Exudative Retinal Detachment from Malignant Uveal Melanoma: Predictors and Prognostic Significance

Tero Kivelä,1,2 Sebastian Eskelin,1 Teemu Mäkitie,2 and Paula Summanen1

PURPOSE. To determine independent predictors of exudative retinal detachment (RD) in eyes with uveal melanoma and the significance of RD in melanoma-specific survival.

METHODS. The extent of exudative RD was recorded retrospectively in a population-based cohort of 167 consecutive patients with eyes enucleated from 1972 through 1981 because of choroidal and ciliary body melanoma, representing all melanomas treated during that period. Histopathologic features including microvascular loops and networks, microvascular density (MVD), and tumor-infiltrating macrophages were determined. Clinical and histologic predictors of RD were modeled by multiple logistic regression with a split-sample, cross-validation design. Survival was assessed by Kaplan-Meier analysis and adjusted for the effect of competing predictors by Cox proportional hazards regression.

RESULTS. Of 142 (85%) eyes with adequate data, 25% had no RD, 16% had subretinal fluid around the tumor, 43% had clinical RD in one to two quadrants, and 16% had RD in three to four quadrants. The RD was more extensive if the tumor was large (P < 0.0001) and had microvascular loops and networks (P = 0.0094) and less extensive if it involved ciliary body (P = 0.011). High MVD (P = 0.054) and ruptured Bruch’s membrane (P = 0.065) tended to be associated with RD. Multiple logistic regression showed largest basal diameter (odds ratio [OR] 1.43 for each 1-mm change, P < 0.0001), microvascular loops and networks (OR 1.95 for each category change, P = 0.0095), and ciliary body involvement (OR 0.20, P = 0.0039) to be independently associated with RD; ruptured Bruch’s membrane (P = 0.96) and MVD (P = 0.87) were not associated. Clinical RD predicted poor survival (0.59 vs. 0.37 at 20 years; P = 0.029) by Kaplan-Meier analysis, but not after adjusting for other prognostic factors by Cox regression (hazard ratio [HR] 1.00, P = 1.0).

CONCLUSIONS. Tumor size, which may be a surrogate measure for total vascular content and decomposition of choriocapillaris and retinal pigment epithelium, is a strong predictor of exudative RD. Microvascular loops and networks are likewise associated with exudative RD. Exudative RD is not associated with survival after adjusting for tumor size and microvascular loops and networks. (Invest Ophthalmol Vis Sci. 2001;42: 2085–2093)


From the 1Oncology Service and 2Ophthalmic Pathology Laboratory, Department of Ophthalmology, Helsinki University Central Hospital, Finland.

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Corresponding author: Tero Kivelä, Department of Ophthalmology, Helsinki University Central Hospital, Haartmaninkatu 4C, PL 220, FIN-00029 HUS, Helsinki, Finland. tero.kivela@helsinki.fi

E xudative retinal detachment (RD) is detected clinically in up to 75% of eyes with malignant uveal melanoma, and it is the most common abnormality that accompanies this tumor.1 Large- to medium-sized melanomas produce serious damage to the eye, including symptomatic to total RD. Most choroidal nevi do not cause neuroepithelial detachment, let alone exudative RD. Consequently, subretinal fluid over the tumor and asymptomatic exudative RD, which has gravitated from the tumor to the dependent portion of the eye, are useful signs when establishing the diagnosis of uveal melanoma.2,3 Subretinal fluid predicts growth of small melanocytic tumors, and of such lesions, 59% to 86% grow during follow-up.4–7 Preoperative exudative RD is a high-risk indicator for poor visual outcome and enucleation after conservative treatment of uveal melanoma.8–9

The influence of exudative RD on survival is a moot point.7,10 Although the presence of exudative RD was found to be a risk factor for tumor growth, metastasis, and tumor-related death among patients who underwent enucleation and proton beam therapy for choroidal and ciliary body melanoma,9,11 it did not predict which patients would have metastasis after plaque brachytherapy.11,12

Although exudative RD is an established marker of disease activity1–7 and high complication rate8,9 after conservative therapy for uveal melanoma, factors other than large tumor size and posterior location that contribute to the presence of RD are incompletely understood.3,10,13 Textbooks that speculate on this matter suggest that reduced venous return leads to diffuse choroidal leakage, in particular when a posterior melanoma presses against a vortex vein or when Bruch’s membrane is ruptured and acts as a tourniquet around the base of the tumor.1,5,14 Fluorescein angiography indeed reveals diffuse extravasation from tumor and retinal vessels.15,16 Presence of RD has also been linked with rapidity of growth and necrosis of the tumor.3,14 We designed a study to establish to what extent the presence of exudative RD in eyes with malignant uveal melanoma is associated with clinical and histopathologic characteristics of the tumor and with melanoma-specific survival, giving special emphasis to microvascular factors.

PATIENTS AND METHODS

Study Design

The primary purpose of the present study was to determine independent predictors of exudative RD in eyes with malignant uveal melanoma. The secondary purpose was to evaluate exudative RD as a predictor of survival. Tenets of Helsinki Declaration were followed.

Inclusion and Exclusion Criteria

The inception cohort was a consecutive, population-based series of 167 patients with a malignant melanoma of the choroid and ciliary body, validated by obtaining all available follow-up data and histopathologic material.17 In brief, logs of the Ophthalmic Pathology Laboratory, Helsinki University Central Hospital, Finland, were searched backward from 1981 to 1972, and all patients who had had an eye removed because of uveal melanoma were enrolled. Before 1982,
enucleation was the standard treatment for all but the smallest melanomas, some of which were first observed for growth, and all eyes enucleated in the district were submitted to this laboratory, making the series essentially unselected and representative of all malignant uveal melanomas treated during the study period. During this period, patients were mostly evaluated with the Goldman three-mirror lens, but indirect ophthalmoscopy was also used. This series was considered suitable for the present study, because it represented the full spectrum of uveal melanoma, tumor specimens were available from every patient, and long-term follow-up data were also available. Only two thirds of total mortality from uveal melanoma is observed within the first 10 years after treatment.

Eyes that had clinical data on presence or absence of exudative RD were eligible for the analysis of clinical predictors of RD. Eyes in which media opacities precluded adequate examination of the retina (18 patients) or in which clinical data were inadequate (7 patients) were excluded, leaving 142 (85%) of the eyes for clinical analysis. Eyes in which histopathologic data were incomplete were excluded, leaving 124 (74%) of the eyes for histopathologic analysis.

Assessment of Basic Tumor Characteristics

The location (choroid, ciliary body, or both), largest basal diameter (LBD) and height of the tumor, and integrity of Bruch’s membrane (unruptured, ruptured) were ascertained from the original clinical and pathology reports and checked to be consistent with the sections available. Cell type was registered according to the modified Callender classification (spindle, mixed, or epithelioid). If the original report mentioned the presence of epithelioid cells in a tumor classified as spindle-cell type, the tumor was upgraded to the mixed-cell type.

Tumor-infiltrating macrophages were semiquantitatively graded (few, moderate, or many) from sections immunostained with mAb to CD68 epitope of endothelial cells (diluted 1:25; lot 121202; Novocastra Laboratories, Newcastle-upon-Tyne, UK). They were counted from the most highly vascularized area by using an eyepiece with etched graticule corresponding to 0.313 mm² (WK 10×/20L; Olympus, Tokyo, Japan). Any immunolabeled channel, clearly separate from adjacent ones and totally inside the graticule or touching its top or left border, was counted as a microvessel.

Assessment of Retinal Detachment

The clinical extent of RD was assessed according to predefined criteria from patient charts by one investigator masked to histopathologic data. Clinical rather than histopathologic criteria were used, because almost all melanoma-affected eyes have microscopic subretinal fluid, the extent of RD is more difficult to grade from sections, and investigator bias may be caused by awareness of microvascular and other histopathologic features of the tumor. Each eye was classified into one of four categories:

1. No RD: subretinal fluid not mentioned
2. Subretinal fluid: detachment of neurosensory retina over and around the melanoma, without clinical exudative RD extending to the periphery
3. Clinical exudative RD with one to two quadrants of the retina involved, with or without subretinal fluid over and around the tumor (typically, RD in the dependent part of the eye)
4. Clinical exudative RD with three to four quadrants of the retina involved

These categories were easy to apply. In case assignment was not explicit, a second investigator reviewed the chart, and final categorization was based on consensus.

Assessment of Microvascular Factors

Closed microvascular loops and microvascular networks, consisting of at least three back-to-back loops, were identified according to Folberg et al. from sections bleached with potassium permanganate and oxalic acid and stained with periodic acid–Schiff without counterstain, as described previously. They were viewed under a green filter (Watten 58; Eastman Kodak, Rochester, NY).

Microvessels were identified with the mAb QBEND/10 to the CD34 epitope of endothelial cells (diluted 1:25; lot 121202; Novocastra Laboratories, Newcastle-upon-Tyne, UK). They were counted from sections bleached with potassium permanganate and stained with periodic acid–Schiff without counterstain, as described previously. They were viewed under a green filter (Watten 58; Eastman Kodak, Rochester, NY).

Assessment of Survival

Complete follow-up data until December 1999, obtained from the Finnish Population and Cancer Registries, patient charts of hospitals where the patients had been treated for uveal melanoma and other malignancies, pathology laboratories, and death certificates reviewed by previously described routines, were available for 166 of the 167 patients. The median follow-up time was 22 years (range, 18–26) for patients who were still alive. Histopathologic diagnoses of 50 (63%) of 80 metastatic uveal melanomas were reconfirmed by immunohistochemistry, as described. In addition, 14 (17%) tumor-related deaths had been confirmed by fine-needle aspiration biopsy. Nine patients had had a second primary tumor, but histopathologic confirmation of the cause of death was available for all of them.

Statistical Analysis

Analyses were performed by computer (SPSS for Windows ver. 9.0.1; SPSS Inc., Chicago, IL; and StatXact-3 and LogXact-3 software; Cytel Software, Cambridge, MA). All tests were two-sided and used exact probability distributions. Continuous variables between unordered and ordered groups were compared with the Mann-Whitney and Jonckheere-Terpstra tests, respectively. Pearson’s χ², Kruskal-Wallis, and Jonckheere-Terpstra tests were used to compare proportions in unordered, singly ordered, and doubly ordered contingency tables, respectively. If subgroups were analyzed separately, Bonferroni correction was used to adjust probabilities for multiple comparisons.

For statistical analysis, cell type was collapsed into two categories according to the presence of epithelioid cells (spindle, non–spindle) and tumor location according to presence of ciliary body involvement (no, yes). Microvascular loops and networks were analyzed as a three-category variable that considered networks to be an advanced stage of loops (no loops, loops without networks, networks). The extent of RD was analyzed in four categories (no RD, subretinal fluid, clinical RD of one to two quadrants, clinical RD of three to four quadrants), and alternatively as collapsed into two categories based on the presence of clinical RD (described later). LBD and MVD were treated as continuous variables. The latter was square-root transformed to obtain normal distribution.

Multiple logistic regression was used to model exudative RD. Because logistic regression demands a two-category dependent variable, eyes with either no subretinal fluid or subretinal fluid only over and surrounding the tumor (no clinical RD) were compared with those with exudative RD in at least one quadrant (clinical RD). This categorization was made because it provided two groups of approximately equal size and because subretinal fluid is occasionally observed around presumed choroidal nevus. If one of the two categories is small, it is difficult to build a logistic model that outperforms simple assignment of all eyes to the larger group, and subretinal fluid over nevi and small melanomas may have a different set of predictors than clinical exudative RD.

Internal validity of the logistic model was ensured by choosing a split-sample, cross-validation design. The sample was randomly
divided into an analysis and a holdout sample 10 times in a ratio of 3:2 using computer-generated random numbers. The multivariate model was developed on the analysis samples and then applied to the validation samples to obtain the hit ratio (the percentage of eyes correctly classified). Independent variables were allowed in the model if \( P < 0.10 \). Confounding variables were kept in the model, irrespective of statistical significance. Different models were compared with the likelihood ratio test. The hit ratio was compared with maximum-chance criterion, obtained by assigning all eyes to the larger group (clinical RD), and with proportional chance criterion, obtained as \( \left( \frac{\text{proportion of eyes without clinical RD}}{\text{proportion of eyes with clinical RD}} \right)^2 \). The best model obtained was then applied to the entire sample.

Survival time data were analyzed by the Kaplan-Meier product-limit method and log-rank test. Patients judged to have died of causes unrelated to uveal melanoma were censored at the time of death. Equality of follow-up was ascertained by comparing Kaplan-Meier curves with reverse censoring. Power calculation indicated that the present study had an 80% power to detect a 0.25 difference in 20-year melanoma-specific survival as significant. Cox proportional hazards regression was used to adjust survival data for the effect of previously identified prognostic factors. The assumption of proportional hazards was confirmed by adding each covariate by log time interaction to the model and assessing the significance of the product term.

**RESULTS**

**Frequency of Retinal Detachment**

Of the 142 eyes in which the extent of RD was known, 35 (25%; 95% confidence interval [CI], 18–33) had no RD, 23 (16%; 95% CI, 11–23) had subretinal fluid over and around the tumor, 61 (43%; 95% CI, 35–51) had clinical RD involving one to two quadrants, and 23 (16%; 95% CI, 11–23) had RD involving three to four quadrants. No rhegmatogenous detachments occurred. The 124 eyes in which histopathologic factors could be analyzed were comparable in the extent of exudative RD to the 18 eyes excluded from the analysis (Table 1; \( P = 0.12 \), Kruskal-Wallis test).

### Table 1. Presence of Exudative RD, According to Tumor Characteristics in 142 Eyes with Malignant Choroidal and Ciliary Body Melanoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>None</th>
<th>Subretinal Fluid</th>
<th>1–2 Quadrants</th>
<th>3–4 Quadrants</th>
<th>( P )</th>
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<tr>
<td>Clinical covariates (n = 142)</td>
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<td></td>
<td></td>
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<td>Gender, n (%)</td>
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<tr>
<td>Male</td>
<td>14 (22)</td>
<td>13 (20)</td>
<td>23 (35)</td>
<td>15 (23)</td>
<td>0.33*</td>
</tr>
<tr>
<td>Female</td>
<td>21 (27)</td>
<td>10 (15)</td>
<td>38 (50)</td>
<td>8 (10)</td>
<td></td>
</tr>
<tr>
<td>Ciliary body involvement, n (%)</td>
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<td></td>
<td></td>
<td></td>
<td>0.011*</td>
</tr>
<tr>
<td>No</td>
<td>22 (20)</td>
<td>18 (16)</td>
<td>49 (44)</td>
<td>21 (19)</td>
<td></td>
</tr>
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<td>Yes</td>
<td>13 (40)</td>
<td>5 (16)</td>
<td>12 (38)</td>
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<tr>
<td>Largest basal diameter, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>( \leq 10 ) mm</td>
<td>18 (46)</td>
<td>9 (25)</td>
<td>10 (26)</td>
<td>2 (5)</td>
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</tr>
<tr>
<td>&gt;10–15 mm</td>
<td>13 (20)</td>
<td>11 (17)</td>
<td>33 (50)</td>
<td>9 (13)</td>
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</tr>
<tr>
<td>&gt;15 mm</td>
<td>3 (9)</td>
<td>3 (9)</td>
<td>17 (48)</td>
<td>12 (34)</td>
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<td>Height, n (%)</td>
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<td></td>
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<td>0.0002†</td>
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<td>( \leq 5 ) mm</td>
<td>16 (33)</td>
<td>12 (25)</td>
<td>19 (40)</td>
<td>1 (2)</td>
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<tr>
<td>&gt;5–8 mm</td>
<td>12 (24)</td>
<td>5 (10)</td>
<td>25 (50)</td>
<td>8 (16)</td>
<td></td>
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<tr>
<td>&gt;8 mm</td>
<td>6 (14)</td>
<td>6 (14)</td>
<td>16 (38)</td>
<td>14 (33)</td>
<td></td>
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<tr>
<td>Bruch’s membrane, n (%)</td>
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<tr>
<td>Unruptured</td>
<td>23 (31)</td>
<td>7 (10)</td>
<td>38 (51)</td>
<td>6 (8)</td>
<td></td>
</tr>
<tr>
<td>Ruptured</td>
<td>11 (17)</td>
<td>15 (23)</td>
<td>25 (35)</td>
<td>17 (20)</td>
<td></td>
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<td>Histopathologic covariates (n = 124)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Data available, n (%)</td>
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<td></td>
<td></td>
<td></td>
<td>0.12*</td>
</tr>
<tr>
<td>Yes</td>
<td>34 (27)</td>
<td>21 (17)</td>
<td>48 (39)</td>
<td>21 (17)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (6)</td>
<td>2 (11)</td>
<td>13 (72)</td>
<td>2 (11)</td>
<td></td>
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<td>Cell type, n (%)</td>
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<td></td>
<td></td>
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<td>0.18*</td>
</tr>
<tr>
<td>Spindle</td>
<td>22 (28)</td>
<td>18 (22)</td>
<td>29 (36)</td>
<td>11 (14)</td>
<td></td>
</tr>
<tr>
<td>Nonspindle</td>
<td>12 (27)</td>
<td>3 (7)</td>
<td>19 (43)</td>
<td>10 (23)</td>
<td></td>
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<td>Microvascular patterns, n (%)</td>
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<td></td>
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<tr>
<td>No loops</td>
<td>16 (31)</td>
<td>14 (28)</td>
<td>17 (33)</td>
<td>4 (8)</td>
<td></td>
</tr>
<tr>
<td>Loops only</td>
<td>10 (34)</td>
<td>3 (10)</td>
<td>8 (28)</td>
<td>8 (28)</td>
<td></td>
</tr>
<tr>
<td>Networks</td>
<td>8 (18)</td>
<td>4 (9)</td>
<td>23 (52)</td>
<td>9 (21)</td>
<td></td>
</tr>
<tr>
<td>Microvascular density, n (%)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.062†</td>
</tr>
<tr>
<td>1 quartile (1–24 vessels/0.313 mm²)</td>
<td>9 (29)</td>
<td>7 (25)</td>
<td>10 (32)</td>
<td>5 (16)</td>
<td></td>
</tr>
<tr>
<td>2 quartile (25–40 vessels/0.313 mm²)</td>
<td>12 (59)</td>
<td>7 (25)</td>
<td>8 (26)</td>
<td>4 (13)</td>
<td></td>
</tr>
<tr>
<td>3 quartile (41–57 vessels/0.313 mm²)</td>
<td>5 (17)</td>
<td>5 (17)</td>
<td>16 (53)</td>
<td>4 (13)</td>
<td></td>
</tr>
<tr>
<td>4 quartile (58– vessels/0.313 mm²)</td>
<td>8 (25)</td>
<td>2 (6)</td>
<td>14 (44)</td>
<td>8 (25)</td>
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<tr>
<td>Macrophages, n (%)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.79†</td>
</tr>
<tr>
<td>Few</td>
<td>5 (24)</td>
<td>6 (29)</td>
<td>7 (33)</td>
<td>3 (14)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>18 (30)</td>
<td>7 (12)</td>
<td>22 (37)</td>
<td>13 (22)</td>
<td></td>
</tr>
<tr>
<td>Many</td>
<td>11 (28)</td>
<td>7 (18)</td>
<td>17 (44)</td>
<td>4 (10)</td>
<td></td>
</tr>
</tbody>
</table>

* Kruskal-Wallis test.
† Jonckheere-Terpstra test.
‡ Globally highest microvesel count obtained from areas of densest vascularization with mAb QBEND/10 to the CD34 epitope.
§ Evaluated with mAb PG-M1 to the CD68 epitope.
Univariate Analysis of RD in Relation to Tumor Characteristics

No association (Table 1) was noted between the extent of RD and gender, age (Fig. 1A; $P = 0.092$), presence of epithelioid cells ($P = 0.18$ Kruskal-Walls test), and number of tumor-infiltrating macrophages ($P = 0.79$ Jonckheere-Terpstra test). The RD was significantly more extensive in eyes with large tumors, as judged by LBD (Fig. 1B; $P < 0.0001$ Jonckheere-Terpstra test) and height (Fig. 1C; $P < 0.0001$) and in eyes with melanoma that had either microvascular loops or networks (Table 1; $P = 0.0094$), whereas melanomas that involved the ciliary body gave rise to less extensive RD than those limited to the choroid ($P = 0.011$ Kruskal-Wallis test). Melanomas that had ruptured Bruch’s membrane (Table 1; $P = 0.065$) and those with high MVD (Fig. 1D; $P = 0.054$ Jonckheere-Terpstra test) tended to be associated with more extensive RD than those with intact Bruch’s membrane and low MVD.

Because melanomas with ciliary body involvement probably do not have full potential to cause RD, the 110 choroidal melanomas were analyzed as a separate group. The effect of LBD ($P < 0.0001$ Jonckheere-Terpstra test, Bonferroni correction), height ($P < 0.0001$), and microvascular loops and networks ($P = 0.017$) was retained in this group. The effect of a ruptured Bruch’s membrane (P = 0.11 Kruskal-Wallis, Bonferroni correction), presence of epithelioid cells (P = 0.97), and high MVD (P = 0.068 Jonckheere-Terpstra test, Bonferroni correction) did not appreciably change in magnitude. When the analysis was limited to the 32 melanomas involving the ciliary body, only LBD (P = 0.025 Jonckheere-Terpstra test, Bonferroni correction) was associated with the extent of RD.

Multivariate Analysis of RD in Relation to Tumor Characteristics

Presence of exudative RD in eyes with uveal melanoma was modeled by multiple logistic regression. Based on the anatomic fact that ciliary body tumors do not have full potential to leak under the retina because of their location, involvement of the ciliary body was modeled as a confounding variable—that is, as a variable that theory dictates must always be included in the model.

In a starting model, LBD and the status of Bruch’s membrane, the two factors that RD is most often ascribed to in textbooks, were assessed as independent variables—that is, statistical analysis was used to look for evidence of their association with RD (Table 2). High LBD was significantly associated with presence of RD (odds ratio [OR], 1.40 for each 1-mm change; $P = 0.0004$, Wald $\chi^2$ test), but a rupture in Bruch’s membrane was not associated with presence of RD ($P = 0.96$). A model that included presence of epithelioid cells (OR, 1.29; 95% CI 0.39–4.34; $P = 0.79$ Jonckheere-Terpstra test) was also discarded. Consequently, a reduced model that excluded these nonsignificant variables served as a basis for further comparison (Table 2).

A model was then considered in which microvascular factors were assessed (Table 2). MVD was found not to be associated with presence of RD ($P = 0.87$), whereas an ordered three-category variable that considered microvascular networks to be an advanced stage of loops (no loops, loops without networks, loops forming networks) was significantly associated with the presence of RD (OR, 1.98 for a one-category change; $P = 0.052$). When modeled as unordered variables, the presence of loops without networks was not significantly associated with RD (OR, 2.78; $P = 0.22$), whereas the presence of loops forming networks was significantly associated with the presence of RD (OR, 4.30; $P = 0.041$). That the latter OR was approximately 1.5 times larger than the former, supports a dosage effect, lending support to the use of the ordered three-category variable based on hierarchy of loops and networks.

The final model consequently included LBD, microvascular loops and networks, and involvement of the ciliary body (Table 2). It fitted the data significantly better than the reduced model, which included only LBD and ciliary body involvement ($-2$ log likelihood, 81.4–76.9 = 4.50, 1 df; $P = 0.034$, $\chi^2$ test). This was reflected in the fact that the predicted probabilities of RD were located farther from the cutoff score than those predicted by the reduced model (Fig. 2).
As explained in the Methods section, the model was built with an analysis sample that consisted of a randomly chosen subset of patients. To confirm that the final model was valid, and applicable to other patients with uveal melanoma, it was then tested on a validation sample, consisting of the remaining patients. The model correctly predicted the presence of RD in 72.7% of eyes in both analysis and validation samples. This compared favorably with the maximum-chance criteria (obtained by assigning all eyes to the larger group) and the proportional-chance criteria (obtained by randomly assigning all eyes to the two groups according to group size) used to assess the performance of regression models, which correctly predicted the presence of RD in 56% and 51% of eyes, respectively.

After the validity of the final model was confirmed, more precise coefficients were estimated from the entire series of patients (Table 2). These coefficients were entered into the general logistic model, and the probability of exudative RD was calculated for uveal melanomas of various size, location, and microvascular pattern (Table 3). This table can be used as a guide to estimate the risk for exudative RD in clinical practice or to compare the risk between two given tumors. For example, a choroidal melanoma with microvascular networks and 9-mm LBD is readily seen to have a 10 times higher risk (0.50 vs. 0.05) for exudative RD than a ciliochoroidal melanoma of identical size but without any microvascular loops (Table 3).

**Survival in Relation to Retinal Detachment**

At last follow-up, 44 (26%) of 167 patients were alive without evidence of recurrent tumor, 76 (46%) had died of metastatic melanoma, 9 (5%) had died of other cancers, and 37 (22%) had died of other causes. The survival rate of the 142 patients included in the analysis of exudative RD did not differ from that of the 25 patients excluded from the study ($P = 0.39$, log-rank test).

When all four categories of exudative RD were considered, a statistically significant trend was observed among the 142 patients toward higher mortality with increasing extent of RD (Fig. 3A; $P = 0.023$, log-rank test for trend). When analyzed according to the presence of clinical RD, the melanoma-specific probability of survival was significantly higher in patients without RD (Fig. 3B; 20-year survival, 0.59 vs. 0.37; $P = 0.029$, log-rank test).

Multivariate modeling was performed with the 124 patients with histopathologic data according to presence and absence of clinical RD. The survival experience of this subgroup (20-year survival, 0.59 vs. 0.37; $P = 0.029$, log-rank test) was similar to that of the entire series. Univariate Cox regression based on presence or absence of clinical RD (Fig. 3C; 0.56 vs. 0.38; $P = 0.062$, likelihood ratio test) was found to closely parallel corresponding Kaplan-Meier curves representing the observed survival. The survival difference decreased markedly.
DISCUSSION

Large tumor size, posterior location, and ruptured Bruch’s membrane are the characteristics of malignant uveal melanoma that are most frequently linked with presence of exudative RD.\textsuperscript{13} Multiple logistic regression confirmed that tumor size is the single most important predictor of RD in eyes with choroidal and ciliary body melanoma, and that location of the tumor is also important. The impression that ruptured Bruch’s membrane alone would be associated with exudative RD was not substantiated.\textsuperscript{1,14} Although such rupture was moderately associated with RD by univariate analysis, the effect disappeared when LBD was controlled for by logistic regression. Instead, microvascular loops and, in particular, networks formed from back-to-back loops, were associated with the presence of RD in this data set, even when tumor size and location were controlled for.

The logistic model does not reveal the mechanism by which large tumors cause RD; in particular, it does not tell whether LBD is a surrogate measure of one or more underlying tumor and host characteristics that lead to RD. We were able to exclude a number of variables including age and gender, presence of epithelioid cells and infiltrating macrophages, and globally highest MVD. It is not inconceivable that the sheer mass of large tumors may be responsible for RD. For example, the total vascular content and leakage from tumor tissue would be expected to be proportional to tumor volume. Findings in the Collaborative Ocular Melanoma Study\textsuperscript{21} showed that vascularity of large melanomas is more prominent than that of medium-sized ones, and evidence of broken blood–ocular barrier increases with increasing tumor size.\textsuperscript{34,35} Fluid movement from subretinal space into the choriocapillaris is a major force that keeps the retina attached.\textsuperscript{36,37} Large tumors have proportionally larger surface areas and may cause proportionally more widespread decompensation of the choriocapillaris and retinal pigment epithelium (RPE).\textsuperscript{38,39}

Because uveal melanomas that extend to the ciliary body are located only partially under the retina, they intuitively have a smaller than average chance of causing RD than choroidal tumors that lie entirely under the retina. It has also been suggested that anteriorly located tumors have less chance of compressing vortex veins. Indeed, involvement of the ciliary body turned out to be an indicator for a low risk of exudative RD. Entirely choroidal tumors were estimated to have a five times higher chance of causing RD than tumors that extend to the ciliary body, when controlling for tumor size and microvascular loops and networks. Ciliochoroidal melanomas are predicted to cause RD only if they are 3 to 6 mm larger than choroidal melanomas and if they reach a diameter of 15 to 18 mm.

![Figure 2](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932896/)

**FIGURE 2.** Estimated probability of exudative RD from choroidal and ciliary body melanoma in 124 patients with histopathologic data, calculated from (A) a reduced model that included LBD as an independent variable and ciliary body involvement as a confounding variable and (B) the final model that additionally included microvascular loops and networks as an independent variable. Data in (B) show that the probabilities were lower in the group of true negatives and higher in the group of true positives than in (A) and shifted away from the cutoff score (dotted line). However, false negatives and false positives were little affected. Bar: median.

after adjusting for largest basal tumor diameter by multivariate Cox regression (0.49 vs. 0.43, $P = 0.56$) and all but disappeared after microvascular loops and networks were also controlled for (Fig. 3D; 0.48 vs. 0.46, $P = 0.90$). When the survival was adjusted additionally for MVD and ciliary body involvement, the hazard ratio (HR) reached unity (Table 4; HR 1.00, $P = 1.0$).

Data express predicted probability of RD. Calculated from the final multiple logistic regression model given in Table 2, cutoff score is 0.57: $P(X) = 1/[1 + \exp(-(-4.556 + 0.358 \cdot \text{LBD} + 0.667 \cdot \text{MVP} - 1.586 \cdot \text{CBI})]$ where LBD is expressed in millimeters, MVP is microvascular pattern, and CBI is ciliary body involvement, as coded in Table 2. Data in bold type indicate predicted presence of clinical RD (estimated probability, $>0.57$) and data in italics indicate borderline values (estimated probability, $0.57 \pm 0.15$).
Qualitative and quantitative aspects of tumor microvessels have recently been found to be independent predictors of death caused by uveal melanoma, a cancer that can spread only hematogenously unless the conjunctiva is invaded. Logistic regression provided evidence against a major role of “hot spots,” areas of densest vascularization, which are associated with poor prognosis of choroidal and ciliary body melanoma and are postulated to be active sites of metastasis in other tumors. In contrast, the association of RD associated with microvascular loops and networks by multivariate Cox regression (D). Logistic model (A, B), Wald χ² test (C, D).

Table 4. Cox Proportional Hazards Regression of Melanoma-Specific Survival, According to Presence of Clinical Exudative RD in 124 Patients with Choroidal or Ciliary Body Melanoma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient (±SE)</th>
<th>Wald Test*</th>
<th>P</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical RD†</td>
<td>0.511 ± 0.276</td>
<td>3.42</td>
<td>0.064</td>
<td>1.67 (0.97–2.87)</td>
</tr>
<tr>
<td>Largest basal diameter</td>
<td>0.116 ± 0.035</td>
<td>10.79</td>
<td>0.0010</td>
<td>1.12 (1.05–1.20)</td>
</tr>
<tr>
<td>Microvascular patterns‡</td>
<td>0.644 ± 0.157</td>
<td>16.86</td>
<td>&lt;0.0001</td>
<td>1.91 (1.40–2.59)</td>
</tr>
<tr>
<td>Microvascular density§</td>
<td>0.297 ± 0.069</td>
<td>18.5</td>
<td>&lt;0.0001</td>
<td>1.34 (1.17–1.54)</td>
</tr>
<tr>
<td>Ciliary body involvement†</td>
<td>0.919 ± 0.277</td>
<td>11.0</td>
<td>0.0009</td>
<td>2.50 (1.46–4.51)</td>
</tr>
<tr>
<td>Multivariate analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical RD†</td>
<td>0.018 ± 0.343</td>
<td>&lt;0.0001</td>
<td>1.0</td>
<td>1.00 (0.51–1.96)</td>
</tr>
<tr>
<td>Largest basal diameter</td>
<td>0.085 ± 0.041</td>
<td>4.17</td>
<td>0.041</td>
<td>1.09 (1.00–1.18)</td>
</tr>
<tr>
<td>Microvascular patterns‡</td>
<td>0.445 ± 0.167</td>
<td>7.05</td>
<td>0.0079</td>
<td>1.56 (1.12–2.17)</td>
</tr>
<tr>
<td>Microvascular density§</td>
<td>0.202 ± 0.074</td>
<td>7.45</td>
<td>0.0064</td>
<td>1.22 (1.06–1.42)</td>
</tr>
<tr>
<td>Ciliary body involvement†</td>
<td>0.756 ± 0.288</td>
<td>6.89</td>
<td>0.0086</td>
<td>2.13 (1.21–2.38)</td>
</tr>
</tbody>
</table>

* χ², 1 df, two-sided.
† Categories: No, 0; yes, 1.
‡ Categories: No loops, 0; loops without networks, 1; loops forming networks, 2.
§ Square-root-transformed, globally highest microvessel count obtained from areas of densest vascularization with mAb QBEND/10 to the CD34 epitope.

Because the study was a retrospective one, we may have assigned some eyes to the wrong group—for example, because from loops is obtained, the possibility exists that loops are indicators of hidden, more direct tumor or host effects in this analysis.
a dependent RD was missed or not mentioned in the chart. In that case, the logistic model may have classified the eye correctly, but the result would count as a false negative or positive classification when calculating the hit ratio. Although this could have been avoided by a prospective study, in particular with the help of B-scan ultrasonography, it would not have been possible to get unbiased, population-based histopathologic data, because the majority of small- to medium-sized melanomas are now managed conservatively, and statistical results can be extrapolated only to the population from which the sample is drawn. Moreover, a long enough follow-up for survival analysis would not have been available. In the future it may be possible, however, to find microvascular loops and networks clinically by confocal angiography or high-frequency ultrasonography.15,16

Secondly, because logistic regression can handle only a dichotomous dependent variable, it was obligatory to combine eyes with no RD with those that had subretinal fluid over and surrounding the tumor. If local RD were caused by the same factors as clinical RD, it would be a demanding task to separate these two groups from one another, making it understandable that false negative and positive assignments would occur even if the model includes all major variables contributing to RD. This might have been avoided by using multinomial logistic regression, but the sample size was not adequate for such an analysis. It should be explicitly noted that the present model was not designed to predict which small melanomas will involve overlying subretinal fluid rather than clinical exudative RD.4,5,17 We believe that a different set of variables may contribute to local subretinal fluid, not only because it can be associated with presumed nevi but also because steep, collar-button-shaped uveal melanomas sometimes seem to mechanically elevate the retina around the tumor’s base.

Thirdly, the inability to capture all variation in RD and to improve the hit ratio compared with the reduced model indicates that additional variables must contribute to RD. These may include excessive leakage because of high total vascular content or damage to the RPE and choriocapillaris or because of unbalanced influx of fluid from the vitreous cavity and abnormal retinal vessels to the subretinal space caused by changes in osmotic pressure, blocked vortex veins, and reduced suction from the normally elastic chorioid.16,19,47 The role of these latter factors in uveal melanoma is elusive. Although damage to the RPE is frequently given as a cause for exudative RD in eyes with uveal melanoma,16,38,39 experimental data suggest that such damage may also improve outflow of water by allowing the oncotic force of the choroid to suck out subretinal fluid.4,5,30,37,48 Some of these possibilities may be addressed by future prospective clinical studies.

Regarding survival, RD has been an inconsistent indicator of metastatic death caused by uveal melanoma.7,9,10 This is understandable, because previous studies have been based on subpopulations of patients with disease managed by enucleation or some conservative measure and thus are probably unbalanced regarding tumor size.11 We could confirm a modest risk of metastatic death by univariate analysis, but Cox regression definitely showed that the survival difference was entirely due to the association of RD with large tumor size, microvascular loops and networks, ciliary body involvement, and, to a lesser extent, high MVD. When these factors were controlled for, the survival rates of patients with and without exudative RD were identical. Consequently, the presence or absence of RD in eyes with malignant uveal melanoma alone does not carry any information on survival prognosis.

Exudative RD in conservatively managed eyes with uveal melanoma is associated with a higher than average risk of complications.8,9 So far, it has been impossible to reduce the dose or otherwise control the radiation to combat these complications. Better understanding of which factors cause and maintain RD in eyes with uveal melanoma may help ophthalmic oncologists, not only to predict the risk for persistent exudative RD and secondary neovascular glaucoma after irradiation, but also to modulate some of them in the future to reduce this risk.9 Radiation-induced alterations may contribute to exudative RD after brachytherapy and charged-particle treatment, however, and these effects must also be investigated.

References

21. Collaborative Ocular Melanoma Study Group. Histopathologic characteristics of uveal melanomas in eyes enucleated from the...


