

# Specialist management of testicular cancer: Report of the last 10 years at a Portuguese tertiary referral academic centre

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**Summary** *Objectives: To describe our experience on testicular cancer (TC) management, underlining the clinical/pathological scope, administered treatments, outcomes, and challenges. TC incidence is rising globally. The predominant histology is germ cell tumour (GCT). In most patients, orchiectomy is curative. Still, a significant proportion of patients will need further tailored treatment. Specialist Reference Centres have proven themselves successful in this setting. Published data regarding TC in Northern Portugal is lacking. Methods: Retrospective review of consecutive TC patients at a specialist tertiary referral academic centre between January 2010 and December 2020. Statistical analysis was performed using the STATA® version 13.1 software. Multivariate logistic and survival analyses were performed. Results: 125 patients met the inclusion criteria. The median age is 35 (28-40) years; 19% of patients had risk factors for TC – infertility being the most common (11%); 50% of patients wanted sperm cryopreservation prior to treatment; 68% of patients had stage I GCT, 16% stage II, and 17% stage III. Compared to seminoma, non-seminomatous GCT were associated with younger age ( $p < .001$ ) and higher stages at diagnosis ( $p = .02$ ); 24% of stage IA/B GCT underwent adjuvant chemotherapy; 47% of patients with metastatic GCT at presentation had refractory disease, requiring tailored treatment. The median follow-up time is 33 (13-65) months. There was no late relapse. The 5-year OS rate is 98.0%. The 5-year survival of metastatic disease is 95.8%. Conclusions: Despite contemporary excellent cure rates, the challenges of testicular cancer management still endure, especially in advanced stages. Therefore, public awareness is recommended, in order to avoid late presentations - special attention should be given to those who have known risk factors. The existence of Reference Centres is of paramount importance in order to achieve the best outcomes possible.*

**KEY WORDS:** Testicular cancer; Germ cell tumour; Reference centre; Metastatic disease; Relapse; Risk-adapted treatment.

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## INTRODUCTION

Testicular cancer (TC) accounts for approximately 1% of all male cancers worldwide (1). Over recent decades, its

incidence has steadily increased, predominantly in more developed countries, up to 1/10.000 person-years (2).

In many patients, TC is associated with high psychological and physiological burden (3).

Risk factors for developing TC are the presence of the other components of the *testicular dysgenesis syndrome* (TDS) – cryptorchidism, hypospadias, and sub-/infertility (4); familial history of TC in first-grade relatives (5); and personal history of a contralateral TC (6). The predominant histology is *germ cell tumour* (GCT) in over 90% of cases (7). The most common CGT are derived from *germ cell neoplasia in situ* (GCNIS), comprising seminoma and *non-seminomatous* (NS)GCT – embryonal carcinoma, teratocarcinoma, post-pubertal teratoma, post-pubertal yolk sac tumour, choriocarcinoma, and mixed GCT; GCNIS-unrelated GCT include pre-pubertal GCT and spermatocytic tumours; there is also a minority of non-GCT that includes sex cord/stromal tumours (derived from Leydig cells, Sertoli cells or granulosa cells) and secondary cancers (8). TC typically presents as a painless testicular mass or as an incidental *ultrasound* (US) finding, albeit a significant minority of patients refer pain, either scrotal or in the flank (9).

The diagnostic evaluation of TC, with few exceptions, includes physical examination, imaging [testicular US and *computerised tomography* (CT) of the thorax, abdomen, and pelvis], serum tumour markers (alpha-fetoprotein, beta subunit of human chorionic gonadotropin, and lactate dehydrogenase), and radical orchiectomy (1).

The anatomical extent of the disease should be documented in appropriate staging and classification systems (1, 10), in order to initiate adequate early treatment thus improving patients' outcome.

In most patients, orchiectomy is curative, therefore the prognosis is good. Those with metastatic TC may benefit from cisplatin-based chemotherapy regimens [specifically a combination of bleomycin, etoposide, and cisplatin (BEP)], due to generally high GCT chemosensitivity – this results in excellent cure rates, overall (11).

Still, there is a significant minority of patients that need further tailored treatment, such as *retroperitoneal lymph node dissection* (RPLND)/residual mass excision or sal-

vage chemotherapy; in rare cases, high-dose chemotherapy with autologous stem cell support may be needed (12). Thus, there is a worldwide trend towards establishing Reference Centres, which have proven themselves successful by their multidisciplinary approach, meticulous follow-up, and suitable salvage therapies (13). Since 2016, the *Centro Hospitalar Universitário do Porto* is an official Reference Centre in TC management, in collaboration with the *Instituto Português de Oncologia do Porto*, on a national level (Despacho n.º 3653/2016). This study aims to describe our experience on TC management, underlining the clinical and pathological scope, administered treatments, outcomes, and challenges.

## METHODS

A retrospective review was performed, comprising consecutive adult patients who had pathologically confirmed TC at a specialist tertiary referral academic centre, *Centro Hospitalar Universitário do Porto*, between January 2010 and December 2020, after institutional review board approval. All cases were discussed in a multidisciplinary tumour board. Exclusion criteria comprised primary extragonadal GCT, and incomplete data in any of the key variables. Relevant information was collected from medical records regarding age, clinical presentation/referral, risk factors, staging [according to the 2016 Tumour, Node, Metastasis classification of the *International Union Against Cancer*, respective prognostic groups, and the *International Germ Cell Cancer Collaborative Classification* for metastatic testicular cancer (1, 10)], pathology, systemic treatment, follow-up, special management problems and outcome.

### Statistical analysis

Statistical analysis was performed using the STATA® version 13.1 software. Results for continuous variables were expressed as mean  $\pm$  standard deviation or as median (interquartile range) according to its distribution. The chi-square test was applied to compare categorical variables. Independent sample Student t-test and one-way ANOVA were used to compare continuous variables. Univariate and multivariate linear and logistic regression analyses were performed according to the variables and expressed as a coefficient or *odds ratio* (OR) and respective 95% confidence interval (95%CI). A survival analysis was performed in order to calculate the *overall survival* (OS) rate. A *p* value  $< .05$  was considered statistically significant.

## RESULTS

The initial study cohort consisted of 129 patients. Those with primary extragonadal GCT ( $n = 1$ ) and incomplete data ( $n = 3$ ) were excluded to give the final cohort for analysis of 125 patients who met the inclusion criteria. There was a 60% increase in the number of patients with newly diagnosed TC since 2016 (2010-2015  $n = 48$  versus 2016-2020  $n = 77$ ). The median patient age is 35 (28-40) years. All patients are *European Caucasians*. Overall, 24 patients (19%) had a confirmed risk factor for TC – cryptorchidism ( $n = 5$ ,

4.0%), infertility ( $n = 14$ , 11%), family history of TC ( $n = 2$ , 1.6%), and personal history of contralateral TC ( $n = 3$ , 2.4%). The majority of patients presented with a testicular mass ( $n = 73$ , 60%) and/or testicular pain ( $n = 42$ , 35%). A significant proportion of patients presented with an incidental US finding ( $n = 30$ , 25%), some of them in the workup of a retroperitoneal mass ( $n = 10$ , 8.0%) or gynecomastia ( $n = 5$ , 4.0%). Altogether, there was no difference between the number of patients that presented with left sided TC ( $n = 63$ , 50%), versus right sided TC ( $n = 62$ , 50%). One patient presented with synchronous bilateral TC.

After thorough anamnesis and physical examination, a scrotal US was performed on the same day, if not previously done. A minority of patients ( $n = 15$ , 12%) had a scrotal US on the following days. A staging CT was performed upfront preferably, though it did not delay radical orchiectomy, which was performed as quickly as possible, within the reference interval – 7 days after the first contact. The majority ( $n = 75$ , 66%) desired for a testicular prosthesis to be implanted in the same procedure, irrespective of age (OR = .96,  $p = .10$  95%CI [.92-1.00]). All men were offered sperm cryopreservation prior to starting treatment (with a few exceptions of life-threatening disseminated disease), and a significant proportion chose to do so ( $n = 59$ , 50%) – that decision was inversely related to age (OR = .90,  $p < .001$  95%CI [.86-.95]). Pathological exam reported GCT in 87% of patients (Table 1) – of those, the most frequent was pure seminoma, followed by NSGCT, and mixed seminoma-NSGCT. Almost half the NSGCT consisted of embryonal carcinoma ( $n = 22$ , 48%), either pure or as the major component of mixed GCT. The median tumour size was 30 (17-50) millimetres. Notably, there was a histological scar and no evidence of primary tumour in a significant minority ( $n = 6$ , 4.8%) – five patients that were diagnosed with burned-out testis tumour and one patient that underwent chemotherapy before orchiectomy – all these patients had histological confirmation of metastatic GCT.

Two thirds of patients had stage I GCT, while roughly one third presented with advanced disease (Table 1). Compared to seminoma, NSGCT were associated with younger age ( $28.7 \pm 5.3$  vs.  $36.1 \pm 7.8$ ,  $p < .001$ ) and higher stages at diagnosis (22 vs. 13,  $p = .02$ ).

A significant proportion of stage IA/B GCT underwent adjuvant chemotherapy (Table 2), according to risk factors for metastatic relapse – either carboplatin in seminoma or BEP in NSGCT. No patient underwent adjuvant radiotherapy. There were a few stage IA/B GCT that relapsed (Table 2), requiring systemic salvage treatment followed, whenever appropriate, by RPLND – seminoma was found in one case, and fibrosis in another. None of them had had adjuvant chemotherapy.

Regarding metastatic GCT at presentation (that is, stage IS and higher), all patients ( $n = 43$ ) underwent primary BEP chemotherapy, according to prognostic based groups – in good prognosis ( $n = 32$ , 74%), BEPx3 (one patient had cisplatin plus etoposide x4 due to previous pulmonary disease), and in intermediate/poor prognosis ( $n = 11$ , 26%), BEPx4. Chemotherapy started as soon as possible after multidisciplinary discussion. Most patients had tumour marker decline and regressive TC radiologi-

**Table 1.**  
Characteristics of participants at diagnosis by histological type.

	Seminoma	NSGCT	Mixed S-NSGCT	SCST **	Total ***
Patients, n (%)	63 (50%)	34 (27%)	12 (9.6%)	14 (11%)	125
Age, years*	36.1 ± 7.8	28.7 ± 5.3	36.2 ± 7.2	41.7 ± 12.2	35.1 ± 9.3
Stage, n (%)					
I	50 (79%)	17 (50%)	7 (58%)	-	75 (68%)
II	7 (11%)	9 (26%)	1 (8.3%)	-	17 (16%)
III	6 (10%)	8 (24%)	4 (33%)	-	18 (17%)

GCT: Germ cell tumour; NSGCT: Non seminomatous GCT; S NSGCT: Seminoma NSGCT; SCST: Sex cord/stromal tumours; SD: Standard deviation. Estimates were given as mean ± SD\* or frequency (percentage). \*\*: All SCST were Leydig cell tumours; \*\*\*Includes one case of spermatocytic tumour and one case of testicular lymphoma.

**Table 2.**  
Disease management of GCT by histological type.

	Seminoma	NSGCT	Mixed S-NSGCT	Total
Stage IA/B GCT	50 (77%)	9 (14%)	6 (9%)	65
Adjuvant chemotherapy	11 (22%)	3 (33%)	2 (33%)	16 (25%)
Salvage chemotherapy	1 (2.0%)	1 (11%)	1 (17%)	3 (4.6%)
RPLND	0	1 (11%)	1 (17%)	2 (3.1%)
Viable GCT	-	-	1 (100%)	1 (50%)
Teratoma	-	-	-	-
Fibrosis	-	1 (100%)	-	1 (50%)
Persistent/relapsing metastatic GCT	4 (20%)	11 (55%)	5 (25%)	20
Salvage chemotherapy	2 (50%)	2 (18%)	1 (20%)	5 (25%)
RPLND	2 (50%)	11 (100%)	4 (80%)	17 (85%)
Viable GCT	-	3 (27%)	-	3 (18%)
Teratoma	-	4 (36%)	2 (50%)	6 (35%)
Fibrosis	2 (100%)	4 (36%)	2 (50%)	7 (41%)

GCT: Germ cell tumour; NSGCT: Non seminomatous GCT; RPLND: Retroperitoneal lymph node dissection; S NSGCT: Seminoma NSGCT. Estimates were given as frequency (percentage).

**Table 3.**  
Multivariate logistic regression to predict refractory GCT.

Variable	OR	95%CI	p value
Age (years)	1.1	.99-1.2	.09
Histological group			
Seminoma	Reference	-	
NSGCT	12.3	1.9-78.5	< .01
Mixed S-NSGCT	16.3	2.1-125.2	< .01
Stage			
I	Reference	-	
II	4.6	1.0-21.9	.05
III	28.9	6.2-134.1	< .001

GCT: Germ cell tumour; NSGCT: Non seminomatous GCT; S NSGCT: Seminoma NSGCT; 95%CI: 95% confidence interval; OR: Odds Ratio.

cal features at repeated evaluations. Of note, no patient with stage IIA/B seminoma underwent primary radiotherapy.

Almost half the patients with metastatic GCT (n = 20, 47%) presented refractory disease (Table 2), requiring systemic salvage treatment and/or RPLND. The chosen salvage chemotherapy regimen consisted of cisplatin, ifosfamide, and either paclitaxel (n = 3) or vinblastine (n = 2). There was one cisplatin-refractory NSGCT that remitted after second salvage combination of gemcitabine and oxaliplatin. Regarding RPLND (Table 2), viable GCT was found in a significant minority of these

patients, while the majority had either teratoma or fibrosis. Regarding persistent disease/relapse, a logistic model adjusting for age, histological type and stage was found [chi2 (5) = 46.45, p < .001]: when compared to seminoma, NSGCT and mixed seminoma-NSGCT were associated with higher chances of disease persistence/relapse (Table 3); furthermore, higher stages were associated to higher chances of persistent disease/relapse when comparing with stage I GCT.

The median follow-up time is 33 (13-65) months (n = 125). There was no record of late relapses. The 5-year OS rate is 98.0% – there were two patients that died: one with stage IIIC NSGCT, and other with malignant Leydig cell tumour; the remaining patients are in remission. Stratifying by histological type, 5-year OS is lower for NSGCT (96.8%) than for seminoma (100%). Regarding stage, the 5-year survival of metastatic disease is 95.8%. A minority of GCT patients was lost to follow-up within the 5-year period after diagnosis (n = 7, 5.6%).

## DISCUSSION

In this cohort, the majority of patients was in the third/fourth decade of life, which is in concordance with the available literature (2). Since the encompassed population for reference centres in Northern Portugal is not strictly demarcated, and some patients are treated in private practice, no conclusions can be made regarding regional trends in TC incidence. However, our institution has noticed a much higher referral numbers over the last years, since we became an official Reference Centre for TC management.

The main predictor of TC development appears to be the presence of any component of the TDS, which may share genetic and/or environmental triggers (4). In fact, a significant proportion of patients in this cohort consists of patients with TDS whose TC might have gone unnoticed for a longer period had they not undergone testicular imaging. A large proportion of TC (up to 25%) seem to be genetically linked (14). However, in this cohort, only a negligible proportion of patients reported familial history of TC in first grade relatives.

Early detection and referral of TC leads to improved overall survival rates. Actually, routine scrotal US in patients with TDS, specifically those presenting with a personal history cryptorchidism and sub-/infertility, may detect TC in its earlier stages, for which orchiectomy is curative. On the other hand, while testicular pain may lead to earlier presentation, we did not find any difference in TC stages when stratifying by pain. Despite the increasing awareness for TC among young men and their partners, roughly one third of patients presented with metastatic disease. This may arise from ignorance, carelessness, shame, fear, denial, rurality, and reliance in alternative medicine. The definitive reasons cannot be assessed in this cohort.

In this cohort, as reported in literature (1), the majority of GCT consisted of seminoma, whereas NSGCT presented earlier and behaved more aggressively. Overall, GCT accounted for 87% of cases, which is slightly below what is commonly reported (7). This may be due to a higher proportion of sex cord/stromal tumours, namely

Leydig cell tumours, which accounted for 11% of cases, which is roughly 5-fold the proportion historically mentioned in literature (15). We could not establish the reasons for this pathological difference.

The pivotal step of TC treatment is radical orchiectomy, which is a procedure associated with fairly low morbidity as it allows early control of testicular lymphovascular supply, as well as *en bloc* removal of the specimen (1). Usually, with proper counselling, patients are not reluctant to undergo surgery as the possibilities of sperm cryopreservation and prosthesis implantation are reassuring for both fertility and aesthetics, whenever patients may find those issues relevant. Remarkably, the proportion of patients that presented with advanced disease with no histological evidence of a primary TC other than a scar is similar to that of recent reports (16).

After orchiectomy, further treatment depends on both clinical staging and the pathology report. In this cohort, the majority of patients underwent chemotherapy at any point (adjuvant, primary or salvage) with good compliance and tolerance, overall. In this cohort, no patient underwent adjuvant/primary radiotherapy. The scrupulous follow-up plan might have led to timely identification of relapses and quick tailored treatment, which could explain the low mortality in this cohort. In fact, the multidisciplinary approach that exists in our centre, among other factors, seems to lead to a 5-year OS rate of 98.0% and, in metastatic disease, to a 5-year survival of 95.8%, which is higher than what has been recently reported (7, 17).

In this cohort, there seems to exist a stronger association between mixed seminoma-NSGCT and disease persistence/relapse than in other histological types, which is in concordance with recent reports that show a seminoma component in mixed GCT might be associated with more aggressive disease (18). Yet, we could not determine whether it is a true association or not, as it may be confounded by the relative proportion of other NSGCT components.

The major limitation of this study is its retrospective nature, which may have led to some bias, specifically in what concerns risk factors other than those mentioned. Furthermore, the follow-up median is still below 5 years. In addition, genetic studies are not routinely undertaken at our centre, therefore no specific genetic counselling could be offered.

Overall, according to data, our centre offers state-of-the-art treatment for TC. In the future, we hope to help to develop a national database, in order to uniformise medical records and standardise clinical procedures.

## CONCLUSIONS

Despite contemporary excellent cure rates, the challenges of testicular cancer management still endure, especially in what concerns advanced stages. Late presentation, regardless of the underlying causes, may correlate to higher stages, and represents a major shortcoming even in more developed countries, such as Portugal. Therefore, increasing public awareness and education in schools, primary care, and media is recommended – special attention should be given to those who have known

risk factors for testicular cancer. Furthermore, the inclusion of testicular self examination in school curricula might be considered, seeking to detect testicular cancers at a lower stage. The existence of Reference Centres is of paramount importance in order to achieve the best outcomes possible.

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## ETHICS APPROVAL

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The *Institutional Human Investigation Committee* (IRB) approved this study.

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