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Sexual function in men treated for testicular cancer

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ABSTRACT

Introduction: Testicular Germ Cell Cancer (TGCC) patients may be at risk of developing sexual dysfunction after treatment.

Aim: The aim of this study was to assess the prevalence of sexual dysfunctions in TGCC patients 3 to 5 years after treatment, and relate findings to biochemical hypogonadism, treatment intensity and the expected prevalence in the Swedish male population.

Methods: A questionnaire study on 129 consecutive TGCC patients 3 to 5 years post-treatment was performed. Comparators were an age-matched nationally representative group of men (n=916) included in a study on sexual life in Sweden.

Main Outcome Measures: Sexual functions (including erectile dysfunctional distress), time since last intercourse, sexual satisfaction and experience of sexological treatment seeking were assessed by the same questions used in the epidemiological study on sexual life in Sweden. The findings in TGCC patients were correlated to biochemical signs of hypogonadism and type of oncological treatment: Surveillance (SO), adjuvant chemotherapy (ACT), adjuvant radiotherapy (RT) or standard doses of chemotherapy (SCT).

Results: A higher proportion of TGCC patients than comparators were likely to report low sexual desire (OR 6.7 (95 % CI 2.1-21)) as well as erectile dysfunction (OR 3.8 (95% CI 1.4-10)). No significant differences were observed regarding erectile dysfunctional distress, change of desire over time, interest in sex, premature or delayed ejaculation, time since last intercourse, need for or receiving sexual advice or sexual satisfaction. Hypogonadism did not predict erectile dysfunction (OR 1.1 (95% CI 0.26-4.5)) or low sexual desire (OR 1.2 (95% CI 0.11-14)). Treatment modality had no obvious impact on sexual function.

Conclusion: Men treated for testicular cancer had higher risk of having low sexual desire and erectile dysfunction 3 to 5 years after completion of therapy than comparators. These sexual dysfunctions were not significantly associated with treatment intensity or hypogonadism.

INTRODUCTION

Testicular germ cell cancer (TGCC) is the most common malignancy in men between the age of 20 and 40 years. Since the introduction of cisplatin, the overall survival rate has approached 95% [1, 2]. The quality of life (QoL) of survivors, including sexual function, is therefore an important issue. There are several studies reporting a negative impact of treatment on sexual function in TGCC patients [3-5]. However, it is still a matter of discussion to which degree TGCC patients have sexual dysfunctions, and which symptoms are most prevalent. Several factors, such as age at treatment [3, 6] and treatment modality (chemo- and radiotherapy) [5, 7-10], have been suggested to predispose for sexual dysfunction, although the data are somewhat contradictory.

It has previously been shown that TGCC patients with gonadal dysfunction have a reduced quality of life [11]. Since gonadal dysfunction, at least transiently, correlates to treatment intensity [12] it could be anticipated that the stage of the disease and treatment modality could influence sexual function and thereby also quality of life. This also generates the hypothesis that in these patients hypogonadism might be one of the causes and predictors of sexual dysfunction. However, there are no studies to our knowledge showing that hypogonadism is a risk factor for sexual problems in TGCC men.

A specific side effect of TGCC treatment is the absence of antegrade ejaculation, following retroperitoneal lymph node dissection (RPLND) [13, 14]. Apart from this well known association between TGCC treatment and ejaculation, the evidence regarding the possible impact of other types of cancer therapy on indices of sexual function is less clear. Erectile dysfunction was reported to be related to irradiation but other impairments of sexual function were not related to treatment modality [13]**.** A review by Nazareth *et al.* [14] concluded that the disease, its different treatments, and the psychological reactions to both, deserve closer investigation.

None of the reviews evaluated whether sexual dysfunction was considered by the patient to be distressing.

AIMS

Based on the limitations of the available literature as regards sexual dysfunction in TGCC patients, the aims of this article were to study the prevalence of low sexual desire, decreased sexual interest, erectile dysfunction, erectile dysfunctional distress and ejaculatory dysfunctions among TGCC patients 3 to 5 years after completion of cancer treatment. Furthermore, we wished to compare these figures to those of an age-matched representative group of men from the general population. Finally, the aim was to relate our findings to type of oncological treatment and presence of biochemical signs of hypogonadism among TGCC patients.

METHODS

Design and recruitment

Recruitment of TGCC patients

The two inclusion criteria for patients in this study were being included in a fertility study and passing a three-year check-up after treatment. The study was based on a consecutive group of TGCC patients referred to the Department of Oncology, Lund University Hospital, Lund since March 1996 or to the Department of Oncology, Radiumhemmet and Södersjukhuset, Karolinska University Hospital, Stockholm since November 1998. All men below the age of 50 with TGCC diagnosed <5 years prior to inclusion full filled the inclusion criteria and were eligible for the fertility study. In October 2006, a total of 468 patients were eligible. Of these, 75 (16%) declined participation. These men did not differ from the participants in terms of their mean age but received, in general, less heavy treatment. Exclusion criteria for the fertility study were medical or mental conditions leading to difficulties in obtaining informed consent, linguistic difficulties, not being able to understand the questionnaire and bilateral disease. Seven patients were excluded due to compromising mental conditions; two with schizophrenia, two mentally disabled, one with Down's syndrome, one with severe crisis due to his family situation and one with anxiety and aggression towards medical service. Twenty-six were excluded due to linguistic difficulties, treatment for bilateral testicular cancer or physically disability and a further twenty-four moved to another region. Of the remaining 336, about one third (n=129) had passed the three-year check-up and fulfilled the two inclusion criteria and were included in the present study.

All participants gave their informed written consent and the study was approved by the Ethical Board of the University of Lund.

Patient characteristics

All 129 patients were uniformly managed according to the Swedish Norwegian Testicular Cancer Group (SWENOTECA) protocols, for details see *www.ocsyd.se.* They were divided into five treatment groups (Table 1). The surveillance group (SO) was all stage 1 patients, not receiving any further therapy after orchidectomy (n=11). The adjuvant chemotherapy group (ACT) was all stage 1 patients (n=33) receiving 1 to 2 cycles of platinum-based chemotherapy.

Patients receiving standard doses of chemotherapy (SCT) all had disseminated disease and were receiving 3 to 4 cycles of cisplatin-based chemotherapy (n=47). Among these, 21 patients were operated with retroperitoneal lymph node dissection, causing absence of antegrade ejaculation in eight patients. The radiotherapy group (RT) was treated with adjuvant radiotherapy administered to the paraaortic and ipsilateral iliac lymph nodes (n=36). The refractory disease group, which was receiving higher doses of chemotherapy (HDCT), consisted of two individuals who were treated more intensely.

Recruitment of men from the general population

An ad hoc comparator group of all 916 men aged 18 to 54 years who had participated in a cross-sectional, nationally representative investigation on sexual life in Swedes aged 18 to 74 years was selected [15]. The study, performed in 1996, was initiated and financed by the Swedish National Institute of Public Health. Briefly, after initial validation of the content, data were collected by use of structured questionnaires and checklists in combination with structured face-to-face interviews conducted by specially trained professional interviewers. The rationale for selecting this group was its normative value for Sweden, thus, anchoring the results of the patients in the Swedish male population. After exclusion for different reasons (linguistic problems, imprisonment, death, psychiatric reasons, emigration; n=469) and

individuals declining participation (n=1971) a total of 1475 men (and 1335 women) aged 18 to 74 years completed the study, giving a response rate of 59%.

Questionnaires

To investigate the prevalence of self-reported sexual dysfunctions as well as the frequency of sexual activity, sexual satisfaction and the need for treatment-seeking, questions from the above-mentioned epidemiological study were used [15]. These questions were exactly identical for patients and comparators and were answered through subjects filling in structured self-reports. The exact phrasing of the questions and the answering alternatives are given in Appendix.

In order to collect relevant information for the TGCC patients, questions were selected by a multidisciplinary group, involving one psychiatrist/sexologist, one andrologist and two oncologists. The patients answered the questionnaire 3 to 5 years post treatment, and at the same time blood samples were collected. The chosen length of the period from treatment to investigation was based on our earlier findings that the levels of testosterone normalize about three years post-treatment in a significant proportion of TGCC patients [16]. Moreover, medical follow-ups of patients are usually (in Sweden) concluded after 5 years, which makes it less feasible to prolong the follow-up.

MAIN OUTCOME MEASURES

Sociodemographic

The questionnaire (see Appendix) encompassed basic socio-demographic information, including information regarding having/not having a partner, paternity status, sexually transmitted infections (STI), alcohol, smoking and snuffing habits. Body mass index (BMI, kg/m^2) was calculated according to patients´ self-reported weight and height (Table 2).

Measures of sexual functions/dysfunctions

By using the questions validated in the epidemiological study "Sex in Sweden" [15] we were able to obtain a validated population evidence-based comparator group and also an item by item picture of the patients' perception of their sexual life (see Table 3 and the Appendix).

A 6-point answering scale was used for the sexual functions/dysfunctions questions, ranging from never through hardly ever/rather rarely/rather often/nearly all the time/all the time. A patient who stated that the dysfunction occurred rather often/nearly all the time/all the time was judged to suffer from manifest dysfunction *per se*, using the dichotomy described previously [17]. If the dysfunction led to personal erectile distress the same scale was used. Sexual desire was considered low if the patient on a 4-graded scale reported his desire to occur never/rarely; the two other answering alternatives were sometimes/often feeling desire. Time since last intercourse was dichotomized in two different ways, primarily with an approximate 50% distribution (less than 5 days vs. 5 days or more), and secondly with an approximate 10% distribution (3 months or less vs. more than 3 months).

Sexual satisfaction was assessed by the question "How satisfying is your sexual life?" derived from the well-validated generic instrument LiSat-11 checklist [18]. Six alternative answers alternatives ranging from very dissatisfied to very satisfied were offered. The scale is test-retest reliable and it is valid to dichotomize the scale into "satisfied" (very satisfying or satisfying) and "not satisfied" (rather satisfying/rather dissatisfying/dissatisfying/very dissatisfying).

Assessment of biochemical hypogonadism

Blood samples for analysis of serum levels of testosterone and luteinizing hormone (LH) were obtained between 9 am and 3 pm. The details of the hormone analyses performed in patients

recruited in Lund have been presented elsewhere [16]. In Stockholm LH in serum was determined with the AutoDELFIA automatic immunoassay system (Perkin Elmer, USA) and testosterone with the DxI immunoassay system (Beckman Coulter, USA). The reference levels for testosterone and LH were identical in the two centers and the patients were categorized as being hypogonadal if serum testosterone was below 10 nmol/L and/or serum LH was 10 IU/L or more [19].

Statistical analysis

Odds ratios (OR) with 95% confidence intervals (CI) were calculated, by using logistic regression, to evaluate the likelihood for co-occurrence of TGCC and its therapy and sexual function. All analyses were adjusted for age. In addition, potential confounders such as occupation, paternity status, failing to become a biological father, smoking, snuffing, sexually transmitted infections and BMI, were included in the models, one at a time. These items were kept in the model if they changed the age-adjusted effect estimate by more than 15%. Patients reporting absence of antegrade ejaculation were excluded from the analyses concerning premature and delayed ejaculation, need for sexual advice and consulting an expert (Table 4). Our aim was to assess the relative impact of different treatments on the sexual functions of TGCC patients. Hence, the different therapeutic modalities were not compared to the control group but to each other. We chose SCT as the reference group as it was the largest group, and we, a priori, expected the SCT-treated men to be the most seriously affected by their treatment.

For all statistically significant associations between disease/treatment and sexual function outcomes, we then tested whether biochemical hypogonadism was a predictor of sexual dysfunction, using binary logistic regression. Since the blood samples were taken between 9 am and 3 pm and the levels of testosterone but not LH decrease during the day, the possible

associations were re-tested with LH>10 IU/L as the only indicator of hypogonadism. For the variables analyzed by binary logistic regression, the outcomes were dichotomized. Patients on testosterone replacement (n=9) were excluded from this analysis.

SPSS 15.0 software (Chicago, IL) was used for all the statistical analyses. The chosen α level was 0.05.

RESULTS

Sociodemographic characteristics

The distribution of sociodemographic characteristics included in the analysis as potential confounders of sexual function is shown in Table 2. The well-known differences in paternity status and problems becoming a biological father are obvious between patients and comparators. Moreover, patients had a lower prevalence of smoking/snuffing and sexually transmitted infections than the comparators.

Sexual function

Patients were likely to report both manifest low sexual desire (adjusted OR 6.7; 95 % CI 2.1-21.0), and manifest erectile dysfunction (adjusted OR 3.8; 95% CI 1.4-10.0) more often than comparators. 12% of TGCC patients reported erectile dysfunction compared to 3% of controls, whereas the corresponding figures for low sexual desire were closer, at 4% and 2%, respectively. Patients reported manifest erectile dysfunctional distress significantly more often than comparators (OR 6.5; 95% CI 2.6-16). However, this significance disappeared after adjustment for confounders (OR 2.5; 95% CI 0.65-9.8). Low sexual desire and manifest erectile dysfunction per se as well as manifest erectile distress co-occurred in 25% of patients. No significant difference between patients and comparators was found with respect to changes in sexual desire over the last 5 years (33 vs. 32%), decreased sexual interest (14 vs. 15%), premature (6.5 vs. 6.8%) or delayed ejaculation (2.7 vs. 0.86%). Thus, patients assessed their sexual desire as being lower even prior to their diagnosis of testicular cancer. The investigated variables concerning time since last intercourse, sexual satisfaction and need for sexual advice did not differ significantly between patients and the comparators (Table 4).

Sexuality in relation to biochemical hypogonadism

29% of the TGCC patients were hypogonadal, and this was tested as a predictor of positive outcomes, low sexual desire and manifest erectile dysfunction. No significant association between biochemical hypogonadism and low sexual desire (OR 1.2; 95% CI 0.11-14) or manifest erectile dysfunction (OR 1.1; 95% CI 0.26-4.5) was revealed. Inclusion of patients treated with testosterone did not change the OR estimates given above. When LH above 10 IU/L was used as the only indicator of hypogonadism, which was the case in 14% of the patients, it did not change the associations with the two outcomes.

Sexuality in relation to treatment modality

With a few exceptions, the three therapeutic groups SO, RT and ACT did not differ significantly from the SCT-group regarding the age-adjusted ORs for sexual dysfunctions. The only significant intertreatment group differences were that SO patients were more likely than the SCT-treated patients to report manifest erectile dysfunction per se (OR 8.8; 95% CI 1.2-62) and to characterize their sexual life as not satisfying (OR 9.9; 95% CI 1.7-58). Furthermore, a higher proportion of patients in the SCT group than in the SO group had had intercourse during the last five days (OR 9.9; 95% CI 1.7-58).

DISCUSSION

Three to five years after cancer treatment, low sexual desire and manifest erectile dysfunction per se were more common among TGCC patients than in the age-matched general male population. From a clinical point of view, erection seemed to be the most important issue, since as many as 12% of the patients reported frequent erectile dysfunction during the last year compared to only 3% in the general population. These outcomes were not associated with biochemical signs of hypogonadism - low serum testosterone and/or high LH - or treatment intensity. Erectile function and sexual desire might be considered as different ways of measuring the same outcome as it is known that low sexual desire may cause erectile dysfunction and vice versa [17]. In the current study 40% of the comparators, but only 25% of the patients, who stated that they had erectile dysfunction, also had low sexual desire. Our results indicate that the increased risk of sexual dysfunctions should be taken into consideration during the follow-up of men treated for TGCC, optionally in a multidisciplinary reproductive health center [20], since male sexual dysfunctions also might be associated to sexual dysfunctions in the female partner [21] .

A low level of sexual satisfaction generally accompanies all sexual dysfunctions and in particular erectile distress [22]. The finding that the comparators and the patient-group had a similar prevalence of not being sexually satisfied, despite the patients' higher prevalence of erectile and desire dysfunctions, suggests that the patients were reasonably psychologically adjusted to their situation. In line with this are the findings that there was no significant difference in reported erectile distress or in the need for sexual advice between the patients and the comparators.

Interestingly, although sexual desire was low among the TGCC subjects, they did not differ with regard to the incidence of decreased sexual desire during the last five years compared to the general population. These two parameters differ from each other, the first reflecting the

present situation, while the latter refers to change over time. This may indicate that the relatively low sexual desire in TGCC patients is not related to the cancer diagnosis or the therapy, a suggestion supported by the fact that no significant difference was seen in sexual desire between the therapy groups. It is, therefore, tempting to hypothesize that low sexual desire in the TGCC men may instead be associated with the affected patients *per se*.

Impairment of sexual function among TGCC patients, including decrease in sexual desire, ejaculation, orgasm, sexual satisfaction, sexual activity, libido, arousal and erection, has previously been reported by others [5, 23]. However, these studies did not include control groups, and patients with varying post-treatment observation time were included; thus, possible dynamic changes in these conditions related to post-treatment stress and/or possible recovery over time were not considered. The current study also lacks the longitudinal aspect, but it is valid for the specific time of investigation.

Aas *et al.* [3] followed 76 patients longitudinally with a questionnaire before and up to 36 months after treatment. They found that cancer treatment had a negative impact on the patient's satisfaction with his sexual life initially after cancer therapy, but this problem partly resolved later in the follow-up. Lackner *et al.* found no increased risk of erectile dysfunction in TGCC survivors, possibly due to the low number of subjects included [24]. Also in a case-control study on stage 1 and 2 radiotherapy-treated patients, no difference in frequency of sexual dysfunction between patients and healthy controls was observed [25]. However, the follow-up period varied from 1 month to 10 years, which, at least partly, might invalidate the conclusions of this study.

A strength of the current work is that we were able to investigate the possible impact of untreated hypogonadism on sexual dysfunctions overrepresented among the TGCC patients. A further strength is that the questions used to evaluate sexual function and satisfaction had been validated in a large population study, which also provided data for an age-matched

reference group. The 59% response rate for the comparator group may appear somewhat low. However, post-hoc analyses [15] have shown that the studied male population is adequately representative for Swedish men aged 18 to 74 years. Seventy-five of the 468 men (16%) asked to participate declined to take part in the study. In comparison to those 129 who were included in the current study, we found no difference regarding age but they had received significantly less advanced treatment. However, since we did not find any obvious impact of treatment intensity on the risk of sexual dysfunction, we do not think that this selection bias had any impact on our results.

Our findings that indicated lack of association between hypogonadism and the risk of sexual dysfunction are in agreement with a recent report by Wiechno *et al.*, who found no statistically significant correlation between LH or testosterone levels and the International Index of Erectile Function score [26]. Otherwise, studies evaluating the association between sex hormone levels and sexual dysfunction in TGCC patients are lacking.

For diagnosis of androgen deficiency a blood sample should ideally be obtained before 10 am. For logistic reasons, we obtained blood samples at different time points between 9 am and 3 pm. This might blur the difference between truly hypogonadal and eugonadal men, thus reducing the statistical power of that part of the study. However, it has been reported that the diurnal variation in testosterone levels is less pronounced in hypogonadal men [27]. One previous study regarding the association between testosterone levels and metabolic signs of hypogonadism reported no difference in the risk estimates regardless of whether the time of blood sampling had been taken into consideration or not [28]. Furthermore, similar results were found when LH above 10 IU/L was used as the only indicator of hypogonadism. Unlike testosterone, LH does not decrease during the daytime.

Men already on androgen replacement therapy were excluded, which could lead to an underestimation of the prevalence of patients with problems related to hypogonadism and testicular cancer.

Ideally, in testing the impact of therapy, the surveillance group should be used as a reference. However, due to the limited number of SO subjects, all the other therapy groups were compared to the SCT group. We have no explanation as to why some parameters of sexual function were superior in the SCT men compared to the SO men. This might be a chance finding, related to the high number of comparisons performed, a possibility that is supported by Arai *et al.*, who found that surveillance patients had a similar level of sexual function as more intensely treated subgroups [4].

The purpose of the current study was not to evaluate differences in socio-demographic variables. Nevertheless, the large difference in distribution of smokers, snuffers and STI, with a more healthy approach in TGCC patients, is intriguing. This might indicate a change in lifestyle after a cancer diagnosis. These potential confounders were included in the statistical model, and since they were less prevalent among the patients the difference in distribution in comparison to men from the general population does not explain the findings of our study.

CONCLUSIONS

We found that TGCC patients differed from comparators in having manifest erectile dysfunction *per se* and low sexual desire 3 to 5 years after treatment. These findings were neither associated with cancer treatment nor with biochemical hypogonadism. Somewhat surprisingly the 5-year incidence of reduced sexual desire in comparators was equal to that recalled by the patients for the period prior to diagnosis and at least 3 years after the treatment of their cancer.

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Table 1. Characteristics of the 129 TGCC patients included. The Royal Marsden Hospital (RMH) staging system has been used [28].

	SO	ACT	SCT	RT	HDCT	Total
No of patients	11	33	47*	36	2*	129
Age, median (range)	32 (24-51)	33 (20-47)	33 (21-52)	37 (25-49)	40 (33-48)	35 (20-52)
Stage I	11	33	10§	36	1§§	91
Stage II	0	0	25	0	0	25
Stage III	0	0	4	0	0	4
Stage IV	0	0	8	0	1	9

SO	No therapy after orchiectomy
ACT	Adjuvant Chemotherapy (1-2 cycles of platinum based chemotherapy)
SCT	Standard Doses of Chemotherapy (3-4 cycles of platinum based chemotherapy)
RT	Adjuvant radiotherapy
HDCT	Higher Doses of Chemotherapy due refractory or relapsed disease
§	10 with recurrent disease including 3 with marker elevation
§§	1 with contra lateral disease found during follow up
*	Retroperitoneal Lymph Node Dissection was performed in 20 patients

Table 2. Investigated socio-demographic variables, comparison between TGCC patients and a comparator group of nationally representative Swedish men.

	TGCC patients	**Comparator group**
1. Mean age, (Std deviation)	36, (7.2)	39, (8.7)
2. BMI, mean, (Std deviation)	25.4, (3.3)	25.6, (3.2)
	Yes/total (%)	**Yes/total (%)**
3. Occupation:		
Employed/Studying/On paternity leave	102/105 (97)	829/915 (91)
Unemployed/Long time sick-listed	3/105 (2.9)	86/915 (9.4)
4. Paternal status: having one or more children	66/126 (52)	635/899 (71)
5. Failed to fertilize during a period ≥6 months	25/121 (21)	82/878 (9.3)
6. Current or previous smoker	25/105 (24)	407/916 (44)
7. Current or previous snuffer	28/107 (26)	334/914 (37)
8. Current or previous sexually transmitted infection	16/128 (12)	200/914 (22)

Table 3: Questions and answering alternatives corresponding to different outcomes

Outcome	Question(s)	Answer alternatives
Sexual desire	1. How often do you feel sexual desire? 2. If you compare your sexual desire today with 5 years ago is it	1. never/rarely or sometimes/often 2. much greater/slightly greater/unchanged or slightly less/much less
Sexual interest	It happens that people have periods of reduced interest in sex. Has this occurred in your sex life during the past 12 months?	never/hardly ever/rather rarely or rather often/nearly all the time/all the time
Erectile dysfunction (ED)	It happens that the man's penis fails to become erect or to maintain its erection once sexual intercourse starts. Has this occurred in your sex life during the past 12 months?	never/hardly ever/rather rarely or rather often/nearly all the time/all the time or haven't had intercourse during the last 12 months
Personal problems due to ED	Has this been a personal problem in your sex life during the past 12 months?	never/hardly ever/rather rarely or rather often/nearly all the time/all the time or haven't had intercourse during the last 12 months
Premature ejaculation	It happens that the man ejaculates immediately. Has this occurred in your sex life during the past 12 months?	never/hardly ever/rather rarely or rather often/nearly all the time/all the time or haven't had intercourse during the last 12 months
Delayed ejaculation	It happens that the man finds it hard to ejaculate. Has this occurred in your sex life during the past 12 months?	never/hardly ever/rather rarely or rather often/nearly all the time/all the time or haven't had intercourse during the last 12 months
Times since last intercourse	When did you last have sexual intercourse?	less than 24 hours/1-2 days ago/3-4 days ago/5-7 days ago/1-2 weeks ago/3-4 weeks ago/1-3 months ago/ 4-12 months ago/1-2 years ago/ 3-10 years ago/more than 10 years ago or haven't had intercourse
Sexual satisfaction	How satisfying is your sexual life?	very satisfying/satisfying or rather satisfying/rather dissatisfying/dissatisfying/very dissatisfying
Need for sexual advice (treatment seeking)	1. Have you ever felt a need to talk to someone in order to receive advice or help about something related to your sex life?	1.yes/no
	2. Have you ever turned directly to an expert in order to receive advice or help about something relating to your sex life?	2. yes/no

Table 4: Occurrence of sexual dysfunctions, frequency of intercourse, sexual satisfaction and treatment seeking for TGCC patients and a Swedish nationally representative comparators; Distributions and odds ratio (OR) in TGCC patients for variables assessing sexual function.

	Patients yes/total (%)*	**Comparator group yes/total (%)**	**Age-adjusted OR (95 %CI)**	**Adjusted OR** (95 %CI)**
Sexual dysfunctions:				
Low sexual desire	5/126 (4.0)	17/916 (1.9)	2.4 (0.85-6.8)	**6.7[ace] (2.1-21)**
Less sexual desire than 5 years ago	42/126 (33)	294/916 (32)	0.83 (0.56-1.2)	0.83 (0.56-1.2)
Decrease in sexual interest [h]	15/105 (14)	133/912 (15)	0.91 (0.53-1.7)	0.91 (0.53-1.7)
Erectile dysfunction [g]	14/118 (12)	21/819 (2.6)	**6.6 (3.1-14)**	**3.8[be] (1.4-10)**
Erectile dysfunctional distress [g]	9/110 (8)	14/807 (2)	**6.5 (2.6-16)**	2.5[be] (0.65-9.8)
Premature ejaculation [fg]	7/108 (6.5)	55/805 (6.8)	0.90 (0.40-2.0)	0.68[abe](0.29-1.6)
Delayed ejaculation [fg]	3/110 (2.7)	7/806 (0.86)	3.9 (0.94-15.9)	2.4[be](0.45-12.9)
Frequency of intercourse:				
Less than 5 days since last sexual intercourse [h]	51/105 (49)	515/902 (57)	0.71 (0.50-1.1)	0.71 (0.50-1.1)
More than 3 months since last sexual intercourse [h]	13/105 (12)	106/902 (12)	1.1 (0.57-2.0)	1.3[b] (0.67-2.7)
Satisfaction:				
Dissatisfying sex life [h]	19/103 (18)	173/910 (19)	0.84 (0.50-1.4)	0.84 (0.50-1.4)
Treatment seeking:				
Need for sexual advice or help [f]	18/116 (15)	132/911 (14)	0.87 (0.50-1.5)	0.87 (0.50-1.5)
Consulted an expert for sexual advice or help [f]	12/116 (10)	89/855 (10)	0.99 (0.84-1.2)	0.99 (0.84-1.2)

***** Therapy group HDCT is excluded in analysis (2 patients)
******Adjusted for age and one or more of the variables a-e described below.
a=occupation
b=children/have or want to
c=smoking/snuffing
d=sexually transmitted disease
e=Body Mass index
f= eight patients with absence of antegrade ejaculation are excluded
g=nine patients and 69 men from general population not having had intercourse the last twelve months excluded
h=questions added one year after study initiation

Appendix 1. Questionnaire

How tall are you? _____cm
What is your weight? _____kg

At present, what is your main occupation? (Disregard if sick-listed short time)

- Gainfully employed ☐
- Student ☐
- Unemployed ☐
- Conscript ☐
- On parental leave ☐
- Long-time sick-listed ☐
- Other, if so, what? _____

Do you have (or have had) biological children?

Yes☐ No☐

Have you and a partner, during a six month period, tried to attain a pregnancy without succeeding?

Yes☐ No☐

Do you smoke or have you been smoking, regularly, at least five cigarettes per day during at least one year?

No☐ Yes, but not any more☐ Yes☐ Uncertain, don't know☐

Do you snuff or have you used snuff daily?

No☐ Yes, but not any more☐ Yes☐ Uncertain, don't know☐

Have you ever had any sexually transmitted infection?

Yes☐ No☐
If yes, specify what kind of sexually transmitted infection_____

How often do you feel sexual desire?

Never☐ Rarely☐ Sometimes☐ Often☐

If you compare your sexual desire today with 5 years ago is it

Much greater☐ Slightly greater☐ Unchanged☐ Slightly less☐ Much less☐

It happens that people have periods of reduced interest in sex. Has this occurred in your sex life during the past 12 months?

All the time☐ Nearly all the time☐ Rather often☐
Rather rarely☐ Hardly ever☐ Never☐

It happens that the man's penis fails to become erect or to maintain its erection once sexual intercourse starts. Has this occurred in your sex life during the past 12 months?

Haven't had intercourse during the last 12 months ☐ All the time ☐ Nearly all the time ☐
Rather often ☐ Rather rarely ☐ Hardly ever ☐ Never ☐

Has this been a personal problem in your sex life during the past 12 months?

Haven't had intercourse during the last 12 months ☐ All the time ☐ Nearly all the time ☐
Rather often ☐ Rather rarely ☐ Hardly ever ☐ Never ☐

It happens that the man ejaculates immediately. Has this occurred in your sex life during the past 12 months?

Haven't had intercourse during the last 12 months ☐ All the time ☐ Nearly all the time ☐
Rather often ☐ Rather rarely ☐ Hardly ever ☐ Never ☐

It happens that the man finds it hard to ejaculate. Has this occurred in your sex life during the past 12 months?

Haven't had intercourse during the last 12 months ☐ All the time ☐ Nearly all the time ☐
Rather often ☐ Rather rarely ☐ Hardly ever ☐ Never ☐

When did you last have sexual intercourse?

Less than 24 hours ☐ 1-2 days ago ☐ 3-4 days ago ☐ 5-7 days ago ☐
1-2 weeks ago ☐ 3-4 weeks ago ☐ 1-3 months ago ☐ 4-12 months ago ☐
1-2 years ago ☐ 3-10 years ago ☐ More than 10 years ago ☐ Haven't had intercourse ☐

How satisfying is your sexual life?

Very dissatisfying ☐ Dissatisfying ☐ Rather dissatisfying ☐
Rather satisfying ☐ Satisfying ☐ Very satisfying ☐

Have you ever felt a need to talk to someone in order to receive advice or help about something related to your sex life?

Yes ☐ No ☐

Have you ever turned directly to an expert in order to receive advice or help about something relating to your sex life?

Yes ☐ No ☐