Non-Melanoma Skin Cancer Tumor's Characteristics and Histologic Subtype as a Predictor for Subclinical Spread and Number of Mohs Stages required to Achieve Tumor-Free Margins

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Objective: To describe the behavior of non-melanoma skin cancer (NMSC) based on tumor's characteristics.

Methods: A total of 219 of NMSC were analyzed via a retrospective medical chart review. The data obtained from each record included but was not limited to: number of Mohs micrographic surgery (MMS) stages required for tumor clearance, defect size, repair type and size according to the neoplasm's histopathologic subtype.

Results: The mean number of stages required to clear morpheaphorm/infiltrative and micronodular basal cell carcinomas (BCCs) (n= 34) was 2.03, while the nodular and superficial BCCs (n= 125) needed a mean of 1.56 stages (p value= .034). Of the tumors located on a high-risk zone, 59.6% required two or more stages to be cleared while 67.7% of the lesions on a non-high-risk zone were cleared with one stage (p value = 0.001). Recurrent tumors required a mean 2.22 MMS stages to be cleared, whereas primary tumors required a mean 1.61 stages (p value= .006).

Conclusion: Subclinical spread was seen in morpheaform/infiltrative and micronodular BCC histologic subtypes, recurrent tumors, and tumors in high-risk locations. These could help predict aggressive tumor behavior and optimize surgical planning. [*P R Health Sci J 2019;38:40-45*]

Key words: Basal cell carcinoma, Squamous cell carcinoma, Mohs micrographic surgery

Mohs Micrographic surgery (MMS) is considered the gold standard treatment for skin cancer classified as high risk, recurrent or located in aesthetically delicate regions (1, 2, 3).

It minimizes any additional morbidity associated to lesion excision without margin control, as well as improves functionality and cosmetic outcomes by sparing uninvolved skin (4). Although highly effective, MMS can be time consuming and costly. Therefore, identifying skin cancer features that can help predict their behavior may help guide the surgeon, as well as the patient's expectations, prior to MMS.

Basal cell carcinomas (BCCs) tend to grow slowly and are associated with less risk of metastasis (0.1%) when compared to squamous cell carcinomas (SCCs) (2-10%), but can be locally aggressive if left untreated (5). Nodular and superficial BCC (sBCC), as well as BCCs with lack of perineural invasion are considered to be low-risk due to their low recurrence rate (6). On the other hand, micronodular, morpheaphorm, sclerosing, infiltrative, and basosquamous subtypes are considered to be high-risk due to their tendency for recurrence (6, 7, 8). These high recurrence rates are associated to the tumor's diffuse growth pattern and subclinical extension (9). BCCs of non-aggressive histologic subtypes are associated with less MMS stages when compared to their aggressive counterpart (10).

In the US, the 5-year recurrence rate for primary BCCs after MMS is as low as 1.0% (4). When compared with recurrence rates after surgical excision (3.2-10% in primary BCCs and >17% in recurrent BCCs), and taking into consideration the additional treatments these patients will require, MMS seems to be a superior and more cost-effective treatment modality (1, 2).

The histologic grade of (SCCs) and their recurrence rate correlate; moderately and poorly differentiated SCCs are considered high-risk due to their tendency to recur after treatment (6). Perineural and single cell SCCs are also classified under high-risk, whereas the well-differentiated SCCs are considered low-risk tumors (6). High-risk SCCs have also been shown to require more MMS stages for clearance when compared to low-risk SCC subtypes (11).

Tumor characteristics such as location, prior management, and pre-operative size, are also essential in predicting tumor behavior. The nose, ears, eyelids and temples have been identified as high-risk anatomic sites for non-melanoma skin cancer (NMSC) (12, 13) most likely associated to the presence of embryonic fusion planes (12, 14), extensive nerve populations, the perichondrium and periosteum closely associated to the dermis (15), or sebaceous glands that can store isolated groups of malignant cells (16). Tumor location can also serve as a predictor for metastasis, such as the case for SCCs located on the ear or lip (17, 18). Other tumor characteristics attributed to high-risk lesions are location on acral extremities or genitalia as well as tumor size larger than 2 cm (19). In addition, invasive behavior has been linked to recurrent tumors (20). The pathophysiology is most likely explained by a disturbance of a cell's immune function secondary to initial treatment and subsequent scar tissue formation, which locks in tumor cells that can eventually leak causing recurrence (21, 22).

The purpose of this study is to determine risk factors that could identify lesions with increased likelihood of requiring more extensive surgery. It is a retrospective medical chart review comparing tumor characteristics and NMSC histologic subtypes with the extent and complexity of the associated MMS.

Patients and Methods

This study was conducted at the Department of Dermatology of the University of Puerto Rico and the Institutional Review Board granted approval for the study. A retrospective review of medical charts dating from August 2013 to April 2015 was conducted of 312 patients scheduled for surgery with the same Mohs surgeon (S.V.N.). Exclusion criteria are depicted in Figure 1. In patients with multiple and clinically distinct tumors, each lesion was considered a separate tumor.
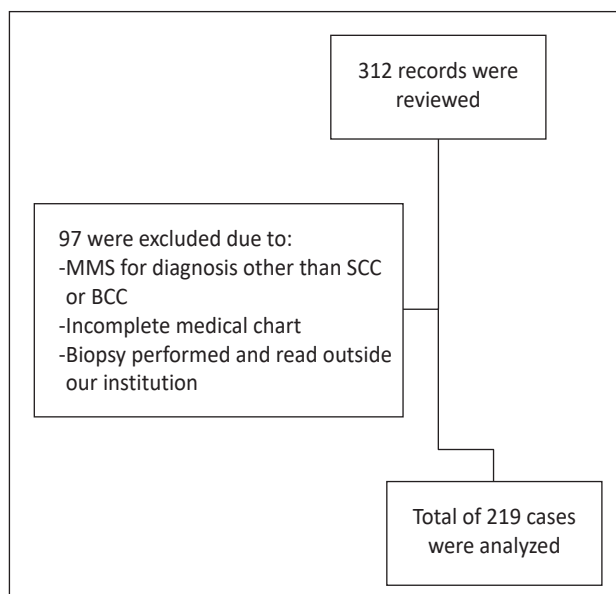

Figure 1. Exclusion criteria

A total of 219 cases were analyzed. BCCs were subclassified as nodular, micronodular, morpheaphorm, superficial, basosquamous and infundibulocystic. Although there are several types of SCCs (e.g. pseudovascular, spindle cell, adenoid, etc.), there are rare and were not present in our cohort. Therefore, SCCs were classified as in situ or invasive. Variables examined included: patients' age and gender, tumor histologic subtype, lesion anatomic location, recurrence status, initial lesion size, number of MMS stages, defect size after MMS, reconstructive technique used, and final closure size. Two or more MMS stages were considered a criterion for extensive subclinical spread.

Previously untreated or incompletely excised neoplasms were classified as primary and those previously treated with apparent clinical or histopathologic success were considered recurrent. Tumors were also classified according to their location. The ear, eyelid, nose, and lip were classified as high-risk anatomic zones while all other locations were considered low-risk. Neoplasms of the ear, nose, and eyelid were sub-classified based on specific subunits.

Clinical visible margins of the lesions were determined prior to MMS and, in most cases; neoplasms were excised with a 2-mm margin per stage. In cases of clinically aggressive SCCs (> 4cm), 4 mm margins were used per stage until a tumor-free plane was reached. The initial biopsy histopathologic slides were collected and reviewed by two dermatopathologists (J.L.S. and J.E.S.) to determine the tumor's histologic subtype. In some cases, a mixed histologic pattern was observed. In this scenario, neoplasms were classified according to the dominant pattern.

Data entry and statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) version 20. Descriptive statistics, one-way ANOVA, Chi-square test and independent T-test were used in data analysis.

Results

The mean patient age was 65.89 years old; 103 (47%) were males and 116 (53%) were females. Most tumors were primary (91.8%), while 18 (8.2%) had been previously treated. Tumor characteristics are described in Table 1. Regarding tumor laterality, 97 (44.3%) were located on the left side and 97 (44.3%) on the right side, whereas midline lesions comprised 11.4% (n=25) of the tumors. Furthermore, 109 (49.8%) were located in a high-risk zone.

Average initial tumor size, final defect size, as well as number of MMS stages needed for tumor removal per histological subtype is illustrated in Table 2. An initial lesion size between 0.50 - 1.50 cm characterized 62% of the neoplasms. A total of 113 (51.6%) tumors were cleared after one stage of MMS and 106 (48.4%) tumors required two or more stages. Tumors with an average initial size of 1.32 cm required one stage, whereas tumors with an average initial size of 1.67 cm required two or more MMS stages for clearance (p value= .011).

Table 1. Tumor characteristics

	n=219	%
Histopathology		
Nodular BCC	121	55.3
SCC invasive	45	20.5
Micronodular BCC	21	9.6
Morpheaphorm BCC	13	5.9
SCC in situ	9	4.1
Superficial BCC	4	1.8
Basosquamous BCC	3	1.4
Infundibulocystic BCC	3	1.4
Location		
Nose	63	28.8
Cheek	37	16.9
Forehead	22	10.0
Eyelid	20	9.1
Ear	15	6.8
Extremities	14	6.4
Temple	12	5.5
Lip	11	5.0
Trunk	10	4.6
Neck	8	3.7
Scalp	6	2.7
Chin	1	0.5
Stages		
1 stage	113	51.6
≥ 2 stages	106	48.4

BCC, Basal Cell Carcinoma; SCC, Squamous Cell Carcinoma

The mean number of stages required to clear micronodular and morpheaform/infiltrative BCCs (n= 34) was 2.03, while nodular and superficial BCCs (n= 125) needed a mean of 1.57 stages (p value= .011). In situ SCCs and invasive SCCs cleared with a mean of 1.56 and 1.67 stages, respectively (p value= .701).

Eighteen tumors (8%) were considered recurrent at initial treatment with MMS. The average initial size of these tumors was 2.35 cm whereas primary tumors had a mean initial size of 1.41 cm (p value < .001). Recurrent and primary tumors had a mean final defect size of 3.42 cm and 2.01 cm, respectively (p value < .001). Among the eighteen recurrent cases, fourteen (77.8%) required two or more stages to be cleared. Furthermore,

Table 2. Average initial tumor and final defect size, and number of MMS stages needed for tumor-free margins per histological subtype

	Mean initial size (cm)	Mean Final defect size (cm)	Mean number of stages
Histopathology			
All (n=219)	1.49	2.12	1.66
Nodular BCC	1.32	1.90	1.57
Micronodular BCC	1.05	1.60	1.95
Infundibulocystic BCC	1.10	1.67	2.33
Morpheaphorm BCC	2.12	3.18	2.15
Basosquamous BCC	.83	1.30	1.00
Superficial BCC	2.18	2.65	1.25
SCC in situ	1.67	2.42	1.56
SCC invasive	1.93	2.64	1.67

BCC, Basal Cell Carcinoma; SCC, Squamous Cell Carcinoma

the mean number of stages required for complete tumor removal was 2.22 for recurrent tumors and 1.61 for primary tumors (p value = .006).

A total of 167 defects (76.3%) were repaired using the following techniques: linear (50.3%), skin graft (23.9%), flap (23.4%), or a combination of these (2.4%). Defects allowed to heal by secondary intention (n= 45) were mostly located on the ear (n=10; 22.2%) and scalp (n=5; 11.1%) A significant association between tumor location and repair type was found (p value < .001). The major contributors to this association were cheek and forehead with linear repair; ear and scalp with secondary intention healing; nose with skin graft; and eyelid with referrals. A total of 7 cases were referred to another service for reconstruction; of these, 4 (57.1%) were eyelid repairs.

Discussion

An increase in the worldwide incidence of NMSCs has resulted in many studies evaluating different surgical and nonsurgical treatment modalities (23-25). Management considerations are based on both patient and tumor characteristics (6). A malignancy's inconspicuous subclinical extension into surrounding tissue suggests that visual estimates of tumor perimeters may be insufficient, resulting in some cases in inadequate removal and increased likelihood of recurrence (18, 26, 27). MMS provides high cure rates as it allows examination of 100% of the peripheral and deep margins of the tumor, whereas, histologic assessment of standard excisions examines only 0.2% of the surgical margins (23, 25, 28, 29). The analysis of tumor characteristics conducted in our study can help identify risk factors associated to NMSC that could help predict their behavior, guide the clinicians management approach, as well as patient's anticipations.

In our data, 85.8% of tumors were located in the head. This predilection may be explained by increased sun exposure of the region (23). Various studies have described how 70-98% of skin cancers occur in the head and neck (6, 23, 30-32). Moreover, in accordance with the findings of Paoli et al. (4), the most frequent location for BCCs in our study was the nose (28.8%). Previously published studies have identified the nose, eyelids, lips and peri-auricular regions as high-risk locations showing deep invasion and higher recurrence rates (4, 12, 23, 33). These locations have a high density of hair follicles and sebaceous glands that may create nests for tumor cells (16). In addition, these locations are embryologic cleavage planes that provide relatively little resistance to tumor invasion (1, 6, 14, 23). As described by Leibovitch et al. (23) and Salasche et al. (16), our data demonstrates how lesions on high-risk zones required more than one MMS stage for tumor clearance. In a study by Batra et al. (26), the highest odds ratio (OR) for predictive risk factors of NMSC with aggressive subclinical extension were location of the lesion (i.e., eyelid, temple, and ear helix), and tumor size (34). Similarly, our study showed a higher prevalence of invasive SCCs on the nose (15.6%) and eyelids (13.3%), which are

considered high-risk anatomic zones, while the most common location for in situ SCCs was the extremities.

Tumor size may also be an indicator of subclinical spread. Large BCC tumors may show extensive subclinical growth known as the "iceberg phenomenon", wherein part of the tumor is not visible to the surgeon (1, 6). Mohs identified a tumor size greater than 2 cm as an indication for MMS based on a higher likelihood of recurrence (35). In this study, a perioperative size ≥ 1.67 cm proved to be a significant predictor of microscopic spread, consistent with other studies that depict gradation of risk with increasing tumor size (1, 6, 13, 26).

Using the number of MMS stages as an indicator of extensive subclinical spread, our study showed that infiltrating/morpheaform/micronodular histologic BCCs subtypes, in comparison with nodular and superficial histologic subtypes, were associated with a significantly higher number of MMS stages. Therefore, these BCC subtypes are more difficult to eradicate and tend to have inconspicuous extension when compared with nodular/superficial BCCs. Aggressive histologic subtypes accounted for 20.6% of the BCC tumors in this study in accordance to previous studies which often cite a 15% frequency of aggressive subtypes (36). Evidence suggests that histologic subtype of BCCs influences tumor behavior (37-41). Sexton et al. (42) and Johnson et al. (43) showed that certain BCC histologic subtypes (morpheaform, infiltrative, micronodular, and mixed patterns) of primary BCCs are more likely to have positive margins after excision. A previous study found that morpheaform tumors were 2.3 times as likely to demonstrate extensive subclinical extension when compared to primary nodular BCC (26, 44). Published data on the incidence and clinical characteristics of SCCs with aggressive subclinical extension are limited. In this study, in situ and invasive SCCs required similar stages for clearance. The degree of SCC differentiation and perineural invasion were not assessed. However, conclusions regarding the behavior of in situ SCCs compared to invasive SCCs are difficult to determine because the low number of SCC cases included in this study (n = 54) hinders the breadth of statistical analysis.

In our study, the initial size for recurrent and primary tumors was 2.35 and 1.41, respectively. Recurrent tumors in our sample required an average 2.22 stages for complete clearance when compared to primary tumors, which required a mean of 1.61 stages to be cleared. The final defect size was also larger for recurrent tumors when compared to primary tumors. Studies have found that recurrent tumors tend to be larger than primary tumors, require more MMS stages, result in larger post-excision defect size and are associated to aggressive histologies (23). Increased risk of recurrence is seen in SCCs that are large, located in high-risk locations, moderately differentiated, poorly differentiated, perineural, and single cell SCC (6, 45). A possible explanation lies in how previous treatments may decrease local host defenses, causing multiple foci of unconnected tumor, or cause entrapment of tumor cells in scar tissue that are subsequently released causing recurrence (21, 22, 26).

The retrospective nature of this study limits its analytic scope. The fact that all cases were obtained from the medical chart of a single, government health facility where patients tend to arrive with more advanced disease is another limitation to consider. Furthermore, MMS frozen sections were not reviewed and most of the initial biopsy specimens were partial tumor shave biopsies therefore preventing complete histologic examination for tumor subtype determination. The histologic subtype declared for an initial biopsy does not always correlate with the subtype of the final Mohs stage. This may be due to the presence of a more aggressive subtype in the depth or periphery of the tumor (46), which is difficult to appreciate in a shave biopsy specimen. Furthermore, SCC histologic subtypes and their correlation with MMS were not assessed.

Conclusions

Our study was characterized by a high percentage of head and neck cases. The distribution of anatomic locations and histologic subtypes described was comparable to other previously mentioned studies. In our study, primary BCCs of the nodular subtype usually required one MMS stage to clear. Furthermore, the most important predictors of extensive subclinical spread for BCC subtypes are morpheaform/infiltrative, micronodular and lesion recurrence as described in our series. Therefore, wider margins should be obtained when excising micronodular, infiltrative, and morpheaform BCCs, as previously reported by other investigators (39, 40, 47). In our data, recurrent tumors were larger than primary tumors, had a larger post-excision defect, a more extensive subclinical extension, and required more stages of excision. High-risk locations and perioperative size could help predict the occurrence of aggressive neoplasms.

By providing a risk scale for subclinical spread and aggressive behavior influenced by histologic subtype, the surgeon can be particularly vigilant when examining frozen sections of high-risk tumors. Furthermore, surgeons can anticipate final defect size, plan for appropriate reconstruction, accommodate their operative schedules depending on the repair's complexity and the surgical time, as well as guide their patients in terms of pre- and post-operative expectations.

Resumen

Objetivo: Describir el comportamiento de cáncer de piel, basocelular y escamoso, basado en las características del tumor. Métodos: Un total de 219 casos de cáncer de piel fueron analizados mediante un estudio retrospectivo de expedientes médicos. La información obtenida incluyó, pero no estuvo limitada a: número de estadios de cirugía micrográfica de Mohs necesarias para obtener márgenes libres de tumor, tamaño del defecto, tipo de reparación y tamaño del tumor de acuerdo a su subtipo histopatológico. Resultados: El promedio de estadios requeridos para lograr márgenes libres en cáncer basocelular morferaforme/infiltrativo (n= 34) fue de 2.03, mientras que

en cáncer basocelular nodular y superficial (n=125) fue de 1.56 (p= 0.34). De los tumores localizados en zonas de alto riesgo, 59.6% requirieron 2 o más estadios para lograr márgenes libres de tumor mientras 67.7% de las lesiones en zonas de bajo riesgo requirieron sólo un estadio (p= 0.001). Los tumores recurrentes requirieron un promedio de 2.22 estadios de cirugía de Mohs mientras tumores primarios requirieron en promedio 1.61 (p= 0.006). Conclusión: Mayor extensión subclínica fue observada en cáncer basocelular del subtipo histopatológico morfeaforme/infiltrativo y micronodular, además en tumores recurrentes y aquellos que estaban en localizaciones de alto riesgo. Estos hallazgos pueden ayudar a predecir el comportamiento agresivo de los tumors y optimizar la planificación pre-quirúrgica.

Acknowledgments

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