Predictors of anxiety and depression two years following treatment in uveal melanoma survivors

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Acknowledgements

We thank Nicola Longrigg and Gary Cheetham of for their assistance with data management

Abstract

Background: We examined the role of post-treatment symptoms and functional problems, and of worry about recurrent disease (WREC), in predicting and probable anxiety and depression cases 24 months after diagnosis in survivors of posterior uveal melanoma (UM). We examined whether WREC mediates links between symptoms, functional problems, and probable anxiety and depression cases. **Methods**: Prospective cohort study of 261 treated UM survivors 6, 12 and 24 months after diagnosis. Hierarchical logistic regression analyses predicting anxiety and depression 24 months after diagnosis identified by Hospital Anxiety and Depression Scale cut-off scores. Symptoms, functional problems and WREC 6 months post-treatment were entered into the analyses as predictors, then the same variables at 12 months. We controlled anxiety or depression at 6 and 12 months and chromosome 3 status, which accurately predicts 10-year survival. Mediation of links between 6-month symptoms and functional problems and 24-month anxiety and depression by 12-month WREC was tested. **Results**: Anxiety caseness at 24 months was predicted by 6-month ocular irritation, headache and functional problems, and 12-month WREC. Depression caseness at 24 months was predicted by 6-month headache and functional problems. WREC at 12-months mediated prediction of anxiety caseness by 6-month symptoms and functional problems. Chromosome 3 status predicted neither anxiety nor depression. **Conclusions:**. Survivors reporting symptoms, functional problems and WREC should be monitored for anxiety and depression. Appropriate reassurance that symptoms do not signify future disease might help prevent anxiety.

Keywords: Cancer; Oncology: Uveal melanoma; anxiety; depression; cancer survivorship; worry about recurrence

Introduction

Ten-year UK survival for all cancers is now estimated to be 50% compared to 24% 40 years ago [1]. Improved survival brings the problems of cancer survivorship into focus. In particular, between 15 and 26% of survivors experience clinically significant anxiety and depression three to five years following treatment [2-4].

Research has focussed on anxiety and depression during diagnosis and treatment [5, 6] but less so on long-term survivors a year or more after treatment. The main approach to understanding long-term anxiety and depression has been to try to predict these from clinical and psychological variables measured at baselines established soon after diagnosis or treatment. A recent review [7] shows that this approach has been largely unfruitful. Reliable predictors are baseline levels of anxiety and depression, personality variables such as neuroticism, and premorbid psychological problems. Whilst helping to identify potentially vulnerable patients, these findings offer limited insights for prevention or treatment. Premorbid conditions cannot be changed and neuroticism and trait anxiety are difficult to change, whilst short-term anxiety and depression are normal responses to a cancer diagnosis that often spontaneously remit [8, 9].

Cancer, and its surgical, radiotherapy and chemotherapy treatments, can cause debilitating symptoms and consequent problems with day-to-day functioning [10, 11]. Symptoms often arise up to a year after treatment. Thus, symptom occurrence and any effects of those symptoms on anxiety or depression will not be captured in research that measures predictors shortly after diagnosis or treatment. Post-treatment symptoms and functional problems predict anxiety and depression symptoms in cross-sectional studies [2, 3], but cross-sectional designs cannot show causality. We are not aware of prospective research that tests whether post-treatment symptoms and functional problems are linked to long-term anxiety and depression.

One reason why symptoms and functional problems might cause anxiety or depression is by inducing worry about recurrent disease (WREC), which, in turn, might lead to anxiety and depression. WREC is common amongst survivors, and usually arises months or years after diagnosis and treatment [12]. Symptoms and functional problems could induce WREC because they create fears of further disease, or because they remind patients of their recent cancer experience [13]. WREC has frequently been linked to anxiety and depression [12, 14], but again studies are cross-sectional so it is unclear whether WREC is a cause or a consequence of anxiety or depression.

Prospective cohort studies examine temporal sequencing associations, providing stronger evidence of causality. The present study used a sample of uveal melanoma (UM) patients to examine whether patients' reports of symptoms and functional problems predict later anxiety and depression caseness, identified by Hospital Anxiety and Depression Scale (HADS) cut-off scores. We also examined whether WREC mediates this relationship. UM provides an ideal model to investigate the influence of post-treatment symptoms on long-term anxiety and depression for two reasons. First, whilst patients experience pre-treatment visual symptoms in uveal melanoma, these symptoms are rarely debilitating [15, 16]. In contrast, post-treatment symptoms and functional problems, including impaired vision, ocular irritation and headaches, can be severe and are linked to anxiety and depression in cross-sectional studies [17-19].

Second, UM serves as a model to understand the origins and influence of WREC because risk of metastatic cancer recurrence can be accurately predicted. A limitation of most WREC research is that objective risks of cancer recurrence cannot be accurately determined [12]. Worry about recurrence should be understood in the context of objective risk. Worry that is proportional to risk can be considered rational, and interventions should help patients to manage the worry [20, 21]. Where worry is disproportionate to objective risk, intervention

goals should include challenging unrealistic or irrational beliefs about risk [12]. About 40-50% of UM patients will develop metastatic disease within 10 years, for which treatment rarely prolongs life [22]. Metastatic disease develops almost exclusively in patients whose tumor shows chromosome 3 deletion (i.e., monosomy 3) [23, 24]. Patients are offered prognostic testing and informed of their prognosis if they accept it. Objective risk, (chromosome 3 status) can be statistically controlled, thus exposing any influence of subjective WREC on anxiety and depression.

Aims

Using a prospective cohort design in UM patients, our first aim was to determine whether impaired vision, ocular irritation, headaches, functional difficulties or WREC assessed 6 and 12 months after diagnosis predicted probable anxiety and depression caseness, identified by the HADS, 24 months after diagnosis. Our second aim was to establish whether WREC at 12 months mediates any prediction of 24-month anxiety or depression caseness by 6-month symptoms and functional problems.

Materials & Methods

Participants

This audit was approved by the Health Research Authority North West – Liverpool Central Ethics Committee (03/06/072/A) and conducted in accordance with the Declaration of Helsinki. The sample comprised a consecutive series of all adult patients treated for posterior uveal melanoma (choroid and ciliary body) between April 1st 2008 and December 31st 2011 at the Liverpool Ocular Oncology Centre (LOOC). Diagnosis and treatment was based on clinical and tumor characteristics described by Damato and Heimann [25]. Most patients had ruthenium plaque radiotherapy or proton beam radiotherapy. If the tumor was unsuitable for radiotherapy, patients underwent trans-scleral local resection, trans-retinal endoresection or

enucleation (i.e., amputation) of the affected eye. Patients who consented to prognostic testing received verbal explanations of their results.

At diagnosis, patients were asked if they were willing to participate in an audit to examine long-term patient reported outcomes of treatment. Patients who gave written consent were posted questionnaires 6, 12 and 24 months following diagnosis with enclosed postage-paid envelopes addressed to the researchers.

Measures

Demographic, clinical and treatment variables and chromosome 3 status were collected from patients' clinical records. These included age, gender, relationship and employment status, whether right or left eye was affected, vision in the unaffected eye at diagnosis, tumour origin (choroid or ciliary body) and primary treatment type including whether the affected eye was conserved or removed. Prognostication was largely determined by chromosome 3 status [25]. Outcomes of testing were categorized as: monosomy 3, disomy 3 (i.e., normal maternal and paternal copies of chromosome 3) and unknown (comprising patients who did not wish to be tested and those whose genetic test failed). Dummy binomial variables were formed to allow comparisons between patients with monosomy 3 and disomy 3 and between patients with monosomy 3 and those whose chromosome 3 status was unknown.

Cut-off scores of ≥8 on anxiety and depression subscales of the HADS [26] were used to identify potential cases. A recent meta-analysis comparing HADS cut-offs to structured interview diagnoses [27] showed the anxiety cut-off of 8 or greater to predict either anxiety or depression with a sensitivity of .73 and specificity of .65. The same cut-off for depression predicts depressive disorders with a sensitivity of .86 and specificity of .81 [27].

Post-treatment symptoms and functional problems were measured using the European Organisation for Research and Treatment for Cancer Ophthalmic Quality of Life Module (QLQ-OPT 30 [28]), validated in UM samples [29]. Subscales related to specific treatments,

such as enucleation, or to activities engaged in by subsets of participants, such as driving, were disregarded. Subscales were: ocular irritation, a 6-item scale with a Cronbach alpha in our sample of .71 at 6 months and .75 at 12 months; vision impairment, a 4-item scale with an alpha of .69 at 6 months and .73 at 12 months; a single item measuring headache, and functional problems a 6-item scale with an alpha of .92 at both 6 and 12 months.

The QLQ-OPT 30 has a 4-item WREC scale. An item on concern about loss of the eye was disregarded. The remaining three items were used, with an alpha of .87 at 6 months and .85 at 12 months. Response format for all QLQ-OPT 30 items is 'Not at all', 'A little', 'Quite a bit' and 'Very much', scored 1-4, respectively. Higher scores indicate poorer outcomes.

Statistical analysis

Preliminary analyses determined whether demographic, clinical and treatment variables, in addition to Chromosome 3 status needed to be statistically controlled. We used Pearson and point-biserial correlations to test whether these variables predicted 24-month anxiety and depression, and conducted interaction analyses to test whether they moderated any associations between predictor variables and 24-month anxiety and depression. Multivariate analyses then examined whether symptoms, functional problems and WREC at 6 and 12 months predicted 24-month anxiety and depression cases. Mediation analysis tested whether WREC at 12 months mediated the prediction of anxiety and depression caseness at 24 months by symptoms and functional problems at 6 months.

Prediction of anxiety and depression caseness at 24 months: Two hierarchical multivariate logistic regression analyses were conducted. Logistic regression provides simple and accurate odds ratio estimation for binary outcomes (30). Objective risk (Chromosome 3 status) and anxiety or depression at 6 & 12 months, were entered as statistical control variables in the first block. Demographic, clinical and treatment variables were entered as control variables in

this block if they were associated with 24-month anxiety or depression in preliminary analyses. The second block comprised 6-month symptoms, functional problems and WREC. The third block comprised 12-month symptoms, functional problems and WREC. Multivariate prediction was tested using odds ratios with 95% confidence intervals.

Mediation analysis: Change scores in WREC from 6 to 12 months were computed, as were changes in anxiety and depression caseness between 12 and 24 months. Potential mediation of 12-24 month changes in anxiety and depression caseness by 6-12 month changes in WREC was tested using bias-corrected and accelerated bootstrapping [31]. Mediation was separately tested for each symptom and the functional problem score. Anxiety or depression caseness at 12 months and WREC at 6 months were controlled in these analyses.

Sample Attrition: This was assessed using multivariate logistic regression to predict the likelihood of retention at 24 months from 6-month demographic, clinical and treatment variables, chromosome 3 status, symptoms and functional problems, WREC, and depression and anxiety caseness.

Results

Of 716 patients who were asked to take part, 554 (77.4%) consented and 411/554 (74.2%) returned 6-month data, 325 returned 12-month data and 291 returned 24-month data. 261 (63.5% of the 411 returned at 6 months) returned data at all three follow-up points and were used in the analysis. Socio-demographic and clinical characteristics are shown in Online Supplement 1[1]. Bivariate analyses showed that female gender and younger age predicted 24-month anxiety and depression caseness. These, as well as chromosome 3 status and 6 and 12-month anxiety or depression caseness were used as covariates in the multivariate analyses.

[1] **Associations between predictor and outcome variables cases were not significantly moderated by demographic variables or Chromosome 3 status**

Table 1 shows anxiety and depression caseness and symptom, functional problem and WREC scores at 6, 12 and 24 months. Associations between them are available in Online supplement 2. Positive associations were generally observed amongst symptoms, functional problems, WREC and anxiety and depression caseness within each time-point and between time-points. 6-month symptoms and functional problems were associated with greater 12-month WREC and a greater likelihood of 24-month anxiety and depression caseness. 12-month WREC was associated with a greater likelihood of 24-month anxiety and depression caseness.

Prediction of anxiety and depression at 24 months

Table 2 shows multivariate predictors of anxiety and depression cases after entry of each predictor block. After entry of the first block, 6 and 12-month anxiety or depression caseness were the only significant predictors; chromosome 3 status predicted neither anxiety nor depression. After including the putative predictor variables measured at 6 months in block 2, ocular irritation, headache and functional difficulties each uniquely predicted anxiety caseness. Headache and functional problems predicted depression caseness. WREC at 6 months did not predict anxiety caseness, but predicted a lower probability of depression caseness. After including the predictor variables measured at 12 months in block 3, no variable predicted depression caseness. WREC at 12 months predicted anxiety. Analyses show that the symptoms and functional problems that predict anxiety and depression caseness at 24 months emerge within 6 months of diagnosis, and that WREC associated with long term anxiety caseness arises between 6 and 12 months[2].

[2] Multicollinearity is problematic when measures are repeated. Tolerances were generally about 0.50 with the lowest tolerances observed for functional problems at 6 (Tolerance=0.29) and 12 months (Tolerance=0.25). These do not constitute problematic levels of multicollinearity [33]. No adjustments were made to the analyses.

Inverse prediction of 24-month depression from 6-month WREC was not expected, with no evidence of univariate prediction. This indicates a possible multivariate suppression effect [32]. On further examination, 6-month headache and functional problems no longer predicted 24-month depression when 6-month WREC was removed. This supports a suppressor interpretation - 6-month WREC suppresses criterion-irrelevant variance in other predictors but has no inherent association with 24-month anxiety.

Mediation analyses

Table 3 shows the outcomes of mediation analyses. WREC changes toward increased worry from 6 to 12 months mediated the prediction of an increased likelihood of anxiety caseness from 12 to 24 months by headache at 6 months. Mediation effects approaching significance were noted for ocular irritation and functional problems at 6 months.

Sample Attrition

Sample attrition analysis showed no evidence of attrition bias. The logistic regression predicting whether patients dropped out or were retained at 24 months from 6-month study variables did not show significant prediction (χ^2=21.00, *df*=21, *p*=.269).

Discussion

Our first aim was to identify predictors of anxiety and depression. Patients who reported symptoms and functional problems 6 months after diagnosis were more likely to score above HADS caseness cut-offs for anxiety or depression. Those reporting worry about recurrent disease at 12 months were more likely to be above anxiety cut-offs at 24 months. The second aim was to prospectively test the hypothesis that 12-month worry about recurrence could

mediate the relationship between symptoms at 6 months and anxiety and depression at 24 months. This hypothesis was supported for anxiety only.

Findings are consistent with cross-sectional studies in UM [17- 19] and other cancers [2, 3], but provide stronger evidence that symptoms, functional problems and WREC could cause anxiety and depression because we show that these precede, and thus cannot be consequences of, anxiety and depression. The finding that 12-month WREC predicts 24-month anxiety is also consistent with cross-sectional evidence [20, 34]. We can be specific about the timeframe. WREC at 6 months did not predict 24-month anxiety, demonstrating that prediction of anxiety is attributable to worry that emerges between 6 and 12 months. To our knowledge, this is the first study to show that worry about disease recurrence mediates effects of symptoms and functional problems on anxiety. Our claim for mediation is strengthened by the prospective design, which eliminates the possibility that any part of the meditational sequence occurs in reverse.

Previous cross-sectional studies show associations between WREC and both anxiety and depression [12, 14]. Our prospective analyses showed WREC to predict only anxiety, suggesting that WREC might cause future anxiety but probably does not cause depression. Worries about recurrence are commonly conceptualized within an anxiety framework [12, 21], and these findings provide empirical support for the idea that WREC is predominantly a risk for anxiety.

WREC predicted anxiety after controlling chromosome 3 status. Thus, worry about disease recurrence cannot be accounted for by objective risk of recurrence. Although worry is suspected to be independent of objective risk [12], our study is the first to statistically control recurrence (i.e., metastasis) risk. Consistent with previous UM research [35], chromosome 3 status itself did not influence anxiety or depression.

Limitations

Although our prospective design strengthens claims of causality, we cannot fully eliminate alternative causal models. For example, patients' perceptions of symptoms and functional problems are subjective, and it is possible that a greater sensitivity to symptoms and functional problems represent early manifestations of anxiety and depression and do not cause it [36]. Also, effects of unmeasured variables cannot be controlled. Another limitation is that we did not take a pre-treatment baseline, and are unaware of the extent to which symptoms such as headaches, existed before diagnosis and treatment. However, we statistically controlled anxiety and depression at 6 months. Thus, it is unlikely that pre-treatment symptoms or functional impairments could influence anxiety or depression at 24 months without influencing these variables at 6 and 12 months. We monitored patients for 24 months, and thus cannot safely make inferences about a longer time period. Nonetheless, our findings are unlikely to represent transient effects because at least 18 months elapsed between measuring 6-month symptoms and functional problems and recording 24-month anxiety and depression. HADS scales are commonly used to find probable anxiety and depression caseness. They have good sensitivity and specificity, but do not provide definitive diagnoses. Findings need to be considered in the context of attrition of 36.5% of the sample. Although attrition analyses showed little bias, bias may exist in unmeasured variables. Last, we did not collect information on socioeconomic status or ethnicity.

Research and Clinical Implications

The key finding is that post-treatment symptoms, functional problems and WREC precede, and possibly contribute to, long-term anxiety and depression in cancer survivors. Thus, a greater focus on the impact of post treatment events on the development of long-term anxiety and depression is warranted. Symptoms and functional problems observed in this study are

not amenable to medical or surgical interventions, thus approaches to prevention and treatment will need to be psychological.

Mediation by WREC demonstrates a specific psychological process, but our findings do not explain (1) why patients worry when they experience symptoms and functional problems, (2) which specific aspects of symptoms and functional problems cause worry, or (3) which patients are likely to be at risk. WREC is likely to be underpinned by the specific interpretations that patients make. For example, a study of breast cancer survivors [13] suggests that patients may see symptoms and functional problems as early manifestations of recurrent disease or as reminders of feelings of risk or vulnerability associated with their cancer experience.

Mediation was only partial. Symptoms and functional problems predicted anxiety and depression independently of WREC. It is important to understand why patients' experiences of symptoms and functional problems directly increase risks of long-term anxiety and depression. One possibility is that symptoms and functional problems cause pain and discomfort that impair daily living over a long time period. The adverse effects of chronic pain and discomfort on long-term anxiety and depression are well established [37], and will need to be treated with support and therapeutic programs [38, 39].

In terms of clinical implications, the focus of attention during follow-up should be on preparing patients to better understand and cope with symptoms and functional problems. This has two immediate implications. First, patients who report concerns about symptoms, functional problems and worry about recurrence should be monitored for early signs of psychological distress. Second, it is important that patients be reassured that symptoms probably do not portend future disease. The final implication is the finding that informing patients of their chromosome 3 status does not influence anxiety or depression. This assuages

concerns that patients may be psychologically harmed, at least in terms of anxiety or depression, by adverse prognoses about metastatic disease.

Conflict of Interest: All authors declare that they have no conflict of interest in devising, conducting or reporting this research.

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Table 1. Psychological and Somatic Variables at Post Diagnosis Observations. *N*=261.

Prevalences of HADS Anxiety and Depression Cases						
		6 months		12 months	24 months	
		N	Percent	N	Percent	N	Percent
Anxiety 'case'		70	26.8	67	27.7	59	22.6
Depression 'case'		26	10.1	30	11.5	30	11.5
Scale Ranges, Means and SDs for Predictors							
	Scale Range	Mean	SD	Mean	SD	Mean	SD
Ocular Irritation	6-24	9.68	3.14	9.70	3.17	9.76	3.31
Visual Impairment	4-16	6.13	2.44	6.08	2.61	5.87	2.39
Headache	1-4	1.57	0.83	1.56	0.82	1.52	0.80
Functional problems	6-24	10.02	4.33	9.89	4.21	9.94	4.23
Worry Recurrent Disease	3-12	7.30	2.71	6.56	2.51	6.29	2.41

Table 2 Multivariate Predictors of 24-Month HADS Anxiety and Depression Cases Using Binomial Logistic Regression

	Anxiety			Depression		
Model Fit	$X^2_{(14)}$=128.17 Cox-Snell R^2=0.396 89.4% classification			$X^2_{(14)}$=75.98 Cox-Snell R^2=0.253 94.3% classification		
Predictors	**Lower 95% C.I.**	**Odds ratio**	**Upper 95% C.I.**	**Lower 95% C.I.**	**Odds ratio**	**Upper 95% C.I.**
Block 1 Covariates†		χ^2=97.6**			χ^2=60.7*	
Age	0.99	1.02	1.05	0.95	0.99	1.03
Sex	0.38	0.86	1.96	0.21	0.61	1.77
6 month Anxiety/Depression	4.08	9.86*	23.86	3.42	12.06*	42.59
12 month Anxiety/Depression	3.33	7.56*	17.15	3.19	9.94*	30.97
M3 (1)	0.24	0.71	2.07	0.50	1.78	6.40
M3 (2)	0.11	0.43	1.65	0.21	1.06	5.30
Block 2: 6 -month		χ^2=16.1**			χ^2=17.7*	
Ocular Irritation	1.04	1.23*	1.45	0.93	1.13	1.37
Visual Impairment	0.78	0.97	1.22	0.65	0.85	1.08
Headache	1.07	1.77*	2.95	1.10	2.32*	4.92
Functional problems	1.00	1.12*	1.25	0.91	1.16*	1.34
Worry Recurrent Disease	0.84	1.01	1.21	0.54	0.71*	0.93
Block 3: 12-month		χ^2=9.69*			χ^2=1.6	
Ocular Irritation	0.73	0.89	1.11	0.83	1.06	1.34
Visual Impairment	0.82	0.97	1.24	0.66	0.93	1.31
Headache	0.86	1.64	3.17	0.71	1.47	3.04
Functional	0.80	0.97	1.18	0.77	0.98	1.24
Worry Recurrent Disease	1.04	1.34*	1.73	0.71	1.01	1.42

† Odds ratios and C.I.s are those observed after entry of each block.; *p<.05; **p<.01

Table 3: Bootstrapping Estimates of the Indirect Effect of 6 Month Symptoms and Functional Problems on 12-24 month Changes on HADS Anxiety Cases Mediated by Changes in 6-12 Month Worry about Recurrence.

	Corrected Estimate	SE	Lower 95%	Higher 95%
6 month Ocular Irritation	.0020[†]	.0016	-.0002	.0064
6 month Visual Impairment	.0005	.0006	-.0035	.0052
6 month Headaches	.0115	.0000	.0010	.0326
6 month Functional Problems	.0027	.0001	-.0003	.0078

[†] Unstandardized beta estimates.

Figure 1: Standardised Beta Coefficients for the Indirect Effect of 6 Month Symptoms and Functional Problems on 12-24 month Changes in HADS Anxiety Caseness Mediated by 6-12 Month Changes in Worry about Recurrence.