Primary Melanoma Thickness Correlated With Regional Lymph Node Metastases

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• **We studied 119 patients with stage I primary cutaneous malignant melanoma, who were undergoing regional lymph node dissection, to determine the relationship of lymph node metastases to thickness of the primary lesion. The lymph nodes in the dissection specimen were each evaluated by serial sections. None of the patients with lesions less than 1.0 mm thick had nodal micrometastases. When lesions exceeded 1.0 mm in thickness, there was no appreciable increase in the incidence of nodal metastases until a thickness greater than 4.0 mm was reached, in which cases the incidence of metastases was 50%. Predictive variables were determined by multiple logistic regression analysis. Only lesions that were at least 4.0 mm thick and were not located on the upper extremities were significant predictors of lymph node metastases; within this category there was a 64% incidence of lymph node metastases.**

(*Arch Surg* 1982;117:921-923)

Recent developments in the microclassification of primary malignant melanoma have enabled more accurate prediction of lymph node metastases, compelling even the advocates of elective lymphadenectomy to reassess their indications.[1-3] Numerous studies have correlated the thickness of primary melanoma, as determined by Breslow's system and Clark's levels of invasion, with the incidence of microscopic regional nodal metastases.[4-6] Pathologic evaluation of lymph node dissection specimens, however, has depended on the study of only one section of each excised lymph node. The presence of micrometastases may thereby be underestimated. Lane et al demonstrated that the survival rate for patients with melanoma and metastatic nodal involvement was highest for those with a single microscopic focus within a lymph node, and that whereas regional lymph nodes might be pronounced normal after thorough but routine pathologic examination, serial sections of the same nodes often demonstrate the presence of microscopic melanoma.[7] To assess the incidence of nodal metastases for varying thicknesses of malignant melanoma with greater accuracy, we performed a prospective study correlating the primary lesion in patients with clinical stage I disease with serial sections of the regional lymph nodes removed at the time of regional lymphadenectomy.

PATIENTS AND METHODS

We studied 119 consecutive patients who had clinical stage I primary malignant melanoma and were undergoing regional lymph node dissection. To be included in our study, the primary lesion had to have been removed by a biopsy so that no residual tumor was noted at the biopsy site in the reexcision specimen. All sections of the biopsy specimen were evaluated and the greatest thickness of the melanoma was measured downward from the top of the granular layer of the epidermis to the deepest melanoma cells in the dermis or subcutis. In addition, Clark's levels of invasion were determined.

Lymph node dissections in this series were done for lesions with levels of invasion III, IV, and V that were thicker than 0.50 mm. Our techniques for regional lymph node dissections have been described elsewhere.[8-10] In this series there were five lesions of the head and neck, 54 of the trunk, 41 of the lower extremities, and 19 of the upper extremities. For trunk lesions, ipsilateral node dissections were performed. Anteriorly, axillary dissections were done for lesions above the umbilicus and inguinal dissections for those below it. Posteriorly, axillary dissections were done for lesions above and inguinal dissections for lesions below the second and third lumbar vertebrae.

The lymph nodes were collected from the dissection specimen. The individual nodes were trisected and appropriately fixed in 10% neutral buffered formaldehyde solution. They were then

Accepted for publication Oct 5, 1981.

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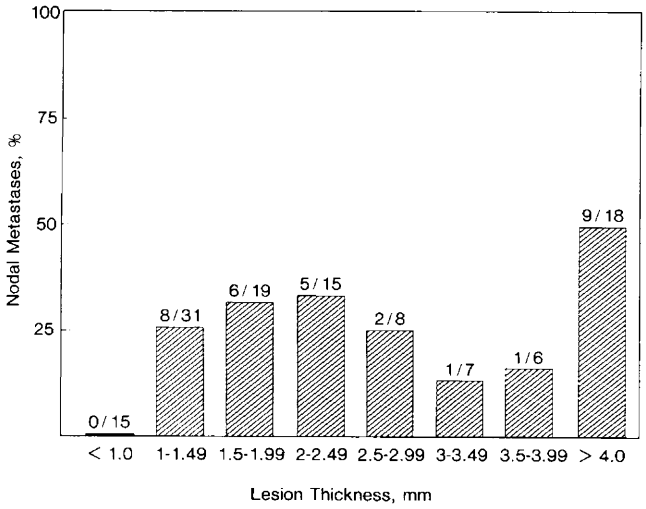

Incidence of regional nodal metastases for increasing thicknesses of primary cutaneous melanoma.

prepared for paraffin embedding and sectioned into 5- to 6-μm strips on a standard microtome. Each trisected lymph node segment was step-sectioned three times, yielding a total of nine sections for each node.

To test for statistically significant differences in the incidence of lymph node metastases, the χ^2 test was used. Significance was determined at the level of .05. We used multiple logistic regression analysis to examine the correlation of lymph node metastases with more than one factor simultaneously.[11] The criterion for inclusion of a factor in the best subset of variables was a step-down significance level of $P = .05$.

RESULTS

The incidence of nodal metastases for increasing thicknesses of primary melanoma is shown in the Figure. No patient with a lesion less than 1.0 mm thick was demonstrated to have nodal micrometastases. Lesions more than 1.0 mm showed no appreciable change in the incidence of metastases for 0.5-mm increases (Figure), until a thickness of 4.0 mm was reached, in which case the incidence was 50%. However, when lesions 1.0 to 3.99 mm thick were grouped together, the difference was significant ($P = .01$) compared with the lesions less than 1.0 mm and greater than 4.0 mm thick. Analysis by Clark's classification showed lymph node metastases in eight of 37 (22%) patients with level III lesions, 21 of 77 (27%) patients with level IV lesions, and three of five (60%) patients with level V lesions. These differences were not significant.

When analyzed by site, the incidence of positive nodes was similar for lower-extremity and trunk lesions, with 29% (12/41) and 33% (18/54) of patients in each group, respectively, having nodal metastases. Of the patients with head and neck lesions, 20% (1/5) had nodal metastases, compared with only 5% (1/19) of those with lesions in the upper extremities. Therefore, upper-extremity lesions were significantly less likely to have nodal metastases than lesions from all the other sites combined ($P = .02$). It should be noted that there were six patients with lesions of the upper extremities thicker than 3.0 mm, of whom only one had nodal metastases. We also noted whether the

Observed Incidence of Lymph Node Metastases

Lesion Thickness, mm	Incidence, %* Upper Extremities	Incidence, %* Lower Extremities, Trunk, or Head and Neck
< 1 (N = 15)	0(0/4)	0(0/11)
1-3.99 (N = 86)	9(1/11)	29(22/75)
≥ 4.0 (N = 18)	0(0/4)	64(9/14)

*Parenthetical proportions indicate number of metastases/number of patients.

dissection was performed in continuity and how many lymph nodes were examined. Neither factor, however, was correlated with lymph node metastases in our group.

In evaluating for potential predictors of lymph node metastases individually, the two important factors were the thickness and site of the lesion. A possible third factor was Clark's level, although there were only five level V lesions, too few to be statistically significant. A multiple logistic analysis was performed to evaluate whether these factors were independently predictive. The 15 patients with lesions less than 1.0 mm thick, none of whom had metastases in the lymph nodes, were excluded. It is not necessary or possible to characterize further the risks in this subgroup. Variables investigated for the multiple logistic model of the remaining 104 patients were thickness, Clark's level, site of the lesions, proximity of the lymph nodes to the melanoma site, and number of lymph nodes examined. Only a thickness of 4.0 mm or greater ($P = .03$) and a location of the lesion other than on the upper extremities ($P = .04$) were significant predictors of lymph node metastases. When we used actual thickness in millimeters instead of a 4.0-mm threshold value, the differences were not as significant ($P = .08$).

The estimate of the risk of nodal metastases for the significant subgroups of patients is given in the Table. The highest-risk patients were those with lesions at least 4.0 mm thick that were not located on the upper extremities; they had a 64% incidence of lymph node metastases. This subgroup was 12% (14/119) of the whole group and it included 28% (9/32) of the patients with lymph node metastases.

COMMENT

The recent use of microclassification systems for primary cutaneous malignant melanoma has provided a better means of gauging both prognosis and the extent of surgery necessary. Several studies in the past have shown that if a lesion is less than 0.75 mm thick, the prognosis is excellent and the incidence of regional node metastases small.[3,4,6] It has been unclear in studies correlating tumor thickness and nodal metastases whether a step-section analysis of regional nodes was performed. Such an analysis should greatly increase the accuracy of diagnosing micrometastases in regional lymph nodes.

Our results indicate that for lesions less than 1.0 mm thick, elective regional lymph node dissections are usually unnecessary. An area of controversy, as reported by Breslow, has been the treatment of patients with lesions

between 0.76 mm and 1.5 mm thick.[6] In our cases, with lesions 1.0 to 1.49 mm thick there was a 26% incidence of metastases in the regional nodes. It is also of interest that for every 0.5-mm increase in thickness above 1.0 mm and up to 4.0 mm, the incidence of nodal metastases shows no significant increase. This suggests that 1.0 mm is a threshold thickness for cutaneous melanoma, above which the incidence of nodal micrometastases with further increases in thickness is not proportionately increased until a thickness of 4.0 mm is attained.

Veronesi has suggested that lymph node dissections may be more appropriate for lesions in direct proximity to the regional nodal group as opposed to those that are at a distance, requiring wide and deep excision not en bloc with the nodal dissection.[12] This is largely because postoperative changes following excision of the primary melanoma in areas of skin covering a lymph node basin may complicate the clinical evaluation of the nodes. However, the incidence of micrometastases in our series was 28% (25/89) for the lymph nodes that were not in continuity, compared with 23% (7/30) for those that were. The low incidence of micrometastases for the upper-extremity melanomas suggests that a more careful analysis by thickness of lesions of this location in the future may be appropriate, as the incidence of regional node disease here appears to be lower than elsewhere.

It must be emphasized that only a lesion that is properly excised and prepared can be relied on to yield precise information, particularly when it is evaluated by the method of Breslow.[13] Prognosis based on Breslow's or Clark's classifications may not take into account the spontaneous resolution that can occur in much of a lesion. It is well established that a clinically occult melanoma may have regional lymph node metastases. The site of the primary tumor may never be discovered in such a case. Likewise, as has been demonstrated by Gromet et al, a primary lesion with metastatic potential may appear thin because the diagnosis is made at a time when a substantial portion of it has undergone regression.[14]

This study was supported by National Cancer Institute grant CA16087 and National Institute of Occupational Safety and Health grant RO1 OH00915.

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