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Prognostic value of tumour thickness in cutaneous malignant melanoma

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SUMMARY The relation between survival and histological features in 91 patients with malignant melanoma was studied and the results were analysed by Clayton's method for interpretation of censored survival data. There was a significant correlation between tumour thickness and survival. The risk of dying from malignant melanoma after 10 years of follow up was less than 15% if the primary tumour was less than 1·5 mm thick but more than 80% if the lesion was thicker than 8 mm.

The type of melanoma, level of invasion, mitotic rate, and presence of ulceration also correlated with survival, but these variables are related to tumour thickness.

The clinical course of cutaneous malignant melanoma is variable.[1,2] Some patients are apparently cured by simple excision but similar treatment in others is followed by the development of metastases and early death. This had led to investigation of histological features which may have prognostic significance. The histological type of melanoma[3–6] mitotic rate,[7–9] extent of dermal invasion (Clark's level),[3,4,10,11] degree of lymphocytic infiltration[12,13] and the presence of ulceration[8,10,14] have all been shown to correlate with survival. Interpretation of some of these features is subjective and although they have statistical meaning their value when dealing with individual patients is often doubtful. A more objective measurement is necessary to help predict prognosis. Breslow[11] measured the diameter, thickness and volume of cutaneous melanomas and established that the thickness of the neoplasm, irrespective of its type, diameter or calculated volume, was a useful guide to subsequent behaviour. Further study of series of melanoma patients in America,[14,15] Canada,[13] Australia[9] and Scandinavia[16] have confirmed this finding but there is still need to define the risks of death or tumour recurrence in relation to various thickness bands. We have conducted a retrospective study of patients with malignant melanoma to assess the value of tumour thickness and other histological features in predicting the outcome of the disease.

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Patients and methods

PATIENTS

The records of 116 patients with cutaneous malignant melanoma treated at Northwick Park Hospital or Mount Vernon between 1949 and 1979 were examined. From these, patients with a single primary lesion of skin away from the subungual region and without evidence of metastasis at presentation were studied. Lentigo maligna without invasive disease was excluded. There were 91 patients for whom adequate pathological material and follow-up data were available.

METHODS

Histological sections

Paraffin-embedded, haematoxylin and eosin stained sections were examined in each case. The material was not considered adequate unless well orientated vertical sections through the main tumour mass were available for study. Melanomas showing marked histological regression, according to the criteria of McGovern[17] were also excluded.

Tumour thickness

A Joyce Loebl "Magiscan" image analysis system was used to measure the thickness of each tumour using an interactive programme (Fig. 1). Measurement was made from the granular layer of the epidermis to the deepest part of the tumour arising from the surface

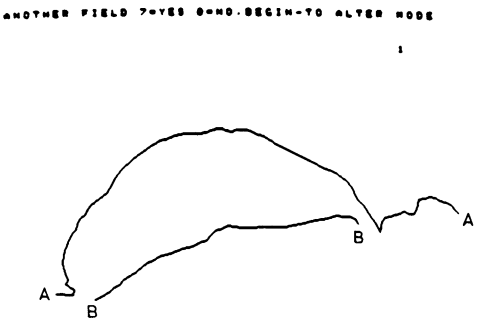

Fig. 1 *The pathologist traces the image of the cutaneous melanoma on the video screen of the "Magiscan" using an electronic light pen. Line A–A delineates the granular layer of the skin, line B–B is the deepest extension of the tumour. Maximum tumour thickness is computed between lines A–A and B–B.*

epithelium, at right angles to the surrounding skin.[18] If the melanoma was ulcerated, measurements were made from the superficial tumour cells in the ulcer base. When there was a dense lymphocytic infiltrate intermingled with the tumour cells the level of tumour penetration was checked on the microscope as the measuring proceeded. The microscope objective used in the system was × 1 and the Magiscan was calibrated on each occasion before use.

Level of invasion

The invasion into the dermis was graded using Clark's levels:

Level I—malignant melanoma confined to the epidermis.

Level II—melanoma invading into the papillary dermis but not extending to the papillary-reticular dermal interface.

Level III—melanoma impinging upon the papillary reticular dermal junction but without significant invasion into the reticular dermis.

Level IV—melanoma infiltrating into the reticular dermis.

Level V—melanoma invading the subcutaneous fat.

Mitotic rate

The mitotic rate was determined by the method of McGovern *et al*[19] except that at least 20 high power fields (× 400) were examined, or in smaller melanomas the entire section was assessed. Three grades of mitotic activity were recognised:

Grade I—an average of less than one mitosis per five high power fields.

Grade II—between two and five mitoses per five high power fields.

Grade III—more than five mitoses per five high power fields.

Inflammation

The intensity of the lymphocytic infiltration was assessed according to Thompson[12]:

Marked—intense lymphocytic infiltration of the whole lesion or of the whole of its base forming a complete basal zone of inflammation.

Intermediate—moderate and easily recognised lymphocytic infiltration but in which the basal zone was incomplete.

Slight—little or no lymphocytic infiltration in a major portion of the tumour.

Other histological features

The variety of melanoma was noted in each case together with the presence of ulceration, and evidence of vascular or lymphatic invasion.

STATISTICAL ANALYSIS

It was anticipated that the incidence rates of both death and tumour recurrence would be related to tumour thickness and to time since diagnosis/treatment. After some trial and error, a model was constructed which reflects such behaviour mathematically.

$$\lambda(t,\theta) = \mu\theta\exp(\beta_1 \log t + \beta_2[\log t]^2) \quad \text{... Equation 1}$$

where t = years of follow-up, θ = tumour thickness (mm), $\lambda(t,\theta)$ is death (or recurrence) rate in year t and μ, β_1 and β_2 are constants determined by fitting the model to the data. Equation 1 gives parallel time-curves which peak at time $\exp(-\beta_1/\beta_2)$, then tail off gradually. The height of the curve (risk) is proportional to the tumour thickness θ. $\lambda(t,\theta)$ is then related to the observed number of deaths (recurrences) $d(t,\theta)$, via the equation.

$$d(t,\theta) = T(t,\theta)\,\epsilon\,(t,\theta) \quad \text{..... Equation 2}$$

where $T(t,\theta)$ is the number of person-years of follow-up in year t for people whose tumour is of size θ and $\epsilon(t,\theta)$ is a random term. $d(t,\theta)$ is assumed to follow a Poisson distribution. Lambda (λ) is assumed to be constant during each year of follow-up but varies from year to year. Equations 1 and 2 may be fitted using the technique of Clayton[20] and the computer program GLIM 3.[21] It was also possible to test whether mitotic rate, inflammation or pigmentation had any additional effect on the prognosis, after taking thickness into account. By combining the incidence-rates $\lambda(t,\theta)$ of Equation 1 one can derive the survivorship functions $S(t,\theta)$ which is the probability that a patient whose tumour was θ mm will survive for at least t years, by forming the product of the one-year survival rates $\exp(-\lambda_t)$—that is,

$$S(t,\theta) = \prod_{j=1}^{t} \exp[-\lambda_j\theta]$$

Examples are shown in Fig. 5 for t = 2, 5 and 10 yr.

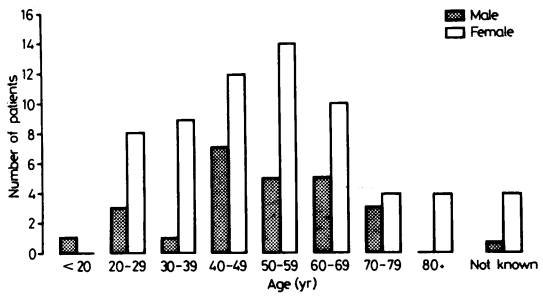

Fig. 2 *Age and sex distribution of malignant melanomas in patients of this study.*

Results

Twenty-six patients were men, with an average age of 49 yr; 65 were women with an average age of 50 yr (Fig. 2). The lower limb was the commonest site in females, and the trunk in males (Fig. 3). In most patients the initial treatment consisted of surgical excision, with or without skin grafting.

Thirty-four of the 91 patients died from metastatic malignant melanoma at times ranging from seven to 108 months after presentation (mean = 33 months). Not all the patients were followed up for the same length of time—that is, the data was "censored." However, Clayton's method[20] takes censoring into account when the death-rate model is fitted to the observed data.

Tumour thickness

Survival was closely associated with the thickness of the primary melanoma (Table 1). The model for death-rates fitted the data well, the constants β_1 and β_2 were significantly different from 0 ($p < 0{\cdot}01$) (Table 2) reflecting the rise and fall of the death/recurrence rate with increasing time since treatment. The residual variations in death-rate could be attributed to the effects of chance. The year of greatest risk of dying from melanoma, regardless of tumour thickness, occurred between 1·4 and 2·4 yr after presentation. This risk was about 31% for patients whose tumour was 8 mm thick, but only 10% when the tumour was 2·5 mm thick (Fig. 4). The survival curves after the 2nd, 5th and 10th yr of follow-up are shown in Fig. 5. Patients whose tumours were less than 1·5 mm thick had a good prognosis, but those with tumours 8 mm thick had only a 20% chance of surviving 10 yr. These estimates were derived from the fitted model equation 1 and Fig. 4.

Table 1 *Cutaneous malignant melanoma—tumour thickness and survival*

Thickness (mm)	*No of patients*	*Deaths*	*Crude survival rate (%)*	*Average follow-up (months)*
<1·50	25	0	100	62
1·50–2·25	8	3	63	117
2·26–3·00	17	8	53	76
3·01–5·00	20	9	55	122
5·01–8·00	13	7	46	97
>8·00	8	7	12·5	72

Table 2 *Estimates for the melanoma death/recurrence model. Standard errors are in parentheses*

Death	−4·00 (0·41)	2·19 (0·82)	−1·27 (0·39)	0·018
Recurrence	−2·86 (0·22)	0·73 (0·52)	−0·72 (0·28)	0·058

Forty-seven of the 91 patients developed recurrent disease, of whom 13 have survived for periods between 12 months and 8 yr. Recurrences were strongly associated with thickness (Table 3). The peak for recurrence was between 0·7 and 1·7 yr after

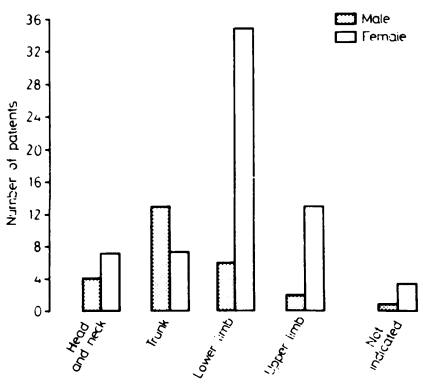

Fig. 3 *Sites of malignant melanoma in patients of this study.*

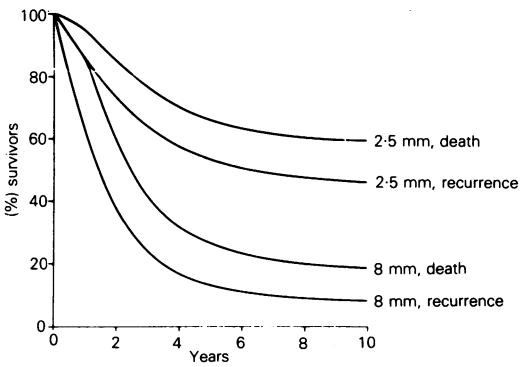

Fig. 4 *Cutaneous malignant melanoma—calculated risk of death or tumour recurrence at times after presentation. Two bands of tumour thickness are illustrated. The risk of dying from melanoma is greater with increased tumour thickness but the curves show maximum risk for each individual thickness band occurring at similar times.*

Table 3 *Cutaneous malignant melanoma—relation between tumour thickness and subsequent development of metastases*

Tumour thickness (mm)	*No of patients*	*No and (%) developing metastases*
<0·76	12	0 (0)
0·76–1·5	13	2 (15)
1·51–2·25	8	4 (50)
2·26–3·00	17	9 (53)
3·01–5·00	20	14 (70)
5·01–8·00	13	10 (77)
>8·00	8	7 (88)

Table 4 *Cutaneous malignant melanoma—relation between Clark's level of invasion and survival*

Clark's level	*Median thickness (mm)*	*No of patients*	*No of deaths*	*% crude survival rate*
I	0·76	6	0	100
II	1·33	15	2	87
III	2·95	26	12	54
IV	2·97	35	14	60
V	7·80	9	6	33

presentation: during those years those with 2·5 mm and 8 mm tumours had recurrence risks of 17% and 40% respectively (Fig. 4).

Level of invasion

The level of invasion of a melanoma into the dermis correlated with survival (Table 4). All six patients with tumours graded as level I survived, whilst six of nine patients with level V melanomas died. Most patients had neoplasms in level III or IV and in these

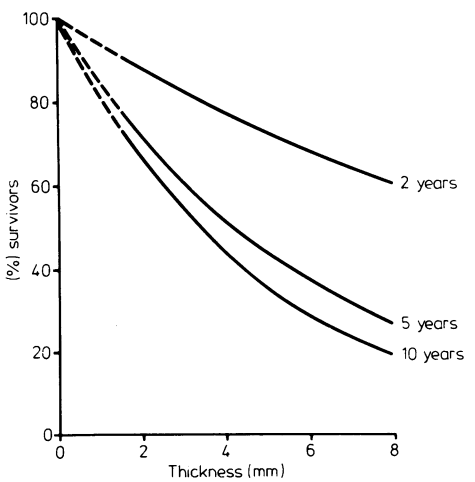

Fig. 5 *Cutaneous malignant melanoma—survival and tumour thickness. The curves demonstrate the chance of surviving 2, 5, or 10 yr with tumours of variable thickness.*

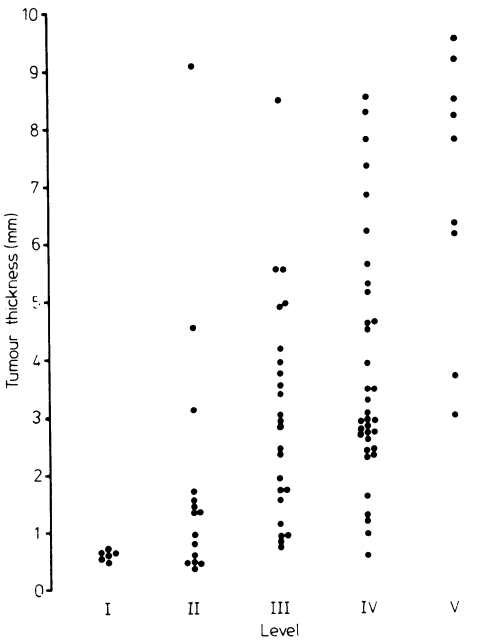

Fig. 6 *Cutaneous malignant melanoma; the relation between Clark's level and tumour thickness is clearly seen. (Spearman's coefficient of rank correlation, $\rho = 0{\cdot}585$ ($p < 0{\cdot}001$)).*

groups the chance of survival was slightly greater than 50% after an average of nearly seven years of follow-up. The level of invasion was also related to tumour thickness. All level I were less than 1 mm thick; only two level II melanomas were thicker than 2 mm but all level V melanomas were thicker than 3 mm (Fig. 6).

Mitotic rate

There is an association between frequency of mitoses and crude survival rate (Table 5), but there is a significant correlation between tumour thickness and mitotic rate (Fig. 7).

Lymphocyte infiltration

There was no significant correlation between survival and degree of lymphocytic infiltration nor between inflammation and thickness.

Table 5 *Cutaneous malignant melanoma—relation between mitotic rate and survival*

Mitotic rate	*No of patients*	*Deaths*	*% crude survival rate*
Grade I	40	8	80
Grade II	38	18	53
Grade III	13	8	38·5

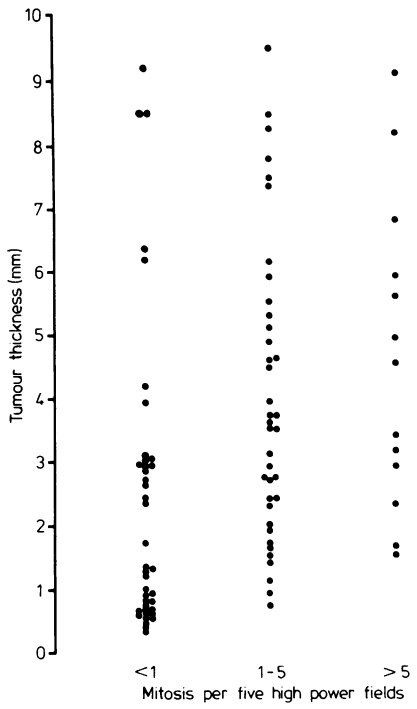

Fig. 7 *Cutaneous malignant melanoma. There is a significant relation between mitotic rate and tumour thickness. (Spearman's coefficient of rank correlation, ρ = 0·433 (p < 0·001)).*

Other histological features

Fifty-three of the melanomas were nodular and 36 were of superficial spreading type. Two were unclassifiable. The survival rate was higher for patients with superficial spreading melanomas (69·4%) than for those with nodular melanomas (59·6%). However the average thickness of the former (2·65 mm) was less than that of nodular melanomas (4·03 mm). Only 27% of superficial spreading melanomas were more than 3 mm thick compared to 58% of nodular melanoma.

Forty-one tumours were ulcerated and this was closely related to the thickness of the tumour (Table 6): in tumours greater than 3 mm thickness more than 70% were ulcerated. Vascular or lymphatic invasion was rarely noted and it was not possible to assess the significance of these variables.

Table 6 *Cutaneous malignant melanoma—relation between ulceration and tumour thickness*

Thickness (mm)	*No of patients*	*No and (%) of ulcerated melanomas*
<0·76	12	0 (0)
0·76–1·5	13	1 (8)
1·51–2·25	8	3 (38)
2·26–3·00	17	7 (41)
3·01–5·00	20	14 (70)
5·01–8·00	13	10 (76)
>8·00	8	6 (75)

Discussion

The prediction of the clinical course of malignant melanoma in an individual patient is difficult. This study has confirmed, however, that measurement of the maximum tumour thickness is a guide to prognosis. Other histological parameters such as level of invasion, type of tumour and presence or absence of ulceration correlate to greater or lesser extent with survival but these features also correlate with tumour thickness. Indeed, McGovern *et al*[9] and Balch *et al*[14] have shown the type of melanoma, mitotic rate and level of invasion are of no additional prognostic significance after determination of tumour thickness.

The significance of an inflammatory infiltrate in cutaneous melanoma is ambiguous. Some studies[12,13] have demonstrated a correlation between large numbers of lymphocytes and survival whilst other series,[7,8,10] including our own, have found no such relation. Balch *et al*[14] reported an inverse correlation between the thickness of the melanoma and lymphocytic infiltrate, but inflammation was not found to be important when other variables were considered.

In this study, measurements identified a group of 25 patients with tumours less than 1·5 mm thick, all of whom survived. Only two in this group, with melanomas 1·33 mm and 1·4 mm thick respectively, required surgery for recurrent disease. However, from calculated predictions, an occasional death would be expected in this group after prolonged follow-up. With increasing thickness of the primary tumour the outlook is less favourable, and of patients with melanomas thicker than 8 mm more than 80% die with metastases within 10 yr.

Our results are in general agreement with previous studies but direct comparison is difficult. Some series include patients at different stages of the disease and others exclude all but patients with localised tumours. A variety of thickness bands have been used for reporting results. In addition whilst some have assessed prognosis in terms of survival others have restricted their study to the development of metastases. These difficulties are compounded, moreover, because many of the studies are retrospective.

Breslow[22] assessed prognosis by recurrence of disease. All patients with melanomas less than 0·76 mm thick remained disease free for at least five years but in 27 patients with tumours of 0·76–1·5 mm, nine

developed metastases. Schmoekel and Braun Falco[7] found a similar recurrence rate (34%) in 56 patients with melanomas from 0·76–2 mm thick. Sondergaard and Olsen[16] report a 64% ten-yr survival rate in 17 patients with primary tumours between 0·76 and 1·5 mm but their study included subungual neoplasms which have a worse prognosis[16] and those with stage 2 disease. Our results, however, indicate a better prognosis for patients with primary tumours up to 1·5 mm thick. This is in agreement with Hansen and McCarten[13] who reported one death amongst 38 patients with tumours < 1·5 mm thick who were followed up for five yr. Wanebo *et al*[15] reported 100% survival in 44 patients with primary melanoma < 1 mm thick. Eldh *et al*[8] reported a greater than 90% survival in 180 patients with tumours < 1·5 mm. Thus although there are differences in the reported figures, it is generally agreed that patients with melanomas less than 1·5 mm thick have a good prognosis and in those with tumours thicker than 4 mm the prognosis is poor. In patients with neoplasms between 1·5 and 4 mm predictions based on thickness can be calculated as in Fig. 5. Most authors agree that metastases are very uncommon in patients with primary melanomas less than 1·5 mm thick have a good prognosis and in extensive areas of regression are excluded. In these cases, measurement of the residual melanoma does not indicate thickness prior to regression, and is an unreliable indicator of clinical behaviour.[23]

In this study, we used a Joyce Loebl "Magiscan" image analysis system which permitted rapid, reproducible measurements of tumour thickness and facilitated examination of a large number of slides. The same interactive technique may be used with a variety of cheaper optomanual instruments and is recommended but, an ocular micrometer can also be used and this is available to every pathologist at minimal cost.

Measurement of tumour thickness in malignant melanoma is a reliable guide to risk of tumour recurrence and death. It should be reported routinely by pathologists.

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