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Adverse effects to quality of life arising from treatment can recover with intermittent androgen suppression in men with prostate cancer ☆

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ABSTRACT

Health-related quality of life (HQOL) research is a means of broadening the assessment of treatment effects. This longitudinal study investigated the dynamic change to quality of life (QOL) and testosterone dependant physiology in men commencing an intermittent maximal androgen blockade program (IMAB). Two hundred and fifty men were accrued to the multi-centre study of IMAB (Flutamide 250 mg TDS, Leuprolide 22.5 mg depot) ceasing treatment after 9 months if PSA <4 ng/ml, and restarting when PSA >20 ng/ml. QOL was assessed every 3 months for 30 months using the EORTC QLQ-C30 and EORTC QLQ-PR25 module. Data completion for the whole study was 90%. At baseline, our cohort was less symptomatic and had better function than the EORTC reference cohort, which may be related to a shift in clinical practice with time. Testosterone suppression (AS) lead to a significant reduction in global HQOL and deterioration in most function and symptom scales. During the off period, there was a trend of progressive improvement in HQOL that paralleled testosterone recovery but was slower than the rate of deterioration during the treatment phase. Maximum recovery of HQOL occurred most frequently by months 9–12. Testosterone recovery was slower and less complete in older men, and lead to concomitant poorer HOQL recovery. Whilst the magnitude of mean change to scale scores was small, there was a consistent and simultaneous deterioration during maximal androgen blockade (MAB) and improvement during androgen recovery. Older men are more likely to show an impaired testosterone recovery, and this was paralleled by a slower HQOL recovery. Newer methods of analysis to describe results in a way that has meaning to the individual patient are warranted.

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1. Introduction

The introduction of the prostate specific antigen (PSA) blood test into routine clinical practice in Australia and the USA in the 1990s has led to earlier diagnosis of prostate cancer.[1,2] Men are often minimally symptomatic or completely asymptomatic and can be expected to survive substantially longer than their historical counterparts.[2,3] More than 2000 men in Australia[4] and more than 80,000 in the USA[2] commence ongoing androgen suppression (AS) each year. Characterization of treatment toxicity and initiatives to reduce it is an important priority in research.[3,5,6] Intermittent androgen deprivation is a treatment initiative that aims to improve quality of life, reduce treatment cost and achieve equivalent or better overall survival than continuous AS.[3,7] However until the results of ongoing phase III studies are available intermittent therapy should remain an experimental approach.

Health-related quality of life (HQOL) research emerged in the late 1980s as a means of broadening the assessment of treatment effects beyond identifying the absence of disease. HQOL is generally applied to five core functions: mental health, physical health, social functioning, role functioning, and global perception of well being.[11] A variety of symptom measures can be included to extend the coverage of the instrument.

In 1998, we initiated a study to examine the dynamic changes to quality of life and testosterone dependant physiology in men commencing an intermittent program of maximum androgen blockade (MAB). This was an Australian multi-centre longitudinal study (GUOG 98.01) that employed a single regimen intermittent maximal androgen blockade (IMAB) program. Our aims in this paper are to establish the reliability and validity of the EORTC QLQ-C30 and QLQ-PR25 prostate module for the Australian population; compare pretreatment HQOL profile of contemporary Australian patients with the normative EORTC reference data for men with prostate cancer; describe the longitudinal changes to HQOL associated with the period of MAB for prostate cancer and testosterone recovery (during the off treatment period) and characterize changes in HQOL associated with disease relapse identified during the study period.

2. Patients and methods

The study committee encouraged accrual from a wide range of clinical practices in Australia (ranging from teaching hospitals to private offices), to reflect contemporary Australian medicine.

2.1. Eligibility and treatment program

For inclusion in the study, all men were required to have histological or cytological diagnosis of adenocarcinoma of the prostate and to have an ECOG performance status of 0, 1 or 2 at baseline. All participating clinicians obtained Institutional Ethics Committee approval and written consent from each participant. Androgen suppression (AS) was achieved by a maximal androgen deprivation program employing Flutamide (Eulexin®) 250 mg tid and Leuprolide (Lucrin®) 22.5 mg three monthly depot. The duration of the first course of testosterone suppressive treatment was scheduled for nine months, at which point patients would cease therapy providing their PSA level was below 4 ng/mL. Assessments were undertaken at three monthly intervals throughout the study period. AS was commenced again when PSA exceeded 20 ng/mL, exceeded the presenting PSA if this was less than 20 ng/mL, or for clinical activity of disease.

Disease extent was prospectively categorized as: locally advanced disease without evidence of metastatic disease but not considered suitable for or declining radical treatment; metastatic disease where metastatic disease had been confirmed and PSA >10 ng/mL; recurrent local disease following radical prostatectomy, or radical radiotherapy and associated with a rising PSA $\geqslant$2 ng/mL, measured on three consecutive occasions, at intervals of at least one month or more apart and without evidence of metastatic disease.

2.2. QOL assessment

After reviewing existing quality of life (QOL) questionnaires for appropriate item content and adequate psychometric properties, we selected the combination of European Organization for Research and Treatment of Cancer EORTC QLQ-C30 version 2.0 core questionnaire and prostate specific module QLQ-PR25 version 3.0 (the QLQ-PR25 has been developed within the EORTC module development group, and is widely employed but the international validation study has not yet been reported[8]). The QLQ-C30 core questionnaire incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality of life scale. Several single item symptom measures were also included (see Table 1). All scales are scored from 0 to 100. High scores for a functional scale represented high or healthy levels of functioning, and similarly for global health or quality of life. High scores for a symptom scale or item represented high levels of symptom or problem. Previous evaluations of the core instrument reported good internal consistency and reliability coefficients.[9] The prostate module QLQ-PR25 is proposed to contain three additional symptom scales (urinary, bowel, sexual) and five treatment related items. All participating clinicians and their staff received detailed verbal and written guidelines for the administration of the QOL questionnaires, which were to be self-administered prior to seeing the doctor at baseline and every third month for a 3-year period.

2.3. Instrument reliability

A factor analysis was performed at baseline, and following 3 months of MAB, to confirm the relationships amongst the 25 items of the QLQ-PR25 in both the pretreatment and on-treatment condition. The number of factors retained was determined by scree plot and parallel analysis and then orthogonal varimax rotation to make the identified factors conceptually meaningful. The three proposed subscales, urinary, sexual and bowel were confirmed (Appendix A).

Table 1 – Pre-treatment scores for QLQ-C30 and QLQ-PR25 prostate module; comparison of Australian scores with EORTC reference data

HQOL domain	Overall score			Locally advanced		Metastatic cohort		Locally recurrent
	Australian	t-Test	EORTC	Australian	EORTC	Australian	EORTC	Australian
Cognitive	84.0	**	79.6	81.3	79.8	84.6	79.2	85.2
Role	86.7	**	72.7	84.3	75.	84.3	62.4	89.4
Physical	88.8	**	73.6	84.5	77.6	87.9	64.2	91.7
Emotional	82.2	ns	79.7	84.8	82.3	80.8	73.5	81.4
Social	87.1	**	79.6	86.6	83.2	87.	70.8	87.4
Global	73.2	**	67.3	71.1	68.6	70.6	61.2	76.
Nausea/vomiting	2.5	**	5.3	2.8	3.5	2.7	9.6	2.3
Appetite	4.4	**	9.9	3.6	5.8	7.4	19.7	3.2
Diarrhoea	6.1	ns	7.2	6.1	6.3	4.4	9.5	7.2
Finance	8.1	*	6	6.1	5.3	8.3	7.8	9.2
Constipation	9.9	**	16.2	12.6	12.3	10.8	25.8	7.8
Pain	14.3	**	24.1	16.7	17.3	17.2	40.6	11.4
Fatigue	18.4	**	33.7	17.7	29.8	22.1	43.1	16.7
Dyspnoea	13.5	**	25.4	17.9	24.7	8.3	26.9	14.1
Sleep	17.8	**	23.7	18.2	19.9	21.9	32.9	15.2
Prostate module								
Sexual function	26.7			19.7		29.2		29.2
Bowel disturbance	5.7			4.2		5.		7.0
Urinary disturbance	20.9			21.9		23.9		18.5

* t-Test significant at $P < 0.05$.
** t-Test significant at $P < 0.01$.

Reliability of the instruments in our Australian population was determined by examining their internal consistency using our own data at baseline. Subscales with internal consistency estimates of less than 0.70 were examined with specific attention to inter-item correlations and item-to-subscale total correlations. Items not consistent with others in the scale were reported as single item scales.

Internal consistency estimates for the QLQ-C30 subscales ranged from 0.32 to 0.92. The physical function scale achieved 0.53 and 0.60 and the removal of items did not improve concordance. Five items were employed, each scored dichotomously and we suggest these estimates are acceptable (QLQ-C30 Version 3.0 employs a four point Likert scale). The cognitive scale achieved 0.54 and 0.58, but it employed only two items, and so these values were considered acceptable.

Internal consistency of the QLQ-PR25 subscales exceeded 0.7 at both time points for the urinary and sexual subscales. Factor analysis did not find association of the urinary discomfort question with the urinary subscale. The optional sexual response questions will be presented in a subsequent report. Internal consistency scores for the bowel scales at baseline and 3 months were 0.42 and 0.63.

2.4. *Scoring and comparative analysis techniques*

To establish comparability with the EORTC reference data, our baseline QLQ-C30 mean scores were compared with the normative EORTC reference data using independent samples ANOVA. Because of multiple scale testing, statistical significance was set at $P < 0.01$. Score change over time was calculated for each scale to investigate the effect of androgen deprivation. Clinical importance was defined as change in mean score greater than 10 percentage points for an individual scale.[10] The influence of other covariates was examined using linear regression analysis. Comparisons were conducted with ANOVA or chi square according to the nature of the data. All statistical assessments were conducted using Stata v.8 statistical software.[11]

3. Results

Recruitment began in July 1999, 250 men were registered, and follow-up closed for this analysis in July 2004. Baseline demographic data is shown in Table 2.

3.1. *Missing data*

Questionnaire return was 90% for the duration of this study analysis. Reasons for missing data are displayed in Fig. 1. Censuring due to retreatment increased as anticipated. Median time to retreatment from end of treatment was 14.5 months. Neither these events, nor death (2.5%), major intercurrent illness (3.2%) and follow-up assessment not yet reached (7.6%) were considered as lost data, but all other causes were. Withdrawal due to protocol violation (6%) or patient request (4%) was uncommon.

3.2. *Baseline HQOL*

The mean scale scores for the QLQ-C30 and prostate specific module are listed in Table 1. Functional domains scored well (82.15–88.8), although overall HQOL was less at 73.23. Of the symptom subscales, fatigue (18.4), sleep problems (17.8), pain (14.3) and dyspnoea (13.5) scored highest. The prostate module identified substantial impairment of sexual function at

Table 2 – Distribution of patients according to performance status, disease extent and descriptive variables $n = 250$

Measure	Descriptive statistics	
Performance status		
Score = 0	172	(68.8%)
Score = 1	71	(28.4%)
Score = 2	7	(2.8%)
Age		
<70 years	86	(34.4%)
70–79 years	130	(52.0%)
>=80 years	34	(13.6%)
Presentation testosterone		
Median	14 ng/ml	
Standard deviation	5.47 ng/ml	
Minimum/maximum	3.50–33.5 ng/ml	
Presentation PSA		
Median	17.75 ug/L	
Minimum/maximum	0.70–2300 ug/L	
Disease extent		
Locally advanced	66	(26.4%)
Metastatic	68	(27.2%)
Locally recurrent	116	(46.4%)
Marital status		
Married	210	(84.0%)
Separated, divorced, widowed	34	(13.6%)
Never married	6	(2.4%)

baseline. Mean values for interest in sex were low at 32.36, and only 45.7% reported any activity.

3.3. *Comparison with EORTC reference data set*

Compared with the overall EORTC reference data set, our Australian cohort reported better function and were less symptomatic, Fig. 2a. Clinically relevant differences were confined to role and physical functions as well as fatigue, dyspnoea and pain symptoms, Table 1. The influence of disease extent was investigated by comparing our locally advanced and metastatic disease subgroups with their respective EORTC reference data sets[12] (currently, reference data is not available for the prostate module). Better scores were again observed for our cohort, but the biggest differences were seen in men with metastatic disease Fig. 2b, with nine scales showing clinically relevant differences, compared with only one cohort with locally advanced disease Fig. 2c.

3.4. *Characteristics of the locally recurrent group*

EORTC do not currently have reference data for this group. Data were collected on a subgroup of 110 men presenting with PSA-only failure attributed to local failure following previous radical surgery or radiotherapy treatment to their prostate. Comparing those with locally recurrent to those with metastatic or locally advanced disease revealed a similar

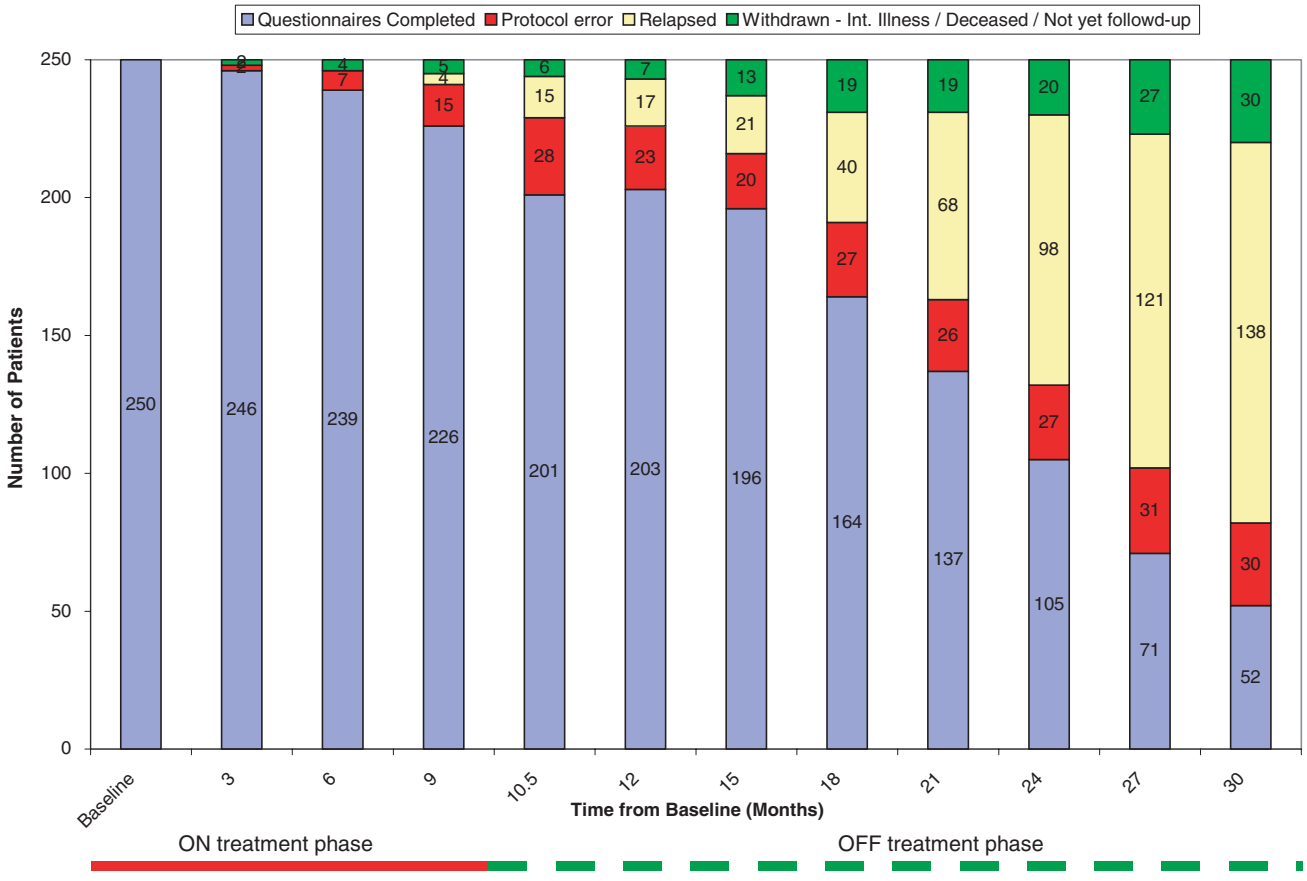

Fig. 1 – Allocation of data return status at each time point for first 9 months of treatment and subsequent 21 months off treatment (protocol error: patient preference, protocol violation, questionnaire not returned, lost to follow-up).

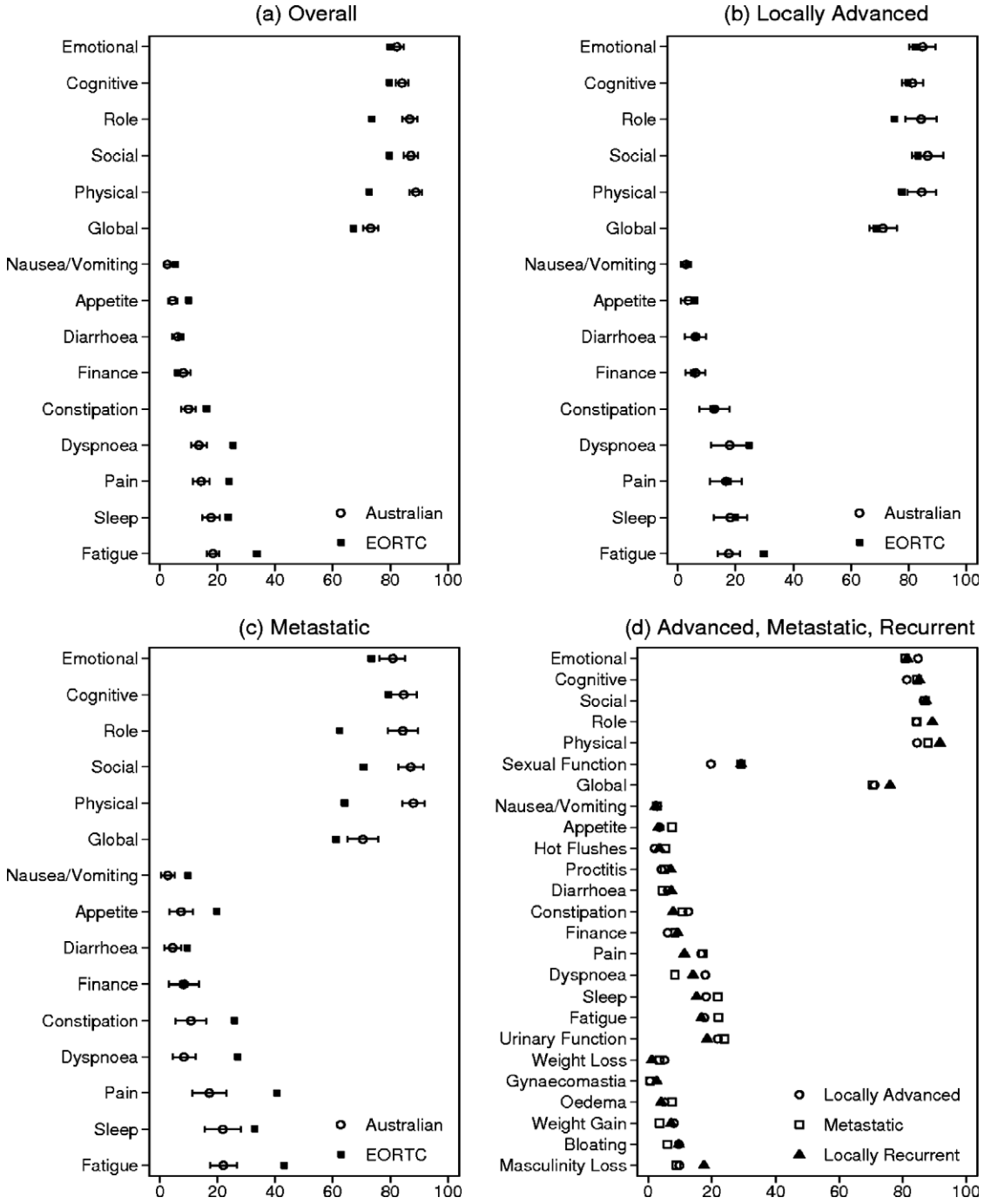

Fig. 2 – Comparison of scale scores at baseline, (confidence intervals included for Australian data): (a) whole cohort scores, Australian vs. EORTC; (b) subgroup – locally advanced disease, Australian vs. EORTC; (c) subgroup – metastatic disease, Australian vs. EORTC; (d) comparison of Australian locally recurrent subgroup with locally advanced vs. metastatic disease subgroups.

pattern of core function across the three groups, Fig. 2d. Better function scores were observed for those with locally recurrent disease but only physical function attained statistical significance. Symptom scores were more variable, but those with locally recurrent disease tended to report lower symptom scores, although the differences were not statistically significant.

3.5. *Changes during MAB (baseline to 9 months) – testosterone and PSA*

At three months 98% of patients achieved biochemical equivalent castrate testosterone levels <2 nmol/L (range 0.2–4.2). Castrate testosterone levels were maintained throughout the AS phase. After 3 months of AS, a fall in PSA of at least

45% was demonstrated by all patients, with 92.4% achieving PSA of 5 ng/mL or less.

3.6. *Changes during MAB (baseline to 9 months) – HQOL*

After 9 months, androgen suppression led to progressive deterioration in scores for 22 of 23 scales, with most of this occurring in the first 3 months. Changes in 12 of these scales were significant. Only one scale, pain, showed an improvement (0.5 points, P = NS). Fig. 3 displays score change over time for scales showing significant change by 9 months.

The degree of change on each scale is shown in Table 3. Significant deterioration was observed for physical and role core functions, but none achieved clinical relevance. In contrast, deterioration in sexual function was clinically relevant. Complete loss of interest in sex increased from 37.2% prior to treatment to 72.2%, and complete sexual inactivity rose from 54.3% to 86.9%. Deterioration in 9 of 17 symptom scales was also significant, but clinically relevant deteriorations were observed for only three of them, hot flushes, sleep disturbance and loss of maleness.

Recognized bowel and hepatic toxicity associated with Flutamide treatment led to dosage adjustment in 25.2% of patients (20.1% ceasing completely) at the 3-month assessment. Subsequently, diarrhoea score returned to baseline levels for the rest of the study period. Flutamide dose adjustment predicted for change in diarrhoea score at three months (score 21.7 vs. 10 points) but did not significantly influence any other scale change. Compliance problems where treatment was prematurely ceased or continued beyond the 9-month schedule were classified as major protocol violations, and the affected patient data was censured from that point (2.1% men).

The influence of baseline factors on score change was investigated. PSA was not significant. Higher baseline testosterone was associated with greater weight gain score by 9 months, but no other scales were influenced. Disease extent at presentation influenced change only to the urine disturbance domain; the locally advanced and metastatic patients reported little change contrasting with a worsening of 6 points for the locally recurrent group. However this difference did not achieve clinical importance.

3.7. *Testosterone and PSA changes during testosterone recovery, months 0–21 off therapy*

Following treatment cessation, testosterone recovery was progressive and median time to eugonadal levels (10 ng/mL) was 9.3 months, after which a gradual decline in mean testosterone level became apparent. PSA rose progressively during this period and was the sole trigger for retreatment (median interval to retreatment 14.5 months).

3.8. *HQOL changes during testosterone recovery period (months 0–21 off therapy)*

Score changes during testosterone recovery mostly showed a biphasic pattern. They initially improved to peak after 9–12 months before declining thereafter (Fig. 3). During the improvement phase, the rate of score improvement was

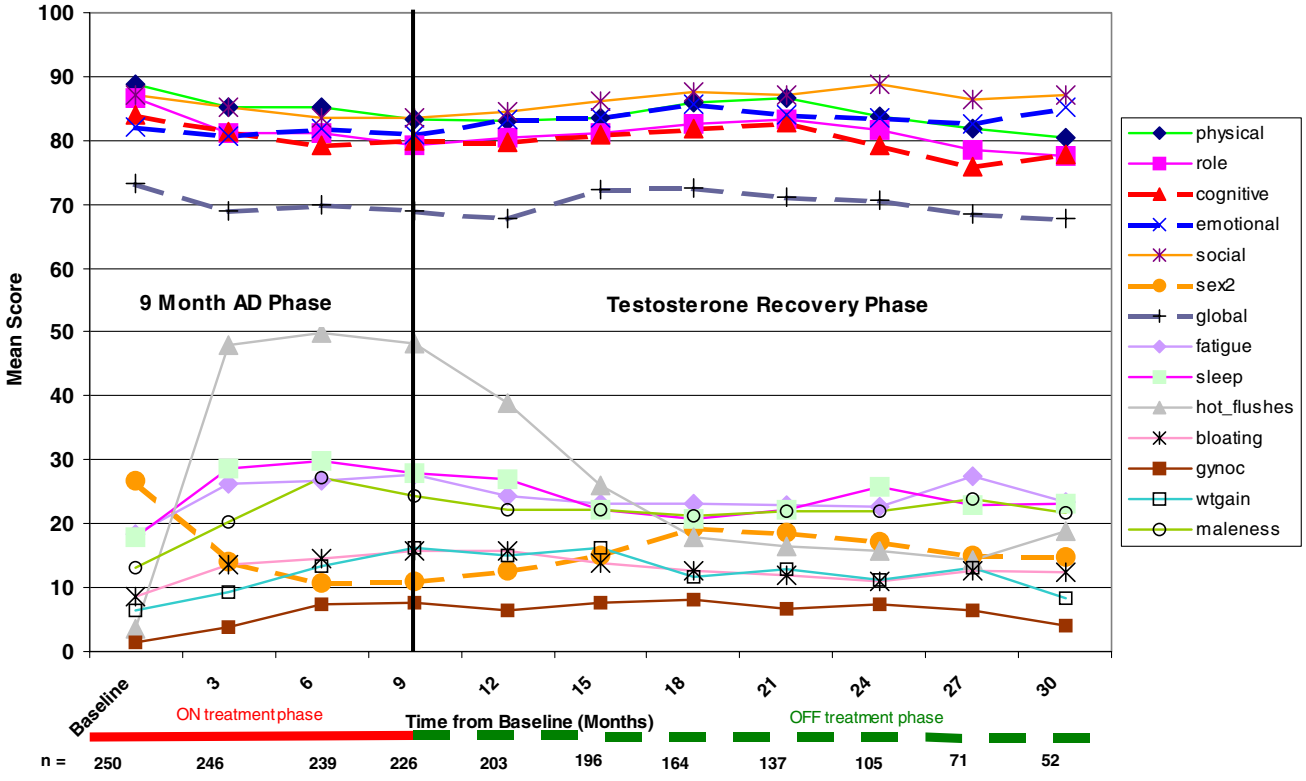

Fig. 3 – Mean scores for men during the 9-month period of maximal androgen blockade treatment and during the subsequent off treatment period of testosterone recovery. (Scales reporting non-significant changes during androgen suppression not included.)

Table 3 – Change in HQOL scale scores during the 'MAB treatment' phase (comparing end of treatment with baseline *n* = 226), and 'Testosterone recovery' phase (comparing 9 month off treatment scores with end of treatment *n* = 164)

	Score change during MAB	Score change during testosterone recovery
QLQ-C30 scales		
Role	−7.3**	3.3
Physical	−5.6**	2.7
Global	−4.2*	3.5
Cognitive	−3.9*	1.8
Social	−3.5	4.0
Emotional	−1.3	4.8*
Diarrhoea	−1.4	−0.04
Finance	−1.2	−2.5
Pain	−0.5	−0.9
Nausea/vomiting	1.6	−2.3*
Appetite	1.8	−1.9
Constipation	4.1*	−3.8
Dyspnoea	9.1**	−4.6
Fatigue	9.3**	−4.7*
Sleep	10.2**	−7.2**
Prostate module scales		
Sexual function	−15.8**	8.4**
Dysuria	−3.9**	−0.5
Bowel disturbance	0.7	−1.0
Weight loss	1.2	−1.9
Urinary disturbance	1.7	−3.4
Oedema	3.7*	−0.7
Gynecomastia	6.2**	0.3
Bloating	7.0**	−3.0
Weight gain	9.8**	−4.6*
Maleness	11.1**	−2.9
Hot flushes	44.5**	−30.1**

* *t*-Test significant at $P < 0.05$.
** *t*-Test significant at $P < 0.01$.

slower than the prior rate of deterioration during MAB. Improvements from end of MAB to peak recovery were significant for emotional function, sexual function, fatigue, sleep and hot flushes, and achieved clinical relevance only for hot flushes. In general HQOL scores returned to the baseline levels during the testosterone recovery phase. Disease extent at baseline was not a factor for recovery. Following peak recovery, there was a general trend of gradual score worsening for those remaining off therapy. We investigated possible explanations for this observation.

3.9. *Factors influencing the biphasic pattern of HQOL recovery*

The number of men remaining off therapy reduced with time so that, by 12 months off therapy, only 111 men remained off therapy. HQOL scores for those being retreated, at the time of retreatment, were as good as or better than the peak recovery scores of the whole off-treatment group. Further, 60.6% had achieved eugonadal testosterone of 10 ng/mL or greater, 59.1% recommenced treatment with PSA <20, and only 6.5% with PSA >40. Hence the unexpected HQOL decline seen after 12 months could be due to selective withdrawal of men with good HQOL scores rather than real deterioration. Accordingly, we dichotomized the off treatment group into those re-commencing treatment at twelve months or earlier from the end of MAB (Early retreatment group), and those remaining off treatment at that time (Late retreatment group). We selected this time point to correspond with the time of peak score recovery for the whole group.

Testosterone recovery was more prompt and substantial in the early retreatment group. At 6 months into the recovery period, mean testosterone for the Early retreatment group was 11.4 compared to 6.9 for the Late retreatment group. The Early retreatment group exceeded eugonadal levels by 6 months, whereas this was not achieved by 12 months in the Late retreatment group. Comparison of their baseline characteristics revealed that the Early retreatment group was significantly younger (73.4 years vs. 77.1years $P < 0.001$) and presented with higher PSA (56.2 vs. 23.3 $P < 0.01$). However, there were no differences in their presentation serum testosterone or HQOL scores at baseline, nor following 9 months of MAB. Finally, examination of the longitudinal score profiles of the individual Late retreatment group scales confirmed a slower and less complete recovery following the completion of MAB, rather than a later decline (data not shown). These results imply that whilst HQOL score recovery is dependant on testosterone recovery, so is disease relapse, and rapid testosterone recovery leads to earlier retreatment, leading to significant selection bias in the group remaining off treatment longest.

4. Discussion

Three compelling findings arise from our observations of QOL change during the androgen suppression and recovery periods. The 9-month period of androgen suppression was associated with a simultaneous and progressive deterioration in a broad range of QOL scores. While androgen recovery was associated with improvement in the affected scores, improvements occurred more gradually, were of smaller magnitude than during the suppression phase, but generally achieved baseline levels. HQOL scores at the time of retreatment were good and approaching baseline levels, suggesting that clinicians are not delaying the initiation of treatment to the time that patients are symptomatic.

At baseline, our Australian cohort reported significantly better HQOL function and lesser symptom scores than their European counterparts. Increasing age is associated with poorer function. The European overall cohort was slightly older (EORTC mean age 74.4 years vs. our 72.2 years $P < 0.01$),[13] however, age differences were not significant in the metastatic (mean 72.2 years EORTC vs. our 70.1 years $P = 0.036$) nor locally advanced subgroup comparisons (EORTC mean 75.2 years vs. our 76.8 years $P > 0.05$). The influence of disease extent was examined in Fig. 2, and the better Australian performance appeared to be strongly influenced by the much better baseline performance of our metastatic subgroup. The largest score difference was observed in the pain scale – 23 points, and was associated with a pattern of worse symptom scores in the reference group that would be consistent with substantial analgesic use; constipation, nausea, loss of appetite, fatigue, disturbed sleeping, and worse physical, role and social core functions. PSA screening is widespread

in contemporary Australia and other Western countries, and is a practice that is recognized to lead to the earlier 'presymptomatic' diagnosis of metastatic disease.[1,3] In contrast, this practice was uncommon in Europe at the time of EORTC reference data collection.[14] Men with metastatic disease were more likely to have presented later, when disease had become sufficiently advanced to be symptomatic. We suggest that many men will now commence treatment without symptoms and hence changes to their QOL will arise as side effects to MAB therapy.

Men with PSA relapse following local treatment are now a common presentation for systemic treatment (44% in our study) but there is no EORTC reference data for this group. Although our cohort was younger, and comprised men who presented with 'PSA only' failure, their presentation HQOL profile differed only marginally from our metastatic and locally advanced cohorts, with a clinically important better physical function score being the only notable difference. This finding is not surprising as they had been deemed fit enough previously to have undertaken radical treatment. Disease extent did not predict changes in HQOL score following AS apart from a 'clinically unimportant' worsening of scores for the urinary disturbance scale for the locally recurrent group. The value of categorizing disease extent as a factor for predicting quality of life appears to have lessened in the PSA era.

The changes to HQOL scores we observed following AS are consistent with the literature; marked loss of potency, significant increase in hot flushes and small magnitude changes to function scales that accompany the initiation of treatment.[9,15–20] However the literature is inconsistent when describing the direction of function change. Some reports describe a general improvement of physical, emotional and overall functions along with pain score,[9,15–17] whilst later reports describe worse outcome.[9,18–20] The latter are in line with our own experience. We suggest that this apparent disparity could be explained by a reduced proportion of men with symptoms of advanced disease in more contemporary reports including our own. Improvements in function or symptom scores attributable to therapeutic reduction of symptoms would be expected to contribute a much smaller effect, and could be overwhelmed by toxicity effects.

During the period of MAB, the number of scales that showed simultaneous score deterioration was striking. The greatest change occurred during the first 3 months with role function and 8 symptom scale changes being significant. By 9 months, deterioration had become significant for weight gain also. In contrast, only the pain scale showed numerical but not significant improvement. Clinically relevant changes were confined to hot flushes and loss of sexual function. Some symptom changes warrant closer review. Pain, a typical manifestation of symptomatic disease, was not prevalent at baseline and scored modestly. Causes of pain other than cancer could be expected to contribute in this age group diluting any possible treatment effect, but it is interesting that improvement only became significant over the longer treatment period, not at 3 months.

The contribution of drug toxicity to the effects of AS appears modest in our group in comparison with others.[16] Diarrhoea is a recognized side effect of Flutamide. In our study this led to 25.2% patients adjusting dosage, with complete resolution of this side effect for the rest of the study period. Dose adjustment was not a factor influencing score change for any of the other scales. In contrast, changes observed following cessation of AS medications were only minimally apparent at six weeks and 3 months. Subsequent changes paralleled the recovery of testosterone. Major compliance problems affected only 2.1% of our patients. Our experience suggests that few contemporary patients will feel better as a result of commencing AS therapy, and common treatment toxicity can be effectively addressed.

As anticipated, there was a trend of HQOL recovery following the discontinuation of AS which was consistent with others.[3,21] The rate of improvement was more gradual than during the prior MAB phase, taking 9–12 months to achieve the best scores. This coincided with the median time to eugonadal recovery, reinforcing their close connection. The subsequent decline in scores (Fig. 3) appeared due to selection bias arising from the earlier withdrawal, because of retreatment, of a group of men who had good HQOL scores. The Late retreatment group had slower and incomplete recovery of testosterone and poorer HQOL score recovery. However, HQOL scores for these 2 groups were indistinguishable at baseline and also at the completion of MAB, so the differences became apparent only in the testosterone recovery period. The Late retreatment group were significantly older and it is recognized that increasing age impairs the functional capacity of the hypothalamic-testis axis.[22] Finally, despite the implication that the higher PSA levels in the Early retreatment group indicated more active cancer, their good HQOL scores at relapse suggest that clinicians did not delay the recommencement of treatment inappropriately.

Our results have to be reviewed with caution. Our patients were a multi-centre sample who gave consent to be in the study, therefore some element of selection bias will be present. However, it was our intention to reflect the range of clinical practice in Australia, and avoid the generalization problems of studies where sampling is drawn from only one practice type – commonly academic units. Our patient age profiles match the Australian prostate cancer profiles closely (data not shown).[4] We employed a within person comparison design because of its greater sensitivity to change over the cross sectional between-patient design or comparison with controls. Missing data was not significant in our study.

Contemporary Australian men with prostate cancer have better function and less symptom problems than the EORTC reference group explainable in part by the changes in clinical practice that have occurred between the EORTC and our sampling periods. There was a consistent and simultaneous deterioration in multiple QOL scales during MAB maximal in the first 3 months of treatment, but which recovered following treatment cessation. However, the rate of improvement followed the androgen recovery, and in older men, this could be significantly delayed. Newer methods of analysis are needed that can summarize the multiple QOL changes in a way that is clinically meaningful to the individual.

Conflict of interest statement

None.

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Appendix A. Prostate cancer specific module QLQ-PR25 (questions ordered according to subscale)

No.	Item	Subscale	Chronbach alpha internal consistency estimate month 0	Chronbach alpha internal consistency estimate month 3
31	Have you had to urinate frequently during the day?	Urine function	0.78	0.80
32	Have you had to urinate frequently at night?			
33	When you felt the urge to pass urine, did you have to hurry to get to the toilet?			
34	Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?			
36	Have you had any unintentional release (leakage) of urine?			
39	Have your daily activities been limited by your urinary problems?			
35	Have you had difficulty going out of the house because you needed to be close to a toilet?	Bowel function	0.43	0.63
40	Have your daily activities been limited by your bowel problems?			
41	Have you had any unintentional release (leakage) of stools?			
42	Have you had blood in your stools?			
50	To what extent were you interested in sex?	Sexual function	0.78	0.76
51	To what extent were you sexually active (with or without intercourse)?			
37	Did you have pain when you urinated?			
38	Answer this question only if you wear an incontinence aid. Has wearing an incontinence aid been a problem for you?			
43	Did you have a bloated feeling in your abdomen?			
44	Did you have hot flushes?			
45	Have you had sore or enlarged nipples or breasts?			
46	Have you had swelling in your legs or ankles?			

(*continued on next page*)

Appendix A – *continued*

No.	Item	Subscale	Chronbach alpha internal consistency estimate month 0	Chronbach alpha internal consistency estimate month 3
47	Has weight loss been a problem for you?			
48	Has weight gain been a problem for you?			
49	Have you felt less masculine as a result of your illness or treatment?			
52	To what extent was sex enjoyable for you?			
53	Did you have difficulty getting or maintaining an erection?			
54	Did you have ejaculation problems (e.g., dry ejaculation)?			
55	Have you felt uncomfortable about being sexually intimate?			

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