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ORIGINAL ARTICLE

Examining trajectories of anxiety in men with prostate cancer faced with complex treatment decisions

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Abstract

Purpose To examine changes in anxiety over time (trajectories) in men with prostate cancer faced with a decision to participate in a clinical trial and to identify demographic and study variables that predict these trajectories.

Methods Our data come from a larger study examining the efficacy of a decision aid on decisional conflict in men with prostate cancer who were deciding whether to participate in a prostate cancer clinical trial. We used latent growth mixture models to identify 'classes' (i.e. groups) of participants with different trajectories of anxiety, as assessed by the State-Trait Anxiety Inventory state scale, and binary logistic regression to determine predictors of anxiety 'class'.

Results In 128 men with prostate cancer (mean age = 63), growth mixture modelling identified two classes defined by different anxiety trajectories. One class ($n = 27$) started with a higher mean anxiety score and did not change over time (stable high), whereas the second class ($n = 101$) started with lower anxiety and significantly reduced over time (low and recovering). None of the demographic and study variables (including age, education, marital status, and decision to join the trial) was predictive of anxiety class.

Conclusions Men treated for prostate cancer who have high levels of anxiety after surgery may continue to have persistent high anxiety levels which do not reduce naturally over time. Patient or disease characteristics do not appear to predict anxiety. It is important, therefore, to monitor for anxiety in this population and refer for psychological interventions where required.

Keywords Prostate cancer · Anxiety · Trajectories · Latent growth mixture model · Patient decision-making

Introduction

The diagnosis and treatment of prostate cancer has a profound psychological impact on men with this disease [1, 2]. Levels of psychological distress vary between individuals and also over time within the same individual. Anxiety in particular has been demonstrated to be prevalent in men with prostate cancer [3, 4], although there is little understanding regarding risk factors for anxiety. One cross-sectional study found that lower physical, social, and functional well-being predicted greater anxiety in men with various stages of prostate cancer [1].

The time course of anxiety has been examined in cancer patients generally [5], as well as in samples of patients with specific primary cancer sites. Dunn et al. [5] used growth mixture modelling, a quantitative method for classifying participants according to different patterns of change over time (trajectories), and identified three trajectories in a sample of oncology patients with different primary cancer sites: (1) low baseline anxiety that remained low, (2) intermediate baseline anxiety that decreased slightly over time, and (3) high baseline anxiety that remained high. Similarly, in a sample of breast cancer patients, Lam et al. [6] also identified groups or 'classes' of women who had low distress at baseline that remained low ('resilient'), high at baseline and remained high ('chronic distress'), and high at baseline but decreased ('recovered'), as

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well as another class that were low at baseline, increased, and then decreased ('delayed recovery'). In another study examining quality of life for individuals with nasopharyngeal cancer, Lam et al. [7] observed anxiety classes representing high-stable, low-stable, high-deteriorating, and recovered anxiety trajectories. One study has examined trajectories of psychological variables in men with 'low-risk' prostate cancer undergoing 'active surveillance' or close monitoring designed to defer or avoid active treatment [8]. Other studies have examined trajectories in relation to the impact of a psychological intervention [e.g. [9]].

Men with prostate cancer exhibiting worse prognostic features might be expected to have higher or different causes of anxiety related to disease recurrence or progression compared to those on active surveillance despite having undergone active treatment; thus, the trajectory of anxiety in this group and the factors influencing it are worthy of investigation. Yet little research has been conducted in this group of men requiring active treatment for their cancer.

Anxiety may be heightened when there is a high level of uncertainty [8, 10]. Patients with prostate cancer sometimes face significant uncertainty associated with choosing between various initial treatment options. Further uncertainties may arise in the clinical trial setting where patients also face the possibility of undergoing treatment of unknown benefit. It is important to determine if the potential benefits of participation in a clinical trial are accompanied by increased anxiety due to an uncertainty about outcomes and the responsibility of making an additional decision. In the present study, we examined trajectories of anxiety in prostate cancer patients who were found to have features predicting a higher chance of recurrence after surgery and who were then faced with a decision about participating in a clinical trial. The trial randomised men to receive adjuvant radiotherapy or close observation with 'salvage' radiotherapy given only if the prostate-specific antigen test rose later during the follow-up period. Alternatively, men could choose to be managed off trial with either immediate or delayed radiotherapy. We sought to determine predictors of anxiety in this group of men, including any impact from a decision to join the trial.

Methods

The data used in this analysis come from a larger study examining the efficacy of a decision aid on decisional conflict in men with prostate cancer who were deciding whether to participate in a prostate cancer clinical trial (the Trans-Tasman Radiation Oncology Group's RAVES 08.03 trial [11]). The information concerning the pros and cons of the RAVES treatment arms was complex, involving uncertain benefits and potentially significant side effects and impact on quality of life. Participants were recruited by either urologists or radiation oncologists. Participants were men aged 18 or older with a diagnosis of prostate cancer treated with radical prostatectomy and who had positive margins and/or disease outside the prostate capsule and/or within the seminal vesicles seen on pathology. Men with insufficient English to read the information provided and complete questionnaires, or with cognitive disorders, were excluded from the study [12]. All patients recruited to this study provided written informed consent.

Consented participants were sent a study package including the standard RAVES participant information sheet and either the decision aid or a blank booklet of the same size. They were prompted to complete the baseline questionnaires first and then to read the information provided. All participants were mailed follow-up questionnaires at 1 month (when all men should have made a decision about participation in the RAVES trial) and at 6 months. Ethical approval was obtained from the Royal Prince Alfred Hospital Human Research Ethics Committee and from site-specific research governance bodies at each participating site (HREC/11/RPAH/433).

Questionnaire

Although several questionnaires were administered (related to the decision aid), only the demographic questionnaire and the questionnaire that assessed anxiety are relevant to the present analysis. The latter questionnaire was the six-item short-form State-Trait Anxiety Inventory (STAI) state scale [13], which has acceptable reliability, validity, and sensitivity to fluctuations in state anxiety. Higher scores indicated a higher state of anxiety.

Statistical methods

In order to examine trajectories of anxiety in prostate cancer patients faced with a decision about participating in a clinical trial, we used latent growth mixture models (LGMM) [14] in Mplus v7.4 [15]. This method classifies participants according to their pattern of change over time, identifying distinct groups (latent classes) with different trajectories, and allows examination of variables (*covariates*) that predict group membership. The method requires pre-specification of the number of classes. We first specified a single-class model without covariates. We then analysed models with one through six classes, again without covariates. The optimal number of classes was determined by examining the following indices: (1) Akaike information criterion (AIC), (2) Bayesian information criterion (BIC), (3) sample-size adjusted BIC; (4) Lo-Mendell-Rubin likelihood ratio test (LM-LRT), and (5) the bootstrap likelihood ratio test (BLRT). Better fit is indicated by smaller values of AIC, BIC, and sample-size adjusted BIC and by statistically significant LM-LRT and BLRT.

Because we found that including covariates in the LGMM models caused estimation problems, we used logistic regression in SPSS v22 instead, with class membership as determined by LGMM modelled using the following predictors: condition (received decision aid vs. did not receive it), age (years), education (dummy coded with year 10 or below as the reference category and four comparison groups: year 12, TAFE, University, higher degree), marital status (unmarried vs. married/de facto), significant medical co-morbidity (yes/no), country of birth (Australia vs. other), investigator specialty (radiation oncologist vs. urologist), and decision to participate in RAVES trials (yes/no). The covariate analysis was binary logistic regression if two classes were identified in LGMM and multinomial logistic regression if more than two classes were observed.

Results

Of 129 participants recruited, all but one provided anxiety scores at all three time points. The characteristics of the 128 participants included in the analysis are summarised in Table 1. The average age of men was 63, and there was a diverse level of education. Most were referred to the study by urologists, and the majority eventually decided not to join the RAVES trial of adjuvant versus salvage radiotherapy.

Table 2 Model fit for six solutions of the latent growth mixture models. Lower AIC, BIC, and sample-size adjusted BIC (SSBIC) indicate better fit. Statistically significant values of LMR-LRT and BLRT indicate superior fit compared to the model with one trajectory fewer

	AIC	BIC	SSBIC	LMR-LRT	BLRT
1 class	1753.48	1776.30	1751.00	–	–
2 classes	1741.71	1773.08	1738.30	0.09	< 0.001
3 classes	1741.26	1781.19	1736.91	0.58	0.25
4 classes	1720.04	1768.53	1713.76	0.36	< 0.001
5 classes	1717.50	1774.54	1711.29	0.41	0.67
6 classes	1717.84	1783.44	1710.70	0.79	0.43

Examination of trajectories of anxiety in prostate cancer patients

Growth mixture modelling revealed that the single-trajectory model had a statistically significant intercept of 10.52 (standardised estimate = 3.42, $p < 0.001$) and a significant slope of − 0.59 (standardised estimate = − 0.62, $p < 0.001$). The two-trajectory model fits the data better than the single-trajectory model (see Table 2). The three-trajectory model had information criteria indicating very similar or slightly worse fit than the two-trajectory model. In addition, one of the trajectories in the three-trajectory model included only three participants. The four-trajectory model had lower information

Table 1 Summary of key demographic variables in participants

		Mean (SD, range)
Age		63.33 (6.47, 42–74)
		Frequency (%)
Education	< year 10	21 (16.4)
	Year 12	15 (11.7)
	TAFE	41 (32.0)
	University	26 (20.3)
	Higher degree	21 (16.4)
	Missing	2 (1.6)
Marital status	Unmarried	12 (9.4)
	Married/de facto	114 (89.1)
	Missing	2 (9.6)
Country of birth	Australia	87 (68.0)
	Other	39 (30.4)
	Missing	2 (1.6)
Significant medical co-morbidity	No	82 (64.1)
	Yes	44 (34.4)
	Missing	2 (1.6)
Investigator specialty of referring clinician	Urologist	92 (71.9)
	Radiation oncologist	36 (28.1)
Decision to participate in the main RAVES study	No	109 (85.2)
	Yes	19 (14.8)

Table 3 Unstandardised estimates from the single- and two-trajectory latent growth mixture models. The values in parentheses are *p* values

		Intercept	Slope	Variance of intercept	Variance of slope	Intercept-slope covariance
1 class	1	10.53 (< 0.001)	− 0.59 (< 0.001)	9.49 (< 0.001)	0.89 (0.37)	− 1.52 (0.22)
2 classes	1	14.33 (< 0.001)	− 0.27 (0.55)	2.98 (0.003)	2.05 (0.04)	− 2.23 (0.03)
	2	9.35 (< 0.001)	− 0.68 (0.001)	5.58 (0.003)	1.30 (0.04)	

criteria than the two- and three-trajectory models, and fit was significantly better than that of the three-trajectory model according to the BLRT. One of the trajectories, however, included only two participants.

Based on the above explorations, the two-trajectory model was selected as the optimal solution. For one trajectory (n = 27), the intercept of 14.33 was significant (standardised estimate = 6.07, $p < 0.001$) but not the slope of − 0.27 (standardised estimate = − 0.24, $p = 0.549$). For the other trajectory (n = 101), the intercept of 9.35 (standardised estimate = 3.96, $p < .001$) and slope of − 0.68 (standardised estimate = − 0.59, $p = 0.004$) were both significant (Table 3). In other words, the analysis identified one class of men who started with a higher mean anxiety score that did not change over time (stable high) and a second group that started with lower anxiety and that significantly reduced over time (low and recovering) (Fig. 1).

The results of the binary logistic regression of trajectory membership on various demographic and study variables are shown in Table 4. None of the potential demographic and other predictors significantly predicted the trajectory class to which an individual man would fall into. The mean baseline anxiety was 9.13 (SD = 2.77) for those who decided to participate in the RAVES trial and 10.66 (3.78) for those who decided not to participate.

Discussion

This study revealed that men with prostate cancer found to have less favourable prognostic features after surgery and who were also dealing with a decision about participation in a clinical trial fell into one of two anxiety trajectory classes:

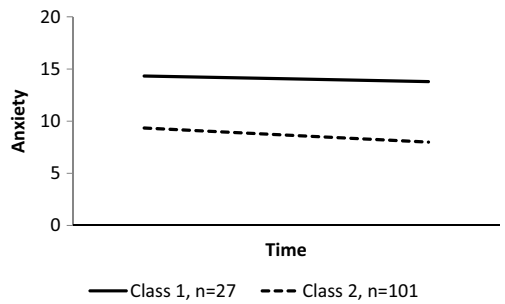

Fig. 1 Intercepts and slopes for the two classes identified by LGMM

(1) initial high anxiety and remaining high, (2) lower level anxiety and improving over time. These groups differ from results from similar analyses of cancer patient anxiety [5–7] in two main ways. Firstly, the previous studies have identified at least three distinct anxiety trajectory classes. Secondly, although 'stable-high' and 'recovering' classes are commonly identified in previous reports (as in this study), these two classes tend to have the same mean baseline scores in other studies. In contrast in the current study, the group in whom anxiety levels 'recovered' started from an overall lower baseline anxiety level.

The implication in the clinical setting is that men with prostate cancer with high-risk features after surgery and who demonstrate a high level of post-surgery anxiety in the post-operative period may have persistently high levels of anxiety over time. These findings suggest that this anxiety does not reduce naturally and may require interventions such as referral to a clinical psychologist or an oncological psychiatric service. A clinical pathway for the management of anxiety and depression in cancer patients has recently been developed [16] and provides more detailed guidance for health professionals in managing and supporting patients such as these.

The observed anxiety trajectories were not explained by any of the variables identified as potential predictors of distress in these men. The findings of the present study suggest that the only potential indicator of likely change of anxiety

Table 4 Results of binary logistic regression of the dichotomous trajectory variable on various covariates

	Odds ratio*	Wald	*p* value
Age	1.06	2.51	0.11
< year 10 vs. Year 12	0.81	0.08	0.77
< year 10 vs. TAFE	3.60	3.50	0.06
< year 10 vs. university	2.88	1.98	0.16
< year 10 vs. higher degree	3.20	2.06	0.15
Marital status	0.91	0.01	0.91
Country	0.95	0.04	0.84
Medical condition	1.27	0.20	0.65
Investigator specialty	0.66	0.56	0.46
Decision to participate in trial	3.48	1.02	0.31

*The odds ratio is the exponent of the unstandardised estimate from the logistic regression

over time is the initial anxiety-level post-surgery, noting that this cohort comprised men who were all given news of a poorer than expected prognosis following their operations. These findings might also apply to men having potentially curative treatment for higher risk prostate cancer with definitive radiotherapy, although this was not tested in this study.

In particular, a man's decision whether to join the clinical trial or not was unrelated to the likelihood of falling into the 'high and persistent' anxiety group. It is reassuring knowing that participating in the clinical trial did not appear to predict for a worse anxiety trajectory. In other words, the inherent uncertainty of the clinical trial, in which participants could not be assured that they were receiving a treatment path proven to be more effective than the other, did not seem to impact on men's anxiety. We did not collect qualitative data from the men involved, so can only speculate on the reasons for this finding. Perhaps, the nature of the trial (testing the timing of radiotherapy rather than two different treatments), assurances of referring clinicians that early salvage radiotherapy was likely to be as effective as adjuvant radiotherapy, the high-quality care received while participating in the trial (the "trial effect"), or increased expectations of treatment success because of trial participation helped alleviate any anxiety induced by trial participation [17].

It is possible that other variables for which data were not collected may have had some explanatory power. Nonetheless, based on the present data, we were not able to identify any disease characteristics that might indicate the trajectory of anxiety in men with prostate cancer with high-risk features after surgery. It is unclear whether this might be generalisable to other men having active treatment as, to the authors' knowledge, this has not been studied. Thus, for clinicians treating and following up men who have had prostate cancer, monitoring for anxiety, ideally with validated screening tools such as 'distress thermometers' [18], should be undertaken. At the very least, recognising the potentially persistent nature of high-level anxiety in these men will assist doctors and nurses caring for these men to be alert to this possibility and intervening where relevant.

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Compliance with ethical standards

Ethical approval was obtained from the Royal Prince Alfred Hospital Human Research Ethics Committee and from site-specific research governance bodies at each participating site (HREC/11/RPAH/433).

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Balderson N, Towell T (2003) The prevalence and predictors of psychological distress in men with prostate cancer who are seeking support. Br J Health Psychol 8:125–134
2. Steginga SK et al (2004) Prospective study of men's psychological and decision-related adjustment after treatment for localized prostate cancer. Urology 63(4):751–756
3. Watts S et al (2013) Depression and anxiety in prostate cancer: a systematic review and meta-analysis of prevalence rates. BMJ Open 4:3
4. Korfage IJ et al (2006) Anxiety and depression after prostate cancer diagnosis and treatment: 5-year follow-up. Br J Cancer 94(8):1093–1098
5. Dunn LB et al (2012) Trajectories of anxiety in oncology patients and family caregivers during and after radiation therapy. Eur J Oncol Nurs 16(1):1–9
6. Lam WWT et al (2010) Trajectories of psychological distress among Chinese women diagnosed with breast cancer. Psychooncology 19:1044–1051
7. Lam WWT, Ye M, Fielding R (2013) Trajectories of quality of life among Chinese patients diagnosed with nasopharyngeal cancer. PLoS One 7(9):e440022
8. Parker PA et al (2016) Relationship between illness uncertainty, anxiety, fear of progression and quality of life in men with favourable-risk prostate cancer undergoing active surveillance. BJU Int 117(3):469–477
9. Dieperink KB et al (2017) Male coping through a long-term cancer trajectory. Secondary outcomes from a RTC examining the effect of a multidisciplinary rehabilitation program (RePCa) among radiated men with prostate cancer. Acta Oncol 56(2):254–261
10. Dale W et al (2005) The role of anxiety in prostate carcinoma. Cancer 104(3):467–478
11. Pearse M et al (2014) A phase III trial to investigate the timing of radiotherapy for prostate cancer with high-risk features: background and rationale of the radiotherapy—Adjuvant Versus Early Salvage (RAVES) trial. BJU Int 113:7–12
12. Sundaresan P et al (2017) A randomised controlled trial evaluating the utility of a patient decision aid to improve clinical trial (RAVES 08.03) related decision-making. Radiother Oncol 125(1):124–129
13. Spielberger CD et al (1983) Manual for the State-Trait Anxiety Inventory. Consulting Psychologists Press, Palo Alto
14. Duncan TE, Duncan SC, Strycker LA (2006) An introduction to latent variable growth curve modeling, 2nd edn. Lawrence Erlbaum Associates, Mahwah
15. Muthén LK, Muthén BO (1998-2011) Mplus User's Guide. Sixth Edition. Los Angeles, CA: Muthén & Muthén
16. Butow P et al (2015) Clinical pathway for the screening, assessment and management of anxiety and depression in adult cancer patients: Australian guidelines. Psycho-Oncology 24(9):987–1001
17. Khoja L et al (2016) Does clinical trial participation improve outcomes in patients with ovarian cancer? ESMO Open 1(4):e000057
18. Chambers SK et al (2014) The validity of the distress thermometer in prostate cancer populations: the distress thermometer in prostate cancer. Psychooncology 23(2):195–203