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Factors associated with feelings of loss of masculinity in men with prostate cancer in the RADAR trial

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Abstract

***Objectives*: To identify the factors underlying prostate cancer (PCa) patients' depression–anxiety, sexual problems, urinary dysfunction and androgen deprivation therapy (ADT)-linked breast changes and hot flushes, and test these as predictors of loss of masculinity (LoM) over 36 months following diagnosis.**

***Methods*: One thousand seventy patients from the TROG 03.04 (RADAR) trial the EORTC QLQ C-30 and PR 25 questionnaires, and the International Prostate Cancer Symptom Score of the American Urological Association at baseline, 3, 7, 12, 18, 24 and 36 months. Selected items from these scales were factor-analysed to identify a four-component solution for responses at 18 and 36 months, and these components were regressed against a single-item measuring LoM.**

***Results*: Depression–anxiety factor was the most powerful predictor of LoM at both time points, followed by sexual problems of ADT side effects (breast changes and hot flushes). Urinary dysfunction was not a consistent predictor of LoM. Depression–anxiety was also the most significant factor distinguishing between those men who reported LoM and those who did not.**

***Conclusions*: Although LoM is often reported as arising from ADT, the relative power of depression–anxiety in predicting LoM, both at the selected time points and using a time-lagged analysis, plus the finding that depression–anxiety was the most consistent difference between men who reported LoM and those who did not, argues for the presence of adverse mood states as being the key ingredient in deciding if PCa patients experience loss of their feelings of masculinity.**

Introduction

Many prostate cancer (PCa) patients report a loss of masculinity (LoM) [1,2], sometimes attributed to the effects of androgen deprivation therapy (ADT) [3,4]. However, quality of life (QoL) data from the randomised controlled RADAR trial for men with locally advanced PCa suggested that the duration of ADT was not a driving issue in overall patient QoL [5]. Further, despite LoM being a component of the ADT-related symptoms domain of the EORTC PR25 organ-specific QoL instrument used in the RADAR trial, the interval change profile of LoM differed substantially from the ADT profile of those patients (shown in Appendix A), suggesting that LoM might be influenced by additional factors to those that lead to other ADT symptoms.

Masculinity is a multi-faceted construct that may undergo significant reframing by men when they experience the challenge of PCa [6], even to the point where the central characteristics that men have held as indicators of their masculinity are altered [7]. Although it is sometimes considered to be an outcome of decreased sexual activity and performance, urinary dysfunction and ADT side effects [8,9], LoM in PCa patients is a multi-faceted construct that may also be influenced by decreases in men's perceptions of their self-reliance, competitiveness, control and ability to provide for others [10], plus mental resilience and vulnerability to stress, emotional control and rationality [11], and ability to cognitively process emotions [12]. These contributors to LoM are likely to increase anxiety and depression [13], and it may be that anxiety and depression are involved in LoM as well as the more traditionally identified sexuality, urinary and ADT factors.

Therefore, because feelings of LoM are significantly aversive for PCa patients, and because there are few reports investigating the possible antecedents that might contribute to LoM, this study aimed to define and then compare the LoM-predictive power of symptoms of depression and anxiety, sexual problems, urinary dysfunction and direct physiological outcomes of ADT that were related to lowered testosterone, using standardised instruments designed to assess QoL in PCa patients. In order to identify any variation over time in the ways that these four aspects of ADT related to LoM, separate analyses were conducted for 18-month and 36-month values collected at those points in time, and for the 'time-lagged' effects of the former upon the latter, as an indication of possible 'causality'.

Methods

Participants

Data previously collected from 1070 patients in the TROG 03.04 (RADAR) trial were used in this study. Patients had a mean age of 67.5 years (SD = 6.9 years, range = 47 to 84 years). The RADAR trial is a randomised, open-label, phase 3 trial involving 23 centres in Australia and New Zealand. Eligible men had histologically confirmed adenocarcinoma of the prostate without lymph node or systemic metastases, and with T stage 2b-4 primary tumours, or T stage 2a primaries of Gleason score ≥7 histologies and baseline prostate specific antigen (PSA) levels ≥10 ng/mL immediately prior to randomisation. Patients had to have an Eastern Cooperative Oncology Group performance status score of 0 or 1 and no concurrent medical conditions likely to significantly reduce prospects of 5-year survival. The trial was approved by the independent ethics committees of participating centres, and all patients provided written informed consent. By using the minimisation technique with a random element and with stratification according to treatment centre, baseline PSA level (<10/10–20/≥20), Gleason score (≤6/≥7) and T stage (T2/T3,4), and use of a brachytherapy boost (yes/no), subjects were randomly assigned in a 1:1:1:1 ratio to one of four treatment arms in a 2 × 2 factorial design.

All subjects received 6 months of leuprorelin (22 · 5 mg i.m. three monthly) commencing at randomisation, 5 months before radiotherapy to the prostate and seminal vesicles. Following this, they received either no further treatment (i.e. 'short term' AS [the control arm: STAS]) or an additional 12 months of leuprorelin (22 · 5 mg i.m. three monthly) (i.e. 'intermediate term' AS [ITAS]). In addition to AS treatment, subjects allocated to the two bisphosphonate treatment arms received ZdA 4 mg i.v. every 3 months for 18 months starting at randomisation (STAS + Z and ITAS + Z).

Follow-up

All patients were routinely followed up every 3 months for up to 30 months, then six monthly up to 5 years post-randomisation and finally annually for a further 5 years. PSA levels were documented, clinician-assessed outcomes were collected and digital rectal examination was performed. Patient-reported outcomes were captured using the EORTC QLQ C-30 and PR 25 questionnaires, and the International Prostate Cancer Symptom Score of the American Urological Association at baseline, 3 months, end of radiotherapy, 12 months, 18 months, 24 months, 36 months, 60 months and then yearly.

Although the EORTC PR25 has sometimes been divided into subscales for urinary and bowel symptoms and sexual dysfunction, other subscales for treatment-related symptoms (including the item relating to LoM) lack satisfactory internal consistency, leading to a call for 'newer methods of analysis that can summarise the multiple QoL changes in a way that is clinically meaningful to the individual' [14, p. 1090]. It has been recommended that individual PR25 items might be used instead of subscales [15]. This caveat regarding the use of PR25 subscales, plus the fact that none of the three scales used here specifically measure the clinical symptoms of anxiety or depression, led to the decision to form a pool of the items from these scales as measures of QoL in this study and then form clusters of items across the three scales.

Items from these three questionnaires were compiled and selected by all authors to form item clusters that (i) tapped symptoms of anxiety and depression as defined by the diagnostic criteria for generalised anxiety disorder (GAD) and major depressive disorder (MDD) from the DSM-V [13], (ii) represented the kinds of sexual problems these patients reported, (iii) were indicators of urinary dysfunction and (iv) reflected the more common physiological side effects of ADT. The complete list of items is shown in Table 1. Several items were combined to form urinary dysfunction scores that were specifically related to (i) difficulties initiating urine flow, (ii) urinary incontinence and (iii) urinary obstruction, and these are shown in italics in Table 1. LoM was defined by responses to item 19 on the EOTRC QLQ-PR25 ('Have you felt less masculine as a result of your illness or its treatment?'). Although it is a single item in the EORTC QLQ-PR25, and is much more global than some of the constructs of masculinity described in the introduction, this measure

Table 1. Items selected to measure anxiety–depression, sexual problems and urinary dysfunction effects of androgen deprivation therapy

Source	Items
EORTC QLQ-C30 v3	11 (trouble sleeping), 12 (irritable), 13 (lacked appetite), 16 (constipated), 18 (tired), 24 (depressed), 22 (worry), 20 (difficulty concentrating), 25 (difficulty remembering), 21 (tense).
EORTC QLQ-PR25	*Urinary Irritative score* = 3 (urge to hurry when urinating) + 7 (pain when urinating), *Urinary Incontinence score* = 6 (urinary leakage), 14 (hot flushes), 15 (sore/enlarged nipples or breasts), 17 (weight loss), 18 (weight gain), 20 (interested in sex), 21 (sexually active), 24 (difficulty with erections).
AUA Symptom Index	*Urinary Obstructive score* = 1 (not emptying bladder) + 5 (weak urinary stream) + 7 (frequency urination at night)

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of masculinity is that which has been developed by the EORTC for assessing that variable [16] and has been used in over 3000 studies of QoL in PCa patients. As such, despite its limitation in terms of bandwidth of masculinity, this item may be accepted in this study to represent a standardised indicator of LoM.

Statistical analyses

Because different samples may report different factor structures [17], SPSS factor analysis (principal components) was used to aggregate the items shown in Table 1 into discrete components for further analysis. Linear and hierarchical regressions were used to assess the relative power of association between the components and LoM for the means of the first 18 and 36 months of recruitment, for the 18 and 36 months observations separately, and for the 'time-lagged' analysis of the effects of the components at 18 months upon LoM at 36 months. The 18 month point was chosen to allow description of patients' states immediately after they had finished ADT. Because they may have had different LoM states after ADT compared with during ADT, the means of the first 18 months allowed the analysis of their states during that ADT period. The 36-month point was chosen at the outset and was pre-specified in the RADAR trial protocol [5], and patient numbers are currently less after this point. The means of the 0 to 36 months period allowed the investigation of patients' states during the overall period.

Results

Mean of first 18 months scores: derivation of components

Principal components analysis (direct oblimin rotation) of the 21 items shown in Table 1 revealed many inter-item correlations $> .3$, a Kaiser–Meyer–Olkin measure of sampling adequacy of .827 (greater than the recommended level of .6) and a significant Bartlett's test of sphericity (4679.453, $df = 105$, $p < .001$), thus justifying factor analysis with these data. A four-factor solution emerged by selection of components with eigenvalues > 1.0 and applying parallel analysis, accounting for 63.65% of the variance (Table 2). The component correlation matrix ranged from .027 to .326, verifying the discreteness of these four 'depression–anxiety', 'sexual problems', 'urinary dysfunction' and 'ADT side effects'.

Mean of first 18 months scores: regression of components on loss of masculinity

Correlations between the four factors and LoM ranged from .140 (sexual problems) to .401 (depression–anxiety). Tolerance values were all above .800 for the factors, and VIF values were less than 1.2, arguing that collinearity was not a problem. Inspection of the normal probability plot (P-P) of the regression standardised residual showed a reasonably straight line, suggesting that no major deviations from normality were present. Linear regression revealed an R^2 of .198 ($F[4, 745] = 45.742$, $p < .001$). The standardised beta values indicated that Factor 1 made the largest significant contribution to LoM ($B = .347$, $t = 9.701$, $p < .001$), followed by Factors 2 ($B = .137$, $t = 4.164$, $p < .001$) and 4 ($B = .125$, $t = 3.582$, $p < .001$), but that Factor 3 (urinary effects) did not significantly predict LoM ($B = .051$, $t = 1.498$, $p = .135$). Hierarchical regression was then used to test for the relative power of each of the four factors in predicting LoM (Table 3).

The same four-factor solution was obtained from patient responses at each of the remaining three time points, with very minor differences only in specific item loadings.

Table 2. Pattern matrix for four-factor solution and per cent variance explained

	Factor 1: Depression and anxiety	Factor 2: Sexual problems	Factor 3: Urinary dysfunction	Factor 4: Androgen deprivation therapy side effects
Percent variance explained	31.582	12.550	10.829	8.688
Items				
Tense	.924			
Irritable	.918			
Depressed	.877			
Worry	.851			
Difficulty concentrating	.618			
Tired	.545			
Difficulty remembering	.520			
Sexually active		.930		
Interested in sex		.927		
Urinary initiative			.872	
Urinary obstructive			.823	
Urinary incontinence			.716	
Breast or nipple change				.710
Weight gain				.697
Hot flushes				.696

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Table 3. Results of hierarchical regression of four factors against loss of masculinity at each time point

Model	R^2 change	F for R^2 change	p for R^2 change
(1) 0–18 month means			
Depression–anxiety	.161	142.838	.000
Depression–anxiety + sexual problems	.002	18.139	.000
Depression–anxiety + sexual problems + ADT side effects	.015	13.411	.000
Depression–anxiety + sexual problems + ADT side effects + urinary dysfunction	.002	2.244	.135
(2) At 18 months			
Depression–anxiety	.144	153.604	.000
Depression–anxiety + ADT side effects	.013	13.752	.000
Depression–anxiety + ADT side effects + urinary dysfunction	.004	3.992	.046
Depression–anxiety + ADT side effects + urinary dysfunction + sexual problems	.002	2.693	.101
(3) 0–36 month means			
Depression–anxiety	.142	88.529	.000
Depression–anxiety + ADT side effects	.018	11.513	.001
Depression–anxiety + ADT side effects + sexual problems	.013	8.326	.004
Depression–anxiety + ADT side effects + sexual problems + urinary dysfunction	.008	5.280	.022
(4) At 36 months			
Depression–anxiety	.111	95.106	.000
Depression–anxiety + ADT side effects	.017	15.219	.000
Depression–anxiety + ADT side effects + sexual problems	.004	3.408	.065
Depression–anxiety + ADT side effects + sexual problems + urinary dysfunction	.000	0.337	.562

ADT, androgen deprivation therapy.

Table 3 presents the four sets of hierarchical regression equations of the four factors described in Table 2 against LoM at each time point.

Depression–anxiety symptoms were the most powerful predictive factor, with ADT side effects being stronger and more consistent than either urinary dysfunction or sexual problems. To investigate Factor 1, the specific items that comprised it were entered into successive regression equations for LoM at each of the four time points. Table 4 shows those items that were significant predictors of LoM at each time point as feeling depressed, feeling tired and difficulty remembering things, which are all symptoms of MDD rather than anxiety.

Table 4. Factor 1 items that were significant predictors of loss of masculinity at four time points

Item	Standardised beta weight	t	p
(i) 0–18 month means			
Tired	.169	4.381	.000
Depressed	.145	2.984	.003
Difficulty remembering things	.083	2.142	.032
(ii) 18 months			
Depressed	.238	5.486	.000
Tense	.165	3.321	.001
Difficulty remembering things	.113	3.217	.001
Tired	.099	2.831	.005
(iii) 0–36 month means			
Tired	.199	4.580	.000
Depressed	.137	2.477	.013
Difficulty concentrating	.094	2.046	.041
(iv) 36 months			
Tired	.207	5.385	.000
Depressed	.151	3.372	.001
Difficulty remembering things	.094	2.482	.013

To explore how the influence of those factors on LoM may have changed over time, standardised beta weights for each of the four factors at the 18-month and 36-month time points were used: depression–anxiety slightly decreased over the 1.5 years from 18 ($B = .326$) to 36 ($B = .289$) months, sexual problems increased slightly ($B = .051$, .064), and both urinary dysfunction ($B = .063$, .020) and ADT side effects ($B = .125$, .014) also decreased. However, those data are outcomes of statistical analyses rather than raw data and show only two points in time (18 and 36 months), making it difficult to derive any implications of causality. Therefore, mean factor scores were calculated for each time point and graphed against LoM scores at those time points for men whose LoM score was > 1.0 at 36 months (i.e. they reported at least some LoM 3 years after commencing treatment compared with other men who reported no LoM at that stage). Figure 1 shows that, whereas LoM increased over the entire 36 months of data collection, urinary dysfunction and ADT side effects had initially peaked at 7 months and then decreased during the remaining 29 months. By contrast, sexual problems described a U-shaped pattern, being very high at point zero, then dramatically decreasing to 7 months, and after which, they gradually increased to 36 months. Depression–anxiety also peaked at 7 months, then decreased to 18 months and gradually increased again.

Some degree of 'causality' may be deduced by measuring the predictive power of 18-month factor scores on 36-month LoM scores. This process is called 'time-lagged' analysis and may be conducted on total scale scores [18], or on

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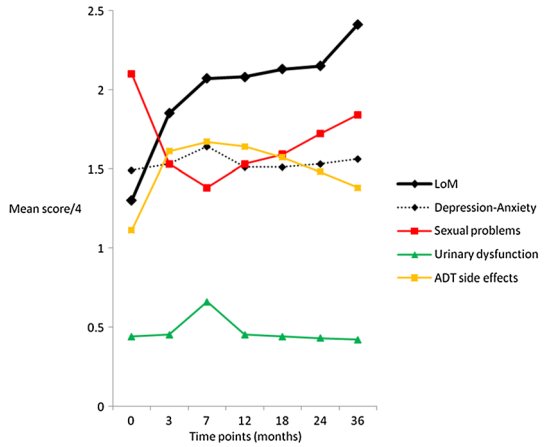

Figure 1. Changes in LoM and factor mean scores over 36 months. ADT, androgen deprivation therapy; LoM, loss of masculinity

derived factor scores [19], as was the case here. Hierarchical regression indicated that anxiety-depression scores at 18 months were the strongest predictor of LoM at 36 months (R^2 change = .043) ($F(1,746) = 33.413$, $p < .001$), and the addition of ADT side effects significantly added to that R^2 square by .009 ($F = 7.401$, $p = .007$), as did urinary dysfunction by .006 ($F = 4.577$, $p = .033$), but sexual problems did not add significantly to the prediction of 36-month LoM scores.

Finally, in order to determine which aspects of the four factors were significantly different across men who reported some LoM at 36 months compared with those who did not report any LoM at that point, the entire sample was divided according to 36-month LoM scores to provide an 'LoM present' versus an 'LoM absent' dichotomy. MANOVA was conducted on differences in the four factor scores from each of the seven points in time when data were collected between those two groups of men. There was a significant main effect ($F[28, 454] = 4.173$ (Wilks' lambda), $p < .001$, partial eta square = .205). After applying a Bonferroni correction for 28 comparisons (bringing the p value to $<.001$), only 12 of the 28 comparisons were statistically significant. These were the following: all seven time point observations for the depression–anxiety factor, the first time point for sexual problems and the last four time points for ADT side effects. In all of these, men with LoM > 1.0 ('none') had significantly higher scores than men with no reported LoM.

Discussion

Examination of the underlying factor structure of the 21 items drawn from the three tests of QoL in PCa patients identified four factors, which were robust and consistent across the four sets of time points. The greater power of depression–anxiety compared with the remaining three factors in predicting LoM was consistently demonstrated. Further, the specific MDD symptoms found to be the most powerful predictors of LoM represented the 'sadness/depressed' diagnostic criterion for MDD (which is required for a positive diagnosis), the fatigue diagnostic criterion and the cognitive functions diagnostic criterion. Because we were able to differentiate the effects of the four factors examined here, these data clarify *how* ADT might lead to LoM and suggest that depression *per se* is a major predictor of LoM in PCa patients, independently of ADT. That suggestion is supported by the fact that the experience of ADT did not consistently predict LoM in these patients. There is clearly an intervening variable in the ADT-LoM equation, and these data argue for that variable being depression.

Clinical implications for treatment of PCa patients who report LoM include the possibility that depression symptoms might be reasonably considered as treatment targets for LoM, whether via antidepressant medication and/or psychotherapies. While the former are commonly considered as the first line response to depression [20], recent evidence suggests that the combination of both medication and psychotherapy offers the most promising treatment model for reducing depression symptoms [21], and this may be of particular value with PCa patients whose depression may be a function of several aspects of their treatment, including ADT and sexual difficulties, and which may benefit from psychotherapy discussions rather than needing direct antidepressant medication.

Figure 1 showed that LoM was increasing throughout the entire data collection period of 36 months, with minimal change in urinary dysfunction and a decrease in frequency of ADT side effects, supporting the suggestion that these factors may not be the most powerful predictors of LoM in PCa patients. Although causality cannot be inferred from the data shown in Figure1, the time-lagged analysis added weight to the suggestion that it is anxiety-depression that contributes most powerfully to LoM, at least from the 18 to 36 months observations.

Limitations to this study include the instruments used, which do not allow for a complete assessment of MDD or GAD; the cultural and geographical nature of the sample; omission of potentially important issues that may have contributed to feelings of LoM (e.g. shrinkage of the genitalia and the need to sit down to pass urine), which were not included in the instruments used during the RADAR trial; and a more probing investigation of the effects of fatigue. Masculinity is multi-faceted, and further research using a wider range of items to measure LoM would be informative. The four factor model explained only 20% of the variance, suggesting that there remain some unexplored factors relevant to feelings of LoM in these men. Finally, it is important to note that the mean age of the RADAR population at randomization was 68 years; LoM during and after therapy may not be as profound in men in this age group as in younger men.

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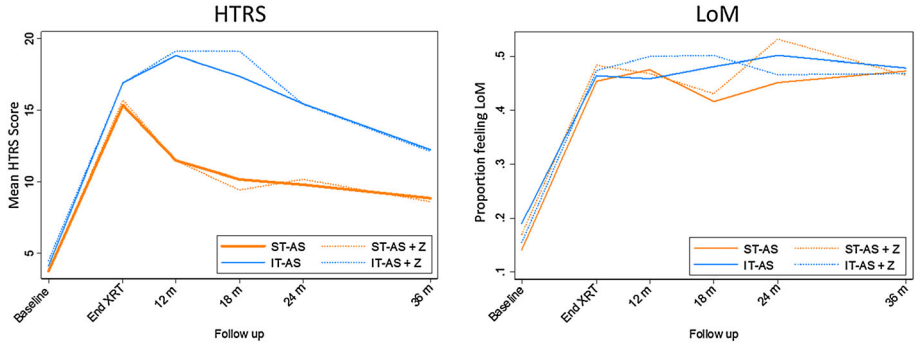
Notwithstanding these limitations, these results argue strongly for further consideration of the role of depression–anxiety aspects of PCa patients' overall illness profile as being more influential in predicting their LoM than their urinary-related or ADT-related issues. Sexual problems appear to be also of lesser importance when understanding LoM in these patients and may also interact with depression–anxiety in ways not able to be determined from these data. Somewhat surprisingly, we were able to determine that this relationship did not appear related to increasing age, although this relationship would benefit from further examination. Finally, the finding that some men did not experience LoM despite receiving ADT argues that it is not the experience of ADT itself that leads to LoM.

Conflict of interest

None to declare.

Appendix A. Androgen deprivation therapy-related symptoms and loss of masculinity in TROG RADAR patients



In the left hand panel EDRTC PR-25 Hormone treatment related symptom (HTRS) scores were greateer in subjects receiving 18 months "intermediate term" androgen suppression with or without 18 months zoledronate (ITAS±Z) at their 12, 18, 24 and 36 month post randomisation visit, than subjects receiving only 6 months androgen suppression with or without 18 months zoledronate ("short term" STAS±Z). In contrast in the right hand panel the proportions of subjects feeling loss of masculinity (LOM) receiving 18 months androgen suppression with or without zoledronate were very similar at the 12,18,24 and 36 month visits to the proportions of subjects receiving 6 months androgen suppression with or without zoledronate. In fact at 36 months no recovery in sense of masculinity has occured in any treatment group regardless of androgen suppression completing at least 18 months earlier.

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