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Cutaneous melanoma: pathological certainties and uncertainties

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SUMMARY. **A historical review is given of the role of histopathology as a prognostic guide to the behaviour of cutaneous melanomas. Problems in the assessment of some of the current parameters are outlined in an attempt to explain the difficulties faced by histopathologists with some types of melanoma.**

The role of histopathology in helping to assess the prognosis of cutaneous melanoma is now well established; it was not always so.

The first suggestion that the microscopic appearance of melanoma could give some clue as to the clinical behaviour of the disease came from Allen and Spitz (1953). They indicated that the prognosis of the disease was worse with increased depth and that mitotic activity within the tumour was also a guide. In the early 1960s Oliver Cromwell Lloyd, working in conjunction with Denis Bodenham and Petersen in Bristol, used the histological profile of the tumours as a prognostic guide (Petersen *et al.*, 1962). He divided melanomas into three "stages" and indicated that thicker lesions did worse than their thinner counterparts.

In 1965 Mehnert and Heard published an article under the title "Staging of Malignant Melanomas by Depth of Invasion. A Proposed Index to Prognosis". The protocol of the Journal in which the article was published required articles to be accompanied by three brief critical summaries from current experts in the field. The discussion comments appended to Mehnert and Heard's paper by two of the three other authors include:

> "...I have considerable reservation about the pathologist's ability to equate the factor of biologic malignancy with the microscopic findings."
> "The cancer question will demand for resolution more basic and sophisticated tools than chi-square and double-blind tests ... All that we are asking is to unravel the very process of life. It seems unlikely that we shall do it with probability tables or statistical legerdemain."

Mehnert and Heard actually proposed that the micro-anatomy of the skin could be sub-divided into four levels and that prognosis would be related to the level reached by the invading melanoma. Mehnert and Heard's names are now virtually unknown.

In spite of the poor reception received by Mehnert and Heard's concept, a number of centres around the world were analysing microscopic features with a view to establishing any prognostic significance. The great breakthrough came from Wallace Clark with his co-workers in 1969 when they expanded the levels indicated by Mehnert and Heard and developed the concept of radial and vertical growth phases in the evolution of cutaneous melanomas. At roughly the same time Alexander Breslow (1970) demonstrated that the physical parameters of a given tumour govern its prognosis and that these physical parameters are conveniently well mirrored by measuring the thickness of the lesion in millimetres as seen on the histology slides.

Over the next few years the implications of these last two papers were assessed around the world and, in 1979, Vincent McGovern and colleagues showed that the thickness of the tumour was the most valuable histological determinant of prognosis over the histogenetic pattern as described by Clark and colleagues (then currently lentigo maligna melanoma, superficial spreading and nodular variants). Thickness was also a better prognostic guide than mitotic activity and evidence of partial regression. The assessment of these relative worths required significant statistical input with the use of single variant analyses and the multivariate analyses used by later workers, thereby more than challenging the criticism of Mehnert and Heard's paper that "all that we are asking is to unravel the very process of life ... with probability tables or statistical legerdemain."

Whilst McGovern and his team had been working on their assessment of the histopathological values, others workers were looking at different microscopic parameters. In particular Balch and his colleagues (1980) found that ulceration of a melanoma was an independent prognostic indicator. In order to establish this, truly complicated statistical analyses were required and it was at this stage that the multivariate technique came into its own (Cox, 1972), to be followed later by even more sophisticated techniques.

In 1981 Day *et al.* indicated that the presence of "microscopic satellites" in the reticular dermis and subcutaneous fat also carried prognostic value. Two years later McGovern and his colleagues (1983) confirmed the usefulness of microscopic satellites and also showed that a polypoid shape had an independent bad influence on prognosis.

In 1983 Maize produced a comprehensive overview of the literature and concluded that "the most important reproducible factor for predicting survival is maximum tumour thickness."

As a result of the work carried out throughout the 1970s and the early 1980s it is now established beyond any doubt whatsoever that the clinical behaviour of cutaneous melanomas is mirrored extremely well by the thickness of the lesion at the time of removal. Lesions < 0.76 mm in thickness carry an extremely good prognosis. Lesions between 0.75 and 1.5 mm carry an intermediate prognosis, often good; lesions thicker than 1.5 mm carry a progressively worse prognosis. In spite of these generalisations there are, nevertheless, exceptions to the rule and a number of further attempts have been made to try to pick out sub-sets of patients who might do badly. One of these was by Christian Schmoeckel and his colleagues in Munich (1983). They suggested that an index produced by a combination of thickness × mitotic rate per square millimetre would give a better guide. This has not found worldwide acceptance.

A further attempt to identify sub-sets came from this Unit in 1984 (Saxby *et al.*) when we studied the thickness of the uninvolved dermis beneath a cutaneous melanoma and produced a ratio of this uninvolved dermis to tumour thickness (DT:TT) as a prognostic index. It was found that if the ratio was > 2 then it was likely to be a very favourable sign. However, there was a very widespread scatter on either side of this ratio and there were many exceptions to its guideline; in particular it did not reliably help identify the small number of bad prognosis cases in what would generally be regarded as a good prognostic group (Briggs *et al.*, 1984). Only one other unit around the world, to our knowledge, has repeated this study. These Italian workers used it as a basis for a poster demonstration at the WHO Conference in Venice in 1985. We ourselves do not use the ratio any longer, but we are re-evaluating its usefulness in another study of a major cohort of patients with at least a 10-year follow-up.

The measurement of simple physical parameters would appear to be easy; nevertheless the biology, and sometimes management, of cutaneous melanoma often renders the assessment of these apparent absolutes extremely difficult.

Firstly, if one considers the management of melanoma, the vast majority of cases are treated by an initial excisional biopsy, either with narrow or wide margins. For one reason or another, however, a small percentage of lesions receive an initial incisional biopsy. In the past such a procedure has been thought to have a detrimental effect on the subsequent prognosis of the patient (Rampen *et al.*, 1980; Heenan *et al.*, 1985). However, it is now clear that this is not so and there is no adverse effect on the outcome of the disease. Nevertheless it does compromise the histological assessment in about 40% of incisional cases (Lees and Briggs, 1991). In consequence full thickness and levels are frequently not assessable.

The above difficulties in histopathological assessment are relatively minor; far greater problems can arise as a result of the biology of the lesion, particularly associated with the clinical variability often seen within individual lesions. This variability is often associated with regression and is completely mirrored microscopically; accurate assessment of maximum tumour thickness depends upon the pathologist actually sampling the area of maximal thickness! Although Sondergaard (1980) demonstrated that maximum tumour thickness is represented in 95% of cases by a single central transverse histological section of the lesion, this still leaves the remaining 5%, and ignores the fact that other parameters may be best assessed elsewhere in the lesion (Table). It is the practice within this laboratory to process the entire melanomatous lesion in transverse blocks. For small lesions this can be as little as three or four sections but, for larger lesions, we occasionally need between 15 and 20 sections. It is only by analysis of all the transverse pieces that a complete image of the clinical variability can be obtained. Inadequate sampling is one of the reasons why there is variability in pathological opinion. Even with the precaution of sectioning the entire lesion, it is still possible to pick up microscopical sub-variations by cutting multiple sections through the individual transverse pieces!

The actual profile of the lesion can produce insurmountable problems. This is particularly so with verrucous melanomas (Fig. 1) where the overall microanatomy is so complex that the relationship of the tumour to the normal levels cannot be accurately assessed. For similar reasons, the maximum thickness is also not assessable in these circumstances.

Similar, but less marked problems arise with polypoid lesions. These also distort the local microanatomy and it is not uncommon to find quite thick melanomas only penetrating to Clark's level 3. In these instances, the thickness and the polypoid shape are

Table Histopathological features routinely assessed in all cutaneous melanomas in this department

Histogenetic type, including any polypoid component	Host lymphocytic response
Thickness	Degree of any regression present
Level	Presence of dermal blood vessel or lymphatic invasion
Cell type and pigment production	Presence of a pre-existing naevus
Mitotic activity/5 HPFs (= 1 sq mm)	Adequacy of local excision
Presence and size of any ulcer	

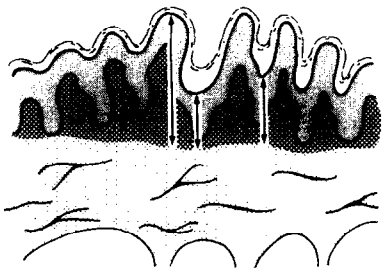

Fig. 1

Figure 1—The complex arrangement often found in verrucous melanomas. The arrows indicate possible points of thickness assessment. Note the marked variation possible. Clark's levels may give a better guide than thickness in these cases, but generally microstaging may be misleading.

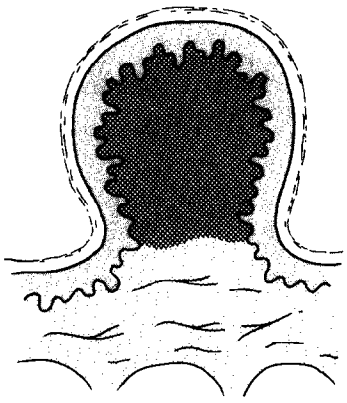

Fig. 2

Figure 2—A polypoid shape distorts the local micro-anatomy. Thickness is of more use than levels in these cases.

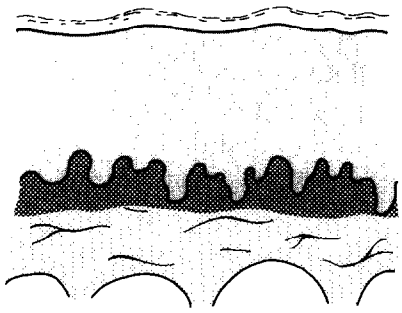

Fig. 3

Figure 3—A spurious thickness can be given in cases where there is marked epidermal hyperplasia; levels give a better guide.

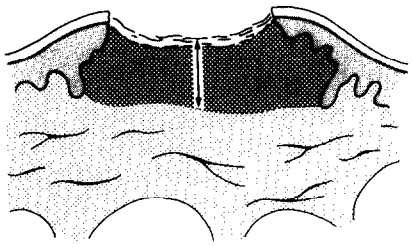

Fig. 4

Figure 4—Thickness in ulcerated cases should be assessed from the base of the ulcer, not by attempting to guess the original profile of the lesion.

overwhelmingly more important than the level (Fig. 2). Conversely, some melanomas are associated with significant epidermal hyperplasia and the majority of the thickness resides within the epidermis with little in the way of underlying deep extension. In these circumstances a melanoma can reach a significant thickness, but only penetrate to level 2 or 3. In this case the levels carry much more prognostic information than the thickness (Fig. 3).

Further complications arise when lesions are ulcerated. As indicated above, ulceration is itself an independent prognostic indicator, but it does mean that the traditional method of measuring thickness, *i.e.* from the top of the granular layer of the epidermis to the deepest extension of the tumour, is not possible. In these circumstances a convention has evolved to indicate that the thickness is measured from the base of the ulcer, minus slough, again to the deepest detectable extension (Fig. 4).

All of the above problems are worsened when a melanoma arises in the presence of a pre-existing naevus. In these circumstances it is often extremely difficult, if not impossible, to state with certainty where the melanoma ends and the naevus begins. In some instances one can detect significant cytological differences between the two types of cells but, in the majority, the cytological difference is such as to be unreliable; clearly naevus cells are present but they merge imperceptibly into what are clearly histologically melanoma cells. In cases like this it is our practice to assess to the bottom of the lesion and issue an "at worst" report, sometimes associated with an attempt to estimate the actual melanoma thickness.

The phenomenon of regression can produce profound interpretational problems. Regression can produce clinical ablation of a melanoma and this too, like other clinical parameters, is mirrored exactly down the microscope. In cases like this it is not uncommon to be able to recognise that the lesion is (or was) a melanoma but, because of the regression, it is impossible to say how thick and deep it was in the past. The prognosis is governed by those past thicknesses and depths, both unassessable on the biopsy material. An extreme example of this is found in those completely ablated cases which may be associated with current nodal metastases, but which have no recognisable melanomatous elements at their primary site, only the signs of their past presence. It is recognised that there is a small percentage of thin melanomas which carries a clinically unexpectedly bad prognosis. It is likely that this bad prognosis is a reflection of the past rather than current thickness of the lesion (Blessing and McClaren, 1992).

In summary it can be said that assessment of the apparent absolute parameters of thickness and levels can be rendered uncertain and of dubious value in some cases by a combination of poor biopsy technique, poor pathological sampling but, above all, by the complex biology which this particular tumour so beautifully clinically and histologically illustrates.

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