Volume as a Prognostic Indicator in Cutaneous Malignant Melanoma

Is volume an additional prognostic indicator that can differentiate those few traditionally “low risk” melanomas that may metastasize and necessitate SLN biopsy?

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It is estimated that in 2007 there were approximately 60,000 cases of invasive cutaneous malignant melanoma (CMM) diagnosed in the US and 8,000 to 10,000 patients receiving the diagnosis would die. This accounts for approximately two to three percent of all cancer deaths and makes cutaneous melanoma the sixth most common cancer. Early diagnosis and adequate surgical excision are essential for cure. Therefore, any additional prognostic factor that assists in the early diagnosis and management of certain types of CMM would be of great value.

A number of factors are presently identifiable and used in the evaluation of primary CMM. They include Breslow tumor thickness, Clark’s levels of invasion, mitotic counts, lymphocytic inflammatory reaction and in particular ulceration. More recently, genetic testing is being investigated and the importance of sentinel lymph node (SNL) biopsy has been established. However, the thickness of lesions described by Breslow in his original work is presently the most accurate single measurement of prognosis. According to the thickness of the lesion, melanoma has been divided into separate risk categories each with a different prognosis (Table 1). If ulceration is present in any category the prognosis is cut approximately by half. Currently, the only other prognostic indicator that can predict with accuracy is tumor mitotic rate. However, there may be some variability in reproductability.

Breslow stated that measurement of thickness was a rough estimate of volume and there is an approximate and inverse relationship between the diameter of the lesion and survival. He implied that the use of volume as a prognostic tool had been neglected. He added that the maximum cross-sectional area should be roughly proportional to the volume. He concluded that the incidence of recurrences and metastatic disease is a factor of thickness and maximum cross-sectional area. The use of cross-sectional area per se is also a simple method of volume estimation according to Temple, et al. In their series the cross-sectional area was positively correlated with tumor thickness; both measurements had similar predictive accuracy. Friedman, et al. agreed that Breslow thickness was considered to be the most reliable prognostic factor in primary cutaneous malignant melanoma. However, the authors argued that thickness was unidimensional and a more accurate measurement of prognosis would be attained by using a three dimensional method. Their results comparing volume to thickness demonstrated that the volume was the superior prognostic indicator. Those patients with volumes of 200mm³ or less had 91.4 percent disease-free survival, compared with survival rate of only 16.7 percent for those patients whose lesions had tumor volumes exceeding 200mm³. Unfortunately, obtaining area measurements in their series was complicated, time-consuming, and labor intensive, making widespread adoption of the technique difficult.

The introduction of the SLN biopsy, although controversial, improves the prognostic accuracy in planning the treatment of certain types of localized invasive melanoma. Experience has dictated that SLN biopsies are not usually done on melanomas less than 1mm in thickness because metastases are rare (but do occur) or on lesions thicker than 4mm because the majority have already metastasized. It is in the intermediate group where most SLN biopsies are carried...
The question is whether volume as an additional prognostic indicator can differentiate those few traditionally "low risk" melanomas that may metastasize and necessitate SLN biopsy. Similarly, can those intermediate risk melanomas that may metastasize be differentiated by volume from those that are unlikely to metastasize? It appears that a small number of high risk melanomas with low volume do not metastasize, whereas higher volume tumors do.

However, if SLN biopsy is performed on this group and is positive, it might indicate the need for node dissection long before nodes are clinically identifiable. Additional prognostic indicators are needed in these categories and volume may be a useful supplement. Therefore, this study has been designed to estimate volume by a clinical and simple method to improve on Breslow thickness as a prognostic tool and, thereby, filling a gap in interpretation.

**Methods**

In order to ascertain the prognostic value of tumor volume, all CMMs (except in situ) from 1998 to 2006 recorded in the Stanford surgical pathology database were reviewed. The relevant material that is applicable for this study both in-house and outside referral was extracted from the clinical and/or pathological reports. This included Breslow thickness and the area of the lesion (the longest vertical and horizontal measurements), either clinical or pathological, also in millimeters and thereby multiplying to obtain volume. It must be emphasized that this method of obtaining volume is approximate and distinctly different from the accurate computer measurements used by Friedman and his colleagues. Our measurement of area obviously does not take into account irregularity of border, and measurement clinically or pathologically may be somewhat different because of shrinkage of the latter. Metastases referred to in the study include those in lymph nodes, skin and distant organs.

Data were analyzed using the SAS System v9.1 (SAS Institute, Cary). The association of volume to metastasis or SNL positivity status, while controlling for Breslow thickness, was assessed by the Mantel-Haenszel test. A Fisher's exact test on each Breslow thickness group was performed, and corresponding exact odds ratio was estimated (only lower limits were produced due to zero counts).

**Results**

The association of volume to metastasis was based on data in Table 2. Overall, after accounting for Breslow thickness, volume and metastasis status are strongly associated (P<0.0001). In particular, consider patients with Breslow thickness ≤1.0. Among those with volume <250, about 92 percent did not have metastasis, but 100 percent of patients with volume >250 had metastasis. Thus, for patients with Breslow thickness ≤1.0, those with volume >250 are at least 14.6 times
more likely to have metastasis than those with volume < 250. Further, among patients with Breslow thickness > 1.0, no patient with volume < 250 had metastasis, but about 80 percent of patients with volume > 250 had metastasis. Thus, for patients with Breslow thickness > 1.0, those with volume > 250 are at least 8.4 times more likely to have metastasis than those with volume < 250.

The association of volume to SNL positivity status was based on data in Table 3. Overall, after accounting for Breslow thickness, volume and metastasis status are strongly associated (P < 0.0001). In particular, consider patients with Breslow thickness ≤ 1.0. Among those with volume < 250, 100 percent did not have SNL positivity status; there were no patients with volume > 250. Thus, no further analysis is possible.

Regarding patients with Breslow thickness 1.1-1.5, among those with volume < 250, no patient had SNL positivity status; 100 percent of patients with volume > 250 had SNL positivity status. Thus, for patients with Breslow thickness 1.1-1.5, patients with volume > 250 are at least 10.2 times more likely to have SNL positivity status than those with volume < 250. Further, regarding patients with Breslow thickness 1.6-2.0, among those with volume < 250, 100 percent of them did not have SNL positivity status, and 100 percent of patients with volume > 250 had SNL positivity status. Thus, for patients with Breslow thickness 1.6-2.0, those with volume > 250 are at least 5.8 times more likely to have SNL positivity status than those with volume < 250. Finally, regarding patients with Breslow thickness ≥ 2.1: Among those with volume < 250, 100 percent did not have SNL positivity status, and 100 percent of patients with volume > 250 had SNL positivity status. Thus, for patients with Breslow thickness ≥ 2.1, patients with volume > 250 are at least 24.9 times more likely to have SNL positivity status than those with volume < 250.

Discussion
In malignant melanoma tumor depth is correlated with increased risk of metastases; however, some thin lesions (five to 10 percent) also metastasize. Using volume in addition to thickness may increase the accuracy of estimating those low risk and intermediate risk melanomas that may metastasize as well as possibly recognize those high-risk melanomas that may not. Moreover, SLN biopsy is not currently recommended for non-ulcerated melanomas less than 1mm thick because metastases are rare. However, our data suggest that tumor volume may help identify lesions in this group that metastasize as candidates for SLN biopsy.

The method for estimating tumor volume in melanoma presented here is based on a clinical application, which is simple, practical, and cost effective. The area measurements are approximate but do not require intensive labor with highly trained technicians and expensive electronic equipment. Even though the number of subjects in this study was small, the evidence suggests that this method has clinical significance in the management of certain categories of cutaneous malignant melanoma and warrants further investigation on a larger scale.