Outcomes in intermediate-risk squamous cell carcinomas treated with Mohs micrographic surgery compared with wide local excision

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Background: Brigham and Women's Hospital stage T2a squamous cell carcinomas, demonstrating a single high-risk feature, have a low risk of metastasis and death but an increased risk of local recurrence. Little evidence exists for the best treatment modality and associated outcomes in T2a squamous cell carcinoma.

Objective: We aimed to compare outcomes for T2a squamous cell carcinoma treated by Mohs micrographic surgery compared with wide local excision with permanent sections.

Methods: Retrospective review of an institutional review board–approved single-institution registry of T2a squamous cell carcinoma.

Results: Three hundred sixty-six primary T2a tumors were identified, including 240 squamous cell carcinomas (65.6%) treated with Mohs micrographic surgery and 126 (34.4%) treated with wide local excision. A total of 32.5% of patients were immunosuppressed and mean oncologic follow-up was 2.8 years. Local recurrence was significantly more likely after wide local excision (4.0%) than after Mohs micrographic surgery (1.2%) (P = .03). Multiple logistic regression demonstrated immunocompromised state (odds ratio [OR] 5.1; 95% confidence interval [CI] 1.1-23.3; P = .03) and wide local excision (OR 4.8; 95% CI 1.1-21.6; P = .04) associated with local recurrence; and wide local excision (OR 7.8; 95% CI 2.4-25.4; P < .001), high-risk head and neck location (OR 8.3; 95% CI 1.8-38.7; P = .004), and poor histologic differentiation (OR 4.7; 95% CI 1.4-15.4; P = .03) associated with poor outcomes (overall recurrence or disease-specific death).

Conclusion: Mohs micrographic surgery provides improved outcomes in Brigham and Women's Hospital T2a squamous cell carcinoma. (J Am Acad Dermatol 2020;82:1195-204.)

Key words: cutaneous squamous cell carcinoma; outcomes; Mohs surgery; wide local excision; dermatologic surgery.

INTRODUCTION

The majority of cutaneous squamous cell carcinomas are readily managed by various modalities, including electrodesiccation and curettage, wide local excision with routine permanent sections, and Mohs micrographic surgery, with low recurrence rates and minimal potential for poor outcomes. Much attention recently has been given to the management of high-risk tumors, especially in the setting of immunosuppression.[1-3] However, variable definitions and staging systems have been applied to stratify tumor risk across studies.

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Although the homogeneity (outcome similarity within stages) and monotonicity (outcome worsening with increasing stage) have been improved in the Brigham and Women's Hospital alternate staging system[4] and in the updated eighth edition of the American Joint Committee on Cancer staging system compared with previous editions, poor outcomes continue to occur in low-stage tumors.[5] Furthermore, staging systems rely on end points occurring with a relatively low frequency in daily practice, including nodal disease or recurrence, distant metastasis, and disease-specific death. In addition to metastasis, locoregional disease recurrence may also be important in contributing to squamous cell carcinoma morbidity, especially in advanced local recurrences in anatomically sensitive areas such as the head and neck. Comparative treatment data between conventional wide local excision and Mohs micrographic surgery are lacking. This knowledge gap is of significant clinical interest, especially in intermediate-risk tumors, which may most strongly benefit from Mohs micrographic surgery. Brigham and Women's Hospital stage T2a squamous cell carcinomas are tumors with a single feature deemed at high risk of a poor outcome (≥ 2 cm, poor differentiation, perineural invasion of nerves of ≥ 0.10-mm caliber, or invasion beyond fat). Although less frequently life threatening than their more aggressive counterparts (T2b and T3), the relative frequency with which T2a tumors are encountered in clinical practice is higher than that of more advanced stages (26%-41.3% of study cohorts).[3,6] This higher frequency, combined with a higher local recurrence (5%-9%) than that of T1 squamous cell carcinomas (0.6%-2%), warrants dedicated study of the T2a tumor stage.[4,6] Previous studies of T2a tumor behavior in mixed-treatment cohorts including wide local excision, Mohs micrographic surgery, and electrodessication and curettage demonstrate higher recurrence rates compared with that for T1 tumors.[4-6] A recent study showed that Mohs micrographic surgery monotherapy is a highly efficacious treatment for squamous cell carcinoma,[3] underscoring a possible role of surgical treatment modality in squamous cell carcinoma prognosis and outcomes. We aimed to study outcomes for intermediate-risk Brigham and Women's Hospital T2a squamous cell carcinomas treated by Mohs micrographic surgery compared with those treated by wide local excision with routine permanent sections.

CAPSULE SUMMARY

- Brigham and Women's Hospital T2a squamous cell carcinomas have a low risk of metastasis and death but an increased risk of local recurrence.
- Mohs micrographic surgery alone provides superior margin control and decreased local recurrence of Brigham and Women's Hospital T2a intermediate-risk squamous cell carcinoma compared with wide local excision.

METHODS

An institutional review board–approved single-institution registry of patients receiving a diagnosis of invasive squamous cell carcinoma between January 1, 2010, and December 31, 2012, was used. Patients receiving a diagnosis of squamous cell carcinoma in situ, receiving adjuvant therapy (including postoperative radiation) after primary tumor treatment, or having incomplete medical records detailing diagnosis or treatment were excluded. All patients were otherwise included irrespective of treating specialty or immune status. Patient data, including demographic, tumor, treatment, and outcome data, were collected from the electronic medical record. Most patients had a single tumor. Multiple tumors were considered independently in the analysis. Tumor anatomic location was categorized as high-risk head and neck (defined by the Mohs appropriate use criteria H zone), non–high-risk head and neck, and non–head and neck.[7] Tumor size was calculated as mean and trichotomized into 3 categories, less than 2 cm, 2 to 4 cm, and greater than or equal to 4 cm. When necessary, Mohs maps and archived histology slides were reviewed. Cases with external biopsy reports not grading squamous cell carcinoma were included and assumed to be nonpoorly differentiated histology unless poor differentiation was encountered in the wide local excision or Mohs micrographic surgery specimen. Oncologic length of follow-up was calculated according to the last visit with a physician (for example, a dermatologist or oncologist) involved in evaluating and treating the tumor in question, whereas overall length of follow-up was based on the last point of contact with our institution (for example, any physician or nurse visits or contact).

Patients were staged according to the Brigham and Women's Hospital T-staging system, and only Brigham and Women's Hospital T2a squamous cell carcinomas were included in the analysis. Brigham and Women's Hospital T2a tumors were defined as having 1, but not multiple, high-risk features (tumor diameter ≥ 2 cm, poorly differentiated histology,

Abbreviations used:

CI: confidence interval
OR: odds ratio

perineural invasion ≥ 0.1 mm, and tumor invasion beyond fat).[6] Tumors were stratified into 2 groups: those treated with Mohs micrographic surgery and those treated with wide local excision with routine permanent sections. All patients had histologically clear margins at the end of therapy. Recurrence was described as previously defined for nonmelanoma skin cancer.[8] Recurrent tumors qualifying as T2a were not included in the primary analysis because the Brigham and Women's Hospital staging system was not validated for recurrent tumors.

Study data were collected and managed with Research Electronic Data Capture (Vanderbilt University, Nashville, TN), a secure, web-based application designed to support data capture for research studies.[9,10]

Statistical analysis

Primary outcomes of interest were overall recurrences (including local recurrence, nodal, regional, and distant metastasis) and overall poor outcomes (recurrence plus disease-specific death). Data were analyzed in JMP Pro (version 14, SAS Institute, Inc., Cary, NC) and SAS (version 9.4, SAS Institute, Inc.) with Pearson χ^2 tests, analysis of variance, competing-risk analysis, Cox proportional hazards analysis, and logistic regression. Results with $P < .05$ were considered statistically significant.

RESULTS

A total of 366 primary T2a squamous cell carcinoma tumors were identified, including 240 tumors (65.6%) treated with Mohs micrographic surgery and 126 (34.4%) treated with wide local excision. The average patient age at diagnosis was 71.9 years. Most patients were men (68.6%) and 32.5% (N = 119) of the cohort was immunosuppressed. The mean follow-up time was 2.8 years (95% confidence interval [CI] 2.5-3.1 years; range 0.0-13.3 years). Characteristics of the entire T2a squamous cell carcinoma cohort, as well as those of tumors with nodal recurrence or disease-specific death, are presented in Table I. The majority of squamous cell carcinomas were 2 to 4 cm in diameter (80.6%), were well differentiated (60.1%), and did not invade beyond subcutaneous fat or into deeper structures (99.7%). Six squamous cell carcinomas (1.6%) had perineural invasion, and 1 (0.3 %) had perineural invasion involving a nerve greater than or equal to 0.10 mm.

Comparison of wide local excision and Mohs micrographic surgery treatment groups revealed a significantly higher proportion of immunosuppressed patients (38.7% for Mohs micrographic surgery and 20.6% for wide local excision; $P < .001$) and high-risk head and neck tumor locations (21.7% for Mohs micrographic surgery and 6.4% for wide local excision; $P < .001$) in the Mohs micrographic surgery group (Table II). Tumor size greater than 2 cm was the most common feature (91.5%) causing T2a designation. In total, there were 17 recurrences, including 8 local ones, 7 nodal ones, 2 in-transit ones, and 0 distant ones, in the cohort during the follow-up time.

Surgical characteristics of the tumors treated by wide local excision were as follows: of the 126 tumors treated with wide local excision, 40.5% (N = 51) were excised by dermatologists, whereas the remaining 75 were excised by nondermatologic providers. Plastic surgeons excised the majority (61%; N = 46) of the squamous cell carcinomas not excised by dermatologists. Sixty-three percent (N = 78) of the wide local excisions had documented margins, and of those 78 tumors, the mean documented excision margin was 5.6 mm (standard deviation 3.2 mm; interquartile range 4-10 mm).

Any recurrence and local recurrence specifically were 2.7 and 3.3 times more likely after wide local excision than Mohs micrographic surgery, respectively ($P = .03$). Univariate analysis demonstrated poor tumor differentiation, high-risk head and neck anatomic site, tumor size greater than 2 cm, and treatment with wide local excision to be associated with poor outcomes (overall recurrence or disease-specific death) (Table III). Multiple logistic regression modeling showed immunocompromised state (odds ratio [OR] 5.1; 95% CI 1.1-23.3; $P = .03$) and treatment with wide local excision (OR 4.8; 95% CI 1.1-21.6; $P = .04$) to be associated with local recurrence, and wide local excision (OR 7.8; 95% CI 2.4-25.4; $P < .001$), high-risk head and neck location (OR 7.3; 95% CI 2.0-26.9; $P = .004$), and poor tumor differentiation (OR 4.7; 95% CI 1.4-15.4; $P = .03$) to be associated with poor outcomes (overall recurrence or disease-specific death) (Table IV). Cumulative incidence functions for local recurrence and poor outcomes across treatment groups are presented in Fig 1. Treatment with wide local excision approached a significantly increased cumulative incidence of local tumor recurrences (subdistribution hazard ratio 3.3; 95% CI 0.8-13.7; $P = .09$) and a significantly increased cumulative incidence of overall disease progression

Table I. Baseline characteristics of the study cohort, as well as characteristic of the tumors that resulted in nodal recurrence or disease-specific death

Variables	Primary T2a cohort (N = 366)	Tumors with nodal recurrence (N = 7)	Tumors with disease-specific death (N = 4)
Mean age at diagnosis (SD), y	71.9 (13.8)	73.3 (10.6)	70.7 (21.2)
Sex, No. (%)			
Men	251 (68.6)	7 (100)	3 (75)
Women	115 (31.4)	0	1 (25)
Immunosuppression, No. (%)			
No	247 (67.5)	6 (85.7)	3 (75)
Yes	119 (32.5)	1 (14.3)	1 (25)
Tumor differentiation, No. (%)			
Well	219 (60.1)	2 (28.6)	0
Moderate	71 (19.5)	0	0
Poor	28 (7.7)	2 (28.6)	2 (50)
Undifferentiated	1 (0.3)	1 (14.3)	1 (25)
Unknown	45 (12.4)	2 (28.6)	1 (25)
Invasion beyond fat, No. (%)			
Yes	1 (0.3)	0	0
No	364 (99.7)	7 (100)	4 (100)
Anatomic location, No. (%)			
High-risk head and neck	60 (16.4)	3 (42.9)	1 (25)
Head and neck	86 (23.5)	2 (28.6)	2 (50)
Nonhead and neck	220 (60.1)	2 (28.6)	1 (25)
Perineural invasion, No. (%)			
Yes	6 (1.6)	0	0
≥0.10 mm	1 (0.3)	0	0
<0.10 mm or unknown	5 (1.3)	0	0
No	360 (98.4)	7 (100)	4 (100)
Mean tumor size (SD), cm	2.6 (1.3)	1.8 (0.7)	1.7 (1.6)
Treatment modality, No. (%)			
Mohs surgery	240 (65.6)	4 (57.1)	1 (25)
Wide local excision	126 (34.4)	3 (42.9)	3 (75)
Mean oncologic follow-up (95% CI), y	2.8 (2.5—3.1)	4.7	2.6
Tumor recurrence, No. (%)			
Yes, type	17 (4.6)	7 (100)	4 (100)
Local	8 (2.2)	0	1 (25)
Nodal	7 (1.9)	7 (100)	2 (50)
In-transit	2 (0.5)	0	1 (25)
Distant	0	0	0
No	349 (95.4)	0	0
Mean time to recurrence (95% CI), y	1.2 (0.5—2.0)	1.2	1.1
Mean overall follow-up (95% CI), y	4.1 (3.8—4.4)	5.1	2.6
Patient vital status at last follow-up, No. (%)			
Deceased	129 (35.3)	4 (57.1)	4 (100)
DSD	4 (1.1)	2 (28.6)	4 (100)
Any cSCC death (non-DSD)	14 (3.5)	0	0
Living	237 (64.7)	3 (42.9)	0

Disease progression is defined as overall tumor recurrence (local, nodal, in-transit, and distant recurrences) or disease-specific death. High-risk head and neck location is defined by areas encompassed by the Mohs appropriate use criteria H zone on the head and neck.
CI, Confidence interval; *cSCC*, cutaneous squamous cell carcinoma; *DSD*, disease-specific death; *SD*, standard deviation.

(subdistribution hazard ratio 2.9; 95% CI 1.1-7.6; $P = .03$) compared with Mohs micrographic surgery.

Across both treatment arms, 4 patients had a death attributable to the T2a tumor included in the study (disease-specific death). Ten additional patients in this study had death attributable to (any) cutaneous squamous cell carcinoma. In those instances, the burden of cutaneous squamous cell carcinoma disease did not allow attribution to a specific index tumor, or the patient succumbed to a cutaneous squamous cell carcinoma not included in this study. T2a-specific and overall cutaneous squamous cell

Table II. Univariate χ^2 comparisons across treatment groups

Variables	Treatment modality (primary tumors only)		Overall cohort	*P* value
	MMS (N = 240, 65.6%)	WLE (N = 126, 34.4%)		
Mean age at diagnosis (SD), y	71.9 (12.8)	72.0 (15.5)	71.9 (13.8)	.94
Sex, No. (%)				
Men	171 (71.2)	80 (63.5)	251 (68.6)	.13
Women	69 (28.8)	46 (36.5)	115 (31.4)	
Immunosuppression, No. (%)				
No	147 (61.3)	100 (79.4)	247 (67.5)	**<.001**
Yes	93 (38.7)	26 (20.6)	119 (32.5)	
Tumor differentiation, No. (%)				
Well, intermediate, or unknown	221 (92.1)	116 (92.1)	337 (92.1)	.99
Poor	19 (7.9)	10 (7.9)	29 (7.9)	
Invasion beyond fat				
Yes	1 (0.4)	0	1 (0.3)	.46
No	238 (99.6)	126 (100)	364 (99.7)	
Anatomic location, No. (%)				
High risk head and neck	52 (21.7)	8 (6.4)	60 (16.4)	**<.001**
Head and neck	67 (27.9)	19 (15.1)	86 (23.5)	
Nonhead/neck	121 (50.4)	99 (78.6)	220 (60.1)	
Perineural invasion, No. (%)				
Yes	3 (1.3)	3 (2.4)	6 (1.6)	.39
≥0.10 mm	0	1 (0.8)	1 (0.3)	
<0.10 mm or unknown	3 (1.3)	2 (1.6)	6 (1.6)	
No	237 (98.7)	123 (97.6)	360 (98.4)	
Tumor size, No. (%), cm				
<2	20 (8.3)	11 (8.7)	31 (8.5)	.17
2 to <4	199 (82.9)	96 (76.2)	295 (80.6)	
≥4	21 (8.8)	19 (15.1)	40 (10.9)	
AJCC8 stage, No. (%)				
T1	17 (14.4)	3 (11.5)	20 (13.9)	**.05**
T2	90 (76.3)	16 (61.5)	106 (73.6)	
T3	11 (9.3)	7 (26.9)	18 (12.5)	
Oncologic length of follow-up (95% CI), y	2.8 (2.4–3.1)	2.8 (2.2–3.4)	2.8 (2.5–3.1)	.90
Tumor recurrence after treatment, No. (%)				**.03**
Yes, type	7 (2.9)	10 (7.9)	17 (4.6)	
Local	3 (1.2)	5 (4.0)	8 (2.2)	
Nodal	4 (1.7)	3 (2.4)	7 (1.9)	
In-transit	0	2 (1.5)	2 (0.5)	
Distant	0	0	0	
No	233 (97.1)	116 (92.1)	349 (95.4)	
Time to recurrence (95% CI), y	0.7 (0.3–1.2)	1.6 (0.3–2.9)	1.2 (0.5–2.0)	.19
Overall length of follow-up (95% CI), y	3.9 (3.5–4.2)	4.6 (4.0–5.2)	4.1 (3.8–4.4)	**.02**
Patient vital status at last follow-up, No. (%)				.09
Deceased	77 (32.1)	52 (41.3)	129 (35.3)	
Death from cSCC	7 (2.9)	7 (5.6)	14 (3.8)	
DSD	1 (0.4)	3 (2.4)	4 (1.1)	
Alive	163 (67.9)	74 (58.7)	237 (64.7)	

This group includes only primary tumors. High-risk head and neck location is defined by areas encompassed by the Mohs appropriate use criteria H zone on the head and neck. Bold values indicate statistical significance with $P < .05$.

AJCC, American Joint Committee on Cancer, eighth edition; *CI*, confidence interval; *cSCC*, cutaneous squamous cell carcinoma; *DSD*, disease-specific death; *MMS*, Mohs micrographic surgery; *SD*, standard deviation; *WLE*, wide local excision.

carcinoma mortality was not significantly associated with treatment modality (wide local excision versus Mohs micrographic surgery). However, disease progression (either overall recurrence or tumor-specific death) was significantly higher with wide local excision treatment than Mohs micrographic surgery (subdistribution hazard ratio 2.9; 95% CI 1.1-7.6; $P = .03$).

Table III. Univariate χ^2 associations with poor outcomes (overall recurrence and disease-specific death)

	Poor outcomes (primary tumors only)			
Variables	**Yes (N = 17, 4.6%)**	**No (N = 358, 97.8%)**	**Overall cohort**	***P* value**
Mean age at diagnosis (SD), y	67.9 (14.6)	72.1 (13.7)	71.9 (13.8)	.23
Sex, No. (%)				
Men	14 (82.3)	237 (67.9)	251 (68.6)	.21
Women	3 (17.7)	112 (32.1)	115 (31.4)	
Immunosuppression, No. (%)				
No	10 (58.8)	237 (67.9)	247 (67.5)	.43
Yes	7 (41.2)	112 (32.1)	119 (32.5)	
Tumor differentiation, No. (%)				
Well, intermediate, or unknown	12 (70.6)	325 (93.1)	337 (92.1)	**<.001**
Poor	5 (29.4)	24 (6.9)	29 (7.9)	
Invasion beyond fat				
Yes	0	1 (0.3)	1 (0.3)	.82
No	17 (100)	347 (99.7)	364 (99.7)	
Anatomic location, No. (%)				
High-risk head and neck	5 (29.4)	55 (15.8)	60 (16.4)	**.03**
Head and neck	7 (41.2)	79 (22.6)	86 (23.5)	
Nonhead/neck	5 (29.4)	215 (61.6)	220 (60.1)	
Perineural invasion, No. (%)				
Yes	0	6 (1.7)	6 (1.6)	.59
≥0.10 mm	0	1 (0.3)	1 (0.3)	
<0.10 mm or unknown	0	5 (1.4)	5 (1.4)	
No	17 (100)	343 (98.3)	360 (98.4)	
Tumor size, No. (%), cm				
<2	5 (29.4)	26 (7.5)	31 (8.5)	**.006**
2 to <4	11 (64.7)	284 (81.4)	295 (80.6)	
≥4	1 (5.9)	39 (11.2)	40 (10.9)	
AJCC8 stage, No. (%)				
T1	2 (18.2)	18 (13.5)	20 (13.9)	.73
T2	7 (63.6)	99 (74.4)	106 (73.6)	
T3	2 (18.2)	16 (12.0)	18 (12.5)	
Treatment modality, No. (%)				
MMS	7 (41.2)	233 (66.8)	240 (65.6)	**.03**
WLE	10 (58.8)	116 (33.2)	126 (34.4)	
Oncologic length of follow-up (95% CI), y	4.4 (2.6−6.2)	2.7 (2.4−3.0)	2.8 (2.5−3.1)	**.03**
Tumor recurrence after treatment, No. (%)				
Yes, type	17 (100)	0	17 (4.6)	**<.001**
Local	8 (47.1)	0	8 (2.2)	
Nodal	7 (41.2)	0	7 (1.9)	
In-transit	2 (11.8)	0	2 (0.5)	
Distant	0	0	0	
No	0	349 (100)	349 (95.4)	
Time to recurrence (95% CI), y	1.2 (0.5−2.0)	N/A	1.2 (0.5−2.0)	N/A
Overall length of follow-up (95% CI), y	4.9 (2.9−6.9)	4.1 (3.8−4.3)	4.1 (3.8−4.4)	.26
Patient vital status at last follow-up, No. (%)				
Dead	8 (47.1)	121 (34.7)	129 (35.3)	.30
Death from cSCC	5 (29.4)	9 (2.6)	14 (3.8)	
DSD	4 (23.5)	0	4 (1.1)	
Alive	9 (52.9)	228 (65.3)	237 (64.7)	

This group includes only primary tumors. High-risk head and neck location is defined by areas encompassed by the Mohs appropriate use criteria H zone on the head and neck. Bold values indicate statistical significance with $P < .05$.

AJCC, American Joint Committee on Cancer, eighth edition; *CI*, confidence interval; *cSCC*, cutaneous squamous cell carcinoma; *DSD*, disease-specific death; *MMS*, Mohs micrographic surgery; *N/A*, not applicable; *SD*, standard deviation; *WLE*, wide local excision.

Table IV. Multiple logistic regression model of factors associated with local recurrence and poor outcomes

Variable	No. (%)	Odds ratio (95% CI)	*P* value
Factors associated with local recurrence			
Immunosuppression			
Immunocompetent	237 (67.5)	1 [Reference]	
Immunocompromised	119 (32.5)	5.1 (1.1—23.3)	.03
Treatment group			
MMS	240 (65.6)	1 [Reference]	
WLE	126 (34.4)	4.8 (1.1—21.6)	.04
Factors associated with poor outcomes			
Treatment group			
MMS	240 (65.6)	1 [Reference]	<.001
WLE	126 (34.4)	7.8 (2.4—25.4)	
Anatomic location			
Nonhead and neck	220 (60.1)	1 [Reference]	.004
Head and neck	86 (23.5)	7.3 (2.0—26.9)	
High-risk head and neck	60 (16.4)	8.3 (1.8—38.7)	
Tumor differentiation			
Well, moderate, or unknown	375 (92.6)	1 [Reference]	.03
Poor	30 (7.4)	4.7 (1.4—15.4)	

Poor outcomes are defined as any recurrence (local, nodal, in-transit, or distant recurrence) or disease-specific death. High-risk head and neck location is defined by areas encompassed by the Mohs appropriate use criteria H zone on the head and neck. Bold values indicate statistical significance with $P < .05$.
CI, Confidence interval; *MMS*, Mohs micrographic surgery; *WLE*, wide local excision.

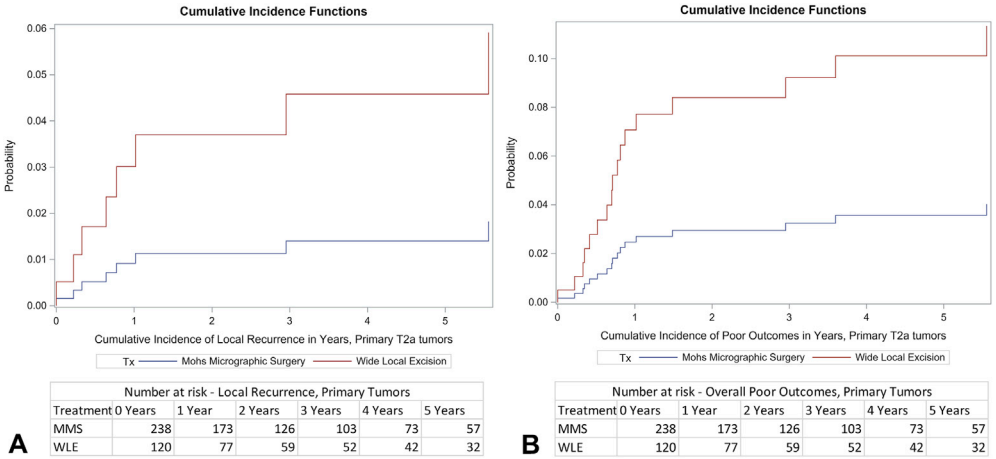

Fig 1. Cumulative incidence functions for local recurrence and disease progression across treatment groups. **A,** Local recurrence. Differences between groups approached statistical significance ($P = .09$). The subdistribution hazard ratio for local recurrence with wide local excision compared with Mohs micrographic surgery was 3.3 (95% confidence interval 0.8-13.7). **B,** Disease progression. Disease progression is defined as any recurrence (local, nodal, in-transit, or distant) or death caused by the index tumor. Pairwise comparisons show that differences between treatment groups were significant ($P = .03$). The subdistribution hazard ratio for disease progression for treatment with wide local excision compared with Mohs micrographic surgery was 2.9 (95% confidence interval 1.1-7.6). *MMS*, Mohs micrographic surgery; *WLE*, wide local excision.

A post hoc analysis was conducted including 39 recurrent tumors, bringing the total cohort to 405 T2a squamous cell carcinoma tumors. Recurrent squamous cell carcinoma tumors were significantly different from primary T2a tumors with respect to frequency of perineural invasion ($P = .01$), tumor size ($P < .001$), and tumor recurrence ($P = .006$) after treatment. Inclusion of previously recurrent tumors demonstrated a future overall recurrence and local recurrence to be 3.6 and 4.8 times more likely after

wide local excision than Mohs micrographic surgery, respectively (P = .001). Univariate analysis retained poor tumor differentiation, tumor size greater than 2 cm, and treatment with wide local excision to be associated with poor outcomes (overall recurrence or disease-specific death) on inclusion of previously recurrent squamous cell carcinoma. Multivariate logistic regression modeling confirmed immunosuppression (OR 3.9; 95% CI 1.2-12.9; P = .002) and wide local excision (OR 7.5; 95% CI 2.1-26.6; P = .002) to be associated with local recurrence and poor tumor differentiation (OR 4.7; 95% CI 1.4-15.4; P = .01) and wide local excision (OR 8.7; 95% CI 2.9-25.7; P < .001) to be associated with overall poor outcomes. Treatment with wide local excision was associated with a significantly increased cumulative incidence of local tumor recurrences (subdistribution hazard ratio 4.9; 95% CI 1.6-15.6; P = .006) and overall disease progression (subdistribution hazard ratio 3.8; 95% CI 1.6-5.9; P = .002) compared with findings after Mohs micrographic surgery.

DISCUSSION

We present a comparative retrospective review of wide local excision versus Mohs micrographic surgery treatment arms for intermediate risk (Brigham and Women's Hospital stage T2a) squamous cell carcinoma. The benefit of Mohs micrographic surgery, even in higher-risk squamous cell carcinoma, has previously been reported.[3,11] The Brigham and Women's Hospital staging system was chosen for our study because it was thought to be more inclusive than the American Joint Committee on Cancer eighth edition. The potential for upstaging to T2a according to several possible variables (size, differentiation, perineural invasion, and depth of invasion) allows the most clinically relevant representation of "intermediate-risk" squamous cell carcinoma.

This study helps to address a significant gap in the literature: the best treatment modality for intermediate-risk T2a squamous cell carcinoma. In brief, wide local excision had 3.3 times the risk of local recurrence compared with Mohs micrographic surgery for primary squamous cell carcinoma and 4.8 times the risk of local recurrence for recurrent squamous cell carcinoma. Treatment with wide local excision was associated with a significantly increased cumulative incidence of local recurrence (subdistribution hazard ratio 4.9; 95% CI 1.6-15.6; P = .006) and overall disease progression (subdistribution hazard ratio 3.8; 95% CI 1.6-5.9; P = .002) compared with Mohs micrographic surgery.

In this cohort of Brigham and Women's Hospital stage T2a tumors, Mohs micrographic surgery had a significantly lower local recurrence of 1.2% versus wide local excision (4.0%) for primary squamous cell carcinoma. These rates are slightly lower than those reported by Rowe et al[12] (Mohs micrographic surgery 3.1% versus wide local excision 7.8%) and arise from a more homogenous cohort. General local recurrence rates after squamous cell carcinoma wide local excision have been reported to be 3.9% to 5%.[13,14] Studies conducted at Brigham and Women's Hospital reported a T2a local recurrence of 8.9% in their initial study[6] and subsequently a local recurrence of 1.5% for T2a tumors[4] treated with multiple modalities, including wide local excision (52%), Mohs micrographic surgery (27%), and electrodesiccation and curettage (15%). Marazzo et al recently reported on Mohs micrographic surgery monotherapy in a cohort of 647 high-risk squamous cell carcinomas. This cohort included 41.3% stage T2a tumors. Overall cohort local recurrence was 2.9%, including a local recurrence of 0.7% for T2a tumors,[3] which is most similar to the findings of the current study. This cohort included fewer immunosuppressed patients, a subgroup known to be at high risk for poor squamous cell carcinoma outcomes.[2,15-17]

T2a staging may occur because of various high-risk features. The most common reason for tumor upstaging from T1 to T2a in our cohort was tumor size (n = 335; 91.5%), followed by histologic differentiation (n = 29; 8.0%), perineural invasion (n = 1; 0.25%), and invasion beyond subcutaneous tissue (n = 1; 0.25%). The risk of local recurrence doubles and that of metastasis triples with tumor sizes greater than 2 cm.[12] In this T2a cohort, tumors smaller than 2 cm were more likely to have a poor outcome (recurrence or disease-specific death), likely because smaller tumors frequently qualified as T2a owing to poor histologic differentiation. Poor histologic differentiation was significantly associated with poor outcomes and was present in 29.4% of cases (P < .001), resulting in a 4.7-fold higher risk of poor outcomes on multiple logistic regression models (P = .03). Tumor invasion beyond the subcutis has been associated with a 28% local recurrence and 27% nodal metastasis risk.[4]

Forty-one recurrent tumors were included in a post hoc analysis. At retreatment, recurrent tumors are known to have worse outcomes than primary tumors.[18] Recurrent tumors frequently occur after wide local excision and, even when treated with Mohs micrographic surgery, have a 10% recurrence rate.[19,20] The metastasis rate may approach 20%.[19] Compared with primary tumors, recurrent tumors had a 7-fold increased local recurrence rate (15.4%

versus 2.2%). This subset of patients was excluded in previous studies[3,4,6] and was not included in the initial validation of the Brigham and Women's Hospital T-staging system. The inclusion of recurrent tumors is an important difference compared with other published cohorts and increases the clinical applicability of our data.

Nodal metastases have been reported in 0.9% to 4.5% of T2a tumors.[4,6] The nodal disease or recurrence risk may exceed the local recurrence risk in T2a tumors treated by Mohs micrographic surgery.[3] This observation was confirmed in our cohort, which had a local recurrence of 1.2% and nodal disease or recurrence of 1.7%. Similar findings were not observed in the wide local excision cohort, which had higher local recurrence rates (4.0%) than nodal disease or recurrence (2.4%). The reason for this is not entirely clear but may be due to micrometastatic subclinical nodal disease present at the primary tumor surgery. This finding highlights the importance of a clinical nodal examination.

Four patients in this study died of their primary T2a squamous cell carcinoma, for a 1.1% mortality rate during the study period. An additional 10 patients died of squamous cell carcinoma other than the index tumor. Our mortality rate is higher than that reported by others. The studies conducted at Brigham and Women's Hospital reported no deaths in their cohort of 67 T2a patients and reported 1 death in their cohort of 332 T2a patients (0.3%). Marazzo et al reported no deaths in their cohort of 267 T2a patients. This difference may be attributable to the inclusion of a higher proportion of immunosuppressed patients.

LIMITATIONS

This study is limited by its retrospective nature and single tertiary care medical center setting. The 2 historical treatment arms were well matched in key variables. Where discrepancies existed, the Mohs micrographic surgery treatment arm had less favorable conditions, including a higher rate of immunosuppression and central facial high-risk head and neck anatomic location. Nevertheless, undocumented high-risk variables may have confounded treatment outcomes. Tumors lacking initial histologic grade were included in this study and were equally present in both treatment arms. If these tumors were to have manifested poor differentiation, upstaging to T2b would have occurred. This would have made 12.4% of our cohort more high risk. Nevertheless, treatment comparisons and conclusions would remain valid and, in fact, support use of Mohs micrographic surgery in even higher-risk tumors. Because 91.5% of our tumors qualified for T2a staging based on size criteria, these findings are most generalizable to tumors qualified as intermediate risk based on size, and other tumor populations with only 1 Brigham and Women's Hospital risk factor may behave somewhat differently. In addition, although the mean wide local excision margin of 5.6 mm fell within the 4- to 6-mm margins recommended by the National Comprehensive Cancer Network guidelines for non–high-risk squamous cell carcinomas,[21,22] only 63% of wide local excisions had documented margins. Furthermore, in the presence of high-risk features, margins of 6 mm are recommended. The local excision cohort could therefore be biased toward increased recurrence and worse outcomes if, for example, tumors undergoing local excision without documented margins were consistently excised with narrower margins than recommended. However, our study reflects the natural distribution of intermediate-risk tumors encountered in normal clinical scenarios and our conclusions would remain valid in these settings. Our mean oncologic follow-up period of 2.8 years is robust, and the majority of nonmelanoma skin cancers recur within 2 years.[19] Our overall mean follow-up of 4.1 years furthermore allows extended tracking of survival status.

CONCLUSION

Treatment modality, tumor size, and tumor recurrence status are associated with increased local recurrence. Wide local excision has 3.3 times the risk of local recurrence compared with Mohs micrographic surgery for primary squamous cell carcinoma and 4.8 times the risk of local recurrence for recurrent squamous cell carcinoma. Mohs micrographic surgery provides superior long-term outcomes for patients with T2a squamous cell carcinoma and has a definitive role in the management of T2a tumors. The inclusion of immunosuppressed patients and recurrent tumors greatly enhances the generalizability of these data. Although worse outcomes should be expected in higher-stage tumors, patients with T2a tumors warrant close clinical follow-up.

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