Histopathologic upgrading of nonmelanoma skin cancer at the time of Mohs micrographic surgery: A prospective review

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Background: Anecdotal experience and data from multiple retrospective studies have suggested that a significant percentage of nonmelanoma skin cancers (NMSCs) display an aggressive histologic subtype that is not diagnosed on initial biopsy.

Objective: To prospectively determine the proportion of NMSCs upgraded at the time of Mohs micrographic surgery (MMS) and examine the surgical parameters of upgraded lesions.

Methods: In this prospective, cross-sectional study, all patients undergoing MMS for NMSC at our institution over the course of 1 year were screened for inclusion. Frozen sections were reviewed independently by 2 fellowship-trained Mohs surgeons.

Results: In total, 265 of 2578 (10.3%) tumors displayed a more aggressive skin cancer histologic subtype on frozen-section analysis at the time of surgery than at the initial biopsy. Upgraded tumors required significantly more stages to reach tumor clearance, had a larger postoperative defect size, and more often required complicated repairs than nonupgraded tumors.

Limitations: Single center study, limited time period, and cross-sectional design.

Conclusion: A significant portion of MMS cases were upgraded at the time of surgery to a more aggressive subtype than that seen at the initial biopsy. Upgraded cases were larger and more surgically challenging than nonupgraded ones. This finding has important implications for primary dermatologists' referral practices and Mohs appropriate use criteria guidelines. (J Am Acad Dermatol 2019;81:541-7.)

Key words: basal cell carcinoma; dermatologic oncology; Mohs micrographic surgery; squamous cell carcinoma.

Current Mohs micrographic surgery (MMS) appropriate use criteria (AUC) guidelines support the use of MMS for aggressive subtypes of nonmelanoma skin cancers (NMSCs), regardless of tumor location.[1] However, aggressive subtypes might not be identifiable on initial biopsy, depending on the type and depth of the biopsy. Studies comparing excisional specimens of basal cell carcinoma (BCC) to initial biopsies have demonstrated that initial biopsies miss features of aggressive cancer subtypes in 11%-26% of cases.[2-8] More recently, multiple retrospective studies have examined the rates of tumor upgrading at the time of MMS, with rates ranging 10%-33%.[9-13]

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Tumors upgraded to a more aggressive subtype during MMS might require more extensive surgeries than initially planned. In this prospective study, we examine the characteristics of NMSC tumors upgraded during MMS over a year-long period at a single institution. We hypothesize that ≥10% of NMSCs would be upgraded on the basis of previous publications and that upgraded tumors would likely be larger and require more complicated (flap or graft) repairs.

CAPSULE SUMMARY

- A significant percentage of nonmelanoma skin cancers referred for Mohs surgery display aggressive histology not evident on initial biopsy.
- Tumors upgraded to more aggressive subtypes during Mohs surgery are larger and require more extensive surgery. Dermatologists should consider the limitations of superficial biopsies for detecting aggressive histology when weighing treatment options.

METHODS

All patients undergoing MMS for BCC, squamous cell carcinoma (SCC), or SCC in situ from July 1, 2016 to June 30, 2017 at our institution were prospectively screened for inclusion. Other types of skin cancers (eg, melanoma, sebaceous carcinoma, mucinous carcinoma, dermatofibrosarcoma protuberans) were excluded. The study was approved by the Institutional Review Board of Washington University School of Medicine (#201607016).

Mohs surgery was conducted at Washington University by 2 fellowship-trained surgeons (Dr Hurst and Dr Council) according to standard practices on the interpretation of frozen sections stained with hematoxylin and eosin. Curettage is routinely performed before the first Mohs stage, and curettage specimens are processed and examined separately from the first stage. No immunohistochemical stains were used.

During the study period, each surgeon noted the presence of an aggressive histologic subtype on frozen sections of either the first Mohs stage or the curettage specimen. All patients whose cancer was upgraded to a more aggressive subtype were included. Aggressive subtypes of BCC included infiltrative, micronodular, morpheaform, and metatypical.[14-16] Metatypical BCC was defined as a tumor with loss of basaloid elements, such as peripheral palisading and stromal retraction, and gain of squamous differentiation as evidenced by cells with eosinophilic cytoplasm related to premature cornification and large nuclei. BCCs with only keratinization in the absence of corresponding squamous atypia were not classified as metatypical. Collision tumors and rare cases in which MMS revealed a new and distinct skin cancer subtype were excluded. Frozen sections were rereviewed independently by both Dr Hurst and Dr Coucil for concordance.

Data were collected regarding patient demographics and pathologic features. Preoperative and postoperative sizes represent the largest measured diameter of the lesion. Tumor location was stratified into areas H, M, and L according to published MMS AUC guidelines. Area H includes mask areas of the face, hands, feet; area M includes cheeks, forehead, scalp, neck, jawline, and pretibial shin; and area L includes the remaining areas of the trunk and extremities.[1]

Comparative statistics on the surgical parameters between the upgraded cancers and nonupgraded cancers were completed by using a deidentified surgical case log, which contained limited information regarding tumor location and size, number of stages performed and specimens collected to achieve clearance, and repair type. For continuous data (age, numbers of specimens and stages, preoperative and postoperative sizes), differences between groups were analyzed by an unpaired 2-tailed Student *t* test with posthoc correction for multiple comparisons. For categorical data (location, repair type), nonupgraded and upgraded tumors were compared by using a 2-sided Fisher's exact test. Corrected *P* values $<.05$ were considered significant. Analyses were performed in Microsoft Excel and GraphPad Prism version 7.02.

RESULTS

Of the 2578 tumors treated with MMS at our institution during the study period, 265 tumors (10.3%) in 253 patients were upgraded on frozen-section analysis during MMS to a more aggressive subtype than that found on the initial biopsy. The upgrade rate was similar between providers (Dr Hurst 10.1%, Dr Council 10.6%). Average patient age was 71 years, there was a male predominance (59%), and most patients had skin types I or II. Recurrent tumors made up 7% of upgraded cancers, and the average delay from biopsy to MMS was 111 days (±standard deviation 71 days). Demographic data are summarized in Table I.

In total, 15% (230/1563) of BCCs were upgraded to a more aggressive subtype. The most commonly observed subtypes were infiltrative and metatypical, and many tumors contained >1 subtype (Table I).

Abbreviations used:

AUC: appropriate use criteria
BCC: basal cell carcinoma
NMSC: nonmelanoma skin cancer
MMS: Mohs micrographic surgery
SCC: squamous cell carcinoma

Two cases with a preoperative diagnosis of superficial BCC were upgraded to aggressive subtypes of BCC (1 metatypical, 1 metatypical and infiltrative). Three cases with a preoperative diagnosis of unspecified carcinoma and 1 case with a preoperative diagnosis of basaloid neoplasm were diagnosed as infiltrative BCC.

About 3% (11/351) of SCC in situ cases were upgraded to invasive SCC; 2 of these cases were moderately differentiated SCC. Also, 3% (20/662) of well-differentiated SCC cases were upgraded to moderately (n = 16) or poorly (n = 4) differentiated SCC. One tumor with a preoperative diagnosis of squamoproliferative lesion was diagnosed during MMS as moderately differentiated SCC. Of the 5 tumors upgraded to poorly differentiated SCC at the time of MMS, 4 (80%) required referral for additional surgical resection after several stages of MMS did not result in their clearance. Of these 4 tumors, 3 were on the ear and ultimately required auriculectomy, and 1 was on the finger and required amputation of the digit.

In 2 cases, the diagnosis changed entirely after frozen-section pathology. In 1 case, a tumor biopsy diagnosed as SCC was later found to be infiltrative and metatypical BCC. In another case, BCC was later found to be SCC. In these instances, the initial biopsy pathology and frozen-section pathology were reviewed by a board-certified dermatopathologist (Dr Rosman), who agreed with the findings.

Surgical parameters for upgraded and nonupgraded tumors are shown in Table II. Upgraded tumors required significantly more stages and specimens for tumor clearance. The postoperative defect size for upgraded lesions was also significantly larger than the size for nonupgraded lesions (2.4 cm vs 1.7 cm for BCC and 2.5 cm vs 1.8 cm for SCC in situ). Although the preoperative size was larger for upgraded tumors, the difference between the measured preoperative and postoperative defect sizes was also significantly larger for the upgraded tumors than the nonupgraded tumors (1.1 cm vs 0.8 cm for BCC and 1.1 cm vs 0.7 cm for SCC in situ).

For BCC, there was no significant difference between groups for tumor location (Table III). For SCC, there was a tendency toward a higher proportion of upgraded tumors on the head and neck (P = .057, unpaired Fisher's exact test, area H compared with other locations, upgraded vs nonupgraded). Only 1 tumor of the upgraded SCC in situ group appeared in area L compared with 12% of the tumors in the nonupgraded lesion group.

The type of surgical repair used to construct each defect was classified as complicated, linear, granulation, or outside repair (Table IV). For the purposes of this study, complicated repairs included any flap or

Table I. Demographic and tumor characteristics of patients with upgraded nonmelanoma skin cancers

Characteristic	Value*
Demographic	
Age, years, mean ± SD	71 ± 13
Sex	
M	148 (59)
F	102 (41)
Skin type	
I	48 (19)
II	194 (78)
III	5 (2)
IV	1
V	1
History of nonmelanoma skin cancer	170 (68)
Smoker	24 (9)
History of radiation	4 (2)
Immunosuppressed	29 (11)
Tumor characteristic	
Initial diagnosis	
BCC	225
Superficial BCC	2
SCC in situ	11
SCC well differentiated	21
SCC moderately differentiated	1
Other†	5
Postoperative diagnosis	
BCC to infiltrative	168
BCC to metatypical	102
BCC to micronodular	37
BCC to morpheaform	1
SCC in situ to SCC	11
Well-differentiated SCC to moderately or poorly differentiated SCC	20
Initial biopsy type	
Shave	260 (98)
Punch	2
Excisional	2
Curette	1

Missing data were excluded from analyses. For postoperative diagnosis, some BCCs demonstrated multiple subtypes.
BCC, Basal cell carcinoma; *SCC*, squamous cell carcinoma; *SD*, standard deviation.
*Values are n (%) unless indicated otherwise.
†Includes 3 cases of unspecified carcinoma, 1 squamoproliferative lesion, and 1 basaloid neoplasm.

Table II. Surgical data for nonupgraded and upgraded tumors

Parameter	Nonupgraded BCC	Upgraded BCC	*P* value	Nonupgraded SCC in situ	Upgraded SCC in situ	*P* value
Age, years	69 ± 12	70 ± 13	NS	72 ± 12	73 ± 11	NS
Specimens*	2.4 ± 1.1	3.3 ± 1.5	<.001	2.0 ± 0.9	3.0 ± 1.1	<.001
Stages†	1.6 ± 0.7	2.2 ± 0.9	<.001	1.4 ± 0.6	2.0 ± 0.6	<.001
Preoperation defect size,‡ cm	0.9 ± 0.6	1.2 ± 0.8	<.001	1.1 ± 0.6	1.5 ± 0.7	<.001
Postoperation defect size,§ cm	1.7 ± 1	2.4 ± 1.2	<.001	1.8 ± 0.8	2.5 ± 1.0	<.001
Size change, cm	0.8 ± 0.6	1.1 ± 0.7	<.001	0.7 ± 0.5	1.1 ± 0.6	<.001

Values are mean ± standard deviation. Unpaired 2-tailed Student *t* test, nonupgraded versus upgraded, with Bonferroni posthoc correction for multiple comparisons.
BCC, Basal cell carcinoma; *NS*, not significant; *SCC*, squamous cell carcinoma.
*Total number of tissue sections examined during Mohs micrographic surgery.
†Total number of stages needed for clearance of tumors.
‡The largest measured tumor diameter on the basis of the clinical impression before surgery.
§The largest measured diameter of the postoperative surgical wound.

Table III. Location of nonupgraded and upgraded SCC in situ and BCC tumors

Tumor and area	Nonupgraded tumors, n (%)	Upgraded tumors, n (%)	*P* value*
BCC			
H	783 (59)	140 (61)	NS
M	492 (37)	82 (36)	NS
L	58 (4)	8 (4)	NS
SCC in situ			
H	425 (44)	21 (60)	.057
M	438 (44)	13 (37)	NS
L	117 (12)	1 (3)	NS

BCC, Basal cell carcinoma; *NS*, not significant; *SCC*, squamous cell carcinoma.
*Compared by using 2-sided Fisher's exact test.

Table IV. Repair types used to close the postoperative surgical defect after Mohs micrographic surgery

Repair type	Nonupgraded tumors, n (%)	Upgraded tumors, n (%)	*P* value*
Complicated†	355 (15)	106 (40)	<.001
Linear	1293 (56)	109 (42)	<.001
Granulation	475 (21)	12 (5)	<.001
Outside‡	190 (8)	34 (13)	.0125

*Compared by using 2-sided Fisher's exact test.
†Complicated repairs included advancement flaps, rotation flaps, transposition flaps, interpolation flaps, and split or full-thickness skin grafts.
‡Outside designates a repair done by a surgeon other than Dr Hurst or Dr Council.

graft; linear repairs included any linear closure, including complex and intermediate layered linear closures; and outside repairs included those referred to other surgical specialists, such as otolaryngology or oculoplastics. Upgraded tumors were much more likely than nonupgraded tumors (40% vs 15%) to require a complicated repair. Upgraded tumors were less frequently allowed to heal via second intention (5% vs 21%) and more frequently referred to outside physicians for repair (13% vs 8%) than nonupgraded tumors. These findings remained significant, even when controlling for the number of stages and postoperative surgical defect size.

In total, 11% (29/265) of patients with upgraded tumors were immunosuppressed, including 17 patients with a history of solid organ transplant, 7 patients with hematologic malignancy, and 5 patients with autoimmune disease. Only 7% (16/226) of patients with upgraded BCC were immunosuppressed. Approximately 36% (4/11) of tumors upgraded from SCC in situ to SCC and 45% (10/35) upgraded from well-differentiated SCC to moderately or poorly differentiated SCC occurred in the setting of immunosuppression. Perineural invasion was noted in 3 of the 20 cases upgraded to moderately or poorly differentiated SCC, and all 3 of these aggressive tumors occurred in the setting of immunosuppression.

Four patients with upgraded tumors had a history of radiation therapy to the affected area (either radiation for a previous cancer or historical treatment of acne vulgaris). The associated tumors had a preoperative diagnosis of nodular BCC and were upgraded to metatypical (3 cases) and/or infiltrative (3 cases).

DISCUSSION

This prospective study shows that a significant portion of NMSC cases referred for MMS display histologic features of aggressive cancers that were not seen on the initial biopsy. Our results are consistent with previous studies examining the

discordance between biopsy and intraoperative pathology. Retrospective studies comparing biopsy and excisional specimens of BCC have shown that histologic features consistent with aggressive subtypes seen on excision were not identified in 11%-26% of initial biopsies.[2-8] In most of these studies, the histology of excisional specimens were compared with that of initial punch biopsies.

More recent studies have detailed discrepancies between biopsy and intraoperative pathology during MMS. Chuang et al completed a prospective study on 29 cases of SCC in situ treated by MMS, of which 9 (31%) were upgraded to invasive SCC.[9] Moioli et al analyzed 55 cases of SCC in situ treated with MMS at a single institution and found that 16% of cases were upgraded to invasive SCC.[13] Stiegel et al studied 323 cases of NMSC referred for MMS over a 1-year period at a single institution and reported upgrade rates of 25% for SCC and 36% for BCC; however, they excluded cases that cleared on the first stage.[12] If those cases were included, as they were in this study, the overall upgrade rate would have been 16%, which is closer to the rate reported here.

Many of the cases included in our study displayed >1 aggressive histologic subtype within a single tumor. This finding is consistent with previous publications reporting high rates of mixed histologic features within BCCs (40%-43%).[17,18]

There is a recognized trend toward smaller biopsies in the field of dermatology, with superficial shave biopsies of suspected NMSC increasingly utilized.[19] Likewise, most clinicians in our referral base use shave biopsy to sample suspected NMSCs, and 98% of the biopsies in this study were performed using a shave method. Haws et al reported that shave biopsy was less accurate at identifying aggressive histologic subtypes of BCC than punch biopsy (81% vs 89% accuracy, respectively).[2] In another study, the overall accuracy of shave and punch biopsy for BCC subtype diagnosis were comparable, but infiltrative BCC was misidentified in 50% of shave biopsies and 21% of punch biopsies.[20] Westers-Atterma et al compared 105 cases of punch biopsy with excisional specimens and found that TNM stage was underestimated by punch biopsy in 15% of cases.[7] Knackstedt et al conducted a study of 51 SCC in situ cases that were transected on initial biopsy and found evidence of invasive SCC in 9.8% upon Mohs debulk analysis.[11]

The decision regarding which sampling technique to use for diagnosis of a suspected NMSC is complex and must take into consideration clinician experience, patient preferences, and the appearance of the neoplasm on physical examination. There is also substantial variation in surgical technique within a shave biopsy, and deeper saucerization biopsies are probably more accurate than superficial shave biopsies at identifying aggressive histologic subtypes of NMSC. More studies are needed to compare biopsy methods with regard to tumor upstaging.

The rate of upgrading in this study was higher for BCC (15%) than SCC and SCC in situ (3%). This might be due to sampling bias, considering clinicians tend to perform deeper biopsies for suspected SCC than for suspected BCC. Logically, superficial biopsies might fail to detect more aggressive histopathology. Clinicians should consider the importance of sampling an adequate amount of tissue to enable accurate diagnosis when one of these aggressive subtypes, which are associated with increased risk for recurrence, are suspected.[14,15,21-24] The use of treatment modalities that do not provide margin control might be inappropriate after a superficial shave biopsy in a high-risk area or in a high-risk (eg, immunosuppressed) patient.

Here, we present the first prospective study of tumor upgrading on surgical outcomes. Upgraded tumors required significantly more stages for clearance and produced larger postoperative defect sizes. Upgraded lesions required more complicated repairs and were less often allowed to heal by second intention. Interestingly, upgraded tumors had larger preoperative sizes than nonupgraded tumors, suggesting that larger tumors might have an increased risk for harboring aggressive histology not sampled on the initial biopsy. Upgraded lesions also demonstrated a larger degree of size change from preoperative to postoperative defect size. Since preoperative size correlates with clinical impression, this suggests that occult aggressive tumors are more likely to have subclinical extension only evident on frozen-section examination.

Comparative analysis of tumor location between upgraded and nonupgraded BCCs found no significant differences. For SCC, a higher proportion of upgraded lesions were located in area H, with only 1 upgraded SCC in situ located in area L. Although these data did not reach statistical significance (P = .0574, 2-sided Fisher's exact test), we suspect that with a larger cohort we could have concluded that SCCs located in area H have a higher risk for upstaging to a more aggressive histologic subtype than apparent on initial biopsy.

Importantly, in this study, the histologic features were only evaluated in lesions that were already referred for MMS. In our referral catchment area, the vast majority of referrals for MMS are classified as appropriate (AUC 7-9) according to published MMS AUC guidelines.[1] Accordingly, only 4% of BCCs in this study were located in area L. Thus, these results might not be generalizable to all NMSCs. It is possible

that upgrading rates would be lower for small tumors in low-risk areas.

Immunosuppression significantly increases the risk for NMSC, particularly SCC.[25-27] Immunosuppressed patients with SCC are at increased risk for recurrence and nodal metastasis.[28-31] In this study, nearly half of tumors upgraded to moderately or poorly differentiated SCC occurred in the setting of immunosuppression. This finding further substantiates the potential for aggressive behavior of SCC in the setting of immunosuppression, and clinicians should consider this information when planning treatment options for SCC in immunosuppressed patients or when performing a biopsy on a suspected SCC in the setting of immunosuppression.

This study has several limitations. It is important to note that the upgraded group included only tumors found to contain a previously undiagnosed aggressive subtype during MMS. The nonupgraded group included tumors with a preoperative diagnosis of one of these aggressive subtypes. Further analyses on tumor subtype were not possible as the deidentified surgical log did not contain detailed information on tumor subtype. If tumors with a preoperative diagnosis of an aggressive subtype had been excluded from the nonupgraded group, it is possible that the differences between groups may have been more dramatic.

In addition, the results represent 1 academic center's experience over a 1-year time frame. The results might be influenced by referral bias and variation in surgical referral practice patterns in our catchment area. There is inherent subjectivity in the classification of NMSC subtypes among both dermatopathologists and Mohs surgeons and variance in the reporting of these subtypes. Unlike some previous studies, we did not section through the frozen tissue block to exhaustively identify the presence of small foci of aggressive histology. Future studies could explore the long-term outcomes of upgraded tumors to determine whether histologic features of occult aggressive tumors correlate with an increased risk for recurrence or, in the case of SCC, development of metastatic disease.

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