ORIGINAL RESEARCH

Actionable Risk Thresholds for Adjuvant Radiation Therapy and Surveillance Imaging in High-Risk Cutaneous Squamous Cell Carcinoma

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ABSTRACT

Aim: Assess the actionable clinical risk thresholds for patients with high-risk cutaneous squamous cell carcinoma (cSCC) that clinicians use to guide adjuvant radiation therapy (ART) and surveillance imaging decisions and how the 40-gene expression profile (40-GEP) test impacts management decisions.
Methods: Physician, Physician's Assistant, and Nurse Practitioner clinicians with at least ten recent or 12 total 40-GEP requisitions were invited to complete an online survey.
Results: In total, 244 out of 752 (32%) invited clinicians completed the survey. Preferred formalized staging or risk assessment strategies (AJCC, BWH, NCCN, or individual risk factors) were highly variable. Clinicians most commonly reported recommending ART at 20% risk of local recurrence or regional/distant metastasis and surveillance imaging for patients who had at least a 10% risk. ART was considered at a minimum risk threshold of 10% for local recurrence or regional/distant metastasis. A 40-GEP Class 2B result was ranked among the top two most important high-risk factors for ART and surveillance image decision-making, along with extensive perineural invasion.
Conclusion: Clinicians considered 10% and 20% risk of local recurrence or regional/distant metastasis as clinically relevant thresholds for recommending use of surveillance imaging or ART, respectively. Clinicians reported the 40-GEP test results to be one of the most important factors in assessing risk of disease progression used to guide management decisions regarding ART and surveillance imaging, and the 40-GEP can be used to guide risk-aligned management in patients with high-risk cSCC.

INTRODUCTION

For patients diagnosed with invasive cutaneous squamous cell carcinoma (cSCC), a variety of formalized risk assessment systems have been developed to determine the risk of disease progression in order to guide considerations for follow-up frequency, surveillance imaging, and adjuvant radiation therapy (ART). These include the National Comprehensive Cancer Network Guidelines© (NCCN),[1] the American Joint Committee on Cancer (AJCC) version 8 staging system for

tumors on the head or neck,[2] and the Brigham and Women's Hospital (BWH) T-staging system.[3] These approaches broadly classify patients into risk groups based on the presence of various combinations of high-risk clinicopathologic factors which are used to guide management decisions such as the need for ART, surveillance imaging, and/or more frequent follow-up visits.[4,5] The need for improvement in risk stratification is highlighted by the continued modifications to these clinicopathologic systems and their limited accuracy. For example, since the initial validation of the BWH system,[3] the need for improvement in risk stratification has led to suggestions for potential refinements to the system including a T2a-high grouping, further stratification of the T1 subset with "minor risk factors", and the suggestion that the T2b stage can be further refined by separating patients by the number of risk factors present.[6–8] However, none of these suggested modifications have been formally incorporated or validated for clinical use. Separately, AJCC also underwent significant modifications between the previous version 7 and the current version 8, which is limited to tumors on the head and neck.[9–11]

Treatment pathway recommendations for patients with high-risk cSCC are made based on a clinician's patient-specific assessment of the risk of disease progression. While formal staging systems exist to assess the risk of progression (primarily BWH staging and AJCC v8 staging), these systems are limited in application by low accuracy. On average, 35% of patients who experience regional and distant metastasis are classified as low-stage and at least 75% of patients who are classified with high-stage disease do not experience poor outcomes.[11–14] The result is that the majority of high-risk patients with high-stage disease do not experience a poor outcome and are being over-treated, while a substantial number of high-risk patients with early-stage disease do experience poor outcomes and are currently being under-treated. As a result of these limitations, staging systems are not consistently utilized by clinicians, nor incorporated into guidelines, such as NCCN or AAD, to direct patient management. As such, clinicians have traditionally made decisions to guide ART and surveillance imaging based on individual risk factors as a surrogate or estimate for an individual patient's risk of disease progression. The specific factors each clinician uses to guide ART are subject to clinical interpretation, and as such, risk factors are not consistently applied by clinicians to guide treatment decisions. In fact, Moody et al. found that ART is not consistently implemented in patients when guided by clinicopathologic risk factors alone; there was no difference in clinical or pathological risk profiles in patients treated or not treated with ART.[15] Likewise, there is no difference in clinical and pathological risk factors associated with use of imaging surveillance.[13] Improved risk stratification for patients with SCC with one or more high risk factors (i.e., NCCN high-risk (HR) and very-high-risk (VHR)) is an important unmet clinical need to guide the use of both ART and surveillance imaging.

Following surgical removal of the primary tumor, typically by Mohs surgery or peripheral and deep en face margin assessment, patients with negative margins who have either an NCCN HR or VHR risk factor follow a single treatment pathway regarding consideration of ART and surveillance imaging. Specifically, patients in either of these risk groups are eligible for consideration of ART in the presence of "poor prognostic features", or in patients who have "high risk for regional or distant metastasis".[1] However, there are no criteria in guidelines to identify which specific patients will have a high individual likelihood

of progressing to regional or distant metastasis and meet these designations.[1] Additionally, there are no known clinicopathologic factors that predict response to ART.[3,6,10–12,16] As such, accurate selection of patients likely to benefit from ART and surveillance imaging remains challenging and unstandardized, especially in cases with complete surgical resection.[1,15,17] Improving risk assessment and predicting responsiveness to ART for a given patient is critical to avoid under- or over-treatment.

The 40-gene expression profile (40-GEP; DecisionDx®-SCC) test has been shown to provide valuable prognostic information for patients with cSCC with one or more risk factors (i.e., NCCN HR or VHR disease), enhancing the accuracy of prediction of metastasis beyond the NCCN, AJCC, or BWH systems alone.[18,19] Patients with one or more high-risk factors are eligible for 40-GEP testing, and the 40-GEP stratifies patients into three groups based on risk of regional or distant metastasis of: Class 1 (low risk), Class 2A (higher risk), or Class 2B (highest risk).[20] Wysong et al. demonstrated that the 40-GEP adds independent prognostic information to BWH, AJCC, and NCCN risk classification systems, and Class 2A and Class 2B 40-GEP results were also significant and independent predictors of poor outcomes when compared to individual risk factors.[19] The 40-GEP has also been shown to predict risk of local recurrence in patients with NCCN HR cSCC following Mohs surgery with negative margins. (see concurrent publication by Ratner et al. in this issue of SKIN). Additionally, the test has also been shown to predict response to ART.[15,21,22] Specifically a Class 2B result is associated with a 50% reduction in metastasis compared to untreated matched controls. Conversely, patients with a Class 1 result did not benefit from ART, and, given their low metastatic rate, could likely defer treatment.[21,22]

The goal of this clinical impact study was to understand how 40-GEP test results, clinicopathologic high-risk factors, formalized risk assessment systems, and specific absolute risk thresholds for local recurrence or metastasis are currently being employed to guide decisions around the use of ART and surveillance imaging for patients with cSCC.

METHODS

A survey with questions on topics related to cSCC management was distributed to participants. The survey was carried out between March 19, 2025 and April 4, 2025 under an Institutional Review Board-approved protocol, and all responses were collected anonymously. Clinicians were sent an email invitation to participate in the survey if they met all of the following criteria: 1) Clinical credentials of MD/DO, Physician's Assistant (PA), or Nurse Practitioner (NP); 2) Familiarity with 40-GEP test results, defined as at least ten documented requests for 40-GEP testing for a patient from January 2023 – October 2024 or at least 12 total requests since the first clinical availability of the test in September 2020; 3) Documented receipt of both Class 1 (low risk) and Class 2 (Class 2A, higher risk or Class 2B, highest risk) test results to ensure adequate familiarity with 40-GEP result interpretation. Respondents were only permitted to complete the survey once. The protocol allowed for the survey to be closed after three weeks or when approximately 250 responses had been received.

All data analysis was performed using open-access packages running in R (v4.1.2). All questions regarding preferences for

'*consideration*' or '*recommendation*' to pursue ART– due to risk of local recurrence or metastasis– were asked specifically in situations where clear surgical margins had been achieved. Finally, clinicians were asked to select which risk factors (from a list of 22) they deemed important for a given management decision (e.g., ART, surveillance imaging). As a supplemental analysis, to get the specific view of the most highly qualified and experienced respondents, we analyzed responses separately for dermatologist physicians with >5 years in practice who see >10 patients with cSCC every three months.

RESULTS

In total, 752 clinicians with sufficient experience managing patients with 40-GEP test results were invited to participate in the survey. Following removal of incomplete surveys, 244 completed responses were analyzed (32%). Clinicians represented all geographic regions of the United States (**Table 1**). Most (87%) worked in a community practice setting, and less than 5% were at an academic or cancer center (**Table 1**). All respondents self-reported medical credentials; 78% were physicians (MD, DO, or MD/PhD), 15% were PAs, and 7% were NPs (**Table 1**). Of the 190 physicians, 69% indicated specialization in Dermatology/Mohs Surgery and 23% in Dermatology. Overall, 86% of clinicians had been in practice for more than five years, and 70% had seen at least 40 patients with a newly diagnosed, primary invasive cSCC within the last three months (**Table 1**).

Clinicians (n=244) were asked a series of questions about which classification system was their predominant method for risk assessment for cSCC tumors presenting in their practice. For traditional risk assessment

Table 1. Demographics of survey respondents (n=244). **Abbreviations**: cSCC, cutaneous squamous cell carcinoma.

Demographic variable	No. of respondents (%)
Primary specialty	
Dermatology/Mohs	136 (55.7)
Dermatology	93 (38.1)
Other[a]	8 (3.3)
Surgical oncology	5 (2.0)
Dermatology/dermatopathology	1 (0.4)
Prefer not to answer	1 (0.4)
Medical credentials	
MD/DO	188 (77.0)
Physician's Assistant	37 (15.2)
Nurse Practitioner	17 (7.0)
MD/PhD	2 (0.8)
Practice type	
Community practice	212 (86.9)
Academic/cancer center	11 (4.5)
Other	10 (4.1)
Hospital-based	9 (3.7)
Prefer not to answer	2 (0.8)

Practice region in US	
Southeast	75 (30.7)
Midwest	65 (26.6)
Northeast	40 (16.4)
West	36 (14.8)
Southwest	27 (11.1)
Prefer not to answer	1 (0.4)
Years in practice	
Residency/fellowship	1 (0.4)
0-5	33 (13.5)
6-10	75 (30.7)
11-20	80 (32.8)
≥20	55 (22.5)
Newly diagnosed invasive primary cSCC patients (No./3 months)[b]	
≤10	16 (6.6)
10-39	58 (23.9)
40-79	53 (21.8)
80-160	58 (23.9)
>160	58 (23.9)

[a] Includes responses for: general surgeon specializing in dermatologic surgery, head and neck surgeon, oculofacial plastics or skin cancer, plastic surgery, radiation oncology, surgery.
[b] Question had n=243 respondents (one missing response).

systems (e.g., AJCC, BWH, or NCCN) and individual risk factors, respondents were markedly divided in their preferences; for example, 32% reported using individual risk factors, 28% reported using BWH, and 26% reported using some combination of staging approaches. When asked specifically for which cSCC patients they employed their preferred risk assessment system, 64% did so with suspected high-risk patients only, and 30% used it for all cSCC patients.

Clinicians were then asked to give free-text responses regarding what treatment recommendations they consider for patients who present with a specific stage or risk level tumor (excepting the lowest risk category for each system: i.e., NCCN Low Risk, AJCC T1, or BWH T1). After filtering responses to focus on clinicians who predominantly use one specific system in their practice, consideration of ART was tabulated for each stage. Of the clinicians who favored NCCN Guidelines, 73% considered ART for NCCN HR patients and 86% considered ART for NCCN VHR patients. Of clinicians predominantly using BWH, 32% considered ART as an option for T2a patients, 69% for T2b, and 71% for T3.

When asked about the use of ART to manage patients with high-risk cSCC, just under half of all clinicians (n=114; 47%) responded that they themselves make the clinical decision to consider or recommend ART (termed “ART Decision Makers”). Most other clinicians said that they refer some or all patients to another specialty to make this recommendation, and only one respondent answered “No, I do not use adjuvant radiation therapy to manage patients with high-risk cSCC.”

Of the clinicians responding as ART Decision Makers, the minimum risk for metastasis

(defined as nodal and distant) at which ART was considered in patients with clear margins was 10% that was elected by the largest group of respondents (36%). When substituting the stronger language of '*recommend*' ART in place of '*consider*', responses shifted toward higher metastatic risk selections and the most common response was ≥20% risk of metastasis, which was chosen by 36% of respondents (**Figure 1A**).

The consideration of ART specifically regarding the risk of local recurrence was approached in a separate series of questions. Again, ART Decision Makers, most commonly responded that they '*consider*' ART if the patient has a risk for local recurrence of at least 10% (42% of respondents). Similarly, the most common response to '*recommend*' ART was for patients with ≥20% risk of local recurrence (41% of respondents) (**Figure 1B**).

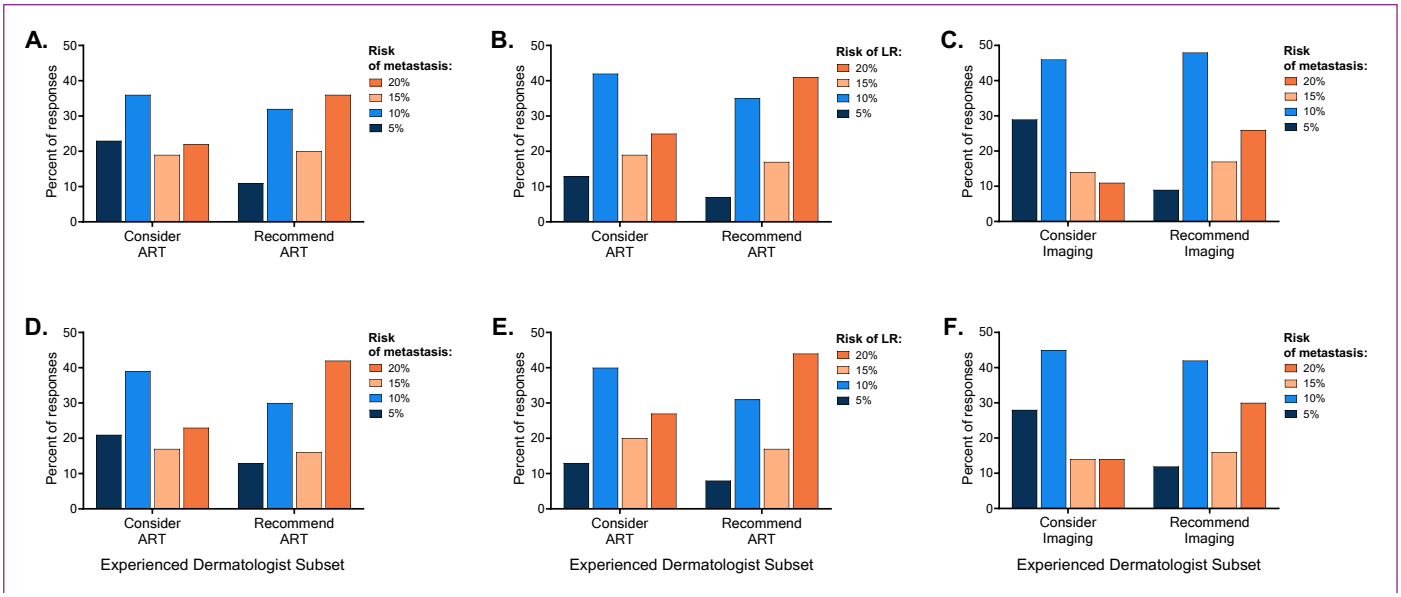

Figure 1. Clinician attitudes on the level of metastatic or local recurrence risk required to prompt decision-making for ART and surveillance imaging. Clinicians were asked a series of questions about the minimum level of risk for metastasis or local recurrence at which they would consider / recommend ART in patients with clear margins. Clinicians were also asked a series of questions about the minimum level of risk for metastasis at which they would consider / recommend surveillance imaging in patients. Clinicians who elected that they make the clinical decision to consider or recommend ART (n=114) or surveillance imaging (n=123) were asked to select a single response. Response proportions are plotted for risk thresholds (5% - 20%). Responses including "Other" or "Prefer not to answer" were excluded from analysis. Risk threshold selections by (A) "ART Decision Makers" responses for the minimum risk of metastasis for considering ART and (B) the minimum risk of local recurrence for considering ART, as well as (C) "Surveillance Imaging Decision Makers" responses for the minimum risk of metastasis to prompt decisions to perform surveillance imaging. Risk threshold selections were also plotted for a subset of specialized dermatologists (i.e., >5 years of practice experience and >10 cSCCs seen per quarter) showing (D) "ART Decision Makers" responses for the minimum risk of metastasis for considering ART and (E) the minimum risk of local recurrence for considering ART, as well as (F) by "Surveillance Imaging Decision Makers" responses for the minimum risk of metastasis to prompt decisions to perform surveillance imaging.

Respondents were next presented with a list of 22 high-risk factors taken from either 40-GEP test results (Class 2A or 2B), NCCN Guidelines, AJCC, or BWH staging[1–3,19,23] and asked whether the presence of each factor alone would elevate their concern to the level of considering or having a conversation about ART. At least 95% answered 'Yes' for extensive PNI, PNI with invasion into nerve sheath/≥0.1mm nerve, or a 40-GEP Class 2B (highest risk) result (**Table 2**). The highest stages (BWH T3 and AJCC T4), LVI, poor differentiation, depth >6mm or beyond subcutaneous fat, and tumor diameter >4cm were also important high-risk factors for ART consideration, selected by >80% of clinicians (**Table 2**). A substantial proportion of respondents also identified multiple individual NCCN HR factors as important to guide ART, including tumor diameter >2cm but ≤4cm (45%), immunosuppression (51%), neurologic symptoms (77%), and location on the head and neck with presence of another NCCN HR factor (67%) (**Table 2**).

Table 2. Most frequently used risk factors for consideration of adjuvant radiation therapy. Survey participants (n=244) were asked, "*Please consider each risk factor and answer Yes or No as to whether the presence of the factor(s) alone would elevate your concern to the level of considering or having a conversation about adjuvant radiation therapy (ART)*." 40-GEP test results are shown in bold font.

Risk factors elevating concern for consideration of ART	Respondents answering 'Yes' (%)
Extensive PNI (invasion of 5 or more distinct nerves within histological section)	97
40-GEP Class 2B	**96**
PNI with tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1mm	95
Lymphatic or vascular involvement (LVI)	89
BWH T3	89
Poor differentiation	85
Size >4cm (any location)	83
AJCC T4	83
Depth >6mm or beyond subcutaneous fat	82
BWH T2b	77
Neurologic symptoms in the tumor area	77
AJCC T3	75
Located on the head or neck AND presents with another NCCN high-risk factor	67
Desmoplastic cSCC	61
Any PNI	60
40-GEP Class 2A	**51**
Immunosuppression	51

Size >2cm but ≤4cm	45
BWH T2a	30
AJCC T2	29
Located on the head or neck	27
Moderate differentiation	26

Abbreviations: 40-GEP, 40-gene expression profile; CI, confidence interval; AJCC, American Joint Committee on Cancer Version 8 T-staging; BWH, Brigham & Women's Hospital Tumor Staging; NCCN, National Comprehensive Cancer Network Guidelines; PNI, perineural involvement.

Almost all survey respondents indicated that surveillance imaging is a part of their management plan for at least some of their patients with high-risk cSCC. Half of respondents answered that they made the clinical decision to consider or recommend surveillance imaging themselves (n=123; termed "Surveillance Imaging Decision Makers"), 29% responded that they referred some, and 20% that they referred all of their patients to another specialty to make imaging recommendations. The minimum risk of metastasis at which Surveillance Imaging Decision Makers '*consider*' surveillance imaging was most commonly reported as a 10% risk of metastasis threshold (46% of respondents). Similarly, the most common risk threshold for which these clinicians would '*recommend*' surveillance imaging was at least 10% risk of metastasis (48% of respondents) (**Figure 1C**).

Clinicians were again presented with the same list of 22 high-risk factors and asked to consider each risk factor and whether the presence of that factor alone would elevate their concern to have a conversation about the use of surveillance imaging. The most frequently chosen risk factor was a 40-GEP Class 2B test result, indicated by 95% of respondents. Extensive PNI, BWH stage T3, LVI, and AJCC stage T4 were also selected by >80% of clinicians. Also, a 40-GEP Class 2A result was selected by more than half of respondents as a risk factor that would elevate their concern to consider surveillance imaging (**Table 3**).

In the subset of physician respondents with the more specialized experience (i.e., dermatologists with >5 years of practice experience and >10 cSCCs seen on average each quarter; n=145), results mirrored that seen in the whole respondent cohort (**Figure 1: D-F**). Namely, the risk threshold for considering ART for regional/distant metastasis and local recurrence was 10%, and for recommending ART was 20% (n=85 ART Decision Makers). Further, a 10% risk threshold was reported for considering or recommending surveillance imaging (n=78; Surveillance Imaging Decision Makers). Finally, risk factors for consideration of ART (**Table 4**) and surveillance imaging (**Table 5**) among these experienced dermatologists (n=145) were similar to those reported by the entire cohort.

DISCUSSION

This study evaluated clinical use of the 40-GEP test results, risk assessment factors, staging systems, and specific absolute

Table 3. Most frequently used risk factors for consideration of surveillance imaging. Survey participants (n=244) were asked, "*Please consider each risk factor and answer Yes or No as to whether the presence of the factor(s) alone would elevate your concern to the level of considering or having a conversation about surveillance imaging.*" 40-GEP test results are shown in bold font.

Risk factor for consideration of surveillance imaging	Respondents answering 'Yes' (%)
40-GEP Class 2B	**95**
Extensive PNI (invasion of 5 or more distinct nerves within histological section)	92
BWH T3	87
Lymphatic or vascular involvement	86
AJCC T4	82
PNI with tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1mm	78
Neurologic symptoms in the tumor area	73
Depth >6mm or beyond subcutaneous fat	69
AJCC T3	67
Size >4cm (any location)	67
Poor differentiation	66
BWH T2b	65
40-GEP Class 2A	**58**
Located on the head/neck AND presents with another NCCN high-risk factor	56
Any PNI	41
Desmoplastic cSCC	34
Immunosuppression	31
Size >2cm but ≤4cm	23
AJCC T2	18
BWH T2a	18
Located on the head/neck	14
Moderate differentiation	9

Abbreviations: 40-GEP, 40-gene expression profile; CI, confidence interval; AJCC, American Joint Committee on Cancer Version 8 T-staging; BWH, Brigham & Women's Hospital Tumor Staging; NCCN, National Comprehensive Cancer Network Guidelines; PNI, perineural involvement.

percent risk thresholds to guide decisions regarding the use of ART and surveillance imaging for patients with high-risk cSCC. The results demonstrate a wide range of preferences for use of any given formalized risk assessment system, similar to previously published findings by Patel et al.[24]

Based on current risk assessment systems, there is substantial incongruence regarding the risk factors most useful for prognostication.[1–3] Refinements to the AJCCv8 system introduced in 2017 improved performance somewhat over AJCCv7,[9] but outcomes between T2 and T3 were not significantly different in some studies, and AJCCv8 is limited to head and neck tumors only.[10,11] While the BWH system continues to undergo suggested changes to improve accuracy, none of these improvement have demonstrated clinical utility or have been formally incorporated.[6–8] It has previously been demonstrated that the 40-GEP test significantly improves risk prediction accuracy when incorporated with NCCN risk assessment, AJCC staging, and BWH staging by adding independent risk information not available from clinical and pathological risk assessment, improving the likelihood of accurately predicting metastasis by 2-fold over use of these systems alone.[3,11,18,19.25-27] Due to the overlapping high-risk clinical and pathologic features in the BWH, NCCN, and AJCC systems, the use of a clinicopathologic-based staging system along with the objective and independent information provided by the 40-GEP test provides the most accurate risk assessment for any given patient.[19] Across all validation studies, within all risk and staging groups, the 40-GEP identifies patients that have a 40-50% reduction in metastatic risk with a Class 1 result, an increase in risk with a Class 2A result equivalent to the addition of another clinical or pathological risk factor, and a risk similar to or greater than that of BWH T2b tumors with a Class 2B result.[18–20]

This study contributes to the body of clinical utility evidence for the 40-GEP and the 10% and 20% thresholds articulated for ART and surveillance imaging, and our results are in line with previously published findings (**Table 6**).[4,8,24,28] Based on the identification of these thresholds, the 40-GEP can guide use of ART in patients with NCCN HR and VHR disease, such that patients with Class 2B results are recommended for use of ART, patients with Class 2A results are considered for ART in the context of other clinicopathologic risk factors, and patients with Class 1 results can defer ART. Further, the 40-GEP should also be used to guide the use of imaging surveillance in patients with NCCN HR disease, such that patients with Class 2A or Class 2B results should be recommended for use of surveillance imaging and Class 1 patients can defer use of imaging based on low rates of local recurrence and metastasis. (see concurrent publication by Ratner et al. in this issue of SKIN). Of note, based on the elevated risk of metastasis in patients with NCCN VHR disease, use of surveillance imaging should not be guided by the 40-GEP in this subset.

In this context, we assessed the impact of 40-GEP test results on patient management in the intended use population (**Table 7**).[19] When considering the clinical utility thresholds for ART of 10% and 20%, use of the 40-GEP in the context of NCCN risk classification would identify 42% of NCCN VHR patients who could forgo ART (due to a Class 1 result, risk of metastasis <20% and no clinical benefit from ART) and 2% of NCCN HR patients who should be recommended for ART (risk of metastasis >20%, demonstrated benefit due to a Class 2B result). If you assume Class 2A patients are recommended for ART with NCCN VHR

and deferred from ART in NCCN HR, this results in recommendation for ART treatment in 22% of all 40-GEP-tested patients, a 33% decrease from use of NCCN classification alone. This strategy captures 60% of metastatic events, a similar sensitivity to the use of NCCN alone in this cohort (**Table 7**). As it relates to surveillance imaging, the use of the 40-GEP within the NCCN risk classification strategy provides a utility to

Table 4. Most frequently used risk factors for consideration of adjuvant radiation therapy by experienced dermatologist physicians. Experienced dermatologist physicians (n=145 meeting the criteria defined in the Methods), were asked, "*Please consider each risk factor and answer Yes or No as to whether the presence of the factor(s) alone would elevate your concern to the level of considering or having a conversation about adjuvant radiation therapy (ART).*" 40-GEP test results are shown in bold font.

Risk factors elevating concern for consideration of ART	Respondents answering 'Yes' (%)
Extensive PNI (invasion of 5 or more distinct nerves within histological section)	98
PNI with tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1mm	98
40-GEP Class 2B	**96**
BWH T3	92
Lymphatic or vascular involvement (LVI)	90
Poor differentiation	89
AJCC T4	86
Size >4cm (any location)	81
BWH T2b	79
AJCC T3	79
Depth >6mm or beyond subcutaneous fat	79
Neurologic symptoms in the tumor area	78
Located on the head or neck AND presents with another NCCN high-risk factor	63
Desmoplastic cSCC	56
Any PNI	56
40-GEP Class 2A	**50**
Immunosuppression	46
Size >2cm but ≤4cm	45
BWH T2a	30

Moderate differentiation	28
AJCC T2	25
Located on the head or neck	22

Abbreviations: 40-GEP, 40-gene expression profile; AJCC, American Joint Committee on Cancer Version 8 Tumor Staging; BWH, Brigham & Women's Hospital Tumor Staging; NCCN, National Comprehensive Cancer Network Guidelines; PNI, perineural involvement.

detect and manage patients with moderately elevated risk of metastasis that are not recommended to receive ART to further reduce potential for patient harm. If you assume use of imaging in NCCN VHR, and not in NCCN HR, patients with NCCN HR

Table 5. Most frequently used risk factors for consideration of surveillance imaging by experienced dermatologist physicians. Experienced dermatologist physicians (n=145 meeting the criteria defined in the Methods) were asked, "*Please consider each risk factor and answer Yes or No as to whether the presence of the factor(s) alone would elevate your concern to the level of considering or having a conversation about surveillance imaging*." 40-GEP test results are shown in bold font.

Risk factors elevating concern for consideration of surveillance imaging	Respondents answering 'Yes' (%)
40-GEP Class 2B	**95**
Extensive PNI (invasion of 5 or more distinct nerves within histological section)	93
BWH T3	92
Lymphatic or vascular involvement (LVI)	87
AJCC T4	85
PNI with tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1mm	79
Neurologic symptoms in the tumor area	74
AJCC T3	70
BWH T2b	68
Size >4cm (any location)	67
Depth >6mm or beyond subcutaneous fat	66
Poor differentiation	66
40-GEP Class 2A	**57**
Located on the head or neck AND presents with another NCCN high-risk factor	50
Any PNI	36
Immunosuppression	30

Desmoplastic cSCC	26
Size >2cm but ≤4cm	19
BWH T2a	16
AJCC T2	12
Located on the head or neck	9
Moderate differentiation	8

Abbreviations: 40-GEP, 40-gene expression profile; AJCC, American Joint Committee on Cancer Version 8 Tumor Staging; BWH, Brigham & Women's Hospital Tumor Staging; NCCN, National Comprehensive Cancer Network Guidelines; PNI, perineural involvement.

Table 6. Previously published risk thresholds for ART and surveillance imaging compared with the current study.

Citation	Journal	Evidence type	Risk of metastasis threshold for considering/recommending ART
Current study	*SKIN: J Cutan Med*	Consensus expert medical opinion: Survey of N=244 dermatology clinicians	10% (negative surgical margins) for consider ART 20% (negative surgical margins) for recommend ART
Rentroia-Pacheco, et al. 2023 [4]	*eClinical Medicine*	Consensus expert medical opinion: Survey of N=53 members of the SCOUT consortium	20% median (IQR 10, 20) "*Above which 5-year metastatic risk probability would you consider discussing adjuvant radiotherapy to the local tumour bed following clear margin surgery with your cSCC patient?*"
Patel, et al. 2022 [24]	*Cancer Medicine*	Consensus expert medical opinion: Survey of N=156 dermatologists	BWH stage T2b "*For which BWH stage do you consider post-operative ART for a patient with high-risk cSCC?*"
Citation	**Journal**	**Evidence type**	**Risk of metastasis threshold for recommending imaging**
Current study	*SKIN: J Cutan Med*	Consensus expert medical opinion: Survey of N=244 dermatology clinicians	10% (negative surgical margins)
Gupta, et al. 2021 [8]	*J Am Acad Dermatol*	Original research of N=1342 BWH Stage T2a tumors and evidence-based practice recommendation	8% (BWH Stage T2a-High)

Wang, et al. 2025 [28]	*JAMA Dermatol*	Original research of N=216 high-stage patients and evidence-based institutional convention recommendation	10%

Abbreviations: ART, adjuvant radiation therapy; BWH, Brigham & Women's Hospital Tumor Staging; cSCC, cutaneous squamous cell carcinoma; IQR, interquartile range.

tumors and Class 2A results comprise an increase of 21% of tumors that should be surveilled by imaging due to elevated risk of metastasis (Class 2A and Class 2B results) than use of NCCN alone. This also captures 70% of metastases that occurred within the NCCN HR patient population which could be missed if these patients were treated based on their NCCN risk classification alone.[19]

Taken together, the combined uses of 40-GEP to guide ART and imaging in NCCN HR and VHR patients correctly identifies 90% of all metastatic events in the cohort as high risk, effectively recommending these patients for either ART or surveillance imaging, and misses only 10% of all metastatic events (**Table 7**). Furthermore, a recently published study estimated the annual predicted direct

Table 7. Management guidance based on 40-GEP results from Wysong et al. 2024[19] within the NCCN High-Risk and Very High-Risk framework.

NCCN High Risk Baseline risk of metastasis: 6.5% Baseline risk of local recurrence: 8.6% Per NCCN Guidelines: Consider ART[1] and use of imaging surveillance		
40-GEP class result (%)	**Post-test risk assessment**	**Clinical recommendation based on 40-GEP results**
Class 1 (42%)	No ART benefit 3.0% metastatic rate 5.8% local recurrence rate	Defer ART Avoid imaging surveillance
Class 2A (21%)	May have ART benefit in some patients 11.6% metastatic rate 14.5% local recurrence rate	Consider ART in context of risk factors Recommend imaging surveillance
Class 2B (2%)	Benefit from ART 30.7% metastatic rate 29.6% local recurrence rate	Recommend ART Recommend imaging surveillance
NCCN Very High Risk Baseline risk of metastasis: 25.9% Per NCCN Guidelines: Consider ART[1] and use of imaging surveillance		
40-GEP class result (%)	**Post-test risk assessment**	**Clinical recommendation based on 40-GEP results**

Class 1 (15%)	No ART benefit 16.9% metastatic rate	Defer ART Imaging surveillance per guidelines
Class 2A (18%)	May have ART benefit in some patients 29.1% metastatic rate	Consider ART in context of risk factors Imaging surveillance per guidelines
Class 2B (3%)	Benefit from ART 54.1% metastatic rate	Recommend ART Imaging surveillance per guidelines

Abbreviations: 40-GEP, 40-gene expression profile; ART, adjuvant radiation therapy; NCCN, National Comprehensive Cancer Network Guidelines.

cost savings for Medicare-eligible patients to be $972 million when the 40-GEP is used to guide ART decision-making (foregoing for patients with Class 1 results, treating some with Class 2A, and treating all who had Class 2B results).[29]

Our study found that the most common risk threshold for metastasis and local recurrence where clinicians *consider* ART was 10%. It has previously been shown that BWH T1 patients have an overall risk of metastasis of 6.5%, and the 40-GEP can identify individuals that exceed this 10% risk of metastasis threshold if they have a 40-GEP Class 2A (11.3% rate of metastasis) or Class 2B (33.3%) result, compared with the 3.0% rate of metastasis for Class 1 patients.[19] Similar results were seen for BWH T2a, who had an overall rate of metastasis of 13.4%, where those with a 40-GEP Class 2A result had an 18.8% rate of metastasis and those with Class 2B had a 36.4% rate of metastasis, whereas patients with a Class 1 result had a 7.4% rate of metastasis, less than the 10% risk threshold identified in the current study, appropriate for de-escalation of treatment and follow-up intensity.[19]

Our analysis demonstrates that clinicians who use the 40-GEP consider a highest-risk Class 2B test result to be among the most important risk factors they consider when making management decisions for ART. Overall, 40-GEP test results were a frequently used risk factor for considering ART and surveillance imaging for high-risk cSCC, on par with multiple other high-risk factors such as large/extensive PNI, poor differentiation, LVI, and the highest-stage tumors (BWH T3 or AJCC T4). Two large multi-center studies have shown that the 40-GEP test predicts response to ART.[21,22] To date, clinicopathologic factors have not been shown to predict response to ART.[15] Use of risk factors to guide ART decisions is inconsistent, likely due to the inconsistent definitions of high risk employed across NCCN guidelines, BWH staging, and AJCC staging systems.[1–3,5,30] For ART decision making in our study, nearly all physicians selected risk factors with well-established association to high risk of metastasis, including PNI in nerves deeper than the dermis, extensive PNI, and the 40-GEP Class 2B result. Interestingly, in addition to these risk factors, the assessment of risk factors considered to refer patients to ART suggests that over 60% of highly experienced dermatology physician respondents refer for ART on the basis of the presence of individual NCCN high-risk factors as well; this reinforces the need to identify Class 1 patients within NCCN HR and VHR cSCC subsets who can safely forgo ART. For surveillance imaging, risk factors with well-established association with regional or distant metastasis were nearly universally used to guide decisions for surveillance imaging, including 40-GEP Class 2B results; Class 2A results were also used to guide surveillance imaging decisions by over half of the respondents.

Limitations

Because the study was focused on the use of 40-GEP testing for high-risk cSCC, the respondent population was limited to clinicians with significant experience managing patients after receipt of 40-GEP test results. As such, these results could differ if a similar series of questions were posed to a broader community of dermatologic clinicians. However, our results concerning appropriate risk levels for upgrading follow-up considerations and considering the use of ART were similar to previous studies.[4,24] Over 94% of clinicians surveyed reported working in a Dermatology setting, so other specialties such as medical oncologists, head and neck surgeons, and radiation oncologists were not as well represented in our study [24] Furthermore, 87% of our respondents reported working in community practice settings. However, this is a more representative population of US dermatology professional settings, as only about 15% of dermatologists practice in an academic tertiary care center.[31]

CONCLUSION

In conclusion, this study further strengthens the 10% and 20% thresholds for the established interventions of ART and surveillance imaging which are incorporated into established management strategies for patients with high-risk cSCC based on their known ability to improve patient outcomes when directed to patients at high risk to experience poor outcomes. The survey results found a general lack of agreement on which formalized risk assessment strategies based on clinicopathologic factors are preferred, while also identifying high levels of clinical incorporation of the 40-GEP test result into clinical decision making in the context of a patient's known risk factors. Based on previous data confirming the independent risk stratification of the 40-GEP, clinicians should use 40-GEP testing to inform ART and surveillance imaging to identify patients above and below established risk thresholds to more closely risk-align established management strategies to improve outcomes for patients with high-risk cSCC.

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