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Efficacy of 2-cm Surgical Margins for Intermediate-Thickness Melanomas (1 to 4 mm)

Results of a Multi-institutional Randomized Surgical Trial

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Background

A prospective, multi-institutional, randomized surgical trial involving 486 localized melanoma patients was conducted to determine whether excision margins for intermediate-thickness melanomas (1.0 to 4.0 mm) could be safely reduced from the standard 4-cm radius.

Methods

Patients with 1- to 4-mm–thick melanomas on the trunk or proximal extremities were randomly assigned to receive either a 2- or 4-cm surgical margin.

Results

The median follow-up time was 6 years. The local recurrence rate was 0.8% for 2-cm margins and 1.7% for 4-cm margins (p value not significant [NS]). The rates of in-transit metastases were 2.1% and 2.5%, respectively (p = NS). Of the six patients with local recurrences, five have died. Recurrence rates did not correlate with surgical margins, even among stratified thickness groups. The overall 5-year survival rate was 79.5% for the 2-cm margin patients and 83.7% for the 4-cm margin patients (p = NS). The need for skin grafting was reduced from 46% with 4-cm surgical margins to 11% with 2-cm surgical margins ($p < 0.001$). The hospital stay was shortened from 7.0 days for patients receiving 4-cm surgical margins to 5.2 days for those receiving 2-cm margins (p = 0.0001). This reduction was largely due to reduced need for skin grafting, since the hospital stay for those who had a skin graft was 2.5 days longer than that for those who had a primary wound closure ($p < 0.01$).

Conclusion

Margins of excision can be safely reduced to 2 cm for patients with intermediate-thickness melanomas. The narrower margins significantly reduced the need for skin grafting and shortened the hospital stay.

The surgical management of melanoma becomes more important each year as an ever larger number of individuals are afflicted with this disease, which is increasing in incidence at an alarming rate. Of the more than 32,000 patients who developed the disease in 1990,[1] about 12,800 (40%) had intermediate-thickness melanomas (*i.e.*, 1.0 to 4.0 mm), for which the optimal excision margins have not been previously defined in a controlled surgical trial. Determining the appropriate margins is vitally important because of the adverse effects associated with suboptimal margins. If the margins are too narrow, residual tumor cells might eventually result in a local recurrence, a life-threatening process since 60% to 80% of such patients eventually die of their disease.[2] If the surgical margins are too wide, the large surgical defect may have to be covered with a split-thickness skin graft (STSG) or a complicated flap, which results in greater disfigurement, prolongs hospitalization, and increases costs.

Historically, the recommended surgical margins for melanoma have been a 4- to 5-cm radius around the primary tumor or the biopsy site. During the past decade, however, surgical margins have been reduced, largely based on empirical observations and retrospective studies.[3-9] Retrospective studies have noted a correlation among the surgical margins, tumor thickness, and the incidence of local recurrences.[2,10-12] Only one prospective, randomized trial has been conducted, and it was restricted to melanomas thinner than 2.0 mm.[13,14] In this trial of 584 melanoma patients with tumors thinner than 2.0 mm, the World Health Organization (WHO) Melanoma Program concluded that it is safe to excise thin melanomas (< 1.0 mm thick) with a 1-cm radial margin. However, a 4% local recurrence rate was encountered with 1-cm margins for melanomas thicker than 1.1 mm, but no local recurrences occurred when 3-cm margins were used.[14] Three of these five patients with local recurrences died of disease. No definitive conclusions could be reached about the appropriate surgical margins for melanomas thicker than 1.0 mm.

The current study is the first to address the optimal surgical margins for intermediate-thickness melanomas (1.0 to 4.0 mm). We postulated that the lateral extent of these melanomas (including microsatellites) is less than 2 cm in a radial direction from the primary tumor or biopsy site.

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The participating members of the Intergroup Melanoma Committee are listed in the Appendix.

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METHODS

Patients

All patients had cutaneous melanomas with thicknesses of 1.0 to 4.0 mm and no evidence of metastatic melanoma in regional lymph nodes or at distant sites. Patients who had had cancer previously (except for skin cancer) or who had received chemotherapy, radiotherapy, or any other adjunct to surgery were excluded. Patients with lentigo maligna melanoma were also excluded. Written informed consent was obtained from all patients.

Patients with clinically localized melanomas (*i.e.*, Stages I and II according to American Joint Committee on Cancer staging criteria) and intermediate-thickness melanomas located on the trunk or a proximal extremity (*i.e.*, proximal to the elbow or knee) were randomly assigned to receive either 2- or 4-cm margins around the melanoma biopsy site. Each patient was also randomly assigned to receive elective (immediate) lymph node dissection (ELND) or observation of the regional lymph nodes with delayed lymph node dissection only if clinically indicated. Follow-up for this portion of the trial is not yet sufficiently mature to report the results. Patients receiving ELND were evenly distributed between the two treatment arms involving surgical margins, so any survival differences that may result from ELND would not influence the survival outcome from the surgical margin issue.

All patients were examined for the presence of recurrent or metastatic melanoma at 3-month intervals during the first 2 postoperative years, at 6-month intervals in years 3 to 5, and annually thereafter. These surveillance examinations included a history and physical examination, chest x-rays, and measurement of serum liver enzymes; computed tomograms or nuclear scans were obtained to confirm signs or symptoms of metastatic melanoma.

Surgical Technique and Quality Control

Pathologically confirmed cutaneous melanomas were surgically excised with 2- or 4-cm margins of normal-appearing skin around the melanoma biopsy site. The surgical margins were measured with a ruler before excision and dictated in the operative report. It was permissible to excise a lesion with a larger margin in one direction to create an elliptical defect that could be closed with advancement flaps. Full-thickness flaps or STSG could be used to close the surgical defect at the discretion of the surgeon. The underlying subcutaneous tissues, down to or including the underlying muscular fascia, were incor-

porated into the surgical specimen; excision of the muscular fascia beneath the melanoma was optional. Definitive resection was performed within 45 days after biopsy.

All surgeons were board-certified and were accredited members of an established Cancer Cooperative Group (*i.e.*, Eastern Oncology Group, Southwestern Oncology Group, National Surgical Adjuvant Breast Project, National Cancer Institute of Canada, Cancer and Leukemia Group B, Piedmont Oncology Group, Mid-Atlantic Oncology Group, and Danish Melanoma Group). Each surgeon signed a Quality Assurance Form for each patient that stated the surgical margins actually used. A Quality Control Committee met periodically and corroborated the data by reviewing the operative note and measurements described in the pathology report.

Pathology

A representative histologic section of each primary melanoma was independently reviewed by a pathologist from the participating Cooperative Group, and at least 66% of the slides were also reviewed by a panel of melanoma pathologists at the Pathology Reference Center, Massachusetts General Hospital, Boston, Massachusetts.

Surgical Complications

A Surgical Toxicity Form was submitted within 3 months of surgery that described the presence and severity of wound infection, wound separations, seroma or hematoma, skin graft failure, limb edema, or prolonged pain. Other surgical complications such as thrombophlebitis and pneumonia were also reported.

Local Recurrences

A local recurrence was defined as a pathologically documented melanoma that recurred within 2 cm of the surgical scar after a definitive excision of the primary melanoma. All local recurrences were treated with complete excision of the lesion. If a patient with multiple in-transit (intralymphatic) metastases had a lesion within 2 cm of the scar, it was not counted as a local recurrence. Once the patient had distant metastases, synchronous tumor recurrences in and around the surgical scar were not counted as a local recurrence because they were more likely a manifestation of distant metastasis.

Statistical Analysis

Standard statistical techniques were used. Proportions were compared using chi square analysis or Fisher's exact test when appropriate. Mean comparisons were made using analysis of variance and t tests. Survival and disease recurrence curves were constructed using the Kaplan–Meier product limit method. These curves were analyzed for comparisons by the log-rank procedure. Proportional hazards analysis was used to associate covariates to time-dependent endpoints such as recurrence and survival.

The frequency of local recurrences increased as a function of time. To determine when the data base was sufficiently mature to close the study, Dr. Seng-jaw Soong examined the cumulative frequency of local recurrences among 294 patients with intermediate-thickness melanomas from the Alabama/Sydney Melanoma Data Base. More than 75% of local recurrences occurred within 24 months. Because the median follow-up time in this prospective, randomized trial has reached 72 months (and 80% of patients have been observed for more than 2 years), the number of patients still at risk for development of a local recurrence is small. Therefore, a decision was made to close the study and report the results.

RESULTS

Characteristics of Study Patients

Of the 486 patients entered in the study, 95.1% could be evaluated for response. Pathologic criteria rendered 1.2% ineligible for inclusion in the analysis; an additional 1.4% were excluded because their surgery violated protocol guidelines, and 2.3% were lost to follow-up.

The clinical and pathologic characteristics of the patients and their tumors are shown in Table 1. The patients in the 2-cm and 4-cm margin subgroups were evenly distributed according to sex, age, anatomic site of the tumor, tumor thickness, and the presence or absence of tumor ulceration.

Skin Grafting Rate

Reducing the surgical margins significantly diminished the incidence of skin grafting (Table 2). Thus, among patients who had 4-cm surgical margins, 46% required an STSG, compared with 11% of those who had 2-cm surgical margins ($p < 0.001$).

Duration of Hospital Stay

For the entire patient cohort, the length of hospital stay was shortened by almost 2 days for those who received 4-cm excision margins compared to those who received 2-cm margins (7.0 *vs.* 5.2 days, $p < 0.001$) (Table 2). For patients who did not have ELND, the hospital stay was reduced from 5.2 days for those who received 4-cm margins compared to 3.0 days for those who received 2-cm margins ($p < 0.001$) (Table 2).

Table 1. CLINICAL AND PATHOLOGIC CHARACTERISTICS OF MELANOMA STUDY PATIENTS AND TUMORS

Characteristic	Surgical Margin	
	4 cm	2 cm
Total no. of patients	242	244
Sex (%)		
Male	57	57
Female	43	43
Anatomic site (%)		
Trunk	61	63
Proximal extremity	39	37
Thickness (%)		
1.00–1.99 mm	54	58
2.00–2.99 mm	28	30
3.00–4.00 mm	18	12
Average (mm)	1.98	1.94
Median (mm)	1.8	1.8
Ulceration (%)		
Present	23	23
Absent	77	77
Age (yr)		
Median	47.6	45.3
Range	18–81	19–79.0

This reduction in hospital stay was largely due to the reduced requirements for skin grafting. Thus, the duration of hospital stay was reduced by 2.5 days for those patients who only received a skin graft but no ELND compared to those who had a primary closure (6.5 days *vs.* 3.0 days, p = 0.001). For those patients who had an ELND, the hospital stay was also reduced by 2.4 days when an STSG was not used (9.5 days *vs.* 7.1 days, p = 0.001).

Surgical Complication Rates

The wound infection rate at the primary melanoma excision site was 5.4% for patients receiving a 2-cm excision margin and 4.6% for those patients with a 4-cm margin (p = NS); the wound dehiscence rates were 4.6% and 4.2%, respectively (p = NS). The extended hospital stay in patients who underwent skin grafting (with or without ELND) was influenced by a prolonged postoperative management (including delayed ambulation) and a slightly higher infection rate compared to those who had primary closure (5.7% *vs.* 2.8%, p = 0.07). None of the other complications occurred with enough frequency to be analyzed statistically.

Analysis of Prognostic Factors

A multifactorial analysis of factors predicting survival was performed (Table 3). As expected, increasing tumor thickness correlated strongly with a decreasing survival rate (p = 0.001). The presence of ulceration correlated with decreased survival (p = 0.01) as did trunk location of the melanoma (p = 0.04). The margin of excision did not correlate with survival, even after accounting for all other prognostic factors.

Recurrence Rates

After a median follow-up time of 72 months, the overall local recurrence rate was 0.8% (two patients) for those who received 2-cm excision margins and 1.7% (four patients) for those who received 4-cm margins (p = NS). The two patients with a local recurrence after a 2-cm margin had tumor thicknesses of 1.7 and 2.1 mm, while those with 4-cm margins had tumor thicknesses of 2.4, 2.9, 3.0, and 3.4 mm. Of these six patients, five have died of metastatic disease thus far. This finding reinforces previous conclusions that local recurrence is associated with a high mortality rate.[2,15] The rates of in-transit metastases were virtually the same for both groups (2.5% *vs.* 2.1%, respectively). The relapse rates for distant metastases were also comparable (10.9% *vs.* 8.5%, respectively; p = NS).

Table 2. INFLUENCE OF SURGICAL MARGIN ON RATE OF STSG AND HOSPITAL STAY (ALL PATIENTS)

	No. of Patients	% STSG	Mean Hospital Stay (days) (±SD)	p Value*
All patients	486	28	6.1 (4.8)	
4-cm margin (± ELND)	242	46	7.0 (5.1)	< 0.001
4-cm margin plus ELND	130	45	8.6 (5.5)	< 0.001
4-cm margin only	112	46	5.2 (4.0)	
2-cm margin (± ELND)	244	11	5.2 (4.5)	
2-cm margin plus ELND	133	11	7.0 (4.6)	< 0.001
2-cm margin only	111	10	3.0 (3.1)	

* p value difference in hospital stay for each cohort.

Table 3. MULTIFACTORIAL ANALYSIS OF PROGNOSTIC FACTORS

Features Predicting Survival (Cox Proportional Hazards Model)	Coefficient	95% Confidence Interval	Relative Risk	p Value
Thickness	0.5534	0.225, 0.881	1.738	0.0008
Ulceration	0.7909	0.181, 1.400	2.205	0.0095
Anatomic subsite	0.6529	0.021, 1.284	1.919	0.0389
Surgical margin	0.4237	−0.154, 1.000	1.526	0.1421

Survival Rates

There was no difference in overall survival between patients who received surgical margins of 2 or 4 cm (Fig. 1). The overall 5-year survival rate was 79.5% for the 2-cm margin patients and 83.7% for the 4-cm margin patients (p = NS).

DISCUSSION

The results of this prospective, randomized trial demonstrated that it is safe to use 2-cm excision margins for intermediate-thickness melanomas. The local recurrence rates and survival rates were the same regardless of whether 2- or 4-cm surgical margins were used. In light of this finding, a 2-cm margin is clearly preferable because it significantly reduced the need for disfiguring skin grafts, was associated with a shortened hospital stay, and, by implication, reduced health care costs. Such a narrow excision could often be performed as outpatient surgery, thus eliminating the need for hospitalization altogether. At M. D. Anderson Cancer Center, for example, the mean hospital stay in 1992 for a 2-cm excision of cutaneous melanoma was only 1.4 days (median, 1.0 days), and 40% of patients had their surgery performed on an outpatient basis (Lee J, Lacy C. Unpublished observation).

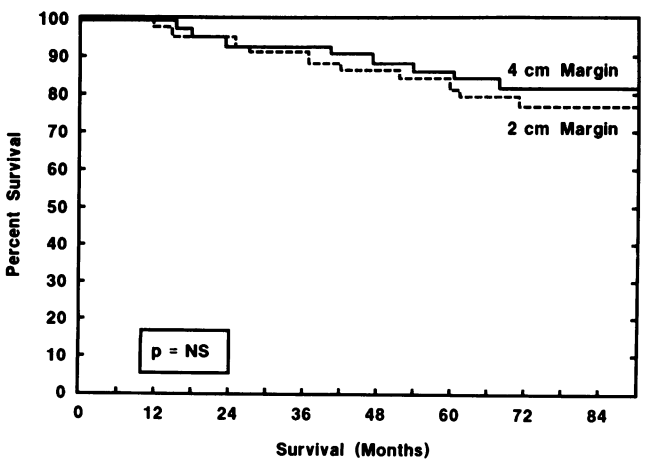

Figure 1. The overall survival of patients randomly allocated to receive either a 2-cm or 4-cm margin of excision. There is no significant difference in overall survival or disease-free survival (data not shown) after a median 72 months of follow-up.

Increased local recurrence rates were not found for patients in any subgroup of tumor thickness, anatomic site, or excision margin. In contrast, in the previous WHO Melanoma Program randomized surgical trial, a clustering of local recurrences was noted in patients with 1.1- to 2.0-mm–thick lesions who had 1-cm margins of excision, indicating that a 1-cm margin may be too narrow for this tumor thickness.[14]

There are two possible biological explanations for local recurrence. First, retained primary tumor cells or microsatellites that were left behind after an inadequate incision may continue to grow and become clinically manifest as a local recurrence. Alternatively, circulating metastatic melanoma cells may grow in the surgical scar of the excised primary melanoma as the initial clinical manifestation of distant metastasis. Currently, it is impossible to distinguish between these two biological entities, and both may contribute to the incidence of local recurrence. Until we can distinguish between these two possibilities, it is appropriate to presume that a local recurrence may result from inadequate surgical excision. The surgeon should tailor the excision margins to minimize this risk without sacrificing an unnecessarily large amount of tissue.

Based on the results of this randomized surgical trial and the previous randomized surgical trial conducted by the WHO Melanoma Program, we recommend the following margins of excision around a primary melanoma. For melanomas thinner than 1.0 mm, a 1-cm margin of excision is sufficient based on the WHO Melanoma Program trial results. For intermediate-thickness melanomas (1.0 to 4.0 mm), a 2-cm margin is appropriate. For patients with melanoma arising on the face, hands, or feet, it is sometimes impossible to excise the tumor with a 2-cm surgical margin. In these circumstances, the surgeon must use his or her best judgment and excise the melanoma with the widest possible margin (up to 2 cm) given its anatomic location and tumor thickness.

As with other forms of cancer, the most successful treatments are those initiated at the earliest possible stage of disease. Early detection of melanoma results in the highest rate of cure and the least magnitude of surgical treatment. After years of recommending surgical

margins based on empirical observations in retrospective studies, a definitive recommendation for surgical management of most melanomas can now be made based upon the results of prospective, controlled surgical trials.

Acknowledgments

Carolyn Sankey was the Executive Secretary for the Intergroup Melanoma Committee from its inception. Her dedicated efforts and organizational abilities are directly responsible for the accuracy, completeness, and timeliness of the data. Dr. Edwin M. Jacob, Clinical Professor of Medicine (Oncology), University of California at San Francisco, and formerly Associate Chief, Clinical Investigations Branch, National Cancer Institute (NCI), had a major role in initiating this surgical trial, while Dr. Michael Friedman, Chief, Clinical Investigations Branch, NCI, was instrumental in facilitating this study. The central pathology reviews were performed by Drs. Martin Mihm, Raymond Barnhill, and Ben Bronstein at the Massachusetts General Hospital. Dr. Seng-jaw Soong, Director of Biostatistics, Comprehensive Cancer Center, University of Alabama at Birmingham, performed the statistical analysis of the Alabama/Sydney Melanoma Clinic data about the timing and natural history of local recurrences described in the Methods section.

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Appendix: Participating Institutions

Roswell Park Memorial Institute	
UT M. D. Anderson Cancer Center	(A. Boddie, D. Hohn, J. Jessup, 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 Centre, 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	

In addition to the authors, surgeons who entered five or more patients are listed in parentheses after each institution.

Discussion

DR. MURRAY F. BRENNAN (New York, New York): Mr. Chairman, Members and Guests, I would like to thank Dr. Balch for asking me to comment on this paper and for the opportunity to review the manuscript. He is to be congratulated, along with his colleagues, for his tenacity in getting this trial started almost 10 years ago and carrying it through to such fruition. I have three comments to make.

First, if local recurrence is not caused by leaving tumor cells behind (*i.e.*, a smaller margin did not increase local recurrence), what does cause local recurrence? Is it merely that the circulating tumor cells at the time of operation localized to an area of injury? Or does he have some other explanation?

Second, this trial contained two components: a component of wide local excision and a component of randomization to lymph node dissection or not. He briefly alluded to the observation that one quarter of these patients had a 2-cm excision and no lymph node dissection; however, in the manuscript, they had a 3-day hospital stay. It may not be feasible for us to