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Original Paper

Androgen Replacement and Quality of Life in Patients Treated for Bilateral Testicular Cancer

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Gonadal hormones and quality of life (QL) were assessed in bilaterally orchiectomised patients with testicular cancer who received intramuscular androgen replacement (ARP). 43 patients were to have serum analyses of testosterone LH, FSH and SHBG, preferably performed at the end of the interval between two intramuscular injections. They also completed a QL questionnaire consisting of the EORTC QLQ-C30, GHQ-28, IES and PAIS (sexuality). 17 of 31 evaluable patients had subnormal testosterone levels, and 9 highly elevated LH. Blood levels indicating hypogonadism were more often observed in the 25 patients whose ARP was scheduled at ≥3 week intervals than in the 18 patients with ≤2 weeks between ARP injections. A total of 11 patients reported hot flushes. The patients' QL was similar to that of a control group. However, 8 (20%) patients were 'cases' according to GHQ-28/IES, independent of their hormone levels. Current standard intramuscular ARP is not optimal in approximately 1/3 of the patients who have undergone bilateral orchiectomy for testicular cancer, particularly if scheduled at ≥3 week intervals. Schedules for ARP have to be improved. In spite of intermittent hypogonadism most patients are psychosocially and sexually well adjusted to their health situation. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

THE PREVALENCE of patients treated for bilateral testicular cancer is increasing, due to the fact that more than 90% of patients with unilateral testicular cancer are cured today [1], and approximately 4–5% of the patients with unilateral testicular cancer develop a germ cell malignancy in the contralateral testicle during their lifetime. This incidence is not influenced by the routine treatment of the first germ cell malignancy [2, 3]. The standard treatment of the second testicular cancer is orchiectomy, often combined with radiotherapy and/or chemotherapy [1]. Most of the young patients are, therefore, faced with the fact that they have to be surgically castrated. Thereafter life-long androgen replacement (ARP) is required. The patient who faces this situation regularly asks the clinician about the morbidity he has to expect after the second orchiectomy. Questions of particular interest concern quality of life (QL) and sexual functioning. The overall clinical impression indicates no major morbidity in these patients with testosterone substitution. However, a *Medline* review of the last decade reveals only one publication, dealing with these issues in 7 patients [4].

At the Norwegian Radium Hospital (NRH), a comprehensive cancer centre in Oslo, approximately 100 new patients with testicular cancer are seen each year. The 15 year cumulative risk of bilateral cancer has been reported to be 3.9% [2]. In 1995 a questionnaire-based investigation was performed to evaluate the adequacy of the patients' intramuscular testosterone replacement together with important dimensions of physical and psychosocial functioning in patients who had undergone bilateral orchiectomy for testicular cancer.

PATIENTS AND METHODS

From the NRH's patient registry 55 relapse-free alive patients were identified. Between 1952 and 1994, all had been referred to the NRH after bilateral orchiectomy due to

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bilateral testicular cancer. All patients were known to have received parenteral ARP.

The patients were invited by mail to participate in a questionnaire-based research project evaluating their physical and psycho-social well-being. A total of 43 men (78%) consented to participate in the study. All 43 patients received regular intramuscular injections of Primoteston Depot^R (Schering AG, Berlin, Germany). This drug is available as two different formulations: Primoteston Depot^R 100 mg/ml: 110 mg testosterone enantate + 25 mg testosterone propionate, equivalent to 100 mg testosterone; or Primoteston Depot^R 180 mg/ml: 250 mg testosterone enantate, equivalent to 180 mg testosterone. In Norway intramuscular application of Primoteston Depot^R 180 mg/ml at 3-week intervals is regarded as standard ARP after surgical castration for bilateral testicular cancer. All patients start with this dose schedule immediately after the second orchiectomy. Individual changes from this schedule are subsequently performed based on patient satisfaction with the standard ARP, guided by regular serum testosterone controls.

The questionnaire covered details about a patient's occupational situation, educational level, family situation, major comorbidity, frequency and duration of sick-leave during the preceding 6 months and the regular use of drugs. Patients also reported the type of their testosterone injections (type of drug, mg per injection, scheduled interval). They were asked to have a blood sample drawn at their general practitioner's office for determination of serum testosterone, luteinising hormone (LH), follicle stimulating hormone (FSH) and sex hormone binding globulin (SHBG). This blood sample should have been taken immediately before they were to have their next injection after completion of the questionnaire.

All blood samples were analysed at the Hormone Laboratory, Aker University Hospital, Oslo, Norway. Testosterone serum levels were measured by radioimmunoassay (Orion Diagnostica, Espoo, Finland). The intra- and interassay coefficient of variations (CVs) were 6 and 7–12%, respectively. LH and FHS serum levels were measured by two-site immunofluorometric assays (Delfia, Wallac OY, Turku, Finland). The intra- and interassay CVs for both assays were 1–3 and 2–5%, respectively. SHBG serum levels were measured by two-site immunoradiometric assay (Orion Diagnostica). The intra- and interassay CVs were 3-6 and 7–12%, respectively. The normal ranges for the serum hormone levels in males, aged 20–50 (–70) years, are: testosterone 10–40 nmol/l; LH 1–12 IU/l; FSH 1–12 IU/l; SHBG 10–40 nmol/l. The ratio serum testosterone/SHBG was calculated as a measure of 'free testosterone'. The normal range of this parameter is 0.3–1.5.

On a visual analogue scale the patients indicated to what degree they were troubled by hot flushes, and whether they were satisfied with their ARP.

The patients completed the EORTC QLQ C-30 (version 2) [5]. The EORTC QLQ-C30 assesses functioning and symptoms generally encountered by cancer patients, such as impaired physical and emotional function or pain and sleep disturbances. The instrument has been tested extensively and is frequently used in QL research in oncological patients. Responses to EORTC QLQ C-30 from a Norwegian 'normal' age-matched population were used for comparison [6].

The QLQ C-30 was supplemented by a self-constructed previously published testicular cancer module [7] which evaluates somatic morbidity (hair loss, polyneuropathy, fertility, dry ejaculation) and sexuality. One question assesses the patient's fear of eventual relapse of his germ cell malignancy. Scores on the Likert scale ranged from 1 (not at all) to 4 (very much).

In addition to the questions on sexuality from the testicular cancer module, post-treatment sexual interest, ability, enjoyment and satisfaction, relationship with partner, sexual identity and changes in frequency of coitus were assessed by questions from Section IV (sexual relationship) from the PAIS questionnaire (Psychosocial Adjustment to Illness Scale) [8]. A Global Sexual Functioning Score (SEX) (range 0–4, no sexual life to normal) was constructed, slightly modified from the previously described procedure used in patients with penile cancer [9]. The internal consistency of this SEX scale corresponded to a Cronbach α coefficient of 0.66. The Pearson's correlation coefficient between the SEX scale and the sexuality scale from the testicular cancer module was 0.62 ($P<0.001$).

Patients were asked to complete the impact of event scale (IES) [10] and general health questionnaire (GHQ-28) [11]. By a 6-point scale (0–5) the 15 items of the IES assess the patient's psychological response after a traumatic life event, as experienced during the last 7 days. The intrusion subscale (seven items) evaluates the patient's thoughts and impressions when remembering the stressful event. The avoidance subscale (eight items) evaluates the patient's denial of the traumatic event and of its consequences. The scores of each subscale were categorised as follows: slight distress, 0–8; moderate distress, 9–19; servere distress, >19. The 28 item version of GHQ, scored as 0–0–1–1, assesses general well-being and social functoning. The sum of the patient's score is calculated. Using GHQ-28 and IES the published criteria of caseness were used: intrusion or avoidance score >19, or a summarised GHQ-28 score of >5.

The EORTC QLQ C-30 (including the testicular cancer module) was analysed according to published guidelines for the former instrument [6]. Correlations between two parameters were estimated by Pearson's correlation coefficient. Differences between distributions were tested by the Chi-square test (or Fisher's exact probability test). Means were compared by the Student *t*-test. A P value <0.05 was considered to be statistically significant (or a difference of ≥ 10 points considering the EORTC QLQ-C30).

RESULTS

Completion of the questionnaires

One patient did not respond to one item of GHQ-28, and one answer was lacking for one IES item for another patient. 2 patients did not answer, respectively, 1 or 2 questions addressing sexual function. These missing answers were substituted by the mean of the corresponding item values obtained from all responding patients. 4 additional patients did not respond to any of the sexual function questions and were excluded from all sub-analyses as regards sexuality.

Demographics

As regards initial staging and treatment of their bilateral testicular cancer the 43 responding patients were comparable with the 12 patients who refused to return a completed questionnaire (Table 1). 18 of the 43 patients had between 1 and 4 children, 1 of their spouses conceived between the patient's first and second orchiectomy.

Table 1. *Demographics*

	Evaluable patients		Non-compliant patients	
No. patients:	43		12	
Median age (range) at study	41 (31–75) years		46 (33–71) years	
Initial stage	1st orchiectomy	2nd orchiectomy	1st orchiectomy	2nd orchiectomy
1	32	35	8	10
2	4	5	3	2
3	3	1	0	0
4	4	2	1	0
Seminoma	19	27	8	9
Non-seminoma	24	16	4	3
Treatment				
Surveillance	7	27	1	8
Radiotherapy	25	8	7	1
Retroperitoneal surgery only	5	0	0	1
Chemotherapy±others	6	8	4	3
Testicular prothesis				
Unilateral	5		1	
Bilateral	5		0	
Major comorbidity	12		n.a.	

n.a., not available.

Somatic concerns

In general, patients recorded limited somatic morbidity evident by low mean scores on the testicular cancer module: hair loss, 1.2, pain or numbness in hands or feet, 1.5; Raynaud-like phenomena, 1.3; tinnitus/hearing loss, 1.2. Most patients expressed no or limited fear of relapse of their malignancy (mean 1.8 of a scale from 1 to 4) and little concern as to their fertility status (mean 1.5).

Androgen replacement

The scheduled intervals between the parenteral testosterone injections varied considerably from 7 to 70 days. 18 patients received their ARP at ≤2 weeks intervals (subgroup 1), whereas in 25 patients at least 3 weeks elapsed between two injections. 9 of these latter patients (subgroup 2) recorded a scheduled injection interval of ≥4 weeks. The individual testosterone doses per injection varied analogously from 35 mg to 180 mg. Single doses of less than 180 mg were usually given at intervals of less than 2 weeks. No patient had an ARP schedule with intervals between 2 and 3 weeks.

For all 35 evaluable patients there was a significant negative correlation between the level of serum testosterone and the time which had elapsed since the last injection of testosterone (expressed as the percentage of days which had elapsed since the last testosterone injection compared with the scheduled interval, 100%) ($R = -0.56$, $P<0.001$). When more than 80% of the scheduled interval between 2 injections had elapsed, 17 of 31 evaluable patients had serum testosterone levels below the lower limit of the normal range (10 nmol/l) (Figure 1; Table 2). 16 of these 17 patients were scheduled for standard ARP (Primoteston Depot^{R} 180 mg/3 weeks). Among 30 patients who were evaluable at the end of

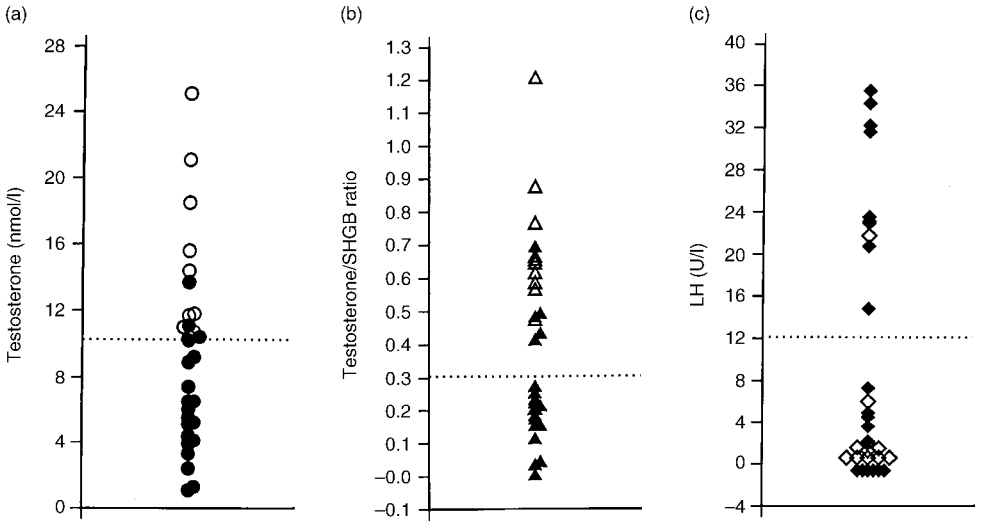

Figure 1. Serum hormone levels in patients assessed after ≥80% of scheduled interval has elapsed. Open symbols, ≤2 weeks interval; solid symbols, ≥3 weeks interval; ···, lower/upper limit of the normal range. (a) Testosterone. (b) Testosterone/sex hormone binding globulin. (c) LH. SHGB, sex hormone binding globulin; LH, luteinising hormone.

Table 2. Hormone levels and distress during Androgen replacement (ARP)

	Median (range)	Number of cases
Testosterone (nmol/l) ($n=31$)	8.9 (1.1–25.10)	–
>10, 0 nmol/l	–	17
Testosterone/SHBG ($n=29$)	0.29 (0.28–1.17)	–
<0.3	–	15
LH (U/l) ($n=31$)	2.2 (0.6–35.5)	–
>20.0 u/l	–	9
Hot flushes		
No		32
Sometimes		6
Bothersome		5
Satisfied with on-going ARP?		
No		7
Yes		34
Not evaluable		2

Table 4. Quality of life dimensions as assessed by EORTC QLQ C-30

	Patients (n=43)	Normal population [6]
Functioning*		
Physical	94.8†	93.6†
Role	73.3	95.6
Emotional	85.3	84.2
Social	86.0	87.4
Cognitive	89.9	87.8
Symptoms‡		
Fatigue	18.9	25.0
Pain	6.6	17.2
Sleep	10.1	15.9
Economics	3.1	8.3
QL [6]	83.3	75.8

*Scaling from 0 (worst) to 100 (best). †Mean values of the normalised scores. ‡Scaling from 0 (no symptoms) to 100 (maximal symptoms).

the interval, 15 patients displayed testosterone/SHBG values below the lower limit of the normal range, 11 of them in patients on standard ARP. Serum LH was elevated in 9 patients, 8 of whom received standard ARP. Hot flushes (of any frequency and degree) were reported by 11 patients. Of 41 evaluable patients 34 were satisfied with their testosterone replacement, and 7 indicated dissatisfaction.

Sexual function

In general, the patients indicated satisfying global sexual life function on the SEX scale, without a statistical relation to the schedule of ARP (Table 3). Evaluating each of the sexual items separately, the mean score of intercourse frequency was significantly lower in patients on standard ARP (3.1) than in those receiving ARP with <2 week intervals (3.6; $P=0.02$, data not shown).

Psychosocial well-being

Moderate or severe post-traumatic distress was evident in 5 patients as concerns avoidance. No case of severe intrusion was observed. Overall, 8 of the 43 patients were classified as 'cases' (IES avoidance: 2, GHQ-28: 5, Both IES + GHQ: 1).

Table 3. Sexual life and psychological well-being

	n
Global sexual function (0–4)*	
Mean ± S.D.	3.0 ± (0.86)
Score <3	7
IES intrusion	
Slight	38
Moderate	5
Severe	0
IES avoidance	
Slight	38
Moderate	2
Severe	3
GHQ-28	
Score>5	6

*(0, not at all; 4, 'normal'). S.D., standard deviation.

Quality of life

Most of the mean scores for the individual QL dimensions of EORTC QLQ C-30 were comparable with those from the age-matched normal male population, with exceptions for fatigue, economics, pain and role function (Table 4). For these 4 dimensions the patients with bilateral testicular cancer scored better than the control group, the difference being statistically significant for pain ($P=0.01$). Patients with bilateral testicular cancer scored significantly lower on the Role Functioning Scale than the comparable normal population. Furthermore, the 8 patients classified as 'cases' based on psychological wellbeing, displayed significantly lower role functioning than patients not considered to be 'cases' (Median score: 50 versus 100; $P=0.004$). In particular, the ability to continue with professional work outside the personal household was impaired in 'cases' (5 of 8) as compared with 'non-cases' (8/35; $P=0.08$). Patients reported significantly better overall QL than the control group.

Comparison of subgroups

Patients from subgroup 1 displayed significantly higher testosterone levels ($P<0.01$) and lower LH values ($P<0.01$) compared with subgroup 2 (Table 5). No statistically

Table 5. ARP scheduling, hormone levels and psychosocial distress (including global quality of life)

	Subgroup 1*	Subgroup 2†
No. of patients	18	25
Median age (years)	38	43
Testosterone (nmol/l)‡	11.8	5.8
LH‡	6.1 U/l	1.3 U/l
Psychosocial 'cases'§	3/18 (17%)	5/25 (20%)
Reduced sexual function (score <3)	2/17 (12%)	5/22 (23%)
Dissatisfaction with ARP§	4/18 (22%)	3/23 (13%)
Hot flushes§	4/18 (22%)	7/25 (28%)
Mean global QL score	83	83

*Interval ≤2 weeks between ARP injections. †Interval ≥3 weeks between ARP injections. ‡After ≥80% of the interval. §Cases/evaluable patients. ARP, androgen replacement.

significant difference between the two subgroups was evident for psychosocial caseness, sexual functioning, global QL, satisfaction with ARP or hot flushes.

DISCUSSION

In the present descriptive study we used three frequently validated instruments to assess QL and psychosocial well-being (GHQ-28, IES, EORTC QLQ C-30). In addition, sexuality was covered by a self-constructed scale (derived from PAIS) and by a Testicular Cancer Module. These latter two scales have been used by our group in previous studies in patients with penile or testicular cancer [7, 9, 11]. This experience and the (admittedly limited) psychometric evaluation done in the present study for these dimensions (Cronbach's, Pearson's correlation analysis) suggest a valid evaluation of sexuality by our SEX scale. Considerable inter-patient variation in the scheduled testosterone substitution became evident in our series, most often initiated by the patient's dissatisfaction with standard ARP. From previous studies it is known that intramuscular androgen substitution results in pronounced inter- and intra-patient variations in serum levels of testosterone, LH and SHBG and free testosterone [4, 12]. During the first days of the interval extremely high serum levels of testosterone are observed, whereas subnormal levels are frequently found during the last days of the interval. This was confirmed in the present study which also indicated that these variations are particularly significant in patients on standard ARP. Patients with shorter intervals (and single doses of <180 mg Primoteston Depot^{R}) displayed much less variation in their serum testosterone. Low serum testosterone values were correlated with low values of the testosterone/SHBG ratio and with elevated LH. The finding of elevated serum LH supports the view that 15–20% of our patients displayed signs of 'true' hypogonadism at the end of the interval between two injections.

Complete ablation of testicular androgens has profound consequences on a man's appearance (hair, skin, muscles) and behaviour [13]. Similar but less pronounced distress has to be expected in hypogonadal men with suboptimal ARP [14–16], in the form of reduced sexuality and the unpleasant experience of hot flushes. Indeed, such distress is not rarely encountered by patients treated for bilateral testicular cancer on ARP. Van Basten and colleagues [4] reported loss of libido and excessive sweating in 3 of the 7 patients with bilateral testicular cancer, experienced at the end of the 3 weeks interval of intramuscular ARP. Our results support van Basten and colleagues' observations, in particular in patients on standard ARP who frequently reported reduced intercourse frequency. Also in our series approximately 25% of patients experienced abnormal hot flushes.

The long-term consequences of unphysiological variations of the sex hormones as seen in our patients are less well studied. However, patients with suboptimal ARP may after 20–30 years display an increased risk of late somatic morbidity such as osteoporosis [17]. It is reasonable to speculate whether they also may have an increased risk of prostate cancer due to repeated very high serum levels of testosterone.

The considerable intrapatient variation in serum testosterone during ARP may be reduced by shortening the interval between the injections or by transdermal androgen replacement [15, 18]. According to the present study this would reduce the percentage of patients with subnormal intermittent serum testosterone and LH levels. More frequent performance of organ-saving orchiectomy [19] may be an alternative way to ensure continuously sufficient serum testosterone levels in patients with bilateral testicular cancer.

In spite of the sub-optimal levels of gonadal hormones in approximately 20% of the patients, the majority of men treated for bilateral testicular cancer have only limited post-treatment somatic sequelae. Our patients' perception of ototoxicity, peripheral neuropathy and Raynaud-like phenomena are within the limits seen in patients with unilateral cancer [7, 20, 21].

The patients' responses on EORTC QLQ C-30 indicate a slightly better, or at least similar, psychosocial situation as the age-matched control group, except for role functioning. One explanation for these favourable results may be that the patients' previous experience of two life-threatening malignant diseases, even though cured, has decreased the patients' level of expectations. This may in particular be relevant for the experience of pain where the patients scored much better than the control individuals. Another interesting observation was that fatigue was no major problem in the cured testicular cancer patients contrary to observations in cured patients with Hodgkin's disease [22].

However, 8 of 43 patients (19%) were categorised as 'cases' according to IES/GHQ-28 without clear association to the type of ARP. This is considerably higher than the percentage of 3.6% observed in the general population with comparable instruments [23], but is only half that of the psychosocial morbidity seen in cured patients for penile cancer [11]. In contrast to patients with penile cancer, intrusion did not represent a major distress response in patients with bilateral testicular cancer [11]. One explanation may be that men experience the diagnosis and treatment of penile cancer as more serious and life-threatening than the management of bilateral testicular cancer, whose favourable prognosis is well recognised. Our percentage of avoidance (3 of 43) is similar to that reported by Tjemsland and colleagues [24] for women assessed 1 year after radical treatment for breast cancer.

In conclusion, in patients who have undergone bilateral orchiectomy for testicular cancer, current intramuscular standard ARP is not optimal and implies a risk of intermittent hypogonadism in approximately 20–30% of patients. Intramuscular ARP should be scheduled with ≤ 2 weeks interval. The psychosocial and sexual adjustment is satisfactory in the majority of the patients. However, approximately 20% of the patients are 'cases' according to internationally accepted psychosocial screening instruments.

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