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Original Article

Factors Influencing the Response Rate and Survival of Testicular Germ Cell Tumors: A Single Institution Experience from Egypt

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Abstract

Background: Testicular germ cell tumors (TGCTs) are the most common cancer in young adult males, and they represent one of the most curable solid tumors. The treatment modalities of different stages are variable among centers.

Aim: To describe the management of TGCTs and its outcome in an Egyptian cancer center.

Methods: The medical records of patients with TGCT treated between January 2012 and December 2016 were retrospectively reviewed. Thirty-two patients were included. Demographic, clinical, treatment, and outcome data were analyzed.

Results: The median age of the patients was 34.5 years. The most common presentation was unilateral painless testicular mass (87.5%). Seminoma represented 53% of cases and almost half of them had Stage I disease. For all patients, the clinical stage and International Germ Cell Cancer Collaborative Group (IGCCC) risk classification were significantly associated with survival outcomes. Five-year overall survival for stage I patients was 100%, compared to 87.5% for stage II ($p<0.0001$). Patients with good risk had a 5-year OS of 87.4% while none of the poor risk group survived for 5 years ($p =0.002$). The 5-year disease-free survival for stage I was 83% for those who remained under active surveillance versus 87.5% for those who received adjuvant carboplatin ($p=0.364$).

Conclusions: Stage I TGCTs has an excellent overall survival regardless of the treatment modality received. In advanced disease, the clinical stage and IGCCC risk stratification remain valid prognostic risk factors.

Keywords: Testicular germ cell tumors, Treatment, Prognosis, Egypt
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Introduction

Testicular cancer is the most commonly diagnosed malignancy in young adult men [1]. There is marked geographical variation in the age-standardized incidence rate for testicular cancer, ranging from as low as 1.86/100,000 in Egypt [2] to as high as 9.2/100,000 in Denmark [3].

Although the overall incidence of testicular tumors is rare (about 1% of all male malignancies), testicular germ cell tumors (TGCT) are the most common among them. In post pubertal males, 95% of testicular tumors arise from germ cells and the majority of cases occur between the ages of 20 to 35 years [4].

TGCTs are classified into seminoma and nonseminoma (NSGCT). Classic seminoma account for 50% of TGCT with peak age of 40 –50 years. NSGCT include embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratoma, and mixed tumors [5, 6].

There is a paucity of data on testicular germ cell cancer management in Egypt. In the present study, our objective was to describe the treatment of these rare tumors in a single Egyptian institution and to determine factors that may impact survival results. This is expected to guide further improvement in the quality of care of our patients.

Methods

This is a retrospective study of the medical records of patients with pathologically proven TGCTs who had been treated at Kasr Al-Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK) from January 2012 to December 2016. Only patients with complete clinical data were enrolled in the present study.

The collected data included: demographic characteristics, date of diagnosis, presenting symptoms, comorbidities, pathological subtype, tumor size, clinical stage, tumor markers (alpha fetoprotein [AFP], Beta human chorionic gonadotropin [B-HCG], and lactate dehydrogenase [LDH]), treatment received, and survival outcome.

Staging was carried out according to the updated 8th edition of the AJCC/UICC staging system for testicular cancer [7]. Stage IIA or higher were further stratified according to International Germ Cell Cancer Collaborative Group risk classification (IGCCC) into good, intermediate, and poor risk groups.

Radiotherapy for para-aortic lymph nodes was given as 3D conformal RT using A-P/P-A fields on a LINAC machine. The dose ranges from 21.6 Gy/12 fractions to 30 Gy / 15.

Regarding response assessment, complete remission (CR) was defined as the absence of tumor mass by computerized tomography scan after chemotherapy or residual mass <3cm in seminoma or <1cm in NSGCT, with normal tumor markers. Partial remission (PR) was defined as having residual mass after chemotherapy that did not match the definition of CR, while progressive disease (PD) was defined as growing mass or increasing markers.

Statistical analysis

Categorical variables were described as numbers and percentage and compared between groups using Chi-square / Fisher exact test. Abnormally-distributed continuous variables were described as median and range. The Kaplan-Meier method was used for survival analysis and survival curves were compared using the log-rank test. Disease-free survival (DFS) was calculated as the time of months elapsed between the date of achieving complete remission (after surgery and / or chemoradiotherapy) and the date of recurrence / death. Overall survival (OS) was calculated from the date of diagnosis to the date of death. A *p-value* less than 0.05 was considered significant.

The IBM SPSS software, version 23.0. (Armonk, NY: IBM Corp.) was used for data management and analysis.

Results

During the study period, 46 patients presented to our institute with the diagnosis of TGCT. Fourteen patients were excluded due to incomplete data and the remaining 32 patients were included.

All patients underwent a thorough clinical examination, scrotal ultrasound, computed tomography scan of the chest, abdomen, and pelvis with contrast and measurement of AFP, B-HCG, and LDH levles. All patients underwent upfront unilateral inguinal orchiectomy. The delay period from surgery to presentation to our department ranged from 3 to 62 days, with a median of 21 days. Details on the clinical and pathological characteristics of the studied population are presented in Table 1.

The first-line treatment received and the response to it according to different stages are presented in Table 2. In the 3 patients with stage II who did not achieve CR, the retroperitoneal lymph nodes were the only site of residual disease. Those patients were successfully managed as follows: one patient with NSGCT underwent retroperitoneal lymph node dissection while the other 2 patients with seminoma, were treated by radiotherapy.

In patients with stage III diseases who did not achieve CR (3 with PR and 1 with progression); three patients with NSGCT had retroperitoneal residual disease and retroperitoneal lymph node dissection was performed, while the remaining patient developed brain metastasis and died from disease progression.

At the time of data analysis (June 2020), the median follow up of patients was 42.5 months (95% CI: 23.0 – 63.1 months). Four (12.5%) patients died; two from chemotherapy toxicity (septic shock) and the other 2 from disease progression (liver cell failure and respiratory failure).

The 5-year DFS and OS for the entire group was 76 % and 84%, respectively. The median DFS and OS were not yet reached. As shown in Table 4, the stage of disease and the IGCCC risk stratification were the only factors that had a significant impact on survival. Disease-free survival and OS for patients with stage I were 86% and 100%, vs 79%

Table 1: Characteristics of 32 patients with testicular germ cell tumors

Characteristic	*n* (%)
Comorbidities	
Ischemic heart disease	3 (9.4)
Diabetes mellitus	2 (6.3)
HCV infection	2 (6.3)
Renal insufficiency	1 (3.1)
None	24 (75)
Side	
Left	17 (53.1)
Right	15 (46.9)
History of undescended testis	2 (6.2)
Clinical presentation	
Unilateral painless testicular mass	28 (87.5)
Flank pain	2 (6.25)
Asymptomatic	2 (6.25)
Stage	
IA	15 (46.9)
IB	2 (6.3)
IIA	1 (3.1)
IIB	5 (15.6)
IIC	4 (12.5)
IIIB	1 (3.1)
IIIC	4 (12.5)
Pathological subtypes	
Seminoma	17 (53.1)
Classic seminoma	15 (46.9)
Spermatocytic seminoma	2 (6.3)
NSGCTs	15 (46.9)
Yolk sac tumour	1 (3.1)
Embryonal carcinoma	1 (3.1)
Mixed	13 (40.6)
Lymphovascular Invasion	7 (21.8)
Elevated tumour markers (pre-surgery)	
B-HCG	10 (31.2)
AFP	11 (34.4)
LDH	10 (31.2)
IGCCC risk stratification (for stage≥ IIA)	
Good	10 (66.7)
Intermediate	2 (13.3)
Poor	3 (20)
	Median (range)
Age	34.5 (21-58)
Tumor size in max dimensions (cm)	5.8 (1.5-14)

NSGCT: Nonseminomatous germ cell tumor, **B-HCG:** Beta human chorionic gonadotropin, **AFP:** Alphafetoprotein, **LDH:** Lactate dehydrogenase, **IGCCC:** International Germ Cell Cancer Collaborative Group

and 87.5% for stage II (p<0.0001). Stage III patients were only 5 and survived for less than 5 years.

The relationship between achieving CR and the studied variables is shown in Table 3. The clinical stage was the only significant factor.

As presented in Figure 1, the 5-year DFS was 87.5% in patients who received adjuvant chemotherapy vs. 83% in patients kept on active surveillance only, with no statistically significance difference between the 2 groups (p=0.364).

Three patients (out of 17) with stage I had relapse (relapse rate 17.6%). Two of them were under active surveillance, and one patient received adjuvant carboplatin. The median time to relapse was 20 months and para-aortic lymph nodes was the only site of relapse. All the 3 patients were successfully salvaged by BEP.

Discussion

Testicular germ cell tumors represent a heterogeneous group of neoplasms in terms of pathology, age at diagnosis, treatment modalities, and prognosis.

Although testicular cancer is a rare tumor (about 1% of all male malignancies), it represents one of the most curable solid tumors with a 10-year survival rate of 90-95% [3].

The median age of the patients included in this study was 34.5 years. Pure seminoma constituted 53% of our cases, while NSGCT represented 47%. This coincides with the worldwide epidemiological incidence data in which classic seminoma account for 50% of testicular GCTs and the age ranges from 20-35 years [5].

Fifty-three percent of our testicular germ cell tumor population presented with stage I. Active surveillance was adopted in 40% of patients, while the other 60% received active treatment. The 5-year DFS was comparable in both groups. The relapse rate was 17.6%, this matches data from numerous prospective studies that showed that the relapse rate is approximately in the range of 15% in unselected populations with stage I TGCT [8, 9]. However, a large retrospective analysis from the Danish group found that the relapse rate after orchiectomy in stage I NSGCT was 30.6% [3]. Considering that Denmark is one of the few

Table 2: First line treatment and response according to different stages for both seminoma and NSGCT

Stage	First line treatment		Response	
	Regimen	***n* (%)**	**Criteria**	***n* (%)**
Stage I (n=17)	Active surveillance	7 (41.2)	CR	17 (100)
	Carboplatin AUC 7 x 1	5 (29.4), seminoma		
	BEP x 2	4 (23.5), NSGCT		
	Radiotherapy to PALN	1 (5.9), seminoma		
Stage II (n=10)	BEP x 4	6 (60)	CR	7 (70)
	EP x 4	2 (20)	PR	3 (30)
	VP x 4 (renal impairment)	1 (10)		
	Radiotherapy to PALN	1 (10)		
Stage III (n=5)	BEP x 3 (intermediate risk)	2 (40)	CR	1 (20)
	BEP x 4 (poor risk)	3 (60)	PR	3 (60)
			PD	1 (20)

AUC: Area under the curve, **BEP:** Bleomycin – etoposide – cisplatin, **CR:** Complete remission, **NSGCT:** Non-seminomatous germ cell tumor, **PALN:** Paraortic lymph nodes, **PD:** Progressive disease, **PR:** Partial remission, **VP:** vinblastine – paclitaxel

Table 3: The relationship between variables and the achievement of complete remission

Variable	CR	No CR	*p* value
	***n* (%)**	***n* (%)**	
Age			
≤35	14 (82.4)	3 (17.6)	0.678
>35	11 (73.3)	4 (26.7)	
Comorbidities			
No	19 (79.2)	5 (20.8)	1
Yes	6 (75)	2 (25)	
Pathology			
NSGCT	11 (73.3)	4 (26.7)	0.678
Seminoma	14 (82.4)	3 (17.6)	
Side			
Left	14 (82.4)	3 (17.6)	0.678
Right	11 (73.3)	4 (26.7)	
Stage			
I	17 (100)	0	0.001
II	7 (70)	3 (30)	
III	1 (20)	4 (80)	
IGCCC risk (for stage>I)			
Good	7 (70)	3 (30)	0.103
Intermediate	1 (50)	1 (50)	
Poor	0	3 (100)	

IGCCC: International Germ Cell Cancer Collaborative Group, **NSGCT:** Nonseminomatous germ cell tumor

countries in which all stage I patients are followed on a surveillance program, this explains their higher relapse rate. The median time to relapse in our patients was 20 months. In one of the largest published series by Mortensen et al., the median time to relapse in 1,954 patients with stage I seminoma was 13.7 months, but 22% of relapses occurred between 3 and 5 years [10]. Similar results were reported by the German Testicular Cancer Group [11]. Consequently, follow-up beyond 3 years is warranted. In our study, all the relapsed stage I patients were successfully salvaged by BEP and their 5-year DFS and OS were 83% and 100% respectively, comparable results have been published by Fischer et al [12].

The Spanish Germ Cell Cancer Cooperative Study Group has developed a risk-adapted approach for the treatment of stage I testicular seminoma. It is based on tumor size and rete testis invasion, with surveillance reserved for low-risk patients and adjuvant 2 cycles of carboplatin for high-risk patients [13].

Between 1950 and 1990, adjuvant radiotherapy was the standard treatment of stage I seminoma. However, growing evidence has raised concerns about the late effects of radiation therapy [14]. In the current study, only 2 patients with seminoma received radiotherapy. Travis et al. combined 14 population-based registries with more than 10,000 patients with stage I seminoma treated with

Table 4: Univariate analysis of disease-free and overall survival

Variable	5-year DFS		5-year OS	
	Rate	*p* value*	Rate	*P* value*
Age				
≤35	100%	0.016	78%	0.356
>35	80%		92%	
Pathology				
NSGCT	100%	0.257	60%	0.103
Seminoma	86%		94%	
Side				
Left	92%	0.486	92%	0.25
Right	88%		74%	
Stage				
I	86%	0.245	100%	<0.0001
II	100%		88%	
III	100%		0	
IGCCC risk **				
Good	----	----	88%	0.002
Intermediate / poor	----		0	

*Logrank test, **No DFS events, **DFS:** Disease-free survival, **IGCCC:** International Germ Cell Cancer Collaborative Group, **OS:** Overall survival

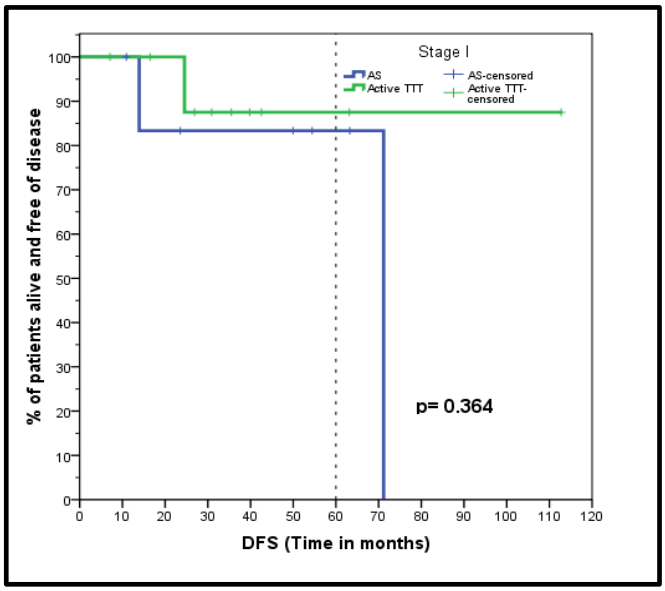

Figure 1: Kaplan–Meier curves of disease-free survival for stage I patients: active surveillance vs. active treatment

radiation therapy; the estimated cumulative 40-year risk of a second malignancy was 36% compared with 23% in the normal population [15]. With a median follow-up of 30 months (8-120), none of our patients developed second malignancy with either chemotherapy or radiotherapy.

In our series, patients with advanced stages (stage II and III) were 15 patients, 10 were of good risk, 2 with intermediate risk, and 3 with poor risk. Good-risk patients had a 5-year DFS and 5-year OS rate of 78.5% and 87.4%, respectively. All of the 10 patients with good risk received chemotherapy, with the majority (6/10) had 3 cycles of BEP, while 4 patients received 4 cycles of EP regimen. The largest reported series from the Groupe d'Etude des Tumeurs Urogénitales (GETUG), Memorial Sloan Kettering Cancer Center (MSKCC), Swedish Norwegian Testicular Cancer Study Group, and UK Medical Research Council used four cycles of EP as a standard of care for the management of good-risk metastatic testicular GCT with very favorable outcomes [16-19]. Similar efficacy has been reported with 3 cycles of BEP [20].

In the current study, patients with NSGCT and retroperitoneal lymphadenopathy who did not achieve CR with chemotherapy were managed by RPLN dissection. None of the surgically managed cases had pure mature teratoma pathology. Although data from Heidenreich et al. showed that the incidence of finding mature teratoma in residual NSGCTs is about 40% [21]. The group from Indiana University reported their long-term experience with 141 patients and from their patients who had retroperitoneal recurrence (4.5%), the sole predictor of relapse and cancer-specific survival was the IGCCC risk classification [22]. Historically, the outcomes of patients with IGCCC with poor risk were disappointing, with 5-year PFS and OS rates of 41% and 48%, respectively [23]. A more recent retrospective analysis of 223 poor prognosis patients reported 5-year PFS and OS rates of 55% and 64%, respectively [24]. In the present study, we had only 3 patients with poor-risk IGCCC and all died within the first 2 years.

Our data should be taken with caution, given the retrospective nature of the study and the small number of patients. Better documentation of our patient's files is a must as we were not able to include 12 more patients due to insufficient data.

Finally, integration of PET/CT in the assessment of response for our seminoma patients should be performed.

Conclusion

Stage I TGCTs has an excellent overall survival regardless of the treatment options. In advanced disease, the clinical stage and IGCCC risk stratification remain valid prognostic risk factors. Prospective studies are required for patients with poor risk NSGCT to improve their outcome.

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Authors' contribution

Conception or design: HHZ, AS, WE; Acquisition, analysis, or interpretation of data: HHZ, NOO; Drafting or revising the manuscript: HHZ, WE; Approval of the manuscript version to be published: All authors; Agreement to be accountable for all aspects of the work: All authors.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

Data availability

Deidentified individual participant data used to produce the results of this study are available from the corresponding author (HHZ) upon request.

Ethical considerations

This study was approved by the Research Committee of Kasr Al-Ainy Center of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Cairo University.

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Study registration

None.

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