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A study of thin (< 1.5 mm) malignant melanomas with poor prognosis

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SUMMARY. **555 cases of malignant melanoma less than 1.5 mm in depth were studied. 30 recurred locally or metastasised during follow-up. The width and depth of excision was similar in those with and without recurrence. There were no local recurrences in tumours < 1.0 mm which had been completely excised, irrespective of the width of excision. Other variables, the size of the primary tumour ($p < 0.03$), the depth of uninvolved dermis deep to the lesion ($p < 0.01$), the Clark level ($p < 0.03$) and the presence of lesional regression ($p < 0.001$), identify a sub-group of thin melanomas which have a poor prognosis irrespective of local treatment.**

In the 1960's Mehnert and Heard introduced the concept of levels of invasion as a prognostic indicator for cutaneous malignant melanomas,[1] this was further refined by Clark *et al.* in 1969[2] and in 1970 Breslow published results showing cross sectional thickness to be of major prognostic significance.[3] Today, Breslow depth is generally accepted as the most sensitive prognostic indicator.[4,5] Many studies have divided melanomas into 3 groups, *i.e.* those measuring less than 1.5 mm having a good prognosis, those measuring 1.5–3.5 mm an intermediate and those greater than 3.5 mm a poor prognosis.[6,7] The extent of primary surgery and any adjuvant treatment has been determined according to these criteria.[5,8]

Increased public awareness of the importance of melanomas, together with health education programmes, has meant that a larger proportion of patients are presenting with the better prognostic group of thinner lesions, *i.e.* measuring less than 1.5 mm.[9] Although this has reduced the requirement for mutilating surgery, and has greatly improved the outlook, a small percentage of thin lesions will still metastasise.[10] It is therefore necessary to discover additional factors which may allow a refinement of prognosis in thin lesions. In particular it is important to assess whether differences in the primary surgical management can account for those patients with progressive disease in what should be a good prognostic group. In this paper clinical details and correlation with histological findings are described in 30 patients with melanomas < 1.5 mm who developed recurrent or metastatic disease. The histological details of this study have been reported in detail elsewhere.[11]

Patients and methods

The registration of all primary cutaneous melanomas by the Scottish Melanoma Group (SMG), founded in 1978/9, provides accurate information from over 95% of melanoma patients in Scotland. Clinical and pathological details are registered at the time of presentation and subsequent follow-up requested annually from both clinicians and general practitioners. Further clinical details were obtained in this study by contacting the relevant clinicians and general practitioners, and reviewing case records.

Using this data base it was possible to identify all patients with cutaneous melanoma in the East of Scotland, with tumours less than 1.5 mm in depth, who had recurrent disease. Clinical details including age, sex, size and anatomical location of the primary melanoma were documented. Width of excision margins, method of skin closure and if lymph node dissection was performed were also recorded. In addition, details of the timing and sites of recurrent disease were recorded, as was the date and cause of death if this occurred. In all cases the histology of the primary lesion was studied by reviewing the original slides (an average of 3–4 per case) and in each case taking deeper levels of the original blocks to confirm the depth of invasion.

Those patients diagnosed between 1979 and 1987 who subsequently developed metastases/recurrent disease during follow-up were compared with a randomly selected control group of patients with melanomas < 1.5 mm diagnosed in the same period, but who were disease free after a minimum of 5 years.

Details of the two groups were analysed using chi-squared tests, and Students' test.

Results

In the East of Scotland, in the 8-year period from 1979–1987 there were 1299 malignant melanomas diagnosed; 555 of these measured less than 1.5 mm and 38 of these were registered as having recurrent disease. Review of the histology of these 38 cases resulted in the exclusion of 8 cases from further comparisons. In 1 case the documented recurrence was actually an inflammatory lesion at the site of a skin

graft to the primary defect. When deeper levels of the primary lesions were examined it was found that 4 cases were actually greater than 1.5 mm. Typographical errors in documentation had meant that a further two thick lesions had been wrongly classified as being less than 1.5 mm in depth and in one patient with metastatic disease there were two primary lesions, one of which measured more than 1.5 mm.

There were, therefore, 30 patients with melanomas < 1.5 mm who had either locally recurrent or metastatic disease. Throughout the period of study there was no uniform treatment policy but all patients did undergo excision of the primary lesion with either direct closure or split skin grafting. Four patients with metastatic disease had lymph node involvement at the time of presentation; these patients underwent regional lymph node dissection at this time but no other patients received immediate lymph node dissections.

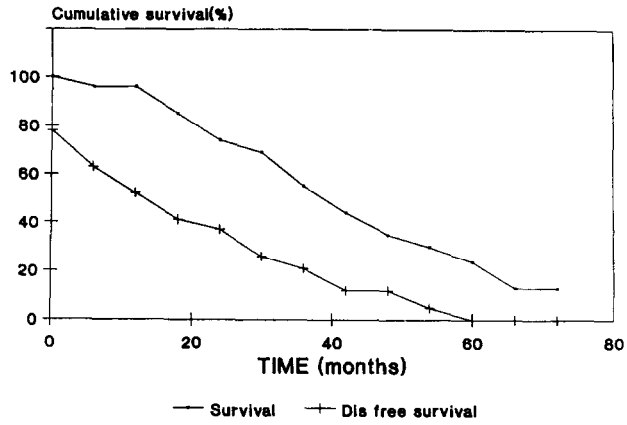

Fig. 1

Figure 1—Cumulative probability of disease free and overall survival in patients with malignant melanomas (< 1.5 mm) who developed recurrence.

Local recurrence

Local recurrence occurred in 4 patients, including 2 patients in whom there was histological evidence of atypical melanocytic cells at the excision margins. These two cases were situated on the face and on the heel, where there may have been a tendency to limit the extent of primary resection. In one of the remaining cases there was marked histological regression, making an accurate assessment of the tumour depth difficult. This lesion had been excised with a 3 cm skin margin. The fourth local recurrence was from a primary situated on the nose; this measured 1.0 mm and had been excised with 1 cm skin margins. There were, therefore, no local recurrences in tumours which were adequately excised and measured less than 1.0 mm in depth.

Metastatic disease

There were 26 cases of thin melanomas with metastatic disease, including the 4 patients with lymph node involvement at presentation *i.e.* stage II disease. Of these 4 patients there was no further evidence of disease following regional node dissection in one case, but in the other 3 there has been disease progression, with death between 3 and 71 months following surgery. In all but two of the other cases, the regional lymph nodes were the site of initial recurrent disease, occurring between 1 and 72 months (median 18 months) following surgery. In 2 patients there were in-transit skin deposits in addition to nodal disease and in 1 of these there were also pulmonary metastases. In total, 18 patients in this group with metastatic disease have died, one from a cerebrovascular accident, the remainder related to their melanomas between 22 and 77 months (median 42 months) after surgical treatment (Fig. 1).

There was no difference between the patients with recurrent disease and the controls in terms of excision margins (mean width of excision 1.7 cm and 1.6 cm in the cases and the controls respectively) or method of closure, except that in the group of recurrent tumours there were the two patients with local recurrence and evidence of tumour at the excision margins (Table 1).

Table 1 Width of excision margins and methods of skin closure in patients with progressive disease and control patients

	< 1 cm		*1–3 cm*		*< 3 cm*		*Mean excision margin*
Margins	*dir*	*graft*	*dir*	*graft*	*dir*	*graft*	
Cases*	7	2	7	6	2	4	1.6 cm
Controls	12	8	4	8	—	8	1.7 cm

* 2 other cases had involved margins

Table 2 A comparison of histological features of patients with progressive disease and controls, who were disease free at 72 months

	Cases (N = 30)	*Controls (N = 40)*	*Significance*
Follow up† (months)	97 (22.7)	105 (30.4)	
Breslow depth (mm)	0.84	0.75	N/S*
Size (cm^2)	3.10	2.06	$p < 0.005$*
Depth of uninvolved dermis	0.84	1.57	$p < 0.001$*
Clark level II	2	13	
III	9	22	
IV	7	5	$p < 0.003$*
Regression			
present	11	1	$p < 0.001$**
absent	7	39	

* Student's test, **, chi squared test
† mean (s.d.)

Details of the factors found to be statistically different between thin melanomas with locally recurrent and metastatic disease compared with controls (disease free after a minimum of 5 years follow-up) are shown in Table 2. It is clear that although there was no difference in the Breslow depth of the tumours in each group, there were significant differences between the groups in terms of lesion size, depth of uninvolved dermis deep to the tumour, Clark level, and presence of regression in the primary tumour. The latter 3

factors have been previously shown to be independent predictors of survival.[11]

Discussion

Allen and Spitz first suggested a correlation between the thickness of melanomas and prognosis but they also noted that a number of clinically innocuous lesions behaved paradoxically and gave rise to widespread metastases.[12] Although Breslow felt that metastases did not occur from melanomas unless they reached a certain thickness,[3] many authors have since described metastases from thin melanomas,[13–15] and in the current series 6% of patients with melanomas less than 1.5 mm were found to have, or develop, metastases. Although the Breslow depth is recognised as the single most important prognostic factor for melanomas in general, it is clear that for thin lesions other factors are of importance.[16] Treatment factors have been investigated in this study and apart from 2 cases of incomplete excision there was no difference between the extent of skin excision in the patients with recurrent disease and in the controls.

Throughout the period studied there was no uniform policy about the width of excision margins and the extent of surgical excision remains controversial.[8] The "5 cm rule" recommended by Handley[17] has been challenged and in a WHO trial there was no difference between the survival of patients with melanomas < 2 mm who were treated by 1 cm or 3 cm skin excisions.[18] This trial has recently been criticised as having an inadequate follow-up period in view of the findings of Crowley and Sieglat that 70% of recurrent disease after a period of 10 years was in the skin surrounding the local excision.[8,19] This is unlikely, however, to represent residual disease and in view of the cosmetically inferior results of wide excision a 1 cm excision margin is recommended in patients with thin melanomas. It has also been shown that primary skin closure does not compromise cure rates[20] and in the present study there was no difference between the cases and the controls regarding the method of wound closure.

Specimens should be appropriately reviewed and further excision considered if the clinical impression differs from the pathology report, if there is histological evidence of involvement of the skin margins, or if significant regression makes an assessment of depth difficult. The thickest part of the tumour should always be blocked and it is particularly important in the case of thin lesions that the whole tumour is embedded. Histological features of thin lesions which metastasise rather than treatment options appear to be the most significant determinants of poor prognosis and we have previously shown lesional regression to be the most significant feature predicting a poorer outlook.[11] Metastases were also more common in patients whose tumours reached Clark level IV and who had a relatively thin layer of uninvolved dermis deep to the tumour. Kelly *et al.* previously described a subgroup of aggressive thin melanomas of Clark level IV, involving the reticular dermis,[21] and Briggs *et al.* suggested that melanomas with a relatively thin width of uninvolved dermis relative to the tumour thickness had a poor prognosis.[15] It is possible, therefore, that the microenvironment of the reticular dermis facilitates permeation of cells both locally and into lymphatics. It would be expected, therefore, that thin melanomas occurring in areas with thin skin, such as the head and neck, might be expected to have a worse prognosis than those lesions from areas such as the back, where the skin is thicker. We have not, however, been able to demonstrate a relationship between site and prognosis in this series.

The histological features of significance identified in this study are independent of local treatment and it is therefore unlikely wide local excision would be of benefit to patients showing them in their tumours. They should be carefully followed up for signs of recurrent disease. Further prospective studies are required to quantify the risks associated with each of these features.

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