The Natural History and Treatment Outcomes of Perineural Spread of Malignancy within the Head and Neck

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Abstract

Keywords

- ▶ perineural invasion
- ▶ head and neck
- ▶ skin cancer
- ▶ squamous cell carcinoma
- ▶ skull base surgery
- ▶ perineural spread

Understanding the natural history of diseases enables the clinician to better diagnose and treat their patients. Perineural spread of head and neck cancers are poorly understood and often diagnosis is delayed resulting in poorer outcomes and more debilitating treatments. This article reviews a large personal series of head and neck malignancy presenting with perineural spread along almost exclusively the trigeminal and/or facial nerves. A detailed analysis of squamous cell carcinoma of cutaneous origin is presented including an analysis of likely primaries, which most often have occurred months to years prior. The importance of early detection is reinforced by the highly significant ($p < 0.0001$) differences in disease specific survival, which occur, depending on how far along a cranial nerve the disease has been allowed to spread.

Introduction

Perineural spread (PNS) of malignancy is a unique form of tumor cell metastasis. Primary tumor cells invade small adjacent peripheral nerves to access the perineural space, a process termed *perineural invasion* (PNI). The perineural space is a potential space beneath or between layers of perineurium, the middle layer of the peripheral nerve sheath. Tumor can spread contiguously along the nerve away from the primary within a plane of relative low resistance. This process is gradual and the direction of spread is primarily retrograde toward the brainstem, yet at nerve branching points it can be antegrade toward the skin. The disease progressively advances along cranial or spinal nerves and into the relevant ganglia, and can spread to the brainstem or rarely the spinal cord and seed the meninges via the cerebrospinal fluid.

PNI can be categorized into two forms. PNI that is incidentally detected on histopathology of a cutaneous malignancy excised from an asymptomatic patient is known as incidental PNI and remains readily treatable. On the other hand, PNS or clinical PNI refers to more advanced disease that has spread

into large caliber nerves manifesting radiologically and/or clinically with symptoms or signs of cranial nerve neuropathy. This is classified using a zonal system on imaging, as previously detailed in article “The Imaging of Large Nerve Perineural Spread”.¹ PNS or clinical PNI is associated with worse outcomes, with overall survival at 5 years ranging from 50 to 64%.^{2,3}

PNS can be misinterpreted as a benign cranial neuropathy such as Bell’s palsy or trigeminal neuralgia, resulting in significant costly delays in diagnosis. Understanding PNS epidemiology and natural history can increase awareness of the disease and minimize diagnostic and treatment delays so as to maximize outcomes. The majority of available data pertain to PNS from cutaneous squamous cell carcinoma of the head and neck (CSCCHN), which will be the focus of this review.

Incidence and Demographics

Queensland (Australia) has the highest recorded rates of non-melanoma skin cancer (NMSC) in the world.^{4,5} The true incidence of NMSC is unknown as it is not a notifiable condition. The

proportion of NMSCs that go on to develop PNS is also unclear. It has been estimated that incidental PNI is detected in less than 5% of skin cancers.⁶ Approximately 25 patients with PNS of various pathologies are managed through our institution annually with a total 181 cases having been managed. In the literature, the majority of case series of PNS are from regions with a high incidence of NMSC, such as Queensland (Australia), Texas, and Florida (United States).^{2,7-9}

We recently analyzed the epidemiological features of 120 consecutive patients with PNS from CSCCHN.¹⁰ Men were affected over five times more frequently than women. The average age at diagnosis was 66 years, with an age range of 34 to 91 years.¹⁰ The majority of patients (85.8%) had a previous history of skin cancer (reflecting significant previous sun exposure); however, 7.5% had no prior history. In addition, despite the known association of immunosuppression with increased risk of cutaneous malignancy, the majority of patients presenting with PNS were immunocompetent (96.7%).^{10,11}

Primary Tumor Features

PNS of cutaneous SCC is the most common tumor subtype managed at our institution ($n = 145$). Other tumor types managed include other non-SCC skin cancers (basal cell carcinoma/melanoma, $n = 15$) and salivary gland tumors (i.e., adenoid cystic/carcinoma ex pleomorphic, $n = 9$). Some patients with PNS from an unknown primary tumor are not medically fit for treatment or biopsy due to advanced age or disease and as such are classed as unknown pathology ($n = 12$). Although the majority of available data pertain to PNS from cutaneous SCC, generalizations are limited due to the known differing biology between tumor types.

A major finding from our recent analysis was that more than 20% of patients presented with PNS in the absence of a known primary index lesion (T0; AJCC 7th edition).^{10,12} Patients may present without any history or evidence of skin cancers or mucosal primary in the region of interest, and the only sign may be sun-damaged skin. This feature may reflect subclinical disease or immune-mediated tumor regression.¹³ Many primary tumors on retrospective review were classed as unassessable (TX; 21.7%), due to either cryotherapy or laser treatment of skin cancers with no biopsy (7.3%), incomplete pathology reports, or a history of multiple potential primary skin lesions in the region of interest.

Patients typically present months to years after treatment of a primary tumor. The median time from primary tumor treatment to the onset of PNS symptoms was 16 months (range: 1–86 months).¹⁰ This reflects the slow, progressive spread of disease along the perineural space. The cheek was the most frequent primary tumor location (15.8%), with other sites detailed in ► **Table 1**.

Another key finding from this series was that over a third of patients with PNS did not have PNI reported in the histology of the primary tumor. The significance of this is that patients may still have PNS despite no evidence of PNI identified in a primary tumor. Although the reasons for this are unclear, detecting PNI in a specimen can be challenging due to small caliber nerves branching randomly through a given histolog-

Table 1 Primary tumor location in patients with PNS of cutaneous SCC

Location	n	%
Unknown	45/120	37.5
Cheek	19/120	15.8
Nose	12/120	10
Temple	12/120	10
Forehead	10/120	8.3
Preauricular	10/120	8.3
Lip	3/120	2.5
Scalp	3/120	2.5
Eyelid	3/120	2.5
Chin	1/120	0.8
Postauricular	1/120	0.8
Ear	1/120	0.8

Source: Adapted from Warren et al.¹⁰

Note: 120 patients with PNS from cutaneous SCC.

ical section. Involved nerves can therefore be overlooked due to technical processing artifact or inadequate specimen assessment.¹⁴⁻¹⁶ Careful specimen processing and staining is required to minimize false negatives. Standardized pathology reporting of all skin lesions is necessary to enable complete primary tumor assessment.

Presentation

The symptoms and signs of the disease are dependent on the nerve(s) involved and are typically progressive in nature as the disease slowly spreads. This is an important differentiator from benign causes of cranial nerve neuropathy such as trigeminal neuralgia and Bell's palsy. The diagnosis can often be delayed, and the median time between PNS symptom onset and diagnosis of PNS was 6 months (range: 2 weeks to 5 years).^{2,17} The trigeminal (ophthalmic V₁, maxillary V₂, and mandibular V₃ divisions) and facial (VII) cranial nerves are the most commonly involved nerves, and cross-branching between V and VII does occur.^{2,8,18}

The common symptoms and signs of PNS at presentation are detailed in ► **Table 2**. Unilateral facial palsy was present in 39.2%, and was typically partial (59.6%) affecting one or more of the peripheral branches. A complete unilateral facial palsy at presentation was seen in 40.4%, and this was frequently progressive in onset (89.5%) compared with sudden onset (10.5%). In comparison, Bell's palsy is typically characterized by a sudden-onset complete facial palsy that may resolve over time. Trigeminal nerve involvement presents as numbness, pain, paraesthesia, or formication (sensation of crawling ants) in the distribution of the involved nerve. Over time, the distribution of the affected area can spread to involve all divisions of the trigeminal nerve once retrograde invasion of the ganglion occurs. Disease can also spread antegrade down a nerve branch toward the skin.

Approximately a third of patients also presented with a subcutaneous mass overlying the cranial nerve exit foramina,

Table 2 Presentation features of perineural spread

Presentation	n	%
Numbness	68/120	56.7
Neuropathic pain	52/120	43.3
Paraesthesia	37/120	30.8
Formication	18/120	15
Burning	4/120	3.3
Subcutaneous mass	41/120	34.2
Facial palsy	47/120	39.2
Partial palsy	28/47	59.6
Complete palsy	19/47	40.4
Nodal disease ^a		
N0	113/120	94.2
N1	4/120	3.3
N2b	3/120	2.5

Source: Adapted from Warren et al.¹⁰

Note: 120 patients with PNS from cutaneous SCC.

^aAJCC TNM, 7th edition (2010), criteria.

typically the infraorbital or supraorbital foramen.² Great auricular nerve involvement, although uncommon, can also occur, and may present as a palpable thickened cord over the sternocleidomastoid muscle and dysesthesia in the nerve's dermatomal distribution.¹⁹

Patients with suspected PNS are typically assessed with magnetic resonance imaging with neurography protocol, which determines disease extent using the zonal system and guides treatment. In our series of 120 patients with PNS of CSCCHN, disease was detected at presentation in Zone 1 in 31.5%, Zone 2 in 42.3%, and Zone 3 in 25.2%.¹⁰ Importantly, the majority of patients present with PNS of tumor alone, with only 5.8% having regional nodal involvement.¹⁰ Distant metastases at presentation are also uncommon (0.08%). This suggests that PNS is an inherently different form of tumor metastasis when compared with hematogenous or lymphatic metastasis, possibly from differing unknown tumor biological properties or factors within the tumor microenvironment.

Natural History and Outcomes

Outcome analysis using an electronic prospective database of 120 consecutive patients with PNS from CSCCHN assessed and/or treated at our institution between 1998 and 2013 was undertaken. The treatment details for these patients are summarized in ►Table 3. Of the 120 patients, 60% received surgery and postoperative radiotherapy, 6.7% received surgery alone (no radiotherapy as either ineligible or declined), 12.5% received radiotherapy alone (typically due to Zone 3 disease), and 1.7% received chemoradiotherapy. The remainder were palliated (19.2%) predominantly due to advanced Zone 3 disease or because the patient was not fit for treatment. Of the patients treated with surgery, 13.8% had a neck

Table 3 Management of perineural spread

Treatment	n	%
Intent		
Definitive	80/120	66.7
Salvage	17/120	14.2
Palliative	23/120	19.2
Type		
Surgery and postoperative radiotherapy	72/120	60.0
Surgery	8/120	6.7
Radiotherapy	15/120	12.5
Chemoradiotherapy	2/120	1.7
Palliative radiotherapy	10/120	8.3
Palliative chemotherapy	2/120	1.7
Palliation	11/120	9.2
Surgery		
Yes	80/120	66.7
No	40/120	33.3
Intent		
Definitive	63/80	78.8
Salvage	17/80	21.3
Neck dissection		
Yes	11/80	13.8
No	69/80	86.3
Orbital exenteration		
Yes	30/80	37.5
No	50/80	62.5
Radiotherapy		
Yes	98/120	81.7
No	22/120	18.3
Intent/dose		
Definitive	17/98	17.3
Dose range	50 to 70 Gy (25–35 fractions)	
Adjuvant	72/98	73.5
Dose range	45 to 63 Gy (25–30 fractions)	
Palliative	9/98	9.2
Dose range	30 to 60 Gy (10–30 fractions)	
Regional nodal irradiation		
Yes	12/120	10.0
No	108/120	90.0

dissection and 37.5% required orbital exenteration. Radiotherapy is typically adjuvant postoperative, with the dose given ranging from 45 to 63 Gy over 25 to 30 fractions. Regional nodal irradiation was only provided to 10%.

Table 4 Treatment outcomes for perineural spread

	<i>n</i>	%
Status		
Alive without disease	53/120	44.2
Alive with disease	10/120	8.3
Alive, disease status unknown	1/120	0.8
Died from disease	40/120	33.3
Died from other causes	8/120	6.7
Died, cause of death unknown	1/120	0.8
Lost to follow-up	7/120	5.8
Recurrence details		
Recurrence		
Yes	38/97	39.2
No	59/97	60.8
Recurrence by type^a		
Local (in-field)	25/44	56.8
Local (out-field)	7/44	15.9
Regional (in-field)	2/44	4.5
Regional (out-field)	2/44	4.5
Central	6/44	13.6
Distant	2/44	4.5
Treatment for recurrence		
Yes	24/38	63.2
No	14/38	36.8
Response to treatment for recurrence		
Yes	9/24	37.5
No	15/24	62.5
Multiple recurrences		
Yes	9/38	23.7
No	29/38	76.3

Note: Median follow-up: 29 months (range, 2 weeks to 171 months).

Median time to death from disease: 21 months (mean, 32 months).

Median time to recurrence: 16 months (range, 7–76 months)

^aSix patients had more than one type of recurrence.

Outcome analysis, summarized in ►Table 4, demonstrates the aggressive nature of the disease. After a median follow-up of 29 months (range: 2 weeks to 171 months), one-third of patients died from disease, 44.2% were alive without disease, and 19.2% of patients were palliated at presentation. The median time to death from disease was 21 months (mean: 32 months).

In patients who received treatment, 60.8% remained disease-free at follow-up. Recurrence of disease following treatment was seen in 39.2%. The median time to any recurrence was 16 months (range: 7–76 months). Recurrence was categorized into local, regional, central (at skull base/dura/brainstem), or distant, and further subdivided based on whether the recurrence was within the radiation field (in-field) or out of the radiation field (out-field). The majority were local in-field recurrences (56.8%), demonstrating that the control of

diffuse disease in the skin and small peripheral nerves remains one of the more challenging aspects of management. The majority of recurrences received treatment (63.2%), with 37.5% of these successfully salvaged with surgery, supporting our practice of close follow-up (see article “Post-operative Imaging and Surveillance of Large Nerve Perineural Spread” in this issue). Also, 23.7% of patients who recurred had more than one episode of recurrence. Regional and distant recurrences were uncommon, with 4.5% regional in-field recurrence, 4.5% regional out-field recurrence, and 4.5% having recurrence with distant metastases. These low rates again reflect differing tumor biology with a neurotropic tendency rather than lymphatic or hematogenous spread.

Current AJCC staging classifies all NMSC with PNS to the skull base as T4 disease.¹² This system therefore does not differentiate between disease prior to the skull base, at the skull base, and at the brainstem, and does not help as a prognostic or treatment indicator. At our institution, we classify PNS according to zonal extent on imaging, which helps guide management and prognosis.² Patients with Zone 3 disease had significantly worse disease-specific survival (DSS) than those with Zone 1 or Zone 2 disease (DSS at 5 years: Zone 1, 84%; Zone 2, 63%; Zone 3, 16%; $p < 0.0001$; see ►Fig. 1). This demonstrates that detecting disease early is associated with significantly improved outcomes.

Patients with single nerve involvement had significantly better DSS at 5 years (DSS, 67%) than those with multiple nerve involvement (DSS, 36%; $p = 0.03$; see ►Fig. 2). Patients treated with surgery that achieved a clear or close (<5 mm) margin did better than those with involved margins (DSS at 5 years, 72 vs. 46%; $p = 0.04$; see ►Fig. 3; recurrence-free survival at 5 years 59 vs. 36%; $p = 0.08$).

Conclusion

PNS of malignancy is a unique mechanism for tumor cells to metastasize with a potentially devastating impact on patient prognosis. It is a progressive process with characteristic progressive symptomatology. Patients can have PNS without a known index primary lesion or without PNI detected in the primary.

Fig. 1 Kaplan-Meier curve of disease-specific survival for patients with perineural spread from cutaneous squamous cell carcinoma comparing zonal extent of disease ($n = 120$; $p < 0.0001$).

Fig. 2 Kaplan-Meier curve of disease-specific survival for patients with perineural spread from cutaneous squamous cell carcinoma comparing single nerve versus multiple nerve involvement ($n = 120$; $p = 0.03$).

Fig. 3 Kaplan-Meier curve of disease-specific survival for patients with perineural spread from cutaneous squamous cell carcinoma treated with surgery comparing clear/close margin (<5 mm) versus involved margin ($n = 80$; $p = 0.04$).

PNS demonstrates an innate tendency for neurotropic spread without associated nodal involvement. Patient outcomes are significantly better in the earlier stages of the disease. An appreciation of the natural history of PNS can enable prompt diagnosis and treatment and can improve outcomes.

Key Points

- PNS is typically a slowly progressive disease with the median time from primary tumor treatment until onset of PNS symptoms being 16 months (range: 1–86 months), and the symptoms and signs are typically progressive.
- PNS can be mistaken for benign causes of cranial nerve dysfunction, and the diagnosis is often delayed with the median time from PNS symptom onset until diagnosis being 6 months (range: 2 weeks to 5 years).
- Over 20% of patients can have PNS without an obvious primary tumor.
- PNI is likely underappreciated on histology with over one-third of patients with PNS having no PNI seen in the primary tumor.
- Regional nodal and distant metastatic spread is uncommon.

- The disease can be aggressive with up to 20% of patients palliated at presentation, and one-third dying from the disease.
- The zonal system for disease extent on imaging is helpful for disease prognostication and classification.
- Achieving clear surgical margins is associated with improved outcomes compared with positive surgical margins.
- Patients with multiple nerve involvement do worse than patients with single nerve involvement.

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