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CLINICAL STUDY

# Bilateral testicular germ cell tumors – 50 years experience

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**ABSTRACT**

OBJECTIVE: This study analysed the characteristics and outcome of the patients with bilateral germ testicular cell cancer (TC), especially synchronous.

METHODS: Among 2.124 TC patients diagnosed between 1970 and 2020, 96 (4. 5%) developed the 2nd TC. Nine occurred synchronously and 87 were metachronous. Patients were analysed according to the age and histological type of bilateral TC in comparison with unilateral TC.

RESULTS: The mean follow-up of all 2,124 patients was 14.9 years. Unilateral TC occurred in 2.028 patients (the mean age of 32.4 years), 707 of them had seminoma, 1.310 nonseminomatous (NS) TC and 11 spermatocytic tumours. The 1st tumour of metachronous bilateral disease was diagnosed at a significantly younger age (27.1 years) compared to the unilateral disease (32.4 years). The mean interval between the 1st and the 2nd TC was 8.2 years. Patients with NSTC had a longer mean interval (9.2 years) between the 1st and the 2nd TC in comparison with seminoma patients (6.7 years). The mean age at diagnosis for seminoma was significantly higher (31.3 years) compared to the NSTC (24.1 years). Bilateral seminoma occurred in 5 synchronous bilateral TC patients, four patients had discordant histology, none presented with bilateral NSTC.

CONCLUSIONS: Bilateral TC is a rare and requires individualized management of patients *(Tab. 5, Fig. 4, Ref. 32)*. Text in PDF *www.elis.sk*

KEY WORDS: bilateral testicular cancer, interval, synchronous, metachronous tumours, seminoma, nonseminoma, discordant.

## Introduction

Testicular cancer (TC) represents a relatively rare neoplasm, accounting for 1–2 % of cancer in men and 5 % of urologic tumours in general (1). However, TC is the most common malignancy in young adult men (aged 15–40 years) with a consistent increase in incidence in European population (2, 3). The recognised risk factors include a past or current history of cryptorchidism or undescended testis, Klinefelter syndrome, familiar history of TC, infertility and maternal oestrogen exposure (4, 5). The presence of tumour or testicular intraepithelial neoplasia (TIN) is recognised as a risk factor for the development of contralateral tumour (6). The development of bilateral tumour is not a new phenomenon. The first documented case of bilateral germ cell TC was described by Bidard in 1853 (7). Hamilton and Gilbert (8) believed that the likelihood of cancer in the contralateral testis was from several hundred to several thousand times greater than expected in chance association. In various medical centres all over the world, the incidence of bilateral TC varies between 1–7.8 % (6, 9, 10). Bilateral TCs are either synchronous (occurring simultaneously) or metachronous (developing consecutively after a certain time interval). Synchronous tumours are apparent at the time of diagnosis or within the first three months after the diagnosis. In one of the largest studies including 29,515 TC patients, the 15-year risk of contralateral TC was 1.9 %, with 62 % occurring metachronously and 38 % synchronously (10). The risk appears to be higher in younger patients and in those with a seminoma histology. The incidence of bilateral TC had increased over the last decades due to the long-term survival of patients after treatment for their 1st tumour (11). Such observations appear to be related to better management and higher cure rates of TC patients treated over recent decades, mostly related to advances in chemotherapy, particularly the efficiency of cisplatin-based regimens (12). Metachronous disease is about twice as frequent comparing to bilateral synchronous TC. In the systematic study published in 2012 with 50.376 patients, the incidence of bilateral TC was 1.82 %, including metachronous (1.26 %), and synchronous (0.56 %) cases (13). The current guidelines for the treatment of TC contain little information related to bilateral involvement and most of the published articles concerning patients with synchronous TC are case reports or a small series. Bilateral germ cell TC tend to have the

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same histological structure. The majority of the synchronous cases are bilateral seminomas (50 %), following by discordant histology (34 %), and bilateral nonseminoma (16 %) (10).

The aim of the present paper was to analyse a group of patients with bilateral TC from the single centre database focusing on synchronous bilateral TC and to interpret the need for an individualized treatment approach.

## Material and methods

Between 1970 and 2020 a total of 2,124 patients with primary TC were collected and followed-up in our centre. The group comprised 2,028 (95.5 %) patients with unilateral TC and 96 (4.5 %) patients with bilateral TC. This group of patients was analysed according to the age and histological type of the 1st and the 2nd tumour in comparison to the group of patients with unilateral TC.

*Statistical analysis*

The patients' characteristics were analysed using descriptive statistics. Continuous variables are reported as the means with standard deviations (SD) and medians with ranges, and upper and lower quantiles ($Q_1$–$Q_3$). Categorical variables are presented as counts and relative frequencies as well as differences between the groups were evaluated using Pearson's $chi^2$ test or Fisher's exact test. Statistical analyses were performed using StatsDirect 3.0.191 software (Stats Direct Ltd., Cheshire, UK) and Statistica 13 software (Dell-StatSoft, Inc. Tulsa, OK, US). All the p values were considered significant at a two-tailed $p < 0.05$.

## Results

The mean follow-up of all the 2,124 patients was 14.9 years (median 13.7; 25–75 % quantile 6.3 and 22.2 years, range 1–50.3 years). The mean age of 2,028 patients with unilateral TC was 32.2 years. In the group of patients with unilateral TC, there were 707 patients with a pure seminoma (the mean age of 37.0 years) 1,310 patients with nonseminomatous (NS) TC (the mean age of 29.8 years) and 11 patients with spermatocytic tumour (the mean age of 48.9 years). The difference was statistically significant ($p < 0.001$) (Tab. 1).

In the group of 96 patients with bilateral TC, we observed 87 patients with metachronous occurrence, where the 1st TC was diagnosed in the mean age of 27.1 years and the 2nd TC in the mean age of 35.2 years (median 34 years, 25–75 % quantile was 30 and 40 years, range 18–57). In patients with metachronous bilateral disease, the 1st TC was diagnosed significantly earlier compared to TC in patients with unilateral disease ($p < 0.0001$) (Tab. 2).

**Tab. 1. Age of patients with unilateral TC.**

| Patients | Number | Mean | Median | 25–75% quantile | range |
|---|---|---|---|---|---|
| All | 2.028 | 32.2 | 31 | 26 and 38 | 1.0–79 |
| Seminoma | 707 | 37.0 | 36 | 30 and 42 | 15–73 |
| NS | 1.310 | 29.8 | 28 | 24 and 34 | 1.0–79 |
| Sperm. Tumour | 11 | 48.9 | 50 | 39 and 59 | 32–67 |

**Tab. 2. Age of patients with metachronous bilateral TC.**

| Patients | Number | Mean | Median | 25–75% quantile | range |
|---|---|---|---|---|---|
| All | 87 | 27.1 | 27 | 23 and 32 | 1.0–49 |
| Seminoma | 36 | 31.3 | 31 | 27 and 34.5 | 21–49 |
| NS | 51 | 24.1 | 24 | 20 and 29 | 1.0–35 |

**Tab. 3. Interval between manifestation of the 1st and 2nd bilateral TC.**

| Patients | Number | Mean | Median | 25–75% quantile | range |
|---|---|---|---|---|---|
| All | 87 | 8.2 | 6 | 3.8 and 10.9 | 0.3–34.3 |
| first seminoma | 36 | 6.7 | 5 | 2.7 and 9.4 | 6.7–23.3 |
| first NS | 51 | 9.2 | 6.9 | 4.3 and 12 | 7.7–33.4 |

In the group of 87 patients with metachronous TC, there were 36 patients (the mean age 31.3 years) with pure seminoma in the 1st TC and 51 patients with NSTC (the mean age 24.1 years). The difference was statistically significant ($p < 0.001$) (Tab. 2).

The difference between the mean age of 707 patients with pure seminoma in unilateral TC (37 years) and 36 patients with pure seminoma in the 1st TC of bilateral disease (31.3 years) was statistically significant ($p < 0.001$).

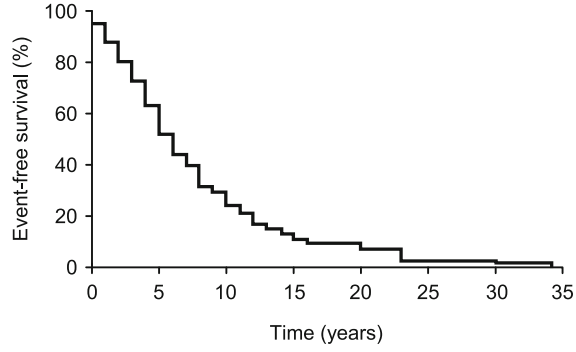


**Fig. 1. Time intervals between the first and second tumours in patients with metachronous bilateral TC.**

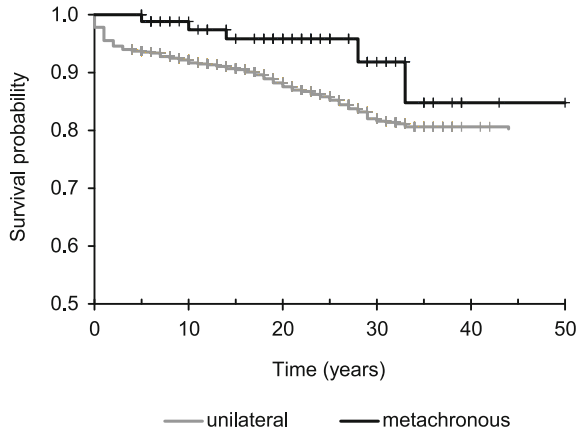


**Fig. 2. Comparison of survival of patients with metachronous bilateral and unilateral TC.**

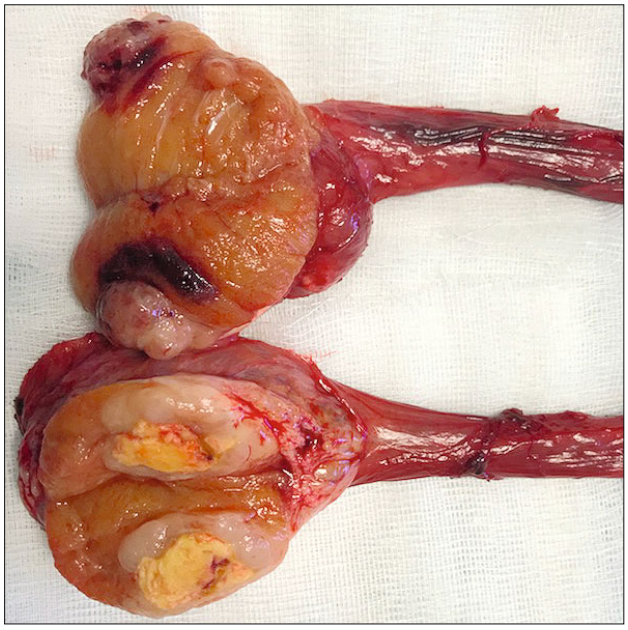

**Fig. 3. Macroscopic specimens of removed testicles with simultaneous bilateral TC.**

Similarly, a statistically significant was the difference between the mean age of 1,310 patients with primary NSTC in unilateral TC (29.8 year) and 51 patients with primary NSTC in the 1st TC of bilateral disease (24.1 years) ($p < 0.001$). The first TC in patients with bilateral disease occurred significantly earlier.

Patients with pure seminoma in the 1st TC (the mean age 31.3 years) are significantly older than patients with NSTC in the 1st tumour (the mean age 24.1 years) ($p < 0.001$).

In the group of 87 patients with metachronous TC, the mean interval between the manifestation of the 1st and the 2nd TC was 8.2 years (median 6 years; 25–75 % quantile was 3.8 and 10.9 years; range 0.3–34.3 years) (Tab. 3). The 2nd TC occurred within 5 years in 32 patients (36.8 %), within 10 years in 29 patients (33.3 %), after 10 years in 18 patients (20.7 %), after 20 years in 6 patients (6.9 %), and even appeared after 30 years of follow up in two (2.3 %) patients (Fig. 1).

The mean interval between the manifestation of the 1st TC with pure seminoma histology and the 2nd TC was 6.7 years and between the manifestation of the 1st NSTC and the 2nd TC 9.2 years. The difference between these intervals was not statistically significant ($p = 0.0685$) (Tab. 3).

After a follow-up of 20 years, a statistically significant difference in the overall survival was observed ($p = 0.0091$). Patients with metachronous bilateral TC reached 96.7 % survival rate at 20 years (95% CI: 91.4–100 %) compared to 87.6 % (95% CI: 85.8–80.1%) in unilateral TC (Fig. 2).

Familial occurrence was observed in two non-twin brothers with metachronous bilateral seminoma.

In nine (9.4 %) patients, TC was considered to be synchronous (the interval between occurrence of the 1st and 2nd TC was < three months) with the mean age of 34 years (median 29 years, 25–75 % quantile was 27 and 43 years, range 24–45 years). Four of them presented with a discordant histological type (the mean age 27.5 years; 25–75 % quantile was 26.5 and 28.5; range 26–29). The mean follow-up of these 9 patients was 161.7 months (13.5 years), range 12-337 months (28.1 years) (Tab. 4).

For illustration, we present macroscopic specimens of removed testicles with simultaneous bilateral cancer with discordant histologic type (Fig. 3). Based on our own experience, we confirm that contrast MRI can distinguish between NSTC and seminoma (Fig. 4A, B).

## Discussion

Patients with a history of TC are at significantly higher risk for developing a tumour in the remaining testis. Of the 2,124 patients, who were treated and/or diagnosed at our centre, 96 (4.5 %) patients developed contralateral TC. This study group represents one of the largest cohorts of bilateral TC cases published in literature. First registered patient with bilateral TC in our study was diagnosed in year 1970 and the presented study evaluated the outcome of 50-years of experience in the centre. Furthermore, 9

**Tab. 4. Characteristics of patients with simultaneous bilateral TC.**

| Order of patient | Age | Histology I | Histology II | Clinical stage | Postorchiectomy | Follow-up (months) |
|---|---|---|---|---|---|---|
| 1 | 27 | S | NS | I | Surveillance | 337 |
| 2 | 29 | S | NS | III | 4xBEP | 304 |
| 3 | 26 | S | NS | IIB | 4xBEP | 295 |
| 4 | 45 | S | S | I | 20.0 Gy | 195 |
| 5 | 24 | S | S | III | 4xBEP | 157 |
| 6 | 43 | S | S | IIB | 3xBEP | 70 |
| 7 | 45 | S | S | IIB | 3xBEP | 64 |
| 8 | 39 | S | S | IIA | 3xBEP | 21 |
| 9 | 28 | S | NS | I | 1xBEP | |

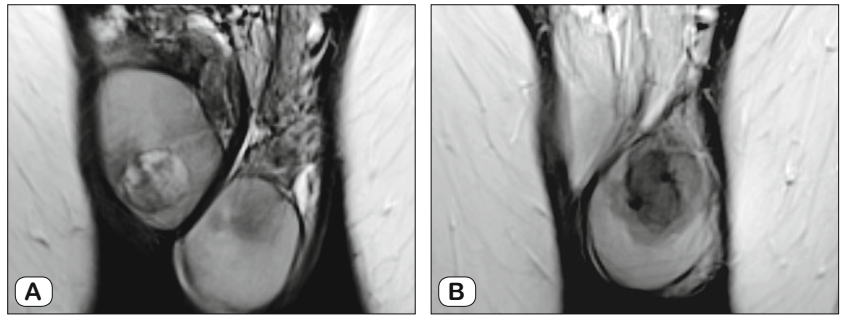


**Fig. 4. Distinguishing NSCT from seminoma testis using MRI.**

**Tab. 5. Characteristics of tumour type in patients with metachronous bilateral TC.**

| Histology I | Histology II | Number of patients |
|---|---|---|
| S | S | 25 |
| S | NS | 11 |
| NS | S | 22 |
| NS | NS | 29 |

patients (9.4 %) presented with an extremely rare synchronous bilateral TC. Although published data state that metachronous TC represents 62 % of bilateral TC cases (10), our data showed that 83.5 % (87 of 96 patients) developed a metachronous tumour and a synchronous disease was scarce.

According to the large meta-analysis of 51 studies with 916 cases of bilateral TC (13), men with metachronous tumours had the average age of 30.02 years at diagnosis of the 1st tumour, while men with synchronous tumours were older, with the average age of 33.54 years ($p < 0.001$). The results of our current study confirmed this trend, however we registered a lower median of age both in metachronous and in synchronous cohort, 27.1 and 34 years, respectively.

Several authors described differences in the incidence of bilateral TC between the patients with a previous history of seminoma and NSTC (11, 13, 14, 15). Pure seminoma was the most common histology type in the group of patients aged 31–40 years. Patients with seminoma at a younger age (≤ 30 years) had a greater risk of developing TC in the contralateral testis. NSTC was most common in the age group of 21–30 years. There was no significant difference in the incidence of bilateral TC between these patients in the different age groups (4).

Interestingly, in metachronous TC, we registered higher rates of discordant histology 37.93 % and bilateral NSTC 25.23 % than pure seminoma in both tumours 28.73 % (Tab. 5), unlike previously published data from Fossa et al (10), where the majority of the metachronous cases were bilateral seminomas (42.85 %), discordant histology (41.12 %) and bilateral NSTC (16.03 %).

Results of our current study confirmed the previous findings (14), that the patients with NSTC in the 1st tumour were significantly younger (22.8 years) compared to the patients with seminoma (30.7 years).

Theodore et al (16) described that patients with bilateral TC were younger compared to the men with unilateral TC. The mean age at diagnosis of the 1st tumour in patients with bilateral disease in our study was 25.8 years in comparison with the mean age at diagnosis of TC in patients with unilateral disease of 31.7 years.

Andreassen et al (17) described a statistically longer interval between 1st and 2nd TC for patients with primary NSTC (6.3 years) compared to the patients with a primary seminoma (4.6 years). Our results showed no statistical significance between these intervals (9.2 years vs 6.9 years).

Che et al (11) analysed the group of 20 patients with metachronous tumours, where the 2nd tumour occurred within 5 years in 14 patients (70 %) and between 10–15 years in the other 6 patients (30 %).

In our group of 87 patients with metachronous TC, the 2nd tumours occurred within 5 years in 32 patients (36.8 %), within 10 years in 29 patients (33.3 %), after 10 years in 18 patients (30.7 %), after 20 years in 6 patients (9.5 %), even after 30 years in two (3.2 %) patients.

Synchronous bilateral TC are exceedingly rare. When a synchronous bilateral TC develops, it is suggested that, because of the absence of lymphatic/vascular connections between the two testicles, each lesion starts independently as a primary tumour (18). The predominant histology type of synchronous TC is seminoma, identically in both lesions (19). The treatment is in principle the same as that of solitary primary germ cell TC. Tumour histology and stage determines the prognosis of synchronous tumours. Synchronous development occurred in 16.1 % of bilateral TC reported in 29 studies published since the early 80-ties (20). Dieckmann et al (21) in their review of literature reported a total of 151 cases of bilateral synchronous cancer and 114 of these (75.5 %) demonstrated seminoma in both testicles. Only 19 patients (12.6 %) had a discordant histology. This finding has, however, been challenged by more-recent data. Holzbeierlein et al (22) in their series found that 70 % patients presenting with a synchronous bilateral TC had different histology. Additionally, other series found 54 % (11) and 33 % (22) patients presented with a discordant histology. In our study, we observed 9 cases of synchronous bilateral occurrence (9.6 %) and four of them (44.4 %) presented with a discordant histology. Overall, synchronous TC were associated with a more advanced disease (higher stage) (24) and presented less favourable survival rates than metachronous TC (25).

Although bilateral orchiectomy has been largely accepted as the standard treatment for bilateral TC, several current studies reported organ-sparing approaches. In such cases, tumour diameter should not exceed 20–25 mm, to preserve enough testosterone producing parenchyma. Enucleation/resection should always be performed under a cold ischaemia to preserve the function of Sertoli and Leydig cells (26). Preoperative imaging (ultrasound and/or MRI) played a quite important role in guiding the surgical approach in patients with synchronous occurrence of TC (27).

The need to perform a routine biopsy of the contralateral testis in patients with unilateral TC is a matter of ongoing discussion (10). Some European investigators (mainly in Denmark) recommend a biopsy in all TC patients (28), some recommend this approach only for high-risk patients (29), and some do not support contralateral biopsy at the diagnosis of primary TC, although the long-term follow-up of these patients is needed (30).

Bilaterally orchiectomized TC patients need a life-long testosterone substitution in attempt to minimize the long-term adverse effects and risks associated with hypogonadal symptoms, metabolic syndrome, osteoporosis, type II diabetes, cardiovascular disease etc. (31, 32).

**Learning points**

All the patients with unilateral TC have an increased risk of developing a contralateral TC, even decades after diagnosis. Chemotherapy for the 1st TC does not eliminate the risk of de-

veloping a contralateral tumour. Management of the 2nd tumour should be individualized for each patient according to the histological type, treatment modality and clinical stage of the 1st tumour with a long-term follow-up and long-life testosterone substitution. Synchronous bilateral TC are extremely rare. Their treatment is, in principle the same as that of solitary primary germ cell TC.

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