Carcinoma in situ of contralateral testis in patients with testicular germ cell cancer: study of 27 cases in 500 patients

HANS VON DER MAASE, MIKAEL RØRTH, SVEN WALBOM-JØRGENSEN, BENT L SØRENSEN, IVAN STRØYER CHRISTOPHERSEN, TAGE HALD, GRETE KRAG JACOBSEN, JØRGEN G BERTHELSEN, NIELS E SKAKKEBÆK

Abstract

Carcinoma in situ in the contralateral testis was diagnosed in 27 of 500 patients (5.4%) with unilateral testicular germ cell cancer. Eight of the 27 patients received intensive chemotherapy for spread of their initial testicular cancer. Follow up biopsy studies did not detect changes of carcinoma in situ in any of these patients, and none developed a contralateral testicular tumour (observation time 12-88 months). Of the remaining 19 patients with carcinoma in situ, seven developed contralateral testicular cancer. The estimated risk of developing invasive growth was 40% within three years and 50% within five years. None of the 473 patients without carcinoma in situ detected by screening biopsy developed contralateral testicular cancer (observation time 12-96 months). No serious complications arose from the biopsy procedures.

All patients with unilateral testicular germ cell cancer should be offered biopsy of the contralateral testis.

Introduction

Patients with unilateral germ cell cancer of the testis have an increased risk of developing a tumour in the contralateral testis. The magnitude of this risk has been reported to be between 1% and 2%.^{1,2} These cancers are probably always preceded by carcinoma in situ.^{3,4} On the other hand, carcinoma in situ in the contralateral testis has been found in roughly 5% of patients at the time of treatment for the initial testicular cancer.⁵

The spontaneous course of carcinoma in situ in the contralateral testis is unknown and may be influenced by the treatment given for the initial cancer. It has therefore been our policy not to perform a contralateral orchidectomy or employ other therapeutic interventions for carcinoma in situ unless invasive growth becomes apparent during follow up.

We describe the course of carcinoma in situ of the contralateral testis detected in 27 patients during screening of 500 patients with unilateral testicular germ cell cancer.

Patients and methods

During July 1972 to January 1985, 500 patients with unilateral testicular germ cell cancer were examined for carcinoma in situ of the contralateral testis. In the first six years only one surgical department participated in the screening project, and in this period only 13 biopsy specimens were examined. Thereafter an increasing number of surgical departments participated, and since 1980 a biopsy specimen from the contralateral testis has

FIG 1—Carcinoma in situ of testis. (a) Section of testicular biopsy sample showing several seminiferous tubules with carcinoma in situ (CIS) and single normal tubule (N). (b) Higher magnification of (a) showing seminiferous tubules with carcinoma in situ (left) and tubule with normal spermatogenesis (right). Tubules with carcinoma in situ contained two types of cells—characteristic atypical germ cells (G) and normal Sertoli cells (S). Note difference between characteristic atypical germ cells and normal spermatogonia (Sg). No invasive growth to interstitial tissue seen where normal Leydig cells (L) present. (Cleland fixation; iron-haematoxylin and eosin.)

Finsen Institute, Rigshospitalet, DK-2100 Copenhagen, Denmark

HANS VON DER MAASE, MD, senior registrar, department of oncology ONB
MIKAEL RØRTH, MD, DRMED, chief oncologist
SVEN WALBOM-JØRGENSEN, MD, chief oncologist
BENT L SØRENSEN, MD, DRMED, chief surgeon

University Hospital, Herlev, Copenhagen

IVAN STRØYER CHRISTOPHERSEN, MD, chief oncologist
TAGE HALD, MD, DRMED, professor and chief urologist

University Hospital, Gentofte, Copenhagen

GRETE KRAG JACOBSEN, MD, DRMED, chief pathologist

Laboratory of Reproductive Biology, Department of Obstetrics and Gynaecology, Rigshospitalet, Copenhagen

JØRGEN G BERTHELSEN, MD, DRMED, senior registrar
NIELS E SKAKKEBÆK, MD, DRMED, consultant andrologist (professor and chief paediatrician, University Hospital, Hvidovre, Copenhagen)

Correspondence and requests for reprints to: Dr von der Maase.

FIG 2—(a) Carcinoma in situ and early invasive growth in atrophic testis without palpable tumour. (b) Higher magnification of (a). Note cells identical with characteristic atypical germ cells (G) both inside and outside seminiferous tubules, in which both mitotic figures (M) and normal Sertoli cells (S) also present. Adjacent to extratubular germ cells several groups of Leydig cells (L) present. (c) Higher magnification of (a). Rete testis. Note invasion by characteristic atypical germ cells, located under cylindrical epithelium of rete testis. (Cleland fixation; iron-haematoxylin and eosin.)

been examined in about 80% of all new patients in eastern Denmark with unilateral germ cell cancer. Roughly three quarters of the specimens were taken during the initial orchidectomy, the remainder being obtained at one of the two oncological centres before further treatment. All patients were observed for at least 12 months.

In all cases investigations, treatment, and follow up after orchidectomy were carried out either by the department of oncology, University Hospital, Herlev, or by the department of oncology ONB, Finsen Institute, Copenhagen. Histological classification of the tumours⁶ and the staging procedures⁷ were performed according to the Danish testicular carcinoma study. The treatment strategy for the initial testicular cancer has been described.⁸⁻¹⁰

Patients with carcinoma in situ of the contralateral testis were treated according to the initial testicular cancer in all respects, independently of the exact changes diagnosed. They were followed up by clinical examination of the remaining testis including measurement of the testis by an orchidometer every three months, ultrasound scanning once or twice a year, and biopsy sampling every one to two years. If invasive growth was diagnosed orchidectomy was performed and the patient resubjected to routine staging procedures.

Testicular biopsy specimens were fixed in Stieve's or Cleland's fixative, embedded in Paraplast, serially sectioned at 4 μ m, and stained with iron-haematoxylin and eosin. Sections were examined for carcinoma in situ by light microscopy at $\times 400$ -1000.¹¹ All specimens were examined by the same investigator (NES). Carcinoma in situ was defined as the presence of intratubular atypical germ cells¹² (fig 1). These cells are larger than normal

spermatogonia and have a large hyperchromatic nucleus containing several prominent nucleoli. The atypical germ cells are usually located in one layer close to the basement membrane, though several layers may be found. Atypical germ cells may also invade the interstitial tissue, a phenomenon denoted as early invasive growth of undifferentiated tumour cells (fig 2).

Results

Of the 500 patients screened, 27 (5.4%) had carcinoma in situ of the contralateral testis. Table I gives selected clinical data for these 27 patients. Characteristics such as age, histological tumour type, and distribution of staging were similar to those of patients with testicular cancer in general.⁷

During follow up six patients developed a contralateral testicular cancer seven to 45 months after the diagnosis of carcinoma in situ, whereas one patient had early invasive growth of undifferentiated germ cell cancer adjacent to the changes of carcinoma in situ in the initial biopsy specimen. Table II gives the details of the initial and contralateral tumours. Diagnosis of contralateral testicular cancer was based on routine biopsy in three cases, detection of tumour by ultrasound in three, and growth of the testis in the remaining case. All patients were classified as having stage I disease at the time of the second orchidectomy and received no further treatment (table II). One patient developed metastases in the supraclavicular lymph nodes 36 months after the first and 15 months after the second orchidectomy. Both testicular tumours as well as the lymph node metastases were classified as pure seminomas. The patient subsequently received combina-

TABLE I—Data related to initial testicular cancer in 27 patients with carcinoma in situ of contralateral testis

Histological germ cell tumour type*	Median age in years (range)	Location (right/left)	Stage	No of patients	Treatment
Seminoma	33 (26-48)	8/8	I	13	Radiotherapy†
			II	2	Radiotherapy
			III	1	Chemotherapy
Non-seminoma	28 (24-45)	4/7	I	6	Radiotherapy or observation†
			II	4	Chemotherapy
			III	1	Chemotherapy

*"Seminoma" refers to tumour consisting entirely of seminoma components; "non-seminoma" refers to all other germ cell tumour types whether seminoma component present or not.

†One patient in each group received chemotherapy at relapse after 43 and four months respectively.

tion chemotherapy with cisplatin, vinblastine, and bleomycin (PVB).¹⁰ The patient was alive and without evidence of disease 38 months after finishing chemotherapy.

Development of a contralateral testicular cancer during follow up occurred only among patients who had not received any systemic treatment. The only treatment in these cases was irradiation of the regional para-aortic and pelvic lymph nodes, whereas the remaining testis was carefully shielded. The scattered radiation dose to the testis was 0.3-0.8 Gy (30-80 rads).

The spontaneous course of carcinoma in situ in the contralateral testis is illustrated in a life table¹³ (fig 3) based on data from the 19 patients who received no systemic treatment and from two further patients who were included up to the time that they received systemic treatment for disseminated relapse of the initial cancer. The estimated risks of developing invasive cancer within three and five years were 40% and 50%, respectively.

In the group of patients not given systemic treatment carcinoma in situ was detected repeatedly in all follow up biopsy samples, save for the first one in two patients. In both these cases the changes of carcinoma in situ were seen again in the next follow up biopsy sample a year later. Thus spontaneous disappearance of carcinoma in situ was not observed.

Eight patients with carcinoma in situ in the contralateral testis received

FIG 3—Life table¹³ showing relation between time after diagnosis of carcinoma in situ and proportion of patients escaping invasive growth. Estimate based on data from 19 patients not having systemic treatment and from two further patients in period up to time that they received chemotherapy for relapse of initial tumour. Fine lines represent 95% confidence limits.

TABLE II—Data from seven patients developing contralateral testicular cancer

Case No	Initial testicular cancer			Time from diagnosis of carcinoma in situ to invasive growth (months)	Contralateral testicular cancer			Observation time from second orchidectomy (months)	Present state
	Histological type	Stage	Postorchidectomy treatment		Histological type	Stage	Postorchidectomy treatment		
1	Seminoma	I	Radiotherapy	45	Early invasive growth	I	None	102	Alive. NED†
7	Seminoma	I	Radiotherapy	21	Seminoma	I	None*	57	Alive. NED
12	Seminoma	I	Radiotherapy	13	Seminoma	I	None	30	Alive. NED
13	Seminoma	II	Radiotherapy	27	Early invasive growth	I	None	16	Alive. NED
15	Seminoma	I	Radiotherapy	12	Seminoma	I	None	6	Dead. NED‡
16	Embryonal carcinoma + teratoma + endodermal sinus tumour	I	Radiotherapy	7	Seminoma + embryonal carcinoma	I	None	32	Alive. NED
17	Seminoma	I	Radiotherapy	0	Seminoma	I	None	35	Alive. NED

*This patient received chemotherapy 15 months later because of supraclavicular lymph node metastases.

†NED = No evidence of disease.

‡Suicide without evidence of disease.

chemotherapy, either as primary treatment after orchidectomy (six patients) or for relapse (two). The chemotherapeutic regimen consisted of cisplatin, vinblastine, and bleomycin in seven patients and vinblastine and bleomycin in one. None of these eight patients developed contralateral cancer of the testis during follow up periods of 12, 14, 15, 21, 24, 60, 84, and 88 months, respectively. Each of the eight patients had one or more biopsy specimens examined after chemotherapy, and in all cases the changes of carcinoma in situ had disappeared.

A total of 58 follow up biopsies were performed in the 27 patients (median two, range 0-7). No serious complications arose from biopsy sampling, though local discomfort was usually present for several days.

Three of the 27 patients died, one from spread of the initial cancer and two from other causes (suicide and drug addiction).

The biopsy specimens did not show carcinoma in situ in 473 patients. None of these patients developed a contralateral testicular cancer during the period of observation (median 46 months, range 12-96 months).

Discussion

This study has elucidated the spontaneous course of carcinoma in situ in the contralateral testis of patients with unilateral testicular germ cell cancer. The estimated risk for untreated carcinoma in situ to progress to invasive cancer was 40% within three years and 50% within five years. A similar risk has been estimated for carcinoma in situ in the testes of infertile men.⁴ The estimate was based on data from patients receiving irradiation of the regional lymph nodes or no additional treatment after the initial orchidectomy. The scattered radiation dose to the testis of less than 0.8 Gy (80 rads) in the former group was, in this respect, considered insignificant.

Our data strongly support the concept that testicular germ cell tumours are preceded by carcinoma in situ. Thus patients with carcinoma in situ of the testis had a high risk of developing an invasive tumour, whereas none of the patients without carcinoma in situ in the screening biopsy sample developed a contralateral cancer. The concept also accords with the fact that carcinoma in situ is nearly always present in the tissue adjacent to testicular germ cell tumours.^{14 15}

Spontaneous disappearance of carcinoma in situ did not occur in our series. Nevertheless, we still do not know whether carcinoma in situ invariably progresses to invasive growth. Some cases may persist in a premalignant state, which may help to explain the difference between the high incidence of carcinoma in situ (5.4%) and the presumed incidence of bilateral testicular cancer (1-2%). The influence of chemotherapy on the course of carcinoma in situ may be another explanation for this apparent discrepancy. Finally, the previous reported incidence of bilateral testicular cancer may have been underestimated.

Combination chemotherapy with cisplatin, vinblastine, and bleomycin appears to eradicate carcinoma in situ. Nevertheless, a longer follow up period will be needed to show whether this effect is permanent. It should be noted that development of a contralateral cancer has occasionally been observed despite prior combination chemotherapy including regimens containing cisplatin, vinblastine, and bleomycin.¹⁶ Furthermore, we have unpublished data on four patients who developed contralateral testicular cancer after having

received bleomycin and vincristine simultaneously with irradiation. These patients were treated according to an early protocol of the Danish testicular carcinoma study for non-seminoma stage I,⁹ before establishment of the screening procedure for carcinoma in situ in the contralateral testis. Thus, though we have no information about changes of carcinoma in situ before treatment of these four patients, this chemotherapeutic regimen is probably not enough to eradicate carcinoma in situ of the testis. On the other hand, intensive chemotherapy with all three agents is too toxic for the treatment of premalignant disease. Hence chemotherapy should be given only in accordance with the classification of the initial testicular cancer and not for carcinoma in situ of the contralateral testis.

None of our patients died as a result of progression of the carcinoma in situ. All patients developing cancer of the contralateral testis appeared to have been cured by orchidectomy alone. One patient developed metastases in supraclavicular lymph nodes 15 months after the second orchidectomy but it was impossible to determine whether this was relapse related to the initial or to the second testicular cancer.

It appears that patients receiving chemotherapy for the initial testicular cancer have a minimal risk of developing a contralateral tumour. These patients should be offered continuous clinical observation, including follow up biopsies, without any further treatment. Patients with carcinoma in situ not receiving chemotherapy have a high risk of developing a contralateral cancer. For these patients it is important to devise an effective and at the same time acceptable treatment for the changes of carcinoma in situ in order to avoid a second orchidectomy and subsequent androgen insufficiency. We are investigating the efficacy of localised irradiation of the testis, and our preliminary results show that a dose of 20 Gy (2000 rads) given over 10 days may eradicate carcinoma in situ of the testis without appreciably affecting Leydig cell function.¹⁷

In conclusion, our findings show the importance of performing a biopsy of the contralateral testis in patients with testicular cancer. If the biopsy specimen is without carcinoma in situ the patient may be assured that the risk of developing a contralateral cancer is

extremely small. If carcinoma in situ is present it is possible to diagnose invasive growth at an early stage by a suitable follow up programme to eradicate the changes of carcinoma in situ and avoid invasive growth. We therefore recommend that all patients with unilateral testicular germ cell cancer should be offered a contralateral testicular biopsy.

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Cryptorchidism: an apparent substantial increase since 1960

JOHN RADCLIFFE HOSPITAL CRYPTORCHIDISM STUDY GROUP

Abstract

A total of 1849 boys born to mothers resident in a defined area around Oxford were examined for cryptorchidism. Those born in hospital were examined at birth and again after three months

if cryptorchid at the earlier examination. The incidence of cryptorchidism at three months adjusted to the birthweight distribution of England and Wales was 1.58%. By comparison, in a very similar study conducted around 1960 the incidence was 0.96%. Hence the cryptorchidism rate had apparently increased by 65% over the two decades, which contrasted with the twofold increase in the national orchidopexy rate. The proportion of boys undergoing orchidopexy appeared consistently to be roughly twice the proportion of boys with an undescended testis at 3 months of age.

The increase in cryptorchidism and disparity with the rate of orchidopexy are not easily explained and are the subjects of continuing study.

Introduction

Cryptorchidism is an important and the only well established risk factor for testicular cancer, some 10% of patients with testicular cancer having a history of the condition.¹ Moreover, this frequency of past cryptorchidism among patients with testicular cancer appears to have changed little, if at all, over the past 50 years, which

John Radcliffe Hospital Cryptorchidism Study Group

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Pat Ansell, SRN; Jean Barton, SRN; Diana Bull; M B Jackson, MRCP; Anne Pike, RN; M C Pike, PhD

INSTITUTE OF CANCER RESEARCH, SUTTON, SURREY
Clair Chilvers, MSC

JOHN RADCLIFFE HOSPITAL, HEADINGTON, OXFORD

N E Dudley, FRCS; M H Gough, MS; D M Griffiths, FRCS; C Redman, FRCP; A R Wilkinson, FRCP

OXFORDSHIRE AREA HEALTH AUTHORITY, RADCLIFFE INFIRMARY, OXFORD
A Macfarlane, FRCP

Report prepared by M B Jackson, Clair Chilvers, M C Pike, Pat Ansell, Diana Bull

Correspondence to: Dr M C Pike, ICRF Cancer Epidemiology Unit, Radcliffe Infirmary, Oxford.