Histopathological features of clinical perineural invasion of cutaneous squamous cell carcinoma of the head and neck and the potential implications for treatment

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ABSTRACT: *Background.* Nonmelanoma skin cancer (NMSC) with perineural invasion (PNI) is most commonly seen in cutaneous squamous cell carcinoma of the head and neck (SCCHN). The cranial nerves are a conduit for skin cancer to reach the brainstem.

Methods. The histopathological features of 51 tissue specimens from 49 patients with cutaneous SCCHN and clinical PNI were assessed with consecutive transverse and longitudinal sections.

Results. No skip lesions were identified. Tumor spread was contiguous in all specimens. No tumor spread into the perineural space from surrounding or adjacent tumor was seen. Proximal large cranial nerves showed epineural involvement in 3.9% in areas with large tumor bulk, extensive PNI, and intraneural invasion.

Conclusion. Perineural tumor spread in cutaneous SCCHN was contiguous and no skip lesions were evident in nerve specimens assessed in this series. Spread beyond cranial nerve perineurium was uncommon, reflecting its multilayer barrier function at this level. These findings may have treatment implications. © 2013 Wiley Periodicals, Inc. *Head Neck* 00: 000–000, 2013

KEY WORDS: skin cancer, head and neck neoplasms, peripheral nerve neoplastic infiltration, perineurium, squamous cell carcinoma

INTRODUCTION

Australia has the highest recorded rates of nonmelanoma skin cancer (NMSC) in the world, with at least 2% of the population being diagnosed each year.[1] The head and neck is the most common site, with squamous cell carcinoma (SCC) being the second most frequent pathology after basal cell carcinoma.[1]

The detection of perineural invasion (PNI) in a cutaneous squamous cell carcinoma of the head and neck (SCCHN) declares the tumor to be aggressive, with a worse prognosis because of higher rates of locoregional recurrence and reduced survival.[2–7] It is more frequent in men and typically associated with large tumors (>2 cm), mid-face location, recurrent tumors, and/or poor differentiation.[5,8,9] The overall incidence of NMSC with PNI is generally estimated at 5%. PNI is a poor prognostic indicator in several malignancies including prostate,[10] pancreas,[11] cervix,[12] stomach,[13] colorectum,[14] and head and neck.[15]

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Peripheral nerves are composed of nerve fiber bundles enclosed by a sheath with 3 distinct layers. The inner layer, or endoneurium, envelopes the axons, Schwann cells, and capillaries in a loose matrix of connective tissue. The middle layer, or perineurium, binds groups of axons and surrounding endoneurium to form a fascicle. It is comprised of multilamellar, concentric perineural cells, which have tight cell-cell junctions (zonulae occludentes) and intervening layers of basement membrane.[16,17] The perineurium is a major component of the blood-nerve barrier with highly selective permeability that keeps nerve fibers contained from the surrounding potentially harmful environment.[16,18] The outer layer is the epineurium and it binds fascicles together with fibrocollagenous connective tissue to form a peripheral nerve.

We define PNI as the invasion of tumor cells into the "perineural space" of a peripheral nerve (ie, the space beneath or between the layers of perineurium). PNI precedes perineural spread (PNS), which describes the extension of these tumor cells via the perineural space along a peripheral nerve and this is preferentially retrograde/centripetal (ie, proximal or toward the brain) yet can be antegrade/centrifugal (ie, distal or toward the skin). This process of tumor spread is distinct from metastasis via a lymphatic or hematogenous route, and often exists independently.[7,19,20]

The majority of PNI cases are asymptomatic and involve small adjacent peripheral nerves only detectable on microscopy, otherwise known as incidental PNI.[21]

This is typically managed by complete surgical excision and consideration of postoperative radiotherapy.[2,3,8]

PNS can progress to involve cranial nerves (particularly the facial [VII] and trigeminal [V] nerves) and ganglia, and eventually spread into the brainstem or cause leptomeningeal carcinomatosis (ie, central failure).[22,23] When radiological or clinical evidence of PNS is present (ie, facial palsy or trigeminal nerve distribution numbness, paresthesia, formication, or pain) this is termed "clinical PNI." Although clinical PNI is seen in approximately 30% to 40% of all PNI cases, it carries a significantly worse prognosis than incidental PNI necessitating a more aggressive treatment approach.[4,7,21,24] Assessment and treatment is best guided by magnetic resonance (MR) neurography. Using a zonal classification of disease extent, MR neurography can accurately detect and define the anatomic extent of disease when matched to histopathological findings in the majority of cases.[25,26]

The management of clinical PNI is often complex and dependent on the extent of disease, yet typically involves surgery and/or radiotherapy.[2,27,28] At our institution, radiation is recommended for all clinical PNI with fields typically covering involved nerve territory with a margin.

The "skip lesion" concept has made the demarcation of clinical PNI disease extent difficult for many clinicians.[3,9,20,29–31] This describes the histopathological finding of perineural tumor with intervening segments of disease-free nerve. Some clinicians advocate irradiation to include the skull base or brainstem, despite a clear peripheral surgical margin because of the risk of skip lesions.[3,21,31–33] We have not identified radiographic evidence of skip lesions on any patient presenting to our institution with NMSC and PNS. Although this can have a profound impact on management, no dedicated study to specifically prove this theory exists. Our objective was to examine the histopathological characteristics of cutaneous SCCHN with clinical PNI to identify any features such as skip lesions that influence treatment paradigms.

MATERIALS AND METHODS

Fifty-one tissue specimens of cutaneous SCCHN with clinical PNI from 49 patients were examined after surgery undertaken between 2000 and 2009. Ethics approval for the study was granted by the Princess Alexandra Hospital Human Research Ethics Committee (2003/197). Patients were only included if they were undergoing surgery for cutaneous SCCHN with clinical PNI at our institution for either: (1) definitive management of operable disease with curative intent; and/or (2) diagnostic purposes (ie, nerve biopsy). One additional nerve specimen was collected at autopsy from a patient (with informed consent) who died of clinical PNI after initial surgical treatment. Patients with other forms of cutaneous malignancy (ie, melanoma or basal cell carcinoma [BCC]) were excluded because of low numbers. Further details of primary tumors were obtained from pathology archives. This study involved histopathologic analysis and did not include radiographic and clinical follow-up data. Further studies are being undertaken to evaluate patterns of long-term failure.

The American Joint Committee on Cancer classifies all cutaneous malignancy with PNI of the skull base as T4.[34] We, however, have classified the primary tumors without taking account of the clinical PNS for 2 reasons. First, to allow the reader to understand the types of tumors that give rise to clinical PNS, and second, to use instead a zonal classification of the degree of PNS identified by MR neurography, which has been shown to correlate with survival (Table 1).[28] Zone 1: V1 (ophthalmic division) to the superior orbital fissure; V2 (maxillary division) to the external aperture of the foramen rotundum; V3 (mandibular division) to the external aperture of the foramen ovale; VII (facial nerve) to the external aperture of the stylomastoid foramen. Zone 2: V1, V2, V3: from zone 1 to the Gasserian ganglion cistern; VII: from zone 1 up to the lateral end of the internal auditory canal, including the geniculate ganglion and the labyrinthine segment. Zone 3: (all nerves) proximal to the ganglion, into the cisterns, or into the brainstem.[25] Operable disease was determined by imaging disease extent in zone 1 or zone 2. Zone 3 is generally deemed inoperable, yet is considered on a case-by-case basis. This is because of the advanced nature of the disease and increased risk of iatrogenic tumor spread through the cerebrospinal fluid during surgery. Patients with inoperable disease at our institution are offered definitive radiotherapy for disease not involving the brainstem, or palliative radiotherapy if this is involved.

Surgical resection of the involved nerve(s) was undertaken after informed consent with curative intent, as described previously.[27] The extent of surgery (and thus the length of nerve specimen assessed) was determined by the imaging zonal extent of disease on preoperative imaging and involved en bloc resection of skin (if involved) and cranial nerve via a skull base or subcranial approach, generally with the aim of obtaining a clear surgical margin (Figure 1).[27] Diagnostic nerve biopsies involved resection of a continuous segment of nerve of at least 2.5 cm length. Tissue orientation was achieved with a marking suture at the proximal end of the nerve and tissue inking. Specimens of either a segment of tissue containing the nerve or the nerve segment alone were processed in the laboratory. Any bone was decalcified before formalin-fixation of the specimen to minimize tissue disruption. When tissue containing the nerve was received (ie, infratemporal fossa or pterygopalatine fossa resection), dissection of the nerve was undertaken using marking sutures for orientation. To assess the proximal (ie, brainstem aspect) and distal (ie, skin aspect) margins, nerve segments were placed in a cassette so that sections could be taken parallel to the long axis of the nerve (ie, longitudinal). Serial transverse sections were taken perpendicular to the long axis of the nerve. The transverse and longitudinal sections were processed consecutively for a complete assessment. Transverse shaved frozen sections of the proximal margin were also used to assess margin status.

Formalin-fixed paraffin-embedded tissue sections were initially stained with hematoxylin-eosin. Staining with broad-spectrum keratin (AE1/AE3), cytokeratin (MNF116), and/or S-100 was performed in cases in which the tumor was suspected clinically yet not confirmed on hematoxylin-eosin staining. This was also utilized: (1) in specimens with undifferentiated tumor to accurately identify tumor type; and (2) in specimens in which an inflammatory reaction

TABLE 1. Features of cutaneous squamous cell carcinoma of the head and neck with clinical perineural invasion.

Patient	Sex	Primary T-classification (AJCC*)	Primary location	Nerve involved	Imaging zone extent	source	Nerve diameter, mm	Margin	Histologic grade	Pattern of spread	Skip lesion	Epineural spread peripheral nerve	Epineural spread cranial nerve, distal	Epineural spread cranial nerve, proximal
1	M	TX	Pre-auricular	VII	2	Resection	2	Clear	3	PN, IN	0	0	0	0
2	M	T2	Nose	V1, V2	2	Resection	2	Clear	3	PN, IN	0	1	0	0
3	M	T2	Forehead	V1, V2	2	Resection	2	Clear	3	PN, IN	0	1	0	0
4	M	T0	Unknown	V2	2	Resection	3.5	Clear	2	PN, IN	0	0	0	0
5	F	T1	Pre-auricular	V3	2	Resection	3	Clear	2	PN, IN	0	1	0	0
6	F	T0	Unknown	V2	2	Resection	3.5	Clear	2	PN, IN	0	0	0	0
7	F	T1	Nose	V2	1	Resection	2.5	Clear	3	PN, IN	0	0	0	0
8	M	T0	Unknown	V3, VII	2	Resection	2.5	Close	2	PN, IN	0	0	0	0
9	F	T2	Nose	V3, VII	2	Resection	2.5	Clear	3	PN, IN	0	0	0	0
10	F	T2	Nose	V2	3	Resection	3.5	Close	4	PN, IN	0	0	0	0
11	M	T1	Cheek	V2	3	Biopsy	0.5	N/A	2	PN, IN	0	0	0	0
12	M	T1	Temple	V1	1	Biopsy	3	N/A	2	PN, IN	0	0	0	0
12	M	T1	Temple	V1	1	Resection	2.5	Clear	2	PN, IN	0	0	0	0
13	M	T2	Temple	VII	N/A	Resection	1.5	Clear	3	PN, IN	0	0	0	0
14	M	T0	Unknown	VII	2	Resection	2	Clear	2	PN, IN	0	0	0	0
15	M	T2	Temple	VII	N/A	Resection	0.2	Clear	2	PN, IN	0	0	0	0
16	M	TX	Unknown	V1, V2	2	Resection	3.5	Clear	3	PN, IN	0	0	0	0
16	M	TX	Unknown	V3, VII, VIII	N/A	Autopsy	5	N/A	2	PN. IN	0	1	0	0
17	M	T4	Cheek	V2	2	Resection	5	Involved	2	PN, IN	0	0	1	0
18	M	T1	Temple	VII	1	Resection	1.5	Clear	2	PN	0	1	0	0
19	F	T2	Temple	V1	2	Resection	3	Clear	3	PN, IN	0	0	0	0
20	M	TX	Unknown	V3	1	Resection	3.5	Clear	3	PN, IN	0	1	0	0
21	M	T2	Cheek	GA	N/A	Resection	1	Clear	4	PN, IN	0	0	0	0
22	M	T2	Cheek	V3, VII	1	Resection	1.5	Clear	2	PN, IN	0	1	0	0
23	M	T0	Unknown	V2	2	Resection	3.5	Involved	4	PN, IN	0	0	0	0
24	M	T0	Unknown	V1	2	Resection	4	Involved	3	PN, IN	0	0	1	0
25	M	T2	Cheek	V1, V2, V3	2	Resection	6	Involved	3	PN, IN	0	1	0	0
26	M	T2	Forehead	V1, V2	1	Resection	4	Clear	3	PN, IN	0	0	0	0
27	M	TX	Unknown	V1	2	Resection	2	Clear	3	PN, IN	0	0	0	0
28	M	T2	Cheek	V3, VII	1	Resection	1.6	Clear	3	PN, IN	0	1	0	0
29	M	T2	Nose	V2	1	Resection	3	Clear	3	PN, IN	0	1	0	0
30	M	T2	Forehead	V1	1	Resection	1.7	Clear	3	PN, IN	0	1	0	0
31	M	T1	Cheek	V2	2	Resection	5	Clear	3	PN, IN	0	1	0	0
32	F	TX	Unknown	V2	2	Resection	4	Clear	2	PN, IN	0	1	0	0
33	M	TX	Unknown	V3	1	Resection	2	Clear	1	PN, IN	0	1	0	0
34	M	TX	Unknown	V2	2	Resection	7	Involved	2	PN, IN	0	0	0	0
35	F	T2	Nose	V2	2	Resection	5	Clear	1	PN, IN	0	1	0	0
36	M	T1	Nose	V2	2	Resection	5	Clear	2	PN, IN	0	1	0	0
37	M	T2	Nose	V2	2	Resection	2.5	Clear	2	PN, IN	0	0	0	0
38	M	T0	Unknown	VII	2	Resection	0.7	Clear	3	PN, IN	0	0	0	0
39	M	T2	Cheek	V2	2	Resection	5	Involved	3	PN, IN	0	0	0	0
40	M	T2	Cheek	V2	1	Resection	0.8	Involved	2	PN, IN	0	1	0	0
41	M	T2	Cheek	V2, V3	2	Resection	4.5	Clear	2	PN, IN	0	1	0	0
42	F	T2	Cheek	V2	1	Resection	3.5	Clear	3	PN, IN	0	0	0	0
43	M	T2	Temple	V2, V3	1	Resection	6	Close	2	PN, IN	0	0	0	0
44	M	T2	Pre-auricular	V2	2	Resection	1.5	Involved	2	PN, IN	0	1	1	0
45	M	T2	Temple	V1	2	Resection	2.5	Clear	2	PN, IN	0	1	0	1
46	M	T2	Cheek	V2, V3	2	Resection	2.5	Involved	2	PN, IN	0	0	0	0
47	M	T2	Lip	GA	N/A	Resection	1.2	Clear	2	PN, IN	0	0	0	0
48	M	TX	Unknown	V1	1	Resection	0.5	Clear	2	PN, IN	0	0	0	0
49	M	T2	Forehead	V1	2	Resection	2	Involved	2	PN, IN	0	1	0	1

Abbreviations: AJCC, American Joint Committee on Cancer; PN, perineural; IN, intraneural; N/A, not applicable; GA, great auricular; V, trigeminal nerve; V1, ophthalmic division; V2, maxillary division; V3, mandibular division; VII, facial nerve; VIII, vestibulocochlear; GA, great auricular.

* Nominal classification of the primary tumor if there were no perineural spread using 7th Ed AJCC 2011.[34] By AJCC criteria, all perineural spread specimens assessed in this study are T4.

Imaging zone extent described in Gandhi et al.[26] Tumour histologic grade/differentiation: 1 = well, 2 = moderate, 3 = poor, 4 = undifferentiated. Distal signifies towards skin. Proximal signifies toward skull base/brainstem. Skip lesion/epineural spread: present = 1, absent = 0.

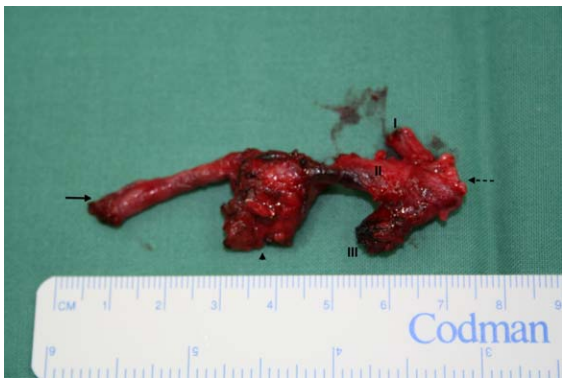

FIGURE 1. Surgical specimen comprising infraorbital nerve at distal or skin aspect of specimen (arrow), pterygopalatine fossa contents (arrowhead), trigeminal nerve divisions (I = ophthalmic stump; II = maxillary; and III = mandibular stump) and Gasserian ganglion at proximal aspect of specimen (broken arrow). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

was present around the nerve yet no tumor was clearly identifiable on initial hematoxylin-eosin staining.

The following histopathological features were assessed: (1) nerve involved; (2) tumor differentiation; (3) tumor invasion pattern: perineural (within the perineural space); intraneural (invading endoneurium); or epineural (invading epineurium); (4) presence of "skip lesions" (ie, discontinuous tumor cells within a perineural and/or intraneural location); and (5) maximum transverse nerve diameter. Epineural spread was assessed by level: peripheral (subcutis); distal cranial nerve (deep to subcutis and in the vicinity of the superficial musculoaponeurotic system); or proximal cranial nerve (in the vicinity of the skull base).

RESULTS

Fifty-one nerve specimens from 49 patients were assessed, and details are included in Table 1. Forty-eight patients underwent surgical resection with curative intent. Two patients underwent diagnostic nerve biopsy: 1 proceeded to surgical resection (specimens 12 and 13) and 1 received palliative care with radiotherapy (specimen 11). One patient who died of disease after surgical treatment consented to the harvesting of involved nerves at autopsy (specimens 17 and 18). Disease affected men (81.6%) more commonly than women (18.37%). In 15 of 49 patients (30.6%), the primary tumor was unassessable (TX $n = 8$) or there was no evidence of one (T0 $n = 7$). There were 9 patients classified as T1, 25 patients classified as T2, and 1 patient classified as T4, if we were to ignore the influence of the large nerve PNS in all specimens. The patient with T4 disease had tumor invading the maxilla and infraorbital nerve. In 14 of 49 patients (28.6%), primary tumor location was unknown (ie, TX or T0). The most common known primary tumor location was the cheek in 13 of 49 patients (26.5%). No evidence of skip lesions was seen in any patient imaged preoperatively with MR neurography. Fifteen patients had zone 1 disease, 29 patients had zone 2 disease, and 2 patients had zone 3 disease. Two patients did not undergo preoperative MRI. Two patients underwent MR neurography with continuous disease evident in the great auricular nerve only, a nerve which is not provided for in zonal classification.

Cranial nerve V was the predominant nerve involved in 44 of 49 patients (89.8%), with 8 of 44 involving more than 1 major division (18%; V_1, V_2, and/or V_3). Of those with V nerve involvement, the most commonly involved division was V_2 (61.4%; 27 of 44), with V_1 involvement seen in 31.8% (14 of 44), and V_3 in 27.3% (12 of 44). Cranial nerve VII was involved in 24.5% (12 of 49) of all patients. Involvement of more than 1 cranial nerve was seen in 14.3% (7 of 49). Other affected nerves were the great auricular (2 cases, with 1 extending to the third cervical spinal nerve root) and vestibulocochlear (1 case). Clear margins were obtained in 72.9% (35 of 48; excluding nerve biopsies and autopsy specimen). Three patients had close margins (ie, <5 mm clearance), whereas 10 patients had involved margins.

Tumor spread was contiguous along the perineural space and no skip lesions were identified in any of the assessed nerve specimens (Figures 2A–2D). In the instances in which skip lesions were initially suspected, further sectioning with AE1/AE3 or MNF116 staining identified contiguous tumor cells consistently with no skip in spread (Figure 2C).

PNI with coexistent intraneural invasion was the predominant pattern of spread (98%; 50 of 51; Figure 3A). There was no evidence of invasion into the perineural space from tumor surrounding or abutting a peripheral nerve. Epineural tumor was only detected in areas in which overall tumor bulk was large and with concomitant PNI and intraneural invasion. Predominant epineural tumor spread was seen in distal small peripheral nerves (ie, subcutis; 43.1%; 22 of 51). In the distal aspect of large cranial nerves, tumor spread into the epineurium was observed in 5.9% (3 of 51). In the proximal aspect of large cranial nerves, extension into the epineurium was seen in 3.9% (2 of 51; Figure 3B). The epineurium and perineurium seemed to act as a barrier to local spread in the majority of large cranial nerves (Figure 3) and was useful as a margin of resection in the absence of gross adjacent tumor involvement of soft tissue. Spread beyond the proximal cranial nerve epineurium into the surrounding soft tissues was rare and only with concomitant bulky perineural disease (1 case). In this case, perineural tumor from V_1 invaded the soft tissue surrounding the optic nerve sheath, without penetration through the sheath.

DISCUSSION

Australia has the highest recorded incidence of NMSC in the world, and the detection of PNI denotes a worse prognosis.[1] The definition is dependent on the histopathological features, yet is variable in the literature.[35–37] The contiguous nature of PNS is generally well understood, however, the idea of a skip in tumor growth continues to pervade the literature.[3,9,20,31,33,38–40] This can greatly influence patient management and lead to overtreatment. This case series demonstrates 2 key features of cutaneous SCCHN with clinical PNI: (1) PNS was contiguous and no skip lesions were evident in the nerve specimens assessed in this study; and (2) the proximal perineurium

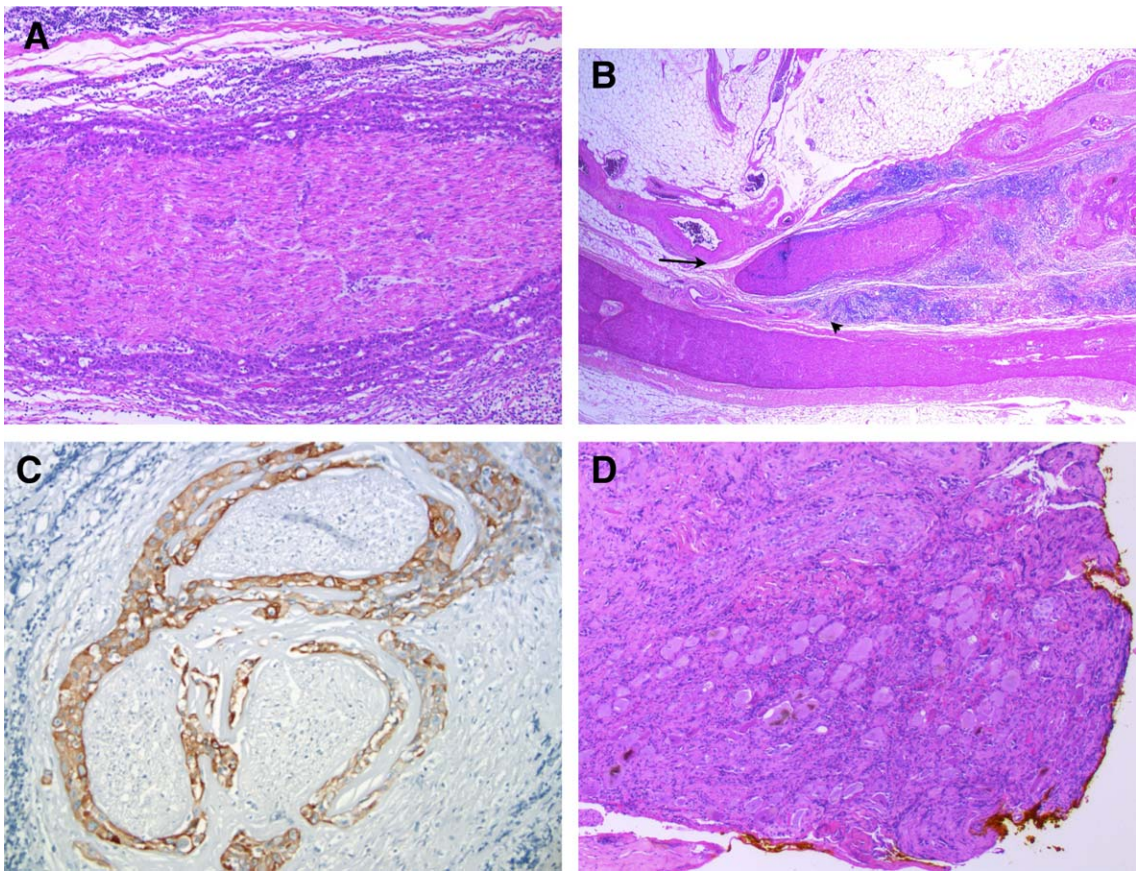

FIGURE 2. Cutaneous squamous cell carcinoma of the head and neck (SCCHN) with contiguous perineural invasion (PNI). (A) Cranial nerve with "onion-skin" pattern and contiguous PNI (hematoxylin-eosin, longitudinal, original magnification ×100). (B) The proximal extent of PNI with uninvolved nerve on the left (arrow) and contiguous PNI on the right (arrowhead, hematoxylin-eosin, longitudinal, original magnification ×20). (C) Cranial nerve with perineural squamous cell carcinoma (SCC) using AE1/AE3 staining to show virtual circumferential perineural space involvement (original magnification ×100). (D) Contiguous PNI of cranial nerve into ganglion with positive resection margin (yellow ink; hematoxylin-eosin, original magnification ×100). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

was a barrier to tumor spread in the majority of cranial nerves reflecting the multilayered structure of the perineurium at this level.

Another important observation in this series was the high number of patients with no evidence of primary tumor (T0) or primary tumors that were unassessable (TX). TX classification was applied to any patient with missing or nonexistent pathological documentation of an index primary skin lesion. In only 1 patient was the location known, yet the precise features were missing (ie, missing pathological report). The remaining 7 patients classified as TX had nonexistent pathological records either because of: (1) a vague history of skin lesions in the vicinity of the region of interest, yet no treatment; or (2) a history of skin lesions previously treated with cryotherapy, shave, or curettage with no tissue diagnosis or pathological record. The diagnosis of clinical PNI should therefore always be considered even in patients with no obvious primary tumor.

Absence of skip lesions

Despite the fact that skip lesions were disputed previously,[23,41–43] they are still frequently propagated in the literature as a cause for concern in regard to margin control.[3,9,20,25,31,40] PNI was initially thought to arise from perineural lymphatics.[6,44] This could theoretically lead to skip lesions via an embolic process producing a false-negative margin. However, the existence of perineural lymphatics was discounted.[45,46] If skip lesions were observed, they could be explained by processing an artifact during sectioning and/or staining[42] or regression of tumor because of an inflammatory or immunological response.[47]

PNI can be overlooked unless a high degree of suspicion is applied with careful histological technique.[48–50] The haphazard course of nerves makes sectioning and tracing nerves a challenge, and routine 2D sections may not appreciate the complete 3D structure. In addition, involved fascicles can have asymmetric axial extension and/or noncircumferential disease, which could give the impression of a skip lesion on a particular longitudinal section. When this was suspected, deeper histological sections were taken and contiguous disease consistently demonstrated. These issues are particularly important with cranial nerve VII within the parotid gland because of the nerve's diverging ramification pattern. The well-described mimics of PNI, such as peritumoral fibrosis, re-excision

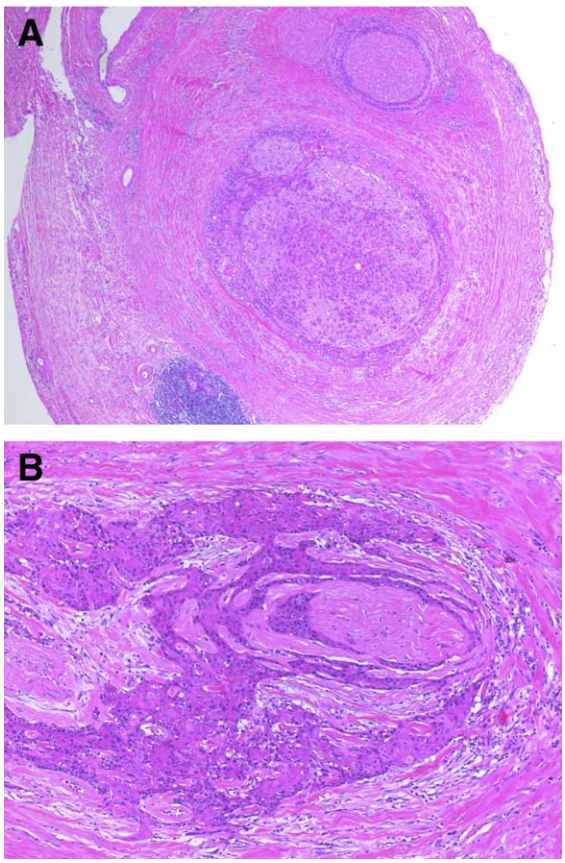

FIGURE 3. Perineural invasion (PNI) of cranial nerve by cutaneous squamous cell carcinoma of the head and neck with the perineurium and epineurium as a barrier to spread. (A) Cranial nerve with perineural and intraneural spread of squamous cell carcinoma with no epineural involvement (hematoxylin-eosin, original magnification ×40). (B) Perineural and epineural invasion with disease contained by outer epineurium (hematoxylin-eosin, original magnification ×100). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

PNI, reparative perineural infiltration, or epithelial sheath neuroma also need consideration and exclusion.[51]

Cottel[47] discussed perineural "skip areas" in Mohs chemosurgery cases. "Skip areas" were apparent and the presence of inflammation was the harbinger of underlying undetected perineural disease. This necessitated further horizontal sectioning to trace the nerve for evidence of disease, an approach he considered superior to routine vertical sectioning.[41,47,52] However, many studies that report skip lesions are earlier Mohs chemosurgery case series.[47–50] Matorin and Wagner[42] recognized the specific limitations of Mohs surgery to assess PNI because of the reliance on horizontal sections with inherent technical processing issues, and the skip lesion was seen as a possible product of this.[53]

Immune-mediated regression of cutaneous tumors is well documented in melanoma and SCC.[54,55] The intensity of inflammation associated with perineural tumor is variable yet can be florid. It is plausible that complete regression of perineural tumor segments could occur after an intense inflammatory reaction, leaving a "skip" in the residual lesion.[23] However, scarring of the nerve would be recognizable on histological sections. Complete regression of perineural tumor was not observed here, even in cases with intense inflammatory infiltrate. In addition, no significant scarring of the nerve without tumor was seen, unless the nerve had been surgically manipulated in a previous operation (ie, biopsy).

In our experience, PNS is only contiguous and skip lesions (while not seen) are likely a product of processing artifact. NMSC with high-risk features should raise the index of suspicion in the surgeon and histopathologist.[8] When this is applied in conjunction with appropriate sectioning and staining (hematoxylin-eosin, AE1/AE3, MNF116, and/or S100), PNI can be more accurately assessed.[48]

Perineurium as a barrier to spread

As a cranial nerve approaches the skull base (ie, proximal), the perineurium is multilayered and blends with the pia-arachnoid to make the perineural space continuous with the subarachnoid space.[56] In the periphery (ie, distal aspect), it gradually thins to become single-layered or absent.[18] In the dermis, the perineurium either fuses to be a component of the terminal endings of sensory nerves (Pacinian corpuscles, muscle spindles) or forms funnel-like openings at motor end plates.[17,57]

Shattock[44] recognized the barrier function of the perineurium as an "obstacle to invasion" by tumor, and that axial extension to the central nervous system was inevitable. He theorized that invasion occurred where the perineurium was "attenuated as the nerve diminishes in size." PNI likely first occurs at the primary tumor site, when tumor invades the perineural space of adjacent small nerves where the perineurium is thin or absent.[6] Tumor spreads in a contiguous fashion in a centripetal direction taking the relative path of least resistance.[45,46] Inevitably, this continues to ganglia and branching points to also enable secondary centrifugal spread.[6,58] In our experience, spread seems to be preferentially toward the brainstem.

The perineurium was a barrier to tumor spread in the majority of proximal large cranial nerves, preventing tumor spread into or out of the peripheral nerve sheath and promoting axial extension over radial expansion (Figure 3).[50] We use the epineurium as a margin for resection of disease when disease is confined to the nerve preoperatively on MR neurogram.

The differing definitions of PNI contribute to the confusion as to precisely what constitutes PNI.[35–37] Batsakis[37] described neurotropism as the invasion of tumor "in, around, and through peripheral nerves." Liebig et al[35] agreed with this definition, yet added that "tumor in close proximity to nerve and involving at least 33% of its circumference or tumor cells within any of the 3 layers of the nerve sheath" also qualified as PNI. However, in our experience, any tumor surrounding or abutting a nerve to any extent should not constitute PNI in the absence of perineural space involvement. This finding merely represents focal abutment, yet can be supportive of PNI in equivocal cases, as Dunn et al[36] proposed. We use a simplified definition of PNI based on the histopathological features that is in accordance with previously proposed

definitions: the finding of tumor cells in the perineural space.[30,36,59]

CONCLUSION

Any high-risk features of NMSC need to be communicated to the assessing histopathologist so that all specimens are carefully assessed for the presence and extent of PNI.[8] A vigilant approach should demonstrate contiguous perineural tumor. If not, further sections and stains should be applied until disease extent and margin status are clarified. The perineurium and epineurium of cranial nerves were a barrier to tumor spread, and can be used as a margin of resection when disease is confined to the nerve.

This study was limited because of the relatively small sample size in an uncommon disease, and by the fact that an entire cranial nerve could not be resected and therefore assessed in its entirety from skin to brainstem. However, skip lesions were nonexistent and only contiguous PNS evident in the surgically resectable nerve segments were assessed in this series of patients with clinical PNI. The concept of a skip lesion affects patient assessment and treatment significantly and likely reflects processing artifact. Further studies are currently being undertaken to assess long-term outcomes. These histological findings should be taken into consideration when deciding how far beyond a radiologically or histologically involved nerve should be treated.

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