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EDITORIAL – MELANOMAS

Editorial: Should We Abandon TNM Staging in Favor of Gene Profiles in Node-Positive Melanoma?

Kathryn E. Engelhardt, MD[1,2], Jeffrey D. Wayne, MD[3], and Karl Y. Bilimoria, MD, MS[1,2,3,4]

[1]Surgical Outcomes and Quality Improvement Center (SOQIC), Department of Surgery and Center for Healthcare Studies, Feinberg School of Medicine, Northwestern University, Chicago, IL; [2]Center for Healthcare Studies, Feinberg School of Medicine, Northwestern University, Chicago, IL; [3]Department of Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL; [4]Northwestern Institute for Comparative Effectiveness Research (NICER) in Oncology, Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL

Patients with sentinel lymph node (SLN)-positive stage III melanoma have heterogeneous outcomes ranging from 23 to 87 %.[1] Due to this variability, it is challenging to provide prognostic information to patients, stratify patients appropriately for clinical trials, and make decisions regarding adjuvant therapy. Thus, there would be value in identifying a gene signature that would allow discrimination of patients with stage III melanoma into high- and low-risk groups.

The article by Hao et al. published in this current edition of Annals of Surgical Oncology[2] leverages the pathologic specimens from the Sunbelt Melanoma Trial (SMT),[3] a randomized controlled trial that recruited 774 patients with intermediate-thickness melanoma undergoing an SLN biopsy (SLNB).

The current study by Hao et al. sought to identify a gene signature using SLN tissue to better predict survival in stage III patients. Using the SLN specimens collected in the SMT, training and validation datasets were created to compare cases with recurrence versus those without recurrence. After starting with 54,675 probes, only two genes still had significant differential expression: PIGR and TFAP2A. It is particularly interesting that these SLN samples were primarily lymph node tissue and not just melanoma tumor cells or macrometastases, thus the gene signature is thought to be indicative of the immune environment rather than the tumor itself. An additional advantage is that the test can be applied even in the setting of low burden of disease in the SLN.

The study then further analyzed the prognostic ability of the gene signature and compared it with the current standard, the American Joint Committee on Cancer (AJCC) TNM staging.[4] A significant difference in disease-free survival (DFS) was observed between the high- and low-risk gene groups, but no difference in overall survival (OS) was observed. When the high- and low-risk groups were defined based on AJCC TNM staging alone (IIIA compared with IIIB), no difference in the study population for DFS or OS was observed between groups in the validation cohort, but a significant difference was observed in the training cohort. It should be noted that this validation dataset, upon which the final analysis was performed, only included 30 patients and only had follow-up data up to 3 years; however, 3 years should be sufficient as recurrence is usually identified in this population in this time frame.[5,6] Moreover, when Breslow thickness and ulceration were incorporated into the definition of high and low risk, along with the two-gene signature, a significant difference was found in both DFS and OS. In summary, for those patients in the SMT with positive SLNs, the gene signature was superior to the AJCC TNM staging system for predicting DFS and OS. However, the most superior model for individual prognostication included both the gene signature and the clinicopathologic features of Breslow thickness and ulceration.

The value of the gene signature is rooted in our continued need for individual prognostication. The AJCC TNM staging currently offers prognostic information by stage group based on data from a large number of patients,[7]

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K. Y. Bilimoria, MD, MS
e-mail: kbilimoria@nm.org

but, even within stage groups, there is heterogeneity in outcomes.[1] Given this range of outcomes in stage III melanoma, the AJCC staging system does little to predict an individual patient's risk of recurrence and survival. This is especially important in the current setting of evolving systemic therapies for melanoma. The optimal adjuvant therapy for these patients has yet to be defined, but we undoubtedly need better prognostic tools to determine when to employ certain adjuvant therapies. The two therapies approved for use in this country carry significant toxicities and, to date, show benefit in only one prospective, phase III, randomized trial each.[8,9] Thus, there is a great deal of activity in the study of alternative adjuvant therapies, including trials to define the groups that benefit most from current therapies (e.g., EORTC trial 18081), trials examining checkpoint inhibitors that block the PD-1 pathway (e.g., Checkmate 238), and trials evaluating molecularly targeted therapies (e.g. COMBI-AD).[9] We also need to better group patients into similar prognostic categories in clinical trials so we can best interpret the trial findings. Once we move closer to defining the preferred adjuvant therapy or combination of therapies, it will still be necessary to define the population that benefits most from this therapy in order to guide management for individual patients.

The study by Dr. McMaster's group is a step toward defining high- and low-risk patients more precisely than our current standard. To date, therapeutic options are partly based on clinical and pathologic data encompassed in the AJCC TNM staging system. However, staging systems do not allow for accurate individual prognostication, or sufficient discrimination between stage groups, to guide treatment decisions. Gene expression profiles (GEP) are used in other solid tumors (uveal melanoma, soft tissue sarcoma, breast cancer, glioblastoma, and mesothelioma) and, most recently, a GEP for cutaneous melanoma, DecisionDx-Melanoma™ has been introduced.[10–14] The 31-gene DecisionDX GEP seeks to define high- and low-risk patients with node-negative melanoma. The tissue for this assay can be from any melanoma tissue (primary, nodal, or metastatic disease). Based on the results of the assay, patients are divided into two groups, with the survival of these two groups differing considerably. The test applies to all stages but, thus far, no published stage-specific prognostic data are available.[11]

There are notable limitations of Dr. Hao's study. First, the SLN gene signature was developed based on tissues procured at the time of sentinel node biopsy. Thus, a patient must undergo SLN staging in order for these data to be accurately used. This is appropriate for the intended population of the test (stage III) but it does limit the generalizability of this gene signature. Second, the sample size of the validation dataset included only 30 patients. While this sample size was sufficient to show a significant difference in DFS, the relatively limited number of subjects may explain why the AJCC staging system underperformed in predicting DFS and OS in Dr. Hao's study. Others have previously been able to show the prognostic accuracy of the AJCC system.[4,7]

Currently, National Comprehensive Cancer Network (NCCN) guidelines do not endorse use of DecisionDx-Melanoma™ outside of a clinical trial, but these gene assays clearly hold promise for guiding our treatment decisions. Ideally, additional work should evaluate the application of DecisionDx-Melanoma™ to the primary tumors in stage III patients, and compare the prognostic value of both the SLN gene signature and the primary tumor DecisionDx-Melanoma™ GEP. These tests can be compared as individual predictors, but also that data may be combined together into a potentially stronger model. Once the utility of the assays is better defined, the next steps involve prospective trials of adjuvant therapy utilizing these gene assays to stratify treatment groups. This additional work would serve to validate the assays as clinically useful prognostic tools. In the meantime, without a prospective trial incorporating these tools as a guide to select patients for adjuvant therapy, that decision will still have to be based on individual discussions between oncologists and their patients. However, defining an optimal gene assay test is an important step toward the goal of personalized adjuvant therapy in stage III melanoma.

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