ORIGINAL RESEARCH

Tumor Characteristics Predicting Perineural Invasion in Cutaneous Squamous Cell Carcinoma Identified by Stepwise Logistic Regression Analysis

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ABSTRACT

Background: Perineural invasion (PNInv) is a significant risk factor for metastasis and death in cutaneous squamous cell carcinoma (cSCC). Despite this known association, factors contributing to the presence of PNInv are not well characterized.
Aims: To determine risk factors associated with the presence of PNInv using the high-risk cSCC criteria developed by the National Comprehensive Cancer Network (NCCN).
Methods: After receiving Institutional Review Board approval for this retrospective review, the presence of NCCN high-risk factors for cSCC were recorded for patients treated at a tertiary referral academic medical center, from January 1, 2010 to March 31, 2012. Stepwise logistic regression was used to identify factors associated with the presence of PNInv.
Results: PNInv was present in 34 of 507 (6.7%) cSCCs. Moderately or poorly differentiated histology ($p<0.001$, OR 6.6 [95% CI, 3.2-13.7]), acantholytic, adenosquamous, or desmoplastic subtype ($p=0.01$, OR 1.8 [95% CI, 0.8-4.2]), and tumors in areas M (≥10mm) and H (≥6mm) ($p =0.05$, OR 5.0 [95% CI, 1.2-21.0]) were significantly associated with the presence of PNInv.
Conclusions: This data suggests clinicians should have a higher suspicion and may be able to identify PNInv in high-risk cSCC based on the presence of specific high-risk factors.

INTRODUCTION

Perineural invasion (PNInv) in cutaneous squamous cell carcinoma (cSCC) has been established as a significant independent risk factor for metastasis and death.[1-5] Accordingly, PNInv is included as a high-risk factor in the National Comprehensive Cancer Network's (NCCN) cSCC guidelines.[4] While the association of PNInv with poor outcomes is well known, factors contributing to the

presence of PNInv in cSCC are not well characterized. Our aim was to determine risk factors associated with the presence of PNInv using the high-risk cSCC criteria developed by the NCCN.

METHODS

After receiving Institutional Review Board approval, electronic medical records (EMR) were queried for all patients diagnosed with cSCC of the head and neck treated at a tertiary referral academic medical center from January 2010 to March 2012. Patients were seen across multidisciplinary settings including the departments of Dermatology, Otolaryngology-Head and Neck Surgery, Hematology and Oncology, Radiation Oncology, Surgical Oncology, and Plastic Surgery. Patient demographic data as well as the presence of the NCCN high-risk factors for head and neck cSCC were recorded.

NCCN defines high-risk location/size as ≥10 mm in area M (forehead, scalp, cheek, neck, and pretibia) and ≥6 mm in area H, "mask areas of the face" (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet.

Breslow Depth (BD) and Clark Level (CL) were available for 6 of 507 tumors (1.2%); thus, tumors were not excluded if they had incomplete BD or CL. Tumors with incomplete EMR data, other than BD or CL, were excluded. PNInv was defined as tumor cell invasion within the perineurium or endoneurium as identified on the biopsy or excision pathology, or during Mohs Micrographic Surgery. PNInv was determined by reviewing the dermatopathology and surgical pathology reports. Stepwise logistic regression was used to identify NCCN cSCC high-risk factors associated with the presence of PNInv. Alpha was set at 0.05.

RESULTS

There were a total of 520 cSCCs of the head and neck identified and 13 were excluded due to incomplete EMR data. The analysis included 507 tumors from 471 patients. PNInv was present in 34 of 507 cSCCs (6.7%) from 34 patients (29 male and 5 female). The average age of the PNInv cohort was 77 years (SD 13.1 years). The mean size of tumors with PNInv was 2.6 cm (median 1.6 cm, range 0.6-8 cm) compared to a mean of 1.3 cm (median 1.0 cm, range 0.3-8.5 cm) for the overall cohort (Table 1). The majority (58.8%) of tumors with PNInv were ≤ 2.0 cm. The most common anatomic locations of cSCC for the overall and PNInv cohorts were the ear (19.5% vs. 14.7%), scalp (15.4% vs. 17.6%), and cheek (15.0% vs. 14.7%). Areas M (> 10 mm) and H (> 6 mm) contained 12 (35.3%) and 20 (58.8%) of cSCCs with PNInv, respectively.

The logistic regression model identified three statistically significant NCCN high-risk factors associated with the presence of PNInv in cSCC: moderately or poorly differentiated histology (P<0.001, OR 6.6 [95% CI, 3.2-13.7]), acantholytic, adenosquamous, or desmoplastic subtype (P =.01, OR 1.8 [95% CI, 0.8-4.2]), and tumors fitting NCCN criteria for areas M and H (P = .05 OR 5.0 [95% CI, 1.2-21.0]) (Table 2).

Table 1: NCCN Patient and Tumor data.

	Overall Cohort N = 507 (%)	PNInv cohort n = 34 (%)	*P* value
Location/size as a high-risk feature, No. (%)	393 (77.5)	32 (94.1)	0.03
Area M >10 mm[a], No. (%)	137 (27.0)	12 (35.3)	0.10
Area H > 6 mm[b], No. (%)	256 (50.5)	20 (58.8)	0.41
Moderately or poorly differentiated	72 (14.2)	16 (47.1)	<.001
Acantholytic, adenosquamous or desmoplastic subtypes	76 (15.0)	8 (23.5)	0.23
Depth >2mm or Clark Level IV, V[c], No. (%)	5 (1.0)	1 (2.9)	0.89
Rapidly growing	78 (15.4)	12 (35.3)	0.002
Poorly-defined borders	68 (13.4)	2 (5.9)	0.28
Recurrence	50 (9.9)	8 (23.5)	0.014
Immunosuppression	34 (6.7)	3 (8.8)	0.88
Site of prior radiation therapy or chronic inflammatory process	5 (1.0)	2 (5.9)	0.04
Neurological symptoms	1 (0.2)	0 (0)	1.00
Vascular Involvement[d]	1 (0.2)	1 (2.9)	0.08

PNInv, perineural invasion; No., number.
[a]Area M: ≥10 mm on the forehead, scalp, cheek, neck, and pretibia.
[b]Area H: ≥ 6 mm on the "mask areas of the face" (central face, eyelids, eyebrows, periorbital, nose, lips (cutaneous and vermilion), chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet.
[c] Depth or Clark Level was rarely recorded, 6 of 507 tumors.
[d]PNInv and vascular invasion are considered as a single grouping for the NCCN criteria.

Table 2: Multivariable predictors of perineural invasion.

	Entire cohort N = 507 (%)	PNInv cohort n=34 (%)	*P* value	Odds Ratios (95% C.I.)
Moderately or poorly differentiated	72 (14.2)	16 (47.1)	<.001	6.6 (3.2-13.7)
Acantholytic, adenosquamous or desmoplastic subtypes	76 (15.0)	8 (23.5)	0.01	1.8 (0.8-4.2)
Location/size as a high-risk feature	393 (77.5)	32 (94.1)	0.05	5.0 (1.2-21.0)
Area M >10 mm[a]	137 (27.0)	12 (35.3)		
Area H > 6 mm[b]	256 (50.5)	20 (58.8)		

PNInv, perineural invasion.
[a] Area M: ≥10 mm on the forehead, scalp, cheek, neck, and pretibia.
[b] Area H: ≥ 6 mm on the "mask areas of the face" (central face, eyelids, eyebrows, periorbital, nose, lips (cutaneous and vermilion), chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet.

DISCUSSION

In this study, moderately or poorly differentiated histology, acantholytic, adenosquamous, or desmoplastic subtypes, and tumors fulfilling NCCN criteria for areas M and H were significantly associated with the presence of PNInv in cSCC (Table 2). This data suggests clinicians should have a higher suspicion and may be able to identify PNInv in cSCC based on these specific high-risk factors. As independent risk factors for cSCC, tumor size, location on the face, and moderately or poorly differentiated histology have been associated with metastasis and death,[1-6] while acantholytic, adenosquamous, or desmoplastic subtypes

of cSCC have received considerably less attention in the literature.

The identification of patients with high-risk cSCC is critical to the subsequent management of these tumors, as well as improving patient outcomes. By identifying cSCCs with PNInv and other high-risk characteristics early, prompt and aggressive management can be initiated providing patients the best outcomes possible. This includes initial treatment with complete margin assessment, such as Mohs micrographic surgery, to maximize complete tumor removal. Waiting until PNInv is symptomatic likely means involvement of larger diameter nerves, which is associated with an aggressive clinical course.[1-3,6]

Though further validation is needed, cSCCs with PNInv may not possess traditional high-risk features for metastasis, such as increased size >2cm or lip location. Interestingly, in the PNInv cohort the majority (n=20, 58.8%) were ≤2 cm and only 1 tumor was on the lip. Of note, the scalp and cheek two frequent sites for PNInv in this analysis are classified in area M, which requires a larger tumor (≥ 10 mm) to be considered high-risk compared to area H (≥ 6 mm).

Established cSCC high-risk factors excluded from the model due to lack of statistical significance with PNInv included the following: poorly-defined borders, recurrence, immunosuppression, site of prior radiation therapy or chronic inflammatory process, neurologic symptoms, depth > 2mm or CL IV, V, and vascular involvement (Table 1). The lack of statistical significance for many established cSCC high-risk factors was unexpected, but could be related to the characteristics of the sample or its size. The excluded factors may be rare enough in presentation not to merit inclusion in the model or they may have been present, but were infrequently recorded. Of note, BD and CL were rarely recorded (6 of 507 tumors, 1.2%). Consequently, the minimal data on BD and CL impacted our ability to fully examine their association with PNInv. In our experience, there are significant inter-institutional differences in the routine collection of BD and CL.

CONCLUSION

In summary, the results reported herein are informative and advocate for clinicians having a higher suspicion for PNInv in cSCC with moderate or poor differentiation, acantholytic, adenosquamous, or desmoplastic subtypes, and those tumors in areas M (≥ 10 mm) and H (≥ 6 mm). Additionally, we identified that tumors ≤ 2cm in diameter were often (58.8%) associated with PNInv.

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