Clinical outcomes in high-risk squamous cell carcinoma patients treated with Mohs micrographic surgery alone

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Background: There is little evidence to predict patient outcomes after the treatment of high-risk cutaneous SCC (hrSCC) using Mohs micrographic surgery (MMS).

Objective: We sought to report the rates of poor outcomes in patients with hrSCC treated by MMS alone and to determine if any specific clinical factors may be more predictive of these outcomes.

Methods: We conducted a retrospective chart review of all patients with hrSCC who were treated in our clinic between October 2011 and December 2015.

Results: We identified 647 hrSCC tumors that met the inclusion criteria. During the follow-up period, there were 19 local recurrences (2.9%), 31 nodal metastases (4.8%), 7 distant metastases (1.1%), and 7 disease-specific deaths (1.1%). Two factors, poor differentiation and invasion beyond the subcutaneous fat, were positively associated with local recurrence, nodal metastasis, and disease-specific death through multivariate analysis.

Conclusions: Invasion beyond the subcutaneous fat and poor histologic differentiation may carry a greater risk of poor outcomes than other factors in hrSCC. MMS alone provides excellent marginal control with low rates of local recurrence, nodal metastasis, and disease-specific death. (J Am Acad Dermatol 2019;80:633-8.)

Key words: cutaneous oncology; cutaneous squamous cell carcinoma; dermatologic surgery; high-risk squamous cell carcinoma; Mohs micrographic surgery.

Although most cases of cutaneous squamous cell carcinoma (cSCC) are cured by surgery, there exists an important subset of patients with high-risk cutaneous squamous cell carcinoma (hrSCC) that have been defined by their appreciable risk of local recurrence (LR), nodal metastasis (NM), and disease-specific death (DSD).[1-3] hrSCC has not been consistently defined, however, contributing to the clinical equipoise surrounding its management. Several studies have attempted to identify the prognostic factors that are predictive of poor outcomes in cSCC with the hope of further refining the definition and guiding appropriate management. In 2010, the

Abbreviations used:

AJCC-SS:	American Joint Committee on Cancer staging system
BWH-SS:	Brigham and Women's Hospital staging system
cSCC:	cutaneous squamous cell carcinoma
DM:	distant metastasis
DSD:	disease-specific death
hrSCC:	high-risk cutaneous squamous cell carcinoma
LR:	local recurrence
MMS:	Mohs micrographic surgery
NM:	nodal metastasis
WLE:	wide local excision

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Funding sources: None.
Conflicts of interest: None declared.
Accepted for publication September 7, 2018.

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Published online September 20, 2018.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.09.015

American Joint Committee on Cancer first created a staging system (AJCC-SS) specifically for cSCC, separating it from other nonmelanoma skin cancers, to reflect the natural history and stage-specific outcomes of cSCC.[4,5] However, the AJCC-SS has demonstrated poor ability to prognosticate which patients are at risk for NM, with the T2 stage representing 80% of tumors and 92% of NMs in 1 study of prospectively collected cSCC.[6]

To better stratify tumors, Brigham and Women's Hospital defined and validated an alternate staging system (BWH-SS) separating patients who were more likely to have poor outcomes from those with better outcomes.[7] Seventy-three percent of cSCC patients in their 2 BWH-SS publications, however, underwent treatments other than Mohs micrographic surgery (MMS).[8] The accuracy of this staging system could be compromised by recurrences caused by inadequate excision rather than histologic or clinical features of the tumor.

The goals of our study are to report the rates of LR, NM, DM, and DSD in patients with hrSCC (as stratified by both the AJCC-SS and the BWH-SS) treated by MMS alone, and to determine if any specific clinical factors may be more predictive of poor outcomes.

CAPSULE SUMMARY

- Various factors are linked to poor outcomes in squamous cell carcinoma, but poor differentiation and invasion beyond the subcutaneous fat may greater predict the risk of locoregional disease and disease-specific death.
- Mohs micrographic surgery alone provides excellent marginal control of high-risk squamous cell carcinoma and may lower rates of measured poor outcomes.

METHODS

This study received institutional review board approval from the Western Institutional Review Board (protocol no. 20152364). Using practice management software (MedEvolve, Little Rock, AR), all primary cSCCs treated between October 1, 2011 (the first date at which SCC was differentiated from nonmelanoma skin cancer by *International Classification of Diseases, 9th revision* codes) and December 1, 2015 were identified. None of the included patients received preoperative imaging or had sentinel lymph node biopsy specimens obtained. All lesions were treated with MMS, with an initial margin of ≥2 mm and 2-mm margins at each subsequent stage. All included lesions had no clinical signs of locoregional metastasis and histologically clear margins at the conclusion of MMS, and none received postoperative radiation therapy. A comprehensive chart review of all treated cSCCs was then conducted to identify cases that featured at least one of the following factors: poor differentiation, preoperative tumor diameter ≥2 cm, perineural invasion (PNI), depth beyond the subcutaneous fat, or involvement of the ear, lip, or temple. Invasion beyond the subcutaneous fat was interpreted as tumor invasion through the subcutaneous fat layer requiring extirpation of fascia, periosteum, perichondrium, or bone for tumor clearance. This information was garnered from pathology reports, surgical notes, and Mohs maps with special annotations of the findings during surgery. When necessary, archived MMS slides were examined. Information extracted from each of these identified cases included age, sex, lesion site, preoperative lesion size, presence of poor differentiation, diameter ≥2 cm, presence of PNI, presence of invasion beyond the subcutaneous fat, AJCC 7th edition stage, BWH stage, immune status, LR, NM, DM, DSD, and all-cause death. Patients who had undergone solid organ transplantation, iatrogenic immunosuppression, and who had chronic lymphocytic leukemia were considered immunosuppressed. Cases treated <1 year before the chart review were excluded because of insufficient follow-up time. Recurrent tumors were excluded from our study, principally to maintain uniformity with the BWH-SS validation study, which also excluded recurrent tumors.

Next, follow-up data were collected regarding occurrence of LR, NM, DM, and DSD after tumor extirpation by MMS. Patients with identified hrSCC were contacted and interviewed by telephone regarding the occurrence of poor outcomes. Sixty-two percent of the patients were followed clinically at the authors' clinics and did not require telephone interviews. Follow-up was gathered via telephone interview for 248 patients. LR was defined as a biopsy-proven cSCC within the excision scar. NM was defined as biopsy-proven cSCC in the draining lymph node basin. DM was defined as biopsy-proven cSCC in an organ system other than the skin or lymphatics. DSD was defined as death occurring from metastatic or locally advanced cSCC. The 5 patient claims of poor outcomes garnered through telephone interview were confirmed via contact with the referring provider. All 7 cases of DSD were confirmed through existing correspondence (within the medical record). Cases

Table I. Number of tumors by stage, American Joint Committee on Cancer T-staging system, and summary of staging system

AJCC tumor stage	Summary	Patients, n (%)
T0	In situ squamous cell carcinoma	—
T1	≤2 cm in greatest dimension with <2 high-risk factors	232 (35.9)
T2	≥2 cm in greatest dimension or with two or more high-risk factors	411 (63.5)
T3	Tumor with invasion of orbit, maxilla, mandible, or temporal bones	4 (0.6)
T4	Tumor with invasion of other bones or direct perineural invasion of skull base	0 (0.0)

American Joint Committee on Cancer high-risk factors include ≥2 mm thickness, Clark level ≥IV, perineural invasion, primary site ear, primary site non–hair-bearing lip, or poorly differentiated histology.
AJCC, American Joint Committee on Cancer.

Table II. Number of tumors by stage, Brigham and Women's Hospital alternative T-staging system, and summary of staging system

BWH tumor stage	Summary	Patients, n (%)
T0	In situ squamous cell carcinoma	
T1	0 risk factors	235 (36.3)
T2a	1 risk factor	267 (41.3)
T2b	2-3 risk factors	129 (19.9)
T3	4 risk factors or bone invasion	16 (2.5)

Brigham and Women's Hospital risk factors include tumor diameter ≥2 cm, poorly differentiated histologic characteristics, perineural invasion, and tumor invasion beyond the subcutaneous fat (excluding bone invasion, which automatically upgrades tumor to alternative stage T3).
BWH, Brigham and Women's Hospital.

required ≥1 year of confirmed follow-up to be included in the final study group.

Means, standard deviations, and standard errors and median and interquartile ranges were calculated for normally and nonnormally distributed interval variables respectively. Frequency distributions were produced for nominal and ordinal variables. Group means and medians were tested using parametric and nonparametric methods as appropriate. For nominal variables, proportions were calculated for each group and statistical association tested with the chi squared or Fisher's exact test. Odds ratio or Cramer's V was used to indicate the strength of association for significant tests. For multiple comparisons, the familywise error rate was set at 0.05 with the Bonferroni method.[9] Survival differences among groups were tested with the log rank test. Cox proportional hazard models were developed for each outcome of interest and reduced by backward elimination. Statistical analysis was performed using R software (v 3.2.4; Vienna, Austria).[10]

RESULTS

The chart review of all SCC cases resulted in the identification and inclusion of 647 hrSCC tumors. A total of 116 (15%) cases were identified but excluded because of absent or insufficient follow-up data. No statistically significant differences regarding age, gender, tumor location, tumor characteristics, AJCC or BWH stage, or rate of immunosuppression were found between included and excluded cases (data not shown.) Summaries of both staging systems and total number of tumors per stage are shown in Tables I and II.

Demographic, clinical, and pathologic information can be found in Table III. Most patients in the cohort had single tumors. For patients with multiple tumors, each tumor was considered independent during analysis. The mean age at time of treatment was 74.8 years (standard deviation [SD] 11.2 years.) Most patients were male (78.7%.) Sixty-four patients (10.5%) were immunosuppressed. The median follow-up was 36 months (range 12-192 months).

The median tumor size was 2.1 cm (interquartile range 1.4 cm), with 373 tumors (57.7%) ≥2 cm. Three hundred twenty-seven tumors (50.6%) arose in the high-risk areas of the ear, lip, or temple. All T1 lesions (in both staging systems) were from these high-risk locations but had no other high-risk features. Fifty-eight tumors (9%) were poorly differentiated, 52 (8%) had PNI, and 134 (20.7%) invaded beyond the subcutaneous fat. The mean follow-up time was 43.2 months (SD 29.2 months). During the follow-up period, there were 19 LRs (2.9%), 31 NMs (4.8%), 7 DMs (1.1%), and 7 DSDs (1.1%).

Using the AJCC-SS, there were 232 T1 tumors (35.9%), 411 T2 tumors (63.5%), and 4 T3/T4 tumors (0.6%) (see Table I for staging criteria). Using the BWH-SS, there were 235 T1 tumors (36.3%), 267 T2a tumors (41.3%), 129 T2b tumors (19.9%), and 16 T3 tumors (2.5%) (see Table II for staging criteria). Table IV shows the proportion of measured poor outcomes that occurred within each stage for the 2 staging systems.

Multivariate analysis using Cox proportional hazard models and reduction by backward elimination conducted to determine the correlation between the observed factors (high-risk location, immune status, and the 4 BWH staging system criteria) and the

Table III. Cohort patient and tumor characteristics

Characteristic	
Participant factors	
Mean age at treatment, y (SD)	74.8 (11.2)
Mean follow-up, months	43.2
Median follow-up, months	37
Gender, n (%)	
Female	138 (21.3)
Male	509 (78.7)
Immunosuppression, n (%)	
None	579 (89.5)
Iatrogenic	4 (0.6)
Leukemia/lymphoma	20 (3.1)
Transplant	44 (6.8)
Tumor factors	
Mean preoperative diameter, cm (SD)	2.2 (1.4)
Tumor body location, n (%)	
Cheek	50 (7.7)
Ear	171 (26.4)
Forehead	33 (5.1)
Hand/finger	16 (2.5)
Lip	74 (11.4)
Nose	21 (3.3)
Other	121 (18.7)
Scalp	74 (11.4)
Temple	87 (13.5)
High-risk location, n (%)	
Non–high-risk	320 (49.5)
Ear	165 (25.5)
Lip	78 (12.1)
Temple	84 (13.0)
Poorly differentiated, n (%)	
No	589 (91.0)
Yes	58 (9.0)
Diameter ≥2 cm, n (%)	
No	274 (42.4)
Yes	373 (57.7)
Perineural invasion, n (%)	
No	595 (92.0)
Yes	52 (8.0)
Deep invasion, n (%)	
No	513 (79.3)
Yes	134 (20.7)

SD, Standard deviation.

measured poor outcomes. Results of multivariate analysis are displayed in Table V. Holding other variables at fixed value, having a tumor with deep invasion beyond the subcutaneous fat increases the hazard of LR 746% and the hazard of NM 902%. Holding other variables at fixed value, a poorly differentiated tumor increases the hazard of LR 453%, increases the hazard of NM 236%, and increases the hazard of NM by 3300%. Age, gender, tumor location, immunosuppression, tumor diameter, or PNI were not statistically significant after multivariate analysis.

All but 1 of the patients with LR in our cohort were successfully locally salvaged by repeat MMS (median follow-up of 37 months). For patients that developed NM during active observation, the rate of regional (nodal) control after lymph node dissection with or without radiation in our cohort was 30 of 31 patients (median follow-up of 31 months). Twenty-four of 31 patients with nodal metastasis had survived, with 6 developing DMs and suffering DSD and 1 succumbing to regionally advanced disease. Ultimately, all but 1 patient with DMs died of cSCC.

DISCUSSION

MMS has previously been demonstrated to be a highly effective modality in the treatment of cSCC.[11] A single article regarding MMS for hrSCC demonstrated extremely low rates of poor outcomes, but was published before the BWH-SS and makes no mention of AJCC stage.[12] In the cohort Schmults et al[3] used to develop the BWH-SS, 27% were treated with MMS while the remainder underwent wide local excision (WLE) or other destructive modalities. Our cohort experienced the lowest rates of LR, NM, and DSD published thus far for hrSCC using the BWH staging system. Additional data by stage and by treatment provided by Dr Schmults (Chrysaline Schmults, MD, personal communication, October 16, 2016) shows that improved outcomes with MMS may extend to BWH stage T2b and T3 lesions.[8] Our MMS T2b patients had a LR rate of 7.8% compared with the 17.2% LR rate observed in T2b patients treated with WLE with or without radiation. Our MMS T3 patients (n = 16) suffered 5 LRs and 3 DSDs, while 6 of 9 T3 patients (n = 9) treated with WLE with or without radiation suffered LRs, and all 9 succumbed to DSD. While the 2 cohorts likely differed, our more population-based cohort advances the generalizability of the BWH-SS. Additional study is needed to directly and statistically compare rates of poor outcomes by different treatment modalities. The observation of lower NM and DSD, however, may be attributable to the ability of MMS to completely extirpate the primary tumor, halting the natural history of disease progression. This theory is supported by data that show that incomplete excision of cSCC leads to a 4-fold increase in DSD.[13]

Anecdotally in our clinic, the identification of high-risk patients changes follow-up to every 2 to 3 months and places an emphasis on the teaching of weekly self-palpation of the draining lymph node basins. With achieving negative margins and treating only palpable nodes, our survival rate is high, and salvage of patients with nodal disease is comparable to the 95% rate of regional control published in the otorhinolaryngology literature, sparing unnecessary

Table IV. Proportion of measured outcomes occurring within each stage (for both American Joint Committee on Cancer T stage and Brigham and Women's Hospital stage)

Stage	n (%)	n/N (%)			
		Local recurrence	Nodal metastasis	Distant metastasis	Disease-specific death
AJCC					
T1	232 (35.9)	1/19 (5.3)	3/31 (9.6)	0/7 (0)	0/7 (0)
T2	411 (63.5)	18/19 (94.7)	27/31 (87.1)	6/7 (85.7)	7/7 (100)
T3/T4	4 (0.6)	0/25 (0)	1/31 (3.2)	1/7 (14.3)	0/7 (0)
BWH					
T1	235 (36.3)	2/19 (10.5)	3/31 (9.6)	0/7 (0)	0/7 (0)
T2a	267 (41.3)	2/19 (10.5)	4/31 (12.9)	0/7 (0)	0/7 (0)
T2b	129 (19.9)	10/19 (52.6)	19/31 (61.3)	3/7 (42.9)	4/7 (57.1)
T3	16 (2.5)	5/19 (26.3)	5/31 (16.1)	4/7 (57.1)	3/7 (42.9)

AJCC, American Joint Committee on Cancer; *BWH*, Brigham and Women's Hospital.

Table V. Results of multivariate analysis: Increased hazard rates of measured outcomes by tumor factors

	Measured outcome, %		
	Local recurrence	Nodal metastasis	Disease-specific death
Tumor factor			
Poor differentiation	746	236	3300
Invasion beyond fat	453	902	Not significant

Factors that were not significant included high-risk location, size ≥2 cm, immunosuppression, Breslow depth, and perineural invasion (which was not stratified by nerve caliber).

surgery for many patients without clinical nodal disease.[14]

The principal objective was to investigate which different clinical and pathologic factors were independently and significantly associated with our measured outcomes. On multivariate analysis following reduction by backward elimination, only 2 factors, poor differentiation and invasion beyond the subcutaneous fat, remained significantly associated with poor outcomes. Anaplasia has long been linked with poorer outcomes in a multitude of solid tumors.[13] Like our study, Brinkman et al[15] found that poor histologic differentiation was closely linked with nodal metastasis and overall survival in cSCC. Invasion beyond the subcutaneous fat, which is intrinsically tied to tumor depth of invasion, has also been similarly intimately linked to poor outcomes in hrSCC. In fact, tumor thickness >6 mm is the only stand-alone prognostic variable demonstrated prospectively.[16] Further prospective studies are required to determine if these 2 tumor factors are exclusively the principal predictors of poor outcomes. It may be that MMS mitigates the risk conferred by factors such as size >2 cm or PNI.

In evaluating poor outcomes by both AJCC-SS and BWH-SS in our cohort, several key observations are worth noting. In our cohort, AJCC T3 and T4 tumors (requiring bone invasion) represented only 0.6% of all tumors. This meant that nearly all tumors, with any combination of high-risk features, was designated AJCC T2 stage. This aggregation of high-risk tumors with significantly variable biologic behaviors and patient outcomes within 1 AJCC T-stage renders the AJCC-SS meaningless to the clinician. Conversely, the BWH created different break points based on risk factors to better stratify each stage with an increased risk of poor outcomes. Only 23% of tumors in our cohort were BWH T2b and T3 stage, yet they accounted for 79% of LRs, 77% of NMs, and 100% of DMs and DSDs. Our T2b/T3 lesions had a LR rate of 10.3%, a NM rate of 16.5%, and a DSD rate of 4.8%, notably higher than the mean rate for the overall cohort. This consolidation of poor outcomes in the higher 2 stages mirrors the results of Schmults et al[3] in their previous 2 applications of the staging system.[7,8] This division between favorable stages (T1 and T2a) and higher-risk stages (T2b and T3) makes the BWH-SS a valuable prognostic tool for the clinician and allows it to serve as a guide for patient selection in future prospective trials. The 8th edition of the AJCC-SS has recently been released and incorporates many of the high-risk factors into staging. Additional studies are necessary to determine its efficacy as a prognostic tool.

Several limitations were noted. One limitation is the retrospective gathering of demographics, clinical and pathologic information, and application of the 2 staging systems, and an inability to accurately gather the time from treatment to measured outcome. Some risk factors that could not be retrospectively studied, such as tumors arising within scar/nonhealing wounds or tumors with other specific histologic

patterns previously described as high-risk (adenoid, infiltrative, etc) were not included and may be statistically significant. Another limitation is the absence of follow-up data on a small proportion of all identified cases. This subset of cases represented only 15% of the overall 763 hrSCCs found during our chart review, and no statistically significant differences exist between the cases with and without follow-up. Another limitation involves PNI. The BWH-SS first introduced and proposed in 2013, which was used to stage our subset of patients, did not take nerve caliber into account. The current iteration of the BWH-SS now focuses on PNI ≥0.1 mm. Our cohort of PNI cases likely contains at least some proportion of PNI that is <0.1 mm. Most of the PNI in our cohort was noted at the peripheral margin of an MMS stage, however, which may be biologically distinct from other forms of PNI. Another limitation is that 26% of patients had <2 years of follow-up. Longer follow-up may have revealed a greater number of poor outcomes, identifying other statistically significant risk factors.

In conclusion, invasion beyond the subcutaneous fat and poor differentiation may be the principal predictors of poor outcomes in patients treated with MMS. In addition, our cohort affirmed the role of the BWH-SS in stratifying cSCC into relatively indolent (T1/T2a) and aggressive (T2b/T3) subtypes. Continued refinement of what constitutes hrSCC will help to identify which tumors may benefit from adjuvant prognostic testing, such as obtaining a sentinel lymph node biopsy specimen or genetic expression profiling, which is now being explored in cSCC. In the face of a rising epidemic, improved identification and management of hrSCC will lead to reduced morbidity and mortality for our patients.

We thank Chrysalyne Schmults, MD, of Brigham and Women's Hospital for assisting us in the correct application of the BWH-SS and in providing additional data about the BWH cohort.

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