Depression, Anxiety, and Regret Before and After Testing to Estimate Uveal Melanoma Prognosis

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**IMPORTANCE** To our knowledge, longitudinal assessment of depression, anxiety, and decision regret (a sense of disappointment or dissatisfaction in the decision) in patients undergoing prognostication for uveal melanoma does not exist.

**OBJECTIVE** To report on depression, anxiety, and decision regret before and after testing to estimate uveal melanoma prognosis.

**DESIGN, SETTING, AND PARTICIPANTS** Prospective interventional case series conducted at an institutional referral practice of 96 patients with clinical diagnosis of uveal melanoma who underwent prognostication at the time of primary therapy.

**MAIN OUTCOMES AND MEASURES** Depression, anxiety, and decision regret prior to prognostication (baseline) and at 3 and 12 months afterwards. The Hospital Anxiety and Depression Scale (HADS) and Decision Regret Scale were self-administered by the patients prior to prognostication (baseline) and at 3 and 12 months afterwards. Data were summarized using means and standard deviations for continuous measures, frequencies, and percentages for categorical factors. A mixed model was used to assess the trajectory of HADS anxiety and the associations between HADS anxiety and baseline HADS depression, baseline decision regret, prognostication test result, and adjuvant therapy, respectively, while adjusting for age and sex.

**RESULTS** Ninety-six patients (median age 60.7 years) completed baseline questionnaires. The mean (SD) HADS anxiety score at baseline (7.4 [4.0]) was higher than at 3 months (5.4 [3.7]; \( P < .001 \)) or 12 months (4.7 [3.4]; \( P < .001 \)), and decreased with older age (coefficient estimate [SD], −0.06 [0.02]; \( P < .001 \)). The decision regret score was associated with baseline HADS depression score (coefficient estimate [SE], −1.17 [0.43]; \( P < .007 \)), and HADS depression score increased with baseline HADS anxiety score (coefficient estimate [SE], 0.39 [0.06]; \( P < .001 \)).

**CONCLUSIONS AND RELEVANCE** Our study raises questions about decision regret in patients who agree to have a prognostic test that may not help guide treatment. Although decision regret appears to lessen or dissipate with time, study on larger numbers of patients is necessary to elucidate factors that may be addressed to mitigate decision regret.

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Uveal melanoma is a rare tumor of the eye with an annual incidence rate of 5.3 per million people in the United States. Most patients undergo radiotherapy or enucleation shortly after initial diagnosis. Approximately 50% of these patients will go on to develop metastases, despite having had no evidence of metastases on conventional imaging at the time of diagnosis. Unfortunately for those patients with metastatic disease, there is no effective therapy, and the majority of these patients will die within 1 year.

Depression and anxiety in patients with cancer is very common, with approximately 25% of cancer patients requiring assessment and treatment during the course of their cancer care. The rates of depression and anxiety vary with different cancer types. One study of patients with uveal melanoma demonstrated the highest rate of depression at 3 months following treatment of the primary tumor. Chabert et al. reported that 27.9% of the patients were anxious and 23.7% were depressed when assessed with the Hospital Anxiety and Depression Scale (HADS)–Anxiety Subscale and the HADS–Depression Subscale. In the Collaborative Ocular Melanoma Study, patients who underwent brachytherapy had more symptoms of anxiety compared with those who underwent enucleation, although depression levels were equal between the 2 groups (post-treatment).

Many patients with uveal melanoma are offered the option of prognostic testing, wherein primary tumor cells are genotyped to determine whether the patient has low risk (0%-5%) or high risk (60%-100%) of metastases. That the loss of a chromosome 3 is associated with the development of metastasis is well established, and a variety of techniques are being used clinically to test tumors for detection of monosomy 3 and gene expression profiling. The purpose of this testing is somewhat different from that of most other prognostic tests in patients with newly diagnosed cancer. Typically, prognostic tests are used to guide adjuvant therapy recommendations. In uveal melanoma, adjuvant therapy has not been shown to improve outcome. In the absence of easy access to an adjuvant treatment trial, the prognostic information is either used to increase the frequency of systemic surveillance to detect preclinical metastatic disease or to help the patients in end-of-life planning.

Decision regret is the sensation of disappointment or distress about a decision that one has made. Although everyone has regrets from time to time, it can occur more often when a person has major depression or an anxiety disorder. When a patient is making medical decisions, physicians want to be certain that their patient fully understands the decision. Knowing what factors can play into decision regret will be helpful for both physicians and patients.

To our knowledge, to date, there are no studies that provide longitudinal assessment of depression, anxiety, and decision regret in patients undergoing prognostication for a cancer for which effective therapies to prevent and treat metastasis do not exist. The goal of this study was to evaluate depression, anxiety, and decision regret in patients undergoing prognostication of uveal melanoma.

Methods

This study was approved by the institutional review board at the Cleveland Clinic, Cleveland, Ohio, and was undertaken to evaluate decision regret and depression and/or anxiety in patients who were enrolled in an established study of uveal melanoma prognostic testing. Patients with a high-risk genotype were offered inclusion in a systemic adjuvant therapy trial. Patients were given self-administered questionnaires at 3 points: baseline (immediately prior to treatment of the primary tumor), 3 months, and 12 months following treatment of the primary tumor. A trained interviewer was present for any clarifications.

Inclusion Criteria

Patients invited to participate in the study were able to read English, were their own guardians, and had a clinical diagnosis of uveal melanoma without any prior local or systemic therapy. All eligible patients were informed of the investigational nature of this study; those who provided written informed consent were enrolled. Patients younger than 18 years and those with metastasis at presentation were excluded.

Hospital Anxiety and Depression Scale

The HADS is a 14-item questionnaire that patients self-administer. The HADS has been validated in patients with a wide variety of cancers. Items are grouped into 2 components: one component assesses anxiety (HADS–Anxiety Subscale), and the other screens depression (HADS–Depression Subscale). The range of scores is from 0 to 21 on each subscale. A score of less than 7 on either subscale indicates unlikely clinically significant anxiety or depression. With a score of 8 to 10, a patient is considered to have possible anxiety or depression, and with a score greater than 10, a patient is considered to have either probable anxiety or depression.

Decision Regret Scale

The decision regret scale was modified to include the following 6 questions at initial evaluation:

- I am satisfied that I am adequately informed about the issues important to my decision.
- The decision I made was the best decision possible for me personally.
- I am satisfied that my decision was consistent with my personal values.
- I expect to successfully carry out (or continue to carry out) the decision I made.
- I am satisfied that this was my decision to make.
- I am satisfied with my decision.

Decision regret was significantly associated with depression. Psychosocial assessment, including decision regret, should be integrated into future adjuvant treatment trials.
Interviews at 3 to 12 months included following 5 questions:
• It was the right decision.
• I regret the choice that was made.
• I could go for the same choice if I had to do it over again.
• The choice did me a lot of harm.
• The decision was a wise one.

Patients were asked by the trained interviewer to reflect on the decision that they had made about obtaining a prognostic profile. They were asked to show how strongly they agreed or disagreed with these statements by circling a number from 1 to 5 that best fit their view about their decision (1 = strongly agree, 2 = agree, 3 = neutral, 4 = disagree, 5 = strongly disagree). Decision regret was scored at baseline as no regret: 6 to 12, some regret: 13 to 23, and full regret: 24 to 30. Decision regret was scored at follow-up as no regret: 5 to 10, some regret: 11 to 19, and full regret: 20 to 25.

Prognostication Test
Chromosome 3 status was assessed by fluorescent in situ hybridization using both directly labeled SpectrumGreen (Abbot Laboratories) and SpectrumOrange (Abbot Laboratories) enumeration probes for the alphacentromeric locus of chromosome 3 (CEP3) and a locus-specific probe. A total of 200 interphase cells were scored using a Zeiss fluorescent in situ hybridization workstation to determine the percentage of signals for each locus. We used a cutoff value of 20% to define monosomy for chromosome 3 (high-risk genotype, poor prognosis).17

Statistical Analysis
Categorical data were summarized using frequency and percentage. Continuous data were summarized using mean and standard deviation. Scores of HADS anxiety, HADS depression, and decision regret were compared among time points using paired t test.

For decision regret, possible scores at baseline were between 6 and 30 and possible scores at follow-up were between 5 to 25. For analysis purpose, decision regret scores were transformed to a 0 to 100 scale for both baseline and follow-up.

Scaled decision regret score at baseline = (decision regret score at baseline − 6)/(30 − 6)/100. After transformation, an original score of 6 will be 0, and an original score of 30 will be 100.

Scaled decision regret score at follow-up = (decision regret score at follow-up − 5)/(25 − 5)/100. After transformation, an original score of 5 will be 0, and an original score of 25 will be 100.

A mixed model was used to assess the trajectory of HADS anxiety score and the associations between HADS anxiety score and baseline HADS depression score, baseline decision regret score, prognostication test result, and use of adjuvant therapy, respectively, while adjusting for age and sex. An unstructured covariance structure was assumed for the mixed model to account for the correlations among observations from the same patient. Similar analyses were performed for HADS depression score and decision regret score. All tests were 2-sided and performed at an overall significance level of .05. A Bonferroni-adjusted significance level was used for multiple comparisons. All analyses were performed using SAS version 9.2 (SAS Institute).

Results
A total of 96 patients enrolled in this prospective study. The mean (SD) age was 60.7 (14.8) years, and 44% were women. The tumors of 42 patients (44%) manifested the high-risk genotype, monosomy 3, and 21 of these 42 (50%) enrolled in the adjuvant therapy trial (Table 1).

At 3 months, 68 patients completed the HADS psychological assessments, and 65 completed the decision regret scale. At 12 months, 79 patients completed the HADS psychological questionnaires, and 77 completed the decision regret scale.

At Baseline/Follow-up
Hospital Anxiety and Depression Scale
At the baseline, 49% (n = 47) of patients had scores that indicated either possible or probable anxiety, and 9% (n = 9) had either possible or probable depression. At the 3-month visit, 55% (n = 24) had scores that indicated either possible or probable anxiety, and 4% (n = 3) had either possible or probable depression. At the final assessment (12 months), 20% (n = 16) had either possible or probable anxiety, and 9% (n = 7) had either possible or probable depression (Figure).

Decision Regret
At the baseline, 10% (n = 10) of patients had some or full decision regret. At 3 months, 17% (n = 11) had some or full decision regret, while at 12 months, 10% (n = 8) had some or full decision regret. Of those patients with decision regret at any time, 55% (n = 12) were women. There were 12 patients who had no decision regret at baseline, but who expressed some regret at 3 months (8 [67%]). Two of these patients had monosomy 3 or poor prognosis (neither patient reported any decision regret at 12 months).

Trends
For all 3 outcomes (depression, anxiety, and decision regret), there was a general decreasing trend over time both in estimated differences in scores (Table 2) and prevalence of different classifications of the measures (Figure).

Four models were used to assess the longitudinal trends in scores for the 2 HADS subscales (anxiety and depression) and decision regret scores, prognostication test result, and use of adjuvant therapy, respectively, while adjusting for age and sex.

The HADS anxiety score increased as baseline HADS depression score increased (estimated coefficient [SE], 0.65 [0.08]; P < .001). There was no association between anxiety score over time and decision regret score at baseline (P = .70), results of prognostication test (P = .96), or entry into adjuvant therapy trial (P = .85). Statistical analysis revealed that anxiety score at baseline was higher than at 3 months (mean
Depression, Anxiety, and Regret During Uveal Melanoma Prognosis Testing

Table 1. General Characteristics of 96 Patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Overall</th>
<th>Men (n = 50)</th>
<th>Women (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, mean (SD), y</td>
<td>60.7 (14.8)</td>
<td>59.3 (15.8)</td>
<td>62.2 (13.6)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>95 (99)</td>
<td>50 (100)</td>
<td>45 (98)</td>
</tr>
<tr>
<td>African American</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Prognostication outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>42 (44)</td>
<td>20 (40)</td>
<td>22 (48)</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>12 (12)</td>
<td>8 (16)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Poor</td>
<td>42 (44)</td>
<td>22 (44)</td>
<td>20 (44)</td>
</tr>
<tr>
<td>Adjuvant therapy trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>75 (78)</td>
<td>40 (80)</td>
<td>35 (76)</td>
</tr>
<tr>
<td>Yes</td>
<td>21 (22)</td>
<td>10 (20)</td>
<td>11 (24)</td>
</tr>
</tbody>
</table>

* There was no difference between men and women in the distributions of any of these characteristics.

[SD], 7.4 [4.0] and 5.4 [3.7], respectively; P < .001) or 12 months (4.7 [3.4]; P < .001) (Table 3). The HADS anxiety scores also decreased with older age (coefficient estimate [SE], −0.06 [0.02]; P < .001). Female sex was not associated with higher HADS anxiety.

The HADS depression score increased with increase in baseline HADS anxiety scores (estimated coefficient [SE], 0.39 [0.06]; P < .001). No other significant associations were found in other analyses.

Decision regret score was significantly associated with baseline HADS depression score (estimated coefficient [SE], 1.17 [0.43]; P = .007). No other significant associations were found.

Discussion

This was a 12-month, prospective study in which patients who underwent prognostication testing of uveal melanoma were assessed at baseline and followed up longitudinally for depression, anxiety, and decision regret. We found that depression and anxiety decreased over time (estimated differences in scores [Table 2] and prevalence of different classifications of the measures [Figure]) and that decision regret was associated with depression. This prospective study differs from other studies, as patients were followed up longitudinally from just prior to the prognostic testing for up to 12 months after treatment of the primary tumor. Further, it examined the possible coexistence of, and the potential confounding role of, depression and anxiety with decision regret.

Previous studies have reported that patients do want cytogenetic/prognostic testing and did not regret deciding to have the testing.18 Cook and colleagues18,19 observed that patients did not even view that a decision needed to be made. In the same study, they observed that patients expected to be reassured if informed of a good prognosis; however, in our study, patients reported that this was not the case.

Beran and colleagues20 retrospectively surveyed patients with uveal melanoma and reported that 97% of those who had not been offered cytogenetic prognostic testing would have wanted prognostication and the majority of all patients, regardless if they underwent prognostication, felt that supportive counseling should be integrated at the time of discussion of results. The patients with less favorable results did perceive the testing to be less useful than those with a more favorable prognosis.20 Their study was consistent with previous reports that showed a gradual decrease in depression and anxiety over time.18,20 We also observed reduction in the number of patients reporting anxiety symptoms over time. However, our data did differ in that an unexpectedly low number of patients (9%) endorsed symptoms of depression.20 We observed a higher rate (10%) of decision regret in our patients compared with previous studies.18,20 This could be because our patients were asked about decision regret at the time of clinical diagnosis and periodically through the first year of follow-up. In the previous studies, patients were asked about decision regret well after the prognosis and surveillance period.18,20 It could be that decision regret is more common during the initial postprognostication period. Our findings show that 10% of patients had
Decision regret even prior to becoming aware of the prognostication test results. At 3 months after prognostication, 17% of patients had decision regret and in the 12-month follow-up data, this number dropped to the baseline value of 10%. In a previous study, it had been suggested that patients may have regret if found to have a poor prognosis after undergoing prognostication.\(^6\) While this did happen in 2 patients in our study, the majority of patients with decision regret did not follow this pattern.

Depression and anxiety can cause people to question their decisions. Because of this, one could expect that those patients with higher depression and anxiety ratings would more frequently express decision regret. In our study sample, this was the case, and decision regret score was significantly associated with baseline HADS depression score. Therefore, support or intervention directed to alleviate self-reported depression could improve the decision-making capacity for patients undergoing prognostic testing.

Limitations of our study include small sample size, and we recommend that these factors be studied in larger populations. Although the study sample size provided adequate statistical power to detect medium- to large-effect changes, a larger sample size would be required to detect smaller changes. Asking someone about decision regret can result in one questioning their decision, and this may have resulted in bias, regardless of when the question was asked. One of the major strengths of our study is the longitudinal data collection from baseline to 12-month postintervention. To our knowledge, such longitudinal data collection has not been done in prior studies.

In summary, in this prospective, longitudinal study of patients undergoing prognostic testing for uveal melanoma, we observed that depression and anxiety declined over a period of 12 months and that decision regret was significantly associated with depression score. Our study raises questions about decision regret in patients who are having a test that may not help guide treatment. Although decision regret appears to lessen or dissipate with time, study on larger numbers of patients is necessary to elucidate factors that may be addressed to mitigate decision regret. Given that prognostication tests will eventually be used to identify patients eligible for enrollment into adjuvant treatment trials, psychosocial assessment, including decision regret, should be integrated into such trials, ideally prior to any testing.

Table 2. Comparisons of Outcomes Among Baseline, 3 Months, and 12 Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline vs 3 mo</th>
<th>Baseline vs 12 mo</th>
<th>3 mo vs 12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Estimated Difference (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>68</td>
<td>-1.63 (-2.39 to -0.87)</td>
<td>.001</td>
</tr>
<tr>
<td>HADS Depression</td>
<td>68</td>
<td>-0.34 (-0.98 to 0.31)</td>
<td>.31</td>
</tr>
<tr>
<td>Decision regret(^a)</td>
<td>65</td>
<td>-0.51 (-5.10 to 4.07)</td>
<td>.83</td>
</tr>
</tbody>
</table>

\(^a\)P values were from paired t test. A Bonferroni-adjusted significance level of 0.05/3 = 0.0167 was used to account for multiple comparisons.

\(^b\)Scaled score. For analysis purpose, decision regret scores were transformed to a 0 to 100 scale for both baseline and follow-up. Scaled decision regret score at baseline = (decision regret score at baseline − 6)/(30 − 6)/100. After transformation, an original score of 6 will be 0 and an original score of 30 will be 100. Scaled decision regret score at follow-up = (decision regret score at follow-up − 5)/(25 − 5)/100. After transformation, an original score of 5 will be 0 and an original score of 25 will be 100.

Table 3. Summary Statistics of Outcomes at Baseline and Follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>3 mo</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean (SD)</td>
<td>No.</td>
</tr>
<tr>
<td>HADS Anxiety Score</td>
<td>96</td>
<td>7.4 (4.0)</td>
<td>68</td>
</tr>
<tr>
<td>HADS Depression Score</td>
<td>96</td>
<td>3.1 (1.0)</td>
<td>68</td>
</tr>
<tr>
<td>Decision regret score(^a)</td>
<td>96</td>
<td>12.5 (21.4)</td>
<td>65</td>
</tr>
</tbody>
</table>

\(^a\)Scaled score. For analysis purpose, decision regret scores were transformed to a 0 to 100 scale for both baseline and follow-up. Scaled decision regret score at baseline = (decision regret score at baseline − 6)/(30 − 6)/100. After transformation, an original score of 6 will be 0 and an original score of 30 will be 100. Scaled decision regret score at follow-up = (decision regret score at follow-up − 5)/(25 − 5)/100. After transformation, an original score of 5 will be 0 and an original score of 25 will be 100.
multidisciplinary investigation of uveal melanoma, part of which is reported herein. Funding organizations listed above did not have any role in collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES


