Curr Oncol Rep (2013) 15:128–133
DOI 10.1007/s11912-012-0288-y

Perineural Invasion of Head and Neck Skin Cancer: Diagnostic and Therapeutic Implications

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Published online: 27 December 2012

Abstract Perineural invasion of head and neck skin cancer is a poorly understood and often misdiagnosed pathological entity. Incidental or microscopic perineural invasion is identified by the pathologist and often leads to confusion as to how the patient should be further treated. The less common but more aggressive clinical perineural spread presents with a clinical deficit, which is too commonly misinterpreted by the clinician. This review will try to clarify the terminology that exists in the literature and explore the mechanisms of invasion and spread. It will look at the recent advances in diagnosis and comment on the limitations inherent in current classification schemes. A review of outcomes will be included and current treatment strategies utilized discussed.

Keywords Perineural invasion · Neurotropism · Skin cancer · Squamous cell carcinoma · Skull base surgery · Staging

Introduction

Perineural invasion (PNI) is a unique form of tumor dissemination occurring when tumor cells gain access to the perineural space and then, in some cases, manage to spread along the nerves to distant locations. In the head and neck region this usually involves the trigeminal (V) and facial (VII) nerves with their rich network of cutaneous endings in a region most often exposed to UV radiation. The rates of invasion vary but are generally in the range of 0.18 – 10 % of basal cell carcinomas (BCC) and 2.5 – 14 % of squamous cell carcinomas (SCC) [1, 2].

The disease is often under recognized leading to a delay in the diagnosis and the terminology used can be confusing resulting in possible inappropriate treatment. The exact mechanism of spread has not been elucidated and there are no identified prognostic markers. The natural history of perineural spread (PNS) is a slow central progression of the disease, usually taking years, with eventual central (intracranial) failure [3].

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Definition and Terminology

The terms commonly used and often analyzed together, but with very different prognostic significance, are small nerve, microscopic or incidental, and large nerve, named nerve or clinical.

PNI occurs when a skin cancer gains access to the perineural space of a peripheral nerve. This likely occurs where the perineurium is thin or absent in the subcutis. This represents incidental, microscopic or small nerve invasion. If the tumor then manages to spread along the perineural space of the nerve away from the original tumor mass (i.e. PNS), then eventually a clinical deficit occurs manifesting as paresthesia (V) or a palsy (VII). This is termed clinical or large nerve spread and carries a worse prognosis [4–6].

Confusion arises with the terminology of small and large nerve as the incidental or microscopic group may have the nerve size assessed as a prognostic indicator of outcome [7]. A diameter of less than 0.1 mm is called small and greater

than 0.1 mm is identified as large. Most clinical or named nerves will be on the order of millimeters in size. Hence, the terms incidental or microscopic, and clinical or named are to be preferred and should form separate prognostic groups for analysis.

In addition, the terms perineural invasion and spread should be limited to tumor involving the perineural and endoneural spaces of the nerve. External compression of a nerve causing a deficit should not be grouped with this form of spread and nor should direct tumor spread along the fissures and foramina of the skull base which follow different anatomical planes.

Finally, perineural invasion can also occur with far advanced cutaneous malignancies invading the skull base. In these cases small nerves within the tumor mass can be invaded, indicating a more aggressive tumor. These cases, however, may not have extension along a named nerve away from the edge of the tumor mass and if so should not be considered clinical PNS [8].

Pathology and Natural History

Incidental perineural invasion is reported by the histopathologist but no standardized reporting scheme is recognized. It is known that there is an increased incidence of recurrence and that nerve size may predict outcome [7]. No information is available in terms of outcomes with respect to (i) degree of nerve involvement, (ii) number of nerves involved, (iii) involved nerve margin to tumor and surgical edge, and (iv) involved nerve relationship to tumor. The Queensland Perineural Invasion Group is currently studying these factors, in addition to maximal involved nerve size, type and site of tumor, prospectively.

Clinical perineural spread is a less common entity and probably represents the spread along an invaded small nerve into a larger named nerve. It carries a much worse prognosis [4–6]. Clinical PNS with positive imaging findings has reduced 5-year local control rates (25 – 38 %) compared to incidental PNI (80 – 90 %) [4–6, 9•]. It is also associated with reduced 5-year disease-specific survival (54 – 61 %) compared to incidental PNI (73 – 90 %) [4–6, 9•]. These studies assessed treatment with surgery and/or radiotherapy.

In our experience, spread is continuous along the nerve, without evidence of skip lesions, with eventual central failure if not treated [3]. The misconception of skip lesions probably originated from an article by Cottel where he discussed skip areas being a result of inappropriate analysis of Moh's surgical specimens [10]. We have not found any evidence in the literature to support the concept of skip lesions even though expert groups continue to report its existence [11]. We have submitted for publication an analysis of over 50 surgical specimens of clinical PNS of SCC were we could not identify any evidence of a skip lesion. We also found the perineurium to be an excellent barrier to tumor spread with infrequent epineural involvement (3.7 % cases, each of these occurring in the proximal portions of the named nerves, i.e., close to the skin).

The concept of leptomeningeal carcinomatosis or drop metastasis is well accepted and relates to the spread of the disease into the subarachnoid space once beyond the Gasserian or Geniculate ganglia or as a result of iatrogenic spread during surgery in advanced cases. In addition, retrograde or centrifugal spread at nerve branch points toward the skin can occur, but is less common [11].

As PNS tends to occur slowly and is under recognized, patients are often diagnosed late [12]. It is not uncommon for symptoms to be present for years and the diagnosis can be missed by a multitude of medical specialties [12]. In symptomatic patients the absence of either a known primary cutaneous malignancy or microscopic PNI in the primary should not lead to the diagnosis of clinical PNS being dismissed. In our recent analysis of 50 consecutive cases of clinical PNS of cutaneous SCC treated with surgical intervention and post-op radiotherapy, no known or assessable primary was identified in over a third of patients and of those who had an index lesion no microscopic PNI was reported in almost half [13].

Diagnosis and Staging

Clinical PNS appears to occur in regions with high incidence of cutaneous malignancies with most of the published data coming out of Texas and Florida in the USA and Queensland in Australia [3–6, 14]. The age range in our series is variable (34 – 91 years) with a predominantly male incidence (82 %) [13]. Features of non-melanoma skin cancer (NMSC) considered high risk for PNI include large tumor size (>2 cm), cheek or mid-face location and tumors which are poorly differentiated and/or multiply recurrent [15]. The V and VII nerves are most commonly involved and may occur in combination. There is infrequent involvement of the great auricular nerve and the nerves of extraocular movement [16].

Usually the patient will present with a slowly progressive dysesthesia in the distribution of one of the branches of the trigeminal nerve. The complaint is commonly of formication (a sensation of ants crawling), which will spread many months later to the other branches of the trigeminal when the Gasserian ganglion has been invaded. Facial nerve involvement usually presents as slowly progressive facial nerve palsy with involvement of a peripheral branch prior to the whole nerve being paralyzed. This should be distinguished from the rapid involvement of all branches with a Bell's palsy.

High resolution focused magnetic resonance imaging (MRI or MR neurography) is accepted as the imaging modality of choice for large nerve spread as computed tomography (CT) will only pick up late disease such as bone erosion and/or foraminal expansion [9•, 17–19]. We find the zonal system as proposed by Williams et al. to be the best assessment of disease spread [9•]. This describes the spread of tumor along the nerve away from the main tumor specimen and is described in Table 1. Our experience is that MR neurography is good at defining the extent of the disease in 83 % of cases [19].

MRI will show intensity or enlargement of the involved nerve with some obliteration of surrounding fat planes at foraminal openings. In addition, denervation changes of involved motor nerves (V3, VII) cause T2 hyperintensity and abnormal enhancement with Gadolinium of the supplied muscles. We have seen this misinterpreted as primary pathology in the muscle.

There are reports in the literature of MRI negative assessments for clinic PNS disease, ranging from 22 – 47 %, which has made it difficult to compare treatment strategies [4, 20]. These patients fared much better than if the disease was identifiable on an MRI. Although not statistically significant, these patients had better local control rates (64 %) when compared to imaging-positive clinical PNS patients (38 %) at 5 years in a small study (n=21; p=0.67) [4]. Another study demonstrated significantly improved 5-year disease-specific survival when imaging-negative disease (100 %) was compared to imaging-positive disease (zone 1, 56 %, zone 2/3, 61 %) following surgery and/or radiotherapy (p=0.02)[20]. It is common for patients with surgical excision of a primary skin tumor to have dysesthesia post treatment. If the primary tumor had incidental perineural invasion this could then be misclassified as clinical disease. As the disease will be MRI negative and no further surgery will be undertaken, this would not be confirmed by surgical pathological analysis. There are no reports in the literature of reported MRI negative clinical PNS disease having a named nerve analyzed histopathologically.

In our recent analysis MRI was positive in over 95 % of cases. One case of early partial facial nerve palsy caused by disease in the peripheral branches of the VII nerve within an irradiated parotid bed was not detected. All patients with V nerve symptoms were identified on MRI [9•]. We feel to be classified as clinical PNS a patient must have (i) dysesthesia and a positive MRI, (ii) palsy in the setting of PNI, or (iii) histological proof of an involved named nerve.

The staging by the American Joint Committee on Cancer (AJCC) of all cutaneous malignancy with clinical PNS is T4 [21]. This is regardless of primary site or extension along the nerve. Specifically, T4 is for "perineural invasion of skull base" which accounts for zones 2 and 3 disease but not zone 1. We favor using a combination of size of primary to predict for regional nodal disease and the zonal system on imaging which has been shown to be a predictor of overall survival (p=.025) [3] (Table 1).

Table 1 Suggested staging of primary cutaneous malignancy and perineural invasion (adapted from AJCC 7th Edition). For nodal and metastasis staging, see AJCC criteria. (AJCC)

Tx	• Primary tumor cannot be assessed
T0	• No evidence of primary tumor
Tis	• Carcinoma *in situ*
T1	• Tumor 2 cm or less in greatest dimension with less than two high-risk features
	○ >2 mm thick, Clark level≥IV, perineural invasion, primary site ear or non-hair bearing lip, poorly differentiated or undifferentiated.
T2	• Tumor >2 cm in greatest dimension OR
	• Tumor any size and two or more high-risk features
T3	• Tumor with invasion of maxilla, mandible, orbit or temporal bone
T4	• Tumor with invasion of skeleton (axial or appendicular)
PN1	• Clinical PNI Imaging zone 1
	○ V1 (ophthalmic nerve) to the superior orbital fissure; V2 (infraorbital nerve) to the external aperture of the foramen rotundum; V3 (mandibular nerve) to the external aperture of the foramen ovale; VII (facial nerve) to the external aperture of the stylomastoid foramen.
PN2	• Clinical PNI Imaging zone 2
	○ 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.
PN3	• Clinical PNI Imaging zone 3
	○ Zone 3: All nerves: proximal to the ganglion, into the cisterns, or into the brain stem.

Treatment and Outcomes

Treatment depends on stage of disease, health of the patient and patient wishes. Cure with consideration of form and function is the goal. As with most advanced head and neck cancer surgical clearance and post-operative radiotherapy is the current standard of care [22]. In far advanced disease such as disease into the brainstem or gross intradural spread supportive care and/or palliation in the form of radiotherapy to the central component is recommended.

Surgical treatment is designed to remove en-bloc the involved nerves and distributions and to halt the central progression of the disease. As the retrograde or centrifugal spread of the disease is not common, it is not designed to remove this potential spread. Here, we rely on post-operative radiotherapy and reserve disfiguring surgery for salvage when subcutaneous nodular recurrence occurs. As the nerve is already non-functioning, the additional

morbidity is related to having extensive surgery rather than a new deficit.

Three features, as discussed above, support the design of operations to remove the disease: (i) the accuracy of current focused MRI in the assessment of tumor spread; (ii) the likely non-existence of skip lesions and (iii) the barrier function of the perineurium. As nerves travel antegrade or centripetally toward the brain branching also needs to be taken into account.

Our current surgical paradigm is outlined in Table 2. We believe there are limitations to surgical intervention and are cognizant of not disturbing barriers to spread, which can result in tumor, spread and decreased survival. We do not offer operations on MRI zone 3 disease but have fully resected pathological zone 3 disease not evident on MRI; however, patient numbers are too small to recommend guidelines. In addition, V1 tumor extending past the supraorbital ridge results in an orbital exenteration as we have not been successful in preserving orbits that require irradiation. Interestingly, orbits preserved following Gasserian ganglion resection without radiation to the globe have all avoided exenteration or lid closure.

In our first series of 21 consecutive immunocompetent patients (MRI-positive or histopathologically proven SCC) with clinical nerve spread treated with surgery +/− radiotherapy, the 5-year disease specific survival rate was 64.3 % with a 5-year local control rate of 64 % [23]. We have recently analyzed an extension of this homogenous group involving 50 consecutive patients with clinical PNS from SCC with outcomes that mirror these results [13].

We must, however, be aware of any change to the natural history of the disease with our current treatment policy. We know we have improved the control of central spread of disease and survival but we have observed an increase in delayed peripheral failure. One must ask whether improved cure rates and the additional time given to a patient with the change in failure, and its consequences, from central to peripheral is justified.

Radiotherapy plays a key role in the management of perineural spread yet there are no standardized recommendations of treatment. For cutaneous tumors with incidental PNI a margin of 2 – 3 cm is generally used provided vital structures such as the orbit are not nearby. With clinical PNS the cutaneous branches are covered and the named nerve irradiated back to the ganglion for zone 1 disease, to the prepontine aspect of the nerve for zone 2 and up to the brainstem for zone 3. In addition, recently, with the ready availability of intensity modulated radiation therapy (IMRT), consideration should be given to field coverage 2 – 3 cm across the facial midline, as we have seen six cases of delayed contralateral spread of disease (presentation between 6 months and 6 years), four of whom may have benefited from extended fields [24].

Regional nodal disease is uncommon with clinical PNS, occurring in 8 % of our series and 14 % of that reported by Balamucki et al. [6, 13]. This is probably related to the extent of the primary disease rather than the degree of spread in a nerve and is supported by the absence of lymphatics in nervous tissue [25, 26]. Regional nodes should therefore be addressed dependant on radiological findings and the clinical assessment of the cutaneous primary if present.

Current Research

Research is directed towards elucidating the mechanism of PNI and PNS. PNI is a poor prognostic indicator in several

Table 2 The surgical management of clinical perineural invasion. All patients are considered for radiotherapy (XRT) and most will receive a free flap reconstruction. Ptyergopalatine fossa (PPF), Infratemporal fossa (ITF), internal acoustic meatus (IAM), trigeminal nerve ophthalmic division (V1), maxillary division (V2), mandibular division (V3), facial nerve (VII)

Nerve Involved	Zone 1	Zone 2	Zone 3
V1	• to supraorbital ridge: resect nerve(s) • beyond ridge: orbital exenteration +/− superior orbital fissure	• include ganglion via a lateral craniotomy or transorbital approach	• XRT alone • consider subtotal resection
V2	• infraorbital nerve resection + PPF contents + maxillary division via transfacial (endoscopic or sublabial)	• include ganglion via combined anterior and lateral craniotomy approach	• XRT alone • consider subtotal resection
V3	• ascending mandibulectomy + ITF contents via combined superior and inferior approach	• include ganglion via a lateral craniotomy	• XRT alone • consider subtotal resection
VII	• radical parotidectomy + mastoid segment of VII	• include ganglion via temporal bone resection	• XRT alone • consider surgery: geniculate ganglion + surrounding dura + contents of IAM
VII + V3	• radical parotidectomy + ascending mandibulectomy + ITF contents via combined superior and inferior approach	• include ganglion via lateral approach and temporal bone resection	• XRT alone • Consider subtotal resection

other malignancies and the majority of molecular studies thus far have involved prostate and pancreatic cancer [27•, 28, 29]. The tumor microenvironment clearly plays an important role, with co-culture in vitro models suggesting that signals between tumor and nerve stimulate simultaneous tumor and neurite growth that culminate in invasion [28, 30]. These signals could include various growth factors such as nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) which have variously demonstrated over-expression in tissue specimens and cell lines [31]. The genetic factors remain unclear and our group is preparing for publication the results of whole genome expression profiling of cutaneous head and neck SCCs with microscopic and clinical PNI. This will hopefully contribute to the understanding of PNI mechanisms and ideally lead to the identification of novel biomarkers, which could be utilized in detecting those patients at risk of disease progression who would benefit from early intervention.

Conclusion

Perineural invasion and spread in head and neck cutaneous malignancy remains a difficult to treat problem with only moderate survival and potentially morbid treatment. It is still misunderstood by most of the specialties that come in contact with the disease resulting in delayed diagnosis and poorer outcomes. The greatly improved imaging techniques available with focused MRI should allow an improved pick up and earlier treatment.

Distinguishing between incidental (microscopic) and clinical disease will help direct research to more robust treatment recommendations for each of these groups. Studying the features of incidental PNI will guide the need for additional treatment to prevent local recurrence, while the genetic factors may lead to markers for those at risk of progression to clinical disease.

The accuracy of current MR imaging techniques and the understanding of patterns of spread supports the use of skull base techniques in trying to obtain clear surgical margins for improved survival. IMRT techniques give improved delivery of radiation therapy, allowing for greater preservation of critical structures and also allows consideration to be given to treat beyond the midline to prevent the contralateral spread of disease.

Finally, consideration should be given to modify the current staging system for NMSC, which essentially incorporates a method of metastasis into the primary classification. The tumor that has spread away from its primary deserves its own classification similar to that available for nodal (N) and metastatic (M) disease.

Disclosure No potential conflicts of interest relevant to this article were reported.

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