of relapses

Most patients were treated and did not relapse. The data set in this category was not complete and we were missing information of 2 patients. Of the patients we know relapsed, only 2 demised and both presented iwithStage 4.

The following table details the participants who demised. Of note is participants 18 and 30, who despite having histology in keeping with an Immature Teratoma presented with Stage 4 disease hence, is more likely to be a Mixed GCT. Participant 100 had an undefined tumour but in view of elevated AFP in an 8 year old was probably a GCT.

Table 1: Participants who demised

Number	Year of Diagnosis	Year of death	Duration of survival	Age at Diagnosis	Histology	Locations	Stage	Treatment modality	Relapse	Died from	Tumour marker
15	2006	2007	25 months	11years	Dysgerminoma	Pelvic	3	None	NO	Complications of tumour	BetaHCG 395
18	2006	2006	0months	8 years	Immature Teratoma	Sacrococcyx Thorax	4	Surgery then Chemotherapy PEB	YES	Metastases	
20	2007	2008	17 months	Neonate	Immature Teratoma	Face	1	Surgery then Chemotherapy: JEB, BEP, Other	NO	Complications of tumour	AlphaFP 5236
30	2009	2009	0	2 years	Immature Teratoma	Sacrococcyx Liver	4	Chemotherapy: BEP	NO	From Metastases Had paralysis	AlphaFP 78780
37	2005	2007	25months	Neonate	Mature Teratoma	Sacral	1	Surgery	NO	From complications of treatment	AlphaFP 62874
48	2011	2011	8months	12 years	Embryonal Carcinoma	Ovary, lung, liver, spine	4	Surgery	NO	From Metastases	AlphaFP 4
50	2011	2011	0	10 years	Mixed GCT	Ovary, Pleural and peritoneal Metastases	4	Chemotherapy: BEP	NO	Complications of tumour: SVC syndrome	AlphaFP 16814
56	2011	2011	0	Neonate	Immature Teratoma	Cervical	1	No treatments	NO	Complication of tumour	
68	2013	2013	3months	Neonate	Immature Teratoma	Sacral	1	Chemotherapy after surgery: BEP	NO	Sudden death at home	AlphaFP 36852
78	2014	2014	0	2 years	Undefined	Abdomen	3	Chemotherapy: BEP	NO	Complication from tumour	AlphaFP 57927
93	2016	2016	5months	8months	Mature Teratoma	Upper Abdomen	1	Surgery	NO	Unrelated: Fits at home	AlphaFP 4.3
94	2017	2017	0	Neonate	Mature Teratoma	Sacrococcyx	1	No treatment	NO	Complication of tumour	AlphaFP121000
100	2017	2017	0	8 years	Undefined	Pelvis Ovary	3	Chemotherapy: PEB	NO	From Tumour	AlphaFP 5789
107	2019	2020	3months	18months	Embryonal Yolk Sac Tumour	Testes abdomen, lungs	4	Chemotherapy: PEB	NO	Unrelated: Drowning	AlphaFP >60000
110	2020	2020	0	6 years	Dysgerminoma	Ovary, lungs, abdomen	4	No Treatment	NO	From Tumour	AlphaFP 89293

Discussion:

The South African Children's Tumour Registry reported an age-standardized ratio of 1.7 per million for GCTs. (14) Our findings are higher than that seen in other areas at 6.42 ASR per million per year. (Appendix G) This is due to the inclusion of patients from Lesotho and other provinces of South Africa, other than the Free State. In comparison, the USA has 2.5 per million in white children and 3.0 per million in their African American counterparts, ASR 11.5/100000 person years in Norway and ASR in Uganda as 0.3/100000 person years. In India, male incidence of ASR 1.3-12.9 and female incidence ASR 0.2-1.3 per million. (27) In the Australian population from 1983-2006 had an incidence 6.4 ASR per million per year. (23)

In 2021, there were no patients who presented with MEGCTs. This may be attributed to the COVID-19 pandemic and the increased difficulty in accessing healthcare. It would be worthwhile and interesting to see if the age of presentation will be older in the subsequent years from 2022 when the restrictions of the pandemic were lifted.

Age of presentation is as expected highest in the neonatal period and in the group less than 5-years-old, but unusually we have a similar presentation in the 5-10-year-old age group. This can be explained by late presentation due to difficulties in accessing healthcare or delayed health seeking behaviour. This is further suggested by the histological profile of the tumours seen in our context. By far the majority is mature and immature teratomas, which is more in keeping with the expected paediatric profile described in other studies.(4,13,23,31) We would expect dysgerminomas and seminomas to become more frequent in the age group older than 15 years.(4,13,23,24,31) In the future, studies designed to understand reasons as to why the 5–10-year-old age group is having a higher-than-expected incidence may assist in understanding the disease progression, increasing healthcare education, and improving access to healthcare.

The histological distribution of the tumours (majority mature and immature teratoma) is in keeping with the international trends seen in the paediatric population. The most common anatomical sites (gonadal, sacrococcygeal and pelvic) are also in keeping with the expectations for the histological types. (13)

Understandably, patients from urban areas closer to the POU presented in larger numbers, like Mangaung.

Most of the MEGCTs were surgically excised (n= 99) and of those 36 received chemotherapy as adjuvant or neoadjuvant.

Limitations:

As this study is retrospective, there are gaps in the data and information is limited to what was collected in the database which was setup more than 30 years prior.

Conclusion: This retrospective study shows the incidence per year of EGCTs in our drainage area as being higher than those in other areas in SA and the USA, England but lower than Norway. Age of presentation was surprisingly high in all age groups although in other data a bimodal distribution is described in childhood and adolescence/early adulthood. The histological and anatomical distributions are in keeping with international data. Surgical intervention remains the mainstay of treatment low-stage MEGCTs.

Acknowledgements:

Prof JP du Plessis – Supervisor of research and submission, Head of Paediatric Oncology Unit.

Prof D Stones – Former head of the Oncology Unit and set up of the database.

Dr C van Rooyen - Biostatistics
Competing interests: No competing interests
Author contributions: Dr K Thottekkat: Article, research, data collection
Funding: No funding was obtained
Data availability: Data is protected for patient safety and will be shared with relative parties only after consideration by the author and supervisor.

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3. APPENDICES

A Letter of FINAL approval from Research Ethics Committee

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

16-Jan-2023

Dear Dr Krishna Thottekkat

Ethics Clearance: **The incidence, subtypes and demographics of patients with Germ Cell Tumours at Universitas Paediatric Oncology Services from 2000 to 2021**
Principal Investigator: **Dr Krishna Thottekkat**
Department: **Paediatrics and Child Health Department (Bloemfontein Campus)**
Submission Page

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2022/1157/3101**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

Research conducted in any Department of Health facility: Researchers are required to sign and return the HSREC approval letters to the provincial Department of Health where they applied. It is also a requirement for researchers to submit electronic copies of their final research findings, and/or make a presentation of their findings and recommendations at departmental research days when and where indicated.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2020); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; International Council for Harmonisation (ICH) Harmonised Guideline, Integrated Addendum to ICH E6(R1), Guideline for Good Clinical Practice (GCP) E6(R2), 2016, SAHPRA Guidelines as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

The Principal Investigator (PI) bears final responsibility for the RIMS application. In the event of any misconduct or improper activities perpetuated by a third party, the PI will be held vicariously liable. The HSREC will bear no responsibility or liability for any actions of a PI and/or third party or breach of confidentiality caused by the PI and/or third party.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Prof. A. Sherriff
Chairperson: Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00011992; REC 230408-011; IORG 0010096; FWA 00027947
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B Permission from FSDOH

health
Department of Health
FREE STATE PROVINCE

27 October 2022

Dr. K Thottekkat
Paediatrics and Child Health Department
University of the Free State

Dear Dr. K Thottekkat

Subject: The Incidence, Subtypes and Demographics of Patients with Germ Cell Tumours At Universitas Paediatric Oncology Services From 2000 To 2021

- Please ensure that you read the whole document, Permission is hereby granted for the above-mentioned research on the following conditions:
- Participation in the study must be voluntary and written consent by each participant must be obtained.
- Serious adverse events to be reported to the Free State department of health and/ or termination of the study.
- Ascertain that your data collection exercise neither interferes with the day-to-day running of **Universitas Hospital** nor the performance of duties by the respondents or health care workers.
- The DOH expects that the researcher will be the responsible data manager according to the POPI Act. The responsibility thus lies with the researcher to ensure that the processing of all participants' personal information and research data is lawful according to the stipulations of the POPI Act (Protection of Personal Information Act 4 of 2013).
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- Department of Health to be fully indemnified from any contravention of the POPI Act as you conduct this study.
- **Research results and a complete report should be made available to the Free State Department of Health upon completion of the study (a hard copy plus a soft copy).**
-
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and to the Free State Department of Health.
- Any amendments, extensions, or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to the Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to Scheelats@fshealth.gov.za/Gwantshuws@fshealth.gov.za before you commence with the study**
- No financial liability will be placed on the Free State Department of Health.
- **Please discuss your study with the Institution Manager on commencement for logistical arrangements.**
- Department of Health is to be fully indemnified from any harm that participants and staff experience in the study.
- As part of feedback you will be required to present your study findings/results at the Free State Provincial health research day.

Trust you find the above in order.

Kind Regards

~~MR. M~~NG MAHLATSI
HEAD: FREE STATE DEPARTMENT OF HEALTH

Date: 28/10/2022

Head: Health
PO Box 227, Bloemfontein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and Harvey Road, Bloemfontein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail: khusemj@fshealth.gov.za / chikobvup@fshealth.gov.za
www.fs.gov.za

C Permission from HOD

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

MASTER OF MEDICINE

This is to certify that the Departmental Research Meeting approved of the following MMed research protocol:

DATE OF MEETING	20 May 2022

DEPARTMENT	Paediatrics and Child Health
STUDENT NUMBER	2020904450
INITIALS AND SURNAME OF CANDIDATE	K Thottekat
NAME OF DEGREE	MMed (Paed)
SUPERVISOR	Prof JP du Plessis
CO-SUPERVISOR	N/A

TITLE OF THE RESEARCH PROJECT
The incidence, subtypes and demographics of patients with Germ Cell Tumours at Universitas Paediatric Oncology Services from 2000 to 2021.

RESEARCH CHAMPION — DATE: 23 May 2022

JP du Plessis

SUPERVISOR(S) — DATE: 23·05·2022

HEAD OF THE DEPARTMENT — DATE: 23/05/2022

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA
UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

The Chair: Health Sciences Research Ethics Committee
Prof A Sherriff
For Attention: Mrs M Marais
Block D, Room 104,
Francois Retief Building
Po Box 339 (G40)
Nelson Mandela Drive
Faculty of Health Sciences
University of the Free State
Bloemfontein
9300

23 May 2022

Dear Prof Sherriff

Dr K Thottekat (Student number: 2020904450)

The incidence, subtypes and demographics of patients with Germ Cell Tumours at Universitas Paediatric Oncology Services from 2000 to 2021.

I, Dr DC Alexander, hereby grant Krishna Thottekat permission to conduct the above mentioned research project. The research will be completed in accordance with myself as Head of Department of Paediatrics and Child Health and Prof JP du Plessis as supervisor of this study.

Yours faithfully

23/05/2022

Dr DC Alexander
(Acting Head of Department)

Date

Department of Paediatrics and Child Health / Departement Pediatrie en Kindergesondheid
205 Nelson Mandela Drive/Rylaan, Park West/Parkwes, Bloemfontein 9301, South Africa/Suid-Afrika
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D Copy of the FINAL research protocol as approved by he HSREC

University of Free State Faculty of
Health Sciences
Department of Paediatrics and Child Health

The incidence, subtypes and demographics of patients with Germ Cell Tumours at Universitas Paediatric Oncology Services from 2000 to 2021

Protocol for a research project submitted in fulfilment of the requirements for the degree Magister of Medicine (Paediatrics) in the Department of Paediatrics and Child Health Faculty of Health Sciences at the University of the Free State (UFS)

Candidate: Dr Krishna Thottekkat

Student no.: 2020904450

Contact details:
Address: 6 Willowood, Kamoa Crescent, Wild Olive Estate, Bloemfontein, 9301
Cell: 0828486663
Email: thottekkatk@yahoo.com

Supervisor: Prof J du Plessis, Paediatric Oncology

Date: 03/10/2022

Executive Summary

Germ Cell Tumours (GCTs) are a recognised rare oncological entity and most of the information available comes from the developed world. There is a paucity of information regarding these tumours (especially from a Paediatric Oncology standpoint) in South Africa and the world.

This research endeavours to describe the incidence, subtypes and demographics of patients with MEGCTs in the Free State and associated drainage areas, and see how it compares to available published data on the matter.

To achieve this, an observational descriptive study approach will be adopted, and data will be collected from patients who have attended the Paediatric Oncology Unit at Universitas Academic Hospital in the last 21 years. An existing database has been created by the heads of department, which has separate approval for this collection from UFS HSREC.

The research outputs are firstly to describe the incidence per year, subtypes, demographics, 5-year survival, morbidity, mortality and treatment modalities of patients with GCT who have presented to the Universitas Paediatric Oncology Services from 2000 until 2021. Secondly, to compare our findings with other South African studies, studies from other parts of Africa, Asia and developed regions.

The impact of this study does not lie solely in the information it provides but in the possible questions it will raise. With the careful and studied analyses of the available data, this research can provide information that can be used as a platform on which to build further research questions so as to better clinical practice. Without adequate data collection and analyses in the current South African setting, the South African population is incumbent on the use of data collected in dissimilar populations and with different challenges. By filling this niche, we can better direct future research, focus and resources, for the benefit of this studied population.

Table of Contents

4. Abbreviations

ACCIS	: Automated Childhood Cancer Information System
AFP	: Alpha foeto-protein
AFRCN	: African Cancer Registry Network
APC	: Annual Percentage Change
ASR	: Age Standardised Rate
CI5	: Cancer Incidence in Five Continents Volumes V – XI (CI5PLUS)
DOH	: Department of Health
GCNIS	: Germ Cell Neoplasm In Situ
GCT	: Germ Cell Tumour (GCTs – Plural)
GDP	: Gross Domestic Product
HSREC	: Health Science Research Committee
MaGIC	: Malignant Germ Cell Tumour International Consortium
MEGCT	: Malignant Extracranial Germ Cell Tumour
NORDCAN	: Cancer Database of Nordic countries: Denmark, Finland, Iceland, Norway, Sweden, Faroe Islands and Greenland
NPCR	: National Program of Cancer Registries (USA)
PGC	: Primordial Germ Cell
PGCTs	: Paediatric Germ Cell Tumours
PLAP	: Placental Alkaline Phosphatase
POU	: Paediatric Oncology Unit
SEER	: Surveillance, Epidemiology and End Results
UAH	: Universitas Academic Hospital
UFS	: University of Free State
USA	: United States of America
WHO	: World Health Organisation
β-hCG	: Beta Human Chorionic Gonadotropin

5. Background, Literature Review and Research Problem

Introduction:

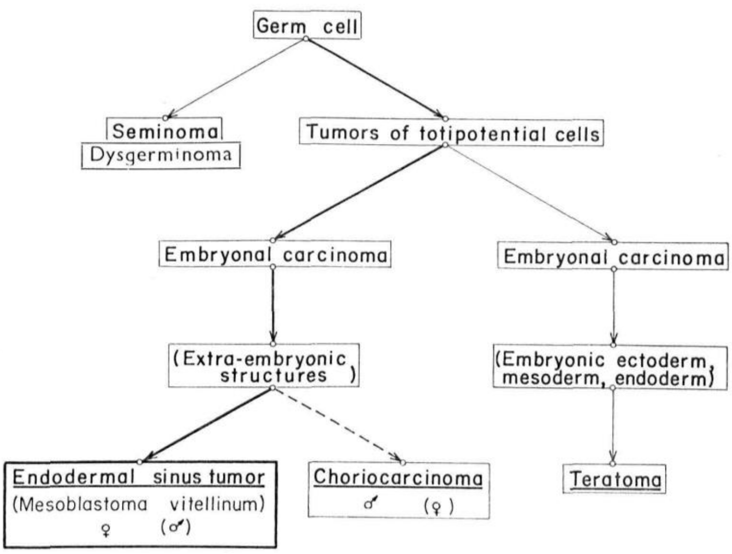
Neoplasms arising from primordial germline cells in patients less than 18 years, are known collectively as Paediatric Germ Cell Tumours (GCTs). (1) Primordial germ line cells are totipotent, meaning that they have the potential to differentiate into any cell of the organism and indeed, an individual organism as well. Neoplasm refers to an abnormal growth of cells or an inability to initiate appropriate apoptosis. These GCTs are commonly found in extragonadal sites in younger children and gonadal sites in the older age group (2) and this is attributed to the embryonal migration of the primordial cells to the genital ridge. (3)

<u>Embryological development, Types and Classification of Germ Cell Tumours</u>

Arising from the yolk sac endoderm, primordial germ cells migrate around the hindgut to their final destination on the genital ridge on the posterior aspect of the abdominal wall and here becomes part of the developing gonads. Due to the path of migration set out in this manner, germ cell tumours when they arise, can be seen anywhere in these midline sites from the pineal gland area to the ovaries/testes with the most common site being the sacrococcygeal region. (4)

The migratory primordial germ cell undergoes proliferation and if a deviation from the norm arises at this point, then it may result in the formation of teratomas especially those consisting of all cell lines (endoderm, mesoderm, ectoderm.) There also may be differentiation into the yolk sac tumour which under normal differentiation and proliferation would have given rise to the extra-embryonic structures. After migrating to the genital ridge, further sex- specific differentiation takes place and in the normal course this will eventually form the mature gametes. In the event of neoplastic change, a precursor known as Germ Cell Neoplasm In Situ (GCNIS) is noted prior to differentiation into malignant types of GCT. These cells have also been found surrounding malignant cells. (1,4)

Characteristics of the tumours are largely variable, as they can be attributed to the development of the tumour as both a reflection of and a deviation from normal embryonal development. This variety lends to the complexity of the classification of this group of tumours.



Although GCTs were widely known prior, it was only in 1965 that Telium proposed a classification that has been widely accepted as the pathologic classification. (5)

This is the schematic from Telium's paper. He used the term Endodermal Sinus Tumour which is currently referred to as Yolk Sac Tumours.

More in keeping with advancements in knowledge, Oosterhuis and Looijenga proposed a classification based on epidemiology, clinical presentation, phenotypic characterization, chromosomal constitution and genomic imprinting. This distinction was recognized in 2004 by the World Health Organization as the preferred classification system for testicular GCTs. Advancements in cytogenetic analysis have led to the identification of isochromosome 12 p (i12p) as a specific abnormality in more than 80% of germ cell tumours in post-pubertal patients. (4)

Treatment orientated studies tend to group the tumours by site: this is largely as extracranial and intracranial tumours as it becomes necessary to make this distinction due to the different treatment modalities employed for these 2 groups. In other studies, the authors prefer to classify the tumours as either gonadal or extragonadal and then histologically as Seminomatous or Non-seminomatous. Within these subsets there are further histological subtypes and, in some cases, separate gradings may exist (for eg. Teratomas.)

Table 1 | **The five types of germ-cell tumour**

Type	Anatomical site	Phenotype	Age	Originating cell	Genomic imprinting	Genotype	Animal model
I	Testis/ovary/ sacral region/ retroperitoneum/ mediastinum/ neck/midline brain/other rare sites	(Immature) teratoma/ yolk-sac tumour	Neonates and children	Early PGC/ gonocyte	Biparental, partially erased	Diploid (teratoma). Aneuploid (yolk-sac tumour): gain of 1q, 12(p13) and 20q, and loss of 1p,4 and 6q	Mouse teratoma
II	Testis	Seminoma/ non-seminoma	>15 years (median age 35 and 25 years)	PGC/gonocyte	Erased	Aneuploid (+/– triploid): gain of X, 7, 8, 12p and 21; and loss of Y, 1p, 11, 13 and 18	Not available
	Ovary	Dysgerminoma/ non-seminoma	>4 years	PGC/gonocyte	Erased	Aneuploid	Not available
	Dysgenetic gonad	Dysgerminoma/ non-seminoma	Congenital	PGC/gonocyte	Erased	Diploid/tetraploid	Not available
	Anterior mediastinum (thymus)	Seminoma/ non-seminoma	Adolescents	PGC/gonocyte	Erased	Diploid/tri-tetraploid	Not available
	Midline brain (pineal gland/ hypothalamus)	Germinoma/ non-seminoma	Children (median age 13 years)	PGC/gonocyte	Erased	Diploid/tri-tetraploid	Not available
III	Testis	Spermatocytic seminoma	>50 years	Spermatogonium/ spermatocyte	Partially complete paternal	Aneuploid: gain of 9	Canine seminoma
IV	Ovary	Dermoid cyst	Children/adults	Oogonia/oocyte	Partially complete maternal	(Near) diploid, diploid/tetraploid, peritriploid (gain of X, 7, 12 and 15)	Mouse gynogenote
V	Placenta/uterus	Hydatidiform mole	Fertile period	Empty ovum/ spermatozoa	Completely paternal	Diploid (XX and XY)	Mouse androgenote

PGC, primordial germ cell.

(Figure source: (3))

These developmental, typological and classificational differences hold very important implications in gathering information about GCT, as there is loss of standardization between different texts, making comparison laboured. Although once identified, standardization becomes clearer due to established and recognized staging systems for the different subsets of GCTs, this differentiation has again meant that we may be able to represent the number of each subset and their incidence, severity and complications but cannot then look at the larger group with the same ease. The sites of the tumours have also led to difficulties in gathering information: Urology is responsible for testicular cancers, gynaecology for ovarian, a general surgeon or physician may be the first point of contact for an intra-abdominal mass.

Epidemiology

150 children per million below the age of 15 years are diagnosed with cancer annually. The incidence of GCTs are varied among sources of different geographical origins. In the USA the incidence is quoted as 2.5 per million in white children and 3.0 per million in their African American counterparts, with the overall incidence accounting for 2-3% of all paediatric malignancies under the age of 15. (4)The incidence increases in adolescents and young adults.(1)

Due to the apparent rarity of their incidence, the epidemiological data collected on GCTs is not as extensive or as well represented as other more life-threatening childhood cancers. Notably, the landmark Children's Cancer Survival Study did not include GCTs.

Such numbers are largely sourced from data provided by first-world countries, in particular America's SEER programme. Even in the higher income countries, there has been recognition of the paucity of data and to combat this, there has been a move to establish the Malignant Germ Cell Tumour International Consortium (MaGIC) in 2009 which involves different groups from America, UK, Australia, New Zealand, Japan and one centre in India. They are facilitating many different trials in these countries, that focus on GCTs and their treatment.
Reliable information from low and middle-income countries tends to be from single institutions, if even available, or small registries, and thus is hard to make reliable conclusions.

There are 2 distinct peaks in incidence: young children from birth to 4 years and a second peak beginning in puberty. There are important histological and molecular biological differences between childhood and adolescent GCTs, with adolescent GCT behaving more like the adult counterpart. (1) This bimodal differentiation has led to a difficulty in consolidating the available data, as paediatricians are most likely to see and deal with the first peak of incidence and in many South African hospitals only see children until the age of 12. This means that gynaecology, urology and general surgery see the bulk of the next peak in incidence, even though paediatric GCT are defined as those below the age of 18. American data is represented as those below the age of 15 (at best still an arbitrary cut-off.) Most data that tries to be inclusive of all ages are done in adults and due to unavoidable retrospective data collection problems like the reliability of memory and sourcing very old files, summaries or other documents, further holes are poked in the proverbial bucket of information. (13)

In South Africa the South African Children's Tumour Registry was established in 1987 by the South African Children's Cancer Study Group (www.saccsg.co.za), and reported an age-standardized ratio of 1.7 per million for GCTs. This number comes from data collected from 9 paediatric oncology institutions all over South Africa from 1987 to 2007. The article however does not provide in-depth details about GCTs as the aim of the article was to give an overview of the spread of paediatric oncology in that 20-year span. (14)

Gurney, et. al., published in European Urology in 2019 a summary of international trends in the incidence of testicular cancers that span over 35 years from 1978 to 2012, and cover 41 countries. The data was obtained from Cancer Incidence in Five Continents (CI5) volumes V – XI CI5plus and the NORDCAN databases. There is only one country (Uganda) representing the 54 countries in Africa. In using this method, one sees that the authors have inadvertently introduced a bias that has come from very little available high-quality data. Though a useful resource in a setting where data is scarce, the article clearly shines a light on problems spoken about previously, such as the difficulty in classifications used by different areas and indeed over a long time-span when there have been various iterations of the same classification system. Similarly, Asia is represented by India, China, Thailand, Philippines and Japan and the Middle East by only Israel and Kuwait. Europe is subdivided into 4 areas with a total of 24 countries contributing to the data. Some places have more than one registry contributing to the data like from the UK there are 11 registries contributing, Canada there are 8, Australia has 5 and although places like USA and Norway only have one registry noted, we know that in the USA the SEER registry actually comprises of many other local registries (but only 9 are mentioned in this study) and in countries like Norway, the national registries are kept quite meticulously and are reflective of the entire population due to their healthcare system.

The following table summarises information obtained from multiple sources and serves to highlight the difficulties in standardizing this data. These studies will be further quoted after data collection and analysis, as they (amongst others) will be used for comparison to the data obtained for this research endeavour.
(13,16–25)

		Study/ Journal – Type of cancer	Period	Country/ Population/ Registries	Available DATA	Cons	Pros
WORLD	1	Gurney, et al./ European Urology 2019 - Testicular cancers	1978 -2012	Data from 41 countries: CI5*, CI5plus, NORDCAN	ASR Norway (Highest): 11.5/100000 person years ASR Uganda (Lowest): 0.3/100000 person years	As discussed above	
	2	Stiller, et al. / Cancer Treatment Reviews 2007 MEGCTs	1978 - 2003	Data from multiple registries: ACCIS#, SEER and NPCR@, CI5, Cancer in Africa	USA (Age 15 -19, 1993–2003) • Non-Hispanic Blacks: 9.5/1000000 person years (Male) 16.6/1000000 person years (Female) • Non-Hispanic Whites: 42.0/1000000 person years (Male) 13.6/1000000 person years (Female)	Classification systems used are not uniform	Provides more details in some categories like Africa
AFRICA	3	Babatunde, et al./ Paediatrics and International Child Health, 2015 MEGCTs	1991 - 2010	University College Hospital, Ibadan	3.4 % incidence of PGCT, total 625 children diagnosed with malignant tumours. 0.3 M:F Median age 2 years	Total 21 children over 20 years, 5 males and 16 females with PGCT, this suggests the data collection is poor or something has drastically changed in the management and prevention of childhood cancers	Included data from past Ibadan studies: 1960 -1972: 1.6 % (Williams 1975) Total 1326 cases 1973 -1990: 1.4% (Akang 1996) Total 1881 cases

ASIA	4	Suita, et al./ Journal of Paediatric Surgery, 2002 Paediatric Solid Malignant Tumours	1975 - 2000	Committee for Paediatric Solid Malignant Tumours in Kyushu Area	Focuses on treatment outcomes and prognostic factors.	No incidence rates worked out and small number in study	
	5	Joel, et al./ eCancer 2021 Mediastinal GCTs	April 2001 – June 2019	Christian Medical College and Hospital Vellore	Mediastinal tumours common symptoms, therapy.	Focuses only on mediastinal tumours	
Europe/ Australia	6	Pesola, et al./ British Journal of Cancer 2017 GCTs	1971 - 2013	English children and adolescents	Age 0-14 yr. Male: 1989: 0.5 ASR per million, 2009: 0.7 ASR per million, 2029 projection: 0.8 ASR per million Female: 1989: 0.7 ASR per million, 2009: 0.8 ASR per million, 2029 projection: 1.1 ASR per million		APC also included and Adolescent group from 15 -24 years also included
	7	Paapsi, et al. / BMC Cancer 2020 GCTs	1970 - 2016	Estonia	Total cases: 75 (4.6%) Avg annual cases: 2% ASR/ per million: 1970 – 1994: 4.7 1995 – 2016: 8.3 APC 2.5%	Very narrow population group	Also includes survival rates and addresses essentially one country with two different healthcare systems and makes comparisons of the data
	8	Baade, et al./ British Journal of Cancer 2010 GCTs	1983 - 2006	Australian population	Total cases 511 Avg cases per year: 25.1 (4.1%) ASR/million per year: 6.4		Further includes age group incidence, incidence for each sex, APC

	9	Magnanti, et al./ BMC Cancer 2008 GCTs	1968 - 2005	Northern England	Total cases: 534 (14.9 %) ASR/million: 0-14years: Male: 5.2 Fem: 5.5 ASR/million:15-24years Male: 34.8 Fem: 15.4		Further breaks it down as Gonadal and Extra gonadal Includes APC, and breaks it down into further into 3 time periods

CI5 - Cancer incidence in 5 continents volumes V-XI

Automated Childhood Cancer Information System

@ Surveillance, Epidemiology and End Results and National Program of Cancer Registries (USA)

ASR – Age Standardised Rate

APC – Annual Percentage Change

Another important source for African Cancer statistics is the Cancer in Sub- Saharan Africa report. From this resource, data from various African regions are summarised in the table below. All countries in the report have not been summarised in the table. Of note, is that Egypt has not contributed data to this report as this only includes sub- Saharan countries, which may have been a valuable country for comparison as it has the second highest GDP on the continent after Nigeria. This data is from the latest volume (Vol 3) which includes data up to and including 2017. Of interest is the number of registries included in the analysis from each country. Where indicated with a plus sign these registries were from different regions in the same country and/or looking at different time periods. AFRCN (African Cancer Registry Network) required that submitted data included >70% of expected national rates to be registered for the report. One may suspect that there is an abundance of information when looking at these numbers however one must keep in mind that registries are from specific regions within cities/hospitals and further provide data to the registry only for specific years where the data has been collected accurately and reliably. The expected rates are worked out from previous reports or comparing to previous reports which inherently introduces bias to the report. Another very important criticism in relation to the aim of this research in using this data, is that it has been presented as site specific tumours, so numbers for testicular tumours and ovarian tumours can be ascertained but one cannot be sure which of these account for malignant GCT not to mention which of the other tumours account for extra-gonadal malignant GCTs. This type of classification is much more pertinent to adult medicine than paediatrics. Also looking at the raw numbers, it becomes evident that the representation of those under 15 is severely deficient. (26)

	Country	**Number of registries**
1	Botswana	**17**
2	Kenya	**4 + 5**
3	Nigeria	**28+29+30+31**
4	Ethiopia	**2**
5	Ghana	**25**
6	Eswatini	**18**
7	Mozambique	**7 + 8**
8	Namibia	**19**
9	South Africa	**20 + 21**
10	Uganda	**10**
11	Zimbabwe	**15 + 16**

India, interestingly does have a registry of their own, but in 2013 this included only 25 population-based cancer registries and only covered 7.45% of the total population. Germ cell tumours were reported from this data as Male incidence ASR 1.3-12.9 and female incidence ASR 0.2-1.3 per million, covering the years 2009 to 2011. (27)

The inclusion of these other data sets is important to this comparative analysis as the South African diaspora is one of diverse and mixed ethnicities and economic status.

Diagnosis

As PGCTs can occur in any part of the body the clinical presentation can vary as such. Some types may present with distinct clinical entities like an ovarian dysgerminoma which in the post pubertal child may present with either amenorrhea or menorrhagia.

Certain markers in the blood may assist in the diagnosis of GCT. Depending on the histopathological type the tumour may secrete AFP, β-hCG and/or Placental ALP (PLAP). Yolk Sac tumours exhibit the highest AFP levels with embryonal carcinomas exhibiting intermediate levels, however teratomas of only histological type or pure teratomas usually do not exhibit higher AFP levels and if present may be a prompt for further evaluation. β-hCG levels are often elevated in embryonal carcinomas and choriocarcinomas. Although these markers are useful, they are not specific and so results must always be interpreted with age of the patient and other comorbidities in mind.

The following table details histological identifiers as well as the markers that may be exhibited by the tumour.(Sourced from (4))

Histologic Variant	Morphology	Common Sites of Origin	Markers*		
			AFP	β-hCG	PLAP
Germinoma	Cells are round with discrete membranes, abundant clear cytoplasm. Round nucleus with one to several prominent nucleoli. Cells arranged in nests or lobules separated by fibrous stroma. Areas of necrosis with granulomatous reaction Multinucleated giant cells may be present	Ovary: dysgerminoma Testis: Seminoma Anterior mediastinum	−	−	+
Mature teratoma	Mature tissue derived from Ectoderm: squamous epithelium, neuronal tissue Mesoderm: muscle, teeth, cartilage, bone Endoderm: mucous glands, gastrointestinal and respiratory tract lining No mitoses seen	Sacrococcygeal/ presacral Gonads Mediastinum	−	−	−
Immature teratoma	Immature tissue derived from the three germinal layers. Lesions are graded histologically: Grade 1: Some immaturity with neuroepithelium absent or limited to a rare low magnification (×40) field and not more than one such field in any slide Grade 2: Immaturity and neuroepithelium present but does not exceed three low-power microscopic fields in any slide Grade 3: Immaturity and neuroepithelium prominent; occupying four or more low-magnification microscopic fields	Sacrococcygeal/ presacral Gonads Mediastinum	−	−	−
Embryonal carcinoma	Tumor cells polygonal with abundant pink vacuolated cytoplasm with ill-defined cellular membranes. Nucleus irregular and pleomorphic with prominent nucleoli. Cells arranged in solid sheets with scanty stroma or in tubules, acini, or papillary structures. Typical and atypical mitoses present.	Testis (young adult)	−	±	±
Yolk sac tumor (Endodermal sinus)	Five characteristics are seen microscopically: 1. Aggregates of small undifferentiated embryonal cells 2. Areas of stellate mesodermal cells 3. Areas of perivascular formation consisting of a mesodermal core with a capillary in the center lined by columnar cells (Schuller-Duvall body) 4. Cystic structures which form small cavities lined by flat cells continuous with the parietal lining of the endodermal sinuses 5. Intra- and extracellular hyaline globules that are PAS positive and that contain α-fetoprotein, α_1-antitrypsin, albumin, or transferrin as demonstrated by immunohistochemical staining	Testis (Infant) Ovary Presacral	+	−	−
Choriocarcinoma	Presence of 1. Syncytiotrophoblastic cells that have multiple hyperchromatic nuclei and abundant eosinophilic cytoplasm AND 2. Cytotrophoblasts that have a single nucleus with abundant clear cytoplasm and well-defined cell borders. The two cell populations are often arranged in biphasic plexiform pattern	Ovary Mediastinum Pineal region	−	+	−

Treatment modalities

In order to decide on the most effective treatment modalities for GCT, one must first determine the histological subtype, site of origin and stage of disease. As most GCT are benign surgical resection is the treatment of choice. Low stage malignant tumours may also be treated in this way. Staging is done by subtype and site of origin as these are not standard for all GCTs. Cisplatin /Carboplatin and Etoposide and Bleomycin, 3weekly for 4 cycles with re-evaluation at week 12, is the first line of chemotherapy if a responsive subtype is identified. If there is complete remission chemotherapy is stopped, if there is still residual tumour present then the patient may require surgery and then a further 2 cycles of chemotherapy. Radiotherapy is reserved for persistent cases and mixed germ cell tumours. (4)

The South African Children's Cancer Study Group aim to develop a national treatment protocol, which will be investigated prospectively. In preparation of this, retrospective data was collected from 9 paediatric oncology units in SA, anonymized and then pooled. This study is focusing on treatment-related data, although demographics will be included and the information is as yet unpublished. (29)

Survival and rates of relapse

Most Germ cell tumours have excellent cure rates if found early enough. For example, ovarian dysgerminomas have 95% 5-year survival rate if found in Stage 1 but presentation at Stage 4 reduces that 5-year survival rate to 33%. Location plays an important role in treatment and therefore survival. For example, in mediastinal tumours there may be problems with primary resection regardless of stage due to the proximity to vital structures. Teratomas are highly favourable in the less than 2-month age group as only 7% is malignant in female and 10% is malignant in males in this age group. However, over the age of 2 months the percentage of malignant tumours rises drastically to 48% in females and 67% in males.(4)

The data set of this research endeavour will also look at the outcomes of patients and compare this to data from other regions. There is still a large gap in foundational knowledge that can allow for further advancement in the field of GCTs.

3. Aim and Objectives

Study aim

The aim of this study is to profile the epidemiological data, especially concerning incidence, subtypes and demographics of Malignant Extracranial Germ Cell Tumours seen at the Paediatric Oncology Unit, Universitas Academic Hospital from 2000 to 2021 and see how it compares to similar studies.

Study objectives

- Firstly, to describe the incidence per year, subtypes, demographics, tumour stage at presentation, HIV status, 5-year survival, morbidity, mortality and treatment modalities of patients with GCTs who have presented to the Universitas Paediatric Oncology Services from 2000 until 2021.
- Secondly to compare our findings with other South African studies as well as international studies.

4. Methods

4.1 Study design: Descriptive cross-sectional retrospective study from the data available in the Paediatric Oncology database.

4.2 Study setting: Universitas Academic Hospital Paediatric Oncology Unit.

4.3 Study population and sampling

4.3.1 **Study population**

- All patients with Malignant Extra-Cranial Germ Cell Tumours attending the Universitas Academic Hospital Paediatric Oncology Unit between 2000 and 2021.
- **Inclusion criteria:**
  - Patients below the age of 15 at the time of diagnosis with Germ Cell Tumours
  - Patients for whom clinical records are available in the existing database. Based on the experience of the study leader, the estimated number of participants is 110.
- **Exclusion criteria:** Patients above the age of 15 at the time of diagnosis and patients diagnosed with intracranial GCTs.

4.3.2 **Sampling method:** An existing database will provide all patients treated in the unit.

4.3.3 **Sampling size:** All patients fulfilling inclusion criteria from the database

4.4 Measurements

- Measurement instrument: REDCap will be used to extract data from existing database
- Pilot study: The data capture tool will be piloted against the information of

patients from the database in order to detect the suitability of the tool and if there are any flaws present.

- The original data was collected with the purpose of creating an extensive and comprehensive database for use in a myriad of research endeavours and so was collected in a much broader scope. This lends to the reliability and validity of the data but the usability will have to be assessed during data collection.
- HSREC approval of the database: ETVOS NR 108/02

5. Data Management

The data provided by the participants will be treated with respect and confidentiality. The data will only be used in conjunction with this particular study and will not be made available to any third parties. The data will be de-identified by using a participant number. A unique number will be allocated to each participant for data analysis and write-up phases of this research study and will thus protect the confidentiality of the patient.

6. Data Analysis

A statistician from the Department of Biostatics of the University of the Free State (UFS) will assist with the analysis of the data after collection.

Data points that are continuous will be described with statistical measures such as means, standard deviations, medians or percentiles. Data that is of a categorical nature will be quantified using frequencies and percentages.

This research paper aims to comment on the incidence of Germ cell tumours. This will be looked at as an overall incidence over the 21 years designated and then broken down to a yearly incidence as well, using age standardised ratios. Furthermore, the annual percentage change in incidence will be calculated.

Breakdowns in the incidence by subtype and locations will be done, to see any trends/patterns. Other parameters to look at will be age, sex, HIV status, treatment modalities used and outcomes. Different groups will be evaluated using appropriate statistical tests and confidence intervals for unpaired data.

The first 5 participants' data will be evaluated as part of the pilot study.

7. Ethical Considerations

The protocol will be submitted to the Health Sciences Research Ethics Committee (HSREC) of University of Free State (UFS) for approval. An application will also be submitted to the Free State Department of Health (DOH) for provincial approval to conduct the study at UAH.

No patient consent is required as this is a retrospective study and the data is already part of the POU's patient information database UAH. The data will be collected from the POU's patient information database at UAH. Permission to use this database has been granted by the principal data collector (see permission in Appendices.) There will be no face-to-face, telephonic or written communication between the researcher and the patients or their caregivers.

Patients' names and hospital numbers will be omitted in the collection and only the participant numbers will be used to collect data, which will ensure anonymity and confidentiality, when the data is analysed and written up. As there will be no interaction between the researcher and participants or their caregivers, and as there will be no intervention employed as part of the research, the study will be of no harm to the participants.

Data will be collected using REDCap and will be password protected. Only the principal investigator and the supervisor will have access to the data. The data will be stored for a maximum of five years and the principal investigator will be responsible for deleting it once the storage period has elapsed. Upon completion of this project, the data will not be used for any other research activities. This study is not linked to any other institution and no personal information will be transferred to another country.

Study limitations

As this is a retrospective study, some data might not be available from the database. Only the available data will be recorded. Our population group will only be those that present to the Universitas Paediatric Oncology Unit. Although noting these numbers is indeed part of the analysis, one has to keep in mind that there will be an proportion of patients affected by the general socio-economic, cultural and indeed geographic difficulties. These will always make comparisons to other and especially higher income countries unequal. In a recent estimate, the International Agency for Research on Cancer noted that in "developing countries", about 3 dollars was spent on each cancer patient being included into a registry whereas in "first world countries" the norm was more in the region of 70 dollars. Although a limitation of the study, this will also be an important factor to be highlighted in the discussion section of the results obtained.

8. Logistics, Time Schedule and Action Plan

Please see GANTT Chart included at the end with the appendices.

9. Budget/Resources

Expenses expected to be incurred:

Paper	R340
Printing	R250
Total	**R590**

They are to be covered by the researcher.

10. Reporting of Results

Results will be published in the form a mini-dissertation for Masters in Medicine and as a publication in a journal as per the direction of the research supervisor.

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12. Appendices

GANTT CHART

DATA COLLECTION TOOL PROTOTYPE

GANTT CHART

	2021				2022												2023				
	JUN/JUL	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY
NAMA Course	x																				
Literature study		x	x	x	x																
Protocol writing				x	x	x	x	x	x	x											
Protocol submission											x	x									
Ethics board amendments													x	x	x						
Data collection																x					
Data processing																	x				
Statistical analysis																		x			
Final paper preparation																			x	x	
Final paper submission																					x

DATA COLLECTION TOOL PROTOTYPE

Demographics	Participant number	Comments
Age at presentation		
Year of presentation		
ICD code of tumour type		
Histological type		
Tumour stage at presentation		
Treatment modality		
HIV status		
Ethnicity		To allow comparison to relevant international data
Geographical location		
Outcome		Alive/Dead
Comorbidities		Each risk factor will be assessed against established, accepted or suspected risk factors. In these three categories, the raw data will be analysed and then organised into numerical categories for data analysis. For example, if the patient developed another tumour type as a consequence of radiation then this will be assigned as category 1 and then all category 1 complications can be quantifiable
Risk factors		
Complications		

E Forms for collecting data - e.g., questionnaire/data capture instrument(s)

Codebook

Data Dictionary Codebook

04-09-2023 16:45

Collapse all instruments

#	Variable / Field Name	Field Label *Field Note*	Field Attributes (Field Type, Validation, Choices, Calculations, etc.)
Instrument: **Data Tool** (data_tool)			Collapse
1	record_id	Record ID	text
2	sex	Sex	dropdown 1 Male 2 Female
3	location	Geographical location	dropdown 1 Mangaung Metropolitan Municipality 2 Xhariep District Municipality 3 Lejweleputswa District Municipality 4 Thabo Mofutsanyane District Municipality 5 Fezile Dabi District Municipality 6 Northern Cape 7 Eastern Cape 8 Lesotho 9 Gauteng 10 North West
4	hiv_status	HIV positive	truefalse 1 True 0 False
5	ethnicity	Ethnicity	dropdown 1 Sotho 2 Xhosa 3 Indian 4 Afrikaans 5 European 6 Mixed 7 Zulu

6	year_of_presentation	Year of Presentation	dropdown 2000 2000 2001 2001 2002 2002 2003 2003 2004 2004 2005 2005 2006 2006 2007 2007 2008 2008 2009 2009 2010 2010 2011 2011 2012 2012 2013 2013 2014 2014 2015 2015 2016 2016 2017 2017 2018 2018 2019 2019 2020 2020 2021 2021
7	age_at_presentation	Age at Presentation	dropdown 1 Neonate 2 1month - < 1 year 3 1years - < 2 years 4 2 years - < 3 years 5 3 years - < 4 years 6 4 years - < 5 years 7 5 years - < 6 years 8 6 years - < 7 years 9 7 years - < 8 years 10 8 years - < 9 years 11 9 years - < 10 years 12 10 years - < 11 years 13 11 years - < 12 years 14 12 years - < 13 years 15 13 years -< 14 years 16 14 years - < 15 years 17 15 years - >15 years

8	histology	Tumour histology	dropdown 1 Mature Teratoma 2 Immature teratoma 3 Yolk sac tumour 4 Mixed GCT 5 Embryonal carcinoma 6 Choricarcinoma 7 Gonadoblastoma 8 Germinoma 9 Dysgerminoma 10 Seminoma 11 Sertoli-Leydig Cell Tumours 12 Juvenile Granulosa Cell Tumour 13 Undefined
9	tumour_site	Tumour Site	checkbox 1 tumour_site___1 Left Gonad 2 tumour_site___2 Right Gonad 3 tumour_site___3 Pelvic 4 tumour_site___4 Sacrococcygium 5 tumour_site___5 Abdomen 6 tumour_site___6 Thorax 7 tumour_site___7 Neck 8 tumour_site___8 Face 9 tumour_site___9 Intracranial
10	stage	Stage at Presentation	dropdown 1 Stage 1 2 Stage 2 3 Stage 3 4 Stage 4
11	outcome Show the field ONLY if: 2	Outcome	dropdown 1 Alive 2 Dead
12	if_dead Show the field ONLY if: [outcome] = '2'	If DEAD	dropdown 1 from Metastases 2 from complications of treatment 3 from complications from tumour 4 From unrelated cause 5 Unknown
13	relapse	Relapse	yesno 1 Yes 0 No

14	treatment_modality	Treatment modalities	checkbox 1 treatment_modality___1 Chemothrapy PRIOR to radiotherapy 2 treatment_modality___2 Chemotherapy AFTER radiotherapy 3 treatment_modality___3 Chemotherapy PRIOR to surgery 4 treatment_modality___4 Chemotherapy AFTER surgery 5 treatment_modality___5 Chemotherapy 6 treatment_modality___6 Radiotherapy PRIOR to Surgery 7 treatment_modality___7 Radiotherapy AFTER Surgery 8 treatment_modality___8 Radiotherapy 9 treatment_modality___9 Surgery 10 treatment_modality___10 No treatment
15	type_of_chemotherapy Show the field ONLY if: [treatment_modality(1)] = '1' or [treatment_modality(2)] = '1' or [treatment_modality(3)] = '1' or [treatment_modality(4)] = '1' or [treatment_modality(5)] = '1'	IF Chemotherapy	checkbox 1 type_of_chemotherapy___1 JEB 2 type_of_chemotherapy___2 PEB 3 type_of_chemotherapy___3 BEP 4 type_of_chemotherapy___4 Other
16	tumour_marker_1	AFP	text
17	tumour_marker_2	CEA	text
18	tumour_marker_3	Beta HCG	text
19	complications	Complications	checkbox 1 complications___1 Paralysis 2 complications___2 Incontinence 3 complications___3 Gynaecomastia 4 complications___4 Superior vena cava syndrome 5 complications___5 No complications 6 complications___6 TB 7 complications___7 nephrectomy
20	data_tool_complete	Section Header: *Form Status* Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete

F Calculation of the Age Standardised Rate (ASR) per million per year:

- Total incidence/ 21 years = average incidence per year over 21years
- Average incidence per year over 21years/population under the age of 15years in Mangaung (2011 census) x 1000000 = Age Standardised Ratio per million people per year.

2011 Census: 778624 people under the age of 15

G Instructions to authors of South African Journal of Oncology

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format. Systematic reviews should follow the same basic structure as other original research articles. The aim and objectives should focus on a clinical question that will be addressed in the review. The methods section should describe in detail the search strategy, criteria used to select or reject articles, attempts made to obtain all important and relevant studies and deal with publication bias (including grey and unpublished literature), and how the quality of included studies was appraised, the methodology used to extract and/or analyse data. Results should describe the homogeneity of the different findings, and clearly present the overall results and any meta-analysis.

Original Research Article full structure

Title:

- Full title: Specific, descriptive, concise, and comprehensible to readers outside the field. Max 95 characters (including spaces).
- Tweet for the journal Twitter profile: This sentence/statement will be used on the journal Twitter profile to promote your published article. Max 101 characters (including spaces). If you have a Twitter profile, please provide us your Twitter @ name. We will tag you to the Tweet.

Abstract: The Abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. The Abstract should not exceed 250 words. Please minimize the use of abbreviations and do not cite references in the abstract. Refer to the relevant article type's guideline you are submitting for the abstract sections.

Introduction: The Introduction should put the focus of the manuscript into a broader context and explain its social and scientific value. Address this to readers who are not experts in this field and include a brief review of the key literature. If there are relevant controversies or disagreements in the field, they should be mentioned. Conclude with a brief statement of the overall aim of the experiments and a comment about whether that aim was achieved. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

Methods: The Methods section should provide clarity about how and why a study was done in a particular way. It should provide enough detail for the reproduction of the findings. Protocols for new methods should be included, but well-established methodological procedures may simply be referenced. A full description of the methods should be included in the manuscript itself rather than in a supplemental file. Only information that was available at the time the plan or protocol for the study was being written must be included; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.
The methods section should include:

- The selection and description of participants or description of materials.
- The aim, design and setting of the study.
- The description of the processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses.

- The type of statistical analysis used, including a power calculation if appropriate.

The Methods section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

Results: Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods Section. Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample." Separate reporting of data by demographic variables, such as age and sex, facilitates the pooling of data for subgroups across studies and should be routine unless there are compelling reasons not to stratify reporting, which should be explained.

Conclusion: It is useful to begin the discussion by briefly summarizing the main findings, and exploring possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your findings in the context of the totality of the relevant evidence. State the limitations of your study, and explore the implications of your findings for future research and for clinical practice or policy. Discuss the influence or association of variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses, when warranted and label them clearly.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

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1.1 Background, Literature Review and Research Problem

Introduction:

Neoplasms arising from primordial germline cells in patients less than 18 years, are known collectively as Paediatric Germ Cell Tumours (GCTs). (1) Primordial germ line cells are totipotent, meaning that they have the potential to differentiate into any cell of the organism and indeed, an individual organism as well. Neoplasm refers to an abnormal growth of cells or an inability to initiate appropriate apoptosis. These GCTs are commonly found in extragonadal sites in younger children and gonadal sites in the older age group (2) and this is attributed to the embryonal migration of the primordial cells to the genital ridge. (3)

Embryological development, Types and Classification of Germ Cell Tumours:

Arising from the yolk sac endoderm, primordial germ cells migrate around the hindgut to their final destination on the genital ridge on the posterior aspect of the abdominal wall and there becomes part of the developing gonads. Due to this path of migration, GCTs when they arise, can be seen anywhere in these midline sites from the pineal gland area to the ovaries/testes with the most common site being the sacrococcygeal region. (4)

The migratory primordial germ cell undergoes proliferation and if a deviation from the norm arises at this point, then it may result in the formation of teratomas especially those consisting of all cell lines (endoderm, mesoderm, ectoderm). There also may be differentiation into the yolk sac tumour which under normal differentiation and turnitin

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Title: The demographics of patients with Germ Cell Tumours at a South African Hospital from 2000 to 2021

Authors: Dr K Thottekkat (University of Free State Paediatric Registrar, Free State Department of Health)

Prof J Du Plessis (University of Free State Professor in Paediatric Haematology and Oncology, Head of Clinical Unit at Universitas Academic Hospital)

Abstract:

Background: Paediatric Malignant Extracranial Germ Cell Tumours (MEGCTs) are a rare type of cancer. Available data comes from mostly high-income countries. Aim: To profile the epidemiological data of MEGCTs. Setting: Universitas Academic Hospital (UAH), Bloemfontein. Methods: Retrospective data from the Paediatric Oncology Unit's (POU) database was analysed from January 2000 to December 2021. Results: Over the course of 21 years, 111 patients with germ cell tumours presented to the unit. The average incidence of GCT in our population is 6.4 Age Specific Rate (ASR) per million per year from 2000 until 2021. Mature and Immature Teratomas are the most common histological subtypes seen in our demographic. Conclusion: This study shows the incidence of MEGCTs is higher than that noted in the rest of South Africa (SA), Africa, and other regions of the world. Contribution: Dr K Thottekkat (Author of article, data collection) Prof J du Plessis (Supervisor)

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Report: Chapter 1 - Literature Review

Chapter 1 - Literature Review

by Krishna Thottekkat

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Chapter 2 - The demographics of patients with Germ Cell Tumours at a South African Hospital from 2000 to 2021

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