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Pilot phase II trial of Neoadjuvant Immunotherapy in Locoregionally Advanced, Resectable Cutaneous Squamous Cell Carcinoma of the Head and Neck

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*From the **Clinical Cancer Research**. June 2021*

Purpose: In locoregionally advanced, resectable cutaneous squamous cell carcinoma of the head and neck (CSCC-HN), surgery followed by radiotherapy is standard but can be cosmetically and functionally devastating, and many patients will recur.

Experimental Design: Newly diagnosed or recurrent stage III-IVA CSCC-HN patients amenable to curative-intent surgery received two cycles of neoadjuvant PD-1 inhibition. The primary endpoint was ORR per RECIST 1.1. Secondary endpoints included pathologic response [pathologic complete response (pCR) or major pathologic response (MPR; ≤10% viable tumor)], safety, DSS, DFS, and OS. Exploratory endpoints included immune biomarkers of response.

Results: Of 20 patients enrolled, 7 had recurrent disease. While only 6 patients (30%; 95% CI: 11.9–54.3) had partial responses by RECIST, 14 patients (70%; 95% CI: 45.7–88.1) had a pCR (n=11) or MPR (n=3). No SAEs occurred during or after the neoadjuvant treatment. At a median follow-up of 22.6 months (95% CI: 21.7–26.1), one patient progressed and died, one died without disease, and two developed recurrences. The 12-month DSS, DFS, and OS rates were 95% (95% CI: 85.9–100), 89.5% (95% CI: 76.7–100), and 95% (95% CI: 85.9–100) respectively. Gene expression studies revealed an inflamed tumor microenvironment in patients with pCR or MPR and CyTOF analyses demonstrated a memory CD8+ T-cell cluster enriched in patients with pCR.

Conclusions: Neoadjuvant immunotherapy in locoregionally advanced, resectable CSCC-HN is safe and induces a high pathologic response rate. Pathologic responses were associated with an inflamed tumor microenvironment.

Summary Statements

- This is a Phase II pilot study assessing the safety and activity of neoadjuvant immunotherapy in cSCC of the head and neck with locoregionally advanced, resectable disease. All patients received 2 cycles of cemiplimab q3 weeks preoperatively. They then underwent surgery at least 21 days after completing their second cycle. Pre and post treatment imaging was obtained, and extent of surgery was based on pre-treatment imaging. Clinical surveillance and imaging were performed every 3-4 months for the first two years after completion of therapy

- 20 patients total were enrolled. Overall response rate by RESIST criteria on imaging was 30%. Two patients had progression of disease based on RESCIST criteria. Pathologic response rate (pCR and MPR) was 70%.
- Adjuvant treatment was decided based on pathologic response and was determined on a case-by-case basis by the multidisciplinary team. 11 patients (55%) were not recommended previously planned radiation based on pathologic response. 5% declines adjuvant therapy. 8 patients (40%) received adjuvant radiation and 2 (10%) received chemoradiation.
- At mean follow up time of 22.6 months 3 patients (15%) recurred none of whom had achieved either imaging or pathologic response. At 12 months DSS was 95%, DFS was 89.5% and OS was 95%.
- Upon examination of tumor environment, patients with inflamed tumor microenvironment were associated with favorable pathologic responses. There were higher infiltration of T cells and immune genes involved in TCR and PD1 signaling pathways. In contrast, an immune suppressive microenvironment was found in patients without a pathologic response.
- 35% of patients had treatment relates adverse events. However, none of the adverse events were serious and all fully resolved. None of the adverse events resulted in delay of proposed surgery.

Strengths

- This is the first study to report safety and efficacy of PD-1 inhibitors in locoregionally advanced cSCC in the head and neck. This was performed in a prospective manner which adds to the strength of the data.
- Comparison of imaging versus pathologic response rates further validates prior studies showing that imaging often underestimates pathologic response.
- Inclusion of the analysis tumor microenvironment adds important information to the growing body of literature on cancer biology.

Weaknesses

- Despite encouraging results, this is a pilot Phase II trial at a single institution with a small cohort of patients that was non-randomized and followed over a relatively short follow up period. Results should be further validated with a larger, multicenter phase II study.
- There was variability in adjuvant treatment given following surgery. While this did not seem to affect recurrence rates in this small population, it could potentially have a greater affect in a larger multi-institutional trial.

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Systematic review and meta-analysis of local recurrence rates of head and neck cutaneous melanomas after wide local excision, Mohs micrographic surgery, or staged excision

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From the ***Journal American Academy of Dermatology.*** *September 2021*

Background: Prospective trials have not compared the local recurrence rates of different excision techniques for cutaneous melanomas on the head and neck.

Objective: To determine local recurrence rates of cutaneous head and neck melanoma after wide local excision (WLE), Mohs micrographic surgery (MMS), or staged excision.

Methods: A systematic review of PubMed, EMBASE, and Web of Science identified all English case series, cohort studies, and randomized controlled trials that reported local recurrence rates after surgery for cutaneous head and neck melanoma. A meta-analysis utilizing a random effects model calculated weighted local recurrence rates and confidence intervals (CI) for each surgical technique and for subgroups of MMS and staged excision.

Results: Among 100 manuscripts with 13,998 head and neck cutaneous melanomas, 51.0% (7138) of melanomas were treated by WLE, 34.5% (4826) by MMS, and 14.5% (2034) by staged excision. Local recurrence rates were lowest for MMS (0.61%; 95% CI, 0.1%-1.4%), followed by staged excision (1.8%; 95% CI, 1.0%-2.9%) and WLE (7.8%; 95% CI, 6.4%-9.3%).

Limitations: Definitions of local recurrence varied. Surgical techniques included varying proportions of invasive melanomas. Studies had heterogeneity.

Conclusion: Systematic review and meta-analysis show lower local recurrence rates for cutaneous head and neck melanoma after treatment with MMS or staged excision compared to WLE

Summary Statements

This systematic review analyzed 100 retrospective studies comparing 3 common surgical techniques (wide local excision (WLE), Mohs micrographic surgery (MMS), and staged excision) for melanoma and melanoma in situ (MIS) of the head and neck and found WLE to have the highest risk of local recurrence

- Many limitations detailed below limiting the generalizability of the conclusions of this study

Strengths

- Addresses an important question about resection technique for melanoma focused specifically on the head and neck where no prospective comparative studies exist

- Large number of studies reviewed (100) with a relatively large number of patients in each cohort

Weaknesses

- Significant opportunity for selection bias with each technique included in the analysis
- Authors note moderate kappa between reviewers (.61) and high risk of bias in all included studies
- No staging information or tumor details collected for comparison of the groups, and the definition of local recurrence varied amongst the included studies

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Higher metastasis and death rates in cutaneous squamous cell carcinomas with lymphovascular invasion

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From ***Journal of American Academy of Dermatology.*** *April 2022*

Background:
Lymphovascular invasion (LVI) is an aggressive histologic finding but is excluded from current staging systems due to its lack of demonstrated independent prognostic significance.

Objective:
To evaluate the impact of LVI on cutaneous squamous cell carcinoma tumor outcomes.

Methods
In total, 10,707 cutaneous squamous cell carcinoma tumors from a 20-year, retrospective, multicenter cohort were stratified by the presence (LVI^+) or absence (LVI^-) of LVI. Outcomes (local recurrence, in-transit metastasis, nodal metastasis, disease-specific death) were compared based on low (Brigham and Women's Hospital [BWH] stage T1/T2a) and high (BWH T2b/T3) tumor stages.

Results
Of the 10,707 tumors, 78 had LVI. The analysis of low-stage BWH tumors showed the LVI^+ group had a significantly higher 5-year cumulative incidence of local recurrence (LVI^+: 12.3%; LVI^-: 1.1%; $P < .01$), metastasis (LVI^+: 4.2%; LVI^-: 0.4%; $P < .01$), and disease-specific death (LVI^+: 16.2%; LVI^-: 0.4%; $P < .01$). The analysis of BWH high-stage tumors showed the LVI^+ group maintained a higher 5-year cumulative incidence of metastasis (LVI^+: 28.5%; LVI^-: 16.8%; $P = .06$) and disease-specific death (LVI^+: 25.3%; LVI^-: 13.9%; $P = .03$), however, there was no difference in local recurrence (LVI^+: 16.3%; LVI^-: 15.8%; $P = .11$).

Limitations

Retrospective study design.

Conclusion
LVI^+ cutaneous squamous cell carcinomas have higher rates of metastasis and death at 5 years. Future staging systems should consider incorporating LVI.

Summary Statements

- Lymphovascular invasion (LVI) is a high-risk feature associated with metastatic disease and disease-specific death in patients with cSCC, but is not incorporated in staging systems due to lack of sufficient data to demonstrate independent prognostic significance
- This is a retrospective multi-institutional study that evaluated 10,707 cSCC tumors from a pathology database and tumor-specific variables, outcomes measures including local recurrence, metastasis (including in-transit and nodal), and disease specific death, as well as surgical approach and adjuvant treatment were collected and analyzed. Tumors were stratified into Brigham and Women's Hospital (BWH) low stage (T1-T2a) and BWH high stage (T2b-T3).
- They demonstrated that LVI was associated with higher 5-year cumulative incidence of local recurrence, metastasis, and disease-specific death (DSD) in low-stage BWH tumors, and with higher 5-year cumulative incidence of metastasis and DSD in high-stage BWH tumors. LVI was also associated with a 12.2x increased risk of local recurrence, 9.9x increased risk for metastasis, and a 41.4x increased risk for DSD in low-stage BWH tumors.

Strengths This is the largest and first multi-institutional study of over 10,000 tumors that demonstrated LVI to be an independent prognostic indicator of poor outcomes including local recurrence, metastasis, and disease-specific death.

- This study provides evidence that LVI influences the development of poor outcomes in cSCC in the absence of other risk factors, supporting the need to use LVI as high-risk factor in treatment decisions and staging criteria.

Weaknesses
The study population is primarily from high-volume academic centers and thus may not represent the general cSCC population and management of patients who are treated in smaller institutions or private centers.

- This is a retrospective study which by nature is limited by the completeness of how LVI and other tumor risk factors are being reported, which may impact the results of the study.

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Risk factors for metastatic cutaneous squamous cell carcinoma: Refinement and replication based on 2 nationwide nested case-control studies

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From ***Journal of American Academy of Dermatology.*** *March 2022*

Background:
Risk factors for cutaneous squamous cell carcinoma (cSCC) metastasis have been investigated only in relatively small data sets.

Objective:
To analyze and replicate risk factors for metastatic cSCC.

Methods:
From English and Dutch nationwide cancer registry cohorts, metastatic cases were selected and 1:1 matched to controls. The variables were extracted from pathology reports from the National Disease Registration Service in England. In the Netherlands, histopathologic slides from the Dutch Pathology Registry were revised by a dermatopathologist. Model building was performed in the English data set using backward conditional logistic regression, whereas replication was performed using the Dutch data set.

Results:
In addition to diameter and thickness, the following variables were significant risk factors for metastatic cSCC in the English data set (n = 1774): poor differentiation (odds ratio [OR], 4.56; 95% CI, 2.99-6.94), invasion in (OR, 1.69; 95% CI, 1.05-2.71)/beyond (OR, 4.43; 95% CI, 1.98-9.90) subcutaneous fat, male sex (OR, 2.59; 95% CI, 1.70-3.96), perineural/lymphovascular invasion (OR, 2.12; 95% CI, 1.21-3.71), and facial localization (OR, 1.57; 95% CI, 1.02-2.41). Diameter and thickness showed significant nonlinear relationships with metastasis. Similar ORs were observed in the Dutch data set (n = 434 cSCCs).

Limitations:
Retrospective use of pathology reports in the English data set.

Conclusion
cSCC staging systems can be improved by including differentiation, clinical characteristics such as sex and tumor location, and nonlinear relationships for diameter and thickness.

Summary Statements
Nested cohort study of a national (English, Jan 2013 to Dec 2015) cohort of 1774 excised cutaneous squamous cell carcinoma with 1:1 matching based on minimum follow-up time then analyses were externally validated using 434 from a national Dutch cohort (2007/2008)

- Sex, location in the face, diameter, thickness, differentiation, deep involvement of the tumor, and perineural invasion were found to be associated with increased odds of

regional or distant metastasis. This was validated in the Dutch cohort with the exception of perineural invasion.
- Risk of metastasis significantly increased with diameter over 3cm and thickness over 8mm.

Strengths
Study based in a comprehensive national cohort capturing both high and low risk tumors. Detection of metastasis previously validated in a prior study. Missingness low for many variables and where missing, imputation used to maximize inclusion in the final model.
- External validation completed with a comprehensive national registry
- Nonlinear relationships between diameter, thickness and metastatic disease considered

Weaknesses
- Multiple primary tumors unable to be considered in the study
- Immunosuppression defined through patient administration systems and may underestimate this risk factor.
- Measurement of thickness not standardized in the primary cohort.
- Distant and regional metastasis considered equal as an endpoint, though the cohort included a very small number of patients with distant metastatic disease.

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Enhanced metastatic risk assessment in cutaneous squamous cell carcinoma with the 40-gene expression profile test

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From ***Future Oncology.*** *March 2022*

Aim: To clinically validate the 40-gene expression profile (40-GEP) test for cutaneous squamous cell carcinoma patients and evaluate coupling the test with individual clinicopathologic risk factor-based assessment methods.

Patients & methods: In a 33-site study, primary tumors with known patient outcomes were assessed under clinical testing conditions (n = 420). The 40-GEP results were integrated with clinicopathologic risk factors. Kaplan-Meier and Cox regression analyses were performed for metastasis.

Results: The 40-GEP test demonstrated significant prognostic value. Risk classification was improved via integration of 40-GEP results with clinicopathologic risk factor-based assessment, with metastasis rates near the general cutaneous squamous cell carcinoma population for class 1 and ≥50% for class 2B.

Conclusion: Combining molecular profiling with clinicopathologic risk factor assessment enhances stratification of cutaneous squamous cell carcinoma patients and may inform decision-making for risk-appropriate management strategies.

Plain Language Summary

Plain language summary Cutaneous squamous cell carcinoma is a common skin cancer, with approximately 2 million cases diagnosed each year in the USA. Because substantial numbers of patients experience metastasis, which can result in death, accurate metastatic risk assessment is important. Clinicians use clinicopathologic factors to determine risk for disease progression. However, traditional methods miss pinpointing many patients who experience metastasis and sometimes categorize patients as at risk who do not develop metastasis, indicating that additional tools are needed. A molecular test, the 40-gene expression profile (40-GEP), was developed to predict metastatic risk based on the biology of the tumor. This study demonstrates that the 40-GEP, either as an independent tool or together with traditional methods, accurately identifies patients' risk of metastasis. Using the 40-GEP could improve patient management to improve patient outcomes.

Summary Statements

Accurate risk stratification remains an active area of investigation for a growing population of patient with cutaneous squamous cell carcinoma

- The authors have developed a 40-gene expression profiling-based algorithm (40-GEP) to assign risk (Class 1A – low, Class 2A- moderate, and Class 2B – high) levels for the development of metastatic disease.
- The current study examined a cohort of 420 patients, collected from multiple clinical centers and retrospectively reviewed to validate that the 40-GEP can significantly improve the identification of patients at risk of metastatic disease when combined with accepted clinicopathologic risk factors/staging strategies.

Strengths

- This study evaluates a relatively large cohort of patients
- Methodology is rigorous, with consideration and inclusion of important risk factors (eg. stratification by AJCC 8th edition staging, Brigham and Women's staging, immunosuppression, among others) and sound statistical approaches to demonstrate the validity, significance, and utility of the 4-GEP.
- Conclusions not overstated, as authors acknowledge that real-world prospective incorporation and study of the 40-GEP are needed and actively being pursued.

Weaknesses

This is a retrospective cohort study, and there may be some selection bias present in the process of collating the study cohort.

- Despite a large sample size (n-420 with 63 metastatic events recorded), the cohort is still limited to draw conclusions from the multivariable analysis, as the events become infrequent across strata (as evidenced by the fairly large 95% confidence intervals for the class 2B sub-cohort in the multivariable analyses).

- The association of 40-GEP risk strata with metastasis in this retrospective cohort needs to be studied for performance in a large prospective cohort to support clinical utility and 'real-world' validity/implementation.

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Factors predicting outcomes of patients with high-risk squamous cell carcinoma treated with Mohs micrographic surgery

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From ***Journal American Academy of Dermatology.*** *March 2019*

Background: There is limited literature on the long-term outcomes and prognostic factors of high-risk cutaneous squamous cell carcinomas (hrSCC) treated with Mohs micrographic surgery (MMS).

Objective: To determine the rates of local recurrence, metastatic disease, and disease-specific death in hrSCCs treated with MMS and patient or tumor factors associated with poor outcomes.

Methods: Single-institution, retrospective cohort analysis of hrSCC treated with MMS alone and MMS with adjuvant therapy.

Results: A total of 882 cases of hrSCC treated with MMS were identified, of which 842 were treated with MMS alone, with a median follow-up time of 2.4 years. The rate of local recurrence was 2.5%, of metastatic disease was 1.9%, and of disease-specific death was 0.57%. Perineural invasion, poor differentiation, and immunosuppression were significantly associated with poor outcomes. In propensity score-matched case patients treated with adjuvant therapy and control patients treated with Mohs alone, there was no significant difference in progression-free survival, but matching was imperfect.

Limitations: Single-institution, retrospective review.

Conclusions: MMS remains an effective treatment for hrSCC. Current SCC staging systems may be limited by inconsistent inclusion of poor differentiation. Immunosuppression, especially transplant, should be considered a high-risk clinical feature. Further study is needed on the effect of adjuvant treatment.

Summary Statements

- Rates of recurrence, metastasis and disease specific death were evaluated in univariate modeling categorized into BWH staging or AJCC8 staging as well as immune status (Table II). Further review evaluating rates of these outcomes using high risk features: poor diff, >2cm, PNI, Invasion of nerve >0.1mm in caliber, invasion beyond subcutaneous far, vermilion lip, ear, or temple (Table III).
- Immunosuppression, PNI and poor tumor differentiation were significantly associated with poor patient outcomes.

- Poor differentiation should be considered within staging systems and immunosuppression, especially transplant, as a high-risk clinical feature

Table II. Proportion of outcomes at each stage using BWH staging system and AJCC8 staging system with 2-year cumulative incidence

Tumor stage	Overall, n (%)	Recurrence*	Metastatic*	Disease-specific death*
BWH				
T1	499 (56.6)	8/499 (1.6)	3/499 (0.60)	0/499 (0)
		0.015 (0.0068 to 0.03)	0.0021 (2e-04 to 0.011)	0 (NA, no events)
T2A	339 (38.4)	7/339 (2.1)	8/339 (2.4)	3/339 (0.88)
		0.022 (0.0097 to 0.043)	0.021 (0.0095 to 0.042)	0.01 (0.0028 to 0.028)
T2B	32 (3.6)	4/32 (12.5)	4/32 (12.5)	1/32 (3.2)
		0.13 (0.04 to 0.28)	0.13 (0.039 to 0.27)	0.034 (0.0024 to 0.15)
T3	12 (1.4)	3/12 (25)	2/12 (16.7)	1/12 (8.3)
		0.26 (0.055 to 0.54)	0.17 (0.023 to 0.43)	0.13 (0.0047 to 0.46)
AJCC8				
T1	514 (58.3)	11/514 (2.1)	6/514 (1.2)	2/514 (0.39)
		0.021 (0.011 to 0.036)	0.0078 (0.0027 to 0.019)	0.004 (0.00083 to 0.014)
T2	277 (31.4)	2/277 (0.72)	5/277 (1.8)	1/277 (0.36)
		0.0078 (0.0016 to 0.026)	0.015 (0.005 to 0.036)	0.0039 (0.00037 to 0.02)
T3	83 (9.4)	7/83 (8.4)	5/83 (6.0)	1/83 (1.2)
		0.093 (0.04 to 0.17)	0.065 (0.024 to 0.14)	0.017 (0.0014 to 0.083)
T4	8 (0.9)	2/8 (25)	1/8 (12.5)	1/8 (12.5)
		0.27 (0.029 to 0.62)	0.12 (0.0048 to 0.44)	0.17 (0.0047 to 0.55)
Immune status				
Not immunosuppressed	685 (77.7)	11/685 (1.6)	8/685 (1.2)	2/685 (0.3)
		0.016 (0.0082 to 0.028)	0.011 (0.0048 to 0.021)	0.0038 (0.00079 to 0.013)
Iatrogenic	25 (2.8)	0/25 (0)	0/25 (0)	0/25 (0)
		0 (—)	0 (—)	0 (—)
Leukemia/lymphoma	46 (5.2)	0/46 (0)	2/46 (4.3)	1/46 (2.2)
		0 (—)	0.043 (0.0078 to 0.13)	0.022 (0.0017 to 0.1)
Transplant	118 (13.4)	10/118 (8.5)	7/118 (5.9)	2/118 (1.7)
		0.088 (0.045 to 0.15)	0.043 (0.016 to 0.091)	0.017 (0.0033 to 0.055)
HIV	8 (0.9)	1/8 (12.5)	0/8 (0)	0/8 (0)
		0.12 (0.0048, to 0.44)	0 (—)	0 (—)

AJCC8, American Joint Committee on Cancer Staging Manual, eighth edition; *BWH,* Brigham and Women's Hospital; *SD,* standard deviation.
*Values in the first row are n/total (%); values in the second row are the estimated 2-year cumulative incidence (95% confidence interval).

Table III. Results of univariate analysis for local recurrence, metastatic disease, any progression, disease-specific death, and all-cause death and multivariate analysis for any progression

	Univariate models										Multivariate model	
	Recurrence		Metastasis		Disease specific death		Overall death		Recurrence/metastasis/disease specific death			
Characteristic	HR	*P* value	HR	*P* value	HR	*P* value	HR	*P* value	HR	*P* value	HR	*P* value
Age												
<70 (reference)												
70-80	**0.27 (0.09-0.82)**	**.021**	0.79 (0.27-2.27)	.66	0.69 (0.11-4.11)	.68	1.29 (0.84-1.99)	.25	0.45 (0.18-1.09)	.077		
>80	0.36 (0.1-1.24)	.1	0.7 (0.19-2.63)	.6	**0 (0-0)**	**<.001**	1.84 (1.15-2.93)	.11	0.56 (0.21-1.54)	.26		
Male	0.83 (0.24-2.79)	.76	2.06 (0.27-15.47)	.48	**26,771.88 (10,897.09-65,772.93)**	**<.001**	**2.33 (1.02-5.29)**	**.044**	1.09 (0.33-3.59)	.89		
Immunosuppressed	**3.5 (1.52-8.05)**	**.0033**	**3.87 (1.49-10.01)**	**.0054**	5.05 (0.85-30.13)	.075	**3.45 (2.39-4.98)**	**3.64×10^{-11}**	**3.51 (1.67-7.34)**	**.00088**	**2.63 (1.20-7.77)**	**.016**
Size ≥ 2 cm	0.84 (0.35-2)	.69	2.04 (0.77-5.43)	.15	0.37 (0.04-3.33)	.38	1.32 (0.92-1.91)	.13	1.27 (0.6-2.66)	.54		
Poorly differentiated	**12.7 (4.9-32.94)**	**1.70×10^{-7}**	**25.37 (9.69-66.42)**	**4.60×10^{-11}**	**127.21 (15.5-1044.15)**	**6.40×10^{-6}**	**2.72 (1.26-5.85)**	**.011**	**14.32 (6.21-33.02)**	**4.20×10^{-10}**	**7.20 (1.88-27.55)**	**.0039**
Perineural invasion	**8.26 (3.04-22.43)**	**3.50×10^{-5}**	**8.4 (2.75-25.64)**	**.00019**	**17.65 (2.99-104.24)**	**.0015**	**2.39 (1.16-4.91)**	**.018**	**7.77 (3.14-19.25)**	**9.40×10^{-6}**	2.34 (0.54-10.21)	.26
Deep invasion	**8.81 (3.33-23.32)**	**1.20×10^{-5}**	4.27 (0.97-18.71)	.054	7.58 (0.84-68.38)	.071	1.12 (0.35-3.53)	.85	**6.61 (2.57-16.98)**	**8.70×10^{-5}**		
Site												
Trunk/extremities (reference)												
Head/neck	3.92 (0.48-32.31)	.2	3.95 (0.48-32.7)	.2	**162,405.85 (52,188.18-505,395.27)**	**<.001**	1.9 (0.97-3.75)	.063	5.67 (0.72-44.97)	.1		
Acral	2.68 (0.17-43.24)	.49	5.21 (0.47-58.26)	.18	1 (0.67-1.49)	>.99	1.52 (0.59-3.92)	.39	5.34 (0.48-59.73)	.17		
Temple	3.55 (0.42-29.87)	.24	1.78 (0.18-17.39)	.62	**55,508.21 (7812.44-394,391.93)**	**<.001**	0.8 (0.37-1.74)	.57	3.57 (0.42-30.03)	.24		
Lip	2.2 (0.2-24.36)	.52	1.1 (0.07-17.72)	.95	1 (0.74-1.35)	>.99	0.77 (0.31-1.92)	.58	2.21 (0.2-24.48)	.52		
Ear	1.59 (0.18-13.76)	.67	0.99 (0.1-9.68)	.99	**29,796.62 (4179.57-212,423.31)**	**<.001**	1.16 (0.59-2.27)	.66	2.26 (0.28-18.53)	.45		

Bold indicates statistical significance.
HR, Hazard ratio.

Strengths

- Large cohort, but only 5-10% of patients with advanced stage (see weakness below)
- Side by side comparison of two staging systems as well as inclusion of data regarding immunosuppression and high-risk features.
- Convincing data demonstrating significance of poor outcomes in poorly differentiated tumors.

Weaknesses

- Retrospective review with a median follow-up of 2.4 years. Exclusion criteria included less than 3 months follow-up. Unclear how many patients had only 3 months - 1 year follow-up. Anything less than a one-year follow-up is unacceptably short for high-risk cutaneous squamous cell cancer.

- Very low rates of advanced staged tumors with high-risk features.
    - AJCC T3/T4: N=91
    - BWH T2B/T3: N=44
- Authors admit great variability in consistent reporting in tumor depth and did not retrospectively analyze the pathologic specimens either. Thus, deep invasion was noted through either the biopsy or Mohs intraoperative or debulk pathology reports.

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