*Prognostic Factors for Patients with Clinical Stage I Melanoma of Intermediate Thickness (1.51–3.99 mm)**

A Conceptual Model for Tumor Growth and Metastasis

CALVIN L. DAY, JR., M.D., MARTIN C. MIHM, JR., M.D., ROBERT A. LEW, PH.D., MATTHEW N. HARRIS, M.D., ALFRED W. KOPF, M.D., THOMAS B. FITZPATRICK, M.D., PHD., TERENCE J. HARRIST, M.D., FREDERICK M. GOLOMB, M.D., ALLEN POSTEL, M.D., PATRICK HENNESSEY, M.D., STEPHEN L. GUMPORT, M.D., JOHN W. RAKER, M.D., RONALD A. MALT, M.D., A. BENEDICT COSIMI, M.D., WILLIAM C. WOOD, M.D., DANIEL F. ROSES, M.D., FRED GORSTEIN, M.D., DARRELL RIGEL, M.D., ROBERT J. FRIEDMAN, M.D., MEDWIN M. MINTZIS, M.D., ARTHUR J. SOBER, M.D.

From the Departments of Dermatology and Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, and the New York University School of Medicine, New York, New York

Fourteen variables were tested for their ability to predict visceral or bony metastases in 177 patients with clinical Stage I melanoma of intermediate thickness (1.51–3.99 mm). A Cox multivariate analysis yielded a combination of four variables that best predicted bony or visceral metastases for these patients: 1) mitoses > 6/mm^2 ($p = 0.0007$), 2) location other than the forearm or leg $p = 0.009$), 3) ulceration width > 3 mm ($p = 0.04$), and 4) microscopic satellites ($p = 0.05$). The overall prognostic model chi square was 32.40 with 4° of freedom ($p < 10^{-5}$). Combinations of the above variables were used to separate these patients into at least two risk groups. The high risk patients had at least a 35% or greater chance of developing visceral metastases within five years, while the low risk group had greater than an 85% chance of being disease free at five years. Criteria for the high risk group were as follows: 1) mitoses > 6/mm^2 in at least one area of the tumor, irrespective of primary tumor location, or 2) a melanoma located at some site other than the forearm or leg and histologic evidence in the primary tumor of either ulceration > 3 mm wide or microscopic satellites. The low risk group was defined as follows: 1) mitoses ≤ 6/mm^2 and a location on the leg or forearm, or 2) mitoses ≤ 6/mm^2 and the absence in histologic sections of the primary tumor of both microscopic satellites and ulceration > 3 mm wide. The number of patients in this series who did not undergo elective regional node dissection (N = 47) was probably too small to detect any benefit from this procedure. Based on survival rates from this and other studies, it is estimated that approximately 1500 patients with clinical Stage I melanoma of intermediate thickness in each arm of a randomized clinical trial would be needed to detect an increase in survival rates from elective regional node dissection.

THE MOST FREQUENT QUERIES to physicians from patients with melanoma concern prognosis. Answers to these inquiries affect not only patients' personal plans for the near future but also subsequent surgical and medical oncologic therapies. For patients with distant metastases (Stage III) and for patients with primary lesions ≤ 0.75 mm who have no other clinical evidence of disease (Stage I), prognostic appraisal is not difficult. The former group rarely survive their disease, while the latter group rarely have metastases. Recently, Balch et al.[6] confirmed earlier studies[27,29,30] that demonstrated a 90% or greater chance of death from melanoma at ten years for patients with clinically suspicious regional lymph nodes that are confirmed by

Supported in part by the National Cancer Institute Grant R 10 CA 13651-01 CCI and the Marion Gardner Jackson Trust, Massachusetts General Hospital, Fruit Street, Boston, MA 02114.

* A publication of the Melanoma Clinical Cooperative Group. The following individuals are of were members of the Melanoma Clinical Cooperative Group at Massachusetts General Hospital or New York University Medical Center. Massachusetts General Hospital: T. B. Fitzpatrick, M.D., Ph.D., Principal Investigator, A. J. Sober, M.D., Director, Melanoma Registry, A. B. Cosimi, M.D., C. L. Day, M.D., A. R. Rhodes, M.D., R. A. Lew, Ph.D., J. Kaiser, M.D., R. A. Malt, M.D., M. C. Mihm, Jr., M.D., B. Pearson, M.S., J. Raker, M.D., and W. Wood, M.D. New York University: Alfred W. Kopf, M.D., Principal Investigator, A. B. Ackerman, M.D., D. Baker, M.D., R. S. Bart, M.D., R. H. Blum, M.D., Mr. J. Brown, J. C. Bystryn, M.D., P. Casson, M.D., J. Cooper, M.D., N. Dubin, Ph.D., R. J. Friedman, M.D., F. M. Golomb, M.D., W. R. Grier, M.D., S. L. Gumport, M.D., M. N. Harris, P. Hennessey, M.D., M. Levin, M.D., G. Lipkin, M.D., M. M. Mintzis, M.D., Ms. M. MOSESON, F. M. Muggia, M.D., B. S. Pasternack, Ph.D., Postel, M.D., A. Ragaz, M.D., D. S. Rigel, M.D., D. F. Roses, M.D., H. Sage, M.D., Ms. Z. Scheiner, F. Valentine, M.D., Mr. F. Viau and Mrs. G. Richards.

Reprint requests: Dr. Arthur J. Sober, Department of Dermatology, Massachusetts General Hospital, Boston, Massachusetts 02114.

Submitted for publication: June 1, 1981.

0003-4932/82/0100/0035$00.95

TABLE 1. *Variables Tested for Their Value in Predicting Visceral or Bony Metastases in 177 Patients with Clinical Stage I Melanoma of Intermediate Thickness (1.51–3.99 mm)*

Clinical variables
sex
age
location
adjuvant therapy received
surgical treatment (wide local excision only vs wide local excision and elective regional lymph node dissection)
Histologic variables
histologic type
level of invasion
thickness
ulceration width determined histologically
mitotic rate
lymphocytic response
histologic regression
microscopic satellites
pathologic stage

pathologic examination to harbor metastases (*i.e.* clinical Stage II, pathologic Stage II). Like the first two mentioned groups above, the eventual outcome for this latter group of patients is relatively certain (although the interval to death is a relatively uncertain).

For the remainder of patients with primary cutaneous melanoma eventual outcome is less certain. For example, clinical Stage I melanoma patients with microscopic metastases in regional nodes (clinical Stage I, pathologic Stage II) have about a 50% chance (or less) of surviving. Investigation of prognostic factors for these patients revealed that one subgroup had an 80% five-year survival rate in spite of having regional node metastases.[14] In patients with pathologic Stage II melanoma who had clinically suspicious nodes (clinical Stage II), thickness of the primary tumor was of no aid in predicting outcome.[6,14] In contrast, thickness was the dominant variable for patients with pathologic Stage II disease if nodes were not abnormally enlarged prior to surgery (clinical Stage I).[14]

Another group of patients whose prognosis falls somewhere between the extremes of almost certain death from melanoma and excellent prospects for a continued normal life are those patients with clinical Stage I melanoma of intermediate thickness. In April 1979 we suggested that these patients stand to gain the most from elective regional node dissection (ERND) because they frequently have regional node metastases without coexistent systemic disease.[39] To better understand the important clinicopathologic determinants of biologic behavior for these melanomas, a Cox multivariate analysis was performed using 14 variables on 177 patients with clinical Stage I melanoma of intermediate thickness (*i.e.* 1.51–3.99 mm).

Patients and Methods

Six hundred forty-four patients with primary cutaneous malignant melanoma were evaluated consecutively and entered prospectively into a study group at one of two institutions, New York University Medical Center or the Massachusetts General Hospital, from September 1, 1972 through May 30, 1977. The characteristics of this population have been described previously.[14–21,34] Histologic sections were reviewed by one pathologist.

Of the 644 patients entered in the study, 177 had clinical Stage I melanoma 1.51–3.99 mm in thickness, and these 177 patients are the subject of this paper. Each patient was followed for evidence of visceral or bony metastases at three-month intervals or less for the first two years, at six-month intervals for the next three years, and annually thereafter. The time interval to the last follow-up examination or time to visceral or bony metastases was computed from the date of definitive surgery.

Disease-free survival at five years (*i.e.* free of visceral or bony metastases) was computed according to the method of Kaplan and Meier.[26] Probability values for comparing two sets of life-table data were determined using the end results and standard error at five years.† The best combination of variables for predicting visceral or bony metastases was determined by a Cox (multivariate) proportional hazards analysis.[12]

Clinical Variables[5] (Table 1)

The five clinical variables tested were sex, age, location of the primary tumor, adjuvant therapy received, and the type of surgical treatment *i.e.* wide local excision (WLE) only versus wide local excision and elective regional node dissection (WLE & ERND). Multiple single tumor locations and combinations of different locations were tried in the Cox multivariate analysis. This allowed the Cox model to choose the best and/or worst location or combination of locations for predicting metastases.

Primary Tumor Histologic Variables[9] (Table 1)

The primary tumor histologic variables tested were histologic type[11,32] (nodular, superficial spreading, acral lentiginous, and lentigo maligna melanoma), level of invasion, thickness of the primary tumor, ulceration width determined histologically,[11] lymphocyte response at the base of the tumor, histologic evidence of regres-

† Three patients had the onset of their first visceral or bony metastases at 62 months. Thus, the survival rates were actually calculated at 62 months rather than 60 months.

sion,[25] mitoses/mm^2, the presence or absence of microscopic satellites,[18] and pathologic stage. The lymphocyte response was graded as nearly absent, minimal, moderate or marked. Only the lymphocyte response at the most deeply invasive portion of the tumor was considered. Thus, a tumor with marked lymphocyte response at the superficial portion of the tumor but a minimal response at the deepest portion was graded as minimal. Mitoses were not counted by high power fields but rather by using a micrometer disc grid in which the area counted could be more precisely determined. As in previous studies,[14-21,34] the tumors were first scanned on low power to look for the area of highest concentration of mitoses. The mitoses were then counted in that area. Ulceration width was used rather than ulceration per se because we found that those patients with focal ulceration (*i.e.* ≤3 mm wide) had a prognosis comparable to those patients with nonulcerated lesions.[18] Microscopic satellites were defined as discrete accumulations or nests of melanoma cells > 0.05 mm in diameter below the main body of the tumor and separated from the main tumor mass on at least one histologic section by intervening normal reticular dermal collagen or fat.[18] Histologic type, level of invasion, and regression were determined prospectively. The other histologic parameters were ascertained retrospectively.

Results

Overall

Of the 177 patients evaluated, 34 (19%) are dead of melanoma, and three are alive with visceral metastases. The overall actuarial disease-free survival rate (*i.e.* absence of bony or visceral metastases) at five years was 74 ± 4%. Nine patients had recurrent disease at nonvisceral, nonskeletal sites that were removed surgically.‡ These nine patients are now clinically disease-free. Four of these nine patients had initial WLE and ERND while five had WLE only.

Results for Single Variables (Tables 2 and 3)

Only the following five variables were *not* useful in predicting visceral or bony metastases for this group of patients (p > 0.05); age, histologic regression, level of invasion, histologic type, and type of surgical treatment (*i.e.* WLE vs WLE & ERND). Each of the remaining nine variables when studied as a single factor was prognostically useful (p ≤ 0.05).

‡ Regional lymph node metastases—six patients; distant skin metastases—one patient; and in-transit metastases—2 patients.

TABLE 2. *Five-year Disease-free Survival Rates ± SE by 14 Variables for 177 Patients with Clinical Stage I Melanoma of Intermediate Thickness (1.51–3.99 mm)*

Variables *not* useful in explaining biologic behavior (p > 0.05)

Variable	Number of Patients	Five-year Disease-free Survival ± SE (%)
Histologic Regression		
no	99	79 ± 5%
yes	78	68 ± 7%
Age		
<40 yrs	36	75 ± 7%
40–60 yrs	90	71 ± 6%
>60 yrs	51	78 ± 8%
Level of invasion		
level II or III	53	77 ± 7%
level IV or V	124	72 ± 5%
Histologic type		
superficial spreading	110	79 ± 5%
nodular	39	71 ± 8%
acral lentiginous	13	74 ± 13%
lentigo maligna	5	50 ± 35%
unclassified centrifugal growth phase	3	—
indeterminate	7	—
Surgical treatment		
wide local excision only	47	66 ± 8%
wide local excision plus elective regional lymph node dissection	130	73 ± 5%

Multivariate Analysis Results (Table 4)

A combination of the following four variables best explained the observed biologic behavior for this particular group of patients: mitoses > 6/mm^2 (p = 0.0007), location on the leg or forearm (p = 0.009), ulceration >3 mm in width (p = 0.04), and microscopic satellites (p = 0.05). The overall model chi square was 32.40 with 4° of freedom ($p < 10^{-5}$).

Life Tables for the Prognostic Model Variables (Table 5)

The following algorithm demonstrates one useful way to arrange the variable interaction. Twenty-seven patients, each with a mitotic rate of >6/mm^2, had an actuarial five-year disease-free survival rate (*i.e.* free of bony or visceral metastases) of 40 ± 11%. For 118 of the remaining 150 patients, the primary melanoma arose at sites other than the forearm or leg. Of these 118 patients, 49 had either microscopic satellites or histologic ulceration >3 mm wide. Their survival rate was 53 ± 8%. In contrast, the 69 patients without microscopic satellites or histologic ulceration >3 mm wide had a survival of 86 ± 6%. Finally, the remaining 32 patients (*i.e.* mitoses ≤ 6/mm^2 and a tumor located on

TABLE 3. *Five-year Disease-free Survival Rates ± SE by 14 Variables for 177 Patients with Clinical Stage I Melanoma of Intermediate Thickness (1.51–3.99 mm)*

Variables useful for predicting metastases to viscera or bone ($p \leq 0.05$)		
Variable	Number of patients	Five-year Disease-free Survival ± SE (%)
Mitoses		
≤6/mm²	150	81 ± 4%
>6/mm²	27	40 ± 11%
Location		
forearm	10	100%
leg	29	79 ± 11%
arm	18	79 ± 11%
thigh	14	76 ± 13%
trunk	69	74 ± 6%
hand or foot	17	66 ± 12%
head or neck	20	46 ± 16%
Ulceration width determined histologically		
no ulceration	94	79 ± 5%
ulceration width ≤ 3.0 mm	35	88 ± 6%
ulceration width 3.01–6.0 mm	32	52 ± 10%
ulceration width > 6.0 mm	16	54 ± 11%
Microscopic Satellites		
present	42	54 ± 11%
absent	135	79 ± 4%
Received Adjuvant Therapy		
No	153	77 ± 4%
Yes	24	49 ± 13%
Pathologic Stage		
negative nodes	107	77 ± 5%
positive nodes	24	53 ± 13%
Lymphocytic Response		
nearly absent, minimal, or moderate	149	71 ± 5%
marked	28	87 ± 7%
Sex		
male	92	68 ± 6%
female	85	81 ± 5%
Thickness		
1.51–2.00 mm	57	85 ± 6%
2.01–2.50 mm	47	74 ± 8%
2.51–3.00 mm	39	71 ± 9%
3.01–3.99 mm	34	54 ± 10%

TABLE 4. *Cox Multivariate Analysis of 177 Patients with Clinical Stage I Melanoma of Intermediate Thickness (1.51–3.99 mm)*

Variable	p Value*
Mitoses > 6/mm²	0.0007
Location on the leg or forearm	0.009
Ulceration > 3 mm in width	0.04
Microscopic satellites	0.05

The overall model chi square = 32.40 with 4 D.F. $p < 10^{-5}$.

* Probability value associated with the standardized regression coefficient. The most influential variables in the model have the smallest associated p-values.

the forearm or leg) had an actuarial five-year disease-free survival rate of 93 ± 7%.

Discussion

There are at least two hypotheses to explain the histologic variables selected by the Cox multivariate analysis. Some of the authors have suggested that mitoses, histologic ulceration, and microscopic satellites are simply morphological features associated with clones of cells with high metastatic potential. In this hypothesis, the cell surface characteristics and other properties indigenous to the different cell lines may be more important than the rate of growth per se; and the above three histologic variables are indirect measurements of these other properties.

An alternative hypothesis places more emphasis on tumor doubling time than on other cellular properties. The above three histologic variables, in this hypothesis, are direct measurements of the doubling time. The rapid increase in size of the melanoma, as evidenced most directly by clusters of mitoses, has secondary effects immediately above (*i.e.* ulceration) and below (*i.e.* microscopic satellites) the tumor. The epidermis thins and eventually ulcerates as a result of internal trauma (expanding mass) and/or external trauma (excoriation) and/or loss of blood supply (tumor compression) with resultant cell death and necrosis.

In this hypothesis, as the tumor rapidly proliferates, it also expands downward. "Buds" of cells develop at less restrictive dermal structures such as the loosely organized adventitial dermis of appendages resulting in deeper spread. In some histologic sections these "buds" appear as "satellites" (*i.e.* not connected to the main body of the tumor). It is conceivable that during this "budding" or "expansile" phase, cells permeate into lymphatics and blood vessels for similar reasons. These lymphatic and blood vessel nests also appear as "satellites."

Irrespective of the true meaning of the histologic findings, the above three variables were probably additive prognostically as a result of histologic sampling techniques. That is, because mitoses, ulceration, and microscopic satellites are focal phenomena, they were not all present or all absent in available histologic sections. Mitoses/mm², for example, varied even within the same histologic section. Furthermore, counting mitoses in random fields did not prove as prognostically fruitful as actively searching for clusters of mitoses and counting in those areas (data not shown).

The remaining variable in the model (*i.e.* location on the forearm or leg) is more difficult to explain. Removal of location from the list of variables did not result in replacement by another variable in the final model. This

would suggest that the location finding is real and not simply a substitute for one of the other variables studied. Some of the authors have suggested that location on the forearm or leg is simply an indirect measurement of early recognition and treatment because of easy visibility. This possibility is currently directly "untestable." However, when tested against known histologic indicators of "early" vs "late" recognition and treatment, location remains as an independent variable. We have suggested elsewhere that perhaps the benefit of ERND is "site dependent."[14-17,20,21] Evidence from these studies suggests that *patients with melanomas of the hands, feet, head, neck, and posterior arm are the least likely to benefit from ERND, while patients with melanomas at other sites (i.e. trunk, forearm, leg, thigh, anterior arm) are the most likely to benefit from ERND.*[14-17,20,21] It is, thus, tempting to suggest that the excellent survival for the patients in the present study, with forearm or leg melanoma, was due to the ERND performed on 90% (36 of 40) of the patients in this group.

TABLE 5. *Risk Groups Defined by a Cox Multivariate Analysis for 177 Patients with Clinical Stage I Melanoma of Intermediate Thickness*

Risk Group Characteristics	Number of Patients in Each Group	Five Year Disease* Free Survival ± SE
Mitoses > 6/mm²	27	40 ± 11%
Mitoses ≤ 6/mm²		
1. lesion location at a site other than the leg or forearm		
a. microscopic satellites and/or ulceration width > 3 mm wide	49	53 ± 8%
b. neither microscopic satellites nor ulceration > 3 mm in width	69	86 ± 6%
2. lesion located on the leg or forearm	32	93 ± 7%
Total	177	74 ± 4%

* Free of visceral or bony metastases at 62 months.

Level of Invasion

The Clark system of levels of invasion[11] places special emphasis on the reticular dermis as a barrier to metastases. If the reticular dermis blocks the development of metastases then there should have been a sharp drop in survival rates between level III and level IV patients. In six studies comparing the prognostic value of level of invasion to thickness,[2,9,13,22,33,38] thickness dominated in all six studies. In three of these studies, levels had a small added effect to thickness,[9,22,38] while the other three studies demonstrated on added prognostic effect of levels to thickness.[2,13,33] Furthermore, the level of invasion was not an independent risk factor for recurrent disease in multivariate analyses of four different clinical Stage I subgroups of the MCCG.[14-17] The multivariate analyses of Balch et al.[2,3,6] also did not list level of invasion as an important interacting covariate. In the authors' experience, level of invasion was most useful (prognostically) for lesions < 1.7 mm or lesions > 3.6 mm in thickness.[20,21] In any event, the essential differences between the biologic model proposed by Clark et al. and the one proposed here is the concept that the rate of expansion of the vertical growth phase is the important determinate of metastases and not the existence of the vertical growth phase (*i.e.* nodule) per se or the infiltration of melanoma cells into the reticular dermis per se.

Histologic Type

McGovern et al.[28] demonstrated better survival rates for Lentigo maligna melanoma over a given thickness range when compared to other melanomas of the head and neck. That study compared "cheek melanoma" to "melanoma of the scalp and posterior neck." Specific sites are very important in determining prognosis given comparable thickness.[15-17,20,21] Patients with melanoma of the scalp and posterior neck do very poorly compared with melanoma at other sites even after correcting for thickness.[31] That a histologic grading system based on the radial growth phase would significantly affect prognosis would be mechanistically sound only if one could demonstrate a correlation between the currently used histologic types and different types of vertical growth phase components. The authors are currently investigating this possibility. The only subgroup in our series where histologic type was an independent risk factor was for those clinical Stage I patients with lesions > 3.6 mm in thickness located on the trunk.[21] Irrespective of the role of histologic typing in prognosis, it remains useful to pathologists and tumor biologists in classifying melanomas and possibly in understanding melanoma epidemiology, respectively.

Thickness

The survival rates over the thickness range of 1.51 to 3.99 varied by 31% (Table 3). This is especially important to keep in mind when comparing survival rates between different centers over this thickness range. For example, one might expect a higher survival rate for a group of patients whose mean thickness is 2.0 when compared with a group whose mean thickness is 3.0 even though both groups have no patients outside the defined thickness range of 1.51–3.99 mm. This wide variation in survival rates is not observed, however, when one uses the natural thickness groupings of < 0.85 mm, 0.85 through 1.69 mm, 1.70 through 3.64 mm, and ≥ 3.65 mm.[20,21,40]

TABLE 6. *Actuarial Survival Rate (Death from Melanoma Only) Comparisons for Patients with Clinical Stage I Melanoma 1.51–3.99 mm in Thickness who had Only a Wide Local Excision (no Elective Node Dissection)*

Study Group	Number of Patients	Five Years	Seven Years	Ten Years
MGH-NYU	47	76%	68%[19]	—
Eldh[23]	106	76%	70%	68%
Cascinelli[10]	88	69%	67%	
Balch et al.[3]‡	24	37%	0%*	—

* Eight year results.
† Distal 2/3 of the extremities only.
‡ The survival rates shown by Balch et al. are lower than the other three studies.

Lymphocyte Response

While lymphocyte response did not dominate prognosis for this group of patients, it was the best prognosticator for lesions ≥ 3.65 mm.[21] The authors interpret these findings as follows: for lesions of intermediate thickness (*i.e.* 1.51–3.99 mm), the best prognosticators are those parameters that tell one whether or not a lesion has metastasized. However, most (>75%) of lesions ≥ 3.65 mm eventually demonstrate some type of metastases. Whether a patient with a very thick lesion (*i.e.* ≥ 3.65 mm) subsequently develops a visceral or bony metastases with resultant death then apparently depends on host response parameters (*i.e.* the degree of lymphocyte response).[21]

Age and Sex

Neither age nor sex have proved to be independent risk factors for recurrent disease or death from melanoma in seven multivariate analyses of various clinical Stage I melanoma subgroups conducted by the NYU-MGH Melanoma Clinical Cooperative Group.[14–17,20,21] Multiple cross-tabulations have revealed that the somewhat better survival for females and for younger patients were usually accounted for by considerations of different combinations of thickness and "subsite." In other words, there was little difference in survival by age or sex once "subsite" and thickness had been determined. It is especially important to consider the hands and feet separately from the remainder of the extremities.[21] Patients with thick melanomas of the hands and feet have lower survival rates than patients with thick melanomas located elsewhere irrespective of age. However, these patients as a group are older than patients with thick melanomas at other sites.[21] Failure to stratify by "subsite" (*i.e.* hands and feet vs other locations) in this situation results in a substitution of age for hands and feet in the Cox multivariate analysis. This may possibly have been the reason that Balch et al. showed age to be an important prognostic factor in a recent multivariate analysis that examined the effect of adjuvant therapy on high risk clinical Stage I patients.[7]

Pathologic Stage

Although pathologic stage was the dominant variable in the multivariate analyses of Balch and co-workers when they analyzed a mixture of clinical Stage I and clinical Stage II patients,[1] it (pathologic stage) was notably absent when they used it as a variable in their analysis of clinical Stage I patients.[2] It was also absent from the prognostic models of four different subgroups of clinical Stage I patients analyzed by the NYU-MGH Melanoma Clinical Cooperative Group.[14–17] One might predict its absence from the above models 1) if a significant number of subclinical metastases were missed by pathologic sampling (*i.e.* a good proportion of the patients with negative nodes were actually positive) or 2) if ERND was done when metastases were localized to regional nodes resulting in a higher than predicted survival rate for these patients. Our data support the latter possibility.[11] That a significant number of microscopic metastases was missed by pathology is not consistent with the following data: 18% (24 of 130) of the node dissections done resulted in the finding of positive nodes. This compares with the five-year actuarial incidence of subsequent node metastases in the 47 patients who did not receive ERND of 21%. As discussed elsewhere,[14] the finding of positive nodes is useful prognostically for clinical Stage I patients only in the following two instances 1) ≥4 or mode nodes are found to be positive regardless of the total number removed or 2) ≥20% of the nodes removed are histologically positive even though the total number of positive nodes number three or less (*e.g.* a group of patients who have nine nodes removed with microscopic deposits in three of these do much worse than a group of patients who have 30 nodes removed and who also have microscopic tumor deposits in three).

Nineteen of the 24 patients in this series with positive microscopic node metastases had neither four or more positive nodes nor had microscopic deposits of tumor in ≥20% of the total number of nodes removed. The survival rate for these 19 clinical Stage I, pathologic Stage II patients of 70% was not significantly different than the survival rate of 76% for the patients in this study with negative nodes. We interpret this similarity in survival results as evidence of a benefit for ERND in this group of patients.

Surgical Treatment

How can we claim a benefit for ERND in this group of patients with lesions of intermediate thickness yet

TABLE 7. *Difference in Five- and Ten-year Survival Results (Death from Melanoma) for Patients with Clinical Stage I Melanoma*

Study	Year	Number of Patients	Five-year Survival Rate	Ten-year Survival Rate	Per Cent Difference
McNeer & Das Gupta[29]	1964	359	71%	62%	9%
Knutson[27]	1971	116	53%	47%	6%
Sugarbaker & McBride[35]*	1976	128	65%	55%	10%
Epstein & Bragg[24]†	1980	193	83.5%	75.4%	8%
Eldh[23]‡	1981	106	76%	68%	8%

* Melanoma of the trunk treated with wide local excision only.
† Patients with positive nodes were excluded.
‡ 1.51–3.99 mm in thickness treated with wide local excision only.

fail to show a difference in survival results between those who did and those who did not have ERND? There are at least three reasons for this inconsistency.

First, this prospective study was designed as a natural history study and not as a clinical trial for ERND (*i.e.* not randomized). Nearly all patients in our series who could undergo ERND did so. Thus, patients who did and could undergo ERND are compared with those who were not candidates for ERND initially. Inferences drawn from such a study may be quite valuable. However, definite conclusions regarding different therapies (*i.e.* adjuvant therapy and ERND) require randomized trials. Nevertheless, the survival rates for the 47 patients treated with WLE only in this study are very similar to those of two other studies[10,22] which did contain patients with lesions of intermediate thickness who *were* candidates for ERND (Table 6). One can infer from these survival results that the magnitude of the benefit of ERND is probably small (see discussion below) and possibly less than that suggested by Balch et al.[3]

Second, the survival rates for patients in each of the two surgical treatment groups continued to diverge after five years of follow-up in the series of Balch et al.[3] Thus, five years may be too short an interval to evaluate results of melanoma surgery. However, two other studies[23,35] (Table 7) showing survival results for patients with clinical Stage I disease treated with WLE only demonstrated only an 8–10% difference in survival rates at five and ten years. Notice that the Eldh[23] series contained 106 patients with lesions 1.51–3.99 mm treated with WLE only. These survival rates do not differ from three other studies[24,27,29] containing other Stage I patients (Table 7). Thus, the Balch et al. contention that there is a marked increase in death from melanoma after five years for Stage I patients treated with WLE only, compared with those treated with ERND & WLE is not supported by these other studies. The Balch et al. study contained only 24 patients treated with WLE only. This small number is probably the source of differences between their series and the other series.

Although the above explanations for the failure to find a significant difference in survival results for the different surgical treatment groups are plausible, it is more likely that the sample size in this study was just too small to detect a beneficial effect of ERND. Both the WHO study[10,36] and the present study had less than 200 patients in the intermediate thickness range. Using the assumptions listed below, the authors calculate that a series of 3000 or more is required to detect a statistically significant effect.

1. *The real incidence of subclinical regional node metastases for these patients ranges from 20–30%.* The incidence of subsequent regional node metastases in 101 patients in the WHO study who had lesions 1.0–3.99 mm and no ERND was 32%.[37] The incidence of subsequent regional node metastases in the 106 patients with lesions 1.51–3.99 mm and no ERND in the series by Eldh was 31%.[23] The five-year actuarial incidence of subsequent nodal metastases in the 47 patients in the present series was 21%. This figure varies with the mean thickness of the group. For example, the 34 patients in the present series with lesions 3.1–3.99 mm had six times the incidence of nodal metastases§ as the 57 patients with lesions 1.51–2.0 mm (*i.e.* 42 vs 7%). Thus, the differences between the present study and the WHO study for the percentage of these patients with subclinical positive nodes (*i.e.* 21 vs 32%, respectively) probably results from a greater proportion of patients towards the thinner end of the thickness range (Table 3) in the present study. The WHO had approximately equal numbers of patients over each thickness increment.[37]

2. *The melanoma survival rate (death from melanoma only) at ten years for patients with clinical Stage I melanoma of intermediate thickness who undergo ERND is approximately 70%. (Table 8).* The MCCG survival rates for those patients who did undergo ERND (Table 8) very closely parallel those of Balch et al.[3] when stratified by thickness of the primary tumor. The

§ Microscopic deposits of melanoma found by ERND or subsequent metastases to nodes in those patients treated by WLE Only.

TABLE 8. *Actuarial Survival Rate (Death from Melanoma Only) Comparisons for Patients with Clinical Stage I Melanoma 1.51–3.99 mm in Thickness who had Both a WLE and an ERND*

	Five-year Survival Rate	Number of Patients
Cascinelli[10]*	84%	90
Balch et al.[2]†	83%	—
NYU-MGH†	79%	130

* Distal 2/3 of the extremities.
† All sites.

WHO also had similar results.[10] The estimated ten-year survival rate for these patients of 70% is derived from the five-year survival results shown in Table 8, and the difference between five- and ten-year survival results in Table 7.

3. *The survival rate of those patients with clinical Stage I melanoma of intermediate thickness who have subclinical regional node metastases found by ERND is 50% or more.* The authors have reviewed[14] the published survival rates for 468 patients with positive elective nodes pooled from 24 series and found that the overall survival rate was 45%. However, the survival rate for those patients with microscopically positive nodes and primary lesions ≤ 3.5 mm was higher (*i.e.* 59%) than the overall survival rate of 45% for this group of patients.

4. *The survival rates of those patients who initially have subclinical node metastases but are treated initially with WLE only and subsequently with a therapeutic node dissection is 35% or less.* McNeer and DasGupta demonstrated a 31% five-year survival rate for this group of patients.[29] The WHO group had similar results at five years for this group of patients (*i.e.* 30%).[36] Balch et al. showed strikingly similar results (*i.e.* 28%).[6] As McNeer and DasGupta[29] pointed out, these survival rates are higher than for patients who have clinically suspicious nodes at the time of initial diagnosis. Both Balch et al.[6] and the MCCG[14] demonstrated that thickness of the primary tumor was not useful prognostically for this group of patients with clinically palpable histologically positive nodes. Thus, patients with lesions ≤ 3.5 or 4.0 mm who develop nodal metastases during the follow-up period probably do not have higher survival rates than patients with thicker lesions who subsequently develop node metastases.

5. *With appropriate selection of cases the mortality of ERND (anesthesia and complications of the extra surgical procedure itself) is less than 1 per 1000.* The authors have purposely avoided consideration of cost and morbidity of ERND for two reasons. First, if there is indeed no increased survival from ERND, then cost and morbidity need not be considered. Second, if there is a patient salvage from ERND, the above two issues then become a value judgement that depends in part on the magnitude of the effect of ERND.

Calculations

The above five assumptions require that approximately 1500 patients with clinical Stage I lesions of intermediate thickness enter each arm of a randomized trial to detect a benefit of ERND. The source of the problem is illustrated as follows.

Assumptions 2 and 3 predict only a 15% difference in survival rates between the ERND arm and non-ERND arm even if all of these patients have subclinical (microscopic) lymph node metastases. However, assumption 1 predicts that 30% (and not 100%) of these patients will have such metastases. The difference in survival rates between the two surgical treatment arms in, thus, reduced to 4.5% (*i.e.* 15% survival difference with 100% incidence of nodal metastases times the actual incidence of nodal metastases of 30% = 4.5%).

In selecting the sample size for a comparative clinical trial, one usually relies on the extensions of the method given by Armitage.[1] Using the assumptions listed above, a statistical power exceeding 80%, and a probability value of 0.05, this method computes a required sample size of approximately 3000 patients. One may show that the required sample size shrinks if one increases the ten-year survival rate for the ERND patients, increases the proportion with subclinical nodes, increases the proportion who benefit from ERND, and tests only that ERND is better than no ERND. For example, with a ten-year ERND survival rate of 75%, with 33% of patients with subclinical nodes, with 30% higher survival rate among patients with subclinical nodes treated with ERND, and testing only superiority of ERND, the sample size shrinks to 360 patients. *This is still approximately twice the number of patients in the WHO study with lesions of intermediate thickness.* It is concluded that the reason for the similarity in survival results in the present study between the two surgical treatment groups was partially caused by both a specific location mismatch (*i.e.* ERND may be more beneficial for melanomas at some locations than others) and by early follow-up results (*i.e.* five years rather than ten years). However, the primary reason for our negative findings for ERND was caused by an inadequate number of patients.

Large randomized trials of clinical Stage I patients with lesions of intermediate thickness testing ERND vs no ERND are needed to settle this debate pending development of techniques which allow accurate presurgical determination of those patients with subclinical regional node metastases.

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