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Independent prognostic factors for distant metastases and survival in patients with primary uveal melanoma

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Abstract

Adjuvant treatment strategies in uveal melanoma require determination of prognostic factors. Patients, who received primary therapy in 1994 and 1995 at our institution, were analysed. Of 271 patients 85% and 71% were available for follow up of $\geqslant 4$ and $\geqslant 5$ years. Forty three patients (15.9%) developed metastases. Kaplan–Meier analysis revealed a 5-year progression free survival (PFS) of 79% for the whole patient cohort. Extraocular tumor growth (EOG), ciliary body involvement or a largest tumor diameter (LTD) >14 mm were associated with a significantly lower 5-year PFS of 28%, 61.4% or 67.6%. In multivariate analysis time to progression was significantly associated with ciliary body involvement and LTD, and survival was associated with ciliary body involvement. Ciliary body involvement profoundly increased the risk for metastases (hazard ratio 6.9, $P<0.001$) within the first 3 years. This study determined patients with ciliary body involvement to be candidates for future adjuvant therapeutic interventions.

Keywords: Uveal melanoma; Prognostic factors; Metastases; Survival

1. Introduction

Uveal melanoma is the most common primary malignant tumor of the eye with an annual incidence of six cases in one million [1]. Studies in the early 1990s demonstrated that approximately 35% of patients will develop metastatic disease at various time points after primary therapy [2]. Metastases at the time of first presentation are rare, indicating early hematogenous spread [3]. Whereas primary uveal melanoma is subject to curative surgery or radiotherapy, only palliative treatment can be offered to patients with metastatic disease. Prognosis is poor with a median survival between 2 and 9 months after detection of metastases [4–6].

Clinical prognostic factors for metastases and survival have been identified in the 1970s and 1980s when enucleation was the standard therapy for uveal melanoma. These factors include ciliary body involvement, the largest tumor diameter (LTD) and the tumor height [7–9]. Since various studies demonstrated that

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prognosis was not influenced by the primary treatment modality [10–13], local radiotherapeutic approaches are the standard therapy for uveal melanoma today. Yet prognostic factors have not been analysed in patients treated with these modern therapeutic strategies avoiding enucleation.

Until now there is no effective adjuvant therapy available after surgery or radiotherapy. Since the efficacy of systemic chemotherapy in metastatic disease is low, adjuvant chemotherapeutic approaches are not promissing. Vaccination approaches targeting tumor associated antigens in melanoma have demonstrated efficacy in phase I and II trials in cutanous melanoma patients with low tumor burden [14–16]. Vaccination approaches are therefore good candidates for treatment of patients at high risk for development of metastatic disease in uveal and cutanous melanoma. A recent study showed the induction of tumor reactive T lymphocytes against tyrosinase in patients after primary treatment of uveal melanoma by employing human leucocyte antigen (HLA)-class I-restricted peptides derived from the melanoma differentiation antigen tyrosinase [17].

In this retrospective study we identified prognostic factors predicting the development of metastatic disease in a homogenous cohort of 271 uveal melanoma patients, who received primary therapy in our institution in 1994 and 1995.

2. Patients and methods

We investigated the course of all patients, who underwent primary therapy for uveal melanoma in the Department of Ophthalmology of the Free University of Berlin in 1994 and 1995. We determined the characteristics of the primary uveal melanoma including tumor location, tumor size and therapy from the patient's charts. To evaluate follow-up we contacted the patient's Ophthalmologists and/or General Physicians by fax and phone call. In patients with unknown primary physicians we directly contacted the patient.

Descriptive analysis includes means, medians, standard deviations and ranges for continuous variables. Time to event (survival, metastasis) was analysed using the Kaplan–Meier method including confidence limits for survival rates, the log-rank test and the Cox-proportional hazard model. The proportional hazards assumption was examined using the method of time dependent covariates. The level of significance was 0.05 (two-sided) for all statistical tests. All analyses were performed using commercially available software (SPSSWIN, release 11.5). Time dependent hazard analysis was performed using the R open software.

3. Results

3.1. Patient characteristics

In 1994 and 1995 271 patients received primary therapy for uveal melanoma in the Department of Ophthalmology at the Free University of Berlin. 52% of patients were female, median age was 58 years with a range of 8–86 years (Table 1). 3.7% of the tumors had extraocular growth (EOG) of the tumor at the time of first diagnosis. In 24% of patients the ciliary body was infiltrated by the melanoma. In 35.4% and 40.6% of patients the tumor was located anterior or posterior of the equator without involvement of the ciliary body. The median of the LTD was 12.3 mm (range 3–22 mm), the median of the tumor hight was 5.6 mm (1.4–15.8 mm).

3.2. Primary therapy

The majority of patients (70%) received local radiotherapy only. In 7% enucleation followed radiotherapy. 10% had enucleation as the only primary therapy. The overall enucleation rate was 18.1% (Table 2).

3.3. Follow-up data

Complete 4- and 5-year follow-up data were available for 231 (85.2%) and 191 (70.4%) patients, respectively (Table 1). The most frequent reason for being lost to follow-up was a change of address or migration. However, at the time of the last contact to the Ophthalmologist or General Physician there was no evidence of disease progression in all of these patients. During the follow-up period 43 patients (15.9%) developed metastatic disease. Ten patients (4%) had an ocular relapse. Fifty nine patients (21.8%) died, in 37 (62.7%) metastatic melanoma was the cause of death, 18 patients died from other causes (30.5%). In 4 patients (6.8%) the cause of death is unknown, but there was no reported clinical evidence of metastatic disease.

3.4. Progression free survival and survival analysis

Kaplan–Meier analysis revealed a 5-year progression free survival of 79% (CI 73.5–84.5%) (Fig. 1a) and a 5-year over all survival of 74.6% (CI 68.8–80.4%) (Fig. 1b). The melanoma-related death rate was 18% (CI 12.7–23.3%) at 5-years.

Patients with EOG had a significantly shorter time to progression. The 5-year progression free survival was 28% (CI >0–60%) for patients with EOG and 80.6% (CI 75.2–86%) for patients without EOG ($P<0.001$, log-rank test, see Fig. 2a). The median time to progression was 35 months (range: 8–68 months) for patients with EOG. The risk factor EOG, however, was present in only 10 patients. 5-year survival was 50% (CI 12.8–87.2%) in

Table 1
Patient characteristics

	Number of patients
All patients	271 (100%)
Female	141 (52%)
Male	130 (48%)
Median age (range)	58 years (8–86)
Extraocular tumor growth (EOG)	10 (3.7%)
Ciliary body involvement	65 (24%)
Anterior tumor growth	96 (35.4%)
Posterior tumor growth	110 (40.6%)
Median of LTD (range)	12.3 mm (3–22 mm)
LTD $\leqslant$11 mm	87 (32.1%)
LTD 11–14 mm	81 (29.9%)
LTD $\geqslant$ 14 mm	86 (31.7%)
LTD unknown	17 (6.3%)
Median of tumor height (range)	5.6 mm (1.4–15.8 mm)
Lost to 4-year follow-up	40 (14.8%)
Lost to 5-year follow-up	80 (29.6%)

LTD, largest tumor diameter; EOG, extraocular tumor growth; mm, millimeter.

Table 2
Primary therapy

	Number of patients
All patients	271 (100%)
Enucleation alone	27 (10%)
Radiotherapy (RT) alone	191 (70%)
Ruthenium RT alone	152 (56%)
Iodine RT alone	36 (13%)
Ruthenium + Iodine RT	3 (1%)
Radiotherapy + enucleation	18 (7%)
Radiotherapy + excision	7 (3%)
Radiotherapy + excision + enucleation	2 (1%)
Excision only	0 (0%)
Other therapy	19 (7%)
Enucleation + other therapy	2 (1%)
Radiotherapy + other therapy	5 (2%)

RT, Radiotherapy.

patients with EOG and 83.3% (CI 78.1–88.5%) in patients without EOG ($P = 0.0027$, log-rank test, Fig. 2b).

Patients with ciliary body involvement had a significantly shorter time to progression. The 5-year progression free survival was 61.4% (CI 48%–74.8%) in patients with ciliary body involvement. In contrast, the 5-year progression free survival was 79% (CI 70.2–87.8%) and 89.8% (CI 83.4–95.2%) in patients with tumors located posterior or anterior of the equator without involvement of the ciliary body. The difference in progression free survival was significant with a P-value <0.001 when analysed with the log-rank test (Fig. 3a). 5-year overall survival was 58.9% (CI 45.5–72.3%) in patients with ciliary body involvement and 82.0% (CI 73.6–90.4%) or 76.9% (CI 67.9–85.9%) in patients with anterior or posterior tumor growth without involvement of the ciliary body. This difference also was significant with a P-value<0.01 when analysed with the log-rank test (see Fig. 3b). The melanoma-related death rate at 5 years was 31.4% (CI 18.6–44.2%) in patients with ciliary body involvement and 10.7% (CI 3.5–17.9%) or 15.1% (CI 7.3–22.9%) in patients with anterior or posterior tumor growth without involvement of the ciliary body.

Tumor size>14 mm was also associated with a significantly shorter progression free survival. 5-year progression free survival was 67.6% (CI 56.6–78.6%) in patients with a LTD >14 mm and 84.8% (CI 76.2–93.4%) for patients with a LTD <11 mm and 82.9% (CI 73.3–92.5%) for patients with a LTD of 11–14 mm (see Fig. 4a). 5-year overall survival was 67.5% (56.1–78.9%) in patients with a LTD >14 mm and 75.2% (CI 65.6–84.8%) for patients with a LTD <11 mm and 85.3% (CI 76.7–93.9%) for patients with LTD of 11–14 mm (see Fig. 4b). The differences in 5-year progression free survival (PFS) between patients with a LTD >14 mm and LTD of 11–14 mm or <11 mm was significant with a P-value<0.01. The

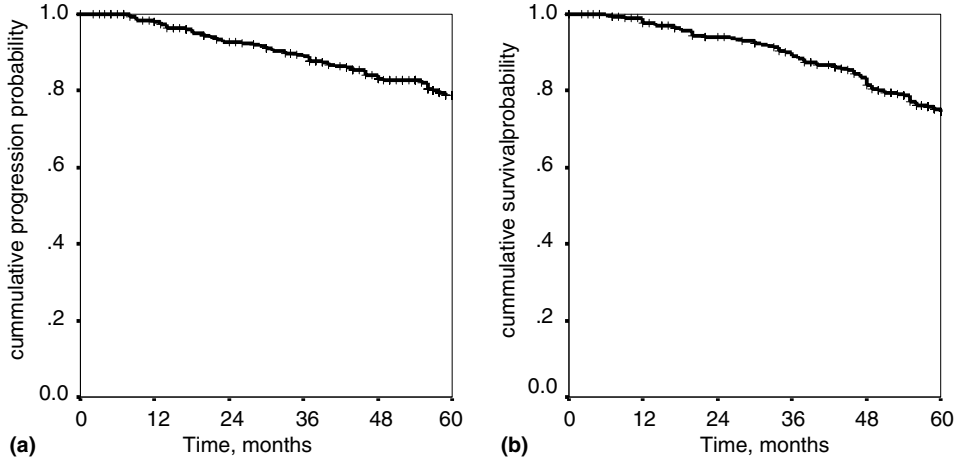

Fig. 1. Kaplan–Meier estimates for (a) PFS and (b) OS of the entire patient cohort.

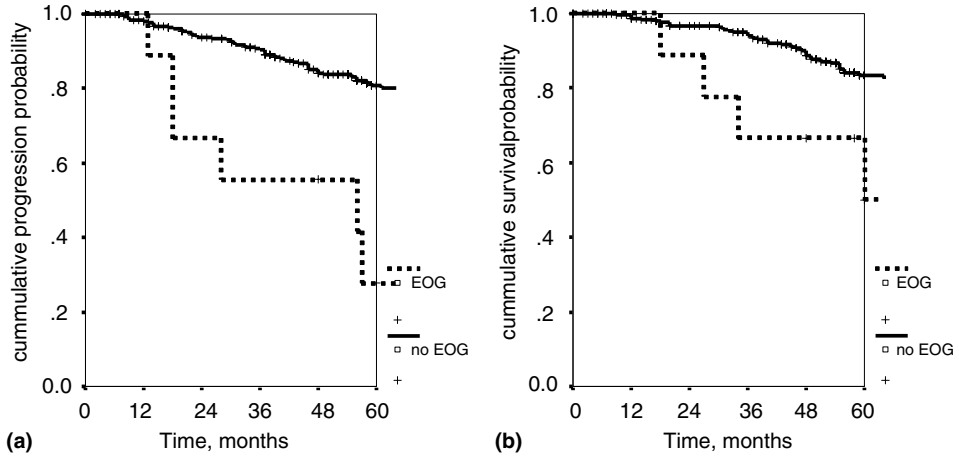

Fig. 2. Kaplan–Meier estimates for (a) PFS and (b) OS by extraocular tumor growth (EOG).

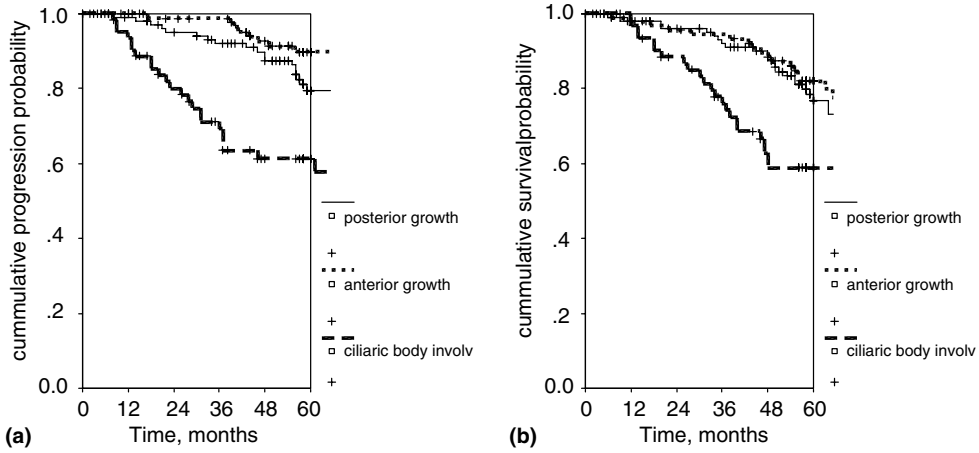

Fig. 3. Kaplan–Meier estimates for (a) PFS and (b) OS by ciliary body involvement *versus* anterior or posterior growth without ciliary body involvement.

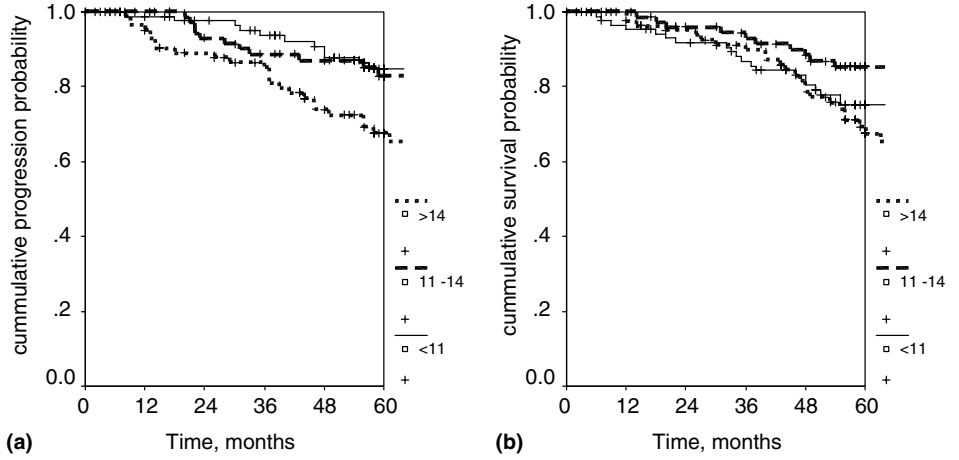

Fig. 4. Kaplan–Meier estimates for (a) PFS and (b) OS by largest tumor diameter (LTD) <11 mm *versus* 11–14 mm *versus* >14 mm.

Table 3

	Time to metastases		Time to metastases or local recurrence		Survival	
	Hazard ratio	*P*-value	Hazard ratio	*P*-value	Hazard ratio	*P*-value
Age at diagnosis	–	0.84	–	0.69	1.3[b]	0.019
Ciliary body involvement	2.6	<0.001	3.1	<0.001	2.4	<0.001
Extra ocular growth	–	0.21	2.5	0.05	–	0.55
Largest diameter	1.7[a]	0.023	1.5[a]	0.05	–	0.30
Tumor height	–	0.39	–	0.23	–	0.52

[a] Per increase of 5 mm.
[b] Per decade.

melanoma-related death rate at 5 years was 29.2% (CI 18.0–40.4%) for patients with LTD >14 mm and 8.9% (CI 1.9–15.9%) or 15.3% (CI 6.7–23.9%) for patients an LTD of 11–14 mm or <11 mm.

3.5. Independent prognostic factors

In a multivariate analysis time to metastasis was significantly associated with ciliary body involvement and largest tumor diameter. Survival was significantly associated with ciliary body involvement and patients age (Table 3).

The prognostic impact of ciliary body involvement was not persistant during the entire follow up period ($P = 0.03$, Cox Regression). In the first three years of follow up, ciliary body involvement increased the risk for metastases (hazard ratio) by 6.9 ($P<0.001$) as compared to patients without ciliary body involvement (Fig. 5). Among those patients, who had survived the first three years without metastasis, ciliary body involvement did not have prognostic relevance for the further course of the disease (hazard ratio 1.2, $P = 0.7$).

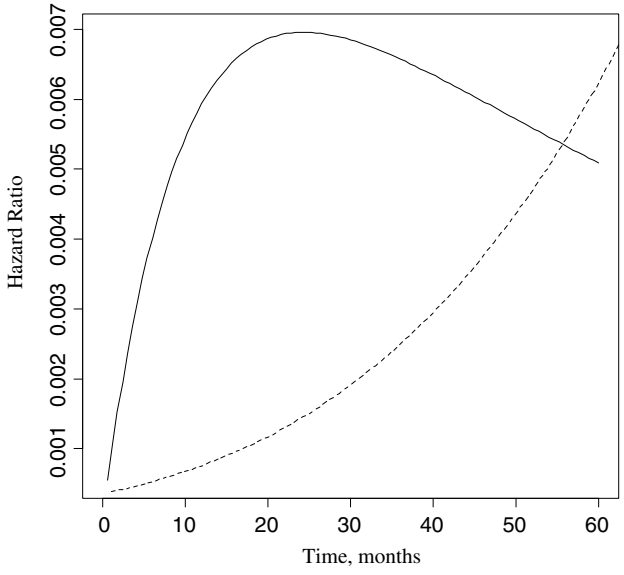

Fig. 5. Hazard ratio over time for ciliary body involvement (—) *versus* no ciliary body involvement (----).

4. Discussion

This analysis identified ciliary body involvement to be the most important independent clinical prognostic factor for early systemic disease progression and survival in this homogenous cohort of patients. The role of ciliary body involvement was dominant over the initial three years of follow up, as determined by time dependent hazard analysis. One earlier study evaluating 267 patients treated with enucleation also demonstrated that ciliary body involvement was predictive for survival in a multivariate analysis [7]. This earlier study also analysed histopathologic factors and found that the poor prognosis of ciliary body melanoma was independent of tumor size and cell type [7]. The fundamental difference between the study reported here and all previous analyses is, that while the enucleation rate in our study was 18.1%, in previous studies only patients with enucleation had been considered. The increased 5-year mortality of 31.4% in patients with ciliary body involvement observed in our study is in accordance with that of 22% and 41% reported from other studies investigating the outcome of patients with ciliary body melanoma treated with local radiotherapy [18,19].

A meta-analysis considering data published between 1966 and 1988 on the 5-year mortality rates of patients treated by enucleation demonstrated three distinct prognostic subgroups when representing tumor size by the combination of tumor height and tumor base diameter determined histologically after enucleation [2]. In our study the largest tumor diameter (LTD) was significantly associated with the time to progression, but not with survival. Tumor height and the combination of LTD and tumor height also were not predictive for survival. Since LTD and tumor height were not re-assessed histologically due to an enucleation rate of only 18.1% in our study, our results might

not be fully comparable with data determined in studies with an enucleation rate of 100% [2,7]. Ciliary body involvement and EOG were identified to be the most important prognostic factors in our study. However, only 27% of patients had one of these tumor characteristics. 73% of patients had anterior or posterior tumor growth without EOG or ciliary body involvement, of whom 10% to 20% of patients also developed metastases. For this group of patients we could not identify a predictive factor for metastases.

Earlier studies were able to investigate histopathologic, cytogenetic and molecular factors on the prognosis of patients with uveal melanoma treated by enucleation. The following factors associated with a worsened prognosis have been described: number of epitheloid cells, mitotic activity, presence of a vascular network, high number of tumor-infiltrating lymphocytes (TILs), high DNA-index and high expression of Ki-67 and proliferating cell nuclear antigen (PCNA), the presence of monosomy 3, 8q duplication and c-myc expression reviewed in [20]. More recently, expression of cyclin D1, p53, MDM2 protein expression and epidermal growth factor receptor were shown to be associated with an unfavourable outcome in uveal melanoma [21,22], whereas S-100-beta serum concentration did not have prognostic value [23]. However, since several retrospective studies demonstrated that local radiotherapy is equally effective as enucleation in the primary treatment of uveal melanoma [10–12], access to tumor biopsies or resected tumors for determination of histopathologic or molecular prognostic factors is very limited nowadays, which underlines the importance of clinical prognostic factors.

The study presented here is the largest single center series with 271 patients treated within a two year period. The large analysis published by Li and collegues [24] from the Harvard Cyclotron Laboratory included 1204 patients treated within a 13 years time period. This group reported a 5-year metastastic death rate of 12.8%, which is comparable to 18% (CI 12.7–23.3%) observed in our analysis. Tumor baseline characteristics of our cohort and the cohort from the Harvard Cyclotron Laboratory were similar with a median of the LTD of 12.3 mm (range 3–22 mm) and a median height of 5.6 mm (range 1.4–15.8 mm) in our study and 12.0 mm (range 6–22 mm) and 5.1 mm (4.2–15.0 mm) in the Harvard study [24]. However in the Harvard study no data on the percentage of patients with extraocular tumor growth or involvement of the ciliary body are given.

In contrast to our analysis, a much higher metastatic death rate of 36% was reported in the collaborative ocular melanoma study group (COMS) trial [25], which might be explained by inclusion of only patients with large primary uveal melanoma into that trial, which studied enucleation alone *versus* enucleation preceded by external beam irradiation in a randomized setting.

Taken together, ciliary body involvement and a large tumor diameter can serve as clinical inclusion or stratification criteria in adjuvant treatment trials.

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