

Sexual Function in Men with Castrate Levels of Testosterone: Observations of a Subgroup of Sexually Active Men with Prostate Cancer Undergoing Androgen Deprivation Therapy

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Abstract

Purpose: To identify possible factors that influence sexual function in men undergoing maximal androgen deprivation therapy (ADT). **Patients and Methods:** A descriptive exploration was performed looking at characteristics of twenty-two men reporting sexual activity after nine months of maximal ADT. This previously published Phase II study, involved 250 prostate cancer patients undergoing intermittent ADT. An analysis between this cohort and the group that did not maintain sexual function was performed to ascertain if age, testosterone level, functional status or maintenance of quadriceps strength had an impact upon sexual function. **Results:** There was no difference in age, testosterone level or ECOG performance status between the sexually active and non-sexually active groups. Over the course of 9 months of ADT, the sexually active group appeared to maintain quadriceps muscle strength as measured with physical stands, and maintained overall health as measured by quality of life questionnaires, compared to the non-sexually active group. **Conclusions:** This retrospective study suggests that exercise during ADT may reduce the impact of ADT on sexual function. This warrants further testing, and could be the focus of future randomised controlled trials.

Keywords

Prostate Cancer, Intermittent Androgen Suppression, Exercise, Sexual Function,

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Leuprolide, Flutamide

1. Introduction

Prostate cancer is the second most common male cancer worldwide [1]. More than 2000 men in Australia commence androgen deprivation therapy (ADT) each year as part of their treatment for prostate cancer [2].

We have previously published data on the influence of testosterone suppression on sexual function on 250 men with prostate cancer, undergoing intermittent ADT [3]. These data found a subgroup of men, who in spite of ADT which lead to castrate levels of testosterone, reported maintenance of sexual activity. In this report, we aim to identify factors that may predict for, or result in, maintenance of sexual function by comparing the characteristics of patients in this subgroup with the cohort who did not maintain sexual function.

2. Methods

2.1. Eligibility and Treatment Program

This multicentre study began in July 1999, registered 250 men across Australia and closed to follow up in July 2004.

Study participants were required to have a histological or cytological diagnosis of adenocarcinoma of the prostate and Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 2. Full details of this cohort are described in an earlier publication [4]. Androgen suppression therapy (ADT) was achieved by maximal androgen deprivation using Flutamide (Eulexin®) 250 mg tds and Leuprolide (Lucrin®) 22.5 mg three monthly depot, and continued for a scheduled nine months (ONPhase), at which point patients ceased therapy providing their PSA level was equal to or below 4 ng/mL (OFFPhase). Assessments were undertaken at baseline, and three monthly intervals throughout the study period.

2.2. Sexual Function and Quality of Life Questionnaire

Participants completed the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 2.0 core quality of life (QOL) questionnaire and prostate specific module QLQ-PR25 version 3.0, results as previously described [3]. Questions used to assess sexual function assessment are presented in **Table 1**, where scores were graded on a Likert scale. Questions used to assess general health are presented in **Table 2**.

Table 1. Questions pertaining to sexual function.

During the last 4 weeks,	Not at all	A little	Quite a bit	Very much
Q49 Have you felt less masculine as a result of your illness or treatment? (Masculinity)	1	2	3	4
Q50 To what extent were you interested in sex? (Libido)	1	2	3	4
Q51 To what extent were you sexually active (with or without intercourse)? (Activity)	1	2	3	4
Please answer the next question only if you have been sexually active over last 4 weeks,				
Q53 Did you have difficulty getting or maintaining an erection? (Potency)	1	2	3	4

Table 2. Questions pertaining to general health.

Q1	Do you have any trouble doing strenuous activities like carrying a heavy shopping bag or suitcase?		Y	N			
Q2	Do you have any trouble taking a long walk?		Y	N			
For the following question please circle the number between 1 and 7 that best applies to you.							
Q29	How would you rate your overall health during the past week?						
	1	2	3	4	5	6	7
	Very poor						Excellent

Our previous publication [3] identified a subgroup of patients who were sexually active after 9 months of ADT. This paper explores the longitudinal data set associated with this subgroup and contrasts the characteristics of these men with the non sexually active cohort. The responses to the activity question “To what extent were you sexually active (with or without intercourse)” were examined. Excluding patients not sexually active at baseline, after 9 months of ADT, 22 men responded being sexually active (sexually active group). Characteristics of these men were compared to the remaining cohort (non-sexually active group) using the following measures.

2.3. Age and Testosterone Levels

Patient age was recorded at study entry. Serum testosterone was measured at baseline, at the three month mark of ONPhase, and three monthly during OFFPhase, until testosterone levels returned to baseline.

2.4. Quality of Life Questionnaire

Questions 1, 2 and 29 were selected as measures to assess general health.

2.5. Quadriceps Strength Measurement

The time required for patients to complete 20 full stands from a sitting position was measured. This was done in a separate part of the trial to measure quality of life and long term physiological changes associated with ADT. Use of the arms to assist standing was not allowed. Participants were encouraged to perform the task as quickly as possible. The time taken was measured in seconds (s). Measurement of the time to complete 10 stands was also recorded.

3. Statistical Analysis

Characteristics of the subgroup of 22 men, who were sexually active after 9 months of ADT were compared to the remaining cohort.

For continuous variables we carried out two sample t-tests, whilst for categorical variables, chi-squared tests were used. P-values are presented in **Table 3** and **Table 4**.

4. Results

Between 1999 and 2004, 250 men were recruited to the study investigating the effects of intermittent ADT. They all underwent maximal ADT, and have been analysed as two groups: sexually active and non-sexually active, as described above. Castrate level of testosterone was confirmed at 3 months in all patients, which was defined as less than 2 nmol/L.

Age, testosterone levels, ECOG Performance Status, responses to general health assessment and quadriceps strength measurement were compared for the two groups.

There was no statistically significant impact demonstrated for age, baseline testosterone levels and baseline ECOG performance status, on sexual activity at 9 months as seen in **Table 3**.

4.1. General Health Assessment

For all three general health questions analysed, there was no significant difference between the sexually active group and non-sexually active group at baseline. The sexually active group maintained better general health scores for all three questions after 9 months of ADT, as detailed in **Table 4**.

Between baseline and the 9-month time point, the sexually active group demonstrated no significant change in their responses with regards to the ability to perform strenuous activities (Q1). Conversely more patients in the non-sexually active Group reported trouble with strenuous activities at 9 months ($p < 0.01$).

Similarly, the sexually active group reported no significant change in terms of trouble taking a long walk (Q2) between baseline and 9 months, whereas the sexually inactive group reported a significant change in this ability during the same time period ($p < 0.01$).

Furthermore, with respect to overall health (Q29), the sexually active group had no significant change in their self-rated scores between baseline and 9 months, while a significantly lower self-assessment of overall health

Table 3. Physical characteristics between sexually active group versus non-sexually active group after 9 months of ADT.

	Sexually Active	Non-Sexually Active	P values
Age (years)	69.32	69.95	0.7460
ECOG Status (within the group, % of men with ECOG 0)			
At Baseline	73	75	0.7804
After 9 months of ADT	59	68	0.7434
Testosterone Levels (nmol/L)			
At Baseline	16.12	14.86	0.3290

Table 4. General health assessment.

General Health Questionnaire			
	At Baseline	After 9 months of ADT	
Q1 (% responded Y)			
Sexually Active	14	19	0.9398
Non-Sexually Active	15	36	0.0021
Q2 (% responded Y)			
Sexually Active	18	33	0.1573
Non-Sexually Active	24	44	0.0003
Q29			
Sexually Active	5.95	5.32	0.0129
Non-Sexually Active	5.53	5.10	0.0020
Quadriceps Strength Measurement (sec)			
Sexually Active	20.77	16.87	0.0007
Non-Sexually Active	22.38	20.93	0.0371

was noted in the non-sexually active group, after 9 months of ADT ($p < 0.01$).

4.2. Quadriceps Strength Measurement

There was a significant difference in quadriceps strength measurement after 9 months of ADT between the sexually active and non-sexually active groups. At baseline, mean time taken to complete 10 stands was similar between the sexually active group and non-sexually active group; 20.77 s and 22.38 s respectively. After 9 months of ADT, mean time taken to complete 10 stands, when comparing groups, was 16.87s in the sexually active group, versus 20.93 s in the non-sexually active group ($p < 0.01$). Noting the time taken for the sexually active men decreased, suggesting improved quadriceps strength.

5. Discussion

Results from this subgroup analysis suggest maintaining muscle strength during ADT may in some way counteract the adverse effect of ADT on sexual function.

In a previous publication data were presented where at baseline, prior to administration of ADT, participants had a median age of 71 and 46% were still sexually active [3]. These men underwent maximal ADT, and despite castrate levels of testosterone, a subgroup of 22 men remained sexually active. These 22 men represented 20% of patients who were sexually active at baseline.

There are several known facts about sexual activity. Firstly, that sexual activity decreases with age [5]. Secondly, sexual activity decreases with decreasing levels of testosterone [3]. The men in this trial, who underwent ADT, all reached castrate levels of testosterone. Hence there was some speculation that the subgroup of sexually active men on ADT were perhaps younger, or had a slightly higher levels of testosterone. Analysis of this subgroup has shown this was not the case.

Quadriceps muscle strength, which was measured as part of the trial to document muscle loss over the course of ADT, turned out to be significant between the sexually active and non-sexually active men. At baseline, quadriceps muscle strength, measured as timed stands, was similar between the two groups. However after 9 months of ADT, the sexually active group appeared to have superior quadriceps muscle strength, compared to the non-sexually active group. Of note, in both groups the time it took to complete 10 stands was shorter after 9 months post commencement of ADT compared to baseline (pre-ADT). The drop in the non-sexually active group was not statistically significant. The decrease in time in both groups may be attributable to patients having become familiar with the timed stands task, whilst the significant reduction in time in the sexually active group may reflect an increase in muscle mass, potentially due to exercise.

Exercise has shown benefits in multiple trials, ranging from reduction in cardiovascular disease and type II diabetes mellitus [6] [7]. In the setting of ADT, exercise has been shown to be effective in reducing muscle and bone loss as well as combating fatigue. A recent randomized controlled trial involving 57 patients has also reported that short-term exercise during ADT results in maintenance of sexual function in the exercise group [8]. The results of this current analysis raise the interesting hypothesis that the men who exercise and maintain their muscle mass over the course of ADT have a higher probability of maintaining sexual function.

The subgroup of sexually active men showed improved quadriceps strength, when compared to the non-sexually active men. One possibility is that fitter men were more likely to maintain sexual function, but this seems less likely given baseline measurements, and general health assessment questions, in this trial failed to detect any difference in the two groups. A more likely possibility is that the men, who exercised and maintained their muscle mass over the course of ADT, had a higher probability of maintaining sexual function. This is as demonstrated by quadriceps strength assessment and general health assessment results.

There are several limitations of this study. These include the retrospective nature of the data, and the small number of patients in the sexually active subgroup. Assessment of general health was subjective in nature, with the answering of questionnaires. Despite a formal protocol being in place, the measurement of quadriceps muscle strength may not have provided highly reliable data, given that different clinic nurses at multiple participating sites collected the measurements. Although an interesting hypothesis, validation of this concept requires further investigation, with more sophisticated and rigorous testing.

6. Conclusion

This study generates the hypothesis that exercise during ADT may impact favourably on the side effect profile of ADT from the perspective of sexual function. This warrants further testing, and could be the focus of future randomised controlled trials.

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