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Fear of cancer recurrence and adverse cancer treatment outcomes: predicting 2- to 5-year fear of recurrence from post-treatment symptoms and functional problems in uveal melanoma survivors

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Abstract

Objective The fear of cancer recurrence (FCR) in later survivorship can lead to poorer mental health, quality of life and physical and functional recovery. Later-occurring FCR may be a consequence of late-emerging physical symptoms and functional problems from cancer or its treatment. Based on the self-regulation model, we predicted that persistent or escalating symptoms and functional problems would prospectively predict FCR observed 2–5 years after diagnosis and treatment.

Methods This is a five-year study of 708 uveal melanoma (UM) patients, measuring self-reported visual and ocular symptoms, functional problems and FCR at 6, 12, 24, 36, 48 and 60 months post-diagnosis. A mixed measures design over four levels with observations staggered to represent prospective prediction. Criterion variables were FCR at 24, 36, 48 and 60 months. Predictors were symptom and function scores measured at the previous two observations to FCR. Controls were FCR measured at the previous observation to the criterion FCR measure and demographic, clinical and treatment variables.

Results Linear mixed modelling showed that FCR was uniquely predicted by enduring symptoms, those that emerged two observations previously, but not symptoms arising at the previous observation. FCR was predicted by functional problems, which emerged in the observation prior to FCR, but not the observation previous to that.

Conclusions Persistent or emerging post-treatment symptoms and functional limitations are probable risk factors for late-occurring FCR in UM survivors.

Implications for Cancer Survivors Monitoring symptoms and functional limitations assists in identifying at-risk survivors and targeting preventive interventions. Self-regulation theory suggests that helping survivors to more realistically appraise symptoms and functional problems may prevent FCR.

Keywords Oncology · Uveal melanoma · Fear of cancer recurrence · Symptoms · Functional limitations

Background

Fear of cancer recurrence (FCR) is the fear, worry or concern that cancer will return [1]. FCR is widespread and usually experienced as aversive to survivors across a range of cancers [2]. FCR does not necessarily confer lasting psychological harm [1], particularly if it is experienced early in survivorship and dissipates [3, 4]. However, higher levels of FCR are problematic if they occur later in survivorship. Persistent, late-emerging, worsening or recurrent fear trajectories [3, 4] predict depression and anxiety, poorer quality of life, higher health service use and poorer physical and functional recovery [5–8].

Theoretical models of FCR [1–9] suggest that physical symptoms trigger and shape emotional responses to illness,

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particularly when sensations are severe, longstanding or worsening [10]. One explanation for late-occurring FCR is that physical and functional sequelae of cancer treatment, such as pain or discomfort, sometimes emerge during survivorship. Empirically, these are associated with FCR [11]. However, little is known about links between somatic symptoms and FCR after the first 2 years of survivorship. We report a theoretically guided examination of the extent to which symptoms and functional problems associated with cancer treatment predict FCR during years 2 to 5 of cancer survivorship.

Theoretical background

Current theoretical models of FCR [12–16] view somatic sensations as triggers for FCR, particularly those in body regions adjacent to the initial cancer. Sensations initiate a sense of threat imbued with uncertainties about life expectancy, implications for life goals and repetition of aversive experiences associated with cancer and its treatments. Once triggered, FCR can be aggravated and prolonged by factors such as prior anxiety, intolerance of uncertainty or dysfunctional thoughts about either illness or worry itself [15, 16]. FCR can be largely independent of objective risks or outcomes and is resistant to objectively based reassurance [13, 17].

Less attention has been paid to how and why somatic experiences initially induce a sense of threat and the nature of specific experiences that do so. The self-regulation model [10] (SRM) provides probably the most detailed description of how somatosensory experiences influence emotional and behavioural responses to illness [10]. Anchored in early findings that patients tether anti-hypertensive, antibiotic and asthma medication use to experienced symptoms rather than abstract propositional knowledge (e.g. knowledge that regular medication use is necessary to treat underlying but unseen disease processes) [10], the SRM emphasises the primacy of concrete perceptual processing — that behavioural and emotional responses are primarily influenced by individuals' perceptual experiences not by propositional knowledge [18, 19]. The effects of perceptual experiences on emotional responses are seen to be mediated by intuitive heuristics that are associated with specific sensation attributes such as sensation location, persistence, severity or escalation [19, 20]. For example, instead of deliberating on an aversive sensation by exploring different hypotheses to explain it, a person may simply fear it because it is painful or repulsive [14, 21]. Leventhal, Brissette and Leventhal [19] describe how specific heuristics are linked to sensation attributes (Table 1).

Evidence for this proposition is currently sparse. In FCR research, cross-sectional and short-term prospective studies show correlations between FCR and perceptions of symptom frequency and severity [22, 23]. Indirect support for the role of specific heuristics comes not from FCR research but from qualitative studies of how people misinterpret, and thus fail to report, initial cancer symptoms. Symptoms corresponding to location, pattern, duration, rate of change and severity heuristics are considered likely to be dangerous, and symptoms not corresponding to these do not [24]. One study explicitly shows that people use heuristics to infer danger from symptoms [21].

Current study

Cancer treatments can cause localised symptoms and functional problems, that survivors experience as severe, persistent and escalating, which may cause FCR. According to the SRM, FCR could potentially be reduced or prevented by identifying and changing initial appraisals of these symptoms. There is limited prospective research into predictors of later-occurring FCR, and existing studies have focussed on demographic and clinical predictors, anxiety and smoking cessation rather than symptoms or functional impairments [3, 25–27]. We prospectively examined whether symptom characteristics representing severity, persistence and escalations would predict FCR observed up to 5 years after diagnosis in a sample of uveal melanoma (UM) survivors.

Table 1 Heuristics associated with symptom attributes

Heuristic	Definition
Location rule	Body areas at or adjacent to previous illnesses sites are more likely to be regarded as threatening
Pattern rule	Symptoms that are striking and troubling are likely to be threatening. Diffuse, mild, ambiguous or vague symptoms are less likely to be interpreted so
Severity (of interference) rule	Symptoms that disrupt functioning indicate the presence of illness, whereas those that allow normal functioning will indicate less severe illness
Duration rule	Symptoms that are persistent or prolonged (compared to previous experience or expectations), rather than short lived or intermittent, can indicate seriousness
Rate of change rule	Symptoms that are worsening, or increasing in number, and symptoms that have a sudden rather than gradual onset, can indicate more severe illness. Symptoms that are getting better/improving, stable, or decreasing in number, can indicate absence of illness

UM is advantageous in studies of FCR because objective risk of recurrence is knowable. After UM treatment, symptoms and functional problems emerge in survivorship but rarely portend local recurrence which is extremely uncommon [28]. This allows a more convincing demonstration of the role of concrete perceptual processes in FCR, as any links between symptom characteristics and fears of local recurrence would belie objective reality. Metastatic risk is also objectively knowable. About 40–50% of treated patients die of non-preventable metastatic disease, with metastatic risk almost wholly determined by a single genetic mutation, deletion of one of the pairs of chromosome 3 (monosomy 3, M3), which is reliably detected through prognostic testing [29]. Patients with disomy 3 (two chromosomes. D3) are unlikely to develop metastatic disease. Prognostic outcomes at the time of the study was therefore either good (little risk of metastasis; D3), poor (almost certain metastasis; M3) or not known. If links between symptoms and functional problems are unaffected by knowledge of metastatic recurrence, patterns of association should not differ between these outcomes.

Hypotheses

We observed FCR in later survivorship using discrete observations made 24, 36, 48 and 60 months post-diagnosis. We hypothesised that symptoms and functional impairments, measured one and two observations previously to each observation, would predict FCR at those observations (e.g. 24-month FCR is predicted from 6- and 12-month symptoms and functional impairments and 36-month FCR from 12- and 24-month symptoms and functional impairments).

Hypotheses 1a and 1b operationalised the pattern rule that more troubling visual and ocular symptoms will predict FCR:

Hypothesis 1a: Based on the rate of change heuristic, higher symptom scores on the previous observation will predict FCR.
Hypothesis 1b: Based on the duration heuristic, higher symptom scores on the penultimate (previous but one) observation will predict FCR.

Hypotheses 2a and 2b were based on the severity of interference rule that higher functional impairment scores will predict FCR:

Hypothesis 2a: Based on the rate of change heuristic, higher functional impairment scores on the previous observation will predict greater FCR.
Hypothesis 2b: Based on the duration heuristic, higher functional impairment scores on the penultimate observation will predict FCR.

Method

Participants and procedure

We conducted a secondary analysis of data from an audit of patient-reported outcomes with patient consent for research use, reviewed by the Liverpool Central Ethics Committee (03/06/072/A) consistent with the Declaration of Helsinki. The sample was consecutive adult patients from England or Wales treated for posterior (choroid or ciliary body) UM between April 1st, 2008, and December 31st, 2014, at the Liverpool Ocular Oncology Centre (LOOC). Ruthenium plaque radiotherapy and proton beam radiotherapy were first considered treatments. If the tumour was unsuitable for radiotherapy, patients underwent trans-scleral local resection, trans-retinal endoresection or enucleation (eye removal; treatment protocol is described in Damato and Heimann [30]). These treatments commonly cause delayed ocular and visual symptoms and functional problems [31]. Prognostic testing was offered and explained to patients. Decision-making assistance was offered by cancer nurses and a psychologist. Prognosis was communicated and explained to patients, as an individualised risk of metastatic spread over 10 years was explained by their ocular oncology team.

A consecutive series of UM patients were approached after diagnosis. Those agreeing to participate were surveyed at six observations after diagnosis (observations at 6, 12, 24, 36, 48 and 60 months). Treatments were completed, and test results were communicated before the 6-month observation. Patients who gave written consent were posted questionnaires with postage-paid return envelopes.

Measures

We measured FCR and the extent to which patients felt troubled by ocular irritation, visual impairments, headaches and functional problems such as using stairs and pouring drinks. All variables were measured using scales within the European Organisation for Research and Treatment for Cancer Ophthalmic Quality of Life questionnaire (EORTC QLQ-OPT 30 [29]). The EORTC QLQ-OPT 30 is designed for UM patients, and scales show good reliability and convergent and discriminant validity in UM samples [32, 33]. Response format for all items was 'Not at all', 'A little', 'Quite a bit' and 'Very much', scored 1–4, respectively, and all items were worded in terms of poorer outcomes. Item means were used for all EORTC subscales.

FCR is operationalised in the EORTC QLQ-OPT 30 scale 'worry about cancer recurrence' measuring worry

about local and secondary recurrence (Cronbach's alphas in this study of 0.82–0.86). 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 [34]. Three items used were used: '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's alphas in this study 0.70–0.77); visual symptoms (4 items, e.g. 'Were you troubled by any defects in side vision', alphas 0.72–0.75); and headache (single item 'Did you have headaches?'). The three symptom scales — ocular irritation, visual disturbance and headache — were strongly intercorrelated at each observation with correlations ranging from 0.44 to 0.74. 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 = 0.98 and RMSEA = 0.06. To minimise potential predictor collinearity in multivariate analyses, we computed a single mean of the three subscales that we labelled visual and ocular symptoms.

Functional limitations are measured by the EORTC QLQ-OPT 30 functional limitations scale (5 items, e.g. 'Difficulty seeing steps or pavements?', alphas 0.92–0.93).

Six-month anxiety was assessed using the Hospital Anxiety and Depression Scale (HADS) anxiety subscale [35]. The scale has seven items scored from 0 to 3 with higher scores signifying greater symptomology (range = 0–21, alpha 0.82). The anxiety subscale predicts diagnosed cases with good sensitivity and specificity, with a clinical cut-off of eight and above [36].

Age, gender, chromosome 3 status (M3, D3, not tested or test failed) and primary treatments were taken from patient records.

Analysis

We used a mixed measures design with four levels. Observations of variables were staggered to represent prospective prediction within each level. Later survivorship was arbitrarily defined as 24 months. Most primary UM treatments conclude after 6 months, and few survivors receive secondary or preventive interventions. Outcome variables were FCR at 24, 36, 48 and 60 months (representing levels 1–4). Predictor variables at each level were two sets of symptom and function scores; one measured two observations before the outcome (6, 12, 24 and 36 months, respectively) and the other one observation before the outcome (12, 24, 36 and 48 months, respectively). This allowed prospective prediction of FCR by predictors measured one and two observations previously (Table 2). FCR scores at the previous observation (12, 24, 36 and 48 months) were used as control variables. Other control variables were 6-month age, gender, treatment modality, prognostic testing outcomes and 6-month anxiety. Previous studies have shown enucleation patients to differ from other treatments on FCR [31, 37]. A dummy variable (enucleation versus other treatments) was used in the analyses.

We addressed missing data by a three-step process. First, we deleted without replacement cases who did not contribute

Table 2 Timeline showing timing of predictor observations across four levels of the mixed model analysis

	Clinical records	6-month observation	12-month observation	24-month observation	36-month observation	48-month observation	60-month observation
Level 1	Covariates	Symptoms and functional impairments	Symptoms and functional impairments/ FCR covariate	Criterion FCR measure			
Level 2	Covariates		Symptoms and functional impairments	Symptoms and functional impairments/ FCR covariate	Criterion FCR measure		
Level 3	Covariates			Symptoms and functional impairments	Symptoms and functional impairments/ FCR covariate	Criterion FCR measure	
Level 4	Covariates				Symptoms and functional impairments	Symptoms and functional impairments/ FCR covariate	Criterion FCR measure

data at the 24-month or who did not contribute at least three time points. Second, data were replaced for cases who had missed a single time point but returned at the next time point. Data estimation used unbiased full information likelihood estimation (FILA) based on adjacent time points and covariates [38]. Third, data were estimated for participants who missed two or more consecutive time points using a pattern-matching approach with dummy covariates coded for dropout occasion [39].

SPSS v27 was used in all analyses. Means and *SD*s were estimated for continuous variables and frequency counts and percentages for categorical variables. Pearson and split-half correlations were used for univariate tests. Temporal trajectories across the six time points were estimated using six-level factorial mixed models of slopes and intercepts of scores for each variable at each observation.

Hypotheses were tested using a single mixed model analysis employing maximum likelihood estimation with diagonal covariance for correlated random effects. Initial models included all control and predictor variables plus intercept and slope. FCR, symptoms and functional problems were treated as random effects. Final model selection was based on minimising the Bayesian information criterion through backward selection of control variables (symptom and functional problem variables were used in all models).

Follow-up moderation analyses examined whether prognostic group (e.g. participants' knowledge of their metastatic risk) influenced relationships between symptoms and functional problems and FRC; we conducted follow-up analysis to identify whether prediction patterns differed between M3, D3 and not tested groups. Two interaction terms were added to the above model: one between M3 status (M3 versus other groups) and symptoms and functional limitations and the other between D3 status (D3 versus other groups) and symptoms and functional limitations. Significant interactions would suggest that chromosome 3 status influenced links between predictor variables and FCR.

Results

All patients were approached ($n = 1{,}374$), of whom 1,014 provided data at least once. We eliminated 305 cases who did not satisfy data provision criteria, including 107 who died before 24 months. Of the remaining 709 cases, data replacement was carried out for 112 cases at 6 months, 83 at 12 months, 63 at 24 months, 120 at 36 months, 180 at 48 months and 290 at 60 months. The mean age was 69.03 (SD = 12.12), and 49% were female. Table 3 shows sample characteristics.

Table 3 Demographic and clinical characteristics of participants

	Number	Percentage
Sex		
Males	363	51.3%
Females	340[†]	48.0%
Marital status		
Married or with partner	516	74.5%
Widowed	90	12.3%
Divorced/separated	85	13.0%
Single	2	0.3%
Treatment		
Enucleation	155	21.9%
Plaque radiotherapy	327	46.2%
Proton beam radiotherapy	167	23.6%
Resection	34	4.8%
Other	25	3.5%
Chromosome 3 status		
Disomy 3	179	25.3%
Monosomy 3	192	27.1%
Unknown	296	41.8%
Test failed	41	5.8%
Eye		
Left	342	48.3%
Right	366	51.6%
Visual acuity affected eye (LogMar)	Mean = 0.14	SD = 0.28
Visual acuity unaffected eye (LogMar)	Mean = 0.15	SD = 0.28

[†] where raw frequencies do not total 708, discrepancies are attributable to missing data

Means and SDs in Table 3 (replacement data are included) between 2.54 and 2.15 over the six observations show some worry (verbal labels are 2 = 'A little' and 3 = 'Quite a lot') that declined significantly, but by only about 15%, over 5 years (linear model $F = 20.18$, $df = 5$, $p < 0.01$). The first three observations were significantly higher than the sixth. This is consistent with previous prospective studies showing small declines in FCR in late survivorship populations [3, 25–27]. Symptoms showed a smaller but broadly linear decline (linear model $F = 2.42$, $df = 5$, $p < 0.05$), with the first two observations significantly higher than the sixth. No trajectory was noted for functional impairment (linear model $F = 1.67$, $df = 5$, $p = 0.140$) (Table 4).

Hypothesis tests

Appendix 1 shows Pearson and point-biserial correlations between FCR and predictors at each of the four levels used for hypothesis testing. FCR was positively associated with all predictors. FCR was associated with younger age at all

Table 4 Temporal trends in study variables

	6 months	12 months	24 months	36 months	48 months	60 months
Age	69.03 (12.12)					
Anxiety	5.39 (4.13)					
FCR	2.54 (1.17)	2.37 (1.12)	2.22 (0.99)	2.18 (1.02)	2.17 (1.01)	2.15 (0.92)
Symptoms	1.79 (1.21)	1.72 (1.20)	1.70 (1.23)	1.66 (1.05)	1.69 (1.13)	1.64 (0.85)
Functional problems	1.76 (1.16)	1.72 (1.04)	1.72 (1.05)	1.69 (1.05)	1.78 (1.06)	1.69 (0.74)

levels and female gender at the first level only. Positive associations were noted with M3 and enucleation treatment. D3 did not predict FCR and was not used as a covariate in the multivariate analyses.

The best fit multivariate mixed model (BIC = 6,821.34) included the intercept, M3 status, anxiety, level, previous FCR score and times 1 and 2 functional impairment. Of the control variables, higher FCR scores were predicted by greater anxiety at 6 months, monosomy 3 and greater FCR at the previous observation. Time 1 symptoms and time 2 function were positively associated with FCR. Time 2 symptoms and time 1 functional impairment were not predictors (Table 5).

Moderation analyses

Including interactions between chromosome 3 status and predictors into the model did not improve the BIC (BIC = 7,052.29) nor were any of the two way interactions significant (see Appendix 2). This suggests that patterns of association did not differ between chromosome 3 groups.

Discussion

Treatment-related symptoms and functional problems are probable risk factors for FCR in UM survivorship. Consistent with the duration heuristic, symptoms predicted FCR only when they persisted for at least a year. Functional problems predicted FCR at the immediately subsequent observation, which is consistent with the rate of change heuristic. These relationships did not differ according to chromosome 3 status, suggesting invariance across differing objective (metastatic) recurrence risk levels.

The study makes two contributions. First, we show that treatment-related symptoms and functional problems predict future FCR, at least in UM survivors. Unlike previous cross-sectional studies [22], prospective associations show sequence, thus strengthening causal claims. Symptoms and functional problems differ from previously established risk factors in one important respect. Previous FCR risk factor studies have used predictors measured at diagnosis or treatment cessation [4]. We suggest that origins of some FCR might lie in events — symptoms and functional problems — occurring *during* survivorship and not necessarily predictable at its commencement. Monitoring patients during their survivorship could identify survivors at higher risk of FCR.

Second, findings are consistent with the SRM idea that specific somatic experiences — localisation, escalation, durability and severity — are key drivers of emotional responses to illness. Associations between FCR, symptoms and functional problems belie the reality that the latter do not portend local recurrence. Moreover, associations did not differ according to prognostic group — the effects were similar in those who were told that they would be almost certainly free from metastatic spread and those told that

Table 5 Multivariate mixed model predictors of FCR; *beta*s and confidence intervals for predictors of FCR at 24, 36, 48 and 60 months

	Low 95% C.I	*beta*	High 95% C.I
Intercept	1.01	1.15	1.28
M3 positive	.03	.12	.22
Anxiety	.06	.07	.08
FCR T1	.08	.13	.18
Level	− .01	.01	.03
Symptoms at previous observation	− .03	.01	.05
Symptoms two observations previously	.05	.11	.17
Functional problems at previous observation	.03	.08	.17
Functional problems two observations previously	− .03	.03	.15

metastatic spread is highly likely. Our findings are consistent with the idea that FCR is mediated by the heuristics specified by Leventhal, Brissette and Leventhal [19], although we did not measure heuristics directly and cannot empirically show mediation.

We do not know why FCR lagged symptom detection by over 12 months (duration heuristic), but no lag was found for functional problems (rate of change heuristic). We are unconvinced that the observed symptoms led to FCR only after they caused functional problems, because links between symptoms and FCR were statistically independent of later functional problems. A better explanation is that symptom meanings were ambiguous [21]. Thus, survivors may have been willing to overlook them or wait until symptoms persisted before evaluating them as dangerous. This explanation is supported in studies of cancer symptom recognition, where people often do not appreciate the danger of cancer symptoms until those symptoms persist and force a re-evaluation of initial perceptions [24].

Another explanation is that survivors experienced dissonance; they perceived symptoms as threatening but knew that the risk of local recurrence was low. Similar to many dual process models [40], when modes conflict the SRM suggests that people might give immediate reference to deliberative 'top down' modes of thought because they desire rational solutions [10]. However, preferencing knowledge over intuition is often an effortful activity that may consequently be time-limited [19]. Thus, intuitive thought often eventually prevails in influencing emotion and behaviour [10].

Limitations

We did not examine mediators of associations between symptoms, functional problems and FCR. Thus, we infer mechanisms for our effects but do not know that survivors used pattern, severity, duration or rate of change heuristics and cannot rule out the possibility that survivors drew their conclusions about symptoms and functional limitations through other means. Our claim for the importance of symptoms in FCR rests on the assumption that patients knew that symptoms and functional problems do not portend local recurrence and knew their probabilities of metastatic spread because they were informed of these. This is consistent with our clinical experience, but we did not directly assess their subjective beliefs about recurrence risk. Whilst there is evidence from other cancers that objectively harmless symptoms are associated with FCR [22], we caution that the effects noted here are located in UM and may not generalise readily to other cancers.

Implications for survivors

Currently, FCR interventions focus on the amelioration of FCR using multicomponent psychoeducation, CBT, mindfulness, metacognitive and relaxation packages [41]. In focussing on the initiation of FCR, our findings suggest a different approach that FCR can be prevented by identifying survivors at risk, through monitoring symptoms and functional problems and developing preventive interventions that address somatosensory appraisals. The SRM literature underpins interventions that are currently used to prepare patients for stressful medical procedures [42] and may be adaptable to symptoms and functional problems. Preparation involves explicitly describing procedures, their implications and patients' likely somatic experiences. The rationale is to curtail anxiety in patients by providing safe, plausible and accessible schemata, allowing them to process aversive sensations without catastrophising[43]. This approach may help cancer patients by helping them to understand and tolerate symptoms and functional problems but requires development and testing. Another area requiring investigation is innovative ways that practitioners can reduce FCR by explaining symptoms and functional problems during routine follow-up consultations.

A clear research priority is a mediational research to determine whether heuristics, derived from the characteristics of symptoms and functional problems, mediate relationships with FCR. It is also important to show that heuristics mediate FCR independently of competing explanations. A second priority is to establish psychological, social and other contextual conditions that facilitate or moderate the development of FCR when symptoms and functional limitations are experienced.

Conclusions

Cancer patients experiencing symptoms and functional problems at any point in the first four years of survivorship are at risk of experiencing elevated FRC, even though they may objectively know that recurrence risk is low. Future research is required to understand both inductive and deductive mechanisms for this effect.

Appendix 1

Table 6 Pearson and point-biserial correlations between FCR and predictors

	FCR Observation 3	FCR Observation 4	FCR Observation 5	FCR Observation 6
Age	− 11*	− .09*	− .04	− .11*
Sex	.07*	.02	.07	.05
M3 positive	.10*	.12*	.07	.17*
D3 positive	− .03	− .03	.02	− .06
Enucleation treatment	.00	.09*	.09*	.04
6-month anxiety	.39*	.33*	.33*	.42*
FCR previous observation	.51*	.45*	.37*	.43*
Symptoms two observations previous	.16*	.21*	.23*	.33*
Symptoms time 2	.37*	.25*	.23*	.30*
Functional problems two observations previous	.20*	.19*	.34*	.18*
Functional problems previous observation	.29*	.19*	.24*	.18*

*, $p < .05$; *M3*, monosomy 3 = 1; rest of sample = 0. D3, disomy 3 = 1; rest of sample = 0. Time 2, observation previous to DV. Time 1, two observations previous to DV

Appendix 2

Table 7 Multivariate mixed model predictors of FCR; *beta*s and confidence intervals for main effects and M3 positive by symptom and functional limitation interactions

	Low 95% C.I	*beta*	High 95% C.I
Intercept	1.22	1.49	1.77
M3 positive	− .32	− .02	.29
Anxiety	.06	.08	.08
FCR T1	− .05	− .01	.03
Level	− .01	.01	.03
Symptoms T1	− .04	.07	.08
Symptoms T2	− .17	− .06	.05
Functional problems T1	.00	.07	.13
Functional problems T2	− .02	.09	.20
Poor prognosis* symptoms T1	− .23	− .10	.03
M3 positive* symptoms T2	− .11	.01	.14
M3 positive*	− .10	− .02	.06
M3 positive*	− .09	.04	.17

T1, measure taken one observation previous to outcome; *T2*, measure taken two observations previous to outcome

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Data availability Data available on request from the first author. Ethical clearance may be required.

Declarations

Consent to participate All participants provided written consent after provision of a patient information statement.

Conflict of interest The authors declare no competing interests.

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