ORIGINAL ARTICLE

Correlation of basal cell carcinoma subtype with histologically confirmed subclinical extension during Mohs micrographic surgery: A prospective multicenter study

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Background: Traditionally "aggressive" histologic subtypes (HSs) of basal cell carcinoma (BCC) are more likely to quantitatively exhibit subclinical extension (SCE), requiring more stages during Mohs micrographic surgery (MMS) and, therefore, larger margins upon excision. However, the tendency for SCE has never been compared between HSs of BCC in a prospective manner.

Objective: To prospectively correlate the HS of BCC with the likelihood of SCE as defined by the number of MMS stages required to clear the tumor.

Methods: In a prospective, multicenter study involving 17 Mohs surgeons in 16 different practices across the United States, data regarding 1686 cases of BCC undergoing MMS were collected. Patient demographics, tumor characteristics, number of MMS stages required for tumor clearance, and specific BCC subtypes noted on both index biopsy and the final MMS stage were recorded.

Results: Analysis of the average number of MMS stages for each HS required to clear tumor revealed 2 distinct degrees of SCE ($P < .0001$): high (higher than average) risk of SCE (1.9 stages, 1.0 SD) and low (lower than average) risk of SCE (1.6 stages, 0.9 SD). Subtypes of BCC within the high category were morpheaform (2.1), infiltrative (1.9), metatypical (1.9), mixed (1.8), and superficial (1.8). The low category included BCC subtypes of basosquamous (1.6), micronodular (1.6), nodular (1.6), and unspecified (1.5). Three hundred twenty-four cases (22.0%) manifested HS drift or a change in subtype from index biopsy to the final MMS stage. Superficial BCC was the only subtype that showed an increase in prevalence from index biopsy to the final MMS stage (from 16.0% to 25.8%; $P < .0002$).

Limitations: HSs from index biopsy may not be representative of all HSs present, resulting in sampling bias.

Conclusion: SCE of superficial BCC was as likely as SCE of BCC subtypes that are considered "aggressive" and are deemed "appropriate" for MMS by the appropriate use criteria. Our study also found that when HS drift occurs, the most likely subtype to extend subclinically is superficial BCC. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2022.02.037.)

Key words: basal cell carcinoma; drift; histologic subtype; Mohs micrographic surgery; subclinical extension; superficial.

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INTRODUCTION

Histologic subtypes (HSs) of basal cell carcinoma (BCC) are used as predictors of subclinical extension (SCE). Subtypes considered aggressive are characteristically more likely to exhibit SCE and require wider clinically tumor-free margins upon excision.[1-3] Historically, aggressive HSs of BCC have included infiltrative, morpheaform, micronodular, and metatypical subtypes.[4-6] Mohs micrographic surgery (MMS), with its precise and exhaustive margin examination, is especially well suited to methodically and precisely identify occult tumor extension.[7-12]

The purpose of this study was to correlate the HS of BCC with the likelihood of SCE as defined by the number of MMS stages required to clear the tumor. Prior studies that have used MMS as a tool to assess SCE among BCC subtypes have been retrospective.[13,14] Therefore, we sought to conduct, to our knowledge, the first prospective, multicenter study to determine whether certain BCC subtypes were more likely than others to exhibit SCE. Secondarily, we sought to validate the notion that subtypes traditionally considered aggressive were more prone to exhibit occult extension beyond clinical margins than those not considered aggressive.

CAPSULE SUMMARY

- Subclinical extension is a prominent feature of histologically aggressive subtypes of basal cell carcinoma (BCC), and superficial BCC exhibits frequent subclinical extension akin to that of "aggressive" subtypes.
- Clinicians should be aware of the higher likelihood of occult subclinical extension with superficial BCC and consider therapies with exhaustive histologic margin evaluation, such as Mohs micrographic surgery.

METHODS

Study design, setting, and participants

This study received institutional review board exemption from the Western Institutional Review Board (protocol number: 20152364). Data for this cohort were prospectively collected from patients undergoing MMS for BCC from the Cutaneous Oncology Research Cooperative data registry, which consists of 17 Mohs surgeons located in 16 different dermatology practices across the United States. Of the 17 Mohs surgeons, 16 were trained in the same fellowship program and performed MMS in a uniform fashion, taking 1- to 2-mm margins for each stage. Generally, curettage was performed prior to the first MMS stage for all subtypes. All cases in this study were obtained from biopsy-confirmed BCCs, with data collection occurring over 20 consecutive surgical days in 2012, immediately prior to the implementation of the appropriate use criteria (AUC) for MMS. Case data were submitted online directly into the Cutaneous Oncology Research Cooperative data registry.

Patient demographics, tumor characteristics, number of MMS stages required for tumor clearance, and specific BCC subtypes noted on index biopsy as well as the last positive MMS stage were recorded. Subtypes of BCC included superficial, nodular, infiltrative, metatypical, micronodular, morpheaform, keratotic, mixed, and unspecified categories. The mixed category was defined as >1 subtype identified. The investigators chose to include an unspecified category to represent those realistic clinical cases in which BCCs referred to Mohs surgeons did not have a subtype explicitly stated on the index biopsy pathology report. Subtypes that were identified as basosquamous, fibrosing/sclerosing, and adenoid were grouped together with metatypical, morpheaform, and nodular, respectively. The anatomic locations were grouped in accordance with the American Academy of Dermatology's AUC on MMS.[4]

SCE and HS drift

SCE, the primary end point, was defined as a BCC requiring >1 MMS stage, regardless of whether the tumor was apparent at the peripheral margin, deep margin, or both. To provide information that was most applicable to the clinical setting, SCE was measured as a function of the original index biopsy subtype rather than subtypes that were identified upon subsequent MMS stages. Large SCE was defined as 3 or more MMS stages required to clear the tumor. As a secondary end point, the change between the index biopsy BCC subtype and the BCC subtype of the final MMS stage was documented and termed "HS drift." For HS drift analysis, 212 cases of BCC were excluded because the tumor was cleared after a single MMS stage and no subtype could be identified on margin analysis. Additionally, the "mixed" category was divided into its constituent BCC subtypes to attribute HS drift to a specific subtype.

Abbreviations used:

AUC: appropriate use criteria
BCC: basal cell carcinoma
HS: histologic subtype
MMS: Mohs micrographic surgery
sBCC: superficial basal cell carcinoma
SCE: subclinical extension

Statistical analyses

For normally and nonnormally distributed interval variables, means and standard deviations as well as median and interquartile ranges were calculated, respectively. Data were analyzed using frequency distributions for nominal and ordinal variables, Pearson χ^2 test, or Fisher's exact (probability) test for nominal variables. The 1-way analysis of variance, Welch 2-sample *t* test, and Tukey multiple comparison test was used to determine statistically significant differences between the means of nominal variables. For multiple comparisons, the family-wise error rate was defined as 0.05 using the Holm method. The primary outcomes were BCC-SCE per subtype and BCC-SCE per AUC-defined anatomic location. The secondary outcome was HS drift. Multivariate analyses were conducted using binomial logit models.

RESULTS

Cohort characteristics

Patient and tumor characteristics are shown in Table I. Data regarding a total of 1686 cases of BCC were prospectively collected. Clearance of any BCC regardless of subtype required an average of 1.7 MMS stages (0.9 SD).

SCE

Of 1686 total cases, 784 manifested SCE in this cohort (Table I). The number of MMS stages required to clear the tumor per BCC subtype is shown in Table II. The morpheaform subtype yielded the highest mean MMS stages at 2.1 (0.9 SD), whereas the unspecified group exhibited the lowest mean MMS stages at 1.5 (0.7 SD). Analysis of the mean number of MMS stages required to clear tumor per subtype revealed 2 distinct degrees of SCE ($P < .0001$; Table II): high (1.9, 1.0 SD), or higher than average risk of SCE, and low (1.6, 0.9 SD), or lower than average risk of SCE. Subtypes of BCC within the high-risk category were morpheaform (2.1), infiltrative (1.9), metatypical (1.9), mixed (1.8), and superficial (1.8). The low-risk category included BCC subtypes of keratotic (1.6), micronodular (1.6), nodular (1.6), and unspecified (1.5). Subtypes within the high-risk category constituted 47.7% of large SCE but only 33.7% of non–large SCE ($P = .006$; Supplementary Table I, available via Mendeley at https://doi.org/10.17632/45mdghgcrr.1).

Age and sex were not statistically correlated to SCE (data not shown). Recurrent tumor status as well as superficial basal cell carcinoma (sBCC) subtype were each independently and significantly correlated to SCE (odds ratio, 1.6; $P = .0003$ and $P = .005$, respectively; Supplementary Table II, available via Mendeley at https://doi.org/10.17632/45mdghgcrr.1). After controlling for recurrent tumor status, sBCC status was still associated with SCE (odds ratio, 1.5; $P = .0008$).

The mean number of MMS stages per AUC-defined anatomic location is shown in Table III. Area H exhibited the highest average MMS stages to clear (1.8, 1.0 SD), followed by area M (1.6, 0.9 SD) and area L (1.4, SD 0.7; $P < .0001$). Subgroup analysis of the mean number of MMS stages per BCC subtype for area L is shown in Supplementary Table III (available via Mendeley at https://doi.org/10.17632/45mdghgcrr.1).

HS drift

After excluding 212 cases in which the presence—and therefore the subtype—of the tumor was not identified on the final MMS stage, 324 cases (22.0%) exemplified HS drift, in which different BCC subtypes were identified on the final MMS stage compared with index biopsy subtype. Table IV illustrates the HS drift per BCC subtype in which the mixed BCC subtype was divided among its constituent single subtype categories. Nodular, superficial, and unspecified BCC subtypes all exhibited a statistically significant HS drift ($P < .0002$). Nodular and unspecified subtypes diminished from index biopsy to the final MMS stage (56.4% to 48.3% and 5.4% to 2.8%, respectively; Fig 1), whereas sBCC increased in frequency (16.0% to 25.8%). The remaining subtypes of keratotic, infiltrative, metatypical, and morpheaform did not significantly change from the index biopsy to the last MMS stage.

DISCUSSION

The biologic behavior of BCC according to subtype has been previously characterized.[6,15-17] Micronodular, infiltrative, and morpheaform subtypes have been traditionally categorized as "more aggressive" than nodular and superficial subtypes. Histologically aggressive BCCs tend to be large, locally destructive, recurrent, or metastatic.[18] In addition, they have been characterized as being more likely to exhibit positive tumor margins after surgical excision.[6] During MMS, histologically aggressive subtypes require more stages to achieve

Table I. Patient demographics and tumor characteristics

Characteristic	All subjects	
Sex	*N*	%
Female	691	41.0
Male	995	59.0
Total	1686	
Age, y	*N*	%
18-29	9	0.5
30-39	30	1.8
40-49	114	6.8
50-59	262	15.5
60-69	427	25.3
70-79	449	26.6
80-89	343	20.3
90+	52	3.1
Total	1686	
Number of BCCs	*N*	Mean (SD)
	1686	1.7 (0.9)
Tumor history	*N*	%
Primary	1521	90.2
Recurrent	165	9.8
Total	1686	
Tumor anatomic site	*N*	%
Ear	141	8.4
Lower extremity	54	3.2
Upper extremity	78	4.6
Eyelid	108	6.4
Face	555	32.9
Genitalia/groin	1	0.1
Lip	64	3.8
Neck	81	4.8
Nose	443	26.3
Scalp	71	4.2
Trunk	90	5.3
Total	1686	
Tumor anatomic region	*N*	%
H	917	54.4
M	547	32.4
L	222	13.2
Total	1686	

Number of BCCs per number of MMS stages required for clearance	*N*	%
1 layer	902	53.5
2 layers	557	33.0
3 layers	146	8.7
4 layers	52	3.1
5 layers	21	1.3
≥6 layers	8	0.5
Total	1686	
Index tumor subtype	*N*	%
Infiltrative	131	7.8
Keratotic	22	1.3
Metatypical	16	1.0
Micronodular	35	2.1
Mixed	249	14.8
Morpheaform	44	2.6
Nodular	793	47.0
Superficial	159	9.4
Unspecified	237	14.1
Total	1686	
Final tumor subtype	*N*	%
Infiltrative	177	10.5
Keratotic	25	1.5
Metatypical	13	0.8
Micronodular	47	2.8
Mixed	74	4.4
Morpheaform	41	2.4
Nodular	693	41.1
Superficial	361	21.4
Unspecified	43	2.6
TMN	212	12.6
Total	1686	
Number of index tumor subtypes	*N*	%
Single	1197	71.0
Multiple	252	15.0
Unspecified	237	14.1
Total	1474	
Histologic subtype drift*	*N*	%
No	1150	78.0
Yes	324	22.0

BCC, Basal cell carcinoma; *MMS*, Mohs micrographic surgery; *TMN*, tumor not identified.
*Histologic subtype drift is defined as the change in subtype identified from the index biopsy to the final MMS stage. Two hundred twelve cases in which the tumor was not identified on the final MMS stage were excluded.

tumor-free margins, most often due to peripheral (48.9%) rather than deep (11.7%) SCE.[3] Without the use of histologically controlled margin surveillance, such BCCs are prone to recurrence as a direct consequence of SCE.

Our prospective, multicenter study reaffirms that certain BCC subtypes are more prone to exhibit SCE. However, our findings unexpectedly challenge the notion that sBCC is an innocuous, low-risk subtype. Current guidelines, including the AUC for MMS, do not consider sBCC to exhibit aggressive biologic behavior. Furthermore, the appropriateness of MMS for sBCC has been scrutinized, claiming that "current data supporting MMS for sBCC are at best uncertain."[19,20] Still, currently available evidence has strongly illustrated the tendency of sBCC to exhibit SCE with MMS, a technique inherently well suited for the identification of SCE. A retrospective study of 342

Table II. Mean number of Mohs micrographic surgery stages required to clear tumor per subtype and degrees of subclinical extension

Index biopsy tumor subtype	Mean	(SD)	*P* value	Mean (SD)	*P* value
Morpheaform	2.1	(0.9)	<.0001	High degree of SCE	
Infiltrative	1.9	(1.0)		1.9 (1.0)	
Metatypical	1.9	(1.5)			
Mixed	1.8	(1.1)			
Superficial	1.8	(0.9)			<.0001
Keratotic	1.6	(1.1)		Low degree of SCE	
Micronodular	1.6	(0.9)		1.6 (0.9)	
Nodular	1.6	(0.9)			
Unspecified	1.5	(0.7)			

SCE, Subclinical extension.

Table III. Average number of Mohs micrographic surgery stages required to clear tumor per appropriate use criteria—defined anatomic location

Tumor anatomic region	Mean	(SD)	*P* value
Area H	1.8	(1.02)	<.0001
Area M	1.6	(0.88)	
Area L	1.4	(0.71)	

Table IV. Histologic subtype drift of basal cell carcinoma*

	Index biopsy		Final MMS stage (all cases)		
Subtype	*N*	%	*N*	%	*P* value
Infiltrative	210	12.4	209	13.5	.958
Keratotic	24	1.4	27	1.7	.672
Metatypical	24	1.4	16	1.0	.203
Micronodular	63	3.7	63	4.1	1.000
Morpheaform	56	3.3	45	2.9	.265
Nodular	959	56.4	749	48.3	<.0002
Superficial	272	16.0	400	25.8	<.0002
Unspecified	91	5.4	43	2.8	<.0002
Total	1699		1552		

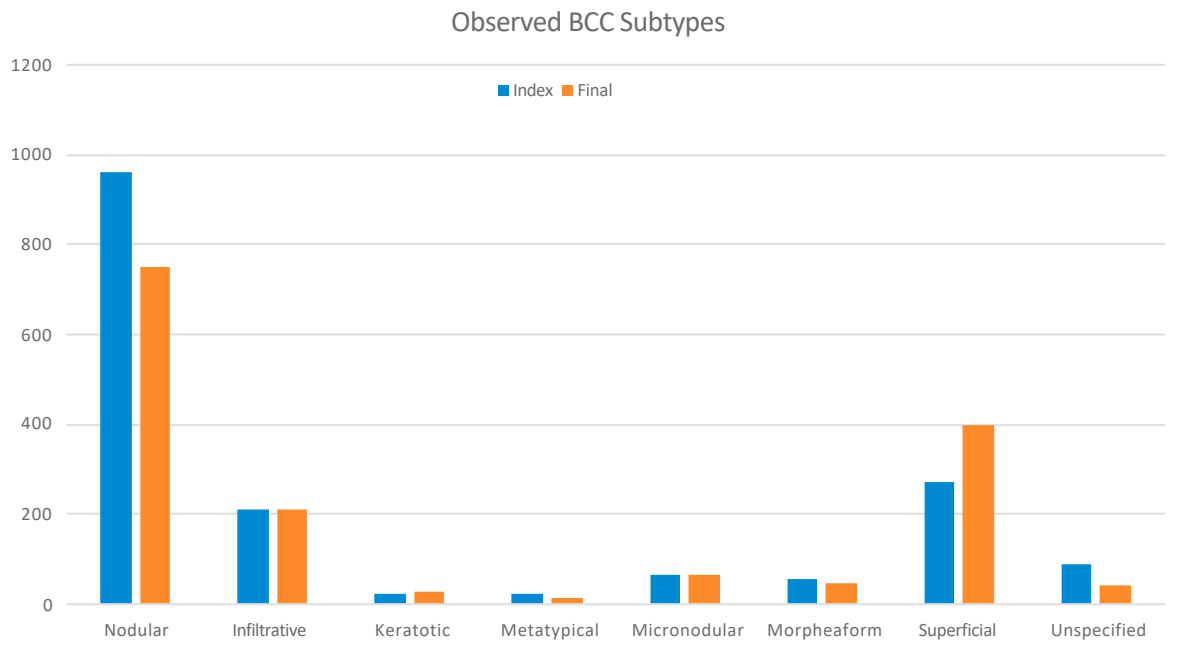
MMS, Mohs micrographic surgery.
*Histologic subtype drift is defined as the change in subtype identified from the index biopsy to the final MMS stage. Two hundred twelve cases in which a tumor was not identified on the final MMS stage were excluded.

primary BCCs showed that 54.4% of sBCCs were cleared only after 3 or more stages of MMS.[3] Another retrospective review of 158 sBCCs of the head and neck treated with MMS showed that an average of 2.6 stages were required for clearance.[2] sBCC also exhibits more SCE leading to larger surgical margins, having twice the odds of large SCE (defined as at least 3 MMS stages and a final surgical margin of at least 1 cm) after controlling for age, sex, Fitzpatrick skin type, prior history of BCC, and location of BCC.[1,14] Our study corroborates these findings, as sBCC was independently associated with a high risk of SCE akin to historically defined "aggressive" BCC subtypes.

The location of BCC according to AUC-defined anatomic location was significantly associated with SCE. Area H, area M, and area L followed predictable high-, medium-, low-degrees of SCE, respectively. The central face and ears include prominent anatomic structures with chronically sun-exposed areas, and these locations are well characterized high-risk locations for the development of BCC,[2,21-26] as well as showing a propensity for significant SCE.[14] However, even in area L, sBCC was among the subtypes with the highest degree of SCE.

A few studies have evaluated HS drift or the tendency for the subtypes to change over the course of MMS. An early prospective study of 129 BCCs treated with MMS showed that approximately 40% change subtypes at the SCE.[27] Other studies have described a transformation of primary nonaggressive BCC into "more aggressive" recurrent subtypes (ie, nodular, infiltrative, or morpheaform) after topical therapy or photodynamic therapy.[28-31] Recent retrospective investigations of sBCCs treated with MMS or excision with frozen sections have demonstrated higher rates of mixed histology on the head and neck as well as previously undetected, more invasive BCC subtypes.[32,33] Interestingly, this prospective study found the opposite trend—the need for additional MMS stages was significantly related to an increase in the frequency of sBCC but not a "more aggressive" subtype. This was evident by the fact that sBCC was the only subtype to exhibit a statistically significant increase in prevalence at the tumor perimeter.

The findings herein contradict the assertion that sBCC is an easy-to-treat subtype. A wide variety of treatment modalities exist for sBCC, including topical



Observed Subtypes	Nodular	Infiltrative	Keratotic	Metatypical	Micronodular	Morpheaform	Superficial	Unspecified
Index	959	210	24	24	63	56	272	91
Final	749	209	27	16	63	45	400	43

Fig 1. Histologic subtype drift per histologic subtype of BCC. Superficial BCC was the only subtype seen significantly more often at the perimeter of tumors after multiple Mohs micrographic surgery stages. Histologic subtype drift is defined as the change in subtype identified from the index biopsy to the final Mohs micrographic surgery stage. Two hundred twelve cases in which a tumor was not identified on the final Mohs micrographic surgery stage were excluded. *BCC,* Basal cell carcinoma.

or intralesional therapies, destruction, or standard excision, and recent literature has proposed that nonsurgical therapies as well as nonexcisional surgical treatments are effective for most sBCCs.[19] Despite US Food and Drug Administration approval of topical 5-fluorouracil 5% cream and imiquimod 5% cream for the treatment of sBCC,[34-37] clinical recurrence rates have been reported to be 31.8% within 3 years of treatment with 5-fluorouracil and 19.6% to 22.1% within 5 years of treatment with imiquimod.[38-41] Similarly, treatment of sBCC with photodynamic therapy has yielded an 84.4% cure rate.[36] Of note, head and neck BCCs are underrepresented in these studies, with more than two-thirds of tumors located on the trunk and extremities.[38,41] Large variability in efficacy exists for treatments that include cryosurgery, with recurrence rates ranging between 1% and 39%.[42-47] By contrast, MMS has demonstrated a 5-year recurrence rate of 1.0% and 5.6% for primary and recurrent BCCs, respectively, regardless of subtype, and it offers the added benefits of margin verification and tissue conservation in addition to excellent cosmesis and cost effectiveness.[48,49]

Our study is limited by sampling bias in that the HSs of the primary tumor on index biopsy may not be representative of all HSs present. Discordance rates between BCC subtypes identified at the time of biopsy and those identified after MMS and excision have been evaluated in previous studies, with 18% to 38% discordance rates and up to 40% having a more histologically aggressive subtype not previously identified from the initial biopsy.[36,50-57] Given the multicenter prospective nature of the present study, the study population broadly reflects that which is seen in clinical practice.

CONCLUSION

In conclusion, we show that the HS of BCC is correlated with SCE as well as HS drift. Specifically, our data challenge the perception of sBCC as a low-risk subtype. Rather, sBCC exhibits a high degree of SCE akin to that of more historically "aggressive" BCC subtypes. BCCs of any HS may also exhibit

occult extension as a result of drifting to become sBCC at the margin, which is contrary to the notion that additional stages are most often related to the presence of previously undiagnosed, traditionally aggressive BCC subtypes. Therefore, sBCC has been shown to have significant potential to be clinically occult and may lead to recurrence without margin verification. Given this finding, it is reasonable to consider MMS as potentially beneficial in the treatment of sBCC.

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Conflicts of interest

None disclosed.

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