

# Low- and High-risk Malignant Melanoma—III. Prognostic Significance of the Resection Margin\*

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**Abstract**—The influence of the resection margin on the prognosis of malignant melanoma was investigated in 577 cases (stage I), 285 with later recurrences and 292 disease-free for at least 5 yr. The resection margins varied considerably, with  $\leq 10$  mm in 172 cases and ca. 50 mm in 85 cases. Low- and high-risk melanomas (determined by means of tumor thickness and mitotic index) were found to be distributed evenly, with only minor variations for different resection margins. The occurrence of metastases was found to be independent of the resection margin, and several statistical methods were used (correlation coefficients, chi-square tests, discriminant analyses). This was also true when high-risk cases were analyzed separately. In contrast, for low-risk melanoma (68 cases), the six metastatic cases had a resection margin  $\leq 20$  mm (11.8% vs 0%,  $P=0.3$ ). Furthermore, local recurrences (40 in 482 cases) were seen more frequently in cases with a resection margin  $< 30$  mm (10.0 vs 2.9%,  $P=0.02$ ). However, local recurrences did not appear to be responsible for disseminated disease, as 82.1% were at high and 10.3% were at medium risk. The benefit of a 5-cm resection margin could not be substantiated in this study. A 3-cm resection margin may be necessary to lower the risk of local recurrences and a 2-cm margin appeared to be sufficient for low-risk melanoma.

## INTRODUCTION

SURGICAL excision constitutes the main step in treatment of stage I malignant melanoma. However, the extent of the resection margin [1] and the type of anesthesia necessary remain matters of debate, since few studies analyzing these issues have been reported.

We are presenting the findings in 577 surgically treated cases in which the prognostic significance of various clinical and histological parameters have been studied [2, 3]. Since the resection margins applied varied considerably (and even cases with minimal margins were numerous), and since nearly 50% of the patients developed later metastases (the others were disease-free for at least 5 yr), we were able to statistically examine the influence on prognosis of these different surgical procedures.

## MATERIAL AND METHODS

The same cases studied in the two preceding articles [2, 3] were analyzed. In 577 patients treated in different dermatology clinics in West Germany (240 in Munich) from 1965 to 1975, the minimal resection margins were indicated in surgery reports and shown in most cases on pre-operative photographs with the planned resection lines painted on the skin along with a grading scale. Local anesthesia was used in 46 cases; the others had regional or general anesthesia.

Two hundred and ninety-two patients were disease-free for at least 5 yr and 285 had later recurrences. Local recurrences were observed in 40 cases (in 104 cases, all with later metastases, exact information as to the presence of local recurrences could not be obtained at the time of this multicentric investigation). In four cases local recurrences developed after a distant metastasis had occurred; in four other cases no further metastases occurred.

In these patients clinical (age, sex, site and

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horizontal diameters) as well as histological (level of invasion [4], tumor thickness [5], mitotic index [6, 7], prognostic index [6, 7], ulceration, vascular invasion, tumor breadth [2], tumor elevation, cellular atypia, cell type, inflammatory reaction, histogenetic type and adjacent nevocellular nevus) parameters were determined and computerized along with the resection margins. The following analyses and statistical evaluations were carried out:

(1) *The influence of resection margins on the rate of recurrences and local recurrences*

The percentages of cases with metastases and local recurrences for different resection margins (differentiated in 6 different groups) and for cases with amputation (e.g. ears, fingers and toes) were determined. The results were analyzed by means of chi-square tests, correlation coefficients and discriminant analyses.

(2) *The influence of resection margins on the rate of recurrences differentiated for low- and high-risk cases*

The percentages of metastatic cases for different resection margins in five different thickness and prognostic index groups were determined and analyzed statistically by means of the chi-square test.

(3) *Analysis of a possible selected distribution of cases according to different resection margins*

The mean values (including the standard deviation and Student's *t* test) of tumor thickness and prognostic index were determined for cases with and without metastases according to different resection margins. These parameters were also determined for cases with local recurrences.

A possible correlation between the two major prognosticators analyzed and the resection margin as well as local recurrences were examined by means of correlation coefficients for orientation and by means of chi-square tests.

(4) *The influence of local anesthesia on the rate of metastatic cases*

In cases with local anesthesia the medium tumor thickness and prognostic index as well as the resection margins were determined.

## RESULTS

(1) *The influence of resection margins on the rate of recurrences and local recurrences*

The percentages of cases with metastases for different resection margins are shown in Fig. 1. The results are statistically significant by means

of the chi-square test ( $P = 0.003$ ), apparently indicating fewer recurrences for very small and medium resection margins. However, the correlation coefficient between the resection margin and the occurrence of metastases was very low ( $0.0033$ ;  $P = 0.5$ ), and discriminant analyses excluded the resection margin as an (independent) prognosticator.

The percentages of cases with local recurrences for different resection margins are shown in Fig. 2. Only three cases (2.9%) with a resection margin  $>30$  mm had local recurrences, compared to 36 with  $\leq 30$  mm (10.0%). This was statistically significant ( $P = 0.02$ ).

(2) *The influence of different resection margins on the rate of recurrences differentiated for low- and high-risk cases*

The percentages of metastatic cases were analyzed for five different tumor thickness and prognostic index levels. There were some variations for tumor thickness which were less pronounced for the prognostic index. The results were statistically insignificant ( $P > 0.04$ ) on each prognostic index level; high-risk cases (258 with a

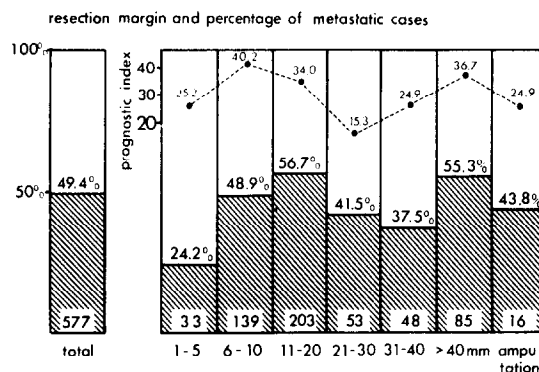


Fig. 1. Percentages of metastatic cases and the total number of cases for different resection margins.

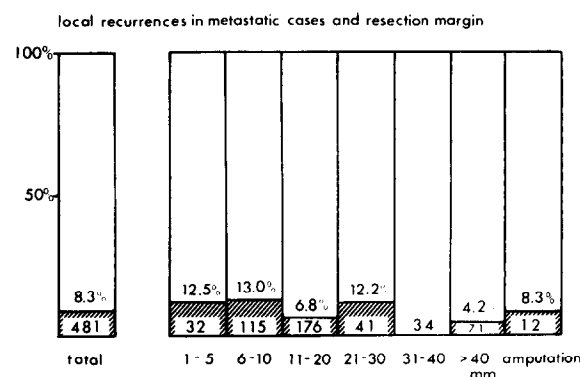


Fig. 2. Percentages of cases with local recurrences and the total number of cases for different resection margins.

prognostic index  $\geq 13$  and 20 additional cases with vascular invasion or ulceration with tumor thickness  $\geq 3.0$  mm and 12 (30.8%) were prognostic were 65.2% recurrences for a resection margin  $> 30$  mm ( $n = 69$ ) and 77.0% for a resection margin  $\leq 30$  mm ( $n = 209$ ). This was statistically insignificant ( $P = 0.07$ ).

Since tumor thickness alone was not sufficient to effectively determine low-risk melanomas, cases with a mitotic index  $> 10.0$  mit/mm<sup>2</sup> were excluded. In this group of 68 cases (Fig. 4), the six metastatic cases had a resection margin  $\leq 20$  mm; therefore for a resection margin  $\leq 20$  mm the percentages of metastatic cases was 11.8% (51 cases) and for  $> 20$  mm 0% (16 cases). This is statistically insignificant ( $P = 0.35$ ) due to the small number of cases.

For medium-risk cases minor variations of the percentages of metastatic cases were noted: 1–5 mm, 33.1% (13 cases); 6–10 mm, 18.2% (55 cases); 11–20 mm, 41.0% (78 cases); 21–30 mm, 28.6% (28 cases); 31–40 mm, 21.7% (23 cases);  $> 40$  mm, 46.2% (39 cases).

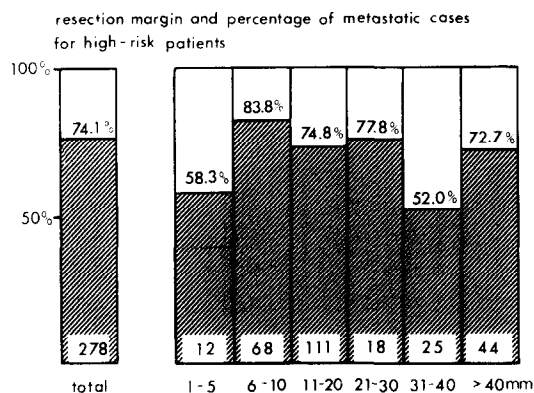


Fig. 3. Percentages of metastatic cases in high-risk melanomas [prognostic index  $\geq 13$  ( $n = 258$ ) or vascular invasion or ulceration with tumor thickness  $\geq 3.0$  mm ( $n = 20$ )] for different resection margins.

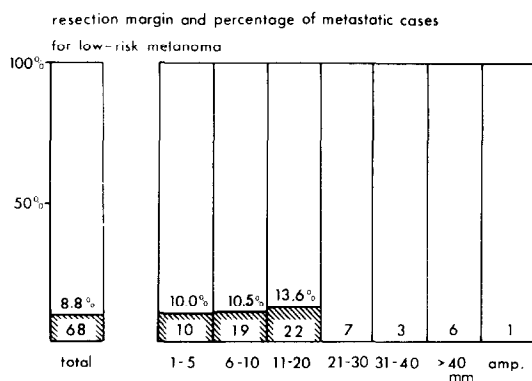


Fig. 4. Percentages of metastatic cases in low-risk melanomas (tumor thickness  $< 0.76$  mm, mitotic index  $< 10$  mit/mm<sup>2</sup>) for different resection margins.

### (3) Analysis of a possible selected distribution of cases according to different resection margins

The mean values of the resection margins, of tumor thickness and of the prognostic indices for all cases and for cases without metastases, with metastases and with local recurrences are shown in Table 1. The average resection margin for local recurrences is noted to be definitely smaller. The mean values of these three parameters differentiated for six different groups of resection margins are shown in Table 2. Variations of percentages of metastatic cases for different resection margins can be partly explained by variations of the average prognostic index (Fig. 1).

In addition, a correlation was seen between site and the resection margin (by means of the chi-square test,  $P \leq 0.001$ ): melanomas with an unfavorable location (trunk, palms and soles) were seen more frequently in the two groups with the highest percentages of metastatic cases (11–20 and  $> 40$  mm) compared to the rest of the tumors. Therefore some minor variations were seen for the prognostic index and location which may partly account for the differences in the percentages of metastatic cases. However, the percentages varied also when low- (Fig. 4) and high-risk cases (Fig. 3) were analyzed separately, but the number of cases

Table 1. Average resection margin, tumor thickness and prognostic index for all cases (except cases with amputation), cases without metastases, with metastases and with local recurrences

	mean: resection margin	tumor thickness	prognostic index
all cases ( $n = 561$ )	24.54 mm	2.64 mm	33.1
no metastases ( $n = 233$ )	24.48 mm	1.85 mm	11.1
with metastases ( $n = 278$ )	24.60 mm	3.44 mm	55.4
local recurrences ( $n = 39$ )	19.36 mm	4.23 mm	72.1

Table 2. Average resection margin, tumor thickness and prognostic index (including standard deviation) for different resection margins

resection margin (mm)	n	mean resection margin (mm)	mean tumor thickness (STDev.) (mm)	mean prognostic index (STDev.)
1-5	33	4.3	2.37 (2.27)	25.2 (48.5)
6-10	139	9.6	2.64 (2.79)	40.2 (91.7)
11-20	203	17.3	2.63 (1.99)	34.0 (51.5)
21-30	53	28.3	2.25 (1.79)	15.3 (22.0)
31-40	46	37.5	2.81 (2.22)	24.9 (28.4)
> 40	87	50.2	2.65 (2.20)	36.7 (97.0)

decreased considerably, limiting the significance of these results.

These analyses also revealed that most of the cases with local recurrences were at a high risk of developing metastases: 25 (64.1%) had a tumor thickness 3.0 mm and 12 (30.8%) were medium-risk (0.76–2.9 mm); 32 (82.1%) had a prognostic index  $\geq 13$  and 4 (10.3%) were medium-risk (1.1–12.9 mm). Only two cases were low-risk (tumor thickness  $\leq 0.75$  mm), and all three cases with local recurrences and with a resection margin  $> 30$  mm had a prognostic index  $> 6$ . Furthermore, the mean values of tumor thickness and the prognostic index were considerably higher compared to the rest of the tumors (Table 1).

*(4) The influence of local anesthesia on the rate of recurrences*

In 46 cases with local anaesthesia 16 (34.8%) developed later metastases. The resection margins were  $\leq 30$  mm, and in 34 cases  $\leq 10$  mm. For low-risk melanomas (tumor thickness  $\leq 0.75$  mm, mitotic index  $< 10$  mit/mm<sup>2</sup>) the rate of recurrence was 0% (12 cases). For medium-risk melanomas the rate of recurrence was 16.7% (18 cases). For high-risk melanomas (prognostic index  $\geq 13$ ) the rate of recurrence was 81.3% (16 cases). Since the number of cases was relatively small, no statistical analysis was carried out.

## DISCUSSION

In the treatment of malignant melanoma the minimum resection margin without decreasing chances of survival is still a matter of debate. Few studies analyzing this issue have been published, as several limitations are obvious: hundreds of well-documented cases with sufficient follow-up are necessary because many prognosticators, in particular, tumor thickness [5], mitotic activity [6, 7] and location [8–10], need to be considered. Furthermore, since a wide excision is generally performed, few cases with a very small resection margin are available for evaluation.

In this multicentric study of 577 cases the resection margin varied considerably because treatment procedures varied during different periods and in different clinics. The possibility of resection margins being influenced clinically with early and advanced melanomas being treated differently was largely excluded.

Since malignant melanoma constitutes a heterogeneous group of neoplasms, prognostically homogeneous groups are necessary for determining the effectiveness of therapeutical modalities. In this study [2, 3] tumor thickness

and mitotic activity were found to be the predominant histological prognosticators which were combined as the prognostic index. For high-risk melanomas ulceration and vascular invasion added little additional information. This was particularly true for clinical criteria such as sex and site.

Our results reveal no overall favorable effect of a wide excision on the prognosis of malignant melanoma. Some variations, in particular, a slightly higher-than-average percentage of metastatic cases for a resection margin  $> 40$  mm (the average margin was 50.2 mm), correlated with variations of the mean prognostic index. In addition, when high- and medium-risk cases were analyzed separately, the rate of metastatic cases appeared to be independent of the resection margin. For low-risk melanomas, however, the six metastatic cases had a resection margin  $\leq 20$  mm. None of the patients had received local anaesthesia, four were located on the trunk (three of them were males) and two of them were lentigo-maligna melanomas located on the faces of females. The relevance of these findings, suggesting the necessity of a 2-cm margin even in low-risk malignant melanomas, remains to be seen, as thin melanomas even with narrow resection margins have been reported not to metastasize [11, 12]. Our findings, particularly the relatively high percentage (13.9%) of metastases in these thin melanomas (most of these patients have since died due to metastatic spread) is unusual and may be influenced by an unbalanced selection of cases as the rate of recurrences (49.7%) is relatively high. Therefore disease-free cases, and in particular early cases with a good prognosis, are probably less numerous in this study than would be expected.

Another problem is that local recurrences are seen more frequently here in cases with a resection margin  $\leq 30$  mm. Similar results were reported by others [13–15]. However, it appears doubtful that distant metastases were caused by local recurrences and could have been prevented by a wider excision. Most of the cases with local recurrences in this study were at a high risk of developing metastases, as indicated by tumor thickness and by the prognostic index. Since it cannot be proven that distant metastases are unrelated to local recurrences, a resection margin  $> 3$  cm decreasing the risk of local recurrences may be necessary. This opinion was recently expressed by Rampen [16] analyzing the results of Cascinelli *et al.* [14].

Another interesting question in the surgical treatment of malignant melanoma is whether local anesthesia can be used safely. Our findings in 46 cases so treated did not show any major unfavorable effect, but the number of cases is too

low, precluding a profound statistical analysis. In this respect it is interesting to note that excisional biopsy (probably performed with local anes-

thesia) followed by wide excision was not found to be related to a lower 5-yr survival rate in malignant melanoma [17].

## REFERENCES

1. DAY CL, JR, MIHM MC, JR, SOBER AJ, FITZPATRICK TB, MALT RA. Narrower margins for clinical stage I malignant melanoma. *N Engl J Med* 1982, **306**, 479-482.
2. SCHMOECKEL C, BOCKELBRINK A, BOCKELBRINK H, KOUTSIS J, BRAUN-FALCO O. Low- and high-risk malignant melanoma—I. Evaluation of clinical and histological prognosticators in 585 cases. *Eur J Cancer Clin Oncol* 1983, **19**, 227-235.
3. SCHMOECKEL C, BOCKELBRINK A, BOCKELBRINK H, BRAUN-FALCO O. Low- and high-risk malignant melanoma—II. Multivariate analyses for a prognostic classification. *Eur J Cancer Clin Oncol* 1983, **19**, 237-243.
4. CLARK WH, JR, FROM L, BERNARDINO EA, MIHM MC. The histogenesis and biologic behavior of primary human malignant melanoma of the skin. *Cancer Res* 1969, **29**, 705-726.
5. BRESLOW A. Tumor thickness, level of invasion and node dissection in stage I cutaneous melanoma. *Ann Surg* 1975, **182**, 572-575.
6. SCHMOECKEL C. *The Prognostic Index in Malignant Melanoma*. Dallas, TX, American Academy of Dermatology, 1977.
7. SCHMOECKEL C, BRAUN-FALCO O. Prognostic index in malignant melanoma. *Arch Dermatol* 1978, **114**, 871-873.
8. DAY CL, JR, MIHM MC, JR, SOBER AJ *et al*. Prognostic factors for melanoma patients with lesions 0.76-1.69 mm in thickness: an appraisal of 'thin' level IV lesions. *Ann Surg* 1982, **195**, 30-34.
9. DAY CL, JR, MIHM MC, JR, LEW RA *et al*. Prognostic factors for patients with clinical stage I melanoma of intermediate thickness (1.51-3.99 mm): a conceptual model for tumor growth and metastasis. *Ann Surg* 1982, **195**, 35-43.
10. DAY CL, JR, LEW RA, MIHM MC, JR *et al*. A multivariate analysis of prognostic factors for melanoma patients with lesions  $\geq 3.65$  mm in thickness: the importance of revealing alternative Cox models. *Ann Surg* 1982, **195**, 44-49.
11. BRESLOW A, MACHT SD. Optimal size of resection margin for thin cutaneous melanoma. *Surg Gynecol Obstet* 1977, **145**, 691-692.
12. BALCH CM, MURAD TM, SOONG S-J, INGALLS AL, RICHARDS PC, MADDOX WA. Tumor thickness as a guide to surgical management of clinical stage I melanoma patients. *Cancer* 1979, **43**, 883-888.
13. ELIAS EG, DIDOLKAR MS, JOEL JP. A clinicopathological study of prognostic factors in cutaneous malignant melanoma. *Surg Gynecol Obstet* 1977, **144**, 327-334.
14. CASCINELLI N, VAN DER ESCH P, BRESLOW A, MORABITO A, BUFALINO R. Stage I melanoma of the skin: the problem of resection margins. *Eur J Cancer* 1980, **16**, 1079-1085.
15. BAGLEY FH, CADY B, LEE A, LEGG MA. Changes in clinical presentation and management of malignant melanoma. *Cancer* 1981, **47**, 2126-2134.
16. RAMPEN F. Melanoma of the skin: the problem of resection margin (letter to the editor). *Eur J Cancer* 1981, **17**, 589-590.
17. ELDH J. Excisional biopsy and delayed wide excision versus primary wide excision of malignant melanoma. *Scand J Plast Reconstr Surg* 1979, **13**, 341-345.