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Low- and High-risk Malignant Melanoma—II. Multivariate Analyses for a Prognostic Classification

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Abstract—*Multivariate and discriminant analyses were carried out in 585 cases of stage I cutaneous malignant melanoma, 294 disease-free for at least 5 yr and 291 with later metastases. Clinical and histological criteria were examined as to how they could be used, alone or combined, to determine a low and high risk of later recurrences, taking into account both quality (the degree of probability of prognostication) and quantity (the number of patients identified). For low-risk malignant melanoma a tumor thickness* $\leqslant 0.75$ mm *and a mitotic index* < 10.0 mit/mm^2 *were necessary (in 68 cases 8.8% recurrences). A horizontal diameter* > 3.0 cm *may be an additional risk factor. For high-risk malignant melanoma (74.6% recurrences in 291 cases) the following criteria had to be fulfilled: prognostic index* $\geqslant 13$, *ulceration (in tumors with a thickness* > 3.0 mm*) or vascular invasion. Remaining cases constituted the medium risk group (recurrences in 29.6% of 226 cases). Within these three prognostical subgroups sex appeared insignificant and site seemed a minor influence on the rate of recurrences (site was significant for female high-risk cases only). Even better results were achieved by means of the discriminant analysis, in which eight parameters, each combined with a weight factor, were found to be relevant. In this way the probability of a correct prognostication of later metastases can be obtained directly. This classification of low-, medium- and high-risk malignant melanoma may prove helpful in the selection of different therapeutical modalities for individual patients and in evaluating their efficacy.*

INTRODUCTION

NUMEROUS factors have been shown to have a bearing on the prognosis of stage I malignant melanoma, tumor thickness [1] possibly being the most important one. The question now arises as to how other criteria can be combined with tumor thickness in order to improve prognostication. This is difficult, as all of these criteria seem more or less related to and dependent of each other. The degree of dependency therefore needs to be investigated. A total dependency would exclude the parameter, whereas a partial dependency would indicate a limited usefulness. Therefore, these criteria cannot be simply combined in prognostic score sheets [2, 3] because they do not necessarily improve prognostication.

Different parameters can be combined in two different ways: the first approach is mathematical, using computerized data and multivariate analyses; the computer decides how the parameters are weighed and combined.

A second approach is to determine as best as possible the malignant potential of the tumors by means of histological, tumor-related criteria only, first establishing a prognostical classification of malignant melanoma and then testing the prognostic effect of clinical, host-related criteria in these histologically defined prognostical subgroups. It will then be possible to see whether the histologically determined prognosis needs to be corrected using clinical criteria.

MATERIAL AND METHODS

The same cases studied in the preceding article [4] were analyzed. The data of 585 cases of

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cutaneous malignant melanoma (stage I), 294 disease-free for at least 5 yr and 291 with later metastases, were computerized and analyzed. The following criteria were considered: sex, site, age, histogenetic type, horizontal diameters, level of invasion [5], tumor thickness [1], mitotic index [6, 7] prognostic index [6, 7], ulceration, vascular invasion, tumor breadth [4], tumor elevation, cellular atypia, cell type, inflammatory reaction, adjacent nevocellular nevus and resection margin.

In order to determine a prognostic classification whereby metastatic and non-metastatic cases can most effectively be distinguished, two different approaches were utilized:

(1) Combining histological criteria simply and comprehensibly

In a first step histological criteria were sought in order to best determine low-, medium- and high-risk melanoma patients. Two aspects were considered: (a) quantity—as many cases as possible for the low- and high-risk groups; (b) quality—as low a percentage of metastatic cases as possible for the low-risk group and as high a percentage as possible for the high-risk group. In a second step the two most important clinical parameters determined in the first part of this study (sex and site) were examined statistically within these subgroups by means of χ^2 tests.

(2) Combining clinical and histological criteria by means of discriminant analyses

The computerized data were investigated by numerous discriminant analyses [8], carried out separately for males and females as well as for nodular and superficial spreading melanomas.

Comparison of different prognostical methods

The discriminant analysis was compared with the approach by histological criteria quantitatively and qualitatively. In this comparison the level of invasion and tumor thickness alone were included by determining the number of metastic cases in four different risk groups as percentages to all metastatic cases ($n = 291$).

RESULTS

(1) Simple, comprehensible combination of histological criteria

(a) Low-risk malignant melanoma. Seventy-two cases had a tumor thickness < 0.76 mm, 10 of which (13.9%) had later metastases. With a mitotic index $\leqslant 10$ mit/mm^2, four metastatic cases were eliminated, decreasing the recurrence rate in 68 cases to 8.8%. By also eliminating cases with a mitotic index > 5.0 mit/mm^2 and/or clinical diameter > 30 mm, eleven more cases (two of which only had later metastases) were excluded without significantly lowering the rate of metastatic cases (Fig. 1). Eight thin melanomas had a diameter > 30 mm, and two of these (25%) had later metastases (in one the mitotic index was 10.7 mit/mm^2). Six thin melanomas had a mitotic index > 5.0 and < 10.0 mit/mm^2, and one of them had recurrences. No other clinical or histological criteria were clearly related to the metastatic cases.

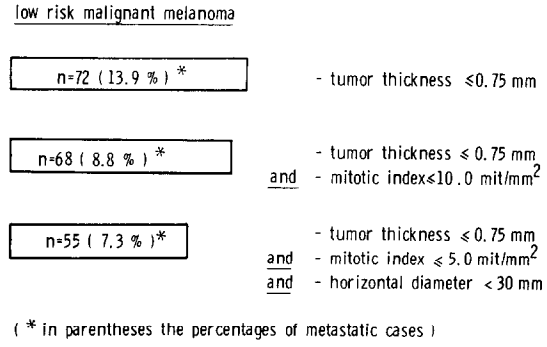

Fig. 1. Low-risk malignant melanoma. Evaluation of effectiveness of prognosticators: as quality improves (decreasing percentages of metastatic cases) quantity worsens (the total number of cases decreases).

(b) High-risk malignant melanoma. The highest percentages of metastatic cases were found by means of vascular invasion and by means of the mitotic index: 57 cases showed vascular invasion, and 47 had > 25 mit/mm^2, 94.7 or 97.9% of which developed later metastases.

By combining different criteria it was possible to increase the number of high-risk cases, but the percentage of metastatic cases was always lower. The best results were obtained when the following criteria were fulfilled: prognostic index $\geqslant 13$, vascular invasion or ulceration in thick tumors (tumor thickness $\geqslant 3.0$ mm). Two hundred and seventy-one cases (with metastases in 76.4%) had a prognostic index $\geqslant 13$, 11 more cases were added with vascular invasion and 10 more cases

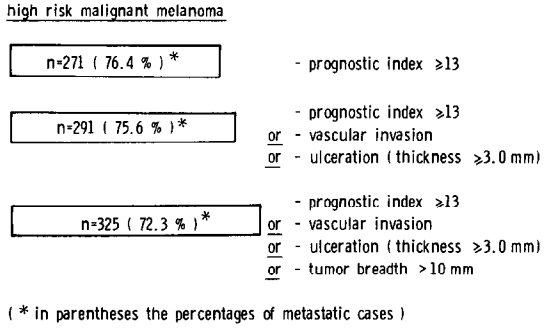

Fig. 2. High-risk malignant melanoma. Evaluation of effectiveness of prognosticators: as quantity improves (increasing number of cases), quality worsens (the percentages of metastatic cases decrease).

with ulceration (in tumors with a thickness $\geqslant 3.0$ mm). With the combination of vascular invasion and ulcerated thick tumors, 20 more cases were included in the high-risk group (one case was positive for both criteria); thus the high-risk group contained 291 cases, 220 of which (74.6%) had later metastases (Fig. 2).

By also adding cases with the small lymphocyte-like cell type or particularly with a tumor breadth >10 mm the high-risk group was further increased (315 or 325 cases). However, there was a decrease in the percentage of metastatic cases (73.0 or 72.3%), and the percentage of metastatic cases in these added cases were 41.7 and 44.1% only. By also including cases with severe cellular atypia, only three more cases were added, and two of them did not develop later metastases.

(c) Analysis for sex and location.

(I) High risk malignant melanoma. The group with a prognostic index $\geqslant 13$, with vascular invasion or with ulceration (thickness $\geqslant 3.0$ mm) was chosen for further analyses because the percentage of metastatic cases was relatively high (74.6%) and the group relatively large ($n = 291$).

The results are shown in Table 1: the percentages of metastatic cases varied between 55.6 and 100% for different locations in female patients; this was statistically significant ($P = 0.005$). They varied between 66.7 and 100% in the male patients, but this was statistically insignificant ($P = 0.6$). Furthermore, there was no significant sex difference within the same location.

(II) Medium-risk malignant melanoma. All other cases not grouped as low- or high-risk malignant melanomas showed statistically insignificant results when analyzed for sex and site (Table 2).

Table 1. High-risk melanomas (see Table 3): variations of the percentages of metastatic cases for sex and site

	trunk	head	neck	legs/ arms	palms/ soles	Σ	P
♀	91.2 % (34)	60.0 % (15)	55.6 % (9)	63.7 % (102)	100 % (9)	70.4 % (169)	0.005
♂	82.4 % (68)	85.7 % (7)	66.7 % (3)	74.4 % (39)	100 % (5)	80.3 % (122)	0.6
Σ	85.3 % (102)	68.2 % (22)	58.3 % (12)	66.7 % (141)	100 % (14)	74.6 % (291)	0.001
P	0.4	n.s.	n.s.	0.3	n.s.	0.08	

Significant differences for location in female patients only were found. Prognostic index $\geqslant 13$ *or* vascular invasion *or* ulceration (thickness $\geqslant 3.00$ mm). The total number of cases are in parentheses.

Table 2. Medium-risk melanomas (see Table 3): variations of the percentages of metastatic cases for sex and site

	trunk	head	neck	legs/ arms	palms/ soles	Σ	P
♀	34.5 % (29)	16.7 % (18)	50.0 % (2)	25.9 % (112)	25.0 % (8)	26.6 % (169)	0.6
♂	45.2 % (31)	36.4 % (11)	—	30.0 % (20)	33.3 % (3)	38.5 % (65)	0.7
Σ	40.0 % (60)	24.1 % (29)	50.0 % (2)	26.5 % (132)	27.3 % (11)	29.9 % (234)	0.3
P	0.6	n.s	—	0.9	n.s	0.2	

No statistically significant results were found. Tumor thickness >0.75 mm, prognostic index <13, no vascular invasion, no ulcerated thick tumors ($\geqslant 3.0$ mm). The total number of cases are in parentheses.

(2) Combining clinical and histological criteria by means of discriminant analyses

Different discriminant analyses were carried out and slightly different results were achieved when nodular or superficial spreading melanomas were analyzed separately (differentiated for male and female patients).

The most simple equation (valid for all 585 cases studied) was achieved as follows:

$D = 0.1613 \times$ thickness (mm) $+ 0.0477 \times$ tumor breadth (mm) $+ 0.0736 \times$ mitotic index (mit/mm^2) $+ 0.2348 \times$ infiltration* $+ 1.1550 \times$ vascular invasion* $+ 0.3162 \times$ ulceration* $- 0.0099 \times$ prognostic index $+ 0.7636 \times$ lymphocytic-like cell type* $+ 0.3796 \times$ trunk* $- 1.7586$ (* dummy variable, scoring 1 when present, 0 when absent).

All variables not appearing in the discriminant function gave no further information (a few variables with no relevant discriminating influence were discarded).

When the individual values of a patient's parameters were inserted in the function, the individual scores D of the patient were obtained (Figs 3 and 4). The mean value of the non-

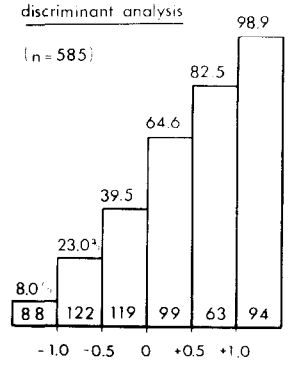

Fig. 3. Discriminant analysis in malignant melanoma (n = 585 cases). The percentage of metastatic cases and the total number of cases for six different groups of the discriminant score D *are given.*

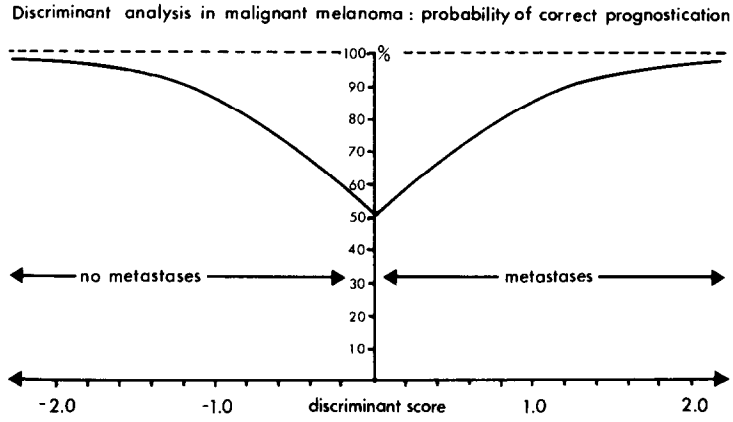

Fig. 4. Results of the discriminant analysis in 585 cases, showing a diagram in which for a particular score D the probability of a correct classification in the metastatic (right) or the non-metastatic (left) group can be determined.

metastatic cases was -0.602, of the metastatic cases 0.586.

In this way the prognosis as well as the degree of probability of the forecast can be determined for individual patients.

Comparison of different prognostical methods

By combining histological criteria a prognostic classification with four different risk groups was reached (Table 3). Comparing this approach with the discriminant analysis, only minor differences were found (Fig. 5) as the number of cases and their percentages of metastatic cases were very similar. Only the percentages of false forecasts (the sum of false-positive and false-negative cases in relation to the total number of cases) was slightly lower by means of the discriminant analysis: 22.0 vs 25.3% (for comparison see Table 3 in part I of this study [4]). In addition, the number of metastatic cases in four different risk groups were determined as percentages to the total number of metastatic cases ($n = 291$), and the level of invasion and tumor thickness alone were also included in this analysis (Fig. 6). The latter two prognosticators were clearly less effective in the identification of metastatic cases; the two other more refined methods allowed more patients with a higher degree of probability to be identified. Furthermore, the presentation of these results (Fig. 6) facilitates the comparison with other studies.

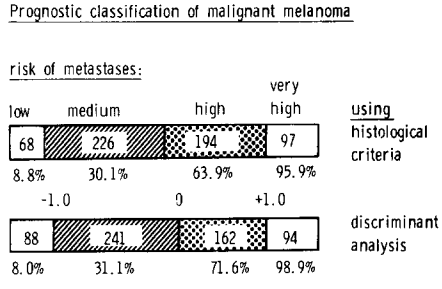

Fig. 5. Prognostic classification of malignant melanoma: comparison of two different methods, one by histological criteria only (see Table 3) in the upper line, the other by discriminant analysis in the lower line. The total number of cases and the percentages of metastatic cases are shown.

DISCUSSION

Prognostic information is necessary to determine treatment modalities for stage I melanoma patients and to restrict those with a risk of serious side-effects to certain subgroups in which improvement is most likely. Furthermore, prognostically homogeneous groups are necessary to evaluate their effectiveness. When analyzing the prognosis for an individual melanoma patient, the most important question is whether metastases

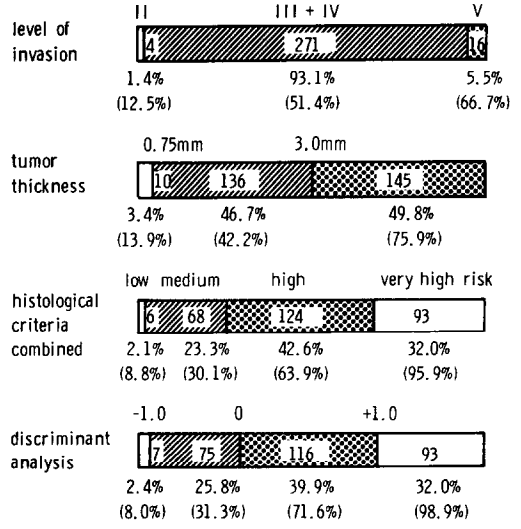

Fig. 6. Effectiveness of various parameters in the identification of metastatic cases. The number of metastatic cases are shown as well as their percentages relative to all metastatic cases (n = 291). The percentages of these metastatic cases relative to all metastatic and non-metastatic cases within these risk groups are given in parentheses.

Table 3. Proposed prognostic classification of melanoma with a minimum criteria allowing optimum prognostication

1) Low-risk malignant melanoma
(recurrences in < 8 %)
- tumor thickness ≤0.75 mm
and - mitotic index <10 mit/mm^2
(no signs of regression, ulceration and vascular invasion; cases with a clinical diameter >3 cm should be classified as medium-risk)

2) Medium-risk malignant melanoma
(recurrences in ca. 30 %)
cases other than low-, high-, or very high-risk

3) High-risk malignant melanoma
(recurrences in ca. 65 %)
- prognostic index ≥13
or - ulceration in tumors with thickness ≥3.0 mm

4) Very high-risk malignant melanoma
(recurrences in ca. 95 %)
- mitotic index ≥25 mit/mm^2
or - vascular invasion (unequivocally)
or - high-risk melanomas with palmar/plantar/subungeal location

will occur and whether such a development can be prevented through therapeutical measures. However, an exact prognosis can never be made for individual cases, and only an estimate with a certain degree of probability can be given; only a low or a high risk of later recurrences can be determined. Clues should be examined in each case as best as possible, allowing a low or high risk to be ascertained. In addition, the probability of an exact forecast should be as high as possible. Furthermore, a prognostic classification should be as simple and reproducible as possible in order to be applied routinely.

Combining different parameters should theoretically improve prognostication by increasing the probability of a correct prognosis and by decreasing the number of medium-risk cases for which a forecast cannot be made. This is problematic, particularly because more than two variables have to be investigated which are also more or less dependent on each other. This can be achieved using multivariate analyses [9–15] of computerized data only. Stepwise multiple regression analyses were executed [13, 14] or the Cox model [16] was used [9–12]; but some shortcomings in these studies should be pointed out: not only the total number of cases (in clinical stage I and with at least a 5-yr follow-up), but also the number of metastatic cases needs to be sufficiently high. The last prerequisite is not always fulfilled: less than 70 metastatic cases were analyzed by Balch *et al.* [9] and Eldh *et al.* [13], slightly over 100 by Day *et al.* [10–12] and Larsen and Grude [14] and only the study by van der Esch *et al.* [15] contained a large number (*ca.* 240) of metastatic cases. In some studies tumor thickness [14] or vascular invasion [9–12] were not evaluated. The mitotic activity was either not determined at all [9] or only insufficiently as different degrees; in particular, very low (<1.0 mit/mm^2) or very high (>25 mit/mm^2) mitotic indices were not analyzed separately (with several degrees of freedom in the chi-square test). Various results had to be inevitably insignificant simply because the number of cases and, as mentioned above, the number of metastatic cases in the various subgroups was too small. In contrast, statistically significant results are not necessarily clinically relevant when their effect is small, and this also needs to be examined. In this respect the Cox model [16], introduced to study survival rates in leukemic patients within certain time periods ('age-specific failure rate'), does not seem to be the most appropriate method. In these studies [9–12] it is difficult to comprehend how different parameters could be combined and how great their clinical relevance when combined really is. Since we were not primarily interested in survival rates of stage I melanoma patients, but in whether they would develop recurrences, different approaches were attempted.

For this purpose our series with 585 cases (with a complete set of data including 'tumor breadth' [4] never examined before) and later recurrences in *ca.* 50% of them was most suitable. First, discriminant analyses [8] were carried out. The mathematical objective was to 'weigh' and combine discriminating variables. The procedure works stepwise in that the variables are selected by their discriminating power, taking into account their correlations with each other. The 'weights' (discriminating coefficients) for the selected variables are utilized to maximize the separation of metastatic and non-metastatic cases. In this way a discriminant score D for the patient can be computed. This score D allows the classification into the metastatic or non-metastatic groups, and it also gives an estimate of degree of probability of the forecast (Fig. 4).

Since this approach is hardly comprehensible or verifiable with common sense, a different approach was tried. Different parameters were examined as to whether they could be used to determine as effectively as possible low- and high-risk cases (Table 3).

A 50% risk in our opinion is not high enough for a case to be classified as high-risk, as a 65% and even a 95% risk can now easily be determined. A prognostic index [7] $\geqslant 13$ was more effective than a tumor thickness $\geqslant 3.0$ mm as more cases were identified [4]. Thick tumors ($\geqslant 3.0$ mm) with a low mitotic index ($\leqslant 5.0$ mit/mm^2) had a recurrence rate of 50% only ($n = 38$). In contrast, we feel a 20% risk [15] to be unacceptably high for the low-risk group; we obtained 8.8% metastatic cases in this group, but as our series of 585 cases contains a higher than normal rate of metastatic cases, a recurrence rate of 5% should usually be expected when defining the low-risk group in this way (Table 3). Comparing this approach with the discriminant analysis (Fig. 5), the differences appear to be minor; therefore the classification by histological criteria (Table 3) seems to be simple as well as sufficient for clinical use.

Once the malignant potential of melanomas was analyzed histologically, the question arose whether clinical parameters could be shown to have an influence within these prognostical subgroups. A horizontal diameter >3 cm appears to be a weak additional unfavourable parameter in the low-risk group. Sex and site were not significantly related to the recurrence rate, except for the location in female high-risk patients (Table 1). The question is whether the location itself also determines the prognosis or whether there is a benign variant of malignant melanoma, particularly in female patients and predominantly associated with certain locations. It may also be necessary to differentiate the locations more meticulously [10–12]. These questions require further investigation.

Summarizing our results, the possibility of determining a low (recurrences in 5%), high (recurrences in 65%) or very high risk (recurrences in 95%; 75% when the last two groups are combined) has to be pointed out. Clues alone or combined, allowing classification of individual cases into one of these groups, should be searched and mentioned in histopathological reports (the probability of a correct forecast should also be given). In this way the number of medium-risk cases should be kept as small as possible. Obviously several independent studies need to be analyzed and compared before general agreement can be reached as to how the prognosis in malignant melanoma can be determined most effectively. To facilitate the comparison of our results with those in other and future studies, the effectiveness of different prognostical methods in the identification of metastatic cases is analyzed and compared in Fig. 6; for this purpose the results are shown as percentages of the total number of metastatic cases only.

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