Metastasis-free survival prediction with the 40-gene expression profile (40-GEP) test in patients with cutaneous squamous cell carcinoma of the head and neck (HNcSCC) risk stratified according to the Brigham and Women's Hospital (BWH) tumor staging criteria

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Introduction

- Patients with cSCC located on the head or neck (**HNcSCC**) may be considered at increased risk of metastasis compared with tumors on other sites based on inclusion of site-specific risk factors in the National Comprehensive Cancer Network (**NCCN**) Guidelines and American Joint Committee on Cancer (**AJCC**) staging criteria,[1-3] but not in the Brigham and Women's Hospital (**BWH**) tumor staging criteria.[4]
- The 40-gene expression profile (**40-GEP**) test has been shown to independently stratify patients' risk of metastasis as low (**Class 1**), higher (**Class 2A**) or highest (**Class 2B**) for with at least one NCCN High-Risk or Very High-Risk factor.[5]
- The 40-GEP also increases the accuracy of risk stratification when used in conjunction with any of these formalized risk assessment strategies.[6,7]

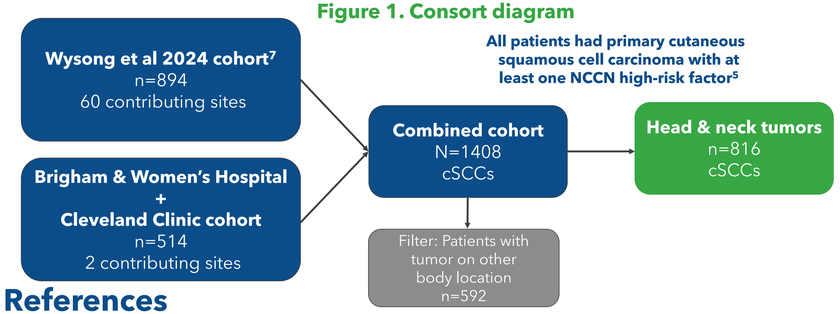
Objective

- Using the largest combined cohort to date, the current study sought to assess whether the 40-GEP stratifies risk of metastasis in patients with HNcSCC (a high-risk feature by some staging criteria), and whether the 40-GEP adds value to BWH staging in this patient subset.

Patients & Methods

- Under an IRB-approved, 60-institution retrospective study, patients with primary cSCC from a previously published cohort (n=894)[7] with at least one NCCN high-risk factor[1] were combined with a novel cohort from two academic centers (n=514) (**Figure 1**). Patients with a tumor on the head or neck (n=816) were included in analysis. Enrollment in the novel cohort required tumor diameter ≥2 cm, poor or moderate differentiated histopathology, >6 mm depth of invasion or invasion into or beyond subcutaneous fat, small or large caliber PNI, LVI, or desmoplastic subtype. Patients from both cohorts were excluded if they had macroscopic positive margins or had received adjuvant radiation therapy (**ART**). Kaplan-Meier survival analysis was used to estimate 3-year regional or distant metastasis-free survival (**MFS**). Cox multivariable analysis was used to compute hazard ratios for each system and to compare prognostic models with or without incorporation of the 40-GEP test. BWH staging[4] was grouped into low stage (T1+T2a) and high stage (T2b+T3).

Figure 1. Consort diagram



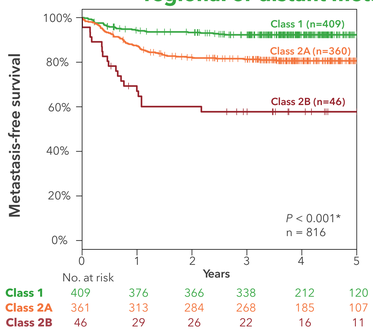
Results

Table 1. Patient demographics: n=816 patients with HNcSCC

Risk Factor	All patients n=816	Class 1 n=409 (50.1%)	Class 2A n=361 (44.2%)	Class 2B n=46 (5.6%)	P-value*
Patient characteristics					
Age in years, median (range)	**73 (26-90+)**	71 (26-90+)	75 (28-90+)	72.5 (40-90+)	0.001
Male, n (%)	**671 (82.2%)**	332 (81.2%)	298 (82.6%)	41 (89.1%)	ns
Immunosuppression, n (%)	**224 (27.5%)**	130 (31.8%)	79 (21.9%)	15 (32.6%)	<0.01
Follow-up in years, median (range)	**4.2 (0.2-14.8)**	4.2 (0.2-14.8)	4.4 (0.3-11.8)	3.8 (0.5-11.9)	ns
Tumor characteristics & treatment					
Tumor diameter** ≥2 cm, n (%)	**293 (38.7%)****	119 (31.3%)**	149 (43.8%)**	25 (65.8%)**	<0.001
Poorly differentiated (G3), n (%)	**152 (18.6%)**	57 (13.9%)	81 (22.4%)	18 (39.1%)	<0.001
Mohs as definitive surgery, n (%)	**631 (77.3%)**	340 (83.1%)	266 (73.7%)	25 (54.4%)	<0.001
Staging, n (%)					
BWH[7] T1	**359 (44.0%)**	215 (52.6%)	134 (37.1%)	10 (21.7%)	<0.001
T2a	**308 (37.8%)**	139 (34.0%)	153 (42.4%)	16 (34.8%)	
T2b	**126 (15.4%)**	51 (12.5%)	59 (16.3%)	16 (34.8%)	
T3	**23 (2.8%)**	4 (1.0%)	15 (4.2%)	4 (8.7%)	
Disease progression events, n (%)					
Non-local metastasis	**121 (14.8%)**	33 (8.1%)	69 (19.1%)	19 (41.3%)	<0.001

*p-values reported for Person Chi-squared or Wilcoxon F test, as appropriate; **n=58 cases without tumor diameter available.

Figure 2. Performance of the 40-GEP to stratify patients for risk of regional or distant metastasis from HNcSCC

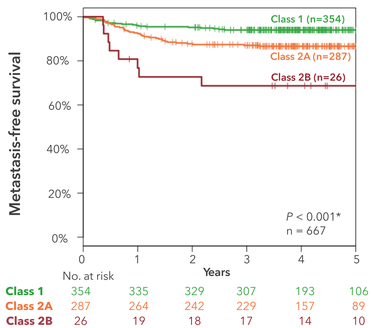


Full H&N cohort

40-GEP Risk Class	3-year MFS (95% CI)	Overall Event Rate*
Class 1	92.3% (89.7-94.9%)	8.1%
Class 2A	81.3% (77.3-85.4%)	19.1%
Class 2B	57.8% (44.9-74.2%)	41.3%
Overall Cohort	85.5% (83.1-87.9%)	14.8%

*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.

Figure 3. The 40-GEP risk stratifies patients with BWH T1/T2a HNcSCC



BWH T1/T2a only

40-GEP Risk Class	3-year MFS (95% CI)	Overall Event Rate*
Class 1	94.0% (91.5-96.5%)	6.5%
Class 2A	87.0% (83.2-91.0%)	13.2%
Class 2B	68.7% (52.8-89.3%)	30.8%
T1/T2 Overall	90.0% (87.7-92.3)	10.3%

*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. Multivariable analysis for 40-GEP test results and the BWH staging system

Group	HR (95% CI)	P-value
40-GEP **Class 1**	Reference	
40-GEP **Class 2A**	2.24 (1.48-3.40)	<0.001
40-GEP **Class 2B**	4.46 (2.50-7.95)	<0.001
BWH Low Stage (T1+T2a)	Reference	
BWH High Stage (T2b+T3)	3.56 (2.46-5.15)	<0.001

Binary categorizations of BWH staging were employed: Addition of interaction terms to the multivariate analysis revealed no significant interactions (P>0.05).

Table 3. Metastatic risk prediction of the BWH staging system is significantly improved when 40-GEP is included

Model*	X^2 (2 degrees of freedom)	ANOVA
BWH Staging, binary	27.88	P<0.001
BWH Staging + 40-GEP		

***The models employed binary staging of BWH T1/T2 vs BWH T2b/T3, and three groups for the 40-GEP: Class 1, Class 2A, and Class 2B.

- When the performance of a staging-alone model was compared to a multivariate model that included the 40-GEP, a significant improvement in predictive accuracy of metastatic events was observed. Inclusion of interaction terms revealed no significant interactions (P>0.05), verifying the 40-GEP as contributing independent prognostic value to the prediction of metastatic risk relative to staging alone.

Conclusions

- Some patients with HNcSCC will experience metastasis, and the 40-GEP can help identify those patients who may be at substantially higher risk of metastasis within the HNSCC patient population.
- BWH staging and the 40-GEP were both significant predictors of metastasis in this cohort of HNcSCC tumors.
- Incorporation of the 40-GEP test result with BWH staging increases the accuracy of metastatic risk prediction over staging-alone to optimize personalized management decisions.

References

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