Survival in Patients With Presymptomatic Diagnosis of Metastatic Uveal Melanoma

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Objective: To determine if patients diagnosed as having metastatic uveal melanoma before the onset of symptoms experience more favorable survival outcomes than patients diagnosed after the onset of symptoms.

Methods: A retrospective cohort study was performed among 90 patients who were diagnosed as having metastatic uveal melanoma after proton beam irradiation by routine surveillance testing (asymptomatic group) compared with 259 patients who were diagnosed as having metastatic uveal melanoma after development of symptoms (symptomatic group). The median survival times and cumulative rates of melanoma-related death after diagnosis of metastasis were compared between the 2 groups.

Results: No differences were noted between groups in known prognostic factors for melanoma-related death, including age and tumor size. Cumulative rates of melanoma-related death were higher for patients in the symptomatic group vs the asymptomatic group (P < .001, log-rank test) owing to differences in mortality observed in the first year after diagnosis of metastasis (87.8% vs 68.5%). By the second year after diagnosis of metastasis, cumulative rates had reached 90% or higher in both groups. The median time to melanoma-related death after primary tumor diagnosis was 40.6 months in the asymptomatic group vs 45.1 months in the symptomatic group (P = .61).

Conclusion: Presymptomatic detection of metastatic uveal melanoma by routine surveillance testing seems to confer a survival advantage only in the first year after diagnosis of metastasis, which is likely because of lead-time bias.

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Despite excellent rates of local control of primary intraocular tumor, metastatic disease remains the leading cause of death in patients with uveal melanoma.1 Prior investigations of metastasis after proton beam irradiation for uveal melanoma revealed that the cumulative probability of metastasis at 5 years after primary treatment was 20%, with a median time to metastasis of 2.1 years after treatment.2 Similarly, cumulative rates of metastasis in the Collaborative Ocular Melanoma Study2 at 5 years and 10 years after treatment were 25% and 34%, respectively. Once metastases develop, median survival is short, typically less than 1 year.4,5 The site and extent of metastases affect length of survival. Patients in whom metastases are confined to extrahepatic locations have significantly longer survival (median, 19-28 months).6 However, most patients who develop metastases have liver involvement, which results in 1-year survival of approximately 10% to 15%.6

Various systemic chemotherapy regimens have proven ineffective against metastatic uveal melanoma.5,6 Results of several uncontrolled studies suggest improved survival after aggressive local therapies for metastatic disease, such as surgical resection of hepatic metastases5,6 and hepatic artery infusion chemotherapy,10 leading some investigators to advocate for more frequent or more extensive surveillance examinations to detect smaller isolated metastatic lesions.

To determine the effect of earlier detection of metastatic disease on survival of patients with uveal melanoma, we compared outcomes in asymptomatic patients diagnosed as having metastatic disease by routine surveillance testing vs those whose metastases were discovered after the onset of symptoms. As a measure of potential improvement in treatment protocols over the past 2 decades, we also evaluated differences in survival between patients diagnosed as having metastatic disease before January 1990 vs those diagnosed between January 1990 and December 1997.
STUDY DESIGN

A waiver of informed consent and Health Insurance Portability and Accountability Act authorization was granted by the Institutional Review Board of the Massachusetts Eye and Ear Infirmary, Boston. Three hundred forty-nine patients treated with proton beam irradiation at the Massachusetts Eye and Ear Infirmary for primary uveal melanoma who subsequently developed metastases were classified into the following 2 groups according to how and when metastasis was detected: (1) diagnosis at the time of routine surveillance testing or incidentally in the absence of symptoms (asymptomatic group) and (2) diagnosis after development of symptoms (symptomatic group). These categories were used as a surrogate measure of early and late diagnoses. For routine metastasis surveillance, most patients had annual liver function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total and direct bilirubin, lactate dehydrogenase, γ-glutamyltranspeptidase, and 5′-nucleotidase levels), and computed tomographic images of the liver were obtained if abnormalities were found.

Diagnosis of melanoma metastasis was confirmed by biopsy in 77.8% of the asymptomatic group and in 76.2% of the symptomatic group. For patients in whom biopsy was not performed, the diagnosis was established by imaging studies (eg, ultrasonography, magnetic resonance imaging, or computed tomography), by autopsy, or in rare cases (2.2% of the asymptomatic group and 1.9% of the symptomatic group) by report from a physician or next of kin or by death certificate. Only 2 patients in the symptomatic group had an unconfirmed diagnosis.

The median survival times and cumulative rates of melanoma-related death after diagnosis of metastasis were compared between the 2 groups. Vital status was obtained through active surveillance of most patients; approximately 50% of patients in both groups returned to the Massachusetts Eye and Ear Infirmary after proton beam irradiation for ocular and systemic follow-up, while the remainder were followed up through their referring ophthalmologists or internists. Patients who did not return regularly to the Massachusetts Eye and Ear Infirmary for follow-up care were instructed to have annual liver function tests, and their local physicians were contacted on an annual basis to ascertain data on ocular and survival outcomes.

Vital status for these patients was also determined by a search of the Social Security Death Index, which provides date and place of death. This was followed by a search of the National Death Index, which provides cause of all deaths occurring in the United States, Puerto Rico, and the US Virgin Islands beginning in 1979.

The role of treatment for metastatic disease was also assessed in this study by comparing differences in survival between patients diagnosed as having metastatic disease during the following 2 periods: before January 1990 vs between January 1990 and December 1997. This analysis looked for a possible cohort effect related to advances in the treatment of metastatic disease.

STATISTICAL ANALYSIS

Differences in patient and tumor characteristics were assessed using the Fisher exact test for discrete variables and the Wilcoxon rank sum test for continuous variables. Melanoma-related death rates were calculated using the Kaplan-Meier method.

RESULTS

Among the asymptomatic group, metastasis was diagnosed by routine surveillance testing in 90 patients (25.8%). Among the symptomatic group, metastasis was diagnosed in 259 patients (74.2%) after the onset of symptoms, such as anorexia or abdominal pain. Patients in the 2 groups had similar known prognostic factors for melanoma-related death such as age, tumor diameter, and tumor location (Table 1). The proportion of patients receiving treatment for metastatic disease was similar between the 2 groups: 66.7% of the asymptomatic group and 59.5% of the symptomatic group underwent some type of treatment. No statistically significant differences were noted in the types of treatment administered to each group.

The median time from primary tumor diagnosis to diagnosis of metastasis was 31.4 months in the asymptomatic group vs 40.3 months in the symptomatic group (P=.14, Wilcoxon rank sum test).

Table 1. Known Prognostic Factors for Metastasis-Related Death and Distribution of Treatment Types for Metastatic Disease in Asymptomatic vs Symptomatic Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asymptomatic Patients (n=90)</th>
<th>Symptomatic Patients (n=259)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at proton beam irradiation, median (range), y</td>
<td>61 (25-88)</td>
<td>64 (28-90)</td>
<td>.12a</td>
</tr>
<tr>
<td>Tumor characteristic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Largest diameter, median (range), mm</td>
<td>16 (8-24)</td>
<td>16 (6-24)</td>
<td>.21a</td>
</tr>
<tr>
<td>Anterior margin posterior to equator, No. (%)</td>
<td>22 (24.4)</td>
<td>70 (27.0)</td>
<td>.39</td>
</tr>
<tr>
<td>Treatment type, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>32 (53.3)</td>
<td>71 (46.7)</td>
<td>.14</td>
</tr>
<tr>
<td>&gt;1 Type</td>
<td>22 (36.7)</td>
<td>52 (34.2)</td>
<td></td>
</tr>
<tr>
<td>Irradiation</td>
<td>0</td>
<td>13 (8.6)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>2 (3.3)</td>
<td>4 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Otherb</td>
<td>4 (6.7)</td>
<td>12 (7.9)</td>
<td></td>
</tr>
</tbody>
</table>

aWilcoxon rank sum test. Fisher exact test for other P values.

bImmunotherapy, for example.
Cumulative rates of melanoma-related death were higher for patients in the symptomatic group vs patients in the asymptomatic group ($P<.001$, log-rank test) because of differences in mortality observed in the first year after diagnosis of metastasis (87.8% vs 68.5%, respectively). By the second year after diagnosis of metastasis, cumulative rates had reached 90% or higher in both groups (Figure 2). The median survival time after diagnosis of metastasis was 6.1 months in the asymptomatic group vs 2.7 months in the symptomatic group ($P=.001$, Wilcoxon rank sum test).

Secondary analyses to look for a possible cohort effect related to advances in the treatment of metastatic disease over time revealed no significant trends. Patients whose metastases were detected before January 1990 (cohort 1) and those whose metastases were detected between January 1990 and December 1997 (cohort 2) seemed balanced with respect to known prognostic factors (Table 2). There was no difference between the 2 cohorts in the percentage of patients receiving treatment for metastatic disease. Most significantly, the median survival time after diagnosis of metastasis was almost identical between the cohorts (3.6 months in cohort 1 vs 3.4 months in cohort 2; $P=.96$, Wilcoxon rank sum test). Melanoma-related death rates were similar between the 2 cohorts through 3 years after diagnosis of metastasis ($P=.44$, log-rank test) (Figure 4). At 1 year after diagnosis of metastasis, there was no difference in mortality between both cohorts. Among asymptomatic patients, mortality rates at 1 year were 71.4% in cohort 1.0

### Table 2. Known Prognostic Factors for Metastasis-Related Death and Proportion of Patients Receiving Treatment for Metastatic Disease in Cohorts Diagnosed Before 1990 vs Between 1990 and 1997

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cohort 1 (n=166)</th>
<th>Cohort 2 (n=183)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at proton beam irradiation, median (range), y</td>
<td>62 (28-83)</td>
<td>63 (25-90)</td>
<td>.69</td>
</tr>
<tr>
<td>Tumor characteristic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Largest diameter, median (range), mm</td>
<td>16 (9-24)</td>
<td>16 (7-24)</td>
<td>.17</td>
</tr>
<tr>
<td>Anterior margin posterior to equator, No. (%)</td>
<td>39 (23.5)</td>
<td>53 (29.0)</td>
<td>.57</td>
</tr>
<tr>
<td>Treatment for metastatic disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>by site of metastasis, No. (%)</td>
<td>(n=112)</td>
<td>(n=100)</td>
<td></td>
</tr>
<tr>
<td>Liver only</td>
<td>54 (48.2)</td>
<td>50 (50.0)</td>
<td>.11</td>
</tr>
<tr>
<td>Liver and other</td>
<td>51 (45.5)</td>
<td>37 (37.0)</td>
<td>.12</td>
</tr>
<tr>
<td>Extrahepatic only</td>
<td>7 (6.2)</td>
<td>13 (13.0)</td>
<td>.10</td>
</tr>
</tbody>
</table>

$^a$Wilcoxon rank sum test. Fisher exact test for other $P$ values.
In this large series of patients who developed metastases after proton beam irradiation for uveal melanoma, those whose metastatic disease was detected while asymptomatic survived slightly longer after the diagnosis of metastasis than those whose symptoms prompted the diagnosis of metastasis (median, 6 vs 3 months; \( P < .001 \)). However, there was no difference in survival after the primary tumor diagnosis between symptomatic and asymptomatic patients.

Similar findings were reported from a study\(^\text{11}\) of Finnish patients with metastatic uveal melanoma, 37% of whom were diagnosed on the basis of signs or symptoms. Asymptomatic patients had longer survival after diagnosis of metastasis compared with symptomatic patients (median survival, 12.1 vs 5.7 months; \( P = .03 \)), as did those who participated in annual surveillance examinations vs those who did not (median survival, 8.9 vs 4.3 months; \( P = .08 \)). However, there was no difference in survival after primary tumor diagnosis. Therefore, the increased survival in patients after diagnosis of metastasis by surveillance testing is most likely because of lead-time bias.

We acknowledge that the presence or absence of symptoms is not an accurate surrogate marker for metastatic tumor burden and accept that there might be asymptomatic patients with widespread or advanced metastatic disease, and vice versa. However, the observation that symptom status correlates with survival time after diagnosis of metastasis among patients in this study and in prior studies\(^\text{1,11}\) suggests that this criterion is associated with severity of metastasis. Because of the retrospective nature of our study, limited information regarding the extent of metastatic disease at initial detection was available for these patients. Therefore, evaluation of patient groups based on symptom status was the only feasible method for this study.

It could also be argued that our surveillance protocol had less sensitivity for detecting hepatic metastasis compared with protocols that use liver imaging and did not detect metastatic disease at a stage early enough for successful intervention. However, the median time from primary tumor diagnosis to detection of metastasis (metastasis-free interval) for our asymptomatic group (31.4 months) is comparable to that for asymptomatic patients in other studies\(^\text{2,13}\) that included imaging as part of the surveillance protocol, suggesting that diagnosis of metastasis was not significantly delayed with our procedures. Even when liver imaging is used, the proportion of patients who are eligible for regional therapies is limited.

In a French study\(^\text{15}\) of 602 patients having uveal melanoma who were screened using abdominal ultrasonography every 6 months, 63 patients developed hepatic metastasis and were evaluated for potential liver resection, followed by hepatic artery infusion chemotherapy. A survival benefit of treatment in this study was only seen in the group of patients who were able to have complete resection of all gross metastatic disease and who had fewer than 10 lesions (median survival, 25 vs 15 months for the overall group). However, despite frequent ultrasonographic examinations, more than 90% of patients in this series had metastatic involvement of both liver lobes, and 70% had more than 10 lesions. In addition, complete resection of gross metastases was achieved in only 50% of patients who underwent surgery because of the discovery of miliary liver metastases undetected by preoperative imaging. Ultimately, only 22% of 63 patients had complete resection of gross metastases. Therefore, the authors concluded that semiannual ultrasonographic surveillance was ineffective in early detection of liver metastases due to uveal melanoma.

In addition to the frustrating lack of efficacy of current surveillance tools, our data reveal no advances in the treatment of metastatic uveal melanoma. Our cohort analysis showed no difference in treatment rates or survival times between patients diagnosed as having metastatic disease before 1990 and those diagnosed more recently. No survival benefit was seen in the more recent cohort, even for patients who were asymptomatic when metastases were discovered. This analysis is limited by the lack of data regarding proportions of patients in each cohort receiving regional therapies such as hepatic artery infusion chemotherapy or surgical resection of hepatic metastases. However, the percentage of patients with metastatic disease limited to the liver who received treatment was similar in both cohorts (Table 2). This suggests that, even for patients with isolated hepatic metastases, treatment options remain limited, and any regional therapy advances in the 1990s have had marginal effect on survival for the overall group of patients with metastatic uveal melanoma.

We were unable to assess the effect of more recent treatment advances, but a 2009 review\(^\text{14}\) of the existing literature on efficacy of treatments for metastatic uveal melanoma concluded that the current evidence for any treatment-related survival benefit is weak and is subject to significant bias, including selection bias, lead-time bias, and publication bias. Therefore, given current treatment options, earlier diagnosis of metastatic uveal melanoma through surveillance protocols may result in increased morbidity, with little effect on mortality for most patients. Patients most commonly selected for aggressive treatments associated with the highest morbidities are those who are asymptomatic and most likely to enjoy good quality of life for a longer period without intervention. Going forward, the prediction of metastatic risk based on molecular profiling of the primary tumor may be the ultimate surveillance tool.\(^\text{15}\) However, the benefit of such surveillance requires development of adjuvant chemotherapy protocols (administered at the time of primary ocular tumor diagnosis) that are proven to reduce mortality from metastatic disease.

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REFERENCES


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