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Bilateral Testicular Tumours: Prevalence and Clinical Implications

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In a series of 773 patients with the diagnosis of a testicular germ cell tumour, treated at Hannover University Medical School between 1972 and 1985 and with a median follow-up of 9 years (60–210 months), bilateral testicular tumours occurred in 27 (3.5%) patients. None of 157 patients receiving chemotherapy for metastatic disease of the first tumour developed a metachronous bilateral tumour. Of 24 patients with metachronous tumours 23 had stage I and 1 patient had stage II at the time of initial diagnosis. The second testicular tumour was stage I in 18 patients, stage II in 5 and stage IV in 1 patient. 3 patients (13%) relapsed after treatment for their second germ cell tumour (surveillance 13 patients, radiotherapy 7 patients, lymph node dissection 2 patients and chemotherapy 2 patients), 1 of which died after refusing further treatment. The cure rate was 96% in patients with bilateral disease. Routine biopsy of the contralateral testis to identify existing carcinoma *in situ* (CIS) is recommended. Patients with CIS must be informed about their increased risk of a second testicular tumour. Irradiation of CIS or close clinical follow-up might both constitute appropriate strategies for the management of these patients.
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INTRODUCTION

TESTICULAR CANCER is a rare disease with an estimated incidence of 5 in 100 000 males. A considerable increase has been demonstrated in most western countries during the past decades [1]. Meanwhile, several risk factors for the development of testicular cancer have been identified [2], among which the history of a testicular neoplasm in the contralateral testis is one of the most important. The prevalence of bilateral testicular cancer in large studies ranges between 2.6 and 5.0% [2–4]. Skakkebaek and coworkers have shown, that a testicular tumour can develop from carcinoma *in situ* (CIS). They recommended contralateral biopsies in all patients with testicular cancer [5]. However, it remains unclear whether the development of a contralateral testicular tumour affects the long term survival of these patients. In a recent Italian study including 1587 patients with germ cell cancer, 20 of 23 patients who developed a second testicular tumour remained alive and disease-free after appropriate therapy [6]. The charts of 773 consecutive patients treated at the University of Hannover were analysed to estimate the relative risk for second germ cell tumours and to identify potential risk factors.

PATIENTS AND METHODS

The clinical charts of all 773 patients with malignant germ cell tumours of the testis, diagnosed and/or treated at Hannover University Medical School between 1972 and 1985, were reviewed. The median follow-up for the study population since initial diagnosis of testicular cancer was 9 years (60–210 months). The overall survival of this study population was 78%. The patients' characteristics, including histology and tumour stages according to the Royal Marsden Classification [7] are presented in Table 1. Patients were seen every 3 months in the first 2 years after initial diagnosis; twice a year up to 5 years and annually thereafter. 13 patients (1.6%) were lost to follow-up. Synchronous tumours were defined as being detected within 4 months after the first tumour, any tumours occurring thereafter were recorded as metachronous.

RESULTS

Prevalence, histology and tumour stages

The overall prevalence of bilateral testicular cancer in our study population was 3.5% (27 of 773 patients).

The contralateral tumour was diagnosed metachronously in 24 of 27 patients (89%) and synchronously in 3 of 27 (11%). Metachronous tumours were diagnosed after a median of 60 months (6–186 months). 2 patients with bilateral tumours had a history of testicular maldescent.

All 3 patients with synchronous bilateral tumours had pure seminoma in one and non-seminomatous germ cell tumour (NSGCT) in the other testicle. Tumour stages at diagnosis were stage I in 1 patient and stage II in 2 patients.

Table 1. Characteristics of the study population of 773 patients including histology and tumour stages according to the Royal Marsden Hospital (RMH) classification

Total no. of patients	773
Tumour stages (RMH)	
I	421 (54.4%)
II	213 (27.6%)
III	47 (6.1%)
IV	92 (11.9%)
Histology	
Pure seminoma	299 (38.7%)
Non-seminoma	474 (61.3%)
History of maldescent	69 (8.9%)

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In the 24 patients with metachronous tumours, the first tumour was pure seminoma in 15 (62.5%) and NSGCT in 9 (37.5%) patients. The tumour stages at initial diagnosis were: stage I in 14 patients and stage II in 1 for the patients with seminoma and stage I in all 9 patients with NSGCT. The histology of the contralateral tumour was seminoma in 13 (54%) and NSGCT in 11 (46%) patients. There was no concordance in the histological findings between the first and the second testicular tumour (Table 2).

Treatment of the contralateral tumour, follow-up and survival

Of the 18 patients with stage I disease at the time of their second testicular tumour 13 underwent surveillance and 5 patients with pure seminoma were treated with adjuvant radiotherapy. Both patients with stage II NSGCT received surgery plus adjuvant chemotherapy. 2 patients with stage II seminoma were treated by radiotherapy alone and the third patient underwent surgery. The only patient with stage IV disease was treated with cisplatinum-based combination chemotherapy and achieved a complete response (Table 3).

The occurrence of metachronous cancer according to the type of treatment for the first tumour is shown in Table 4. No metachronous tumours were observed in patients who had received chemotherapy compared with 24 second tumours in 461 patients not receiving chemotherapy ($P < 0.007$).

3 of 24 patients (13%) relapsed after treatment for their second testicular tumour. Both patients with NSGCT were salvaged (one by radiotherapy and one by lymph node dissection and adjuvant chemotherapy). 1 patient with disseminated seminoma refused further treatment and died. After a median follow-up of 9 years 26 of 27 patients (96.3%) are alive and without evidence of disease.

DISCUSSION

Synchronous bilateral cancer of the testis is a rare condition [8]. Dieckmann *et al.* cumulated 89 published cases and estimated an incidence of synchronous bilateral cancer of 1/1000 patients with germ cell cancer [9, 10]. In our study population of 773 patients, 3 (0.4%) presented with synchronous bilateral testicular cancer.

Metachronous contralateral germ cell tumours were observed in 24 of 773 patients corresponding with a prevalence of 3.1%.

Table 2. Histology and tumour stages of first and second tumours in 24 patients with metachronous bilateral testicular cancer

First tumour and stage		Second tumour and stage	
Seminoma	15	Seminoma	9
Stage I	14	Stage I	8
Stage II	1	Stage II	1
		Non-seminoma	6
		Stage I	6
Non-seminoma	9	Seminoma	4
Stage I	9	Stage I	2
		Stage II	2
		Non-seminoma	5
		Stage I	2
		Stage II	2
		Stage IV	1

Table 3. Treatment of first and second testicular tumours in 24 patients with metachronous bilateral disease. The number of patients is given in parentheses

	Treatment
First tumour	
Seminoma	(15)
	Stage I (14): radiotherapy (11), surveillance (3)
	Stage II (1): radiotherapy (1)
Non-seminoma	(9)
	Stage I (9): surgery (5), radiotherapy (2)*, surveillance (2)
Second tumour	
Seminoma	(13)
	Stage I (10): radiotherapy (5), surveillance (5)
	Stage II (3): radiotherapy (2), surgery (1)†
Non-seminoma	(11)
	Stage I (8): surveillance (8)
	Stage II (2): surgery + chemotherapy (2)
	Stage IV (1): chemotherapy (1)

*Both patients were treated prior to the introduction of cisplatinum based chemotherapy.
†Patient with abdominal lymph nodes > 5 cm.

The median interval between first and second tumour was 60 months (6–186 months). Though follow-up in our series was 9 years, second tumours have been reported as late as 32 years after primary diagnosis [3]. Therefore, the prevalence of bilateral tumours might further increase with longer follow-up. All but one second tumour were detected in early stages, usually by routine follow-up visits or self examination.

Osterlind *et al.* [2] investigated the relative risk of second metachronous testis cancer in 2850 men. Based on 73 cases and 24.588 person-years of observation, the relative risk for the development of a second germ cell cancer was 24.8 (95% confidence interval: 19–38) compared to an age-matched control group. A higher risk ratio was reported for patients with NSGCT compared to patients with seminoma. In our population 15 of 311 (4.8%) patients with seminoma developed a metachronous testicular cancer compared to only 9 of 492 (1.8%) patients with NSGCT ($P < 0.027$).

The impact of the treatment modality given for the first tumour on the probability of a metachronous second tumour remains controversial. Kleinerman and Hellbardt reported a higher percentage of patients treated with radiotherapy developing a second tumour compared to patients without radiotherapy [11, 12]. Thompson found a higher incidence of second tumours in patients receiving surgery or radiotherapy (5/27) opposed to patients receiving chemotherapy (0/120) [4]. While no difference was seen between patients treated with surgery alone or radiotherapy in our series, no patient treated with chemotherapy developed a second tumour ($P < 0.007$). This may indicate, that chemotherapy as a systemic treatment modality could be able to prevent or delay the development of contralateral testicular tumours. However, second testicular tumours have been reported after prior chemotherapy [6, 10] and were also observed at our institution in 2 patients with extragonadal germ cell tumours after prior chemotherapy.

In a series of 897 patients reported by Hay, metachronous testicular tumours occured mainly within the first 5 years of follow-up, whereas in the period 15–19 years after irradiation secondary cancers originating from the bladder or the gastro-

Table 4. Metachronous testicular tumours according to histology and prior treatment

	All	Treatment modality		
		Surveillance	Radiation +/− Surgery	Chemotherapy
Seminoma	15/263	3/19	12/223	0/21
Non-seminoma	9/355	7/182	2/37	0/136
All	24/618 (3.9%)	10/201 (5.0%)	14/260 (5.4%)	0/157* (0%)

The calculations are based on all patients at risk after a median follow-up of 5 years. (*$P < 0.007$ for patients with prior chemotherapy versus patients with surveillance or radiation +/− surgery).

intestinal tract were dominating [13]. This time pattern might suggest, that the metachronous testicular tumour represents rather a biological phenomenon of the same disease than a treatment-induced second malignancy. The occurrence of metachronous testicular tumours in patients on surveillance programmes, who did not receive potentially carcinogenic treatment modalities, further supports this hypothesis.

A history of testicular maldescent, generally acknowledged as a risk factor for testicular cancer, was not more common in patients developing bilateral cancer (2/27) as opposed to those with unilateral disease (67/746). In our series the histology of the first testicular tumour did not predict the histological type of the metachronous tumour (Table 2). This supports the hypothesis of Skakkebaek *et al.* [14], that CIS represents the common precursor of both seminomatous and non-seminomatous germ cell tumours.

Berthelsen *et al.* reported CIS-like changes in biopsy specimens of the contralateral testicle in 13 of 250 (5.2%) men with unilateral testicular cancer; 2 patients with CIS later developed a second germ cell tumour [15]. Dieckmann *et al.* reported an incidence of 3.4% (19 of 551) of contralateral CIS in German patients with testicular cancer [16]. Routine biopsies of the contralateral testis were not performed in our patients and none had received irradiation of the remaining testis.

Since a contralateral biopsy has no adverse effect itself, it can be recommended as a routine procedure for all patients. It still remains controversial, whether all patients with CIS should receive irradition of the contralateral testis, which will result in definite infertility and might also affect Leydig cell function [17, 18]. Though the fertility of patients with CIS is generally poor [19], it may occasionally be sufficient to father children. Of interest, 1 patient developing a metachronous testicular cancer in our series has fathered a healthy child during the surveillance period. Therefore, close clinical follow-up might also be an appropriate strategy in patients with documented CIS who either possess a strong wish to preserve fertility or fear the late effects of radiotherapy.

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