

Long-Term Results of a Prospective Surgical Trial Comparing 2 cm vs. 4 cm Excision Margins for 740 Patients With 1–4 mm Melanomas

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Background: The Intergroup Melanoma Surgical Trial began in 1983 to examine the optimal surgical margins of excision for primary melanomas of intermediate thickness (i.e., 1–4 mm). There is now a median 10-year follow-up.

Methods: There were two cohorts entered into a prospective multi-institutional trial: (1) 468 patients with melanomas on the trunk or proximal extremity who randomly received a 2 cm or 4 cm radial excision margin and (2) 272 patients with melanomas on the head, neck, or distal extremities who received a 2 cm radial excision margin.

Results: A local recurrence (LR) was associated with a high mortality rate, with a 5-year survival rate of only 9% (as a first relapse) or 11% (anytime) compared with an 86% survival for those patients who did not have a LR ($P < .0001$). The 10-year survival for all patients with a LR was 5%. The 10-year survival rates were not significantly different when comparing 2 cm vs. 4 cm margins of excision (70% vs. 77%) or comparing the management of the regional lymph nodes (observation vs. elective node dissection). The incidences of LR were the same for patients having a 2 cm vs. 4 cm excision margin regardless of whether the comparisons were made as first relapse (0.4% vs. 0.9%) or at anytime (2.1% vs. 2.6%). When analyzed by anatomic site, the LR rates were 1.1% for melanomas arising on the proximal extremity, 3.1% for the trunk, 5.3% for the distal extremities, and 9.4% for the head and neck. The most profound influence on LR rates was the presence or absence of ulceration; it was 6.6% vs. 1.1% in the randomized group involving the trunk and proximal extremity and was 16.2% vs. 2.1% in the non-randomized group involving the distal extremity and head and neck ($P < .001$). A multivariate (Cox) regression analysis showed that ulceration was an adverse and independent factor ($P = .0001$) as was head and neck melanoma site ($P = .01$), while the remaining factors were not significant (all with $P > .12$).

Conclusion: For this group of melanoma patients, a local recurrence is associated with a high mortality rate, a 2-cm margin of excision is safe and ulceration of the primary melanoma is the most significant prognostic factor heralding an increased risk for a local recurrence.

Key Words: Melanoma—Surgical excision margins—Neoplasm staging—Cox regression—Risk factors.

Throughout most of the 20th century, the standard surgical treatment of cutaneous melanoma was to radically excise the primary lesion with a 4–5 cm radial

margin of surrounding skin. Such a large defect required closure with a split thickness skin graft (STSG). Moreover, the surgical rationale for a STSG closure was that it enabled the surgeon to better detect a local recurrence

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that might otherwise be obscured by a full thickness flap closure. Finally, it was known that a local recurrence was associated with a very high risk for distant metastases and mortality, so that undertreatment of the primary melanoma with a narrow margin of excision might contribute to an increased risk of local recurrence and patient demise.¹⁻⁴ It was postulated that thin melanomas could be treated conservatively,⁵⁻⁸ but there were no randomized trials delineating what specific margin was safe and whether it should be adjusted according to the biology of the tumor as measured by advancing tumor thickness.

The World Health Organization Melanoma Program conducted the first randomized trial that addressed this issue.^{9,10} Their surgical protocol (Trial #10) compared 1-cm vs. 3-cm radial margin of excision in a limited eligibility group of patients with melanoma thickness of 2.0 mm or less. This patient group was selected because the risk of a local recurrence was low, and therefore it would be safe to test a more skin-sparing margin of excision. Long-term results of this trial showed that a 1-cm margin of excision is safe, and that there was no difference in survival rates compared with a 3-cm radial margin. However, there was a clustering of local recurrence rates up to 4.5% confined to patients who had a tumor thickness of 1.1 to 2.0 mm and who had a 1-cm margin of excision (Cascinelli, N; personal communication).

The Intergroup Melanoma Surgical Trial has been conducted since 1983 in a cohort of 740 patients with intermediate thickness melanomas (i.e., 1.0–4.0 mm) to prospectively determine: (1) whether a 2-cm radial margin of excision is equivalent (or safe) compared with a 4-cm radial margin with respect to survival and local recurrence rates; and (2) whether currently available prognostic factors could identify subgroups of patients with intermediate thickness melanomas who had a high risk for local recurrence and for whom a wider margin of excision would reduce the risk of local recurrence. Patient eligibility was confined to those patients with melanomas located on the trunk or proximal extremity to ensure that the more radical 4-cm margin could be carried out if they were randomly assigned to receive such a treatment. All patients were also randomly selected to receive an elective lymph node dissection (ELND) or observation of their clinically uninvolved nodes as their initial management. The results of the ELND portion of the randomized surgical trial have been published.^{11,12}

This is the largest randomized surgical trial ever conducted to address the definitive surgical management of a primary melanoma and to confirm the validity of prognostic factors to define risk groups. For the purposes of identification, these patients will be referred to in this article as “Group A” or the randomized group. An in-

terim report that showed no overall survival difference in 2-cm vs. 4-cm margins were compared and published after 6 years and 7.6 years of follow-up with the limitation that a number of patients were still developing potentially fatal distant metastasis.^{13,14} The data set is now matured to make definitive conclusions because the relapse rates for all stages have plateaued.

A second group of patients were prospectively entered into the surgical protocol whose melanoma was located on the distal extremity or head and neck area, as long as they could have a 2-cm radial margin of excision. Such patients were assigned randomly to receive either an ELND or nodal observation as described above. These patients are referred to as “Group B” or non-randomized patients for a standardized surgical margin because it was technically not feasible to perform a 4-cm radial surgical margin; all such patients had a 2-cm surgical margin of excision.

METHODS

Patients

Eligible patients were those with intermediate thickness melanomas (1.0 to 4.0 mm) and for whom the anatomic location of their melanoma would permit the surgeon to perform either a 2-cm or a 4-cm radical margin of skin excision (Group A) or a 2-cm radical margin of excision (Group B). Eligible patients were pre-chosen randomly to their surgical treatment according to the method described by Zelan.¹⁵ Written informed consent was obtained for all patients. The policies for follow-up and surveillance testing have been described.^{12,13}

All surgeons were board certified and accredited members of an established cancer cooperative group. Rigorous quality control was used throughout the study, which included standardized descriptions of the lymphadenectomy procedures, educational sessions at group meetings, centralized surgical quality control review, and use of quality control data forms as previously described.¹³ An experienced pathologist from the participating cooperative group reviewed the slides and at least two thirds of the slides were also reviewed by a central panel of melanoma pathologists who independently reviewed a representative histologic section of each primary melanoma. Regular audits were performed on all research records by one or more members of the Intergroup Melanoma Surgical Committee. The principle investigator reviewed the circumstances and medical documentation of all deaths and was blinded as to the surgical treatment received.

A local recurrence (LR) was defined as any melanoma recurrence within 2 cm of the surgical scar after a definitive surgical excision. The LR rates were also recorded separately when they were the first manifestation of relapse (1st LR) or that occurred at anytime in the course of progressive metastatic disease (anytime LR group). The rates of LR are expressed as the cumulative rate with an average follow-up of 10 years. Because all the local recurrences occurred within 8 years, it is unlikely that these rates would change with a longer follow-up period beyond the mean 10-year follow-up available now.

Statistical Analysis

Standard statistical techniques were used. Proportions were compared using χ^2 analysis. Disease-specific survival from melanoma and disease recurrence curves were constructed by using the Kaplan-Meier product limit method. These curves were analyzed for comparisons by the log-rank procedure. The *P* value indicated after comparison of the 10-year survival rates was calculated based on comparisons of the survival curves. Multivariate analysis based on Cox's regression model was used to associate covariates to time-dependent endpoints such as survival. Results are reported based on "randomized intent" which included those patients who refused the randomized treatment assigned.

RESULTS

Characteristics of the Study Patients

This was a multi-institutional study that involved 93 surgeons practicing in 77 institutions located in 4 coun-

tries (U.S., Canada, Denmark, and South Africa); over 75% of the patients were entered from 15 major institutions (see Appendix).

Patient accrual began in 1983 and stopped in 1989. More than 94% of the patients entered into the study were eligible and were able to be evaluated. There is now a 92% long-term follow-up of at least 5 years or until death. This is a mature database with a median follow-up of 10 years and a range up to 16 years. The clinical and pathological characteristics of the patients are exactly balanced among prognostic factors as previously published.^{11,13,14}

Overall Survival and Incidence Rates of Local Recurrences (LR)

Overall, there were 13 patients who had a LR as a first relapse and a total of 28 patients who had a LR at anytime in the course of their metastatic melanoma. A local recurrence was associated with a highly significant difference in survival compared with patients who never experienced a LR (Fig. 1), regardless of whether survival rates compare 1st LR events alone or those that occurred at anytime (Fig. 2). Thus, those patients who had a LR all died of metastatic melanoma within 10 years.

Among the 468 Group A patients (randomized to 2-cm vs. 4-cm margin), there were only 3 patients (0.6%) who had a first LR and 11 (2.3%) who had a LR anytime. Among the 272 Group B patients (non-randomized with a 2-cm margin), there were a somewhat higher rate of LR, with 10 patients having a first LR (3.7%) and 17 patients (6.2%) who had a LR anytime.

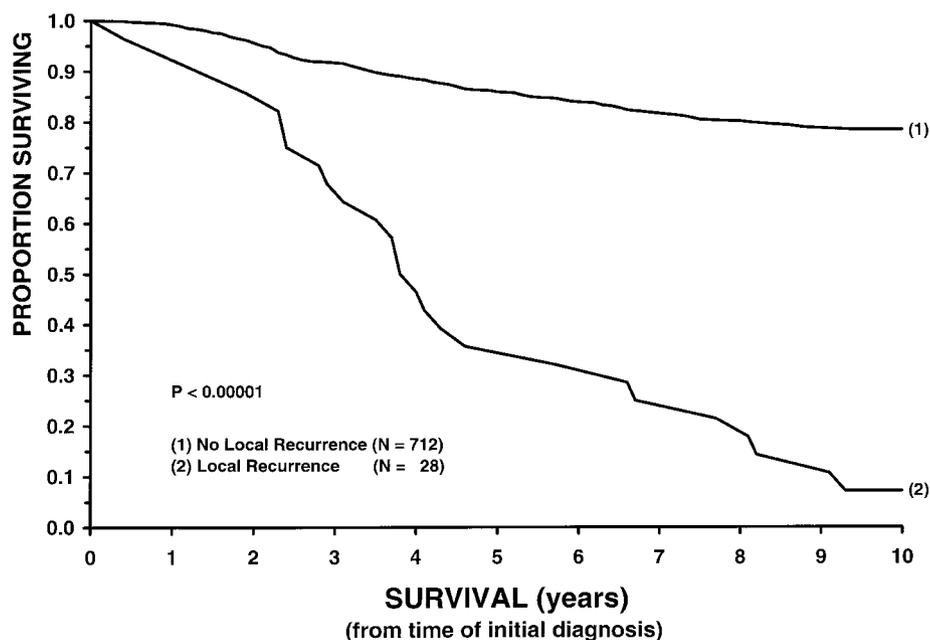


FIG. 1. Disease-specific (actuarial) survival for all 740 melanoma patients comparing those 28 patients who had a local recurrence at any time during the course of their metastatic disease with those 712 patients who never had a local recurrence. The survival differences were highly significant ($P < .00,001$).

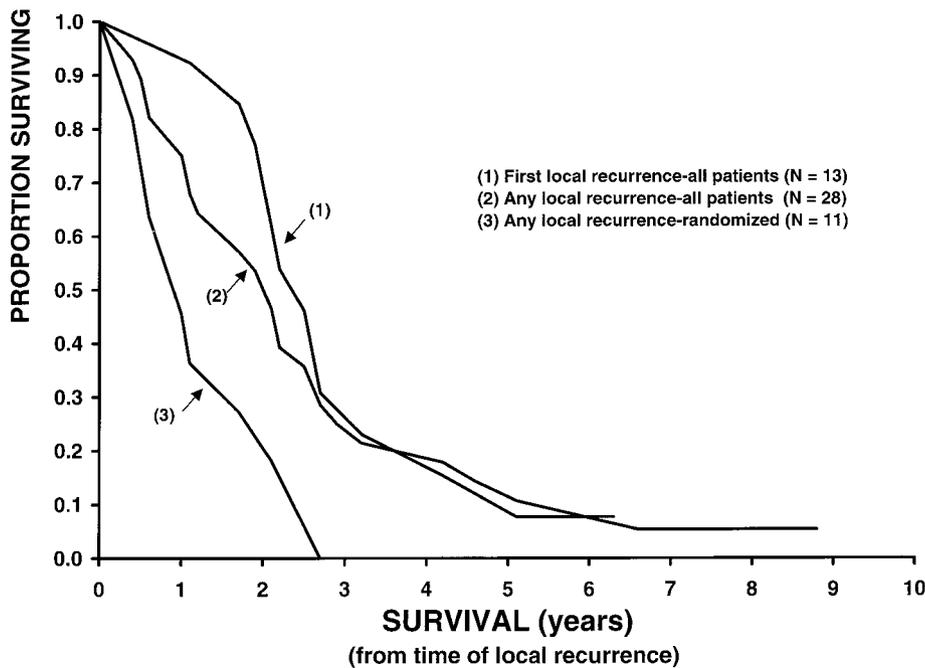


FIG. 2. Disease-specific (actuarial) survival for all 28 patients who had a local recurrence comparing those 13 patients who had a local recurrence as their first sign of relapse with those 11 patients who had a local recurrence later in the course of their metastatic disease. There were no significant differences between these groups and virtually all patients eventually died of metastatic melanoma.

For the entire group of 740 patients, the anatomic site of the primary melanoma significantly correlated with the LR rate ($P < .001$). Thus, the LR rate (anytime) for 177 patients with a melanoma arising on the proximal extremity was only 1.1%, while it rose to 3.1% for the 291 patients with trunk melanoma, to 5.3% among the 208 patients with distal extremity melanomas, and 9.4% among the 64 patients with melanomas of the head or neck.

The correlation of thickness and ulceration remained when the analysis was conducted within the prospectively defined cohorts of Group A and Group B patients. Among Group A patients (i.e.: with trunk or proximal melanoma melanomas), the local recurrence rates (anytime) increased from 1.0% for melanomas of 1.0–2.0 mm thick, to 4.6% for 2.1–3.0 mm melanoma, and to 4.1% for those 3.1–4.0 in thickness (Table 1) ($P < .05$). Among Group B patients (i.e.: with distal extremity or head and neck melanomas), the LR rates were higher, ranging from 3.8% for 1.0 to 2.0 mm melanomas, 5.6% for 2.0 to 3.0 mm melanomas and 23.1% for 3.0 to 4.0 mm melanomas ($P = .05$ by single factor analysis, but $P = .14$ by multifactorial analysis).

Ulceration of the primary melanoma was associated with a dramatic increase in LR rates, when it was present (Table 1). There was a 6-fold increase in LR rates (anytime) in the Group A patients (1.1% for non-ulcerated melanomas vs. 6.6% for ulcerated melanomas); among the Group B patients, there was an 8-fold increase in LR rates (2.1% vs. 16.2%) ($P < .001$).

Survival and Incidence Rates Among the Randomized Patients (Group A)

There were no differences in survival rates overall or incidence rates of LR comparing patients who had a 2-cm vs. 4-cm surgical margin (Fig. 3; Table 2). For the 238 patients who had a 2-cm margin, the incidence of LR was 0.4% as a first relapse and 2.1% at anytime. For those 230 patients that had a 4-cm margin, the LR rates was 0.9% as a first relapse and 2.6% at anytime. Ten year survival rates for the two groups had no significant differences, being 70% 10 year disease-specific survival for those who had a 2-cm margin vs. 77% for those who had a 4-cm margin ($P = .074$, Figure 3). When the survival rates were further divided based upon whether the patients had ELND or not, there was still no survival difference ($P = .16$) (Table 2). The median time to local recurrence was 1.7 years and the median survival after LR was only 1 year.

Multivariate Prognostic Factors Analysis

A multifactorial step-wise regression analysis based on the Cox model was performed for the entire group of 740 patients (Table 3). The only two factors that were related significantly to poorer survival were the presence of tumor ulceration ($P < .001$), and the head and neck site ($P = .02$). Notably, the surgical margins of excision (2 vs. 4 cm) did not correlate with LR rates, having taken into account all other factors in the model. Whether or not an elective node dissection was

TABLE 1. Effect of melanoma thickness and ulceration on local recurrence rates (anytime) for the randomized Group A whose melanomas were located on the trunk and proximal extremity and the nonrandomized Group B whose melanomas were located on the distal extremity or the head and neck area

Surgical margin	Ulceration		Tumor thickness (mm)		
	absent	present	1.0–2.0	2.1–3.0	3.1–4.0
Group A (468 pts)	1.1%	6.6%	1.0%*	4.6%*	4.1%*
Group B (272 pts)	2.1%	16.2%	3.8%	5.6%	23.1%

The correlations of increasing risk for thicker and ulcerative melanomas was significant ($P < 0.001$ except *values which were $P = 0.05$).

performed or not had no impact on LR rates. When the analysis was performed within the two separate cohorts (Groups A and B), only melanoma ulceration was a significant and independent prognostic factor associated with an increased risk of a local recurrence (Table 4).

Does a Wider Surgical Margin Decrease the Local Recurrence Rates?

The incidence of LR rates were examined within the Group A patients to correlate surgical margins with adverse prognostic factors. As shown in Table 5, those patients who had the more radical 4-cm radial margin of excision did not have any lower rate of local recurrences compared with those who had a narrower 2-cm margin.

Patterns of Metastases After a Local Recurrence

Patterns of metastases were examined among the 28 patients who developed a local recurrence. The next site of metastatic relapse was at a distant site (sometimes

with simultaneous regional metastases) in 62% of patients while it was at a regional site (sometimes with a simultaneous local recurrence) in 28% of patients. When the relapse patterns were examined for the next site of distant metastasis, the most frequent sites were skin and subcutaneous metastases (39%), lung (19%), brain,¹⁷ widespread or multiple sites (15%), liver (6%), and bone (4%).

DISCUSSION

This surgical trial complements and extends the findings of the WHO Melanoma Group Trial #10 which was confined to patients with melanomas <2.0 mm in thickness. The Intergroup Melanoma study has demonstrated that a reduced 2-cm radial margin of surgical excision is safe for even more advanced melanomas, those up to 4.0 mm in thickness. In the randomized portion of this trial, there was no advantage of a more radical 4-cm surgical margin, either in terms of disease-specific survival or

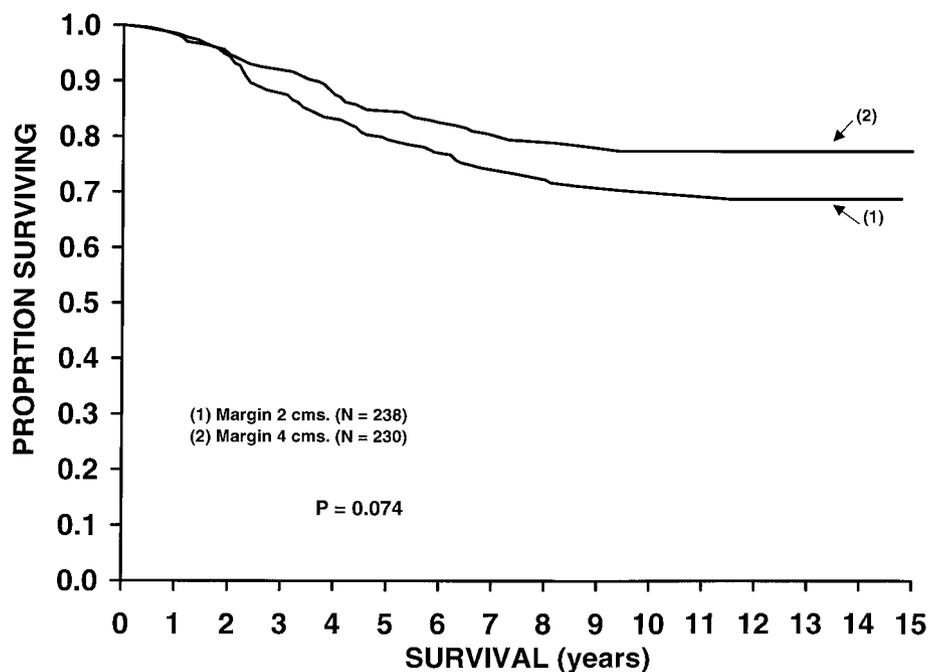


FIG. 3. Disease-specific (actuarial) survival comparing patients with trunk and proximal extremity melanomas (of intermediate thickness) who were randomized to receive either a 2 cm or 4 cm radial margin of surgical excision around their primary melanoma. The differences in survival were not significant by either single factor analysis ($P = .07$) or by multifactorial analysis ($P = .85$).

TABLE 2. Ten-year survival and local recurrence (LR) rates of group A patients who were randomized to a 2 cm. vs. 4 cm. surgical margin

Surgical margin	No. pts.	10-Year survival			LR rates	
		all pts.	ELND	WLE only	1 st relapse	anytime
2 cm	238	70%	74%	66%	0.4%	2.1%
4 cm	230	77%	76%	79%	0.9%	2.6%

ELND, elective lymph node dissection; LR, local recurrence; WLE, wide local excision.

There were no differences in 10-year survival rates for the entire cohort of patients ($P = 0.07$ by log rank test) and for subgroups based upon their second randomization to undergo observation of the regional lymph nodes or an elective lymph node dissection. $P = 0.162$ by log rank test.

TABLE 3. Multivariate analysis (Cox model) of risk for local recurrence (anytime) among all 740 patients

Factor	Risk ratio	P value
Tumor ulceration	6.3	0.0001
Anatomic site:		
Head/Neck	9.4	0.01
Extremity	3.5	0.14
Trunk	2.5	0.24
Tumor thickness (<2.0 mm vs. >2 mm)	2.0	0.14
Surgical Margin (2 cm vs. 4 cm)	1.0	0.79
Regional Nodes (ELND vs. observation only)	0.9	0.87
Surgical wound closure (skin graft vs. primary closure)	0.9	0.75

decreasing the rate of local recurrences. The incidence of LR was lower than that for the WHO Trial for the overlapping 1.0 to 2.0 mm thickness patients (4.5% LR for the WHO Trial #10 vs. 0.6% for the Intergroup Trial). Therefore, we would recommend a 2-cm surgical margin whenever it is anatomically feasible and where the surgical defect can be closed primarily without a STSG.

Two randomized trials in Europe compared 2-cm vs. 5-cm radial margins for melanomas up to 2.0 mm in thickness and showed no survival advantage for the more radical surgical margin.^{16,17} The Swedish Melanoma Study Group patients had local recurrence rates of 0.8% for those 373 patients who had a 2-cm margin and a 1.0% rate for those 396 patients who had a 5-cm margin after a follow-up period of 5.8 years. These rates are comparable with those of the present Intergroup study, although their follow-up period is shorter.¹⁶

This study also demonstrated that a LR is associated with a strikingly high mortality rate. The 10 year survival rate was only 5% for those patients who had a LR, either as a first relapse or at anytime in the course of metastatic disease. We had postulated at the outset of the trial that a LR may have been a manifestation of retained primary melanoma cells or neighboring intralymphatic satellites.

TABLE 4. Multivariate analysis (Cox Model) of risk for local recurrence rates (anytime) for the randomized Group A patients and nonrandomized Group B melanoma patients

Factor	Group A (468 pts)		Group B (272 pts)	
	risk ratio	P value	risk ratio	P value
Tumor ulceration	4.2	0.03	8.4	0.005
Anatomic site:	2.5	0.24	2.8	0.048
Tumor thickness (<2.0 mm vs. >2 mm)	2.8	0.16	1.7	0.360
Surgical Margin (2 cm vs. 4 cm)	1.1	0.85	N/A	N/A
Regional Nodes (ELND vs. observation only)	0.8	0.77	1.2	0.76

Group A: trunk and proximal extremity.

Group B: distal extremity or head and neck area.

TABLE 5. Local recurrence rates

Surgical margin	Ulceration		Tumor thickness (mm)		
	absent	present	1.0–2.0	2.1–3.0	3.1–4.0
2 cm	1.1%	5.8%	2.0%	3.0%	0%
4 cm	1.2%	7.4%	0%	6.4%	7.7%

A wider (i.e.: 4 cm) surgical margin did not reduce the risk of a local recurrence compared to a narrower surgical margin (2 cm). P values of correlation were not significant.

However, the patterns of metastases analysis showed that a LR was more likely a manifestation of Stage IV melanoma. First, the next site of relapse in 62% of patients was at distant sites, not regional sites as would be expected if a LR followed the patterns of recurrences of a primary melanoma or satellite metastasis which would next relapse at a regional site in the majority of patients. Second, a LR was associated with a higher rate of metastases in the skin and subcutaneous tissues than with any other metastatic site. It is probable, therefore, that a LR is equivalent to a skin or subcutaneous metastasis that coincidentally occurs in or around the surgical scar of a primary melanoma excision. This does not exclude the possibility that some LR reflect the biological manifestation of regrowth of retained primary melanoma cells or intralymphatic metastases that are very aggressive with regard to their metastatic behavior.

This study extends previous reports and validates the powerful predictive value of melanoma ulceration that is associated with a strikingly high incidence of local recurrences and metastatic melanoma.^{3,4,6,18–24} An ulcerated melanoma is, in every respect, a locally advanced and aggressive cancer. The presence of ulceration thus portends a more invasive metastatic property of a melanoma and a substantially higher risk for regional and distant metastases. This study demonstrates the striking influence of ulceration on local recurrence rates where

the incidence of LR increased 6-fold to 8-fold compared with non-ulcerated melanomas of intermediate thickness. Increasing tumor thickness correlated significant with the risk of a LR, with the risk increasing by 4-fold to 6-fold as the melanoma thickness increased from 1.0 up to 4.0 mm. The risk of a local recurrence was substantially increased when comparing the Group A and Group B patients of equivalent thicknesses, demonstrating the importance of anatomic site of the primary melanoma as a predictive factor for a LR.

In this study, as with the preponderance of other publications, anatomic site was an independent predictor of outcome, with patients having their melanomas arising on the head and neck having a worse prognosis compared with other anatomical sites.^{3,14,25-29}

Given this knowledge of prognostic factors predicting the risk of a LR, can the surgeon prevent a local recurrence with a wider surgical margin in those patients with a "high risk" for this event? Intuitively, one would postulate that a wider surgical margin for an ulcerated melanoma might be associated with a lower risk of a LR. This would especially be true if a wider excision of skin and subcutaneous tissue were removing lateral extensions of primary melanoma cells or microsatellites to a greater extent than a narrower surgical margin. This was not the case, however, further substantiating the conclusion that a LR is a first manifestation of a Stage IV melanoma. Thus, the analysis comparing local recurrence rates in patients having a 4-cm excision was no lower than those having a 2-cm excision when compared for equivalent thickness groups or ulceration status (Table 5).

This trial also dispels the previous notion that a skin graft would enable the clinician to better detect a local recurrence earlier through a thin coverage of the surgical defect. First, the incidence is too low to justify an approach that is more expensive and disfiguring. Second, since all patients with a LR eventually died, regardless of width of margin or closure by STSG, it is highly unlikely that any patients would be salvaged by a slightly earlier detection of a LR. And finally, the multifactorial analysis showed that closure by STSG or a primary closure with a full-thickness flap had no impact on survival rates, even after accounting for all the other factors that influence the risk of a LR (Table 3).

This surgical trial does not specifically address the surgical management of several important groups of melanoma patients. Those patients with lentigo maligna melanoma and desmoplastic melanomas were excluded as were patients with thick melanomas (>4.0 mm). Subsequent surgical trials will need to address the optimal surgical management of these patients as well as examining whether even narrower margins might be safe in

some subgroups.²⁴ For the present, however, those patients comprising the vast majority of melanoma patients can have an appropriate excision margin of their melanoma with a risk of local recurrence of <1.0% and no compromise in their survival rates if they have a 1-cm radial margin for a melanoma up to 1 mm in thickness and a 2-cm margin for up to 4.0 mm melanomas. In both circumstances, the surgical defect can (and should) be closed primarily with a full thickness flap.

APPENDIX

Surgeons from the following cancer cooperative groups participated in this study: Eastern Cooperative Oncology Group, Southwest Oncology Group, National Surgical Adjuvant Breast Project, Cancer and Leukemia Group B, NCIC, MAOP, Pediatric Oncology Group, and the Danish Melanoma Group.

The following institutions participated in this melanoma surgical trial. The first 15 institutions listed below entered 77% of the total patient accrual. In addition to the authors, those surgeons who entered five or more patients are listed in parentheses after each institution.

Roswell Park Memorial Institute
 University of Texas-M.D. Anderson Cancer Center (A. Boddie, D. Hohn, K. Jessup, D.D. Ota, R. Pollock, M. Romsdahl, M. Ross)
 University of Alabama at Birmingham (W. Maddox)
 McGill University (A. Loutfi, H. Shibata)
 University of Florida (K. Bland)
 Case Western Reserve University (E. Mansour)
 City of Hope Medical Center (J. Terz)
 Ohio State University (W. Farrar)
 Tom Baker Cancer Center, University of Calgary
 Danish Melanoma Group (C. Krag)
 Emory University (D. Murray)
 Washington Hospital Center (M. Cohen)
 Scott and White Medical Center (C. Verheyden)
 Medical Center of Delaware
 The University of Virginia
 Spartanburg CCOP (J. McCulloch)
 Indiana University Medical Center (J. Bennett)
 University of Kansas Medical Center
 University of Pretoria South Africa
 Tufts University
 University of California at San Diego
 Washington University Medical Center
 Tulsa University (J. Lockhart)
 University of Arkansas (D. Chu)
 Good Samaritan Hospital (R. Welling)
 Baptist Medical Center, Oklahoma (K. Boatman)
 Letterman Army Center

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