

Impact of Gene Expression Profile Testing on the Management of Squamous Cell Carcinoma by Dermatologists

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ABSTRACT

Background: The incidence of cutaneous squamous cell carcinoma (cSCC) is increasing likely due to improved detection and a growing elderly population. Although the prognosis of cSCC is excellent with complete surgical excision, many patients who go on to develop metastasis are initially classified as low-risk. The most commonly used staging systems, American Joint Committee on Cancer (AJCC) and Brigham Women's Hospital (BWH), have low sensitivity and low positive predictive value for predicting metastasis. A gene expression profile test (cSCC-GEP) is in development to identify patients with cSCC at high risk for metastasis and death.

Objective: To determine the impact of cSCC-GEP test results on management decisions made by dermatologists for cSCC patients.

Design, Setting, and Participants: 402 dermatologists attending a national dermatology conference completed an online survey designed to determine the impact of cSCC-GEP test results on management decisions in a variety of clinical situations. Participants answered a series of questions related to three cSCC patient vignettes, each featuring different patient and lesion characteristics.

Main Outcomes and Measures: Proportion of dermatologists who would recommend radiation, chemotherapy/immunotherapy, or sentinel lymph node biopsy (SLNBx) for each patient vignette (without cSCC-GEP results, with a lower risk result, or with a higher risk result). The effect of the test results on the follow-up intervals recommended by dermatologists was also examined.

Results: In the majority of vignettes, a lower risk cSCC-GEP test result led to a statistically significant decrease in the proportion of dermatologists who would recommend radiation, chemotherapy/immunotherapy, SLNBx, or quarterly follow-up. Conversely, a higher risk cSCC-GEP result significantly altered management toward increased intensity (more recommendations for radiation, chemotherapy/immunotherapy, SLNBx, or quarterly follow-up) in all vignettes.

Conclusions and Relevance: The results of a cSCC-GEP test appear to significantly impact decisions made by dermatologists regarding subsequent management, SLNBx, and follow-up intervals for patients with cSCC.

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BACKGROUND

Nonmelanoma skin cancer (NMSC) is the most common malignancy in the United States. It is estimated that cutaneous squamous cell carcinoma (cSCC) represents 20% of NMSC cases with an approximate annual incidence of over 700,000, which is increasing yearly.[1,2] While the exact incidence of cSCC is not included in national cancer registries, a recent study showed an increase of 263% in the incidence of cSCC between 2000-2010 compared to 1976-1984.[3] This increasing incidence is likely due to both improved detection and the growing elderly population.[4] Although the prognosis of cSCC is generally excellent with complete surgical excision, a recent study showed that roughly 4% of cases develop nodal metastases and 1.5% die from this disease.[2]

To more accurately identify cSCC's at high risk for metastasis or death, there are two main staging systems, American Joint Committee on Cancer (AJCC) and Brigham Women's Hospital (BWH). However these staging systems have low sensitivity (23-46%) and low positive predictive value (12-13%).[5-8] Many patients who develop metastasis are initially classified as low-risk, and conversely, some patients who are classified as high-risk do not go on to develop metastatic disease. Thus, accurate identification of high risk cSCC patients is critical. Additionally, the definitive work-up and treatment indicated for high-risk cSCC remains unknown.[9] Given the recent FDA-approval of Cemiplimab[10] for the treatment of advanced cSCC and its significant side effect profile, it is particularly important that the appropriate patients are selected for this therapy.

A gene expression profile (GEP) test is currently under development (Castle Biosciences Inc., Friendswood, TX). The goal of the 40-gene test is to improve upon current staging systems and identify patients with cSCC at high risk for metastasis and death. Previous analyses have identified 73 genes as associated with cSCC recurrence and metastasis.[8] A recent study performed microarray analysis of 80 cSCC lesions to further identify novel genes differentially expressed in high-risk cSCC's.[11] Based on the patient's expression of these genes, machine learning can

TABLE 1.

Clinical Characteristics of Patient Vignettes							
Vignette	Gender, Age	Location	Lesion Size	Invasion on Imaging	Perineural Invasion	Margins	Other Medical History
1	Male, 70	Upper Arm	3 cm x 4 cm	None	None	Clear	None
2	Male, 64	Scalp	4 cm x 4 cm	None	None	Unclear	None
3	Female, 35	Thigh	1.5 cm x 2.2 cm	None	None	Clear	CLL

Abbreviations: Cm centimeter, CLL chronic lymphocytic leukemia.

be applied to gene expression data in order to predict cSCC outcomes and predict high-risk patients. A cSCC gene expression profile test (cSCC-GEP) has been validated on residual tumor from primary cSCC biopsies and can classify lesions as either Class 1 (low risk) or Class 2 (high risk). The goal of this study was to determine the impact of this genomic technology on the clinical management of cSCC patients.

METHODS

Dermatologists who attended a national Dermatology conference completed an online survey with three cSCC patient vignettes. Each vignette presented an image and described patient characteristics such as age, gender, and anatomic location of lesion, as well as lesion characteristics (e.g. tumor size, margin of resection, invasion of bone, and perineural invasion). (Table 1) Respondents answered a series of questions using pre and post-test methodology to evaluate the effect of Class 1 (low risk) and Class 2 (high risk) cSCC-GEP test results on management (adjuvant radiation therapy, chemotherapy/immunotherapy, referral for SLNBx, and recommended length of follow-up interval [q3 months, q6 months, and q12 months]).

The primary outcomes were the proportion of respondents who would alter their decision to perform a SLNBx or recommend adjuvant radiation therapy and/or chemotherapy/immunotherapy with the addition of cSCC-GEP test results, as well as the proportion who would alter their recommended follow-up interval. McNemar's test was performed for assessing categorical variables, and the Wilcoxon signed-rank test was performed for assessing ordinal variables. Clinical recommendations for Class 1 and Class 2 cSCC-GEP test results were compared to baseline (without cSCC-GEP test result).

RESULTS

Respondent and Patient Vignette Characteristics

Overall, 435 dermatologists participated in the survey with a completion rate of 92.4% (N=402). Of the respondents, 33% reported being in practice for 11-20 years followed by 28% for 1-10 years and 20% for 21-30 years. (Table 2) Over 50% of dermatologists reported seeing an average of 1-5 high-risk cSCC patients per year and almost 25% of dermatologists reported seeing greater than 10 high-risk cSCC patients per year. The majority of respondents (>60%) reported using the AJCC system to stage cSCC, however over 35% of dermatologists reported not using a staging system at all.

Impact of cSCC-GEP Test Results on Decision to Recommend Adjuvant Radiation Therapy

A Class 1 cSCC-GEP test result led to a statistically significant decrease in recommended adjuvant radiation therapy by dermatologists in all vignettes. (Table 3) For all vignettes with a Class 2 cSCC-GEP test result, there was a statistically significant increase in adjuvant radiation therapy recommendations.

Impact of cSCC-GEP Test Results on Decision to Recommend Adjuvant Chemotherapy or Immunotherapy

A Class 1 cSCC-GEP test result led to a statistically significant decrease in recommended adjuvant chemotherapy or immu-

TABLE 2.

Sample Characteristics (N=402)		
		%
Years in Practice	Resident/Fellow	3.0
	1-10 Years	27.9
	11-20 Years	32.8
	21-30 Years	20.1
	30+ Years	16.2
High Risk SCC Patients Encountered	0	4.2
	1-5	55.2
	6-9	18.2
	>10	22.4
SCC Staging System Used	AJCC	60.2
	BWH	7.2
	UICC	0.2
	I am not aware/ do not use these systems.	36.6
Mohs Surgeon	Yes	18.9
	No	81.1

Abbreviations: SCC = squamous cell carcinoma. AJCC = American Joint Committee on Cancer. BWH = Brigham Women's Hospital. UICC = Union for International Cancer Control.

TABLE 3.

Impact of cSCC-GEP Results on the Decisions of 402 Dermatologists to Order Adjunctive Tests for Three Hypothetical Patients With Cutaneous Squamous Cell Carcinoma

	Squamous Cell Carcinoma Vignette					
	70yo Male, Upper Arm, 3cm x 4cm, No Invasion, Mar-gins: Clear, No Hx		64yo Male, Scalp, 4cm x 4cm, No In-vasion, Margins: Unclear, No Hx		35yo Female, Thigh, 1.5cm x 2.2cm, No Invasion, Margins: Clear, Hx of CLL	
Recommend Radiation	%	*P*-value[a]	%	*P*-value[a]	%	*P*-value[a]
No GEP	6.0	-	90.3	-	14.4	-
Class 1 GEP	3.2	0.027	64.7	<0.001	8.2	<0.001
Class 2 GEP	72.4	<0.001	96.3	<0.001	75.4	<0.001
Recommend Chemotherapy/ Immunotherapy	%	*P*-value[a]	%	*P*-value[a]	%	*P*-value[a]
No GEP	6.2	-	45.0	-	9.2	-
Class 1 GEP	6.0	1.000	18.4	<0.001	6.0	0.007
Class 2 GEP	43.0	<0.001	73.9	<0.001	46.8	<0.001
Recommend SLNBx	%	*P*-value[a]	%	*P*-value[a]	%	*P*-value[a]
No GEP	4.2	-	55.0	-	10.0	-
Class 1 GEP	2.2	0.057	21.4	<0.001	3.7	0.021
Class 2 GEP	51.7	<0.001	81.3	<0.001	60.2	<0.001

[a]McNemar's test. Yo = years old. Hx = history. GEP = gene expression profiling. SLBNx = sentinel lymph node biopsy. CLL = chronic lymphocytic leukemia.

notherapy by dermatologists in 2 of 3 vignettes. (Table 3) For all vignettes with a Class 2 cSCC-GEP test result, there was a statistically significant increase in adjuvant chemotherapy or immunotherapy recommendations.

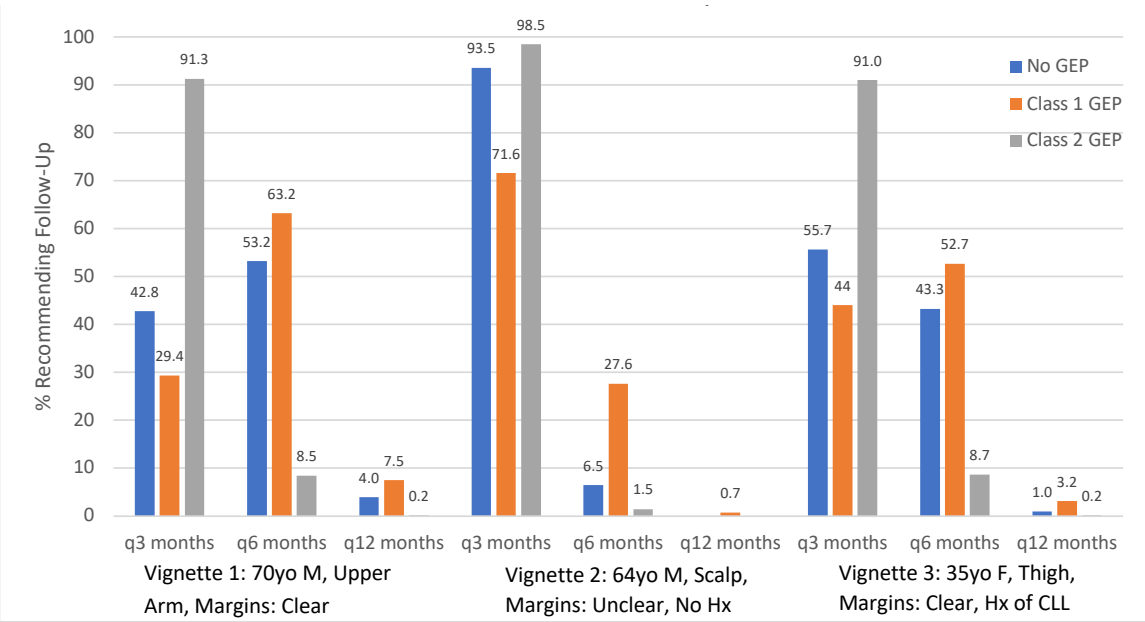
Impact of cSCC-GEP Test Results on Decision to Refer for SLNBx

A Class 1 cSCC-GEP test result led to a statistically significant decrease in the proportion of SLNBx recommended by dermatologists in 2 of 3 vignettes. (Table 3) For all vignettes with a Class 2 cSCC-GEP test result, there was a statistically significant increase in SLNBx recommendations.

Impact of cSCC-GEP Test Results on Recommended Follow-up Interval

A Class 1 cSCC-GEP result led to a statistically significant increase in the number of respondents who would recommend

FIGURE 1. Effect of cSCC-GEP test results on dermatologist recommendation for follow-up interval.*



*Analysis performed via Wilcoxon signed-rank test found statistically significant changes in follow-up interval for all cases when comparing no GEP result to Class 1 or Class 2 GEP result (p<0.0001).
Abbreviations: cSCC-GEP = cutaneous squamous cell carcinoma gene expression profile. GEP = gene expression profile. Yo = years old. M = male. F = female. CLL = chronic lymphocytic leukemia.

a longer follow-up interval for all vignettes. (Figure 1) Similarly, a Class 2 cSCC-GEP result was associated with a statistically significant increase in the proportion who would recommend shorter follow-up interval for all vignettes.

DISCUSSION

The results of this study indicate that additional information provided by GEP can improve management for cSCC patients. In most situations, a lower risk cSCC-GEP result was associated with a significant reduction in recommendations for SLNBx, adjuvant radiation therapy and chemotherapy/immunotherapy, as well as a tendency to lengthen the recommended follow-up interval. Conversely, a higher risk result was associated with a significant increase in recommendations for SLNBx, adjuvant radiation therapy and chemotherapy/immunotherapy, as well as a shorter follow-up interval in most cases. As these patients are at a higher risk for development of subsequent metastases and/or local recurrence, they would likely benefit from close monitoring. For these reasons, the results from this study suggest that cSCC-GEP test results could lead to decreased morbidity and mortality.

In the field of melanoma, GEP tests are currently being utilized to identify high-risk patients and determine their need to receive adjuvant radiation, chemotherapy, and other forms of therapy.[12] These tests are impacting physician management decisions for melanoma patients. The present study shows that GEP testing has the potential to improve clinical decision-making for cSCC cases as well.

More than one third of participants stated they did not use any system to stage their cSCC patients. This represents a clear knowledge gap and opportunity to improve clinical practice. The cSCC-GEP test may act as an additional piece of information, that in combination with a traditional staging system such as AJCC, could better optimize patient outcomes. A previous study of GEP in melanoma showed that adding GEP results to AJCC staging had an additive positive effect on prognostic accuracy.[13] Future studies are warranted to determine if the cSCC-GEP test can have a similar impact.

A new immune therapy, Cemiplimab (PD-1 inhibitor), has been FDA-approved and shown to be efficacious for management of metastatic and locally advanced cSCC.[10] Current staging systems are mainly histologic in nature, and genomic testing may more effectively identify high risk cases that would benefit from treatment with Cemiplimab. cSCC-GEP testing can aid in targeting this expensive therapy to high risk patients, while minimizing adverse effects for patients with lower risk disease who may not benefit from the drug.

Limitations to this study include the possibility that the clinical vignettes used are not complete representations of real-world patient cases. Moreover, this study used a cross sectional design and therefore, the results cannot be used to make inferences about causation. Additionally, the sample of dermatologists attending the national conference may not accurately represent the larger population of dermatologists practicing across the United States.

CONCLUSIONS

The results of this study suggest that the information provided by the cSCC-GEP test can significantly impact dermatologist management recommendations, including the decision to perform a SLNBx and recommendations for adjuvant radiation therapy and chemotherapy/immunotherapy, while remaining within the context of established guidelines. Further, study physicians utilized the information from cSCC-GEP to alter management in the risk appropriate direction. This indicates significant theoretical clinical utility and suggests that the improved prognostic information provided could potentially lead to more efficient resource allocation and targeted treatment for cSCC patients.

DISCLOSURE

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