Routes of Extraocular Extension of Uveal Melanoma

Risk Factors and Influence on Survival Probability

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Purpose: To correlate extraocular spread with other survival predictors and with metastatic death and determine whether there was any relationship between the size of the extraocular tumor and survival.

Design: Nonrandomized retrospective case series.

Participants: Eight hundred forty-seven patients with uveal melanoma treated by primary enucleation between January 1993 and December 2006.

Methods: Baseline variables were age, gender, largest basal tumor dimension, tumor height, anterior tumor margin, route of extraocular spread (i.e., aqueous channels, vortex veins, ciliary arteries, or ciliary nerves), tumor cell type, mitotic rate, closed connective tissue loops, and monosomy 3. Determination of death was based on the National Health Service Cancer Registry.

Main Outcome Measures: Prevalence and route of extraocular extension and correlation with intraocular tumor characteristics and metastatic death.

Results: The 847 patients had a mean age of 64 years. Extraocular tumor extension was recorded in 124 patients and occurred via aqueous channels (37, 29.8%); ciliary arteries (34, 27.4%); vortex veins (28, 18.5%); ciliary nerves (11, 8.9%); optic nerve (1, 0.8%), and a variety of rare combinations of these routes (13, 10.4%). Extraocular spread via aqueous channels occurred in 15.2% of tumors involving ciliary body or angle, but through other channels in <6% tumors at risk. Extraocular spread correlated with anterior tumor extension, large basal tumor diameter, epithelioid cellularity, closed loops, high mitotic rate, and monosomy 3. Extraocular spread along aqueous drainage channels correlated inversely with intraocular tumor dimensions. Venous spread correlated with large basal tumor diameter. Arterial spread correlated with location near optic disc. Neural spread correlated weakly with mitotic rate. Log rank analysis showed metastatic death to correlate with extraocular extension, irrespective of the route. Multivariate Cox analysis showed the correlation between metastatic death and extraocular spread to be weaker than with largest basal tumor diameter, closed loops, epithelioid cells, and mitotic rate. Size of extraocular tumor was not significant (P = 0.3).

Conclusions: Extraocular spread correlated with increased mortality because it was associated with increased tumor malignancy and, in the case of posterior tumors, more advanced disease. Type of scleral route and size of extraocular tumor were unimportant regarding risk of systemic dissemination and tumor-related death.

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The prognostic significance of the size of extraocular tumor has been addressed by several authors, most of whom have concluded that larger extraocular tumor dimensions are associated with increased orbital recurrence rates and with mortality.\(^2\)\(^4\)\(^5\)\(^8\)\(^9\)

To address gaps in the published literature concerning extraocular extension of uveal melanoma, we investigated the correlation between route of extraocular spread and other survival predictors in a large series of patients with detailed histologic, cytogenetic, and clinical data. We also investigated the relationship between metastatic death and presence of extrascleral spread, taking into account route and the size of the extraocular tumor as well.

**Patients and Methods**

**Patients**

Patients were included in this study if they were (1) referred to our center with uveal melanoma between January 1993 and December 2006, (2) treated by primary enucleation, whether this was performed by us or, after our examination of the patient, by the referring ophthalmologist, and (3) if pathologic examination of the enucleated eye was performed at our center. Patients with extraocular tumor were identified by searching our customized ocular oncology database and pathology archives.

**Clinical Management**

Full ophthalmologic examination including echography was performed by one of the authors (BD) in all cases. Largest basal tumor diameter and tumor thickness were measured by B-scan echography (I3, Innovative Imaging, Sacramento, CA).

Before ocular treatment, systemic clinical examination including biochemical liver function tests (including lactate dehydrogenase, alkaline phosphatase, bilirubin, and γ-glutamyl transpeptidase) were performed routinely but liver ultrasonography was undertaken only if there was an increased risk of metastatic systemic disease (largest basal tumor diameter >16 mm).

Enucleation was performed if the patient was not motivated to undergo eye-conserving therapy or if such therapy was unlikely to succeed. This surgery was routinely undertaken at our hospital unless the patient preferred to be treated close to home.

Postoperatively, patients were referred to an oncologist for systemic screening only if cytogenetic tests showed monosomy 3. Ocular surveillance for local tumor recurrence and other complications was delegated to the referring ophthalmologist once the senior author (BD), on the basis of previous outcomes analyses, considered the chances of such problems occurring to be ≤1%.

**Histopathologic Examination**

After a thorough macroscopic examination, the entire globe was embedded in all cases. At least 3 levels were taken from each of the calottes. The pupil–optic nerve block was leveled 5 times. If there was any evidence of intrascleral tumor extension, additional levels were performed to exclude the presence/absence of microscopic extraocular growth. The diagnosis of melanoma was made on hematoxylin and eosin sections and, if necessary, confirmed immunohistochemically using Human Melanoma Black-45, melan A, tyrosinase, and/or NK1 C3 stains. Spindle and epithelioid cell types were assessed using the modified Callendar system.\(^1\)\(^4\) Extravascular matrix patterns were assessed as previously described using the periodic acid–Schiff (PAS) reagent, without counterstaining, to facilitate recognition of closed loops.\(^1\)\(^5\) The mitotic rate was measured by counting the number of mitoses in 40 high-power fields. The size of the extraocular tumor was measured macroscopically (if visible) in 3 dimensions, otherwise on histologic sections using digital analysis (Olympus Soft Imaging Solutions, Munster, Germany), with the largest perisceral diameter of the extraocular extension being recorded.

**Cytogenetic Studies**

As previously described,\(^1\)\(^5\) fluorescence in-situ hybridization studies of interphase and metaphase cells were performed on touch preparations and short-term cultures, respectively. Fluorescence in-situ hybridization was performed in the standard manner. We used centromere enumeration probes and a locus-specific indicator probe (Vysis Inc, Downers Grove, IL). These detected the centromeres for 3 and 8 along with the c-myc oncogene at 8q28.

**Statistical Analyses**

Clinical, pathologic, and cytogenetic data were entered into a custom computerized database prospectively. Tumors were categorized as involving ciliary body if they extended anterior to the ora serrata and were recorded as having epithelioid cells irrespective of the proportion of such cells in the tumor. When transverse ultrasonographic measurement of basal tumor diameter were not possible because of annular spread around ciliary body or angle, the chord length of the largest basal tumor diameter was estimated from the number of clock hours of circumferential tumor spread up to a maximum of 6 clock hours. Extraocular extension was defined as tumor spreading beyond the outer scleral surface. The route was categorized as aqueous (along aqueous drainage channels), venous (merging intra- and perivortex vein spread); arterial (including tumors with both peripherial and optic nerve spread); and neural (along channels for posterior ciliary nerves). Tumors with only optic nerve spread or with various combinations of venous, neural, and arterial spread were excluded from further statistical analysis because of small numbers.

To determine rates of extraocular tumor spread along each scleral route, we first categorized tumors according to their anterior and posterior extent and determined the rate of extraocular growth along each route for every category. Next, for each scleral route, we analyzed only tumors having a >1% rate of spread along that route (because they clinically involved or extended close to that scleral channel). For example, only tumors extending anterior to ora serrata were assessed for risk of extension along aqueous channels, tumors involving postequatorial choroid were considered for spread along vortex vein channels, and tumors involving choroid were considered from spread along channels for ciliary arteries or nerves.

We notified the National Health Service Cancer Registry of all newly diagnosed patients with ocular melanoma. These were flagged at the registry, which informed us automatically and within 2 months of the date and cause of any deaths. If we did not receive such information about any patient by the close of the study, we assumed that the patient was alive.

Depending on the wording of the death certificate, death from metastatic disease was coded as definitely or probably caused by uveal melanoma unless another primary malignancy was specified as the cause in the death certificate. Follow-up time was estimated from the time of treatment to the date of death or to July 19, 2006, when the data were downloaded.
Data analysis was done by one of us (IC) using a statistical program (SPSS, SPSS Inc, Chicago, IL) and figures were redrawn using a bespoke program to show 95% confidence intervals and numbers at risk (www.ircsoftware.org). Correlations between baseline risk factors were analyzed by the Pearson chi-square test (without Yates’s adjustment); by the “N/H110211” chi-square test wherever some expected values were 5; or by the Mann-Whitney test where variables were continuous. Predictive factors were correlated with melanoma mortality using the Cox proportional hazards model. Multivariate analysis was performed as a forward stepwise procedure. The Kaplan-Meier method was used to compute metastatic mortality (terminating curves when 5 cases were under follow-up) and groups were compared using the log rank test. P 0.05 was considered to be statistically significant. All statistical tests were 2-sided.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Consent for the use of tissues and data for research was obtained from all patients. Institutional Review Board/Ethics committee approval was not required because this study is an audit of routine clinical practice.

Results

The 847 patients had a mean age of 64.1 years (range, 21.6–96.9). The tumors had a mean largest basal diameter of 14.9 mm (range, 2.2–23.6) and a mean thickness of 7.6 mm (range, 0.5–17.7). Baseline tumor characteristics are summarized in Table 1.

Extraocular tumor extension was recorded in 124 patients (14.6%) and occurred by the following routes: (1) aqueous drainage channels (37 patients, 29.8%); (2) ciliary arteries (34 patients, 27.4%); (3) vortex vein (28 patients, 18.5%); (4) ciliary nerves (11 patients, 8.9%); (5) optic nerve and ciliary arteries (6 patients, 4.8%); (6) ciliary arteries and ciliary nerves (3 patients, 2.4%); (7) optic nerve (1 patient, 0.8%); (8) drainage channels and ciliary arteries (1 patient, 0.8%); (9) drainage channels and ciliary nerves (1 patient, 0.8%); (10) vortex vein and ciliary nerve (2 patients, 1.6%; Fig 1). When we considered only tumors whose location and extent gave rise to a 1% risk of extraocular spread along a particular route were considered, the prevalences of such extraocular extension were 15.2% (95% confidence interval [CI], 10.6–19.7%) for aqueous drainage channels in 244 eyes at risk, 4.0% (95% CI, 2.6–5.4%) for venous channels in 751 eyes at risk, 5.3% (95% CI, 3.8–6.8%) for arterial channels in 828 eyes at risk, and 2.1% (95% CI, 1.1–3.0%) for neural channels in 828 eyes at risk.

Extraocular spread correlated strongly with angle involvement (P<0.001), large basal tumor diameter (P<0.001), epithelioid cells (P = 0.002), closed loops (P = 0.002), and monosomy 3 (P = 0.001; Table 1).

Table 1 shows the prevalences of the various routes of extraocular tumor extension, according to other factors predictive of...
metastatic death in tumors involving or extending close to the scleral channel in question. Extraocular spread along aqueous drainage channels correlated strongly with angle involvement \( (P = 0.001) \) and inversely with largest basal tumor diameter \( (P = 0.005) \) and tumor height \( (P < 0.001) \). Venous spread correlated strongly with ciliary body involvement \( (P = 0.001) \) and large basal tumor diameter \( (P = 0.001) \) and weakly with sagittal tumor location \( (P = 0.05) \), being commoner with superior location. Arterial spread correlated strongly with nasal tumor location \( (P=0.002) \) and with posterior tumor extension to disc \( (P = 0.008) \). Neural spread correlated strongly with large basal tumor diameter \( (P = 0.002) \) and weakly with high mitotic rate \( (P = 0.03) \).

The basal diameter of the extraocular tumor was known in 123 of the 124 cases and had a median of 1.2 mm (range, 0.3–16.0). This median basal diameter of the extraocular tumor was 1.5 mm (range, 0.3–9.0) along drainage channels; 1.0 mm (range, 0.3–6.0) along vortex veins; 1.2 mm (range, 0.5–16.0) along ciliary arteries; and 1.0 mm (range, 0.5–11.0 mm) along posterior ciliary arteries.

Survival was analyzed in 744 patients living in mainland Britain, 114 of whom had a tumor with extraocular extension. There were 319 deaths (42.9%); 222 were caused by metastatic disease (29.8%). The median time to death or to the close of the study was 3.59 years (range, 0.02–14.6). Figure 2 shows the metastatic mortality rates according to the route of extraocular extension. Log rank analysis showed metastatic death to correlate with presence of extraocular extension along drainage channels \( (P = 0.03) \), venous channels \( (P = 0.02) \), arterial channels \( (P = 0.009) \), and neural channels \( (P = 0.01) \). Multivariate Cox analysis was performed correlating metastatic death with the presence of extraocular spread (by any route), size of extraocular spread, largest basal tumor diameter, tumor height, ciliary body involvement, epithelioid cellularity, closed loops, and mitotic rate. Significant correlations were found between metastatic death and largest basal tumor diameter, closed loops, epithelioid cells, mitotic rate, and extraocular spread; however, extraocular spread was the least significant of these risk factors \( (Wald = 12.314; \text{Table 2}) \). Cox multivariate analysis was performed to correlate metastatic mortality with 2 variables: presence of extraocular extension (through any route) and basal diameter of extraocular extension. Extraocular extension was highly statistically significant \( (P<0.001) \). Basal diameter of extra-ocular extension was not significant \( (P = 0.1; \text{Table 3}) \). For the individual routes, the numbers of cases were too small for meaningful conclusions to be drawn.

**Discussion**

The main findings of this study was that extraocular spread was most common along aqueous drainage channels, occurring in 15% of tumors involving ciliary body...
Figure 1. (A–C) Microphotograph demonstrating melanoma infiltration of the anterior chamber with involvement of the angle and drainage channels, resulting in an episcleral nodule. (D) Tumor thrombus within a vortex vein. (E) Perivascular spread in the outer episcleral layer. (F) Perivascular spread in the region of the long posterior ciliary artery close to the optic nerve (optic nerve meninges, upper right corner). (G) Higher magnification demonstrating the nests of epithelioid melanoma cells. (H, I) Rare deep choroidal melanoma infiltration of the optic nerve head (hematoxylin and eosin staining).
or angle; in contrast, 6% of tumors extending to other scleral channels showed extracocular growth through those channels. Extraocular spread was associated with tumor size and location, and hence with the likelihood of tumor extending to scleral channels. Extraocular spread also correlated with histologic and cyogenetic features of tumor malignancy. Each route of extraocular spread was associated with increased mortality from metastatic disease. Size of extraocular tumor did not correlate significantly with mortality.

The main strengths of this study are the large number of patients, the analysis according to the route of extraocular spread, and the length of follow-up. To our knowledge, no other studies have investigated these factors in such detail and on such a large number of cases. Despite this, our study has several weaknesses. First, there was selection bias because our investigation restricted to patients treated by primary enucleation; however, the inclusion of patients treated by local resection, radiotherapy, or phototherapy would have resulted in large amounts of missing histologic data, possibly obscuring significant correlations. Second, the diagnosis of cause of death was based on death certificates, which are known to be inaccurate. Third, tumor cell types were categorized by microscopic examination, which remains controversial and subjective. Fourth, tumor lethality was assessed by fluores-

Table 2. Cox Multivariate Analysis Correlating Metastatic Mortality with Risk Factors for Metastatic Death

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95.0% CI for Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Largest basal tumor diameter</td>
<td>0.166</td>
<td>0.024</td>
<td>48.37</td>
<td>1</td>
<td>&lt;0.001</td>
<td>1.18</td>
<td>1.127</td>
</tr>
<tr>
<td>Closed loops</td>
<td>0.859</td>
<td>0.178</td>
<td>23.313</td>
<td>1</td>
<td>&lt;0.001</td>
<td>2.36</td>
<td>1.666</td>
</tr>
<tr>
<td>Epithelioid cellularity</td>
<td>0.949</td>
<td>0.225</td>
<td>17.778</td>
<td>1</td>
<td>&lt;0.001</td>
<td>2.583</td>
<td>1.662</td>
</tr>
<tr>
<td>Mitotic rate</td>
<td>0.04</td>
<td>0.01</td>
<td>15.72</td>
<td>1</td>
<td>&lt;0.001</td>
<td>1.041</td>
<td>1.02</td>
</tr>
<tr>
<td>Extraocular spread</td>
<td>0.562</td>
<td>0.16</td>
<td>12.314</td>
<td>1</td>
<td>&lt;0.001</td>
<td>1.754</td>
<td>1.282</td>
</tr>
</tbody>
</table>

B = B statistic; CI = confidence interval; df = degrees of freedom; Exp = exponential; SE = standard error; Sig = statistically significant; Wald = Wald statistical test (maximum likelihood estimate).
currence in-situ hybridization, which can miss vitally important partial deletions of chromosome 3.15 Fifth, despite the large sample size, the number of patients with extraocular spread was small. We did not address delayed orbital tumor recurrence after enucleation, which we may investigate in a future study.

As suggested previously by others,4,5,8,9,17 the route of extraocular spread depended mostly on intraocular tumor location and hence with the likelihood of the tumor extending to a scleral channel. For example, extension along venous channels correlated positively with large basal tumor diameter, possibly because larger tumors were more likely to spread to a vortex vein channel. Interestingly, aqueous drainage channel spread correlated inversely with tumor thickness and basal tumor diameter; this was probably because of early tumor detection as a result of visible tumor extraocularly and/or in the iris.

To determine the rate of extraocular tumor spread along a particular scleral route, we selected only those tumors at risk of infiltrating that type of scleral channel; otherwise, these results would have reflected the distribution of tumors within the eye rather than their ability to grow through the relevant scleral route. Tumors categorized according to their anteroposterior location and hence with the likelihood of the tumor extending to a scleral channel. For example, extension along venous channels correlated positively with large basal tumor diameter, possibly because larger tumors were more likely to spread to a vortex vein channel. Interestingly, aqueous drainage channel spread correlated inversely with tumor thickness and basal tumor diameter; this was probably because of early tumor detection as a result of visible tumor extraocularly and/or in the iris.

When all routes of extraocular spread were considered together, histologic and cytogenetic features of increased malignancy (i.e., epithelioid cell type, increased mitotic rate, presence of closed connective tissue loops, and monosomy 3) also correlated with extraocular spread. There are conflicting data regarding cell type and risk of extraocular spread in the literature, with the proportions of spindle, mixed, and epithelioid tumors within cohorts varying considerably.5,9,10 This may be explained by the persisting variability in the definition of “mixed” and “epithelioid” tumors between pathologists.14

When the different scleral routes were considered individually, histologic and cytogenetic indicators of malignancy showed little or no statistical correlation with extraocular spread; this is probably because of small numbers. Nevertheless, the different scleral routes showed similar trends between these indicators and extraocular spread. This suggests that route of spread is not important.

As in previous studies, the presence of extraocular tumor extension correlated with poorer survival.2–10,12 On multivariate analysis, however, it showed less statistical significance than 4 other risk factors (largest basal tumor diameter, closed connective tissue loops, epithelioid cell type, and mitotic rate). This suggests that extraocular spread is merely an indicator of increased tumor malignancy and size rather than a cause of systemic metastases. Other studies have reached similar conclusions.2–4,5,8

In our study, all routes of extraocular spread correlated similarly with metastatic death. This result differs significantly from the conclusions of Zografos,13 who reported that only extraocular spread along vortex veins predicted increased metastatic mortality. Our findings suggest that, in Zografos’ study, tumors spreading along vortex vein channels correlated with poorer survival because they were relatively large.

Some authors have suggested that size of extraocular tumor was important for melanoma recurrence in the orbit2,9 and was associated with a worse prognosis,5 although the latter was not demonstrated as being statistically significant on multivariate analysis. One would expect to see a correlation between size of extraocular extension and mortality, if only because of lead-time bias. In our series of patients treated with primary enucleation for uveal melanoma, however, the size of the extraocular tumor extension, measured as described, was not significant with respect to metastatic death. This may reflect the small size of most extraocular tumors in this series (median, 1.2 mm), and is in agreement with previous reports.9,18

In conclusion, extraocular spread indicated greater malignancy of the intraocular melanoma and, with posterior tumors, there was also an association with more advanced stage of disease. Route of extraocular spread reflected only the location and extent of the intraocular tumor and was relatively unimportant with respect to survival prognosis.
References


Footnotes and Financial Disclosures

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