Original Article

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Evaluation of General Features of Patients with Testicular Cancer

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Abstract

Objective: Testicular cancers (Tca) are most common in men aged 20-34. Despite the increase in its incidence, the mortality rate from Tca decreases. In our study, it was aimed to evaluate the general characteristics, the treatments and survival of the patients who were followed up and treated with the diagnosis of Tca.

Materials and Methods: In this study, patients who were admitted to Okmeydanı Training and Research Hospital and Abant İzzet Baysal University, Medical Faculty, Medical Oncology Outpatient Clinic between January 2004 and December 2014 with the diagnosis of Tca, were evaluated retrospectively.

Results: In 324 (96.7%) of 332 patients included in the study with the diagnosis of Tca, testicular germ cell tumor (TGCT) was present. Of the patients, 150 (46.3%) had seminoma and 174 (53.7%) had non-seminoma tumors. The median age of patients with TGCT was 32 (minimum 18-maximum 81) years. Non-seminoma group was diagnosed at a younger age ($p<0.05$). The most common histology in the non-seminoma group was mixed germ cell tumor which was found in 135 patients (77.6%).

The stage in which the patients were most diagnosed was stage I (seminoma 73.3% and non-seminoma tumor 44.3%, $p<0.001$). Distant metastasis was present in 3.5% of patients with seminoma and 32.7% of patients with non-seminoma tumor ($p<0.001$). It was observed that 98% of the patients in the seminoma group and 85.6% of the patients in the non-seminoma group were in the good prognostic group ($p<0.001$). Radiotherapy, which was applied in 90 (81.8%) patients, was the most applied treatment in the group with stage I seminoma. In stage I non-seminomatous group, the most common treatment was cisplatin-based combination treatments, which was given to 58 (75.3%) patients.

The median follow-up period of patients with stage I seminoma was 60 (minimum 3-maximum 134) months, and the median follow-up period of patients with non-seminoma tumor was 69 (minimum 8-maximum 178) months. Three hundred twelve (96.3%) patients with TGCT survived and 145 (96.7%) in the seminoma group and 167 (96%) patients in the non-seminoma group survived ($p>0.05$).

Conclusion: The majority of our patients were diagnosed at an early stage and were in the good prognostic group. Most of our patients survived during our follow-up period.

Keywords: Survival, testicular cancer, testicular germ cell tumor

Introduction

Although testicular cancer (Tca) constitutes 1% of all cancers seen in men, it is the most common solid malignant tumor in men aged 20-34 (1,2). Although the incidence can vary from country to country, there has been an increase in the incidence of Tca in the last 20 years (3,4,5).

Cryptorchidism is one of the most important risk factors in its etiology. Other risk factors include family history, ethnicity, Testicular Feminization syndrome, and contralateral Tca history (1,6,7).

Of the Tca, 95% originate from the germinal tissue. Testicular germ cell tumors (TGCT) are divided into two groups as seminomatous and non-seminomatous germ cell tumors (GCT) (7).

The prognosis in Tca depends on the histological type, stage, tumor markers and metastasis of the tumor (8,9). Today, thanks to the developing surgery, radiotherapy techniques and chemotherapies, the survival rates of patients in especially good prognostic group are at 95% (1,10).

In this study, it was aimed to evaluate the demographic characteristics, histological subtypes of the tumor, the serum

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level of tumor markers, the stage at the time of diagnosis, the groups according to their prognostic features, treatment options, relapse and survival status of the patients who were diagnosed as having Tca, followed-up and treated.

Materials and Methods

For this study, approval was obtained from Abant İzzet Baysal University Faculty of Medicine Ethics Committee with the approval number: 2015/86, date: 13.08.2015. In this study, patients who were ≥18 years old, admitted to Okmeydanı Training and Research Hospital and Abant İzzet Baysal University, Faculty of Medicine, Medical Oncology Outpatient Clinic between January 2004 and December 2014 with the diagnosis of Tca, followed-up and treated, were included. Patients with missing file data were excluded from the study. Patient data in computer records and patient files were analyzed retrospectively.

The age of diagnosis, whether there was cryptorchidism, location of the tumor, histopathological diagnosis, serum level of tumor markers, stage at the time of diagnosis, risk categories, primary treatment type and date, whether there was recurrence, last control date and last status of the patients were recorded. The clinical staging of the patients was performed according to the American Joint Committee on Cancer Tca tumor node metastasis staging (11). Metastatic TGCT was classified according to the International Germ Cell Concensus Group as good, moderate and poor prognosis (12).

Statistical Analysis

The collected data were recorded and evaluated with SPSS 20.0 program. While the values showing homogenous distribution were expressed as "mean ± standard deviation"; parameters showing non-homogeneous distribution were expressed as "median (minimum-maximum)". The differences between the data of the seminoma and non-seminoma groups were evaluated using the Student t-test for numerical parameters showing homogeneous distribution, and the Mann-Whitney U test for parameters not showing homogenous distribution. The chi-square test, Fisher test was used to compare nominal data such as the location of the primary tumor, history of cryptorchidism, and the stage at the time of diagnosis, between the independent seminoma and non-seminoma groups. The correlation between the stage of the tumor and the serum level of tumor markers was evaluated by Spearman and Pearson Correlation tests. A p value <0.05 was considered statistically significant.

Results

It was determined that there were 343 patients who were admitted to the two centers with the diagnosis of Tca, treated and followed up. Eight of the patients were excluded from the study because the age at diagnosis was under 18 years and 3 patients were excluded because their file data were not available.

The remaining 332 patients with Tca were included in the study. Distribution of all patients according to histopathological subtypes is given in Table 1.

The median age of 324 patients with TGCT was 32 (minimum 18-maximum 81) years. In the seminom group, the median age was 36 (minimum 18-maximum 77) years; in the non-seminomatous group, it was 28 years (minimum 18-81). Patients in the seminoma group were most frequently diagnosed in the 30-39 age group (40%), whereas in the non-seminomatous group, they were most frequently diagnosed in the 20-29 age group (51.7%). The patients in the non-seminomatous group were diagnosed at a younger age. The distribution of age groups at the time of diagnosis between the two groups was statistically significantly different (p<0.05).

Table 1. Distribution of patients with testicular cancer by histological subtypes

	n	%
Testicular germ cell tumors	324	97.6
-Seminomatous	150	-
-Non-seminomatous	174	-
Embryonal carcinoma	28	-
Teratoma	6	-
Yolk sac tumor	3	-
Choriocarcinoma	2	-
Mixed germ cell tumor	135	-
Gender cord stromal tumor	**4**	**1.2**
-Leydig cell tumor	2	-
-Sertoli cell tumor	2	-
Other non-specific stromal tumors	**4**	**1.2**
-Diffuse large B cell lymphoma	1	-
-Leiomyosarcoma	1	-
-Liposarcoma	1	-
-Rhabdomyosarcoma	1	-
Total	**332**	**100**

Cryptorchidism was detected in 7.4% of patients with TGCT. It was present in 8% of the seminoma group and 6.9% of the non-seminomatous group. There was no statistical difference in terms of cryptorchidism between groups (p>0.05).

Of TGCT, 50% were located in the right testicle, 48.5% in the left testicle and 1.5% were in bilateral testicles. No statistical difference was found between the groups in terms of tumor location (p>0.05).

The most common histological subtype among the non-seminomatous group was mixed GCT, which was detected in 135 patients (77.6%) patients. Of 135 patients with mixed GCT histology, 111 (82.2%) contained histological component of embryonal carcinoma, 72 (53.3%) teratoma, 67 (49.6%) yolk sac tumor, 51 (37.8%) seminoma, and 8 (5.9%) choriocarcinoma. The most common combination was the embryonal carcinoma/teratoma combination seen in 26 patients (19.3%).

Of patients with TGCT, 0.3% were diagnosed as having stage 0 disease, at diagnosis, 57.7% as stage I, 17.6% as stage II, and 24.4% as stage III disease at the time of diagnosis. The stages of patients diagnosed as having seminoma and non-seminomatous tumors are given in Figure 1.

Distant metastases were present in 62 (19.1%) of 324 patients with TGCT at the time of diagnosis. The most common site of

metastasis was lung (48.4%). Multiple organ metastasis was present in 30.6% of the patients. Distant metastasis was present in 5 (3.5%) patients in the seminoma group and 57 (32.7%) in the non-seminomatous group. The difference between the two groups in terms of the presence of distant metastases at the time of diagnosis was statistically significant (p<0.001).

Distribution of patients diagnosed as having seminoma and non-seminomatous tumor by prognostic groups is given in Figure 2.

There was a positive correlation between the stage of the tumor and serum alpha feto protein and beta human chorionic gonadotropin (β-hCG) levels in patients in the non-nematomatous group (p<0.05).

When the primary treatments received by 110 patients diagnosed as having stage I seminoma were examined; radiotherapy was preferred in 90 (81.8%) of the patients, carboplatin chemotherapy in 11 (10%), and observation in 7 patients (6.4%). Two patients (1.8%) received treatment outside of the standard protocols.

The median follow-up period of patients diagnosed as having stage I seminoma was 60 (minimum 3-maximum 134) months.

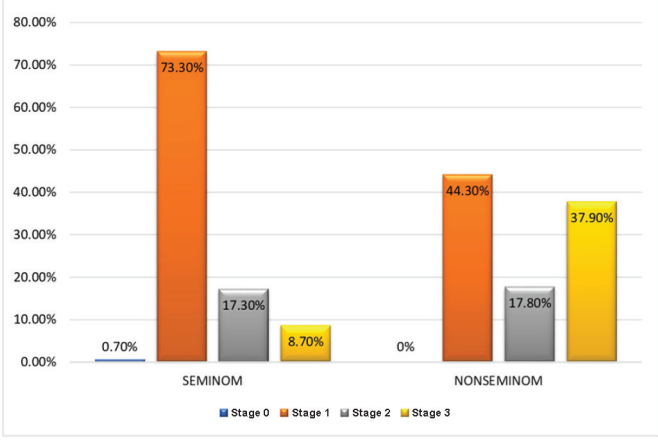

Figure 1. The disease stages at the time of diagnosis in patients with seminomas and non-seminomatous tumors

Stage 0, stage 1, stage 2, stage 3

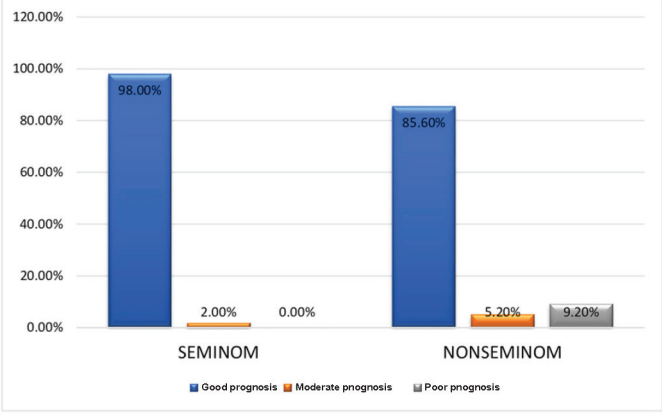

Figure 2. The distribution of patients with seminoma and non-seminomatous tumor according to prognostic groups. Good prognosis, moderate prognosis, poor prognosis

Median disease-free survival (DFS) duration was 14 (minimum 6-maximum 71) months. Disease recurrence was observed in 3 (3.3%) of 90 patients receiving radiotherapy, 2 (18.2%) of 11 patients who received carboplatin chemotherapy, and 2 (28.6%) of 7 patients in observation. The difference between preferred treatment methods in terms of recurrence was statistically significant (p<0.05).

The recurrence site was lymph nodes (regional and non-regional) in patients with stage I seminoma with recurrence after radiotherapy. The place of recurrence after treatment with carboplatin was lymph nodes (regional) and lung. Recurrence site was found to be lymph nodes (regional) in patients under observation. There was no statistically significant difference in terms of location of recurrence between three treatment options (p>0.05).

It was found that only 1 patient (0.9%) in the seminoma group died as a result of acute abdomen as a complication of adjuvant radiotherapy, and other patients were alive.

The median follow-up period of patients in stage I non-seminomatous group was 69 (minimum 8-maximum 178) months. The median time from the time of diagnosis to the relapse was 65 (minimum 3-maximum 137) months.

'Of 77 patients diagnosed as having stage I non-seminomatous tumor, observation was preferred in 11 (14.3%), 58 (75.3%) received cisplatin based chemotherapy, 4 (5.2%) preferred RPLND, and 4 (5.2%) patients did not accept treatment. Recurrence was observed in 3.4% of patients receiving chemotherapy, 18.1% of patients in observation, and 75% of patients who refused treatment. There was a statistically significant difference in terms of recurrence between treatment groups (p<0.001). It was found that only 2 (2.6%) of the patients died due to disease progression and other patients were alive.

In the follow-up; 318 (95.8%) of 332 patients diagnosed as having Tca, 312 (96.3%) of 324 patients with TGCT, 145 of 150 (96.7%) patients in the seminoma group, and 167 (96%) of 174 patients in the non-seminomatous group were found to be alive.

Discussion

TGCT is rare below the age of 15 and above the age of 60, but makes a peak at the age of 30-34 (7). In a study published in 2014 on this issue, it was found that patients were diagnosed most frequently in the second decade (13). While the median age at the time of diagnosis in seminomatoous GCT is 35-39 years, the median age is 10 years younger in the non-seminomatous GCT and it is 25-29 years (5).

Mixed GCT is the most common histological subtype in non-seminomatous GCT with a rate of 40% (14). Mixed GCT is the second most frequent tumor in the TGCT after seminoma (15). In a study conducted in Denmark, it was found that the most common component in mixed GCT was embryonal carcinoma (80%) and the most frequently observed combination was embryonal carcinoma/teratoma (16). In our study, it was concluded that the incidence of TGCT and the rate of histological subtypes were similar to the literature data.

History of cryptorchidism is one of the most important risk factors associated with the development of TGCT. In the study

of Wood and Elder. (17), it was found that the relative risk of Tca development in patients with cryptorchidism was between 2.75-8. In a study on this subject, cryptorchidism was detected in etiology in 10.7% of patients with TGCT (13). In our study, unlike these data, cryptorchidism was found lower in etiology. It was thought that this was because of our study was retrospective and cryptorchidism was not mentioned in the records of some patients.

Stage and prognosis have been shown to be directly related to early diagnosis in Tca (1,8,10). In a study conducted by Opot and Magoha (18) in Kenya, 64.1% of patients diagnosed as having Tca had advanced metastatic disease. Also, in a study conducted in Nigeria, 62.5% of patients were admitted with advanced stage metastatic disease (19). According to the data of the European Tca guideline, less than 20% of patients diagnosed as having TGCT present with a widespread metastatic disease with moderate or poor prognosis. While 90% of seminomatous GCTs have a good prognosis, 56% of non-seminomatous GCTs have a good prognosis (10). In our study, 60% of our patients with TGCT were diagnosed at an early stage. Of the patients in the seminoma group, 98% were in the good prognosis group, and 85.6% of the patients in the non-seminomatous group were in the good prognosis group. With the ease of access to health services in developed countries, high level of education and informing patients about self-examination, rate of admission with early stage disease is high. In the undeveloped countries, the vast majority of patients are admitted with metastatic disease for reasons such as difficulty in accessing health services, beliefs in traditional medicine, and low educational and socioeconomic level (13). We though that majority of patients were admitted with early stage disease and good prognostic features due to easy admission to health institutions in our country.

The first choice in the treatment of Tca is orchiectomy (10). Postoperative radiotherapy or carboplatin chemotherapy or observation are standard treatment options in patients with stage I seminoma (1,10,20). In a study comparing 1 cure carboplatin chemotherapy and adjuvant radiotherapy by Oliver et al. (20), it was shown that there was no difference between treatments in terms of relapse rate after 5 years of median follow-up, time to relapse, and survival rates. In a meta-analysis on this subject, the median DFS rate was 94.7% in patients receiving carboplatin during the 6.5-year follow-up period, and 96% in patients receiving radiotherapy. Although radiotherapy and carboplatin chemotherapy reduced the likelihood of relapse compared to the observation option, the cumulative survival rates were similar in all three treatment options (21). The most important disadvantage of the follow-up protocol in patients with stage I seminoma is the need for more intensive follow-up due to the possibility of recurrence (22,23). It was thought that the radiotherapy option might have been more preferred since the radiation oncology clinic had been actively working before the medical oncology clinic in one of our hospitals. It was thought that the reason why the observation option was less preferred was that it required more frequent follow-up, more frequent computed tomography and that patients preferred this option less because of fear of not being treated for cancer.

In non-seminomatous GCT, treatment options after orchiectomy vary according to stage, observation, chemotherapy and retroperitoneal lymph node dissection (RPLND) (1). The predominance of embryonal carcinoma component and/or the presence of lymphovascular invasion in the pathology of patients with stage I disease may change the treatment method to be followed. Active observation may be sufficient in patients without those at the time of diagnosis. However, if one of these factors is present, chemotherapy or RPLND may be considered in addition to active observation (1,10,24). In our study, it was seen that patients preferred the chemotherapy option instead of RPLND. As a result of this, it was concluded that high complication rates depending on the surgeon's experience and the surgical technique itself may have affected this preference.

According to the data of the 2019 European Tca guideline, the 5 year survival rate is 92% in patients with non-seminomatous GCT in the good prognosis group, while the 5 year survival rate in patients with seminomatous GCT is reported as 86% (10). Even in advanced disease, survival increases with advances in diagnosis and treatment. Prognosis improves, mortality decreases and survival results are satisfying due to early diagnosis, advances in treatment methods and follow-ups with frequent intervals. In recent years, 10 year survival rates are approaching to 95% with effective treatments (1,25). In the undeveloped countries where those cannot be achieved, survival rates are still very low. In the study conducted by Chalya et al. (13) in Tanzania, the survival rate was reported as 22.2%, and the survival rate in the study by Opot and Magoha (18) in Kenya was reported as 38.89%. In our study, in the median 60 month follow-up period, 95.8% of patients diagnosed as having TGCT were alive. Of patients diagnosed as having seminomatous GCT, 96.7% were alive and 96% of patients diagnosed as having non-seminomatous GCT were alive at the end of follow-up period. These survival results were very satisfactory and similar to the survival results of developed countries.

Although long survivals are achieved in patients diagnosed as having Tca, malignant neoplasms and cardiovascular disease secondary to treatment appear as important survival problems in the long term. In addition, patients may experience hearing loss, tinnitus, neurotoxicity, nephrotoxicity, pulmonary toxicity, hypogonadism, infertility, anxiety, depression, and cognitive impairment as adjuvant treatment side effects (26). In this regard, we believe that it will be appropriate to follow up the patients diagnosed as having Tca in terms of treatment complications.

Conclusion

Although the incidence of Tca has increased in recent years, there is a decrease in mortality due to early diagnosis and treatment methods. Unfortunately, admission rates with metastatic stage disease are still high and survival rates are low in some underdeveloped and developing countries. In our study, the majority of our patients were diagnosed at an early stage and were in a good prognostic group. During our follow-up period, 96.3% of our patients were alive. Radiotherapy was preferred as an adjuvant treatment among patients with stage I seminomatous GCT among the options of observation, radiotherapy and chemotherapy. Recurrence rate was low in those receiving radiotherapy. In patients diagnosed as having stage I non-seminomatous GCT, cisplatin-based combination

therapy was mostly applied. Recurrence was also very low in this treatment group. However, it has been concluded that there is a need for prospective studies that can screen the side effects of treatments more closely, clarify the choice of treatment, especially in patients with stage I TGCT, and also prevent data loss.

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Ethics

Ethics Committee Approval: Approval was obtained from Abant İzzet Baysal University Faculty of Medicine Ethics Committee with the approval number: 2015/86, date: 13.08.2015.

Informed Consent: Retrospective study.

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Authorship Contributions

Concept: M.E.G., Ü.Ü., Design: M.E.G., Ü.Ü., Data Collection or Processing: M.E.G., Ü.Ü., Ç.G., Analysis or Interpretation: M.E.G., Ü.Ü., Literature Search: M.E.G., Ü.Ü., Writing: M.E.G.

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