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Synchronous and metachronous bilateral germ cell tumours of the testis

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Background. *We reported fourteen patients with bilateral testicular tumours, and discussed the need for contralateral testicular biopsy during orchiectomy to detect carcinoma in situ (CIS).*

Patients and methods. *Fourteen patients with bilateral testicular tumours were reviewed in order to establish the incidence, histologic findings, predisposing factors, interval between the development of two primaries, type of treatment administered and the overall outcome.*

Results. *Bilateral tumours were identified fourteen times between 1984 and 1996. The tumours occurred simultaneously in five patients, and a contralateral malignancy developed in the others after a time ranging between 6 and 107 months. The most frequent histologic diagnosis was seminoma and was confirmed in 10 cases. Four patients had a history of undescended testis. One patient also had persistent müllerian duct syndrome. All patients were initially treated with radical orchiectomy. According to their stage, all patients were treated with radiotherapy and/or chemotherapy. Four patients died in the period between 6 and 33 months after the diagnosis. The remaining 10 are still alive with, no evidence of disease.*

Conclusions. *The second tumour is diagnosed more often due to prolonged follow-up examinations; periodic self-examination by patients; ultrasonography of the testis; tumour markers AFP and beta-HCG and a contralateral testicular biopsy during orchiectomy. CIS of the contralateral testis evolves into invasive cancer in probably most of the patient germ cell tumours and usually cured by radiotherapy. Despite that, we do not advocate a routine biopsy of the contralateral testis in the patients with unilateral testicular tumour due to the following reasons: 1. CIS of the testis is the precursor of most malignant testicular germ cell tumours except for spermatocytic seminoma, Teratoma and Paediatric yolk sac tumours. 2. CIS is not diagnosed in about 95 % of all cases with testicular tumours. 3. CIS may be randomly distributed and a single biopsy may not detect it. 4. Testicular biopsy does not only devoid minor complications but also affects spermatogenesis. 5. Development of a germ cell tumour in general takes 3 and 5 years, a non-palpable testicular tumour can be localised by ultrasonography and ultrasound scanning occasionally identifies CIS based on irregular pattern secondary to the normal tubules. 6. Scar lesions in the testis after biopsy may render sonographic interpretation more difficult. 7. The natural history of CIS is unknown and the precise method of treatment is controversial. 8. There is no data that CIS has an impact on survival. 9. A careful follow-up is warranted to all germ cell tumour patients, including those with negative biopsies. So, a watchful waiting policy to the problem of the CIS should be the choice.*

Key words: testicular neoplasms-pathology; orchiectomy; carcinoma in situ - diagnosis; germinoma

Introduction

Testicular carcinomas are relatively rare tumours; however, they are the most common solid tumours occurring in males between the ages of 20 and 34 years. The incidence of testicular tumours is 2.1 to 2.3 per 100 000 males.[1]

The metachronous appearance of second tumours deserves a particular attention because it has been reported that once a patient has a malignant tumour of one testis, the risk of developing a tumour on the opposite side is much higher than that of the general population.[1] The increase of the bilateral testicular cancer may be due not only to higher survival rates obtained with cisplatin based chemotherapy but also to its early detection by the ultrasound of the testes.

The aim of the present paper was to analyse a group of patients with bilateral germ cell tumours of the testis and to discuss the need for a biopsy of the contralateral testis during orchiectomy for the first primary.

Patients and methods

From 1984 to 1996, 876 patients, 17 to 68 years of age, were treated for a testicular germ cell tumour in Ankara Oncology Education and Research Hospital. We reviewed the medical records of these patients to identify and study bilateral testis tumours (BTT) with respect to their incidence, histopathologic findings, predisposing factors, interval between the development of two primaries, type of treatment administered, and the overall outcome.

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Results

Bilateral invasion was identified in fourteen patients (1.6%). The tumours occurred simultaneously in five patients (0.57%). In nine cases, a contralateral malignancy developed after a time interval ranging between 6 and 107 months. The age of patients ranged from 21-58 years (median 34.5 years). Seminoma was the most frequent pathologic diagnosis (10/14 cases), followed by mixt tumours (2/14 cases: seminoma + embryonal carcinoma, seminoma + teratocarcinoma), and each one had embryonal carcinoma and teratocarcinoma (Figure 1). Four of fourteen patients (28.5%) had a history of undescended testis. One of these patients also had persistent Müllerian duct syndrome with bilateral abdominal testicular seminoma.[2]

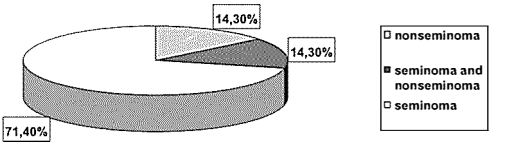

Figure 1. Histologic findings in consecutive bilateral testicular tumors.

Initially, all patients were treated with radical orchiectomy. In accordance with the staging system used in our hospital[3] the patients were classified as follows:

- stage I: four patients
- stage IIb: one patient
- stage IIc: five patients
- stage III: one patient
- stage IV: three patients

Four of ten seminoma patients in stages I and IIb, and seminoma + teratocarcinoma case in stage I, received radiotherapy. Of the remaining eight patients in stages between IIc and IV were treated with the reduced dose PVB chemotherapy protocol (cisplatin, vinblastine, bleomycin).[3] Three months after radiotherapy, the seminoma + teratocarcinoma case in stage I was also treated with

chemotherapy because the level of tumour marker AFP was noted to be high. Four patients died 6, 9, 20 and 33 months, respectively after the diagnosis of the second tumour. Three of four patients died due to central nervous system metastases, and the fourth died because of myocardial infarction. All other patients are still alive and the longest survival time is 8 years and 11 months.

Discussion

Although the average incidence of testicular tumours is in the range of 2.1 to 2.3 per 100.000 males, it seems to have increased in the last three decades. It remains the most common solid tumour in men between the ages of 20 and 34 years.[1,4,5]

In patients who survive one testicular malignancy, the risk of developing a contralateral testicular malignancy is 500 to 1000 times greater than in healthy male subjects. The risk is again increased by the factor 2 to 4 in cases of previous cryptorchidism.[6-8] The risk factors like cryptorchidism in unilateral malignancy were reported to range between 7 and 35% of the total number of patients with testicular cancer.[9,10]

In our series, the incidence of cryptorchidism is 2.7% (24 patients) and 28.5% of these (4 patients) had BTT. More recent studies document an increased incidence of BTT. The relative incidence of BTT reported in the literature from 1981 to 1995, can be calculated as 2.36%.[8,11-15] In the current study, BTT is 1.7% of the total incidence of testicular carcinomas.

In principle, bilateral tumours can occur synchronously or metachronously, i.e. at different times. Recent literature suggests that approximately two thirds of the metachronous testicular tumours occur within 5 years of the first diagnosis.[16] Our study disagrees with this maintaining that 33.3% of all metachronous tumours occurred within 5 year of the first diagnosis and that 66.6% were diagnosed after a period of more than 5 years (Figure 2). The incidence of synchronous BTT have been reported in the range of 16.6% to 31.5%.[16-18] Our incidence is 35.75%.

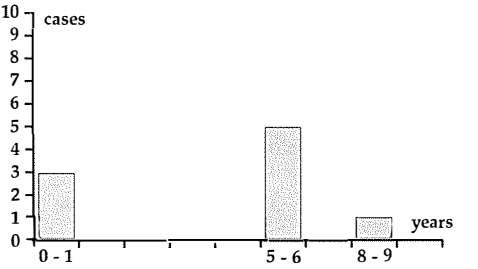

Figure 2. Time-interval until the diagnosis of the contralateral testicular tumour.

In Denmark, the incidence of carcinoma *in situ* (CIS) in the contralateral testis in patients with testicular malignancy has been reported to be 5% to 6%; however, 50% of these men had a history of cryptorchidism. Though the reports of sequentially diagnosed BTT are increasing in number, routine biopsy of the opposite testis remains controversial. CIS is a characteristic pattern within the seminiferous tubules. In typical cases, such tubules contain two types of cells: CIS germ cells and Sertoli cells, and CIS is the precursor of most types of malignant testicular tumours, except of teratoma, spermatocytic seminoma, paediatric yolk sac tumours and epidermoid cyst (monodermal teratoma).[19] Thus, CIS is found in only 5% of patients with the primary tumour of the testicle. Biopsy carries the risk of a transscrotal procedure in consecutive tumour and scar lesions in the testis may render sonographic interpretation more difficult.

A technique that seems to have a bright future is non-invasive CIS detection employing ejaculate examination for the presence of aneuploid cells in flow cytometry or detection of tumour cells in the ejaculate using a specific monoclonal antibody.[20] There is no doubt that an impalpable testicular tumour

can be localised by ultrasound, and ultrasound scanning occasionally identifies CIS based on irregular pattern secondary to the abnormal tubules.[5] Thus, no risk of implanting the carcinoma in the scrotal wall or altering the lymphatic drainage has been involved. Realistically, we do not recommend a routine biopsy of the contralateral testicle to detect CIS during radical orchiectomy, except in cryptorchidic patients, as cryptorchidism is an important indication for biopsy of the other testicle and as a tumour in the contralateral testicle occurs in around 50% of all these cases.

The management plan of the tumour in the contralateral testis depends upon the time interval between the development of the two tumours, extent of the therapy of the original tumour and the histologic type and stage of the second tumour. There is no standard therapy for patients with consecutive tumour, and each patient requires an individual therapeutic approach. The prognosis of patients depends on the same factors that affect the prognosis of unilateral testis tumours. In the absence of an identifiable disease, a policy of watchful waiting and for identifiable metastases cisplatin based chemotherapy should be treatment of choice.[20,21]

Treatment at each major site of urologic malignancy has characteristic side effects on sexuality and fertility. Bilateral orchiectomy have a negative effect not only on potency but also on sexual life because serum testosterone reaches castrate levels in mean of 3 hours.[22] An abnormally low level of testosterone may cause difficulty in achieving full erection, a loss of sexual desire, reduced ejaculate, a need for prolonged stimulation to reach orgasm and often a decrease in the intensity of pleasure produced during penile caressing and orgasm.[23,24] The rates of sexual dysfunction in our cases are shown in Table 1. The reduction of the testosterone levels secondary to an orchiectomy provokes a counter-regulatory effect with an intra-hypothalamic increase of adrenergic activity from which hot flushes result. Although these flushes are not dangerous, they can sometimes be extremely bothersome and, as a result, can potentially reduce the quality of life of patients.[24] Only one of our cases experienced hot flushes. Since in the case of post-menopausal hot flushes in women, sufficiently high-doses of oestrogen lead to complete disappearance of their complaint, a replacement of testosterone for bilaterally orchiectomised patient with BTT is however indicated.

Table 1. Sexual dysfunction in patients treated for bilateral testicular cancer

	Number of patients	Total (%)
No current sexual activity	1	10
Erectile dysfunction	4	40
Low sexual desire	8	80
Reduced ejaculate	10	100
Reduced orgasmic intensity	2	20

Conclusions

Second tumors are being increasingly diagnosed due to the following reasons: (1) Prolonged follow-up examinations; (2) Periodic self-examination by patients; (3) Ultrasonography of the testis; (4) Tumour markers AFP and beta-HCG; (5) A contralateral testicular biopsy at the time of orchiectomy.

CIS of the contralateral testis evolves into invasive cancer in probably most of the patients with germ cell tumours and cured by radiotherapy. Although CIS of the testis is the precursor of most malignant germ cell tumours we do not advocate routine biopsy of the contralateral testis with unilateral testicular tumour. It is estimated that only the typical form of seminoma could be diagnosed and CIS occurs in the testicle containing seminoma in more than 85% of the cases.[25,26]

The natural history of CIS is unknown and the precise method of treatment is controver-

sial. In a large study involving 87 institutions in Europe, the prevalence of TIN in the contralateral testis was found to be 4.9%. Testicular atrophy was reported to be an independent factor for prevalence in a multivariate analysis.[27] Since CIS is not randomly dispersed throughout the testis a single biopsy may not detect it.[28] There is a small but definite false-negative detection rate, and there are reported cases of the development of neoplasia despite the earlier negative biopsy for testicular intraepithelial neoplasia.[28]

A 3 mm surgical testicular biopsy has a diagnostic sensitivity close to 100%, it is not devoid of minor complications such as infection, superficial serous exudates, localised induration and pain. It has been suggested that biopsy of the contralateral testis affects spermatogenesis.[29] Thus, ultrasound scanning occasionally identifies CIS based on irregular pattern secondary to the normal tubules and scar lesions in the testis after biopsy may render sonographic interpretation more difficult. On the other hand, searching for more disease in the contralateral testis and facing treatment of CIS, since 95% of patients does not have CIS in the other testis, may impose unnecessary emotional stress in some patients.[27,30]

Radiotherapy can eradicate CIS and, thereby, prevent cancer development; but, to date, there is no data whether Leydig cell function is affected or not at even low doses (14 Gy).[31] Furthermore, close follow-up is warranted to all germ cell tumour patients, including those with negative biopsies. So, to our opinion, a watchful waiting policy to the problem of CIS in the contralateral testis should be the choice.

The treatment principles of secondary tumours should be similar to that for primary tumours. In order to prevent sexual dysfunction and hot flushes, administration of androgens may be mandatory in some cases. Thus, an artificial testicular implant can be performed if psychological resistance occurs.

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