Original Article

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Effect of Primary Testicular Tumor Localization on Prognosis and Survival of Non-seminomatous Testis Cancer Patients

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Abstract

Objective: Unlike left testicular vein, right testicular vein drains into inferior vena cava. Consequently, the systemic spread of testicular cancers in each side is expected to differ based on the vascular structures of the right and left testis. In this study, we investigated the effect of tumour localization on survival of non-seminomatous testicular cancer patients.

Materials and Methods: We included three hundred and twenty-one (321) non-seminomatous testicular cancer patients who were followed-up at Gülhane Training and Research Hospital between January 1981 and December 2015.

Results: The primary tumour found in the left testis in 152 (47.2%) patients, while 170 (52.8%) patients had the primary tumour in the right testis. The lungs (n=62, 42.5%) was the most common site of metastasis. During follow-up and primary treatment, 74 (23.1%) patients had recurrence, which was common in retroperitoneal lymph nodes (10.3%) and lung (5%). Median follow-up period was 88.3 (range: 1-386) months, while median survival was 337 months in all cases. Median 10 year survival rate was 74.1%, while median 20 year survival rate was 70.7%. We found that survival of patients with the primary tumour was significantly different between the left and right testis (337.6 months vs denotes not reached, p=0.001). The recurrence rate was significantly higher (84.7% vs 68.2%; p=0.002) in patients with right testicular tumour when compared to patients with left testicular tumour.

Conclusion: The survival of the patients with tumour localized in the right testis was higher than patients with tumour localized in the left testis.

Keywords: Germ cell tumours, survival, testicular cancer

Introduction

Testicular cancer, which constitutes 1% of all solid tumours, is the most common solid malignancy in men aged between 15 and 35 years (1). Germ cell tumours, which constitute 95% of testicular cancers, are classified as pure seminoma and non-seminomatous germ cell tumour. The 5 year survival rate of testicular cancer patients treated with platinum-based combination chemotherapy is 95% (2). Despite having extensive organ metastasis and/or high serum tumour markers, patients can be cured with effective combination chemotherapies (2). In spite of this remarkable cure rates, additional treatments may be required in patients with refractory and/or relapse arising from first-line treatment (3). International Germ Cell Cancer Collaborative Group divided patients into three (good, intermediate and poor) based on prognostic factor-based staging classification (4). According to a meta-analysis published in 2006, survival rates with standard treatment were significantly increased (71%) among patients with poor prognosis following the publication of the International Germ Cell Consensus Classification (5). However, some patients do not benefit significantly from the treatment despite having better Prognostic score (4). Therefore, there is an urgent need for additional prognostic factors.

Similar to other solid cancers, non-seminomatous testicular cancer also spreads through lymphatic and vascular pathways (6). When the vascular structures are evaluated, we observe that the venous drainages of both testicles are different. While the collector vein of the right testis is connecting to the inferior

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vena cava directly, the collecting vein of the left testis is initially drains into the collector vein of the left kidney, and then joins approximately 8-10 cm proximal to the inferior vena cava. Therefore, the left testis is exposed to more pressure and have relatively slower blood flow than the right testis. There is a hypothesis that the systemic spread will be higher due to the direct drainage into the heart, and due to the low pressure in the vascular structure of the right testis (7).

This study aimed to investigate the effect of tumour localization (right and left testis) on survival of non-seminomatous testicular cancer patients.

Materials and Methods

Setting and Study Population

This was a single-center retrospective study including non-seminomatous testicular cancer patients diagnosed at a medical oncology clinic of a university hospital between January 1981 and December 2015.

Information regarding demographic characteristics of patients, biochemical findings including beta-human chorionic gonadotropin, alpha-fetoprotein and lactate dehydrogenase, tumour localization and histopathology, T stage, lymph node infiltration status, distant metastasis, orchiectomy status, response to chemotherapy, response to radiotherapy (if administered), relapse and refractory status, stem cell transplantation and tumour localization, progression-free survival, and overall survival were obtained from patients' files, retrospectively. Histopathology of tumour was determined according to World Health Organization classifications (8).

The tumour stage in the patients was defined according to the American Joint Committee on Cancer and Union for International Cancer Control (9). Local ethics committee approval was obtained, and the study protocol conformed to the ethical guidelines of 1975 Declaration of Helsinki (approval number: 19/26, date: 12.02.2019).

Statistical Analyses

Descriptive statistics for continuous (quantitative) variables were presented as mean, standard deviation, minimum and maximum values. The categorical variables were presented as number (n) and proportion (%). Independent t-test and One-way analysis of variance were used for comparison. Chi-square test was used to the determine relationship between categorical variables. The adopted statistical level of significance (p) was 5%. Progression-free survival was estimated as the time from diagnosis to progression/recurrence or death. Total survival (OS) was estimated as the period from diagnosis to death. All statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 18.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

A total of three hundred and twenty-one (321) non-seminomatous testicular cancer patients aged ≥18 were included in the study. Demographic characteristics and treatment methods are summarized in Table 1. Median age of patients was 34 (range: 18-77) years. The primary tumour was located in the left testis in 152 (47.2%) patients, and in the right testis in 170 (52.8%) patients. The most common histopathology was mixed non-seminomatous germ cell tumour (39.4%), while the most rare tumour type was immature teratoma (4.7%). Exactly 146 (44.3%) cases were metastatic at the time of diagnosis, while 176 (54.7%) cases were localized. The most common site of metastasis was the lungs (n=62, 42.5%). The second most common site of metastasis was in multiple visceral organs (n=37, 25.3%). There were elevated tumour markers in 30 (9.3%) patients.

After analysis of treatments details, 6 cases (1.9%) in the suitable stage were closely followed-up. Adjuvant chemotherapy following radical orchiectomy was administered to 277 (86.3%) patients. Exactly 9 (2.8%) patients received adjuvant radiotherapy, and in three of these cases, the radiotherapy site was the pelvic region. Retroperitoneal lymph node dissection was performed in 109 cases, and only 3.7% of these cases had metastasis in the liver. Metastasectomy was performed in 41 (12.8%) patients. Although bleomycin-etopocyte-cisplatin chemotherapy (of three or four cycles) was the most preferred protocol in first-line therapy, single-agent carboplatin, etoposide-cisplatin and etoposide-ifosfamide-cisplatin protocols were other plausible options.

Exactly 74 (23.1%) patients had recurrence in the follow-up period and during primary treatment. The most common recurrence sites were retroperitoneal lymph nodes (10.3%) and lung (5%).

Median follow-up period was 88.3 months (range: 1-386), while median survival was estimated as 337 months in all cases. Median 10-year survival rate was 74.1%, while 20-year survival rate was 70.7%. Primary tumour localization, left and right testis, was significantly different in terms of survival of patients (337.6 months vs denotes not reached (NR), p=0.001). No statistically significant difference was observed between the groups based on factors affecting survival (Table 2). The recurrence rate in patients with right testicular tumour was significantly higher (84.7% vs 68.2%; p=0.002). In one case, high dose chemotherapy was needed for salvage treatment. Third-line chemotherapy was required for 83 patients. The most preferred salvage regimen was vinblastine-ifosfamide-cisplatin (17.1%). Following salvage treatment, complete response, partial response, and stable disease were observed in 24 (7.5%), 32 (10%), and 13 (2.8%), respectively. The unresponsiveness to salvage treatment was 3.4%. Autologous stem cell transplantation was performed in 40 (12.5%) patients. Overall, exactly 251 cases were healthy, while 70 (21.7%) patients died.

Lung and retroperitoneal lymph node recurrence were more common in patients with right testicular tumour (p=0.02) than in patients with left testicular tumour. The effect of tumour localization on survival was independent of metastasis, histopathology, site of metastasis, and disease stage at the time of diagnosis.

Discussion

Based on the human anatomy, it is observed that the lymphovascular structures of each organ are asymmetrical. Due

Table 1. Demographic characteristics and treatment details							
		Right		Left		Total	
		n	n%	n	n%	n	n%
Metastasis site		74	49	103	60.6	177	55.1
	brain	5	3.3	5	2.9	10	3.1
	multiple organ metastasis	22	14.6	15	8.8	37	11.5
	other	5	3.3	8	4.7	13	4
	liver	8	5.3	2	1.2	10	3.1
	bone	3	2	3	1.8	6	1.9
	pulmonary	32	21.2	30	17.6	62	19.3
	supradiaphragmatic lymph node	2	1.3	4	2.4	6	1.9
Stage	1	29	-	55	-	84	-
	2	48	-	52	-	100	-
	3	74	-	63	-	137	-
Treatment	chemotherapy	132	87.4	145	85.3	277	86.3
	radiotherapy	5	3.3	4	2.4	9	2.8
	no treatment	14	9.3	21	12.4	35	10.9
First-line chemotherapy status	CT was given	132	87.4	147	86.5	279	86.9
	no CT	19	12.6	23	13.5	42	13.1
First step chemotherapy protocols		19	12.6	23	13.5	42	13.1
	BEP 2 cycle	18	11.9	32	18.8	50	15.6
	BEP 3 cycle	50	33.1	52	30.6	102	31.8
	BEP 4 cycle	59	39.1	55	32.4	114	35.5
	carboplatin single dose	0	0.0	2	1.2	2	0.6
	EP 3 cycle	0	0.0	1	0.6	1	0.3
	EP 4 cycle	3	2	4	2.4	7	2.2
	EP 6 cycle	1	0.7	1	0.6	2	0.6
	VIP: Etop + ifos + cisplatin	1	0.7	0	0.0	1	0.3
Marker status							
	normal	125	82.8	143	84.1	268	83.5
	high	15	9.9	15	8.8	30	9.3
Relapse	non-recurrent	97	64.2	137	80.6	234	72.9
	recurrent	48	31.8	26	15.3	74	23.1
Relapse place		103	68.2	144	84.7	247	76.9
	lung	10	6.6	6	3.5	16	5
	brain	2	1.3	1	0.6	3	0.9
	inguinal	0	0.0	1	0.6	1	0.3
	liver	4	2.6	0	0.0	4	1.2
	bone	4	2.6	1	0.6	5	1.6
	mediastinal lymph node	7	4.6	5	2.9	12	3.7
	retroperitoneal lymph node	21	13.9	12	7.1	33	10.3
Autologous transplant	done	21	13.9	19	11.2	40	12.5

BEP: Bleomycin-etopocyte-cisplatin, EP: Etoposide-cisplatin, VIP: Etoposide-ifosfamide-cisplatin, CT: Chemotherapy

to asymmetrical arrangement, the incidence and prognosis of diseases affecting the right and left locations in organs are different (10). During cancers development process in different organs of the body is evaluated, differences in development mechanisms and various clinical outcomes are observed. In a study conducted by Roychoudhuri et al. (7), the impact of

Table 2. Distribution of tumour according to localization of testicle						
		Right		Left		*p
		n	n%	n	n%	
Pathology	embryonal cell carcinoma	**8**	**5.3**	**9**	**5.3**	0.052
	immature teratoma	6	4	9	5.3	
	mixed non-seminoma	65	43	62	36.5	
	mixed seminom + non-seminoma	29	19.2	39	22.9	
	pure coriocarcinoma	12	7.9	20	11.8	
	teratoma	20	13.2	8	4.7	
Yolk sac tumour		11	7.3	23	13.5	
Metastasis	yes	76	50.3	70	41.2	0.100
	no	75	49.7	100	58.8	
	brain	5	3.3	5	2.9	
	multiple organ	22	14.6	15	8.8	
	other	5	3.3	8	4.7	
	liver	8	5.3	2	1.2	
	bone	3	2	3	1.8	
	pulmonary	32	21.2	30	17.6	
	supradiaphragmatic lymph node	2	1.3	4	2.4	
	marker status normal	125	82.8	143	84.1	
	high	15	9.9	15	8.8	
Relapse	-	6	4%	7	4.1	0.002
	non-recurrent	97	64.2	137	80.6	
	recurrent	48	31.8	26	15.3	
Relapse place	lung	103	68.2	144	84.7	0.020
		10	6.6	6	3.5	
	brain	2	1.3	1	0.6	
	inguinal	0	0.0	1	0.6	
	liver	4	2.6	0	0.0	
	bone	4	2.6	1	0.6	
	mediastinal lymph node	7	4.6	5	2.9	
	retroperitoneal lymph node	21	13.9	12	7.1	

tumour localization on survival of patients with breast, lung, kidney, testis and ovarian was evaluated. They found that patients with left testicular cancer have better survival rate. In our study, a significant difference was found between cases with right and left testicular tumour in terms of survival (n=337.6 months vs NR, p=0.001). Our results are in consonant with that of the only literature so far (11).

In this study, the median follow-up period was 88.3 (range: 1-386) months, while the median survival was 337 months in all cases. The 10 year survival rate was 74.1%, while the 20 year survival rate was 70.7%. According to a meta-analysis by van Dijk et al. (5) including ten different studies, the 5 year survival rate of non-seminomatous testicular cancer patients with intermediate and poor prognosis were 83% and 71%, respectively. The 10 and 20 year survival rates of patients included in our study were consistent with the aforementioned literature.

In a study including 769 diffuse large B cell lymphoma patients, the OS was 4.4 years in patients with left testicle cancer, and 4.7 years in patients with right testicle cancer (p=0.039) (11). Authors were of stated that their results were inconsistent with the findings of Roychoudhuri et al. (7). However, they did not provide reasons for these contradictory result.

In our study, we included 45 seminoma patients and investigated the effect of tumour localization on their survival. The survival of the patients with tumour originating from the left testis was significantly higher than that arising from the right testis (n=205.1 month vs NR, p=0.002). This finding indicates that patients whose tumour originated from the right testis had poor survival.

Study Limitations

This is the first study on the localization of a rare type of primary tumour conducted retrospectively. This study was single-centred as it was included a large group of patients having a long follow-up period.

Conclusion

The survival of patients with localized tumour in the right testis was significantly better than that of patients with localized tumours in the left testis. The effect of tumour localization on survival was independent of the metastasis, histopathology, site of metastasis, and disease stage, as at the time of diagnosis.

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Ethics

Ethics Committee Approval: Local ethics committee approval was obtained, and the study protocol conformed to the ethical guidelines of 1975 Declaration of Helsinki (approval number: 19/26, date: 12.02.2019).

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Authorship Contributions

Concept: B.Y., N.K., Design: B.Y., N.K., İ.E., Data Collection or Processing: B.Y., N.K., B.B.B., Analysis or Interpretation: E.E., B.B.B., Literature Search: N.K., B.B.B., R.A., Writing: B.Y., N.K., E.E.

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