Surgical Management of Perineural Spread of Head and Neck Cancers

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Abstract

Keywords

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The surgical management of perineural spread of head and neck cancers has become an integral part in the contemporary treatment of this pathology. We now understand that tumour spreads within the epineurium and in a continuous fashion. We also can rely on the accuracy of magnetic resonance neurography in detecting and defining the extent of disease. With modern skull base techniques and a greater understanding of the anatomy in this region, specific operations can be designed to help eradicate disease. We review the current approaches and techniques used that enable us to better obtain tumour free margins and hence improve survival.

Introduction

Recognition and diagnosis of perineural invasion (PNI) and perineural spread (PNS) related to cancer can be difficult. It is often missed clinically and on pathological diagnosis. In cutaneous malignancy so-called “incidental” PNI is a subtype of the disease wherein the patient is asymptomatic. The diagnosis is typically the result of biopsy and/or surgical excision of the primary tumor with histological sectioning. A high index of suspicion is important.¹ When the tumor cell invades extensively enough to cause clinically apparent deficits in the involved nerve, it is referred to as “clinical” PNI or PNS. The trigeminal nerve (cranial nerve [CN] V) and facial nerve (CN VII) are the most commonly involved, and prognosis is typically poor.² Patients present with progressive nerve symptoms in the involved nerve distribution, such as numbness, paresthesias, facial palsies, and neuropathic pain. In addition, these large CNs provide a direct route to their respective ganglia and onto the skull base and central nervous system (CNS). There is evidence that V2 (maxillary branch of the trigeminal nerve) PNS from squamous cell carcinoma (SCC) of the cheek is most common with clinical PNI, however,

patients with V3 (mandibular branch of the trigeminal nerve) involvement may have worse outcomes in some reports.³

Classification and understanding of PNI are topics of debate. Staging of PNI by the American Joint Committee on Cancer recognizes all PNS that has invaded the skull base as T4. PNI in the primary tumor is staged as T1 or T2 depending on the presence of high-risk features.⁴ However, this system has limited use in clinical practice due to the fact that it fails to categorize the precise extent of invasion, which influences management and outcomes.⁵ Williams et al⁶ created a zonal system of classifying PNS based on magnetic resonance imaging (MRI) and the extent of retrograde (centripetal) perineural spread. Importantly, studies have shown that clinical PNI/PNS can be identified by MR neurography the vast majority of the time.^{7,8} Zone 1 for the trigeminal and facial nerves describes the involvement from the face to the superior orbital fissure for V1 (ophthalmic branch of the trigeminal nerve), and to the external apertures of foramen rotundum, foramen ovale, and the stylomastoid foramen for V2, V3, and CN VII, respectively. Zone 2 for all of CN V extends from zone 1 to the Gasserian ganglion, and for CN VII from

zone 1 to the lateral end of the internal auditory canal. The distinction of zone 3 refers to invasion proximal to the ganglion and into the cisternal segments of the nerves and brainstem, and this may result in CNS seeding when there is gross disease if resection is attempted. This zonal system provides an important framework for management and expected outcomes. A more in depth description of the zonal classification is available in the radiology article of this issue.

Management of PNS has also been a topic of study and debate. Different institutions have different approaches to management, with some advocating radiation therapy in place of surgical management due to the challenges involved.^{2,9} However, there is significant evidence that surgical resection followed by postoperative radiotherapy (PORT) leads to improved patient outcomes.^{3,5,8} This involves a diverse surgical team with appropriate experience, and there are several important features that must be learned and studied. The aim of this article is to discuss and outline the surgical management of clinical perineural spread by providing rationale, specific guidelines, evidence for its use, and outcomes with surgical treatment.

Surgery for Clinical Perineural Spread

Surgical management of PNS requires a multidisciplinary team involving otolaryngologists, neurosurgeons, and plastic/reconstructive surgeons. The zonal system by Williams et al is helpful in formulating a surgical plan. Following sound

oncologic principles, the goal of surgery is to excise the involved nerve and its branches en bloc with clear margins. With the proximal tumor invasion toward the skull base and brainstem, this can be a challenge. Nevertheless, in previous studies of PNS from SCC of the head and neck (SCCHN) treated with surgery and postoperative radiotherapy, patients with clear or close margins had significantly improved overall survival compared with those with involved margins.^{5,8}

In the past, "skip lesions," referring to the discontinuous spread of tumor cells presumably resulting from dissemination via perineural lymphatic vessels, were hypothesized. The literature demonstrates that PNS is most likely continuous, and skip lesions are probably the result of technical artifact from heterogeneous tumor burden along the nerve.¹⁰⁻¹² In a study by Panizza et al, the histopathological features of 51 tissue specimens from 49 patients with cutaneous SCCHN and clinical PNI were assessed with consecutive transverse and longitudinal sections. No skip lesions were identified and tumor spread was contiguous in all specimens. These findings suggest that skip lesions are unlikely to occur.¹² In addition, as the perineurium thickens as it approaches the skull base, we have documented its barrier to spread in the majority of proximal trigeminal and facial nerves.¹² This knowledge constitutes the fundamental justification that supports an aggressive surgical approach. As a tumor can spread at nerve branching points consideration needs to be given to en bloc resection in these regions. As examples the pterygopalatine fossa, superior orbital fissure, and infratemporal fossa need to

Table 1 Surgical management of perineural spread¹³

Nerve	Zone 1	Zone 2	Zone 3
V1	To supraorbital notch: resect nerve; ~1 cm beyond notch; orbital exenteration ± superior orbital fissure	Include ganglion via a lateral craniotomy or transorbital approach	XRT alone; consider subtotal resection
V2	Infraorbital nerve resection ± pterygopalatine fossa contents ± maxillary division via transfacial (endoscopic or sublabial)	Include ganglion via an anterior or lateral craniotomy approach	XRT alone; consider subtotal resection
V3	Mental to Inferior alveolar nerve: Mandibulectomy as required to clear involved nerve; if past mandibular foramen: ascending mandible and ITF contents via a superior and inferior approach	Include ganglion via a lateral craniotomy	XRT alone; consider subtotal resection
	Auriculotemporal nerve to inferior alveolar nerve: Ascending mandibulectomy + ITF contents as above; ensure lingual branch clear of centrifugal spread		
VII	Radical parotidectomy + mastoid segment of VII	Resect nerve as required to ensure 5 mm margin; via mastoidectomy to second genu; via an enlarged posterior tympanotomy to first genu (including chorda tympani) or via a temporal bone resection to include ganglion	XRT alone; consider surgery: geniculate ganglion + surround dura + contents of IAC
VII + V3	Radical parotidectomy + ascending mandibulectomy + ITF contents	Include ganglion via lateral approach and temporal bone resection	XRT alone; consider subtotal resection

Abbreviations: VII, facial nerve; IAC, internal auditory canal; ITF, infratemporal fossa; V1, ophthalmic branch of the trigeminal nerve; V2, maxillary branch of the trigeminal nerve; V3, mandibular branch of the trigeminal nerve; XRT, radiotherapy.

be en bloc resected with their respective nerves, V2, V1, and V3 when involved up to that region.

Clinical PNI or PNS, denotes tumor aggressiveness and carries a worse prognosis than incidental PNI, having invaded and spread along the nerve substantially enough to cause symptoms.² The natural history is central spread and failure, and the goals of surgery are to prevent that outcome while maintaining as much form and function as possible. It is also critical to encompass potential spread down side branches as discussed, which can result in diffuse disease. Due to the nature and disease location, however, these surgeries can be disfiguring. Surgery can involve subcranial resection, referring to resection without a craniotomy (i.e., transfacial resection), or skull base resection, when dissection proceeds intracranially. Preoperative evaluation with MR neurography and the utilization of the zonal system provides the primary framework for management. A study by Gandhi et al⁷ found that MRI correctly identified the extent of disease spread in 25 of 30 nerves (83.3%). This is important in both achieving complete tumor resection and allowing as much preservation of nerve and tissue as possible.

Once the zonal extend of the PNS has been defined, specific management can be considered. ►Table 1 summarizes our current thoughts on the surgical resection required based on

zonal extent and specific nerve(s) involved.¹³ All zone 3 extent, regardless of the nerve involved, should be managed on a case by case basis, but will often be treated with radiotherapy alone. This is due to the risk of introducing the tumor cells into the CNS with subsequent leptomeningeal spread and drop metastasis. Consideration of a subtotal preganglionic resection should be given for disfiguring disease or pain control in addition to any radiotherapy.

For CN V1, if PNS of the tumor is limited to the supraorbital nerve 1 to 2 cm beyond the supraorbital notch, the nerve is resected (►Fig. 1). For extent beyond this, the orbit is typically exenterated. Zone 2 invasion is managed with resection of the Gasserian ganglion via a lateral craniotomy or, as the orbit would have been exenterated for extensive zone 1 disease, a transorbital approach.

Management of V2 zone 1 spread involves resection of the infraorbital nerve including the pterygopalatine fossa contents as needed along with the maxillary division via an endoscopic or sublabial transfacial approach (►Fig. 2). This is the commonest nerve involved and carries minimal morbidity. The type of approach depends on previous surgery, or if there is a subcutaneous mass, which is seen in about half of the patients. Almost all patients present either having had a skin cancer removed months to years before or not having had

Fig. 1 Patient with clinical perineural spread in the supraorbital nerve. (A) Intraoperative markings of the proposed surgical resection; (B) dissection down to the supraorbital rim; (C) endoscopic intraorbital dissection of the supraorbital nerve; (D) final specimen including subcutaneous tissue.

Fig. 2 Endoscopic cadaveric dissection of the infraorbital nerve and pterygopalatine fossa. The extent of nerve resection usually undertaken via an anterior approach in a patient with V2 perineural spread is outlined. V2, maxillary branch of the trigeminal nerve; DPN, descending palatine nerves; GG, gasserian ganglion; ICA, internal carotid artery; SPA, sphenopalatine artery; SPG, sphenopalatine ganglion.

any identifiable skin cancer in the distribution of the nerve (see article “The Natural History and Treatment Outcomes of Perineural Spread of Malignancy within the Head and Neck” in this issue). If there is a previous scar then often it is easiest just to access the resection through this (►Fig. 3) or if there is a subcutaneous mass where skin will need to be resected and repaired via a cervicofacial rotation flap this corridor can be used (►Fig. 4). When there are no scars we prefer a sublabial transantral approach, which gives the appropriate trajectory in detaching the infraorbital nerve and drilling out the pterygoid base and medial middle cranial fossa floor. As almost all patients receive postoperative radiotherapy we are reluctant to perform a transnasal endoscopic Denker procedure as there is no need to remove the normal lateral nasal wall, which will lead to an exacerbation of posttreatment crusting. An anterior or lateral craniotomy is required for zone 2 spread to resect the Gasserian ganglion.

For V3 the main trunk is usually involved from the auriculotemporal branch, which supplies the auricle and skin in the temporal region. The nerve branching here is complex and requires an en bloc resection of the infratemporal fossa with special attention to ensure distal clearance of the inferior alveolar and lingual nerves if involved. Zone 1 surgery involves an ascending mandibulectomy with resection of the infratemporal fossa contents via a combined

Fig. 3 A 43-year-old patient with zone 3 perineural spread of squamous cell carcinoma along V2 with a previous cutaneous squamous cell carcinoma excised from his face 20 months prior. Old scar used as access point. (A) Arrow heads pointing to old scar; (B) scar outlined; (C) final specimen after combined anterior and lateral resection; arrow points to the distal infraorbital nerve and arrowhead to the preopontine trigeminal nerve. GG, Gasserian ganglion; PPF, pterygopalatine fossa; V1, ophthalmic branch of the trigeminal nerve; V2, maxillary branch of the trigeminal nerve; V3, mandibular branch of the trigeminal nerve.

Fig. 4 Patient with zone 1 perineural spread along V2 with a facial mass. (A) A cheek advancement flap was designed to cover the skin excised with the facial mass (M) and this was used as access point for the nerve; (B) final result after closing the defect; (C) final specimen; arrow points to the distal infraorbital nerve and arrowhead to the nerve transected at the dura after drilling out the foramen rotundum. V2, maxillary branch of the trigeminal nerve.

superior and inferior approach with preservation of the uninvolved VII nerve. This is accomplished via a frontotemporal preauricular cervical approach with detachment of the masseter muscle from the mandible to preserve the facial nerve. A mandibulotomy just above the angle from a cervical approach is combined with a subtemporal drill out from above to free the mandibular condyle and resect the V3 nerve. Zone 2 spread is managed via a lateral craniotomy performed to access the Gasserian ganglion (see article “Intracranial Management of Perineural Spread in the Trigeminal Nerve” in this issue). ▶ **Figs. 5** and **6** demonstrate zone 2 spread along V2/V3 branches.

Occasionally, the mental nerve is involved in tumors of the chin with direct spread into the inferior alveolar nerve (▶ **Fig. 7**). Once the tumor is into the inferior alveolar nerve spread preferentially occurs cranially but it can access the inferior dental nerve branches. Attempted stripping of the nerve will potentially leave microscopic disease in the mandible and we routinely resect that portion of the mandible en bloc to obtain clearance and reconstruct it with an osteocutaneous free flap. When the disease spreads to the inferior alveolar foramen resection just beyond the foramen with additional nerve is undertaken (▶ **Fig. 8**). If the spread is zone 2 then the whole hemimandible with the contents of the infratemporal fossa are resected.

CN VII involvement with zone 1 spread requires a radical parotidectomy, including the peripheral branches of the nerve, with resection of the mastoid segment of the nerve. The facial nerve as required will be resected for zone 2 disease, and this is best managed via a simple mastoidectomy up to the second genu and with a temporal bone resection beyond that. Facial nerve palsy is more likely to present early, when compared with dysesthesia, and as such the nerve involvement is often limited to the mastoid portion and is usually sampled at the second genu for frozen section confirmation. Should it be positive or suspicious the first genu can be reached via a posterior tympanotomy, which is larger than that for middle ear surgery as the fallopian canal is incorporated into the tympanotomy.

Importantly, simultaneous involvement of the trigeminal and facial nerves can occur due to their extensive communication.^{14,15} In our previous study,⁵ this occurred most commonly with V3. If this occurs, zone 1 extent is managed with radical parotidectomy with ascending mandibulectomy along with removal of the infratemporal fossa contents. The additional morbidity of surgical resection is surprisingly limited given that V3 and VII palsies already exist. Both ganglia should be resected with a lateral approach and temporal bone resection for zone 2 spread (▶ **Figs. 9** and **10**). (See article “Reconstruction of the Base of Skull Defect—Lessons Learned over 25 Combined Years” in this issue.)

Fig. 5 Preoperative MRI of a patient with perineural spread along V2/V3 extending to the Gasserian ganglion. (A) Axial contrast-enhanced T1 sequence demonstrating grossly enlarged V3 in the foramen ovale (white arrow) just anterior to the horizontal petrous carotid artery (black arrow); (B) axial contrast-enhanced T1 sequence demonstrating tumor filling the pterygopalatine fossa; (C) coronal contrast-enhanced T1 sequence demonstrating retrograde spread along the infraorbital nerve (black arrow) and the greater palatine (white arrow) necessitating en bloc resection of lateral nasal wall and posterior ipsilateral palate; (D) coronal contrast-enhanced T1 sequence shows tumor extending superiorly in V3 intracranially to Meckel cave (black arrow) and retrograde into V2 (white arrow). MRI, magnetic resonance imaging; V1, ophthalmic branch of the trigeminal nerve; V2, maxillary branch of the trigeminal nerve; V3, mandibular branch of the trigeminal nerve.

As discussed, PNS occurs retrograde (centripetal), but it can also occur anterograde (centrifugal) less commonly. This can potentially result in diffuse cutaneous spread as the tumor cells travel distally down the branches as nerve junctions are reached. The surgical team should not aim to remove the entire dermatome of potential cutaneous peripheral spread, which in our experience occurs infrequently and late in the disease process. Encompassing nerve branches with the goal of preventing spread is achieved with the dissection of the orbit, the pterygopalatine fossa, and the infratemporal fossa, when applicable. Any subcutaneous mass should be excised accordingly, however, resecting the entire dermatome of an involved nerve would be extremely disfiguring and should not be performed. We rely on radiotherapy to manage the distal spread of disease, and excise if and when there is distal recurrence which usually manifests as a subcutaneous mass.

Studies have varying results on the incidence of nodal metastases associated with PNS. Nonetheless, most reports have shown a low rate of nodal metastases, thus a neck dissection is recommended for neck-positive disease or if required as part of the reconstruction. This finding is also suggestive that the mechanisms leading to PNS are unique.^{3,8,16}

Outcomes

Past data on the treatment outcomes and the success of surgery for PNS have numerous limitations. Historically, there exist common misconceptions that interfere with appropriate study designs. Examples include varying definitions of incidental PNI and clinical PNI, failure to recognize the different behaviors of SCC versus basal cell carcinoma (BCC), varying treatment methodologies, unclear definitions on what actually constitutes PNI, and including patients with no evidence of PNS on MRI in a series of “clinical” PNS.^{6,17,18} This creates issues with an appropriate subgrouping of study participants, which skews study results. As mentioned previously, SCC carries an overall poorer prognosis, and the pooling of SCC and BCC participants may create inaccuracies. Errors also occur due to mistaking postsurgical numbness following surgical excision of skin cancer as clinical PNI, when, in reality it was not the tumor invasion that caused the symptoms.³ More relevant data are obtained with appropriate and clear study grouping.

Our group has published several reports that study PNS with scientifically relevant patient subgrouping.^{3,5,7,12} Included in these studies are patients who underwent surgical resection of clinical PNI along with their epidemiological

Fig. 6 Specimen and postoperative photos from the patient presented in ►Fig. 5. The resection encompasses the ipsilateral palate (preserving the premaxilla), lateral nasal wall, contents of pterygopalatine fossa and infratemporal fossa with final superior margin through V2/V3 portion of Gasserian ganglion. (A) Medial view of the surgical specimen demonstrating the margin through V2/V3 portion of Gasserian ganglion (white arrow) and the distal infraorbital nerve (black arrow); (B) lateral view of the specimen where the en bloc mandible, infratemporal fossa contents, and maxillectomy specimens can be seen, as well as the distal infraorbital nerve (black arrow); postoperative view of the patient and intraoral reconstruction on day 3 (C and D). V2, maxillary branch of the trigeminal nerve; V3, mandibular branch of the trigeminal nerve.

Fig. 7 Axial (A) and sagittal (B) contrast-enhanced fat-saturated T1-weighted images demonstrating perineural spread into the inferior alveolar nerve (arrows).

parameters and treatment outcomes. Panizza et al, in 2011,³ reviewed a prospective database of 21 patients who underwent surgery as their primary treatment modality and found a 64.3% 5-year disease-specific survival and a survival rate for the entire group of 90% at 4 years. In this cohort three complications arose: extradural hemorrhage, cerebrospinal

fluid leak, and wound infection, each requiring additional management.³ Solares et al⁵ reported on 29 patients undergoing surgery of SCCN PNI for curative intent, along with 7 patients receiving palliation. Patients undergoing subcranial and skull base resection had a 5-year disease-free survival of 50 and 53.6%, respectively, compared with 0% for those

Fig. 8 Mandibulectomy specimen from patient in ▶**Fig. 7**. Arrow head points to the proximal inferior alveolar nerve.

undergoing radiation and palliative therapies. Importantly, none of the patients treated with skull base resection had central recurrence, while all patients who received palliation had a central failure. An updated report published by Warren et al⁸ reviewed the PNS features and long-term survival of 50 consecutive patients who underwent surgery and postoperative radiotherapy for clinical PNI due to SCCHN. With surgery, 35 patients (70%) had clear central nerve margins and 5 patients (10%) had margins under < 5-mm clearance.

Overall survival at 5 years was 64%, and disease-specific survival was 75%. Overall, 10 complications arose. These included a wound breakdown ($n = 2$), radionecrosis ($n = 4$), corneal abrasion with resulting orbital exenteration ($n = 2$), and visual impairment due to microangiopathy from PORT ($n = 2$).⁸ An update on the Queensland Skull Base Unit figures can be found in article “The Natural History and Treatment Outcomes of Perineural Spread of Malignancy within the Head and Neck” in this issue.

As discussed above, surgery for PNS from SCCHN is large and complex. Complications do occur and should be managed as they arise. The price of surgery does compare positively with the improved survival rates provided.

Summary and Conclusions

The results discussed indicate that surgery for PNS of SCCHN offers beneficial survival and outcomes with an acceptable rate of complications. There are many factors to consider, and a patient should be thoroughly evaluated and appropriately imaged and staged before attempting surgery. Surgical treatments vary depending on the nerve involved and the zonal extent, with the ultimate goal of en bloc resection with clear margins for prevention of spread along other branches and to prevent central failure. Clear margins are associated with a better outcome and should be the ultimate goal. It is important to keep in mind when surgery should be avoided due to the good chance of failure and tumor spread (zone 3).

Fig. 9 Patient with zone 2 perineural spread along V3 and zone 1 spread along VII. (A) MRI demonstrating enhancement of V3 and VII (arrowheads); (B) facial flaps has been elevated, a temporal craniotomy has been performed and epidural dissection of the Gasserian ganglion is being performed; (C) microscopic view of the V2/V3 portion of the Gasserian ganglion being transected (white arrow); (D) final defect. The suction is pointing to the horizontal petrous internal carotid artery and the arrow to the cut end of the mandible. VII, facial nerve; MRI, magnetic resonance imaging; V2, maxillary branch of the trigeminal nerve; V3, mandibular branch of the trigeminal nerve.

Fig. 10 Patient with zone 2 spread along V3/VII. (A) Intraoperative view demonstrating temporal bone specimen completely mobilized; (B) lateral view of the surgical specimen with en bloc resection of the temporal bone (arrow), ramus mandibularis, infratemporal fossa, and neck dissection (double arrow); (C) view of the postoperative defect with the parapharyngeal (double arrow) and horizontal petrous carotid completely skeletonized (arrow). The arrowhead points to the cut end of the mandible; (D) immediate postoperative view demonstrating the soft tissue free flap reconstruction with a transverse rectus abdominus myocutaneous free flap (Photo courtesy: Dr. James Emmett, Plastic Surgeon); (E) immediate postoperative scan demonstrating absence of the temporal bone and the soft tissue free flap reconstruction. VII, facial nerve; XI, accessory nerve; XII, hypoglossal nerve; IJV, internal jugular vein; V3, mandibular branch of the trigeminal nerve.

Numerous studies have been discussed that attempt to appropriately draw conclusions on surgical treatment outcomes. Surgery combined with radiotherapy portends the best chance for success in zone 1 and zone 2 disease. Resulting histopathological findings feed into the postoperative radiation fields. The radiation oncologist, surgeon, and radiologist ultimately formulate this decision. Frozen section is a tool for intraoperative decision-making, but its use should be used cautiously as its accuracy can be limited.

Outcomes of surgery for PNS associated with SCCHN are positive, and offer the best survival benefit when combined

with postoperative radiotherapy based on the evidence. Skull base surgery for zones 1 and 2 spread may provide the best chance of preventing central failure. Patients may require orbital exenteration for V1 spread 1 to 2 cm past the supraorbital notch, although with radiation therapy it is difficult to preserve the function of the eye regardless. Corneal irritation from radiotherapy may result in the need for orbital exenteration postoperatively. Importantly, prior results show that surgery for SCCHN with PNS has a low-intraoperative mortality, with none of the patients experiencing perioperative deaths.

SCCHN associated with PNS is a complex phenomenon with many nuances. At the present time there is still discontinuity on treatment methods and the understanding of disease features. Further controlled studies with appropriately grouped cohorts are important but difficult as numbers treated are limited. However, the evidence is mounting that surgical treatment along with radiation for clinical PNS of SCCHN offers the best chance outcomes.

Conflict of Interest

None.

Financial Disclosure

None.

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