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Volume of Malignant Melanoma Is Superior to Thickness as a Prognostic Indicator

Preliminary Observation

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Cutaneous malignant melanomas (MMs) exhibit a wide range of biologic behavior. The best histologic predictor of metastases or death, or both, from MM is the greatest thickness of the primary neoplasm.[1-3,5,10,11] Those tumors in which the features of malignancy are limited to the epidermis (MM in situ) behave in a biologically benign fashion if completely excised. In contrast, thick MMs that have penetrated into the deeper dermis often lead to metastases or death, or both.[1-3,5,10,11] Thickness is a unidimensional measurement; however. A more reliable predictor of metastatic potential might be one that takes into account the three-dimensionality of a neoplasm. Tumor volume was considered as a prognostic factor for MM first by Breslow[2] in 1970 and more recently by Gebhart and Knobler.[8] Our preliminary study shows that calculation of tumor volume from step-sec-

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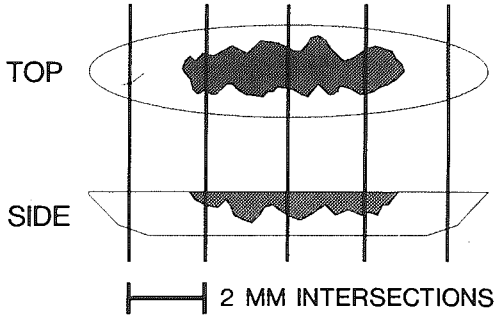

Figure 1. Sections of the primary MM were made at 2-mm intervals.

tioned MMs may be a more reliable predictor of outcome than is the measurement of greatest thickness.

MATERIALS AND METHODS

The histologic step-sections of 35 cutaneous MMs from patients entered into the New York University Melanoma Cooperative Group data base between 1973 and 1979 were studied. These patients met the following criteria for selection: Each patient either had an intact primary MM on entry into the study or had had the MM removed within 30 days of entry. All patients had complete excisional biopsies, with blocks prepared from parallel step-sections at 2-mm intervals throughout the surgical specimen (Fig. 1). Histologic slides were prepared, with sections measuring 4 μm in thickness from each block. All patients were followed up for at least 5 years for the development of metastases. A metastasis was defined as either regional lymph node or systemic involvement. Calculations of tumor thickness and tumor volume were made without knowledge of the patients' outcomes.

Thickness was measured with an ocular micrometer from the top of the granular zone to the deepest MM cell by Breslow's[2] method. To calculate MM volume, the thickest dermal portion of the neoplasm was measured on each section by calculating the distance from the middle portion of the dermal papilla to the deepest neoplastic cell (Fig. 2). Then, the greatest width of the dermal component of the neoplasm in each section was measured. The cross-sectional morphology of the neoplasm in each of the step-sections was approximated by fitting the thickness and width of the dermal component of the lesion to a hemiellipse (Fig. 3). The accuracy of a hemielliptical approximation for sectional areas was verified with the use of a calibrated projection microscope. The cross-sectional areas of 10 MMs, as determined on a calibrated projection microscope, were compared with the areas calculated using the hemiellipse model. An average difference between the two methods of less than 6% was found, leading to the conclusion that the hemielliptical method would serve for the study.

The volume of the lesion between two adjacent sections (intersectional volume) was computed with the use of the formula

$$\int_{x=0}^{x} \underset{X}{\tfrac{1}{2}\pi\,(a + x\,[A - a])} \underset{X}{(b + x\,[B - b])}\,dx$$

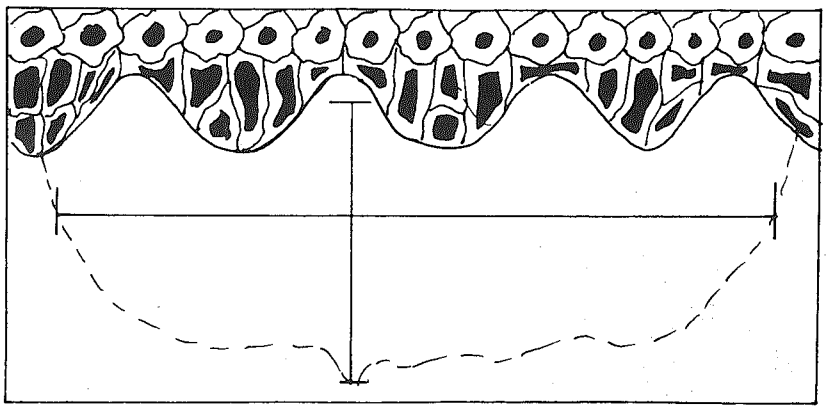

Figure 2. To calculate volume, the greatest thickness and width of the dermal component were measured as shown.

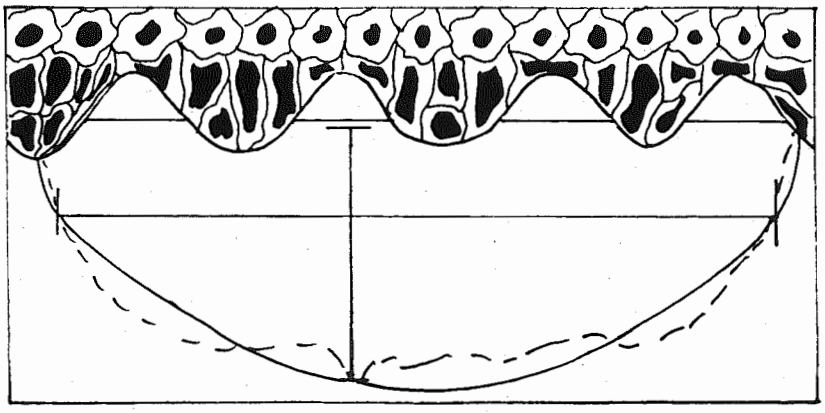

Figure 3. A hemiellipse was created to approximate the cross-sectional morphology of the MM.

Where: X = inter-section distance (2 mm)
a = dermal lesion thickness of the nth section
b = ½ dermal width of the nth section,
A = dermal lesion thickness of the nth + 1 section, and
B = ½ dermal lesion width of the nth + 1 section.

For a 2-mm distance between sections, this formula reduces to

$$\tfrac{1}{6}\,\pi\,[a\,B + A\,b + 2\,AB + 2\,ab]$$

The lesion was estimated to extend 1 mm beyond the last section positive for tumor (end volume) in each direction. The end volume was calculated using the formula above; with X = 1, the formula reduces to $\tfrac{1}{12}\,\pi\,[AB]$. The volume of the lesion was then computed as the sum of the volumes between sections and end volumes.

Chi-square analysis comparing tumor volume ranges with actual patient outcomes was performed. Five-year disease-free survival rates were computed with the use of the Kaplan-Meir method.[9] A Cox proportional-hazards-risk model[9] was used to compare the prognostic significance of tumor volume versus thickness.

RESULTS

Of the 35 patients in this study, 23 (66%) remained metastasis-free after initial surgical therapy, but 12 (34%) subsequently developed metastases (Table 1). Eleven of the 12 patients who developed metastases died: 10 of metastatic MM and 1 of unrelated causes.

For the 23 patients who remained metastasis-free, the thickness of their primary MMs ranged from 0.4 to 5.4 mm (mean = 2.19 ± 1.69) as compared with thicknesses of 1 to 12 mm (mean = 4.66 ± 3.10) for the 12 patients who developed metastases. A comparison of MM volumes for these two groups of patients revealed a mean of 68.92 ± 62.99 mm^3 (range 8–210) for the patients remaining metastasis-free, versus a mean of 445.49 ± 318.67 mm^3 (range 96–1081) for patients with metastases. In reviewing the data, the volume of 200 mm^3 appeared to delineate those patients who developed metastases from those who did not. Only two of the 12 patients (17%) who developed metastatic MM had volumes < 200 mm^3, but 10 of the 12 patients (83%) who developed metastatic MM had tumor volumes > 200 mm^3 (Fig. 4). In contrast, tumor thickness did not correlate as closely with the development of metastases (Fig. 5). A 5-year disease-free survival rate of 91.4% was computed for patients with tumor volume < 200 mm^3, compared with one of 16.7% for patients with tumor volumes > 200 mm^3 ($P < 0.0001$) (Fig. 6).

A Cox proportional-hazards-risk analysis was performed to compare tumor volume ranges with tumor thickness ranges that have been suggested to be significant.[4] Tumor volumes < 200 mm^3 and > 200 mm^3 were compared with thickness ranges of < 1.70 mm, 1.70 to 3.64 mm, and > 3.65 mm. The results are summarized in Table 2. In our series, tumor volume was a more significant predictor of survival rate than was thickness.

Table 1. *Thickness and Volume Measurements of the 35 MMs in Relation to Metastases*

CASE NO.	THICKNESS (MM)	VOLUME (MM^3)	TIME TO METASTASIS (MONTHS)	TOTAL FOLLOW-UP (MONTHS)
1	4.20	96.15	7	29
2	1.60	41.81	NM	143
3	5.20	209.89	NM	95
4	3.00	841.84	9	59
5	0.70	54.49	NM	142
6	1.70	40.81	NM	144
7	1.10	30.33	NM	145
8	0.65	217.60	21	33
9	4.20	698.21	6	20
10	8.20	741.40	2	11
11	5.20	201.18	NM	186
12	5.40	167.96	NM	191
13	2.80	131.30	NM	144
14	5.00	233.97	5	11
15	1.50	38.47	NM	135
16	0.40	14.24	NM	119
17	4.60	172.19	NM	127
18	0.55	30.09	NM	136
19	3.90	95.76	NM	119
20	0.60	13.13	NM	128
21	12.00	1081.17	9	39
22	1.00	268.62	42	142
23	1.00	22.31	NM	138
24	3.40	47.12	NM	130
25	3.20	58.05	NM	108
26	7.40	467.61	0*	3
27	3.10	213.61	23	65
28	1.40	41.36	NM	145
29	2.50	338.18	3	6
30	2.40	30.15	NM	130
31	2.65	148.11	5	13
32	2.10	88.00	NM	106
33	0.50	22.80	NM	125
34	0.65	25.49	NM	131
35	0.55	8.20	NM	144

* Metastasis present at entry into study. NM = No metastasis (nodal or systemic).

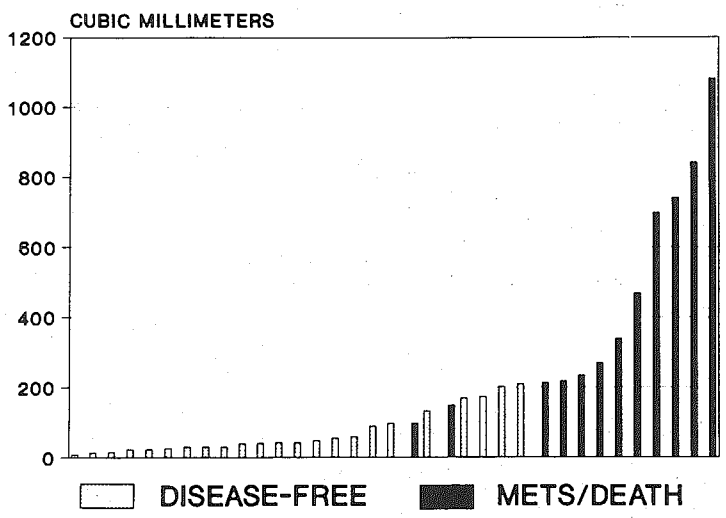

Figure 4. Volume versus survival. Ten of the 12 patients who developed metastases (mets) had tumor volumes >200 mm^3.

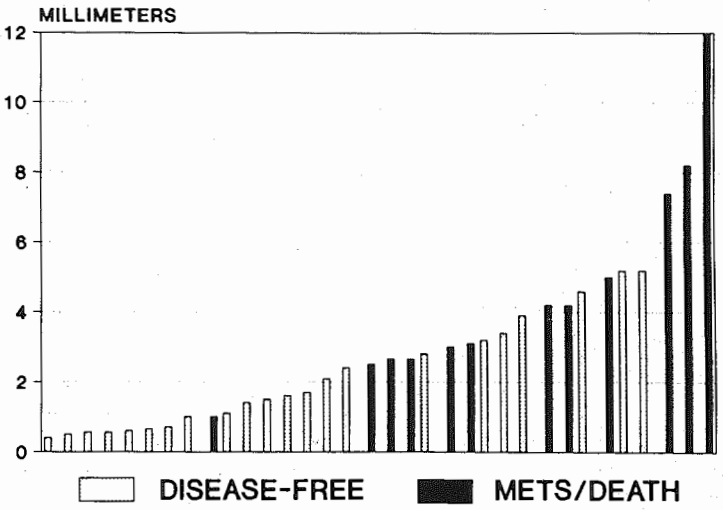

Figure 5. Thickness versus survival. Of those patients with tumor thicknesses >1.7 mm, 11 patients developed metastases (mets), whereas 10 patients did not develop metastases. Compare with Figure 4.

DISCUSSION

On the basis of previous multivariate analyses, it is generally accepted that Breslow thickness[2] is the best histologic predictor of survival rates of clinical stage I patients with primary cutaneous MM.[1,5,10] Although the small number of cases in this preliminary study did not enable us to do extensive analyses of the numerous interacting prognostic factors in a Cox proportional-hazards-risk model, we found tumor volume to be a more reliable prognostic factor than was thickness. Thickness considers only one dimension (vertical) of the tumor. Therefore, it is only a crude estimate of tumor volume in comparison to the calculation of tumor volume based on step sections.

The lethal nature of a MM is due to its ability to penetrate blood and lymphatic vessels and spread to distant sites.[6] As a MM penetrates from the epidermis (in situ) into the papillary dermis and then into the reticular dermis and subcutis, it enlarges three-dimensionally. Once its tumor volume exceeds that which is nutritionally supportable by diffusion, the neoplasm must stimulate the formation of new blood vessels.[7] These neovascular structures can probably be more easily penetrated by the cancer cells than are normal vascular structures, thereby increasing the chance of metastases. Therefore, we measured the volume of the dermal component of each primary melanoma.

Although the calculation of tumor volume of primary cutaneous malignant melanomas, as described in this preliminary study, is a tedious procedure, we consider the concept to be important because volume may prove to be a superior determinant of the survival rate of patients with this neoplasm. With newer computer technology, this complicated process of determination of tumor volumes of MMs may be markedly simplified.

In summary, there are numerous important clinical and histologic prognostic factors known to predict the outcome of patients with primary cutaneous MM. Thickness of the

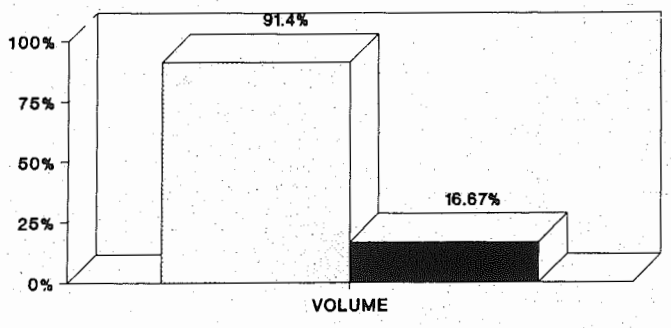

Figure 6. Tumor volume versus disease-free survival. The 5-year disease-free survival for patients with tumor volumes <200 mm^3 *(gray area)* compared with that of those with tumor volumes ≥ 200 mm^3 *(black area)*. N = 35, $P < 0.001$.

Table 2. *Cox Proportional-Hazards-Risk Model, Comparing Tumor Volume with Breslow Thickness*

	χ^2	*P* VALUE
Volume (<200 mm^3 vs. >200 mm^3)	22.04	<0.0001
Thickness >3.65 mm	4.10	<0.0428
Thickness 1.70–3.64 mm	6.41	<0.0114

tumor is at present the most useful histologic variable; however, in our study, the volume of the dermal component proved to be of greater significance than thickness in predicting disease-free survival rates. These are preliminary observations that require validation by application of the same methodology to other series of patients with primary cutaneous MM.

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