

Testicular germ cell tumours: Outcomes at a tertiary hospital in the Western Cape, South Africa



Authors:

Gérard Grobler¹ 
 Petrus V. Spies¹ 
 Henriette Burger² 
 Heidi van Deventer¹ 
 André van der Merwe¹ 

Affiliations:

¹Department of Urology,
 Faculty of Health Sciences,
 Stellenbosch University,
 Cape Town, South Africa

²Department of Radiation
 Oncology, Faculty of Health
 Sciences, Stellenbosch
 University, Cape Town,
 South Africa

Corresponding author:

Gérard Grobler,
 gerard.grobler@gmail.com

Dates:

Received: 16 Mar. 2023
 Accepted: 08 Sept. 2023
 Published: 01 Nov. 2023

How to cite this article:

Grobler G, Spies PV, Burger H,
 Van Deventer H, Van der
 Merwe A. Testicular germ cell
 tumours: Outcomes at a
 tertiary hospital in the
 Western Cape, South Africa.
 S. Afr. j. oncol. 2023;7(0),
 a268. [https://doi.org/
 10.4102/sajo.v7i0.268](https://doi.org/10.4102/sajo.v7i0.268)

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Background: Testis cancer is a rare malignancy, and there are limited data describing Africa's clinical characteristics and outcomes.

Aim: We summarised 16 years of South African data, comparing it to available data for Africa and international data.

Setting: The retrospective review included males > 12 years with testicular germ cell tumours diagnosed and treated at Tygerberg Hospital from 01 January 2005 to 31 December 2020.

Methods: Self-declared racial status included Caucasian, mixed ethnicity, African and Asian. Patients were identified from uro-oncology and pathology records indicating any form of testicular cancer. Data were extracted for demographics, staging, treatment and outcomes. In addition, patients were contacted or tracked as part of a living status report by the Department of Home Affairs to determine the last contact date for survival outcomes.

Results: There were 142 patients in the study. The most common risk factor was cryptorchidism (14.1%), but most patients reported no known risk factors (82.4%). Seminomas presented 10 years later than non-seminomatous germ cell tumours (NSGCTs). Having no risk factors seems to be protective hazard ratio (HR) 0.18 and being diagnosed after 40 years carries an increased risk of death. The histopathological classification was fairly equal, with 70 seminoma and 72 NSGCTs. There was no statistical difference in the stage distribution between seminoma and NSGCTs. The overall 5-year survival was 91% for seminoma compared with 78% in NSGCTs. With a time horizon of 15 years, a patient was expected to survive 16% (1.9 years) longer in the seminoma group. Clinical stage (CS) three patients had a higher risk of dying compared with CS1 and CS2, and there was no difference between seminoma and NSGCTs (HR = 12.6).

Conclusion: The clinical characteristics of our patient population correspond to international data. There is a need for better health education to ensure patients present earlier and have access to appropriate medical care.

Contribution: Our data represent the largest series of testis cancer outcomes at a single centre in Africa and the aim is to motivate other centres to describe and analyse their oncological outcomes to ensure we provide the best possible care to all our patients in South Africa's future.

Keywords: Africa/South Africa; testis cancer; demographics; staging; treatment; outcomes.

Introduction

Testicular cancer (TCA) accounts for around 0.5% of malignancies and is primarily found in young males between the ages of 15 and 40 years, with a marked global increase in the incidence over the last five decades.^{1,2,3} The worldwide incidence of testicular germ cell tumours (TGCTs) is between 6 and 11 per 100 000 men and seems to have doubled among Caucasians during this period.³ The increased incidence has been accompanied by decreased mortality because of earlier presentation, standardisation of treatment, a multidisciplinary team approach to management and the use of Cisplatin-based chemotherapy.⁴

The development of the disease is influenced by well-known risk factors such as cryptorchidism, previous TGCT in the contralateral testicle, germ cell neoplasia in situ (GCNIS), testicular microlithiasis, family history of TGCT, and genetic syndromes including testicular dysgenesis syndrome,⁵ a condition characterised by hypospadias, subfertility and disorders of sexual differentiation (DSD).¹

Testicular cancer is currently classified into GCNIS-derived and non-GCNIS-derived tumours as per the 2016 updated WHO pathological classification.⁶ This study mainly focuses on patients with GCNIS-derived tumours and divides them into seminoma and non-seminomatous germ cell

tumours (NSGCTs), comparing clinical staging, treatment and outcomes.¹

The lack of access to gold-standard medical care and resources in low- and middle-income countries (LMICs) may influence the available treatment and outcomes for patients with cancer.⁷ Despite South Africa being a middle-income country, our institution had available resources for complete staging and treatment of TGCT throughout the 16-year reporting period for this cohort. Patients in this cohort were treated according to the most updated European Association of Urologists (EAU) or National Comprehensive Cancer Network (NCCN) TGCT guidelines.

Testicular germ cell tumour is a rare malignancy, and there are limited data describing clinical characteristics and outcomes from African cohorts. A 2020 review by Cassel et al. summarised the findings from eight published retrospective sub-Saharan African TCA cohorts. Of note was the wide variations in staging and management practices, making comparisons of outcomes difficult.⁷ Cassim et al. explored the influence of race on clinical TGCT characteristics in the Western Cape Province of South Africa and found a very low prevalence of black African men among a 15-year tertiary multi-institutional TGCT cohort.³ A recent AORTIC supported survey on patterns of care of TGCT in Africa suggested that TGCTs were predominantly diagnosed at advanced stages, but that resources were available to effectively treat patients. Regional networking through tumour-board discussions was put forward as one strategy to strengthen expertise in low-volume centres and work towards standardisation of staging and management approaches.⁸ Our study aims to report South African data from a 16-year retrospective cohort.

Methods

Data were retrospectively reviewed for males > 12 years of age with TGCTs, diagnosed and treated at Tygerberg Hospital from 01 January 2005 to 31 December 2020. Racial status was self-declared and included Caucasian, mixed ethnicity, African and Asian people. Patients were identified from uro-oncology and pathology records indicating any form of TCA in the National Health Laboratory Service database. Data were extracted for demographics, staging, treatment and outcomes. Patients were contacted directly or tracked as part of the Medical Research Council living status report by the Department of Home Affairs to determine the last contact date or date of death for survival outcomes. Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University.

Patients were staged according to the International Union Against Cancer (UICC) TNM system, for which stage grouping has remained the same from 2002 (6th edition) to 2017 (8th edition), using histological results, CT and post-orchidectomy or pre-chemotherapy tumour markers (human chorionic gonadotropin [HCG], alpha-fetoprotein [AFP] and lactate dehydrogenase [LDH]).⁶ Those who presented with

metastatic disease were further classified according to the 1997 International Germ Cell Cancer Collaborative Group (IGCCCG) risk grouping system.⁸

During follow-up, treatment response was monitored using clinical examination, tumour markers and repeat imaging to determine oncological outcomes: remission, refractory disease and relapse (early or late). Outcomes are reported by histopathological subgroup and stage.^{9,10}

All retrospective data were captured in a de-identified REDCap (Research Electronic Data Capture) database. The REDCap is a secure web application for building and managing online surveys and databases. The demographic and clinical variables were summarised in tables and graphs to represent the study's primary objective. Descriptive statistics such as frequencies, percentages, means and standard deviations were calculated overall and by cancer type. Then, cross-tabulations by cancer type with categorical variables were carried out and the chi-square test was performed to test for associations. Survival analysis for time to death was performed with surviving participants censored at the date of the last follow-up. The Kaplan-Meier survival curves of the cancer type and age group were compared using a log-rank test. The restricted mean survival times with 95% confidence intervals were estimated for cancer types for a 15-year truncation time. A multiple Cox regression model was used to model the time to death on cancer type, cancer stage, age, presence of cryptorchidism, no known risk factor present and ethnicity. Hazard ratios were estimated with 95% confidence intervals. A significance level of 5% was used. Stata 17 software was used to perform the analysis.

Ethical considerations

Ethical clearance to conduct this study was obtained from the Stellenbosch University Health Research Ethics Committee (No. S20/08/193).

Results

Clinical characteristics

There were 142 patients included in the study, of which 88 overlapped with the cohort reported on by Cassim et al.³ The mean age was 32 years (range 16–63 years, standard deviation [s.d.]: 9.21), with patients with NSGCT presenting 10 years younger than those with seminomas ($p < 0.01$). The histological subtype of tumours described was mainly derived from GCNIS and divided equally among the two groups into seminoma (49.3%) and NSGCTs (50.7%). Detailed clinical characteristics are reported in Table 1.

The most common risk factor identified was cryptorchidism (14.1%), followed by testicular atrophy (3.5%). Most of the patients self-identified as mixed ethnicity (52.8%), followed by Caucasians (38%). There was no statistically significant correlation between ethnicity and histological TGCT subtype.

Staging

Figure 1 shows the stage distribution according to the Union of International Cancer Control (UICC) stage groups. There was no statistically significant difference in the stage distribution by histological subtype ($p = 0.116$), although there was a higher prevalence of clinical stage (CS) 3 cases in NSGCTs (41.7%) as compared with seminoma (27.1%).

Treatment

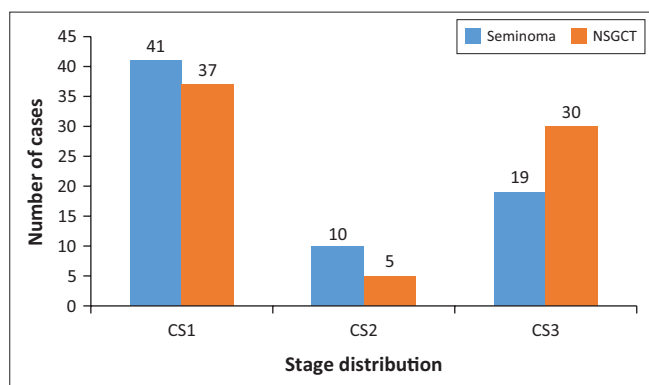
First-line treatment by histological subtype and CS is shown in Table 2 and second-line treatment in Table 3.

Outcomes of patients after receiving primary treatment are described in Table 4.

TABLE 1: Clinical characteristics of total number of participants in the study.

Variable	n	%	Mean age	Distribution
Histological subtype	-	-	32	16–63
Seminoma	-	-	37	19–63
NSGCT	-	-	27.1	16–44
Seminoma	70	49.3	-	-
Pure	67	95.7	-	-
With syncytiotrophoblast cells	3	4.3	-	-
NSGCT	72	50.7	-	-
Mixed GCT	58	80.6	-	-
Embryonal carcinoma	10	13.9	-	-
Yolk sac tumour, post-pubertal type	3	4.2	-	-
Teratoma, post-pubertal type	1	1.4	-	-
Risk factors			-	-
None stated	117	82.4	-	-
Cryptorchidism	20	14.1	-	-
Testicular atrophy	5	3.5	-	-
Family history of TGCT	2	1.4	-	-
Subfertility	2	1.4	-	-
Previous contralateral TGCT	1	0.7	-	-
Associated DSD	1	0.7	-	-
Ethnicity			-	-
Mixed ethnicity	75	52.8	-	-
Caucasian	54	38.0	-	-
African people	8	5.6	-	-
Asian people	5	3.5	-	-

NSGCT, non-seminomatous germ cell tumour; GCT, germ cell tumour; TGCT, testicular germ cell tumour; DSD, disorders of sexual differentiation.



NSGCT, non-seminomatous germ cell tumour; CS1, 2, 3, clinical stage 1, 2, 3.

FIGURE 1: Stage distribution according to the Union of International Cancer Control stage groups.

Survival outcomes

The median follow-up time was 6.1 years (range 0.04–17.2 years). The Kaplan–Meier survival estimates comparing the overall survival between seminoma and NSGCT are shown in Figure 2, and a summary of the available 15-year data in Table 5. Using a restricted mean survival analysis with a time horizon of 15 years, we calculated and included the mean expected survival in Table 5. There was a significant difference in the overall survival curves between the two histological subtypes ($p = 0.03$), with a 5-year OS for NSGCT of 78% and 91% for seminoma.

The Kaplan–Meier survival estimates comparing overall survival of seminoma and NSGCT by their CS can be seen in Figure 3. A summary of the available 15-year data is shown in Table 6. The numbers were limited for 10- and 15-year survival outcomes, with the CI over 30%. Clinical stage 3 seminomas had no events after 2 years, which is the only

TABLE 2: First line treatment by histological sub-type and clinical stage.

Primary treatment	CS1		CS2		CS3	
	n	%	n	%	n	%
Seminoma (n = 70)						
Orchidectomy alone (defaulted)	1	1.4	1	1.4	0	-
Orchidectomy and surveillance	4	5.7	0	-	0	-
Orchidectomy and chemotherapy	36	51.4	9	12.9	18	25.7
Definitive RT and chemotherapy	0	-	0	-	1	1.4
NSGCT (n = 72)						
Orchidectomy alone (defaulted)	1	1.4	0	-	1	1.4
Orchidectomy and surveillance	5	6.9	0	-	0	-
Orchidectomy and chemotherapy	31	43.1	5	6.9	27	37.5
Orchidectomy and chemotherapy and RPLND	0	-	0	-	2	2.8

NSGCT, non-seminomatous germ cell tumour; RT, radiotherapy; RPLND, retroperitoneal lymphnode dissection; CS, clinical stage.

TABLE 3: Second line treatment by histological sub-type and clinical stage.

Secondary treatment	CS1	CS2	CS3
Seminoma (n = 6)			
Salvage chemotherapy	1	0	1
Radiotherapy	0	0	2
Salvage chemotherapy and other† treatment	0	0	2
NSGCT (n = 14)			
Salvage chemotherapy	1	0	2
Salvage chemotherapy and other† treatment	3	1	6
Defaulted	0	0	1

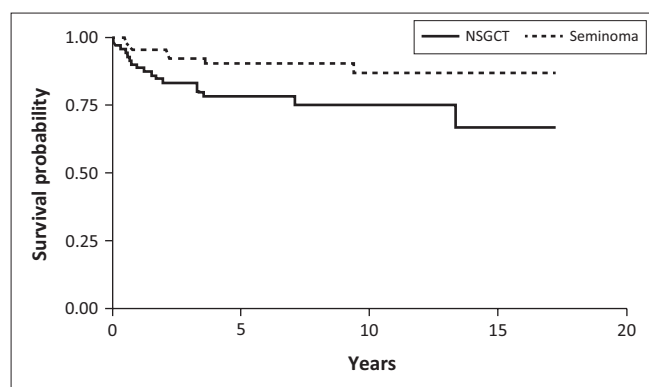
NSGCT, non-seminomatous germ cell tumour; CS, clinical stage; RPLND, retroperitoneal lymphnode dissection.

†, 'Other' is defined by +/- RPLND, radiotherapy and residual mass excision – it was not offered as a single treatment option in this group.

TABLE 4: Outcomes after receiving primary treatment.

Outcomes	Total		Seminoma	NSGCT
	n	%		
Defaulted	4	2.8	2	2
Relapse	7	4.9	2	5
Early	4	-	1	3
Late	3	-	1	2
Refractory	13	9.2	4	9

NSGCT, non-seminomatous germ cell tumour.



NSGCT, non-seminomatous germ cell tumour.

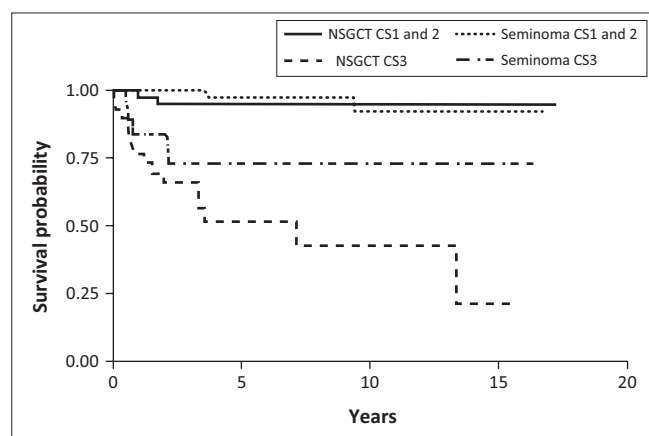
FIGURE 2: Kaplan–Meier survival estimates comparing the overall survival between seminoma and non-seminomatous germ cell tumour.

TABLE 5: Summary of available 15-year data.

Histological subtype	5-year OS (%)	10-year OS (%)	15-year OS (%)	Mean expected survival†
Seminoma (n = 70)	91	87	87	13.6 years
NSGCT (n = 72)	78	75	67	11.7 years

NSGCT, non-seminomatous germ cell tumour; OS, overall survival.

†, Median survival was not reached because less than 50% of patients died during our study timeline; therefore, the mean expected survival is reported.



NSGCT, non-seminomatous germ cell tumour; CS1, 2, 3, clinical stage 1, 2, 3.

FIGURE 3: Kaplan–Meier survival estimates comparing the overall survival between seminoma and NSGCT and their clinical stage.

difference comparing CS3 survival curves between the seminoma and NSGCTs ($p = 0.508$). Overall, CS3 patients had a higher risk of dying than CS1 and CS2 (HR = 12.6 [95% CI: 4.0–39.4], $p < 0.001$).

Tumour type, age, ethnicity and the presence of risk factors were not significant predictors of mortality. When comparing age groups, the highest risk of death was found in patients older than 40 years (29.2%). Four of the eight black African patients died (causes of death are unconfirmed), and the other half went into remission. The four black African patients who died all presented with stage 3C disease.

Discussion

Our study analysed the clinical characteristics and outcomes of TGCT patients who were treated at a single tertiary hospital in the Western Cape Province of South Africa over a 16-year

TABLE 6: Testicular germ cell tumours overall survival estimates by histological subtype and clinical stage.

Clinical stage and histological subtype	5-year OS (%)	10-year OS (%)	15-year OS (%)	Median OS (years)
CS1 and CS2				
Seminoma (n = 51)	98	93	93	†
NSGCT (n = 42)	95	95	95	†
CS3				
Seminoma (n = 19)	73	73	73	†
NSGCT (n = 30)	52	43	21	7 years

NSGCT, non-seminomatous germ cell tumour; CS, clinical stage; OS, overall survival.

†, The available data did not provide enough information to calculate median overall survival for the other groups, as there were too few patient deaths in those groups.

period. The ratio of seminoma to non-seminoma in this cohort was 1:1, which is nearly identical to the ratio reported for sub-Saharan Africa by Cassel et al. (1.1:1) and international reported trends.^{7,11}

Age at presentation also aligns with international findings that seminomas (mean age 37 years) present on average 10 years later than NSGCTs (mean age 27 years).^{1,11} The ethnic distribution in the cohort did not follow the Western Cape Province's demographic distribution of mixed ethnicity (49%), African (33%), Caucasian (17%) and Asian (1%) (2011 STATS SA census). It showed a marked predominance of men of mixed ethnicity (53%) and Caucasians (38%) and significant underrepresentation of black African males (6%). This finding is in keeping with the data from Cassim et al., demonstrating an increased prevalence among these two groups and confirming the low incidence in the local black African population.³ Cryptorchidism is typically found in the history of about 5% – 10% of patients with TCA. There was a slightly higher prevalence of 14.1% in our group.¹² A possible contributing factor to the higher prevalence could be the late presentation and delays in corrective surgery for patients with cryptorchidism in our population.^{13,14}

Clinical stage 1 disease is found at diagnosis in 75% – 80% of seminoma and about 55% – 64% of NSGCTs in developed countries. In our study, only 58.6% of seminomas and 51.4% of NSGCT were CS1. These findings suggest that seminomas are diagnosed at later stages in our study population. True CS 1S is usually found in about 5% of NSGCT diagnoses, but in our cohort, around 41.7% had persistent elevated tumour markers post-orchidectomy.¹⁵ This could suggest the presence of micro-metastasis and radiological understaging in these patients.

Surveillance after orchidectomy was only offered to a small number of patients in the CS1 group because of the increased need for labour-intensive follow-up and historically poor patient retention patterns in our population.¹⁶ One patient in the NSGCT CS1 group relapsed on surveillance within 2 years of his orchidectomy. All other patients received Cisplatin-based adjuvant combination chemotherapy per the EAU guidelines for their CS. The relapse rate after adjuvant chemotherapy for CS1 disease was 6%, higher than the current rate of 3% reported in high-volume centres.⁹ This may be explained by the high incidence of CS 1S disease.

A study in the Netherlands by Verhoeven et al. demonstrated a 5-year survival of 99% – 100% in CS1 seminoma patients, 93% – 100% in CS2 patients and 73% – 88% in CS3 patients. Non-seminomatous germ cell tumour had a 5-year relative survival for CS1 of 98% – 99%; CS2 varied between 94% and 98%; and patients with CS3 varied from 78% to 85%.¹⁷ The 5-year overall survival outcomes for this cohort by CS are comparable to those reported in developed countries for CS1 and CS2 TGCT (seminoma 98%, NSGCT 95%) and even for CS3 seminoma (73%). The outcomes for CS3 NSGCT are, however, inferior at 52%. Our survival outcomes were much closely aligned with outcomes from the developed world than with those reported from the African continent where 5-year OS ranged from 22.2% to 47%.^{7,18,19,20,21} This may be because of more accurate staging and appropriate upfront treatment, as well as offering RPLND as primary or secondary treatment options when indicated. The increased mortality in CS3 patients may be attributed to their extensive disease and late presentation, making access to standard medical care even more difficult.⁷

This study was limited by its retrospective design, the potential for incomplete records and smaller sample sizes in the 10–15-year survival groups, which decreases the possibility of finding statistical significance. In addition, the ethnicity was self-reported by patients. Finally, the study was conducted at a major academic referral centre in the Western Cape but may not represent the outcomes for the whole country and therefore decreases the generalisability of the study findings.

Conclusion

This study demonstrated that our patient population has similar clinical characteristics to those described internationally. Outcome measures are mostly comparable to those from developed countries, with room for improvement in the management of CS3 NSGCT. Access to gold-standard medical care and appropriate resources can improve outcomes, as seen when comparing our data with data from other sub-Saharan African countries.⁷ There is a need for better health education to ensure patients present earlier follow up and access appropriate medical care. There is potential for supportive collaboration using modern technology to connect high-volume treatment centres such as ours with other centres in Africa to improve TGCT outcomes across the continent.

Acknowledgements

The authors would like to acknowledge C.J. Lombaard from the Division of Epidemiology and Biostatistics, Department of Global Health, University of Stellenbosch, Bellville, Cape Town, South Africa, assisted with the statistical analysis.

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

G.G. conceptualised the research with the support of P.V.S., H.B., H.v.D. and A.v.d.M. G.G. wrote the protocol and applied for ethical approval with the help of H.v.D. G.G. collected the data. G.G. wrote the manuscript with the support of the co-authors P.V.S., H.B., H.v.D. and A.v.d.M.

Funding information

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data availability

De-identified data that support the findings of this study are available from the corresponding author, G.G., upon reasonable request.

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