Semen parameters and testicular pathology in men with testicular cancer and contralateral carcinoma in situ or bilateral testicular malignancies

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We evaluated 14 patients with bilateral testicular tumour, one-sided tumour and contralateral carcinoma in situ (CIS) of the testis or testis tumour in single testis with respect to their fertility. We analysed semen parameters, serum hormones [follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone], testicular sonography, testicular volumes and testicular histology prior to further anti-cancer treatment. Ten out of 14 patients showed normal or reduced sperm concentrations, while 4/14 patients were azoospermic. Serum FSH levels showed a significant negative correlation with sperm concentrations in patients with testicular malignancies (r = -0.64, P = 0.025). Testicular volumes revealed a significant positive correlation with semen parameters in patients with testes that were affected by CIS (r = 0.733, P = 0.038). We conclude that even bilateral testicular cancer and/or CIS do not preclude fertility and, therefore, patients should be offered andrological investigation and therapy, including possibly surveillance strategy or the chance for cryopreservation of the semen prior to further treatment in order to preserve their chances for paternity.

Key words: carcinoma in situ/cryopreservation of semen/male infertility/scrotal sonography/testis tumour

Introduction

Testicular cancer is the most common tumour occurring in young men. A total of 70% of tumours become manifest between 20 to 40 years of age with a maximum for seminomas at 37 years and non-seminomatous tumours at 28 years. Contralateral testicular biopsy reveals in about 5% of patients testicular carcinoma in situ (CIS) (synonymous: testicular intraepithelial neoplasia, TIN) and bilateral testicular tumours can be found in 2% of patients (von der Maase et al., 1987; Dieckmann et al., 1993; Giwercman et al., 1993b; Dieckmann and Loy, 1996).

As testicular cancer has become a curable illness with more than a 90% chance of survival due to surgery, chemotherapy and radiotherapy, long-term toxicity of treatment becomes an important factor contributing to the patient’s quality of life (Fossa et al., 1996). One of these aspects arises from the young age of the patients, who are often not married and have not fathered children at the time of manifestation of their disease. Therefore, fertility is one important aspect to be considered and discussed with the patient prior to anti-cancer treatment.

In patients with testicular cancer, fertility may be reduced before any potentially toxic treatment affects the gonads. The reasons for reduced spermatogenesis involving both the tumorous and the contralateral testis are poorly understood (Fossa et al., 1982; Berthelsen and Skakkebaek, 1983; Hansen et al., 1991; Kliesch et al., 1996). However, patients with unilateral testicular tumour have the chance that spermatogenesis may recover after orchidectomy. If further treatment (chemotherapy or radiotherapy) is necessary, it depends on the treatment modalities, doses and individual susceptibility, whether spermatogenic capacity of the contralateral testis will recover after the end of treatment or whether fertility will be further reduced (Hansen et al., 1991). In cancer patients with CIS of the contralateral testes and in patients with bilateral testicular tumours the situation is even more difficult. So far very little data on the fertility of patients with bilateral testicular cancer or CIS of the contralateral tests are available (Frens, 1983; Giwercman et al., 1993a). Therefore we evaluated 14 patients with either simultaneous or consecutive bilateral testicular tumour and/or contralateral CIS with respect to fertility. These patients were extracted from a database of 300 testis cancer patients in our department and were included for analysis if semen analysis, serum parameters and testicular sonography were available.

Materials and methods

Fourteen patients presented either with testicular tumour and CIS of the contralateral testis, simultaneous or consecutive bilateral testicular tumour or testis tumour in one single testis (Table I). Testicular tumour had been suspected due to increased testicular mass palpated by the patient or the physician, or by ultrasonography performed during clinical investigation. CIS was suspected in some patients because of irregular, inhomogeneous testicular parenchyma during scrotal sonography.

Ultrasonography

Scrotal sonography was performed with a 7.5 MHz scanner. Hominogeneity and echogenicity of testicular parenchyma were documented and testicular volumes were sonographically determined using the rotation-ellipsoid formula described earlier (Behre et al., 1989; Behre et al., 1995). Only testes affected by CIS cells were considered for evaluation of testicular volumes (patients no. 4, 5, 6, 8, 9, 10, 11, 12, 13, 14).
Table I. Patients’ characteristics

<table>
<thead>
<tr>
<th>Patient no. (age, years)</th>
<th>Histology (right/left)</th>
<th>Sperm concentration (×10⁹/ml)</th>
<th>Progressive sperm motility (%)</th>
<th>Normal sperm morphology (%)</th>
<th>FSH (IU/l)</th>
<th>Testosterone (nmol/l)</th>
<th>AFP (ng/ml)</th>
<th>βHCG (mIU/ml)</th>
<th>Testicular volume (ml) (right/left)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (29) S/S</td>
<td></td>
<td>2.2</td>
<td>36</td>
<td>5</td>
<td>n.d.</td>
<td>n.d.</td>
<td>2.9</td>
<td>23.9</td>
<td>25/15</td>
</tr>
<tr>
<td>2 (37) S/S</td>
<td></td>
<td>0.0</td>
<td>–</td>
<td>–</td>
<td>14.5</td>
<td>16.9</td>
<td>1.9</td>
<td>0.2</td>
<td>24/92</td>
</tr>
<tr>
<td>3 (24) S/Tb</td>
<td></td>
<td>0.4</td>
<td>3</td>
<td>22</td>
<td>15.7</td>
<td>12.1</td>
<td>2.9</td>
<td>0.5</td>
<td>n.d.</td>
</tr>
<tr>
<td>4 (37) CIS/CIS</td>
<td></td>
<td>0.0</td>
<td>–</td>
<td>–</td>
<td>26.6</td>
<td>11.7</td>
<td>2.0</td>
<td>0.3</td>
<td>-12</td>
</tr>
<tr>
<td>5 (29) CIS/S</td>
<td></td>
<td>2.6</td>
<td>14</td>
<td>9</td>
<td>8.7</td>
<td>14.9</td>
<td>2.9</td>
<td>0.0</td>
<td>18/15</td>
</tr>
<tr>
<td>6 (25) CIS/S</td>
<td></td>
<td>0.15</td>
<td>9</td>
<td>6</td>
<td>5.9</td>
<td>25.9</td>
<td>1.9</td>
<td>6.4</td>
<td>20/35</td>
</tr>
<tr>
<td>7 (41) unknown²/S</td>
<td></td>
<td>0.0</td>
<td>–</td>
<td>–</td>
<td>10.0</td>
<td>29.5</td>
<td>4.3</td>
<td>22.7</td>
<td>-30</td>
</tr>
<tr>
<td>8 (29) S/CIS</td>
<td></td>
<td>0.0</td>
<td>–</td>
<td>–</td>
<td>41.8</td>
<td>5.1</td>
<td>1.5</td>
<td>1.9</td>
<td>-5</td>
</tr>
<tr>
<td>9 (26) S/CIS</td>
<td></td>
<td>4.9</td>
<td>53</td>
<td>8</td>
<td>2.6</td>
<td>20.8</td>
<td>1.9</td>
<td>16.7</td>
<td>-23</td>
</tr>
<tr>
<td>10 (25) S/CIS</td>
<td></td>
<td>3.8</td>
<td>40</td>
<td>50</td>
<td>n.d.</td>
<td>n.d.</td>
<td>3.9</td>
<td>12.3</td>
<td>-10</td>
</tr>
<tr>
<td>11 (24) CIS/EC + T</td>
<td></td>
<td>1.5</td>
<td>54</td>
<td>14</td>
<td>6.3</td>
<td>4.1</td>
<td>2.8</td>
<td>92.3</td>
<td>14/-</td>
</tr>
<tr>
<td>12 (24) EC + T/CIS</td>
<td></td>
<td>35.5</td>
<td>60</td>
<td>25</td>
<td>9.8</td>
<td>11.6</td>
<td>6.6</td>
<td>0.5</td>
<td>-21</td>
</tr>
<tr>
<td>13 (29) T/CIS</td>
<td></td>
<td>25.5</td>
<td>64</td>
<td>51</td>
<td>10.9</td>
<td>21.5</td>
<td>3.2</td>
<td>0.0</td>
<td>-72</td>
</tr>
<tr>
<td>14 (27) YS + T/CIS</td>
<td></td>
<td>9.4</td>
<td>18</td>
<td>6</td>
<td>4.0</td>
<td>9.8</td>
<td>436.0</td>
<td>7.0</td>
<td>-15</td>
</tr>
</tbody>
</table>

¹Remaining testes at the time of semen analysis and hormone determinations.
²Orchidectomy 1987 and four cycles of polychemotherapy with cisplatin, etoposide, bleomycin.
³Orchidectomy 1993.
⁴Orchidectomy at the age of 3 (1957) because of maldescended testis.
CIS = carcinoma in situ; EC = embryonic carcinoma; FSH = follicle stimulating hormone; S = seminoma; AFP = alpha-fetoprotein; T = teratoma; βHCG = β human chorionic gonadotrophin; YS = yolk sac tumour; n.d. = not done.

12, 13 and 14, as testes with manifest tumours may have increased volumes due to tumorous mass.

Tumour marker and hormone analysis
Prior to surgical intervention blood samples were routinely drawn to determine testicular tumour markers, alpha-fetoprotein (AFP) and β-human chorionic gonadotrophin (HCG). Serum hormone concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone (T) were determined at the time of semen analysis.

AFP and βHCG were analysed by immuno-enzymometric assays, LH and FSH were determined by time-resolved fluorometric assays and T by radioimmunoassay as published earlier (Behre et al., 1992). Normal limits were <7 ng/ml for AFP and <5 mU/ml for βHCG. Normal ranges were 2–10 IU/l for LH and 1–7 IU/l for FSH. The lower normal limit for T was 12 nmol/l.

Semen analysis
In patients with suspected bilateral testicular tumours, either simultaneously (patients no. 1 and 2) or consecutively (no. 3), or sonographically suspicious findings for CIS or tumour in a single testis (no. 14, 7), semen analysis and cryopreservation of the ejaculate were offered to the patient prior to any surgery. In men suspected to have unilateral tumour, semen analysis and cryopreservation of semen were offered before (patients no. 5 and 6) or after orchidectomy (patients no. 8–14) prior to further treatment of patients.

Semen analysis was performed according to WHO guidelines (WHO, 1992). Sperm concentration was normal with ≥20×10⁹ spermatozoa/ml, sperm motility was normal with ≥50% progressively motile spermatozoa (rapidly and slowly motile spermatozoa) and morphology was regarded as normal with ≥30% normally formed spermatozoa (WHO, 1992). Cryopreservation was performed as described elsewhere (Kliesch et al., 1996).

Statistics
Descriptive statistics of untransformed variables are given as the arithmetic mean and the standard error of the mean (SEM) or the standard deviation (SD), as indicated. P values < 0.05 were considered significant. All variables were checked for normal distribution. The sperm concentrations were log-transformed before analysis to achieve normal distribution. Analysis of linear regression was performed to determine the dependence of semen parameters from serum hormone levels and testicular volumes only in patients with CIS in the remaining testis. Analyses were performed using the statistical software Statgraphics®, version 7.1 (STSC Inc., Rockville, MD, USA).

Results

Patients
A total of 14 male patients were investigated at a mean age of 29 years (±5 years SD; range 24–41 years). Seven patients were married at the time of investigation, none of them had demonstrate CIS (Figure 1) (Hustin et al., 1987; Bergmann and Kliesch, 1994).
fathered children before. Four patients sought medical help because of unexplained infertility (patients no. 2, 3, 4 and 5) and testicular tumour or CIS were suspected during andrological work-up. Ten patients were referred to the clinic because an increase of testicular mass was observed that caused suspicion of testicular tumour. Two of them retrospectively reported unexplained infertility for several years. Moreover, two patients had a history of maldescended testes either of the right side (no. 7) or of both testes (no. 9).

Patients suffered from simultaneous ($n = 2$) or consecutive ($n = 1$) bilateral testicular tumours, or simultaneously diagnosed testicular tumour and contralateral CIS ($n = 9$). Another patient had had an orchidectomy due to maldescended testis during childhood and developed a seminoma in the other testis; one patient had an orchidectomy due to CIS and was diagnosed to have CIS in the contralateral testis 2 years later (Table I). All patients are still alive and show progression free survival, the longest being 4 years and 7 months (6–55 months).

**Scrotal sonography**

On scrotal sonography all testicular tumours revealed suspicious findings with hypoechogetic and hyperechogetic inhomogeneous lesions of the testicular parenchyma. Only one of the patients was not suspected to have a tumour by palpation of the testes (patient no. 1). Testes with CIS without manifest tumour in the histology showed more often inhomogeneous testicular structures with hyperechogetic spots in 7 out of 10 patients, while three testes with carcinoma *in situ* revealed a homogenous testicular parenchyma in scrotal sonography (patients no. 6, 9 and 14).

Sonographically determined testicular volumes in testes with CIS ranged between 5 and 23 ml and were in the normal range.
Semen parameters in men with testicular tumour and contralateral carcinoma in situ

Figure 2. Sperm concentrations and testicular volumes of patients having one remaining testis with carcinoma in situ at the time of semen analysis. Note the logarithmic scale for sperm concentration. Broken line indicates lower normal limit for sperm concentration (\(\geq 20 \times 10^6/\text{ml}\)).

in 8 of 10 patients (\(\geq 12 \text{ ml}\)) (Table I). Testicular volumes of single testes (at the time of semen analysis) affected with CIS showed a significant correlation with sperm concentrations (\(r = 0.733, P = 0.038\)) (Figure 2).

Testicular histopathology

Testicular tumours were histologically evaluated and classified to belong to stage pT1 (restricted to the testis) or in the case of CIS pTis, with the exception of one patient (no. 8) whose testis tumour revealed penetration of the epididymis and vas deferens (pT3). Seminomas were found in 11 testes (nine patients). Five patients with seminomas, one patient with embryonic carcinoma/teratoma and another one with yolk sac tumour/teratoma had elevated serum \(\beta\)HCG levels. Four patients had non-seminomas with elevated AFP serum levels in one case (Table I).

Contralateral CIS or CIS in a single testis was found in 10 patients by morphological and immunohistochemical analysis of testicular biopsies (Table I). In azoospermic men, testes with CIS did not reveal any testicular tubule with round or elongated spermatids.

Testicular sperm extraction

Two patients (no. 2 and 7) who revealed azoospermia prior to orchidectomy wanted to have testicular tissue cryopreserved. Multiple testicular biopsies were taken distant to the tumour during operation. However, no spermatids could be found.

Semen analysis

Semen analysis revealed azoospermia in four patients, oligoasthenoteratozoospermia in six and oligoteratozoospermia in two patients. Normal sperm concentrations were observed in two men with teratozoospermia in one case (Table I). The median sperm concentration (of all men) was \(1.9 \times 10^6/\text{ml}\) (mean \(6.1 \pm 2.9 \times 10^6/\text{ml}\) SEM). Of the azoospermic men, two had CIS in the remaining testis (no. 4 and 8), one patient had a seminoma in the residual testis (no. 7) and one man revealed simultaneous bilateral seminoma (no. 2). The patients with normal sperm concentrations had CIS in the contralateral testes (no. 12 and 13). The oligozoospermic men included those with bilateral seminoma (no. 1) and simultaneous contralateral CIS (no. 5, 6, 9, 10, 11 and 14), and one patient with consecutive seminoma 7 years after having received polychemotherapy with cisplatin-etoposide-bleomycin because of previous testicular cancer (no. 3) (Table I). Sperm concentrations increased significantly with testicular volumes determined by ultrasonography in men with single remaining testis with CIS (Figure 2) (\(r = 0.733, P = 0.038\)).

Hormones

Mean serum hormone levels were for \(\text{LH}\) 6.4 IU/l (\(\pm 1.3 \text{ IU/l}\) SEM, range 2.4–14.5 IU/l), for \(\text{FSH}\) 15.0 IU/l (\(\pm 3.7 \text{ IU/l}\) SEM, range 2.6–41.8 IU/l) and for \(\text{T}\) 15.3 nmol/l (\(\pm 2.3 \text{ nmol/l}\) SEM, range 4.1–29.5 nmol/l) (Table I). While LH and \(\text{T}\) did not show any correlation with testicular volumes or sperm concentrations, \(\text{FSH}\) showed a significant negative correlation of –0.64 with sperm concentration (\(P = 0.025\)) in men with single remaining testis with CIS or testis tumour at the time of investigation (Figure 3).

Discussion

A total of 10/14 patients with carcinoma in situ of the contralateral testis or bilateral testicular tumours (simultaneous or consecutive) revealed semen parameters that may be compatible with fertility, in particular if methods of assisted fertilization are considered. Sperm concentrations were reduced in most patients, but may exceed the lower normal limit. The results of semen analysis were not correlated with the histopathological findings, either with CIS, seminoma or non-seminoma.

Objectively determined testicular volumes may reflect spermatogenic activity. Azoospermia or extremely low sperm concentrations were correlated with reduced testicular volumes determined by ultrasonography in patients with the remaining
testis affected by CIS. Moreover, we found significantly more often inhomogeneous rather than homogeneous testicular parenchyma in CIS testis during ultrasonography. Thus hyper-echogenic testicular lesions not only reflect impaired spermatogenesis as previously shown in infertile men, but may also reflect CIS of the testis (Lenz et al., 1987; Behre et al., 1995).

In addition, serum FSH levels may reflect testicular function, with highest levels in severely impaired spermatogenesis. These results confirm recent findings in infertile men with increased FSH concentrations that were correlated with the occurrence of unilateral or bilateral focal Sertoli-cell-only syndrome in testicular histology (Bergmann et al., 1994). However, elevated FSH levels may also originate from the tumorous testis itself or from the unilaterally missing testicle after orchidectomy. In our study, sperm concentrations showed a significant negative correlation with FSH in men with CIS in the remaining testes. However, in three patients (patients no. 9, 11 and 14) FSH serum levels were low with low sperm concentrations. In these patients false low levels of FSH may be measured due to elevated βHCG (patients no. 9 and 11) or AFP (patient no. 14) levels that negatively influence the hypothalamic–pituitary–gonadal axis.

In patients with CIS of the testis and viable spermatozoa in the ejaculate, the delay in therapy possibly in combination with techniques of assisted fertilization may be the chosen treatment, until fatherhood has been achieved. With the standard treatment of CIS, namely radiotherapy with 18–20 Gy, spermatogenic capacity will be irreversibly destroyed. If a surveillance strategy is not feasible, or in men with manifest bilateral tumour of the testes in which the delay in cancer treatment cannot be recommended, cryopreservation of semen must be offered to the patients prior to further therapy in order to preserve fertility (Kliesch et al., 1996, 1997). In men with bilateral testis tumour the enucleation of a tumour may also be an alternative. The chance to use cryopreserved spermatozoa and semen samples of extremely low quality (severe oligoasthenoteratozoospermia) in combination with assisted fertilization techniques to induce a pregnancy in the female partner have increased tremendously with the introduction of intracytoplasmic sperm injection.

Moreover, the following aspects deserve further consideration. It remains difficult to answer the question of whether an increased genetic risk exists for the offspring of patients suffering from malignancies or treated by oncological chemotherapeutic or radiotherapy (Kliesch et al., 1997). It has been demonstrated that malignant germ cells are present in the seminal fluid (Giwerzman et al., 1990) and the available cytogenetic investigations in spermatozoa from patients after chemotherapeutic or radiotherapy show a significantly increased proportion of structural chromosomal anomalies in comparison to controls (Genescà et al., 1990; Rousseaux et al., 1993). However, these in-vitro results are not supported by clinical data and reports on paternity of testicular cancer patients with uni- or bilaterally affected testes do not suggest increased rates of anomalies in children born (Dieckmann and Loy, 1993; Babosa et al., 1994; Heidenreich et al., 1997). Possibly exogenous hazards may contribute to the increasing incidence of testicular cancer (James, 1997) more than the reproduction of cancer patients themselves. Another aspect involves the possible risk of genetically determined disease in the offspring when using assisted fertilization techniques with fresh or frozen spermatozoa. However, the reported data of in-vitro fertilization centres and the data obtained from offspring of oncological patients (including testis cancer patients) both indicate no increased risk for malformations (Dodds et al., 1993; Meschede et al., 1995). Nevertheless, the offspring of testis cancer patients should be carefully included in the follow-up of these patients, as an increased chance to develop a testis cancer in sons should be taken into consideration.

In summary, we have demonstrated that in patients with CIS of the testis or bilateral manifest testicular tumour, spermatogenic activity is still present. Therefore, the chance to father a child generally exists. Clinical parameters, such as testicular volumes and serum FSH levels, correlate with semen parameters and may indicate testicular function in men with testicular malignancies. Therefore, an andrological investigation including testicular sonography, determination of testicular volumes, sperm hormone and semen analysis in patients with unilateral or bilateral testicular tumour and/or CIS may be helpful. As the minimum, we recommend the performance of a semen analysis to verify the presence or absence of spermatozoa in the ejaculate. Patients should finally be offered a risk-adopted therapeutic strategy, including the possibility of surveillance in cases of CIS, tumour enucleation in cases of bilateral testis tumour and the cryopreservation of their semen prior to further treatment. The preservation of fertility may have an important impact on the young patient’s quality of life.

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