CLINICAL SCIENCE

Prognostic value of clinical and histopathological parameters in conjunctival melanomas: a retrospective study

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Aim: To determine prognostic factors for recurrence of disease and tumour related mortality in patients with conjunctival melanoma.

Methods: A retrospective analysis of clinical and histopathological data of 69 patients with histologically verified conjunctival melanoma.

Results: As univariate analysis showed, significant risk factors for the development of recurrence were: irregular pigmentation (RR = 2.0, p = 0.0007), incomplete surgical excision (RR = 3.5, p = 0.008), tumour invasion deeper than in substantia propria (RR = 3.9, p = 0.008), and presence of epithelioid tumour cells (RR = 2.9, p = 0.05). For tumour related mortality a significantly increased risk was found for tumour location in palpebral conjunctiva, caruncle, plica, or fornices (RR = 5.9, p = 0.001), for tumour infiltration deeper than the substantia propria (RR = 5.5, p = 0.001), for incomplete surgical excision (RR = 4.4, p = 0.05), and for nodular or mixed (nodular and superficial) growth pattern of the tumours (RR = 1.2, p = 0.002). The use of an adjuvant therapy for the surgical excision of the melanomas had no statistically significant influence upon the development of recurrent disease nor upon the tumour related mortality.

Conclusion: These data present similar clinical and histopathological risk factors for patients with conjunctival melanoma as reported previously. The present study also addresses the failure of retrospective studies on conjunctival melanoma to prove the efficacy of a supplementary therapy to surgical excision.

Conjunctival melanoma is a rare malignancy of the human with an estimated incidence of 0.02–0.08 per 100 000 inhabitants in the Western population.[1 2] Metastatic spread to the regional lymph nodes occurs in about one third of the patients. After clinical detection of disseminated disease survival rate is extremely low. The 10 year tumour related mortality is approximately 30%.[1–4]

The primary therapy of conjunctival melanoma is the surgical excision of the tumour, wherever possible. The recurrence rate is very high and almost 50% of the patients will experience one or multiple recurrences. Therefore, numerous supplementary treatments (cryotherapy, topical application of chemotherapeutical agents, brachytherapy, teletherapy) are used either alone or in combination with the surgical removal of the tumour.[1 5–8]

The prognosis of conjunctival melanoma has been positively correlated with various clinical and histopathological features.[9 10] Established markers for poor prognosis include distinct tumour locations (palpebral conjunctiva, fornices, plica, and caruncle) and tumour depth as a sign of tumour invasion into the subconjunctival layers.[11–13] There is considerable controversy concerning the predictive impact of recurrent disease, histological cell type, and the clinical origin of the tumour.[9]

In the present study, we undertook a retrospective analysis of the clinical and histopathological data of 69 patients with conjunctival melanomas. Statistical analysis to determine prognostic factors for recurrent disease and tumour related mortality was performed.

PATIENTS, MATERIALS, AND METHODS

We reviewed all records of patients with "suspected" conjunctival melanotic lesions (n = 391) who were examined between 1969 and 1997 at the university eye clinic in Essen. Twenty four patients were excluded since their records were not available in our archive. Out of the remaining 367 patients, histologically proved conjunctival melanoma was present in 56 cases. We excluded two more cases because these patients lived abroad and no sufficient follow up data were available. In addition, we reviewed the records of 15 consecutive patients who underwent surgical excision for conjunctival melanomas between 1992 and 1997 in the eye clinic of the Free University in Berlin. In total, 69 patients (Essen 54, Berlin 15) were included into this study. In both centres a wide range of treatments (surgery, brachytherapy with ruthenium and strontium, cryotherapy, mitomycin C, external irradiation, proton beam irradiation) are available for the treatment of conjunctival melanomas.

We processed clinical and histological data into a databank using the File Maker Pro 4.0 software package. The following parameters were assessed: sex, age (at the date of diagnosis), laterality and location of the lesion, clinical origin as found by the histopathological examination (primary acquired melanosis (PAM), de novo, naevus), multifocality, grade of pigmentation (melanotic, amelanotic, mixed), growth pattern as documented by the clinical examination (nodular, superficial, mixed), grade of invasion (substantia propria, or deeper), histological cell type (spindle, epithelioid, mixed), classification of the primary histologically examined tumour material (excision with tumour free margins, excision with tumour infiltrated margins), type and date of primary treatment, time to first recurrence (months), type and date of treatment for recurrence, cause and date of death (melanoma related, cardiovascular disease, other malignancy, others), site of metastases (orbit, lymph nodes, distant).

Table 1 Primary treatment of the 69 patients with conjunctival melanoma

	No	%
Excision in toto*		
no additional therapy	14	20.3
with ruthenium plaque	1	1.4
with cryotherapy	2	2.9
with strontium plaque	2	2.9
with mitomycin C	1	1.4
with external irradiation	3	4.5
Excision not in toto*		
no additional therapy†	12	17.4
with ruthenium plaque	15	21.7
with cryotherapy	2	2.9
with ruthenium plaque and cryotherapy	1	1.4
with strontium plaque	3	4.5
with strontium plaque and mitomycin C	1	1.4
with mitomycin C	1	1.4
with external irradiation	7	10.1
with proton beam irradiation	2	2.9
Exenteration	2	2.9
Total	69	100

* As observed by histological examination of the specimens.
† These patients were clinically monitored by their referral ophthalmologists. In eight cases the referral ophthalmologist considered further treatment not necessary since no clinical signs for tumour persistence were detectable. Four additional patients refused any further treatment.

To compare the associations between the clinical and the histopathological features, we used the Spearman test. For the survival analysis, we categorised the tumour location as "favourable" (bulbar and limbus) and as "unfavourable" (palpebral, caruncle, plica, fornices) as already proposed in former studies,[4 11 12] and in order to preserve comparability of our results with previous observations. Survival time was defined as the time from the primary therapy to the date of death caused by conjunctival melanoma (event), or to the last time that the patient was known to be alive (right censored), or to the date of death for patients whose demise was considered to be unrelated to conjunctival melanoma (right censored). Follow up data were obtained by contacting the general practitioner or the local ophthalmologist.

The influence of prognostic factors on tumour related survival was assessed by Kaplan-Meier estimates and the log rank test for univariate analysis. We checked the assumption of Cox proportional hazards by complementary log plots. We calculated hazard ratios (RR) with 95% confidence intervals (95% CI). All p values are presented two sided without adjustment for multiple testing. We did not perform multivariate analysis taking into account that (i) our sample size was relatively small, and (ii) there was no association among the prognostical significant parameters, as they were detected by the bivariate analysis and, therefore, there was only a minimum of potential confounding among these parameters. We performed all statistical analysis with the SPSS 9.0 software package.

RESULTS

Our study cohort consisted of 41 (59.4%) female and 28 (40.6%) male patients. The youngest patient was 14 years of age and the oldest 88 years old (median 60 years). The right eye was affected in 36 (52.2%) cases, and the left eye globe in the remaining 33 (47.8%); there was no case of a bilateral conjunctival melanoma. While the melanoma was unifocal in 53 (72.5%) patients, two to four foci of the tumour were present in 16 (27.5%) patients. Thus, a total of 99 lesions were initially observed. Out of the 99 lesions, 57 (57.6%) were located at the bulbar conjunctiva, 14 (14.1%) at the palpebral conjunctiva, seven (7.1%) on the caruncle, three (3%) on the plica, 11 (11.1%) on the fornices, and seven (7.1%) in more than one of these locations.

Table 2 Univariate Cox proportional hazard regression analysis for recurrence free survival of 34 out of 69 patients with conjunctival melanomas who developed local recurrence

Parameter	RR (relative risk)	95% CI	p Value*
Age >60 years Ref: ⩽60 years	1.01	0.6–1.7	0.96
Multifocality (continuous)	1.17	0.78–1.75	0.45
Growth pattern Nodular or mixed Ref: superficial	1.06	0.98–1.14	0.14
Sex Male Ref: female	0.86	0.42–1.77	0.86
Histological cell type Epithelioid and mixed Ref: spindle	**2.9**	**1.0–8.48**	**0.05**
Grade of invasion Deeper than subst propria Ref: subst propria	**3.9**	**1.42–10.71**	**0.008**
Location† Unfavourable Ref: favourable	0.87	0.42–1.77	0.69
Surgical excision Not in toto Ref: in toto	**3.55**	**1.38–9.1**	**0.008**
Adjuvant therapy No Ref: yes	1.25	0.79–1.96	0.34
Grade of pigmentation Amelanotic or mixed Ref: melanotic	**2.0**	**1.35–3.07**	**0.0007**
Clinical origin PAM or de novo Ref: naevus	0.87	0.49–1.53	0.63

*All p values are two sided.
†As "favourable" were classified melanomas located on the bulbar conjunctiva and limbus and as "unfavourable" those located at the palpebral conjunctiva, caruncle, plica, or fornices.

The growth pattern was nodular in 33 (47.8%) patients, superficial in 19 (27.5%), and mixed in the remaining 17 (24.7%). In 34 (49.3%) cases, the tumours were melanotic, in four (5.8%) cases the tumours had no pigmentation (red or yellow coloured), and in 31 (44.9%) patients the tumours showed a mixed pattern of pigmentation. The histological cell type appeared with pure spindle cells in 11 (15.9%) melanomas, predominantly epithelioid in 18 (26.1%) melanomas, and was of mixed cell type in 36 (52.2%) melanomas; in four (5.8%) cases this information was not available. Conjunctival melanomas infiltrated and expanded into the substantia propria in 58 (84.1%) cases, and invaded the deeper layers (that is, episclera, muscle) in 11 (15.9%) lesions. The origin of the melanomas was PAM in 29 (42.1%) patients, de novo in 11 (15.9%) patients, naevus in 27 (39.1%) patients, and unknown in two (2.9%) patients.

The bivariate analysis showed that patients older than 60 years of age had more superficial and multifocal lesions, whereas in patients younger than 60 years of age predominantly unifocal and nodular lesions were present ($p = 0.001$). Multifocality was more often found in superficial lesions and

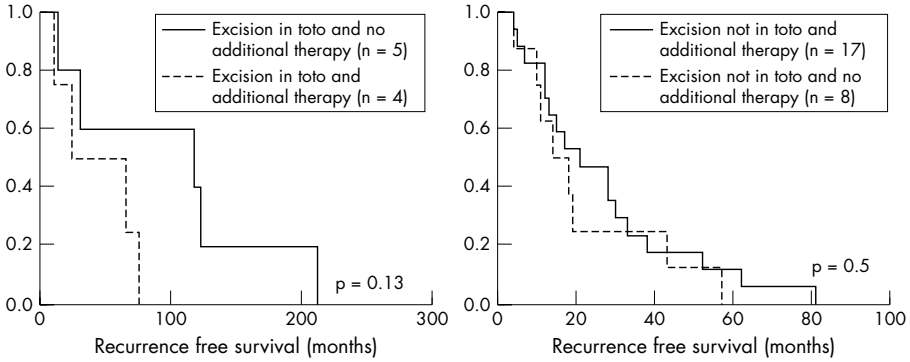

Figure 1 Kaplan-Meier analysis for recurrence free survival. The log rank test for univariate analysis was assessed.

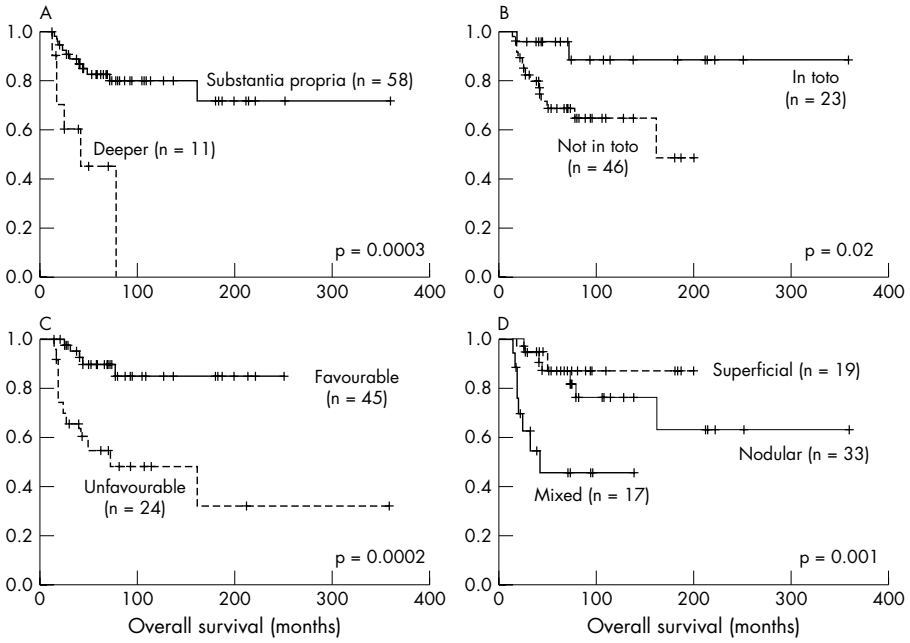

Figure 2 Kaplan-Meier analysis for overall tumour related survival. The log rank test for univariate analysis was assessed.

in tumours of PAM origin (p = 0.001 for growth pattern; p = 0.01 for origin of the tumour).

The type of primary therapy applied in the 69 patients is summarised in Table 1. As various therapeutic approaches were used and the total number of the patients was relatively small it was not possible to perform sufficient analysis for each treatment. In total, 34 (49.3%) patients developed recurrent disease. The presence of epithelioid cells in tumour, tumour extension deeper than in the substantia propria, irregular tumour pigmentation, and incomplete surgical excision were significant parameters for the development of recurrence (Table 2). The use of a supplementary therapy showed no impact on the recurrence of the tumour (Table 2, Fig 1).

The assessment of the follow up data disclosed that 19 (27.5%) patients developed metastases. Seventeen (24.6%) patients died as a result of conjunctival melanoma, and 12 (17.4%) patients died from causes considered to be unrelated to their conjunctival melanomas. The median follow up time was 67 months (range 15–360). The 5 year tumour related mortality was 32%. The Kaplan-Meier analysis for overall tumour related survival showed that tumour location, grade of invasion, surgical excision, and the pattern of growth were of prognostic value in our patient cohort (Fig 2). These findings were also verified by the univariate Cox proportional hazard regression analysis (Table 3).

DISCUSSION

One of the main problems in the clinical management of conjunctival melanoma remains the high rate of recurrent disease. The surgical excision of the primary lesion is possible in the majority of the cases although very often the tumour can not be completely removed. In the present study, 46 out of the 69 primary tumours were histologically not removed in toto. As expected, the presence of recurrence was, within these patients, higher than in those that were primarily removed in toto. Possible reasons for the relatively high rate of incompletely removed tumours may be, firstly, the large extension and inconvenient location of the tumours when patients first presented in our departments since both eye clinics (Essen and Berlin) are national referral centres for ocular malignancies and, secondly, the involvement of many surgeons over the examined period (1969–97) which might lead to the use of various surgical techniques.

As our data showed, the presence of recurrent disease was also associated with the grade of tumour invasion, with the extend of pigmentation of the lesions, and with the histological cell type of the tumours. These observations are in accordance with the clinical experience that tumour margins of irregular pigmented tumours are not always precisely visible and that the tumour, therefore, can not be always totally removed. Similarly, microscopically invasion of the sclera or of

Table 3 Univariate Cox proportional hazard regression analysis for overall tumour related survival of 69 patients with conjunctival melanomas

Parameter	RR (relative risk)	95% CI	p Value*
Age			
>60 years	0.96	0.48–1.93	0.92
Ref: ⩽60 years			
Multifocality (continuous)	1.09	0.6–1.9	0.7
Growth pattern			
nodular or mixed	**1.16**	**1.06–1.28**	**0.002**
Ref: superficial			
Sex			
male	0.98	0.37–2.59	0.97
Ref: female			
Histological cell type			
Epithelioid and mixed	3.65	0.48–27.74	0.21
Ref: spindle			
Grade of invasion			
Deeper than subst propria	**5.54**	**1.97–15.6**	**0.001**
Ref: subst propria			
Location†			
Unfavourable	**5.86**	**2.06–16.66**	**0.001**
Ref: favourable			
Surgical excision			
Not in toto	**4.44**	**1.0–19.72**	**0.05**
Ref: in toto			
Adjuvant therapy			
No	1.48	0.78–2.8	0.23
Ref: yes			
Grade of pigmentation			
Amelanotic or mixed	1.52	0.91–2.53	0.11
Ref: melanotic			
Recurrence			
Yes	0.87	0.32–2.33	0.78
Ref: no			
Clinical origin			
PAM or de novo	0.97	0.48–1.94	0.93
Ref: naevus			

*All p values are two sided.
†As "favourable" were classified melanomas located on the bulbar conjunctiva and limbus and as "unfavourable" those located at the palpebral conjunctiva, caruncle, plica, or fornices.

the muscle is not detectable and this tumour mass can be easily overlooked by the surgical excision. In total, 49.3% of our patients (n = 69, median follow up: 5.5 years) developed recurrent disease which is within the range of previous reports (Paridaens[4]: recurrence rate (RR): 55.1%, n = 256, median follow up 6.3 years; Shields[10]: RR: 35%, n = 150, mean follow up 7.0 years; Lommatzsch[1]: RR: 23.5%, n = 81, median follow up 5.5 years).

On the other hand, although there was a trend in our data of a reduced recurrence rate after additional treatment to tumour excision this was not statistically significant (Fig 1, Table 2). Unfortunately, because of the limitation of our study—the result of the use of a variety of treatments in a relatively small patient cohort—it was not possible to evaluate the efficacy of a particular type of supplementary therapy. While a number of studies[3 10 14] could demonstrate no beneficial effect of exenteration on patient survival when compared with eye salvaging conservative treatment procedures there is no clear benefit of any supplementary therapy to surgical excision addressed so far. Lommatzsch[1] recommended the use of locally applied β irradiation but no analysis of the treatment effect is presented in their original work. Shields and colleagues demonstrated, in a previous report,[6] a clear benefit of cryotherapy on the development of recurrence after surgical excision of conjunctival melanomas. Nevertheless the same group failed to reproduce this result in a later analysis of their patients obviously also including the patients referred to before.[10] Further reports about mitomycin C[5] and proton beam irradiation[8] should be addressed as preliminary because of the limited patient number enrolled and follow up period provided. Thus, so far no supplementary therapy to surgical excision of conjunctival melanoma with proved efficacy exists.

The survival analysis for overall tumour related survival was in accordance with previous reports showing that tumour location and tumour invasiveness are prognostic markers in patients suffering from conjunctival melanomas.[4 11–13] The prognostic impact of the growth pattern though statistically significant was not strong enough (relative risk 1.16) in our study and thus is of limited clinical value. The age of the patients at the time of diagnosis, the histological cell type of the tumour, the development of recurrent disease, the use of an adjuvant therapy, as well the clinical origin of the tumour had no prognostic value in our investigation.

There are several limitations of the present study. Firstly, we used a wide variety of therapeutical regimens in a relatively small cohort of patients and therefore (i) it was not possible to evaluate the efficacy of each regimen used, and (ii) this probably biased the presence of recurrence disease. Secondly, we report on only 69 patients and this does not allow us to perform more extensive statistical analyses such as multivariate analysis for potential prognostic markers. Thirdly, we possibly studied a preselected group of patients since only patients with advanced disease are likely to be referred to ocular oncology centres. However, our results are in accordance with most of the previous reports verifying the "classic" risk factors for tumour related survival and development of recurrence in patients with conjunctival melanoma. We also demonstrated that the use of an adjuvant therapy had no impact on the development of recurrent disease in our patient cohort. Indeed, no prospective study is provided with a sufficient number of patients to investigate the influence of any supplementary therapy after tumour excision. This lack of proved efficacy so far is much more a result of methodological problems of studies with conjunctival melanomas than an evidence of insufficient biological effectiveness of the examined methods. Owing to the low incidence of conjunctival melanomas it is not possible for one specialised centre to recruit enough patients. As already stated by other ocular oncologists[1 10] such a clinical trial can only be realised as an international multicentre effort.

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