Annual Oration for 1976

Malignant Melanoma—A Therapeutic Approach Related to Biologic Behavior

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Capricious, unpredictable, virulent, grave and peculiar have all been applied to descriptions regarding the behavior of cutaneous malignant melanoma. Recently Peacock, in editorial comment, remarked "as yet, it is not possible to correlate prognosis, the need for secondary surgery, or the best type of chemotherapy or immunotherapy with any general scheme for classification of the disease."[1] On the contrary, we disagree with the above and in this report will attempt to outline our strategies in treating cutaneous melanoma. These are based upon identifiable parameters which correlate well with the biologic behavior of this disease.

The Developmental Biology of Primary Cutaneous Melanoma

In 1969, Clark and his coworkers described a relationship between the depth of dermal invasion by cells of the primary tumor with patient survival following treatment.[2] More important, however, was their observation that in several clinical types of melanoma (i.e., lentigo maligna, volar, superficial spreading) these invasive tumors can exist in a form which lacks the capacity to produce metastases. This phase of radial growth has been well documented, can be present for several years and has been identified by the invasion of tumor cells into, but not completely through, the papillary dermis (level II). If uninterrupted, these tumors undergo a change (called intralesional transformation by Clark) which has been characterized by the development of a phase of vertical growth. Tumor cells have penetrated more deeply into the dermis (level III-papillary reticular dermal level, level IV-reticular dermal level, level V-subcutaneous level) and frequently polyconism can be seen microscopically. Characteristically a nodule(s), occurring within the primary tumor, heralds this change. Nodular melanomas lack an antecedent radial growth phase and present initially with vertical growth. Tumors at these stages have the capacity to produce metastases. A superb and comprehensive review of this subject by Clark et al. is suggested for more complete details.[3] In addition to the above, other prognostic variables including tumor thickness and host lymphocyte response to tumor, have been employed as supplemental predictors of tumor behavior.

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

The Role of Surgery

Surgical excision is presently the only curative treatment available in melanoma. The two areas potentially controllable by surgery include the primary lesion site and the lymph node regions into which they drain. Our experience with 117 cutaneous melanomas occurring in 115 patients comprises the basis for this report. They were seen initially between January 1971 through July 1976; had a median follow up of 3 years; and with the possible exception of an occasional biopsy were evaluated, treated and followed by the author. The composition of this group is shown in Table 1. Accurate microstaging of

TABLE 1. Type + Level of Cases

Microstage	Type					Male	Female	Ages (median)
	LMM	*SSM*	*NM*	*VOL*	*UNC*			
II	2	39	0	0	0	16	25	18-75 (46)
III	1	26	11	1	2	18	23	17-72 (44)
IV	0	18	10	3	0	21	10	21-78 (50)
V	0	1	0	1	0	2	0	—

LMN—Lentigo Maligna Melanoma, SSM—Superficial Spreading Melanoma, NM —Nodular Melanoma, Vol—Volar Melanoma, Unc—Unclassified Melanoma

the primary tumor was carried out by serial block sectioning[2] and all patients were further evaluated by physical examination, chest x-ray, liver function studies and radionuclide scanning of brain, liver and bone. By these techniques the overall extent of disease was determined (i.e., Stage I-localized disease without metastases, Stage II-tumor confined to the regional nodes and Stage III-disseminated melanoma). Surgical therapy has been confined to Stages I and II.

Treatment of the Primary Area

The principle of "wide surgical removal in a three dimensional plane" was advocated by Sampson-Handley in 1907 because centrifugal, dermal lymphatic permeation was frequent.[4] The extent of excision, a measured distance of 3 to 5 cm. about the tumor in all directions to and including the deep fascia, aims at resection of this potentially involved lymphatic plexus. A skin graft is usually required for closure. This should be obtained prior to excision of the primary area with protection of the donor site from tumor cell seeding.

Certain types and sites of melanoma deserve special mention. Level II lentigo maligna melanoma is one example. In these, local excision (with visibly free margins) and primary closure fortunately affords both adequate treatment and satisfactory cosmetic results. Subungual tumors usually require amputation in order to achieve adequate resection margins. These are best accomplished through the appropriate metatarsal or metacarpal-phalangeal joint. Lesions on the sole of the foot cause concern because of the questionable ability of split-thickness grafts to tolerate weight bearing. We feel that initial free-grafting is

almost always indicated, in most instances long-term function is adequate and revisions can be performed when necessary.

Our treatment of the primary lesions in this series is shown in Table 2. A measured wide excision was carried out in the majority, and most of these required skin grafting for closure. In 11 cases (all trunk lesions) primary wound

TABLE 2. Primary Lesion*

Microstage	Procedure				
		Wide Excision		Local Excision	Amputation
	Total	Graft	Primary Closure		
II	43	31	7	4	1
III	41	39	2	0	0
IV	31	29	2	0	0
V	2	1	0	0	1
	117	100	11	4	2

*117 primary lesions in 115 patients

apposition was possible. Local excision (LMM) and minor amputations (Vol) were used when conditions dictated. To date no local recurrences have developed, therefore strengthening our continued endorsement of the treatment outlined above.

Treatment of the Regional Lymph Nodes

The excision of clinically involved regional lymph nodes prompts little argument; however, the management of those which appear normal remains controversial.[5,6] In an attempt to improve the yield of tumor-positive lymph nodes, we retrospectively correlated nodal findings with microstaging, and found metastases only in association with those primary tumors invasive to level III or beyond.[7] For this reason, we performed prophylactic regional lymphadenectomy in all patients with level III, IV or V disease whose tumors drained to a single lymph node basin. Lymphadenectomy was not done in level II disease, or in those more deeply invasive tumors located in ambiguous sites (drained by more than one nodal region). In-continuity dissections were preferred and used whenever feasible. In the others, nodal and primary excisions were performed disparately during the same operation.

While our major aim was to remove potential areas of metastatic disease, we were also able to correlate the depth of dermal invasion with the physical status of the regional nodes (as determined by a single observer) and the eventual nodal microscopic findings. These can be seen in Table 3. To date no level II patient has either presented with, or developed, delayed nodal metastases. Withholding lymph node dissections from this group appears justified.

In 45 regional lymphadenectomies performed at primary operation (5 others were performed when delayed metastases appeared), 3 patients were found with clinically postive nodes. Two 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 23 cases with level III invasion, was confirmed histologically in 22 (4% clinical false negatives), thereby providing satisfactory correlation between the clinical and microscopic findings at this level. This was not the case in the 26 lymphadenectomies performed for level IV disease. Five clinically negative nodal regions (5 of 19) were found to contain tumor at microscopy, while 5 others (5 of 12, not treated initially by regional node dissection (because of ambiguous location), developed delayed, microscopically confirmed nodal metastases (false negatives—26% and 42% respectively).

These findings have prompted an alteration of our views regarding the presence of tumor-involved lymph nodes at the time of "prophylactic" regional lymphadenectomy in level III patients. Since there was good correlation between the physical and microscopic lymph node findings, as well as an absence, to date, of "delayed" nodal metastases, we presently withhold regional lymphadenectomy from level III patients without clinical evidence suggesting nodal metastases. On the other hand, at levels IV and V, the potential for occult nodal metastases exceeds 25%, and therefore prophylactic dissection appears justified.

Emphasis must again be placed on the ability to cure some patients with positive lymph nodes as well as using these findings in gauging prognosis. Tumor in lymph nodes is clearly associated with a high risk for recurrence, and this information can be used for placing these patients into some form of adjuvant therapeutic program (see below). Although the excision of uninvolved lymph nodes may theoretically produce an immunologic deficit, no firm evidence exists to either support or contradict this hypothesis. Since the potential for nodal metastases can be reasonably predicted, the performance of elective regional lymphadenectomy continues to outweigh any hypothetical disadvantage.

Results of Surgical Therapy

While the results of these data encompass a median followup of only 3 years, certain preliminary observations can be made. These are shown in Table 4. All patients have been followed at 3 month intervals by physical examination supplemented by routine laboratory studies, chest x-rays and radionuclide scans at defined times. To date, 19 patients have developed recurrences or died from metastatic melanoma. One level II patient developed a subcutaneous metastasis in the same extremity as, but quite a distance from, the site of primary tumor 18 months following her initial treatment. In the others, the frequency of recurrence related directly to the depth of dermal invasion originally noted (level III—7%, IV—45%, V—50%). Further, the presence of lymph

TABLE 3. Correlation of Microstaging With Nodal Status

Microstage	Number of Patients	Prophylactic Regional Lymphadenectomy Performed						Not Performed	
		Number of Patients	Micro+ Clinical −	Micro+ Clinical +	Micro− Clinical −	Micro− Clinical +		Number of Patients	Delayed Nodal Metastases
II	41	0						41	0
III	41	24	•	•	•	•		17	0
IV+V	33	21	1	1	22	0		12	5
			5	2	14	0			

•Nodes not dissected

TABLE 4. Recurrences as Related to Microstage and Nodal Status

Microstage	Number of Patients	Recurrence Total (%)	Recurrence Nodes Negative	Recurrence Nodes Positive	No Recurrence Total	No Recurrence Nodes Negative	No Recurrence Nodes Positive
II	41	1 (2%)	•	•	40	•	•
III	41	3 (7%)	2	1	38	20	1
IV	31	14 (45%)	7	7	17	10	3
V	2	1 (50%)	1	0	1	1	0

•Nodes not dissected

node metastases had ominous significance, since eight of these patients have already developed recurrences or died from their disease. This is not unexpected, since these patients' tumors have already demonstrated their biologic aggressiveness by metastasizing to lymph nodes. Four patients with nodal metastases remain free of disease (3, 6, 31 and 42 months following surgery). Each had microscopic tumor discovered in clinically negative nodes.

The Role of Adjuvant Therapy

Adjuvant therapy represents an additional approach in the care of patients with melanoma. Its aim is the treatment of those patients who are clinically well without evidence of disease, but at appreciable risk for the development of recurrence. As noted above, this can be predicted to a great degree by combining the level of invasion with the presence or absence of lymph node metastases. Several recent reports employing BCG immunotherapy appear promising.[8, 9] Mastrangelo et al.[10] have treated 44 Stage II (previously operated and presumably without residual disease) with dimethyl-triazeno imidazole carboxamide (DTIC). Thirty-four of these patients have been at risk for at least 1 year with the range encompassing 1 through 49 months. When compared to historical controls, both the disease-free interval and the survival of those treated appeared significantly better.

Several contrary reports have also been presented. Hill et al.[11] determined that DTIC was of no value in Stage II melanoma. Similarly, Pinsky et al.[12] and Cunningham et al.[13] have reported that BCG failed to improve the survival of patients in identical stages when compared with those treated by surgery alone. Many factors may account for these discrepancies, including the types of controls, drugs employed, dosages and their schedules. In any event, further clarification is necessary. While the efficacy of the present treatment regimes may be questionable, the ineffectiveness of surgery alone in these high risk groups demands continued exploration in this area.

Summary

This review has attempted to demonstrate that rational therapeutic decisions relative to cutaneous malignant melanoma can be based on defined prognostic variables. Among these are the clinical type of tumor, its depth of dermal invasion and the presence or absence of lymph node metastases. The role of surgery and the potential value of adjuvant therapy have been described.

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