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Squamous Cell Carcinoma with Aggressive Subclinical Extension: 5-year Retrospective Review of Diagnostic Predictors

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Abstract

Background—Squamous cell carcinoma with aggressive subclinical extension (SCC-ASE) is a tumor whose extensive spread becomes revealed during or post-surgical pathologic review, particularly during Mohs surgery. Limited clinical awareness of such lesions may result in unanticipated longer surgical times and larger post-operative defects. SCC-ASE associated clinical risk factors are not well studied.

Objective—Evaluate the incidence of and risk factors associated with SCC-ASE.

Methods—Retrospective analysis of SCC treated with Mohs from 2007 to 2012 at a single academic surgical center. SCC-ASE was defined as a lesion requiring at least 3 Mohs stages with a final surgical margin of at least 1 cm.

Results—Of 954 cases studied, 31% were SCC-ASE. In multivariable analysis, sex ($p=0.001$), history of prior non-melanoma skin cancer ($p<0.001$), skin types II and III ($p=0.004$, <0.001), immunosuppression due to solid organ transplant ($p<0.001$), and cigarette use ($p<0.001$) were significant predictors of SCC-ASE.

Limitations—Single academic center selection bias, not-controlled for sun exposure differences, no information on medication regimens of solid organ transplant patients, and a small sample size.

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Conclusion—Easily attainable demographic factors, especially immunosuppressed status and cigarette use, can help predict the occurrence of SCC-ASE and thereby optimize surgical planning and patient preparedness.

Keywords

aggressive; cigarette; immunosuppression; Mohs; smoking; squamous cell carcinoma; subclinical

Introduction

There are approximately 700,000 new SCC cases per year¹ and 2% of all patients die from metastatic disease.¹ SCCs with aggressive subclinical extension (SCC-ASE) are those that appear nonaggressive on clinical examination, but are found to be subclinically aggressive during Mohs Micrographic Surgery (MMS).² Clinical assessment may underestimate the margins of SCC-ASE tumors, resulting in increased surgical times and infection rates from what is expected. Thus, preoperative prediction of subclinical aggression is critical for appropriate surgical planning and patient preoperative counseling.

Thus far, the data on the incidence and clinical characteristics of SCC-ASE is limited. Batra et al.² conducted a retrospective analysis of 1095 MMS patients in order to identify predictive risk factors for NMSC with ASE. The highest odds ratio (OR) yielding variables were location of the lesion (eyelid, temple, ear helix), and tumor size; immunosuppression and age were not found to be significant.² However, in highly cosmetically sensitive areas such as the eyelid, nose, lip, or the ear, smaller clinical margins are often taken per MMS stage. These lesions may require multiple stages because of technique and cosmetic concerns, rather than due to true subclinical aggression. Therefore, post-operative margin size is important to consider when defining ASE as it may help distinguish truly aggressive lesions from those which required multiple stages purely due to cosmetic reasons. Therefore, we propose a more stringent definition for SCC-ASE in order to filter any confounding non-aggressive lesions located in cosmetically sensitive areas: three or more MMS stages and a final surgical margin of 1cm or more.

We present a 5-year retrospective review of SCC-ASE cases in a single-academic institution to determine the predictive significance of clinical variables.

Methods

Our retrospective review was performed at the Dermatologic and Mohs Surgery Center of University of California, San Diego (UCSD). This study was approved via expedited review by the UCSD Institutional Review Board.

All MMS cases with a biopsy-confirmed diagnosis of SCC, presenting between March 2007 and February 2012, were assessed. Data was gathered via electronic medical record review with secondary confirmation within paper records of all MMS cases occurring before 2008. SCC-ASE was defined as a lesion requiring at least 3 MMS stages and having a final surgical margin of at least 1 cm. Cases were arranged into two statistically independent groups (SCC and SCC-ASE) to avoid double inclusion of same participants within both

groups—324 cases were removed. (Figure 1) Current cigarette use was defined as activity within 6 months of MMS. Immunocompromised state was defined as having a solid organ transplant (SOTR) (kidney, liver, heart or lung), being on chronic immunosuppressive therapy, chemotherapy, having a diagnosis of blood cancer (leukemia or lymphoma), or being HIV-positive. Clinical aggression was defined as having any-axis pre-procedure size exceeding 20mm. Lesion location was separated into zones consistent with the 2013 NCCN Guidelines³ in order to strengthen the power of each area; Zone 1 (“mask areas” of face-central face, eyelids, eyebrows, periorbital, nose, lips (cutaneous and vermillion), chin, mandible, preauricular and postauricular skin/sulci, temple, ear, genitalia, hands, and feet); Zone 2 (cheeks, forehead, scalp, neck, and pretibial); Zone 3 (trunk and extremities excluding pretibial, hands, feet, nail units, and ankles). These anatomical areas respectively correspond to the H, M, and L areas, as delineated in the American Academy of Dermatology's appropriate use criteria (AUC) for MMS.⁴

Data was analyzed via Independent T-test for continuous variables, Fisher's exact test for binary variables, and logistic regression model with backward likelihood ratio technique with removal set at $p=0.1$, in SPSS Version 21. The primary outcome of interest was the development of SCC-ASE, the primary exposure of immunosuppression, and secondary exposure of cigarette use. Confounding covariates included skin type, age, sex, location, clinical aggression, and history of prior NMSC.

Results

During the focused 5-year interval 4037 MMS cases were completed; 954 cases of SCC were included in analysis with 653 (68%) cases of SCC, and 301 (32%) cases of SCC-ASE. The mean age of SCC and SCC-ASE groups were 70 and 68 years old ($p=0.1$), respectively. (Table 1) Males were found to have 2.2 times the odds of having SCC-ASE than females. Distribution of skin type was similar amongst both groups with Fitzpatrick-type II predominating. When compared to all other skin types, skin type I had a significant OR of 1.6 $p=0.042$. The spread of lesion by location was similar in both SCC and SCC-ASE groups, and any difference was not statistically significant. When the location was analyzed by anatomic sites with chest/back serving as reference, neither ear nor vermillion lip were found to be significant ($p=0.48$, 0.8 , respectively); nose and leg (excluding pretibial, ankle, foot) had significant protective ORs ($p=0.048$, 0.002 , respectively.)

Fifteen percent of SCC cases and 34% of SCC-ASE cases were immunosuppressed ($p<0.001$). An immunosuppressed patient diagnosed with SCC has 3 times the odds of having an SCC-ASE than a non-immunosuppressed patient ($p<0.001$). SOTR and blood cancer patients had significantly higher odds of having SCC-ASE when compared to the rest of the study population—3.6 ($p<0.001$), and 2.1 ($p=0.029$) respectively.

Current cigarette use was a significant determinant of SCC-ASE (OR=5, $p<0.001$). Lifetime cigarette use also significantly varied between the two groups (35% vs. 46%, $p=0.001$). History of prior NMSC was significantly different between the two groups (OR 2.7, $p<0.001$).

In adjusted analysis, sex, SOTR, skin types II and III, current cigarette use and history of NMSC remained significant predictors for SCC-ASE. (Table 2) Patients diagnosed with SCC and who are current smokers have a 4.7 times the odds of having SCC-ASE than non-smokers when controlled for all of the aforementioned variables. Those with history of prior NMSC had 1.9 times the odds of having SCC-ASE ($p < 0.001$) if diagnosed with SCC. Additionally, when compared to the rest of the study population, SOTR patients have 1.7 times the odds of having SCC-ASE ($p < 0.001$).

We also assessed for any interaction between the primary outcome of immunosuppression and other significant predictor variables from the regression model on the development of SCC-ASE. An interaction describes a situation in which the immediate multiplicative effect of combining two variables on an outcome is greater than the contribution of either alone. In our analysis, all of the interactions between immunosuppression and the predictor variables were insignificant, suggesting that our additive model was the best fit. We also assessed for a dose response of SCC-ASE development in cigarette users according to pack-years reported; we had limited information on pack-year history among our cohort and did not see a significant association between the number of packs and SCC-ASE development.

Within the logistic regression model, the predictive capacity of the chosen variables allows for a determination of the probability of SCC-ASE. Based on our model, a 70 year-old male, current smoker, with history of NMSC, SOTR, with Fitzpatrick skin type II, has 71% probability of having an SCC-ASE if diagnosed with SCC. Whereas, for a 70 year-old female, also skin type II but without history of NMSC, non-smoker and non-immunosuppressed, the probability of having an SCC-ASE when diagnosed with SCC is 22%. (See Table 3)

Discussion

Our single-center retrospective review revealed the importance of easily attainable demographic predictors on the development, diagnosis and prediction of SCC-ASE. In multivariable analysis sex, SOTR, skin type, current cigarette use, and history of NMSC were found to be significant predictors of SCC-ASE.

Males were found to have significantly higher odds of developing SCC-ASE in both unadjusted and adjusted models. This may be a simple reflection of the higher incidence of SCC in men as compared to women.⁵ However, although our results do not have the power to explain causality, our findings may signal to an underlying difference in SCC amongst the sexes. Men tend to underutilize and delay medical care⁶ and have the highest annual exposure to UV among adults over the age of 40.⁷ Thus, through excessive UV exposure and lack of timely treatment, men may not only have increased risk for developing SCC, but possibly also higher odds of more aggressive types of tumors. Further studies are necessary to evaluate this theory.

History of prior NMSC was also significantly associated with the development of SCC-ASE. Before the age of 65, 40-50% of Americans will develop at least one BCC or SCC.⁸ Probably due to the factors contributing to the development of the primary skin cancer,

having one NMSC predisposes to another one—with the cumulative 3-year risk of developing a subsequent SCC after an index SCC being 18%, which is 10-times the incidence of the developing of a first tumor in a similar healthy population.⁹ The development of the more aggressive SCC-ASE in those with NMSC history within our cohort suggests that dermatologists may need to educate patients with a history of prior NMSC on their risks for developing secondary skin cancers, which may be larger and more subclinically aggressive.

Our findings demonstrate that immunosuppressed patients with a diagnosis of SCC were almost three times more likely to have SCC-ASE. Past studies have demonstrated a clear relationship between immunodeficiency and NMSC, with a predominance of SCC over BCC in the immunosuppressed population and a reported incidence ratio of 4:1.¹⁰ Immunosuppressed state has been shown to increase the risk of developing SCCs.¹¹ SOTRs have more than sixty times the risks of developing SCCs, and these cancers tend to be “high-risk” due to increased rates of recurrence and metastasis.¹² Among the different types of immunosuppression, SOTRs have the highest levels of SCC compared to patients with HIV, or other causes of immunosuppression. In addition to increased incidence of SCC, SOTRs are at increased risk of developing more aggressive tumors manifested by increased risks of recurrence, metastases.¹² Our results are consistent in that SOTRs had the highest risk for SCC-ASE among our cohort when controlled for all other covariates. Although Batra et al.⁶ included immunosuppression in their analysis, it was not found to be a significant predictor for aggression.² However, their study may have been confounded by misclassification bias due to the omission of final surgical margin as part of the criteria for subclinical aggressiveness. Thus, we propose inclusion of immunosuppression as a predictor for SCC-ASE as it may help Mohs surgeons anticipate such lesions and prepare patients accordingly.

In our cohort, cigarette use was more predominant among the SCC-ASE patients and was an independent risk factor for the development of SCC-ASE when results were controlled for other confounders. However, to date, there are no studies examining the differential effect of cigarette use on cutaneous SCC aggression. Our results meet biologic plausibility of how cigarette components may be associated with increased risk for skin cancer. Cigarette carcinogens may act directly or through systemic effects on the skin. Tobacco smoke condensate is a carcinogen, and topical application of smoke in animals has been found to induce cutaneous SCC.¹³ Carcinogenic compounds within cigarettes, including polycyclic aromatic hydrocarbons, nitrosamines, and phenolic compounds ultimately alter DNA and lead to mutagenesis and cancer development. Animal studies utilizing individual cigarette components have directly linked benzo[a]pyrene diol epoxide (a type of polycyclic aromatic hydrocarbons) to skin carcinogenesis.¹⁴ Lastly, cigarette components have been found to be immune system-suppressive and thus, may affect patients’ ability to suppress tumor growth. Our results suggest that cigarette use is an important predictor for SCC-ASE and may help physicians anticipate such lesions preoperatively and prepare the Mohs surgeons and the patients for more complex procedures. Additionally, as studies show that public awareness of the association between smoking and skin cancer is low¹⁵, increasing public education regarding this association may help decrease such risky behavior amongst patients at risk for skin cancer.

Conclusion

SCC-ASE are frequently missed with traditional diagnostic techniques leading to inappropriate surgical margin selection, unanticipated treatment durations, and possible lesion recurrence or metastasis. Our data and predictive model suggest that clinical factors, especially immunosuppression and cigarette use status can help predict the occurrence of SCC-ASE and thereby optimize surgical planning and patient preparedness.

Our study had several limitations. The conduction of the study at a single-center academic institution may have contributed to a selection bias as our patients may have had more advanced disease than other patients seen in the community. Additionally, information on sun exposure differences among our cohort was not available. Nevertheless, all of the participants were from San Diego County, as reported by zip-code, which has a UV index mean of 7, and overall has a higher incidence of SCC than northern parts of the US. Thus, our cohort may be different from the general population in its intrinsically higher risk for NMSC due to the sun exposure. We were unable to assess the medication regimens of our immunosuppressed SOTR patients and this may also serve as a confounder in the development of SCC. Finally, we have a small sample size which may have limited our power in assessing associations.

Future studies evaluating the prognostic potential of the here-in reported significant risk factors are necessary. Specifically, although the 2010 American Joint Committee on Cancer (AJCC) staging system¹⁶ includes location of the lesion (ear and vermillion lip) in their criteria, we did not find location of the lesion to be a significant risk factor for subclinical aggression. Additionally, although immunosuppression was a significant risk factor for subclinical aggression in our results, it was not included in neither AJCC, International Union Against Cancer (IUAC), nor the Brigham and Women's alternative staging system as described by Schmults et al in 2013.¹⁷ However, the Schmults' et al study was not powered to detect differences in final outcomes amongst immunosuppressed patients as their study included only 35 immunosuppressed subjects.¹⁸ Moreover, the prognostic impact of a SCC-ASE diagnosis on final outcomes such as nodal metastasis, local recurrence, disease-specific and all-cause death must be evaluated in order to assess if incorporating such a diagnostic criteria into a staging system will change lesion stratification into various stages, and ultimately change treatment guidelines.

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Abbreviations

BCC	basal cell carcinoma
MMS	Mohs Micrographic Surgery

NMSC	nonmelanoma skin cancer
SOTR	solid organ transplant recipient
SCC	squamous cell carcinoma
SCC-ASE	squamous cell carcinoma with aggressive subclinical extension

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Capsule Summary

- A subset of squamous cell carcinomas demonstrate aggressive subclinical extension
- Our analysis identified several diagnostic factors associated with this phenomena, particularly immunosuppression
- Our model can help predict the occurrence of subclinically aggressive squamous cell carcinoma and thereby optimize surgical planning and patient preparedness

Figure 1.
Study design

Table 1

Demographics^{# *}

	Total=N 954	SCC N=653 (%=68)	SCC-ASE N=301 (%=32)	OR	P value
Age (mean, SD)	-	70 (13.6)	68.46 (13.7)	-	0.107
Sex (n, %)	F 323 (34)	255 (39)	68 (23)	0.5	<0.001
	M 631 (66)	398 (61)	233 (77)	2.2	
Skin type (n, %)	I 103 (11)	61 (9)	42(14)	1.6	0.042
	II 681(71)	468 (72)	213 (71)	0.9	0.861
	III 82 (9)	64 (10)	18 (6)	0.6	0.080
	IV 7	5 (1)	2 (1)	0.9	1
Location of lesion ^a (n, %)	[I] 424 (44)	290 (44)	134 (45)	1.0	1
	[2] 435 (46)	297 (46)	138 (46)	1.0	0.944
	[3] 95 (10)	66 (10)	29 (9)	1	0.908
Clinical aggression ^b (n, %)	52 (5)	33 (5)	19 (6)	1.3	0.444
Immunosuppression (n, %)	Total 200 (21)	97 (15)	103 (34)	3.0	<0.001
	HIV+ 37 (4)	22 (3)	15 (5)	1.5	0.278
	Blood cancer 44 (5)	23 (4)	21 (7)	2.1	0.029
	SOTR ^c 115 (12)	48 (7)	67 (22)	3.6	<0.001
	Other ^d 4	4 (1)	-	1.0	0.999
CD4 Count (mean, range)	-	381.7 (4-934)	490.133 (18-2164)	-	0.428
Cigarette use ^e	234 (25)	95 (15)	139 (46)	5.0	<0.001
Pack years (mean, SD)	-	22.02 (2.24)	17.859 (1.46)	-	0.110
Lifetime cigarette use	365 (38)	226 (35)	139 (46)	1.6	0.001
History of prior NMSC	500 (52)	293 (45.2)	207 (68.8)	2.7	<0.001
Mohs stages (mean, SD)	-	1.6 (0.5)	3.5 (0.8)		<0.001
Surgical Margin ^f (mm) (mean, SD)	-	6.5 (5.8)	19.4 (11.3)		<0.001

Zone 1: "H": "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips (cutaneous and vermillion), chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet

Zone 2: "M": cheeks, forehead, scalp, neck, and pretibial

Zone 3: "L": trunk and extremities excluding pretibial, hands, feet, nail units, and ankles

[#] Percentages reflect proportion of cases amongst the corresponding column

^{*} Abbreviations: NMSC- nonmelanoma skin cancer, OR- odds ratio, SCC-ASE- squamous cell carcinoma with aggressive subclinical extension, SCC- squamous cell carcinoma, SD- standard deviation, SOTR- solid organ transplant recipient

^a NCCN Guidelines Version 1.2013 of Squamous cell skin cancers:

^b Clinical aggression defined as pre-operative size of lesion is >20mm on the smallest axis

^c Solid organ transplant recipients included kidney, heart, lung, liver transplants

^d Other included stem cell transplant and immunosuppressive medications

^e Cigarette use in the last 6 months prior to MMS procedure

^f Surgical margin defined as the difference in millimeters in size between the post-operative largest measurement, and the pre-operative largest measurement

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Table 2

Adjusted Results^{* **}

	<i>B</i>	P-value	OR	95% CI
Age	−0.001	0.826	1.0	0.9, 1.0
Sex (F)	−0.571	0.002	0.6	0.5, 0.8
SOTR	0.544	<0.001	1.7	1.3, 2.2
Skin type II	−.0338	0.004	0.7	0.6, 0.9
Skin type III	−0.460	<0.001	0.6	0.5, 0.8
Current Cigarette Use	1.540	<0.001	4.7	3.3, 6.6
History of NMSC	0.632	<0.001	1.9	1.3, 2.6

* Variables included in logistic regression model: fixed: age ; backward likelihood ratio with threshold of 0.10: sex, skin type, location, clinical aggression, immunosuppression, type of immunosuppression, cigarette use, history of prior NMSC. Only variables included in final model step are displayed. One binary outcome of SCC-ASE (yes/no).

** Abbreviations: NMSC- nonmelanoma skin cancer, OR- odds ratio, SCC-ASE- squamous cell carcinoma with aggressive subclinical extension, SCC- squamous cell carcinoma, SOTR- solid organ transplant recipient

Table 3

SCC-ASE Percentage Probability Prediction^{1,2}

		SOTR	NMSC Hx	SOTR and NMSC Hx	Current Smoker	Smoker and SOTR	Smoker and NMSC Hx	Smoker, SOTR, and NMSC Hx
Female	skin type II	22	24	35	43	57	59	71
	skin type III	20	21	32	40	54	56	69
Male	skin type II	33	35	48	57	70	72	81
	skin type III	32	34	47	56	69	70	80

¹ Prediction derived with the linear predictor formula: $P=1/1+e^{-a}$; all predictions based on a 70 year-old individual; all values represent %. Since age was not a statistically significant predictor in our model, variability in the predicted SCC-ASE probability due to age was not significant and was not included.

² Abbreviations: Hx- history of, NMSC- nonmelanoma skin cancer, SCC-ASE- squamous cell carcinoma with aggressive subclinical extension, SCC- squamous cell carcinoma, SD- standard deviation, SOTR- solid organ transplant recipient