Integration of the 40-Gene Expression Profile (40-GEP) for Management and Treatment of High-risk Cutaneous Squamous Cell Carcinoma (cSCC): A Real-world Algorithm

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Background

- The prognostic 40-gene expression profile (40-GEP) test has established both analytical and improved clinical validity for risk stratification when compared to current staging systems. The test categorizes patients as low (Class 1), moderate (Class 2A), or high (Class 2B) risk for regional or distant metastasis within 3 years of diagnosis.[1-3]
- Clinical utility studies of the 40-GEP test have demonstrated its appropriate use for the intended high-risk population, and its ability to direct personalized risk-aligned patient management while also increasing clinician confidence in treatment decisions. [4-8]

Clinical Issue and Objective

For high-risk cSCC patients, the limitations of risk-stratification tools, along with broad treatment guidelines, has led to disparities in clinical practice and management, creating a diversity of patient outcomes.[8]

The objective of this study is to provide guidance to clinicians regarding how to incorporate the results of the 40-GEP test into common treatment modalities for their high-risk cSCC patients.

Methods

- Private practice Mohs surgeons who have utilized 40-GEP results for prognostication of high-risk SCC patients merged their risk-aligned management approaches into a singular algorithm focused on how to incorporate 40-GEP test results within the management guidelines proposed by the National Comprehensive Cancer Network (NCCN)[9] (**Figure 1**).
- Real-world cases were compiled by the authors to evaluate the following treatment modalities: surveillance imaging, sentinel lymph node biopsy (SNLB), adjuvant radiation therapy (ART), and clinical follow-up.

Cases Presentations

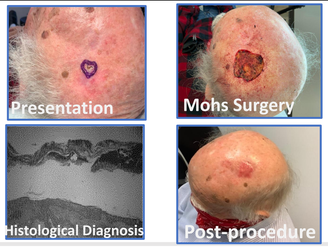
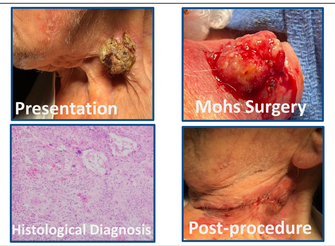
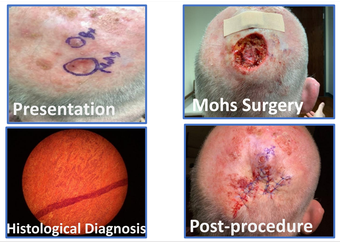
	Case Report 1	Case Report 2	Case Report 3
Clinicopathologic risk factors	• 74-year-old male • 2.2 cm diameter, moderately differentiated • Located on the left posterior scalp	• >90 year-old male • 3.1cm diameter, moderately differentiated • Located on left central lateral neck	• 63-year-old male • >2cm diameter, invasion beyond subcutaneous fat • located on head region
Disease presentation and progression			
American Joint Committee on Cancer (AJCCv8) and Brigham and Women's Hospital (BWH) Stage	AJCC v8: T2 BWH: T2a	AJCC v8: T2 BWH: T2a	AJCC v8: T3 BWH: T2b
Rationale for 40-GEP	2.2 cm diameter, multiple stages of Mohs surgery, larger defect size (4.2 x 4.2cm)	multiple stages of Mohs surgery, larger defect size (4.4 x 4.1cm)	Multiple stages of Mohs surgery, poor clinical margins, patient with a history of multiple cSCCs
Treatment approach pre-40-GEP	CT scan, RT, and follow-up every 1-month	SLNB, RT, and follow-up every 6 months	Imaging to evaluate for distant metastasis was considered
40-GEP Result	Class 1 (Low Risk)	Class 2A (Moderate Risk)	Class 2A (Moderate Risk)
Treatment approach post-40-GEP	Forgo RT and CT scan; follow-up for monthly wound check and nodal exams every 6 months	Forgo SLNB and radiation with follow-up scheduled for every 3 months	Surveillance of lymph nodes with ultrasound imaging every 6 months for two years and clinical follow-up every 3 months with lymph node exam
Outcomes	One-year post-treatment, the wound healed with no evidence of recurrence or metastasis.	3 months post treatment, the wound has healed with no evidence of recurrence or metastasis	16 months post-treatment the wound healed with no evidence of disease

Figure 1. Treatment algorithm for incorporation of 40-GEP test results into treatment decisions for a high-risk cSCC patient

Patient diagnosed with primary invasive cSCC and one or more risk factors

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Due to complexities in patient's clinicopathologic risk factors, clinician decides further assessment is needed

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Patient qualifies for 40-GEP testing;
Clinician sends primary tumor FFPE for biologic metastatic risk prediction

Management Decisions within NCCN guidelines

Treatment*	Class 1	Class 2A	Class 2B
Surveillance Imaging	No action if extensive disease is not present	**Discuss MRI, US and/or CT	**Consider MRI, US and/or CT
Nodal Assessment	No action if low T-stage & negative palpation	Surveillance suggested for high and very high risk	Discuss and consider SLNB and/or surveillance for high and very high risk
Adjuvant Radiation Therapy	No action if high risk and negative surgical margins	Consider for very high risk and high T-staged high risk	Recommend for very high risk and high T-staged high risk
Clinical Follow up	Every 6 mo for 2 yr	Every 3-6 mo for 1 yr	Every 2-3 mo for 1 yr

*multidisciplinary board should be considered; **choice of imaging technique dependent on number and type of high-risk factors; US= ultrasonography; CT= computed tomography; FFPE=Formalin-Fixed Paraffin-Embedded

Conclusions

- For high-risk cSCC patients, whose management is currently broad under existing guidelines, clinicians can identify risk-aligned treatment pathway improvements by use of the 40-GEP within their existing clinical practices.
- One such algorithm to incorporate the 40-GEP is presented here as a mechanism to implement guideline recommendations for personalized management of patients based on their risk for poor outcomes.

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Disclosures

GS is a consultant for Castle Biosciences Inc. (CBI); ASF is an advisor for CBI and Regeneron; SNT declares no relevant conflicts of interest. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed herein.

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