Efficacy of Elective Lymph Node Dissection in Patients with Intermediate Thickness Primary Melanoma

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One of the most controversial areas in the management of malignant melanoma concerns the efficacy of prophylactic lymph node dissection. During a retrospective computer-aided data review of over 3000 melanoma patients referred to the Duke University Cancer Center, 613 patients with complete staging along with surgical and pathologic data, having trunk and extremity melanoma, were identified with Breslow thickness in the range of 0.76 to 4.0 mm. One hundred eighty-seven of these clinically node-negative patients received an elective lymph node dissection (WLE/ND). The remaining patients were treated only with an initial wide local excision (WLE) at the time of diagnosis of their melanomas. There was no difference in age at diagnosis or male-female ratio between the treatment groups. A higher percentage of the WLE/ND group (36% *vs.* 31%) showed ulceration of their primary lesions and a greater mean tumor thickness (1.81 ± 0.80 mm *vs.* 1.60 ± 0.73 mm) than the WLE patients. Despite the force of these two adverse prognostic factors in the WLE/ND group, only ten deaths (5%) have occurred in the elective lymph node group compared to 51 (12%) in the control group. Using a multifactorial analysis to control for the prognostic contribution of the two most informative variables in stage I melanoma, Breslow thickness and ulceration, WLE/ND had an independent favorable effect on survival (p = 0.01). There was no apparent additional benefit to lymph node dissection in patients whose primary lesion measured less than 0.76 mm or greater than 4.0 mm in thickness. The surgeon may use survival estimates with and without elective node dissection based on a prognostic equation ("prognostigram") as a quantitative aid to treatment planning.

NEW METHODS of microstaging introduced by Clark[1] and Breslow[2] and multivariable statistical techniques for survival analysis are important new tools for studying malignant melanoma. This disease was previously characterized as highly variable in its prognosis, but much of this variability can now be explained by measurable features of the primary site lesion. The acquisition of a statistical method capable of adjusting for the effects of prognostic factor imbalances in the assignment of treatments when evaluating results has enabled us to use the large body of experience incorporated in the Duke University melanoma data bank to address open questions in the management of melanoma.

One such issue is the role of prophylactic lymph node dissections as an adjunct to wide local excision of the primary (WLE/ND) in the treatment of stage I melanoma of the trunk and extremities. Many clinicians use the negative results of randomized controlled trials of WLE/ND from the World Health Organization[3] and Mayo Clinic[4] as their justification for offering the procedure infrequently, if at all. Proponents of the WLE/ND cite many descriptive series purporting to show a favorable outcome with this procedure.[5–8] Milton, Balch, et al.[9] have presented large retrospective series from Alabama and New South Wales using multifactorial techniques which demonstrate a markedly better outcome for patients undergoing WLE/ND compared to concurrent and otherwise similar patients who had WLE only. We report here our experience in the identification of prognostic factors for stage I cutaneous melanoma and evaluation of the effect of elective lymph node dissection on survival in melanoma patients. These data are of particular relevance to community practice since they represent the results from over 30 community surgeons contributing to the patient material.

Materials and Methods

Patient Population

Since its inception in 1972, the Duke University Compehensive Cancer Center has registered over 3000 melanoma patients into a comprehensive data bank as part of an ongoing study of the immunologic aspects of mel-

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anoma. The subset of stage I patients with cutaneous melanomas of the trunk and extremities for whom complete clinical and pathologic information was available was extracted for study. Attention was focused on patients with tumor thickness between 0.76 mm and 4.0 mm. The population was categorized into those receiving an elective lymph node dissection (WLE/ND) in addition to the standard wide local excision of the primary melanoma *vs.* those who did not have a node dissection. There were 187 patients who received an ELND and 426 who only had wide local excision (WLE). Follow-up on this subgroup of melanoma patients was 100%, with a range of 2 to 10 years. All deaths in the series were due to metastatic melanoma.

Treatment

All operative reports and pathology reports were reviewed by one of the authors (DSR) and categorized as WLE or WLE/ND. Patients in whom a biopsy of a few superficial nodes was performed were not considered to have had a lymph node dissection. Most patients' surgery was performed by the referring physicians prior to the referral to Duke for adjunctive therapy. Adjuvant therapy was confined to a specific active immunotherapy protocol.

Pathology

Two pathologists (KM and RV) examined resection specimens from the primary tumors. Pathologic review included Breslow thickness, Clark level, and the presence or absence of ulceration.

Statistical Methods

Actuarial survival curves were obtained by the Kaplan-Meier method.[10] The log rank test[11] was used for survival time differences between subgroups. A univariate analysis was performed in which each variable was considered individually to estimate its prognostic value. The proportional hazard regression model, suggested by Cox,[11] was used for multifactorial analysis of prognostic factors. In this model, the hazard ratio $\lambda_i/\lambda_0 = \exp(\sum_j B_j(X_{ij} - \bar{X}_j))$ where λ_i and λ_0 are the hazard (death rate) functions for the individual i and the overall group, $\bar{X}_j$ and B_j are the mean and regression coefficient for the jth variable, and X_{ij} is the value of the jth variable in the ith individual. Significance testing on $h_0{:}b_j = 0$ makes use of the approximate asymptotic chi-square distribution of twice the increment in log likelihood, resulting from addition of a variable or variables to the model.[11] When the hazard ratio $\exp(\sum_j B_j(X_{ij} - X_j))$ is greater than 1, a patient would have a higher predicted hazard rate than the overall group, while hazard ratios less than 1 predict more favorable than average survival. Individual prognostic predictions (prognostigrams) can be generated for a patient with known factors incorporating the overall patient experience by the formula $S_i(t) = S_0(t)^k i$ where S_i and S_0 are the survival estimates for the individual and the overall group and k_i is the hazard ratio computed for the individual. Two survival estimates, one assuming WLE/ND and another WLE only, express expected outcomes for the individual patient under each of the two treatment modalities.

TABLE 1. *Prognostic Factor Distribution*

Variable	ELND	No ELND
Number	187	426
Age (mean)	45.7	45.5
Number dead	5%	12%
Sex		
Male	45%	45%
Female	55%	55%
Primary site		
Trunk	33%	58%
Upper extremity	35%	13%
Lower extremity	32%	29%
Histological type		
Lentigo maligna	0%	2%
Superficial spread	74%	77%
Nodular	25%	21%
Clark level		
2	0.5%	2%
3	44%	53%
4	53%	43%
5	2.5%	2%
Thickness	1.81 ± 0.80 mm	1.60 ± 0.73 mm
Ulceration	35%	31%

Results

Distribution of Prognostic Factors

Table 1 summarizes the prognostic factor distributions among WLE/ND and WLE patients. There was no appreciable difference in age at diagnosis or male/female ratio between the two groups. A higher percentage of WLE/ND patients had upper extremity primary sites. WLE/ND patients had a greater mean thickness of the primary and a higher incidence of ulceration. Referring surgeons were more likely to perform WLE/ND on patients whom they judged to be at higher risk for metastasis.

Treatment Results

A smaller proportion of patients undergoing WLE/ND (5%) had died of melanoma at the time of evaluation than in the WLE group (12%). Actuarial survival estimates for the two groups are given in figure 1. The dif-

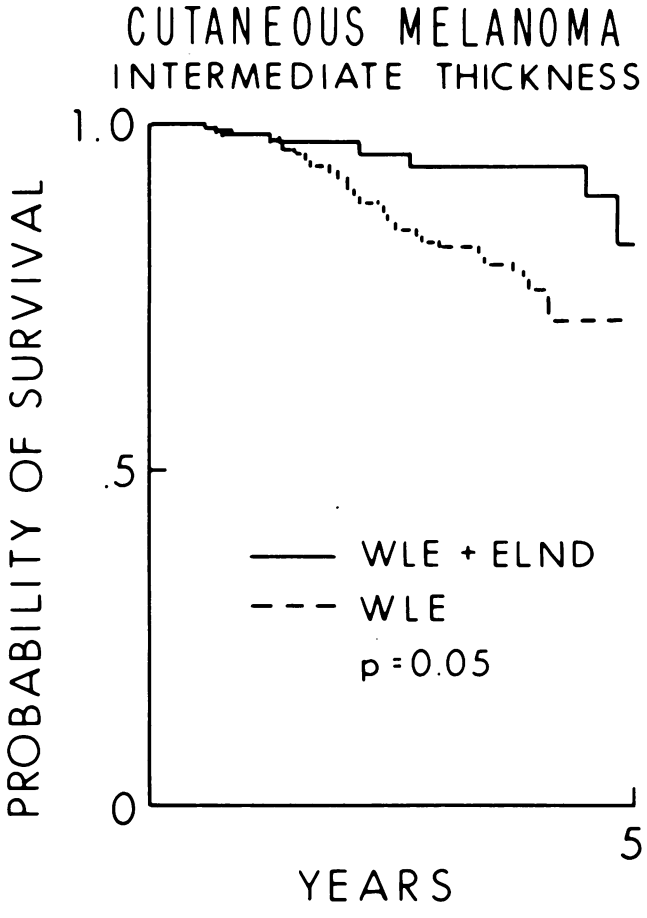

FIG. 1. Actuarial survival curve of intermediate thickness melanoma demonstrating a significant increase in survival in those patients who had an elective lymph node dissection as part of their primary treatment.

ference in survival distributions was of borderline significance (p = 0.05). The 95% confidence intervals on survival estimates broaden beyond 5 years, emphasizing the relatively short follow-up in this group of patients.

Multifactorial Survival Analysis

Four clinical and three pathologic variables were evaluated in a multifactorial analysis of survival prognosis (Table 2). Age and sex were not found to be independently significant. Clark's level had substantial univariate significance but was found to add no further information once thickness had been entered into the model.

TABLE 2. *Cox Model For Stage I Melanoma*

Variable	Univariate p Value	Multivariate p Value	Regression Coefficient	Mean
Ulceration	0.0001	0.0008	0.637	1.66
Thickness	0.002	0.008	0.569	0.64
ELND	0.05	0.01	−1.176	0.32
Clark level	0.005	0.14		3.3
Primary site	0.15	0.08		0.50
Age	0.15	0.25		45.60
Sex	0.14	0.61		1.56

Thickness and ulceration were the two dominant independent factors (Table 2). After adjustment for these factors, WLE/ND was seen to be highly associated with better prognosis (p = 0.01). The estimated death rate for WLE patients was 3.2 times that for comparable WLE/ND patients.

Primary site (trunk *vs.* extremity) was marginally significant as a prognostic factor, with more favorable prognosis accruing to extremity patients. After adjusting for thickness and ulceration, primary site became slightly more significant. When primary site was entered in the model ahead of treatment, WLE/ND lost some of its significance. Similarly, prior entry of treatment nullified the significance of primary site. These observations were not unexpected, given the correlation between primary site and treatment selection.

In order to exclude the possibility that primary site was the primary prognostic factor and treatment was only apparently significant through its correlation with primary site, a separate multifactorial analysis was performed on the WLE group. We reasoned that, were primary site the dominant factor, it should be found significant in the WLE patients alone. Statistically, WLE patients made up the majority of patients (71%) in the study and 83% of the deaths overall. This fact assures recognition of any meaningful contribution to prognosis by primary site. However, no correlation was apparent. Primary site was inconsequential with regard to prognosis among the WLE patients (p = 0.18). We are confident on this basis that primary site variation in treatment allocation does not explain the observed difference in treatment outcome.

Prognostigrams

Using the information in the Cox regression analysis, actuarial survivals for patients having unique prognostic factors were calculated with and without lymph node dissection. The curves are plotted on the same graph as the actuarial survival of the 613 patients on whom the model was based, subgrouped according to WLE/ND and WLE. Figure 2 is an example of a prognostigram for a patient having a superficial melanoma with a Breslow thickness 0.77 mm that was not ulcerated. There is an estimated 5% survival advantage at 5 years for this patient wtih WLE/ND compared to WLE only. Figure 3 illustrates the prognostigram for a patient with a deep 3.9-mm lesion that was ulcerated. This patient has a poorer prognosis than the previous patient with a thin melanoma. However, the patient may expect a 38% increase in survival at 5 years with an WLE/ND *versus*

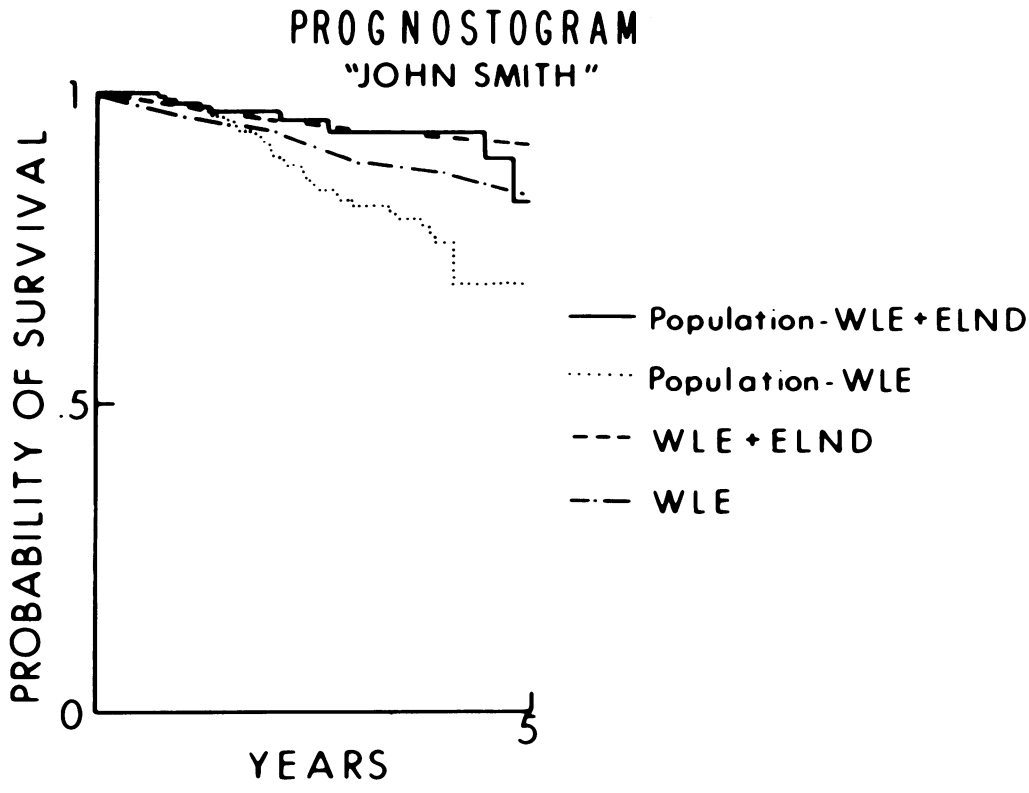

FIG. 2. Prognostigram for patient with a non-ulcerated superficial (0.77 mm) melanoma with (– – –) and without (—·—) elective lymph node dissection. This patient accrues a predicted 5% increase in survival at 5 years after node dissection. His actuarial survival is compared to the model population with (——) and without (· · ·) lymph node dissection.

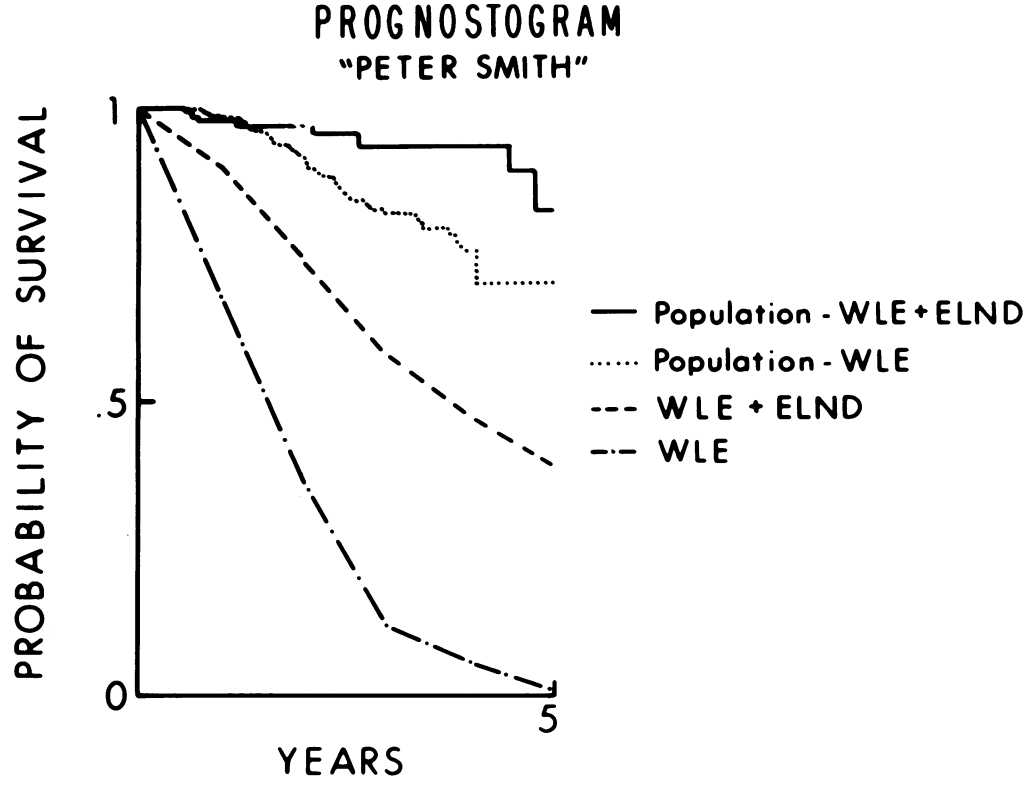

FIG. 3. Prognostigram for particular patient with an ulcerated, deep (3.99 mm) malignant melanoma demonstrating a 38% increase in predicted survival at 5 years with elective lymph node dissection (– – –) compared to wide local excision alone (—·—).

WLE. It is apparent that in patients with deeper lesions or ulcerated lesions, lymph node dissections have a greater absolute influence on survival as compared to patients with more superficial lesions that are not ulcerated.

Discussion

Patients who potentially benefit by WLE/ND are those who harbor metastatic tumor in regional nodes but have no viable tumor dissemination beyond the nodes. The crux of the matter is whether this is a substantial percentage of the patients or an inconsequential fraction. Many of the clinical series,[12,13] presented as evidence supporting or refuting the efficacy of WLE/ND, were reported prior to the advent of microstaging. Since melanoma has such a large natural variation in prognosis, it is evident that interpretation of historical data lacking microstaging information cannot settle the controversy surrounding WLE/ND.

Our study confirms the findings of others[5-9] who were able to detect a strikingly favorable prognosis among patients with intermediate thickness melanomas undergoing WLE/ND after adjusting for known prognostic factors. These findings remain controversial because of results from two contemporaneous prospective randomized trials[3,4] which failed to detect a survival benefit with WLE/ND.

Analysis of our cases yields an estimated death rate that is 3.2 fold greater for a WLE patient compared to a WLE/ND patient of otherwise similar characteristics. This estimate compares to a relative death rate estimate of 2.56 for WLE *versus* WLE/ND in the combined Alabama/New South Wales series of 1069 patients with complete data ($X^2 = 31.6$, $p < 10^{-6}$).[9] Differences of this magnitude have obvious clinical implications.

Acceptance of these results as a basis for establishing treatment policy depends on whether one may confidently attribute the differences in outcome to the different treatments themselves or to other factors fortuitously correlated with treatment. In clinical trials, one can rarely dismiss the possibility that extraneous factors could have been responsible for the differences attributed to treatment. This is true of randomized studies as well as retrospective analyses, although one at least had the advantage of unbiased allocation in a randomized study. It could have been the case, for example, that surgeons in one area who routinely performed WLE/ND were also more effective in managing the primary lesion. If primary site management were the dominant factor producing the difference but went unrecognized, an erroneous conclusion could be reached regarding the efficacy of WLE/ND. We consider this possibility unlikely in the current study, but confirmation by randomized controlled trial would be reassuring.

A large United States cooperative clinical trial studying WLE/ND *versus* WLE is underway at the present time, but useful results will not be available for a minimum of 6 to 10 more years. In the meantime, the individual surgeon must weigh all the evidence in developing an informed therapeutic approach to each patient. Our belief is that the results of retospective analyses,[5-9] controlled as they are for the important prognostic determinants, offer the most useful guideline for treatment selection.

We have developed a clinical report, the "prognostigram," which summarizes the prognostic and therapeutic information gleaned from this investigation. Certain individuals, *e.g.*, those with thin melanomas, have a marginal gain of 3% to 5% by WLE/ND compared to WLE. Others are projected to have as much as 40% or greater difference in long-term survival. This type of information can provide as a useful quantitative basis for the surgeon and patient in balancing the operative risks of WLE/ND against the anticipated gains in outcome.

In contrast to the report by Balch, Soong, Milton, et al.,[9] where "virtually all" of the surgical procedures were performed or supervised by four surgeons, our material represents the accumulated experience of a large number of community surgeons. It is reassuring to know that the beneficial results of WLE/ND as practiced in cancer centers can be transferred successfully into community practice.

This study also underscores the great value of regional data banks as a means of addressing treatment questions which can not possibly be answered by any one physician or hospital. The data base approach to medical decision making is particularly effective in a highly charged situation such as that with WLE/ND, where clinicians on either side of the issue are reticent to submit their patients to a randomized trial. Assuming the existence of prognostic factors capable of explaining much of the inherent variability of a disease, reliable information regarding treatment efficacy can often be obtained from data banks of this type.

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Discussion

DR. ALFRED S. KETCHAM (Miami, Florida): This material serves to offer a specific, reproducible handle from which we can determine the prognosis and presumably the local recurrence and metastatic rates for malignant melanoma. That is, the specific measurement in millimeters from the top of the melanotic lesion, whether it be an elevated nodular lesion or an excavated ulcerative lesion, to the deepest point of tumor invasion into the dermis or the subcutaneous tissue (Breslow). Clark's levels are interesting and helpful but remain controversial.

This presentation leads me to change the title of my local surgical society lecture, which I have entitled "The Surgeon's Paradise in Treating Melanoma," whereby any and all surgeons are treating this disease. This so called simplicity of treating melanoma was based upon the poorly documented, highly selected patient material coming from a multi-institutional collective analysis published recently through the auspices of the World Health Association. It suggested that for stage I melanoma, simple local excision and conservative lymph node observation is all that was indicated. So I feel that it is time to change my melanoma lecture title back to that of "The Surgeon's Challenge in Treating Melanoma," challenged by the local recurrence and the regional node disease problems that we in referral patient institutions are seeing in increased numbers, this conservative trend has been due to the inappropriate belief that melanoma behaves more like basal cell carcinoma than like squamous cell carcinoma. I used the word challenge because we are challenged by the need to learn again how to do a complete lymph node drainage basin resection, rather than a sampling procedure, in order to minimize the disastrous complications of melanoma regrowth in a surgerized groin, neck or axilla. Finally, challenged by the absolute need to seek from our pathologists an accurately measured, not an estimated, extent of actual tumor invasion, determined by evaluating more than one slide made from representative areas of the primary tumor.

I realized that this was not meant to be an encompassing dissertation on melanoma, but they have studied so many cases in preparing this data that I am impelled to ask them what I am sure they are preparing for presentation to us next year: (1) How reliable, and by what means, do you decide on which lymph node draining the area should be dissected, in those frequent occurrences of midline or approaching midline primary lesions? Can you give us an impression of the value, or the lack of satisfaction, for modified dissection, such as leaving the sternocleidomastoid muscle, the spinal accessory nerve or the mandibular branch of the facial nerve, when dissecting the neck? Does the pectoralis minor have to be transected in the axillae? When do you the deep ileo-obturator node dissection and are you also observing less leg edema, when the deep groin dissection is performed through a separate transabdominal incision, when of course there is an indication for the deep groin dissection?

When you classified a lesion as ulcerative in your presentation, did this mean irritation bleeding or was there true ulceration and dermal erosion? Finally, as you retrospectively view your data, is the trend towards less grafting of the primary tumor site and doing more and more primary closures, a viable approach? As more and more are doing less and less for this potentially lethal disease, few of us have found anything really worthwhile to offer the melanoma failure patient. This paper emphasizes how we can again decrease the alarming incidence of local recurrence and regional failure by performing adequate surgery; for it is adequate surgery which most often avoids the necessity of performing radical surgery.

DR. DONALD L. MORTON (Los Angeles, California): As Dr. Ketcham mentioned, one of the problems with treatment of melanomas of the trunk, particularly lesions near the midline or the umbilicus, is distinguishing between lymph node groups which might be affected with metastatic melanoma. We have developed a lymphatic scan, using sulfur technetium colloid, to determine the direction of lymphatic shed. The area of the lesion is injected with this radioactive substance, and when the drainage pattern is established, the node groups which are possibly affected are removed.

We have recently reviewed our data from a prospective 5-year study in which this scan was used for 118 patients, and in terms of depth of invasion of the primary, there were no significant differences between those who had lymph node resection that was apparent on the scan v those who did not. However, there were significant differences in the recurrence rates, 34% for those who had wide excision only, compared to 14% for patients who had wide excision and lymphadenectomy. The differences in the number of deaths, 25% versus 9.3%, were also statistically significant. We examined a number of factors that are known to influence prognosis for patients with melanoma and have yet to find any single factor except lymphadenectomy as an explanation for these differences.

In fact, every single institutional retrospective study in which this question of the effectiveness of prophylactic lymph node dissection for melanoma has been a part has shown benefit for the patients who had elective lymph node dissection. This benefit is not large, depending upon the depth of the primary melanoma, in the order of five to as high as 20%, but, overall, it probably averages about 10% in most retrospective single-institution studies. However, in the multi-institutional study to which Dr. Ketcham referred, 25 centers entered 500 patients over a 10-year period, and the results supposedly showed the ineffectiveness of lymph node dissection. A review of these data does show a difference. Survival rates from wide excision only at 5 years were 58%, but with node dissection survival was 70% for Clark's Level IV and 69% versus 78% if Breslow depth of invasion was considered.

The problem was that the number of patients entered into that trial whose primary melanomas were in these categories was not large enough for these differences to be statistically significant. Unfortunately, then, the conclusion was that because the differences were not statistically significant with the numbers of patients studied, there was no difference in survival between the two groups. I submit to you that such a conclusion is not the proper use of biostatistics. The proper conclusion should have been that there was an observed difference, but with the numbers of patients admitted to the trial in those categories it is impossible to determine the significance of these differences.

I would like the support of this organization for counteracting a fallacy. We as surgeons have been so honest and eager to admit that we cannot cure every patient with lymph node metastases that some of our colleagues in medical oncology have assumed that we cannot cure any patient. As a result, those of us in the centers are continually seeing patients with lymph node metastasis from melanoma, or breast cancer, or whatever, who have been told by their medical oncologist in the community, "You have disease in your lymph nodes; therefore, you have systemic disease; therefore, you are incurable and will not be helped by surgical resection of these nodes."