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Excision Margins in High-Risk Malignant Melanoma

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ABSTRACT

BACKGROUND

Controversy exists concerning the necessary margin of excision for cutaneous melanoma 2 mm or greater in thickness.

METHODS

We conducted a randomized clinical trial comparing 1-cm and 3-cm margins.

RESULTS

Of the 900 patients who were enrolled, 453 were randomly assigned to undergo surgery with a 1-cm margin of excision and 447 with a 3-cm margin of excision; the median follow-up was 60 months. A 1-cm margin of excision was associated with a significantly increased risk of locoregional recurrence. There were 168 locoregional recurrences (as first events) in the group with 1-cm margins of excision, as compared with 142 in the group with 3-cm margins (hazard ratio, 1.26; 95 percent confidence interval, 1.00 to 1.59; P=0.05). There were 128 deaths attributable to melanoma in the group with 1-cm margins, as compared with 105 in the group with 3-cm margins (hazard ratio, 1.24; 95 percent confidence interval, 0.96 to 1.61; P=0.1); overall survival was similar in the two groups (hazard ratio for death, 1.07; 95 percent confidence interval, 0.85 to 1.36; P=0.6).

CONCLUSIONS

A 1-cm margin of excision for melanoma with a poor prognosis (as defined by a tumor thickness of at least 2 mm) is associated with a significantly greater risk of regional recurrence than is a 3-cm margin, but with a similar overall survival rate.

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THE RISK OF DEATH FROM CUTANEOUS melanoma is determined mainly by the thickness of the tumor, as described by Breslow,[1] the presence or absence of tumor ulceration and microdeposits of melanoma in sentinel lymph nodes,[2,3] the site of the tumor, and the patient's sex.[4] Spread occurs by lymphatic and hematogenous routes. Micrometastases from primary tumors migrate through cutaneous lymphatics to the regional lymph nodes. Traditionally, wide margins of excision have been used to prevent lymphatic spread, but over the past decade, margins have become smaller because previous trials have suggested that narrower margins are safe.[5-7] The issue remains controversial because inadequate excision margins increase the risk of local recurrence and in-transit metastases, both of which are associated with a high mortality rate.[8] Conversely, unnecessarily large margins of excision are associated with greater morbidity and increased cost.

The width of the excision margin has been investigated in three randomized trials of patients with predominantly[8] or exclusively[9,10] thin tumors with a good prognosis. Wide and narrow margins were associated with similar rates of recurrence and survival, but these trials may have been too small to detect an adverse effect of a narrow margin owing to an insufficient number of events. The Intergroup Melanoma Surgical Trial[8] found no difference in results between 2-cm margins and 4-cm margins for melanomas that were 1 to 4 mm thick, but the mean thickness of the melanomas was 1.96 mm, and only 207 patients (44 percent) had melanomas that were more than 2 mm thick. We conducted a multicenter clinical trial to investigate the effect of the margin of excision on the outcome in patients with high-risk malignant melanoma.

METHODS

STUDY DESIGN

The randomized trial was performed under the auspices of the United Kingdom Melanoma Study Group, the British Association of Plastic Surgeons, and the Scottish Cancer Therapy Network. It was coordinated by the Clinical Trials and Statistics Unit at the Institute of Cancer Research, Sutton, United Kingdom. Recruitment began in January 1993 and ended in July 2001. Eligible patients had a single, primary, localized cutaneous melanoma 2 mm or greater in thickness on the trunk or limbs (excluding the palms of the hands or the soles of the feet), where a 3-cm excision margin was technically possible. Patients had to be at least 18 years old and could not be pregnant. Patients who had a history of cancer (other than basal-cell carcinoma) or who were receiving immunosuppressive therapy were ineligible. Elective lymph-node dissection, sentinel-node biopsy, or adjuvant therapy was not allowed. Investigations other than chest radiography to determine the stage of disease were deemed unnecessary.

Participating surgeons chose one of two primary treatment approaches. The primary tumor could be excised before randomization, with either a 1-mm or a 1-cm margin to confirm the diagnosis and determine the thickness of the lesion. The patients were then randomly assigned to receive a 1-cm or 3-cm margin after the 1-mm primary excision or to receive no further treatment or an additional 2-cm margin after the 1-cm primary excision. The trial surgery was to be performed within 45 days after the primary excision, and all excisions were to extend to or include the deep fascia. The wound-closure techniques used were at the discretion of the surgeon.

Local recurrence was defined as a recurrence within 2 cm of the scar or graft. In-transit recurrence was defined as a recurrence from beyond the first 2 cm of the scar or graft to the regional nodes. All locoregional recurrences were detected clinically and confirmed by biopsy. The thickness of the tumor was measured at the referral centers before randomization. The presence or absence of ulceration was assessed by means of a centralized review. Data on the quality of life were collected from a sample of 426 patients and are reported separately.

STATISTICAL ANALYSIS

Randomization was performed by telephone at a central site and was stratified according to the center and the extent of primary surgery (1-mm initial margin of excision or 1-cm initial margin of excision). Permuted blocks of random size were used for randomization, and the allocation ratio was 1:1. All analyses were conducted according to the intention-to-treat principle. An independent data-monitoring committee regularly reviewed the trial results and reported its conclusions in a blinded fashion to the trial management group. The time to an event was measured from the date of randomization. The originally specified primary end points were the time to the first local or in-transit recurrence (the study had 90 percent power to detect an absolute increase in the rate from 10 percent to 20 percent at three

years; 82 events were required) and regional lymph-node or distant metastasis (90 percent power to detect an absolute increase in the incidence from 40 percent to 55 percent at three years; 238 events required). A secondary end point was overall survival (90 percent power to detect an absolute difference of 15 percent in the mortality rate corresponding to a 40 percent rate, as compared with a 55 percent rate; 238 events required). The target enrollment was originally intended to be 600 patients.

We anticipated that the three-year rate of local or in-transit recurrence in the groups as a whole would be 15 percent, but it was found to be approximately half this figure. The data-monitoring committee and the trial management group therefore agreed that the sample size should be increased to 900 patients and the end points altered by combining the rates of local or in-transit recurrence with the rate of nodal recurrence into the single primary end point of locoregional recurrence. This decision coincided with the publication of the results of the Swedish Melanoma Study Group trial,[9] which had combined local recurrence, in-transit recurrence, and regional-node metastases into the single end point of locoregional recurrence. The trial management group was unaware of the emerging results of our trial when the end points and the study size were changed. Locoregional recurrence and disease-free survival therefore became the primary end points. Since most first events in clinical practice are locoregional recurrences, these two primary end points are not independent events, and consequently no adjustment was made for multiple comparisons.

Life-table curves were calculated according to the Kaplan–Meier method,[11] and the effect of prognostic factors was assessed with the use of Cox regression analysis.[12] Tests for heterogeneity were used in all cases except those that examined the effect of tumor thickness, which was fitted as a linear trend. In the analysis of the time to locoregional recurrence, follow-up was truncated at the time of the first local, in-transit, or nodal recurrence (event) or distant metastasis (the censoring event) owing to the fact that only the first "nodal or distant" recurrence was recorded on the case-report form. Death without recurrence was counted as an event in the calculation of disease-free survival (for which the event was recurrence or death). Two-sided significance tests were used throughout.

The independent data-monitoring committee regularly reviewed the progress of the trial; the alpha spending function used a P value of less than 0.001 for interim analyses and a P value of 0.05 for the final analysis. Ten patients (1.1 percent) were lost to follow-up immediately after randomization. A P value for interaction of 0.01 was predefined as the level to be achieved before a subgroup result would be considered to override the overall treatment result.

The ethics committee at each center approved the study. All patients gave written or oral informed consent.

RESULTS

Table 1 summarizes the features of the trial and characteristics of the patients. A total of 900 patients were enrolled, 453 of whom were assigned to a 1-cm margin of excision and 447 to a 3-cm margin of excision. Of these patients, 742 initially had a 1-mm margin of excision and 158 a 1-cm margin of excision. There were protocol deviations in 14.0 percent of the patients (Table 1); the majority were minor. The median tumor thickness was 3.0 mm in the group with 1-cm margins of excision and 3.1 mm in the group with 3-cm margins of excision. The site of the melanoma had the expected distribution within the two sexes. Among the men, 48.1 percent had tumors on the back and 18.1 percent had lower-limb tumors, whereas 18.4 percent of the women had tumors on the back and 52.9 percent had lower-limb tumors.

Of the patients in the group with 3-cm margins of excision, 66.4 percent had an inpatient procedure with a general anesthetic, as compared with 32.1 percent of the patients in the group with 1-cm margins of excision (P<0.001). The rate of surgical complications was 7.8 percent among patients who had a 1-cm margin of excision and 13.9 percent among the patients who had a 3-cm margin of excision (P=0.05). The median follow-up was 60 months, and there was no significant difference in the pattern of loss to follow-up between the two groups.

Table 2 lists the distribution of events, and Table 3 summarizes the end points. Univariate analysis showed that the overall relative rate of locoregional recurrence was 26 percent higher in the group with 1-cm margins of excision than in the group with 3-cm margins (hazard ratio, 1.26; 95 percent confidence interval, 1.00 to 1.59; P=0.05) (Tables 3 and 4 and Fig. 1A). The protocol-defined end points refer to event rates at three years, because most recurrences occur within this period; the hazard ratio for locoregional recurrence up to three

Table 1. Features of the Trial and Characteristics of the Patients.

Variable	1-cm Margin of Excision	3-cm Margin of Excision
Trial features		
No. randomized	453	447
No. eligible	388	386
No. with protocol deviations	65	61
Tumor thickness <2 mm on review	30	32
Sentinel-node biopsy performed	14	13
Previous or synchronous cancer	6	1
Surgical timing incorrect	3	4
3-cm margin not possible because of site of tumor	4	2
Tumor not melanoma	1	2
Metastatic disease	1	1
Other	6	6
No. completing treatment	446	444
No. with an event	206	172
No. who died	144	137
No. actively followed up	303	302
No. lost to follow up	6	8
Patients' characteristics		
Age (yr)		
Mean	57	58
Range	16–86	19–92
Sex (%)		
Male	54	49
Female	46	51
Tumor thickness*		
Median (mm)	3.0	3.1
Range (mm)	1.7–18.0	1.0–17.0
Distribution (%)		
<2.0 mm	0.2	0.4
2.0–2.5 mm	35.3	32.5
2.6–3.0 mm	18.4	17.0
3.1–4.0 mm	20.6	22.2
>4.0 mm	25.7	28.3
Site (%)†		
Limb	54.7	53.5
Distal	30.6	31.7
Proximal	24.1	21.8
Trunk	45.3	46.5
Ulceration (%)‡		
Absent	63.4	60.2
Present	36.6	39.8
Surgery (%)		
1-mm initial margin and either 1-cm or 3-cm final margin of excision	82.1	82.8
1-cm initial margin and either no further treatment or an additional 2-cm margin	17.9	17.2

* The tumor thickness was determined at the referral centers before randomization and the histologic review. Data were missing for one patient in the group with 1-cm margins of excision and two patients in the group with 3-cm margins of excision.

† Seven patients were excluded from the analysis: in two patients the site could not be classified, and in five the site meant that the patient was ineligible for enrollment.

‡ The presence or absence of ulceration could not be assessed in 120 patients: 60 in the group with 1-cm margins of excision and 60 in the group with 3-cm margins of excision.

years was 1.34 for the group with 1-cm margins of excision, as compared with the group with 3-cm margins of excision (95 percent confidence interval, 1.06 to 1.71; P=0.02); beyond three years it was 0.69 (95 percent confidence interval, 0.36 to 1.37; P=0.30), on the basis of only 36 events. The difference in disease-free survival approached statistical significance, but the largest component of the combined end point was locoregional recurrence (hazard ratio for death or recurrence for the group with 1-cm margins as compared with the group with 3-cm margins, 1.21; 95 percent confidence interval, 0.99 to 1.46; P=0.06) (Table 3 and Fig. 1B).

There were 144 deaths in the group with 1-cm margins of excision, as compared with 137 in the group with 3-cm margins of excision (hazard ratio, 1.07; 95 percent confidence interval, 0.85 to 1.36; P=0.6); 128 and 105 deaths, respectively, were attributable to melanoma (hazard ratio, 1.24; 95 percent confidence interval, 0.96 to 1.61; P=0.1) (Table 3). There were no significant differences between the groups in either melanoma-specific survival (Fig. 1C) or overall survival (Fig. 1D). Subsidiary analyses showed that the hazard ratio for local or in-transit recurrence, as a first or secondary recurrence, was 1.51 in the group with 1-cm margins of excision, as compared with the group with 3-cm margins of excision (95 percent confidence interval, 0.91 to 2.51; P=0.1), and for regional-node recurrence, as a first or secondary recurrence, it was 1.21 (95 percent confidence interval, 0.96 to 1.53; P=0.1).

A total of 769 patients had complete data on all the factors included in the multivariate analysis; evaluation of ulceration was possible in 780 patients, the tumor site was unclassifiable in 5 patients, 4 patients lacked follow-up data, and in 2 patients the tumor thickness at the time of randomization was unknown. The effect of a 1-cm margin width, as compared with a 3-cm margin width, was increased by multivariate analysis adjusting for known prognostic factors (hazard ratio for locoregional recur-

Table 2. Distribution of Events in the Two Groups.

Event	1-cm Margin of Excision	3-cm Margin of Excision	Total
	no. of events		
First event			
Local recurrence	15	13	28
In-transit recurrence	10	7	17
Nodal recurrence	135	118	253
Local or in-transit recurrence and nodal recurrence	7	3	10
Distant metastasis	38	30	68
Local or in-transit recurrence and distant metastasis	1	1	2
Total no. of locoregional events	168	142	310
Total no. of first events	206	172	378
Death			
From melanoma	128	105	233
From other causes			
After recurrence			
Cardiovascular causes	1	6	7
Other cancers	0	1	1
Other	3	1	4
Without recurrence			
Cardiovascular cause	8	15	23
Other cancers	1	4	5
Other	3	4	7
Cause unknown	0	1	1
Total	144	137	281

Table 3. Incidence of Primary and Secondary End Points.*

End Point	1-cm Margin of Excision	3-cm Margin of Excision	Hazard Ratio (95% CI)	P Value
	no. of events			
Primary				
Locoregional recurrence	168	142	1.26 (1.00–1.59)	0.05
Recurrence or death	220	195	1.21 (0.99–1.46)	0.06
Secondary				
Local or in-transit recurrence	37	25	1.51 (0.91–2.51)	0.1
Regional-node recurrence	149	129	1.21 (0.96–1.53)	0.1
Death from melanoma	128	105	1.24 (0.96–1.61)	0.1
Death from any cause	144	137	1.07 (0.85–1.36)	0.6

* Local or in-transit recurrence and nodal recurrence occurring after other types of recurrence were included in the assessment of these two end points to avoid informative censoring. CI denotes confidence interval.

Table 4. Univariate Analysis of the Time to Locoregional Recurrence.*

Factor	No. of Patients	Hazard Ratio (95% CI)	P Value
Margin of excision			
3 cm†	443	1.00	
1 cm	447	1.26 (1.00–1.59)	0.05
Sex			
Female†	425	1.00	
Male	465	1.43 (1.14–1.79)	0.002
Age			
<60 yr†	473	1.00	
≥60 yr	417	0.95 (0.76–1.18)	0.6
Tumor thickness‡			
2 mm	244	0.66 (0.53–0.83)	
3 mm†	279	1.00	
4 mm	152	1.34 (1.07–1.68)	
5 mm	80	1.69 (1.35–2.11)	
6 mm	132	2.03 (1.63–2.54)	<0.001
Site§			
Distal limb†	276	1.00	
Proximal limb	203	1.25 (0.91–1.72)	
Trunk	406	1.37 (1.05–1.79)	0.06
Ulceration¶			
Absent†	477	1.00	
Present	298	2.12 (1.68–2.68)	<0.001

* The analysis includes 890 patients because 10 patients were lost to follow-up immediately after randomization. CI denotes confidence interval.
† This group served as the reference group.
‡ The tumor thickness was determined at the referral center and fitted as a linear trend. Data were missing for three patients.
§ Five patients were excluded from the analysis because the site meant the patient was ineligible.
¶ The presence or absence of ulceration could not be assessed in 115 patients (58 in the group with 1-cm margins and 57 in the group with 3-cm margins).

rence, 1.34; 95 percent confidence interval, 1.06 to 1.70; P=0.02) (Table 5). Similar hazard ratios were obtained when all patients with protocol deviations (Table 1) were excluded from the analysis (data not shown). Table 5 shows that male sex, increasing tumor thickness, and ulceration were each independent risk factors for all end points and that a distal-limb site was an indicator of a good prognosis with respect to melanoma-specific survival and, possibly, overall survival.

Pairwise interactions between margin width, sex, and tumor thickness were tested for statistical significance with respect to the risk of locoregional recurrence. None of the interactions reached a P value of less than 0.01; there was therefore no evidence that the poorer prognosis associated with the 1-cm margin was confined to any subgroup of patients. However, there was a suggestion of an interaction of margin width with sex. In men the hazard ratio for locoregional recurrence was 1.59 (95 percent confidence interval, 1.18 to 2.14; P=0.002), but in women the hazard ratio was 0.89 (95 percent confidence interval, 0.63 to 1.26; P=0.51; P for interaction=0.014). This is a qualitative interaction, since it implies that there is an effect in males but not females — such interactions are usually considered implausible.

We anticipated that patients with a recurrence after the more extensive surgery would have more aggressive disease than those with a recurrence after less extensive surgery. Examination of overall survival after locoregional recurrence in the two groups supported this hypothesis: the overall survival rate after locoregional recurrence was higher in the group with 1-cm margins of excision than in the group with 3-cm margins of excision (hazard ratio for death, 0.75; 95 percent confidence interval, 0.56 to 1.00; P=0.05). Median survival after locoregional recurrence was 27.9 months in the group with 1-cm margins of excision and 18.5 months in the group with 3-cm margins of excision.

DISCUSSION

In this randomized trial of the surgical treatment of high-risk melanoma, we found a greater risk of locoregional recurrence when melanomas that were at least 2 mm thick were excised with a 1-cm margin, rather than a 3-cm margin. A result of similar magnitude was reported by the Swedish Melanoma Study Group,[9] which compared 2-cm and 5-cm margins of excision for tumors with a depth of 0.8 to 2.0 mm. The hazard ratio for locoregional recurrence in our trial — 1.26 (95 percent confidence interval, 1.00 to 1.59; P=0.05) — was marginally larger when we used multivariate analysis to adjust for known prognostic factors; this was also the case when the analysis was restricted to the first three years of follow-up. We have presented two-sided P values, but it is implausible that a narrower margin would decrease the risk of locoregional recurrence. Taking all these factors together, we do not believe that the outcome of this trial is simply a chance finding. An interaction of margin width with sex just failed to reach statistical significance, but to our knowledge, such an interaction has never been reported before and should therefore be regarded as a hypothesis requiring further investigation.

Since approximately 40 percent of patients with tumors of this thickness ultimately die of melanoma,[2] the expected total number of deaths from melanoma in our trial should be 360. With this number of deaths, it would be possible to detect an increase

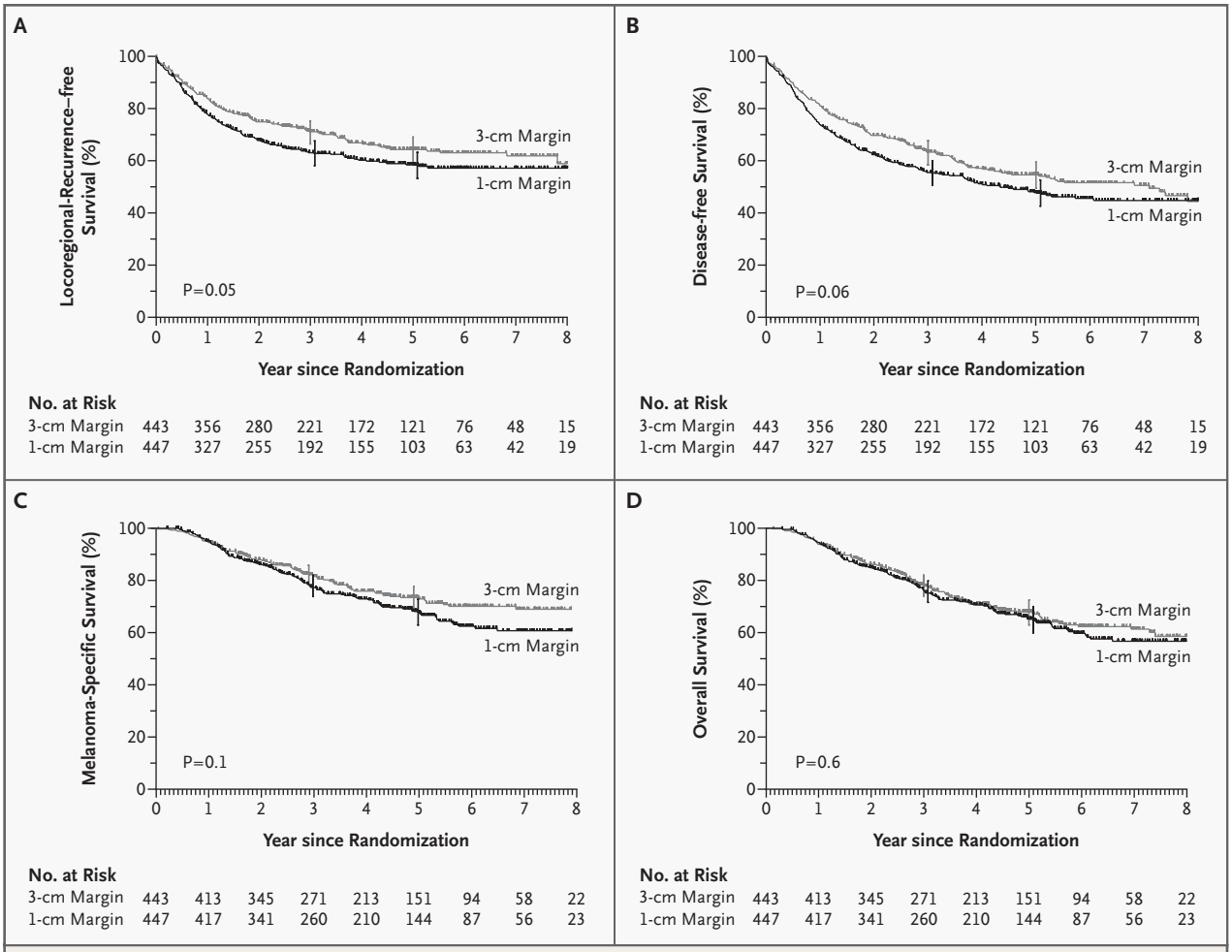

Figure 1. Rates of Survival without Locoregional Recurrence (Panel A), Disease-free Survival (Panel B), Melanoma-Specific Survival (Panel C), and Overall Survival (Panel D).

The vertical bars show the 95 percent confidence intervals at specific time points. Six patients in the group with 1-cm margins of excision and four patients in the group with 3-cm margins were lost to follow-up immediately after randomization and were not included in the analyses. In Panel A, there were 168 locoregional recurrences in the group with 1-cm margins of excision, as compared with 142 in the group with 3-cm margins of excision (hazard ratio, 1.26; 95 percent confidence interval, 1.00 to 1.59; P=0.05). In Panel B, there were a total of 220 events in the group with 1-cm margins of excision, as compared with 195 in the group with 3-cm margins of excision (hazard ratio, 1.21; 95 percent confidence interval, 0.99 to 1.46; P=0.06). In Panel C, there were 128 deaths from melanoma in the group with 1-cm margins of excision, as compared with 105 in the group with 3-cm margins of excision (hazard ratio, 1.24; 95 percent confidence interval, 0.96 to 1.61; P=0.1). In Panel D, 144 patients died in the group with 1-cm margins of excision, as compared with 137 in the group with 3-cm margins of excision (hazard ratio, 1.07; 95 percent confidence interval, 0.85 to 1.36; P=0.6).

in the death rate by a factor of 1.4 with 90 percent statistical power. Since margin width most likely has less of an effect on melanoma-specific deaths than on locoregional recurrence (i.e., less than our estimated hazard ratio of 1.26), it may never be possible to reach a clear conclusion about the effect of the width of the excision margin on survival on the basis of our results alone. Although we did not find a statistically significant effect of margin width on melanoma-specific survival, the hazard ratio for death from melanoma was 1.24 for a 1-cm margin of excision, as compared with a 3-cm margin of excision (95 percent confidence interval, 0.96 to 1.61; P=0.1).

The effect on melanoma-specific survival in the Swedish Melanoma Study Group trial[9] was similar, with a hazard ratio of 1.22 for a 2-cm margin of excision, as compared with a 5-cm margin of exci-

Table 5. Multivariate Analysis of Locoregional Recurrence, Recurrence or Death, Death from Melanoma, and Death from Any Cause.*

Factor	No. of Patients	Primary End Points				Secondary End Points			
		Locoregional Recurrence		Recurrence or Death		Death from Melanoma		Death from Any Cause	
		hazard ratio(95% CI)	*P value*	*hazard ratio (95% CI)*	*P value*	*hazard ratio (95% CI)*	*P value*	*hazard ratio (95% CI)*	*P value*
Margin of excision			0.02		0.03		0.07		0.3
3 cm†	383	1.00		1.00		1.00		1.00	
1 cm	386	1.34 (1.06–1.70)		1.25 (1.02–1.55)		1.29 (0.98–1.70)		1.14 (0.89–1.47)	
Sex			0.03		0.01		0.02		0.02
Female†	351	1.00		1.00		1.00		1.00	
Male	418	1.34 (1.03–1.74)		1.35 (1.07–1.70)		1.46 (1.07–1.98)		1.41 (1.07–1.86)	
Tumor thickness‡			<0.001		<0.001		<0.001		<0.001
2 mm	200	0.70 (0.54–0.91)		0.74 (0.59–0.94)		0.77 (0.57–1.05)		0.79 (0.59–1.04)	
3 mm†	247	1.00		1.00		1.00		1.00	
4 mm	137	1.28 (0.99–1.67)		1.24 (0.98–1.56)		1.2 (0.89–1.64)		1.19 (0.90–1.57)	
5 mm	70	1.56 (1.20–2.02)		1.46 (1.16–1.84)		1.39 (1.02–1.89)		1.35 (1.02–1.79)	
6 mm	115	1.82 (1.40–2.37)		1.67 (1.32–2.11)		1.57 (1.15–2.13)		1.51 (1.14–2.00)	
Ulceration			<0.001		<0.001		<0.001		<0.001
Absent†	472	1.00		1.00		1.00		1.00	
Present	297	1.74 (1.37–2.24)		1.71 (1.38–2.12)		2.00 (1.51–2.65)		2.04 (1.58–2.64)	
Site			0.9		0.21		0.03		0.06
Distal limb†	244	1.00		1.00		1.00		1.00	
Proximal limb	172	1.10 (0.78–1.54)		1.27 (0.94–1.71)		1.64 (1.09–2.48)		1.45 (1.00–2.09)	
Trunk	353	1.06 (0.78–1.44)		1.24 (0.95–1.63)		1.63 (1.11–2.37)		1.45 (1.04–2.02)	

* A total of 769 patients had complete data on all the factors included in the multivariate analysis. Factors that did not have independent predictive ability in the multivariate analysis were included in order to be able to make comparisons across end points (i.e., the margin of excision was included in the models for melanoma-specific and overall survival, and site was included in the models for locoregional recurrence and disease-free survival). CI denotes confidence interval.
† This group served as the reference group.
‡ The tumor thickness was determined before randomization and histologic review.

sion (95 percent confidence interval, 0.88 to 1.69; P=0.24). In addition, the hazard ratio for death from melanoma in the Intergroup Melanoma Surgical Trial[8] was approximately 1.36 in the group with narrow margins of excision, as compared with the group with wide margins (95 percent confidence interval, 0.97 to 1.92; P=0.07). We based this estimate on 10-year survival rates of 70 percent in the narrow-margin group and 77 percent in the wide-margin group and on the P value for the difference between the two groups. Our review of these three trials suggests that there is a significant increase in the risk of death from melanoma associated with a narrow margin of excision, as compared with a wide margin (hazard ratio, 1.26; 95 percent confidence interval, 1.06 to 1.50; P=0.008). In both our study and that of the Swedish Melanoma Study Group,[9] there were fewer deaths from other causes in the group with narrow margins of excision, but this difference was not statistically significant.

The necessary margin of excision is controversial,[13] but it is clear that inadequate margins can increase the risk of locoregional recurrence and, hence, may be associated with increased mortality.[8,14] This issue is crucial, because doubts remain about the efficacy of adjuvant treatment with interferon.[15,16] Interferon increases the disease-free interval but probably not overall survival.[17] If we had allowed sentinel–lymph-node biopsy in our trial, the pattern of recurrence would have differed, but the extent of the difference between the two groups and its effect on the outcome of the trial are a matter of conjecture. The most likely outcome would have been an increased incidence of local or in-transit recurrence, as recently reported in patients with a positive sentinel node[18,19] and as was found after elective lymph-node dissection.[20-23] Our findings confirm that metastasis is an ongoing phenomenon over time. Melanoma cells may not have reached the sentinel node by the time sentinel–lymph-node biopsy is performed, which may partly explain the false negative results that are obtained.

Which margin should be recommended? Many national and international guidelines[7,24] support the use of 2-cm margins as a result of the Intergroup Melanoma Surgical Trial,[8] whereas the Australian guidelines[25] allow the use of a minimal 1-cm margin for tumors between 2 and 4 mm in thickness. Our findings suggest that, in a small number of patients, the melanoma cells that remain after excision with a 1-cm margin will prove fatal. We therefore recommend that the use of a 1-cm margin should be avoided in patients with melanomas that are at least 2 mm thick. Our study provides no data to support the preferred use of either a 2-cm or 3-cm margin, and it would seem reasonable, pending further data, for the patient to make the choice after an informed discussion of the surgical options. It may be prudent to use a 3-cm margin of excision in patients with deeper tumors (those more than 4 mm thick), because such patients have a higher risk of locoregional recurrence.

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APPENDIX

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