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Impact of Testicular Germ Cell Tumor Laterality on Survival After Autologous Stem Cell Transplantation and High-Dose Chemotherapy

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ABSTRACT

Introduction: This study aimed to evaluate the effect of tumor localization on survival in patients undergoing autologous stem cell transplantation (ASCT), high-dose chemotherapy (HDCT) for recurrent/refractory testicular germ cell tumors (GCT).

Methods: The investigation encompassed 144 individuals with testicular germ cell cancers who had HDCT and ASCT from November 2016 to January 2024. Clinical and demographic information was retrospectively collected from the hospital's computerized database and patient records. Individuals lacking medical records and those under the age of eighteen were not included in the analysis. The study examined the clinical and demographic characteristics of the patients, overall survival (OS) following HDCT, the association between OS and tumor location, and other factors influencing OS.

Results: The median follow-up was 46.2 months. The 1-year and 3-year OS in the right testis group were 88% and 72%, respectively. The 1-year and 3-year OS in the left testis group were 70% and 56%, respectively. Although the right testis group had a better OS numerically, it was not statistically significant.

Conclusion: In this research, the impact of primary tumor lateralization on survival was evaluated in individuals having relapsed/refractory testicular GCT who had HDCT and ASCT treatment. While left testicular tumors were associated with worse numerical survival, this was primarily due to higher risk profiles in these patients. Tumor lateralization was not observed to independently impact OS.

Keywords: Testicular cancer, tumor lateralization, germ cell tumor, autologous stem cell transplantation

Introduction

The most common solid tumor in males aged 15 to 35 is testicular cancer. However, this accounts for a minimal percentage of all cancers in males, with germ cell tumors (GCT) constituting 95% of testicular cancer cases. Testicular GCTs are categorized into two distinct histopathological groups: seminoma and non-seminoma. Seminoma accounts for approximately 60% of all testicular GCT cases (1). Testicular cancer is one of the most easily treatable solid tumors with a 95% five-year survival rate (2). Despite these advances, approximately 20% of patients receiving first-line chemotherapy relapse and need salvage treatment. Salvage surgery may be conducted in individuals with anatomically limited diseases and disease recurrence (3). Nevertheless, most patients need substantial doses of salvage chemotherapy or chemotherapy. Data show that 60% of patients are cured with high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) (4). The right and left testes have different lymphatic drainage systems. The right testis drains into the vena cava, whereas the left testis drains into the left renal vein (5). Thus, the left testis is subjected to more pressure and has a slower blood flow than the right testis. It is hypothesized that the risk of systemic dissemination would be greater due to direct drainage to the heart, and lower pressure in the vascular structure of the right testis (6). In the majority of cases, tumors in the right testis tend to metastasize predominantly to the aortocaval nodes, while those in the left testis typically metastasize to the paraaortic nodes (7). There are a limited number of studies investigating the effects of primary tumor lateralization on survival. Our study aimed to determine whether tumor lateralization is a risk factor for survival in individuals with recurrent or refractory testicular GCT who had HDCT and ASCT.

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Methods

Participant selection: Male individuals with recurrent or refractory testicular germ cell cancer who had HDCT followed by ASCT and were at least 18 years old were included in this retrospective research. From November 2016 to January 2023, the investigation was carried out at University of Health Sciences Türkiye, Gülhane Training and Research Hospital's Bone Marrow Transplant Unit. Participants who qualified had undergone at least one course of platinum-based chemotherapy but experienced disease relapse. Before ASCT and intensified HDCT, they were administered induction chemotherapy with either paclitaxel, ifosfamide, and cisplatin or cisplatin, ifosfamide, and etoposide. Patients under the age of 18 or those not having accessible medical records were not included. The study comprehensively analyzed factors such as patient age, tumor histology, primary tumor location, number of metastatic sites, prior treatments, the beta-human chorionic gonadotropin (HCG) and the serum alpha-fetoprotein (AFP) values before HDCT, risk assessments based on the International Prognostic Factor Study Group (IPFSG) and International Germ Cell Cancer Collaborative Group (IGCCCG) systems, tumor response pre- and post-HDCT, overall survival (OS), and determinants influencing OS.

Chemotherapy regimens, stem cell, transplantations and endpoints: For the collection of CD34+ stem cells, a subcutaneous injection of granulocyte colony-stimulating factor at a dose of 10 mcg/kg was administered for five days. Patients received either carboplatin and etoposide (CE) or ifosfamide, carboplatin, and etoposide (ICE) HDCT regimen. Patients receiving the CE regimen were administered carboplatin (700 mg/m^2) and etoposide (700 mg/m^2) on days 1-3. Patients on the ICE regimen received ifosfamide (12 g/m^2), carboplatin (1.2 g/m^2), and etoposide (1.2 g/m^2) in 6 equal doses on days 1-6. After two days of recuperation, stem cell reinfusion was carried out. To prevent infections, all patients were given oral levofloxacin 500 mg, oral acyclovir 400 mg, and oral fluconazole 400 mg. The treatment regimen also incorporated prophylactic antiemetics and oral care products. A complete blood count was performed daily until engraftment was achieved. Platelet engraftment was defined as achieving a minimum platelet count of 20,000/mm^3 sustained for 3 consecutive days, while neutrophil engraftment was characterized by a neutrophil count reaching at least 2000/mm^3. To maintain platelet levels at 20,000/mm^3 and hemoglobin levels at 8 g/dL, platelet and erythrocyte suspensions were transfused as needed. OS, which is the investigation's main endpoint, is defined as the period between transplantation and either the patient's death or their last recorded follow-up. Radiological evaluations were conducted three months post-ASCT using positron emission tomography/computed tomography, and results were assessed with respect to RECIST 1.1 standards. A complete response (CR) was identified by the lack of active lesions that can be detected by radiography, and negative serum indicators. A 50% decrease in the sum of the longest diameters of detectable lesions or decrease more than 90% in elevated blood biomarkers were considered partial responses (PR). The absence of notable changes in tumor burden or size of lesions was defined as stable disease (SD). Increases in lesion size of over 25%, the emergence of additional lesions, or increased serum biomarker levels were indicators of progressive disease (PD).

Statistical Analysis

Statistical evaluations were performed through SPSS version 25.0. Mann-Whitney U tests and Student's t-tests were utilized to analyze independent variables. Continuous variables were presented as mean ± standard deviation, for normally distributed data, while non-normally distributed data were presented as medians. Kaplan-Meier survival analysis and log-rank tests were applied to assess cumulative survival and treatment-related correlations. Categorical variables were analyzed with chi-square and Fisher's exact tests. A p-value below 0.05 was accepted as statistically significant.

Results

The investigation involved 144 individuals. The median age at diagnosis was 32 years (18-64 years). In 77 (53.5%) patients, the primary tumor was localized in the right testis, and in 67 (46.5%), it was in the left testis. Sixteen patients (11.1%) had seminoma histology, and 128 patients (88.9%) had non-seminoma histology. Retroperitoneal lymph nodes and lungs were the most common sites of metastasis, [137 (95.1%) and 65 (45.1%) patients, respectively]. Clinicopathological features were classified based on whether they pertained to the right or left testes (Table 1). The aim was to evaluate the heterogeneity between the groups. The left testis group consisted of younger patients (p=0.02). The distribution of the two groups was normal for histological subgroups (p=0.11). When we analyzed the IPFSG and IGCCCG risk groups, we observed that the left testicular group comprised higher-risk patients (p=0.009 and p=0.001, respectively). There was no difference between metastatic sites except for lung metastases. The rate of lung metastasis was greater in the left testis group (p=0.03). No significant difference was observed in the number of metastatic sites (p=0.1). Likewise, no difference was seen between the number of lines, AFP, and beta-HCG levels before HDCT + ASCT. In the response evaluation before HDCT + ASCT, CR was seen in 22 patients (28.6%), PR in 47 patients (61%), SD in 7 patients (9.1%), and PD in 1 patient (1.3%) within the right testis group. In the left testis group, CR was seen in 13 patients (19.7%), PR in 40 patients (59.7%), SD in 11 patients (16.4%), and PD in 3 patients (4.5%). There was no difference in treatment responses among the two groups (p=0.25). Under the HDCT regimen, 138 received CE and 6 received ICE. Distribution between groups was normal (p=0.86). In the evaluation of response after HDCT + ASCT, CR was seen in 51 patients (66.2%), PR in 13 patients (16.9%), SD in 3 patients (3.9%), and PD in 10 patients (13%) in the right testicular group. In the left testis group, CR was seen in 34 individuals (50.7%), PR in 12 individuals (17.9%), SD in 8 individuals (11.9%), and PD in 13 individuals (19.4%). There were no difference in treatment responses among the 2 groups (p=0.14). No difference was seen among the groups with regard to progression status after HDCT + ASCT, but the rate of death was statistically higher in the left testis group (43% vs. 27%) (p=0.04). The median follow-up time was 46.2 months. The 1-year and the 3-year OS rates of the right testis group were 88% and 72%, respectively. One and 3-year OS rates of the left testis group were 70% and 56%, respectively. As a result of univariate analysis: non-seminoma histology (p=0.002), left testicular localization (p=0.03), IPFSG intermediate high-risk (p<0.001), IGCCCG poor risk (p<0.001), 2 or more metastatic sites (p=0.004), high AFP (p<0.001), and beta-HCG values (p<0.001) before HDCT + ASCT were linked with worse OS (Table 2). Multivariate analysis showed that the IPFSG very high-risk group (p<0.001), and AFP >1000 IU (p=0.003) before transplantation were independent variables affecting OS.

Table 1. Patient characteristics according to right and left

Patient characteristics						
n		**Right**		**Left**		**p**
		%	**n**	**%**		
Age	≤32	34	44.2	42	62.7	**0.026**
	>32	43	55.8	25	37.3	
Histology	Seminoma	12	15.6	4	6.0	0.11
	Yolk sac	4	5.2	6	9.0	
	Embryonal carcinoma	11	14.3	4	6.0	
	Choriocarcinoma	3	3.9	6	9.0	
	Teratoma	7	9.1	4	6.0	
	Mixed germ cell tumor	40	48.2	43	64.2	
IPFSG	Very low	9	11.7	2	3.0	**0.009**
	Low	22	28.6	18	26.9	
	Intermediate	27	35.1	13	19.4	
	High	9	11.7	17	25.4	
	Very high	10	13.0	17	25.4	
IGCCCG	Good	29	37.7	23	34.3	**0.001**
	Intermediate	25	32.5	7	10.4	
	Poor	23	29.9	37	55.2	
Metastatic site	Lung	29	37.7	36	53.7	0.03
	Liver	14	18.2	12	17.9	0.14
	Retroperitoneum	72	93.5	65	97.0	0.99
	Brain	4	5.2	10	14.9	0.06
	Bone	9	11.7	6	9.0	0.63
Metastatic site number	1	38	49.4	24	35.8	0.10
	≥2	39	50.6	43	64.2	
Number of treatment lines before HDCT	2	62	80.5	48	71.6	0.21
	3	8	10.4	14	20.9	
	≥4	7	9.1	5	7.5	
AFP before HDCT	<1000 IU/L	57	74.0	43	64.2	0.20
	≥1000 IU/L	20	26.0	24	35.8	
B-HCG before HDCT	<1000 IU/L	66	85.7	56	83.6	0.72
	≥1000 IU/L	11	14.3	11	16.4	
Tumor response before HDCT	CR	22	28.6	13	19.7	0.25
	PR	47	61.0	40	59.7	
	SD	7	9.1	11	16.4	
	PD	1	1.3	3	4.5	
HDCT regimen	CE	74	96.1	64	95.5	0.86
	ICE	3	3.9	3	4.5	
Tumor response after HDCT	CR	51	66.2	34	50.7	0.14
	PR	13	16.9	12	17.9	
	SD	3	3.9	8	11.9	
	PD	10	13.0	13	19.4	
Progression after HDCT	Present	43	55.8	36	46.3	0.25
	Absent	34	44.2	31	53.7	
Exitus status	Alive	56	72.7	38	56.7	0.04
	Dead	21	27.3	29	43.3	
Median follow-up time (months)	46.25					
	Right		**Left**			
1-year OS (%)	88		70			
3-years OS (%)	72		56			

IPFSG: International Prognostic Factor Study Group, IGCCCG: International Germ Cell Cancer Collaborative Group, HDCT: High-dose chemotherapy, AFP: Alpha-fetoprotein, B-HCG: Beta-human chorionic gonadotropin, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease OS: Overall survival, CE: Carboplatin and etoposide, ICE: Ifosfamide, carboplatin, and etoposide

Discussion

To date, the effect of testicular tumor laterality on survival is not known. Our study is one of the few studies investigating the effect of tumor lateralization on survival in patients with testicular GCT. In our study, we found that tumor localization did not affect OS in patients with testicular GCT who underwent HDCT + ASCT. However, the 1- and 3-year OS of patients who had right testicular tumors were numerically better (Figure 1). Similar to other solid cancers, seminomatous and non-seminomatous testicular cancers are spread by lymphatic and vascular routes (8). However, each testis has different vascular and lymphatic drainage systems. While the collecting vein of the right testicle is directly connected to the inferior vena cava, the collecting vein of the left testicle initially drains into the collecting vein of the left kidney. It is hypothesized that the left testicle is subjected to more pressure and has a relatively slower blood flow than the right testicle. There is a hypothesis that systemic spread will be higher due to direct drainage to the heart, and lower pressure in the vascular structure of the right testicle (9). Davila Dupont et al. (10) also tested this hypothesis. In a series of 37 patients by Davila Dupont et al. (10), 2-year relapse-free survival was 100% for the left testis and 77.3% for the right testis. Despite the small number of patients, the researchers showed that there was a tendency for earlier relapse in right testicular GCTs (10). The study by Yıldız et al. (11) is among the few studies investigating laterality in testicular GCTs. In their study, the patients with left testicular tumors had improved survival outcomes. However, HDCT + ASCT was performed in a small number of patients. Although the patient population in the compared study was larger than ours, most of the participants were early-stage. The number of high-risk patients was significantly lower than anticipated in our study. Only 40 patients underwent HDCT + ASCT (11). Miao et al. (12) studied the effect of tumor laterality on survival in 1213 individuals with diffuse large B-cell lymphoma (DLBCL) of testicular origin. Although no significant effect of laterality on survival was demonstrated, both

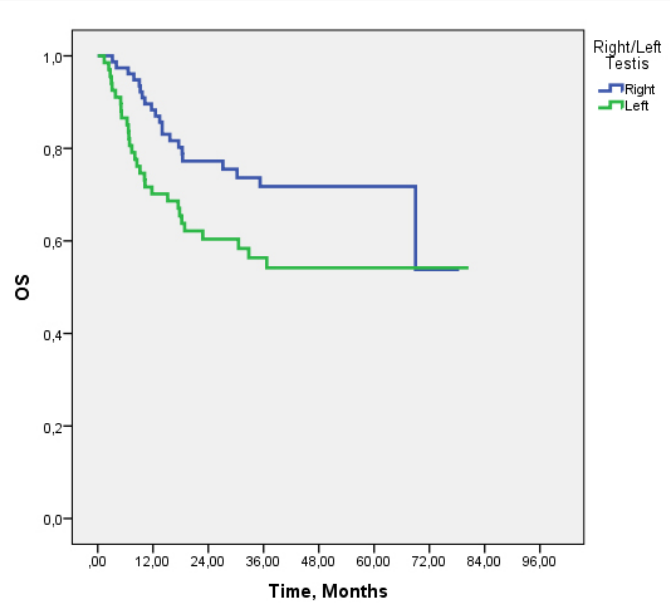

Figure 1. Kaplan-Meier curves for overall survival-tumor lateralization relationship
OS: Overall survival

Table 2. Analysis of patiens for OS according to clinicopathological factors

		Median OS (months) univariate	p	HR (95% CI) multivariate	p
Age	≤32	69.0	0.581		
	>32	NR			
Histology	Seminoma	NR	0.023	0.60 (0.07-4.72)	0.63
	Non-seminoma	59.0			
Localization	Right	NR	0.030	1.25 (0.70-2.24)	0.44
	Left	NR			
Metastatic site number	1	NR	0.004	1.17 (0.58-2.33)	0.65
	≥2	69.0			
IPFSG	Very low	NR	<0.001	2.04 (1.47-2.83)	<0.001
	Low	NR			
	Intermediate	69.0			
	High	NR			
	Very high	9.0			
IGCCCG	Good	NR	<0.001	1.19 (0.81-1.74)	0.37
	Intermediate	NR			
	Poor	30.5			
AFP	<1000 IU/L	NR	<0.001	2.37 (1.33-4.25)	0.003
	≥1000 IU/L	18.6			
HCG	<1000 IU/L	NR	<0.001	1.68 (0.88-3.22)	0.11
	≥1000 IU/L	14.0			

IPFSG: International Prognostic Factor Study Group, IGCCCG: International Germ Cell Cancer Collaborative Group, AFP: Alpha-fetoprotein, HCG: Human chorionic gonadotropin, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, NR: Not reached

10-year cancer-specific survival and OS were better in the left testis group (12). In a study by Gundrum et al. (13) in 769 individuals with testicular DLBCL, left testicular origin was shown to be a poor prognostic factor. This was the largest study in the literature that showed results similar to ours. There are a limited number of studies in the scientific community investigating the effect of testicular tumor lateralization on survival, and the results are contradictory. In our study, the survival of the left testis group was numerically worse, but this difference was not statistically significant. The main reason for this is thought to be that the left testicular group consisted of higher risk patients. When both IPFSG and IGCCCG risk scores are analyzed, it is evident that the left testis group has a higher risk. Many studies have shown that IPFSG and IGCCCG scores are important in determining prognosis (14,15). In our study, both IPFSG and AFP >1000 IU were found to be independent variables for OS.

Study Limitations

Our investigation has some limitations. In addition to being single-center and retrospective, our patient population is relatively small.

Conclusion

In conclusion, our study included 144 patients who underwent HDCT + ASCT. All patients were metastatic and had experienced recurrence. Although there are articles supporting the early recurrence of right testicular tumors, there are few studies on survival, and the two most significant studies were on testicular DLBCL. The results of these two studies contradict each other. Our paper describes one of the largest cohorts investigating the effect of lateralization on OS in patients with testicular GCT, and it found no effect of testicular tumor lateralization on survival. Since all our patients received HDCT + ASCT treatment, performing this study on a rare group increases its value. Further studies with larger patient populations are needed to confirm these findings and better understand the role of tumor laterality in testicular cancer prognosis.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Gülhane Training and Research Hospital Ethics Committee (approval number: 2024-215, date: 24.04.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Concept - A.T., B.K., N.K.; Design - A.T., A.D., E.K.T.; Data Collection or Processing - Ö.F.K., E.K.T., G.A.; Analysis or Interpretation - A.T., B.K., N.M., G.A.; Literature Search - A.T., A.D., Ö.F.K., N.M.; Writing - A.T., G.A., N.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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