A prospective evaluation of the clinical, histologic, and therapeutic variables associated with incidental perineural invasion in cutaneous squamous cell carcinoma

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Background: The prognosis and management of incidental perineural invasion (PNI) in patients with cutaneous squamous cell carcinoma (CSCC) has not been well defined.

Objective: We sought to investigate the clinical, histologic, and treatment characteristics associated with incidental PNI, histologic PNI extending beyond the tumor bulk, in patients with CSCC.

Methods: We conducted a multicenter prospective analysis of patients with CSCC undergoing Mohs micrographic surgery.

Results: The incidence of PNI was 4.6% in 753 CSCC cases. PNI was significantly associated with tumors of the head and neck ($P = .039$), larger tumor diameter ($P < .001$), presence of clinically palpable lymphadenopathy ($P = .012$), and recurrent ($P < .001$) and painful ($P < .001$) tumors. Further, PNI was significantly associated with poor tumor differentiation ($P < .001$), greater tumor thickness ($P < .001$), a greater number of Mohs stages ($P < .001$), and larger estimated maximum Mohs margin ($P < .001$) required to clear the tumor.

Limitations: The low numbers of patients demonstrating incidental PNI limits this study.

Conclusions: The association of incidental PNI with clinicopathological indicators of poor prognosis suggests that incidental PNI may serve as a marker to improve the precision in the prognostic assessment of patients with CSCC. (J Am Acad Dermatol 2014;70:630-6.)

Key words: Mohs micrographic surgery; perineural invasion; prognostic factors; squamous cell carcinoma.

Although no definitive, comprehensive clinicopathological system for cutaneous squamous cell carcinomas (CSCC) has yet been adopted, the presence of tumor cell invasion into and/or approximating a nerve (perineural invasion [PNI]) has been suggested to be an indicator of poor prognosis.[1-14] The incidence of PNI in CSCC has been reported to range from 2.4% to 14%.[1,2,12,15-28] The presence of PNI is frequently associated with those tumors demonstrating extensive soft-tissue spread, frequent recurrences, and a decreased overall survival.[1,2,19,20,28-30] Given its potential role in the clinical course of CSCC, some recommend that patients with PNI be treated with wider surgical margins, undergo sentinel lymph node dissection, and/or be treated with postoperative radiation therapy.[25,31-36]

Although PNI has been suggested to be a marker for more aggressive disease, it must be stressed that, with the exception of 1 study,[24] most of the available

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information regarding PNI in CSCC has been obtained from a small number of heterogeneous retrospective studies.[1,2,15-31] Many of these studies have failed to present a unified definition of PNI, have used conventional techniques to evaluate histopathology, and have not taken into account heterogeneity of the patient populations investigated or histopathological characteristics of the lesions analyzed. Moreover, none of the available studies have presented a clear distinction between PNI that is an incidental finding on histology and PNI that is associated with gross neurologic deficits. The latter, often referred to as clinical PNI, has clearly been shown to be associated with poor prognosis.[1,2] On the other hand, there is a paucity of information available regarding PNI that is not discovered on normal pathologic specimens but discovered incidentally separate from the tumor bulk through histologic evaluation during surgical resection in asymptomatic patients with CSCC, ie, incidental PNI.

CAPSULE SUMMARY

- The prognosis of patients with cutaneous squamous cell carcinoma showing incidental perineural invasion is not well defined.
- This study demonstrates the clinical, histologic, and treatment characteristics associated with incidental perineural invasion.
- This information strengthens our ability to identify and stratify those patients with cutaneous squamous cell carcinoma at risk of perineural invasion.

The limited information available regarding incidental PNI in CSCC has led to uncertainty in its treatment in patients. This uncertainty is evidenced by both the nonevidence-based consensus recommendations, developed by multidisciplinary panels,[13,14] and the variation in concordance rates between surgeons on how to treat these patients.[37] The goal of this work is to perform a multicenter prospective evaluation of the clinical, histologic, and treatment characteristics associated with incidental PNI in patients with CSCC. The results reported herein are the preliminary findings published in anticipation of a 5-year follow-up study.

METHODS

A prospective, multicenter analysis of the clinical, histologic, and treatment characteristics of patients undergoing Mohs micrographic surgery for CSCC within 4 academic and 11 private practice Mohs micrographic surgery sites was conducted over 25 working days. Institutional review board approval was obtained from the Western Institutional Review Board (protocol No. 20100110). Fellowship-trained Mohs micrographic surgeons treated all patients and recorded all data.

The criterion for inclusion was all cases of histologically confirmed CSCC treated with Mohs micrographic surgery. Table I summarizes the clinical, pathologic, and treatment parameters that were assessed. The clinical variables immune suppression, radiation exposure, and scarring skin conditions were defined as: (1) organ transplant recipients, patients with chronic lymphocytic leukemia, patients with AIDS and/or patients on immunosuppressive medications; (2) patients with a history of ionizing radiation or psoralen plus ultraviolet A exposure; and (3) patients with a history of burn injury, chronic nonhealing wound, or immunobullous or connective tissue disease. All patients demonstrating cranial nerve deficits were excluded from the study. The degree of anaplasia was based on subjective assessment of differentiation. The categories were well, moderately, and poorly differentiated, when the percentage of anaplastic cells in the lesions were less than 25%, between 25% and 50%, and greater than 50%, respectively.

All surgeons used the previously described standard frozen section Mohs micrographic surgery technique.[38] The treating Mohs micrographic surgeons carried out all excisions, mapping, and tissue examination.

Tumor thickness was established by comments made in the original biopsy report. In those cases where no depth was available on the original biopsy report, measurements of tumor depth were made on the debulked tumor by the treating Mohs micrographic surgeons.

The diagnosis of PNI was defined as the presence of tumor cell invasion into and/or the partial or complete encasement of a nerve resulting in histologically discernible tumor encircling or partially encircling a nerve either described in the biopsy report or as identified in the debulking specimen or Mohs sections. Cases that did not demonstrate PNI in the original biopsy specimen or in any Mohs stage were classified as negative.

Statistical analysis

All data were included in the original analysis. Patients were separated by PNI status and variables were compared between categories using independent *t* tests or χ^2 tests, as appropriate, using software