

## Research Article

# Single Center Experience: Testicular Cancer Case Series

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### Abstract

**Objectives:** Testicular cancer is the most common tumor in men aged 15-35 years. It constitutes 1-2% of cancers seen in men and 5% of urological cancers. In this study, we aimed to evaluate the testicular cancer cases followed in our center.

**Methods:** In our study, 71 patients who had orchiectomy and histopathologically diagnosed with testicular cancer, were analyzed retrospectively based on the archive information of Medical Oncology Department.

**Results:** The mean age of the cases was 31.6 years (range 18-65). 35 (49.3%) of the cases were found to be pure seminoma, while 36 (50.7%) were found to be non-seminomatous germ cell tumors (NSGCTs). Most of the cases (47 cases-67%) had limited disease at diagnosis, while the number of locally advanced cases was 15 (21.3%); the number of metastatic cases at diagnosis was 9 (12.7%). Death occurred in 4 of 71 testicular cancer cases.

**Conclusion:** Consistent with the literature, the most common seminoma and mixed germ cell tumors were found. In our cases, 67% localized disease, 21.3% regional involvement and 12.7% distant metastases were similar to the literature. Median overall survival and disease-free survival data could not be calculated statistically in our cases.

**Keywords:** Testicular cancer, seminoma, non-seminomatous germ cell tumors

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Testicular cancer is the most common tumor in men aged 15-35 years. It constitutes 1-2% of cancers seen in men and 5% of urological cancers. New cases are encountered in 3-10 of 100 thousand men every year.<sup>[1,2]</sup> While the incidence is high in Scandinavian countries (9 per 100 thousand); It is lower in Asian and African countries (1-3 per 100 thousand), while in the United States (USA) it is 5-6 per 100 thousand.<sup>[3,4]</sup> In our country, it is 3.7 per 100 thousand according to the 2015 Turkey cancer statistics of the Ministry of Health. According to 2015 data, it is the most common cancer in men between the ages of 15-24 in our country.

About 95% of testicular cancers are composed of germ cell tumors and the remainder are mostly rare stromal tumors (for example; Leydig cell, Sertoli cell and granulosa cell tumors).<sup>[5]</sup> Germ cell tumors are divided into two groups as

seminoma and non-seminomatous germ cell tumors (NSGCTs) due to clinicopathological differences. Seminomas account for 52% and NSGCTs for 48%.<sup>[5]</sup> NSGCTs reach the highest level in terms of incidence in the 3<sup>rd</sup> decade and seminoma in the 4<sup>th</sup> decade. The most common presentation type of testicular cancer is localized seminomas.<sup>[5]</sup> NSGCTs include mixed germ cell tumors, embryonal cell carcinoma, choriocarcinoma, yolk sac tumors, and teratomas.

There has been an increase in the incidence of testicular cancer in the last 30-40 years all over the world, especially in Western societies, Europe and developed industrial countries, and this rate has doubled globally.<sup>[1,3,4,6]</sup> Contrary to the increase in incidence, mortality rates due to testicular cancer; decreased by 0.2-0.3% in Western European countries such as Switzerland, Netherlands, Germany, France and the

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USA; It decreased to the level of 1-1.4% in Eastern European countries such as Bulgaria, Romania and Hungary.<sup>[7-9]</sup>

When all stages of testicular cancer are covered, the 5-year overall survival rate is 96%. Testicular cancer is one of the rare malignancies that can be cured even in metastatic disease. 5-year survival in localized, regional and distant metastases, respectively; 99.2%, 96.0%, and 73.1%, showing curability even in advanced germ cell tumors.<sup>[8, 9]</sup>

Radical inguinal orchiectomy provides information on diagnosis and staging along with treatment. With orchiectomy, the pathological T phase of the tumor is determined according to the presence of lymphovascular invasion and the depth of invasion (tunica vaginalis, spermatic cord, scrotal involvement). Measurement of serum tumor markers, thorax imaging (with radiography or tomography), abdominal and pelvic imaging (with tomography or magnetic resonance) should be performed for a complete staging.

Testicular cancers often metastasize via lymphatic rather than hematogenous route. Metastases to retroperitoneal lymph nodes often develop due to embryonal development. Right-sided tumors typically spread to the interaortic lymph nodes, and left-sided tumors to the left para-aortic lymph nodes. Distant hematogenous spread can be most commonly to the lungs, liver, brain, bones, kidney, adrenal glands, gastrointestinal system and spleen. T stage is determined after orchiectomy, and lymph node status, distant metastasis status, serum tumor markers and S stage are determined by the further examinations performed. A complete staging should be done according to the most commonly used American Joint Committee on Cancer (AJCC). (AJCC Cancer Staging Handbook, 8<sup>th</sup> edition).<sup>[10]</sup>

High cure rates are available with orchiectomy alone in stage I germ cell tumors. With radical orchiectomy, 80% of early-stage seminomas and 60-70% of early-stage non-seminomatous tumors can be treated curatively. Adjuvant chemotherapy is recommended for T2 and higher tumors in stage I or in cases with high serum tumor marker levels at diagnosis. In advanced disease (cases with stage II retroperitoneal lymph node or stage III distant metastases), a high rate of cure is possible with platinum-based chemotherapy, retroperitoneal lymph node dissection (RPLND), retroperitoneal radiotherapy or radical orchiectomy with some combined treatments.<sup>[11]</sup>

Treatment of advanced tumors is managed by risk stratification. A common classification system has been developed by the International Germ Cell Cancer Collaborative Group (IGCCCG). In the IGCCCG classification system, patients are divided into good, moderate, and poor risk groups for both progression-free and overall survival. Tumor histology (seminoma, non-seminoma), primary tumor

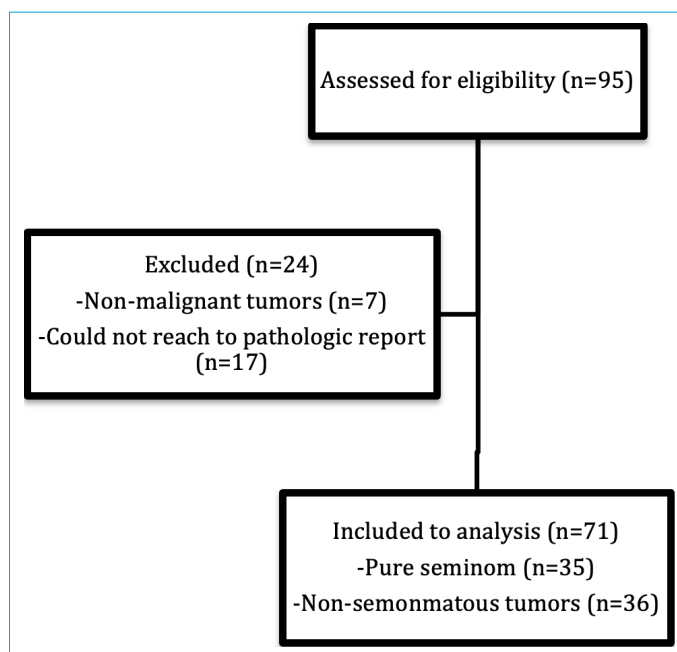
site, metastatic involvement sites, and serum tumor markers were defined as risk factors.

Independent high risk factors identified for NSGCT; presence of mediastinal primary tumor, presence of non-lung visceral metastases (liver, bone, brain, etc.), and increased levels of tumor markers, including  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG), alpha-fetoprotein (AFP), and lactate dehydrogenase (LDH). The significant prognostic factor for seminoma patients is the presence of extrapulmonary visceral metastases; if there is metastasis, it is in the moderate risk group if there is no metastasis, it is in the good risk group and there is no high risk group in seminomas.

Although a relapse-free survival of more than 80% is observed in the good-risk group after first-line chemotherapy, additional treatment is required in 60% of moderate or bad-risk patients due to relapse.<sup>[12]</sup> Patients with relapsed seminoma have better outcomes than those with NSGCTs. Long-term disease-free survival is observed in 50% of those with seminoma and 35% of NSGCTs in standard dose regimens for relapsed or refractory disease.<sup>[13]</sup> In this study, we aimed to retrospectively examine clinicopathologic, treatment and prognostic features of 71 testicular cancer cases.

## Methods

In our study, 71 patients who had orchiectomy and histopathologically diagnosed with testicular cancer were examined retrospectively based on the file archives of Afyonkarahisar Health Sciences University of Medical Oncology Department (Fig. 1 consort diagram). Case records have been obtained since 2011, and the last recorded patient



**Figure 1.** Consort diagram.

diagnosis date belongs to the end of September 2021. There are 95 cases in these records, and 24 of them were not included in the analysis due to various reasons (due to incorrect archiving, unavailability of pathology report, lack of radiological and laboratory data, etc.).

The histopathological classification of cases with testicular cancer was made according to the 2016 World Health Organization testicular neoplasms classification.<sup>[14]</sup> Staging was done according to the American Joint Committee on Cancer (AJCC) (AJCC Cancer Staging Handbook, 8<sup>th</sup> edition).<sup>[10]</sup> Risk situations have been determined according to the classification developed by the International Germ Cell Cancer Collaborative Group (IGCCCG). Clinicopathological characteristics of the cases, such as age, localization, tumor size, laboratory findings, and treatment and follow-up information, were obtained from the medical oncology polyclinic file archive reports. The obtained information was processed by using version of SPSS 25.0 and also the statistical data were obtained by using SPSS 25.0.

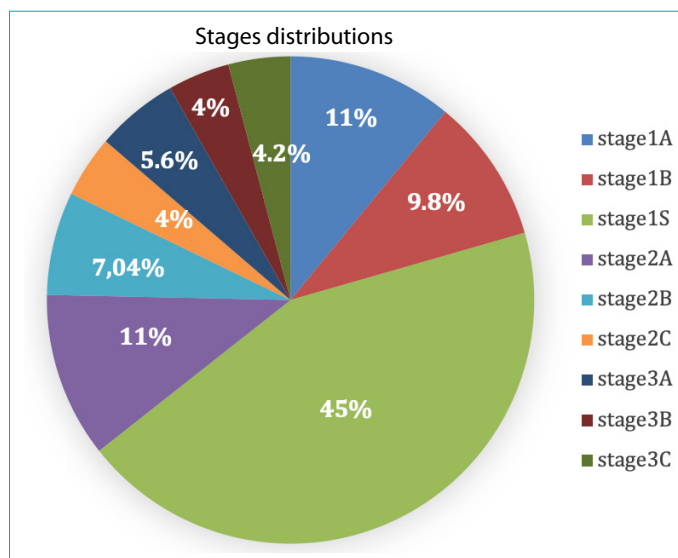
## Results

Data and follow-up information of a total of 71 testicular cancer cases were evaluated. The mean age of the cases was 31.6 years (range 18-64). Of the cases, 35 (49.3%) were found to be pure seminoma and 36 (50.7%) as NSGCTs. Among NSGCTs, mixed germ cell tumors were most common with 32 (45%) cases, embryonal carcinoma 1 (1.4%), yolk sac tumor 1 (1.4%), teratoma 1 (1.4%), choriocarcinoma 1 (1.4%) case was detected (Table 1). Among mixed germ cell tumors, the most common subtype component was embryonal cell carcinoma (16 cases).

Forty-five (63.3%) of the cases presented with the complaint of palpable mass-swelling in the testis, and the number of cases presenting only with testicular pain was 11 (15.5%). 39 (54.9%) of the cases presented with right testicular cancer and 32 (45.1%) with left testicular cancer, no case with bilateral tumor was detected. Most of the

cases (47 cases-67%) had limited (stage 1) disease to the testis at diagnosis, while the number of locally advanced cases (with retroperitoneal lymph node metastasis) was 15 (21.3%); the number of metastatic cases at diagnosis was 9 (12.7%). Most of the cases (32 cases-45%) had stage 1S at diagnosis (Fig. 2).

According to the 5 stage, most of the cases (40 cases-56.3%) entered the S1 stage, there were 9 cases in the S2 stage and only 1 case in the S3 (table 2). In the risk grouping used in advanced disease (stage 2 and stage 3), 16 of 24 patients with advanced disease were defined as good risk, 7 patients at medium risk, and 1 case in bad risk group (Table 2). 57 (80.2%) of the cases received primary chemotherapy treatment (adjuvant or curative), 9 of them had distant metastases. Two patients died after primary treatment, one due to generalized pneumonia (according to bleomycin toxicity) and the other due to progressive disease. A total of 4 cases received second-line chemotherapy for progression. Three of these cases were metastatic at diagnosis and received second-line chemotherapy for progression. Two of them died due to progression, and the third patient



**Figure 2.** Percentages distribution of patients according to the stage at diagnosis.

**Table 1.** Distribution of testicular cancer cases according to histopathological diagnoses

Histopathological diagnose	Patients n=71 (%)
Pure seminoma (%49.3)	35 (49.3)
Non-seminomatous tumors (%50.7)	
Mixt germ cell tumors	32 (45.1)
Embryonal cell carcinoma	1 (1.4)
Choriocarcinoma	1 (1.4)
Yolk sac tumor	1 (1.4)
Teratom	1 (1.4)
Total	71 (100)

**Table 2.** Distribution of testicular cancer cases by IGCCCG stage and risk groups

IGCCCG stage	Patients n=71 (%)	Risk group	Patients n=24 (%)
S0	21 (29.7)		
S1	40 (56.3)	Good risk	16 (66.6)
S2	9 (12.6)	moderate risk	7 (29.1)
S3	1 (1.4)	poor risk	1 (4.3)
Total	71(100)	Total	24 (100)

achieved complete remission. In one case, although there was no metastasis at the beginning, he received second-line chemotherapy due to progression after primary treatment, and complete remission was achieved in this case.

In the primary treatment, 40 (70%) cases received BEP (bleomycin, etoposide, platinum), 17 (30%) cases received carboplatin chemotherapy. All of the cases who received carboplatin treatments were early-stage seminoma cases. TIP (taxane, ifosfamide, platinum) chemotherapy was given in 3 of 4 patients who received second-line chemotherapy, and VeIP (vinblastine, ifosfamide, platinum) chemotherapy was given in 1 patient. Radiotherapy was applied in 5 cases in total, and it was applied to retroperitoneal lymph nodes in 3 cases, for brain metastasis in one, and lung metastasis in the other. RPLND was performed in 9 cases and in 2 of these cases, autologous stem cell transplant (ASCT) was performed after progression, one of them went into remission, the other patient died and the remaining 7 cases are still in remission. ASCT was performed in 3 cases (by referral to the reference centre), and complete response was obtained in one case and he is still in remission. The other two cases died after ASCT.

## Discussion

The mean age of our cases was 32.6 years (range 18-64 years), which is consistent with the literature. In the literature, the most common age for testicular tumors is 33 years.<sup>[15, 16]</sup> Again, right testis involvement is more (55%) and is compatible with the literature. Although bilateral involvement is reported at a rate of 1-4% in the literature, bilateral involvement was not detected in our cases. Seminoma cases (35 cases) constitute approximately half of our cases and this is proportionally compatible with the literature. Approximately 50-52% of germ cell tumors are seminomas. Mixed germ cell tumors are the most common subtype in NSGCTs. In our cases, 32 (88%) of 36 NSGCT cases showed mixed germ cell features. Again, in mixed germ cell tumors, the most common subtype was found to be embryonal carcinoma, in accordance with the literature.

The most common complaints in testicular cancer are swelling and pain in the testis. In our cases, the most common form of admission was isolated swelling (64%), testicular pain and swelling together (16%), and isolated testicular pain (15%). This situation often allows early diagnosis in testicular cancers. In the SEER analysis, 68% of the patients present with localized disease, 19% with regional involvement and 12% with distant metastasis. In our cases, 67% localized disease, 21.3% regional involvement and 12.7% distant metastasis were present, which were almost at the

same rates as the literature.

In 14 of the cases, there was no need for chemotherapy or additional treatment due to early diagnosis. 33 cases received primary adjuvant chemotherapy after orchiectomy, 15 cases received curative chemotherapy for regional (retroperitoneal lymph node) metastases and 9 cases for distant metastases. According to tumor markers, only 9 patients had S2 and 1 patient had S3 stage. 16 of 24 patients with advanced disease (stage 2 and 3) were in the good risk group and only 1 patient in the bad risk group according to the risk classification. Although this shows that the patient population is generally at low risk and the majority of early stage patients, most of the cases had chemotherapy indication and received treatment. The chemotherapy regimens of the cases were platinum-based in accordance with the guidelines and 70% BEP and 30% carboplatin treatments were used in the primary treatment of the cases. Patients with seminoma were treated with single-agent carboplatin in the primary treatment. In the second line treatment, in 3 cases TIP and in 1 case VeIP regimens were used. RPLND was applied in 9 cases. ASCT was applied in 3 cases in total. Death occurred in 4 of 71 patients.

Because of the severe and potentially fatal pulmonary toxicity associated with bleomycin in the good-risk group of testicular cancer, the four-cycle EP (etoposide-cisplatin) regimen has been evaluated as an alternative regimen to bleomycin-etoposide-cisplatin (BEP). In the European Organization for Research and Treatment of Cancer (EORTC) study, 395 patients were randomized to 4 cycles of EP and 4 cycles of BEP. Higher complete response rates (85% vs. 95%) were found in the BEP arm.<sup>[17]</sup> Grouped Etudedes Tumeurs In the Uro-Genital (GETUG) T93BP study, 257 patients were randomized to 3 cycles of BEP and 4 cycles of EP.<sup>[18]</sup> Overall response rates were similar in both arms (96% vs. 97%). At 53-month follow-up, the EP arm had a low 4-year recurrence-free survival rate (86% vs. 91%,  $p=0.135$ ) and a high mortality rate (5 vs. 12,  $p=0.096$ ). As a result of these studies, it has been shown that the results of 4 cycles of EP with 3 cycles of BEP are similar but possibly somewhat inferior. For this reason, 4 cycles of EP are recommended for patients with low pulmonary capacity, impaired renal function and those over 50 years of age, but BEP regimen is preferred in the other patient group. Similar efficacy and fewer side effects were observed in the comparison of standard dose 3 cycles of BEP with 4 cycles.<sup>[19, 20]</sup> In the European Organization for Research and Treatment of Cancer (EORTC) study, 812 patients were randomized to both arms. At 25-month follow-up, the 2-year progression-free survival rate was 90.4% in the 3-cycle BEP arm and 89.4% in the 4-cycle BEP arm.

4 cycles of BEP is the standard treatment for advanced stage patients at moderate or bad risk; progression-free survival rates are 75% and 50%, respectively. VIP (etoposide, ifosfamide, cisplatin) can be preferred as an alternative to BEP in patients with underlying lung disease, extensive lung metastases and who are not suitable for bleomycin use. Although other therapeutic approaches for poor-risk diseases include increasing the dose of cisplatin, intensifying the dose with sequential or alternative non-cross-over resistant chemotherapy regimens, and using high-dose chemotherapy protocols, its superiority over 4 cycles of BEP or VIP could not be demonstrated.<sup>[21,22]</sup>

Patients diagnosed with relapsed or refractory testicular cancer should be referred to a cancer center with a multidisciplinary team. When using cisplatin-based regimens at this stage, results are less successful than when used in primary care or as an adjuvant. The most commonly used standard dose regimens are triple drug combinations containing ifosfamide and cisplatin; TIP (Paclitaxel-ifosfamide-cisplatin), VeIP (Vinblastine-ifosfamide-cisplatin), VIP (Etoposide-ifosfamide-cisplatin). VIP applies to patients who have not used etoposide in their initial chemotherapy regimen. For patients previously treated with VIP, optimal second-line chemotherapy is not well defined. Alternatives include high-dose chemotherapy with carboplatin and etoposide, combinations of PVB (cisplatin, vinblastine and bleomycin) and gemcitabine, paclitaxel and cisplatin or oxaliplatin.<sup>[12]</sup> Other treatments for recurrence are high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT). The 2-year progression-free survival rate reported from a center in which HDC and ASCT was applied is 90% in seminoma and 52% in non-seminoma.<sup>[23]</sup>

Median overall survival and disease-free survival data could not be calculated statistically in our cases. The reason for this may be explained by the low number of recurrences or progressions after primary treatment, and the low number of deaths in general, and possibly the need for more cases and follow-up period.

As a result; although increases in the frequency of testicular cancers have been reported in recent decades, a general decrease in mortality has been reported. It can be said that the reason for this decrease is the adoption of multidisciplinary approaches in treatment, especially in refractory disease, the success of platinum-based chemotherapy agents in curative treatment, the widespread use of testicular self-examination and the availability of more technical opportunities for early diagnosis.

## Disclosures

**Ethics Committee Approval:** Afyonkarahisar university of health sciences clinical research Ethics Committee, date: 02.12.2022, meeting number: 2022/16, research number: 606.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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