Comparison of Sentinel Lymph Node Micrometastatic Tumor Burden Measurements in Melanoma

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BACKGROUND: Multiple methods have been proposed to classify the micrometastatic tumor burden in sentinel lymph nodes (SLN) for melanoma. The purpose of this study was to determine the classification scheme that best predicts nonsentinel node (NSN) metastasis, disease-free survival (DFS), and overall survival (OS).

STUDY DESIGN: A single reviewer reanalyzed tumor-positive SLN from a multicenter, prospective clinical trial of patients with melanoma ≥1.0 mm Breslow thickness who underwent SLN biopsy. The following micrometastatic disease burden measurements were recorded: Starz classification, Dewar classification (microanatomic location), maximum diameter of the largest focus of metastasis, maximum tumor area, and sum of all diameters. Univariate and multivariate models and Kaplan-Meier analysis were used to evaluate each classification system.

RESULTS: We reviewed 204 tumor-positive SLNs from 157 patients. On univariate analysis, all criteria except Starz classification were statistically significant risk factors for NSN metastasis. On multivariate analysis, including Breslow thickness, ulceration, age, sex, and NSN status, maximum diameter (using a cut-off of 3 mm) was the only classification system that was an independent risk factor predicting DFS (hazard ratio 2.31, $p = 0.0181$) and OS (hazard ratio 3.53, $p = 0.0005$). By Kaplan-Meier analysis, DFS and OS were significantly different among groups using maximum diameter cut-offs of 1 and 3 mm.

CONCLUSIONS: Maximum tumor diameter outperformed other measurements of metastatic tumor burden, including microanatomic tumor location (Dewar classification), Starz classification, maximum tumor area, and sum of all diameters for prediction of survival. Maximum tumor diameter is a simple method of assessing micrometastatic tumor burden that should be reported routinely. (J Am Coll Surg 2014;218:519–529. © 2014 by the American College of Surgeons)

Sentinel lymph node (SLN) biopsy is now the cornerstone of nodal staging for cutaneous melanoma. The status of the SLN is the most important prognostic factor for patients with a Breslow thickness of at least 1.0 mm, and in current practice, SLN biopsy guides treatment decisions regarding completion lymphadenectomy and adjuvant therapy. According to the American Joint Committee on Cancer 2009 melanoma staging classification, status of the SLN is simply designated tumor-positive or -negative, without consideration of the micrometastatic tumor burden in the SLN.[1] Clearly, survival differences exist between stage III patients with SLN-positive (micrometastatic) and palpable nodal (macrometastatic) disease; however, there also remains a great deal of variation in prognosis for patients with micrometastatic disease.[2] In fact, in one study, survival for SLN-positive patients ranged from 14% to 85%.[3] Although patient and primary tumor factors such as age, sex, ulceration, and Breslow thickness are important considerations, the micrometastatic tumor burden may also be an important prognostic factor that can identify patients at high risk for non-SLN (NSN) metastases, recurrence, and death.

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Abbreviations and Acronyms
DFS = disease-free survival
NSN = non sentinel lymph node
OS = overall survival
SLN = sentinel lymph node

Multiple methods of measuring and classifying the degree of SLN metastatic disease have been proposed. The Rotterdam criteria use the linear measurement of the maximum diameter of the largest focus of micrometastatic disease in the SLN; the criteria themselves use categorical cut-offs of 0.1 mm and 1.0 mm to distinguish differences in survival and NSN metastases.[4,5] The maximum tumor cross-sectional area has also been used in addition to maximum diameter for risk stratification.[6,7] In order to consider the entire tumor burden of multiple metastatic deposits, the sum of the maximum diameter of all metastatic deposits has been shown to predict NSN metastases and survival.[8] The Starz classification measures the depth of invasion from the lymph node capsule to stratify patients at risk for death and NSN metastases.[9] The Dewar criteria forego linear measurements in favor of classification of micrometastases according to their microanatomic location within the node to determine the risk of NSN metastases.[10] Although many of these measurements have been validated in separate analyses, few studies have compared some or all of these measurements directly. This study was designed to compare these different micrometastatic tumor burden measurements in order to determine which classification system provides the most accurate prediction of survival outcomes and risk of NSN metastases.

METHODS

This study reviewed original pathologic slides of tumor-positive SLNs from the Sunbelt Melanoma Trial and the University of Louisville Melanoma Database. Details of the Sunbelt Melanoma Trial have been described previously.[11] Briefly, participants in the trial had a primary cutaneous melanoma with Breslow thickness $\geq$1.0 mm and presented without clinical evidence of metastatic disease. All patients underwent SLN biopsy; serial sections and S-100 immunohistochemistry were performed for all patients, while additional immunohistochemical stains (eg, HMB-45, MART-1, Melan-A) were optional. Patients with a tumor-positive SLN by either routine histologic or immunohistochemical examination underwent completion lymphadenectomy. For this analysis, patients with tumor-positive SLN were identified from 3 of the highest enrolling centers from the Sunbelt Melanoma Trial and reviewed. Additional patients from the University of Louisville were also reviewed. The institutional review boards of each participating institution approved this study.

A single reviewer reanalyzed the original pathologic slides. Routine histologic or immunohistochemical stains were used for analysis. An ocular micrometer under light microscopy was used to obtain measurements that were defined based on the following criteria:

1. Maximum diameter of the largest metastatic focus in a single slide yielding the greatest measurement.[4]
2. Maximum cross-sectional area using the perpendicular measurement to the maximum diameter of the largest metastatic focus.[6,7]
3. Sum of the maximum diameters of all metastatic deposits on a single slide yielding the maximum measurement for a given node.[8]
4. The Starz classification of greatest depth of invasion of the deepest focus of metastatic disease measured from the interior margin of the lymph node capsule, categorized as SI ($\leq$0.30 mm), SII (0.31-1.0 mm), or SIII (>1.0 mm).[9]
5. The Dewar critieria, based on microanatomic location of the SLN metastases: subcapsular, parenchymal, combined (subcapsular and parenchymal), multifocal, and extensive.[10]

Outcomes were NSN metastases after completion lymphadenectomy, disease-free survival (DFS), and overall survival (OS). Survival times were calculated from time of SLN biopsy. Simple univariate comparisons for risk of NSN metastases were made across continuous and categorical classifications of SLN tumor burden using Wilcoxon rank sum and chi-square (or Fisher's) testing, as appropriate. Multivariate logistic regression models were also used for risk of NSN metastases. Breslow thickness, age, sex, and ulceration were used as covariates in the multivariate models to provide an adjusted odds ratio for each SLN tumor burden measure. Survival differences in DFS and OS were analyzed by the method of Kaplan-Meier and compared with the log rank test. Univariate and multivariate Cox proportional hazard modeling was also used for DFS and OS comparisons. Breslow thickness, age, sex, ulceration, and NSN status were used as covariates in the multivariate Cox models to provide an adjusted hazard ratio for each SLN tumor burden measure. Nonsentinel node status was used rather than total number of positive lymph nodes in this analysis because we previously found that NSN status outperforms the number of positive nodes in predicting DFS and OS.[12] For the multivariate logistic regression and Cox proportional hazard models, a single SLN tumor burden