



# Oncological Outcomes of Bilateral Testicular Germ Cell Tumors and Evaluation of Prognostic Risk Factors

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## Abstract

**Objective:** The incidence of bilateral testicular germ cell tumours (TGCT) is low and constitutes 0.5%-7% of all testicular tumours. We aimed to evaluate the clinical and pathological features of unilateral and bilateral TGCT, as well as prognostic factors in bilateral cases that may have an impact on oncological outcomes.

**Materials and Methods:** Bilateral TGCT were detected in 10 (11.4%) of 87 patients between January 2010 and July 2016. Patients with 68 unilateral and 10 bilateral tumours (4 synchronous, 6 metachronous) had completely accessible data. We retrospectively evaluated their clinical-pathological data and postoperative follow-up results.

**Results:** Four patients with bilateral synchronous tumours had a seminoma and three (75%) of them had a stage III disease. At a median follow-up of 31.50 (29-37) months, local recurrence, distant metastasis and death were observed in two patients with stage III disease. No recurrence or metastasis was seen in six patients with unilateral TGCT at 33 (24-50) months of follow-up, but metachronous tumours occurred in the contralateral testicles. At a median follow-up of 25 (11-39) months after metachronous tumour development, local recurrence, distant metastasis and death were observed in the contralateral testis of patients with stage III disease. There was no significant difference in bilateral and unilateral cases for disease-free survival, progression-free survival (PFS) and overall survival (OS). PFS and OS were significantly shorter ( $p=0.039$ ) in bilateral synchronous tumours than in metachronous tumours. Moreover, stage III disease was more common (75% vs 33.3%) in synchronous tumours. Family history (OR: 6.556,  $p=0.035$ ), testicular dysgenesis syndrome (OR: 3.876,  $p=0.031$ ), disorders of semen parameters (OR: 2.879,  $p=0.037$ ), undescended testis (OR: 2.561,  $p=0.026$ ), monocyte/lymphocyte ratio  $>0.31$  [odds ratio (OR): 2.234,  $p=0.022$ ], testicular microlithiasis (OR: 2.015,  $p=0.015$ ) and neutrophil/lymphocyte ratio  $>3.23$  (OR: 1.348,  $p=0.025$ ) increased the risk of contralateral tumour development.

**Conclusion:** Bilateral synchronous tumours are detected at a more advanced stage and have lower PFS and OS durations, but survival rates are similar to those of unilateral tumours. Long-term follow-up is necessary for patients with unilateral TGCT having certain risk factors due to the possibility of metachronous tumour development in the contralateral testis.

**Keywords:** Bilateral, metachronous, synchronous, testicular dysgenesis syndrome, testicular germ cell tumour

## Introduction

Although testicular germ cell tumor (TGCT) constitutes 1% of all male malignancies and 5% of urological tumors, it is the most common solid tumor detected in men aged 15-44 years (1). In the treatment of TGCT, which accounts for more than 95% of all testicular malignancies, the standard first approach is radical orchiectomy, and as a result of the developments in adjuvant chemotherapy (CT), high rates of cure can be achieved today (2).

Well-known risk factors in the etiology are testicular dysgenesis syndrome (TDS) components (undescended testis, hypospadias, decreased spermatogenesis), familial TGCT history in first-degree relatives, a history of tumor in the contralateral testicle,

and the presence of intratubular germ cell neoplasia (ITGCN) (3). Bilateral TGCT accounts for 0.5-7% of all testicular tumors (1,4). Synchronous (simultaneous bilateral) tumor is observed in approximately 35% of these patients, and metachronous (second contralateral) tumor is seen in 65% (5).

In general, although it is known that synchronous tumors are seen at more advanced stages and survival rates are lower than metachronous tumors, our knowledge about epidemiological and clinicopathological features and treatment strategies of bilateral TGCT is limited (1). Therefore, we aimed to evaluate the prognostic factors that might affect oncological outcomes in patients with bilateral TGCT by examining the clinical and pathological features of patients diagnosed as having bilateral or unilateral TGCT in our clinic.

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## Materials and Methods

All procedures in our study were conducted in accordance with the ethical standards of the institutional and national research committee including human participants and the principles of the Helsinki Declaration, and since it was a retrospective study, no ethics committee approval was made. Each patient was informed before the surgery that the demographic, clinical, pathological and oncological data of the patients could be used in various oncological studies to be performed in the clinic without specifying the patient names and identity information, and the data of the patients who did not consent was not used in this study.

Pathological findings of 99 patients who underwent radical orchiectomy with a pre-diagnosis of testicular tumor between January 2010 and July 2016 were evaluated retrospectively. The patients of whom pathological examination of orchiectomy specimens showed paratesticular sarcoma (n=5), epidermoid cyst (n=1), inflammatory myofibroblastic tumor (n=1), benign cystic teratoma (n=2), benign leydig cell tumor (n=1), paratesticular fibroma (n=1) and non-Hodgkin lymphoma (n=1) were excluded from the study, and the data of 87 patients with TGCT were evaluated.

Demographic data, histopathological tumor subtypes, clinical tumor stage, tumor localization, tumor size, expression of serum tumor markers (alpha-fetoprotein, beta human chorionic gonadotropin, lactate dehydrogenase), serum hemogram parameters [(neutrophil/lymphocyte ratio (NLR)), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR), mean platelet volume, red cell distribution width], prognostic factors of tumor in pathology samples, follow-up time after orchiectomy, local recurrence, distant metastasis and overall mortality rates of the patients were noted. Family history, the presence of undescended testis, hypospadias or semen parameter disorder (the presence of any disorder in terms of number, motility, morphology or vitality in semen parameters), presence of atrophic testis (testicular volume <12 mL), and the status of microlithiasis in preoperative ultrasonographic examination were also recorded by scanning patient files. Seventy eight patients with TGCT who could be reached were included.

Clinical tumor stages were evaluated according to the 2009 tumor-node-metastasis classification. While early stage tumors consisted of stage IA and IB; advanced stage tumors included stage IS, IIA/IIB/IIC and IIIA/IIIB/IIIC. Histological tumor subtypes were evaluated according to the World Health Organization's classification. According to the European Association of Urology (EAU) 2020 guidelines, for stage I seminoma, presence of rete testicular involvement and tumor size greater than 4 cm; for stage I non-seminoma, the presence of lymphovascular invasion, embryonal carcinoma rate over 50% and proliferation index over 70% were evaluated as pathological prognostic risk factors (3).

The definition of TDS includes the presence of at least two of undescended testicles, hypospadias, decreased spermatogenesis or TGCT (6). Since all patients in our study had TGCT, we classified the patients as having TDS due to whether having at least one of undescended testis, hypospadias or semen parameters disorder.

Patients were divided into two groups without randomization. Group I included patients with bilateral TCHT (n=10), group II with unilateral TGCT (n=68). Both groups were compared in terms of demographic and clinical data, prognostic risk factors, serum hemogram parameters and oncological results. Patients with bilateral TGCT were also evaluated by dividing them into two subgroups as synchronous (n=4) and metachronous (n=6).

## Statistical Analysis

After evaluating the normality status with the Kolmogorov-Smirnov and Shapiro-Wilk tests, when comparing the differences between the two groups, Mann-Whitney U test was used for continuous variables that did not show normal distribution. Pearson chi-square analysis or Fisher's Exact test was used for categorical variables. Kaplan-Meier method was used for the analysis of disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS), while differences between patient groups were evaluated using the log rank test. Logistic regression analysis was used to determine prognostic factors that may affect contralateral tumor development in the follow-up of patients with unilateral tumors at the time of initial diagnosis. Receiver operating characteristic analysis could not be performed to determine the threshold value for serum hemogram parameters due to the small sample size. Instead, the median values of all 78 patients included in the study were taken as threshold values and included in univariate and multivariate models in logistic regression analysis. Analyses were performed using IBM SPSS Statistics 21 (IBM, Armonk, NY USA) software. Values of  $p < 0.05$  were considered statistically significant.

## Results

### Patient Population and General Characteristics

Bilateral tumors were detected in 10 (11.4%) of 87 patients who were diagnosed as having TGCT after radical orchiectomy between January 2010 and July 2016. Four (40%) of them had synchronous tumors and six (60%) had metachronous tumors. Since the data were fully available, the median age of 78 patients included in the study was 31 and during a median of 57.50 (minimum= 6- maximum= 106) months follow-up, 15 (19.2%) developed local recurrence, 17 (21.8%) developed distant metastasis, and 16 (20.5%) cancer-related death was observed. Distant metastases were detected in the lung in 8 patients, liver in 4 patients, and non-regional lymph nodes in 5 patients. Demographic, pathological, clinical data and oncological results of the patients are shown in Tables 1 and 2.

### Synchronous Tumors

The median age at diagnosis was 33 (24-42) in 4 patients with bilateral synchronous TGCT. Two of the patients had a history of undescended testis, 1 had a history of hypospadias, 2 had a defect in semen parameters, 1 had atrophic testis, and 2 had testicular microlithiasis. Two patients were determined to be suitable for the TDS definition. Increased tumor markers were found in 3 (75%) patients, while tumor histopathology was found as pure seminoma on both sides in all patients. After clinical staging, it was determined that one of the patients had

Table 1. Demographic and pathologic data of all patients				
Parameters	Group I (bilateral TGCT) (n=10)	Group II (unilateral TGCT) (n=68)	Total (n=78)	p-value
Age Median (25.-75. percentiles)	27.00 (24.75-36.00)	31.00 (25.25-41.00)	31.00 (25.00-39.50)	†0.342
**Tumor size (cm) Median (25.-75. percentiles)	4.80 (3.45-7.62)	4.00 (2.50-6.40)	4.15 (2.57-6.55)	†0.282
Tumor side (n, %)				
-Left	0 (0.0)	25 (36.8)	25 (32.1)	‡<0.001*
-Right	0 (0.0)	43 (63.2)	43 (55.1)	
-Bilateral	10 (100.0)	0 (0.0)	10 (12.8)	
Histopathologic subtype (n, %)				
-Seminoma	6 (60.0)	35 (51.5)	41 (52.6)	‡0.877
-Non-seminoma	3 (30.0)	24 (35.3)	27 (34.6)	
-Mixed type	1 (10.0)	9 (13.2)	10 (12.8)	
AFP (ng/mL) Median (25.-75. percentiles)	4.35 (2.07-82.02)	6.15 (2.15-76.06)	5.60 (2.17-72.68)	†0.864
β-hCG (mIU/mL) Median (25.-75. percentiles)	5.00 (1.75-370.00)	17.95 (2.55-114.00)	12.45 (2.50-124.00)	†0.899
LDH (U/L) Median (25.-75. percentiles)	608.50 (230.00-1090.75)	308.50 (187.75-717.00)	309.00 (201.35-784.50)	†0.145
Tumor stage				
-I	5 (50.0)	38 (55.9)	43 (55.1)	§0.455
-II	0 (0.0)	8 (11.8)	8 (10.3)	
-III	5 (50.0)	22 (32.4)	27 (34.6)	
ITGCN (n, %)				
Yes	8 (80.0)	30 (44.1)	38 (48.7)	‡0.034*
No	2 (20.0)	38 (55.9)	40 (51.3)	
Rete testis invasion (n, %)				
Yes	2 (20.0)	16 (23.5)	18 (23.1)	§0.582
No	8 (80.0)	52 (76.5)	60 (76.9)	
Tumor diameter >4 cm (n, %)				
Yes	7 (70.0)	33 (48.5)	40 (51.3)	§0.312
No	3 (30.0)	35 (51.5)	38 (48.7)	
Lymphovascular invasion (n, %)				
Yes	4 (40.0)	23 (33.8)	27 (34.6)	§0.478
No	6 (60.0)	45 (66.2)	51 (65.4)	
Embryonal carcinoma rate >50% (n, %)				
Yes	1 (10.0)	18 (26.5)	19 (24.4)	§0.436
No	9 (90.0)	50 (73.5)	59 (75.6)	
Proliferation rate >70% (n, %)				
Yes	1 (10.0)	1 (1.5)	2 (2.6)	§0.241
No	9 (90.0)	67 (98.5)	76 (97.4)	
*p<0.05 Asterisk (*) indicates statistical significance. **In patients with bilateral tumors, the size of the tumor with the largest diameter is given in the table. AFP: Alpha-fetoprotein, β-hCG: Beta human chorionic gonadotropin, ITGCN: Intratubular germ cell neoplasia, LDH: Lactate dehydrogenase, TGCT: Testicular germ cell tumor †: Mann-Whitney U test, ‡: Chi-square test, §: Fisher's Exact test				

stage I disease and the other 3 had stage III disease. At a median follow-up of 31.50 (29-37) months, local recurrence, distant

metastasis and death were observed in 2 patients with stage III disease (Tables 3 and 4).

Table 2. Clinical data and oncologic results of all patients				
Parameters	Group I (bilateral TGCT) (n=10)	Group II (unilateral TGCT) (n=68)	Total (n=78)	p-value
Undescended testis (n, %)				
Yes	4 (40.0)	8 (11.8)	12 (15.4)	§0.042*
No	6 (60.0)	60 (88.2)	66 (84.6)	
Semen parameter disorders (n, %)				
Yes	4 (40.0)	7 (10.3)	11 (14.1)	§0.030*
No	6 (60.0)	61 (89.7)	67 (85.9)	
Hypospadias (n, %)				
Yes	2 (20.0)	1 (1.5)	3 (3.8)	§0.042*
No	8 (80.0)	67 (98.5)	75 (96.2)	
Atrophic testis (n, %)				
Yes	1 (10.0)	4 (5.9)	5 (6.4)	§0.506
No	9 (90.0)	64 (94.1)	73 (93.6)	
Testicular microlithiasis (n, %)				
Yes	5 (50.0)	14 (20.6)	19 (24.4)	‡0.043*
No	5 (50.0)	54 (79.4)	59 (75.6)	
Presence of TDS (n, %)				
Yes	5 (50.0)	12 (17.6)	17 (21.8)	§0.035*
No	5 (50.0)	56 (82.4)	61 (78.2)	
Family history of TGCT (n, %)				
Yes	4 (40.0)	9 (13.2)	13 (16.7)	‡0.034*
No	6 (60.0)	59 (86.8)	65 (83.3)	
Neutrophil/lymphocyte ratio	5.34 (4.33-7.45)	2.76 (1.80-4.42)	3.23 (2.09-4.58)	†0.001*
Monocyte/lymphocyte ratio	0.38 (0.33-0.49)	0.27 (0.18-0.37)	0.31 (0.19-0.38)	†0.006*
Platelet/lymphocyte ratio	190.34 (169.05-248.76)	142.69 (98.16-197.48)	150.01 (107.48-207.86)	†0.013*
Mean platelet volume (fL)	4.29 (3.63-6.04)	5.20 (3.72-7.13)	5.08 (3.74-6.86)	†0.424
Red blood cell distribution width (fL)	14.75 (13.57-15.37)	13.90 (12.72-14.67)	13.90 (12.87-14.80)	†0.081
Follow-up time [median (minimum-maximum), months]	49.50 (29-69)	60.50 (6-106)	57.50 (6-106)	†0.313
Local recurrence rate (n, %)	2 (20.0)	13 (19.1)	15 (19.2)	§0.616
Distant metastasis rate (n, %)	3 (30.0)	14 (20.6)	17 (21.8)	§0.376
Total mortality rate (n, %)	3 (30.0)	13 (19.1)	16 (20.5)	§0.420
*p<0.05 Asterisk (*) indicates statistical significance. TDS: Testicular dysgenesis syndrome, TGCT: Testicular germ cell tumor †: Mann-Whitney U test, ‡: Chi-square test, §: Fisher's Exact test				

### Metachronous Tumors

In 6 patients with bilateral metachronous TGCT, the median age at diagnosis was 26 (20-35) when the first tumor was detected, and 29.5 (22-37) when the contralateral second tumor was detected. Two of the patients had a history of undescended testis, one had a history of hypospadias, 2 had a defect in semen parameters, and 3 had testicular microlithiasis. Three patients were consistent with the TDS definition. During the first tumor diagnosis, elevation in tumor markers was detected in 5 (83.3%) patients, while tumor histopathology was determined as pure seminoma in 2 patients, pure non-seminoma in 3 patients, and mixed type TGCT in one patient. In this subgroup, where 4 patients had stage I disease and 2 patients had stage III disease,

no recurrence or metastasis was observed at a median follow-up of 33 (24-50) months until the contralateral tumor developed (Tables 3 and 4).

When the contralateral second testicular tumor was detected, tumor markers were elevated in 3 (50%) patients, while tumor histopathology was determined as pure seminoma in 4 patients and pure non-seminoma in 2 patients. Although the first tumor was not seminoma in 2 patients, it was observed that the contralateral tumor was seminoma. No significant difference was found in terms of initial tumor size, and contralateral tumor size developed at follow-up [4.75 (3-8) cm vs 4.35 (3.1-6.1) cm, p=0.699]. Unlike the initial tumor staging, stage III contralateral tumor was observed in only one patient and stage I contralateral

Table 3. Demographic and pathologic data of patients with bilateral testicular germ cell tumor				
Parameters	Synchronous tumors (n=4)	Metachronous tumors (n=6)	Total (n=10)	p-value
Age Median (25.-75. percentiles)	33.00 (24.75-41.25)	26.00 (23.75-33.50)	27.00 (24.75-36.00)	†0.334
**Tumor size (cm) Median (25.-75. percentiles)	5.50 (2.40-7.37)	4.75 (3.45-7.77)	4.80 (3.45-7.62)	†0.831
Histopathologic subtype (n, %)				
-Seminoma	4 (100.0)	2 (33.3)	6 (60.0)	‡0.035*
-Non-seminoma	0 (0.0)	3 (50.0)	3 (30.0)	
-Mixed type	0 (0.0)	1 (16.7)	1 (10.0)	
AFP (ng/mL) Median (25.-75. percentiles)	4.10 (1.92-54.50)	33.00 (2.07-430.62)	4.35 (2.07-82.02)	†0.522
β-hCG (mIU/mL) Median (25.-75. percentiles)	1.50 (0.25-120.50)	71.40 (4.27-279.00)	5.00 (1.75-370.00)	†0.088
LDH (U/L) Median (25.-75. percentiles)	1159.00 (407.75-2304.25)	408.00 (230.00-880.00)	608.50 (230.00-1090.75)	†0.394
Tumor stage				
-I	1 (25.0)	4 (66.7)	5 (50.0)	‡0.197
-II	0 (0.0)	0 (0.0)	0 (0.0)	
-III	3 (75.0)	2 (33.3)	5 (50.0)	
ITGCN (n, %)				
Yes	4 (100.0)	4 (66.7)	8 (80.0)	§0.333
No	0 (0.0)	2 (33.3)	2 (20.0)	
Rete testis invasion (n, %)				
Yes	1 (25.0)	1 (16.7)	2 (20.0)	§0.667
No	3 (75.0)	5 (83.3)	8 (80.0)	
Tumor diameter >4 cm (n, %)				
Yes	3 (75.0)	4 (66.7)	7 (70.0)	§0.667
No	1 (25.0)	2 (33.3)	3 (30.0)	
Lymphovascular invasion (n, %)				
Yes	3 (75.0)	1 (16.7)	4 (40.0)	§0.119
No	1 (25.0)	5 (83.3)	6 (60.0)	
Embryonal carcinoma rate >50% (n, %)				
Yes	0 (0.0)	1 (16.7)	1 (10.0)	§0.389
No	4 (100.0)	5 (83.3)	9 (90.0)	
Proliferation rate >70% (n, %)				
Yes	0 (0.0)	1 (16.7)	1 (10.0)	§0.389
No	4 (100.0)	5 (83.3)	9 (90.0)	
*p<0.05 Asterisk (*) indicates statistical significance. **In patients with bilateral tumors, the size of the tumor with the largest diameter is given in the table. AFP: Alpha-fetoprotein, β-hCG: Beta human chorionic gonadotropin, ITGCN: Intratubular germ cell neoplasia LDH: Lactate dehydrogenase, TGCT: Testicular germ cell tumor †: Mann-Whitney U test, ‡: Chi-square test, §: Fisher's Exact test				

tumor in the other 5 patients. At a median follow-up of 25 (11-39) months after the development of the contralateral tumor; local recurrence, distant metastasis and death were observed in one patient with stage III disease. It was noteworthy that the first tumor of this patient was also a stage III tumor. The total follow-up period of 6 patients with metachronous tumors after the first tumor was detected was 64 (48-69) months.

### Clinical Differences Between Bilateral and Unilateral Tumors

While ITGCN (p=0.034) was found with a significantly higher rate in bilateral patients compared to unilateral patients (Table 1), again in these patients undescended testis (p=0.042), semen parameter disorder (p=0.030), hypospadias (p=0.042), the incidence of testicular microlithiasis (p=0.043) and TDS

( $p=0.035$ ) were higher (Table 2). When we divided bilateral patients into two subgroups as patients having synchronous or metachronous tumors, no significant difference was observed between groups in terms of both ITGCN rates (Table 3) and other parameters mentioned (Table 4).

When the rates of local recurrence, distant metastasis and overall mortality were compared, statistical similarity was observed between both bilateral and unilateral patients, and bilateral synchronous-metachronous subgroups (Tables 2 and 4).

While NLR ( $p=0.001$ ), MLR ( $p=0.006$ ) and PLR ( $p=0.013$ ) were found to be significantly higher in bilateral patient; when we divided bilateral patients into subgroups within themselves, no difference was found between synchronous-metachronous subgroups (Tables 2 and 4).

In the median follow-up of 57.5 months for all bilateral and unilateral patients, there was no significant difference in terms of DFS, PFS and OS durations (Figure 1-3). It was observed that PFS and OS durations were significantly shorter in bilateral synchronous tumors compared to bilateral metachronous tumors (Figure 4-6).

Prognostic factors affecting contralateral tumor development in the follow-up of 68 patients with unilateral tumors at the time of diagnosis are shown in Table 5. In multivariate analysis, family history [Odds ratio (OR): 6.556,  $p=0.035$ ], presence of TDS (OR: 3.876,  $p=0.031$ ), impairment in semen parameters (OR: 2.879,  $p=0.037$ ), history of undescended testis (OR: 2.561,  $p=0.026$ ), MLO  $>0.31$  (OR: 2.234,  $p=0.022$ ), presence of testicular microlithiasis (OR: 2.015,  $p=0.015$ ), and NLR  $>3.23$  (OR: 1.348,  $p=0.025$ ) were found to be independent variables that increased the risk of contralateral tumor development.

Parameters	Synchronous tumors (n=4)	Metachronous tumors (n=6)	Total (n=10)	p-value
Undescended testis (n, %)				
Yes	2 (50.0)	2 (33.3)	4 (40.0)	§0.548
No	2 (50.0)	4 (66.7)	6 (60.0)	
Semen parameter disorders (n, %)				
Yes	2 (50.0)	2 (33.3)	4 (40.0)	§0.548
No	2 (50.0)	4 (66.7)	6 (60.0)	
Hypospadias (n, %)				
Yes	1 (25.0)	1 (16.7)	2 (20.0)	§0.667
No	3 (75.0)	5 (83.3)	8 (80.0)	
Atrophic testis (n, %)				
Yes	1 (25.0)	0 (0.0)	1 (10.0)	§0.400
No	3 (75.0)	6 (100.0)	9 (90.0)	
Testicular microlithiasis (n, %)				
Yes	2 (50.0)	3 (50.0)	5 (50.0)	§0.738
No	2 (50.0)	3 (50.0)	5 (50.0)	
Presence of TDS (n, %)				
Yes	2 (50.0)	3 (50.0)	5 (50.0)	§0.738
No	2 (50.0)	3 (50.0)	5 (50.0)	
Family history of TGCT (n, %)				
Yes	1 (25.0)	3 (50.0)	4 (40.0)	§0.452
No	3 (75.0)	3 (50.0)	6 (60.0)	
Neutrophil/lymphocyte ratio	6.13 (4.90-7.83)	4.66 (3.62-7.45)	5.34 (4.33-7.45)	†0.394
Monocyte/lymphocyte ratio	0.35 (0.33-0.45)	0.40 (0.33-0.54)	0.38 (0.33-0.49)	†0.522
Platelet/lymphocyte ratio	210.17 (170.64-277.13)	189.67 (166.30-248.76)	190.34 (169.05-248.76)	†0.670
Mean platelet volume (fL)	3.84 (2.95-5.59)	4.65 (3.82-8.66)	4.29 (3.63-6.04)	†0.286
Red blood cell distribution width (fL)	14.75 (13.80-15.10)	14.55 (13.32-16.40)	14.75 (13.57-15.37)	†0.670
Follow-up time [median (minimim-maximum), months]	2 (50.0)	0 (0.0)	2 (20.0)	§0.133
Local recurrence rate (n, %)	2 (50.0)	1 (16.7)	3 (30.0)	§0.333
Distant metastasis rate (n, %)	2 (50.0)	1 (16.7)	3 (30.0)	§0.333
*p<0.05 Asterisk (*) indicates statistical significance. TDS: Testicular dysgenesis syndrome, TGCT: Testicular germ cell tumor †: Mann-Whitney U test, ‡: Chi-square test, §: Fisher's Exact test				



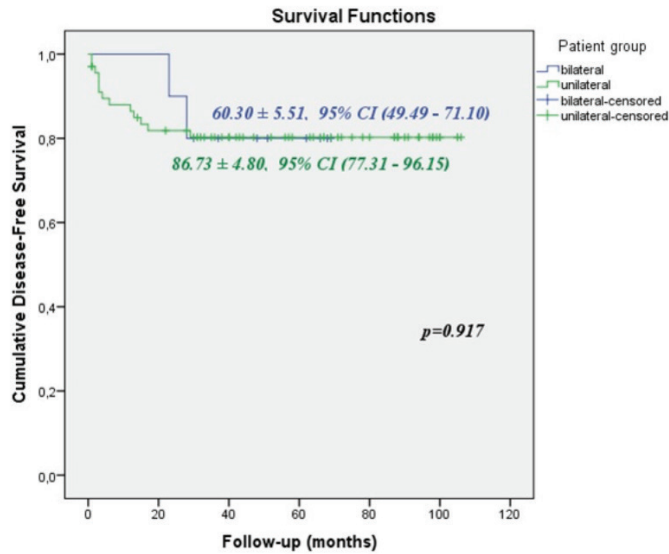


Figure 1. Plot of disease-free survival of bilateral - unilateral testicular germ cell tumors

CI: Confidence interval

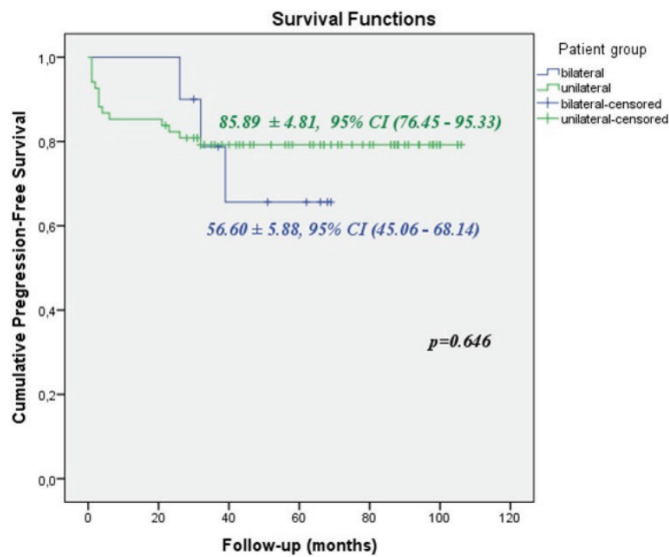


Figure 2. Plot of progression-free survival of bilateral - unilateral testicular germ cell tumors

CI: Confidence interval

## Discussion

Since bilateral TGCT was reported for the first time in 1805, patient survival rates and durations have increased thanks to the developments in adjuvant treatment strategies (7). In parallel with the increasing survival durations, a significant increase is observed especially in metachronous tumor development rates (8). Bilateral TGCT is seen at a rate of approximately 2% (0.5-7%) (7). Of those tumors 64.7-88.9% are metachronous and 6.8-35.3% are synchronous tumors (9). Approximately half of metachronous tumors have the same histopathology with the first tumor detected and the most common histological type is

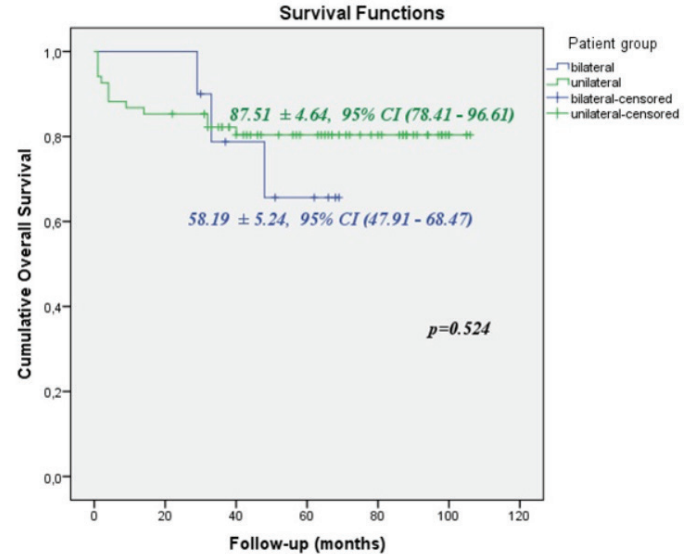


Figure 3. Plot of overall survival of bilateral - unilateral testicular germ cell tumors

CI: Confidence interval

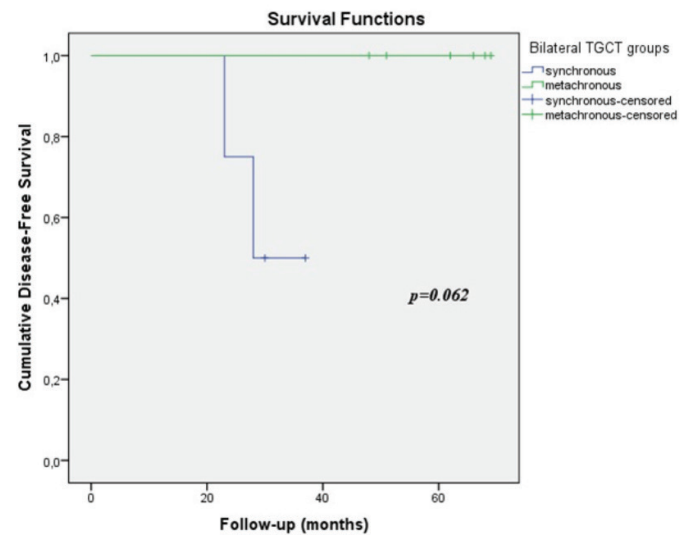
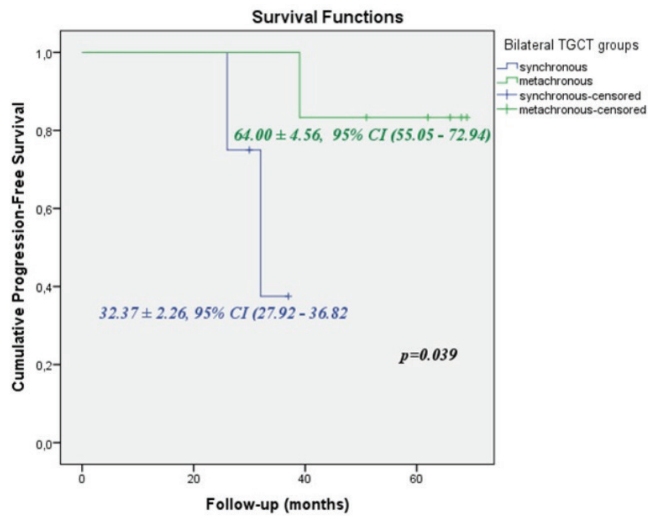


Figure 4. Plot of disease-free survival of bilateral synchronous - metachronous testicular germ cell tumors

CI: Confidence interval, TGCT: Testicular germ cell tumors

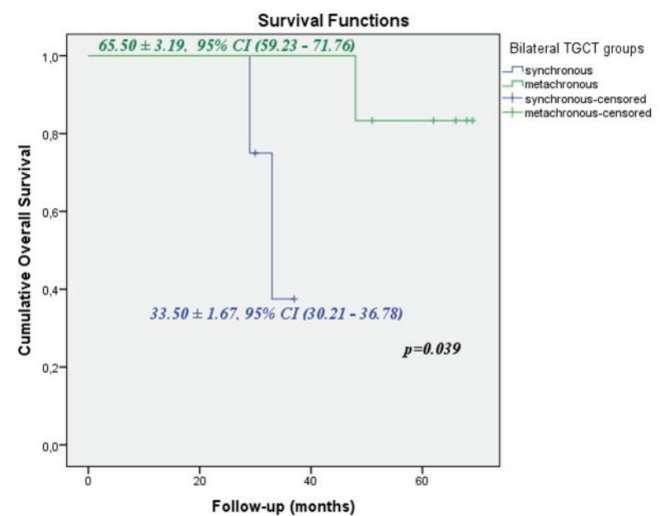
seminoma (7). In synchronous tumors, different histopathological types are less common in both testicles and the histology seen in most of them is also seminoma (1). It has been reported that contralateral tumors develop more in patients with seminoma (1.8% vs 0.6%) compared to patients with non-seminomas (10,11). However, in two studies conducted with limited patient data, it was stated that more contralateral tumors could develop in patients with non-seminoma than patients with seminoma (12,13), and tumor histopathology was reported to have no effect on bilateral tumor development in a case series of 6 patients (14).

In our current study, although we had a small number of patients with bilateral TGCT, we found the rate of bilateral tumors to



**Figure 5.** Plot of progression-free survival of bilateral synchronous - metachronous testicular germ cell tumors

CI: Confidence interval, TGCT: Testicular germ cell tumours



**Figure 6.** Plot of overall survival of bilateral synchronous - metachronous testicular germ cell tumors

CI: Confidence interval, TGCT: Testicular germ cell tumours

**Table 5. Prognostic factors affecting contralateral tumor development in the follow-up of unilateral testicular germ cell tumors**

	Univariate Model				Multivariate Model			
	OR	95% Confidence interval		p	OR	95% Confidence interval		p
		Lower	Upper			Lower	Upper	
Age	1.054	0.966	1.152	0.233				
Tumor size	1.058	0.823	1.361	0.659				
Histopathologic subtype	1.497	0.490	4.578	0.479				
Tumor side (Left vs Right)	1.910	0.533	2.381	0.162				
AFP	1.001	0.988	1.004	0.681				
β-hCG	1.012	0.895	1.058	0.828				
LDH	1.014	0.912	1.095	0.835				
Tumor stage	1.128	0.440	2.890	0.801				
ITGCN (Yes vs No)	2.533	0.434	14.778	0.032*				
Rete testis invasion (Yes vs No)	1.538	0.167	14.084	0.704				
Lymphovascular invasion (Yes vs No)	2.557	0.281	23.255	0.404				
Embryonal carcinoma rate >50%	1.798	0.196	16.393	0.603				
Proliferation rate >70%	3.400	0.725	7.694	0.081				
Undescended testis (Yes vs No)	3.750	0.589	23.867	0.042*	2.561	1.243	13.456	0.026*
Semen parameter disorders (Yes vs No)	4.357	0.672	28.240	0.023*	2.879	1.457	15.457	0.037*
Hypospadias (Yes vs No)	2.400	0.725	7.694	0.041*				
Atrophic testis (Yes vs No)	1.001	0.456	1.965	0.789				
Testicular microlithiasis (Yes vs No)	3.857	0.701	21.216	0.021*	2.015	1.127	9.420	0.015*
Testicular Dysgenesis Syndrome (Yes vs No)	5.182	0.923	29.100	0.042*	3.876	1.523	10.123	0.031*
Family history of TGCT (Yes vs. No)	6.556	1.142	37.621	0.035*	6.556	1.142	37.621	0.035*
NLR >3.23	1.433	1.002	2.052	0.041*	1.348	0.859	3.145	0.025*
MLR >0.31	4.312	2.091	14.177	0.027*	2.234	1.158	7.815	0.022*
PLR >150.01	1.101	0.595	2.017	0.044*				
MPV >5.08	1.084	0.847	1.386	0.522				
RDW >13.90	1.282	0.867	1.896	0.213				

\*p<0.05 Asterisk (\*) indicates statistical significance.

AFP: Alpha-fetoprotein, β-hCG: Beta human chorionic gonadotropin, ITGCN: Intratubular germ cell neoplasia

LDH: Lactate dehydrogenase, MLO: Monocyte/lymphocyte ratio, MPV: Mean platelet volume,

NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, RDW: Red blood cell distribution width,

TGCT: Testicular germ cell tumor, OR: Odds ratio



be 11.4%, above the rates reported in the literature, since we were a selected center where oncology patients were referred. Consistent with the literature, 40% of these patients had synchronous and 60% had metachronous tumors. While pure seminoma was present on both sides of all synchronous tumors; in 2 (33.3%) patients with metachronous tumors, contralateral tumor was observed to be seminoma, unlike the first non-seminoma tumor. When we examined a total of 68 patients with unilateral tumors at the time of diagnosis, contrary to most publications reported in the literature and similar to the studies of Osterlind et al. (13) and Colls et al. (12); we found that more contralateral metachronous tumors developed in patients with non-seminoma (10.8% vs 5.4%) than patients with seminoma.

Survival and remission rates in bilateral patients were found to be similar to unilateral patients in some studies (7). When bilateral patients were compared within themselves, it was observed that the clinical stage was higher in synchronous tumors, and the DFS and OS rates were found to be lower (1). It was observed that DFS and OS rates of metachronous tumors decreased when the clinical stage was higher, when the time until the second tumor development was >60 months, and when the histopathology of the first tumor was seminoma (1). Unlike these findings, Holzbeierlein et al. (15) observed that most of the bilateral synchronous and metachronous tumors were at low stage. Klatte et al. (16), on the other hand, reported that, although bilateral synchronous tumors were diagnosed at a higher stage, if an effective treatment was applied, oncologically similar results could be obtained in synchronous and metachronous tumors compared with unilateral tumors. We also observed similar rates among bilateral and unilateral patients and between bilateral synchronous and bilateral metachronous subgroups in terms of local recurrence, distant metastasis and overall mortality rates in our patients. However, we found that the PFS and OS durations were significantly shorter in bilateral synchronous tumors than in bilateral metachronous tumors, and that stage III disease developed more in synchronous tumors (75% vs 33.3%).

According to the common interpretation of most studies in the literature; since seminomas are thought to be less aggressive than non-seminomas, active surveillance is used more frequently than adjuvant therapy in patients with bilateral synchronous seminomas. It has been suggested that this may be the reason for the greater decrease in DFS and OS durations of synchronous seminomas compared to synchronous non-seminomas (1,17,18). A similar decrease in survival rates was observed in patients with metachronous tumors in whom seminoma developed in the contralateral testicle after the first seminoma compared to metachronous tumors with non-seminoma histopathology, and this situation was attributed to the same cause (1). Zequi et al. (1) observed that seminoma developed at a higher rate in patients who developed tumor in the contralateral testis during a follow-up period longer than 60 months. Depending on the above-mentioned interpretation, they stated that the DFS and OS rates decreased in relation to this situation, since more seminomas were seen when the time until the second tumor development was >60 months. As is known in most solid tumors, the prolongation of the time between the onset of the primary lesion and the recurrence or metastasis is a good prognostic indicator. However, metachronous testicular

tumors were not metastases, and according to Zequi et al.'s argument (1), the prolongation of the time until the detection of metachronous tumors increased the likelihood of development of seminoma and, on the contrary, it was found to be associated with a poor prognosis. Nevertheless, there is no accepted clear consensus to explain this situation and both the findings of Holzbeierlein et al. (15) and Klatte et al. (16) and our findings do not support the mentioned relationship.

It was found that the frequency of metachronous tumor development was lower in patients who underwent adjuvant CT. In addition, it was observed that more seminoma was observed in metachronous tumors developing in patients who underwent CT compared to metachronous tumors developing in the follow-up of patients who did not undergo CT, regardless of the initial tumor histology (1). Although there were publications predicting that adjuvant CT would reduce the risk of contralateral tumor development (16,19), there were also studies in which this relationship was not observed (1,20). We realized that adjuvant radiotherapy (RT) was applied to patients who were diagnosed as having stage I seminoma and were treated between 2010 and 2013 in our study, as part of the treatment protocol of that period. However, adjuvant RT has been replaced by single-dose carboplatine in the treatment of these patients in the EAU guidelines since 2014 (3). Of our 68 patients with unilateral tumors at the time of diagnosis, contralateral tumors were observed in 20% of those who were under active follow-up because they had stage I disease and did not have a risk factor for occult metastasis development, while the rate of contralateral tumor development after adjuvant CT or RT was lower (6.25%). In our 2 patients who developed contralateral tumors after active follow-up, we observed that the rate of development of seminoma was higher, consistent with the findings of Zequi et al. (1).

While the incidence of TGCT development is 0.005% in the general population, the rate of tumor development in the contralateral testicle in individuals with a history of TGCT is up to 5% (1). Despite this increased risk, it was observed that the tumor detected in the contralateral testis in patients with metachronous tumors was mostly (95.2%) stage I tumor and the developing second tumor was smaller than the first tumor (10,11). Therefore, it has been emphasized that self-examination and early diagnosis are important in patients with a history of TGCT (10). The time until the second tumor development has been reported as a median of 39-47 months (4 months-32 years) in different studies (1,7,16,17). Among our 68 patients with unilateral tumors at the time of diagnosis, contralateral tumors were detected in 8.1% of them during a follow-up of a median 57.5 months, and a second tumor emerged within 5 years, after the first tumor was detected in all metachronous tumors. But we did not observe a significant difference in the size of the second tumors in our patients.

ITGCN is defined as a precursor lesion in the development of TGCT (1). There are still controversies about the application of biopsy to confirm the presence of ITGCN in the contralateral testis during orchiectomy, since the incidence of ITGCN and tumor development in the contralateral testis is low, the developing metachronous tumors are mostly at low stage, and side effects such as infertility and testosterone production

disorders due to local RT to be applied in case of detection of ITGCN, can be observed (16,21). However, it is known that the risk of developing ITGCN in the contralateral testis is >35% in patients with unilateral tumors under the age of 40 with testicular volumes of <12 mL (22). Therefore, contralateral testis biopsy is recommended during orchiectomy in patients under 40 years of age with risk factors for the development of TGCT (testicular volume <12 mL, history of undescended testis or impaired spermatogenesis) (3). In our study, ITGCN was detected in 34 of 68 patients who had unilateral tumors at the time of diagnosis, and 15 of these 68 patients (20.2%) who had the above risk factors did not undergo contralateral testicular biopsy, because none of them accepted it. We observed that 4 (26.6%) of 15 patients with risk factors developed contralateral metachronous tumors. Of these 4 patients, 2 (50%) had a history of undescended testis, 2 (50%) had abnormal semen parameters, while all were under the age of 40, but none of them had atrophic testis. Since our findings are consistent with the data in the literature, we continue to present testicular biopsy as a recommendation to patients with these risks in our clinical practice.

Although the gold standard approach is bilateral orchiectomy in cases of bilateral TGCT, the most important problems related to this are infertility, the need for lifelong androgen maintenance, and the psychological effects observed due to the young age of the patients (7,10). Therefore, if preoperative serum testosterone levels are normal in small-sized (<2 cm in size or tumor volume is less than 30% of testicular volume) synchronous bilateral and metachronous contralateral tumors, testis-sparing surgery (partial orchiectomy) can be used as an alternative approach (3). However, if ITGCN is detected histologically in the remaining testicular tissue, it is recommended to give adjuvant RT to the testis on that side (3). Therefore, patients who want to have children should be given detailed information about this situation. Partial orchiectomy was not performed in any patient among 10 patients with bilateral tumors in our study considering that there would not be enough testicular parenchyma to be preserved, because tumor size was not less than 2 cm or the estimated tumor volume/testicular volume ratio was not less than 30%.

Individuals with a family history are at higher risk for developing TGCT, and the rate of bilateral tumor development is higher in these individuals compared to sporadic patients (10). In our patients with bilateral tumors, family history was significantly higher than in patients with unilateral tumors (40% vs 13.2%). When bilateral tumors were examined within themselves, we found that although no significant difference was found between synchronous and metachronous tumors in terms of family history, family history was the risk factor that increased tumor development 6.5 times in the contralateral testicle.

Recently, the effects of inflammation markers and hemogram parameters on oncological outcomes have been more popularly investigated, and it has been reported that high NLR and platelet levels in TGCT may cause development of metastasis and a decrease in disease-specific survival (23,24). When we examined the effects of serum hemogram parameters on our patients, it was found that NLR, MLR, PLR values at the time of

diagnosis were higher in bilateral tumors compared to unilateral tumors. We found that high NLR (>3.23) and MLR (>0.31) values increased the risk of contralateral TGCT by 1.3 and 2.2 times, respectively.

The effects of molecular and genetic risk factors on the development of TGCT have not been fully elucidated yet. Recently, there are publications defending that c-kit mutations are more common in bilateral patients than unilateral patients (25), and also opposite results have been encountered (26,27). Although no genetic and biomolecular markers were examined in our study, we observed that the development of TGCT in the contralateral testis significantly increased in the presence of family history, testicular microlithiasis, undescended testis with increased NLR, MLR, TDS and TDS components, and impairment in semen parameters. Although it is known that metachronous contralateral TGCT develops within the first five years in 60% of the patients, it has been reported in the literature that metachronous contralateral TGCT may develop even after 32 years and long-term follow-up is required in all patients, especially in individuals with the risk factors mentioned above (16).

### Study Limitations

The retrospective design of our study, the limited power of the statistical analysis performed due to the small number of patients, lack of randomization while determining the groups, short follow-up periods, and the fact that the follow-up results belonging to a single center, were the main limiting factors. In addition, since our hospital was a center where oncology patients were referred, the patients we included in the study mostly represented a selected group with advanced stage disease. For this reason, bilateral TGCT detection, recurrence, progression and death rates in our study were higher than the rates reported in the literature. We think that these rates may not reflect the real population incidence.

### Conclusion

According to our findings, although bilateral synchronous tumors were detected at a more advanced stage at the time of diagnosis, we showed that the survival rates of bilateral tumors were similar to unilateral tumors thanks to appropriate treatments, although a significant decrease in PFS and OS times was observed. Nevertheless, we observed that patients with unilateral tumors at the time of diagnosis increased the risk of development of contralateral tumors in cases of family history, TDS, impaired semen parameters, undescended testicular history, presence of testicular microlithiasis, NLR >3.23 and MLR >0.31. If patients with a history of TGCT carry these risk factors, it is important to follow-up the contralateral testis regularly, as the possibility of development of bilateral metachronous tumors in long-term follow-up increases.

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**Contribution:** There is not any contributors who may not be listed as authors.

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

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## Ethics

**Ethics Committee Approval:** All procedures in our study were conducted in accordance with the ethical standards of the institutional and national research committee including human participants and the principles of the Helsinki Declaration, and since it was a retrospective study, no ethics committee approval was made.

**Informed Consent:** Each patient was informed before the surgery that oncological follow-up information such as recurrence, metastasis development, and survival analysis can be used in various oncological studies to be performed in the clinic without specifying the patient names and identity information, and the data of patients who did not consent were not used.

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

## Authorship Contributions

Surgical and Medical Practise: A.I.A., M.S.B., H.B., Concept: A.I.A., M.S.B., Design: I.S., H.B., Data Collection or Processing: I.S., Analysis or Interpretation: I.S., A.I.A., Literature Search: I.S., Writing: I.S.

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