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Bilateral germ cell cancer of the testis: a report of 11 patients with a long-term follow-up

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Objective To describe the incidence, clinical characteristics, treatment methods and long-term follow-up of bilateral germ cell tumours of the testis (GCTT) in patients treated at one institution.

Patients and methods Of 552 patients with GCTT, 11 (2%, mean age 26.9 years) developed bilateral disease; all 11 underwent radical orchidectomy. Additional treatment was planned according to the histological type and clinical stage of the tumour, and previous treatments. Intramuscular testosterone was administered periodically after total castration. The data on survival, sexual status and treatment complications were reviewed.

Results Of the 11 patients, seven developed a second tumour metachronously (median interval 87 months) and four had synchronous bilateral GCTT. Cryptorchidism, infertility or atrophic testis was associated with the development of bilateral GCTT in seven of the 11 patients. All synchronous tumours and most of the sequential tumours had identical histology on both sides. Although all sequential tumours presented at an early clinical stage, three of four synchronous bilateral GCTTs presented at an advanced stage. Five patients received platinum-based chemotherapy; three patients underwent post-chemotherapy resection of the retroperitoneal residual mass. Sexual libido and potency were conserved in all patients. No significant morbidity was recorded as being caused by any of these treatments. At a median follow-up of 11.6 years, all patients were alive with no evidence of cancer.

Conclusions All patients with unilateral GCTT have an increased risk of developing a contralateral testicular tumour, even decades after diagnosis. Management should be adapted to each patient. As all patients in this series survived in the long-term, developing a second germ cell cancer does not necessarily predict a poor prognosis.

Keywords Germ cell tumours, testis, bilateral, prognosis

Introduction

Germ cell tumours of the testis (GCTTs) are still the most common solid cancers in men aged 15–34 years [1]. Fortunately, more than 80% of patients are cured even if they have advanced clinical stage disease, a unique feature of this cancer. However, there is a greater risk of developing a secondary GCTT in the remaining testis. Many investigators have reported an increase in the incidence of bilateral GCTT [2,3]. Since the first report by Bidard in 1853 [4], the incidence of bilateral GCTT has been reported to be 1–5.8% [5,6]. Although the second tumour is usually metachronous, synchronous tumours also occur [2,3,7,8]. Several risk factors, e.g. cryptorchidism, a previous history of infertility, atrophic testis and carcinoma *in situ* (CIS) of the testis, have been associated with the increased risk of developing a secondary GCTT [7]. Herein we present the incidence of bilateral GCTT, the clinical characteristics of the patients, diagnostic procedures, treatment methods and long-term follow-up of patients from a consecutive series of GCTTs treated at one institution.

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Patients and methods

Between 1980 and 1998, 552 patients with GCTT were treated in our department; of these, 11 (2%) developed bilateral GCTT. The diagnostic procedure included a history, physical examination, serum markers (AFP and βhCG), ultrasonographic evaluation of the testicles and abdomen, a chest X-ray and CT of the thorax, abdomen and pelvis. Clinical staging was conducted according to the Royal Marsden Hospital Staging System [9]. All patients underwent radical orchidectomy as an initial treatment and for histological diagnosis. Subsequently, the treatment strategy was determined according to the histological type and clinical stage of the cancer. Patients with clinical stage I or IIA seminoma received radiotherapy to the retroperitoneum, if not given previously. Patients who had clinical stage I seminoma as a secondary cancer after previous radiotherapy were entered into an active surveillance programme with no

further therapy. Patients with clinical stage I nonseminomatous cancer developed either primarily or secondarily were also managed by active surveillance. Patients with an advanced clinical stage of either seminoma or nonseminoma received platinum-based polychemotherapy regimens (Table 1). Patients with normal serum markers and in partial remission underwent surgery after chemotherapy. An intramuscular depot of testosterone was administered to all patients after total castration, every 3–4 weeks. Patients were assessed at follow-up visits every 1–2 months in first year after diagnosis, every 3 months in the second and every 6 months thereafter. The duration of follow-up was calculated from the date of first diagnosis. The results for disease control and survival, sexual status and treatment complications were recorded.

Results

Of the 11 patients with bilateral GCTT, seven developed the second tumour metachronously after a median interval of 87 months (range 12–256) and four synchronously. The mean age at presentation was 27.5 and 26.6 years in patients presenting synchronous and metachronous tumours, respectively. Two of seven patients developed metachronous tumours 2 years after the original diagnosis. The remainder developed the second tumour at least 5 years after the first tumour, although two of them developed secondary cancer more than 10 years after the first tumour (12 and 21.7 years, respectively). There was a history of cryptorchidism unilaterally in two patients, one of whom had nonseminomatous histology. Three patients had been investigated for infertility problems. Only one of the seven patients with metachronous tumours fathered a child in the interval between the diagnosis of the first and the secondary tumour. Also, four patients had a history of atrophic testis on one or both sides. Although seven patients had at least one of these risk factors, there was no association between the risk factors and the development of bilateral GCTT in five patients.

Of the seven patients with sequential tumours, five had identical histology bilaterally and two had different histological types (Table 1). All four patients with synchronous tumours had identical histology on both sides. Although three of the four patients with synchronous tumours had an advanced clinical stage at presentation, none of the secondary cancers presented as metastatic disease in metachronous bilateral GCTT. The treatments given to all 11 patients are shown in Table 1; five received platinum-based polychemotherapy regimens. Three patients underwent resection of the retroperitoneal residual mass after chemotherapy; antegrade ejaculation was preserved in these patients. Sexual libido and potency were conserved in all patients by the testosterone depot. One patient had a sleep disorder and another a peptic ulcer, possibly associated with testosterone replacement. The median (range) duration of the follow-up after the first diagnosis of GCTT and after the diagnosis of bilateral GCTT was 11.6 (2.7–23.1) and 4.4 (1.4–9.8) years, respectively. All patients were alive with no evidence of cancer at their last follow-up visit.

Discussion

A review of a series of GCTTs from the Mayo Clinic

Table 1 Patient age, clinical stages and histological types of the first and secondary germ cell testicular cancer, treatment methods and follow-up results

	First tumour			*Second tumour*					
Patient no. /age (years)	*Histology*	*Clin. stage*	*Therapy*	*Interval (months)*	*Histology*	*Clin. stage*	*Therapy*	*Diag. method*	*Follow-up (months/ status)*
1/36	Sem	IIC	Chemo	0	Sem	IIC	4 BEP	Synch	36/NED
2/24	Sem	IIA	RT	0	Sem	IIA	RT	Synch	32/NED
3/27	ECA + YST	IV B M + L3	Chemo + surg	0	ECA + YST	IV B M + L3	Chemo + surg	Synch	48/NED
4/38	Terat	IIICN +	Chemo + surg	0	Terat	IIICN +	Chemo + surg	Synch	20/NED
5/28	Terat	I	Surv	12	Sem	I	RT	Clinical	91/NED
6/24	Terat	IIC	Chemo + surg	93	Sem	I	RT	Clinical	146/NED
7/32	Sem	I	RT	87	Sem + ECA	I	Surv	Clinical	199/NED
8/31	Sem	I	RT	47	Sem	I	Surv	Clinical	163/NED
9/21	Sem	I	RT	144	Sem	I	Surv	Clinical	262/NED
10/24	ECA	I	Surv	71	ECA	IM	Chemo	Clinical	139/NED
11/17	Sem	I	RT	260	Sem	I	Surv	Clinical	277/NED

Chem, chemotherapy; NED, no evidence of disease; RT, radiotherapy to retroperitoneum; ECA, embryonal carcinoma; YST, yolk sac tumour; Surv, surveillance; sem, seminoma; synch, synchronous.

showed that only three patients with bilateral GCTTs were recorded between 1935 and 1944, although there were 16 such patients between 1977 and 1986 [2]. Many authors have presented explanations for this increase in incidence [2,3,10,11]. First, platinum-based chemotherapy has improved survival; second, an increase in the incidence of GCTT leads to an increase in bilateral GCTT. Finally, GCTT is a disease of young men with no comorbidity, so they survive to develop a new germ cell cancer. As shown by numerous studies, in men with GCTT in one testis, the risk of developing cancer in the remaining testis is 500–700 times more than their unaffected peers [5,12,13].

The incidence of CIS in the contralateral testis has been reported to be 5–10% at diagnosis in patients with unilateral GCTT [14], and is associated with a high risk of developing invasive cancer in untreated cases [15]. In a Danish study, Berthelsen *et al.* [16] reported that of the 250 patients with unilateral GCTT screened, 13 (5.2%) had contralateral testicular CIS. The authors noted a relationship between the development of contralateral CIS and an atrophic contralateral testis, a history of undescended testis, or both, in 85% of their patients. Later, the same group documented the persistence of CIS on repeat biopsies and reported an estimated risk of 50% for developing invasive cancer within 5 years [17]. Furthermore, none of their patients with unilateral GCTT and a negative contralateral testicular biopsy developed secondary germ cell cancer [17], confirming the concept that CIS precedes testicular germ cell cancers [14]. Therefore, simultaneous contralateral biopsy has been recommended in cases with unilateral GCTT to diagnose and treat the neoplastic changes at a pre-invasive stage, so that total castration is avoided [17]. On the other hand, the negative predictive value of a negative biopsy has been questioned [18] and other concerns raised, e.g. ultrasonographic interpretation that might be complicated by testicular scar tissue developed after biopsy, and a theoretical risk of scrotal contamination [11].

No biopsies were taken from normal-appearing contralateral testes in the present patients with unilateral GCTT. In this series, the risk of developing metachronous bilateral GCTT was 1.3% (seven of 548 patients). Thus, more than 75 patients would require screening for contralateral CIS to prevent one invasive cancer developing in the future. These retrospective results from relatively few patients cannot be taken to support the avoidance of contralateral testicular screening. Total castration could not be avoided in most of the present patients with metachronous bilateral GCTT by excluding such screening. Nonetheless, secondary GCTT was diagnosed at stage 1; the long-term survival was good and testosterone replacement was satisfactory in all patients.

In addition to an atrophic testis and cryptorchidism, infertility has also been associated with the development of bilateral GCTT [5,7]. The present results support this view, as in patients with bilateral GCTT, cryptorchidism and a history of infertility were 6.5 and 2.5 times more common than in patients with unilateral GCTT. Indeed, only one patient fathered a child in the period between the first and second cancer. From these findings and given that a third of these patients had a history of atrophic testis, men with any of these risk factors should be followed carefully to detect any developing bilateral cancer. Such an association may not always be present; Dieckmann and Loy [19], reviewing a multicentre series, detected no significant difference in the incidence of cryptorchidism between patients with bilateral and unilateral GCTT. Likewise, almost half of the present patients with bilateral GCTT had none of the risk factors. Thus, it must be considered that every patient with unilateral GCTT has a significant risk of developing a new cancer in the remaining testis.

Numerous studies have shown that more than half of patients develop secondary cancer within 5 years of the initial diagnosis, and most within 10 years [2,10,20]. The diagnosis of bilateral cancer has been reported as long as 32 years after the primary diagnosis [10]. Therefore, a life-long follow-up for the early diagnosis of contralateral GCTT is usually recommended. Because an annual follow-up is usually conducted 3–5 years after diagnosis, there may be a delay in the diagnosis of a contralateral cancer. Kristianslund *et al.* [20] emphasized the value of educating patients in self-examination to prevent any delay in diagnosis. All our patients with unilateral GCTT are informed about the increased risk of a new cancer in the remaining testis, and are trained in self-examination; this is important in the diagnosis of metachronous tumours at early stage, and thus in achieving long-term survival. It is difficult to explain why some synchronous bilateral GCTTs presented at an advanced stage; perhaps patients with bilateral GCTT defer seeking medical advice because they are anxious about total castration [21].

Although bilateral orchidectomy has been largely accepted as the standard treatment for bilateral GCTT, several recent studies reported testis-sparing approaches to preserve function and cosmesis [22,23]. All patients managed with a testis-sparing approach had small tumours and contiguous testicular structures were not involved. We did not use testis-sparing tumour resection as in the present series most patients had large tumours. However, the patients tolerated total castration well and the functional outcome with periodic testosterone replacement was satisfactory. The rationale for retaining the testis should be questioned and the risk of local and systemic recurrence recognized.

Synchronous bilateral GCTTs have generally been reported to have identical histological types [2,24], frequently so in metachronous bilateral GCTTs [10,25]. Kristianslund *et al.* [20] reported that nearly all patients with initial seminoma had an identical histological type in the contralateral tumour, and about half of their patients with nonseminoma had a seminoma on the other side. In the present series, all synchronous tumours had identical histology (seminoma in half). Most patients with seminoma on one side later developed a seminoma on the other side. Moreover, two of the five patients with initial nonseminoma developed seminoma in the other testicle. These results are in accord with previous work and confirm seminoma to be the most frequent histological type in bilateral GCTT.

The role of therapy given for a first GCTT in the development of the secondary cancer is controversial. Thompson *et al.* [25] reported that five of 57 patients treated by orchidectomy only or orchidectomy plus radiotherapy developed cancer on the other side, although none of the 63 patients treated with chemotherapy developed secondary cancer. The authors claimed that chemotherapy protects against contralateral cancer. However, many reported series contradict this statement [3,10,11]. Although six of seven patients in the present study developed a contralateral cancer after surveillance only or radiotherapy for their GCTT, one patient treated with four courses of polychemotherapy developed GCTT in the remaining testicle. These results further emphasize that chemotherapy does not completely prevent secondary cancer.

As adverse effects of each therapeutic procedure accumulate and previous treatment changes the mode of metastasis [11], there are limiting factors in the treatment of the secondary GCTT, particularly depending on previous therapy. Radiation dosage is limited by the initial therapy [10] and retroperitoneal lymph node dissection is not possible if it has been performed previously [10]. Patients with clinical stage I seminoma who had been irradiated were followed expectantly. One patient who had undergone a resection of retroperitoneal residual mass after chemotherapy for advanced nonseminoma was treated successfully with radiation for the secondary cancer (stage I seminoma).

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