Squamous cell carcinoma with aggressive subclinical extension: 5-year retrospective review of diagnostic predictors

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

Objective: We sought to evaluate the incidence of and risk factors associated with SCC-ASE.

Methods: We conducted a retrospective analysis of SCC treated with Mohs micrographic surgery between 2007 and 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 ≥1 cm.

Results: Of 954 cases studied, 31% were SCC-ASE. In multivariable analysis, sex (P = .001), history of previous nonmelanoma skin cancer (P < .001), Fitzpatrick skin types II and III (P = .004 and <.001, respectively), immunosuppression related to solid organ transplant (P < .001), and cigarette use (P < .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 are all limitations of our study.

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. (J Am Acad Dermatol 2015;73:120-6.)

Key words: aggressive; cigarette; immunosuppression; Mohs; smoking; squamous cell carcinoma; subclinical.

There are approximately 700,000 new cases of squamous cell carcinoma (SCC) per year,[1] and 2% of these 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

Abbreviations used:

BCC:	basal cell carcinoma
MMS:	Mohs micrographic surgery
NMSC:	nonmelanoma skin cancer
SCC:	squamous cell carcinoma
SCC-ASE:	squamous cell carcinoma with aggressive subclinical extension
SOTR:	solid organ transplant recipient

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margins of SCC-ASE tumors, resulting in increased surgical times and infection rates from what is expected. Preoperative prediction of subclinical aggression is therefore critical for appropriate surgical planning and patient preoperative counseling.

The published data on the incidence and clinical characteristics of SCC-ASE are limited. Batra et al[2] conducted a retrospective analysis of 1095 patients who had undergone MMS in order to identify predictive risk factors for nonmelanoma skin cancer (NMSC) with ASE. The highest odds ratio (OR)—yielding variables were location of the lesion (ie, eyelid, temple, and 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 true subclinical aggression. Therefore, postoperative margin size is important to consider when defining ASE because it may help distinguish truly aggressive lesions from those which required multiple stages purely for cosmetic reasons. Therefore, we propose a more stringent definition for SCC-ASE in order to filter any confounding nonaggressive lesions located in cosmetically sensitive areas: ≥3 MMS stages and a final surgical margin of ≥1 cm.

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

CAPSULE SUMMARY

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

METHODS

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

All patients who underwent MMS with a biopsy-confirmed diagnosis of SCC and who presented between March 2007 and February 2012 were assessed. Data were 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 ≥3 MMS stages and having a final surgical margin of ≥1 cm. Cases were arranged into 2 statistically independent groups (SCC and SCC-ASE) to avoid double inclusion of same participants within both groups—324 cases were removed (Fig 1). Current cigarette use was defined as activity within 6 months of MMS. Immunocompromised state was defined as being a solid organ transplant recipient (SOTR; ie, of the kidney, liver, heart, or lung), being on chronic immunosuppressive therapy, chemotherapy, having a diagnosis of blood cancer (ie, leukemia or lymphoma), or being HIV-positive. Clinical aggression was defined as having any-axis preprocedure size >20 mm. Lesion location was separated into zones consistent with the 2013 National Comprehensive Cancer Network guidelines[3] in order to strengthen the power of each area; zone 1 (ie, "mask areas" of face-central face, eyelids, eyebrows, periorbital, nose, lips (ie, cutaneous and vermillion), chin, mandible, preauricular and postauricular skin/sulci, temple, ear, genitalia, hands, and feet); zone 2 (ie, cheeks, forehead, scalp, neck, and pretibial); zone 3 (ie, trunk and extremities, excluding pretibial, hands, feet, nail units, and ankles). These anatomic 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 were analyzed with the independent *t* test for continuous variables, the Fisher exact test for binary variables, and a logistic regression model with backward likelihood ratio technique with removal set at $P = .1$ (all analyses conducted with SPSS software [v 21; SPSS, Inc, Chicago, IL]). The primary outcome of interest was the development of SCC-ASE, the primary exposure of immunosuppression, and the secondary exposure of cigarette use. Confounding covariates included skin type, age, sex, location, clinical aggression, and history of previous NMSC.

RESULTS

During the focused 5-year interval, 4037 MMS cases were completed; 954 cases of SCC were included in the 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, respectively ($P = .1$; Table I). Men were found to