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Clinical predictive factors for development of recurrence and metastasis in conjunctival melanoma: a review of 68 cases

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Abstract

Sixty eight cases of histologically proved conjunctival melanoma were reviewed in order to determine the clinical factors that were predictive of local recurrence and distant metastasis. All patients were treated with surgical excision and most had supplemental cryotherapy. The mean follow up was 7·5 years. Histopathologically, the conjunctival melanoma arose from primary acquired melanosis in 56%, from naevus in 26%, and de novo in 18%. Of the 68 patients, 38 (56%) developed at least one local tumour recurrence and 22 (32%) developed more than one recurrence. The method of initial treatment and the eventual development of metastasis were the two parameters statistically associated with tumour recurrence. Those patients treated initially with tumour excision alone had a statistically significant higher recurrence rate than those treated initially with excision and supplemental cryotherapy (p=0·001). Fourteen patients (21%) developed metastasis and the mean period between treatment and metastasis was 3·6 years. Twelve (18%) died from metastatic melanoma with a mean interval of 4·4 years from the time of initial surgery until death. The only clinical parameter that was statistically associated with distant metastasis was local tumour recurrence (p=0·015). Based on these observations, the authors make recommendations regarding the treatment of conjunctival malignant melanoma. It appears that initial complete excision of the tumour with supplemental cryotherapy offers the patient the best chance of remaining free of recurrence and metastasis.

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Although there have been several reports on the prognostic histological factors for cutaneous melanoma and uveal melanoma, there is little information available on clinical prognostic factors associated with conjunctival melanoma. The prognosis of conjunctival melanoma has been correlated with its histological origin[1-4] and histological features,[4-11] location and extension,[1 2 5 10 12 13] and the development of recurrences.[1 3 5] Several authorities have pointed out the difficulties and controversies in the management of melanoma of the conjunctiva.[1 4 10 12 14 15] The goals of treatment of conjunctival melanoma should be to eradicate the tumour, prevent local recurrence, and, above all, to prevent metastatic disease and death. This study was undertaken to determine the clinical parameters that are predictive of local recurrence and metastasis of malignant melanoma of the conjunctiva.

Materials and methods

We reviewed the records of all patients with histologically proved primary conjunctival melanoma who were evaluated and managed on the Ocular Oncology Service at Wills Eye Hospital between April 1972 and June 1992. The factors evaluated included the age, race, and sex of the patient, the anatomical site of the tumour (bulbar conjunctiva, palpebral conjunctiva, forniceal conjunctiva, caruncle, cornea, and eyelid margin, or combination of these), clinical tumour pigmentation (pigmented or non-pigmented), and treatment of tumour. Therefore, in this study, we analysed only the clinical parameters related to prognosis.

The clinical parameters were then statistically analysed for association with the development of local tumour recurrence and distant tumour metastasis. We used the ordered χ^2 test when the data was ordered. For simple dichotomies, we used the Fisher's exact test. Otherwise, conventional χ^2 tests were used. Means were compared by the t test.

Results

There were 68 patients with conjunctival melanoma who were evaluated and treated: all were white. Of the 68 conjunctival melanomas, 37 (54%) involved the right eye, 31 (46%) the left eye, and none were bilateral. The tumour either appeared as a new conjunctival lesion or a change (increase in pigmentation or size) in a previously static conjunctival lesion as noted by the patient or the ophthalmologist. The mean follow up was 7·5 years (range 0·4–28·3 years; median, 6·8 years).

Among the 68 patients with conjunctival melanoma there were 43 patients (65%) who were treated initially at another institution and referred to us for evaluation and further treatment because of the histopathological diagnosis of conjunctival melanoma. Twenty five patients (35%) were evaluated and treated initially at our institution by us using our standard techniques.[16] To ensure that there was no bias in our analysis, we elected to evaluate this subgroup of 25 patients separately in order to determine the clinical parameters that were significantly associated with local recurrence and metastasis and compare this with the total group of 68 patients.

The presumed origin of the conjunctival

melanomas had been categorised by our pathology department on the basis of histological criteria previously described in the literature.[7 14] From a histological standpoint, 38 (56%) of the conjunctival melanomas arose from primary acquired melanosis (PAM), 18 (26%) from pre-existing naevus, and 12 (18%) from areas without any histological evidence of a pre-existing lesion (classified as de novo).

Table 1 Relation between development of recurrence and various clinical characteristics in 68 patients with histologically proved conjunctival melanoma. Data are not adjusted for difference between groups in members of years at risk

Subgroups	Number of patients: Recurrence n=38 (56%)	Number of patients: No recurrence n=30 (44%)	Degrees of freedom	Test statistic	p
Age (years) at symptoms:					
<40	10	6			
>40 to 60	11	7			
>60	17	17			
Mean (range)	56 (22–83)	60 (25–89)	66	$t=1\cdot01$	0·3
Age (years) at histology:					
<40	7	4			
>40 to 60	11	7			
>60	20	19			
Mean (range)	58 (22–84)	63 (31–89)	66	$t=1\cdot15$	0·2
Sex:					
Male	18	19			
Female	20	11	–	Fisher's exact test	0·2
Number of contiguous anatomical locations involved:					
One	20	16			
Two	13	13	1	Ordered $\chi^2=0\cdot17$	0·7
Three	5	1			
Clinical pigmentation:					
None	31	29			
Yes	7	1	–	Fisher's exact test	0·07
Type first treatment:					
Excision biopsy	35	17			
Excision biopsy + Cryotherapy	3	13	–	Fisher's exact test	0·001
Metastasis:					
None	26	28			
Yes	12	2	–	Fisher's exact test	0·02

Table 2 Relation between development of metastasis and clinical various characteristics in 68 patients with histologically proved conjunctival melanoma. Data are not adjusted for difference between groups in numbers of years at risk

Subgroups	Number of patients: Metastasis n=14 (21%)	Number of patients: Metastasis n=54 (79%)	Degrees of freedom	Test statistics	p
Age (years) at symptoms:					
<40	1	15			
>40 to 60	4	14			
>60	9	25			
Mean (range)	62 (40–79)	56 (22–89)	66	$t=1\cdot09$	0·3
Age (years) at histology:					
<40	0	11			
>40 to 60	4	14			
>60	10	29			
Mean (range)	64 (41–80)	59 (22–89)	66	$t=1\cdot01$	0·3
Sex:					
Male	7	30			
Female	7	24	–	Fisher's exact test	0·8
Number of contiguous anatomical locations involved:					
One	8	28			
Two	3	23	1	Ordered $\chi^2=0\cdot03$	0·9
Three	3	3			
Clinical pigmentation:					
None	2	6			
Yes	12	48	–	Fisher's exact test	0·3
Type first treatment:					
Excision biopsy	12	40			
Excision biopsy + Cryotherapy	2	14	–	Fisher's exact test	0·5
Recurrence:					
0 Recurrence	2	28			
≥1 Recurrences	12	26	–	Fisher's exact test	0·015

AGE OF PATIENT

The ages of patients at the time of clinical onset of conjunctival melanoma are shown in Tables 1 and 2. The age ranged from 22 to 89 years with a mean of 57 years. Sixteen patients (24%) were younger than 40 years, 18 (26%) were between 40 and 60 years, and 34 (50%) were older than 60 years. There was no statistical correlation between age at onset of symptoms and the development of eventual melanoma recurrence or metastasis.

The ages of the patients at the time of histological confirmation of the conjunctival melanoma are shown in Tables 1 and 2. Eleven (16%) were less than 40 years old, 18 (26%) between 40 and 60 years, and 39 (58%) more than 60 years. The mean age at the time of histological diagnosis was 60 years (range 22–89 years). The mean interval between the initial recognition of the tumour and the initial resection was 2·6 years. There was no significant relation between delay in surgical excision and recurrence or metastasis. The age of the patient at the time of histological confirmation was not a statistical indicator of melanoma recurrence or metastasis.

RACE

All patients were white. There were no black or oriental patients with conjunctival melanoma in this series.

SEX

Of the 68 patients, 37 (54%) were male and 31 (46%) were female. Among the 37 men, 18 (49%) experienced recurrences and seven (19%) developed distant metastases. Among the 31 women, 20 (65%) developed recurrences and seven (23%) developed distant metastases. There were no statistical correlation between the sex of the patient and the development of recurrence or metastasis (Tables 1, 2).

ANATOMICAL LOCATION AND EXTENT

All of the conjunctival melanomas were solitary tumours. At the time of initial surgery, 36 of the tumours were confined to one anatomical location (Tables 3 and 4). Thirty one involved only the bulbar conjunctiva, two were confined to the palpebral conjunctiva, two were confined to the caruncle, and one was confined to the fornix.

Twenty six of the conjunctival melanomas were more extensive and involved more than one contiguous anatomical location. Twenty were located in the bulbar conjunctiva with corneal extension, four in the bulbar conjunctiva with forniceal extension, and two in the bulbar conjunctiva and caruncle.

Four patients had contiguous involvement of the bulbar conjunctiva, caruncle, and eyelid margin. Two patients had contiguous involve-

Table 3 Relation between the development of recurrence and the initial anatomical location of conjunctival melanoma in 68 patients

Extension	Anatomical site	Number of patients: Recurrence Number	%	No recurrence Number	%
1 Location	Bulbar conjunctiva	17	44·8	14	46·8
	Palpebral conjunctiva	1	2·6	1	3·3
	Caruncle	1	2·6	1	3·3
	Fornix	1	2·6	0	0·0
		20	52·6	16	53·4
2 Contiguous locations	Bulbar conjunctiva+cornea	10	26·3	10	33·3
	Bulbar conjunctiva+caruncle	1	2·6	1	3·3
	Bulbar conjunctiva+fornix	2	5·3	2	6·7
		13	34·2	13	43·3
3 Contiguous locations	Without lid margin involvement	2	5·3	0	0·0
	With lid margin involvement	3	7·9	1	3·3
		5	13·2	1	3·3
	Total	38	100%	30	100%

Table 4 Relation between the development of metastasis and the initial anatomical location of conjunctival melanoma in 68 patients

Extension	Anatomical site	Number of patients: Metastasis Number	%	No metastasis Number	%
1 Location	Bulbar conjunctiva	5	35·8	26	48·1
	Palpebral conjunctiva	1	7·1	1	1·9
	Caruncle	1	7·1	1	1·9
	Fornix	1	7·1	0	0·0
		8	57·1	28	51·9
2 Contiguous locations	Bulbar conjunctiva+cornea	1	7·1	19	35·2
	Nasal conjunctiva+caruncle	1	7·1	1	1·9
	Bulbar conjunctiva+fornix	1	7·1	3	5·5
		3	21·3	23	42·6
3 Contiguous locations	Without lid margin involvement	1	7·1	1	1·9
	With lid margin involvement	2	14·3	2	3·7
		3	21·4	3	5·6
	Total	14	100%	54	100%

ment of the bulbar, forniceal, and palpebral conjunctiva without extension to lid margins (Tables 3, 4).

Because of the small number of patients displaying each specific conjunctival melanoma location, no statistical conclusions could be reached regarding the relation between the development of recurrence and metastasis and the initial location of conjunctival melanoma.

The development of tumour recurrence or metastasis was not statistically related to the number of anatomical sites initially involved (Tables 1, 2). Although patients with simultaneous involvement of more than one site at the time of the initial evaluation had a higher incidence of distant metastasis, this was not statistically significant.

CLINICAL PIGMENTATION

Among the 68 patients, 60 (88%) displayed clinical signs of brown pigmentation within the conjunctival melanoma and 28 (12%) were completely amelanotic on initial examination. Thirty one (52%) of the pigmented conjunctival melanomas developed recurrences and 11 (18%) were associated with subsequent metastatic disease. Although there was a slight tendency towards increased recurrences in patients with pigmented tumours, the trend was not statistically related to the development of metastases (Table 2).

TYPE OF TREATMENT

Of the 68 patients with conjunctival melanoma, 52 (76%) were treated initially with excisional biopsy only and 16 (24%) were treated initially with a combination of excisional biopsy and cryotherapy. Forty three patients (65%) were initially treated in other institutions before being referred to us for further management. This accounted for the high number of patients initially treated with excisional biopsy alone, without cryotherapy. Most of the patients treated by us since the mid 1970s have received cryotherapy at the time of excision of the tumour.

By including all patients in our analysis we found that the type of treatment was statistically associated with the development of recurrence ($p=0·001$) (Table 1). Those patients treated with excisional biopsy without supplementary cryotherapy had a higher incidence of local tumour recurrence in comparison with those treated with a combination of excisional biopsy and cryotherapy. The type of the initial treatment was not statistically associated with metastatic conjunctival melanoma (Table 2). No patients were managed initially by orbital exenteration or radiotherapy.

By analysing the subgroup of 25 patients treated exclusively in our department, we found that the type of initial treatment was also statistically associated with development of local recurrence ($p=0·005$) (Table 5). Patients who were initially managed with wide excision and cryotherapy were less likely to develop local recurrence. We also found that the type of initial treatment was not statistically predictive of distant metastasis (Table 6).

RECURRENCE

Of the 68 patients, 30 (44%) had no recurrences and 38 (56%) experienced one or more than one recurrence. Twenty two patients (32%) experienced more than one recurrence. The mean time interval between the first treatment and the first recurrence was 2·5 years (range 0·4–14 years). Among the 22 patients with two or more recurrences, 12 have had five or more recurrences. One patient with PAM experienced 13 recurrences of a very anaplastic tumour over a 13 year course and has still not developed distant metastasis.

Among the 16 patients initially treated with a combination of excisional biopsy cryotherapy, three (18%) developed local recurrence. Among the 52 patients initially treated with excisional biopsy alone, 35 (68%) developed local recurrence. This difference was significant ($p=0·001$, Fisher exact test).

The presence of one or more conjunctival melanoma recurrence was statistically associated with an increase incidence of distant metastasis ($p=0·015$) (Table 2). The time interval of 29 months (range 3–168 months) between the initial tumour excision and the development of recur-

Table 5 Relation between development of recurrence and various clinical characteristics in 25 patients with histologically proved conjunctival melanoma managed exclusively in our department. Data are not adjusted for difference between groups in numbers of years at risk

Subgroups	Number of patients: Recurrence n=9 (36%)	No recurrence n=16 (64%)	Degrees of freedom	Test statistic	p
Type of first treatment:					
Excision biopsy	6	4			
Excision biopsy+ Cryotherapy	3	12	–	Fisher's exact test	0·05
Metastasis:					
None	7	16			
Yes	2	0	–	Fisher's exact test	0·12

Table 6 Relation between development of metastasis and various clinical characteristics in 25 patients with histologically proved conjunctival melanoma managed exclusively in our department. Data are not adjusted for difference between groups in numbers of years at risk

Subgroups	Number of patients: Metastasis n=2 (8%)	No metastasis n=23 (92%)	Degrees of freedom	Test statistics	p
Type of first treatment:					
Excision biopsy	2	8			
Excision biopsy+ Cryotherapy	0	15	–	Fisher's exact test	0·15
Recurrence:					
0 Recurrence	0	16			
≥Recurrences	2	7	–	Fisher's exact test	0·12

rence was not a statistical risk factor for a higher incidence of distance metastasis.

In the subgroup of 25 patients treated exclusively in our institution, the presence of one or more conjunctival melanoma recurrence was statistically not associated with development of metastasis (Table 6).

TREATMENT OF RECURRENCES

The treatment of the first recurrence included excisional biopsy in 21 cases (55%) combination of surgical excision and cryotherapy in 15 cases (40%), application of radioactive plaque and orbital exenteration in single cases each. Further recurrences were managed by excisional biopsy associated with cryotherapy. However, three subsequent recurrent cases were managed by haematoporphyrin photoradiation, three by radioactive plaques, and six by orbital exenteration. Of those treated by radiotherapy, none experienced further recurrences while all three of those treated by haematoporphyrin photoradiation developed subsequent recurrences. Among the seven patients treated by orbital exenteration (one for the first recurrence and six for the subsequent recurrences), four died of metastases over a mean of 2·1 years after the orbital exenteration (range 0·9–3·4 years), and three are free of distant metastases after a mean follow up of 11·7 years.

Table 7 Sites of first metastasis of conjunctival melanoma

Site of spread	Number of cases*
Preauricular nodes	5
Cervical nodes	2
Brain	4
Lung	3
Liver	1
Bone	1

*Two cases presented with simultaneous preauricular and cervical lymph node metastases

METASTASES

None of our patients had recognisable metastatic disease at the time of original diagnosis. Of the 68 patients, 54 (79%) are alive without metastasis and 14 (21%) have developed metastasis. The first sites of the metastasis was preauricular lymph nodes in five cases (40%), brain in four cases (33%), lung in three cases (21%), and liver and bone in single cases each (Table 7). The mean length of time between the histologically proved diagnosis of conjunctival melanoma and the onset of metastasis was 3·6 years (range, 0·6–7·9 years). The 12 patients (86%) who died from metastatic conjunctival melanoma thus far succumbed over a mean of 4·4 years (range, 1·6–8·1 years) after the conjunctival melanoma was initially treated. The time interval between the onset of metastatic disease and death was a mean of 8·6 months (range, 0·5–30 months). Two patients were still alive at 14 and 22 months respectively after the initial presentation of metastatic disease with a total follow up from the initial diagnosis of the conjunctival melanoma of 2·3 and 7·2 years respectively.

MORTALITY

Twenty patients (29%) died during the total mean follow up period of 7·5 years. Twelve patients (18%) died from metastatic melanoma and eight (12%) died from unrelated causes. The time from the histological confirmation of conjunctival melanoma to melanoma related death was 4·4 years (range, 1·6–8·1 years). The non-melanoma deaths were from cardiovascular disease (six patients), pneumonia (one), and breast carcinoma (one).

ANALYSIS OF RESULTS

Because patients had been followed for varying lengths of time, the life table method was used to estimate the proportion of patients developing recurrence and metastasis. The same method was used to estimate the survival rate of patients each year after the diagnosis by analysing metastatic and non-metastatic related mortalities. The global cumulative survival rate was 77% for the first 5 years. The cumulative survival rate of patients treated with excisional biopsy only (77%) was comparable with that of patients treated with combination of excisional biopsy and cryotherapy (75%). The data were analysed separately with regard to the development of local recurrence and to the development of distant metastasis (Tables 1, 2).

Table 1 shows the relationship between development of recurrence and various clinical and histological parameters. The development of local recurrence of conjunctival melanoma was not statistically related to the following parameters: age of the patient at the time of clinical recognition, age at the initial histological confirmation, sex of the patient, and number of sites of contiguous involvement. There was some suggestion of a higher risk of recurrence with clinically pigmented conjunctival melanomas but the probability was not significant (p=0·07) in comparison with patients displaying non-pigmented tumours.

The only features that were statistically associated with tumour recurrence were the type of treatment employed initially (p=0·001) and the eventual development of subsequent metastatic disease (p=0·02). Patients who were managed by combined excisional biopsy and cryotherapy had a statistically significant lower risk of local recurrence than those who had

Table 8 Comparisons of life table values (actuarial method) of cumulative risk to develop metastasis for different subgroups

	Cumulative risk (SE) after					
	1 Year	p	3 Years	p	5 Years	p
Type of first treatment:						
Excision biopsy	2·0% (2·0%)		13·1% (5·0%)		18·1% (5·8%)	
Excision biopsy	0·0% (0·0%)	NS	7·7% (7·4%)	NS	19·3% (12·6%)	NS
Recurrence;						
without recurrence	0·0% (0·0%)		5·0% (4·9%)		11·1% (7·5%)	
with ≥1 recurrence	2·7% (2·6%)	NS	16·5% (6·1%)	NS	22·4% (7·0%)	NS
Recurrence						
without recurrence	0·0% (0·0%)		5·0% (4·9%)		11·1% (7·5%)	
with 1 recurrence	2·7% (2·6%)	NS	16·5% (6·1%)	NS	22·4% (7·0%)	NS
with >1 recurrence	0·0% (0·0%)*		13·6% (7·3%)		18·2% (8·2%)	

Comparisons were made using the *t* test. Where there were more than two groups, the Bonferroni correction for multiple comparisons was applied.

excisional biopsy only. Likewise, patients who developed metastasis were significantly more likely to have had local recurrence before metastasis.

When we analysed the subgroup of 25 patients treated exclusively at our institution, we found that tumour recurrence was statistically associated with the type of initial treatment (p=0·05) (Table 5). Patients treated with excisional biopsy and cryotherapy had a significant lower risk of local recurrence that those treated by excisional biopsy alone.

The same statistical analysis with respect to the development of metastasis is shown in Table 2. The development of distant metastasis was not statistically related to the age of the patient at initial symptoms, age at initial histological diagnosis, sex of patient, number of contiguous sites involved, evidence of clinical pigmentation of the tumour, the type of initial treatment. The only feature that was statistically associated with subsequent metastatic disease was the presence of one or more recurrence (p=0·015) when data are not adjusted for difference between groups in numbers of years at risk. Patients developing one or more than one recurrence had a statistically higher risk to develop distant metastasis in the course of their disease than those who had no recurrence.

When we analysed the subgroup of 25 patients treated exclusively in our institution, we found that development of distant metastasis was statistically not associated with tumour recurrence (Table 6).

The cumulative risk to develop metastasis for different clinical and histological variables is presented in Table 8. We used the *t* test to compare life table values calculated by the actuarial method and applied the Bonferroni correction for multiple comparisons where there was more than a single comparison. We found that the type of initial treatment, the development of tumour recurrence and the number of local recurrences were not significantly associated with a cumulative risk for metastatic disease.

Discussion

Several authors have reviewed the clinical[3-5 17-19] and histopathological[4-11 13 15 20 21] features of conjunctival melanoma and these studies have advanced our understanding of pigmented lesions of the conjunctiva. However, there is still uncertainty regarding clinical and pathological prognostic factors associated with conjunctival melanoma.

Clinical prognostic factors for metastasis have been reported in various series as patient's age at the time of excision,[11] location of the tumour,[11 13] size of the tumour,[12 13] histological origin of the melanoma from primary acquired melanosis (PAM),[1 3] and histological presence of PAM sine pigmento.[4] On the other hand, the presence of PAM[5 18] or naevus[2 5 6] with conjunctival melanoma was shown by others to have no worsened prognosis for metastasis or death.

Our study on the clinical risk factors for conjunctival melanoma is the largest statistical evaluation of the clinical factors of this disease. The mean follow up of 7·5 years (median, 6·8 months) constitutes an appropriate period of follow up. Our goals were to determine the significant clinical risk factors predictive of local tumour recurrence and distant metastasis.

Conjunctival melanoma occurs with greatest frequency in patients over 50 years of age.[3 4 18] There have been few reports on childhood conjunctival melanoma and in patients under age 20 years.[22 23] In our study, the mean age of the patients at the time of clinical recognition was 58 years and at the time of histological diagnosis was 60 years. There were no patients under 20 years of age and we found that the age at the clinical and histological diagnosis was not statistically associated with greater local tumour recurrence or metastasis.

The anatomical location or extent of the conjunctival melanoma was not statistically related to recurrence or metastasis as evaluated in our series. Although we found some evidence that the horizontal extent of the lesion was more important in predicting recurrence than the tumour location, this was not statistically significant. A similar observation was made by Crawford and associates.[11]

According to histopathological observation, most of the conjunctival melanomas arose from PAM (56%), while 26% arose from naevus and 18% de novo. Both Reese[1] and Jakobiec *et al*[4] have reported similar findings. Although 35% of the conjunctival melanomas in our series had clinically detectable PAM associated with the lesion, 56% were shown to have histopathologically detectable PAM. PAM is occasionally quite subtle or difficult to detect clinically over or adjacent to a pigmented conjunctival melanoma, especially if the PAM is minimally pigmented.

The only risk factors statistically associated with local tumour recurrence were the primary method of tumour management and the eventual development of distant metastasis. Those patients treated with excisional biopsy and supplemental cryotherapy had significantly less recurrence than those treated with excisional biopsy alone. For this reason, we included in this study patients with a follow up as short as 0·4 years because tumour recurrence was documented in two cases as soon as 3 months after initial treatment. Patients who presented distant metastasis had a higher incidence of local tumour recurrence during their metastatic process.

Although our retrospective study suggested that combined excisional biopsy and cryotherapy

were associated with a better prognosis, this observational study did not involve randomisation to treatment groups. Morever, a relatively large number of patients were initially treated by different surgeons over several years and methods of excision may have varied considerably. This could also explain the bias between the number of patients initially treated with excisional biopsy alone and that of patients treated with excisional biopsy and cryotherapy. However by analysing the subgroup of patients treated exclusively in our department with a standardised method,[16] the findings are similar regarding the benefit of combined surgical excision and cryotherapy over reducing the incidence of local tumour recurrence. Contrary to the significant association of local tumour recurrence and distant metastasis found in the total group of 68 patients, we did not find in the subgroup of 25 patients a significant predictive effect of tumour recurrence on the incidence of distant metastasis. This can possibly be explained by the higher percentage of patients treated with combined excisional biopsy and cryotherapy compared with the lower percentage of patients treated with excisional biopsy alone in this subgroup. Recognising the benefit of combined treatment, the lower incidence of tumour recurrence in this subgroup is probably associated with a lower risk of metastasis.

In the past, there has been controversy regarding the optimal management of conjunctival melanoma. Reese recommended orbital exenteration with prophylactic radical neck dissection for melanoma arising from naevus and from PAM.[1] Others have suggested complete local excision of the tumour.[10] Lederman[14] advocated local radiotherapy and Zografos *et al*[18] discussed indications for proton beam irradiation. However, Lommatsch *et al* reported no difference in prognosis when comparing conjunctival melanomas treated with surgical excision associated with brachytherapy versus cryotherapy.[12]

More recently, combined surgery and cryotherapy for conjunctival melanoma have been advocated by several authors over the past 10 years.[4 24-28] The selective effectiveness of cryotherapy (at temperatures below −20°C) for melanocytic proliferation of the conjunctiva has been demonstrated both clinically and ultrastructurally.[4 24-28] Our study suggests that local excision and supplemental cryotherapy is more effective in the management of conjunctival melanoma than excision alone. Theoretically, microscopic fronds of residual tumour cells or premalignant cells are controlled by the application of cryotherapy after the main tumour is excised.

Distant metastasis occurred in 21% of the 68 patients over a 7·5 year mean follow up and tumour related deaths occurred in 18%. Folberg and associates[6] reported a 26% death rate over 8 years of follow up and others[4 12 18] have found similar findings. The only significant risk factor associated with metastasis in our series was the presence of one or more than one recurrence when data were not adjusted for number of years at risk.

We prefer wide microsurgical tumour excision with a true 'no touch' technique – that is, excision of the tumour without touching the tumour itself and only handling the normal tissue margin that is removed with the tumour. Conjunctival melanoma is often friable and adheres to instrument tips. Care must be taken to handle the tissue and swab the site with extreme caution or tumour seeding may occur. Once the tumour is completely removed, double freeze thaw cryotherapy should be applied to the conjunctival margins and areas of PAM with care not to freeze the sclera in the ciliary body region.[16] This can be done by lifting the surrounding conjunctiva with forceps. The lesion should be carefully placed flat on a piece of paper or cardboard and then gently put in fixative in the operating room.[16] This facilitates histopathological assessment of margins.

The management of melanoma of the conjunctiva is an important factor in preventing recurrence and eventual metastasis of this malignant tumour. Our study has suggested that the primary management of these patients is crucial and that a carefully planned wide excision of the tumour and supplemental cryotherapy are beneficial in reducing the risk for melanoma recurrence and subsequent distant metastasis.

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