Prevalence of carcinoma in situ of the testis in 207 oligozoospermic men from infertile couples: prospective study of testicular biopsies

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Abstract

Objective: To investigate the prevalence of carcinoma in situ of the testis in a group of oligozoospermic men from infertile couples.

Design: A consecutive group of oligozoospermic men from infertile couples were offered bilateral testicular biopsy. The observed prevalence of carcinoma in situ was compared with the expected prevalence of testicular cancer in a corresponding age matched population of Danish men, assuming all untreated cases of carcinoma in situ progress to tumour stage. This calculation was based on data from the Danish Cancer Registry.

Subjects: 207 men aged 18-50 years who had sperm density below 10 million/ml in two samples within the previous 2 years or sperm density below 20 million/ml in two samples within the previous 2 years and a history of cryptorchidism or one or two atrophic testicles (orchidometer volume less than 15 cm³), or both.

Interventions: Bilateral testicular biopsies.

Main outcome measures: Carcinoma in situ in the biopsy specimen.

Results: No case of carcinoma in situ was found among the 207 men. The expected number in a normal age matched population of corresponding size was 0.8.

Conclusion: There is no increase in risk of carcinoma in situ of the testis in moderately oligozoospermic men of couples referred because of infertility.

Introduction

Carcinoma in situ of the testis is a preinvasive lesion preceding development of all types of testicular germ cell tumours, except the spermatocytic seminoma.^{1,2} Male infertility has been considered a risk factor for carcinoma in situ.³⁻⁹ This assumption was based on retrospective studies of biopsy samples from a heterogeneous group of infertile men, including those with obstructive azoospermia, Sertoli cell only, and Klinefelter's syndrome, who were not expected to have an increased risk of testicular malignancy.

Nevertheless, it has been proposed that testicular biopsy as a screening for carcinoma in situ should be offered to infertile men.⁴ Before screening is recommended, however, the subpopulation of these men who are at particularly high risk of testicular neoplasia should be defined and the magnitude of this risk estimated. Previous studies on risk factors for carcinoma in situ, mainly of men with unilateral testicular cancer who have carcinoma in situ in the contralateral testis, indicated that oligozoospermia, testicular atrophy, and a history of maldescent might be the factors implying increased risk.¹⁰ To evaluate the

need for screening for carcinoma in situ in such men we carried out a prospective study.

Patients and methods

Selection of men for biopsy

The study was performed during 1986-93. All men aged 18-50 years referred because of infertility to one of the three departments of gynaecology in the county of Copenhagen were asked to participate in the study if the following inclusion criteria were fulfilled: sperm density below 10 million/ml in two samples within the previous 2 years or sperm density below 20 million/ml in two samples within the previous 2 years and a history of cryptorchidism or one or two atrophic testicles (orchidometer volume < 15 cm³), or both. The men were excluded if both testes were smaller than 4 cm³ (because of high probability of Klinefelter's syndrome); they had previously been treated for testicular cancer or treated with cytotoxic drugs, or both; they had previously had a testicular biopsy performed; or they were not white (because of racial and geographical differences in incidence of testicular malignancy).

A total of 248 men were invited to participate in the study. Twenty six did not fulfil the inclusion criteria, and two were excluded because of previous testicular cancer or ethnic group. Among the remaining 220 men, 11 did not wish to participate and in two men the biopsy sample was erroneously taken from the epididymis and not from the testis. Thus, a total of 207 men were included in the study. Their characteristics are listed in table 1.

Testicular biopsy

All but six men had bilateral biopsies performed as previously described.^{11,12} Six men had only unilateral biopsy as they had only either the right (3) or the left (3) gonad present in the scrotum.

Calculation of expected number of cases of carcinoma in situ

To estimate the relative risk of carcinoma in situ in the population studied an expected number of cases of testicular cancer was calculated for a corresponding

Table 1 Characteristics of 207 infertile men included in prospective study

Characteristic	Median (range)
Age (years)	31 (20-45)
Duration of infertility (years)	2.5 (0.6-13.0)
Left testis volume (cm ³)	12 (3-25)
Right testis volume (cm ³)	13 (3-25)
Mean sperm count (million/ml)	1.6 (0.0-19.0)

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Table 2 Histological pattern in testicular biopsy specimens from oligozoospermic men in prospective study

Histological pattern	No of men
No carcinoma in situ. Both testes with complete spermatogenesis (including spermatids) in all tubules	94
No carcinoma in situ. Both testes with spermatocytic arrest in all tubules	7
No carcinoma in situ. Both testes with Sertoli cell only in all tubules	18
No carcinoma in situ. No spermatogenesis in any tubules. Hyalinisation in at least some tubules	22
No carcinoma in situ. At least some tubules without ongoing spermatogenesis but minimum 50% of tubules on one side with complete spermatogenesis	47
No carcinoma in situ. Complete spermatogenesis in more than 1% but less than 50% tubules in any of the testes	19
Carcinoma in situ	0

normal population adjusted for age at the time of biopsy and year of birth. The Danish cancer registry is regarded as complete with respect to invasive cancers, whereas carcinoma in situ is less completely reported. The calculation was based on the data from the registry, and the figures for incidence only up to the age of 60 were applied (see below).

The study was approved by the local ethics committees.

Results

No case of carcinoma in situ (95% confidence interval 0 to 3.7; Poisson distribution) was found in testicular tissue from the 207 men included in the study. The distribution of different histological diagnoses is given in table 2.

On the basis of data from the Danish cancer registry, the expected number of cases of carcinoma in situ in a population of Danish men matched for age and year of birth was calculated to be 0.8. Thus, the risk of carcinoma in situ did not deviate from the expected in the group of infertile men included in our study.

Discussion

In our prospective study of oligozoospermic men from infertile couples we could not find any increase in the risk of carcinoma in situ compared with the general Danish male population. Thus, no case of carcinoma in situ was found in the bilateral biopsy specimens from the 207 men, whereas the expected number of cases was 0.8 in a corresponding group with a relative risk of 1. Because of the relatively small number of cases included in our study we cannot exclude the possibility that an existing increase in the relative risk was not found because of a type 2 error. On the other hand, our data show that such an increase, if it does exist, would not be higher than 4.6 (3.7/0.8).

Assumptions in calculating risk

The calculation of expected number of cases was based on several assumptions.

Firstly, testicular biopsy was assumed to be 100% sensitive in the diagnosis of carcinoma in situ. Although not 100% sensitive, experimental and clinical data clearly indicate that this procedure is extremely reliable in the diagnosis of carcinoma in situ.¹³ Thus, in our material of more than 1500 samples from men belonging to high risk groups for testicular neoplasia, we saw only one case of a negative biopsy result followed by development of cancer during an observation period of

over 10 years.¹⁴ Despite the enormous number of testicular biopsies performed, we were able to trace in published work fewer than 10 cases in which men with negative testicular biopsy results went on to develop tumours.¹⁵ The high sensitivity of testicular biopsy in detection of carcinoma in situ is due to the generally dispersed character of this preinvasive lesion.^{16 17}

Secondly, carcinoma in situ is assumed to be of fetal origin, which means that infertile men cannot develop carcinoma in situ after the biopsy had been performed. The few false negative results are probably due to an unusually focal distribution rather than the fact that carcinoma in situ was not present at the time of diagnosis as there is a substantial evidence indicating a fetal origin of carcinoma in situ.¹²⁵

Thirdly, we assumed that carcinoma in situ will always progress to invasive cancer.

Finally, we assumed that all patients develop germ cell cancer not later than the age of 60. Nearly all testicular tumours developed after this age are lymphomas or spermatocytic seminomas not derived from carcinoma in situ. If the above mentioned assumptions are correct the prevalence of carcinoma in situ at the time of biopsy will correspond to the risk of subsequent development of testicular germ cell cancer, and consequently the rates of testicular cancer up to the age of 60 years (as presented in our analysis) can be used in estimating the life time risk of testicular cancer from the age at time of biopsy.

One could also question whether the group of men included in our study was representative of infertile men with low sperm counts. We cannot rule out that some men with poor sperm counts are not referred to infertility clinics by general practitioners because of a rather pessimistic view of the possibilities of treating male infertility. Our study group, however, reflects the population referred to Danish infertility clinics and thereby the potential target group for screening for carcinoma in situ.

Conclusions

It has been suggested that infertile men with low sperm counts should be offered a testicular biopsy as a screening for carcinoma in situ.⁴ Our data indicate that at least mild oligozoospermia, even when associated with a history of cryptorchidism or slight testicular atrophy, or both, does not imply any significant rise in

Key messages

- Testicular cancer can be prevented if it is diagnosed at the preinvasive stage of carcinoma in situ
- Infertile men with atrophic testes were considered as a potential high risk group for testicular neoplasia
- A prospective study of 207 men from infertile couples did not show any increase in risk of carcinoma in situ of the testis in men with moderate oligozoospermia
- A high risk of testicular neoplasia in men with very low sperm counts, atrophic testes, and irregular echo pattern on ultrasonography cannot be ruled out

the risk of carcinoma in situ. A recent retrospective report indicates that the risk of carcinoma in situ may be most pronounced in men with seriously affected spermatogenesis and therefore low sperm counts.¹⁸ In another study of infertile men two cases of carcinoma in situ were found in men with sperm counts below 2.5 million/ml and severe testicular atrophy (≤ 10 cm³).¹⁹ In retrospectively reviewed material from our department we found carcinoma in situ in two of 31 infertile men who had had bilateral biopsy performed because of low sperm counts, testicular atrophy, and irregular ultrasonic echo pattern (unpublished data). Men with such low sperm counts and atrophic testis size comprised less than 20% of our population in the prospective study. There is, therefore, a need for prospective studies to evaluate whether the risk of carcinoma in situ is significantly increased in a subpopulation of infertile men with very severe oligozoospermia and pronounced testicular atrophy accompanied by very irregular echo pattern.

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- 1 Skakkebaek NE, Berthelsen JG, Giwercman A, Müller J. Carcinoma-in-situ of the testis: possible origin from gonocytes and precursor of all types of germ cell tumours except spermatocytoma. *Int J Androl* 1987;10:19-28.
- 2 Müller J, Skakkebaek NE, Parkinson MC. The spermatocytic seminoma: views on pathogenesis. *Int J Androl* 1987;10:147-56.
- 3 Skakkebaek NE. Possible carcinoma-in-situ of the testis. *Lancet* 1972;iii:516-7.
- 4 West AB, Butler MR, Fitzpatrick J, O'Brien A. Testicular tumors in subfertile men: report of 4 cases with implications for management of patients presenting with infertility. *J Urol* 1985;133:107-9.

- 5 Giwercman A, von der Maase H, Skakkebaek NE. Epidemiological and clinical aspects of carcinoma in situ of the testis. *Eur Urol* 1993;23:104-14.
- 6 Nüesch-Bachmann IH, Hedinger C. Atypische Spermatogonien als Präkanzerose. *Schweiz Med Wochenschr* 1977;107:795-801.
- 7 Pryor JP, Cameron KM, Chilton CP, Ford TF, Parkinson MC, Sinokrot J, et al. Carcinoma in situ in testicular biopsies from men presenting with infertility. *Br J Urol* 1983;55:780-84.
- 8 Skakkebaek NE. Carcinoma in situ of the testis: frequency and relationship to invasive germ cell tumours in infertile men. *Histopathology* 1978;2:157-70.
- 9 Schütte B. Early testicular cancer in severe oligozoospermia. In: Holstein AF, Leidenberger F, Hölzer KH, Bettendorf G, eds. *Carl Schirren symposium: advances in andrology*. Berlin: Diesbach Verlag, 1988:188-90.
- 10 Berthelsen JG, Skakkebaek NE, von der Maase H, Sørensen BL, Mogensen P. Screening for carcinoma in situ of the contralateral testis in patients with germinal testicular cancer. *BMJ* 1982;285:1683-6.
- 11 Rowley MJ, Heller CG. The testicular biopsy: surgical procedure, fixation, and staining techniques. *Fertil Steril* 1966;17:177-86.
- 12 Bruun E, Frimodt-Møller C, Giwercman A, Lenz S, Skakkebaek NE. Testicular biopsy as an outpatient procedure in screening for carcinoma-in-situ: complications and the patient's acceptance. *Int J Androl* 1987;10:199-202.
- 13 Dieckmann K-P, Loy V. Prevalence of contralateral testicular intraepithelial neoplasia in patients with testicular germ cell neoplasms. *J Clin Oncol* 1996;14:3126-32.
- 14 Giwercman A, Berthelsen JG, Müller J, von der Maase H, Skakkebaek NE. Screening for carcinoma-in-situ of the testis. *Int J Androl* 1987;10:173-80.
- 15 Dieckmann K-P, Kaup F, Loy V. False-negative biopsy for testicular intraepithelial neoplasia. *J Cancer Res Clin Oncol* 1993;119:1-4.
- 16 Berthelsen JG, Skakkebaek NE. Value of testicular biopsy in diagnosing carcinoma in situ testis. *Scand J Urol Nephrol* 1981;15:165-8.
- 17 Mumperow E, Lauke H, Holstein AF, Hartmann M. Further practical experiences in the recognition and management of carcinoma in situ of the testis. *Urol Int* 1992;48:162-6.
- 18 Bettocchi C, Coker CB, Deacon J, Parkinson C, Pryor JP. A review of testicular intratubular germ cell neoplasia in infertile men. *J Androl* 1994;15:14-6S.
- 19 Chemes HE, Casabé A, Davidzon I. Carcinoma in situ of the testis: incidence in infertility and rapid evolution to invasive seminoma. *J Androl* 1995;suppl:P-24(abstract).

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Comparison of two assays for measuring plasma concentrations of paracetamol

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An overdose of paracetamol can cause fatal hepatic necrosis, but acetylcysteine is an effective antidote if given early.¹ An estimation of plasma concentrations of paracetamol is required if a patient is suspected of having taken a toxic dose. We compared the AcetaSite test card and Stat-Site reflectance meter (GDS Diagnostics, Elkhart, IN), a bedside method of determining paracetamol concentrations that takes 2 minutes, with the Quantase assay (Porton Products, Maidenhead), an established laboratory method.

Patients, methods, and results

Altogether 192 patients were recruited into the study; of these, 92 had taken paracetamol. Patients who had not ingested paracetamol but required venepuncture for other reasons made up the control group. A blood sample was obtained 4 hours after suspected overdose or on arrival if 4 hours had already passed. A drop of this blood was used to measure paracetamol concentration with the AcetaSite card and Stat-Site meter, and the remainder was sent to the laboratory. Medical and nursing staff were trained to use the equipment before the study started.

A statistical method first described by Bland and Altman² was used to assess agreement between the laboratory standard and the AcetaSite test. This method plots the difference between results obtained by a standard and a new test against the mean of these measurements. Logarithmic transformation of the data was performed because the data were not normally distributed.

The figure uses untransformed data to show the relationship between paracetamol concentrations obtained with the laboratory test and those obtained with the AcetaSite test. The limits of agreement are 0.16 and 5.04—that is, in 95% of cases the AcetaSite result was between 0.16 and 5.04 times the laboratory result. The results for five patients fell outside these limits. There were six false negative results but no false positive results. The median time for a result to be available from the laboratory was 28.5 minutes (range 3-166 minutes).

Comment

The wide limits of agreement in this study suggest that there are considerable discrepancies between the two methods in assessing plasma concentrations of

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