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Original Paper

Bilateral Testicular Germ Cell Tumours in Patients with Initial Stage I Disease: Prevalence and Prognosis—a Single Centre's 30 Years' Experience

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Development of second testicular tumours, i.e. bilateral testicular cancer, is influenced by systemic chemotherapy for the first tumour. The prevalence of bilateral testicular cancer was studied in patients with initial stage I disease, in which no systemic treatment was given after orchidectomy. All stage I testicular cancer patients entered a surveillance study with an intensive follow-up since 1982. We hypothesised that after 1982, bilateral testicular cancer was diagnosed at an earlier stage of disease. The prevalence of bilateral testicular cancer was 4.7% (8/170) in stage I patients treated between 1967 and 1981, and 2.9% (8/275) in stage I patients treated between 1982 and 1997 ($P > 0.5$, χ^2-test). In the period 1967–1981, 6 patients had stage I second tumours and 2 patients had stage III second tumours. The former 6 patients are alive with no evidence of disease and the 2 patients with metastatic tumours died of disease or treatment. In the period 1982–1977, all 8 patients had stage I second tumours and all are alive with no evidence of disease. The overall prevalence of bilateral testicular cancer in stage I patients was 3.6% and has slightly decreased over the past three decades. Intensive follow-up, improvement of radiodiagnostic computed tomography techniques, availability of serum tumour markers, and patient education have resulted in earlier diagnosis and lower stage of contralateral testicular tumours, contributing to improved prognosis. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

PROGRESS IN the prognosis of patients with testicular cancer after the introduction of cisplatin-based polychemotherapy is paralleled by an increased concern for the development of secondary malignancies, including malignancies in the remaining testis [1]. In patients who survived unilateral testicular cancer, the risk of developing a contralateral testicular tumour is considered to be 500 times greater than that in healthy men [2]. The increased risk in these patients is much higher than would be expected by chance alone, implying that genetic and/or environmental predisposition might play a role in the development of the second tumour. The prevalence of bilateral testicular cancer in patients with unilateral testicular tumours varies between 1.0 and 5.8% [2–9]. Recent studies demonstrate an increased prevalence of bilateral tumours [4, 10].

Testicular carcinoma *in situ* was first mentioned in 1972 by Skakkebaek who postulated that carcinoma *in situ* is a preinvasive stage of testicular germ cell neoplasms [11]. In patients with unilateral testicular tumours, the prevalence of carcinoma *in situ* in the contralateral testis has been reported in 4.9–5.4% [12, 13]. It has been suggested that cisplatin-based chemotherapy eradicates contralateral carcinoma *in situ*, and thereby reduces the risk of bilateral tumours [5, 14]. The overall influence of cisplatin on the occurence of bilateral testicular cancer seems to be ambiguous: the risk of developing a contralateral tumour is increased as a result of prolonged survival, but, alternatively, cisplatin appears to reduce the risk of a second testicular tumour by eliminating premalignant carcinoma *in situ*. Considering these contradictory effects of cisplatin, the most natural course of bilateral

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testicular cancer development is apparently demonstrated in patients with unilateral stage I disease, since the development of a contralateral tumour is not influenced by systemic treatment in these patients.

In addition to the improved prognosis of testicular cancer patients with the introduction of cisplatin, the staging of patients in the late 1970s was changed when computed tomography (CT) and the serum tumour markers alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) became available [15, 16]. These improved diagnostic possibilities, as well as an effective treatment in case of a relapse, initiated the introduction in the early 1980s of a surveillance policy for patients with stage I non-seminomatous testicular germ cell tumours (NSTGCT) [17, 18]. According to this policy, after orchidectomy all these patients underwent standardised, periodic out-patient check-ups, including the evaluation of serum tumour markers and CT scans of the abdomen and chest. This intensive follow-up advanced the time of diagnosing relapses, with subsequent higher survival rates [18]. In addition to the earlier diagnosis of relapses, we hypothesised that after the introduction of the surveillance policy for stage I patients, combined with a better patient education, second primary testicular tumours are detected at an earlier stage of disease, contributing to an improved prognosis of bilateral testicular cancer patients.

The experience with bilateral testicular cancer over the past three decades in a large population of patients with initial stage I testicular cancer is reported. The prevalence and prognosis of bilateral testicular cancer before and after the introduction of the surveillance policy for stage I disease and the availability of cisplatin in testicular cancer treatment, were studied. Finally, the role of predisposition in the development of bilateral testicular tumours is discussed.

PATIENTS AND METHODS

In the period 1967–1997, 445 patients with stage I testicular cancer were treated at the Groningen University Hospital (GUH). Two cohorts were identified: one cohort of 170 patients (80 NSTGCT, 90 seminomas) who were diagnosed between 1967 and 1981, before the introduction of cisplatin-containing chemotherapy and the surveillance policy, and another cohort of 275 patients (183 NSTGCT, 92 seminomas) diagnosed between 1982 and 1997. All patients underwent orchidectomy and at staging there was no evidence of regional and/or distant metastases. As a result of improved diagnostic possibilities (CT scanning and serum tumour markers), clinical staging methods were obviously different over the two periods. In general, until 1981 staging of disease was performed according to Boden and Gibb with the aid of physical examination, lymphangiography, chest X-ray and lung tomography. Since 1982, patients have been staged according to the Royal Marsden Hospital classification system, using physical examination, serum tumour markers AFP and hCG, chest X-ray, and CT scans of the chest and abdomen [19]. In none of the patients was routine biopsy or ultrasonography of the contralateral testis performed at the time of initial diagnosis.

During the study period, treatment strategies for NSTGCT underwent major changes. Between 1967 and 1981, the majority of patients with stage I NSTGCT underwent a radical retroperitoneal lymph node dissection (RPLND) after orchidectomy. Since 1982, all patients with stage I NSTGCT have been treated according to the surveillance policy after orchidectomy [18]. The treatment of patients with stage I seminoma did not change greatly during the study period and generally consisted of postorchidectomy adjuvant radiotherapy (25 Gy) to retroperitoneal and unilateral iliac lymph nodes, with or without supradiaphragmatic radiotherapy. During the total study period, all patients were discharged from follow-up evaluations after a disease-free interval of 10 years.

The medical records of all patients were reviewed and patients with bilateral testicular cancer were studied in detail. Bilateral testicular cancer in both cohorts was compared with respect to prevalence, age at diagnosis, stage of disease, interval between the first and second testicular tumour, histology, treatment and prognosis. Furthermore, information was obtained about a history of undescended testes and the presence of familial cases with testicular cancer.

RESULTS

The clinical and histological data concerning all patients with bilateral testicular cancer are listed in Tables 1 and 2. The prevalence of bilateral testicular cancer in patients with stage I disease treated between 1967 and 1981 was 4.7% (8 of 170). Four contralateral tumours developed in the cohort of 80 patients with a NSTGCT (5.0%), and four contralateral tumours developed in the cohort of 90 patients with a seminoma (4.4%). Presentation of all bilateral tumours was metachronous, the median interval between the first and the second primary tumour was 7.0 years (range 1–18) (Table 1). At the time of diagnosis of the second testicular tumour, 6 patients had stage I disease and 2 patients had stage III disease (according to Boden and Gibb) (Table 2). 4 patients had bilateral tumours of the same histological types, 2 with non-seminomatous and 2 with seminomatous tumours. However, in 4 patients, there was no concordance in histology. 2 patients with stage III non-seminomatous contralateral disease were treated with chemotherapy. 2 patients with stage I non-seminomatous second tumours were treated according to the surveillance policy. 2 of 4 patients with stage I seminomatous second tumours received adjuvant radiotherapy after orchidectomy. The remaining 2 patients with stage I seminomatous second tumours had previously received radiotherapy in the treatment of the first testicular tumour. 1 of these 2 patients underwent RPLND and the other was treated with surveillance for the second primary tumour.

Table 1. *Characteristics of bilateral testicular cancer patients* (1967–1981 *versus* 1982–1997)

Period	Prevalence bilateral testicular cancer (%)	Mean age at first tumour (years)	Mean age at second tumour (years)	Median interval (years)	Interval (years)			Disease-free survival (%)
					< 5	5–10	> 10	
1967–1981	4.7	32.8 (23–53)	40.8 (29–67)	7.0 (1–18)	4	1	3	75
1982–1997	2.9	32.8 (26–37)	37.0 (26–44)	3.4 (0.5–11)	5	3	0	100
Total period	3.6	32.8 (23–53)	38.9 (26–67)	4.7 (0.5–18)	9	4	3	87.5

Table 2. Clinical and histological characteristics of bilateral testicular cancer patients (1967–1981 *versus* 1982–1997)

No.	Age (years)	Undescended testes	First tumour: Histological type	First tumour: Stage	First tumour: Therapy	Interval (months)	Second tumour: Histological type	Second tumour: Stage	Second tumour: Therapy	Follow-up (months)
1967–1981										
1.	23	No	NS	I	Radiation	108	NS	III	Chemo	Died (12) →sepsis
2.	29	No	NS	I	RPLND	36	Seminoma	I	Radiation	NED (119)
3.	28	No	Seminoma	I	Radiation	60	NS	III	Chemo	DOD (13)
4.	51	No	Seminoma	I	Radiation	189	NS	I	Surveillance	NED (93)
5.	53	No	NS	I	RPLND	14	Seminoma	I	Radiation	NED (155)
6.	18	No	NS	I	RPLND	126	NS	I	Surveillance	NED (97)
7.	28	No	Seminoma	I	Radiation	220	Seminoma	I	Surveillance	NED (9)
8.	32	No	Seminoma	I	Radiation	11	Seminoma	I	RPLND	NED (116)
1982–1997										
1.	32	No	Seminoma	I	Radiation	95	Seminoma	I	Surveillance	NED (74)
2.	36	No	Seminoma	I	Radiation	31	Seminoma	I	Surveillance	NED (72)*
3.	37	No	NS	I	Surveillance	63	Seminoma	I	Radiation	NED (60)
4.	33	No	NS	I	Surveillance	108	NS	I	Surveillance	NED (42)
5.	26	No	NS	I	Surveillance	5	Seminoma	I	Surveillance	NED (94)
6.	26	No	NS	I	Surveillance	51	Seminoma	I	Radiation	NED (64)
7.	36	Bilat	NS	I	Surveillance	13	Seminoma	I	Surveillance	NED (61)
8.	36	No	Seminoma	I	Radiation	18	NS	I	Surveillance	NED (9)

Bilat, bilateral; NS, non-seminoma; RPLND, retroperitoneal lymph node dissection; NED, no evidence of disease; DOD, dead of disease; chemo, chemotherapy. *Received chemotherapy for relapse, 29 months after second orchidectomy.

2 of 8 patients with bilateral testicular cancer died; 1 patient died due to the malignant disease and 1 patient due to chemotherapy-related complications. In both patients the second tumour had become manifest in stage III. The remaining 6 patients are alive with no evidence of disease after a median follow-up of 8.9 years (range 1–13). None of the bilateral testicular cancer patients treated between 1967 and 1981 had a history of undescended testes or familial occurrence of testicular cancer.

In the period 1982–1997, 8 of 275 patients with initial stage I disease (2.9%) had bilateral testicular germ cell tumours, all presenting metachronously (Table 1). Five contralateral tumours developed in the cohort of 183 patients with a NSTGCT (2.7%), and three contralateral testicular tumours developed in the cohort of 92 patients with a seminoma (3.3%). The median interval between the first and the second testicular tumour was 3.4 years (range 0.5–11) (Table 1). All patients had stage I disease at diagnosis of the second tumour (Table 2). 3 of 8 patients showed concordance in histology of the first and second tumour; in 2 patients both tumours were seminomatous and in 1 patient both tumours were non-seminomatous. 5 patients had discordant histology with the first tumour being a non-seminoma in 4 and a seminoma in 1.

2 patients with stage I non-seminomatous second tumours were treated according to the surveillance policy. Of the 6 patients with stage I seminomatous second tumours, 2 received adjuvant radiotherapy and 4 were treated according to the surveillance policy. 2 of the latter 4 patients had previously been treated with radiotherapy for a seminomatous first tumour. 1 of the patients with a seminomatous second tumour treated with surveillance relapsed 29 months after second orchidectomy and was treated with salvage cisplatin-based polychemotherapy. After a median follow-up of 5.3 years (range 1–8), all bilateral testicular cancer patients are alive with no evidence of disease.

1 of 8 patients (12.5%) had a history of bilateral undescended testes. 1 other patient (12.5%) had a non-twin brother who had been treated for unilateral testicular seminoma.

DISCUSSION

The prevalence of bilateral testicular cancer in the literature ranges from 1.0 to 5.8% [2–9], with an increase demonstrated in recent studies [4, 10]. The main reason for this increased prevalence seems to be the availability of cisplatin in the management of disseminated testicular cancer, resulting in improved prognosis and an increasing cohort of survivors at risk for developing a second testicular tumour [4, 6]. The trend of increasing prevalence of bilateral testicular cancer is not confirmed by our data on stage I patients who demonstrate the natural history of second primary tumour development, not influenced by systemic chemotherapy. The prevalence of bilateral testicular cancer in the present series even slightly decreased over the three decades, from 4.7% in the cohort of patients initially treated in the period 1967–1981, to 2.9% in patients initially treated between 1982 and 1997 ($P > 0.5$, χ^2-test). However, the figures in the present study are influenced by the increased number of patients diagnosed with stage I NSTGCT in the second series (from 80 to 183), in contrast to the number of patients with stage I seminomas which remained equal (90 and 92, respectively). The increased number of patients with NSTGCT is mainly due to a changed referral pattern; since the late 1970s all NSTGCT patients within a defined area of the northern part of The Netherlands are referred to the GUH for further management after orchidectomy. Moreover, the stage distribution of NSTGCT patients treated at the GUH has changed, resulting in a higher percentage of stage I

NSTGCT in the 1990s [20]. This might also partially explain the increased number of patients with stage I NSTGCT in the second cohort. Furthermore, it must be mentioned that the prevalence of bilateral testicular cancer in the latter cohort of patients might further increase with prolonged follow-up, in particular of the recently treated patients. According to the literature, the majority of second tumours arise within 5 years after the first tumour diagnosis and, thus, a further increase in the prevalence of bilateral testicular cancer in the second cohort theoretically will only be small [2, 4, 6]. However, data from the first cohort in the present series, with three of eight (38%) second tumours occurring more than 10 years after the first (Table 1), are in contrast with the literature and suggest a higher further increase in the prevalence of bilateral testicular cancer with prolonged follow-up in the second cohort. The overall prevalence of bilateral testicular cancer in this series was 3.6% (16 of 445). The prevalence of contralateral carcinoma *in situ*, a pre-invasive stage of testicular neoplasms, in two large series of patients with a unilateral testicular tumour was found to be slightly higher, namely 4.9–5.4% [12, 13]. There are several explanations for this slight difference between the prevalence of bilateral testicular cancer, studied retrospectively in stage I patients, and the prevalence of contralateral carcinoma *in situ*, detected prospectively at diagnosis of a unilateral testicular tumour.

A proportion of patients with contralateral carcinoma *in situ* received cisplatin-based polychemotherapy for disseminated disease, in contrast with stage I patients in the present series who were treated with locoregional therapy (RPLND, RT). The systemic administration of chemotherapeutic agents possibly eradicated carcinoma *in situ* in the remaining testis, preventing the development of a second primary tumour [5, 14]. In addition, some cases of testicular carcinoma *in situ* which did not progress to testicular neoplasms, even after long intervals, have been reported [21]. Immunological defence mechanisms might have played a role in the prevention of actual tumour development in these cases [22]. Furthermore, a proportion of patients treated for unilateral testicular cancer are lost to follow-up evaluation and, therefore, the possible development of a second primary testicular tumour in these patients is not registered, resulting in an underestimation of the prevalence of bilateral testicular cancer. Moreover, since contralateral tumours can develop after a long interval, some patients might have died of testicular cancer or other causes before developing a second testicular tumour [6, 7]. Considering these explanations for the slightly higher prevalence of contralateral carcinoma *in situ*, the present data on bilateral testicular cancer in stage I patients support the theory of Skakkebaek that carcinoma *in situ* is a pre-invasive stage of testicular germ cell tumours [11].

In the present study, the prevalence of bilateral testicular cancer in patients with a seminomatous first tumour was 3.8% (7 of 182) compared with 3.4% (9 of 263) in patients whose first tumour was a NSTGCT ($P > 0.5$, χ^2-test). These figures are in contrast with two other large studies [5, 7]. Osterlind and colleagues reported a higher risk of second tumour development in patients with NSTGCT [5] whilst Bokemeyer and associates reported a higher prevalence of bilateral testicular cancer in patients with seminoma [7]. However, the prevalence of bilateral testicular cancer in patients with a seminomatous first tumour during the past three decades may have been influenced by the improvement of radiotherapy techniques for seminoma, resulting in reduced radiation scattering to the remaining testis. Since radiation is assumed to have an eradicating effect on carcinoma *in situ*, this reduced scattering may have increased the prevalence of bilateral testicular carcinoma in the last 15 years.

A history of undescended testis is a well-known predisposing factor for developing testicular neoplasms [23]. In patients with unilateral testicular cancer, the incidence of undescended testes varies from 3.6 to 14% [23, 24]. The role of undescended testes in bilateral tumour development remains a moot point. In the present series, 6.3% of bilateral testicular cancer patients (1 of 16) appeared to have a history of undescended testes. This figure is not higher than the reported incidence of undescended testes in unilateral testicular cancer [23, 24], a finding also mentioned in several previous studies [6, 10]. In contrast, others have reported the incidence of undescended testes in patients with bilateral testicular cancer to be higher than in patients with unilateral testicular cancer [2]. However, in view of the inconsistency of data on undescended testes in several reports, the incidence rates of undescended testes in bilateral and unilateral testicular cancer are difficult to compare and have to be judged with some reserve. Nevertheless, it seems obvious that patients with malignancies in both testis, with or without a history of undescended testes, may be considered at high risk of having a genetic predisposition to the malignant disease [25]. The familial occurrence of testicular cancer in one of the bilateral testicular cancer patients in the present series emphasises this genetic predisposition. After the introduction of the surveillance policy for patients with stage I disease in the GUH in the early 1980s, all second testicular tumours were stage I at diagnosis. In the period before the introduction of the surveillance policy, 25% of patients with bilateral testicular cancer had disseminated disease at diagnosis. In addition to the greater extent of disease at contralateral diagnosis, the mean time to second tumour development was also longer in the cohort of patients treated in the period before the introduction of the surveillance policy. Thus, the use of CT scans and the serum tumour markers AFP and hCG in the follow-up management of testicular cancer patients has contributed to earlier detection of the second primary tumour with lower stage of disease. Moreover, patients with unilateral testicular cancer are better informed about the increased risk of developing a second primary tumour and are recommended to perform periodic self-examination of the remaining testis. This also appears to have contributed to the earlier diagnosis of the second tumour. However, the difference in the time to second tumour diagnosis between the two cohorts of patients must be judged with some reserve in view of the shorter follow-up interval of most patients in the cohort 1982–1997. With prolonged follow-up of patients, not only the prevalence but also the mean interval between the first and second tumour may slightly increase. Nevertheless, it seems clear that both intensified follow-up and improved patient education played a role in earlier diagnosis of contralateral tumours in the second cohort. This earlier diagnosis certainly contributed to the improved overall survival. In the present study, all bilateral testicular cancer patients in the second cohort had stage I contralateral tumours and only 1 patient was given cisplatin-based polychemotherapy for relapse. However, in general, the difference in survival of testicular cancer patients between the two eras is principally due to the availability of cisplatin-based polychemotherapy.

In conclusion, the prevalence of bilateral testicular cancer in this large series of patients with initial stage I disease was 3.6% and slightly decreased over the three decades. The prevalence in stage I patients, in whom second tumour development is not influenced by previous treatment, was consistent with the reported prevalence of contralateral carcinoma *in situ* in unilateral testicular cancer patients [12, 13].

Nowadays, the prognosis of bilateral testicular cancer is generally good. However, because the prognosis is influenced more by the stage of the second tumour than purely by its presence, early diagnosis of the contralateral tumour is of particular importance to improve survival. Therefore, long-term follow-up evaluations of patients with unilateral testicular cancer are indicated to detect second primary tumours as early as possible. In addition, patients with unilateral tumours should be advised to perform periodic testicular self-examination. Whether routine biopsy of the contralateral testis to screen for carcinoma *in situ* should be performed in all patients at diagnosis of the first tumour remains controversial.

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