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Special Interest Articles

Prediction of Long-term Gonadal Toxicity after Standard Treatment for Testicular Cancer

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Long-term post-treatment gonadal toxicity was examined (median 3 years after treatment discontinuation) in 125 testicular cancer patients treated with standard regimens: no radiotherapy or chemotherapy (36 patients), infradiaphragmatic radiotherapy (38 patients), and 3–4 cycles of cisplatin-based chemotherapy (51 patients). Radiotherapy and chemotherapy had no impact on serum testosterone, but led to a slight increase in serum follicle-stimulatiing hormone (FSH). The lowest median value of post-treatment sperm cell count was observed after infradiaphragmatic radiotherapy, the highest value after standard chemotherapy. After more intensive cytotoxic treatment recovery of the gonadal function seemed to be delayed. In testicular cancer long-term post-treatment gonadal toxicity is correlated to the patient's pretreatment gonadal function and age rather than to the standard treatment of the malignancy. In patients with pretreatment normal gonadal function the risk of permanent treatment-induced toxicity is minimal after present standard treatment.
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INTRODUCTION

TESTICULAR CANCER is the most common malignancy of adult young men, and about 90% of these patients are cured by modern multimodality treatment [1, 2]. During the last years much interest has been paid to long-term morbidity [3, 7]. The impact of treatment on gonadal function and fertility has been reported in several studies [8, 15]. Both radiotherapy and chemotherapy reduce spermatogenesis, at least transiently. Though the gonadal function recovers in most patients after 2–4 years, irreversible impairment has recently been reported after chemotherapy [15].

Most authors have dealt with the impact of treatment on long-term gonadal dysfunction. The pretreatment gonadal function and the patients' age have not been often considered as predictive parameters of post-treatment spermatogenesis and Leydig cell function. The aim of the present report was to carry out a multivariate analysis in patients who were cured by standard treatment for testicular cancer in order to identify predictive parameters of long-term post-treatment gonadal toxicity.

PATIENTS AND METHODS

About 730 new patients with testicular cancer were treated at the Norwegian Radium Hospital (NRH) between 1980–1987. Details of treatment after orchidectomy have been reported elsewhere [16–19]. Briefly, low-stage seminoma patients (stage I/IIA-B according to the Royal Marsden system [1]) received infradiaphragmatic radiotherapy. More advanced stage seminoma patients were treated with chemotherapy, most often combined with radiotherapy. Patients with clinical stage I non-seminoma underwent retroperitoneal lymph node dissection (RLND). If no metastases were found, no further treatment was given. In 1987 the surveillance policy [20] was introduced for non-seminoma patients with clinical stage I. Non-seminoma patients with metastases and those who relapsed after an initial stage I, routinely received four cycles of cisplatin-based chemotherapy, most often combined with surgery. All patients had regular follow-up examinations at the NRH with 2–6 months' interval for 3 years after treatment discontinuation. Thereafter many of the patients had annual examinations at their local hospitals.

In 1980 a database was established containing information about testicular cancer patients' pretreatment and post-treatment gonadal function and fertility status. At present this database contains information on 500 patients whose gonadal function has been evaluated at least once during the clinical course of their malignancy. From this database 125 patients were identified who fulfilled the following eligibility criteria: a post-treatment evaluation of gonadal function was available 24–48 months after discontinuation of all treatment; the patient was without evidence of disease at the post-treatment evaluation; and the patient had received the last years' routine treatment as outlined above. 96 of the 125 patients also had a comparable pretreatment evaluation (2–3 weeks after orchidectomy but before further treatment).

Group 1 included 36 patients with non-seminoma stage I who

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Table 1. Patients' characteristics

	No. cytotoxic treatment (group 1)	Radiotherapy (group 2)	Chemotherapy (group 3)
No. of patients	36	38	51
Age at orchidectomy (years)	26 (17–59)†	31 (19–72)	27 (15–53)
Seminoma		38	3
Non-seminoma	36		48
Initial stage			
I	35	37	5
II	1	1	39
III			2
IV			5
Interval from treatment discontinuation to evaluation (months)	36 (25–52)	36(24–42)	37 (25–43)
Treatment			
Surveillance	7		
RLND	29		48
Midplane radiation dose			
< 36 Gy		3	
36 Gy		35	
Total dose cisplatin (mg)			760 (570–800)
Total dose bleomycin (mg)			300 (90–305)
Permanent "dry ejaculation" after RLND	4		24

† Median (range).
RLND = retroperitoneal lymph node dissection.

received no chemotherapy or radiotherapy (Table 1). Group 2 included 38 patients with low-stage seminoma who received infradiaphragmatic radiotherapy. Group 3 included 51 patients who received three to four cycles of cisplatin-based chemotherapy [17, 18] (3 cycles: 11 patients; 4 cycles: 40 patients). 32 of the patients received vinblastine only (median accumulated dose 71.5 mg, range 42–104 mg), 11 received etoposide only (median accumulated dose: 400 mg, range: 2775–7600 mg) and 8 received both etoposide and vinblastine together with cisplatin and bleomycin. 48 patients in group 3 underwent RLND. The median time from the end of treatment to evaluation of the post-treatment gonadal function was 3 years. Patients in group 2 were significantly older than those in groups 1 and 3.

Evaluation of the gonadal function included either hormone analysis [21] (25 patients), seminal fluid light microscopy (2 patients) or both (98 patients). In addition, the number of post-treatment pregnancies was recorded (median observation time 5 years).

Follicle stimulating hormone (FSH, normal range 1–12 IU/l), luteinising hormone (LH, normal range 1–12 IU/l) and testosterone (normal range 12–40 nmol/l) were measured. Pretreatment LH measurement was omitted because it may be falsely elevated due to crossreacting human choriogonadotropin. The results of seminal fluid analyses were given as sperm cell count (number of sperm cells × 10^6/ml). A sperm count ≥ 10 × 10^6/ml is considered "normal", i.e. able to lead to fertilisation in most cases [22]. Mobility and morphology of the sperm cells were not considered in the present analysis.

There were another 19 patients who had a 2–4 years' post-treatment evaluation of gonadal function after non-standard treatment. Most of these patients had been treated for relapse or had particularly advanced disease at diagnosis. 9 patients (group 4) had received very high total doses of cytotoxic drugs (more than 4 cycles or high-dose cisplatin regimens). 10 patients (group 5) had been treated with combined chemotherapy and radiotherapy.

Statistics

The PC-based statistical program package "Medlog" was used for calculation of medians and ranges, and for the performance of the Wilcoxon logrank test and the multiple linear regression analysis. A P value less than 0.05 was regarded as statistically significant.

RESULTS

Standard treatment (groups 1–3)

After orchidectomy and before further treatment the median FSH value of group 2 was significantly higher (within the normal range) than for group 3. The pretreatment values of other hormones and sperm cell count did not differ among the three groups (Table 2).

After treatment there was no statistical difference in the median values of post-treatment serum testosterone among the groups (Table 2). After four cycles of chemotherapy the median FSH value was significantly higher than in patients who did not receive cytotoxic treatment. There was a tendency for a higher median FSH value in group 2 than in group 1, but the difference was not statistically significant (P = 0.08). All median FSH values were within the normal range. Post-treatment LH was

Table 2. Gonadal function after standard treatment

	No cytotoxic treatment (group 1)	Radiotherapy (group 2)	Chemotherapy (group 3)
Pretreatment			
Testosterone (nmol/l)	17.9 (1.6–30.8)* 2/28†	16.6 (6.2–31.3) 0/27	17.3 (3.4–39.4) 2/40
FSH (IU/l)‡	7.3 (2.0–19.9) 4/28	8.6 (2.0–29.6) 8/27	4.7 (1.0–28.6) 7/40
Sperm cell count (× 10^6/ml)	15.6 (0–87) 7/28	12.0 (0–156) 9/24	31.0 (0–150) 9/36
Patients with children before treatment	14	17	22
Post-treatment			
Testosterone (nmol/l)	18.4 (0.1–31.1) 5/31	16.6 (6.9–27.9) 4/36	15.8 (6.0–31.0) 6/42
FSH (IU/l)§	7.0 (1.0–31.5) 8/33	9.8 (1.0–36.8) 13/36	9.8 (2.1–40.1) 17/45
LH (IU/l)	5.4 (0.6–16.3) 2/32	6.7 (1.0–14.8) 2/36	6.1 (1.2–18.5) 5/42
Sperm cell count (× 10^6/ml)	19.5 (0–222) 11/24	11.0 (0–76) 9/22	65.0 (0–166) 5/17
No. of post-treatment pregnancies	9	9	8

*Median (range). †Number of patients with pathological values/total number of evaluable patients.
‡FSH: group 1 vs. group 3, P = 0.07; group 2 vs. group 3, $P < 0.01$.
§FSH: group 1 vs. group 2, P = 0.08; group 1 vs. group 3, P = 0.03.
LH: group 1 vs. group 2, P = 0.07.
Sperm cell density: group 2 vs. group 3, P = 0.04.

not significantly different among the groups and the median values were within the normal range.

The sperm cell count was significantly reduced after radiotherapy compared to the chemotherapy group, but without difference if compared to group 1. The highest median value of sperm count was in group 3 (after chemotherapy).

There was no statistical difference in the number of post-treatment pregnancies, though the lowest was in group 3.

Multiple linear regression analysis (groups 1–3)

Low pretreatment serum testosterone and high age (continuous variables) independently predicted the post-treatment testosterone value (Table 3). Standard radiotherapy or standard chemotherapy did not significantly influence the post-treatment testosterone level.

A high pretreatment FSH was a highly significant independent predictor of a high post-treatment FSH. Chemotherapy ($P = 0.09$) and radiotherapy ($P = 0.15$) did not significantly influence the level of post-treatment FSH. Post-treatment LH was independent of all analysed pre-treatment variables and the standard treatment.

A high pretreatment FSH was the only significant determinant of a low pretreatment sperm cell count ($P = 0.017$). High age did not reach significance ($P = 0.086$). Chemotherapy or radiotherapy did not influence on post-treatment spermatogenesis.

Intensive cytotoxic treatment (groups 4 and 5)

High median values of post-treatment FSH were found in patients who received high total doses of cisplatin or received combined chemotherapy and abdominal radiotherapy (Table 4). Post-treatment levels of the median LH and median testosterone were similar to those after standard treatment. Only 1 patient from group 4 and 3 patients from group 5 had a post-treatment seminal fluid analysis. 1 patient from group 5 had a sperm cell count of 10^6/ml, but no sperm cells were identified in the other 3 patients. 3 patients from group 5 fathered a child after treatment.

Table 3. Multiple linear regression analysis (patients treated with standard therapy included in the analysis)

	Coefficient	P
Post-treatment testosterone ($n=74$)		
Pretreatment testosterone	0.245	0.003
Age	− 0.200	0.009
Radiotherapy*	− 0.462	NS
Chemotherapy*	− 0.837	NS
Post-treatment FSH ($n=78$)		
Pretreatment FSH	0.598	< 0.0001
Age	− 0.008	NS
Radiotherapy	2.722	NS (0.152)
Chemotherapy	2.837	NS (0.091)
Post-treatment LH ($n=75$)		
Pretreatment testosterone	0.0001	NS
Age	0.018	NS
Radiotherapy	0.665	NS
Chemotherapy	1.160	NS
Post-treatment sperm cell count ($n=43$)		
Pretreatment sperm cell count	0.100	NS
Pretreatment FSH	− 3.315	0.017
Age	2.263	NS (0.086)
Radiotherapy	−22.992	NS
Chemotherapy	9.079	NS

*Applied vs. not applied.
NS = not significant.

Table 4. Patients with intensive cytotoxic treatment

Patients' characteristics	High-dose chemotherapy (group 4)	Chemotherapy + radiotherapy (group 5)
Patients' characteristics		
No. of patients	9	10
Age at orchidectomy (years)	19 (15–45)*	30 (19–40)
RLND	8	2
Midplane radiation dose (Gy)		36 (36–40)
Total dose cisplatin (mg)	1280 (1000–1410)	750 (530–800)
Permanent "dry ejaculation" after RLND	7	2
Post-treatment gonadal function		
Testosterone (nmol/l)	18.4 (8.6–35.5) 2/9†	16.9 (10.6–24.4) 2/10
LH (IU/l)	8.4 (1.2–53.1) 2/9	7.6 (2.2–16.5) 1/10
FSH (IU/l)	18.7 (8.7–62.3) 6/9	16.3 (5.5–44.8) 6/10
No. of post-treatment pregnancies		3

*Median (range).
†Number of patients with pathological values/total number of evaluable patients.

DISCUSSION

Only 125 eligible patients receiving standard treatment were identified in the data base of 500 patients. One reason for this low percentage was the patients' refusal to produce an ejaculate. The stepwise development of the data base was a further explanation: up to 1988 only those patients were included in whom an ejaculate was obtained. During the early 1980s this was the case only in patients in whom semen cryopreservation was considered. From 1984 to 1988 all testicular cancer patients under 60 were asked to participate in a more systematic evaluation of seminal fluid analysis. From 1988 patients who were unable or unwilling to produce an ejaculate, but in whom serum hormone analysis could be performed, were also included in the data base. No age limit was set for patients who had serum hormone analyses. Not all the physicians seeing testicular cancer patients at the outpatient clinic have paid interest to systematic evaluation of the patients' fertility. These analyses are not part of the routine follow-up examinations. The present study thus comprise selected patients, but we consider the selection to be "at random" and not due to medical or social reasons.

The study examined the long-term gonadal function after standard treatment for testicular cancer. In the recent years minor changes in the treatment protocol have been made: the standard dose of radiotherapy in low-stage seminoma patients is today ≤ 30 Gy. Furthermore, at most oncological centres vinblastine has been substituted by etoposide.

FSH levels and/or sperm cell count can be used to easily evaluate spermatogenesis. A high FSH level reflects a disturbed spermatogenesis [23] and is particularly useful in patients who have "dry ejaculation" after RLND. In the present study only sperm cell count was examined since it had previously been

shown to be significantly related to motility and to the percentage of amorphe sperm cells [24].

Several reports have shown that most patients develop a transient impairment of spermatogenesis after radiotherapy or chemotherapy [4, 10–12, 14]. Gradual recovery can be expected 10–14 months after treatment in the majority of patients. However, in some patients gonadal toxicity may persist for several years or may even be irreversible.

The amount and type of cytotoxic therapy is important for post-treatment gonadal function. Vejby Hansen *et al.* [14] showed that the radiation dose is an independent predictor of post-treatment gonadal function. Furthermore, if radiotherapy is combined with chemotherapy, the post-treatment recovery of spermatogenesis is at least delayed [14]. This is consistent with the findings in our patients in group 5. High total doses of modern chemotherapy (group 4) lead to more profound disturbances of the spermatogenesis than standard treatment with only three or four cycles (group 3). Hartlapp *et al.* [13] indicated that vinblastine is probably less toxic to the male gonads than etoposide, the drug of choice in today's routine treatment of testicular cancer. This finding has so far not been confirmed by other workers. If other cytotoxic drugs are used in addition to cisplatin, vinblastine/etoposide, bleomycin, a different pattern of gonadal function recovery must be expected. In particular, long-term use of alkylating drugs and doxorubicin may lead to long-lasting or irreversible disturbances of the gonadal function [25]. Hartlapp *et al.* [13] suggested more profound and long-lasting gonadal disturbances in patients treated with ifosfamide.

More than the standard treatment itself the pretreatment gonadal function and the patient's age seem to influence post-treatment spermatogenesis and post-treatment Leydig cell function. Increasing age reduces the change of a rapid recovery of spermatogenesis and Leydig cell function, as shown in the present report and in the study by Vejby Hansen *et al.* [14]. In the latter report "high age" starts already at 25 years.

In 40–60% of testicular cancer patients low sperm cell counts are seen after orchidectomy before further treatment [24]. When pretreatment oligospermia or azoospermia is combined with high serum FSH levels, the disturbances of spermatogenesis are most often permanent, independent of the treatment [26]. In about 50% of testicular cancer patients with pretreatment oligospermia or azoospermia, post-treatment recovery of spermatogenesis can be expected, especially if initial FSH levels are normal [26].

Our results are in some contrast to a recent report from Hansen *et al.* [15]. Based on 22 patients, these authors claim that cisplatin-based chemotherapy leads to "persistent impairment of fertility and Leydig cell function in the majority of patients with testicular cancer". However, these investigators used six cycles of chemotherapy instead of only three to four, as in the present study. Furthermore, no details were given about the pretreatment gonadal function of the 22 patients treated with chemotherapy as compared to the 9 control patients from the surveillance program. The median age of Hansen *et al.*'s patients was 32 years, whereas the median age of our patients from group 3 was only 27 years (group 4: 19 years). Even though these age differences were small, they may be of importance for the post-treatment gonadal function. Due to the above mentioned considerations Hansen *et al.*'s results should not without reluctance be evaluated as indicative for the long-term gonadal toxicity which one has to expect in patients with a normal pretreatment gonadal function receiving today's standard treatment for testicular cancer.

We do agree that cisplatin-based chemotherapy leads to disturbances of spermatogenesis and elevation of serum FSH which may persist 3 years after treatment discontinuation, but to a much lesser degree than that stated by Hansen *et al.* [15]. Futhermore, most of the younger patients (most often those with non-seminoma) with normal or almost normal pretreatment gonadal function seem able to a rapid recovery of spermatogenesis. In the older patients (those with seminoma) recovery is impaired.

Hansen *et al.* [15] found elevated LH values which indicated a reduced Leydig cell function after chemotherapy despite normal testosterone values. This could not be confirmed in our study, even in patients treated with intensive cytotoxic treatment. In our series, serum testosterone levels after routine treatment were more related to pretreatment Leydig cell function and age, rather than the treatment itself.

After a median observation time of 5 years, 25 patients from groups 1–3 have fathered at least 1 child. We do not know the number of patients who wanted to father children after treatment. In a previous investigation of cured testicular cancer patients about 60% of stage I/II seminoma patients did not want to have (additional) children [6]. However, about 75% of the younger patients treated with RLND only or combined chemotherapy and surgery did not exclude future paternity. The marginally lower figure of post-treatment pregnancies in the chemotherapy group compared to groups 1 and 2 in the present analysis is probably due to the high incidence of "dry ejaculation" [9] rather than prolonged disturbed gonadal function. In order to preserve fertility limited RLND [9] or nerve-sparing techniques [27] should be adopted whenever possible.

In conclusion, the gonadal function after standard treatment for testicular cancer primarily depends on the pretreatment status of spermatogenesis and Leydig cell function and the patient's age. The standard treatment is of less significance for long-term post-treatment gonadal toxicity. Intensive treatment seems to prolong the period of post-treatment gonadal recovery.

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Psychosocial Well-being in Testicular Cancer Patients

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149 testicular cancer patients with no evidence of disease for 3 or more years filled in a questionnaire which covered the following subjects: psychosocial well-being, working ability and use of analgesics/tranquilisers. The questions were chosen to compare cancer patients' morbidity with that of age-matched controls. The patients had been treated with surgery (32 patients), radiotherapy (39 patients), cisplatin-based chemotherapy plus surgery (46 patients) or chemotherapy plus radiotherapy with or without surgery (32 patients). Since no systematic differences between the treatment groups were found, the analyses were undertaken with all patients combined. The patients felt significantly less exhausted after a working day, were more satisfied with life and felt stronger and more fit than the controls. On the other hand, the patients reported a significantly higher incidence of anxiety and depression than the normal population. The results indicate that patients treated for a malignant disease may have greater fluctuations in mood and affect than the general population.
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INTRODUCTION

TESTICULAR CANCER can be cured in about 90% of cases by the use of multimodal therapy, i.e. surgery, radiotherapy and chemotherapy [1, 2]. During the last years much attention has been paid to the possible long-term sequelae related to the different treatment modalities [3–9]. The most common side-effects are neuropathy, Raynaud-like phenomena, renal impairment, gastrointestinal symptoms and infertility.

Some reports considering long-term psychosocial morbidity in testicular cancer patients have been published [10–17]. The findings have not been consistent. Few investigators have evaluated the general impact of different treatment modalities. In many studies no control group has been used to compare the patients' morbidity with that of a normal population.

The present study was undertaken to investigate psychosocial morbidity in cured testicular cancer patients who had been in complete remission for more than 3 years.