

Impact of Gene Expression Profiling on Decision-Making in Clinically Node Negative Melanoma Patients after Surgical Staging

Darryl Schuitevoerder MBBS,[a] Michael Heath MS,[c] Robert W. Cook PhD,[e] Kyle R. Covington PhD,[e] Jeanine Fortino HIMA,[b] Sancy Leachman MD PhD,[d] and John T. Vetto MD FACS[a,b]

[a]Department of Surgery, Oregon Health & Science University, Portland, OR;
[b]Division of Surgical Oncology, Oregon Health & Science University, Portland, OR;
[c]School of Medicine, Oregon Health & Science University, Portland, OR;
[d]Department of Dermatology, Oregon Health & Science University, Portland, OR;
[e]Castle Biosciences Inc., Friendswood, TX

ABSTRACT

Introduction: The surgeon's role in the follow-up of pathologic stage I and II melanoma patients has traditionally been minimal. Melanoma genetic expression profile (GEP) testing provides binary risk assessment (Class 1-low risk, Class 2-high risk), which can assist in predicting metastasis and formulating appropriate follow up. We sought to determine the impact of GEP results on the management of clinically node negative cutaneous melanoma patients staged with sentinel lymph node biopsy (SLNB).

Methods: A retrospective review of prospectively gathered data consisting of patients seen from September 2015 - August 2016 was performed to determine whether GEP class influenced follow-up recommendations. Patients were stratified into four groups based on recommended follow-up plan: Dermatology alone, Surgical Oncology, Surgical Oncology with recommendation for adjuvant clinical trial, or Medical and Surgical Oncology.

Results: Of ninety-one patients, 38 were pathologically stage I, 42 stage II, 10 stage III, and 1 stage IV. Combining all stages, GEP Class 1 patients were more likely to be followed by Dermatology alone and less like to be followed by Surgical Oncology with recommendation for adjuvant trial compared to Class 2 patients ($P< 0.001$). Among stage 1 patients, Class 1 were more likely to follow up with Dermatology alone compared to Class 2 patients (82 vs. 0%; $P< 0.001$). Among stage II patients, GEP Class 1 were more likely to follow up with Dermatology alone (21 vs 0%) and more Class 2 patients followed up with surgery and recommendations for adjuvant trial (36 vs 64%; $P<0.05$). There was no difference in follow up for stage III patients based on the GEP results ($P=0.76$).

Conclusion: GEP results were significantly associated with the management of stage I-II melanoma patients after staging with SLNB. For node negative patients, Class 2 results led to more aggressive follow up and management.

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INTRODUCTION

The incidence of cutaneous melanoma in the U.S. continues to increase, rising from 1 in 250 persons in 1980 to 1 in 53 in 2010.[1] The American Cancer Society reports 87,110 new cases and 9,730 deaths are predicted in the U.S. for 2017.[2] The majority of patients with melanoma are diagnosed with localized disease (stage I or II) for which surgical management can be curative.[3] However, outcomes and survival of early stage disease are highly variable, with 5-year survival rates for stage I and stage II disease ranging from 92-97% and 53-81% respectively.[2] Furthermore, it is recognized that the majority of patients who die from melanoma are initially diagnosed with sentinel lymph node (SLN) negative disease.[4,5,6] Reasons for this discrepancy include false negative rates associated with SLN biopsy (SLNB), the high numbers of SLN-negative patients, benefits of therapy for SLN-positive patients, and the metastasis of tumor cells through hematogenous rather than lymphatic routes (non-Halstedian model).[7]

Molecular gene expression profiling (GEP) for risk assessment has become standard of care for patients with breast cancer, prostate cancer, and ocular melanoma.[8-10] For cutaneous melanoma, a 23-gene GEP test that classifies melanocytic lesions as benign or malignant has been developed to enhance diagnostic accuracy.[11] Additionally, a prognostic 31-gene GEP test that classifies patients as low risk (Class 1) or high risk (Class 2) for developing metastasis has been reported and independently validated.[12,13] The test accurately identifies over 70% of patients who developed distant metastasis or died from their disease as Class 2, has a negative predictive value of 94% and a positive predictive value of 67% among stage I-II patients, and has been shown

to enhance staging by identifying SLN-negative patients who are more likely to develop metastatic disease.[12,13]

NCCN guidelines currently do not recommend laboratory testing, frequent exams, or imaging for stage IA-IIA disease.[14] With highly variable outcomes and a potentially fatal natural course of disease, management of clinically early stage melanoma patients requires integration of all available clinical and pathologic variables to optimize the evaluation of an individual's recurrence and metastatic risk potential[14]. Molecular tools offer the opportunity to complement current methods for risk assessment. At our institution, starting in mid-2015, the 31-gene GEP test was added to our clinical work-up for newly referred stage I-III patients, but no specific changes were suggested or implemented with respect to follow-up recommendation. The purpose of this study was to determine whether there was a difference in the management of patients with GEP Class 1 or Class 2 tumors, and thus report on any association between GEP testing and clinical decision-making for melanoma patients that have undergone SLNB.

MATERIALS AND METHODS

Patient Treatment and Data Collection

Clinical data were prospectively collected as part of a university-based multidisciplinary melanoma program in accordance with the Oregon Health & Science University (OHSU) institutional review board (IRB) policies; the collection and study of this data was approved by the OHSU IRB (#00001108). All patients included in this study were surgically staged by SLNB as indicated by current NCCN guidelines.[14] Primary melanomas from all patients were assayed by DecisionDx-Melanoma (Castle Biosciences Inc. Friendswood, TX), a 31-gene melanoma GEP test. Patients were excluded from analysis if they had GEP testing without surgical staging. Our method of SLNB has previously been described and has not appreciably changed since that time.[15]

Data Storage and Analysis

Data was entered and stored on REDCap (Research Data Analysis and Capture, Nashville, TN). In order to compare Class 1 and Class 2 gene signatures, cases were assigned to one of four groups based on the method of planned follow-up (all methods included Dermatology follow-up): 1) Dermatology alone; 2) Surgical Oncology; 3) Surgical Oncology plus recommendation for adjuvant trial; or 4) Medical Oncology and Surgical Oncology. Chi-square and Fisher's exact tests were performed for group comparisons.

RESULTS

Clinical Characteristics

GEP testing was performed for 118 cutaneous melanoma patients with clinically node negative disease. Of those, 90 also had SLNB performed as standard of care. Within the group that had GEP testing and SLNB, 52 (58%) had a Class 1 result and 38 (42%) had a Class 2 result. The majority of cases were pathologically stage I or stage II. Not surprisingly, of patients with stage I disease, 87% (33 of 38) were Class 1 compared to 13% (5 of 38) that were Class 2. Within stage II patients, 33% (14 of 42) were identified as Class 1 compared to 66% (28 of 42) that had a Class 2 result. The ten stage III cases included in the study were evenly divided between Class 1 and Class 2 results (Figure 1).

FIGURE 1. Number of Class 1 and Class 2 cases according to clinical stage.

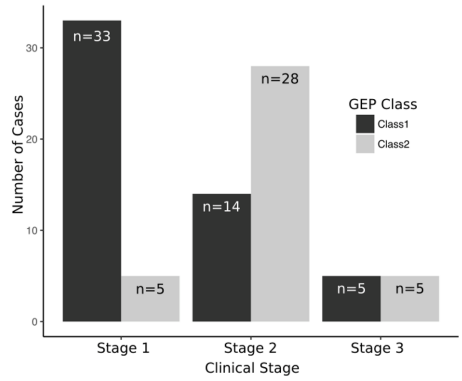
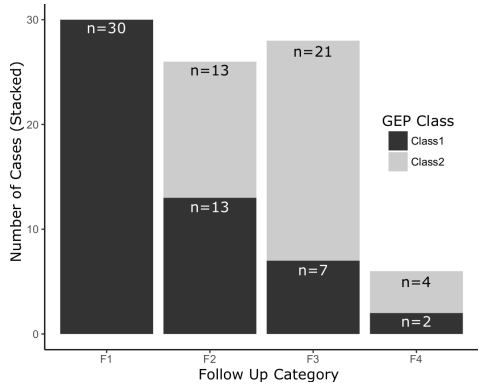


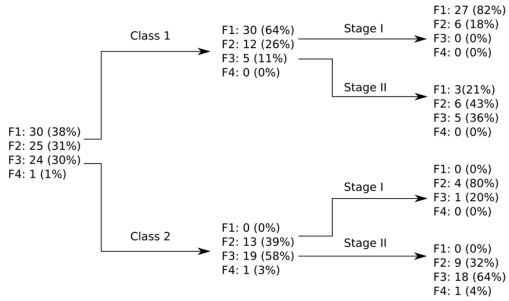
FIGURE 2. Counts of cases by GEP result and follow-up group. Follow-up plans included Dermatology alone (F1), Surgical Oncology + Dermatology (F2), Surgical Oncology plus recommendation for adjuvant therapy (F3), or Surgical Oncology and Medical oncology (F4).



GEP Distribution Within Clinical Follow-up Groups

For stage I patients, GEP Class 1 were more likely to follow up with Dermatology alone compared to GEP Class 2 patients (82 vs. 0%), while Class 2 were more likely to follow up with Surgical Oncology +/- recommendation for adjuvant trial (18 vs 100%; $P<0.001$;). For stage II patients, more GEP Class 1 were followed by Dermatology alone (21% vs. 0%) and more GEP Class 2 patients were followed up with surgery + recommendation for adjuvant trial (64% vs 36%; $P<0.05$).

FIGURE 3. Diagram of the decision tree model derived from analysis of treatment and clinical data. GEP class accounted for 52% of the variable importance and stage accounted for 48% of the variable importance. Follow-up plans included Dermatology alone (F1), Surgical Oncology (F2), Surgical Oncology plus adjuvant therapy (F3), or Surgical Oncology and Medical Oncology (F4).



Among all stages no GEP Class 2 patients were followed by Dermatology alone. Instead, all Class 2 cases were followed by Surgical Oncology with or without recommendation for adjuvant trial or concurrent Medical Oncology follow up. The majority of GEP Class 2 cases (55%) were followed by Surgical Oncology with recommendation for adjuvant therapy. Overall, clinical follow-up recommendations for Class 1 were significantly different from Class 2 (P<0.001), with GEP Class 2 cases receiving a higher level of follow-up (Figure 2).

Statistical Impact of GEP on Clinical Management Decisions

We applied a tree-based prediction model to the data in order to mathematically examine the care decisions that were made. A model that included GEP class and clinical stage (evaluated as a binary stage I/IIA versus stage IIB/IIC, and excluding stage III cases) indicated that the GEP class accounted for 52% of the decision to manage patients according to one of the four follow-up modalities (Figure 3). To evaluate the impact of the GEP test in comparison to independent clinical factors used to determine clinical stage, a model was built that incorporated T-stage, ulceration, and GEP class. In that model, T-stage accounted for 43% of the decision on follow-up care, GEP for 42%, and ulceration for 15% (data not shown).

DISCUSSION

The outcomes and survival of early stage melanoma are highly variable, with 5-year survival rates for stage I and stage II disease ranging from 92-97% and 53-81%, respectively.[2] Recent successes with immunotherapy, particularly in patients with lower disease burden, highlight the importance of early identification of recurrence.[16,17] However, it is neither necessary nor feasible to aggressively image and treat patients with low risk of recurrent disease. In order to help risk stratify patients, our Surgical Oncology group now routinely orders GEP testing for all clinically stage I and II patients. On review of one year of patient data, as outlined in this study, we saw a significant difference in the management and follow up patterns between GEP low vs. high-risk patients. Similarly, Berger et al recently published their experience on the clinical impact of GEP testing in melanoma in a before-and-after study, and found that after GEP results their patient management changed in 53% of cases.[18] While the nature of our study did not permit direct documentation of change in management plans before and after GEP testing, it is clear that both stage I and II patients with a GEP Class 2 result had more aggressive follow up and management. While more aggressive follow up with CT imaging has been shown to increase recurrence detection rates,[19-20] it remains to be seen whether this impacts patient outcomes.

The greatest difference we saw in the follow up and management of patients was that the majority of GEP Class 2 patients were followed by Surgical Oncology and Dermatology or in combination with recommendations for adjuvant trial or consultation by Medical Oncology (100%), while the majority of Class 1 patients were followed by Dermatology alone (58%; P<0.001). This difference was most pronounced in stage I patients, with 82% of GEP Class 1 following up with Dermatology alone and 100% of Class 2 patients being followed by surgical oncology with or without recommendation for adjuvant trial. In the original validation of this specific GEP test, the negative predictive value (NPV) for Stage I and II patients was 94%.[13] Thus, with such a robust NPV, a low risk GEP result coupled with low risk disease and negative SLNB allow for the vast majority of patients in the population to safely follow up with Dermatology alone.

Quantitative evaluation of management changes was performed by implementing tree-based prediction models. Models were built using stage I and II cases because of the initial implementation of GEP testing at OHSU for these stage groups, and because of the small stage III sample size. Each model that was evaluated showed that the management decisions implemented during the study included consideration of the GEP results in combination with either American Joint Committee on Cancer (AJCC) stage, or with the individual clinical factors (tumor thickness and ulceration) used to determine clinical stage. Although the study is limited in its assessment of overall survival outcomes, there is a clear and quantitative impact of the test on management strategies for early stage patients. Future studies will aim to correlate survival with changes in management for patients with stage I, II and III tumors.

National Comprehensive Cancer Network (NCCN) guidelines do not recommend laboratory testing, frequent follow-up examination, or imaging for stage I-IIA melanomas.[14] However, outcomes and survival of patients with early-stage disease are highly variable, and the majority (approximately two-thirds) of patients who die from melanoma are initially diagnosed with early-stage disease.[6] Recent studies reporting the value of

imaging for detection of distant metastatic disease, and successes due to treatment with contemporary immunotherapy, particularly in patients with lower disease burden, highlight the utility and importance of accurate risk assessment and early identification of recurrence.[16,17,19,20] To better estimate risk in our patient population, we continue to include GEP testing of melanoma patients in the clinical algorithms of our university melanoma program, and the results of this study indicate that the test has played a significant role in guiding management and surveillance of patients with node-negative disease. Moving forward, our institution is now enrolling all early stage melanoma patients into an industry-sponsored prospective clinical use trial, and partnering with cooperative oncology groups to design adjuvant trials for node negative patients that include stratification by GEP class.

CONCLUSION

Our study shows that within our multidisciplinary program the follow-up and management patterns of patients with low and high-risk GEP results differed significantly. The molecular biomarkers provided by GEP in patients staged with traditional methods were significantly associated with follow-up and surveillance plans. In the future, continued advances in adjuvant melanoma therapies are expected. Thus, better risk assessment of earlier stage patients could allow for both the appropriate allocation of follow-up resources and the determination of which patients should be considered for adjuvant interventions.

DISCLOSURES

RWC and KRC are employed by Castle Biosciences, Inc. JTV and SL serve as consultants to Castle Biosciences, Inc. All remaining authors report no conflicts of interest in this work. DS, JTV, SL, JF, and MH had primary responsibility for all data and complete control of the final version of this manuscript.

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AUTHOR CORRESPONDENCE

John T. Vetto MD FACS
E-mail:..... vettoj@ohsu.edu