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

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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. (J Am Acad Dermatol 2021;85:588-95.)

Key words: high risk; Mohs micrographic surgery; outcomes; radiation; recurrence; squamous cell carcinoma; staging.

Cutaneous squamous cell carcinoma (cSCC), one of the most common skin neoplasms, can be subcategorized with a high-risk group that shows more aggressive and less predictable behavior.[1-3] These high-risk SCCs (hrSCCs) have been described to have a higher risk of local recurrence (LR), metastatic disease (MD), and disease-specific death (DSD). In an effort to better identify and prognosticate cSCC, multiple staging paradigms have been developed.[4] The *American Joint Committee on Cancer Staging Manual*, eighth edition (AJCC8) and Brigham and Women's Hospital (BWH) staging systems have identified size, location, depth of invasion, poor histologic differentiation, and perineural invasion (PNI) as risk factors that can help stratify these tumors' behavior.[5]

There has been growing literature about the use and efficacy of Mohs micrographic surgery (MMS)

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alone for hrSCC.[6-8] The studies have attempted to better prognosticate these high-risk tumors by identifying patient and tumor characteristics that predict poor outcomes such as LR, MD, DSD, and all-cause death (ACD). Furthermore, the timing and utility of adjuvant therapy in the management of hrSCC, specifically radiation, remains unclear.[9,10] However, recent retrospective studies have shown improved outcomes of patients with hrSCC treated with adjuvant radiation therapy.[11,12]

Our study aims to further analyze the application of MMS in hrSCC tumors in a large cohort of patients. We hope to more clearly define the effectiveness of MMS in hrSCC and identify factors predictive of LR, MD, DSD, and ACD.

CAPSULE SUMMARY

- What are the long-term outcomes for cutaneous high-risk squamous cell carcinomas (hrSCC) treated with Mohs micrographic surgery (MMS) with and without adjuvant therapy, and what are the risk factors that may predict poor long-term outcomes?
- Immunosuppression, perineural invasion, and poor tumor differentiation were significantly associated with poor patient outcomes. Poor differentiation should be considered within the staging systems and immunosuppression, especially transplant, as a high-risk clinical feature. MMS was an effective treatment for hrSCC, suggesting that strict margin control may be the most important treatment factor impacting tumor course and progression.

METHODS

A retrospective chart review was performed on patient electronic medical records at a single academic center and approved by the University of Texas Southwestern Medical Center institutional review board. Patients were identified by the institutional Mohs surgery case logs. All patients diagnosed with cutaneous SCC and treated with MMS from January 1, 2015, to December 31, 2018, were included. Records consisting of the pathology reports, Mohs surgery reports, debulk pathology reports when applicable, and clinic notes were then further reviewed for at least 1 of the following high-risk features and included if present: poor histologic differentiation, defined within our institution as having the following criteria of (1) not keratinizing and (2) staining required to confirm epithelial origin; preoperative tumor diameter of 2 cm or greater; PNI, defined as invasion of nerves equal or greater than 0.1 mm in caliber; deep invasion, defined by invasion beyond subcutaneous fat (invasion of perichondrium or cartilage for the ear); or involvement of the vermillion lip, ear, or temple.

Relevant data were extracted, including age, sex, race, immunosuppression status, tumor site, tumor size, presence of poor differentiation, presence of PNI, presence of invasion beyond subcutaneous fat, AJCC8 stage, BWH stage, number of MMS stages, defect size, use of adjuvant therapies, LR, distant metastasis, nodal metastasis, DSD, and ACD. Of note, immunosuppression was defined by either diagnosis of leukemia or lymphoma, transplant on immunosuppressive regimen, HIV related, or iatrogenic (on immunosuppressive medications for a reason other than transplant). LR was defined as biopsy-proven cSCC at the previous excision site. Metastasis was defined as either biopsy-proven cSCC in the draining lymph node basin or distant organ site. DSD was defined as death resulting from locally advanced or metastatic cSCC.

Exclusion criteria included cases with less than 3 months of follow-up and patients with MD at the time of diagnosis. For patients with less than 3 months of documented follow-up but who were greater than 3 months postsurgery, phone interview was attempted. If reached, patients were interviewed regarding recurrence of the prior skin cancer, the last time they had seen a dermatologist, and the last time they had seen a physician.

Descriptive statistics were calculated for patient, tumor, and treatment characteristics. Frequency of outcomes and 2-year cumulative incidence were calculated by BWH and AJCC8 stage and by immunosuppression subtypes. Progression-free survival was defined as survival without development of LR or MD. Effects of age, sex, site, immunosuppressed status, poor differentiation, PNI, size of 2 cm or greater, and deep invasion were examined in univariate proportional hazard models with and without competing risks for progression-free survival, time to LR, MD, DSD and for overall survival. Given the low rates of events, multivariate modeling was performed only for progression-free survival using proportional hazards models with competing risk. All variables used in univariate models were included, and the final multivariate model was selected via backward elimination. Cumulative incidence curves were generated for LR, MD, and DSD, and Kaplan-Meier survival curves were generated for overall death by factors selected for the multivariate model.

Abbreviations used:

ACD:	all-cause death
AJCC8:	*American Joint Committee on Cancer Staging Manual*, eighth edition
BWH:	Brigham and Women's Hospital
cSCC:	cutaneous squamous cell carcinoma
DSD:	disease-specific death
hrSCC:	high-risk squamous cell carcinoma
LR:	local recurrence
MD:	metastatic disease
MMS:	Mohs micrographic surgery
PNI:	perineural invasion

To test the effect of adjuvant treatment, propensity matching was used to match case patients treated with radiation or adjuvant treatment with control patients treated with Mohs only based on immunosuppression, poor differentiation, PNI, size of 2 cm or greater; deep invasion and cumulative incidence functions for any progression of matched case and control patients were compared by using proportional hazards models with competing risk. Analysis was performed with R software.[13]

RESULTS

We identified 10,267 case patients on initial search. Of those, 986 met the diagnosis of SCC and were high risk based on the inclusion criteria. After exclusion criteria were applied, our final cohort consisted of 882 hrSCC tumors from 715 unique patients with a median follow-up of 2.4 years (interquartile range, 1.6-3.5) (Table I). At first surgery, the average age was 72.2 years (standard deviation, 10.2), 87.6% were men, 19% were immunosuppressed (representing 22.3% of tumors), and 80 patients (11.2%) died during the follow-up period.

Within our tumor cohort, the most common location was the ear (35%), followed by the temple (19.2%). PNI was noted in 3.7% of the cases, deep invasion in 3.5%, size greater than 2 cm in 40.5%, and poor differentiation in 3.4%. Forty tumors were treated with single or combination adjuvant treatment (4.5%) consisting of radiation (3.4%), further wide local excision with or without lymph node dissection (1.6%), and/or chemotherapy (0.5%). Twenty-two of our case patients developed LR (2.5%), 17 developed metastases (1.9%), and 5 died of complications of their hrSCC (0.6%). On review of the patients with multiple tumors treated, we had 11 recurrences, 8 metastases, and 2 deaths from hrSCC. Charts of patients with these events were reviewed, and each event was attributed to specific tumors using the investigators' best clinical judgement of clinic notes, pathology reports, and imaging results. The median time to progression (LR, MD, DSD) was 8.8 months.

Under BWH staging, 499 (56.6%) of our tumors were T1, 339 (38.4%) were T2a, 32 (3.6%) were T2b, and 12 (1.4%) were T3. Using AJCC8 staging, 514 (58.3%) were T1, 277 (31.4%) were T2, 83 (9.4%) were T3, and 8 (0.9%) were T4 (Table II). For less aggressive (T1 and T2a) tumors according to BWH staging, LR was 1.8%, MD was 1.3%, and DSD was 0.4%. More aggressive tumors based on the BWH staging (such as T2b stage and up) had an LR of 15.9%, MD of 13.6%, and DSD of 4.5% (Table II). Of note, the 2 AJCC8 T1 cases that resulted in DSD showed poor differentiation and were in immunosuppressed (lung transplant) patients. Because these risk factors are not accounted for under the AJCC8 staging system, they were T1 under AJCC8 but BWH stage T2a.

Among patients classified as immunosuppressed, 59.9% were transplant patients, 23.4% had a diagnosis of leukemia or lymphoma, 12.7% were iatrogenically immunosuppressed (iatrogenic) not due to transplant, and 4.1% were patients with HIV. There were no cases of LR, MD, or DSD in the iatrogenic cohort. Two cases of MD and 1 of DSD were seen in patients with leukemia/lymphoma. One tumor recurred in a patient with poorly controlled HIV. Ten cases of LR, 7 of MD, and 2 of DSD occurred within transplant patients (Table II).

Our outcomes for cases treated with Mohs alone (n = 842) were similar to those for all cases. BWH stage T1 and T2a tumors had an LR rate of 1.6%, MD rate of 1.3%, and DSD rate of 0.2%. Aggressive tumors based on BWH staging (T2b stage and above) had an LR of 17.6%, MD of 17.6%, and DSD of 5.9%.

In univariate analysis, the factors associated with LR, MD, any progression, DSD, and ACD were PNI (hazard ratios [95% confidence intervals (CIs)], respectively: 8.3 [3.0-22.4], 8.4 [2.8-25.6], 7.8 [3.1-19.3], 17.7 [3.0-104.2], and 2.4 [1.2-4.9]) and poor differentiation (hazard ratios [95% CIs], respectively: 12.7 [4.9-32.9], 25.4 [9.7-66.4], 14.3 [6.2-33.0], 127.2 [15.5-1044.2], and 2.7 [1.3-5.9]). Immunosuppression was associated with LR, MD, any progression, and ACD (hazard ratios [95% CIs,] respectively: 3.5 [1.5-8.1], 3.9 [1.5-10.0], 3.5 [1.7-7.3], 5.1 [0.9-30.1], and 3.5 [2.4-5.0]) but did not reach significance for DSD (5.1 [0.9-30.1], P = .075) (Table III and Fig 1). Deep invasion was found to be significantly associated with LR (8.8 [3.3-23.3]) and any progression [6.6 (2.6-17.0]), although not with MD, DSD, and ACD. Male sex and locations of head/neck, temple, and ear were also significantly associated with increased risk of DSD. However, there were very few DSD events,

Table I. Patient demographics, comorbidities, and tumor characteristics

Clinicopathologic variable	Value
Demographics (N = 715 unique patients)	
Age, y, mean (SD)	72.2 (10.2)
Male, n (%)	626 (87.6)
Race, n (%)	
Asian	1 (0.1)
Black	4 (0.6)
Hispanic	20 (2.8)
Non-Hispanic White	690 (96.5)
Immunosuppressed, n (%)	128 (17.9)
Tumor characteristics (N = 882 tumors)	
In immunosuppressed patients, n (%)	197 (22.3)
Iatrogenic	25 (2.8)
Leukemia/lymphoma	46 (5.2)
Transplant	118 (13.4)
HIV	8 (0.9)
Location, n (%)	
Extremity	71 (8.0)
Trunk	25 (2.8)
Face	88 (10.0)
Hand/foot	35 (4.0)
Scalp/neck	96 (10.9)
Temple	169 (19.2)
Lip	88 (10.0)
Ear	309 (35.0)
Genitals	1 (0.1)
Size of largest dimension, cm, mean (SD)	1.7 (1.2)
Size of smallest dimension, cm, mean (SD)	1.2 (0.8)
High-risk features, n (%)	
Poorly differentiated	30 (3.4)
Perineural invasion	33 (3.7)
Deep invasion	31 (3.5)
Size ≥2 cm	357 (40.5)
Defect largest dimension, cm, mean (SD)	2.6 (1.5)
Defect smallest dimension, cm mean (SD)	2.0 (1.2)
AJCC8 tumor stage, n (%)	
T1	514 (58.3)
T2	277 (31.4)
T3	83 (9.4)
T4	8 (0.9)
BWH tumor stage, n (%)	
T1	499 (56.6)
T2A	339 (38.4)
T2B	32 (3.6)
T3	12 (1.4)
Adjuvant therapies, n (%)	
Adjuvant treatment performed	40 (4.5)
Adjuvant radiation performed	30 (3.4)
Adjuvant chemotherapy performed	4 (0.5)
Wide local excision performed	14 (1.6)

AJCC8, American Joint Committee on Cancer Staging Manual, eighth edition; *BWH,* Brigham and Women's Hospital; *SD,* standard deviation.

and male sex and tumors in these locations made up the majority of our cases. See Table III for further univariate analysis data. In the multivariate proportional hazard models for any progression, selected risk factors by backward elimination were immunosuppression (2.6 [95% CI, 1.2-7.8], $P = .016$), poor differentiation (7.2 [95% CI, 1.9-27.6], $P = .0039$] and PNI (2.34 [95% CI, 0.5-10.2], $P = .26$). Although the hazard ratio for PNI was not significant on its own, it was selected as a factor that increased the explanatory power of the model.

Case patients who received radiation or adjuvant treatment were significantly more likely to have high-risk features or immunosuppression, so it is unsurprising that naïve hazard ratios for radiation or adjuvant treatment estimated significantly increased risk of progression with these treatments (Table IV). Propensity score—matched adjuvant-treated case and control patients treated with Mohs alone were similar across immunosuppressed status and rates of poor differentiation, PNI, size of 2 cm or greater, and deep invasion, although the probability of receiving treatment (thus risk status) was still higher in the treated case patients. After matching, the point estimate for radiation or adjuvant treatment became less than 1; however, a significant difference in cumulative incidence functions between the 2 groups was not found.

DISCUSSION

We report a large cohort of patients with hrSCC treated with Mohs surgery and followed up over years. Mohs alone in the treatment of hrSCC has been shown to be an effective therapy by several recent studies, and our goal was to expand on those findings, specifically investigating risk factors predicting prognosis.[6-8] Similar to the results shown by Marrazzo et al,[6] our cohort of patients with hrSCCs treated with MMS alone showed excellent outcomes for low-risk (BWH staging T1 and T2a) tumors and improved outcomes for high-risk (BWH stage T2b and T3) tumors.[3,6]

The majority of our poor outcomes were in higher-stage tumors. Within our cohort treated with MMS alone, 16 patients experienced LR, 12 MD, and 3 DSD. There were 3 tumors that were BWH stage T2a that led to DSD and 2 tumors that were AJCC stage T1 that led to DSD, representing 3 unique patients. Two of those patients had tumors with BWH stage T2a with only poor differentiation, a feature not included in the AJCC staging system and, thus, only were T1. Additionally, those patients were lung transplant patients. The other patient with DSD had tumor size greater than 2 cm as the only risk feature but had an active diagnosis of leukemia.

Our statistical analysis had similarly found that immunosuppression was associated with poor outcomes of LR, MD, and ACD. Immunosuppressed

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).

status was selected and significant in our multivariate model as well. These data underscore the importance of immunosuppression in prognosticating hrSCC tumors. Further breakdown of immunosuppression by subtype showed higher incidence of all poor outcomes in the transplant patient subtype as well as higher incidence of certain poor outcomes (LR in HIV, MD and DSD in lymphoproliferative disorders) in other subtypes. The literature has clearly shown the significant positive relationship of immunosuppressed status and development of cSCC in addition to higher risk of recurrence and more aggressive disease course.[14-17] However, immunosuppression is not included as a risk factor within our current staging framework (BWH and AJCC8). It is a risk factor within the National Comprehensive Cancer Network management guideline.[18] In the case of AJCC8, it confines its staging system to just tumor features and, thus, patient-specific factors such as immunosuppression are not included. Our results suggest that consideration of immunosuppression, specifically transplant, as a high risk, patient-specific factor should be considered within treatment guidelines.

Within our cohort, poor differentiation remained the strongest prognostic factor associated with LR, MD, DSD, and ACD. Although not included in the AJCC8 staging, this factor is accounted for in the BWH staging and should be given strong clinical weight.

Also, of note, tumor size greater than 2 cm did not predict a poor outcome after MMS treatment in any model and depth of invasion, and locations on the lip, ear, or temple were not associated with poor outcomes consistently and were dropped from the multivariate model. It is possible that the strict margin control during MMS mitigates the effects of these factors on outcome.

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.

Table IV. Comparison of high-risk factors in patients treated with Mohs only and radiation or any adjuvant therapy in whole sample and propensity-matched case and control patients*

	All		Matched		All		Matched	
High-risk factor	**No radiation (n = 852)**	**Radiation (n = 30)**	**No radiation (n = 30)**	**Radiation (n = 30)**	**No adjuvant treatment (n = 842)**	**Adjuvant treatment (n = 40)**	**No adjuvant treatment (n = 40)**	**Adjuvant treatment (n = 40)**
Probability of treatment	**0.0238 (0.088)**	**0.324 (0.263)**	0.234 (0.275)	0.324 (0.263)	**0.0228 (0.0867)**	**0.52 (0.335)**	**0.293 (0.318)**	**0.467 (0.31)**
Immunosuppressed, n (%)	**184 (21.6)**	**13 (43.3)**	14 (46.7)	13 (43.3)	**180 (21.4)**	**17 (42.5)**	20 (55.6)	14 (38.9)
Poor differentiation, n (%)	**19 (2.2)**	**11 (36.7)**	12 (40)	11 (36.7)	**15 (1.8)**	**15 (37.5)**	12 (33.3)	11 (30.6)
PNI, n (%)	**15 (1.8)**	**18 (60)**	11 (36.7)	18 (60)	**10 (1.2)**	**23 (57.5)**	10 (27.8)	19 (52.8)
Size ≥2 cm, n (%)	**338 (39.7)**	**19 (63.3)**	19 (63.3)	19 (63.3)	**330 (39.2)**	**27 (67.5)**	21 (58.3)	23 (63.9)
Deep invasion, n (%)	**20 (2.3)**	**11 (36.7)**	12 (40)	11 (36.7)	**13 (1.5)**	**18 (45)**	13 (36.1)	14 (38.9)
Estimated effect of radiation and any adjuvant treatment on progression-free survival								
HR (95% CI), *P* value	6.9 (2.6-18.2), <.001		0.62 (0.2-1.9), .41		7.9 (3.4-18.7), .001		0.69 (0.3-1.9), .48	

CI, Confidence interval; *HR,* hazard ratio; *PNI,* perineural invasion.
*Bold indicates significant differences between groups. HRs calculated using competing risk models. Matching done via propensity score nearest neighbor matching.

There are conflicting data regarding the role of adjuvant therapy in hrSCC.[9,10] More recently Miller et al[11] and Stevenson et al[12] showed, in their retrospective reviews, improved outcomes of hrSCC treated with radiation therapy and cSCC with any level of PNI treated with radiation therapy, respectively.[11,12] Although this was not the primary goal of our study, within our cohort of patients treated with adjuvant therapy (n = 40), there was no statistical difference in outcomes when matching by high-risk features and immunosuppressed status. Similarly, when analyzing hrSCC treated with MMS plus adjuvant radiation therapy (n = 30) and again matching by the characteristics described, point estimates suggested improved outcomes with treatment, but this was not statistically significant. Given the low rates of progression and high risk factors, limited sample size, and imperfect matching, further study with larger samples or randomized controlled trials may need to be performed to better assess the impact of adjuvant treatment on very-high-risk tumors.

Our study was limited by its retrospective nature and low rates of tumors with some high risk factors and events. Longer-term follow-up for our more recent cases may have revealed more events of interest. Additionally, because the majority of our patients were referrals, White, and with tumors on the head/neck location, a more comprehensive tumor and patient cohort will be necessary in the future to adequately generalize our findings. Similar to Schmults et al,[3] we found great variability in consistent reporting in tumor depth, and we did not retrospectively analyze the pathologic specimens either. Thus, deep invasion was noted through either the biopsy or Mohs intraoperative or debulk pathology reports. For immunosuppressed patients such as those with HIV or leukemia/lymphoma, we did not account for level of disease control. Finally, our study was underpowered to detect a difference in adjuvant treatment modalities. Even with matching of treated and untreated cases, we cannot fully account for the nonrandom decisions to recommend adjuvant treatment.

CONCLUSION

MMS remains an effective treatment for hrSCC. Immunosuppression, PNI, and poor differentiation are significantly associated with poor outcomes. Of those, poor differentiation was the strongest prognostic factor. Immunosuppression should be considered as a high-risk feature although not factored into current staging systems. Further study is needed on the effect of adjuvant therapy on outcomes.

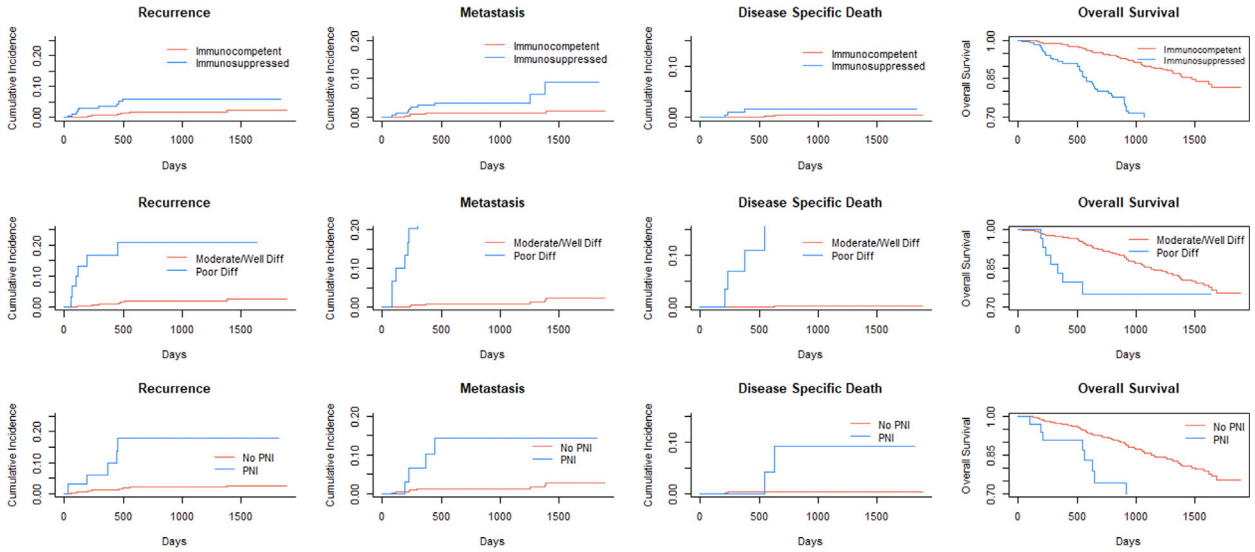

Fig1. Cumulative incidence functions and Kaplan-Meier curves: local recurrence (first column), metastatic disease (second column), disease-specific death (third column), and Kaplan-Meier curves for overall survival (fourth column) by immunosuppressed status, presence of poor differentiation, and perineural invasion (PNI). *Diff,* Differentiation.

Conflicts of interest

None disclosed.

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