The Zonal Classification of Perineural Invasion in Head and Neck Malignancies: A Pictorial Review

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Learning Objectives

To understand the zonal classification system of perineural spread.

To appreciate the targeted MRI sequences required to diagnose perineural invasion within the head and neck.

To appreciate the implications of the degree of invasion on treatment options and patient outcomes.
Background

Australia has the highest rate of skin cancer in the world, with 2 out of 3 Australians diagnosed with skin cancer by the age of 70\textsuperscript{1}. Large nerve perineural spread (PNS) occurs when tumour spreads along the length of a nerve, typically proximally towards the skull base. The incidence of PNS is between 0.5% for basal cell carcinomas (BCCs) and 2-14% for squamous cell carcinomas (SCCs)\textsuperscript{2}. The commonest nerves to demonstrate large nerve perineural invasion are the branches of the trigeminal nerve and the facial nerve\textsuperscript{3}. Patients typically present with symptoms of formication (the sensation of insects crawling on or under the skin), which can progress to sensory loss, pain or motor deficits.

Clinical perineural spread refers to patients with radiological evidence of PNS or cranial neuropathy on physical examination as opposed to patients with incidental microscopic perineural invasion\textsuperscript{4}. These patients demonstrate lower rates of local control\textsuperscript{5} as well as higher rates of metastatic disease and a lower overall survival\textsuperscript{4,6,7}.

Previous studies have commented that patients with imaging negative PNS have a better prognosis that those with imaging positive disease\textsuperscript{4,7}. In our experience, false negative MRI for large nerve perineural spread is very uncommon and is more likely in small nerve (incidental) perineural disease. Paraesthesia and formication following treatment (surgical or radiation) but negative on MRI may also be due to the treatment rather than the disease itself. This type of disease is very different in extent, treatment and prognosis to true clinical, MRI and histopathology confirmed perineural spread in large nerves.

The zonal classification system of large nerve perineural spread in head and neck malignancies was originally described by Williams et al\textsuperscript{6} in 2001, in which the extent of perineural spread was divided into peripheral (zone 1), central/skull base (zone 2) and cisternal (zone 3) (Table 1 on page 4). The extent of disease is crucial in determining the management of the patient, with options including surgical resection, radiation or palliation.
Table 1: Zonal classification for perineural invasion in head and neck malignancies

Imaging Findings OR Procedure Details

Imaging Techniques

The radiological findings associated with PNS are subtle and require targeted imaging techniques to increase the rate of detection. Gandhi et al\textsuperscript{9} (2011) concluded that targeted MRI has a high rate of detection of perineural spread with a sensitivity of 100%. They also found a sensitivity of 83% in the classification of the zonal extent of PNS, with a tendency to underestimate the spread proximal to the Gasserian ganglion.

The recommended imaging technique includes high resolution (small field of view, thin collimation, high-resolution matrix) with the shortest possible acquisition times to limit patient movement, preferentially using a 3T platform. Routine sequences include T2 coronal fat suppressed, T1 axial and coronal, T1 axial and coronal fat suppressed post gadolinium. All sequences are acquired using 32 slices, at 2 mm slice thickness, 0.5 mm interslice gap and 18 cm FOV.

Imaging Findings

In imaging patients with suspected perineural spread, a combination of the clinical symptoms and signs, and primary tumour location assist in directing imaging to likely involved cranial nerves. It is important to have a working knowledge of the cranial nerves and all their branches, both in the clinical assessment and the imaging. Also, a close relationship with the clinician is integral in ensuring accurate assessment of PNS as often the presentation of these patients is complicated, with multi-modality treatment and protracted follow-up.

Finding Suggestive of Perineural Spread\textsuperscript{2,9,10}:

- Asymmetrical thickening of a nerve or ganglion
- Asymmetrical enhancement of a nerve or ganglion Fig. 11 on page 17
- Secondary denervation changes in the muscles of mastication or facial expression
- Loss of the perineural fat pad within a foramina containing a cranial nerve branch Fig. 10 on page 16
- Enlargement of the foramina.
- Enlargement and enhancement of the cavernous sinus or Meckel's cave. Fig. 13 on page 20
A series of images is presented, demonstrating the various zones of perineural spread of the branches of the trigeminal nerve as well as the facial nerve.

Facial nerve:

Zone 1 disease involves the extracranial branches of the facial nerve to the external aperture of the stylomastoid foramen. Fig. 1 on page 8

Zone 2 disease extends to the lateral end of the internal auditory canal, including the geniculate ganglion and the labyrinthine segment. Fig. 2 on page 8

Zone 3 disease extends through the IAC to the cerebellopontine angle cistern. Fig. 3 on page 9, Fig. 4 on page 10

Ophthalmic (V1) nerve:

Zone 1 disease extends to the superior orbital fissure. Fig. 5 on page 11

Zone 2 disease extends from the SOF to the Gasserian ganglion. Fig. 6 on page 12

Zone 3 disease extends proximal to the ganglion and into the cistern or brainstem. Fig. 13 on page 20

Maxillary (V2) nerve:

Zone 1 disease extends to the external aperture of the foramen rotundum. Fig. 7 on page 13

Zone 2 disease extends from foramen rotundum to the Gasserian ganglion. Fig. 8 on page 14

Zone 3 disease extends proximal to the ganglion and into the cistern or brainstem. Fig. 13 on page 20

Mandibular (V3) nerve:
Zone 1 disease extends to the external aperture of the foramen ovale. Fig. 8 on page 14, Fig. 9 on page 15

Zone 2 disease extends to the Gasserian ganglion.

Zone 3 disease extends proximal to the ganglion and into the cistern or brainstem. Fig. 12 on page 18, Fig. 13 on page 20

**Treatment options:**

By accurately determining the extent of PNS, the surgeons can plan an appropriate surgical approach in order to obtain clear margins and therefore improve the prognosis. Possible treatment options include surgical resection with post-operative radiotherapy, radiotherapy alone or palliation. At our institution, the treatment options are considered at a multidisciplinary meeting, taking into account the extent of disease as well as any patient's comorbidities which would preclude surgical options.

Once the PNS reaches beyond the Gasserian or Geniculate ganglia, it is considered inoperable. However, in patients with zone 1 or zone 2 disease, surgical resection with an aim to achieve clear margins followed by post-operative radiotherapy is considered the treatment of choice in order to improve survival and locoregional control. Jackson has also advocated that patients with clinical PNS receive maximal surgery, with high dose radiation, including the tumour bed, cranial nerve to the skull base, and the first echelon nodes. Garcia concluded that in patients with clinical or radiological evidence of PNS, the addition of elective radiotherapy to the first echelon nodes after surgery results in a reduction of treatment failure in the neck.
Fig. 1: Zone 1 disease of the facial nerve in a patient with adenoid cystic carcinoma of the parotid gland. Sagittal T1 post contrast fat suppressed image demonstrates enhancement and thickening of the facial nerve (red arrows), which extends towards, but not into the stylomastoid foramen (blue arrow).

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Fig. 2: Zone 2 disease of the facial nerve. Coronal T1 fat suppressed post contrast image shows enhancement of the mastoid portion of the facial nerve (red arrow) beyond the stylomastoid foramen.

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**Fig. 3:** Zone 3 disease of the facial nerve. Axial T1 fat suppressed post contrast image demonstrates perineural infiltration involving the geniculate ganglion and extending along the intracanalicular portion of the facial nerve towards the cistern.

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Fig. 4: Zone 3 disease of the facial nerve. Coronal T1 post contrast fat suppressed image (same patient as in Figure 3) demonstrates perineural infiltration of the styloid portion as well as the intracanalicular portion of the right facial nerve (red arrows).

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**Fig. 5:** Zone 1 disease of V1. Coronal T1 fat suppressed post contrast image demonstrates enhancement of the left supraorbital nerve.

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**Fig. 6:** Zone 2 disease of V1. Coronal T1 fat suppressed post contrast image shows enhancement and thickening of V1 within the superior orbital fissure.

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Fig. 7: Zone 1 disease of V2. Sagittal T1 fat saturated post contrast image demonstrates thickening and enhancement of the infraorbital nerve, extending along the floor of the orbit towards the foramen rotundum. There is also enhancement within the pterygopalatine fossa.

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Fig. 8: Zone 2 disease of V2. Coronal T1 fat saturated post contrast image demonstrates enhancement of V2 within the foramen rotundum.

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Fig. 9: Zone 2 disease of V2. Axial T1 fat suppressed post contrast (same patient as in Figure 8) demonstrates enhancement of V2 within foramen rotundum, but not extending into Meckels cave (blue arrow).

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Fig. 10: Zone 1 disease of V3 (inferior alveolar nerve). Axial T1 image demonstrates loss of the normal fat within the mandibular foramen on the left, with thickening of the inferior alveolar nerve (red arrow). Normal fat is seen in the right mandibular foramen (blue arrow).

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**Fig. 11:** Zone 2 disease of V3. Coronal T1 fat suppressed post contrast image demonstrates enhancement and thickening of V3 within the foramen ovale. There is associated T2 high signal within the pterygoid muscles suggesting denervation change and a necrotic tumour within the right parotid gland.

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**Fig. 12:** Zone 3 disease of V3. Coronal T1 fat suppressed post contrast image demonstrates widening of foramen ovale (blue arrow), with thickening and enhancement of V3 (red arrow), extending into Meckel's cave.

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<table>
<thead>
<tr>
<th>ZONE 1</th>
<th>ZONE 2</th>
<th>ZONE 3</th>
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<tbody>
<tr>
<td>V1 To the superior orbital fissure</td>
<td>To the Gasserian ganglion cistern</td>
<td>Into the cistern and brainstem</td>
</tr>
<tr>
<td>V2 To the external aperture of the foramen rotundum</td>
<td>To the Gasserian ganglion cistern</td>
<td>Into the cistern and brainstem</td>
</tr>
<tr>
<td>V3 To the external aperture of foramen ovale</td>
<td>To the Gasserian ganglion cistern</td>
<td>Into the cistern and brainstem</td>
</tr>
<tr>
<td>VII To the external aperture of stylomastoid foramen</td>
<td>To the lateral end of the internal auditory canal</td>
<td>Into the cistern and brainstem</td>
</tr>
</tbody>
</table>

**Table 1:** Zonal classification for perineural invasion in head and neck malignancies

**Fig. 13:** Zone 3 disease of the Trigeminal Nerve. Axial T1 fat suppressed post contrast image demonstrates enhancement and enlargement of the Gasserian ganglion extending into the nerve root entry zone in the preoptic cistern.

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Conclusion

As perineural spread is associated with worse outcomes, its' recognition in targeted imaging is important in order to direct appropriate treatment, as well as provide an accurate estimate of prognosis.

If perineural invasion is identified during the initial staging scans, a more comprehensive surgical approach and appropriate radiation fields can be planned. In all surgical procedures, the ideal goal is to achieve negative margins on intra-operative frozen section and formal histopathology.

The zonal system provides a useful framework to direct such treatment and prognosis. At present, zone 3 disease is considered inoperable and therefore accurate assessment of whether a patient has zone 1 or 2 disease versus zone 3 can have life-changing consequences.
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References