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Clinical Characteristics of Metachronous Bilateral Testicular Tumors in the Chemotherapeutic Era

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Abstract

We wanted to present the results of our experience with bilateral testis tumor and to suggest the effects of chemotherapy in suppressing the development of second primary testicular tumors. Between 1978 and 1997,2,345 patients were treated for testicular tumor at The University of Texas M. D. Anderson Cancer Center. Of these, 2,107 had germ cell cancers. There were 22 (0.94%) cases of bilateral testicular tumor in the overall patient population and 21 (1.0%) cases among patients with germ cell cancer. We reviewed the medical records to determine the incidence of the histological subtype, the incidence of metachronous versus synchronous formation of contralateral tumors, and tumor stage in this patient population. We also examined the effect of chemotherapy in treating the first tumor and preventing the occurrence of a second tumor. Finally, we compared the effect of ultrasonography, serum tumor marker elevation, and physical examination in detecting second tumors. Only one contralateral germ cell tumor developed synchronously; all others developed metachronously. Fifty percent of first tumors were seminomas, compared to 55% of second tumors. The histologic concordance rate for first and second tumors was 35%. Tumor stage was higher among first tumors than second tumors. The majority of second tumors in patients who received chemotherapy for first malignancies tended to be metachronous seminomas. Ultrasonography detected 6 of 21 (28.6%) contralateral tumors before they were evident by physical examination or serum tumor marker elevation. Seminomas were more prevalent among patients with bilateral germ cell disease than patients with unilateral disease. Chemotherapy, when used as treatment for first tumors, may have some effect in preventing the development of nonseminomatous germ cell tumors in the contralateral testicle. Close follow-up of the contralateral testis with ultrasonography is essential for early detection of second tumors. The outcome for patients with bilateral testicular germ cell cancer is excellent, secondary to early detection.

Key Words: Testis tumor, bilateral, metachronous

INTRODUCTION

The incidence of bilateral disease of testicular cancer in large studies ranges from 2 to 5%, and this incidence is increasing.[1-4] Seminoma has been shown to be the most common type of metachronous bilateral testicular germ cell disease.[5,6] In most patients with seminoma, the seminoma occurs as the second tumor.[6] No histologic correlation between first and second tumor has been reported;[2] however, the rate of histologic concordance between first and second testicular germ-cell tumors has been reported to be 33%.[6]

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The presence of a blood-testis-barrier has been hypothesized.[7] In studies evaluating chemotherapeutic response, some agents (e.g., cyclophosphamide and vincristine) have been shown to be able to cross the blood-testis barrier.[8,9] However, differential responses to chemotherapy in the testis as treatment for testicular cancer renders the blood-testis-barrier hypothesis inconclusive.

Advances in therapeutic and diagnostic procedures have improved the prognosis for patients with testicular cancer. Chemotherapy, as compared with other treatment modalities, has been shown to be able to reduce the risk for contralateral tumors.[10] Ultrasonography has been useful in the early detection of very small, impalpable testicular tumors.[11,12] In this study, we analyzed the histology of first and second tumors, the process of second tumor detection, and the possibility of contralateral testicular preservation with early detection. As well, we evaluated the effect of chemotherapy in the development of second primary testicular tumors.

Table 1. Cases of Bilateral Testicular Tumors (Germ cell and non-germ-cell; n=22)

Histology	Metachronous	Synchronous	Total
Germ cell tumor	20	1	21
Non-germ-cell tumor	1	-	1
Total	21	1	22

MATERIALS AND METHODS

Between 1978 and 1997, we treated 2,345 patients for testicular tumors at The University of Texas M. D. Anderson Cancer Center. There were 2,107 germ cell malignancies, 210 non-germ cell malignancies, and 28 benign tumors.

Bilateral disease occurred in 22 of 2,345 (0.94%) patients, 21 with germ cell malignancies and 1 with a non-germ cell malignancy (Table 1). The incidence of bilateral germ cell tumor was 1.0% (21 in 2,107 patients). The other 2,086 patients with germ cell tumors had cancer in only one testis (unilateral), which consisted of 672 (32.2%) cases of seminoma and 1,414 (67.8%) cases of nonseminomatous germ cell tumor.

Second tumors occurred metachronously in 21 of 22 patients of bilateral testis tumor, 20 with germ cell tumors and 1 with a non-germ cell tumor. Patient characteristics are listed in Table 2 and include histological classification based on the World Health Organization system, tumor stage according to the American Joint Committee on Cancer Staging, tumor classification according to the Germ Cell Consensus Group system,[13] type of therapy given, and outcome of therapy. The methods used to detect the second tumor and the results of each method are outlined in Table 3. A description of the various chemotherapy regimens used to treat the first tumor and the histology of the subsequent contralateral tumors is given in Table 4.

RESULTS

In 21 of the 22 cases of bilateral testicular tumor, the second tumor developed metachronously; however, in one of these cases (BK), the second tumor actually became apparent on ultrasonography at the time the first tumor was diagnosed. So this tumor may more accurately be considered synchronous, but we have included this case in the metachronous group because of the absence of histologic confirmation at initial presentation. There was one outright case of synchronous formation. Interestingly, one case of bilateral metachronous Leydig cell tumor was diagnosed (SG). Therefore, in this study, 20 of 22 patients with bilateral testicular tumor were classified in the metachronous germ cell tumor group. Of these 20 cases, 10 (50%) of the first malignancies were pure seminoma, including two patients in whom seminoma was mixed with syncytiotrophoblasts; while the other 10 were of nonseminomatous histology. Eleven (55%) of the second malignancies were pure seminomas, and the other 9 were of nonseminomatous histology.

In 7 of 20 (35%) cases, there was histologic concordance between the first and second germ cell tumors, all of which were seminomas. In 7 of 10 (70%) patients whose first-tumor diagnoses were seminomas, including the cases in which seminomas were mixed with syncytiotrophoblasts, the second-tumor diagnosis was also seminoma.

The median age at which the first primary tumors were diagnosed in the 21 patients with metachronous bilateral testicular tumors (including SG) was 28 years (range, 17 to 46 years). The second primary tumors were diagnosed at a median age of 33 years (range, 19 to 58 years).

Thirteen patients received chemotherapy as treatment for the first tumor. In 2 of 13 (15.4%) cases, the second tumor was a nonseminomatous germ cell tumor, excluding cases of teratoma and testicular intraepithelial neoplasia (TIN) (Table 4). By excluding patient BK, in which the evidence of a second tumor was detected during first-tumor diagnosis (indicating synchronous formation), the incidence of second tumors of nonseminomatous germ-cell histology following chemotherapy was 1 of 13 (7.7%).

The stage of first tumors was higher than that of second tumors (Table 2). Diagnoses of retroperitoneal lymph node disease (stage II) or disseminated disease (stage III) were more common in first tumors than in second tumors (10 : 5). In the one case of outright synchronous formation, the tumors were stage I seminoma with bilateral histologic concordance, and they were treated with prophylactic irradiation. Prognostic classification based on the International Germ Cell Consensus was not useful in comparing first and second tumors because of a lack of historical data (Table 2).

The method used to treat the metachronously developed second tumors was dependent on the method

Table 2. Characteristics of Metachronous Bilateral Testicular Tumors

Pt.	Age (yr)	First tumor					Interval (m)	Second tumor					
		Histological status	Stage	IGCCC	Therapy	Outcome		Histological status	Stage	IGCCC	Therapy	Outcome	FU (m)
BS	28	EMB	TxN2M1	N	RPLND, CT	CR	142	SE	T2N0M0	G	S	NED	11
AB	32	EMB,TE	T3N2M1	N	CT	CR	19	SE	T1N0M0	G	S	NED	30
OB	46	SE,Syn	T1N0M0	G	XRT	NED	145	EMB,EST,SE,TE	T1N2M0	G	RPLND, CT	NED	88
MA	26	SE	T1N0M0	G	XRT	NED	60	EMB,SE	T1N0M0	G	S	NED	37
ID	17	TEC	T1N0M0	I	RPLND, CT	CR	28	TE	T1N0M0	G	S	NED	15
HB	23	EMB,TE,CHO	T1N0M0	N	RPLND, CT	CR	116	SE,TE	T1N0M0	G	S	NED	120
BD	31	SE,EST	T2N0M0	G	XRT	NED	40	SE,EST,EMB,TE	T2N0M0	G	CT	NED	19
WK	36	SE	T0N2M0	G	CT, XRT	NED	128	SE	T1N0M0	G	S	NED	11
WM	30	EMB,SE	T1N0M0	G	CT	NED	28	SE	T1N0M0	G	S	NED	9
BK*	30	SE	T1N0M1	G	CT, RPLND	CR	11	EMB	T3NxM1	G	CT	SD	41 †
SG	26	Leydig cell	T1N0M0	-	Orchiectomy	NED	70	Leydig cell	T1N0M0	-	S	NED	12
NJ	37	EMB,EST,TE	T1N0M0	G	CT	NED	38	SE	T1N0M0	G	XRT	NED	27
TR	23	EMB,Syn	T2N2M0	G	CT	CR	44	EMB,TE,CHO,EST	T3N2M1	I	CT	CR	67
GT	29	SE	T1N1M0	G	XRT	CR	118	SE	T1N3M1	I	CT	CR	69
QR	17	SE,Syn	T2N2M0	G	CT	CR	24	SE	T1N0M0	G	S	NED	7
VJ	23	SE	T1N1M0	G	XRT,CT	CR	29	SE	T1N0M0	G	S	NED	173
WR	18	SE	TxN2M0	N	XRT, CT	CR	180	SE,fibrotic	T0N3M0	G	CT, RPLND	NED	95
ZR	25	SE, EMB	TxN3M0	N	RPLND, XRT	NED	14	SE,EMB,CHO	TxNxM1	N	CT	NED	245
WJ	29	SE	T1N0M0	G	XRT	NED	49	SE	T1N0M0	G	S	NED	20
RD	22	SE	T1N0M0	G	XRT	NED	34	SE	T1N0M0	G	S	NED	61
TR	36	EMB,TE,EST,Syn	T1N2M0	G	CT, RPLND	CR	81	TIN	T1N0M0	G	S,TH(TE)	NED	93

*presumptively synchronous, † died of pneumonia.

IGCCC, international germ cell consensus classification; G, good prognosis; I, intermediate prognosis; P, poor prognosis; N, not evaluable; FU(m), follow-up (months); EMB, embryonal carcinoma; TE, teratoma; SE, seminoma; Syn, syncytiotrophoblastic cells; TEC, teratocarcinoma; CHO, choriocarcinoma; EST, endodermal sinus tumor; RPLND, retroperitoneal lymph node dissection; CT, chemotherapy; XRT, irradiation; CR, complete remission; NED, no evidence of disease; SD, stabilization of disease; S, surveillance; TIN, testicular intraepithelial neoplasia; TH, thoracotomy

Table 3. Results of Methods Used to Detect Contralateral Testicular Tumors and Pathologic Findings of the Tumors

Pt.	Detection method			Pathologic findings (size, mm)	Type of orchiectomy
	Physical exam	Ultrasonography	Elevated tumor marker		
BS	Negative	Two lesions less than 4 mm	*HCG	Two foci, TIN, Epididymal extension	Total
AB	Negative	*9 mm lesion	AFP, slight	Two nodule	Total
OB	Negative	*Mixed echo lesion	–	20	Total
MA	*Positive	10 mm lesion	–	10, TIN	Total
ID	Negative	*10 mm mixed echo lesion	–	8	Partial
HB	*Positive	Abnormal echo in entire testis	–	28	Total
BD	Negative	Abnormal echogenicity	*HCG, AFP	18, T. Albuginea inv, TIN	Total
WK	Positive	*Abnormal echogenicity	–	43, TIN	Total
WM	Positive	*Abnormal echogenicity	–	Interstitial spread, TIN	Total
BK	Positive	Not performed	*AFP	Epididymal, Sp. cord, T. Vaginalis inv	Total
SG	Negative	*3 mm lesion	–	Leydig cell tumor	Partial
NJ	Negative	Hypoechoic lesion 15 mm	*AFP, slight	22, TIN	Total
TR	*Positive	Not performed	AFP, HCG, LDH	75, TIN	Total
GT	*Positive	Not performed	HCG	130	Total
QR	Negative	Abnormal echo 12×8×6 mm	*HCG, slight	9, TIN	Total
VJ	*Positive	Hypoechoic, mixed echo 16×10 mm	–	17	Total
WR	*Positive	Not performed	HCG	Fibrotic	Total
ZR	*Positive	Not performed	Not available	25	Total
WJ	*Positive	Mixed echoic lesion	–	Confined to testis	Total
RD	*Positive	Hypoechoic lower pole	HCG	38	Total
TR	*Positive	Not performed	Not available	TIN	Total

*Initial detection method used. HCG, human chorionic gonadotropin; AFP, alpha fetoprotein; LDH, lactic dehydrogenase; TIN, testicular intraepithelial neoplasia; Sp, spermatic; T, tunica; inv, invasion.

used to treat the first tumor, particularly with regard to irradiation. Patients who received radiotherapy to the retroperitoneum as treatment for the first tumor, for example, were not candidates for irradiation of the retroperitoneum for contralateral testis tumor. It was also difficult to perform retroperitoneal lymph node dissection (RPLND) for a second tumor following irradiation for the initial tumor.

The median interval from first-tumor detection to second-tumor development was 44 months (range, 11 to 180 months). None of the patients with bilateral tumors had a history of undescended testis.

The detection methods used to test for the presence of a second primary tumor were ultrasonography, serum tumor marker, and physical examination. In 6 of 21 (28.6%) cases of bilateral testicular germ-cell cancer, the second tumor was initially detected by ultrasonography. Two patients (WK and QR), were evaluated by testicular MRI in addition to ultrasonography for experimental comparison. The results of these two detection methods were nearly the same. In patients whose diagnoses were based on abnormal physical examination or elevated serum tumor marker, large tumor size ($\geq$ 10 cm) or the presence of a TIN (or carcinoma *in situ*) was present, resulting in the need for total orchiectomy. Nine of the second tumors had TIN involvement (Table 3). There was no correlation between the histology of the second tumor and the detection method used in its diagnosis (Tables 2 and 3).

Thirteen of the 21 patients (61.9%) received chemotherapy as treatment for the first tumor. By contrast, 7 of the 21 patients (33.3%) were given anticancer drugs as treatment for the second tumor. Thus, early-stage detection decreased the therapy burden for the second tumor (Table 2). The outcome for patients with a second primary testicular malignancy was excellent and disease cure was expected in most cases. Mean follow-up duration after treatment for the second tumor was 59.5 months (range, 7 to 245 months) (Table 2).

DISCUSSION

Of the 2,107 patients in our study group who had germ cell tumors, 21 (1.0%) had bilateral disease. The overall rate of bilateral disease in our study group

Table 4. Comparison of Chemotherapy Regimen Used to Treat the First Germ Cell Tumor and the Histology of the Second Tumor

Pt.	Chemotherapeutic regimen in first tumor	Histology of second tumor
BS	CISCA / VB	seminoma
AB	CEB	seminoma
ID	BEP, EP	teratoma
HB	CISCA, PVB	seminoma, teratoma
WK	CISCA	seminoma
WM	CEB	seminoma
BK*	BOP, CISCA, POM, ACE	embryonal carcinoma
NJ	CEB	seminoma
TR	CISCA / VB	embryonal carcinoma, teratoma, choriocarcinoma, EST
QR	CTX, carboplatin	seminoma
VJ	CTX, cisplatin	seminoma
WR	CTX, cisplatin	seminoma
TR	PVB	TIN

*presumptively synchronous bilateral tumor.
CISCA/VB: cisplatin, cyclophosphamide, doxorubicin, vinblastin, bleomycin (alternation); CEB: carboplatin, etoposide, bleomycin; BEP: bleomycin, etoposide, cisplatin; EP: etoposide, cisplatin; PVB: cisplatin, vinblastine, bleomycin; BOP: bleomycin, vincristine, cisplatin; POM: vincristine, methotrexate, cisplatin; ACE: actinomycin D, cyclophosphamide, etoposide; CTX, cyclophosphamide; EST, endodermal sinus tumor; TIN, testicular intraepithelial neoplasia

was lower than that reported elsewhere, probably because our study group lacked adequate geographical representation.

Some studies show the relative risk of developing a second primary testicular cancer to be higher among men whose first tumor is nonseminomatous than among men whose first tumor is a seminoma;[2] however, others report that the risk for a second primary testicular tumor is slightly higher when the first tumor is seminoma.[6] In our study, 50% of the first primary tumors were seminomas.

Patients with cryptorchidism are at increased risk for testicular cancer, but are not at increased risk for bilateral disease. There were no patients with a history of undescended testicle in our bilateral testis tumor cases.

Incidence of bilateral disease and implications for treatment

The increasing incidence of bilateral testicular cancer is likely related to advances in chemotherapy, particularly the success of cisplatin-based regimens. This drug has increased the survival rate of patients when given as treatment for a first testicular germ cell malignancy.[6] Therefore, the incidence of bilateral testicular cancer during the chemotherapeutic era may remain stable, whereas: 1) the incidence of bilateral nonseminomatous germ-cell cancer may decrease with the use of chemotherapy for the primary tumor and 2) the incidence of bilateral disease may increase as a result of increased survival among patients after chemotherapy for first testicular tumors. However, the opposite concept, that cisplatin-based chemotherapy does not reduce the risk for second tumors, has also been reported.[1-4] Meanwhile, it is expected that the prevalence of seminoma as the histologic type of the second tumor will increase because chemotherapy, rather than irradiation, is increasingly used as the first-line treatment when the first testicular tumor is seminoma and also because current chemotherapeutic methods are not expected to have a prophylactic effect on the development of seminoma.

Incidence of seminomas versus nonseminomatous germ cell cancers

In our study, seminoma was the most common histology of first tumors (50%) and second tumors (55%). The incidence of seminoma in bilateral germ cell disease was much higher than in unilateral germ cell disease (32.2%). In our study the rate of histological concordance between first and second tumors was 35%, compared with 33% reported in the literature.[6]

Nine of the 20 (45%) nonseminomatous contralateral germ cell tumors in our study had TIN involvement. Seven of these patients received chemotherapy for treatment of the first primary tumor. The effect of systemic chemotherapy on TIN is somewhat debatable, but in our study it was not sufficient to eradicate TIN, secondary to the blood-testis-barrier. This finding is consistent with previous reports.[14-16] The occurrence of 9 cases (45%) of bilateral germ cell tumors with TIN involvement suggests that the presence of TIN does not necessarily indicate the potential for metachronous tumor development.

TIN lesions immediately surrounded the testicular tumor. No TIN lesion was found more than 15 mm from the tumor.[17] This is an important factor in deciding between testis preservation surgery and irradiation. First, there is no definite evidence that

TIN will develop into invasive germ cell cancer, although the risk for TIN in the development of contralateral tumor has been reported. Second, local irradiation for TIN can cause infertility and may also cause Leydig cell dysfunction.[18,19]

Staging and treatment decisions

It is necessary to consider the stage of the first tumor and the method used to treat it when staging and determining treatment for the second tumor. This information is particularly important if further irradiation is planned. When the second tumor is a nonseminomatous germ cell tumor and the first is a seminoma that was treated with irradiation, it is difficult to perform RPLND. Likewise, patients who receive irradiation for a first tumor are not candidates for irradiation in the case of a second tumor. In addition, if RPLND or irradiation are applied to the first tumor, consideration of alternative lymphatic pathways of metastatic spread becomes an important consideration. Considering these factors, the best treatment for a second primary testicular tumor is chemotherapy.

Early detection and follow-up

In our study, serum tumor markers were not helpful in detecting contralateral disease, whereas ultrasonography was very helpful. However, tumor markers were beneficial in follow-up monitoring of metastatic disease associated with a primary tumor.

The early detection of second tumors should facilitate an excellent outcome for patients with bilateral testicular germ cell cancer. The median interval of second tumor detection from time of diagnosis of the first tumor was 44 months. The maximum duration of second tumor development was 180 months. Therefore, very close follow-up at 3 to 6 month intervals for about 4 years after first tumor detection and once a year thereafter should be instituted. Follow-up should include physical examination and ultrasonography. Some reports about the advantages of ultrasonography support this concept.[11,12] It is also important that the patient be trained to perform self-evaluation. These follow-up methods are particularly important in patients who do not receive chemotherapy for their first tumor because they will lack the beneficial effects of chemotherapy (such as in controlling second-tumor development). Routine random biopsy to detect TIN in the contralateral testis is not necessary. Early detection of a second cancer using ultrasonography enables doctors to consider a partial orchiectomy. Intraoperative ultrasonography provides a means of margination for resection and a way to screen for multiple lesions. Frozen section analysis of the surrounding tumor tissue helps rule out multifocal TIN. Careful ultrasonographic follow-up after partial orchiectomy should be instituted every 3 months for 2 years, every 4 to 6 months for the following 3 years, and then yearly throughout the patient's lifetime. These diagnostic and treatment strategies for bilateral testicular cancer are practicable, safe, and essential in the current chemotherapeutic era.

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