New developments in analysis of ocular surface diseases|Nieuwe ontwikkelingen in analyse van ziekten van het oogoppervlak

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CHAPTER 3

CONJUNCTIVAL MELANOMA IN THE NETHERLANDS: A NATIONWIDE STUDY

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Abstract

Purpose. To evaluate risk factors for local recurrence, regional and distant metastases, and mortality associated with conjunctival melanomas.

Patients. 194 patients with histologically confirmed conjunctival melanoma, diagnosed between 1950 and 2002 in the Netherlands. Data were collected from all university centers and many non-tertiary hospitals, using the National Pathology and the Leiden Oncologic Registration Systems. Based on number of incidences, this study included 70% of the conjunctival melanomas reported.

Methods. Clinical and histopathological data for conjunctival tumors were reviewed and compared with data reported in the literature. Risk factors for local, regional, and distant metastases and survival were analysed using Kaplan-Meier and Cox regression analysis.

Results. Of 194 patients with conjunctival melanoma, 112 had a local recurrence (median 1, range 1–9) during follow-up (median 6.8 y; range 0.1-51.5 y). Location was the most important risk factor for development of local recurrence and significantly more were seen for non-epibulbar (Log Rank P=0.044) tumors. Significantly fewer local recurrence were found for tumors initially treated with excision and adjuvant brachytherapy rather than with excision only (Log rank P=0.008) or with excision and cryotherapy (Log rank P<0.038). Forty-one (21%) patients developed regional lymph node metastases, mostly to the parotid or preauricular lymph nodes (n=26; 13%). Risk factors for regional metastases were tumor thickness (Log rank P<0.001), and tumor diameter (Log rank P=0.010). Forty-nine (25%) patients later (mean 4.37 y) developed distant metastases mainly in lung, liver, skin, and brain. Tumor-related survival was 86.3% (95% Confidence interval [CI], 81.0-91.6) at 5 years, 72% (95% CI, 79.7-64.4) at 10 years, and 67% (95% CI, 58.9-76.1) at 15 years. Main mortality risk factors were non-epibulbar location (Log rank P<0.0001) and tumor thickness (Log rank P=0.0004).

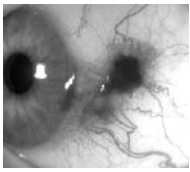
Conclusions. Non-epibulbar tumors more often recur locally and are associated with a shorter survival independent of other risk factors. Tumor thickness is also an important predictor of regional and distant metastases, as well as survival. A prospective study is needed to compare the effect of excision in combination with radiotherapy and excision with cryotherapy on the number of local recurrences, exenteration rate, and survival.

Introduction

Conjunctival melanoma is a rare tumor [1-3] with an incidence of 0.02-0.08 per 100 000 in a Caucasian population,[4-6] accounting for some 1-3% of all ocular malignancies in adults. This malignancy normally occurs around the age of 60 and only rarely before the age of 40 (10%). Conjunctival melanomas may perhaps be associated with sun exposure, like skin melanoma,[8] although they can occur at non sun-exposed sites.[6] In contrast to uveal melanoma,[9] the incidence of conjunctival melanoma is increasing.[6-7]

Local recurrence is reported to be 30–50% at 5 years, 38–51% at 10 years, and 65% after 15 years, depending on treatment.[10-21] Excision without additional treatment is associated with more local recurrences.[22] Main risk factors for patient mortality are thickness and size (basal diameter) as well as a non-epibulbar location (Picture 1) for the primary tumor or one of its recurrences. A contributing factor for prognosis is the origin of the tumor; i.e., 55% are primary acquired melanosis (PAM) and in 25% melanoma de novo, which gives the worse prognosis.[23] Conjunctival nevi rarely develop into a melanoma.[24] The mortality rate is 12-20% at 5 years and up to 30% at 10 years.[10-21] Conjunctival melanomas are known to spread via the lymphatic system, although distant metastases are also found without regional lymph node metastasis.[25]

In this report, data for 194 patients with conjunctival melanoma collected from all university hospitals and many non-tertiary centers in the Netherlands were analyzed to investigate differences in treatment and surgical approach as well as the main risk factors for recurrence, metastasis, and survival.



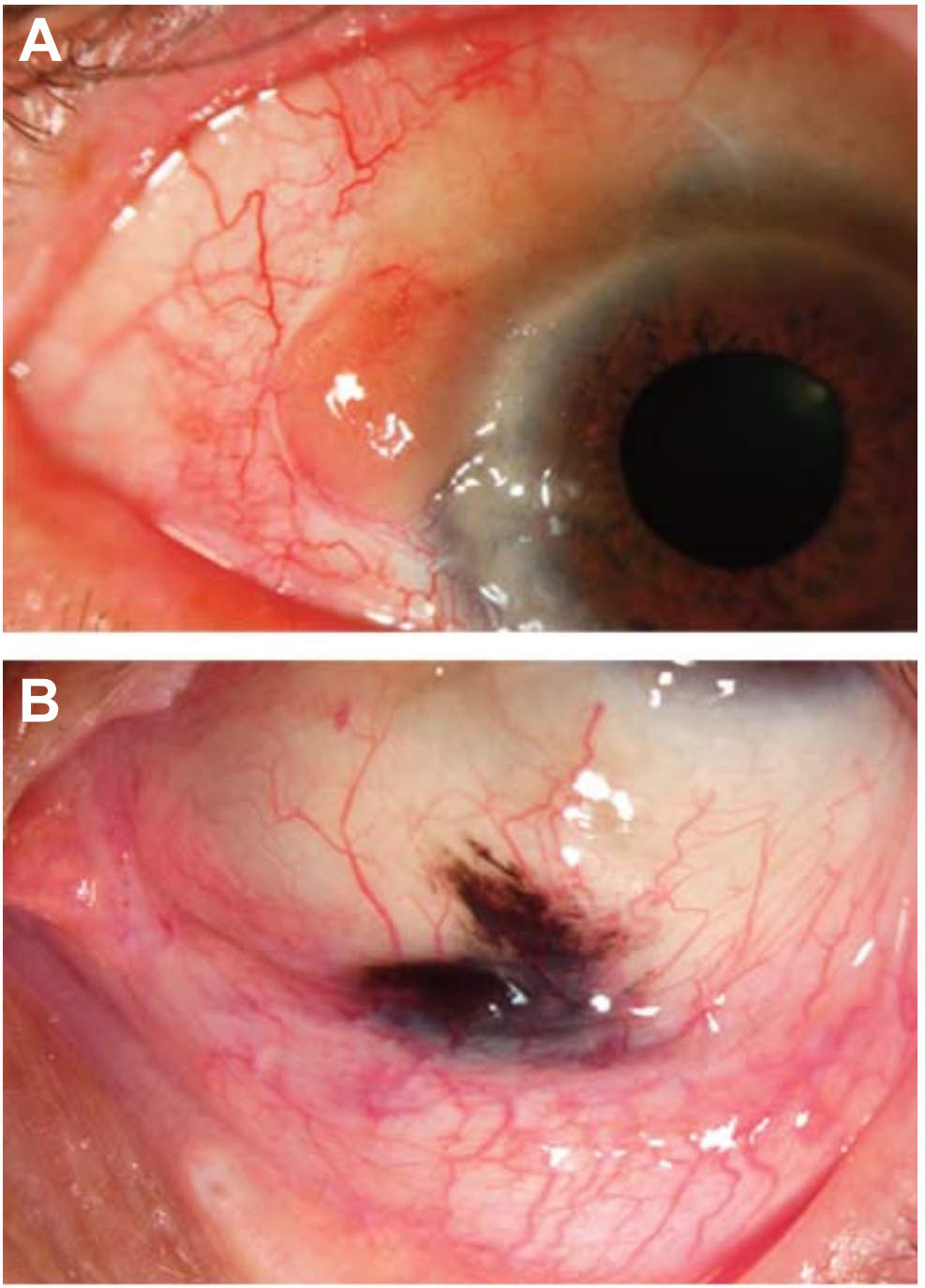
Patients and methods

The Netherlands National Ocular and Orbital Tumor Committee, using the Netherlands Pathology Diagnosis System, helped identify 194 patients diagnosed with malignant conjunctival melanoma between 1950 and 2002. Complete clinical and histopathological data were gathered from patient records and follow-up data were obtained from death certificates, general practitioners, local ophthalmologists, and the Oncologic Registration System of Leiden University Medical Center (LUMC). The mean follow-up was 9.2 years (SD, 8.1 y; median 6.8 y). Only data for patients with histologically proven conjunctival melanoma were analyzed. Patients with a primary eyelid (cutaneous) melanoma were excluded, as were patients with PAM without an invasive component. The study was approved by the Institutional Review Board and adhered to the tenets of the Declaration of Helsinki.

Assessment of tumor characteristics

Of 194 conjunctival melanomas, 178 (92%) primary tumor specimens were reviewed for histopathologic confirmation of the diagnosis at the LUMC while 16 other specimens were assessed by an experienced ophthalmic pathologist elsewhere.

Tumor origin, established on the basis of medical and histopahtological records and photographs, and was classified as ‘nevus’, ‘nevus in combination with primary acquired melanosis (PAM)’, ‘PAM’, and ‘de novo’ melanoma. The clinical variables included age at diagnosis, sex, unilocular (caruncle, fornix, tarsus, limbus, or eyeball) or multilocular (dif-



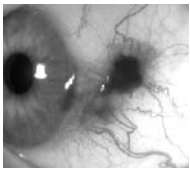
Picture 1. An epibulbar location of a conjunctival melanoma is shown in picture 1A, a non-epibulbar location (inferior conjunctival fornix) is shown in picture 1B.

was 57.4 years (median: 58 y). Regions involved were the limbus (*n*=110, 57%), bulbar conjunctiva (limbus included; *n*=133, 69%), caruncule (*n*=5, 2.6%), tarsus (*n*=11, 5.6%), and fornix (*n*=2, 1%); more than one location was involved in 43 (22%) patients. Origin of the melanomas was PAM (*n*=111, 57.2%), melanoma de novo (*n*=50, 25.7%), nevus in combination with PAM (*n*=9, 5%), and nevus only (*n*=3, 2%). Origin was inconclusive in 21 (11%) patients. Tumor thickness was 2.07 mm (SD 1.9 mm; *n*=153) and the basal diameter was 7.21 mm (SD 4.7 mm; *n*=152).

Primary treatment

Treatment at the moment of histopathological diagnosis (Table 2) was excision alone (*n*=127, 65.5%), excision with topical chemotherapy (Mitomycin C; *n*= 4, 2%), excision and adjuvant cryotherapy (*n*=17, 8.7%), irradiation (*n*=11, 5.6%), and excision with brachytherapy (^{90}Sr/^{90}Y irradiation; 6 x 1000cGy; *n*=20, 10.3%). Exenteration was the primary therapy for advanced conjunctival melanoma in 14 (7.2%) patients and was used in combination with orbital irradiation in 1 patient (0.5%).

Today the standard treatment for primary conjunctival melanoma is excision with adjuvant therapy. However, during the period covered by this study, many different treatment strategies were used (Figure 1). Although in some cases only a few patients represent a certain treatment, we tried to compare different treatments and their outcomes.



Local recurrence analysis and secondary treatments

Within the total follow-up period, 112 patients had a local recurrence (62.6% of the 179 non-exenterated patients). Mean time between the first treatment for histopathologically proven melanoma and first local recurrence was 2.4 years (SD 3.4; median 1.3 y; max 22.6 y). The mean number of local recurrences was 1.6 (range 1–9), resulting in a local recurrence rate of 60.7% (95% CI, 52.9-68.5) after 5 years, 66.8% (95% CI, 59.0-74.6) after 10 years, and 72.2% (95% CI, 63.4-81.0) after 15 years (Figure 2A).

Treatment of the first local recurrence was excision in 63 (56%) patients (4 in combination with topical chemotherapy), 22 of whom ultimately required orbital exenteration for more recurrences or advanced conjunctival melanoma. Twenty-three (20.5%) patients received excision with cryotherapy, with 8 patients ultimately requiring exenteration. Excision with brachytherapy (^{92}Ir irradiation, *n*=3, ^{90}Sr/^{90}Y application, *n*=8) was performed in 11 cases, with two patients being exenterated. One patient was treated for recurrence with irradiation only. In total, 44 (39.3%) patients were exenterated for advanced disease. The probability of recurrence of primary tumors using excision with brachytherapy was lower than when using other treatment modalities (Figure 2B). There were significantly fewer recurrences using excision and brachytherapy of primary tumors (*n*=19) than when using excision with adjuvant cryotherapy (*n*=17; *P*=0.038, log rank test not adjusted for multiple comparisons). Excision with cryotherapy, in comparison to excision only, did not result in less recurrences (*P*=0.759, log rank test, not adjusted for multiple comparisons).

In contrast to other tumor locations, epibulbar involvement showed significantly fewer local recurrences (P=0.044, log rank) (Figure 2C). Analysis showed that local recurrence was not associated with age at time of diagnosis (categories: <50, 50-68, >68y; years; *P*=0.774, log

fuse) location of the primary tumor, date for primary treatment, date for diagnosis of local recurrence, and the presence of regional or hematogenous metastases. Local recurrences at the same or different location in the ocular region, but not PAM without melanoma, were considered 'local recurrence'.[20] The proximity of the melanoma to the limbus was classified as limbal or non-limbal. Basal tumor diameter (mm) was taken from patient records, pathology reports, or photographs, if available (79%), as described by Tuomaala et al[6]. In 42 cases, information about tumor diameter could not be found. Melanoma thickness (mm)was measured by one ophthalmic pathologist on slides of the tumor, according to Breslow.[26] In 41 cases, thickness could not be measured because tumors had been sliced in a tangential plane. Treatment of initial tumors and recurrences were categorized as 'excision only', 'excision and chemotherapy' (topical Mitomycin C), 'excision and cryotherapy', 'external irradiation only', 'brachytherapy after excision', 'orbital exenteration', and 'irradiation and exenteration'. Cryotherapy and ^{90}Sr brachytherapy were available as adjuvant therapy from 1970 onward and were frequently used after 1980 (Figure 1).

Assessment of outcome

Dates of diagnosis and local recurrence were those for histopathologic confirmation of the primary tumor or local recurrence. The interval between diagnosis by a physician and histopathologic confirmation was always less than 2 months. The date for metastasis was taken as the date when dissemination was confirmed by biopsy, imaging, or clinical examination. Regional metastasis was histopathologically confirmed in all 41 cases. Of 49 cases with distant metastases, the metastases were confirmed by histopathology in 24 (49%) patients and by imaging (mostly Computed Tomography) in 25 (51%) patients. Autopsy was performed in three patients. In 12 cases, the location of metastases was not specified. Survival time was defined as the time from histopathological confirmation of the primary tumor to death due to conjunctival melanoma (event), death due to other causes, or time of last presentation.

Statistical analysis

Risk factors for local or regional recurrence and for tumor-related survival were assessed by Kaplan-Meier estimates and with Cox proportional hazards. Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated. Values of $P<0.05$ were considered significant. Statistical analysis was performed using SPSS 11.0 (SPSS Inc, Chicago, IL) and Stata/SE 8.0 software package (StatCorp, College Station, TX). Kaplan-Meier analysis for local recurrence was analyzed for time to the first local recurrence. The Log Rank test was used to compare variables in Kaplan-)Meier analysis. In Cox regression analysis, the variables "origin" and "therapy" were considered nominal categorical variables.

Results

Patient and tumor characteristics

Our study population consisted of 107 (55%) female and 87 (45%) male patients (Table 1), including 99 (51%) left and 95 (49%) right eyes. Mean age at histopathological diagnosis

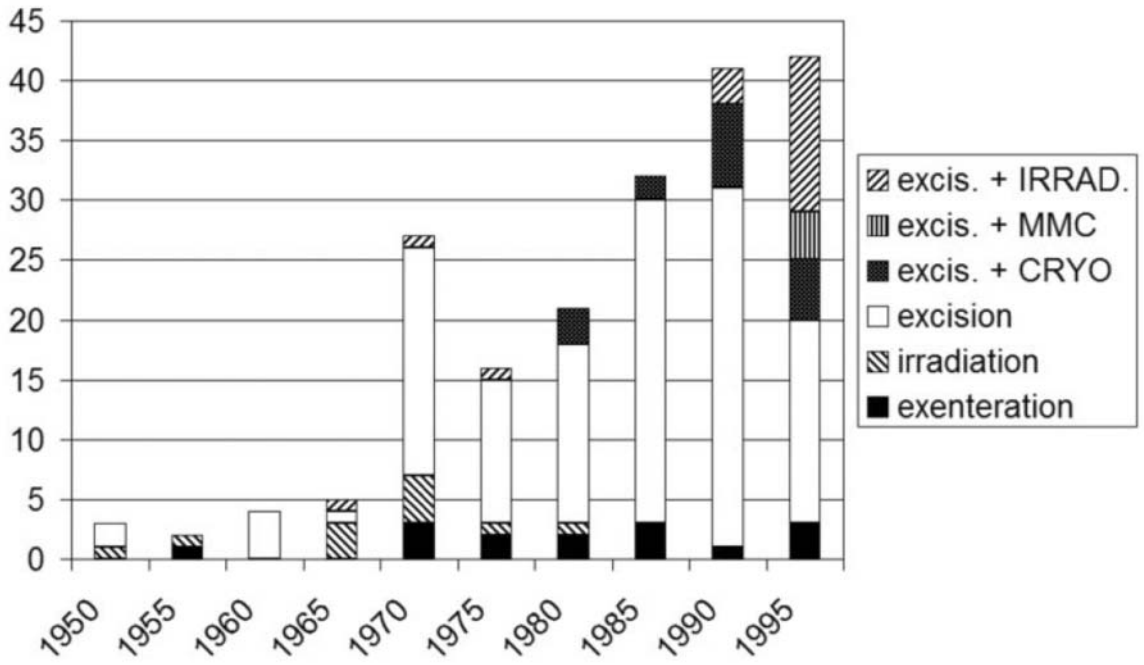
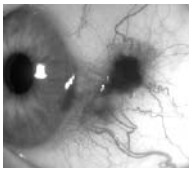


Figure 1. Treatment modality in function of time. The study was made by contributions from all university centers and many general ophthalmologists.



rank test for trend), tumor origin (categories: PAM or non-PAM; *P*=0.61, Log Rank), sex (*P*=0.77, Log Rank), unilocular/multilocular location (*P*=0.82, Log Rank), tumor thickness (<1 mm, 1-2 mm, >2 mm; *P*=0.063, Log Rank test for trend), or basal tumor diameter (0-6 mm, 6-10 mm, >10 mm; *P*=0.571). Cox regression analysis showed that epibulbar location and treatment modality of the primary tumor were the best predictors of local recurrence (see Table 3).

Regional metastases analysis and treatment

Regional metastases developed in 41of 194 patients (*n*=9 regional, *n*=32 regional and distant). Of these 41 patients, 32 were first diagnosed as having only regional dissemination. Mean time between primary tumor diagnosis and regional metastasis was 4.37 years (SD 4.2; median 3.7 y). Mean survival time after metastasis was 8.1 years for regional dissemination only (6 patients still living, 3 died of non-related causes; SD 8.7; median 2.7 y) and 1.72 years for both regional and distant metastases (SD 1.5; median 1.3 y). Regional metastases were found in parotid or preauricular (*n*=26), cervical (*n*=13), sub-mandibular (*n*=9), and axillar (*n*=2) lymph nodes. Both patients with positive axillar lymph nodes had also parotid positive lymph nodes.

Univariate Cox regression analysis (Table 4) indicated that tumor thickness (HR 2.8, *P*<0.001), and basal diameter (HR 1.6, *P*=0.010) were the best predictors of regional metastases. In a multivariate Cox model, only tumor thickness reached statistical significance.

Distant recurrence analysis

Distant metastases developed in 49 patients, of whom 17 cases showed no regional ('skipping') metastases. In 37 patients, the distant metastasis was localized. Metastasis occurred in the lungs (*n*=18 cases), liver (*n*=15), skin (*n*=13), brain (*n*=11), spinal cord (*n*=5), ileum (*n*=3), mesentery (*n*=3), skeletal bones (*n*=3), thyroid gland (*n*= 2), and jaw bone (*n*=2).Mean survival was 1.72 years (SD 1.5; median 1.3 y) for both regional and distant and 0.42 years (SD 0.34; median 0.44 y) for hematogenous metastases. Analysis (Table 5) showed that non-epibulbar lesions were significantly more likely to give rise to a distant metastasis (HR 4.0, *P*<0.001). Univariate Cox analysis showed that increasing tumor diameter was associated with an increasing risk of distant recurrences (HR 2.1, *P*<0.001).

Survival analysis

During the total follow-up period, 47 (24.3%) patients died of metastasis of conjunctival melanoma, 44 (22.7%) of non-melanoma-related causes, and 103 (53%) were still living. Fifty-eight patients (29.9%) developed metastasis. The melanoma-specific survival rate was 86.3% (95% CI 81.0-91.6) at 5 years, 71.2% (95% CI 79.7-64.4) at 10 years, and 67.3% (95% CI 58.9-76.1) at 15 years (Figure 3A).

Survival analysis did not show a significant difference in survival between therapies (overall log rank *P*=0.363). Only patients who underwent a primary exenteration had a significantly lower survival compared to other treatment modalities (*P*=0.036, Log Rank test not adjusted for multiple comparisons). This may be explained by the fact that this group contained significantly larger tumors and at an unfavorable location.

Neither tumor origin (*P*=0.42) nor tumor basal diameter (*P*=0.066, log rank test for trend) showed a significant difference in survival rate. However, survival was significantly better for epibulbar tumors (*P*<0.0001), unilocular location (*P*=0.02), and thin tumors (*P*=0.0004, overall Log Rank for trend). Age at diagnosis (<50 y, 50-68 y, >68 y) was significantly correlated with survival (*P*=0.023, Log Rank test for trend), but older patients had significantly larger (*P*<0.023) and thicker (*P*<0.021) tumors. Cox regression analysis showed the same risk factors as for the development of distant metastases (Table 6), most importantly a non-epibulbar location (HR 3.6, *P*<0.001).

Discussion

Our study suggests that the incidence of conjunctival melanoma in the Netherlands is similar to the previously reported incidence of 0.05/100 000 inhabitants.[4-7] Since 1970, conjunctival melanoma has been diagnosed in 172 patients. With a mean population of 14 575 000 inhabitants in the Netherlands (Central Bureau of Statistics, Voorburg/Heerlen), over the last 30 years an estimated 240 patients would have been diagnosed with this type of melanoma. Thus we probably included more than 70% of possible patients with conjunctival melanoma in the Netherlands after 1970.

Treatment of the local primary tumor has changed in the last decades from irradiation or excision as sole therapy to excision in combination with cryotherapy or brachytherapy. This has enabled us to compare different treatments. For local tumor control, excision in combination with brachytherapy appears to results in fewer local recurrences than when using

Table 1. Patient and tumor characteristics of 194 conjunctival melanoma patients.

Variables	*No. of cases*		*(%)*
Sex			
Male	87		(45)
Female	107		(55)
Location			
Fornix	2		(1)
Caruncular	5		(2.5)
Tarsal	11		(5.5)
Limbal	110		(57)
Epibulbar	133		(69)
Diffuse	43		(22)
Origin of melanoma			
Naevus	3		(2)
Naevus and PAM	9		(4)
PAM	111		(57)
de novo	50		(26)
Inconclusive	21		(11)
Maesurements	*No. of cases*	*Mean*	*SD*
Basal diameter (mm)	153	7.21	4.7
Thickness (mm)	152	2.07	1.9

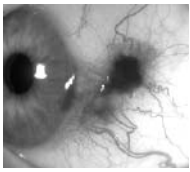


Table 2. Treatment of the primary tumor at moment of its histological diagnosis, and the number of patients with a local recurrence.

Treatment modality	*No. of cases*	*No. of patients with a local Recurrence*	(%)
Excision	127	85	(67)
Excision and Chemotherapy (MMC)	4	4	(100)
Excision and Cryotherapy	17	11	(65)
External Irradiation	11	7	(64)
Excision and Brachytherapy	19	5	(26)
Excision and Brachytherapy and Cryo	1	0	(0)
Exenteration and Irradiation	1	0	(0)
Exenteration	14	0	(0)

MMC = Mitomycin C; intraoperative.

other treatments. Other studies also found a trend toward an increased local recurrence rate after excision without additional treatment compared to excision and ruthenium plaque[27-30] or additional external radiotherapy.[18] Reduction in local recurrences might also reduce the need for secondary exenteration.

The other main risk factor for local recurrences was non-epibulbar location. None of the other variables, such as age at diagnosis, unilocular or multilocular location, origin, thickness, or diameter, were significantly correlated with the local recurrence rate. We confirm the findings of Tuomaala et al.[6] that location is the most important risk factor for local recurrence. The 5-year local recurrence rate was 60.7% (95% CI 53.0-68.5). Others reports have shown lower 5-year rates of between 26% and 52%.[6,11,15,19-20] This difference may be explained by the percentage of tumors treated with adjuvant therapy. However, 10 years after diagnosis, local recurrence seemed to reach comparable levels.[19-20] Therefore, the long-term effect of adjuvant therapy on local recurrences still has to be evaluated. One of our patients had nine local recurrences despite receiving adjuvant brachytherapy and cryotherapy.

Regional metastases occurred in 41 (21%) patients, mostly in the preauricular or parotid (*n*=26) region and cervical (*n*=13) regions. Four patients with only regional metastasis survived for more than 15 years after local treatment, as also reported for parotid gland melanomas.[37-38] This long survival, in the absence of distant metastases, supports an active search for positive lymph nodes in the pre-auricular, cervical, and sub-mandibular regions. This result may also advocate consideration of sentinel lymph node biopsy[39] in trying to treat regional metastases at a sub-clinical stage. Lymphoscintigraphy and sentinel lymph node biopsy is a safe procedure, although its sensitivity is still not known[39-41] and care should be taken to avoid facial paresis. The indication for sentinel lymph node biopsy is still uncertain, but the Cox analysis for regional metastases (Table 4) suggests that tumors thicker than 2 mm with a diameter greater than 10 mm warrant this approach. In our study, primary epibulbar tumors tended to give rise to fewer regional metastases (Table 4), in agreement with Tuomaala et al.[42] who reported significantly fewer regional lymph nodes from limbal tumors.

Forty-seven (24%) patients developed a distant metastasis, mainly in lung, liver, skin, and brain, 40 of these patients had distant metastasis in these four locations. Esmaeli et al.[25] also reported liver and lung as main sites of metastasis. Seventeen patients presented with distant metastasis, without prior or concurrent regional nodal involvement, indicating that not all melanoma patients will benefit from sentinel lymph node biopsy. In contrast to the study of Esmaeli et al, we did not find that the primary tumors that 'skipped' the lymph nodes had a higher rate of local recurrence.

The survival rate was 86.3% at 5 years, 71.2% at 10 years, and 67.2% at 15 years (Figure 3A), similar to other studies (5-year survival 87.6-74%).[4, 21, 25] The total exenteration rate was 30% over a mean follow-up period of 9.2 years, comparable to the 37% reported by Paridaens et al.[33], and the estimated 15-year 32% exenteration rate of reported by Shields and Shields[34]. Main risk factors for distant metastases, as well as for mortality, were non-epibulbar location as well as thick (>2 mm), and multilocular tumors.

Although we found a significant difference in local recurrence analysis, there was no significant difference in survival with different treatment strategies. Only primary exenteration

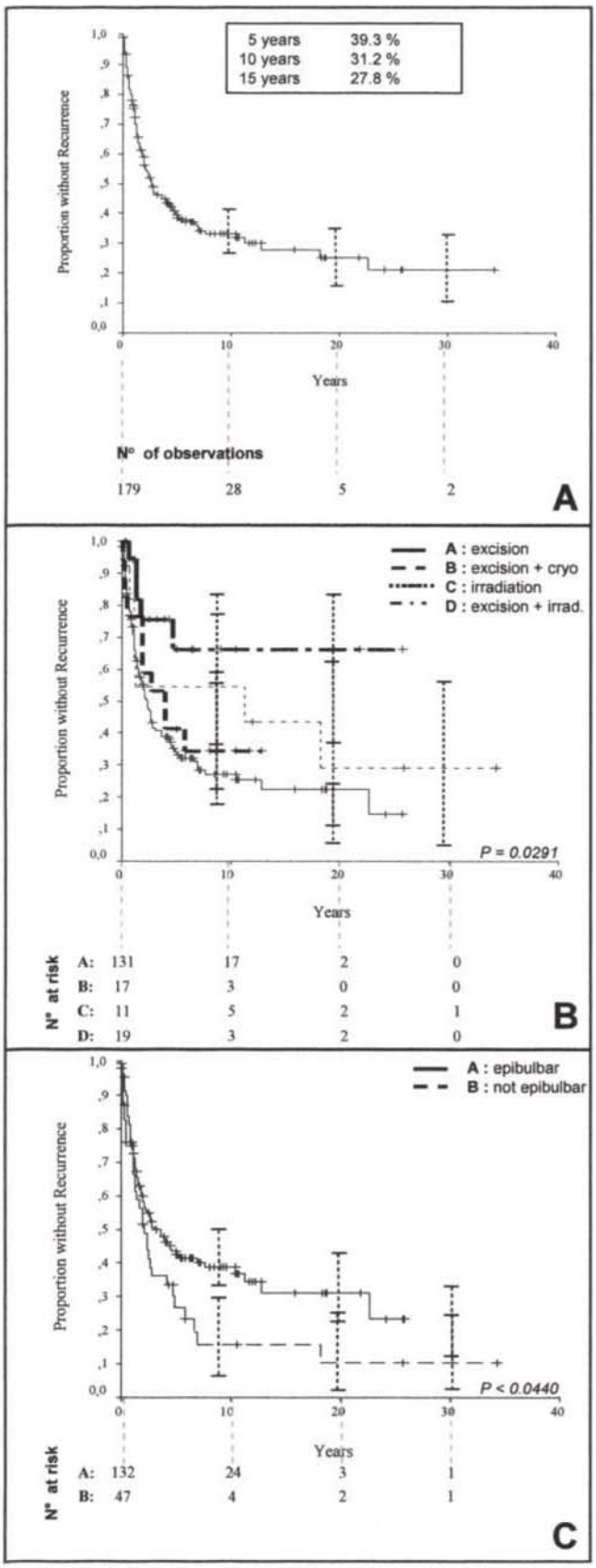


Figure 2. Kaplan Meier recurrence analysis in 179 patients (primary exenterated patients are not included in recurrence analysis). **A**. Overall recurrence rate after the primary treated tumor (time analysed from primary diagnosis to first local recurrence) **B**. Recurrence rate in function of treatment modality of the primary lesion (overall log rank p=0.043). Excision in combination with irradiation had significantly less recurrences (log rank p=0.038). There was no significant difference between excision in combination with cryotherapy when compared with excision only (log rank p=0.759). **C**. Recurrence rate for patients with only a epibulbar component (132 patients) or not (47 patients) (log rank p<0.044).

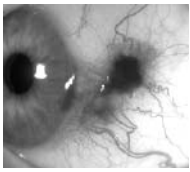


Table 3. Cox regression analysis of the appearance of first local recurrence. Both univariate analysis and a multivariate model are presented. Analysis for 179 patients (patients with primary exenterated tumors are not included in the analysis).

Variable	*Coefficient (SE)*	*Wald ²*	*P*	*Hazard Ratio (95% CI)*
Univariate analysis				
Age at Diagnosis[$]	0.005 (0.005)	0.897	0.344	1.005 (0.994-1.016)
Non-epibulbar location	0.412 (0.206)	3.996	0.046	1.510 (1.008-2.263)
Uni/Multilocular	0.087 (0.170)	0.263	0.608	1.091 (0.782-1.522)
Origin * (referenced to melanoma) [α]		1.768	0.622	
Naevus	-0.515 (0.732)	0.495	0.482	0.598 (0.142-2.509)
Naevus + PAM	-0.624 (0.532)	1.374	0.241	0.536 (0.189-1.520)
PAM	-0.120 (0.219)	0.303	0.582	0.887 (0.578-1.361
Thickness[‡]	0.240 (0.130)	3.433	0.064	1.271 (0.986-1.639)
Basal Diameter[Ÿ]	0.065 (0.115)	0.320	0.571	1.067 (0.852-1.338
Therapy[†] (referenced to excision + brachytherapy) [α]		8.065	0.045	
Excision	1.251 (0.460)	7.404	0.007	3.494 (1.419-8.606)
Excision + cryotherapy	1.129 (0.540)	4.373	0.037	3.093 (1.073-8.911)
Irradiation	0.863 (0.588)	2.151	0.142	2.370 (0.748-7.506)
Multivariate Analysis				
Model (-2log likelihood 1006.905)				
Non-epibulbar location	0.533 (0.211)	6.376	0.012	1.704 (1.127-2.577)
Therapy[†] (referenced to excision + brachytherapy) [α]		9.667	0.022	
Excision	1.331 (0.461)	8.315	0.004	3.783 (1.531-9.347)
Excision + cryotherapy	1.236 (0.542)	5.196	0.023	3.442 (1.189-9.963)
Irradiation	0.768 (0.590)	1.699	0.192	2.156 (0.679-6.848)

$Age at diagnosis : grouped as 0-50 years; 51-67 years; 68-99 years.
*Origin : grouped as naevus, naevus and PAM, PAM or melanoma.
‡Thickness (Breslow): ≤ 1mm; 1 > 2 mm; ≥ 2mm.
ŸBasal diameter : 0-6 mm; 6-10 mm; > 10mm.
†Therapy : excision; excision and cryotherapy; excision and brachytherapy; irradiation.
[α] Origin and Therapy were considered as categorical variates for Cox regression analysis.

for advanced disease was associated with a significantly lower survival, which can be explained by the fact that these tumors were more extensive and had a more frequently unfavorable location. We think that more knowledge of this rare tumor may help us to detect suspect lesions earlier and thus ensure timely referral of patients to ophthalmic oncology centers.

Conclusion

Predictors of poor survival were a non-epibulbar location, tumors thicker than 2 mm, and multifocal location. Survival may be improved by early diagnosis of regional metastases. The long survival rate of some patients with regional metastases also suggests that sentinel lymph node biopsy may increase survival in high-risk patients, e.g., especially in patients with multiple local recurrences, a Breslow tumor thickness of more than 2 mm, and a tumor

Table 4. Cox regression analysis for the appearance of regional metastases in 194 patients. Tumor thickness showed to be the most important risk factor

Variable	*Coefficient (SE)*	*Wald ²*	*P*	*Hazard Ratio (95% CI)*
Univariate analysis				
Age at Diagnosis[$]	0.011 (0.010)	1.234	0.267	1.011 (0.992-1.031)
Non-epibulbar location	0.596 (0.321)	3.456	0.063	1.815 (0.968-3.404)
Uni/Multilocular	0.231 (0.228)	1.027	0.311	1.259 (0.806-1.967)
Origin * (referenced to melanoma) [α]		1.260	0.739	
Naevus	-12.241 (414.426)	0.001	0.976	0.000 (n.a.)
Naevus + PAM	0.312 (0.652)	0.229	0.632	1.366 (0.381-4.903)
PAM	-0.281 (0.370)	0.575	0.448	0.755 (0.366-1.560)
Thickness[‡]	1.019 (0.238)	18.363	<0.001	2.770 (1.738-4.415)
Basal Diameter[Ÿ]	0.489 (0.189)	6.660	0.010	1.631 (1.125-2.364)
Therapy[†] (referenced to excision + brachytherapy) [α]		1.483	0.686	
Excision	0.566 (0.732)	0.597	0.440	1.761 (0.419-7.396)
Excision + cryotherapy	-0.092 (1.001)	0.008	0.927	0.912 (0.128-6.485)
Irradiation	0.741 (0.915)	0.656	0.418	2.098 (0.349-12.602)
Multivariate Analysis				
Model 1 (-2log likelihood 264.401)				
Thickness [‡]	0.874 (0.254)	11.851	0.001	2.397 (1.457-3.942)
Basal Diameter[Ÿ]	0.192 (0.213)	0.811	0.368	1.211 (0.798-1.839)

$,*,‡,Ÿ,†,α : as in Table 3.

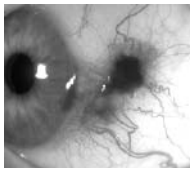


Table 5. Cox regression analysis for the appearance of hematogenous metastases in 194 conjunctival melanoma patients. Epibulbar localisation and tumor thickness are the most important risk factor in our study.

Variable	*Coefficient (SE)*	*Wald ²*	*P*	*Hazard Ratio (95% CI)*
Univariate analysis				
Age at Diagnosis[$]	0.425 (0.180)	5.556	0.018	1.530 (1.074-2.179)
Non-epibulbar location	1.396 (0.289)	23.269	<0.001	4.039 (2.290-7.122)
Uni/Multilocular	0.034 (0.057)	0.343	0.558	1.034 (0.924-1.157)
Origin * (referenced to melanoma) [α]		1.234	0.745	
Naevus	-12.305 (358.641)	0.001	0.973	0.000 (0.000-8.544)
Naevus + PAM	-0.007 (0.637)	0.000	0.991	0.993 (0.285-3.461)
PAM	-0.347 (0.331)	1.100	0.294	0.707 (0.369-1.352)
Thickness[‡]	0.743 (0.196)	14.306	<0.001	2.102 (1.430-3.089)
Basal Diameter[Ÿ]	0.322 (0.172)	3.501	0.061	1.379 (0.985-1.932)
Therapy[†] (referenced to excision + brachytherapy) [α]		3.121	0.373	
Excision	0.711 (0.727)	0.955	0.328	2.036 (0.489-8.471)
Excision + cryotherapy	-0.818 (1.226)	0.466	0.504	0.441 (0.040-4.876)
Irradiation	0.582 (0.918)	0.401	0.526	1.789 (0.296-10.813)
Multivariate Analysis				
Model 1 (-2log likelihood 264.401)				
Non-epibulbar location	1.269 (0.331)	14.694	<0.001	3.557 (1.859-6.805)
Thickness [‡]	0.533 (0.197)	7.345	0.007	1.704 (1.159-2.505)

$,*,‡,Ÿ,†,α : as in Table 3.

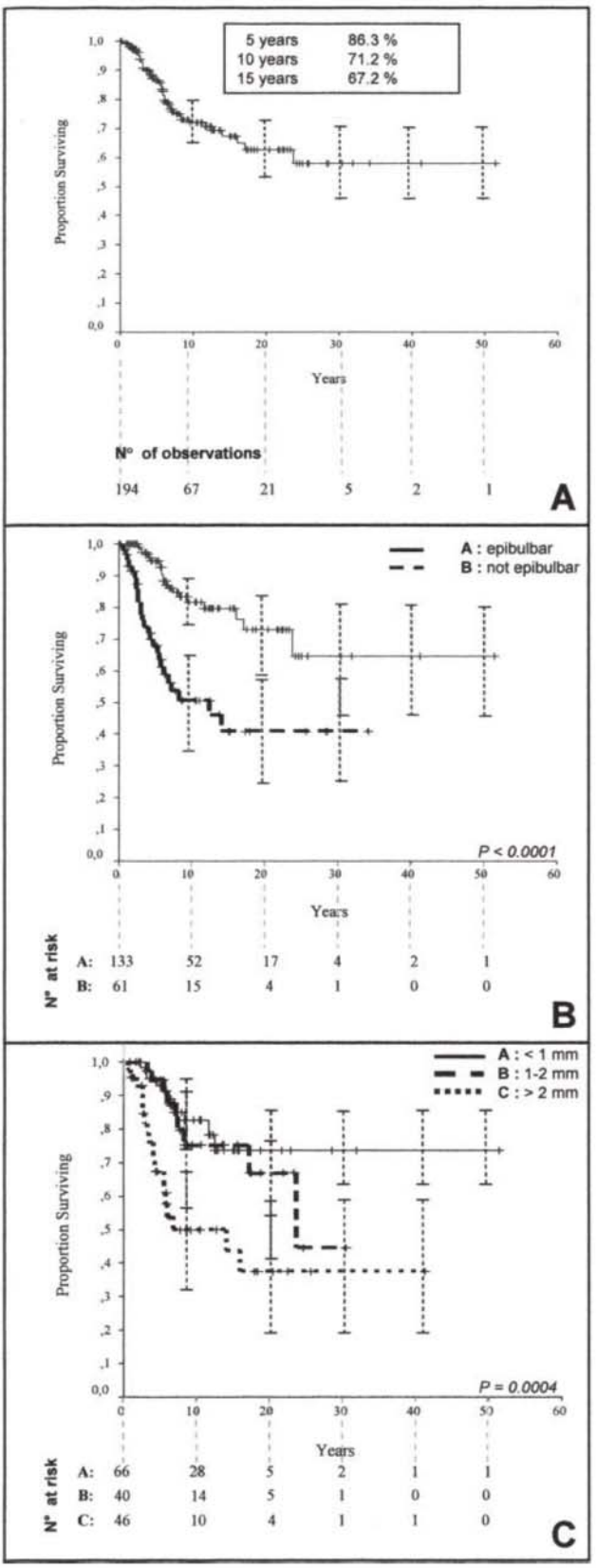
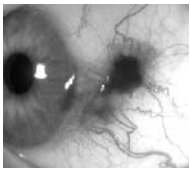


Figure 3. Kaplan Meier survival analysis in 194 patients. **A**. Overall survival in years after primary treated tumor (histopathologically diagnosed conjunctival melanoma). **B**. Survival for epibulbar (61 patients) and non-epibulbar (133 patients) conjunctival melanoma patients. Log rank p<0.0001. **C**. Survival analysis for different tumor thicknesses of the primary lesion (overall Log rank test for trend p=0.0004).

Table 6. Cox regression analysis for survival in 194 conjunctival melanoma patients.

Variable	*Coefficient (SE)*	*Wald ²*	*P*	*Hazard Ratio (95% CI)*
Univariate analysis				
Age at Diagnosis[$]	0.018 (0.010)	3.425	0.064	1.018 (0.999-1.037)
Non-epibulbar location	1.286 (0.294)	19.113	<0.001	3.617 (2.033-6.438)
Uni/Multilocular	0.439 (0.196)	5.210	0.025	1.551 (1.056-2.278)
Origin * (referenced to melanoma) [α]		1.417	0.702	
Naevus	-12.293 (354.707)	0.001	0.973	0.000 (0.000-8.948)
Naevus + PAM	0.192 (0.644)	0.089	0.765	1.212 (0.343-4.279)
PAM	-0.333 (0.341)	0.954	0.329	0.716 (0.367-1.399)
Thickness[‡]	0.678 (0.200)	11.465	0.001	1.969 (1.330-2.916)
Basal Diameter[Ÿ]	0.320 (0.176)	3.299	0.069	1.378 (0.975-1.946)
Therapy[†] (referenced to excision + brachytherapy) [α]		2.788	0.426	
Excision	0.649 (0.728)	0.795	0.372	1.914 (0.460-7.972)
Excision + cryotherapy	-0.819 (1.226)	0.446	0.504	0.441 (0.040-4.873)
Irradiation	0.544 (0.918)	0.351	0.553	1.723 (0.285-10.417)
Multivariate Analysis				
Model 1 (-2log likelihood 264.401)				
Non-epibulbar location	1.148 (0.337)	11.595	0.001	3.152 (1.628-6.103)
Thickness [‡]	0.491 (0.202)	5.914	0.015	1.634 (1.100-2.426)

$,*,‡,Ÿ,†,α : as in Table 3.



diameter greater than 10 mm. Adjuvant brachytherapy may reduce the number of local recurrences. A prospective study is needed to compare the effect of excision in combination with radiotherapy and excision with cryotherapy on the number of local recurrences, exenteration rate, and survival.

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