Mortality After Diagnosis of Small Melanocytic Lesions of the Choroid

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Objective: To evaluate the risk of dying of metastatic choroidal melanoma in patients with small, indeterminate, pigmented lesions of the uveal tract.

Methods: A cohort of 1063 consecutive patients were evaluated in the Ocular Oncology Clinic of the Massachusetts Eye and Ear Infirmary between January 1976 and June 1996 with definite choroidal nevus (n=256), indeterminate lesions (n=334), or small melanoma (n=373). Deaths occurring up to December 1998 were identified through active follow-up or by a search of the National Death Index. Cumulative death rates were compared among diagnostic groups using the Kaplan-Meier method.

Results: Mean lesion diameter was 4.6 mm in the nevi, 7.0 mm in the indeterminate lesions, and 8.1 mm in the small melanomas. Patients ranged in age from 3 to 95 years (median, 64 years). A total of 15 deaths due to ocular melanoma were ascertained (median follow-up of survivors, 8.2 years), 13 in the melanoma group and 2 in the indeterminate lesion group; actuarial tumor-specific death rates at 10 years after evaluation were 5% (95% confidence interval, 3%-8%) and 1% (95% confidence interval 0%-3%), respectively. No deaths due to ocular melanoma occurred in the nevus group.

Conclusions: These data document the very low malignant potential of most indeterminate melanocytic lesions of the choroid and support the current practice of monitoring these tumors, with treatment provided when growth and other signs of malignant transformation are observed.

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Here is considerable evidence that intraocular melanomas arise from benign pigmented precursor lesions (nevus) in the uveal tract. In histopathological sections of uveal melanomas, nevoid cells can be identified at the base of many tumors, and there are documented cases of uveal melanomas arising from preexisting nevi. Also, persons with large numbers of cutaneous and iris nevi are at heightened risk of developing melanomas in the posterior uveal tract (ie, the choroid and ciliary body).

Benign nevi of the choroid are common in white populations. In a survey of 3654 subjects (99% white), the nevus prevalence rate was estimated at 8.9% in women and 8.3% in men, based on fundus photographs. These figures likely underestimate the prevalence, as small, less pigmented nevi are often missed clinically. In comparison, melanomas of the uveal tract are uncommon, with an annual incidence in the United States of about 6 to 7 cases per million persons. An estimated 1 in 8845 choroidal nevi will transform to a malignant tumor per year in the white US population. The tumors metastasize primarily to the liver, and up to 50% of patients may die of the disease within 10 years of diagnosis.

Uveal nevi are generally flat, slate-gray lesions without sharply demarcated margins; their size is limited to about 6 mm in diameter. However, there is considerable overlap in size distributions of nevi and indeterminate lesions compared with small melanomas, and the differential diagnosis can be especially difficult in borderline cases with characteristics of both lesions.

While most studies have evaluated the growth potential of nevi and indeterminate pigmented lesions of the uveal tract, the eventual mortality associated with such lesions is not known. One study evaluated risk factors for metastasis in 1329 small choroidal lesions of 3 mm or less in height and found that 3% of patients developed metastasis. Another study of patients with indeterminate choroidal lesions was restricted to those who were subsequently diagnosed with small melanomas; the 5-year mortality rate after treatment with plaque radiotherapy was 3.9%. In this study, we followed up a large series of patients diagnosed with choroidal nevi or indeterminate lesions to determine long-term survival experience after initial presentation of the uveal tumor. We compared their outcomes with those of patients diagnosed with small melanomas and treated to determine whether an observational approach to managing indeterminate lesions is appropriate.
Patients were referred to the Ocular Oncology Clinic of the Massachusetts Eye and Ear Infirmary (MEEI) between January 1976 and June 1996 for evaluation of a pigmented lesion of the choroid that, based on funduscopic and ultrasound findings, was diagnosed either as a definite choroidal nevus (n=256) or an indeterminate lesion (eg, nevus vs small melanoma; n=334). In general, lesions were categorized as nevi if they were flat (<0.5 mm) and less than 6 mm in diameter. Lesions were categorized as indeterminate if they were less than 2 mm thick and did not exhibit known risk characteristics such as orange pigment, subretinal fluid, or symptoms at presentation. Another 373 patients were diagnosed with a small melanoma (lesions <= 5 mm in height). Small melanomas were treated at our institution by proton irradiation. Lesions in the nevus category ranged from 0.5 mm to 12 mm in diameter and tended to be flat or minimally elevated. Indeterminate lesions (eg, nevus vs small melanoma) managed by observation, and definitive small melanomas (<10 mm in diameter and <5 mm in height) treated at our institution by proton irradiation. Lesions in the nevus category ranged from 0.5 mm to 12 mm in diameter (mean diameter, 4.7 mm) and tended to be flat or minimally elevated. Indeterminate lesions (Figure 1) were

Table 1 presents patient and lesion characteristics, contrasting nevi and indeterminate lesions (eg, nevus vs small melanoma) managed by observation, and definitive small melanomas (<10 mm in diameter and <5 mm in height) treated at our institution by proton irradiation. Lesions in the nevus category ranged from 0.5 mm to 12 mm in diameter (mean diameter, 4.7 mm) and tended to be flat or minimally elevated. Indeterminate lesions (Figure 1) were

Table 1. Characteristics of Patients With Pigmented Choroidal Lesions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Definite Nevus (n=256)</th>
<th>Indeterminate Lesion (n=334)</th>
<th>Small Melanoma (n=373)</th>
<th>Indeterminate Lesion (n=334)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, mean (IQR), y</td>
<td>62 (54-73)</td>
<td>62 (52-73)</td>
<td>59 (49-70)</td>
<td>62 (52-73)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>88 (34)</td>
<td>116 (35)</td>
<td>197 (53)</td>
<td>116 (35)</td>
</tr>
<tr>
<td>Female</td>
<td>168 (66)</td>
<td>218 (65)</td>
<td>176 (47)</td>
<td>218 (65)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Eye involved</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Right</td>
<td>133 (53)</td>
<td>158 (47)</td>
<td>200 (54)</td>
<td>158 (47)</td>
</tr>
<tr>
<td>Left</td>
<td>119 (47)</td>
<td>176 (53)</td>
<td>173 (46)</td>
<td>176 (53)</td>
</tr>
<tr>
<td>Both</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td>.93</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td>.93</td>
</tr>
<tr>
<td>Yes</td>
<td>101 (39)</td>
<td>137 (41)</td>
<td>219 (59)</td>
<td>137 (41)</td>
</tr>
<tr>
<td>No</td>
<td>155 (61)</td>
<td>197 (59)</td>
<td>154 (41)</td>
<td>197 (59)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>Diameter, mean (IQR), mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NR</td>
<td>4.7 (3-6)</td>
<td>7.0 (6-9)</td>
<td>8.1 (7.5-9)</td>
<td>7.0 (6-9)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Height, mean (IQR), mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NR</td>
<td>0.1 (0-0.5)</td>
<td>1.3 (0.8-1.8)</td>
<td>2.7 (2.3-2)</td>
<td>1.3 (0.8-1.8)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; NR, not recorded in the medical record.
larger, on average, than the nevi but smaller than melanomas. Compared with the other groups, patients with small melanomas were significantly younger and more likely to be symptomatic. Patients with melanoma were balanced regarding sex, while those in the benign and intermediate subgroups were almost twice as likely to be female ($P < .001$).

A total of 39 patients with indeterminate lesions and 3 nevi subsequently had treatment for the lesion with proton irradiation after signs of growth and/or other changes, from 2 months to 18 years (median, 4 years) after initial observation at MEEI. Growth may have included expansion laterally as well as in height, and other changes included the development of orange pigment, subretinal fluid, and symptoms. The patients with nevi that progressed during observation (Figure 2) were subsequently treated by proton irradiation 3.4, 7.2, and 9.4 years after initial evaluation. In each case, in the baseline examination, at least 1 dimension of the lesion was larger than the average compared with other nevi in the series. Each of these lesions was also symptomatic, and 2 were associated with the presence of subretinal fluid.

To determine if any clinical factors routinely available in medical records predicted lesion progression, we compared patients followed up at MEEI who progressed during observation and were subsequently treated by proton irradiation with patients whose lesions remained stable during observation at MEEI, and found that tumor height greater than 1.5 mm and presentation with symptoms significantly elevated risk of progression (data not shown).

A total of 4 patients died of metastatic cutaneous melanoma and 2 of ocular melanoma. Both patients who died of ocular melanoma were originally diagnosed with an indeterminate lesion and were later treated with proton irradiation 10 and 20 months (Figure 3) after initial presentation at MEEI. The patients died of metastatic disease 5.5 and 12.8 years, respectively, after presentation at MEEI (4.7 and 11.1 years after receiving treatment).

Of the patients with an indeterminate lesion or nevus ($n = 590$), the observed number of deaths due to melanoma exceeded that expected in the general population (Table 2). For cutaneous malignant melanoma, death rates were 13 times higher than expected in 4682 person-years based on cancer-specific mortality rates in the United States. For ocular malignant melanoma, death rates were 21 times higher than expected in 4682 person-years (Table 2).
States (1985–1995). For ocular melanoma, 2 deaths were observed, while 0.015 were expected (observed vs expected, 133); based on these numbers, 1 death due to ocular melanoma would be expected per year in 2341 patients with indeterminate lesions or nevi [(2/4682) − 1].

Fifteen patients died of melanoma, 2 (0.6%) in the indeterminate lesion group and 13 (3.5%) in the small melanoma group. Death rates for metastasis at 5, 10, and 15 years were 0%, 1%, and 3%, respectively, for indeterminate melanocytic lesions (n = 334) and 2%, 5%, and 7%, respectively, for definite small melanomas (n = 373) (Table 3). No patients with a presumed benign nevus died of melanoma metastasis in the period of follow-up (mean, 8.4 years).

**COMMENT**

The management of small elevated pigmented lesions of the choroid is controversial in ophthalmology, and the usual practice currently is to withhold intervention until there is documented evidence of tumor activity.22 Tumor growth, which occurs within several years in more than a third of uveal lesions suspected for melanoma during observation,23 24 is considered the most important sign of malignancy. However, tumor growth is not always a reliable marker of malignant potential. Benign choroidal nevi may enlarge under observation,25 while uveal melanomas may be stable for long periods of time without progression.26 Other characteristics that have been identified as signs of malignant transformation include orange pigment, subretinal fluid, and the presence of symptoms.27 28 A diagnosis of melanoma is more likely if several of these characteristics are present in addition to growth.

Some argument can be made that any lesion suspicious for intraocular melanoma should be treated promptly to avoid the possibility of metastasis.29 However, the decision to intervene in tumors of the eye is complicated by the fact that any intervention will potentially impair vision and may risk loss of the globe. The current data suggest that the malignant potential of small melanocytic lesions in the eye is very low, with only 1 death expected owing to ocular melanoma in 2340 patient-years after detection (combining nevus and indeterminate lesions). However, about 60% of these patients would be expected to lose useful vision in the eye (to worse than 20/200) if treated by proton irradiation, applying rates observed in the small melanomas (data not shown). It is not clear that early intervention would prevent every case of metastasis,29 whereas studies suggest that a period of observation prior to intervention is not likely to increase death rates when compared with immediate treatment.30 However, a randomized trial would be necessary to definitively address this question.

In this series, patients with a nevus or an indeterminate lesion were significantly older and more likely to be female when compared with patients with a definite melanoma. The 2-fold excess in women was present in the symptomatic lesions as well as those detected by screening (data not shown). It is possible that women have a lower threshold for screening examination or for

### Table 2. Observed and Expected Numbers of Deaths Due to Ocular and Cutaneous Melanoma Among 590 Patients With a Definite Pigmented Choroidal Lesion

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Observed</th>
<th>Expected</th>
<th>O:E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular melanoma</td>
<td>2</td>
<td>0.015</td>
<td>133.3</td>
</tr>
<tr>
<td>Cutaneous melanoma</td>
<td>4</td>
<td>0.31</td>
<td>12.9</td>
</tr>
</tbody>
</table>

Abbreviation: O:E, observed vs expected.

*Expected numbers are based on mortality data (1993 to 1997) provided by the US National Center for Health Statistics; for ocular melanoma, tumors of the eye and orbit are combined.

### Table 3. Actuarial Death Rates of Ocular Melanoma Metastasis in Indeterminate Lesions and Small Melanomas

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients, No.</th>
<th>Deaths Due to Ocular Melanoma, No.</th>
<th>Cumulative Death Rates by Years of Follow-up, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indeterminate lesions</td>
<td>334</td>
<td>2</td>
<td>0 (1-15)</td>
</tr>
<tr>
<td>Small melanomas</td>
<td>373</td>
<td>13</td>
<td>2 (1-4) 5 (3-8) 7 (4-12)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

Figure 3. Fundus photograph taken during evaluation at Massachusetts Eye and Ear Infirmary showing a suspicious lesion (A) that underwent malignant transformation (B) 20 months after the initial evaluation. The patient was treated with proton therapy and subsequently developed metastasis 11 years after treatment.
visiting a doctor with symptoms. However, in a large survey, the prevalence of choroidal nevi was also higher in women. In ocular melanoma, incidence rates are comparable in men and women, with a suggestion in some series of slightly higher rates in men. Why women would be at higher risk of the presumed precursor lesion, though not the cancer itself, is not clear. However, death rates of these tumors are slightly higher in men, which appears to be related to a protective effect of childbearing in women, and it may be that immunologic factors influence progression at various stages of the disease.

There are several issues to consider when evaluating these data. The diagnosis and treatment of small melanomas was based on clinical judgment alone, without the aid of a biopsy for definitive diagnosis. Therefore, it is possible that a small number of treated tumors were not ocular melanomas. This was not a study of the natural history of choroidal pigmented lesions. Many of the patients in this series were referred to MEEI for consultation only, and we lacked data on the clinical course and eventual treatment of their lesions. Thus, an unknown proportion of the patients may have had some intervention at a later date, and the influence of treatment on the current results cannot be evaluated. Also, the NDI search does not include deaths that occur outside the United States, and such deaths go undetected. However, the NDI has been shown to have high sensitivity and specificity for determining deaths and attributing causes. In the present series, the higher-than-expected rates of death due to cutaneous melanoma in a selected series of patients with melanocytic lesions in the eye tends to validate the method. Finally, though follow-up was prolonged in many patients, it should be noted that malignant changes in precursor lesions may require decades to evolve and thus the ultimate prognosis associated with early melanocytic lesions in the eye would require longer follow-up than was available in this series. Despite these limitations, the results of this study revealed low mortality rates in patients with these tumors and support the current management practice of close serial examinations without therapeutic intervention until growth is observed.

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REFERENCES