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Bilateral testicular germ cell tumours: a systematic review

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Testicular cancer is the most common tumour in young men. It is known that a second primary contralateral testis tumour may occur in up to 5% of men with a proior tumour. About 35% of these men present with synchronous tumours, and 65% present with metachronous tumours. However there is little data about bilateral testicular germ cell tumours (BTGCT) in the literature and the most published articles are case reports on a small series of men, which makes it difficult to draw conclusions about therapeutic strategies for the treatment of BTGCTs.

In fact, current guidelines for the treatment of testicular cancer contain little information related to bilateral disease. Therefore, the aim of our study is to provide a broad overview of BTGCT and to update data focusing on incidence, pathological features, and clinical outcomes of men with BTGCTs. Thus, an extensive review containing 94 studies and more than 50,000 patients was conducted.

What's known on the subject? and What does the study add?
Bilateral testicular germ cell tumours (BTGCTs) are rare neoplasms. Most previously published studies consist of case reports or small retrospective case series. Little is known about their epidemiological and clinicopathological characteristics.

BTGCT corresponded to 1.82% of testicular tumours. Metachronous disease was about twice as frequent as synchronous disease. The primary tumour histology, chemotherapy use and the interval between metachronous tumours influenced the histology of the second tumour. Overall, synchronous tumours were associated with more advanced disease and presented less favourable survival rates than metachronous tumours.

KEYWORDS

testis cancer, testis germ cell tumour, bilateral testicular cancer, bilateral testicular germ cell tumour

INTRODUCTION

Testicular cancer is the most common tumour type in males aged 15–44 years. In 2010, an estimated 8400 new cases of testicular cancer were diagnosed in the USA, accounting for <1% of all cancers in the country [1]. The number of diagnosed cases has gradually increased [2], and the current frequency of tumour incidence is 50% higher than it was 30 years ago. However, the causes of this increase remain unclear [3].

Testicular germ cell tumours (TGCTs) represent the majority of testicular tumours (>95%). Men with TGCTs have a higher risk of developing a subsequent tumour. The incidence of TGCTs in the general population is ≈0.005%, and a second primary contralateral testis tumour may occur in up to 5% of men with a prior tumour. When compared by paired analysis according to age, the relative risk of a second cancer can reach 27-times higher in men with TGCT [4]. A possible genetic predisposition of these men for developing second tumours has been proposed, as it is known that men with bilateral testicular tumours are significantly more likely to have brothers with testis cancer than those with unilateral disease [5].

Bilateral TGCTs (BTGCTs) account for 0.5% to 5% of cases of testicular cancer. About 35% of these men present with synchronous tumours, and 65% present with metachronous tumours [6]. Because BTGCTs are rare, most published articles are case reports on a small series of men, which makes it difficult to draw conclusions about therapeutic strategies for the treatment of BTGCTs. Many questions on this subject remain unanswered.

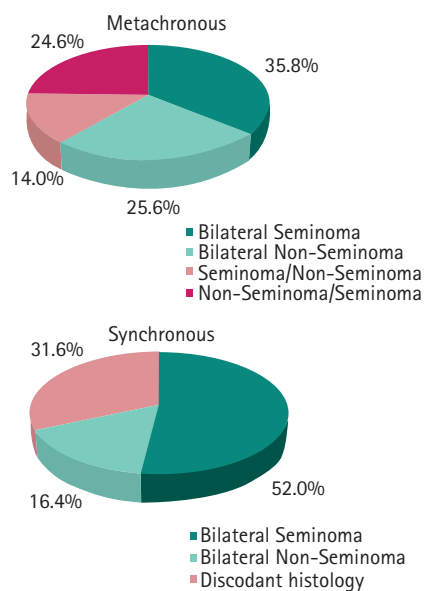The aim of the present systematic review was to provide a broad overview of BTGCT and to update data concerning incidence, pathological features, and clinical outcomes of men with BTGCTs.

PATIENTS AND METHODS

We used methods adapted from the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews, version 1.0, published by the Agency for Healthcare Research and Quality [7].

We comprehensively searched the MEDLINE and Cochrane databases on 4 July, 2011. Search terms included the USA National Library of Medicine's Medical Subject Headings (MeSH): *bilateral testicular cancer, bilateral testicular neoplasm, bilateral testicular germ cell tumour, metachronous testicular tumour, and synchronous testicular tumour*. Both free text and MeSH search for keywords were used. Data from a period of 20 years, from 1991 to 2011, were included in the search.

FIG. 1. Histological characteristics of men with metachronous (above) and synchronous (below) TGCTs.

Metachronous

24.6%
35.8%
14.0%
25.6%

■ Bilateral Seminoma
■ Bilateral Non-Seminoma
■ Seminoma/Non-Seminoma
■ Non-Seminoma/Seminoma

Synchronous

31.6%
52.0%
16.4%

■ Bilateral Seminoma
■ Bilateral Non-Seminoma
■ Discodant histology

The criteria for inclusion in this review were any published studies that included the following:

1. Investigated data on the incidence of BTGCTs.
2. Provided relevant information about clinical and pathological features.
3. Described data related to the clinical outcome of men with these tumours.

The exclusion criteria were as follows:

A. Studies with no clear information on the sample origin.
B. Studies that failed to present data clearly enough or with obviously paradoxical data.

Because BTGCT is extremely rare, we decided to include retrospective studies, regardless of sample size. Additionally, data on five men with BTGCT treated at our institution (corresponding to 1.03% of a total of 432 testicular cancers treated over the past 20 years) were included in the study. When necessary, we contacted study authors for additional data or information. As individual patient data were not available in some of the series, a pooled-analysis level study was performed.

Two reviewers independently assessed each study for inclusion criteria and retrieved the

data from each paper. These data were transferred into a standard format to generate a final database. Discrepancies were resolved by consensus. Studies that met the inclusion criteria were assessed for the following:

- study design
- study population
- epidemiological information
- sample size
- clinical outcomes

STATISTICAL ANALYSIS

Fisher's exact test and the Pearson chi-squared test were used to compare clinical and pathological features between groups. Differences in variables with a continuous distribution across dichotomous categories were assessed with the Mann–Whitney U-test. The Student's t-test was used to compare means of independent groups. The level of significance was set at 5%.

Disease-specific survival (DSS) was defined as the interval between the primary surgery or the last follow-up visit and disease-related death. Overall survival (OS) was defined as the interval between the primary surgery or the last follow-up visit and death. Kaplan–Meier curves were generated to study DSS and OS. The log-rank test was used to compare the estimated curves for each category for a given variable. The confidence interval was set at 5%.

RESULTS

We identified 94 studies that included men with BTGCTs. However, 43 of these studies were excluded based on the inclusion and exclusion criteria. The remaining 51 studies included 39 in English [6,8–45], nine in Spanish [46–55], and one in Italian [56]. These studies encompassed a total of 938 men.

From a total of 51 scientific articles, we obtained 21 case-report studies, 29 case-series studies, and a large population-based cohort study [6]. The large cohort study was included in the final database, but it was only used to calculate epidemiological characteristics of BTGCTs. That study was not used in survival analysis because it did not provide accurate information on clinical and pathological features.

EPIDEMIOLOGICAL DATA

Of the 51 selected studies, 19 described the prevalence of contralateral tumours in cohorts of men with previous TGCTs. In all, 50 376 men were included in the analysis, of which 916 presented BTGCTs, a prevalence of 1.82%. Of these 916, 634 had metachronous tumours (69.2%), and 282 (30.8%) had synchronous tumours.

Men with metachronous tumours had an average age of 30.02 years at diagnosis of the first tumours, while men with synchronous tumours were older, with an average age of 33.54 years ($P < 0.001$). In men with metachronous disease, the histological type of the first tumour was non-seminoma in 50.2% of cases. The remaining tumours presented as 25.6% non-seminoma and 24.6% seminoma in the contralateral testicle (Fig. 1).

On the other hand, seminomatous tumours were more frequent in the second group of tumours, accounting for 60.4% of the secondary tumours. The mean interval between tumours was 65.6 months. In the synchronous disease group, the presence of bilateral seminoma and bilateral non-seminoma was 52% and 14.6% of men, respectively (Fig. 1).

PATIENT CHARACTERISTICS

In all, 50 of the selected articles described clinical and pathological features in addition to the clinical outcome of the men and were included in the survival analysis. Data on 314 men from the aforementioned excluded study [6] were not analysed in this manner. The final database included 602 men: 261 (43.4%) with synchronous tumours and 341 (56.6%) with metachronous tumours. Information regarding patient characteristics is presented in Table 1.

Men with synchronous tumours were older at diagnosis than those with metachronous tumours ($P < 0.001$). Discordant histology was less frequent in synchronous disease compared with metachronous disease. Bilateral seminomatous tumours were more common in men with synchronous tumours (59.4%). In the metachronous group, bilateral seminomatous tumours occurred in 29.9% of cases (Table 1).

Men presenting metachronous tumours were mostly diagnosed as clinical stage I (73.3%), while 49.8% of synchronous tumours were diagnosed as stage I, and 50.2% were identified as stages II or III. Chemotherapy was the most often used complementary therapeutic method used for synchronous tumours (30.3%), whereas radiation was indicated in 38.1% of metachronous tumours (Table 1).

Several clinical and pathological variables were found to predict the histology of the second malignancies in the metachronous tumour group. In all, 68.9% of men presenting a first tumour with seminomatous histology also presented seminomatous histology in the opposite side tumour. Those men who developed a second tumour after an interval of <60 months were associated with a higher rate of seminomatous tumours. There were more cases of seminomatous histology in the second tumours of men who underwent chemotherapy for the treatment of the primary seminoma ($P = 0.003$) or non-seminoma ($P = 0.021$) tumours (Table 2). When chemotherapy was not delivered to the first tumours (seminoma or non-seminoma), the histology of the second tumours were concordant in 64% of cases.

SURVIVAL ANALYSIS

The 5-year OS rates for men in the synchronous and metachronous tumour groups were 88% and 95%, respectively. The 5-year DSS was also significantly lower in the synchronous tumour group than in the metachronous tumour group (89% vs 95%, Fig. 2).

Analysis of the synchronous tumour group showed that higher clinical stage and discordant histology negatively impacted on OS and DSS rates in a univariate analysis. For the metachronous tumour group, higher clinical stage, a time interval between tumours of >60 months (Table 3), and the presence of bilateral concordant histology (mainly seminomatous tumours) negatively influenced OS and DSS rates (Fig. 2).

DISCUSSION

Current guidelines for the treatment of testicular cancer contain little information

TABLE 1 Clinical and pathological characteristics of men presenting with synchronous and metachronous tumours

Characteristic	Synchronous	Metachronous	P
N (%)	261 (43.4)	341 (56.6)	
Mean (SD) age, years	33.54 (5.68)	30.90 (5.20)	<0.001
Mean interval, months	NA	68.03	
N (%):			
Histology:			
Bilateral seminoma	155 (59.4)	102 (29.9)	<0.001
Bilateral non-seminoma	22 (8.4)	107 (31.3)	
Discordant histology	84 (32.2)	132 (38.7)	
Clinical stage:			
I	130 (49.8)	250 (73.3)	<0.001
II	75 (28.7)	74 (21.7)	
III	56 (21.5)	17 (5.0)	
Therapeutics:			
Surveillance	68 (26.1)	37 (10.9)	<0.001
Radiotherapy	62 (23.8)	130 (38.1)	
Chemotherapy	79 (30.3)	79 (23.2)	
RPLND	23 (8.8)	31 (9.1)	
Other	29 (10.7)	64 (18.8)	

RPLND, retroperitoneal lymphadenectomy.

TABLE 2 Metachronous BTGCT clinical and pathological features and association with subsequent contralateral tumour histology

First tumour features	Second tumour seminoma, n (%)	Second tumour non-seminoma, n (%)	P
First tumour histology:			
Seminoma	102 (68.9)	46 (31.1)	<0.001
Non-seminoma	86 (44.6)	107 (55.4)	
Chemotherapy for the first tumour:			
Seminoma:			
Yes	30 (83.3)	6 (16.7)	0.032
No	72 (64.3)	40 (35.7)	
Non-seminoma:			
Yes	54 (52.4)	49 (47.6)	0.021
No	32 (35.6)	58 (64.4)	
Interval, months			
0–60	83 (66.4)	42 (33.6)	0.003
>60	72 (48.6)	76 (51.4)	

related to bilateral disease [57]. As more TGCTs have been diagnosed, especially among infertile men, testis-sparing surgery has been proposed as a therapeutic option for treatment of BTGCT or solitary testis cancer [17,29,43]. Because of these trends, additional information about BTGCT is necessary to assist in managing these men.

Some authors have described an increase in the incidence of BTGCTs [14,36]. Such observations appear to be related to better management and higher cure rates of men with unilateral disease treated over recent decades [6,41]. Several risk factors, e.g. cryptorchidism, testis atrophy, and infertility, have been associated with a higher risk of

developing a second tumour [13–15,25]. In the present study, bilateral tumours accounted for 1.82% of a cohort of 50 376 men. Of the men with bilateral tumours, 1.26% presented metachronous tumours and 0.56% presented synchronous tumours.

These data agree with previous studies that reported a prevalence of bilateral tumours of 1–3% [13–15].

Men with bilateral synchronous disease were an average of 3 years older than men with metachronous disease at diagnosis of primary tumours. This can be explained by the greater presence of seminomatous histology in men with synchronous disease compared with those with metachronous disease (83.6% vs 49.8%, respectively). Seminomatous tumours are known to present later than non-seminomatous tumours [58–62]. Although these differences were statistically significant, we think that these observations will have little impact on the clinical management of men with BTGCTs.

Most initial tumours (50.2%) in the metachronous group corresponded to non-seminomatous tumours, as was previously described [14,63–64]. This is interesting because it has been shown that non-seminomatous tumours usually correspond to 35–45% of TGCTs [3,61,65]. However, an extensive previous study analysing the risk of developing a second tumour described the absence of noticeable differences in the relative risk according to the histology of the first tumour [24].

In the present study, bilateral seminomatous tumours predominated in the synchronous disease group (59.4%), while discordant histology was more frequent in the metachronous group (39.0%). Interestingly, the rate of bilateral non-seminomatous tumours was almost four-times higher in the metachronous group compared with the synchronous group (31.3% vs 8.4%). In other words, 91.6% of cases of synchronous tumours presented seminomatous histology.

*FIG. 2. Survival probability of men with BTGCT. **A**, 5-year OS in men with synchronous and metachronous tumours (P = 0.01). **B**, 5-year DSS in men with synchronous and metachronous tumours (P = 0.03). Survival probability of men with metachronous BTGCT according to histological characteristics. **C**, 5-year OS in men with metachronous tumours (P = 0.01). **D**, 5-year DSS in men with metachronous tumours (P = 0.02).*
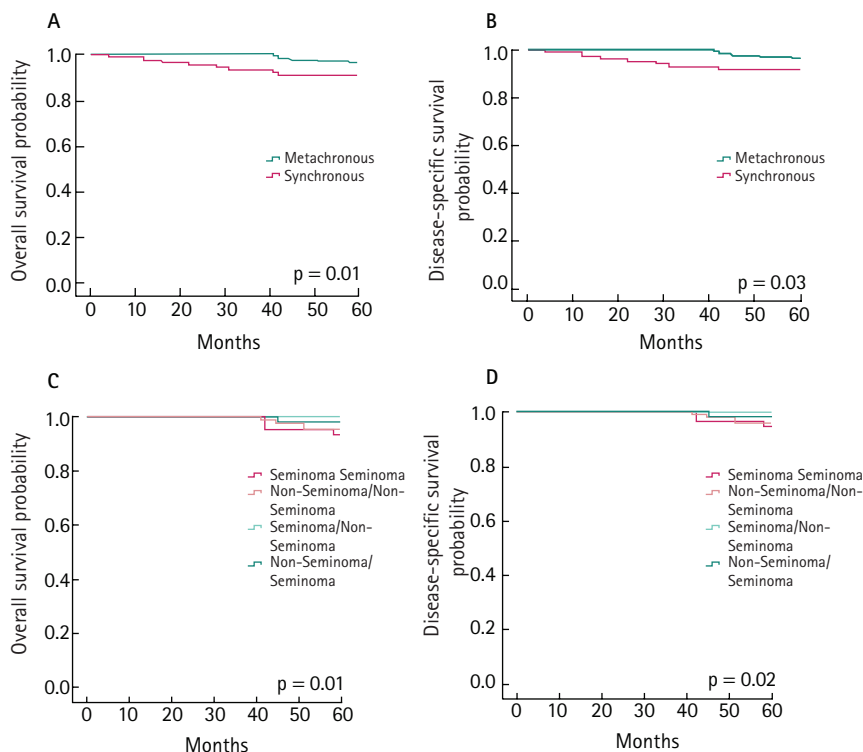

TABLE 3 Univariate survival analysis in men with synchronous and metachronous tumours

	Univariate analysis							
	Synchronous tumours				Metachronous tumours			
Feature	5-year OS, %	P	5-year DSS, (%)	P	5-year OS, %	P	5-year DSS, (%)	P
Histology:								
Concordant S or NS	94.0	<0.001	95.2	<0.001	92.6	0.008	93.1	0.01
Discordant	73.0		74.3		98.4		98.4	
Clinical stage:								
I	100	<0.001	100	<0.001	96.1	0.01	96.5	0.05
II or III	78.1		79.4		90.1		90.1	
Interval, months								
0–60					98.2	0.01	98.2	0.02
>60					94.6		94.6	

S, seminoma; NS, non-seminoma.

Interestingly, despite initially presenting in clinical stage I, in 73.3% of cases, only 10.9% of men with metachronous tumours were included in surveillance protocols. This observation suggests a more aggressive management of these tumours than unilateral tumours with the same clinical stage. Another possible reason for the low proportion of men on surveillance protocols may be the fact that the present review examined a historical series from the last 20 years and the use of surveillance protocols has become more widespread recently [66,67]. However, men in the synchronous group presented with advanced clinical stage (II or III) in 50.2% of cases, suggesting a more aggressive behaviour. In this group, 41% of men received chemotherapy alone or associated with retroperitoneal lymphadenectomy or radiotherapy.

In the present study, primary tumour histology and the interval between metachronous tumours influenced the histology of the second tumour. When the interval between the tumours was <60 months, there was seminomatous histology in 66.4% of cases. In contrast, when the time interval was >60 months, only 48.6% of the tumours were seminomatous ($P = 0.003$). Additionally, the time interval between metachronous tumours did not depend on the first treatment ($P = 0.37$, data not shown). Furthermore, when the first tumour presented seminomatous histology, the same histological type was observed in the second tumour in 68.9% of cases ($P < 0.001$). Similarly, when the first tumour was non-seminomatous, 55.4% of the secondary tumours were also non-seminomatous.

Previous studies have suggested a decreased incidence, as well as a delay, in the appearance of metachronous TGCTs after the use of chemotherapy for treatment of primary low-stage testicular tumours [20,66,67]. A recent clinical trial comprised of 1447 men described a reduced risk of contralateral testicular tumours with adjuvant single-dose carboplatin [68]. As chemotherapy is able to reduce the rates of a second lesion, probably due to some action in the contralateral testis, we investigated whether chemotherapy use influenced the histology of the secondary lesion. In fact, men with seminomatous tumours who received chemotherapy for the first lesion presented seminoma in

subsequent tumours more frequently than those who did not receive chemotherapy (83.3% vs 64.3%, $P = 0.032$). Likewise, men with non-seminomatous primary tumours who received chemotherapy had a significantly higher percentage of subsequent seminomatous tumours (52.4% vs 35.6%, $P = 0.021$). Men with non-seminomatous primary tumours who did not receive chemotherapy more frequently presented non-seminomatous histology in the contralateral testis (64.4% vs 47.6%, $P = 0.021$). Although intratubular germ cell neoplasia is present at birth, it is possible that the potential for progression of intratubular germ cell neoplasia could be influenced by chemotherapy, as it is known that half of patients with intratubular germ cell neoplasia develop invasive cancer.

Overall, synchronous tumours presented less favourable OS (88% vs 95%, $P = 0.01$) and DSS (89% vs 95%, $P = 0.02$) rates than metachronous tumours, a finding which agrees with previous studies [20,41]. Analysis including an adjustment for stage analysis showed no significant difference in OS and DSS rates between the synchronous and metachronous tumour groups (data not shown), suggesting that the higher proportion of men in clinical stage II and III in the synchronous tumour group may have negatively influenced clinical outcomes. Another possible explanation is that more men from the synchronous group than the metachronous group were placed under surveillance (26.1% vs 10.9%, respectively) and received less radiotherapy (23.8% vs 38.1%, respectively, $P < 0.001$). On the other hand, the higher rates of surveillance protocols can be explained by the predominance of seminomatous tumours within the synchronous group; usually seminomatous tumours are considered less aggressive than non-seminomatous tumours.

Discordant histology and advanced clinical stage significantly effected OS and DSS rates in the synchronous group. In contrast, survival rates of men with metachronous tumours were no worse than those with unilateral tumours, which range from 95% to 99%, according to previously published data [68–70]. The prognosis was good for both seminomatous and non-seminomatous tumours. Curiously, survival rates were significantly worse by univariate analysis in men with metachronous tumours in which

repeated seminomatous histology was observed. It is difficult to explain why concordant histology, particularly the combination seminoma/seminoma, predicted a worse survival rate in the metachronous tumour group. This correlation may indicate that these men were subject to a less aggressive treatment approach for their seminomatous tumours, as previously discussed. Furthermore, when analysed individually, the histology of the first or subsequent lesions had no influence on survival rates. In fact, only advanced clinical stage and an interval between tumour development of >60 months effected OS and DSS rates.

Generally, an increased time interval between the primary lesions and metastases of several types of solid tumours is associated with better survival rates [71]. However, it is not possible to compare this generalisation with metachronous BTGCT cases because the second tumours should not be considered as metastatic lesions. Men who presented with longer intervals between tumours (>60 months) had worse outcomes. Clearly, late-onset second tumours deserve special attention during therapeutic decision-making processes (active treatment vs surveillance, for example).

To our knowledge, the present study is the first to perform a systematic review and tabulation of data on men with BTGCTs. Because this tumour type is rare, the vast majority of previously published works consist of case reports and small case series. Although it provides important information about the behaviour of such tumours, the present study has clear methodological limitations. It is a retrospective study without central pathology review and includes an extremely heterogeneous group of patients with no information about serum markers levels. In addition, it includes men treated in different therapeutic eras, which vary profoundly in the treatment of the disease.

Despite the need for further validation, the present study provides important new data on the clinical and pathological features of BTGCTs. We think that the present review will aid in the better understanding and management of men with a disease as rare as BTGCT. Histology of the first tumour, treatment with chemotherapy, and the

interval between metachronous tumours are factors that may influence the histology of the second tumour. Bilateral seminoma with metachronous presentation presents unfavourable survival rates. Men with synchronous disease present tumours at a more advanced clinical stage and have less favourable survival rates than those with metachronous tumours.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **(B)TGCT**, (bilateral) testicular germ cell tumour; **MeSH**, Medical Subject Headings; **DSS**, disease-specific survival; **OS**, overall survival.