A study of the thickness of uninvolved dermis beneath cutaneous malignant melanoma: The ratio of uninvolved dermis to tumour thickness (DT:TT) as a prognostic index

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Summary—The histological material from 147 patients treated for clinical stage I primary cutaneous malignant melanoma between 1968 and 1972 was reviewed. All patients had a minimum follow up of 10 years. Measurements were made of the thickness of uninvolved dermis (DT) deep to the tumour and the tumour thickness (TT) itself.

The ratio of dermal thickness: tumour thickness (DT:TT) was correlated with clinical progress at follow-up and compared as a prognostic index with tumour thickness alone.

The ratio DT:TT was found to be a useful prognostic guide, a value of >2.0 proving to be a very favourable sign.

It is suggested that this simple ratio should be routinely reported in all cases of primary cutaneous malignant melanoma to provide an additional index with a view to assessing its value as a prognostic guide.

Many attempts have been made to devise a reliable method for predicting the prognosis of cutaneous malignant melanoma but most have been thwarted by the capricious nature of the disease. Besides the obvious benefit of being able to assess the prognosis for the individual patient it is also necessary to have specific prognostic indices to plan the extent of the surgery and possible adjuvant therapy that may be required. Some 430 variables may potentially affect the outcome of the disease, although many of these are inter-related and few are of any clinical value (Snodgrass Cowart, 1982). The most important variables currently accepted are the levels of dermal invasion as described by Clark et al. (1969) and the tumour thickness described by Breslow (1970). Although Clark’s levels are precisely defined, they are sometimes difficult to assess objectively in practice and the reproducibility between pathologists is poor (Larsen et al., 1980). A large proportion of tumours fall into levels 3 and 4, for which the prognosis is quite variable.

The measurement of tumour thickness (TT) is an easier and more objective measurement but gives no indication of the degree of invasion into the dermis.

We have therefore sought to study the relationship between the degree of dermal invasion and prognosis by direct measurement of dermal thickness (DT). The thickness of uninvaded dermis at its thinnest point beneath the tumour (DT) has been studied (Fig. 1) and the ratio DT:TT related to the outcome of the disease over a prolonged follow-up period.

The ratio DT:TT depends on three variables:

(i) The thickness of the tumour
(ii) The thickness of the dermis
(iii) The penetration of the tumour into the dermis.
A STUDY OF THE THICKNESS OF UNINVOLVED DERMIS

The present study was undertaken to evaluate the ratio DT:TT and tumour thickness (TT) to long term survival from the disease.

The prognosis for cutaneous malignant melanoma can vary according to the site on the body (Day et al., 1982), with the regions of the backs of the upper trunk, the neck, arms and the scalp (BANS), appearing to have a particularly poor prognosis for tumour thickness in the range 0.76–1.69 mm. The survival rates in the present series have therefore been assessed for these and other sites on the body and related to the DT:TT and to tumour thickness (TT).

Patients and methods

Histological specimens from all patients with stage I primary cutaneous malignant melanoma treated at the Plastic Surgery Unit, Frenchay Hospital, Bristol, for the 5 year period 1968 to 1972 were examined by one worker (PJS). Only those cases of invasive melanoma with adequate histological sections were included in the study: in situ (Clark level 1) lesions and those cases of incisional biopsy were excluded. An optical micrometer was used to measure the maximum tumour thickness from the granular layer (or floor of an ulcerated lesion) to the deepest point of dermal invasion and also to separately measure the thickness of uninvolved dermis deep to the tumour. When the deep surface of the dermis was irregular, an estimate of dermal depth was made at a point where half the dermis had ended, although it was found that this estimation was seldom necessary; measurements of DT and TT were equally easily made. From these two measurements the ratio DT:TT was calculated for each patient. Clinical details were then obtained from a computerised data base of over 1200 patients treated for malignant melanoma since 1967 (Briggs et al., 1984). These details included follow-up data gathered and updated during 1983 to include a record of the nature of any deaths or recurrences during the period 1968 to 1983: the series therefore has a minimum follow-up period of 10 years and a maximum of 15 years.

Of a total number of 238 patients treated during the 5 year period 1968 to 1972, follow-up data were unobtainable for 69, whilst a further 22 patients died of causes unrelated to melanoma. The remaining 147 patients were studied in three groups:

(i) Alive with no further evidence of disease (A)
(ii) Alive with history of recurrent disease (AR)
(iii) Dead due to melanoma (D).

The possible relationship between DT and TT was studied using the Spearman rank correlation. Possible statistically significant differences between DT:TT and TT for the three groups (A, AR and D) were studied using Student's t test. In these analyses the level of significance was taken as p < 0.05.

Patients were subgrouped by values of TT and DT:TT. A two sample test (Kolmogorov Smirnov) was then used to determine if decreasing values for TT and increasing values of DT:TT were associated with significant differences in survival rates. The relationship between anatomical site of the melanoma, DT:TT and the survival was also studied by a two-way analysis of variance, to establish if lower survival rates for lesions arising in some anatomical sites were attributable to either greater maximal tumour thickness or greater tumour penetration of the dermis (reflected in lower values for DT:TT).

Results

Of 147 patients, 27 (18.4%) were male and 120 (81.6%) were female. At the follow-up point in 1983, 71 of the 147 patients (48.3%) were alive and clinically disease-free, 18 of the 147 patients (12.2%) were alive with a history of recurrent disease and 58 of the 147 patients (39.5%) had died of their disease.

Some 29% (17/58) of all deaths occurred five years or more after treatment of the primary tumour. Tumours < 0.76 mm thick represented only 9.5% (14/147) whilst 68% (100/147) were over 1.5 mm thick.

The mean values for DT:TT and TT related to disease outcome (Table 1) shows that the ratio DT:TT for Group A was statistically significantly greater than for Groups AR or D (p < 0.02). Similarly TT for Group A was statistically significantly thinner than TT for Groups AR and D (p < 0.02). The relationship of the various increments of DT:TT and TT to outcome are also illustrated (Figs. 2 and 3).

Survival rates increased with an increase in the value DT:TT and the two sample test showed this association to be significant (p < 0.001) (Table 2). A similar increase in survival was demonstrated with decreasing tumour thickness
Table 1  Relationship of ratio DT:TT and TT to clinical outcome

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Alive and disease free</th>
<th>Alive with recurrence</th>
<th>Non-survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 147</td>
<td>(A) n = 71</td>
<td>(AR) n = 18</td>
<td>(D) n = 58</td>
</tr>
<tr>
<td>Mean ratio DT:TT</td>
<td>0.91</td>
<td>1.18</td>
<td>0.50</td>
<td>0.72</td>
</tr>
<tr>
<td>Mean TT (mm)</td>
<td>2.88</td>
<td>2.06</td>
<td>3.68</td>
<td>3.62</td>
</tr>
</tbody>
</table>

Table 2  Disease-free survival rates related to values of the ratio DT:TT

<table>
<thead>
<tr>
<th>DT:TT</th>
<th>All patients</th>
<th>Alive and disease free</th>
<th>% survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.24–0.34</td>
<td>17</td>
<td>13</td>
<td>35%</td>
</tr>
<tr>
<td>0.25–0.74</td>
<td>47</td>
<td>16</td>
<td>34%</td>
</tr>
<tr>
<td>0.75–1.99</td>
<td>51</td>
<td>32</td>
<td>63%</td>
</tr>
<tr>
<td>&gt;2.00</td>
<td>12</td>
<td>10</td>
<td>83%</td>
</tr>
</tbody>
</table>

Table 3  Disease-free survival rates related to values of TT

<table>
<thead>
<tr>
<th>TT (mm)</th>
<th>All patients</th>
<th>Alive and disease free</th>
<th>% survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3.00</td>
<td>56</td>
<td>17</td>
<td>30%</td>
</tr>
<tr>
<td>2.26–3.00</td>
<td>15</td>
<td>4</td>
<td>27%</td>
</tr>
<tr>
<td>1.51–2.25</td>
<td>29</td>
<td>14</td>
<td>48%</td>
</tr>
<tr>
<td>0.76–1.50</td>
<td>33</td>
<td>25</td>
<td>76%</td>
</tr>
<tr>
<td>&lt;0.76</td>
<td>14</td>
<td>11</td>
<td>79%</td>
</tr>
</tbody>
</table>

(for clarity percentage figures have been given, even though groups contained less than 100 patients).
and this association ($p < 0.001$) was statistically significant (Table 3).

The survival figures for tumours dependent upon their location in the body are given (Table 4): one lesion arising from the genitalia has been omitted here. Survival rates and DT:TT and TT in different regions of the body were found to vary. However no significant difference was found between the ratio DT:TT in each of these groups, nor was there any significant difference found between the values of TT for the groups, with the singular exception of the scalp/back of trunk group where tumours were significantly thicker than in other areas ($p < 0.05$).

Although the small sub-group numbers limit meaningful statistical analysis, the data suggest DT:TT to be a better prognostic guide for lesions of the hands and feet, than TT alone.

### Discussion

The relationship between maximal tumour thickness and prognosis described by Breslow (1970) has become important in the determination of likely prognosis in patients undergoing surgical excision of primary malignant melanoma of the skin. Thin tumours, originally defined as <0.76 mm (Breslow, 1970) and recently modified to <0.85 mm (Day et al., 1981), have been associated with a very good prognosis, whilst lesions of >3.60 mm thick may only be associated with a 38% eight year survival (Day et al., 1981). However, recent studies have shown that some thin tumours may metastasise and kill (Gromet et al., 1978; Trau et al., 1983 and Woods et al., 1983) and, as the present study has shown, some thick tumours (>3.60 mm) can be associated with disease-free survival of more than 10 years (Fig. 3). It seems that the thickness of the intact dermis beneath such tumours might also represent an important factor in determining prognosis in these patients. This has been the factor studied here.

Whilst we have not found any significant correlation between tumour thickness (TT) and thickness of intact dermis (DT), it has been found that poor prognosis was linked not only with tumour thickness of >3.60 mm but also with DT:TT ratios of <0.75.

Clearly in such a retrospective review there must be reservations about the uniformity of histological preparations and any deductions made from measurements on such material. However, it is known that central blocks will provide a tumour thickness which is consistent with the thickness of the whole tumour in 95% of cases (Sondergaard, 1980) and central blocks have been routinely used in this laboratory for many years. In any subsequent prospective study it would be useful to study four quadrants of peripheral dermal thickness around excised malignant melanomata as well as the uninvolved dermal thickness beneath the tumour.

It has been reported that the incidence of thin melanomata (<0.76 mm) is increasing (Little et al., 1980) as high as 57% in one series (Shafir et al., 1982). By contrast, in our series, tumours <0.76 mm represented only 9.5% (14/147) of the lesions, whilst 68% of tumours were thicker than 1.5 mm. Although Breslow (1976) suggested that tumours require a critical thickness to produce metastases this crucial thickness has yet to be defined. In the present series 3 out of 14 patients with lesions <0.76 mm died of their disease, two within 5 years of treatment of the primary lesion.

It must be remembered that maximal tumour thickness is only an indirect index of the biological activity of melanomata. The importance of dermal thickness beneath the tumour has yet to be defined but we consider the findings in this retrospective study sufficient to justify a prospective study of dermal thickness in
relation to primary cutaneous melanoma. In this way we might be able to improve on the current prognostic indices in this unpredictable disease.

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References


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Vincent J. McGovern, MD(NZ), FRACP, FRACPath, FRCPA, (born 1915), Professor of Pathology at the Commonwealth Institute of Health in the University of Sydney and a man with an international reputation for his work in the field of melanomas, was tragically killed in a car accident on the 30th December, 1983. His name ranks along with those of Clark and Breslow for developing the concept, now accepted world wide, of the prognostic help that careful histological micro-staging of melanomas can give to clinicians. He wrote extensively and well mainly, but not exclusively, on malignant melanoma and his published work included several books. The last of these, entitled Melanoma: Histological Diagnosis and Prognosis came out in 1983 and is regarded as one of the very best texts in the world on this subject.

He attained eminence both in the Royal College of Pathologists of Australasia of which he was President from 1975 to 1977 and in the International Academy of Pathology of which he was Vice-President from 1968 to 1982. Although he will be undoubtedly missed for this type of work, it is in his contribution to the study of melanoma where his loss will be greatest.