Health Psychology

Seven-year distress trajectories in uveal melanoma survivors.

--Manuscript Draft--

Manuscript Number:	HEA-2022-3826R2
Full Title:	Seven-year distress trajectories in uveal melanoma survivors.
Abstract:	Objective: Severe or persistent distress is associated with poorer quality of life in cancer survivors. Distress follows distinct trajectories within different population sub-groups. Identifying characteristics and causes of trajectories can assist intervention development and targeting. In a seven-year study of uveal melanoma survivors, we aimed to characterise anxiety, depression and fear of cancer recurrence (FCR) trajectories, and whether concerns about symptoms and functional problems over the first three years of survivorship predict memberships of high distress trajectories. Method: In a closed cohort study, we used growth mixture modelling (GMM) to identify statistically optimal trajectories over 6, 12, 24, 36, 48, 60, 72 and 84-month timepoints post-treatment in 475 patients. We regressed trajectory memberships onto a three-year series of measures of concerns about symptoms and functional problems, controlling demographic, clinical and 6-month anxiety, depression or FCR indicators. Results: Anxiety, depression and FCR were represented by two class linear GMMs. The majority scored consistently low, but 17.5% showed consistently elevated anxiety, 10.9% consistently elevated depression and 19.4% consistently elevated FCR. Higher anxiety trajectory membership was predicted by greater concerns about symptoms at 6 and 24 months, higher depression trajectory membership by symptoms at 24 months and higher FCR trajectory membership by symptoms at 6 and 24 months and functional problems at 12 months. Conclusions: Much of the burden of persistent distress in cancer patients falls on a small proportion of survivors, whose distress is prospectively associated with concerns about symptoms and functional problems.
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Manuscript Classifications:	Anxiety; Cancer survivorship; Depression

Dear Professor Freedland

Please find attached our manuscript 'Identifying and predicting distress trajectories in uveal melanoma survivors over eight years', by Brown, Hope-Stone and Cherry, for your consideration for inclusion into Health Psychology.

The paper addresses a key topic in identifying discrete trajectories of distress and their predictors in subgroups of cancer patients in an eight-year prospective study utilising a large sample. The topic falls within the journal scope statement as we examine distributions of distress within a cancer population and how a time series of predictors may dynamically contribute to them. In particular, we draw attention to the large consecutive sample of 719 and the use of contemporary growth mixture approaches. Currently, there is a dearth of studies that provide long-term prediction of distress in survivors. We also draw attention to our use of a time-series of predictors that allow the capture of dynamic processes that may shape distress trajectories. Finally, we draw new implications for future research on processes contributing to distress and make pragmatic clinical recommendations.

Other papers from the same dataset are as follows:

Brown, S.L., Hope-Stone, L., Fisher, P., Hussein, R.M., Heimann, H., & Cherry, M.G. (2022). Mortality after the first two years of cancer survivorship: Associations between 24-month trajectories in patient reported outcomes and all-cause mortality in uveal melanoma. *Journal of Behavioral Medicine, 45*, 115-123. (IF=2.99) DOI: 10.1007/s10865-021-00252-8

Note: Trajectories referred to in this paper represent population means and do not use the latent class approach employed in the current submission.

Brown, S.L., Cherry, M.G., Hope-Stone, L., Heimann, H., & Damato, B. (2021). Fear of cancer recurrence and adverse cancer treatment outcomes: Predicting 2-5 year fear of recurrence from post-treatment symptoms and functional problems in uveal melanoma survivors. *Journal of Cancer Survivorship* DOI: 10.1007/s11764-021-01129-0Brown, S.L., Cherry, M.G., Hope-Stone, L., Heimann, H., & Damato, B. (2021a). Is accurate routine cancer prognostication psychologically harmful? 5-year effects of life expectancy prognostication in uveal melanoma survivors. *Journal of Cancer Survivorship* DOI: 10.1007/s11764-021-01036-4

Brown, S.L., Hope-Stone, L., Cherry, M.G., Hussein, R.M., Heimann, H., & Damato, B. (2020). Predictors of long-term anxiety and depression in Uveal Melanoma survivors: Cross-lagged five-year analysis. *Psycho-Oncology,* 5514. DOI: 10.1002/pon.5514

Yours Sincerely

Stephen Brown, Laura Hope-Stone and Gemma Cherry

Re:Health Psychology Ms. # HEA-2022-3826
Identifying and predicting distress trajectories in uveal melanoma survivors over eight years.

Many thanks for reviewing this resubmitted manuscript and for inviting a further resubmission. As previously, we have found the reviewing process to be enormously helpful and respond below.

On the manuscript, changes are in red font.

Editor-in-Chief: Thank you for responding to the previous comments. As often occurs, your manuscript expanded when you revised it, and it is now several pages over our 30-page limit. If you can eliminate two or three unnecessary references, that will reduce the length by one page. Also, since half of page 19 is blank, you can save a whole page by eliminating about a half page of text. There are a number of points in the text where you could save a line by eliminating a few words, and there are some blank lines around some of the headings that could be eliminated. Thus, it should be fairly easy to shorten the manuscript by at least two pages.

We have taken your advice on shortening the manuscript, and have reduced it by two pages (to 31 pages).

Associate Editor: The revised manuscript addresses many prior concerns. A few clarifications are requested.

1. Under Participants (page 7), it is stated that "Those agreeing to participate were surveyed using a printed questionnaire over nine observations...." There are only 8 observations in this analysis.

We have corrected this, and the text now reads eight observations (first paragraph, page 7)

2. The reader is directed to Appendices 2-4 for the results reported in the section on "Prediction of Trajectory Groups". Either I am not interpreting the tables presented in the appendices correctly, or there are errors in the numbers reported. For example, the consistently high anxiety trajectory was predicted by higher 6-month symptom scores, and the odds ratio is presented as 3.11, with 95% CI=1.29, 7.52 in the text (page 13). However, Appendix 2 shows the odds ratio (for 6-month symptom scores) as 2.66 with 95% CI= 1.17, 6.06. From what I can see, none of the results reported in that section on page 13 match the results presented in Appendices 2-4. Please resolve these inconsistencies.

We have investigated this discrepancy and corrected the tables in Appendices 2-4.

3. **Discussion section (page 15) - although general population means for the FCR measure are not likely to be available, it would be useful to note whether levels of FCR in this sample of uveal melanoma survivors are comparable to those observed in other samples of cancer patients, such as patients with breast cancer or a mixed sample of patients with different types of cancer**.

We have been able to find two studies that have used the instrument in uveal melanoma samples. This has now been included in the discussion:

'The FCR means of 3.32 and 2.20 (total mean=2.35) on the 4-point scale are similar to a mixed Finnish, Swedish and UK UM patient sample (Individual item means 2.20-2.25; Brandberg, et al., 2004) but higher than an Israeli UM patient sample (Individual item means 1.30-1.41; Frenkel, et al., 2018).' (first paragraph page 14)

4. Table 1 - there is a typo in reporting the percentage of patients who received proton beam radiotherapy (230.7%).

We have corrected the typo, thanks.

5. Figure 1 - it is indicated that 232 patients did <u>not</u> complete the study, but the numbers of those who died and those who dropped out add up to 243 (94 died, 149 dropped out). Does this mean that 232 of the 475 participants (or 48.8%) completed the study?

We have reconfigured and checked Figure 1 in line with suggestions made by Reviewer 2. The correct number of participants retained in the study is 243.

Reviewer #2: With regard to this revision, the authors re-analyzed the data and modified the manuscript based on comments and reviews. The clarification of the data source in the Methods section (Page 6, 7), and of the sampling and attrition analysis in the Results section (Page 14) have strengthened the transparency of this manuscript.

However, the arrow point in the sampling diagram (Figure 1) will still need to be adjusted to follow with CONSORT instructions (https://www.consort-statement.org/consort-statement/flow-diagram). It is suggested to show numbers of the loss-to-follow-up for each time point.

We have amended Figure 1 to be as consistent as possible with CONSORT guidance, allowing for the differences between our observational study and the intervention study typically described in the guidance.

More clinical implication may be added in the Discussion section, such as the time frame for routine screening of psychosocial distress in long-term cancer survivors and recommendation of follow-up for those who are at risks based on the findings.

To further address screening and follow-up, we have added some material to the final paragraph on page 17 (the paragraph consists of new and old text).

'As memberships of concerning trajectories were predicted by elevated anxiety, depression or FCR scores and symptoms and functional problems at six, 12 and 24 months, monitoring at these points should identify most at-risk cases. Once identified, alleviating distress is likely to be challenging. Recent reviews and meta-analyses have shown that intensive psychological interventions based on cognitive behavioural or acceptance and commitment principles delivered by therapists, show stronger and more enduring outcomes than psychological interventions designed for widespread implementation such as self-help materials'

Seven-year distress trajectories in uveal melanoma survivors.

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Author Notes

1. Stephen Brown (ORCID 0000 0002 6142 0995); conceptualisation, formal analysis, investigation, methodology, project administration, supervision, visualisation, writing original draft, writing review and editing
Laura Hope-Stone (ORCID 0000 0001 6069 7231); data curation, project administration, resources, writing review and editing
Mary Gemma Cherry (ORCID 0000 0001 9490 1747); validation, visualisation, writing review and editing
2. No changes in author affiliation.
3. Data are not publicly available because participants did not provide permission for publication of individual data. Data can be obtained from the first author. The authors do not have conflicts of interest. We acknowledge the assistance of Nicola van der Voort in data extraction and preparation.
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Abstract

Objective: Severe or persistent distress is associated with poorer quality of life in cancer survivors. Distress follows distinct trajectories within different population sub-groups. Identifying characteristics and causes of trajectories can assist intervention development and targeting. In a 7-year study of uveal melanoma survivors, we aimed to characterise anxiety, depression and fear of cancer recurrence (FCR) trajectories, and whether concerns about symptoms and functional problems over the first 3 years of survivorship predict memberships of high distress trajectories. **Method**: In a closed cohort study, we used growth mixture modelling (GMM) to identify statistically optimal trajectories over 6-, 12-, 24-, 36-, 48-, 60-, 72- and 84-month timepoints post-treatment in 475 patients. We regressed trajectory memberships onto a 3-year series of measures of concerns about symptoms and functional problems, controlling demographic, clinical and 6-month anxiety, depression or FCR indicators. **Results**: Anxiety, depression and FCR were represented by two class linear GMMs. The majority scored consistently low, but 17.5% showed consistently elevated anxiety, 10.9% consistently elevated depression and 19.4% consistently elevated FCR. Higher anxiety trajectory membership was predicted by greater concerns about symptoms at 6 and 24 months, higher depression trajectory membership by symptoms at 24 months and higher FCR trajectory membership by symptoms at 6 and 24 months and functional problems at 12 months. **Conclusions:** Much of the burden of persistent distress in cancer patients falls on a small proportion of survivors, whose distress is prospectively associated with concerns about symptoms and functional problems.

Key words: Psychological distress; fear of cancer recurrence; cancer survivorship; growth mixture modelling; uveal melanoma

Seven-year distress trajectories in uveal melanoma survivors.

Cancer survivors commonly experience high rates of distress. Approximately 15-25% are affected by clinically-significant anxiety and depression at any one time (Burgess, et al., 2005; Hoffman, et al., 2009; Vargas-Román, et al, 2020; Linden, 2012), whilst survivors can experience aversive and debilitating fear of cancer recurrence (FCR) that often requires clinical intervention (Fardell, et al., 2016). Anxiety, depression and FCR are associated with poorer quality of life (Reed, et al., 2020), increased mortality (Wang, et al., 2020), disease progression (Koch, et al., 2013) and poorer self-management of personal, medical and social challenges of survivorship (Manning, et al., 2011).

Distress is a normal, not necessarily pathological, response to cancer. It is more likely to be problematic if elevated for long periods (Diemling, et al., 2006). Prospective studies show that anxiety in cancer populations commonly peaks immediately after diagnosis then abates over the course of survivorship, whilst any post-diagnosis peak in depression is less pronounced and can subsequently increase or decrease (Burgess, et al., 2005). Less is known about FCR, although fears can persist at least five years into survivorship (Brown, et al., 2021a). However, population means often obscure important sub-population distress trajectories. Latent variable mixture modelling and growth mixture modelling (GMM) analyses can reveal empirically distinct trajectories within sub-groups. Majorities or pluralities of patients show low or transitory distress (Beesley, et al., 2020; Bidstrup, et al., 2015; Duening-Smit, et al., 2022; Costa, et al., 2019; Gonzales, et al., 2017; Kant, et al., 2018; McGinty, et al., 2016; Schapira, et al., 2022; Shim, 2020; Yang, et al., 2018). Smaller sub-groups show concerning trajectories of persistently high distress (Beesley, et al., 2020; Costa, et al., 2019; Duening-Smit, et al., 2022; Kant, et al., 2018; McGinty, et al., 2016; Shim, 2020; Yang, et al., 2018), initially low but increasing distress (Kant, et al., 2018; Schapira, et al., 2022), episodic increases and decreases of distress (Beesley, et al., 2020; Bidstrup, et al., 2015) or changes attributable to events such as

screening (McGinty, et al., 2016). An implication is that much of the distress burden is borne by relatively small numbers of survivors, which emphasises the importance of targeting preventive and ameliorative interventions.

Identifying trajectories of concern allows examination of risk factors for trajectory memberships by identifying predictors. If predictors are causal, interventions that modify them could positively influence personal distress trajectories. Further, a more fine-grained examination of potential risk factors becomes possible because associations between predictors and outcomes is exclusively based on discrimination between trajectory groups, not associations within those groups. However, few trajectory studies have examined risk factors. McGinty and colleagues (2016) found that breast cancer patients with higher FCR trajectories had lower baseline self-efficacy, and higher perceptions of illness risk and increased reassurance seeking. Duening-Smit et al. (2022) found that higher FCR trajectories in head and neck cancer patients were related to lower self-efficacy, higher passive coping and self-reassurance scores, and lower avoidance scores. Gonzales et al. (2017) found that baseline withholding of concerns and greater pain medication use in gynaecological cancer patients predicted depression, poorer quality of life and disability. Kant et al. (2018) found greater symptom burden and lower self-efficacy predict higher breast cancer distress trajectories.

Cancer survivors' concerns about physical symptoms and functional problems may constitute risk factors for higher distress trajectories. Cross-sectional studies show links between cancer symptoms and functional problems and psychological distress (Freeman-Gibb, et al., 2017; MacDonald, et al., 2021). Prospective (latent class and aggregate) studies find similar associations (Brown, et al., 2020; Kant, 2018; Whisenant, et al., 2019). Brown et al. (2021b) propose that temporal and somatic qualities of symptoms and functional problems, such as location, distinction, persistence and seriousness, induce people to infer cancer recurrence that may cause distress. Alternatively, symptoms and

functional problems may induce survivors to re-experience the initial physical and psychological traumas of cancer diagnosis and treatment (Freeman-Gibb, et al., 2017; MacDonald, et al., 2021).

Previous studies of distress trajectories in cancer have two methodological limitations. First, few studies extend over periods longer than the first two years of post-treatment survivorship. This could be problematic because challenges of survivorship develop and change as survivors move from immediate physical, psychological and social adjustments to longer-term living with the existential uncertainties of recurrence and potential foreshortening of healthy life expectancies (Hope-Stone, et al., 2015). Thus, it is unclear whether current findings, from relatively early survivorship, will apply later. Second, most studies employ time invariant predictors, using a single baseline set of predictors to predict trajectory group membership (Kant, et al., 2018; McGinty, et al., 2016). Yet, over the course of survivorship, changes in baseline predictor variables improve prediction of distress at later timepoints (Brown, et al., 2020), and it is likely that time varying predictors measured during survivorship will improve prediction of trajectories.

We aimed to identify the characteristics and predictors of distinct distress trajectories in uveal melanoma (UM) survivors. UM is the most common cancer of the eye. Primary treatment by enucleation (eye removal), radiotherapy or resection is usually successful with a low likelihood of local recurrence. However, treatments can cause ocular symptoms such as irritation, visual loss, and vision related functional problems attributable to peripheral vision and depth perception loss. Loss of visual function is associated with depression in UM and other eye disease populations (Hope-Stone, et al., 2019; Zhang, et al., 2013). In UM, ocular symptoms and functional problems are often not immediate but develop over survivorship, emphasising the importance of using time varying predictors.

As far as we are aware, this is the first study to examine the number and characteristics of cancer distress trajectories over long-term (seven years) survivorship using time-varying predictors. We operationalised distress as anxiety depression and FCR. We first identified the number and characteristics of trajectories in anxiety, depression and FCR by fitting latent class GMMs to a 7-year series of timepoints. We then examined associations between resultant trajectory sub-groups and a 3-year series of measures of concerns about symptoms and functional problems. We expected that initial values and later changes in concerns about symptoms and functional problem would predict memberships of higher anxiety, depression and FCR trajectory groups.

Method

Transparency and Openness

We conducted a secondary analysis of data from an audit of patient reported outcomes, approved by the Liverpool Central Ethics Committee (03/06/072/A). STROBE guidelines were followed in this report (von Elm, et al., 2007). Written consent was sought for research use of data, but not publication of individuals' data. The dataset can be obtained by written request from the first author. Materials were used as described in the text and citations. SPSS and R code are available in Appendix 1. Neither the study nor the analysis was pre-registered.

Participants

We approached a consecutive series of adult patients from England and Wales treated for posterior (choroid or ciliary body) UM between April 1st 2008 and August 31st 2012 at Liverpool Ocular Oncology Centre (LOOC). LOOC is one of three specialist centres in England and is the main referral centre for Northwest England and Wales, but many patients come from across the UK. As LOOC is the main UK provider of prognostic testing it attracts patients from other UK regions. Those agreeing to participate were

surveyed using a printed questionnaire over eight observations after diagnosis (6, 12, 24, 36, 48, 60, 72, and 84 months). Patients who gave written consent were posted questionnaires with postage-paid return envelopes at each timepoint. Three observations are required to permit estimation of non-linear growth curves, and participants who did not provide these were eliminated from the analysis. Re-entry into the study after missed observations was permitted. As this was a secondary analysis, we did not aim for a specific sample size.

Participants underwent either ruthenium plaque radiotherapy, proton beam radiotherapy, trans-scleral local resection, trans-retinal endoresection or enucleation (eye removal). Treatment protocols are described in Damato and Heimann (2013). These treatments commonly cause delayed ocular and visual symptoms and functional problems (Hope-Stone, et al., 2019). UM is associated with approximately 40% 10-year survival rate with death mainly attributable to metastatic melanoma. The probability of metastatic melanoma is largely determined by monosomy 3, a mutation involving the loss of one of the chromosome 3 pair. Disomy 3 is normal. These will be referred to in the text as C3 mutation and C3 non-mutation. A prognostic test, that includes C3 status, provides reliable prediction of life expectancy. The test shows good all-cause mortality prediction with C-statistics 0.79 to 0.80, and 0.81 sensitivity and 0.72 specificity predicting metastatic melanoma (Eleuteri, et al., 2021). Patients are offered prognostic testing, of which about 60% accept. A predicted curtailed life expectancy occurs in about 40-50% of tests. Thus, life expectancy estimates are known to many patients

Prognostic results were communicated by the ocular oncology team as an individualised risk of developing life-threatening metastatic disease over 10 years. Psychology input was offered to all patients by a health psychologist who provides follow-up psychoeducation, supportive and therapeutic services. Treatments were completed and test results communicated before the 6-month observation.

Measures

To measure FCR and participants' concerns about ocular irritation, visual impairments, headaches, and functional problems, we used scales embedded in the European Organisation for Research and Treatment for Cancer Ophthalmic Quality of Life questionnaire (EORTC QLQ-OPT 30; Brandberg, et al., 2004). The EORTC QLQ-OPT 30 is designed for UM and scales show good reliability and convergent and discriminant validity (Brandberg, et al., 2004; Chmielowska, et al., 2013). Response format for all items was *Not at all*, *A little*, *Quite a bit* and *Very much*, scored 1-4, respectively. All items were worded in terms of poorer outcomes. Scale scores represent item means.

FCR is operationalised as worry about local and secondary recurrence (Cronbach alphas across the nine time points ranged from .82 to .86). This scale was developed and used in this study before much of the FCR literature appeared, nonetheless it carries substantial similarities to current FCR measures (Humphris, et al., 2018). The scale comprised three items: 'Were you worried about your health in the future?'; 'Were you worried about the tumour recurring in the treated eye?' and 'Were you worried about the tumour recurring in other areas of your body?' A fourth item on concern about loss of the eye was excluded because it was not relevant to enucleated patients.

Symptom scales of the EORTC QLQ-OPT 30 are; ocular irritation (6 items, e.g., 'Were you troubled by discharge from the treated eye', Cronbach alphas across the nine timepoints; .70 - .77); visual symptoms (4 items e.g., 'Were you troubled by any defects in side vision', Cronbach's alphas; .72-.75); headache (single item 'Did you have headaches?'). The three symptom scales - ocular irritation, visual disturbance and headache - were intercorrelated at each observation with correlations ranging from .44 to .74. A confirmatory factor analysis testing a single latent factor model consisting of equally weighted subscales with fixed error covariances showed satisfactory fit, $X^2_{(2.65)}$=15.87, CFI=.98, RMSEA=.06. To minimise potential predictor collinearity, we

computed a single mean of the three subscales that we labelled visual and ocular symptoms. Functional limitations were measured by the EORTC QLQ-OPT 30 functional limitations scale (5 items, e.g., 'Difficulty seeing steps or pavements?' Cronbach's alphas; .92-.93).

Six-month anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) anxiety and depression subscales (Zigmond & Snaith, 1983). Subscales have seven items scored from 0 to 3 with higher scores signifying greater symptomology (range = 0-21, Cronbach alphas across the nine timepoints; anxiety .87-.88, depression .83-.87). Both predict diagnosed cases with good sensitivity and specificity, with a clinical cut-off of ≥7 (Vodermaier, et al., 2011).

Age, gender, treatment (enucleation versus other treatments (Hope-Stone, et al., 2019)), chromosome 3 status (C3 mutation, C3 non-mutation, not tested/ test failed) were taken from patient records.

Analysis Plan

After descriptive analyses were conducted, we identified latent trajectory classes in anxiety, depression and FCR by fitting 1-4 latent class GMMs. First, we fitted a single class model with random parameters and no covariates. To identify an optimal slope we fitted linear, curvilinear and quadratic slopes. Once the optimal slope model was identified for a single class, we fitted identical GMMs differing by incrementing latent class numbers up to four classes. We used the smallest Bayesian Information Criterion (BIC; Nylund, et al., 2007; Proust-Lima, et al., 2017) to identify the optimal solution. We counteracted potential overfitting by monitoring near-empty classes and rejecting those models (Nasserinejad, et al., 2017). Models of greater than four classes all had two or more empty classes, and thus were not reported. GMM analyses were conducted using the 'hlme' function of the 'lcmm' package in R (Proust-Lima, et al., 2017).

Participants' predicted class memberships were obtained from the above analysis. Logistic regression analyses were used to regress concerns about symptoms and functional problems onto class memberships. Age, gender, treatment and chromosome 3 status (Brown, et al., 2020) are well established predictors of anxiety, depression and FCR (Brown, et al., 2020; Brown, et al., 2021a; Brown, et al., 2021b). These were entered as covariates at stage 1 of the analysis. Enucleation was coded as; enucleation=1 and other treatments=0. Chromosome 3 status was split into two dummy variables. C3 mutation was compared to a combined C3 non-mutation and not tested/test failed category. C3 non-mutation was compared to a combined C3 mutation and not tested/test failed category. The 6-month initial value of the outcome variable (anxiety, depression or FCR) was also included at stage 1. This enables prediction of the slope of trajectories from symptom and functional concerns independently from the starting values of the trajectories. 6-, 12-, 24- and 36-month observations of symptoms and functional problems were entered respectively as stages 2-5. Staging of the entry of predictor variables allows control of autoregressive effects from previous entries, thus any prediction at each stage is attributable to changes in the predictor variable from the previous stage. Descriptive, logistic and multinomial logistic regression analyses were conducted in SPSS v27.

The percentage of missing values was 22.69%, below the 40% upper threshold for viable data replacement (Jakobsen, et al., 2017). For the GMM analysis, full information maximum likelihood was used to replace missing data (Proust-Lima et al., 2017). Unweighted multiple imputation was used to generate imputed datasets in SPSS for the logistic regression analyses (Von Hippel, 2018). Maximum likelihood and multiple imputation approaches provide similar outcomes, with neither likely to show bias where data are missing at random and the data set represents the population (Lee & Sui, 2021).

Unfortunately, a large number of participants died during the study. Based on Wen, et al. (2018), a variable representing the number of months the participant was alive

was used as a covariate for missing data estimation (those who survived the study were allocated 84 months). Post-mortem imputations were consequently removed from data sets. All-cause mortality was ascertained by matching participant's names and dates of birth to information provided by the England and Wales death registry. We examined attrition-related bias through correlations between the proportion of timepoints missed per participant and 6-month study variables. Separate proportions of missed timepoints were calculated for participants who were alive at the time and who had died.

Results

In total, 644 participants of 881 patients meeting eligibility criteria contributed data at 6 months, of which 475 contributed at least three timepoints. Mean age was 69.37 years (*SD*=12.39); 232 (48.8%) were female. Table 1 shows full demographic, clinical and treatment characteristics, and Figure 1 shows the participant flowchart.

Model Selection and Trajectory Characteristics

Linear parameters (weights of 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 for consecutive timepoints) provided best fitting single class models for each outcome. Table 2 shows that two-group solutions had lowest BIC values and acceptable group sizes for anxiety, depression and FCR (Nylund, et al., 2007). Figure 2 shows a *consistently low* anxiety trajectory (82.5% of participants) with an initial mean of 4.21. These scores slightly declined over the study. The remainder (17.5%) showed a *consistently high* trajectory with an initial mean of 10.56 which is greater than the HADS cut-off of ≥7 indicating clinical concern (Vodermaier, et al., 2011).

For depression, the majority (89.1%) had *consistently low* scores, with an initial mean of 2.56. The remaining 10.9% of participants exhibited *consistently high* scores with an initial mean of 8.18 that increased during the study (Figure 3). The majority (80.6%) had a *low* FCR trajectory with an initial mean of 2.20 on a 4-point scale. A *high* FCR

trajectory (19.4%) had an initial mean of 3.32 (Figure 4). Both high and low FCR trajectories showed some evidence of receding over time.

Memberships of higher trajectory groups were correlated over the three outcome variables, without full overlap. Phi coefficients were .42 between anxiety and depression, .386 between anxiety and FCR and .23 between depression and FCR. Cohen (1988) describes estimates of .30-.50 as a medium effect size and .29 or less as a small effect size.

Prediction of Trajectory Groups.

Appendices 2-4 show predictors of outcome trajectories controlling demographic, treatment, chromosome 3 status and the initial 6-month trajectory variables. The logistic regression model predicted membership of the *consistently high* anxiety trajectory (Model $\chi^2(16)$=195.60 - 209.51, -1 Log Likelihood=230.65 – 240.58, Cox & Snell R^2=.338-.357, Nagelkerke R^2=.5747-.590). The *consistently high* trajectory was predicted by higher 6-month (Exp (β)=3.11, 95%C.I=1.29, 7.52) and 24-month (Exp (β)=5.91, 95%C.I=1.36, 25.63) symptom scores (See Appendix 2). A C3 non-mutation was associated with lower likelihood of anxiety trajectory membership (Exp (β)=0.44, 95%C.I=0.19, 0.99).

The logistic regression model predicted membership of the *consistently high* depression trajectory (Model $\chi^2(16)$=141.49 - 155.51.66, -1 Log Likelihood=172.63 - 186.66, Cox & Snell R^2=.258 - .269, Nagelkerke R^2=.516-.549). The *consistently high* trajectory was predicted by higher symptom scores at 24 months (Exp (β)=6.91, 95%C.I=1.59, 30.07; Appendix 3). The logistic regression model predicted membership of the *high* FCR trajectory (Model $\chi^2(16)$=172.19 – 176.39, -1 Log Likelihood=291.56 – 295.58.48, Cox & Snell $R^{2=}$.304 - .309, Nagelkerke R^2=.486 - .494). The *consistently high* trajectory was predicted by higher 6-month symptoms (Exp (β)=2.31, 95%C.I=1.03, 5.18), 12-month functional problems (Exp (β)=2.92, 95%C.I=1.32, 6.44) and 24-month symptoms (Exp (β)=5.84, 95%C.I=1.54, 22.19; Appendix 4).

Inclusion Bias and Attrition Analysis

The 169 excluded participants showed higher 6-month depression scores (4.25, *SD*=4.03 vs 3.16, *SD*=3.23, *t*=3.44, *df*=277.48, $p<.05$) and were less likely to have a C3 non-mutation prognostic testing outcome (18.9% versus 28.6%, χ^2, 1 *df*, =7.22, $p<.05$) than the 475 included participants. Participants provided data at 2,937 at a possible 3,800 timepoints (77.29%). The median timepoints contributed by each participant was seven of a possible eight (interquartile range=3). Unfortunately, 94 participants died during the study, explaining 296 of the missing timepoints. The proportion of missed timepoints for living participants was associated with younger age ($r=-0.21$, $p<.01$) and lower 6-month functional problem scores ($r=-0.11$, $p<.05$). Missing timepoints attributable to death were associated with older age ($r_{(rho)}=0.18$, $p<.05$), enucleation ($r_{(rho)}=0.29$, $p<.05$), C3 mutation ($r_{(rho)}=0.33$, $p<.05$), C3 non-mutation ($r_{(rho)}=-0.25$, $p<.05$), higher 6-month depression scores ($r_{(rho)}=0.10$, $p<.05$) and lower 6-month functional problem scores ($r_{(rho)}=0.21$, $p<.05$).

Discussion

This study makes two contributions. First, we confirmed previously reported trajectories of high anxiety, depression and FCR scores in minorities of cancer survivors, and in addition showed that these persisted at least seven years into survivorship. Second, we showed that higher trajectory memberships could be predicted by measures of participants' concerns about symptoms and functional problems both at the initial 6-month timepoint and also by changes in these measures during the subsequent two and a half years.

Similar to previous studies (Beesley, et al., 2020; Bidstrup, et al., 2015; Costa, et al., 2019; Duening-Smit, et al., 2022; Gonzales, et al., 2017; Kant, et al., 2018; McGinty, et al., 2016; Shim, 2020), large majorities of our participants experienced relatively low anxiety, depression or FCR. Smaller groups of participants showed trajectories characterised by higher distress. The initial high and low anxiety trajectory means of 10.56

and 4.21 (total mean=5.07) are substantially higher and lower, respectively, than age-matched UK population norm of 6.14 (Crawford, et al., 2001). Similarly, the depression means of 8.18 and 2.56 (total mean=3.16) are higher and lower than the population norm of 3.68 (Crawford, et al. 2001). It is noticeable that the overall means did not exceed population norms, and possible that a similar trajectory structure to our sample exists in non-cancer populations. The FCR means of 3.32 and 2.20 (total mean=2.35) on the 4-point scale are similar to a mixed Finnish, Swedish and UK UM patient sample (Individual item means 2.20-2.25; Brandberg, et al., 2004) but higher than an Israeli UM patient sample (Individual item means 1.30-1.41; Frenkel, et al., 2018).

Higher trajectories are concerning both in their extremity and persistence. Higher anxiety and depression trajectories showed means well above the HADS cut-off for clinical concern of ≥7 (Vodermaier, et al., 2011), whilst the initial mean of the high FCR trajectory was close to the highest possible score of 4. Higher scoring trajectories were enduring, with only the *high* FCR trajectory showing evidence of improvement over time. These findings suggest that most of the burden of distress is experienced by relatively small groups of survivors, but these groups experience distress strongly and chronically.

Individuals' trajectories are, however, not fixed, but represent dynamic patterns that emerge over time, possibly in response to changes in concerns about symptoms and functional problems. Our identification of these potential risk factors may help to understand causes of higher trajectories and permit early prediction of their memberships. Baseline (6-month) symptom concerns predicted higher trajectory memberships for anxiety and FCR. As the initial 6-month observation of each trajectory was controlled, trajectory membership could not influence 6-month symptom concerns. This strengthens, although does not prove, the inference that 6-month concerns influenced individuals' subsequent trajectories. Worsening of concerns about symptoms and functional problems over the succeeding two and a half years further predicted higher depression and FCR

trajectory memberships. This suggests that individuals' higher trajectories are dynamically maintained over time by these concerns, and may potentially be curtailed by interventions that reduce concerns. It should be noted though, that we did not control anxiety after the 6-month timepoint. Thus, we cannot eliminate the interpretation that anxiety causes later concerns measured at the 24 and 36-month timepoints.

Findings are consistent with longitudinal (non-latent trajectory) studies linking concerns about symptoms and functional problems to distress (Brown, et al., 2020; MacDonald, et al., 2021; Whisenant, et al., 2019). Concerns may emerge when survivors view symptoms and functional problems as manifestations of recurrent disease or as unwelcome reminders of psychological traumas associated with their cancer experience (Freeman-Gibb, et al., 2017). For example, the FCR literature suggests that somatic experiences of symptoms and functional problems may activate negative assumptions about illness control, consequences, severity and identity and existential implications (Brown, et al., 2021a; Curran, et al., 2020; Fardell, et al., 2016). Prospective tests of these mediators will provide important understandings of the origins of concerns, and why they may cause distress. Theoretical models also suggest that the emergence of concerns may be moderated by negative metacognitive beliefs or intolerance of uncertainty (Curran, et al., 2020; Fardell, et al., 2016), which will give further indications of their origins.

Although superficially similar in shape, trajectories for anxiety, depression and FCR did not represent a homogenous subgroup of participants. Relationships between memberships showed small to medium effect sizes, indicating associations but also substantial independence. Higher trajectory memberships differed numerically with more participants occupying higher anxiety and FCR trajectories than depression. We see these patterns as reflecting specific challenges of UM treatment and survivorship. Primary treatments are generally successful and brief, and, therefore, arguably less physically and emotionally challenging than prolonged treatments such as chemotherapy, immunotherapy

and external beam radiotherapy. Instead, challenges are future-oriented and existential, concerning truncated life expectancy. Thus, future-oriented emotions such as anxiety and fear (Eysenck, et al, 2006) may be more common. Further, FCR appeared to be more responsive to symptoms and functional problems. This may also explain why symptom concerns were generally stronger predictors of higher trajectories than functional concerns. Anxiety, depression and FCR trajectories may benefit from separate conceptualisations, and their importance can differ across specific challenges of other cancers.

Previous studies have found rapid (usually downward) changes in trajectories in small numbers of participants (Beesley, et al., 2020; Kant, et al., 2018). We did not replicate such changes. This may be attributable to several factors. Later survivorship may simply be characterised by stability with only gradual trajectory changes. Other explanations are methodological. Change trajectories in previous research involved numerically small groups, and failure to replicate these may reflect inherent difficulties in reliably detecting trajectories with low numbers (Nasserinejad, et al., 2017). We note that other studies have not found them (Costa, et al., 2019; Duening-Smit, et al., 2022; Gonzales, et al., 2017; McGinty, et al., 2016; Shim, 2020; Yang, et al., 2018). Also, we predominantly made yearly observations and may have missed any rapid changes. All previous studies used shorter between-observation latencies.

Clinical and prognostic variables did not strongly predict trajectories. These are not consistent predictors of distress across the UM literature (Davies, et al., 2022). One reason is that treatments do not entail as great a burden as other cancer treatments. Enucleation can cause trauma, feelings of loss and functional impairment, but, as previously noted, few participants underwent prolonged treatment regimens. Second, the impact of a poor prognosis may be muted; survivors with good prognoses can fail to accept that recurrence risk is low, and, conversely, those with poor prognoses sometimes find alternative ways of building hope for their futures (Hope-Stone, et al., 2015).

This study has limitations. First, our observations started at six months, thus we did not take genuine baseline observations. Consequently, we may have missed shifts in outcome measures, such as reductions in anxiety, occurring soon after diagnosis (Bidstrup, et al., 2015). A second limitation is that measures were not taken before cancer was suspected. Thus, it is unclear whether trajectories were attributable to UM or existed before diagnosis. Participants who failed to meet the three-observation eligibility criterion showed higher 6-month depression scores than included participants. Their exclusion probably reduced our estimate of high depression trajectory membership and may have biased prediction of this trajectory. Many participants failed to complete eight observations, with only 51% completing the final timepoint. The proportion of missed timepoints (whilst alive) was associated with younger age and lower functional problem scores at six months. This is unlikely to bias trajectory estimation (which is not affected by functional problem scores), but may bias estimation of links between functional problems and trajectory memberships. There is added uncertainty about attrition bias because we do not know the causes of individual participants' dropout except when the participant died.

Findings warrant two recommendations. First, interventions may best be focussed on relatively small sub-populations where distress is already severe and chronic. As memberships of concerning trajectories were predicted by elevated anxiety, depression or FCR scores and symptoms and functional problems at six, 12 and 24 months, monitoring at these points should identify at-risk cases. Once identified, alleviating distress is likely to be challenging. Recent reviews and meta-analyses have shown that intensive psychological interventions based on cognitive behavioural or acceptance and commitment principles delivered by therapists, show stronger and more enduring outcomes than psychological interventions designed for widespread implementation such as self-help materials (Park & Lim, 2022; Zhao, et al., 2021). Thus, targeted intensive interventions may be effective, particularly if administered early. Second, concerns about symptoms and

functional problems might contribute to stable patterns of anxiety, depression and FCR. Based on Brown et al. (2021b), one objective is to prevent survivors from making problematic inferences about symptoms and functional problems. Interventions currently used to prepare patients for stressful medical procedures explain the nature and rationale for procedures and likely experiential consequences, thus establishing non-threatening schemas that prevent catastrophising (Suls & Wan, 1989). These might be useful if adapted and implemented before symptoms and functional problems occur.

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Table 1

Sample Parameters of Demographic, Clinical and Chromosome 3 Status Variables.

	Frequency or Mean
Age	69.37 (SD 12.38)
Gender	
Male	243 (51.2%)
Female	232 (48.8%)
Employment status	
Employed	170 (35.8%)
Homemaker	16 (3.4%)
Retired	237 (49.9%)
Sick leave/Medically retired	20 (4.32%)
Other	24 (5.1%)
Not known	8 (1.7%)
Marital status	
Married or co-habiting	355 (74.7%)
Separated	29 (6.31%)
Widowed	61 (12.8%)
Single	28 (5.9%)
Not known	2 (0.4%)
Eye	
Left	240 (50.5%)
Right	235 (49.5%)
Treatment	
Enucleation	118 (24.7%)
Plaque radiotherapy	216 (45.5%)
Proton beam radiotherapy	100 (21.1%)
Resection	26 (5.5%)
Other	15 (3.2%)
Chromosome 3 status	
C3 mutation	142 (29.9%)
C3 non-mutation	131 (27.6%)
Not tested/fail	202 (42.5%)

Table 2

Negative Log Likelihood, Bayesian Information Criterion and Group Sizes for 1-4 Latent Class Models of Anxiety, Depression and Fear of Cancer Recurrence Trajectories.

	Classes	-1 Log likelihood	*df*	BIC	Group membership
Anxiety	1	8473.784	6	16986.11	100
	2	8434.063	9	16925.94	82.49, 17.51
	3	8434.063	12	16945.20	79.29, 20.70, 0.00
	4	8434.063	15	16964.47	78.44, 0.00, 5.28, 16.27
Depression	1	7884.917	6	15808.37	100
	2	7806.460	9	15670.73	89.12, 10.87
	3	7806.460	12	15690.00	88.47, 0.00, 21.53
	4	7806.460	15	15709.27	86.85, 0.00, 23.15, 0.00
Fear Cancer Recurrence	1	3201.752	6	6442.043	100
	2	3165.050	9	6387.910	80.38, 20.19
	3	3165.050	12	6407.180	76.94, 23.05, 0.00
	4	3165.050	15	6426.449	0.00, 75.00, 25.00, 0.00

Figure 1

Participant Flowchart

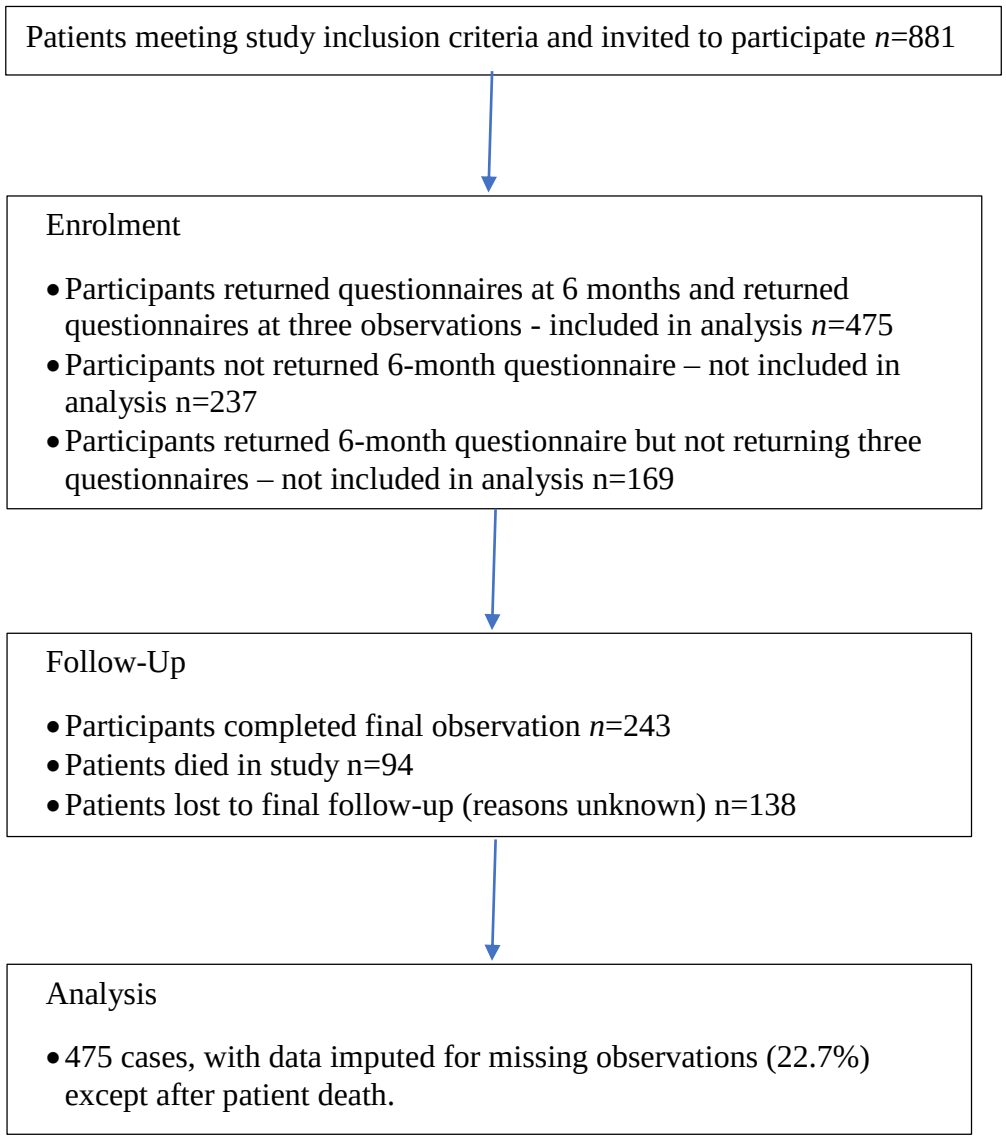
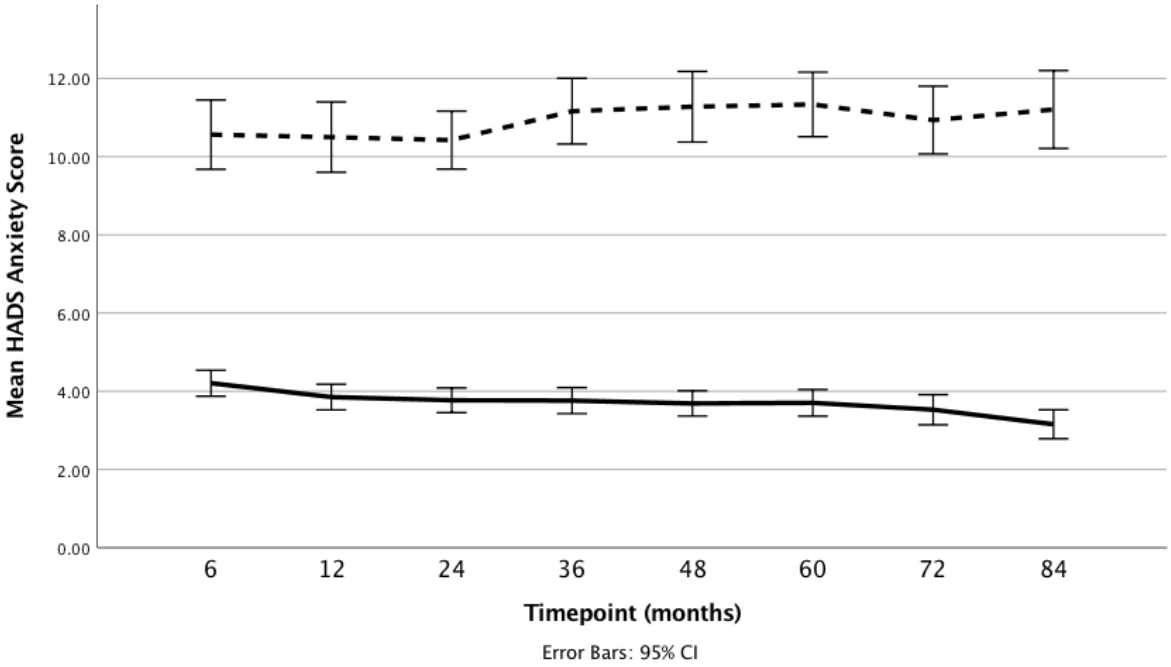


Figure 2

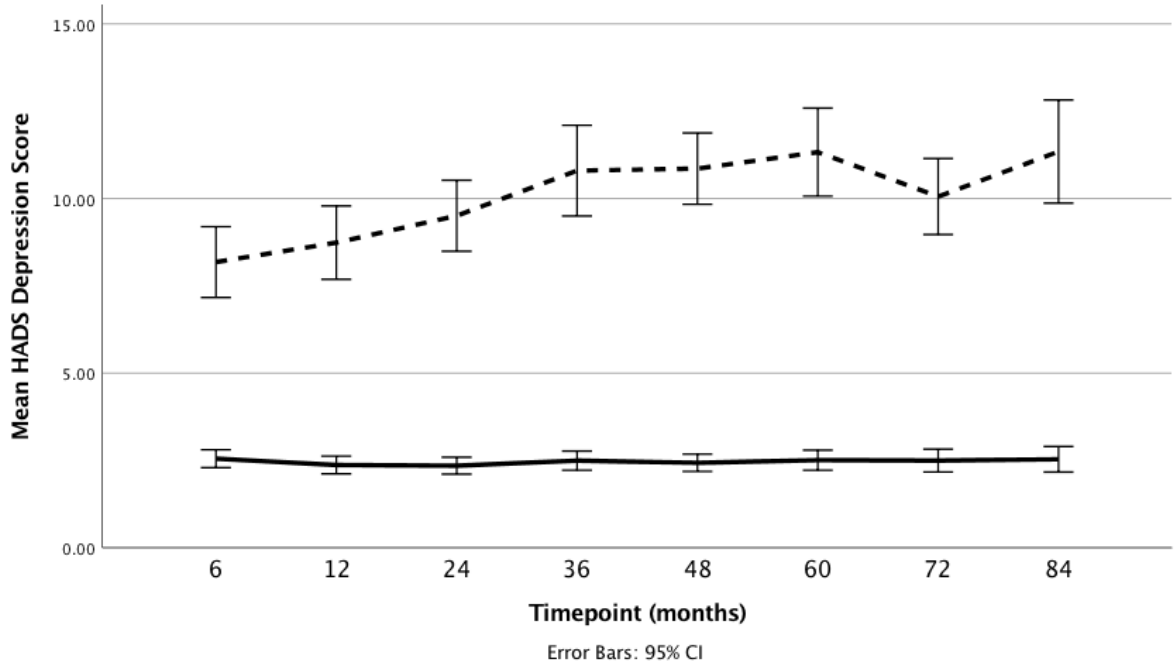
HADS Anxiety Trajectories Over Seven Years



Dotted line refers to consistently high mean scores, solid line consistently low scores.

Figure 3

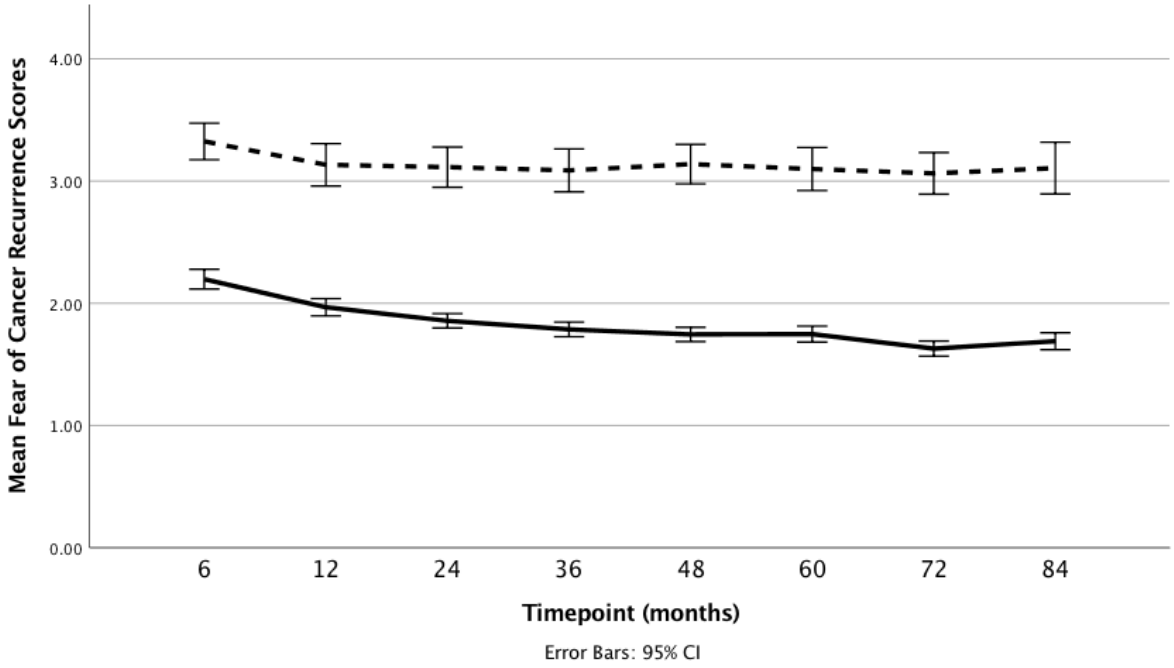
HADS Depression Trajectories Over Seven Years



Dotted line refers to consistently high mean scores, solid line consistently low scores.

Figure 4

Fear of Cancer Recurrence Trajectories Over Seven Years



Dotted line refers to consistently high mean scores, the solid line consistently low scores.

Seven-year distress trajectories in uveal melanoma survivors.

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1. Stephen Brown (ORCID 0000 0002 6142 0995); conceptualisation, formal analysis, investigation, methodology, project administration, supervision, visualisation, writing original draft, writing review and editing
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2. No changes in author affiliation.
3. Data are not publicly available because participants did not provide permission for publication of individual data. Data can be obtained from the first author. The authors do not have conflicts of interest. We acknowledge the assistance of Nicola van der Voort in data extraction and preparation.
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Abstract

Objective: Severe or persistent distress is associated with poorer quality of life in cancer survivors. Distress follows distinct trajectories within different population sub-groups. Identifying characteristics and causes of trajectories can assist intervention development and targeting. In a 7-year study of uveal melanoma survivors, we aimed to characterise anxiety, depression and fear of cancer recurrence (FCR) trajectories, and whether concerns about symptoms and functional problems over the first 3 years of survivorship predict memberships of high distress trajectories. **Method**: In a closed cohort study, we used growth mixture modelling (GMM) to identify statistically optimal trajectories over 6-, 12-, 24-, 36-, 48-, 60-, 72- and 84-month timepoints post-treatment in 475 patients. We regressed trajectory memberships onto a 3-year series of measures of concerns about symptoms and functional problems, controlling demographic, clinical and 6-month anxiety, depression or FCR indicators. **Results**: Anxiety, depression and FCR were represented by two class linear GMMs. The majority scored consistently low, but 17.5% showed consistently elevated anxiety, 10.9% consistently elevated depression and 19.4% consistently elevated FCR. Higher anxiety trajectory membership was predicted by greater concerns about symptoms at 6 and 24 months, higher depression trajectory membership by symptoms at 24 months and higher FCR trajectory membership by symptoms at 6 and 24 months and functional problems at 12 months. **Conclusions:** Much of the burden of persistent distress in cancer patients falls on a small proportion of survivors, whose distress is prospectively associated with concerns about symptoms and functional problems.

Key words: Psychological distress; fear of cancer recurrence; cancer survivorship; growth mixture modelling; uveal melanoma

Seven-year distress trajectories in uveal melanoma survivors.

Cancer survivors commonly experience high rates of distress. Approximately 15-25% are affected by clinically-significant anxiety and depression at any one time (Burgess, et al., 2005; Hoffman, et al., 2009; Vargas-Román, et al, 2020; Linden, 2012), whilst survivors can experience aversive and debilitating fear of cancer recurrence (FCR) that often requires clinical intervention (Fardell, et al., 2016). Anxiety, depression and FCR are associated with poorer quality of life (Reed, et al., 2020), increased mortality (Wang, et al., 2020), disease progression (Koch, et al., 2013) and poorer self-management of personal, medical and social challenges of survivorship (Manning, et al., 2011).

Distress is a normal, not necessarily pathological, response to cancer. It is more likely to be problematic if elevated for long periods (Diemling, et al., 2006). Prospective studies show that anxiety in cancer populations commonly peaks immediately after diagnosis then abates over the course of survivorship, whilst any post-diagnosis peak in depression is less pronounced and can subsequently increase or decrease (Burgess, et al., 2005). Less is known about FCR, although fears can persist at least five years into survivorship (Brown, et al., 2021a). However, population means often obscure important sub-population distress trajectories. Latent variable mixture modelling and growth mixture modelling (GMM) analyses can reveal empirically distinct trajectories within sub-groups. Majorities or pluralities of patients show low or transitory distress (Beesley, et al., 2020; Bidstrup, et al., 2015; Duening-Smit, et al., 2022; Costa, et al., 2019; Gonzales, et al., 2017; Kant, et al., 2018; McGinty, et al., 2016; Schapira, et al., 2022; Shim, 2020; Yang, et al., 2018). Smaller sub-groups show concerning trajectories of persistently high distress (Beesley, et al., 2020; Costa, et al., 2019; Duening-Smit, et al., 2022; Kant, et al., 2018; McGinty, et al., 2016; Shim, 2020; Yang, et al., 2018), initially low but increasing distress (Kant, et al., 2018; Schapira, et al., 2022), episodic increases and decreases of distress (Beesley, et al., 2020; Bidstrup, et al., 2015) or changes attributable to events such as

screening (McGinty, et al., 2016). An implication is that much of the distress burden is borne by relatively small numbers of survivors, which emphasises the importance of targeting preventive and ameliorative interventions.

Identifying trajectories of concern allows examination of risk factors for trajectory memberships by identifying predictors. If predictors are causal, interventions that modify them could positively influence personal distress trajectories. Further, a more fine-grained examination of potential risk factors becomes possible because associations between predictors and outcomes is exclusively based on discrimination between trajectory groups, not associations within those groups. However, few trajectory studies have examined risk factors. McGinty and colleagues (2016) found that breast cancer patients with higher FCR trajectories had lower baseline self-efficacy, and higher perceptions of illness risk and increased reassurance seeking. Duening-Smit et al. (2022) found that higher FCR trajectories in head and neck cancer patients were related to lower self-efficacy, higher passive coping and self-reassurance scores, and lower avoidance scores. Gonzales et al. (2017) found that baseline withholding of concerns and greater pain medication use in gynaecological cancer patients predicted depression, poorer quality of life and disability. Kant et al. (2018) found greater symptom burden and lower self-efficacy predict higher breast cancer distress trajectories.

Cancer survivors' concerns about physical symptoms and functional problems may constitute risk factors for higher distress trajectories. Cross-sectional studies show links between cancer symptoms and functional problems and psychological distress (Freeman-Gibb, et al., 2017; MacDonald, et al., 2021). Prospective (latent class and aggregate) studies find similar associations (Brown, et al., 2020; Kant, 2018; Whisenant, et al., 2019). Brown et al. (2021b) propose that temporal and somatic qualities of symptoms and functional problems, such as location, distinction, persistence and seriousness, induce people to infer cancer recurrence that may cause distress. Alternatively, symptoms and

functional problems may induce survivors to re-experience the initial physical and psychological traumas of cancer diagnosis and treatment (Freeman-Gibb, et al., 2017; MacDonald, et al., 2021).

Previous studies of distress trajectories in cancer have two methodological limitations. First, few studies extend over periods longer than the first two years of post-treatment survivorship. This could be problematic because challenges of survivorship develop and change as survivors move from immediate physical, psychological and social adjustments to longer-term living with the existential uncertainties of recurrence and potential foreshortening of healthy life expectancies (Hope-Stone, et al., 2015). Thus, it is unclear whether current findings, from relatively early survivorship, will apply later. Second, most studies employ time invariant predictors, using a single baseline set of predictors to predict trajectory group membership (Kant, et al., 2018; McGinty, et al., 2016). Yet, over the course of survivorship, changes in baseline predictor variables improve prediction of distress at later timepoints (Brown, et al., 2020), and it is likely that time varying predictors measured during survivorship will improve prediction of trajectories.

We aimed to identify the characteristics and predictors of distinct distress trajectories in uveal melanoma (UM) survivors. UM is the most common cancer of the eye. Primary treatment by enucleation (eye removal), radiotherapy or resection is usually successful with a low likelihood of local recurrence. However, treatments can cause ocular symptoms such as irritation, visual loss, and vision related functional problems attributable to peripheral vision and depth perception loss. Loss of visual function is associated with depression in UM and other eye disease populations (Hope-Stone, et al., 2019; Zhang, et al., 2013). In UM, ocular symptoms and functional problems are often not immediate but develop over survivorship, emphasising the importance of using time varying predictors.

As far as we are aware, this is the first study to examine the number and characteristics of cancer distress trajectories over long-term (seven years) survivorship using time-varying predictors. We operationalised distress as anxiety depression and FCR. We first identified the number and characteristics of trajectories in anxiety, depression and FCR by fitting latent class GMMs to a 7-year series of timepoints. We then examined associations between resultant trajectory sub-groups and a 3-year series of measures of concerns about symptoms and functional problems. We expected that initial values and later changes in concerns about symptoms and functional problem would predict memberships of higher anxiety, depression and FCR trajectory groups.

Method

Transparency and Openness

We conducted a secondary analysis of data from an audit of patient reported outcomes, approved by the Liverpool Central Ethics Committee (03/06/072/A). STROBE guidelines were followed in this report (von Elm, et al., 2007). Written consent was sought for research use of data, but not publication of individuals' data. The dataset can be obtained by written request from the first author. Materials were used as described in the text and citations. SPSS and R code are available in Appendix 1. Neither the study nor the analysis was pre-registered.

Participants

We approached a consecutive series of adult patients from England and Wales treated for posterior (choroid or ciliary body) UM between April 1st 2008 and August 31st 2012 at Liverpool Ocular Oncology Centre (LOOC). LOOC is one of three specialist centres in England and is the main referral centre for Northwest England and Wales, but many patients come from across the UK. As LOOC is the main UK provider of prognostic testing it attracts patients from other UK regions. Those agreeing to participate were

surveyed using a printed questionnaire over eight observations after diagnosis (6, 12, 24, 36, 48, 60, 72, and 84 months). Patients who gave written consent were posted questionnaires with postage-paid return envelopes at each timepoint. Three observations are required to permit estimation of non-linear growth curves, and participants who did not provide these were eliminated from the analysis. Re-entry into the study after missed observations was permitted. As this was a secondary analysis, we did not aim for a specific sample size.

Participants underwent either ruthenium plaque radiotherapy, proton beam radiotherapy, trans-scleral local resection, trans-retinal endoresection or enucleation (eye removal). Treatment protocols are described in Damato and Heimann (2013). These treatments commonly cause delayed ocular and visual symptoms and functional problems (Hope-Stone, et al., 2019). UM is associated with approximately 40% 10-year survival rate with death mainly attributable to metastatic melanoma. The probability of metastatic melanoma is largely determined by monosomy 3, a mutation involving the loss of one of the chromosome 3 pair. Disomy 3 is normal. These will be referred to in the text as C3 mutation and C3 non-mutation. A prognostic test, that includes C3 status, provides reliable prediction of life expectancy. The test shows good all-cause mortality prediction with C-statistics 0.79 to 0.80, and 0.81 sensitivity and 0.72 specificity predicting metastatic melanoma (Eleuteri, et al., 2021). Patients are offered prognostic testing, of which about 60% accept. A predicted curtailed life expectancy occurs in about 40-50% of tests. Thus, life expectancy estimates are known to many patients

Prognostic results were communicated by the ocular oncology team as an individualised risk of developing life-threatening metastatic disease over 10 years. Psychology input was offered to all patients by a health psychologist who provides follow-up psychoeducation, supportive and therapeutic services. Treatments were completed and test results communicated before the 6-month observation.

Measures

To measure FCR and participants' concerns about ocular irritation, visual impairments, headaches, and functional problems, we used scales embedded in the European Organisation for Research and Treatment for Cancer Ophthalmic Quality of Life questionnaire (EORTC QLQ-OPT 30; Brandberg, et al., 2004). The EORTC QLQ-OPT 30 is designed for UM and scales show good reliability and convergent and discriminant validity (Brandberg, et al., 2004; Chmielowska, et al., 2013). Response format for all items was *Not at all*, *A little*, *Quite a bit* and *Very much*, scored 1-4, respectively. All items were worded in terms of poorer outcomes. Scale scores represent item means.

FCR is operationalised as worry about local and secondary recurrence (Cronbach alphas across the nine time points ranged from .82 to .86). This scale was developed and used in this study before much of the FCR literature appeared, nonetheless it carries substantial similarities to current FCR measures (Humphris, et al., 2018). The scale comprised three items: 'Were you worried about your health in the future?'; 'Were you worried about the tumour recurring in the treated eye?' and 'Were you worried about the tumour recurring in other areas of your body?' A fourth item on concern about loss of the eye was excluded because it was not relevant to enucleated patients.

Symptom scales of the EORTC QLQ-OPT 30 are; ocular irritation (6 items, e.g., 'Were you troubled by discharge from the treated eye', Cronbach alphas across the nine timepoints; .70 - .77); visual symptoms (4 items e.g., 'Were you troubled by any defects in side vision', Cronbach's alphas; .72-.75); headache (single item 'Did you have headaches?'). The three symptom scales - ocular irritation, visual disturbance and headache - were intercorrelated at each observation with correlations ranging from .44 to .74. A confirmatory factor analysis testing a single latent factor model consisting of equally weighted subscales with fixed error covariances showed satisfactory fit, $X^2_{(2.65)}$=15.87, CFI=.98, RMSEA=.06. To minimise potential predictor collinearity, we

computed a single mean of the three subscales that we labelled visual and ocular symptoms. Functional limitations were measured by the EORTC QLQ-OPT 30 functional limitations scale (5 items, e.g., 'Difficulty seeing steps or pavements?' Cronbach's alphas; .92-.93).

Six-month anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) anxiety and depression subscales (Zigmond & Snaith, 1983). Subscales have seven items scored from 0 to 3 with higher scores signifying greater symptomology (range = 0-21, Cronbach alphas across the nine timepoints; anxiety .87-.88, depression .83-.87). Both predict diagnosed cases with good sensitivity and specificity, with a clinical cut-off of ≥7 (Vodermaier, et al., 2011).

Age, gender, treatment (enucleation versus other treatments (Hope-Stone, et al., 2019)), chromosome 3 status (C3 mutation, C3 non-mutation, not tested/ test failed) were taken from patient records.

Analysis Plan

After descriptive analyses were conducted, we identified latent trajectory classes in anxiety, depression and FCR by fitting 1-4 latent class GMMs. First, we fitted a single class model with random parameters and no covariates. To identify an optimal slope we fitted linear, curvilinear and quadratic slopes. Once the optimal slope model was identified for a single class, we fitted identical GMMs differing by incrementing latent class numbers up to four classes. We used the smallest Bayesian Information Criterion (BIC; Nylund, et al., 2007; Proust-Lima, et al., 2017) to identify the optimal solution. We counteracted potential overfitting by monitoring near-empty classes and rejecting those models (Nasserinejad, et al., 2017). Models of greater than four classes all had two or more empty classes, and thus were not reported. GMM analyses were conducted using the 'hlme' function of the 'lcmm' package in R (Proust-Lima, et al., 2017).

Participants' predicted class memberships were obtained from the above analysis. Logistic regression analyses were used to regress concerns about symptoms and functional problems onto class memberships. Age, gender, treatment and chromosome 3 status (Brown, et al., 2020) are well established predictors of anxiety, depression and FCR (Brown, et al., 2020; Brown, et al., 2021a; Brown, et al., 2021b). These were entered as covariates at stage 1 of the analysis. Enucleation was coded as; enucleation=1 and other treatments=0. Chromosome 3 status was split into two dummy variables. C3 mutation was compared to a combined C3 non-mutation and not tested/test failed category. C3 non-mutation was compared to a combined C3 mutation and not tested/test failed category. The 6-month initial value of the outcome variable (anxiety, depression or FCR) was also included at stage 1. This enables prediction of the slope of trajectories from symptom and functional concerns independently from the starting values of the trajectories. 6-, 12-, 24- and 36-month observations of symptoms and functional problems were entered respectively as stages 2-5. Staging of the entry of predictor variables allows control of autoregressive effects from previous entries, thus any prediction at each stage is attributable to changes in the predictor variable from the previous stage. Descriptive, logistic and multinomial logistic regression analyses were conducted in SPSS v27.

The percentage of missing values was 22.69%, below the 40% upper threshold for viable data replacement (Jakobsen, et al., 2017). For the GMM analysis, full information maximum likelihood was used to replace missing data (Proust-Lima et al., 2017). Unweighted multiple imputation was used to generate imputed datasets in SPSS for the logistic regression analyses (Von Hippel, 2018). Maximum likelihood and multiple imputation approaches provide similar outcomes, with neither likely to show bias where data are missing at random and the data set represents the population (Lee & Sui, 2021).

Unfortunately, a large number of participants died during the study. Based on Wen, et al. (2018), a variable representing the number of months the participant was alive

was used as a covariate for missing data estimation (those who survived the study were allocated 84 months). Post-mortem imputations were consequently removed from data sets. All-cause mortality was ascertained by matching participant's names and dates of birth to information provided by the England and Wales death registry. We examined attrition-related bias through correlations between the proportion of timepoints missed per participant and 6-month study variables. Separate proportions of missed timepoints were calculated for participants who were alive at the time and who had died.

Results

In total, 644 participants of 881 patients meeting eligibility criteria contributed data at 6 months, of which 475 contributed at least three timepoints. Mean age was 69.37 years (*SD*=12.39); 232 (48.8%) were female. Table 1 shows full demographic, clinical and treatment characteristics, and Figure 1 shows the participant flowchart.

Model Selection and Trajectory Characteristics

Linear parameters (weights of 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 for consecutive timepoints) provided best fitting single class models for each outcome. Table 2 shows that two-group solutions had lowest BIC values and acceptable group sizes for anxiety, depression and FCR (Nylund, et al., 2007). Figure 2 shows a *consistently low* anxiety trajectory (82.5% of participants) with an initial mean of 4.21. These scores slightly declined over the study. The remainder (17.5%) showed a *consistently high* trajectory with an initial mean of 10.56 which is greater than the HADS cut-off of ≥7 indicating clinical concern (Vodermaier, et al., 2011).

For depression, the majority (89.1%) had *consistently low* scores, with an initial mean of 2.56. The remaining 10.9% of participants exhibited *consistently high* scores with an initial mean of 8.18 that increased during the study (Figure 3). The majority (80.6%) had a *low* FCR trajectory with an initial mean of 2.20 on a 4-point scale. A *high* FCR

trajectory (19.4%) had an initial mean of 3.32 (Figure 4). Both high and low FCR trajectories showed some evidence of receding over time.

Memberships of higher trajectory groups were correlated over the three outcome variables, without full overlap. Phi coefficients were .42 between anxiety and depression, .386 between anxiety and FCR and .23 between depression and FCR. Cohen (1988) describes estimates of .30-.50 as a medium effect size and .29 or less as a small effect size.

Prediction of Trajectory Groups.

Appendices 2-4 show predictors of outcome trajectories controlling demographic, treatment, chromosome 3 status and the initial 6-month trajectory variables. The logistic regression model predicted membership of the *consistently high* anxiety trajectory (Model $\chi^2(16)$=195.60 - 209.51, -1 Log Likelihood=230.65 – 240.58, Cox & Snell R^2=.338-.357, Nagelkerke R^2=.5747-.590). The *consistently high* trajectory was predicted by higher 6-month (Exp (β)=3.11, 95%C.I=1.29, 7.52) and 24-month (Exp (β)=5.91, 95%C.I=1.36, 25.63) symptom scores (See Appendix 2). A C3 non-mutation was associated with lower likelihood of anxiety trajectory membership (Exp (β)=0.44, 95%C.I=0.19, 0.99).

The logistic regression model predicted membership of the *consistently high* depression trajectory (Model $\chi^2(16)$=141.49 - 155.51.66, -1 Log Likelihood=172.63 - 186.66, Cox & Snell R^2=.258 - .269, Nagelkerke R^2=.516-.549). The *consistently high* trajectory was predicted by higher symptom scores at 24 months (Exp (β)=6.91, 95%C.I=1.59, 30.07; Appendix 3). The logistic regression model predicted membership of the *high* FCR trajectory (Model $\chi^2(16)$=172.19 – 176.39, -1 Log Likelihood=291.56 – 295.58.48, Cox & Snell $R^{2=}$.304 - .309, Nagelkerke R^2=.486 - .494). The *consistently high* trajectory was predicted by higher 6-month symptoms (Exp (β)=2.31, 95%C.I=1.03, 5.18), 12-month functional problems (Exp (β)=2.92, 95%C.I=1.32, 6.44) and 24-month symptoms (Exp (β)=5.84, 95%C.I=1.54, 22.19; Appendix 4).

Inclusion Bias and Attrition Analysis

The 169 excluded participants showed higher 6-month depression scores (4.25, *SD*=4.03 vs 3.16, *SD*=3.23, *t*=3.44, *df*=277.48, $p<.05$) and were less likely to have a C3 non-mutation prognostic testing outcome (18.9% versus 28.6%, χ^2, 1 *df*, =7.22, $p<.05$) than the 475 included participants. Participants provided data at 2,937 at a possible 3,800 timepoints (77.29%). The median timepoints contributed by each participant was seven of a possible eight (interquartile range=3). Unfortunately, 94 participants died during the study, explaining 296 of the missing timepoints. The proportion of missed timepoints for living participants was associated with younger age ($r=-0.21$, $p<.01$) and lower 6-month functional problem scores ($r=-0.11$, $p<.05$). Missing timepoints attributable to death were associated with older age ($r_{(rho)}=0.18$, $p<.05$), enucleation ($r_{(rho)}=0.29$, $p<.05$), C3 mutation ($r_{(rho)}=0.33$, $p<.05$), C3 non-mutation ($r_{(rho)}=-0.25$, $p<.05$), higher 6-month depression scores ($r_{(rho)}=0.10$, $p<.05$) and lower 6-month functional problem scores ($r_{(rho)}=0.21$, $p<.05$).

Discussion

This study makes two contributions. First, we confirmed previously reported trajectories of high anxiety, depression and FCR scores in minorities of cancer survivors, and in addition showed that these persisted at least seven years into survivorship. Second, we showed that higher trajectory memberships could be predicted by measures of participants' concerns about symptoms and functional problems both at the initial 6-month timepoint and also by changes in these measures during the subsequent two and a half years.

Similar to previous studies (Beesley, et al., 2020; Bidstrup, et al., 2015; Costa, et al., 2019; Duening-Smit, et al., 2022; Gonzales, et al., 2017; Kant, et al., 2018; McGinty, et al., 2016; Shim, 2020), large majorities of our participants experienced relatively low anxiety, depression or FCR. Smaller groups of participants showed trajectories characterised by higher distress. The initial high and low anxiety trajectory means of 10.56

and 4.21 (total mean=5.07) are substantially higher and lower, respectively, than age-matched UK population norm of 6.14 (Crawford, et al., 2001). Similarly, the depression means of 8.18 and 2.56 (total mean=3.16) are higher and lower than the population norm of 3.68 (Crawford, et al. 2001). It is noticeable that the overall means did not exceed population norms, and possible that a similar trajectory structure to our sample exists in non-cancer populations. The FCR means of 3.32 and 2.20 (total mean=2.35) on the 4-point scale are similar to a mixed Finnish, Swedish and UK UM patient sample (Individual item means 2.20-2.25; Brandberg, et al., 2004) but higher than an Israeli UM patient sample (Individual item means 1.30-1.41; Frenkel, et al., 2018).

Higher trajectories are concerning both in their extremity and persistence. Higher anxiety and depression trajectories showed means well above the HADS cut-off for clinical concern of ≥7 (Vodermaier, et al., 2011), whilst the initial mean of the high FCR trajectory was close to the highest possible score of 4. Higher scoring trajectories were enduring, with only the *high* FCR trajectory showing evidence of improvement over time. These findings suggest that most of the burden of distress is experienced by relatively small groups of survivors, but these groups experience distress strongly and chronically.

Individuals' trajectories are, however, not fixed, but represent dynamic patterns that emerge over time, possibly in response to changes in concerns about symptoms and functional problems. Our identification of these potential risk factors may help to understand causes of higher trajectories and permit early prediction of their memberships. Baseline (6-month) symptom concerns predicted higher trajectory memberships for anxiety and FCR. As the initial 6-month observation of each trajectory was controlled, trajectory membership could not influence 6-month symptom concerns. This strengthens, although does not prove, the inference that 6-month concerns influenced individuals' subsequent trajectories. Worsening of concerns about symptoms and functional problems over the succeeding two and a half years further predicted higher depression and FCR

trajectory memberships. This suggests that individuals' higher trajectories are dynamically maintained over time by these concerns, and may potentially be curtailed by interventions that reduce concerns. It should be noted though, that we did not control anxiety after the 6-month timepoint. Thus, we cannot eliminate the interpretation that anxiety causes later concerns measured at the 24 and 36-month timepoints.

Findings are consistent with longitudinal (non-latent trajectory) studies linking concerns about symptoms and functional problems to distress (Brown, et al., 2020; MacDonald, et al., 2021; Whisenant, et al., 2019). Concerns may emerge when survivors view symptoms and functional problems as manifestations of recurrent disease or as unwelcome reminders of psychological traumas associated with their cancer experience (Freeman-Gibb, et al., 2017). For example, the FCR literature suggests that somatic experiences of symptoms and functional problems may activate negative assumptions about illness control, consequences, severity and identity and existential implications (Brown, et al., 2021a; Curran, et al., 2020; Fardell, et al., 2016). Prospective tests of these mediators will provide important understandings of the origins of concerns, and why they may cause distress. Theoretical models also suggest that the emergence of concerns may be moderated by negative metacognitive beliefs or intolerance of uncertainty (Curran, et al., 2020; Fardell, et al., 2016), which will give further indications of their origins.

Although superficially similar in shape, trajectories for anxiety, depression and FCR did not represent a homogenous subgroup of participants. Relationships between memberships showed small to medium effect sizes, indicating associations but also substantial independence. Higher trajectory memberships differed numerically with more participants occupying higher anxiety and FCR trajectories than depression. We see these patterns as reflecting specific challenges of UM treatment and survivorship. Primary treatments are generally successful and brief, and, therefore, arguably less physically and emotionally challenging than prolonged treatments such as chemotherapy, immunotherapy

and external beam radiotherapy. Instead, challenges are future-oriented and existential, concerning truncated life expectancy. Thus, future-oriented emotions such as anxiety and fear (Eysenck, et al, 2006) may be more common. Further, FCR appeared to be more responsive to symptoms and functional problems. This may also explain why symptom concerns were generally stronger predictors of higher trajectories than functional concerns. Anxiety, depression and FCR trajectories may benefit from separate conceptualisations, and their importance can differ across specific challenges of other cancers.

Previous studies have found rapid (usually downward) changes in trajectories in small numbers of participants (Beesley, et al., 2020; Kant, et al., 2018). We did not replicate such changes. This may be attributable to several factors. Later survivorship may simply be characterised by stability with only gradual trajectory changes. Other explanations are methodological. Change trajectories in previous research involved numerically small groups, and failure to replicate these may reflect inherent difficulties in reliably detecting trajectories with low numbers (Nasserinejad, et al., 2017). We note that other studies have not found them (Costa, et al., 2019; Duening-Smit, et al., 2022; Gonzales, et al., 2017; McGinty, et al., 2016; Shim, 2020; Yang, et al., 2018). Also, we predominantly made yearly observations and may have missed any rapid changes. All previous studies used shorter between-observation latencies.

Clinical and prognostic variables did not strongly predict trajectories. These are not consistent predictors of distress across the UM literature (Davies, et al., 2022). One reason is that treatments do not entail as great a burden as other cancer treatments. Enucleation can cause trauma, feelings of loss and functional impairment, but, as previously noted, few participants underwent prolonged treatment regimens. Second, the impact of a poor prognosis may be muted; survivors with good prognoses can fail to accept that recurrence risk is low, and, conversely, those with poor prognoses sometimes find alternative ways of building hope for their futures (Hope-Stone, et al., 2015).

This study has limitations. First, our observations started at six months, thus we did not take genuine baseline observations. Consequently, we may have missed shifts in outcome measures, such as reductions in anxiety, occurring soon after diagnosis (Bidstrup, et al., 2015). A second limitation is that measures were not taken before cancer was suspected. Thus, it is unclear whether trajectories were attributable to UM or existed before diagnosis. Participants who failed to meet the three-observation eligibility criterion showed higher 6-month depression scores than included participants. Their exclusion probably reduced our estimate of high depression trajectory membership and may have biased prediction of this trajectory. Many participants failed to complete eight observations, with only 51% completing the final timepoint. The proportion of missed timepoints (whilst alive) was associated with younger age and lower functional problem scores at six months. This is unlikely to bias trajectory estimation (which is not affected by functional problem scores), but may bias estimation of links between functional problems and trajectory memberships. There is added uncertainty about attrition bias because we do not know the causes of individual participants' dropout except when the participant died.

Findings warrant two recommendations. First, interventions may best be focussed on relatively small sub-populations where distress is already severe and chronic. As memberships of concerning trajectories were predicted by elevated anxiety, depression or FCR scores and symptoms and functional problems at six, 12 and 24 months, monitoring at these points should identify at-risk cases. Once identified, alleviating distress is likely to be challenging. Recent reviews and meta-analyses have shown that intensive psychological interventions based on cognitive behavioural or acceptance and commitment principles delivered by therapists, show stronger and more enduring outcomes than psychological interventions designed for widespread implementation such as self-help materials (Park & Lim, 2022; Zhao, et al., 2021). Thus, targeted intensive interventions may be effective, particularly if administered early. Second, concerns about symptoms and

functional problems might contribute to stable patterns of anxiety, depression and FCR. Based on Brown et al. (2021b), one objective is to prevent survivors from making problematic inferences about symptoms and functional problems. Interventions currently used to prepare patients for stressful medical procedures explain the nature and rationale for procedures and likely experiential consequences, thus establishing non-threatening schemas that prevent catastrophising (Suls & Wan, 1989). These might be useful if adapted and implemented before symptoms and functional problems occur.

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Table 1

Sample Parameters of Demographic, Clinical and Chromosome 3 Status Variables.

	Frequency or Mean
Age	69.37 (SD 12.38)
Gender	
Male	243 (51.2%)
Female	232 (48.8%)
Employment status	
Employed	170 (35.8%)
Homemaker	16 (3.4%)
Retired	237 (49.9%)
Sick leave/Medically retired	20 (4.32%)
Other	24 (5.1%)
Not known	8 (1.7%)
Marital status	
Married or co-habiting	355 (74.7%)
Separated	29 (6.31%)
Widowed	61 (12.8%)
Single	28 (5.9%)
Not known	2 (0.4%)
Eye	
Left	240 (50.5%)
Right	235 (49.5%)
Treatment	
Enucleation	118 (24.7%)
Plaque radiotherapy	216 (45.5%)
Proton beam radiotherapy	100 (21.1%)
Resection	26 (5.5%)
Other	15 (3.2%)
Chromosome 3 status	
C3 mutation	142 (29.9%)
C3 non-mutation	131 (27.6%)
Not tested/fail	202 (42.5%)

Table 2

Negative Log Likelihood, Bayesian Information Criterion and Group Sizes for 1-4 Latent Class Models of Anxiety, Depression and Fear of Cancer Recurrence Trajectories.

	Classes	-1 Log likelihood	*df*	BIC	Group membership
Anxiety	1	8473.784	6	16986.11	100
	2	8434.063	9	16925.94	82.49, 17.51
	3	8434.063	12	16945.20	79.29, 20.70, 0.00
	4	8434.063	15	16964.47	78.44, 0.00, 5.28, 16.27
Depression	1	7884.917	6	15808.37	100
	2	7806.460	9	15670.73	89.12, 10.87
	3	7806.460	12	15690.00	88.47, 0.00, 21.53
	4	7806.460	15	15709.27	86.85, 0.00, 23.15, 0.00
Fear Cancer Recurrence	1	3201.752	6	6442.043	100
	2	3165.050	9	6387.910	80.38, 20.19
	3	3165.050	12	6407.180	76.94, 23.05, 0.00
	4	3165.050	15	6426.449	0.00, 75.00, 25.00, 0.00

Figure 1

Participant Flowchart

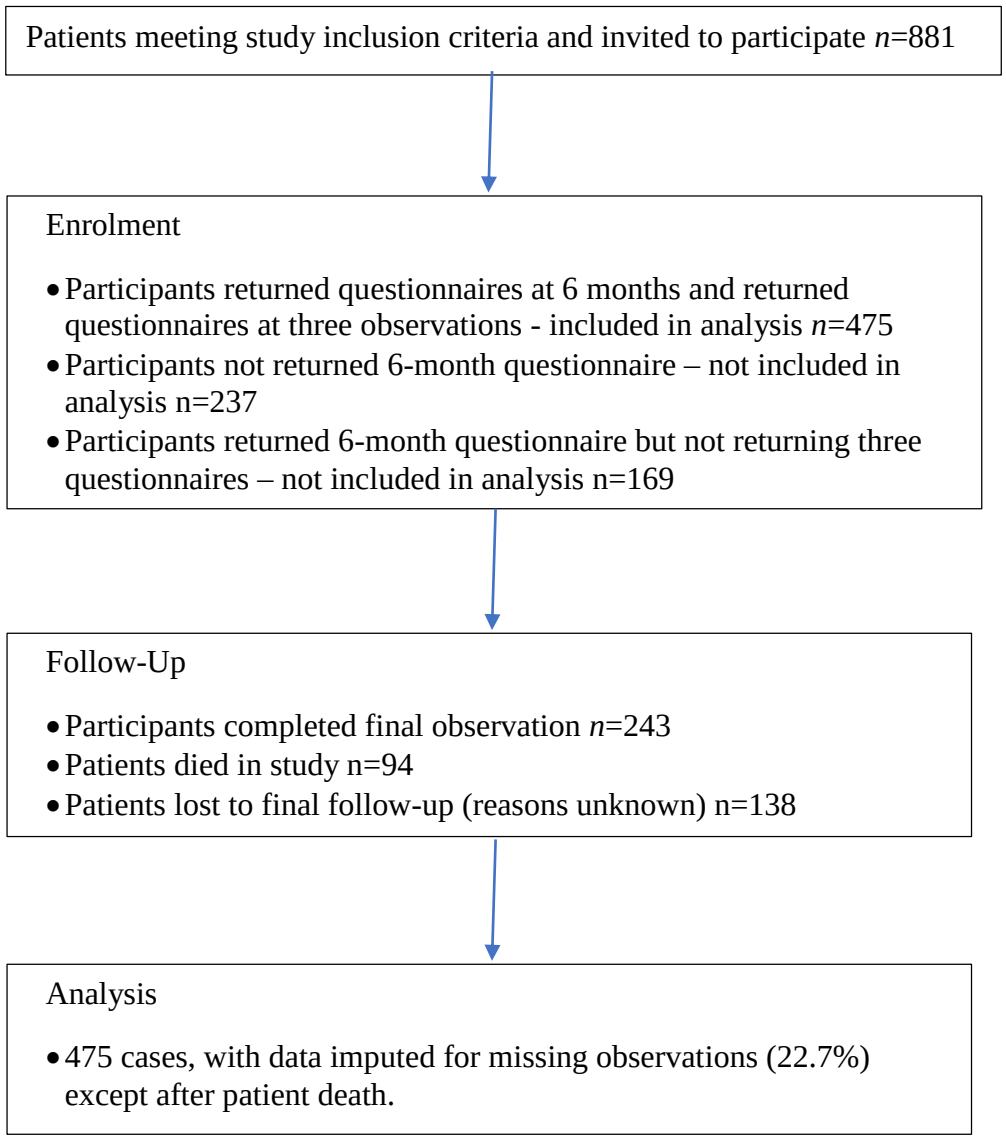
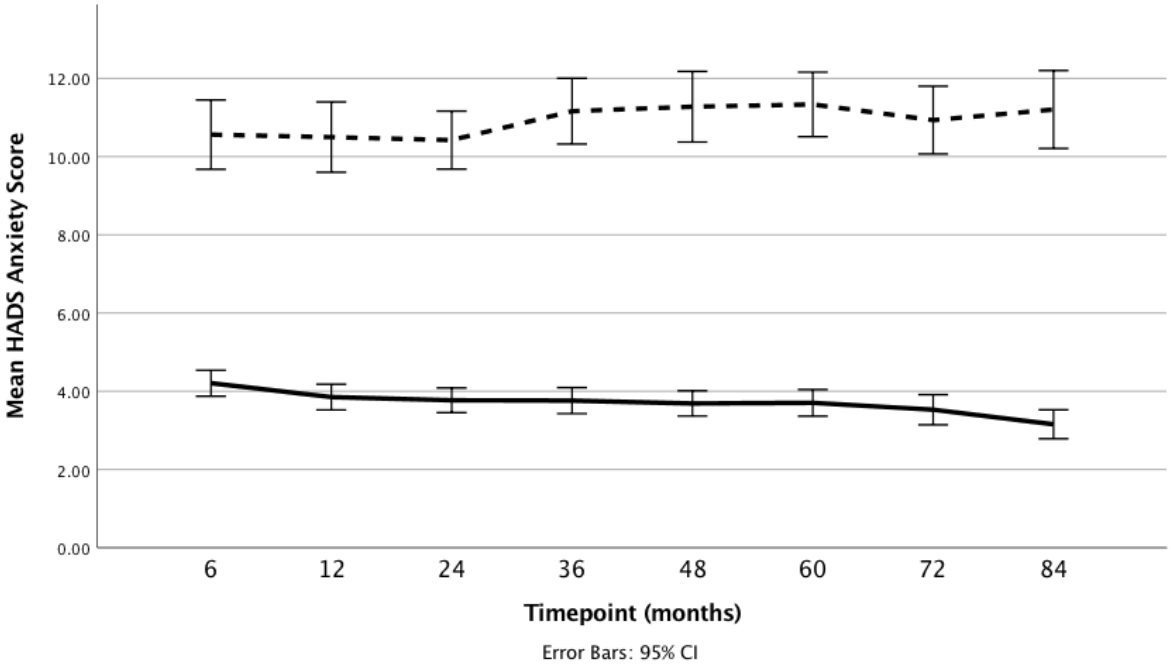


Figure 2

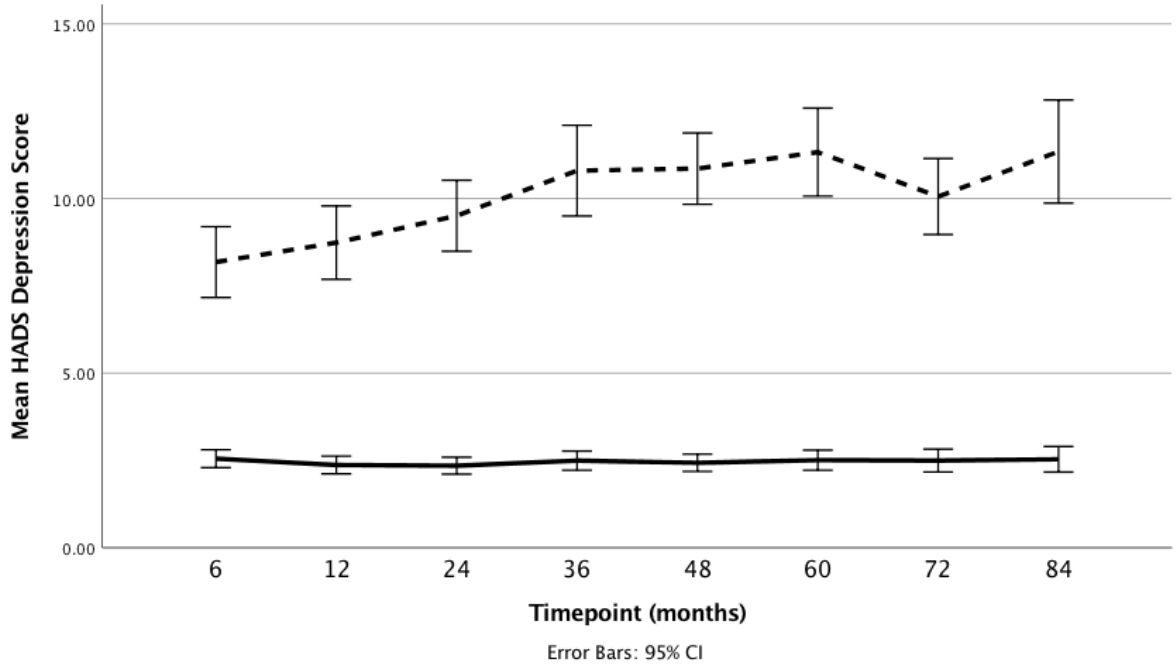
HADS Anxiety Trajectories Over Seven Years



Dotted line refers to consistently high mean scores, solid line consistently low scores.

Figure 3

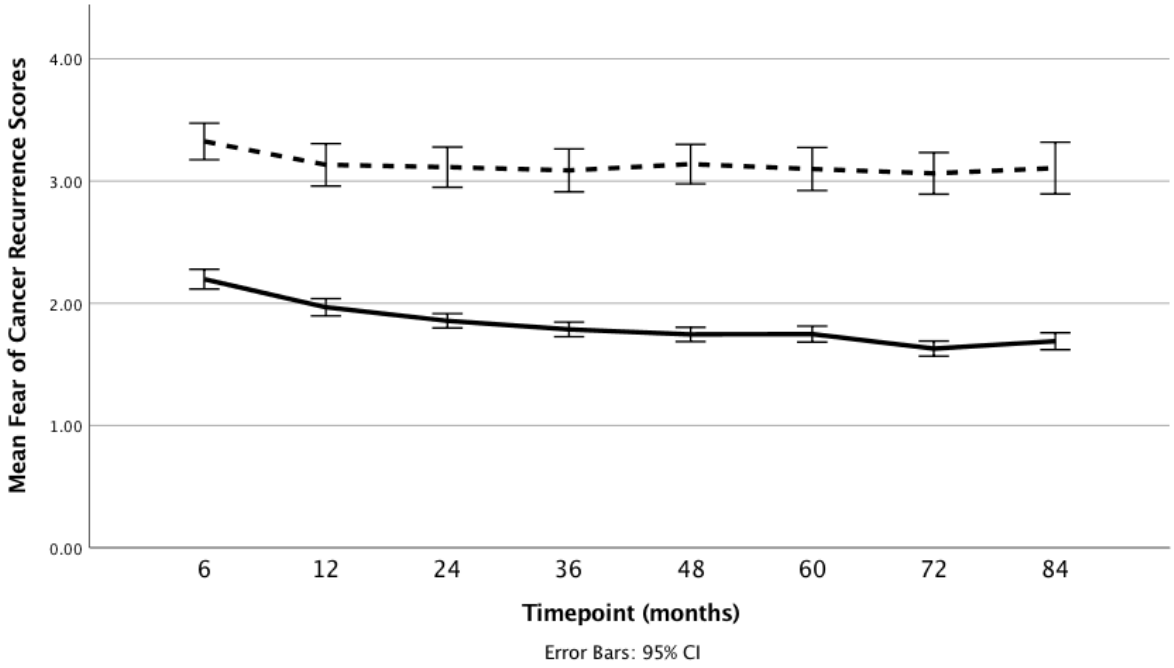
HADS Depression Trajectories Over Seven Years



Dotted line refers to consistently high mean scores, solid line consistently low scores.

Figure 4

Fear of Cancer Recurrence Trajectories Over Seven Years



Dotted line refers to consistently high mean scores, the solid line consistently low scores.