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Quality of Life Compared During Pharmacological Treatments and Clinical Monitoring for Non-Localised Prostate Cancer: A Randomised Controlled Trial

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Abstract

Objectives. This study investigated effects of different management strategies for non-localised prostate cancer on men's quality of life and cognitive functioning.

Design. Participants with prostate cancer were randomly assigned to one of 4 treatment arms: leuprorelin, goserelin, cyproterone acetate, or close clinical monitoring. In a repeated measures design, participants were assessed at pre-treatment baseline and after 6 and 12 months of treatment. A community comparison group of men the same age without prostate cancer participated for the same length of time.

Setting. Public and private urology patients from university teaching hospitals.

Participants. Men with prostate cancer who were eligible for hormonal therapy but did not have symptoms requiring immediate therapy. Eighty-two were randomised: 62 completed the 12 month study. Of 20 community participants, 15 completed the study.

Main outcome measures. Questionnaires on emotional distress, existential satisfaction, physical function and symptoms, social and role function, subjective cognitive function, and sexual function, were combined with standard neuropsychological tests of memory, attention, and executive functions.

Results. Sexual dysfunction increased for patients on androgen-suppressing therapies, and emotional distress increased in patients assigned to cyproterone acetate or close clinical monitoring. Compared with pre-treatment, there was evidence of an adverse effect of leuprorelin, goserelin, and cyproterone acetate on cognitive function.

Conclusions. In deciding the timing of androgen suppression therapy for prostate cancer, consideration should be given to potential adverse effects on quality of life and cognitive function.

One of the recurring and much-debated themes in prostate oncology is the timing of commencement of androgen suppression therapy for patients with non-localised disease. Despite the fact that, on the basis of the indisputable endpoint of survival there is little if anything to be gained by early introduction of various forms of hormonal therapy [1], even minor elevations in serum prostate specific antigen (PSA) levels continue to serve as the trigger for introduction of androgen suppression [2].

This preoccupation with perceived cancer control might be justified if the various forms of palliative hormonal therapy were not associated with unwanted effects. However, significant problems accompany all forms of hormonal manipulation [3], which afflict both the 80-90% of men whose serum PSA readings revert to very low levels with androgen suppression as well as the 10-20% of patients who do not exhibit any durable response comparably.

The usual retorts in support of early commencement of hormonal manipulation are that survival is enhanced and "quality of life" is improved. Studies that used specific measures for quality of life but non-random assignment have reported poorer emotional, physical and sexual function, and increased hot flushes and fatigue, in men using androgen suppressing treatments compared with those on clinical monitoring [4]. However, other studies with similar methods have shown associations between hormonal therapies and improved pain, urinary function, mood, and overall health-related quality of life (HRQoL), compared with pre-treatment [5 6]. There is a need for objective guidance in the form of randomised controlled studies with adequate measurement of quality of life [7 8].

A further issue that has received little attention is the potential for adverse cognitive effects. Luteinising hormone releasing hormone (LHRH) analogues have been associated with self-reported memory decline in 6-56% of female patients treated with these medications for gynaecological conditions [9-11]. Furthermore, objective

decline in verbal memory performance of female patients taking leuprorelin was reversed by oestrogen supplementation but not by placebo [12].

However, evidence on LHRH analogue effects on cognition in men is sparse. In a previous report, we found that 24/50 men with prostate cancer randomised to 6 months of treatment with leuprorelin, goserelin or cyproterone acetate demonstrated clinically significant decline in one or more cognitive tests [13]. Notably, no patient randomised to close monitoring showed a decline in test performance. To our knowledge, this is the first study which objectively has assessed cognitive effects of LHRH analogues in male patients.

Because of a paucity of randomised controlled trials, we examined HRQoL concurrent with neuorocognitive evaluations of patients with non-localised prostate cancer randomised to goserelin, leuprorelin, cyproterone acetate, and close observation. Men of similar age and health who did not have clinical signs of prostate cancer completed the same assessments over the same time periods.

Methods

Participants

Men with non-localised prostate cancer, for whom treatment by hormonal manipulation was considered optional, were eligible. Exclusion criteria were previous hormonal therapy, psychiatric impairment, severe lower tract symptoms (International Prostate Symptom Score > 7), or abnormal serum testosterone. Following power analysis results, eighty-two men enrolled in 1998-1999 and gave written consent, 77 were tested at baseline and 62 (M = 73.5 years, SD = 6.4) completed the 12 month study. Twenty men without prostate cancer were also tested at baseline and 15 (M = 68.7 years, SD = 6.2) completed the study. Demographic characteristics are shown in

Table 1. Patients were recruited through urologists and radiotherapists. Community comparison participants were recruited through media releases and public talks.

Insert Table 1 about here

Tests

Measures are shown in Table 2. All tests chosen are well-established tools used routinely in psychological assessment.

Procedure

When patients were referred, a research nurse obtained informed consent and then randomly allocated participants to one of the four management groups using a table generated by computer before study enrolments began. Patient adherence was observed through periodic serum assays of testosterone and PSA. A clinical psychologist, blinded to the individual patient's management group, conducted cognitive and psychosocial assessments. The psychologist was not blind to the status of participants as being in the randomised study or the community comparison group. Neuropsychological assessments were undertaken after randomisation (one week before treatment) and 6 and 12 months later. Psychosocial questionnaires were completed at home and returned by reply paid mail.

Statistical Analysis

To determine whether there were differences in how the groups responded over time, repeated measures Group (5) x Time (3) Analyses of Variance (ANOVAs) were conducted for the cognitive and quality of life variables. Alpha level .05 was used.

Results

Preliminary Analyses

Five patients consented but withdrew before assessment. Twenty further withdrawals occurred, due to death (2 assigned to cyproterone acetate), illness (2 leuprorelin, 1 goserelin, 3 cyproterone and 4 monitoring), changed treatment decision (1

cyproterone), moving interstate (1 community participant), and refusal (1 cyproterone, 1 monitoring, 4 community participants). Baseline measures of age, years of education, IQ, PSA, testosterone, and number of current or past illnesses did not differ between participants who did or did not complete the study; the data from the latter were therefore excluded from further analysis.

Missing data also resulted from participants omitting to answer questionnaire items. Because measures had high internal reliability, estimates were used to replace missing questionnaire data [14]. A manipulation check with PSA and testosterone measures confirmed that hormonal medications had the anticipated effects on serum variables.

Insert Table 2 about here

HRQoL Changes Over Time

As shown in Table 2, a significant time effect occurred, with worse HRQoL over time in emotional distress, physical/symptom function, social/role function, and sexual function. These time effects were consistent across all groups for physical/symptom and social/role, but showed significant Group x Time interactions for emotional distress and sexual function. There was also a main effect of group for sexual function.

The Group x Time interaction for emotional distress (Figure 1a) occurred because significantly increased distress over time was reported by men assigned to close monitoring, $p = .002$, and those assigned to cyproterone acetate, $p = .041$. However, men in other groups did not report marked changes in distress over time. As Figure 1a shows, the close monitoring group reported the lowest level of emotional distress at baseline, and, even though their distress increased over time, at Time 3 their distress was still lower than that of men assigned to cyproterone acetate or the community comparison group. The interaction for sexual function (Figure 1b) occurred because increased sexual difficulties over time were particularly pronounced for men assigned to

goserelin, $p < .001$, leuprorelin, $p = .033$, and cyproterone, $p = .067$, but did not change markedly for men on clinical monitoring or community comparison participants.

Insert Figure 1 about here

Cognitive Changes Over Time

Significant improvements over time were found for performance of the three memory tasks which repeated the same stimuli each time (Table 2). Main effects of group were found for several tasks, corresponding to the baseline advantage of the community group in IQ.

Three cognitive tasks showed Group x Time interactions (Figure 2). The interaction for a verbal learning task (Figure 2a) was followed with planned comparisons. At Time 1, the community group outperformed men with prostate cancer, $p = .024$ but there was no difference between patient groups. At Time 2, the community group again outperformed men with prostate cancer, $p = .001$, and the men assigned to goserelin recalled significantly fewer words than men assigned to leuprorelin, $p = .008$. At Time 3, the community group recalled more words than men with prostate cancer, $p = .009$, the men on close monitoring recalled more words than men on hormonal treatments, $p = .014$ and there was no difference between the active treatment groups.

The interaction for the coding task, Digit Symbol, is shown in Figure 2b. The community group scored significantly higher than men with prostate cancer at all three time periods. At Time 2, there was an additional trend towards better performance of men assigned to monitoring than those on active treatments, $p = .064$. Men assigned to active treatments did not improve their performance at retest sessions to the same extent shown by men without prostate cancer or those assigned to close monitoring. This was particularly evident for men assigned to cyproterone acetate, who showed worsening performance compared with baseline (see Figure 2b).

There was a further trend towards a Group x Time interaction for the inhibitory task, Stroop colour words (p = .087; Figure 2c). The figure shows that most groups improved their speed over time, whereas the men assigned to cyproterone acetate became slower. This was indicated in group contrasts, in that the community group was only marginally faster than the men with prostate cancer at Times 1 and 2 (p = .056 and p = .046 respectively), but was significantly faster at Time 3, p = .003.

Insert Figure 2 about here

Discussion

HRQoL and cognitive assessments were completed at baseline, 6 months [13 14] and 12 months using established and validated instruments. Both HRQoL and cognitive performance differed over time between participants randomly assigned to different management strategies. The use of random allocation to treatments and validated HRQoL measures were important features of this trial which, to our knowledge, is the first randomised controlled study of HRQoL in men with non-localised prostate cancer that has included clinical monitoring.

Notably, the most striking finding in terms of change in HRQoL was for sexual function with a significant deterioration reported in the men randomised to androgen ablation. This was consistent with previous randomised studies [15 16]. Historically, the importance of sexual function in the elderly has been dismissed or disregarded. In their population study exploring sexual function in elderly men, Helgason et al. reported that even among 70-80 year olds, an intact sexual desire, erection, and orgasm are common [17]. This same group of researchers also directed their attention to prostate cancer reporting on 431 patients 50-80 years diagnosed 1.5 to 2 years previously and 435 age-matched controls. They concluded that waning sexual function in these patients was largely due to effects of treatment which otherwise could not be explained by confounding factors [18].

Although most patients in this study had moderately elevated PSA levels indicating reasonably advanced disease at the time of diagnosis, importantly, there was no clear HRQoL advantage to active treatments compared with clinical monitoring. This was found both in group analyses and in our previously published data on individual responses, which showed that although both decreases and improvements in HRQoL measures were seen for all treatment arms, least variability was present for men randomised to close observation [14]. Furthermore, although numbers were small, there were more instances of worse rather than better HRQoL outcomes with hormonal treatments, affording little solace for advocates of early hormonal intervention.

Cyproterone acetate was associated with both increased emotional distress over time and increased withdrawal from the study (39% for cyproterone cf goserelin 5%, leuprorelin 10%, monitoring 26%, and community 25%). Three treatment withdrawals occurred due to fatigue with cyproterone acetate, whereas neither leuprorelin nor goserelin required cessation due to adverse effects. Findings on emotional distress in leuprorelin and goserelin groups contrasted with previous findings of either improvement [6] or deterioration [4] in emotional function associated with androgen ablation treatments. The latter study used non-random assignment to androgen ablation or close monitoring, so could indicate that patients who are more alarmed about their condition are more likely both to choose active treatment and to experience higher distress. Possible individual preferences for active treatment should also be borne in mind in considering increased distress over time found in the close monitoring group in this study. However, in evaluating increases in emotional distress, it should be noted that mean levels of emotional distress for all groups remained within the normal range.

Patients randomised to pharmacological treatments showed worsening performance relative to comparison groups, for verbal memory, coding, and inhibitory tasks. Cognitive results suggested that androgen ablation, rather than LHRH analogue

treatment per se, was associated with decreased performance of several tasks requiring complex information-processing. No participants in this study required cessation of treatment due to cognitive effects, although cessation of goserelin due to adverse neurological effects has been reported previously [19].

The limited sample size in this study is acknowledged. Power for detecting effects in analysis of variance was adequate (>90%), but larger cell size would have facilitated multivariate analysis and helped to detect group effects against the background of individual variability in HRQoL and cognitive performance. Also, our patient group was representative of the local population for education and IQ, but the community comparison group was typical of study volunteers in having higher than average IQ and education, making cognitive comparisons with this group problematic.

The HRQoL and neurocognitive findings at 6 months' follow-up [13 14] have been maintained at 12 months, this period of monitoring constituting a not inconsiderable proportion of these patients' life expectancies. Given the multiplicity of unwanted effects with hormonal therapy together with these findings, we believe that there is good evidence to re-evaluate our treatment strategies with this mode of palliative therapy, in particular avoiding responses based solely on PSA levels. The Hippocratic dictum of "first do no harm" should prevail. A final corollary is that the litany of unwanted effects from androgen suppression treatments, highlighted in this study, serves to emphasise the urgency for undertaking clinical trials of promising, new systemic therapies with low adverse profiles.

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What This Paper Adds

The introduction of LHRH analogues and antiandrogens has had a greater impact on the management of prostate cancer than any other single scientific development though it has resulted in no change whatever in patient survival. The argument that these treatments benefit quality of life has, to our knowledge, not been tested previously with randomised controlled trials designed to measure quality of life and including a no treatment control arm.

In a randomised controlled trial, we found no evidence that androgen ablation provided superior quality of life to clinical monitoring in symptom-free patients with non-localised prostate cancer over a 12-month period. Indeed, adverse effects were found for sexual and cognitive function. These results imply that decisions about timing of hormonal therapy should consider potential adverse effects on quality of life.

Figure Captions

Figure 1. Graphs of means representing Group x Time interactions, for pre-treatment (T1), 6 month (T2) and 12 month (T3) reports of (a) emotional distress, and (b) sexual dysfunction. Solid symbols represent groups of men with prostate cancer who were randomly assigned to treatments. Open squares represent male community volunteers matched for age and general health. Standard errors are shown for community volunteers; other groups had similar size standard errors.

Figure 2. Graphs of means representing Group x Time interactions, for pre-treatment (T1), 6 month (T2) and 12 month (T3) performance on (a) word list recall, (b) coding, and (c) Stroop inhibitory task. Other explanations as for Figure 1.

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Table 1

Baseline Demographic Characteristics of Participants Who Completed the Study

	Leuprorelin (n=18) M (SD)	Goserelin (n=19) M (SD)	Cyproterone (n=11) M (SD)	Monitoring (n=14) M (SD)	Community (n=15) M (SD)
Age	72.7 (5.8)	73.3 (5.8)	74.2 (9.2)	74.3 (6.0)	68.7 (6.2)
Years of Education	9.1 (2.8)	8.7 (1.6)	9.8 (2.6)	9.5 (2.4)	13.6 (3.4)*
Estimated IQ[a]	102.7 (14.6)	104.5 (13.7)	107.2 (13.6)	113.3 (7.1)	118.1 (9.9)*
PSA (μg/L)[b]	176.2 (497.8)	48.3 (39.4)	50.2 (41.2)	31.7 (19.5)	-
Testosterone[c] (nmol/L)	11.4 (6.4)	11.5 (5.5)	8.2 (4.2)	14.9 (8.1)	-

* Community group significantly higher than patients, p <.001

[a] Missing for 2 men in goserelin, and 1 each in the other 3 prostate cancer groups.

[b] The leuprorelin group included one patient with an outlying PSA value of 2,150 at Time 1. His Time 2 and 3 PSA were 1.6 and 3.8 respectively. Excluding the outlier, the baseline figures for the leuprorelin group are M = 60.1, SD = 74.1.

[c] Missing for 3 patients assigned to leuprorelin, 6 assigned to goserelin, 4 assigned to cyproterone acetate and 2 assigned to monitoring.

Table 2.

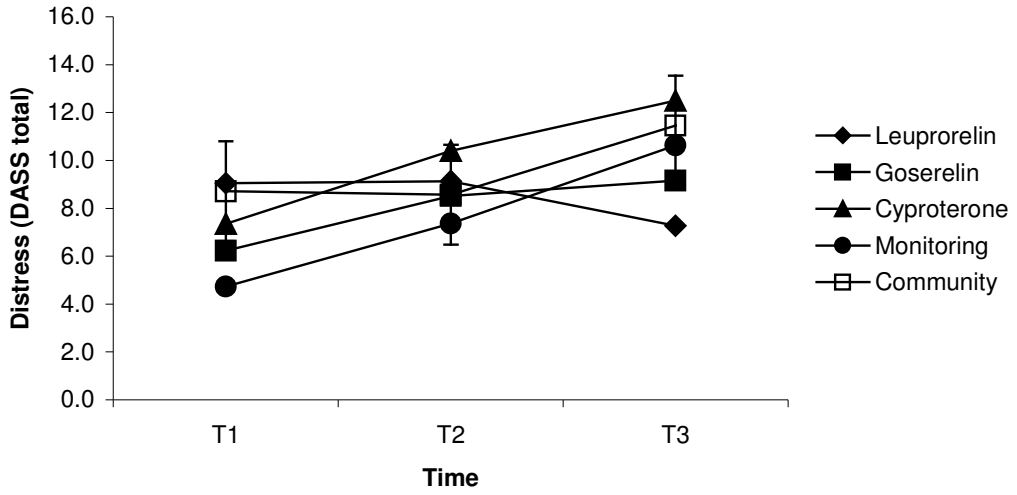
Quality of Life and Cognitive Measures, with Analysis of Variance F Values

Measure[a]	Group	Time	G x T
Quality of Life			
Depression Anxiety Stress Scales	0.17	19.15***	3.14*
Satisfaction with Life Scale	0.94	2.76	0.41
Physical and Symptom Function	1.11	7.20**	0.71
Social and Role Function	0.94	9.65**	0.38
Subjective Cognitive Function	0.47	2.45	0.16
Sexual Function	6.31***	22.31***	3.69**
Memory			
Visual Memory Index	3.08*	15.71***	0.92
Verbal Memory Index	3.48*	58.53***	0.96
Auditory Verbal Learning Test (Trials 1-5)	4.44**	1.00	4.51**
Rey Figure Delayed Recall	5.02**	9.44**	1.65
Attention			
Attention and Concentration Index	3.75**	0.44	0.52
Digit Symbol	3.65*	1.03	2.86*
Trail Making Test Part A	1.82	1.40	0.32
Trail Making Test Part B	3.71*	1.19	0.55
Controlled Oral Word Association Test	1.28	1.23	0.44
Executive Functions			
Stroop test neutral words	2.14	2.13	1.79
Stroop test colour words	1.85	0.42	2.14
Rey Figure Copy	3.93*	0.32	1.19

[a] Sources described previously [13 14]

*$p < .05$ **$p < .01$ ***$p < .001$

(a)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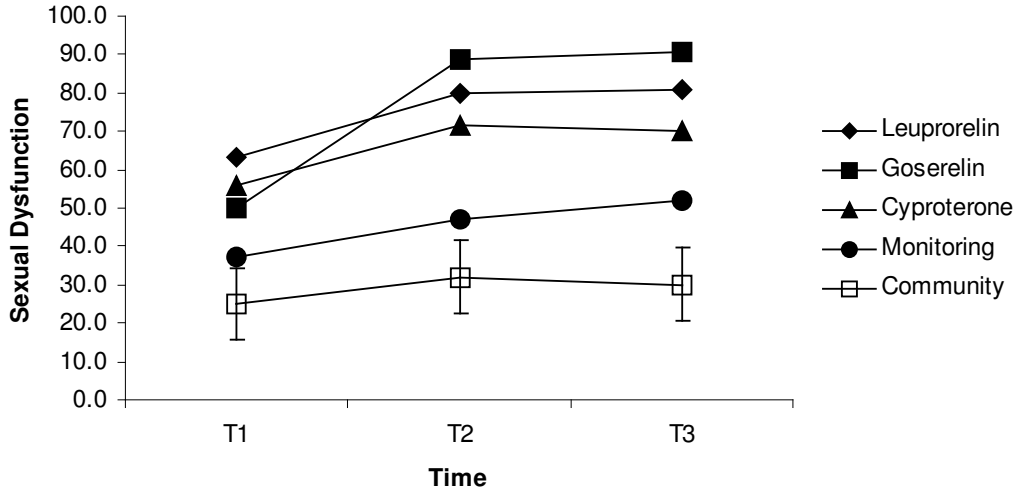
(b)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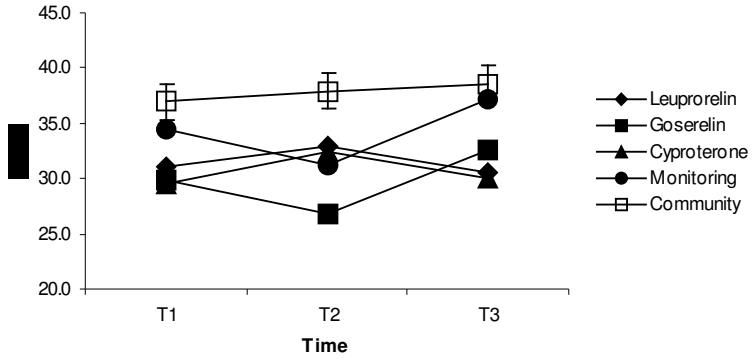
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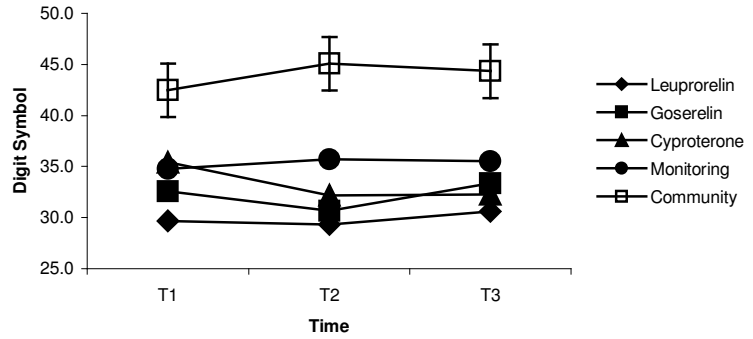
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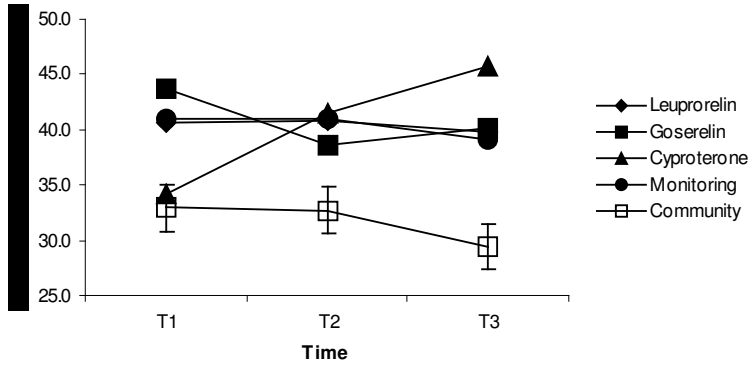
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