The Imaging of Large Nerve Perineural Spread

Mitesh Gandhi¹ Jennifer Sommerville²

¹ The Department of Radiology, Princess Alexandra Hospital and Queensland Xray, Brisbane, Australia

² The Department of Radiology, Princess Alexandra Hospital, Brisbane, Australia

Address for correspondence Dr. Mitesh Gandhi, MBBS, MRCP (UK), FRCP, FRANZCR, 83 Dunne Road, Burbank, Queensland 4156, Australia (e-mail: miteshalka@gmail.com).

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Abstract

Keywords

- ▶ magnetic resonance imaging
- ▶ perineural spread
- ▶ squamous cell carcinoma
- ▶ trigeminal nerve
- ▶ facial nerve

We present a review of the imaging findings of large nerve perineural spread within the skull base. The MRI techniques and reasons for performing different sequences are discussed. A series of imaging examples illustrates the appearance of perineural tumor spread with an emphasis on the zonal staging system.

Introduction

Large nerve perineural spread of malignancy (LNPNS) is a rare but lethal consequence of cutaneous malignancy in the head and neck. The high prevalence of cutaneous malignancy in Australia may explain the relative high numbers of patients who are imaged for this condition in Queensland.¹ In the past diagnosis of this condition was delayed due to a lack of awareness of this entity among both clinicians and radiologists, resulting in whole-brain imaging rather than focused interrogation along the anatomical pathways of the cranial nerves.² This article reviews the use of focused magnetic resonance imaging (MRI) (“MR neurography”) to diagnose and stage this condition, the appearances of perineural spread in various large nerves of the head and neck, the mimics that lead to false-positive diagnoses, and the role of imaging modalities other than MRI.

The diagnosis of LNPNS is often made months to years after the onset of unexplained neurologic symptoms. Symptoms may occur well before the condition is apparent on imaging. The converse is rare in our experience, in terms of LNPNS being apparent on imaging before the patient has symptoms. Dysesthesias along the course of the branches of the trigeminal nerve or an atypical “Bell palsy” should trigger the need for focused MRI although unfortunately many patients will initially have nondiagnostic computed tomography (CT) of the brain.

Magnetic Resonance Imaging Technique and Findings

“Focused” or “targeted” MR of the anatomical pathways of the cranial nerves is also known as “MR neurography” at the centers where the imaging is conducted. While not representative of the heavily T2-weighted MRI neurography as originally described in the literature,³ it is a catchy term that is remembered by clinicians and technicians and allows standardized imaging protocol to be applied for patients being investigated for suspected LNPNS. On both 1.5T and 3T platforms MR neurography shows a high sensitivity of between 95 and 100%.^{4,5}

One of the problems inherent with MRI is long procedure times during which patients have to lie as still as possible, which some patients find hard to tolerate. The resulting movement artifact significantly degrades the quality of the study. It is therefore in everyone's interests to curtail the imaging to a small number of crucial sequences seeking to answer the clinical question rather than detailed whole-brain and neck imaging as part of a fishing expedition.

MRI for LNPNS is optimally performed on 3T platforms allowing the relevant sequences to be performed in a shorter time and with greater resolution when compared with a 1.5T platform. A control study of LNPNS between 1.5T and 3T platforms has not been performed, but in our opinion and in the opinion of our referring clinicians, 3T imaging produces

aesthetically better images particularly with respect to the 3D-isotropic postgadolinium T1-weighted sequence and increases one's confidence in diagnosing and staging the disease.

At our institutions, patients who arrive with diagnoses of potential LNPNS on a 1.5T platform often have a repeat study on a 3T platform prior to surgery. This also raises the point that imaging should be performed within 1 month of surgery as the progression of LNPNS, although usually slow, can be unpredictable and patients initially deemed operable on imaging may be found, after a delay to surgery, to be either inoperable at the time of surgery, or progressed sufficiently to warrant a different surgical approach.

The anatomical coverage for imaging LNPNS is from above the roof of the orbits to the tip of the mandible on axial imaging. Coronal imaging is extended from the globes to the posterior margin of the temporal bones. This covers the trigeminal and facial nerves and their branches. The range of coverage is obviously extended in the few cases of LNPNS involving the cervical plexus and its branches.

Axial and coronal T1 sequences (slice thickness of 2mm with 0.4–1mm spacing, on a matrix of 240–320 pixels with a small field of view) are useful in visualizing asymmetry and infiltration of fat in the juxtaforaminal fat pads of the skull base⁶ and deep face namely the inferior alveolar foramina, the superior and inferior orbital fissures, the pterygopalatine fossae, and the stylomastoid foramina (►Fig. 1).

Coronal T2 fat-suppressed sequences (slice thickness 2 mm with 0.4–1mm spacing on a 240 × 320 matrix) are used to identify denervation changes⁷ in the muscles of mastication and facial expression (►Fig. 2). Denervation changes may be graded as acute (days-weeks), subacute (weeks-months), or chronic (months-years). These are indirect signs of LNPNS. Denervation initially leads to loss of autonomic control with edema of muscles (T2 hyperintensity with an increase in bulk and enhancement postintravenous contrast). Over a period of time, the degree of enhancement, bulk, and T2 hyperintensity decrease as the muscles become atrophic and replaced by fat (T1 hyperintensity, atrophy, and no enhancement). It is important, however, to recognize that

Fig. 1 Juxtaforaminal fat pads. Axial T1 (A) and coronal T1 (B) images demonstrate the normal fat pad in the left pterygopalatine (PG) fossa (red arrow) as compared with tumor infiltration of the right PG fossa (blue arrow). Coronal T1 (C) image illustrates the normal fat pad of the superior and inferior orbital fissures (blue arrow). There is LNPNS infiltrating the right side (red arrow). Axial T1 (D) image with the normal fat pad of the stylomastoid foramen (red arrow) versus tumor in the parotid with LNPNS to the stylomastoid foramen (blue arrow). Axial T1 (E) image with normal fat pad of the mandibular foramen (blue arrow) and LNPNS of the right mandibular foramen (red arrow).

Fig. 2 Denervation changes. Coronal T2 fat-saturated (fs) image (A) shows acute to subacute denervation change with T2 hyperintensity and edema in the muscles of mastication. Coronal T1 fs postcontrast image (B) demonstrates enhancement of the muscles of mastication. T2 hyperintensity and asymmetrical enhancement in the levator labii muscles (the muscles of facial expression supplied by the facial nerve) shown on coronal T2 fs (C) and coronal T1 fs postcontrast (D) images. Coronal T1 (E) shows chronic denervation change in the distribution of the facial nerve with atrophy of the muscles of facial expression on the left (red arrow). Axial T1 (F) shows chronic denervation changes in the distribution of V3 with fatty atrophy of the muscles of mastication.

these changes do not always occur in a sequential order contributing to an overlap in appearances. Identifying denervation changes may alert the radiologist to the existence of underlying LNPNS. In some cases in the past, the acute

denervation changes were mistaken for tumor infiltration and biopsied unnecessarily.

The key sequences are, however, the fat-suppressed post-gadolinium sequences⁸ that consist of a 2D T1 sequence (slice

thickness 2 mm with 0.4–1 mm spacing) and a 3D isotropic T1 sequence with axial, coronal, and sagittal reformats (►Fig. 3). Asymmetrical enhancement of the nerve is the key feature for a diagnosis of LNPNS. The 3D sequences that are now performed on 3T magnets reveal exquisite anatomical detail.⁹

Anatomy of Large Nerve Perineural Spread of Malignancy

The cranial nerves that are commonly involved in LNPNS in our experience and in the literature are the trigeminal nerve (V) and its branches and the facial nerve (VII).¹⁰ The individual nerves most commonly involved in our practice in decreasing incidence

include the infraorbital nerve (►Figs. 3–6), the frontal nerve (►Figs. 7 and 8), the facial nerve (►Figs. 9–11), the auriculotemporal nerve (►Fig. 12), the mandibular nerve (►Figs. 13 and 14), the inferior alveolar nerve (►Fig. 15), and the nasociliary (►Fig. 16) and lacrimal (►Fig. 17) branches of V1 in the orbit. The infraorbital nerve may be associated with a subcutaneous tumor nodule in the cheek (►Fig. 4) or nasolabial fold whereas the frontal nerve may be associated with a subcutaneous tumor nodule in the frontal scalp.

Rarely one sees LNPNS involving the greater auricular nerve¹¹ and the cervical plexus (►Figs. 18 and 19). We have seen one case of LNPNS involving the greater occipital nerve (►Fig. 20) and have identified LNPNS involving the buccal branch of the facial nerve (►Fig. 21).

The skull base radiologist needs to be alert to the possibility of bilateral LNPNS that occurs, albeit rarely, (►Fig. 14) either through multifocal cutaneous squamous cell carcinoma (SCC) or crossover across the front of the face. Skip lesions are rare in our experience (►Fig. 26) and we usually see enhancement of the nerve in continuity. LNPNS occurs both antegradely¹⁰ as well as retrogradely with respect to the nerves of the skull base.

There are anastomoses between the facial and trigeminal nerves at various junctions in the head and neck.¹² On imaging, the most frequently recognized anastomotic points are the auriculotemporal nerve¹³ in its retromandibular location and the greater superficial petrosal nerve,¹⁴ which is a connection between V2 and the geniculate ganglion of VII (►Figs. 22 and 23). Involvement of these sites can potentially lead to LNPNS involving both the trigeminal and facial nerves. However, there are other anatomically described

Fig. 3 3D isotropic reconstructions from a single postcontrast T1 fs acquisition on a 3T magnet showing zone 1 LNPNS of the infraorbital nerve with extension to the pterygopalatine fossa. Images were acquired in the coronal plane (A) and reconstructed into axial (B) and sagittal (C) images.

Fig. 4 Tumor nodule in the subcutaneous left cheek on an axial T1 image. This is often a pointer toward assessment of the infraorbital nerve for LNPNS.

Fig. 5 Axial T1 fs postcontrast showing zone 2 LNPNS of V2 with enhancement of the left V2 extending into the foramen rotundum.

Fig. 6 Zone 3 LNPNS of V2 on axial (A) and coronal (B) T1 fs postcontrast images, with tumor filling Meckel cave and extending along the preganglionic cisternal segment toward the root entry zone in the pons.

trigemino-facial anastomoses that one needs to be aware of—between the infraorbital nerve and the buccal and zygomatic branches of the facial nerve, the supraorbital nerve and the temporal branch of the facial nerve, the zygomaticofacial nerve and the zygomatic branch of the facial nerve, and finally the mental nerve and the facial nerve.¹⁵

Zonal Staging

Once the diagnosis of LNPNS is made on imaging, we stage the disease using the zonal classification system described by Williams et al.¹⁶

Zonal staging of LNPNS (► **Table 1**) allows the skull base surgeon to design the optimal procedure for surgical resection with clear margins. MRI correctly identifies zonal extent of spread in 86% of patients with LNPNS.⁴ The extent of spread in zone 3 disease is underestimated as MR neurography fails to identify microscopic disease in the cisternal segment of the trigeminal nerve. This is of importance as and when there is clear imaging evidence of LNPNS to the prepontine cistern, the patient is deemed as probably inoperable.

False-Negative and False-Positive Studies

Imaging negative LNPNS is rare but does occur especially in the very early stages of the disease, and strong clinical suspicion triggers either close interval follow-up imaging or biopsy of the suspected nerve.

False-positive studies (► **Figs. 24** and **25**) occur when other conditions mimic LNPNS on imaging, particularly viral neuritis, IgG disease, fungal infections, lymphoma, and granulo-

Fig. 7 3D isotropic reconstructions from a single postcontrast T1 fs acquisition with coronal (A), sagittal (B), and axial (C) images showing zone 1 LNPNS of the frontal branch of V1 to the superior orbital fissure.

Fig. 8 Zone 2 LNPNS involving V1 on a coronal T1 fs postcontrast image, with filling of the superior portion of the right cavernous sinus.

matous diseases such as sarcoidosis.¹⁷ Clinical suspicion guides either biopsy or close interval (6–8 week) follow-up.

The Use of Other Imaging Modalities

Other modalities may be used in conjunction with MRI in specific clinical settings. CT diagnosis of LNPNS is made at a relatively late stage when there is foraminal erosion and

Fig. 9 T1 fs postcontrast images in axial (A), sagittal (B), and coronal (C) planes. These are 3D isotropic reconstructions from a single acquisition on a 3T magnet, showing zone 1 disease at the stylomastoid foramen.

bulky mass lesions.¹⁰ CT may, however, be the only option in those patients with implants, which will move or malfunction in a magnetic field. However, in our experience it has not proved useful in identifying early LNPNS. In some situations the device or implant can be stopped or temporarily removed for MRI, for example turning off a pacemaker with a cardiologist in attendance to enable MRI.

CT may be used in the biopsy of equivocal cases particularly of lesions involving V3 in the foramen ovale (►Fig. 27). We have used ultrasound to perform fine needle aspiration of peripheral nerves suspected of involvement by LNPNS, particularly the auriculotemporal and the greater auricular nerves (►Fig. 28).

Diagnosis of LNPNS with positron emission tomography–CT (PET–CT) has been reported in the literature¹⁸; however, it has not been used routinely at our institutions. It has not proven useful in the skull base and around bone margins. FDG-avid LNPNS has been incidentally identified in our practice in the auriculotemporal nerve, (►Fig. 29) which lies surrounded by soft tissues in the retromandibular position and within the masticator space, but often shows a false-negative result. The diagnosis of LNPNS was known about in these cases from MRI studies. PET–CT may prove to have a role at this site and in the imaging of LNPNS involving peripheral nerves and the cervical plexus.

Fig. 10 LNPNS involving the left geniculate ganglion (red arrow) on T1 fs postcontrast images in axial (A) and sagittal (B) planes. Note the tumor in Meckel cave (blue arrow).

Fig. 11 Zone 3 LNPNS of the facial nerve into the internal auditory canal.

Fig. 12 LNPNS of the auriculotemporal nerve.

Fig. 13 Coronal T1 showing LNPNS involving V3 at the foramen ovale and extending into the gasserian ganglion, consistent with zone 2 disease.

Fig. 16 LNPNS involving the nasociliary branch of V1.

Fig. 17 LNPNS involving the lacrimal branch of V1.

Fig. 14 Bilateral LNPNS of V3 through the foramen ovale (zone 2 disease).

Fig. 18 LNPNS involving the cervical plexus and extending to the C2/3 and C3/4 foramina on the left.

Fig. 15 LNPNS involving the inferior alveolar nerve.

Interpretation and Collaboration

MRI studies performed for possible LNPNS are ideally read by radiologists with a skull base interest and an understanding not only of the mechanisms and routes of LNPNS but also knowledge of the potential therapeutic implications of the findings. The best results for the patient are achieved when the radiologist and the skull base surgeon can discuss the imaging together in conjunction with the clinical features and the clinician's level of suspicion. This is often done in an

Fig. 19 LNPNS involving the greater auricular nerve with a characteristic hair pin course around the posterior margin of the left sternocleidomastoid muscle toward the cervical plexus.

Fig. 20 LNPNS involving the greater occipital nerve.

Fig. 21 LNPNS involving the buccal branch of the facial nerve.

informal setting in the radiology department as well as in the formal setting of the Multidisciplinary Tumor Board. One cannot understate the importance of this close collaboration. The outcome of these discussions may vary depending on the level of the experienced clinician's suspicion and the positive or negative findings on the scan. For the patient, this may mean anything from a close interval follow-up (8–12 weeks), a radiological biopsy, a surgical biopsy with the intention to proceed to curative resection and radiotherapy, or palliative measures.

Challenges in Imaging to Improve Outcomes

The challenge in the primary imaging of LNPNS is to identify the disease process at a relatively early stage, thus allowing curative surgery and postoperative radiotherapy. This may be achieved by being able to recognize LNPNS consistently in

Fig. 22 Trigemino-facial anastomosis. Axial T1 fs postcontrast shows V2 in the pterygopalatine fossa (blue arrow). LNPNS extends via the vidian nerve and then the greater superficial petrosal nerve (red arrow) to the geniculate ganglion and the facial nerve.

Fig. 23 The auriculotemporal nerve (red arrow) is the most common trigeminofacial anastomosis involved in LNPNS. Axial (A) and coronal (B) T1 fs postcontrast images demonstrate tumor in the gasserian ganglion (A) (blue arrow) and in the mastoid segment of the facial nerve (B) (blue arrow).

peripheral nerves before the process extends to the skull base through knowledge of imaging defined anatomical locations and pathways (►Fig. 30). Secondly, improvements in MRI technique and resolution will no doubt play a large role in improving the detection of early LNPNS. Newer modalities such as PET-MRI and the use of tumor-specific radionuclide agents may revolutionize the imaging of LNPNS in the future.

Fig. 24 False-positive images in the infraorbital (A) and inferior alveolar nerves (B) in patients with a history of cutaneous SCC. Both were biopsied with a result of “chronic inflammation.”

Fig. 25 Mucormycosis ascending V3, a mimic of LNPNS.

Thirdly, the zonal staging of LNPNS may have to be refined to identify those patients with advanced zone 2 disease, who do not benefit from surgery.

The other challenge of LNPNS imaging is in the posttreatment patient. This important subject will be addressed in a separate article.

Key Points

1. The diagnosis of perineural spread on imaging is performed with high-resolution MRI techniques focused on the anatomical pathways of the cranial nerve branches rather than whole-brain and neck imaging.
2. The most important finding on MRI is asymmetrical enhancement and thickening of the involved nerve.

Fig. 26 Coronal T1 fs postcontrast image in a false-negative case. The change in the superior orbital fissure on the left (arrow) was not thought to be important in this patient with V1 signs but who also had no asymmetry of V1 in the orbit (A). Six months later the enhancement has progressed with extension into the cavernous sinus (B). A history of prior radiotherapy to the forehead and orbit emerged possibly explaining this radiologic “skip” lesion. True skip lesions are rare in our experience.

Fig. 27 CT-guided coaxial core biopsy of the foramen ovale.

Table 1 Zonal classification of perineural invasion in head and neck malignancy

	Zone 1	Zone 2	Zone 3
V1	To the superior orbital fissure	To the gasserian ganglion cistern	Into the cistern and brainstem
V2	To the external aperture of the foramen rotundum	To the gasserian ganglion cistern	Into the cistern and brainstem
V3	To the external aperture of foramen ovale	To the gasserian ganglion cistern	Into the cistern and brainstem
VII	To the external aperture of the stylomastoid foramen	To the lateral end of the internal auditory canal	Into the cistern and brainstem

Adapted from: Williams LS, Mancuso AA, Mendenhall WM. Perineural spread of cutaneous squamous and basal cell carcinoma: CT and MR detection and its impact on patient management and prognosis. *Int J Radiat Oncol Biol Phys* 2001;49(4):1061–1069.

Fig. 28 Ultrasound-guided FNA with a 25-gauge needle (red arrow) of the greater auricular nerve (blue arrow).

Fig. 29 PET-CT demonstrating FDG uptake along the auriculotemporal nerve (arrow).

Important ancillary findings are denervation changes in the muscles of mastication and/or facial expression.

3. The studies are ideally performed on a 3T magnet and may need to be repeated close to the time of surgery.

4. MRI is highly sensitive for the disease and can accurately stage the zonal extent of anatomical spread, thus allowing the design of an appropriate resection.

5. The optimal outcome for the patient is achieved through close collaboration between the skull base surgeon and radiologist.

Fig. 30 LNPNS involving a peripheral subcutaneous branch of the frontal nerve (red arrow) with retrograde spread to the frontal nerve in the orbit (blue arrow).

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