Metastasis-free survival prediction with the 40-gene expression profile test in patients with cutaneous squamous cell carcinoma risk stratified according to the National Comprehensive Cancer Network Guidelines®

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Introduction

- Despite definitive surgical treatment, a subset of cutaneous squamous cell carcinomas (**cSCC**) has an increased risk of regional/distant metastasis making it challenging to identify patients most at risk.[1] The 40-gene expression profile (**40-GEP**) prognostic test improves risk stratification for patients with cSCC with known clinical or histologic risk factors, stratifying patients' risk of metastasis as low (**Class 1**), higher (**Class 2A**), or highest (**Class 2B**) risk.[2]
- The 40-GEP can be used in conjunction with formalized risk assessment strategies[3,4] such as the National Comprehensive Cancer Network (**NCCN**) Guidelines® and tumor staging criteria like Brigham & Women's Hospital (**BWH**).[5,6] However, it has not been shown how the 40-GEP adds prognostic value to BWH staging after first categorizing patients according to NCCN risk stratification into High-Risk or Very-High-Risk subgroups.

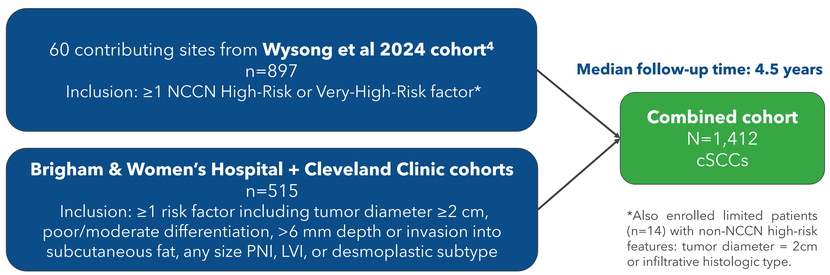
Objective

- To assess how the 40-GEP adds prognostic value for clinicians who may consider both BWH staging and NCCN risk stratification when evaluating treatment and follow-up plans for patients with cSCC.

Patients & Methods

- Under an IRB-approved, 60-institution retrospective study, patients with primary cSCC from a previously published cohort (n=897)[4] having ≥1high-risk factor (closely modeled from NCCN risk stratification[1]) were combined with a novel cohort from two academic centers (n=515) (**Figure 1**).
- Enrollment in the novel cohort required ≥1of the following risk factors: tumor diameter ≥2cm, poor or moderate differentiated histopathology, >6mm depth of invasion or invasion into/beyond subcutaneous fat, small/large caliber perineural invasion (PNI), lymphovascular invasion (LVI), or desmoplastic subtype.
- Patients were excluded if they had received adjuvant radiation therapy (**ART**). Kaplan-Meier survival analysis was used to calculate 3-year regional/distant metastasis-free survival (**MFS**). Cox regression of metastatic risk prediction modeled BWH ± 40-GEP within the context of NCCN risk groups[7], High-Risk (**NCCN HR**) and Very-High-Risk (**NCCN VHR**), and compared using analysis of deviance. BWH staging[6] was grouped into binary categories of low stage (T1+T2a) and high stage (T2b+T3).

Figure 1. Consort diagram



References

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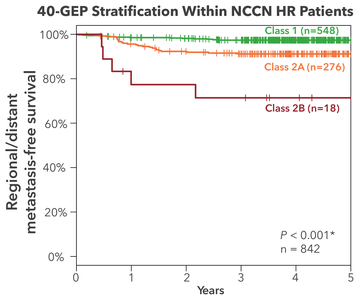
Results

Table 1. Patient demographics

	All patients n=1412	Non-metastatic n=1256 (89.0%)	Metastatic n=156 (11.0%)	*P*-value*
Patient characteristics				
Age in years,** median (range)	**73 (26-90+)**	73 (26-90+)	73 (32-90+)	ns
Male, n (%)	**999 (70.8%)**	871 (69.4%)	128 (82.1%)	0.001
Immunosuppression, n (%)	**372 (26.35%)**	313 (24.9%)	59 (37.8%)	<0.001
Tumor characteristics & treatment				
Tumor diameter,*** median (range)	**1.9 (0.1-22)**	1.8 (0.1-22)	2.3 (0.35-18)	<0.001
Poorly differentiated, n (%)	**210 (14.9%)**	153 (12.2%)	57 (36.5%)	<0.001
Mohs as definitive surgery, n (%)	**967 (68.5%)**	880 (70.1%)	87 (55.8%)	<0.001
Risk stratification, n (%)				
NCCN[5] Low-Risk	**64 (4.5%)**	64 (5.1%)	0	<0.001
High-Risk	**842 (59.6%)**	798 (63.5%)	44 (28.2%)	
Very-High-Risk	**506 (35.8%)**	394 (31.4%)	112 (71.8%)	
40-GEP Class 1	**815 (57.7%)**	770 (61.3%)	45 (28.9%)	<0.001
Class 2A	**538 (38.1%)**	450 (35.8%)	88 (56.4%)	
Class 2B	**59 (4.2%)**	36 (2.9%)	23 (14.7%)	

Percentages shown were calculated as a fraction of the total n of each respective column header.
*P-values reported for Person Chi-squared or Wilcoxon F test, as appropriate
** Ages over 90 years reported as 90+ for privacy
***n=85 cases without tumor diameter available

Figure 2. The 40-GEP provides significant metastatic risk stratification in NCCN High-Risk patients



Added Risk Refinement in the NCCN HR Population

Risk Grouping	3-year MFS (95% CI)	Overall Event Rate*
NCCN HR	**94.8% (93.3-96.3%)**	**5.2%**
NCCN HR+BWH T1/T2a	94.8% (93.3-96.3%)	5.2%
NCCN HR+BWH T1/T2a+Class 1	97.4% (96.0-98.7%)	2.8%
NCCN HR+BWH T1/T2a+Class 2A	91.2% (87.9-94.6%)	8.7%
NCCN HR+BWH T1/T2a+Class 2B	71.4% (53.1-96.2%)	27.8%

*Overall event rate and log-rank test for statistical significance includes total events occurring at any time point during study follow-up, including patients who were followed longer or had later metastatic events than the five years displayed.

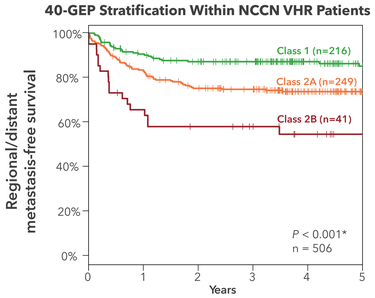
Table 2. Metastatic risk prediction of the BWH staging system is significantly improved when 40-GEP is included for NCCN High-Risk patients

Risk Stratification*	Model Likelihood Ratio	Model ANOVA P-value
BWH Staging	0.21	**<0.001**
BWH Staging + 40-GEP	23.35	

*Models employed binary staging of BWH T1/T2a vs BWH T2b/T3, and three groups for the 40-GEP: Class 1, Class 2A, and Class 2B. (n=842)

- In the **NCCN High-Risk** population, model performance comparison of BWH staging ± 40-GEP showed significantly improved predictive accuracy of metastatic events by the addition of the 40-GEP.
- Inclusion of interaction terms revealed no significant interactions (*P*>0.05), indicating that the 40-GEP adds prognostic information that is independent of BWH staging.

Figure 3. The 40-GEP stratifies metastatic risk in NCCN Very-High-Risk patients, who have a >4-fold overall increase in metastatic event rate vs High-Risk patients



Added Risk Refinement in the NCCN VHR Population

Risk Grouping	3-year MFS (95% CI)	Overall Event Rate*
NCCN VHR	**78.7% (75.1-82.4%)**	**22.1%**
NCCN VHR+BWH T1/T2a	86.0% (82.3-90.0%)	14.7%
NCCN VHR+BWH T2b/T3	66.5% (60.1-73.7%)	34.2%
NCCN VHR+BWH T1/T2a+Class 1	90.0% (85.2-95.1%)	11.2%
NCCN VHR+BWH T1/T2a+Class 2A	83.5% (77.9-89.7%)	16.9%
NCCN VHR+BWH T1/T2a+Class 2B	75.0% (56.5-99.5%)	25.0%
NCCN VHR+BWH T2b/T3+Class 1	81.6% (73.0-91.2%)	19.2%
NCCN VHR+BWH T2b/T3+Class 2A	60.6% (51.4-71.3%)	40.0%
NCCN VHR+BWH T2b/T3+Class 2B	46.8% (30.5-71.6%)	56.0%

*Overall event rate and log-rank test for statistical significance includes total events occurring at any time point during study follow-up, including patients who were followed longer or had later metastatic events than the five years displayed.

Table 3. Metastatic risk prediction of the BWH staging system is also significantly improved when 40-GEP is included for NCCN Very-High-Risk patients

Risk Stratification*	Model Likelihood Ratio	Model ANOVA P-value
BWH Staging	28.45	**<0.001**
BWH Staging + 40-GEP	45.38	

- In the **NCCN Very-High-Risk** population (n=506), model performance comparison of BWH staging ± 40-GEP showed significantly improved predictive accuracy of metastatic events by the addition of the 40-GEP.
- Inclusion of interaction terms revealed no significant interactions (*P*>0.05), indicating that the 40-GEP adds prognostic information that is independent of BWH staging in this patient subset.

Conclusions

- The 40-GEP provided significant metastatic risk stratification in both NCCN High-Risk and Very-High-Risk patients with cSCC.
- Incorporation of the 40-GEP with BWH T-staging significantly improved the accuracy of metastatic risk stratification in both NCCN High- and Very-High-Risk subgroups of patients.
- Integrating the 40-GEP with BWH staging, even within NCCN High or Very-High-Risk profiles, refines risk stratification and supports more accurate clinical decisions, improving personalized care.

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