Integrating the 40-Gene Expression Profile (40-GEP) Test into Management of High-Risk Cutaneous Squamous Cell Carcinoma

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SYNOPSIS

- Cutaneous squamous cell carcinoma (cSCC) is the 2nd most common skin cancer, with **~1,000,000** cases diagnosed per year in the U.S.[1-8] **Incidence is growing** rapidly (>5-fold increase in past 30 years) and it surpasses the incidence of invasive melanoma.
- Regional metastasis rates of 13% have been reported, with most studies reporting ≤6% and most events occurring within 2-3 years of initial diagnosis and treatment.[6] Disease-specific mortality is 1.5-2% and the number of **deaths from cSCC per year is similar to that from melanoma**.[3,7]
- National Comprehensive Cancer Network (NCCN) guidelines accommodate a broad range of treatment plan options for high-risk patients and recommend risk-directed implementation**.** These guidelines and the American Joint Committee on Cancer (AJCC) and Brigham and Women's Hospital (BWH) **staging systems have low positive predictive value (PPV) for identifying patients at high risk for metastasis** (NCCN 15%[9]; AJCC 14-17%[10-11]; BWH 24-38%[11-13]).
- **Improved stratification for implementation of risk-appropriate treatment plans for patients with NCCN-defined high-risk cSCC is needed.**
- Integration of the recently validated 40-gene expression profile (40-GEP) test with AJCC or BWH T stage criteria into management of NCCN high-risk cSCC patients may be key to identifying those high-risk patients who would most benefit from aggressive treatment strategies, while concomitantly reducing unnecessary interventions for those who are low risk for poor outcomes.

OBJECTIVE:

To integrate a validated, prognostic 40-gene expression profile test into clinical decision making for risk-appropriate management of NCCN high-risk cSCC patients

METHODS

- The 40-gene expression profile (40-GEP) test was developed and validated to stratify a patient's risk for regional or distant metastasis at 3 years after diagnosis as low (Class 1), high (Class 2A), or highest (Class 2B) risk for metastasis (Figures 1 and 2).[9]
- As NCCN high-risk cSCC patients are the intended population for the 40-GEP test, cases categorized as such (n=300, Table 1) were used to analyze the effects of integration of 40-GEP risk stratification into patient management decision making. All cases were staged according to either AJCC or BWH staging system criteria for T stage. The numbers of patients in each Class/T stage combination along with metastasis rates were reported and used to align each patient group with risk-appropriate management recommendations.
- Risk-aligned management recommendations based on 40-GEP results and T stage were developed for low, moderate, and high intensity management within the boundaries of acceptable NCCN patient management approaches for patients with high-risk localized disease. Metastasis rates of <10%, 10-50%, and >50% were aligned with low, moderate, and high intensity management recommendations, respectively.

Figure 1. Study design of the 40-GEP discovery, development, and validation

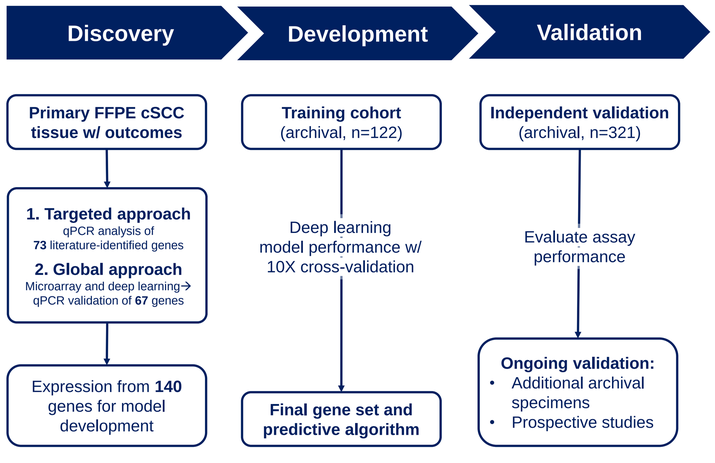
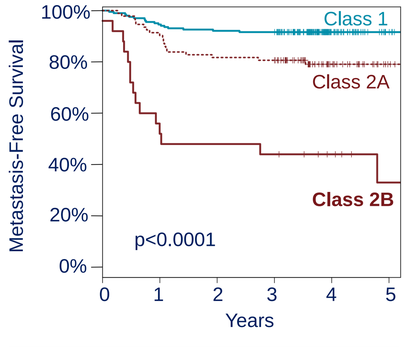


Figure 2. Kaplan-Meier analysis of metastasis-free survival (MFS) by 40-GEP Class (n=321)[9]



40-GEP Class	n	3-year MFS	Overall Event Rate
Class 1	203	91.6%	8.9%
Class 2A	93	80.6%	20.4%
Class 2B	25	44.0%	60.0%

RESULTS

Table 1. Cohort demographics of 300 NCCN high-risk cSCC cases

Feature of Modeling Cohort (% of Cohort)	
Age: Median years (range)	70 (34-95)
Sex: Male	219 (73%)
Immune deficient	76 (25%)
Located on H&N	201 (67%)
Tumor diameter* : mean cm (≥2 cm)	1.85 (36%)
Tumor thickness**: mean mm (>6 mm)	3.90 (16%)
Poorly differentiated	36 (12%)
Clark Level IV / V	62 (21%)
PNI present	36 (12%)
Subcutaneous fat invasion	43 (14%)
40-GEP Result	
Class 1	189 (63%)
Class 2A	87 (29%)
Class 2B	24 (8%)

*275 cases had tumor diameter reported;**109 cases had thickness reported. NCCN, National Comprehensive Cancer Network; H&N, head and neck; PNI, perineural invasion; GEP, gene expression profile

Figure 3. Integration of 40-GEP prognostication into patient management decisions for NCCN high-risk cSCC patients (n=300)

A. Cohort stratification and metastasis rate by 40-GEP Class and T Stage

		AJCC T Stage*		BWH T Stage*	
40-GEP Class	Overall Rate*	T1-T2	T3-T4	T1-T2a	T2b-T3
Class 1	9% (189)	7.5% (159)	16.7% (30)	8.1% (173)	18.8% (16)
Class 2A	21% (87)	15.6% (64)	34.8% (23)	17.8% (73)	35.7% (14)
Class 2B	63% (24)	50.0% (16)	87.5% (8)	58.8% (17)	71.4% (7)

*Metastasis incidence and number (n) of patients in each Class and per T stage.

B. Management intensity determined by risk for metastasis

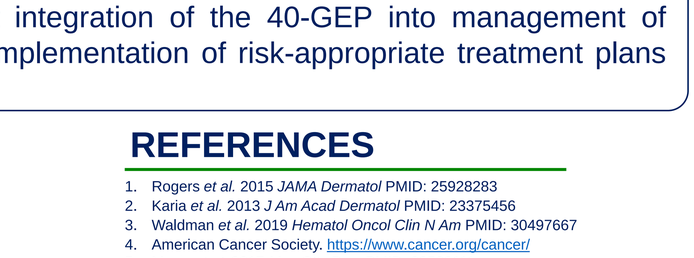


Figure 4. Risk-aligned management recommendations based on 40-GEP and T stage prognosis

*Patients having a single NCCN high-risk feature (e.g., immunodeficiency, ≥2 cm tumor diameter, tumor of the mask area or genitals, or poor tumor differentiation) are deemed high risk by NCCN.
**Risk for metastasis is reported for 40-GEP Class and AJCC 8th Edition T stage.

CONCLUSIONS

- Integration of the 40-GEP test into risk-directed management plans for NCCN high-risk cSCC patients identified a group of patients (Class 1, T1/T2) with risk approaching that of the general population, thereby warranting a low intensity management strategy and sparing these patients unnecessary procedures and potential adverse effects.
- Conversely, those patients with rates of metastasis surpassing 50% (Class 2B) warrant a high intensity strategy that increases follow-up visits, utilizes imaging and/or biopsies for nodal assessment, and offers adjuvant treatments and clinical trials for probable metastatic events.
- The data presented herein support integration of the 40-GEP into management of NCCN high-risk cSCC patients for implementation of risk-appropriate treatment plans for these patients.

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