Eur J Cancer Clin Oncol, Vol. 19, No. 2, pp. 227–235, 1983.
Printed in Great Britain.

0277-5379/83/020227-09$03.00/0

Low- and High-risk Malignant Melanoma—I. Evaluation of Clinical and Histological Prognosticators in 585 Cases

CHRISTIAN SCHMOECKEL, ANGELIKA BOCKELBRINK, HELMUT BOCKELBRINK, JEAN KOUTSIS and OTTO BRAUN-FALCO

Department of Dermatology, University of Munich, Frauenlobstr. 9–11, 800 München 2, West Germany

Abstract—*In 585 cases with primary cutaneous stage I malignant melanoma (294 disease-free for at least 5 yr, 291 with later metastases) prognostic parameters were examined. The most effective proved to be tumor thickness and mitotic activity, particularly when combined as a prognostic index. Furthermore, vascular invasion, ulceration in thick tumors (thickness ≥ 3.0 mm), severe cellular atypia, the small, lymphocytic-like cell type and the absence of an inflammatory reaction were closely associated with a high rate of metastatic cases. Less relevant prognostic factors were the level of invasion, sex, site, tumor breadth, clinical diameters and infiltrative growth. Tumor type, age, duration and an adjacent nevocellular nevus were not significantly associated with the occurrence of later metastases. Furthermore, the growth-type (exo- or endophytic) did not have a bearing on the prognosis.*

INTRODUCTION

PRIMARY cutaneous malignant melanoma constitutes a prognostically heterogenous group of tumors, many of which, in spite of surgical excision, metastasize, usually leading to the death of the patient. Attempts have been made to prevent metastases from developing: by wide excision of the tumor, pre- or post-operative radiotherapy, prophylactic lymphadenectomy, adjuvant immuno- and/or chemotherapy or hyperthermic perfusion therapy. It is still unknown whether these, or some of these, methods really are effective and if they should be performed in all cases or in certain prognostical subgroups only. Therefore prognostical criteria are necessary to determine such subgroups of malignant melanoma.

A first prognostical distinction was made by Allen and Spitz in 1953 [1]. They noted that superficial melanomas had a higher survival rate than cases with a deeper infiltration into the dermis. In 1965 Mehnert and Heard [2] defined four levels of infiltration, and a fifth level was later proposed by Clark *et al.* [3]. The latter definition has become internationally accepted. A different approach was carried out by Breslow [4, 5], who showed that the direct measurement of maximum tumor thickness is a better prognostic parameter. This has been confirmed by several studies [6–12] published in recent years.

Several other clinical and histological criteria are known to have a prognostic significance, and some of them were used to introduce a prognostic score sheet [13] or a prognostic index [14]. Their usefulness, however, is controversial, since they may be more or less related to and dependent on each other. This problem can be resolved through computer-assisted multivariate analyses [7, 8, 15–17], and several such investigations are needed before consensus can be reached.

Prognostic criteria should be simple and reproducible enough to be used clinically. Furthermore, they should be effective both qualitatively and quantitatively: the use of a qualitatively excellent prognosticator (for instance indicating a good prognosis) is quantitatively limited if it identifies only a few cases.

In the following study we report our retrospective findings in a series of 585 cases: in the first section the prognostical significance of various parameters studied will be presented; in the second section the results of multivariate analyses in which the dependency of prognostic criteria

Accepted 7 September 1982.

relative to each other were examined more thoroughly will be given, leading to a prognostic classification of malignant melanoma; and finally, since the resection margins performed in these cases varied considerably, their prognostic significance will be analyzed and discussed in the third section.

MATERIAL AND METHODS

Two thousand, two hundred and forty-two cases with primary cutaneous malignant melanoma have been collected in the 'German Melanoma Study Group'. Of these, 585 cases (stage I) fulfilling the following criteria were studied:

Follow-up

Two hundred and ninety-four cases were disease-free for at least 5 yr; 291 had later histologically proven recurrences.

Treatment

All patients were treated surgically and no previous X-ray or prophylactic lymphadenectomies were performed. In some metastatic cases adiuvant immunochemotherapy with BCG and dacarbazine (DTIC) was applied.

Histology

In all cases histological slides were available. In most cases several sections were examined, but serial or step sections were not made. Cases in which the sections appeared not to represent the center of the tumor were discarded.

Documentation

In nearly all cases black and white photographs and an extensive clinical documentation were present.

The following criteria were determined and computerized:

Clinical criteria

(1) Age; (2) sex; (3) location of the tumor; (4) horizontal diameters (length, width); (5) duration of the lesion (according to the information given by the patients).

Histopathological criteria

(6) Level of invasion according to Clark *et al.* [3]; (7) maximum vertical tumor thickness according to Breslow [4, 5], whereby the distance in mm between the lowermost tumor cells and the str. granulosum (when absent the uppermost undamaged tumor cells) was measured. Intra- and subepidermal infiltration down the hair follicles was not considered; (8) mitotic index, defined as the maximum number of mitoses/mm^2. The area examined varied from 1.0 to 1.5 mm^2 (which corresponds to 7–10 adjoining high-power fields in the microscope used with a radius of 0.215 mm—the area was determined through πr^2), and the number of mitoses was then converted to 1 mm^2. In very thin tumors two sections and/or half high-power fields were used if necessary. In thicker tumors several counts were made whenever possible; (9) prognostic index, defined as the product of tumor thickness and mitotic index [11]; (10) ulceration shown by necrosis of the epidermis; (11) vascular invasion of aggregated tumor cells into blood vessels or lymphatics was recorded if unequivocal only; (12) cellular atypia, graded 0 when absent, 1 when weak, 2 when moderate and 3 when severe; (13) tumor breadth, defined as the horizontal distance in mm of that part of the tumor with at least 75% of maximum vertical tumor thickness (Fig. 13); (14) the four following cell types were differentiated: epithelioid, spindle-shaped, globoid, and small, lymphocyte-like; (15) regression, characterized by a fibrotic papillary dermis with lymphocytes and melanophages without melanoma cells, was recorded only for tumors with level II; (16) infiltrative growth was recorded when strands of tumor cells were seen to protrude from the usually relatively sharply demarcated lower tumor border and to grow between the dermal collagen bundles; (17) inflammatory reaction was graded 0 when few or no lymphocytes or histiocytes were present, 1 when the infiltrate was weak, 2 when moderate and 3 when strong; (18) tumor elevation: the percentage of tumor thickness above the normal skin surface level was determined. The cases were classified into three groups: elevation $<34\%$ (endophytic), 34–66% (intermediate) and $\geqslant 66\%$ (exophytic); (19) tumor type according to Clark *et al.* [3] was determined by combining clinical and histological criteria. Flat, but invasive tumors with sharp demarcations and without an adjacent intra-epidermal component were grouped with primary nodular melanomas (NM) instead of superficial spreading melanoma (SSM). Acral-lentiginous melanomas (ALM) were determined by site (plantar, palmar and subungual locations); by their clinical morphology (lentigo-maligna-like areas); and by numerous atypical, occasionally dendritic melanocytes in the basal layer of the adjacent papillomatous epidermis. Lentigo-maligna-melanomas (LMM) were determined histologically; (20) an associated nevocellular nevus was recorded when it was seen histologically and unequivocally.

(21) *Statistical methods*

The significance of deviation between the distribution of various groups was calculated by Student's t test, the F test or the chi-square test.

Correlation coefficients were determined between each parameter. In order to compare the prognosticators quantitatively, two groups were established for each method—one with good prognoses, another with poor prognoses. The sum of false-negative cases (x) in the first group and of false-positive cases (y) in the second group was then considered as a percentage of the total sum (S) of all cases: $(x+y)100/S$.

RESULTS

Clinical parameters

(1) *Age* did not appear to have a prognostical bearing ($P = 0.2$). A slight rise of metastatical cases with increasing age (Fig. 1) correlated with increasing tumor thickness but less with increasing mitotic activity. The mean age of non-metastatic cases was 48.4 (standard deviation 12.8) and of metastatic cases 50.1 (standard deviation 14.5) years ($P = 0.15$).

(2) *Sex* was prognostically significant ($P \ll 0.001$). Female patients ($n = 384$) had recurrences less often (43.2%) compared to the male patients ($n = 201$; 62.2%). Tumors in men were on average thicker (2.92 mm) and mitotically more active (10.5 mit/mm^2) compared to melanomas in women (2.50 mm and 8.5 mit/mm^2), but this was of borderline significance only ($P = 0.03$ and 0.05). The differences between the sexes were less pronounced when analyzed on each level of tumor thickness and particularly of the prognostic index (Fig. 2). Generally, the rates of metastatic cases were slightly lower in the female patients, but this was statistically significant in two subgroups of tumor thickness only.

(3) *Location* was prognostically significant ($P \ll 0.001$). The following rates of recurrences were noted (in decreasing order): soles, 66.7% ($n = 21$); trunk, 63.7% ($n = 179$); neck, 53.3% ($n = 15$); palms, 50% ($n = 6$); legs (excluding feet and soles), 42.8% ($n = 208$); arms (excluding palms), 41.1% ($n = 73$); feet (excluding soles), 40.0% ($n = 25$). The differences in the rates of metastatic cases were pronounced and statistically significant in three of five thickness levels. They were less distinct for the prognostic index (Fig. 3), and they were significant in the last group (prognostic index >70) only.

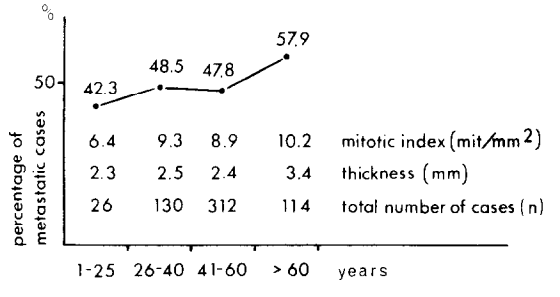

Fig. 1. Age and percentage of metastatic cases. Below, the mean values of the mitotic index and of tumor thickness as well as the number of cases in four different age groups are given.

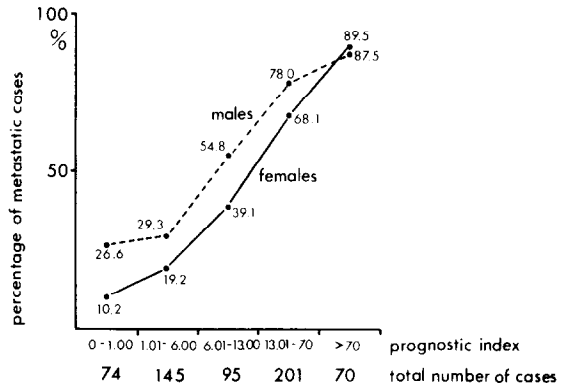

Fig. 2. Sex and prognostic index. Except for the last level, males are noted to have slightly higher (statistically insignificant) rates of metastases.

(4) *Horizontal diameters* (Fig. 4): both length (D_1) and width (D_2) were prognostically significant ($P \ll 0.001$) as well as the area ($D_1 \times D_2 = D_3$). Of 199 cases with $D_1 > 20$ mm 62.8% had metastases compared to 42.4% of 380 cases with $D_1 \leqslant 20$ mm. When analyzed by thickness, this was relevant for thin melanomas ($\leqslant 0.75$ mm) only: 7.4% later metastases for $D_1 \leqslant 20$ mm and 29.4% for $D_1 > 20$ mm.

(5) *Duration* of the lesion was statistically significant ($P = 0.01$) but practically inconclusive as the values varied between 23.3 and 57.1% without a conceivable pattern.

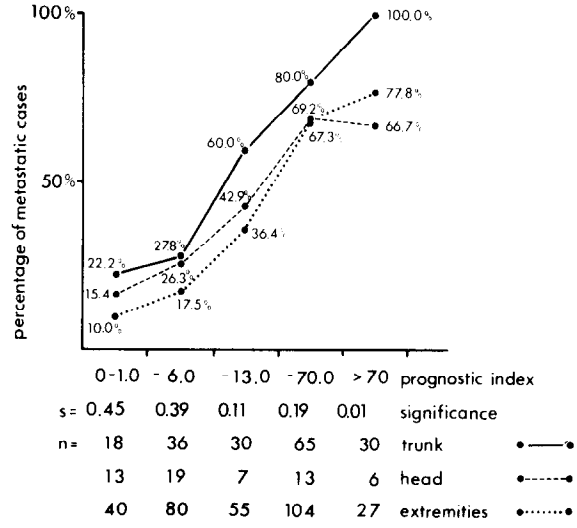

Fig. 3. Location and prognostic index. Even though the trunk had the highest rates of metastases, this was statistically significant on the last level only.

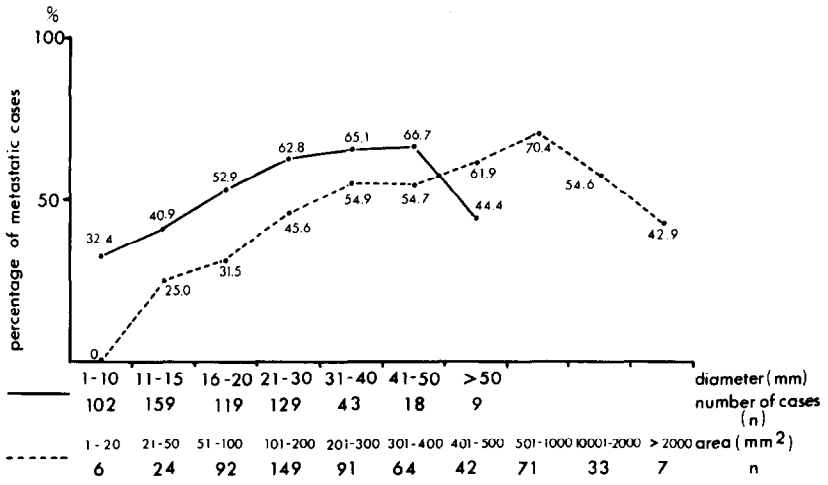

Fig. 4. Largest diameter and area (product of both diameters) and the percentages of metastatic cases.

Histopathological criteria

(6) *Level of invasion* (Fig. 5) was prognostically significant ($\chi^2 = 29.4$ with 3 degrees of freedom; $P \ll 0.001$). However, there were only 32 cases with a good (level II) and only 24 cases with a poor prognosis (level V).

(7) *Tumor thickness* (Fig. 6) was prognostically significant ($\chi^2 = 103.2$ with four degrees of freedom; $P \ll 0.001$) and more effective than the level of invasion (Fig. 10). The relationship between these two parameters is shown in Table 1; no information is gained through the level once thickness has been determined. These two criteria are dependent on each other ($P = 0.001$), the correlation coefficient being relatively high (0.42).

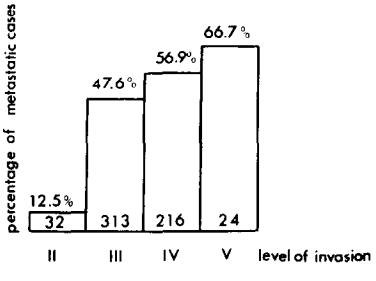

Fig. 5. Level of invasion and percentages of metastatic cases.

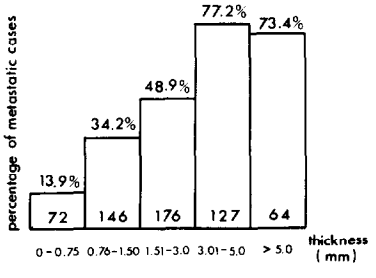

Fig. 6. Tumor thickness and percentages of metastatic cases.

Table 1. Thickness and level of invasion

thickness (mm)	≤ 0.75	→ 1.5	→ 3.0	→ 5.0	> 5.0
level II	29 (6.9%)	3 (33.3%)			
III	43 (18.6%)	108 (34.3%)	86 (52.3%)	54 (75.9%)	22 (81.8%)
IV		35 (34.3%)	87 (44.8%)	68 (77.9%)	26 (73.1%)
V		1 (100%)	3 (66.7%)	5 (80.0%)	16 (62.5%)
p	0.4	0.4	0.5	0.95	0.4

The total number of cases are given (in parentheses the percentages of cases with recurrences). In the lower line the *P*-values, determined by means of the χ^2 test, are shown.

(8) *The mitotic index* (Fig. 7) was prognostically significant ($\chi^2 = 149.9$ with four degrees of freedom; $P \ll 0.001$). It was partly dependent on tumor thickness (correlation coefficient 0.33; $P = 0.001$) and the average mitotic index increased slightly with rising thickness (Fig. 8). However, the individual values varied considerably on each thickness level and the mean mitotic indices were generally twice as high for the metastatic cases compared to the non-metastatic cases. Furthermore, the mitotic index was significant on each thickness level (Table 2).

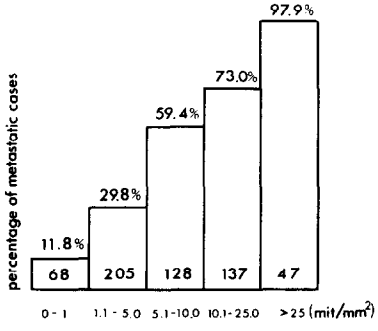

Fig. 7. Mitotic index and percentages of metastatic cases.

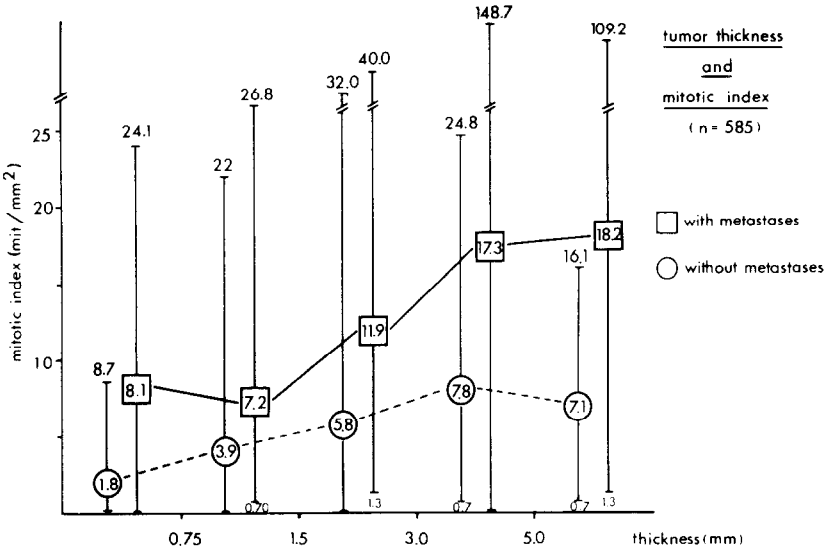

Fig. 8. Relationship between tumor thickness and the mitotic index (maxima and minima are given as well as the average values of cases with and without recurrences).

Table 2. Thickness and mitotic index

thickness (mm)		≤ 0.75	⇤1.5	⇤3.0	⇤5.0	> 5.0
mitotic index (mit/mm²)	0 - 1.0	32 (6.3 %)	18 (16.7 %)	12 (0 %)	4 (75.0 %)	2 (0 %)
	1.1 - 5.0	30 (10.0 %)	79 (25.3 %)	64 (34.3 %)	20 (45.0 %)	12 (58.3 %)
	5.1 - 10.0	6 (16.7 %)	31 (51.6 %)	41 (53.7 %)	34 (76.5 %)	16 (68.8 %)
	10.1 - 25.0	4 (100 %)	16 (56.3 %)	47 (66.0 %)	49 (81.6 %)	21 (76.2 %)
	> 25.0		2 (100 %)	12 (91.7 %)	20 (100 %)	13 (100 %)
	p	<< 0.001	0.002	<< 0.001	0.001	0.002

The total number of cases are given (in parentheses the percentages of cases with recurrences). In the lower line the *P*-values, determined by means of the χ^2 test, are shown.

(9) *The prognostic index* (Fig. 9) appeared to be the most effective prognosticator ($\chi^2 = 167.0$ with four degrees of freedom; $P \ll 0.001$, Fig. 10), as the number of cases with low and high rates of metastases was greatest (Fig. 10) and consequently the intermediate group was smallest.

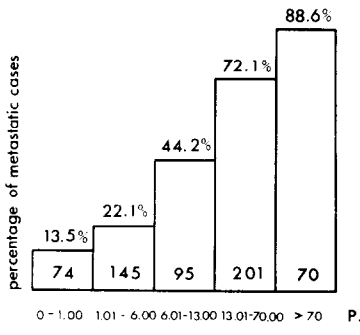

Fig. 9. Prognostic index and percentages of metastatic cases.

Table 3. Quantitative effectiveness of prognosticators

25, 3 %	prognostic index
27, 2 %	mitotic index
32, 8 %	thickness
33, 9 %	location
35, 9 %	breadth
36, 4 %	inflammation
36, 9 %	elevation
39, 2 %	clinical diameter (Dl)
41, 3 %	sex
42, 1 %	cell type
42, 6 %	infiltrative growth
42, 7 %	vascular invasion
43, 2 %	level
45, 1 %	cellular atypia
49, 6 %	type

The sum of false-negative (cases with metastases) and false-positive (cases without metastases) determinations for various parameters as a percentage of the total number of cases.

(10) *Ulceration* was prognostically significant ($P \ll 0.001$). It was seen in 303 cases, 64.4% of which had later metastases; it was not seen in 282

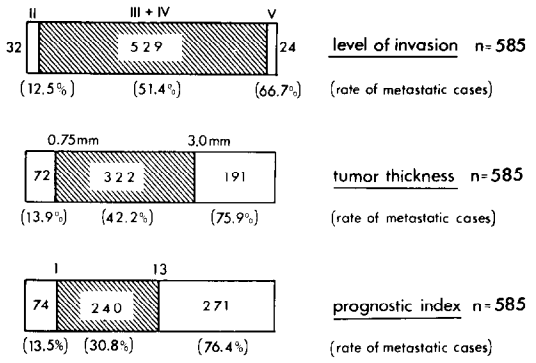

Fig. 10. Quantitative and qualitative comparison of three different prognosticators in groups with low (left), intermediate (middle) and high (right) rates of metastases.

cases, 34.0% of which had later metastases. There was a correlation with tumor thickness (correlation coefficient 0.32) and with the mitotic index (correlation coefficient 0.29). Significant differences in the occurrences of metastases were seen in thick tumors (thickness $\geqslant$3.0 mm) only (Fig. 11) and for a low or high prognostic index. The sum of false-negative and -positive cases was 34.9%.

(11) *Vascular invasion* appeared to be prognostically significant ($P \ll 0.001$). However, it was observed in 57 cases only, with 54 (94.7%) of them having had later metastases. Furthermore, there was a correlation with tumor thickness (66.7% of them were $\geqslant$3.0 mm) and particularly with the prognostic index (84.2% $\geqslant$13). A correlation was also seen with ulceration, infiltrative growth and elevation.

(12) *Cellular atypia* had a moderate prognostic significance ($P = 0.003$). Only severe atypia was associated with a high percentage of metastatic cases (91.7%), but there were only 12 patients in this group. Metastases occurred in 44.9% of 296 cases with no cellular atypia, in 50.8% of 199 cases with weak and in 59.0% of 76 cases with moderate cellular atypia.

(13) *Tumor breadth* (Figs 12, 13) was a significant prognostic parameter ($P \ll 0.001$). For a tumor breadth >10.0 mm a high percentage of metastatic cases (73.1%) was noted on every thickness level, except for thin melanomas. Only for melanomas with intermediate thickness (0.76–1.5 mm) was a continuous rise in the frequency of metastatic cases with increasing tumor breadth observed (Fig. 13).

(14) The presence of different *cell types* was prognostically irrelevant, except for small, lymphocyte-like cells. They were seen in 71 cases, 81.7% of which had later metastases.

(15) *Regression* was observed in three cases with level II, one of which developed later metastases.

(16) *Infiltrative growth* was of limited prognostic significance ($P < 0.001$). It was observed in 214 cases, 59.8% of which developed later metastases.

(17) *The inflammatory reaction* had moderate prognostic significance ($P = 0.003$). There were 100 cases without a noticeable reaction, 65.0% of

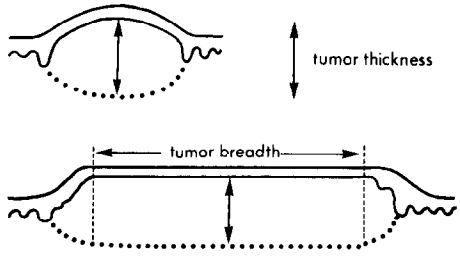

Fig. 12. Schematic definitions of tumor thickness and tumor breadth (details are given in Materials and Methods).

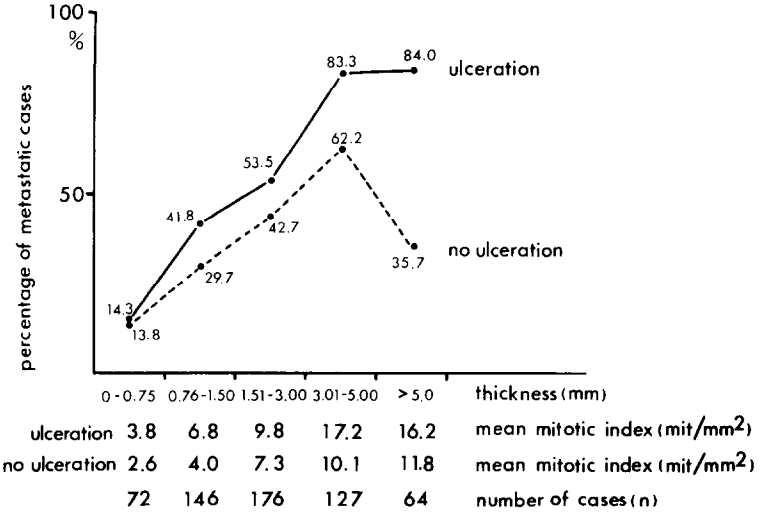

Fig. 11. Ulceration and tumor thickness. Significant differences between ulcerated and non-ulcerated tumors are seen in thicker melanomas only. Ulceration is also seen to correlate with a higher mitotic activity.

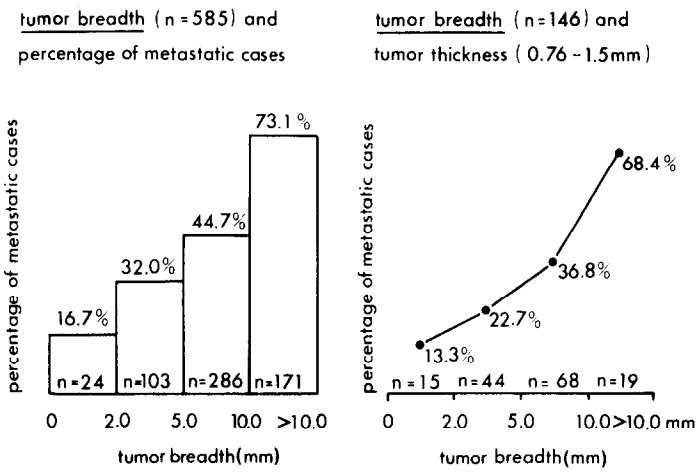

Fig. 13. Tumor breadth and the percentages of metastatic cases in 585 cases (left); tumor breadth and the percentages of metastatic cases in 146 cases with tumor thickness 0.76–1.5 mm (right).

which had later metastases; 36.4% of 44 cases with a very strong inflammatory reaction had later metastases.

(18) *Elevation* was prognostically significant ($P \ll 0.001$). Of 331 elevated melanomas, 61.3% had metastases, compared to 30.8% of 107 endophytic tumors. However, when this analysis was performed on five different thickness levels (Fig. 14) there was no more statistical difference between exophytic, intermediate and endophytic tumors.

(19) *Tumor type* had a limited prognostic significance ($P < 0.001$), with the percentages of metastatic cases in increasing order: LMM, 20.8% ($n = 24$); SSM, 42.5% ($n = 233$); ALM, 53.3% ($n = 15$); and NM, 57.2% ($n = 313$). When analyzed by thickness, LMMs were generally thin (66.7% <0.76 mm; 29.2% 0.76–1.5 mm) and only one (metastatic) case was 1.5 mm; thick tumors (≥3.0 mm) were more common in NMs. The mitotic activity was generally low in LMM, low and intermediate in ALM and more evenly distributed in NM and SSM.

(20) An associated nevocellular nevus was seen in 38 cases (6.5%); 39.5% had later metastases, but this was prognostically insignificant ($P = 0.3$).

(21) A quantitative comparison of the effectiveness of different prognosticators is shown in Table 3 and also in Fig. 10 for the level of invasion, tumor thickness and the prognostic index.

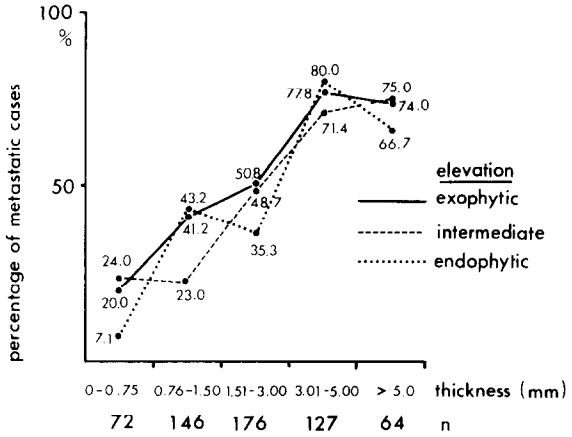

Fig. 14. The degree of elevation (exophytic, intermediate and endophytic growth) and the percentages of metastatic cases on different thickness levels.

DISCUSSION

Among the numerous criteria relevant to the prognosis of malignant melanoma, tumor volume seems to be most important. This is indicated by tumor thickness (probably a parameter of tumor volume) correlating with the occurrences of metastases. In addition, but to a lesser degree, tumor breadth measured histologically and the clinical diameters of the lesions were also shown to be associated with an increasing rate of occurrences. In this respect it was interesting to note that the endophytic or exophytic growth-type of melanomas did not seem to influence the prognosis. Apparently, the tumors are able to induce new vasculature, as indicated by studies with melanoma cells [18]. The prognostic influence of infiltrative growth was limited in this study and the level of invasion [3] was less significant than tumor thickness [4, 5]. These findings indicate the importance of tumor volume for the prognosis of malignant melanoma as compared to the ability of the tumor to infiltrate the underlying tissue. Therefore the level of invasion seems to be mainly a parameter of tumor volume only and this parameter is less effective than tumor thickness, possibly because the exophytic portion of the tumor, when present,

is not taken into consideration. At any rate, a high correlation between tumor thickness and the level of invasion (tumor thickness being the dominant determinant) was found in this study as well as in others [7, 19].

Another important prognosticator appeared to be the mitotic index, defined as the number of mitoses per mm^2 [11, 14]. It proved to be the single most relevant prognosticator (Fig. 7, Table 3) in this study. Our experience has shown that it is easily determined and reproducible enough (provided the same areas are analyzed) to be used routinely. A good tissue-fixation is mandatory; in only a few cases a high pigment load completely concealed eventual mitotic figures. The results of the mitotic index were qualitatively and quantitatively slightly better than those of tumor thickness: the correlation coefficient with the occurrence of metastases (indicating the degree of dependency) was slightly higher (0.4 vs 0.35) and the rate of false-positive and -negative cases was lower (27.2 vs 32.8%). Tumor thickness seems to be more effective in detecting low-risk melanomas, whereas the mitotic index appears to be more effective for high-risk melanomas: 46 of 47 cases (97.9%) with >25 mit/mm^2 had metastases. These two parameters were partly, but not totally, independent of each other, and this has been confirmed by other studies [8, 9, 15–17, 20] but was disputed by McGovern *et al.* [21]. Therefore, by combining tumor thickness and the mitotic index as the product, the prognostic index [11, 14] was justified.

Once tumor thickness and the mitotic activity were assessed, only a few other histological criteria seemed to have a bearing on prognosis. In this study *vascular invasion* was associated with a very high percentage of metastatic cases (94.7%), but it was seen in 57 (9.7%) cases only. It was more common in thick tumors and it was never seen in thin melanomas. These findings are in agreement with results published by others [22, 23]. Only the results of van der Esch *et al.* [9] were not conclusive. *Ulceration*, clearly related to a higher rate of metastatic cases, was significant for thick tumors ($\geqslant 3.0$ mm) only. A similar finding was reported by van der Esch *et al.* [9]. A correlation with tumor thickness was also observed in other studies [19]; Balch *et al.* found ulceration to be significant on each thickness level [24].

Regression was seen in only three cases with level II, one of which developed later metastases. This finding may confirm the report by Gromet *et al.* [25]; once regression is noted in thin melanomas a good prognosis cannot be made. Among the other criteria studied only *severe cellular atypia* and the presence of *small, lymphocyte-like cells* were both associated with a high percentage of metastatic cases.

Studies of this kind are strongly influenced by the selection of cases. In this investigation criteria of selection (as indicated in Material and Methods) were only some indispensible requirements. A high ratio of female patients resulted, but this ratio seems to be normal for central Europe [20, 26]. Of greater importance with regard to a possible uneven selection of patients in this study seems to be the low number of thin tumors (12.3%) and, probably related, the relative low percentage of cases with a disease-free, 5-yr follow-up (50.3%). This seems to account for the relatively high rate (13.9%) of metastatic thin melanomas (most of these patients have died by now). On the other hand, such a high percentage of metastatic cases allows the prognostic significance of various parameters to be studied effectively. Another concern is the lack of serial or step sections in this study, which might have improved the results. But as indicated by Sondergaard [27], central cross-sections are sufficient for such histological investigations.

In the next section of this study ways to effectively combine these prognosticators will be examined.

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