Factors predictive of recurrence, metastasis, and death from primary basal cell carcinoma 2 cm or larger in diameter

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Background: Basal cell carcinoma (BCC) recurrence and metastatic rates are known to be very low. The risk factors for these rare outcomes are subsequently not well studied.

Objective: To identify risk factors independently associated with local recurrence (LR) and metastasis and/or death (M/D) in large (≥2 cm) BCC.

Methods: BCCs histologically confirmed between 2000 and 2009 were retrospectively screened for tumor diameter at 2 academic centers. Medical records of all large BCCs and an equal number of randomly selected small BCCs were reviewed for LR and M/D.

Results: Included were 248 large BCC and 248 small BCC tumors. Large BCCs had a significantly higher risk of LR and M/D than small BCCs (LR: 8.9% vs 0.8%, $P < .001$; M/D: 6.5% vs. 0%, $P < .001$). Because the risks were so low in small BCCs, they were excluded from further analysis. On multivariable logistic regression, head/neck location (odds ratio [OR], 9.7; 95% confidence interval [CI], 3.0-31.3) and depth beyond fat (OR, 3.1; 95% CI, 1.0-9.6) were associated with LR in large BCCs. Risk of LR was lower with Mohs micrographic surgery (OR, 0.14; 95% CI, 0.04-0.5). Head/neck location (OR, 5.3; 95% CI, 1.2-23.2), tumor diameter ≥4 cm (OR, 11.9; 95% CI, 2.4-59.4), and depth beyond fat (OR, 28.6; 95% CI, 6.7-121) were significant predictors of M/D in large BCCs.

Limitations: Retrospective cohort design.

Conclusions: Large BCCs, particularly those with additional risk factors, have a high enough risk of recurrence and metastasis to warrant further investigation to optimize management. (J Am Acad Dermatol 2020;83:832-8.)

Key words: basal cell carcinoma; local recurrence; LR; metastasis; MMS; Mohs micrographic surgery; outcomes; recurrence; risk factors.

With an estimated 2 million cases diagnosed annually in the United States, the incidence of basal cell carcinoma (BCC) exceeds that of any other cancer.[1-3] Most BCCs are easily cured with surgical excision and have low rates of recurrence and metastasis.[4] Local recurrence (LR)

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rates at 5 years for primary BCC range from 1% to 3.2% when treated with Mohs micrographic surgery (MMS) and from 2.3% to 10.1% when treated with standard surgical excision.[5-8] The risk of metastasis is thought to be extremely low, with estimates as low as 0.0028%.[9,10]

Prior studies evaluating BCC have focused on risk factors that increase the rate of LR. Several clinical and histopathologic features have been associated with an increase in LR, including large tumor diameter, head/neck location, recurrent tumors, poorly defined borders, immunosuppression, and perineural invasion.[11-15] Large tumor diameter has in particular been shown to increase the rate of LR. One study reported a 5-year recurrence rate of 15% for BCCs >15 mm in diameter treated with surgical excision and found that increasing lesion diameter was a significant predictor of recurrence when adjusted for scalp, ears, eyes, nose, or face location.[14] Rigel et al[15] also found that BCC LR rates increased with diameter, with a recurrence rate of 2.8% for BCCs with a diameter of 2 cm to 2.9 cm compared with 7.8% for BCCs with a diameter ≥5 cm. Metastatic BCCs have been associated with tumor diameter, depth of invasion, sex, history of radiation at the tumor location, and perineural invasion, but these risk factors have not been well quantified owing to the rarity of metastatic cases.[10,16,17]

This study was undertaken to better understand the risk of LR and metastasis and/or death (M/D) from large BCCs so that higher-risk tumors can be identified early and managed appropriately.

CAPSULE SUMMARY

- Head/neck location, depth beyond fat, and tumor diameter ≥4 cm were independent predictors of metastasis and/or death in large primary basal cell carcinoma (≥2 cm).
- These risk factors could be used to appropriately select basal cell tumors that would benefit from radiologic imaging, close follow-up, and potential adjuvant therapy.

METHODS

Patients with a histologic diagnosis of BCC, BCC with focal squamous differentiation, or basosquamous carcinoma (together referred to as BCC) at Brigham and Women's Hospital and Massachusetts General Hospital were identified between January 1, 2000, and December 31, 2009. Included cases were surgically treated BCCs as determined by excision operative reports (MMS and non-MMS). Duplicate records were excluded. Recurrent tumors and tumors with no primary information were also excluded. If a tumor had positive margins after treatment, a subsequent BCC tumor arising in the same site was defined as a continuation of the primary tumor rather than a recurrence. The Partners Human Research Committee approved this study.

All identified patients with a pathologically confirmed primary BCC were screened for clinical tumor diameter via medical record review. Tumors ≥2 cm in the smallest dimension were classified as "large," and tumors <2 cm in smallest dimension were classified as "small." Medical records for large BCC tumors were reviewed for the following patient and tumor characteristics: age at diagnosis, sex, race, immunosuppression, history of radiation at the tumor location, history of previous skin cancer, history of previous non-skin cancer, basal cell nevus syndrome, smoking history, alcohol history, tumor location, diameter, subtype, squamous differentiation, depth, perineural invasion, treatment modality, final margin status, and adjuvant therapy. In addition, outcomes of interest—LR and M/D from BCC—were recorded.

Because BCC is known to have a very low risk of LR and especially M/D, the analysis was focused on a subgroup of BCC likely to have a high enough risk of LR and M/D that it could be effectively studied without an extremely large cohort. Because the American Joint Committee on Cancer commonly uses 2 cm clinical tumor diameter as a prognostic cut point, a randomly selected group of patients with BCCs of less than 2 cm was analyzed to verify that the risk of LR and M/D from these tumors was less than 5%. If so, it was considered that these small BCCs could be justifiably excluded from the primary analysis because a 5% risk is unlikely to change management.

Tumors were considered to be invasive to the dermis and without perineural invasion unless otherwise stated in the pathology report because Brigham and Women's Hospital/Massachusetts General Hospital pathologists report depth beyond dermis and perineural invasion when present. Basaloid tumor (a term used by pathologists at Brigham and Women's Hospital/Massachusetts General Hospital) was defined as BCCs that have atypical characteristics but are composed of basaloid cells consistent with BCC. Tumors with multiple subtypes were analyzed based on the subtype of highest risk: infiltrative/morpheaform/sclerosing (henceforth

Abbreviations used:

BCC:	basal cell carcinoma
CI:	confidence interval
LR:	local recurrence
mBCC:	metastatic basal cell carcinoma
M/D:	metastasis and/or death
MMS:	Mohs micrographic surgery
OR:	odds ratio

referred to as only "infiltrative") superseded micronodular, which superseded nodular. Superficial BCCs were excluded from the analysis.

For the large BCC cohort, follow-up time was defined as the time from BCC tumor diagnosis to the date of the last visit with a dermatologist, primary care physician, or member of the BCC tumor's treatment team. Baseline demographic characteristics and tumor characteristics were analyzed using descriptive statistics. Patient and tumor characteristics of the LR subset and M/D subset were compared with the subset without LR and M/D using χ^2 and Fisher exact tests.

Logistic regression was used to determine univariable and multivariable associations of risk factors with LR and M/D. Survival analysis via Cox proportional hazards models was also attempted. However, owing to the small number of outcomes of interest, the more robust models were derived via logistic regression. Multivariable models were built using stepwise analysis. Models were corrected for intrapatient correlation using the robust variance estimate because the analysis was tumor case-based rather than patient-based. A subanalysis that excluded basosquamous cases was conducted. Analyses were performed using Stata 14.2 software (StataCorp, College Station, TX). All reported P values were 2-sided, with type I error (α) of <0.05 considered to be statistically significant.

RESULTS

From 11,905 patients with BCC who were screened, 248 large BCC tumors (≥2 cm) were identified in 234 patients. The cohort of small BCC tumors (<2 cm) included 248 cases from 162 patients. The risk of LR and M/D in small BCCs was 0.8% and 0%, respectively, which was less than our 5% threshold, so small BCCs were excluded from further analyses.

The patient and tumor characteristics for disease-related outcomes are provided in Table I. There were 22 LRs and 16 M/Ds. Men had a 13% LR risk and 8% M/D risk, basal cell nevus patients had a 75% LR risk and 50% M/D risk, and patients with a history of radiation at the tumor site had a 33% LR risk and 22% M/D risk. The median primary tumor diameter of LRs and M/Ds was 4.0 cm and 6.3 cm, respectively. Head/neck location had a 17% LR risk and 11% M/D risk, whereas depth beyond fat had a 31% LR risk and 41% M/D risk. Primary tumor treatment of LRs with excision had a 12% risk of recurrence, and MMS had a 4% risk. The patient and tumor characteristics for each disease-related outcome are provided in Supplemental eTable 1 (available at https://doi.org/10.17632/ww52b29yrg.1).

Large BCCs had a significantly higher risk of LR and M/D than small BCCs (LR: 8.9% v. 0.8%, $P < .001$; M/D: 6.5% vs 0%, $P < .001$). There were 8 tumors that developed a LR as well as M/D. Of the 16 cases of M/D, there were 14 cases of metastases (7 of which led to death), and of the 9 deaths from BCC, all but 2 had metastases. MMS was ineligible for 3 M/D patients who required radical surgery and 4 patients presenting with a metastasis at the time of diagnosis. One patient received a partial palliative MMS resection. Thus, the impact on M/D of MMS vs wide excision could not be assessed due to a small number of events (n = 8) in MMS-eligible patients.

Univariable logistic regression of risk factors significantly associated with LR and M/D is detailed in Table II. Perineural invasion was associated with LR (odds ratio [OR], 2.4; 95% confidence interval [CI], 0.8-7.0) and M/D (OR, 12.9; 95% CI, 4.4-38.2). Although it did not reach significance in multivariable modeling, the risk of LR was 17% (5 of 30 cases) and of M/D was 30% (9 of 30 cases) in cases with perineural invasion. Multivariable logistic regression identified multiple independent predictors of disease-related outcomes (Table III). Tumors located on the head/neck were 9.7-times more likely (95% CI, 3.0-31.3) to have a LR and 5.3-times more likely (95% CI, 1.2-23.2) to have a M/D. Tumor depth beyond fat increased the odds of LR and M/D by 3.1 (95% CI, 1.0-9.6) and 28.6 (95% CI, 6.7-121), respectively. Tumor diameter ≥4 cm was associated with a higher M/D (OR, 11.9; 95% CI, 2.4-59.4), and MMS was associated with a lower LR (OR, 0.14; 95% CI, 0.04-0.5). In a subanalysis excluding basosquamous cases, head/neck location remained a significant predictor of LR and MMS remained protective, whereas depth beyond fat lost significance ($P = .076$). Head/neck location, depth beyond fat, and tumor diameter ≥4 cm remained significant predictors of M/D.

DISCUSSION

Our results identify large BCCs (those with clinical diameter ≥2 cm) as having a 6.5% risk of M/D, which is more than 10-times higher than prior estimates of the risk of metastasis in BCC as a whole. Large BCCs

Table I. Patient and tumor characteristics of the overall cohort of ≥2 cm basal cell carcinoma tumors, local recurrence subset, and metastasis/death subset

Variable	Total cases, No. (%)	No LR or M/D, n (%)	LR, No. (% risk of having LR)*	*P*†	M/D, No. (% risk of having M/D)*	*P*†
Patient characteristics	N = 234	n = 206	n = 22 (9)		n = 16 (7)	
Sex				.04		.3
Men	142 (61)	121 (59)	18 (13)		12 (8)	
Women	92 (39)	85 (41)	4 (4)		4 (4)	
Race				.61		>.99
White non-Hispanic	228 (97)	197 (96)	22 (10)		15 (7)	
Other	6 (3)	9 (4)	0		1 (16)	
Basal cell nevus syndrome				.003		.01
Yes	4 (2)	1 (<1)	3 (75)		2 (50)	
No	230 (98)	205 (99)	19 (8)		14 (6)	
Immunosuppression				>.99		.62
Yes	18 (8)	15 (7)	2 (11)		2 (11)	
No	216 (92)	191 (9)	20 (9)		14 (6)	
History of radiation at tumor site				.04		.11
Yes	9 (4)	6 (3)	3 (33)		2 (22)	
No	225 (96)	200 (97)	19 (8)		14 (6)	
Tumor characteristics	n = 248	n = 218	n = 22 (9)		n = 16 (6)	
Age at diagnosis, mean y	67.8	68	64	.16‡	60	.01‡
Total follow-up, median mo	71	71.4	95.3	.01§	47.7	.06§
Tumor diameter, median cm	3	3	4	.01§	6.3	<.001§
Tumor location				<.001		.006
Head or neck	109 (44)	87 (40)	18 (17)		12 (11)	
Other	139 (56)	131 (60)	4 (3)		4 (3)	
Tumor subtype				.1		.003
Infiltrative	129 (52)	104 (48)	17 (13)		16 (12)	
Nodular	74 (30)	72 (33)	2 (3)		0	
Micronodular	11 (4)	10 (5)	1 (9)		0	
Other	12 (5)	11 (5)	1 (8)		0	
Unknown	22 (9)	21 (10)	1 (5)		0	
Squamous differentiation				.58		.34
Yes	53 (21)	44 (20)	6 (11)		5 (9)	
No	195 (79)	174 (80)	16 (8)		11 (6)	
Tumor depth				<.001		<.001
Dermis	192 (77)	182 (84)	9 (5)		0	
Subcutaneous fat	24 (10)	21 (10)	3 (13)		3 (13)	
Beyond fat	32 (13)	15 (7)	10 (31)		13 (41)	
Perineural invasion				.06		<.001
Yes	30 (12)	20 (9)	5 (17)		9 (30)	
No	218 (88)	198 (91)	17 (8)		7 (3)	
Treatment modality				<.001		<.001
Mohs	123 (50)	119 (55)	5 (4)		0	
Standard excision	103 (42)	85 (39)	12 (12)		12 (12)	
Excision and Mohs	9 (4)	7 (3)	1 (11)		1 (11)	
Surgery and radiotherapy	9 (4)	4 (2)	3 (33)		3 (33)	
ED&C	1 (<1)	0	1 (100)		0	
Amputation	1 (<1)	1 (<1)	0		0	
Brachytherapy	1 (<1)	1 (<1)	0		0	
Radiation monotherapy	1 (<1)	1 (<1)	0		0	
Adjuvant therapy				.08		<.001
Radiotherapy	11 (4)	6 (3)	1 (9)		4 (36)	
Chemoradiotherapy	3 (1)	0	1 (33)		3 (100)	
None	234 (94)	212 (97)	20 (9)		9 (4)	

ED&C, Electrodessication and curettage; *LR*, local recurrence; *M/D*, metastasis/death.

*Percentages are row percentages.

†*P* values are derived from the Fisher exact test unless otherwise noted.

‡*t* test.

§Wilcoxon rank sum test.

Table II. Univariable logistic regression of ≥2 cm basal cell carcinoma tumors

	Local recurrence		Metastasis and/or death	
Variable	**OR (95% CI)**	***P****	**OR (95% CI)**	***P****
Sex				
Female	1 [Reference]		1 [Reference]	
Male	3.1 (1.0-9.4)	.047	2.0 (0.6-6.3)	.25
Location				
Other†	1 [Reference]		1 [Reference]	
Head and neck	6.7 (2.2-20.4)	.001	4.2 (1.3-13.3)	.016
Histology				
Other†	1 [Reference]		1 [Reference]	
Nodular	0.2 (0.05-0.94)	.041	—	—
Infiltrative	3.5 (1.2-9.7)	.018	15.5 (2.0-119.5)	.008
Tumor depth				
Other†	1 [Reference]		1 [Reference]	
Fat and beyond	5.0 (2.0-12.2)	<.001	—	—
Beyond fat	7.7 (3.0-19.9)	<.001	48.6 (12.7-185.6)	<.001
Diameter				
Other†	1 [Reference]		1 [Reference]	
≥3 cm	1.8 (.72-4.7)	.206	13.5 (1.8-104.1)	.012
≥4 cm	4.3 (1.7-11.0)	.002	14.4 (3.2-64.8)	.001
≥5 cm	3.8 (1.5-9.3)	.004	14.8 (4.5-48.4)	<.001
Perineural invasion				
No	1 [Reference]		1 [Reference]	
Yes	2.4 (0.8-7.0)	.118	12.9 (4.4-38.2)	<.001
Treatment modality				
Other†	1 [Reference]		1 [Reference]	
Mohs micrographic surgery	0.2 (0.07-0.61)	.005	—	—
Standard excision	1.8 (0.75-4.37)	.185	4.7 (1.48-15.1)	.009
Surgery and radiotherapy	5.8 (1.34-25.0)	.019	8.7 (1.95-38.7)	.005

CI, Confidence interval; *OR*, odds ratio.

*Only risk factors with a *P* value less of ≤ .2 for local recurrence or metastasis and/or death are included in Table II.

†The reference categories of "Other" differ depending on the risk factor being assessed. For example, for the risk factor of histology, nodular basal cell carcinoma (BCC) is compared with a reference of non-nodular BCC, whereas infiltrative BCC is compared with a reference of noninfiltrative BCC.

also had a 9% risk of LR, which was significantly greater than the 0.8% risk in small BCCs. In addition, tumor diameter ≥4 cm, depth beyond fat, and head/neck location were predictors of M/D in large BCCs on multivariable analysis.

Most of the information on metastatic BCC (mBCC) is derived from pooled studies of case reports and case series.[9,10,16,18] These studies have concluded that 64% to 70% of mBCCs arise from primary tumors on the head and neck,[9,18] which is consistent with the results of our study, where 75% (12 of 16) of M/Ds originated from tumors on the head and neck. Previous studies have also examined the relationship between tumor diameter and mBCC. Rates of mBCC have been estimated at 1.9% in tumors ≥3 cm, 45% in tumors ≥10 cm, and 100% in tumors ≥25 cm.[10,16] Our study found tumor diameter ≥4 cm was independently associated with M/D and 88% (14 of 16) of M/Ds originated from primary tumors that were at least 4 cm in diameter.

Additional factors previously associated with mBCC were analyzed, including depth of invasion, sex, history of prior radiation at tumor location, and perineural invasion.[10,16,17] Of these, only depth beyond fat was associated with M/D on multivariable analysis. Depth beyond fat was the strongest predictor of M/D, and 38% of patients with tumors featuring this risk factor developed a metastasis or died from disease.

The only grading system for BCC currently available is the high-risk designation in National Comprehensive Cancer Network guidelines.[12] The criteria for this designation were developed to assist in establishing surgical margins minimizing surgical morbidity rather than to identify a subgroup with risk of M/D. It is thus very broad. For example, the National Comprehensive Cancer Network high-risk designation includes 6 mm BCCs on the mask area of the face, which this study and others have shown are at very low risk for M/D.[9,15]

Table III. Multivariable logistic regression of ≥2 cm basal cell carcinoma tumors

	Local recurrence		Metastasis and/or death	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Location				
Other	1 [Reference]		1 [Reference]	
Head and neck	9.7 (3.0-31.3)	<.001	5.3 (1.2-23.2)	.026
Diameter				
Other	—	—	1 [Reference]	
≥4 cm	—		11.9 (2.4-59.4)	.003
Tumor depth				
Other	1 [Reference]		1 [Reference]	
Beyond fat	3.1 (1.0-9.6)	.049	28.6 (6.7-121.0)	<.001
Treatment modality				
Other	1 [Reference]		—	—
Mohs micrographic surgery	0.14 (0.04-0.5)	.002	—	—

CI, Confidence interval; *OR*, odds ratio.

The risk factors identified in this study could be used to appropriately select BCCs that would benefit from radiologic imaging, close follow-up, and potential adjuvant therapy. Currently, adjuvant therapy is only recommended for BCC with large-nerve/extensive perineural invasion or positive margins after resection.[12] One study reported a 7.7% risk of recurrence in BCC with perineural invasion,[13] which is comparable to our data's risks of both local recurrence (8.9%) and metastasis (6.5%) in large BCC. Whether tumors at greatest risk for M/D may benefit from adjuvant therapy via Hedgehog inhibition (eg, vismodegib or sonidegib) merits further study. Although the adverse effect profiles and cost limit the routine use of these systemic agents, pulse-dosing regimens have been shown to reduce adverse effects while not compromising efficacy, making adjuvant therapy feasible if a high-risk patient subset can be defined.[19]

The risk of LR and M/D in patients with perineural invasion was 17% and 30%, respectively. Similarly, tumors arising in patients with basal cell nevus had a 75% LR risk and 50% M/D risk, whereas tumors arising within a radiated field had a 33% LR risk and 22% M/D risk. These high risks may be clinically relevant; however, some factors, such as perineural invasion, may be highly colinear with the other independent prognostic factors identified in this study such that they are not independent prognostic factors. The current study was only powered to determine the most robust prognostic factors for BCCs ≥2 cm. Larger studies are needed to better define the role of these other potential risk factors in BCC outcomes.

MMS was associated with a lower risk of LR compared with non-MMS excision. These findings support previous literature that details the protective benefit of MMS in BCC overall.[7] Whereas MMS was shown to be protective for LR, the impact of MMS could not be assessed in the M/D model because several cases of M/D were not eligible for MMS. Of the 16 cases of M/D, 3 required surgery under general anesthesia, 1 received no treatment, and 4 tumors presented with metastasis (but were still locally operable), requiring multimodality treatment. The relationship between MMS and metastasis risk requires further analysis in a study with a larger cohort of MMS-eligible tumors.

This study is subject to a few limitations. This cohort was derived from 2 academic centers, which may see more patients with difficult tumors and advanced disease than most dermatologists. However, given that recurrence, metastasis, and death are rare in BCC even at these academic centers, the relative importance of different prognostic factors in this cohort is not likely to differ substantially from patients with BCC in the general population. Given the infeasibility of extracting comprehensive outcome data on all BCCs diagnosed at the 2 hospitals during a 10-year period (which included approximately 12,000 cases screened for clinical diameter ≥2 cm), only a random selection of small BCCs (<2 cm) was analyzed. It is possible that this subset does not appropriately represent all small BCCs. However, this set of 248 cases indicates that the risk of LR and M/D is likely minimal (<1%) in small BCC because only 2 LRs and no M/D occurred in this group. In addition, the study was underpowered to build separate models for metastasis and death. However, given the relatively low occurrence of metastasis and death in BCC ≥2 cm and the high risk of death from metastatic BCC (50% in this study), using a combined end point was considered appropriate. Lastly, this cohort consisted of

patients who received surgical treatment for BCC. Outcomes of interest may possibly have been missed if they occurred in patients who never received surgical treatment (eg, definitive radiotherapy or hospice care). However, radiation is rarely used for BCC treatment at our institution, and we can recall only 1 BCC in a decade that was locally inoperable at primary presentation. Therefore, it is likely that few outcomes of interest were missed.

CONCLUSION

The results reported here represent an important step toward the identification of a subset of BCC with a clinically significant risk of recurrence, metastasis, and death. BCC tumors with a diameter of at least 2 cm were found to have a 9% risk of LR and a 6.5% risk of M/D, which is significantly higher than that of the small BCC cohort and sufficient to warrant further investigation of optimal management. Prognostic factors, including tumor diameter ≥4 cm, head/neck location, and depth beyond fat, were associated with increased risks of LR and M/D. The subset of BCC tumors prone to outcomes should be further defined with quantified risks of recurrence, metastasis and death. Staging criteria can then be developed that separate such high-risk cases from the low-risk large majority of BCC. Continued research on the often-overlooked topic of BCC prognosis is encouraged to improve the care and management of those affected.

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