Optic Nerve Invasion of Uveal Melanoma: Clinical Characteristics and Metastatic Pattern

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Purpose. To determine the frequency of optic nerve invasion in uveal melanoma, to identify clinical factors associated with optic nerve invasion, and to analyze the metastatic pattern and the association with survival.

Methods. All iris, ciliary body, and choroidal melanomas (N = 2758) examined between 1942 and 2001 at the Eye Pathology Institute, University of Copenhagen, Denmark, and the Institute of Pathology, Aarhus University Hospital, Aarhus, Denmark, were reviewed. Cases with optic nerve invasion were identified and subdivided into prelaminar or laminar invasion and postlaminar invasion. Clinical characteristics were compared with those from 85 cases randomly drawn from all ciliary body and choroidal melanomas without optic nerve invasion from the same period. Survival data were obtained by the Kaplan-Meier method, and the Mantel-Cox log-rank test was used to test differences in survival among the three patient groups.

Results. Optic nerve invasion was found in 157 uveal melanomas (5.7%; 95% confidence interval [CI], 4.8%–6.6%). Frequency varied during the observation period between 5% and 7%. Only choroidal and ciliary body melanomas were found to invade the optic nerve. Eighty-five (54%) were confined to the prelaminar or laminar part, and 72 (46%) were confined to the postlaminar part. Increased intraocular pressure (IOP) and juxtapapillary location were associated with prelaminar or laminar invasion and postlaminar invasion. Age older than 70 years, reduced vision to light perception or worse, nonvisible fundus, and large (>15 mm) tumor size were associated with postlaminar spread. In univariate analysis, patients with postlaminar invasion had significantly higher all-cause and melanoma-related mortality than the other patients.

Conclusions. Optic nerve invasion in uveal melanoma is found in 1 in 20 patients. Visible juxtapapillary melanoma or loss of light perception should make the clinician suspicious of melanoma with optic nerve invasion, and special awareness of postlaminar spread should be addressed when increased IOP is present independently of decreased visual acuity and tumor location. (*Invest Ophthalmol Vis Sci.* 2006;47:3268–3275) DOI:10.1167/iovs.05-1435

Uveal melanoma is the most frequent primary intraocular malignant tumor in adults; in Scandinavia, the incidence rate is 5.3 to 8.7 per million person-years.[1–4] The tumor has a great propensity to metastasize and to affect the liver in particular.[3,5,6] Local spread occurs through the overlying Bruch membrane, giving access to the subretinal space, or toward the orbit (through the sclera, most often along ciliary vessels and nerves). Uveal melanoma infiltrates the optic nerve in only 0.6% to 5% of patients and has been associated with high intraocular pressure, non–spindle cell type, juxtapapillary location, and blindness.[3,7–15]

The uveal melanoma material examined between 1942 and 2001 at the Eye Pathology Institute, University of Copenhagen, and the Institute of Pathology, Aarhus University Hospital, was reviewed to determine the frequency of optic nerve invasion and to identify clinical factors associated with optic nerve invasion. Furthermore, the metastatic pattern was investigated, and survival analyses were performed to determine the association between survival and optic nerve invasion.

Materials and Methods

Patients

At the Eye Pathology Institute, University of Copenhagen, and the Institute of Pathology, Aarhus University Hospital, 2758 eyes enucleated for uveal melanoma between 1942 and 2001 were examined. These eyes constituted all enucleated eyes with uveal melanoma during this period in Denmark. All pathology reports and histology specimens were reviewed, and 157 uveal melanomas with optic nerve invasion were identified. A control group of 85 patients was randomly chosen from the same period from the group of patients with choroidal or ciliary body melanoma without optic nerve invasion because no iris melanomas invaded the optic nerve. In total, 242 patients with uveal melanoma were enrolled in this study.

Ethics

The investigation followed the tenets of the Declaration of Helsinki and was approved by the local scientific ethical committee.

Clinical Characteristics

Reports from admitting hospitals were collected, and the following data on each patient were registered: sex, date of birth, date of histopathologic diagnosis, visual acuity, intraocular pressure (IOP), funduscopic examination, signs of extraocular growth at surgery, ocular surgery, radiotherapy, and orbital recurrence. Visual acuity and intraocular pressure were only included if these recordings were obtained within 2 weeks before enucleation. The tumor was classified as juxtapapillary if the clinician observed during funduscopic examination that the tumor was touching the optic disc. Signs of extraocular growth were graded as positive if the admitting physician had noted this in the surgical report or in the admission note. All pathology reports at the Eye Pathology Institute from 1942 to 2005 were also reviewed to detect orbital recurrences. Furthermore, the Danish Can-

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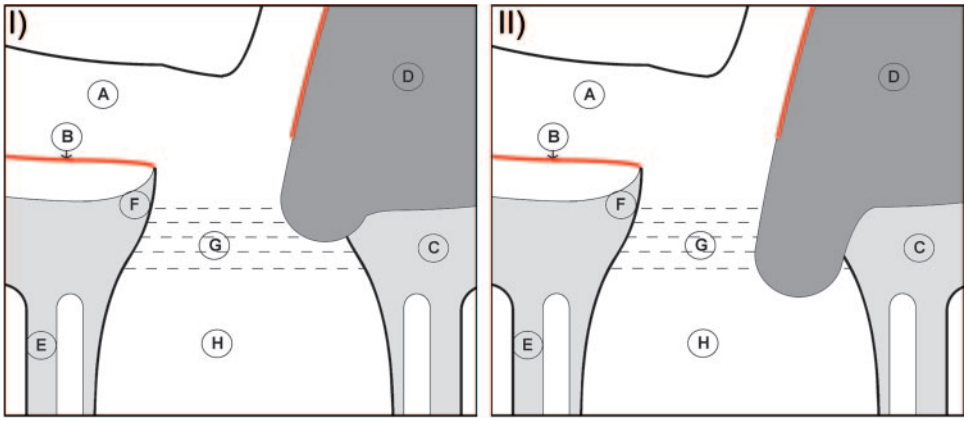

FIGURE 1. Sketch of malignant choroidal melanoma invading the optic nerve. *Left*: Laminar invasion. *Right*: Postlaminar invasion. A, retina; B, Bruch membrane; C, sclera; D, melanoma; E, dura mater; F, border tissue of Elschnig; G, lamina cribrosa; H, optic nerve.

cer Registry (DCR) was studied to detect orbital recurrences not treated with surgery.

Histopathology

All eyes were fixed in buffered formalin, embedded in paraffin, and stained with hematoxylin-eosin for routine histology diagnosis. All specimens were reexamined, and the degree of optic nerve invasion was graded as prelaminar or laminar if tumor cells were present in the optic nerve head or in the lamina cribrosa (Fig. 1, left) and as postlaminar if tumor cells were present in the optic nerve or its sheaths cranial to the lamina cribrosa (Fig. 1, right). Largest basal tumor diameter (LBD) was measured in millimeters, and the tumor was classified as small (≤10 mm), medium (>10–15 mm), or large (>15 mm).

Metastatic Pattern and Survival

Registrations at the DCR and the Registry of Cause of Death were studied, and data on date of death, cause of death, and metastases were collected. Furthermore, autopsy reports were collected. Metastases were registered if they had been confirmed by computed tomography (CT), ultrasonography, surgery, or autopsy. Follow-up data for the cohort of patients was updated to November 1, 2004.

All death certificates were reviewed. If autopsy had been performed, the autopsy report was studied to validate the cause of death. If uveal melanoma metastases were found at autopsy, the patient was coded as having died of melanoma. If no autopsy had been performed and uveal melanoma was registered on the death certificate as the cause of death and the patient had no other malignancies according to the DCR, the patient was coded as having died of melanoma. If uveal melanoma or other malignancies were not noted on the death certificate and the patient was registered exclusively in the DCR with uveal melanoma, the patient was coded as having died of a nonmelanoma cause. If a malignancy other than uveal melanoma was registered as the cause of death on the death certificate and the patient was registered with this malignancy in the DCR, the patient was coded as having died of a nonmelanoma cause. Finally, if a malignancy other than uveal melanoma was registered as the cause of death but this malignancy was not registered in the DCR, the patient was coded as having died of melanoma (12 cases coded on the death certificate as skin melanoma, eight cases as gastrointestinal cancer, and one as unspecified malignancy). In eight cases, the cause of death could not be determined.

Statistical Analysis

Relationships between optic nerve invasion and clinical parameters were examined by contingency tables and were further analyzed by Pearson χ^2 test and Fisher exact test. Mean age and tumor size were analyzed by t test after verification of equal variances by Levene test. The equality of mean of intraocular pressure was tested by the Mann-Whitney U test because a nonnormal distribution was found. Correlations between ordinal parameters and optic nerve invasion were evaluated by Spearman rank correlation test.

Univariate and multivariate binary logistic regression analyses were performed in a forward stepwise manner to evaluate the predictive value of clinical factors for different degrees of optic nerve invasion. Factors with $P < 0.20$ in the univariate analysis were included in the multivariate analysis.

Survival data were obtained by the Kaplan-Meier method, and the Mantel-Cox log-rank test was used to test differences in survival be-

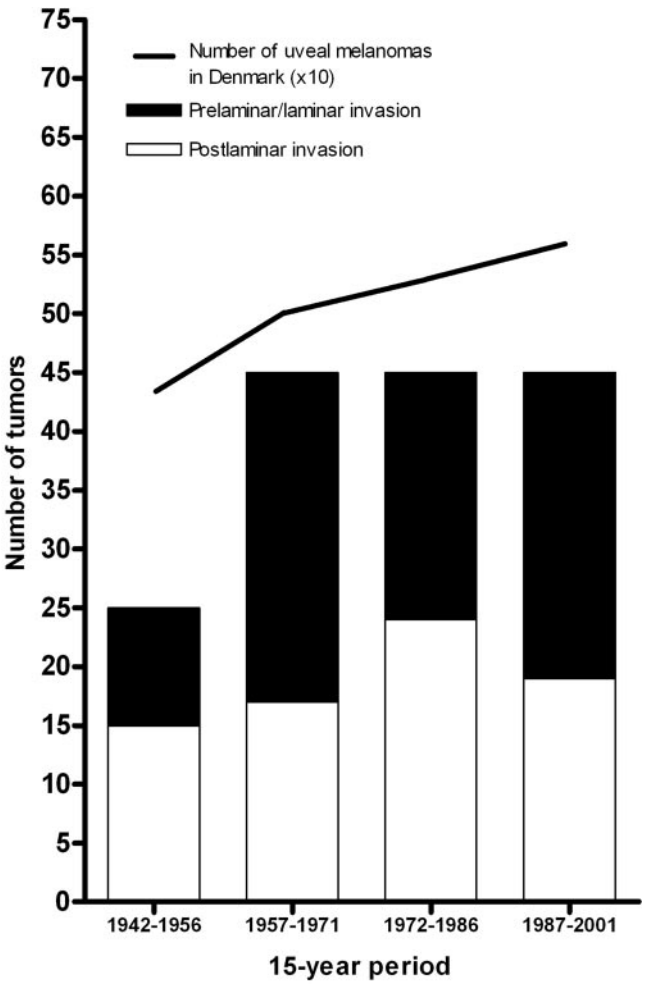

FIGURE 2. Frequency of optic nerve invasion of uveal melanoma in Denmark between 1942 and 2001. Frequency varied between 5% and 7% during the observation period.

tween patient groups. Patients were excluded if no follow-up data were obtainable ($n = 6$). Patients with undetermined causes of death ($n = 8$) were excluded from the analysis of melanoma-related death. One patient with uveal melanoma diagnosed at autopsy was excluded from the survival analyses. Patients who died of causes unrelated to uveal melanoma were censored at the time of death in the analyses of melanoma-related death. $P < 0.05$ was regarded as significant.

Results

For a period spanning 60 years (1942–2001), 2758 eyes with uveal melanoma were examined at the Eye Pathology Institute, University of Copenhagen, and the Institute of Pathology, Aarhus University Hospital. Optic nerve invasion was present in 157 cases (5.7%; 95% confidence interval [CI], 4.8%–6.6%). The frequency of optic nerve invasion in uveal melanoma varied between 5% and 7% of all diagnosed uveal melanomas during the observation period (Fig. 2). Eighty-five (54%) were confined to the prelaminar or laminar part of the optic nerve, and 72 (46%) were postlaminar (Fig. 3). Patient and tumor characteristics are listed in Table 1.

The mean age of patients with postlaminar optic nerve invasion was 70 years (95% CI, 67–73 years) compared with 63 years in patients with prelaminar or laminar invasion (95% CI, 60–65 years; $P < 0.001$) and 61 years in controls (95% CI, 58–64 years; $P < 0.001$).

Visual acuity was significantly reduced in patients with postlaminar invasion compared with the other patient groups (versus prelaminar or laminar, $P < 0.001$; versus control, $P < 0.001$; Table 1). Furthermore, patients with prelaminar or laminar invasion had significantly reduced visual acuity compared with controls ($P = 0.027$; Table 1).

Patients with postlaminar optic nerve invasion had significantly higher IOP (median, 48 mm Hg; 14–70 mm Hg 10th–90th percentiles) compared with other groups (prelaminar or laminar: median, 17 mm Hg; Hg 10th–90th percentiles, 12–50 mm; $P < 0.001$; control: median, 15 mm Hg; 10^{th}–90th percentiles, 10–38 mm Hg; $P < 0.001$; Table 1). In addition, the frequency of increased IOP was higher in patients with prelaminar or laminar optic nerve invasion than in the controls ($P = 0.003$; Table 1).

In 38% (95% CI, 24%–52%) of patients with postlaminar invasion, no view of the fundus was obtainable by direct funduscopic examination, primarily because of vitreous hemorrhage or total retinal detachment, compared with only 8% (95% CI, 2%–14%; $P < 0.001$) among controls.

At direct funduscopic examination, the tumor was observed as juxtapapillary in 66% (95% CI, 48%–83%) of the cases with postlaminar invasion and in 71% (95% CI, 60%–83%) of the cases with prelaminar or laminar invasion (Table 1). In 15% (95% CI, 7%–24%) of the controls, the tumor was observed as juxtapapillary.

A significantly higher proportion of tumors with postlaminar invasion (19%) were thought by the surgeon to include extraocular extension compared with those with prelaminar or laminar invasion (5%; $P = 0.004$). Orbital recurrence was significantly more common among patients with postlaminar invasion (8%; 95% CI, 2%–15%) than in controls (1%; 95% CI, 0%–3%; $P < 0.05$).

Tumors with postlaminar optic nerve invasion (mean LBD, 16 mm; 95% CI, 14–17 mm) were significantly larger than the other tumors (prelaminar or laminar: mean LBD, 13 mm; 95% CI, 11–14 mm; $P = 0.001$; controls: mean LBD, 13 mm; 95% CI, 12–14 mm; $P < 0.001$).

Before enucleation, three patients with prelaminar or laminar optic nerve invasion were treated with Ru-106 brachytherapy; one of those patients was treated twice. Two patients had been treated with transpupillary thermotherapy (TTT) and one (in 1962) with photocoagulation and external radiation. Radiation was used in an attempt to save the eye because the other one was no longer functional. Before enucleation, three patients with postlaminar optic nerve invasion were treated with Ru-106 brachytherapy and two were treated with TTT. In the

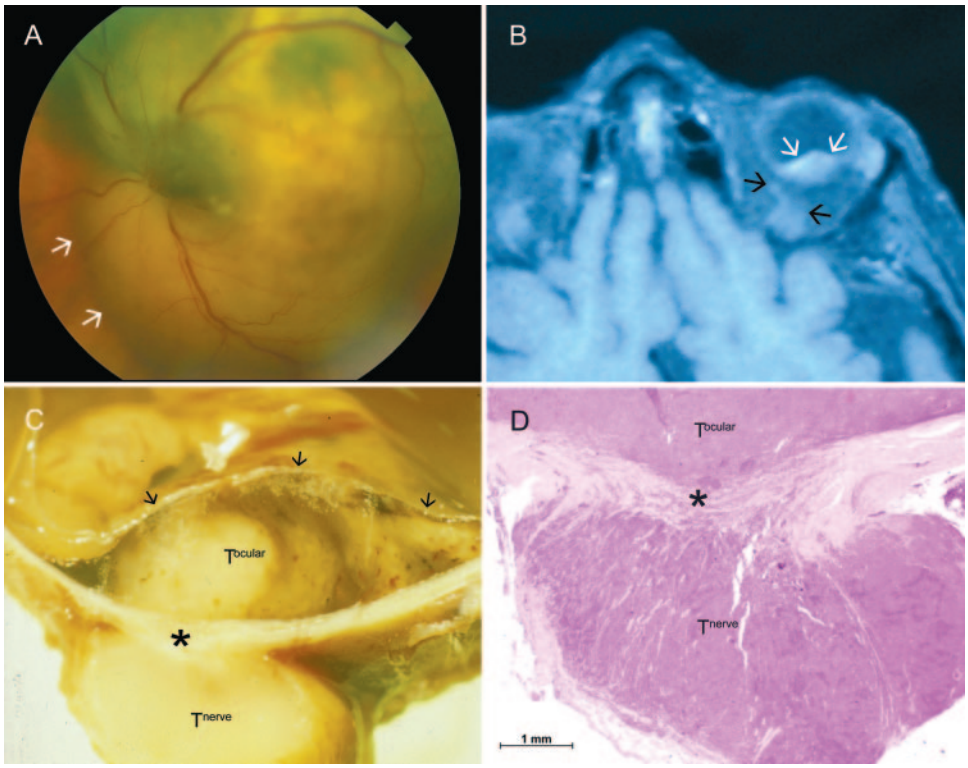

Figure 3. Optic nerve invasion of a uveal melanoma in an 80-year-old woman. (**A**) Funduscopic photograph showing the uveal melanoma with invasion of the optic nerve. *Arrows* mark the nasal tumor margin. (**B**) Magnetic resonance image (MRI) from the same patient. *White arrows* mark intraocular tumor mass, and *black arrows* mark the optic nerve invaded by the melanoma. (**C**, **D**) Photograph and micrograph (hematoxylin and eosin) of the tumor. Retinal detachment (*black arrows*) above the intraocular tumor mass (T^{ocular}) (*lamina cribrosa, T^{nerve} tumor mass in the optic nerve).

TABLE 1. Clinical Characteristics in 242 Patients with Uveal Melanoma with and without Optic Nerve Invasion

Characteristic	Optic Nerve Invasion			*P*
	Prelaminar/ Laminar *n* (%)	Postlaminar *n* (%)	No (control) *n* (%)	
Sex	*n* = 85	*n* = 72	*n* = 85	0.79*§; 0.36†§; 0.22‡§
Male	49 (48)	40 (57)	41 (48)	
Female	36 (52)	32 (43)	44 (52)	
Age, y	*n* = 85	*n* = 72	*n* = 85	<0.001*‖; <0.001†‖; 0.46‡‖
Mean (95% CI)	63 (60–65)	70 (67–73)	61 (58–64)	
Range	31–91	42–92	23–87	
Visual acuity	*n* = 59	*n* = 55	*n* = 76	<0.001*¶; <0.001†¶; 0.027‡¶
6/6-6/12	12 (20)	1 (2)	18 (24)	
6/18-6/60	10 (17)	2 (4)	25 (33)	
5/60-HM	17 (29)	5 (9)	20 (26)	
LP#	6 (10)	12 (22)	6 (8)	
NLP**	14 (24)	35 (63)	7 (9)	
Intraocular pressure (mm Hg)	*n* = 38	*n* = 34	*n* = 68	<0.001*¶; <0.001†¶; 0.003‡¶
≤24 mm Hg	25 (66)	7 (20)	61 (90)	
>24–40 mm Hg	4 (11)	4 (12)	1 (1)	
>40 mm Hg	9 (23)	23 (68)	6 (9)	
Mean	25	44	20	<0.001*††; <0.001†††; 0.065‡††
10th–90th percentile	12–50	14–70	10–38	
Range	8–62	10–79	8–90	
Fundus examination	*n* = 62	*n* = 47	*n* = 78	<0.001*§; <0.001†§; 0.68‡§
Observable fundus	56 (90)	29 (62)	72 (92)	
No view	6 (10)	18 (38)	6 (8)	
Juxtapapillary location	*n* = 56	*n* = 29	*n* = 72	0.58*§; <0.001†§; <0.001‡§
Yes	40 (71)	19 (66)	11 (15)	
No	16 (29)	10 (34)	61 (85)	
Extraocular extension suspected at surgery	*n* = 85	*n* = 72	*n* = 85	0.004*§; 0.12†§; 0.15‡§
Yes	4 (5)	14 (19)	9 (11)	
No	81 (95)	58 (81)	76 (89)	
Orbital recurrence	*n* = 85	*n* = 72	*n* = 85	0.090*§; 0.030†§; 0.56‡§
Yes	2 (2)	6 (8)	1 (1)	
No	83 (98)	66 (92)	84 (99)	
Tumor size (mm)	*n* = 85	*n* = 72	*n* = 85	<0.001*¶; <0.001†¶; 0.88‡¶
Small (≤10 mm)	37 (44)	14 (19)	32 (38)	
Medium (>10–15 mm)	29 (34)	25 (35)	39 (46)	
Large (>15 mm)	19 (22)	33 (46)	14 (16)	
Mean (95% CI)	13 (11–14)	16 (14–17)	13 (12–14)	
Range	3–35	4–40	4–30	<0.001*‖; <0.001†‖; 0.92‡‖

* *P* value for prelaminar/laminar optic nerve invasion versus postlaminar invasion.
† *P* value for postlaminar optic nerve invasion versus controls.
‡ *P* value for controls (no optic nerve invasion) versus prelaminar/laminar invasion.
§ χ^2-test (Fisher exact test).
‖ *t* test (equal variances by Levene test).
¶ Spearman rank correlation test.
# Light perception.
** No light perception.
†† Mann-Whitney U test (not normal distribution).

control group, three patients were treated with Ru-106 brachytherapy and none were treated with TTT.

In addition, before enucleation, six (8%) patients with postlaminar optic nerve invasion, nine (11%) patients with prelaminar or laminar invasion, and eight (9%) patients in the control group had undergone various types of ocular surgery (e.g., iridectomy, sclerotomy).

Univariate binary logistic regression analysis showed that intraocular pressure greater than 24 mm Hg and juxtapapillary location were associated with prelaminar or laminar optic nerve invasion (Table 2). The only clinical factor that was significantly associated with prelaminar or laminar optic nerve invasion of uveal melanoma on a multivariate level was juxtapapillary location (Table 2).

Age older than 70 years, visual acuity reduced to light perception (LP) or no light perception (NLP), intraocular pressure greater than 24 mm Hg, juxtapapillary location, nonvisible fundus, and largest basal diameter greater than 15 mm were significantly associated with postlaminar optic nerve invasion by univariate binary logistic regression (Table 2). Intraocular pressure greater than 24 mm Hg was the only factor associated with postlaminar optic nerve invasion by multivariate regression analysis (Table 2).

Metastatic disease was found in 53% of deceased patients with prelaminar or laminar optic nerve invasion and in 63% of patients with postlaminar optic nerve invasion. Metastatic disease developed in 43 (61%) patients in the control group (Table 3). The liver was the most frequent site of metastasis in all three patient groups, followed by the lungs (Table 3). Evidence of metastasis to the central nervous system (CNS), kidney, heart, or adrenal glands was only found in patients with optic nerve invasion. All five patients with postlaminar optic nerve invasion and metastases to the CNS had invasion of tumor cells into the subarachnoidal space. In two of these patients, the tumor was confined to the subarachnoidal space and the optic nerve sheaths. Significantly more autopsies were

TABLE 2. Association of Clinical Factors with Prelaminar/Laminar and Postlaminar Optic Nerve Invasion of Uveal Melanoma, Evaluated by Univariate and Multivariate Binary Logistic Regression

	Prelaminar/Laminar Optic Nerve Invasion				Postlaminar Optic Nerve Invasion			
	Univariate Logistic Regression		Multivariate Logistic Regression*† (n = 95)		Univariate Logistic Regression		Multivariate Logistic Regression†‡ (n = 86)	
Selected Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Sex								
Female (reference)								
Male	1.46 (0.80–2.68)	0.22			1.34 (0.72–2.52)	0.36		
Age, y		0.97				<0.001		
<50 (reference)								
≥50–60	1.01 (0.39–2.63)	0.98			1.52 (0.42–5.45)	0.52		
≥60–70	1.03 (0.44–2.45)	0.94			1.76 (0.55–5.63)	0.34		
≥70–80	1.14 (0.42–3.08)	0.80			5.55 (1.69–18.2)	0.005		
≥80	1.60 (0.38–6.81)	0.53			12.0 (2.70–53.3)	0.001		
Visual acuity		0.10				<0.001		
6/6-6/12 (reference)								
6/18-6/60	0.60 (0.21–1.69)	0.33			1.44 (0.12–17.1)	0.77		
5/60-HM	1.28 (0.48–3.38)	0.63			4.50 (0.48–42.2)	0.19		
LP	1.50 (0.39–5.77)	0.56			36.0 (3.84–338)	0.002		
NLP	3.00 (0.94–9.62)	0.07			90.0 (10.3–789)	<0.001		
Intraocular pressure, mm Hg		0.016				<0.001		<0.001
≤24 (reference)								
>24–40	9.76 (1.04–91.7)	0.046			34.9 (3.40–357)	0.003	76.0 (6.37–907)§	0.001
>40	3.66 (1.18–11.4)	0.025			33.4 (10.2–110)	<0.001	47.5 (10.6–212)§	<0.001
Fundoscopic examination								
Observable fundus (reference)								
No view	1.29 (0.39–4.20)	0.68			7.45 (2.69–20.6)	<0.001		
Juxtapapillary location								
No (reference)								
Yes	13.9 (5.84–32.9)	<0.001	14.0 (4.67–41.9)§	<0.001	10.5 (3.88–28.6)	<0.001		
Extraocular extension								
No (reference)								
Yes	0.42 (0.12–1.41)	0.16			2.04 (0.83–5.04)	0.12		
Tumor size, mm		0.28				<0.001		
≤10 (reference)								
>10–15	0.64 (0.33–1.26)	0.20			1.47 (0.66–3.27)	0.35		
>15	1.17 (0.51–2.71)	0.71			5.39 (2.22–13.1)	<0.001		

* Log likelihood: −46.377.

† Variables with $P < 0.20$ in the univariate analysis were analyzed in the multivariate analyses.

‡ Log likelihood: −26.977.

§ OR differs slightly from the univariate analysis because fewer patients were included (records for each variable examined by multivariate analysis were not available for all patients in univariate analysis).

performed in patients with prelaminar or laminar invasion than in controls ($P = 0.004$; Table 3).

Two hundred thirty-five patients (126 men, 109 women) were included in the survival analysis (all-cause mortality). Median follow-up time for all patients ($n = 235$) was 50 months (range, 1–660 months), and for patients still alive ($n = 35$) it was 137 months (range, 28 to 660 months). Median follow-up time was 53 months (range, 3–660 months) for patients with prelaminar or laminar invasion, 23 months (range, 1–495 months) for patients with postlaminar invasion, and 65 months (range, 1–478 months) for patients in the control group.

One-hundred eighteen patients died of uveal melanoma, 74 patients died of other causes, and 35 were still alive at the end of follow-up. In eight patients the cause of death was undetermined. These eight patients were excluded from the analysis of melanoma-related death.

Two hundred twenty-seven patients (120 men, 107 women) were included in the analysis of melanoma-related death. Median follow-up time for all patients ($n = 227$) was 49 months (range, 1–660 months), and for patients still alive ($n = 35$) it was 137 months (range, 28–660 months). Median follow-up time was 53 months (range, 3–660 months) for patients with prelaminar or laminar invasion, 23 months (range, 1–495 months) for patients with postlaminar invasion, and 62 months (range, 1–395 months) for patients in the control group.

Significant differences in mortality (all-cause and melanoma-related) were found between patients with postlaminar invasion and controls (all-cause, $P = 0.001$; melanoma-related, $P = 0.017$) and patients with prelaminar or laminar invasion (all-cause, $P = 0.001$; melanoma-related, $P = 0.004$; Figs. 4A, 4B). No significant differences in mortality were found between patients with prelaminar or laminar invasion and controls (all-cause, $P = 0.93$; melanoma-related, $P = 0.49$; Figs. 4A, 4B).

DISCUSSION

Invasion of the optic nerve in uveal melanoma is not as common as it is in retinoblastoma. Invasion is generally limited to

TABLE 3. Autopsy Rates and Metastatic Patterns in Patients with Uveal Melanoma with and without Optic Nerve Invasion

	Optic Nerve Invasion			
	Prelaminar/Laminar *n* (% [95% CI])	**Postlaminar *n* (% [95% CI])**	**No (control) *n* (% [95% CI])**	***P***
Deaths	62	68	71	
Autopsies	22 (35)	16 (24)	10 (14)	0.13*§ 0.15†§ 0.004‡§
Metastases	33 (53)	43 (63)	43 (61)	0.25*§ 0.75†§ 0.40‡§
Metastatic location known‖	26	36	34	
Liver	22 (85[71–99])	27 (75[60–89])	31 (91[82–100])	
Lung	7 (27[10–44])	11 (31[16–46])	6 (18[5–30])	
Bone	5 (19[4–34])	5 (14[3–25])	3 (9[0–18])	
Skin	4 (15[2–29])	4 (11[1–21])	2 (6[0–14])	
CNS	1 (4[0–11])	5 (14[3–25])¶	0 (0)	
Kidney	3 (12[0–24])	3 (8[0–17])	0 (0)	
Heart	4 (15[2–29])	1 (3[0–8])	0 (0)	
Lymph node	4 (15[2–29])	1 (3[0–8])	1 (3[0–9])	
Adrenal gland	5 (19[4–34])	0 (0)	0 (0)	
Other	10 (38[20–57])	3 (8[0–17])	4 (12[1–23])	

* *P* value for prelaminar/laminar optic nerve invasion versus postlaminar invasion.
† *P* value for postlaminar optic nerve invasion versus controls.
‡ *P* value for controls (no optic nerve invasion) versus prelaminar/laminar invasion.
§ χ^2-test.
‖ Since metastases may be present in more than one location, the total percentages exceed 100%.
¶ One patient still alive.

the area anterior to the lamina cribrosa, though postlaminar invasion is seen in 0.6% to 5% of enucleated eyes with uveal melanoma.[3,7–14] An equal number of melanomas with optic nerve invasion was found each 15 of the last 45 years of the observation period, even though an increasing number of uveal melanomas have been diagnosed.[4] The introduction of conservative treatment modalities in the late 1980s might explain this because some tumors invading the optic nerve are not diagnosed histopathologically.

NLP is an uncommon clinical feature in the presence of intraocular melanoma, yet in the present study it was seen in 24% (14/59) of patients with prelaminar or laminar and in 64% (35/55) of patients with postlaminar optic nerve invasion. Lack of light perception as a sign of postlaminar extension of a uveal melanoma is also supported by other case reports and series.[7,15–18] The presence of increased IOP might cause nerve conduction loss, but the sole presence of neoplastic cells in the optic nerve might also disturb the functionality of the nerve fibers. Eight patients with optic nerve invasion and normal IOP in the present study had LP or NLP. Neoplastic cells alone thus appear to produce blindness because of nerve conduction loss.

Age older than 70 years was associated with postlaminar optic nerve invasion in patients with uveal melanoma. Age might be a surrogate for tumor size[19] because melanomas with postlaminar invasion of the optic nerve were on average 3 mm larger in basal diameter than control melanomas and melanomas with prelaminar or laminar invasion. Why melanomas with postlaminar invasion of the optic nerve were larger than control melanomas may be explained by the possible presence of competing diseases affecting visual acuity. Hence, malignant melanomas in these patients may grow larger and more extensively into the optic nerve before they are diagnosed. In addition, the incidence of diseases affecting visual acuity is related to age, which can further exaggerate the age difference between the groups.

Increased IOP is seen in 3% of patients with uveal melanoma.[20] In accordance with Shammas and Blodi[7] and Spencer,[15] increased IOP in the present study was associated with postlaminar optic nerve invasion. After multivariate analysis including tumor size, which is associated with IOP in uveal melanoma,[3] increased IOP was significantly associated with postlaminar invasion of the optic nerve. Increased IOP and chronic vascular occlusive disease may induce optic nerve ischemia and edema, interrupting the integrity of the optic nerve tissue and thus facilitating the growth of malignant tumor cells.[21] Spencer[15] illustrates that blocked aqueous outflow leads to increased IOP and posterior flow in the degenerated vitreous. If the inner limiting membrane has been ruptured by a tumor, detached viable tumor cells can disperse posteriorly through the vitreous, adhere to the optic nerve head, and invade the optic nerve.[15] However, increased IOP can also be a secondary phenomenon to uveal melanoma invading the optic nerve because a tumor in the posterior pole may compromise the posterior blood flow and induce rubeosis iridis and the formation of fibrovascular membranes in the trabecular area. Furthermore, the tumor itself may produce angiogenic factors that also facilitate the growth of fibrovascular membranes in the trabecular area.[22–24] Even though a relation between optic nerve invasion and increased IOP was found, six patients with postlaminar invasion and 25 patients with prelaminar or laminar invasion had normal intraocular pressure, suggesting that factors in addition to increased IOP may be involved in optic nerve invasion. This hypothesis is supported by the transport of intravitreal silicone oil to the optic nerve in normotensive eyes.[25]

At direct funduscopic examination, no view of the fundus was seen in more than one third of cases with postlaminar invasion. This was attributed to total retinal detachment, tumor blocking the visual pathway, and vitreous hemorrhage. Weinhaus et al.[13] use a histopathologic definition of juxtapapillary melanoma as melanoma in contact with the optic disc at any point. Consequently, in the present study, all melanomas with optic nerve invasion were juxtapapillary. Even though histopathologic examination might indicate a tumor is juxtapap-

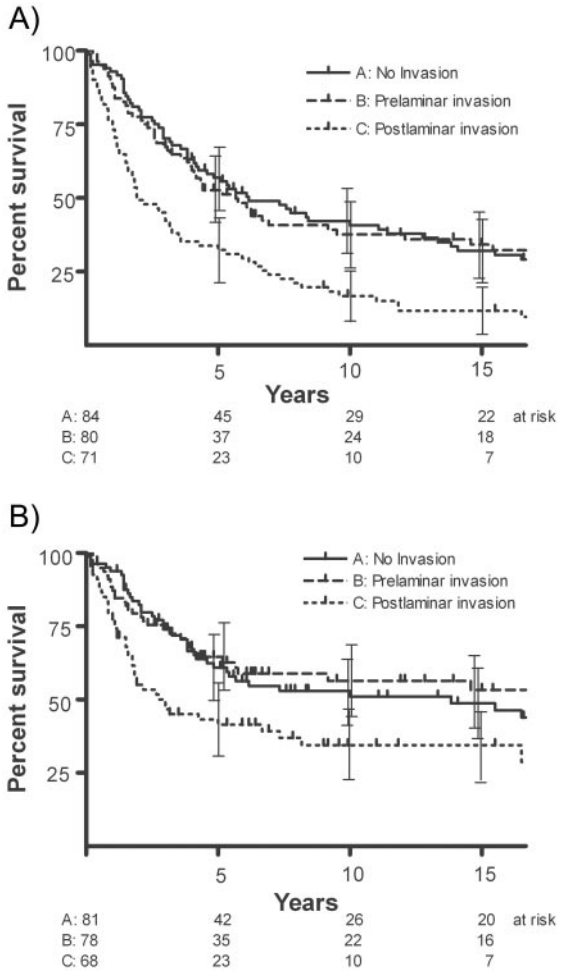

FIGURE 4. All-cause mortality (**A**) of 151 patients with uveal melanoma with different degrees of optic nerve invasion and 84 patients with uveal melanoma without optic nerve invasion. Melanoma-related mortality (**B**) of 146 patients with different degrees of optic nerve invasion and 81 patients with uveal melanoma without optic nerve invasion. Significant differences were seen in both all-cause mortality and melanoma-related mortality between patients with postlaminar optic nerve invasion and the two other patient groups. Bars show 95% confidence intervals.

illary, clinical examination might not reveal it to be in contact with the optic disc. In one third of the cases with visible fundus and uveal melanoma with postlaminar optic nerve invasion, the tumor was not identified as juxtapapillary, perhaps because transscleral illumination was not performed in all cases. This, in addition to the high frequency of a nonvisible fundus in patients with postlaminar invasion, affects the association of juxtapapillary location with postlaminar optic nerve invasion in multivariate analysis.

Orbital recurrence was statistically more frequent in patients with postlaminar optic nerve invasion than in control patients, in accordance with the findings of Affeldt et al.[26] This is not surprising because the probability of total resection of the tumor is smaller if the tumor extends into the optic nerve, especially if no suspicion of optic nerve invasion was present before the enucleation. The higher incidence of orbital recurrence can partly explain why the mortality rate was higher among these patients than among control patients.

The metastatic pattern in uveal melanoma is different from that in cutaneous melanoma. The liver is affected in 80% to 100% of patients with uveal melanoma compared with 14% to 20% of those with cutaneous melanoma.[3,5,6,27–29] Lung, bones, skin, and lymph nodes are other frequent sites of uveal melanoma metastasis.[3,5,6,28,30] This is in accordance with findings in the control patients in the present study (Table 3). Metastases to the heart, kidney, and CNS were found only in patients with optic nerve invasion, perhaps reflecting a different metastatic pattern in uveal melanomas with optic nerve invasion than in uveal melanomas without this feature. However, differences in the number of patients who underwent autopsy might have induced this difference in the present study (Table 3). In addition, metastases to the heart were found almost exclusively at autopsy because clinical symptoms of these metastases are rare.[31,32]

Previous studies have demonstrated the frequency of CNS metastases in patients with uveal melanoma to be 4% to 15%.[3,5,6,28,30,33] Interestingly, all patients in the present study who had metastases to the CNS also had optic nerve invasion. A possible route of dissemination in patients with postlaminar optic nerve invasion was by seeding through the cerebrospinal fluid because all these tumors had gained access to the subarachnoid space. In metastatic cutaneous melanoma, CNS metastases are detected clinically in 40% of patients and at autopsy in 90% of patients.[34,35] The high CNS involvement may result from the common embryonic origin of melanocytes and neuronal subpopulations.[36] This neurotropic propensity seems not to be present in uveal melanocytes, but a subpopulation may exist with this characteristic. Uveal melanoma may differ in response to growth-facilitating factors within the CNS and may interact in different ways with the CNS microenvironment. Differences in gene expression between tumors with and without brain metastases have been recognized in other tumors.[37,38] The same possible difference in gene expression may also affect the propensity for optic nerve invasion of a uveal melanoma (neurotropic uveal melanoma).

The impact of optic nerve invasion on survival has been demonstrated in univariate analyses showing lower survival rates in patients with optic nerve invasion.[3,10,26,39] However, when optic nerve invasion was included in multivariate analyses, the significance on survival disappeared.[10,39]

In the present study, we found a significant difference in survival between patients with postlaminar optic nerve invasion and the other patient groups. Patients with postlaminar invasion were older than the other patients. This affected all-cause mortality because of the higher incidence of competing causes of death. Melanoma-related mortality might have been greater in patients with postlaminar invasion because the tumors were larger and the frequency of orbital recurrence was greater.[14,39–42] Studies have also demonstrated that age affects melanoma-related mortality.[40,43]

CONCLUSION

This study identified juxtapapillary tumor location, reduced visual acuity, and increased intraocular pressure as predictive of invasion of the optic nerve in patients with uveal melanoma. Invasion of the optic nerve was found in 5% of all enucleated eyes with uveal melanoma, and it was associated with poor prognosis because of the large tumor size and the high frequency of orbital recurrences.

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