The Accuracy of Predicting Lymph Node Metastases in Malignant Melanoma by Clinical Examination and Microstaging

L. I. GOLDMAN, W. H. CLARK, JR., E. A. BERNARDINO, A. M. AINSWORTH

From the Temple University School of Medicine
Philadelphia, Pennsylvania

Since 1971, a prospective treatment regimen for primary cutaneous malignant melanoma performed by a single clinician has revealed the following early observations: 1) A significantly higher number of females with level II disease; 2) No recurrences or metastases to date in 29 patients with level II lesions treated by appropriate surgery; 3) The apparent clinical predictability of lymph node metastases in the group microstaged at level III. 4) An inability to predict lymph node metastases (or their delayed development) in patients with level IV disease; 5) A correlation between lymph node metastases and the development of disseminated disease.

In 1969, Clark and co-workers demonstrated a correlation between the extent of microscopic invasion and the biologic behavior of primary cutaneous malignant melanomas.[1] Others have confirmed these findings and have suggested their potential value in planning the therapy of this disease.[2,3,5] These retrospective studies, while providing valuable information, have been limited for the following reasons. Upon review, pathologic material may prove inadequate for accurate microstaging. Further, when several clinicians are involved, less-than-uniform findings can result. This prospective study involved a single clinician (L.I.G.) responsible for total patient care, including surgery, preceded by multisectional microstaging (W.H.C., Jr., E.A.B., A.M.A.). The following questions were asked: 1) Can lymph node metastases be predicted on the basis of clinical examination and/or microstaging? 2) Can survival and/or disease free interval be predicted on the basis of microstaging?

Presented at the conjoint meeting of the Philadelphia Academy of Surgery, the New York Surgical Society, the Boston Surgical Society, and the Baltimore Academy of Surgery, March 10, 1976, at the College of Surgeons, Philadelphia, Pennsylvania.

Supported in part by USPHS grants CA-11536 and CA-05109 from the National Cancer Institute.

Reprint requests: L. I. Goldman, M.D., c/o Temple University School of Medicine, Philadelphia, Pennsylvania 19140.

Method

Eighty-one patients with primary cutaneous malignant melanoma comprised the study group. This study group was selected because, with the exception of an occasional diagnostic biopsy all evaluation, treatment, and followup has been carried out by the senior author. The patients were first seen between January 1971 and July 1975. The primary tumors, usually obtained by total excision at biopsy, were examined by the serial block technique[1] and classified into major clinical subtypes, i.e. lentigo maligna melanoma, superficial spreading melanoma, nodular melanoma and volar-subungual melanoma. Each was further subclassified (level II-papillary dermal level; level III-papillary-reticular dermal interface level; level IV-reticular dermal level; and level V-subcutaneous level) by the maximum depth of histologic invasion. The patients were also evaluated by physical examination, chest x-ray, liver function studies and radionuclide scanning of brain, liver and bone. Initial surgical treatment was of the primary lesions and their draining lymph node regions. The primary sites were widely excised (3–5 cm margins about the tumor, to and including the deep fascia) and closed with split thickness skin grafting. The exceptions were level II lentigo maligna melanoma (local excision and primary closure) and the occasional volar-subungual

TABLE 1. *Type and Level of Cases*

Level	Type				Male	Female
	LMM	SSM	NM	VOL		
II	3	25	0	1	10	19
III	0	16	8	0	10	14
IV	0	17	7	2	19	7
V	0	1	0	1	2	0

TABLE 2. *Clinical Profile of Cases*

	SSM			Nodular		
	Males	Females	P	Males	Females	P
Head & neck	3	4	NS	1	0	NS
Back	8	9	NS	6	1	NS
Chest	5	3	NS	0	0	—
Abdomen	3	1	NS	0	0	—
Arms	6	6	NS	2	0	NS
Legs	2	8	0.13	1	3	0.09
Total	27	31		10	4	

lesions (amputation of involved digit). Simultaneous regional lymphadenectomy was confined to those patients with level III, IV or V disease whose tumors drained to a single nodal basin.

All patients were examined at 3 month intervals during the first two years and at 6 month intervals thereafter. Annual chest x-ray, scans of liver, brain and bone, routine hematology, urinalysis and blood chemistries were performed.

There were 41 males and 40 females with mean ages of 53.2 and 47.2 years respectively. The clinical types of melanoma and their levels of invasion can be seen in Table 1. Their location and distribution by sex are shown in Table 2.

Results

In general the postoperative morbidity was negligible and no operative deaths occurred. One patient required regrafting, all others healed without incident. The specific findings in this study included the following:

The results of 37 regional lymphadenectomies are shown in Table 3. Four patients had clinically positive nodes at the time of operation. Three of these had level IV tumors, the other was found in a level III patient. Tumor was confirmed in each case at microscopy (no clinical false positives). The absence of tumor involved lymph nodes as suggested by the clinical examination in 15 cases with level III invasion was also confirmed histologically (no clinical false negatives) and provided excellent correlation between the clinical and microscopic findings at this level. This was not the case in the 21 lymphadenectomies performed for level IV disease. Four clinically negative nodal regions (4 of 17) were found to contain tumor at microscopy, while 4 others (4 of 9), not treated initially by regional node dissection (because of ambiguous location) developed delayed, microscopically confirmed nodal metastases (false negatives—24% and 44% respectively).

The relationship between microstaging, nodal status and the dissemination of disease can be seen in Table 4. To date no level II patient has developed either recurrence or metastases. Metastatic disease has occurred in 15 of the 52 high risk patients. Two of the 24 at level III (8%), 12 of 26 patients with level IV invasion (46%) and 1 of the 2 level V patients (50%) have developed recurrences. The presence of lymph node metastases had ominous significance, since 10 of these 12 patients have either died or developed disseminated disease. The clinical type of melanoma may have some relationship to recurrence (Fig. 1). While 7 of 34 high risk superficial spreading melanomas have developed recurrences (21%), a greater risk was seen in the nodular-volar group. Eight of 18 (45%) have either died or developed disseminated disease. These differences, however, are not statistically significant (P = 0.14).

TABLE 3. *Correlation of Microstaging with Nodal Status*

Microstage	No. Patients	Prophylactic Regional Lymphadenectomy						
		Performed					Not Performed	
			Micro +		Micro −			
		No. Patients	Clinical −	Clinical +	Clinical −	Clinical +	No. Patients	Delayed Nodal Metastases
II	29	0	*	*	*	*	29	0
III	24	16	0	1	15	0	8	0
IV	26	17	4	3	10	0	9	4

* Nodes not dissected.

TABLE 4. *Recurrences as Related to Microstage and Nodal Status*

Microstage	No. Patients	Recurrence			No recurrence		
		Total (%)	Nodes		Total	Nodes	
			Neg	Pos		Neg	Pos
II	29	0	*	*	29	*	*
III	24	2 (8%)	1	1	22	14	0
IV	26	12 (46%)	3	9	14	6	2
V	2	1 (50%)	1	0	1	1	0

* Nodes not dissected.

Discussion

These data have provided certain preliminary answers to the questions originally posed. Our major interest focused on our ability to predict lymph node metastases by combining clinical and histologic criteria. In this group, no patient with level II disease had either clinical evidence of nodal metastases or had regional lymphadenectomy performed. To date all (median followup 20 months) have remained free of disease. This strengthens our observation[2] that these tumors lack metastasizing potential and, in our judgment, precludes the need for node dissections. In the higher risk groups the clinical assessment of nodal metastases at level III correlated extremly well with microscopic findings. There were neither false negatives or positives nor has any patient developed delayed nodal metastases. On the basis of our observation and the report of Wanebo et al.[4] it is apparent that prophylactic lymph node dissection is unlikely to yield tumor and, therefore, is probably not warranted. It is difficult to reconcile with these observations, Wanebo and associates' finding that level III patients undergoing prophylactic node dissection (almost all of whom had histologically negative nodes) had a better 5-year survival than those who were not operated. Differences in other important prognostic variables (age, sex, etc.) between the treated and untreated groups may account for this paradoxical finding. On the other hand, nodal metastases were unpredictable in the patients with level IV disease. In this group both false negatives and delayed nodal disease were seen. At level IV, the relatively high possibility of occult metastases (or their delayed development) suggests that regional (and perhaps multiregional) lymph nodes be dissected.

Our observation that low risk lesions tend to develop more frequently in females is probably a sampling error since this was not seen in a much larger group of patients (>500) studied by the Melanoma Clinical Cooperative Group. Further, since 5-year followup is incomplete, our findings regarding dissemination and death from disease must be considered preliminary. We anticipate that other patients will likely develop metastases and succumb. Nonetheless, early recurrence was found most frequently in those with lymph node metastases (stage II), an expected finding since these patients have demonstrated biologically aggressive tumors. By combining the gross tumor type with its depth of dermal invasion and presence or absence of lymphatic metastases a reasonable estimate for individual tumor behavior seems feasible.

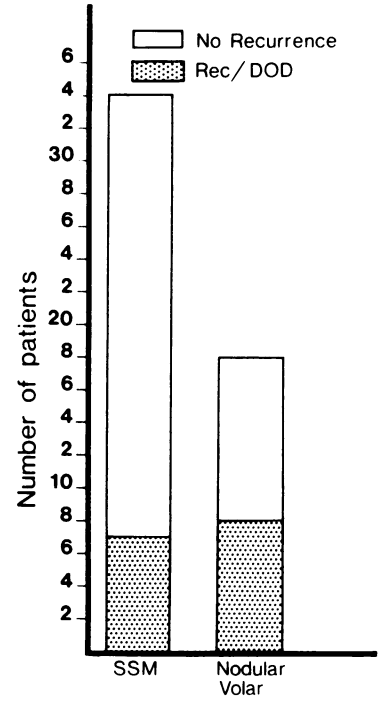

FIG. 1. Relationship between gross type of melanoma with recurrence/dead of disease.

References

1. Clark, W. H. Jr., From, L., Bernardino, E. A., and Mihm, M. C.: The Histogenesis and Biological Behavior of Primary Human Malignant Melanoma of the Skin. Cancer Res., 29:705, 1969.
2. Goldman, L. I.: The Surgical Therapy of Malignant Melanomas. Sem Oncol., 2:175, 1975.
3. Hansen, M. G. and McCarten, A. B.: Tumor Thickness and Lymphocytic Infiltration in Malignant Melanoma of the Head and Neck. Am. J. Surg., 128:557, 1974.
4. Wanebo, H. J., Woodruff, J. and Fortner, J. G.: Malignant Melanoma of the Extremities: A Clinicopathologic Study Using Levels of Invasion (Microstage). Cancer, 35:666, 1975.

Discussion

Dr. E. George Elias (Baltimore, Maryland): Malignant melanoma is a tumor that has a peculiar biological behavior that requires intense study. Dr. Goldman dealt with some of this biological behavior in the early stage of the extraneous type of the disease. It indicates that there are some prognostic values in Clark's level of invasion which can divide the patients into a good-risk group, Level II, and a poor- or guarded prognostic group, Levels III, IV, and V.

This is similar to reports by Breslow, who measures the depth of invasion, and here again, he divides the patients into the 0.75 mm or less, as similar to Clark's Level II, with good prognosis, while patients with a level 0.76 mm or more invasion have poorer prognosis.

The authors have demonstrated that no lymph node dissection is required for Level II, at least in the period studied. The question that needs to be answered is the role of prophylactic versus therapeutic lymph node dissection in Levels III, IV, and V. If we take Level III patients in this study who underwent prophylactic lymph node dissection, we find good correlation between the clinical and the pathological stages of the disease; but we have to keep in mind that the numbers are small. Yet it seems that lymph node dissection did not prevent or delay systemic metastases in one patient with positive lymph nodes that were resected, and in another who had negative lymph nodes.

The first patient had palpable lymph nodes, and that put him in the therapeutic lymph node dissection group, while the other patient had either no lymph node dissection, and could have harbored tumor in his lymph nodes that was not detected clinically, and this places the good clinical-pathological correlation in Level III patients in doubt, or he could have had prophylactic lymph node dissection, and no metastases were seen, but shortly later he developed metastases, and this could express a more aggressive tumor behavior, and indicates that lymph node dissection did not alter the course of the disease.

In Level IV there is a higher incidence of tumor in the regional lymph nodes, and it seems that prophylactic or therapeutic lymph node dissection did not alter or improve the survival or recurrence rate, and this clearly demonstrates poorer prognosis.

It seems, then, that invasion beyond Level II carries graver prognosis, and that regional lymph node dissection has a prognostic, rather than a therapeutic value.

In this prospective study, it is too early to make final conclusions with regard to survival or disease-free interval in the surgically treated group. It would appear, then, that the next logical approach for the control of the melanoma is a national surgical melanoma project, where the pathologists and the surgeons will collaborate in the prospective study of this tumor, at least in the Levels III, IV, and V, with regard to the factors that seem to influence the prognosis; namely, age, sex, race, family history, color and size of the lesion, preexisting mole and duration, site, level of invasion, and the clinical stage of the disease. These are then correlated with a standard surgical approach; namely, wide local excision and skin grafts, with lymph node dissection. This will enable us with a fast patient accrual to study all possible prognostic factors on the course of the disease, with excellent correlation of the clinical and histological findings in the lymph nodes.

Finally, with regard to adjuvant chemotherapy with DTIC (Imidazole Carboxamide) in the melanoma, the Central Oncology Group, Protocol No. 7040, with Dr. George J. Hill, II as the Chairman, has studied the patients with poor prognosis in Stage I, II, and III, according to McNeer & Das Gupta classification. After we studied 140+ patients, there was no statistical difference both in disease free interval & survival. In Stage I disease—there was no difference between the DTIC-treated group and the controls.

After studying over 140 patients with a control arm and DTIC-treated group, there was no significant difference. We treated the invasion with 4.5 mg/kg, which is a higher dose than Dr. Goldman's group, and we repeated every three months. However, the new study is showing that maybe increasing periods, such as every 6 weeks, may be beneficial.

Dr. Matthew N. Harris (New York, New York): Dr. Goldman and I are members of a group, The Melanoma Clinical Cooperative Study Group which includes Harvard University, Temple University, New York University, and the University of California in San Francisco. The protocol, as he presented, has been accepted by our group and has worked quite well.

At the New York University Medical Center we see about 150 new cases of melanoma each year. Our series consists of well over 1200 cases; 800 cases of operable melanoma have been computerized.

The people at Temple have, and it is very important, an excellent pathologist. In order to make a correct diagnosis the pathologist has to be aware of the Clark-Mihm classification, and has to use the classification. This is not done throughout the United States. I might also mention that noted pathologists often differ widely in their interpretation of the histopathology of melanoma.

A second thought is that additional therapy will have to be used in the treatment of melanoma. About 18% of the patients with melanoma have metastases when first seen. It's not the local disease that causes death; it is hematogenous metastasis.

We have recently decided that all our so-called "high-risk" patients, that is, patients with positive nodes, microscopically or clinically, will be treated with adjuvant therapy, either immunotherapy or chemotherapy, or both. To date we are not sure that it has done any good. We all know the capriciousness of malignant melanoma, and I really wonder if the minor statistical differences presented today are really important, considering the vagaries of the disease.

Finally, I might mention the so-called "grey" area of Level III disease, particularly invasions measuring between 0.75 mm and 1.25 mm in depth. We are not sure whether these patients need elective lymph node dissections. Our aim is to achieve the maximum benefit with the least amount of "radical" surgery.

To date, surgery seems to be the only plausible way of treating the disease locally, but the battle is too often lost to hematogenous dissemination.

Dr. L. I. Goldman (Closing discussion): I recognize that there are problems in discussing only three-year results with this disease. However, I would like to call your attention the fact that 50% of people with melanoma who did recur did so within the first two years.

Even in our control series from the Massachusetts General Hospital, we found a better survival than in Dr. Hill's treated group, with the EOG. In terms of retrospective analysis, it is very difficult, for example, to find out whether or not there are clinically positive or negative lymph nodes. One of the reasons that prompted this paper was that all of these cases were operated upon by me, and that the lymph nodes are at least Goldman negative or positive.