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Efficacy of an Elective Regional Lymph Node Dissection of 1 to 4 mm Thick Melanomas for Patients 60 Years of Age and Younger

Charles M. Balch, M.D.,* Seng-Jaw Soong, Ph.D.,† Alfred A. Bartolucci, Ph.D.,†
Marshall M. Urist, M.D.,† Constantine P. Karakousis, M.D.,‡§ Thomas J. Smith, M.D.,‖
Walley J. Temple, M.D.,¶ Merrick I. Ross, M.D.,* William R. Jewell, M.D.,‡
Martin C. Mihm, Jr., M.D.,# Raymond L. Barnhill, M.D.,** and Harold J. Wanebo, M.D.††

From The University of Texas M. D. Anderson Cancer Center, Houston, Texas; University of Alabama at Birmingham,† Birmingham, Alabama; University of Kansas Medical Center,‡ Kansas City, Kansas; the Roswell Park Cancer Institute§, Buffalo, New York; Morristown Memorial Hospital‖, Morristown, New Jersey; the Tom Baker Cancer Centre,¶ Calgary, Alberta, Canada; Albany Medical Center,# Albany, New York; Brigham and Women's Hospital, Harvard Medical School,** Boston, Massachusetts; and Brown University,†† Providence, Rhode Island*

Objective

A prospective multi-institutional randomized surgical trial involving 740 stage I and II melanoma patients was conducted by the Intergroup Melanoma Surgical Program to determine whether elective (immediate) lymph node dissection (ELND) for intermediate-thickness melanoma (1–4 mm) improves survival rates compared with clinical observation of the lymph nodes. A second objective was to define subgroups of melanoma patients who would have a higher survival with ELND.

Methods

The eligible patients were stratified according to tumor thickness, anatomic site, and ulceration, and then were prerandomized to either ELND or nodal observation. Femoral, axillary, or modified neck dissections were performed using standardized surgical guidelines.

Results

The median follow-up was 7.4 years. A multifactorial (Cox regression) analysis showed that the following factors independently influenced survival: tumor ulceration, trunk site, tumor thickness, and patient age. Surgical treatment results were first compared based on randomized intent. Overall 5-year survival was not significantly different for patients who received ELND or nodal observation. However, the 552 patients 60 years of age or younger (75% of total group) with ELND had a significantly better 5-year survival. Among these patients, 5-year survival was better with ELND *versus* nodal observation for the 335 patients with tumors 1 to 2 mm thick, the 403 patients without tumor ulceration, and the 284 patients with tumors 1 to 2 mm thick and no ulceration. In contrast, patients older than 60 years of age who had ELND actually had a lower survival trend than those who had nodal observation. When survival rates were compared based on treatment actually received (*i.e.*, including crossover patients), the patients with significantly improved 5-year survival rates after ELND included those with tumors 1 to 2 mm thick, those without tumor ulceration, and those 60 years of age or younger with tumors 1 to 2 mm thick or without ulceration.

Conclusion

This is the first randomized study to prove the value of surgical treatment for clinically occult regional metastases. Patients 60 years of age or younger with intermediate-thickness melanomas, especially those with nonulcerative melanoma and those with tumors 1 to 2 mm thick, may benefit from ELND. However, because some patients still are developing distant disease, these results should be considered an interim analysis.

The usefulness of elective (immediate) regional lymph node dissection has been debated for decades. Surgeons conducting a myriad of retrospective surgical analyses have been divided equally between those concluding that there is a benefit of elective lymph node dissection (ELND) and those who believe that the regional lymph nodes should be removed only if they are involved clinically.[1] Several institutions have even reversed their recommendations based on serial analysis of their patient data.[2,3] The World Health Organization Melanoma Program conducted the first randomized prospective trial to address this issue (Trial #1), which did not demonstrate a benefit for ELND.[4,5] This classic trial demonstrated that all patients with melanomas do not benefit from ELND, but the design of the trial did not delineate any subgroups based on prognostic factors. Furthermore, this trial was confined largely to female extremity melanomas and included all tumor thicknesses. Another prospective randomized surgical trial conducted by surgeons at the Mayo Clinic did not demonstrate any survival benefit of ELND and also did not address specific subgroups of patients.[6]

The current trial reported was designed from a previous study of prognostic factors and surgical treatment results from prospective melanoma registries of patients treated at the University of Alabama at Birmingham and the Sydney Melanoma Unit. The data suggested that ELND benefited patients with intermediate-thickness melanomas (*i.e.*, 1–4 mm).[2,7–10] Because of the divergent opinions about ELND, we designed a prospective randomized surgical trial. This Intergroup Melanoma Surgical Trial involved the major clinical cancer cooperative groups because of the large sample size required to test the objectives outlined in the protocol.

At the outset of this surgical trial, the stated objective was "to determine whether regional node metastatic disease improves survival rates in those patients selected by prognostic factors analysis." Thus, this trial was designed to test whether the current clinical and pathologic prognostic factors can identify subgroups of patients at higher risk for clinically occult regional metastases and whether, at the time of the initial melanoma diagnosis, ELND improves survival rates. Our hypotheses was that melanomas metastasize first to regional lymph nodes and then to distant sites in subgroups of patients with melanoma, which can be defined by combinations of prognostic factors.

MATERIALS AND METHODS

Patients

Patients with clinically localized melanomas (*i.e.*, stages I and II according to American Joint Committee on Cancer staging criteria) of intermediate-thickness (1–4 mm thick) were eligible for this surgical trial. Patients who previously had cancer (except for skin cancer) or who had received chemotherapy, radiotherapy, or any other adjunctive to surgery were excluded. Patients with lentigo maligna melanoma also were excluded. Written informed consent was obtained from all patients.

Eligible patients were prerandomized to their surgical treatment arms according to the method described by Zelen et al.[11] Patients who had melanomas involving the trunk or a proximal extremity were randomly assigned to receive a 2- or 4-cm radial margin of surgical excision, as reported previously.[1] Patients with head and neck and distal extremity melanomas had a 2-cm radial margin of surgical excision around the primary melanoma. Each patient also was assigned randomly to receive ELND or observation of the regional lymph nodes with therapeutic lymph node dissection only if clinically indicated during follow-up surveillance. The crossover rates for patients who refused the randomized treatment were similar for the two treatments (10% crossed over to ELND and 9% crossed over to observation; Fig. 1). All patients with trunk melanomas had cutaneous lymphoscintigraphy to identify all lymph node areas at risk. All draining lymph nodes basins were dissected in patients with multiple drainage areas as identified by lymphoscintigraphy in patients randomized to receive ELND.

All patients were examined for the presence of recurrent or metastatic melanoma at 3-month intervals during the first 2 years after surgery, at 6-month intervals in

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Address reprint requests to Charles M. Balch, M.D., Office of the Executive Vice President for Health Affairs, Box 323, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030.

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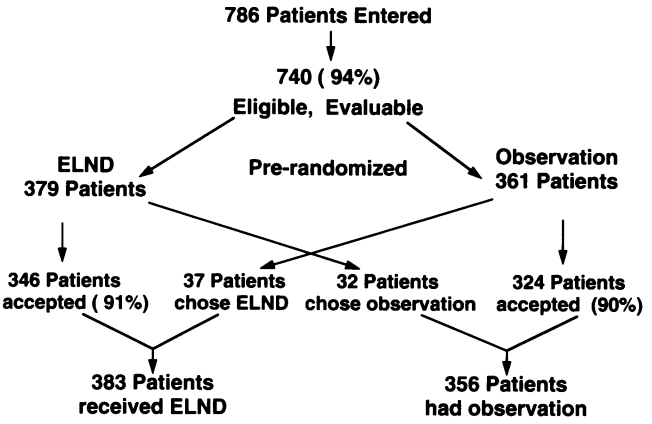

Figure 1. Schema showing patient groups based on "randomized intent" or "treatment actually received." Patients designated in the text as "randomized intent" are those who were prerandomized to either elective lymph node dissection or observation and included those patients who did accept the randomized assignment. The cohort of patients under "treatment actually received" includes the crossover patients from the opposite randomized treatment assignment.

Table 2. PROGNOSTIC FACTORS ANALYSIS BASED ON MULTIVARIATE COX REGRESSION STATISTICAL METHOD

	All Patients		≤60 Years of Age	
Characteristic	Risk Ratio	p Value	Risk Ratio	p Value
Tumor thickness				
1.0–2.0 mm	1.0	—	1.0	—
2.1–3.0 mm	1.6	0.021	2.1	0.002
3.1–4.0 mm	2.2	0.001	2.3	0.003
Tumor ulceration present	2.2	<0.001	2.3	<0.001
Age >60 yr	1.5	0.019	NA	NA
Anatomic site				
Extremity	1.0	—	1.0	—
Head and neck	1.7	0.067	2.1	0.029
Trunk	1.9	0.001	2.2	0.001
Female gender	1.0	0.847	1.3	0.154

NA = not applicable.

years 3 to 5, and annually thereafter. These surveillance examinations included a history and physical examination, chest radiography, and measurement of serum liver enzyme levels. Computerized tomograms and nuclear scans were obtained to confirm signs or symptoms of metastatic melanoma.

Surgical Technique and Quality Control

All surgeons involved in this study 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, or the Danish Melanoma Group). Each surgeon signed a quality assurance form for each patient, which stated the measured surgical margins actually used and the surgical details of the lymphadenectomy (when performed). A quality control committee met periodically and verified the entries in our database by reviewing the surgical notes, pathology forms, and the surgery quality assurance forms completed by the operating surgeon.

Each patient underwent a complete lymph node dissection of the nodal basins identified clinically or by lymphoscintigraphy. A detailed description of the surgical techniques was approved by the surgery committee of

Table 1. CLINICAL AND PATHOLOGIC CHARACTERISTICS

	Randomized Treatment	
Characteristic	Observation	Node Dissection
Melanoma thickness (mm)		
Mean	1.97	1.96
Median	1.80	1.80
Tumor ulceration present (%)	25	23
Age (yr)		
Mean	49	49
Median	48	48
Anatomic site (%)		
Trunk	39	40
Extremities	53	51
Head and neck	8	9
Female gender (%)	51	49

Table 3. SUBGROUPS WITH IMPROVED SURVIVAL FROM ELECTIVE NODE DISSECTION

		p Value	
Subgroup	No. of Patients	Randomized Intent	Actual Treatment Received
Without ulceration	543	0.12	0.02
1.0–2.0 mm	446	0.08	0.03
<60 yr of age	552	0.04	0.09
<60 yr of age, without ulceration	403	0.01	0.007
<60 yr of age, 1.0–2.0 mm	335	0.02	0.003
<60 yr of age, without ulceration, 1.0–2.0 mm	284	0.005	0.0006

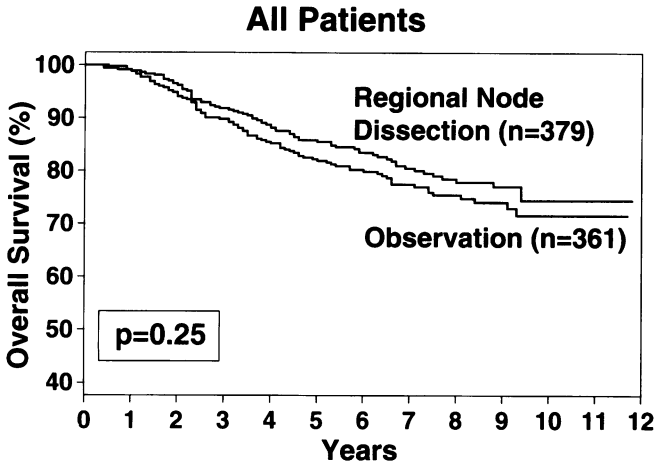

Figure 2. Survival rates for patients receiving elective lymph node dissection *vs.* observation. There was no difference in overall survival based on randomized intent (shown in figure) or actual treatment received (data not shown).

each cooperative group. The description of the surgery had to conform with the surgical guidelines described in the protocol. In addition, each surgeon had to complete a checklist documenting that the critical parameters of surgery quality control were followed. Finally, for specific procedures, the pathologic examination of the surgical specimen had to identify a minimum number of lymph nodes: 5 for an inguinal dissection, 10 for an axillary dissection, and 15 for a cervical nodal dissection.

Each patient who had a groin dissection had a standard inguinal lymph node dissection; iliac dissections were performed only if there were multiple metastases to the femoral lymph nodes. A complete axillary dissection, including removal of level I, II, and III lymph nodes, was performed. When a neck dissection was indicated, a modified neck dissection was performed, sparing the internal jugular vein, the sternocleidomastoid muscle, and the spinal accessory nerve. A parotid lymph node dissection was performed when the primary melanoma was located on the face, anterior scalp, or ear.

Pathology

To confirm the diagnosis, microstaging, and pathologic features, a representative histologic section of each primary melanoma was reviewed independently by a pathologist from the participating cooperative group, and at least 66% of the slides also were reviewed by a central panel of melanoma pathologists at the Pathology Reference Center, Massachusetts General Hospital, Boston, Massachusetts.

Statistical Analysis

Standard statistical techniques were used. Proportions were compared by using chi-square analysis or Fisher's exact test, when appropriate. Mean comparisons were made by using analysis of variance and Student's t test. Survival 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 the comparison of 5-year survival rates was calculated based on the comparisons of the survival curves. Proportional hazards analysis based on Cox's regression analysis model was used to associate variates to time-dependent end points such as recurrence and survival.

Results are reported based on "randomized intent," which includes those patients who refused the randomized treatment assigned. This was the primary basis for

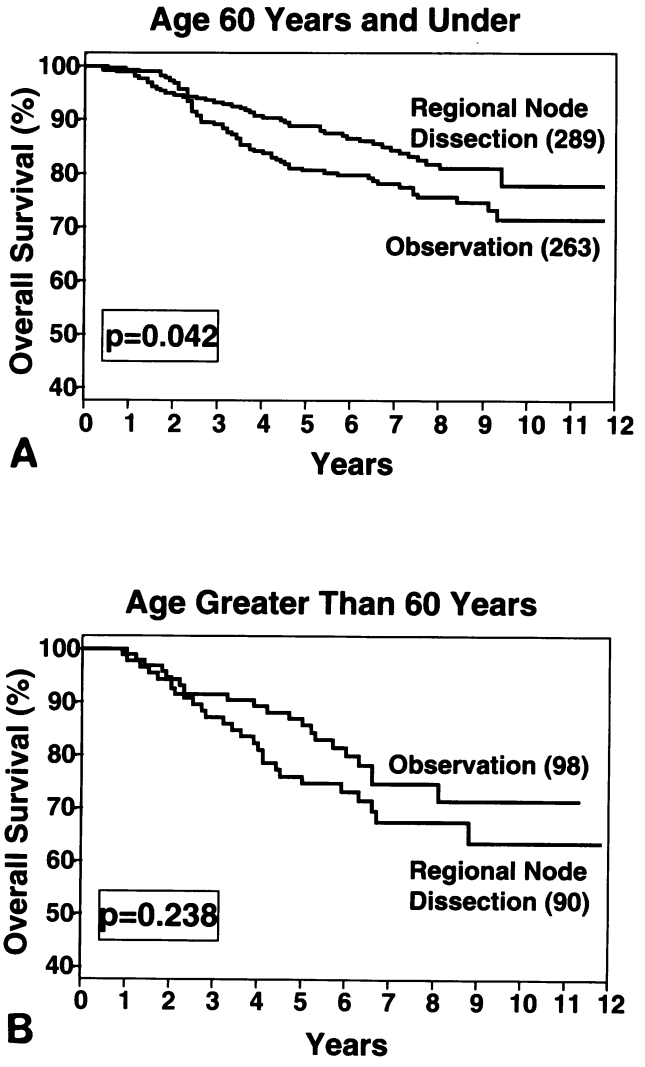

Figure 3. Survival rates by age group based on randomized intent. Patients 60 years of age and younger had higher overall survival rates if their initial treatment included regional node dissection. In contrast, patients older than 60 years of age tended to have a lower survival rate if their initial treatment included regional node dissection.

Table 4. DISTRIBUTION OF PROGNOSTIC FACTORS BY AGE

	≤60 Years (552 patients)	>60 Years (188 patients)
Thickness (%)		
1.0–2.0 mm	61	59
2.1–3.0 mm	29	31
3.1–4.0 mm	10	10
Median thickness (mm)	1.81	1.80
Ulceration (%)	24	24
Female (%)	52	44
Site (%)		
Trunk	42	32
Arm	22	29
Leg	28	29
Head and neck	8	10

interpreting results. Where indicated, results also are based on "treatment actually received," which includes those patients who crossed over from another preassigned treatment (Fig. 1).

RESULTS

Characteristics of Study Patients

Of the 786 patients entered into the study, 740 (94%) were eligible and able to be evaluated. Only 3% of the patients were lost to follow-up. The average length of follow-up was 7.4 years; more than 98% of the patients had a follow-up of 5 years or longer. The clinical and pathologic characteristics of the patients and their tumors are shown in Table 1. The patients were distributed evenly in the two treatment arms according to sex, age, anatomic site of the tumor, tumor thickness, and the presence or absence of tumor ulceration. The patients also were evenly distributed with respect to the width of the surgical margin of the primary melanomas (2- *vs.* 4-cm radial margin), as described previously.[1]

Prognostic Factors of Analysis

A multifactorial (Cox regression) analysis of factors predicting overall survival was performed (Table 2). The factors that correlated most significantly with worse survival rates were the presence of tumor ulceration ($p < 0.001$), greater tumor thickness ($p < 0.02$), trunk site ($p = 0.01$), and older patient age. Patient age was a significant prognostic factor when analyzed as a continuous variable ($p = 0.038$) and when the patients were grouped into cohorts of 60 years or younger *versus* older than 60 years ($p = 0.019$). The gender of the patient did not influence the survival rates.

Overall Treatment Results

The survival rates of patients who received ELND *versus* observation were analyzed according to randomly assigned treatment and by actual treatment received (Fig. 1). Among specific subgroups identified by prognostic factors analysis, the results were virtually the same whether the patients were grouped by randomized intent or actual treatment received (Table 3).

There was no difference in overall 5-year survival between patients whose initial treatment was ELND and those whose lymph nodes were observed (86% *vs.* 82%; $p = 0.25$) (Fig. 2). However, significant differences did appear in subgroups of patients.

Elective Lymph Node Dissection and Age

The most striking differences occurred in patients subgrouped by 60 years of age and younger *versus* older than 60 years of age. Overall, 5-year survival rates of 552 patients 60 years of age or younger (75% of the total patients) had increased survival rates with ELND compared with observation (88% *vs.* 81%; $p = 0.04$; Fig. 3A). In contrast, patients older than 60 years tended to have a lower survival rate if their treatment was ELND rather than nodal observation (74% *vs.* 86%; $p = 0.238$; Fig. 3B). There were no significant differences in the distribution of clinical or pathologic prognostic factors based on the patient's age (≤ 60 years *vs.* ≥ 60 years; Table 4).

The patients 60 years of age and younger were further analyzed by subgroups according to tumor thickness and ulceration. In the 403 younger patients without tumor ulceration, there was a significant increase in 5-year survival with ELND (95% *vs.* 84%; $p = 0.01$; Fig. 4A). In the 335 younger patients with melanomas 1 to 2 mm thick, there also was an improved 5-year survival rate with ELND (96% *vs.* 86%; $p = 0.02$; Fig. 4C). The subgroup showing the most improved 5-year survival rate with ELND were those 284 patients 60 years of age and younger whose melanomas were 1 to 2 mm thick and who had no tumor ulceration (97% *vs.* 87%; $p = 0.005$; Fig. 4E). The improved survival rates were even more significant for ELND when the patient outcome was analyzed for these subgroups based on actual treatment received (Figs. 4B, 4D, and 4F).

Elective Lymph Node Dissection and Tumor Thickness

When treatment results were analyzed by 1 mm tumor thickness subgroups, there were no significant differences among patients whose tumors were thicker than 2 mm (Fig. 5). There was a trend for patients with tumors 1 to 2 mm thick to have improved survival based on randomized assignment ($p = 0.08$; Fig. 5A), and the trend achieved statistical significance when the survival rates were calculated based on actual treatment received ($p = 0.031$; Fig. 6A).

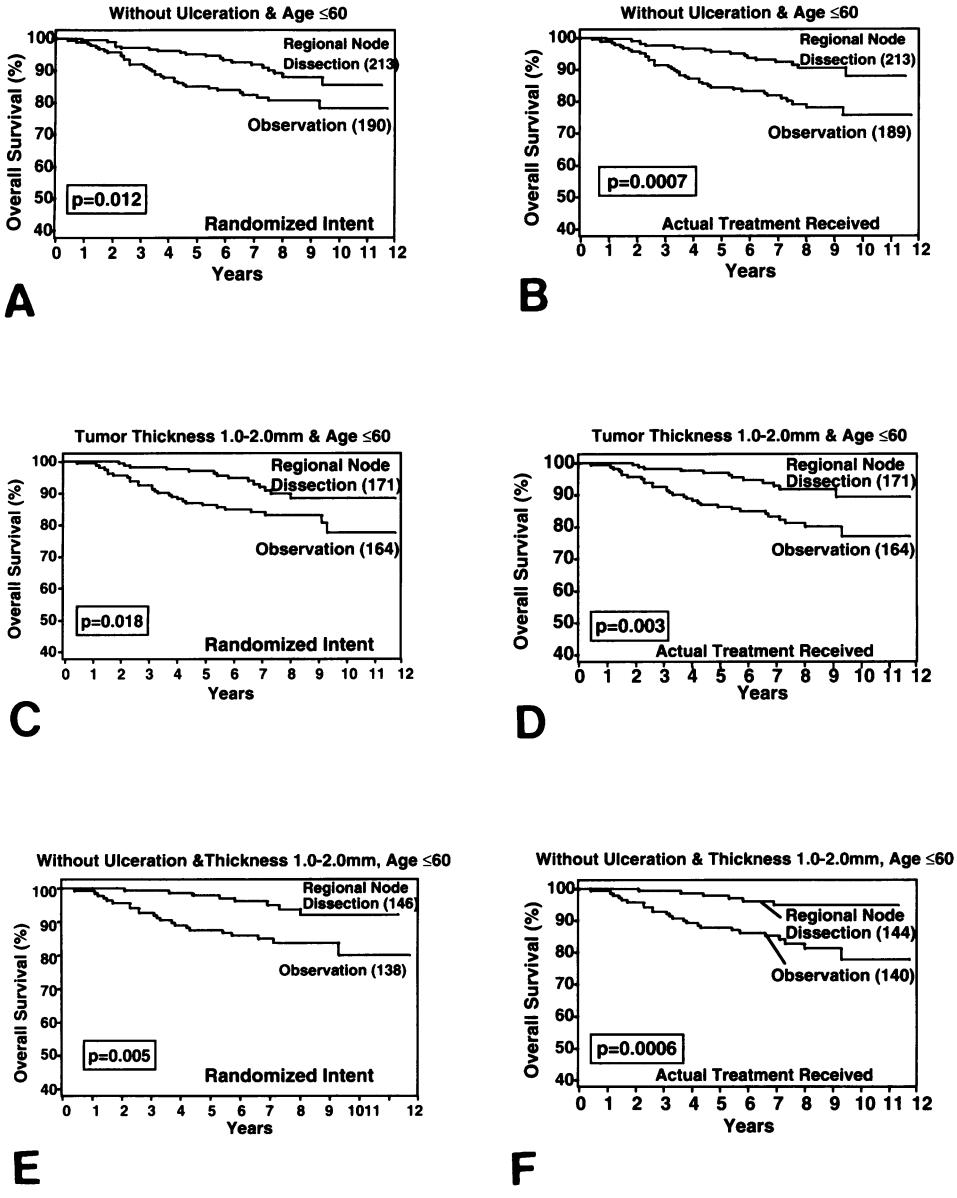

Figure 4. Analysis of subgroups in patients 60 years of age or younger. The left panel shows survival rates based on randomized intent; the right panel compares survival rates based on actual treatment received.

Elective Lymph Node Dissection and Ulceration, Sex, and Tumor Site

Of the 543 patients without ulceration, there was no significant difference in treatment outcome in patients analyzed by randomized treatment intent ($p = 0.12$), whereas patients analyzed by actual treatment received had improved survival with ELND ($p = 0.018$; Fig. 6B).

There was no survival difference in any subgroups of patients when analyzed by gender or by anatomic site of melanoma.

Patterns of Relapse

More than 90% of the patients with regional recurrence had clinical evidence of their relapse within 5 years of follow-up, and distant relapses still were occurring after 9 years of follow-up. The cumulative incidence of distant relapses is shown in Figure 7.

DISCUSSION

This prospective surgical trial identified major subgroups of melanoma patients whose overall survival was significantly better if their initial management included ELND. The benefit of ELND was confined to patients younger than 60 years of age with intermediate-thickness melanomas, especially those without tumor ulceration or with tumors 1 to 2 mm thick. The data are consistent, regardless of whether the surgical treatment analysis was

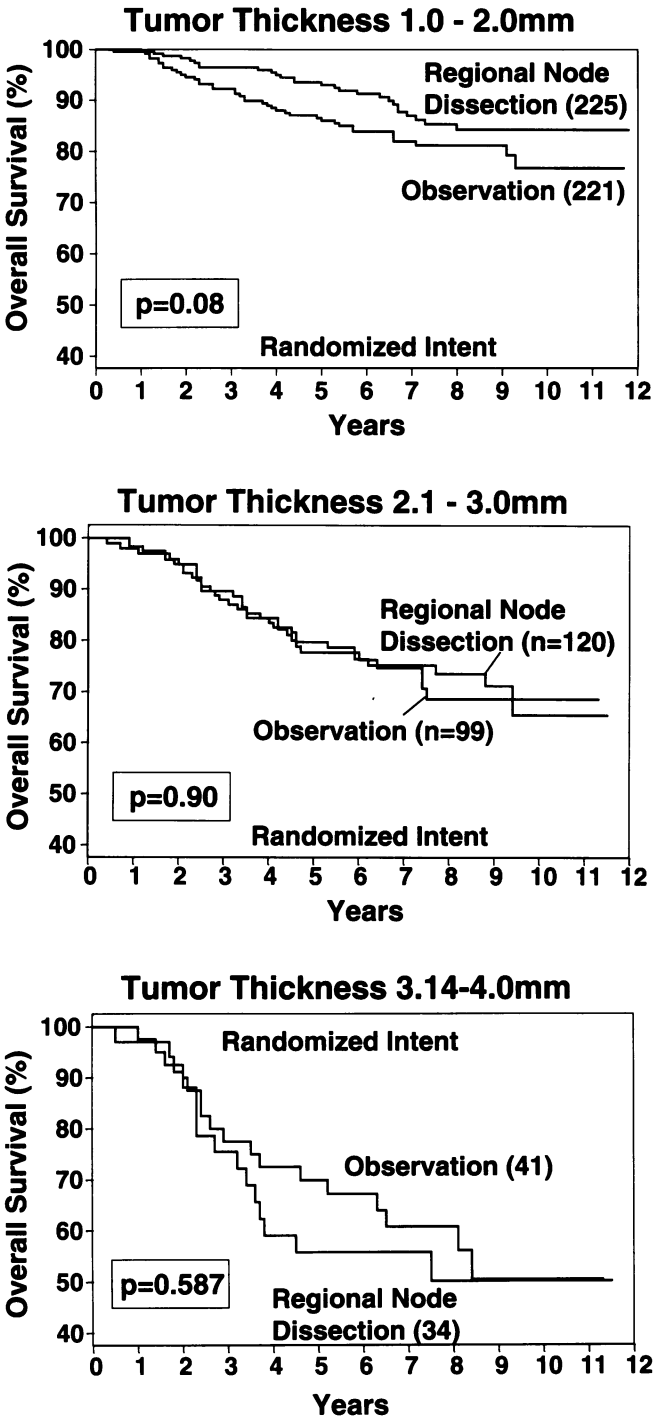

Figure 5. Survival rates by tumor thickness based on randomized intent. There were no significant differences between the two treatment groups, although patients with melanomas 1 to 2 mm thick tended to have a higher survival (p = 0.08).

based on randomized treatment intent or surgical treatment actually received. Therefore, these results should be considered when making surgical decisions about the management of regional lymph nodes. This is the first randomized study to prove the value of surgical treatment for clinically occult metastatic melanoma. To the best of our knowledge, this also is the first controlled surgical trial to demonstrate the curative value of surgical treatment for any form of metastatic cancer.

However, these results should be interpreted with some caution for several reasons. First, at the end of the study, patients still were developing potentially fatal distant metastases, so the treatment comparisons based on overall survival rates may change with longer follow-up. Second, the importance of age was not incorporated into the stratification criteria of the trial, so that one of the independent prognostic factors used for comparing surgical results was identified by the multifactorial analysis at the end of the trial. Third, subgroup analysis can yield

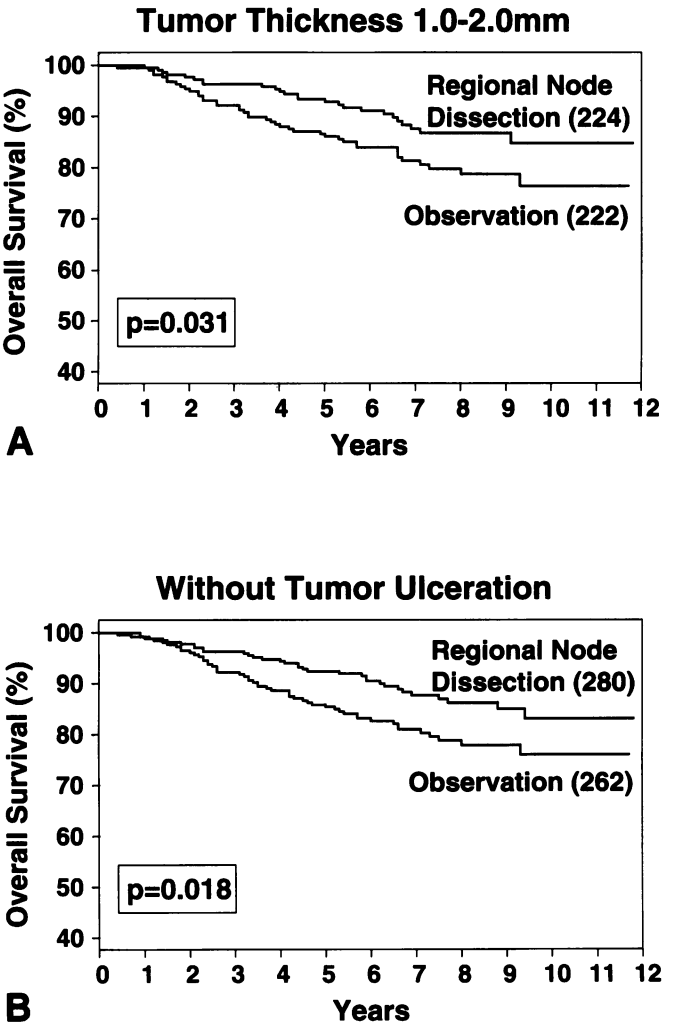

Figure 6. Survival rates by subgroups based on actual treatment received according to tumors 1 to 2 mm thick (A) or without ulceration (B). This includes patients of all age groups. Patients with melanomas thicker than 2 mm or with ulceration did not have any improvement in overall survival with regional node dissection (data not shown).

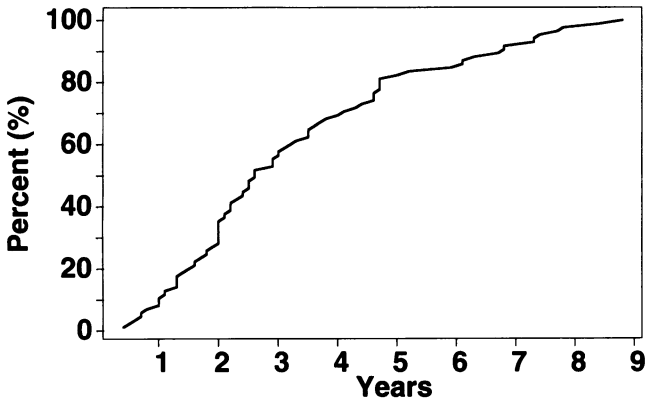

Figure 7. Cumulative incidence of first distant recurrences. Patients are continuing to relapse with distant metastases even after 9 years average of follow-up.

false-positive conclusions; however, the original intent of this trial was to examine subgroups based on prognostic factors. For these reasons, this data analysis should be viewed as an interim analysis; we intend to continue following the patients for several more years.

The results of this trial support the hypothesis that melanoma cells metastasize sequentially from the primary site to regional lymph nodes and then to distant sites, at least in some subgroups of patients. Theoretically, there is a narrow window of time during which regional micrometastases are isolated sufficiently that their removal prevents further dissemination to distant sites. As primary tumors grow or develop ulceration (an invasive property), the risk for distant metastases increases and the benefit of regional lymph node dissection decreases.

An unexpected result of the surgical trial was that the survival benefit was greatest in patients with tumors 1 to 2 mm thick. Several reports of retrospective surgical results suggested that ELND mostly would benefit patients with melanomas more than 2 or even 3 mm thick.[9,10] The results based on randomized intent showed a trend favoring ELND for some patients with thicker tumors, but only for patients patients younger than 60 years of age, and the trend achieved statistical significance only in patients with tumors 1 to 2 mm thick. When the results were compared based on actual treatment received, patients of all ages had improved survival with tumors 1 to 2 mm thick, but especially in patients 60 years of age or younger.

Age was a significant prognostic factor influencing survival rates in these patients. This is not simply because the older patients had more aggressive tumors because the distribution of prognostic factors was fairly even among younger and older patients. We had reported that age significantly influences survival rates but had not incorporated this into clinical decision making.[1,10] In multifactorial analysis of 442 melanoma patients, Austin and colleagues[12] recently reported that patient age was an independent variable influencing outcome.

The impact of age on survival in our surgical trial was dramatic. When patients were subgrouped by decades of age up to 60 years, the patients who had had ELND consistently had better survival rates. However, the survival rates of older patients who had ELND tended to be worse than those of patients who had nodal observation. The lower survival rates in older patients who had ELND offset the benefits seen in younger patients when the entire patient group was analyzed. Whether the poorer survival was due to the immunosuppressive effects of surgery or to other influences cannot be ascertained. Certainly, surgical trials involving melanoma should take into account age, both in the design of the trials and when analyzing surgical outcomes.

Morton and colleagues pioneered the use of sentinel lymphadenectomy for melanoma patients.[13] This selective approach uses intraoperative mapping with a visible blue dye and a radioactive tracer to identify the sentinel (or representative) lymph node within a nodal basin that is most likely to contain melanoma.[13,14] Before this technique is accepted as a standard approach, longer follow-up will be necessary for those patients whose lymph node basins were left intact after sentinel node biopsies were negative for metastatic melanoma. If these results are confirmed by long follow-up, then sentinel lymphadenectomy to guide complete dissection based on pathologic demonstration of metastatic disease might replace the need for ELND, which is based on prognostic factors and a mathematical probability that regional occult metastases are present. An international randomized surgical trial currently is being conducted to confirm these results.

Finally, knowing the pathologic nodal status is important for staging purposes, and adjuvant alpha interferon has been proven to increase survival rates in patients with proven metastatic disease, but not in node-negative patients, including those with T_4 primary melanomas.[15] Thus, surgical excision of the regional lymph nodes may be important for improving survival rates and also for staging patients who should be considered for adjuvant systemic therapy.

Acknowledgments

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study. They also thank Drs. Martin Mihm, Raymond Barnhill, and Ben Bronstein, at the Massachusetts General Hospital, who performed central pathology reviews; Dr. Seng-jaw Soong, Director of Biostatistics, Comprehensive Cancer Center, University of Alabama at Birmingham, who 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; and Dr. Xin Huang, Biostatistics Unit, Comprehensive Cancer Center, University of Alabama at Birmingham, who provided assistance in statistical analysis.

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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. 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 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

Discussion

DR. MURRAY F. BRENNAN (New York, New York): I would like to congratulate Dr. Balch for his organizational skills and, of course, for his tenacity, as he so adequately pointed out, in following this trial now for 10 years, and certain to eventually be 15 or 20.

Dr. Balch, you have shown us that there is no overall survival benefit, that the benefit is to the subgroup under the age of 60 and the difference is approximately 9%. You have to help us by telling us about the morbidity of the procedure of elective dissection so that we can make decisions for our own patients.

You made no mention of whether or not the benefit was to those patients who were identified as having positive nodes. If that were so, did the same number of people who were found to have microscopic disease relapse and need therapeutic node dissection? An understanding of those factors would make it easier for us to decide for the individual patient.

I think it was an extraordinary endeavor. Dr. Balch, I am, however, emotionally very distressed. This paper suggests that dissection benefits only those under 60. As I approach 60, and my children remind me that from every activity from bungee jumping to going to work, "I need to do it now," I am distressed to know that I must have a node dissection soon should I have melanoma.