Perineural Tumor Spread Involving the Trigeminal and Facial Nerves: A Review of Critical Imaging Findings

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INTRODUCTION

Perineural spread (PNS) represents tumor dissemination along a nerve and is seen in 2-5% of head and neck cancers [1] with trigeminal nerve (CN V) and the facial nerve (CN VII) involvement being most common [2,3]. Head and neck malignancies represent a diverse group of neoplasms arising from the oral cavity, larynx, pharynx, salivary glands, and nasal passages. Head and neck cancers are responsible for approximately 4% of all malignancies in the United States [4]. Dissemination of head and neck cancers most commonly occurs through local extension and lymphatic spread to regional cervical lymph nodes with hematogenous and perineural spread being less common. Squamous cell carcinoma (SCC) represents approximately 90% of head and neck cancers and is the most prevalent head and neck tumor to have PNS with a reported incidence of 2-30% [5-7]. Given the prevalence of skin cancer, PNS is most commonly seen with cutaneous SCC. Adenoid-cystic carcinoma (ACC) constitutes 10% of salivary gland tumors but only makes up approximately 2% of head and neck cancers. ACC has the highest relative incidence of perineural dissemination with a reported incidence of approximately 60% [8-11]. Mucosal SCC including palatinal and nasopharyngeal carcinoma (NPC), lymphoma, melanoma, basal cell carcinoma, and other salivary gland tumors such as mucoepidermoid carcinoma are also known to demonstrate PNS [5,12,13].

Even though PNS is a well-known and documented method of spread of head and neck cancers, it remains often overlooked and underdiagnosed on routine preoperative and surveillance imaging. Perineural spread significantly impacts prognosis and management of head and neck carcinomas. Appropriate and optimal treatment of head and neck cancers requires scrutiny of preoperative imaging studies for evidence of PNS prior to initiating therapy. Perineural spread almost always alters treatment and management of head and neck carcinomas. Overlooking and failing to detect PNS on preoperative imaging studies can result in unnecessary or inadequate surgery and ineffective therapy. Radiologists and clinicians involved in the care and management of head and neck cancer patients must be vigilant for imaging or clinical evidence of PNS. Radiologists need to be familiar with the regional anatomy and distribution of the branches of the trigeminal and facial nerve and the imaging findings of PNS. Clinicians must be aware of the common presenting symptoms of PNS and be able to differentiate these symptoms from other benign causes such as Trigeminal neuralgia and Bell’s palsy.

Perineural spread (PNS) and Perineural invasion (PNI)

Perineural spread must be differentiated from perineural invasion (PNI). These are not interchangeable or equivalent terms. Perineural invasion cannot be visualized with imaging and represents microscopic tumor in or around nerves at the primary tumor location. PNI does not imply tumor spread or dissemina-

Keywords
- Perineural tumor
- Larynx
- Pharynx
- Head and neck cancers
tion of tumor from the primary site of origin. Histologically, PNI can be diagnosed when the primary carcinoma has direct contact
with the perineurium of a nerve, surrounds a nerve, and/or demon-
strates neural invasion [14]. Perineural spread and perineural
tumor spread (PNTS) are equivalent terms describing true spread
or dissemination of tumor along a nerve. PNS represents macro-
scopic disease and can be visualized with imaging and is best
visualized and evaluated with magnetic resonance imaging (MRI)
rather than computed tomography (CT) [2,3].

Clinical Significance

Both PNI and PNS adversely affect prognosis resulting in de-
creased survival. The 8th edition of American Joint Committee on
Cancer now recognizes that perineural tumor invasion is part of
the T category for SCC elevating the lesion to T3 classification.
Patients with Perineural spread have a higher incidence of regional
lymph node metastases, local recurrence, and distant metastases
[15-19]. Patients with both clinical symptoms and imaging evi-
dence of perineural spread have the highest rates of local recur-
rence and lower rates of disease specific survival [15]. If PNS is
confirmed or is suggested on preoperative imaging, the extent of
surgical resection necessary to obtain clear surgical margins will
be altered, and adjuvant therapy, neck dissection, and/or a larger
radiation field will need to be considered [5,8,18-20].

Pathogenesis

The mechanism of perineural tumor spread is still not com-
pletely understood. Perineural spread was once thought to rep-
resent spread via direct invasion along low resistant planes or
through lymphatics of the epineurium. It is now known that perineural
spread is not related to direct invasion, hematogenous dissemination
or lymphatic dissemination [14,15]. Currently, it is believed that perineural dissemination is a complex reciprocal
interaction between the tumor and the nerves themselves [14].
There are many potentially important molecular factors involved
in this interaction including neurotrophic factors like nerve
growth factor, brain derived nerve growth factor, neurotrophins,
growth factors and axonal guidance molecules [15,21,22]. The
neoplastic must be able to respond appropriately to these sig-
nals from the neural microenvironment to disseminate along the
nerves [15]. This microenvironment is currently thought to be
one of the key determining factors in PNS with in vitro models
suggesting that reciprocal signals between tumor and nerve are
necessary to stimulate and promote PNS [8,23-27].

Critical Anatomy and Clinical findings

The anatomy as well as the sensory and motor functions of the
trigeminal and facial nerve is intricate and complex. Detection and
diagnosis of PNS requires vigilance and a heightened awareness of
PNS by radiologists and clinicians in combination with a basic
understanding of the anatomy and physiology of the trigeminal
and facial nerve. While up to 40% of patients with PNS are asym-
ptomatic, common sensory symptoms of PNS include formication,
pain, paresthesia, and numbness in the distribution of the trigemi-
nal nerve. Motor symptoms include trouble swallowing and weak-
ness in the muscles of mastication when the mandibular division
of the trigeminal nerve is involved and weakness in the muscles of
facial expression when the facial nerve is involved [28-30]. Clin-
cal symptoms from trigeminal and facial nerve PNS are nonspec-
ific and can overlap common clinical findings of entities such as
trigeminal neuralgia, Bell’s palsy, and stroke. It is critical for the
treating clinician to include PNS in the differential diagnosis of
pain, paresthesia, and numbness in patients with a current or past
history of head and neck cancer to avoid unnecessary delay in the
diagnosis and treatment of perineural tumor spread.

Trigeminal Nerve

PNS most commonly involves the trigeminal nerve secondary
to its large cutaneous distribution [28,31]. CN V is a mixed mo-
tor and sensory nerve which relays sensory information from the
face and head and provides motor input to the muscles of mastication
(masseter, medial and lateral pterygoid, and temporalis). The
trigeminal nerve arises from the mid pons and enters Meckel’s
cave, a CSF-containing pouch in the middle cranial fossa at the
posterior lateral aspect of the cavernous sinus (CS). In the anterior
portion of Meckel’s cave the nerve forms the trigeminal (Gasse-
rian) ganglion [32]. Arising from the trigeminal ganglion are the
three divisions of the trigeminal nerve: the ophthalmic (V1), the
maxillary (V2), and the mandibular nerve (V3).

The ophthalmic nerve is a pure sensory nerve which courses
through the lateral wall of the cavernous sinus and passes through
the superior orbital fissure (SOF) to reach the orbit and provide
sensory innervation to the eye, orbit and forehead [33]. In Figure
1, a cutaneous carcinoma of the forehead spreads along the right
supraorbital nerve (branch of V1) thru the SOF to the cavernous
sinus. Axial noncontrast T1-weighted (T1W) imaging demon-
strates abnormal intermediate signal in the normal high signal
intensity fat along the right supraorbital nerve in the superior and
medial quadrant of the right orbit. The perineural tumor enhances
with contrast on T1W fat suppressed images.

The maxillary nerve (V2) is also a pure sensory nerve and
courses more inferiorly to V1 in the lateral wall of the cavernous
sinus. It exits the middle cranial fossa via the foramen rotundum
(FR) and enters the pterygopalatine fossa (PPF). In the PPF, the
maxillary nerve gives rise to the infraorbital nerve (ION) which
enters the orbit through the inferior orbital fissure (IOF). It cours-
es along the inferior aspect of the orbit to exit through the in-
traorbital foramen and provide sensation to the middle 1/3 of the
face including the upper lip, medial cheek, and nose [33]. Figure
2 and 3 demonstrate perineural tumor involving V2. In Figure 2,
perineural tumor involves a markedly enlarged ION on the right.
Figure 3 demonstrates perineural tumor involving right V2 from
the pterygoid palatine fossa to foramen rotundum and the cavern-
ous sinus without enlargement of the nerve. This case also dem-
onstrates involvement of the vidian nerve (branch of VII) which
will be discussed later.

The mandibular nerve (V3) is the largest trigeminal division
and is a mixed nerve providing motor input to the muscles of mastication as well as sensation to the lower 1/3 of the face including
the chin, lower lip, floor of mouth, and the side of the head [33].
It is the only branch of the trigeminal nerve that does not course
through the cavernous sinus. After branching from the trigeminal
ganglion, the mandibular nerve immediately courses inferiorly
through the foramen ovale (FO) into the infratemporal fossa (ITF).
Within the masticator space (MS), the mandibular nerve gives off
most commonly spreads in a retrograde fashion from the primary tumor toward the central nervous system (CNS). PNS can also disseminate in an antegrade direction away from the CNS [15,34-36]. Figures 6 and 7 illustrate bidirectional perineural tumor spread. In figure 6, a parotid gland neoplasm extends along the auriculotemporal nerve (branch of V3) in a retrograde direction to the masticator space extending to the level of the posterior trunk division of the mandibular nerve into the auriculotemporal and inferior alveolar nerve. The perineural spread continues in a retrograde direction along the mandibular nerve to the skull base and foramen ovale but also spreads in an antegrade direction to the mandible along the inferior alveolar nerve. Figure 7 demonstrates both retrograde and antegrade PNS by a lip carcinoma. The primary lip carcinoma extends in a retrograde fashion along branches of V2 thru the infraorbital canal to PPF and continues thru foramen rotundum to involve the cavernous sinus, gasserian ganglion, and cisternal segment of the left trigeminal nerve. Perineural tumor then spreads along V3 in an antegrade direction thru foramen ovale along the left mandibular nerve.

**Facial Nerve**

The facial nerve controls the muscles of facial expression, and functions in conveying taste from the anterior two-thirds of the tongue and oral cavity. CN VII arises from the mid pons and courses through the cerebellopontine angle cistern to enter the internal auditory canal. It continues through the petrous portion of the temporal bone until it exits the stylomastoid foramen where it eventually pierces the parotid gland fascia and divides into its five terminal branches [37]. In figure 8, PNS involves the left facial nerve from the stylomastoid foramen to the IAC.

**Communications between the Trigeminal Nerve and the Facial Nerve**

There are extracranial communications between the facial and trigeminal nerve which can serve as pathways for PNS to involve both nerves. These patients can have both trigeminal and facial nerve symptoms from PNS. There are three major connec-

The anterior motor branches which innervate the muscles of mastication. The posterior trunk divides into the auriculotemporal nerve (ATN) and the inferior alveolar nerve (IAN). The auriculotemporal nerve provides sensory innervation for the lateral face. The inferior alveolar nerve enters the mandibular foramen (MF) and provides sensory information to the lower teeth and gingiva while traversing the mandibular canal and exiting the mental foramen to supply sensory information to the chin. The auriculotemporal nerve and inferior alveolar nerve are critical terminal branches of V3. Figures 4 and 5 demonstrate PNS extending from cutaneous SCC along right supraorbital nerve (blue block arrows) in the superior orbit thru the superior orbital fissure to cavernous sinus (white block arrows). Note that the tumor is seen best on noncontrast T1W images (A,C,G) because the normal high signal intensity (white) fat has abnormal intermediate signal intensity (dirty fat).

Perineural tumor can disseminate in either a retrograde or antegrade direction and can be bidirectional. Perineural tumor would spread along the posterior trunk division of the mandibular nerve into the auriculotemporal and inferior alveolar nerve. The perineural spread continues in a retrograde direction along the mandibular nerve to the skull base and foramen ovale but also spreads in an antegrade direction to the mandible along the inferior alveolar nerve. Figure 7 demonstrates both retrograde and antegrade PNS by a lip carcinoma. The primary lip carcinoma extends in a retrograde fashion along branches of V2 thru the infraorbital canal to PPF and continues thru foramen rotundum to involve the cavernous sinus, gasserian ganglion, and cisternal segment of the left trigeminal nerve. Perineural tumor then spreads along V3 in an antegrade direction thru foramen ovale along the left mandibular nerve.

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Figure 3 A-L: T1W axial MRI with (A,C,I,J) and without (B,D) contrast, T1W coronal CE FS (E-H), and T1W sagittal CE FS images demonstrate PNS involving the right PPF (blue block arrow). Note the normal fat filled PPF on the left with abnormal enhancing soft tissue within the right PPF. Tumor extends along V2 thru foramen rotundum (small white arrows) to cavernous sinus (white block arrow) as well along vidian nerve (white block arrow) to involve the facial nerve (black block arrow) in the temporal bone and IAC.

Figure 4 A-D: Axial T1W MRI without (A) and with (B) contrast, axial T2W FS, MRI (C) and axial CT (D) images demonstrate PNS from NPC involving V3 (blue block arrow). The left mandibular nerve is enlarged and shows abnormal increased T2 signal and enhancement. The osseous foramen ovale is widened on CT.

Figure 5 A-D: Axial (A,B) and coronal (C,D) T1W CE FS MRI images demonstrate PNS extending along V3 thru foramen ovale (blue arrow) to involve the cavernous sinus (white block arrow), the Gasserian ganglion (white small arrow) and cisternal segment of the right trigeminal nerve (black block arrows).

3. Infraorbital nerve (branch of V2) and the buccal branches of the facial nerve forming the infraorbital plexus [29,38].

The pterygopalatine ganglion is the most recognized neural communication between the trigeminal and facial nerve [3]. The maxillary branch of the trigeminal nerve courses through the pterygopalatine fossa synapsing with the pterygopalatine ganglion before continuing thru foramen rotundum to the cavernous sinus. The facial nerve gives rise to the greater superficial petrosal nerve (GSPN) in the petrous temporal bone, which courses an-

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- **1. Maxillary nerve** and the vidian nerve (branch of VII) in the pterygopalatine fossa.

- **2. Auriculotemporal nerve** (branch of V3) and the facial nerve in the parotid gland.
teromedially to exit the superior surface of the temporal bone. It continues as the vidian nerve in the pterygopalatine canal to enter the pterygopalatine fossa where it synapses with the pterygopalatine ganglion. In figure 3, perineural tumor spreads along the right maxillary nerve to the PPF and continues along V2 to the cavernous sinus but also extends along the right vidian and GSPN to involve the facial nerve in the temporal bone and IAC. PNS involving the vidian nerve is underappreciated and underdiagnosed. In 2000, a retrospective analysis of the CTs and MRIs of 98 untreated patients with head and neck cancer, revealed 10 patients with PNS of the vidian nerve [2].

The auriculotemporal nerve arises from V3 has several connections with the facial nerve in the parotid gland providing another neural connection that allows PNS to involve both the facial and trigeminal nerves (figure 6). Clinically, in the setting of perineural spread along the auriculotemporal nerve, the patient can present with periauricular pain, temporomandibular joint (TMJ) dysfunction or TMJ tenderness [29].

Imaging

In patients with head and neck cancer, imaging is crucial to the diagnosis of perineural dissemination, evaluating the extent of the disease, guiding treatment, and post treatment surveillance. MRI with contrast is the gold standard for detecting and evaluating perineural tumor spread with a reported sensitivity of 95% [39,40]. CT can also demonstrate findings of PNTS and is best utilized to evaluate for widening of osseous skull base foramen. While FDG PET/CT has limited special resolution for the evaluation of perineural dissemination, PNS can be diagnosed on FDG PET/CT [5].

The key imaging findings of PNS are as follows:

Abnormal enhancement (figure 3,8) and/or enlargement (figure 2,4,5) of a nerve or abnormal linear or curvilinear enhancement (figure 6) along the course of cranial nerve V or VII. Contrast enhanced (CE) and fat suppressed (FS) T1W MR images (T1W CE FS) are best to evaluate for abnormal enhancement and enlargement of a nerve (figure 3-6) and is the key sequence to diagnosing perineural tumor spread on imaging [2,41].

Loss of normal fat planes that surround cranial nerves (Figures 1,6,7). Cranial nerves within and below the skull base foramen normally have fat surrounding the nerve. The loss of the normal fat around cranial nerves within and/or below the skull base foramen is an important secondary sign of PNS [42,43]. This finding can be seen on both CT and MRI and when interpreting scans on head and neck cancer patients, a routine imaging search must include visualizing normal fat surrounding the branches of the trigeminal nerve at the skull base foramen and fissures. For the trigeminal nerve this includes the foramen ovale and rotundum, as well as the superior and inferior orbital fissure, and the pterygoid palatine fossa (Figure 3). Precontrast T1-weighted
(T1W) MR images without fat suppression is the best sequence for evaluating the fat planes surrounding the nerves. On T1W imaging, fat has homogeneous high signal intensity. When perineural tumor spreads along the nerve, there is loss of this normal high signal intensity and the fat appears "dirty" with areas of abnormal decreased signal indicating tumor infiltration (figure 1,3).

Expansion of a fossa or canal that contains a nerve (Figures 2,4). CT is the best imaging modality for evaluating osseous structures [44,45] (figure 2). The foramen rotundum and foramen ovale should be closely inspected for enlargement which would indicate PNS [2,41].

Findings related to the denervation of the muscles of mastication or facial expression. When PNS involves a lower motor nerve there are imaging patterns that develop depending on the chronicity of denervation which are best visualized on MRI [44,46]. Acute muscle denervation is seen as intramuscular edema with associated muscle enlargement and is best seen on T2-weighted imaging (Figure 9). In the subacute stage, the muscles will demonstrate milder intramuscular edema on T2-weighted imaging with no muscle enlargement. Chronic denervation results muscle atrophy and fatty infiltration of the involved musculature [45-47] (Figure 10). Chronic denervation can also be seen on CT as asymmetrical muscle atrophy.

CONCLUSION

PNS has significant prognostic and therapeutic implications and is a well-known mechanism of head and neck cancer dissemination that has been adequately described in the literature but is too often overlooked and undetected on routine imaging studies. Vigilance and a heightened awareness of PNS by clinicians and radiologists are critical to avoid unnecessary delays in the diagnosis of perineural spread in head and neck cancer patients. Common symptoms such as facial pain, paresthesia, and motor deficits must not mistakenly be attributed to other etiologies such as trigeminal neuralgia, Bell’s palsy, or stroke. Imaging studies must be appropriately protocoled and scrutinized for evidence of PNS so that subtle imaging findings of perineural spread are not overlooked. While perineural spread can be suspected clinically, PNS is an imaging diagnosis. Assessment and detection of perineural spread should be considered a routine part of the imaging evaluation of the head and neck, and the responsibility of detecting perineural spread belongs to the radiologist protocoling and interpreting the imaging study. Evaluating for evidence of PNS must be considered as important as delineating the primary tumor or detecting metastatic cervical lymph nodes on imaging studies of head and neck cancer patients. Knowledge of the position, expected course, and key anatomic landmarks of the major divisions and branches of the trigeminal and facial nerve are essential in detecting and diagnosing perineural tumor spread. Radiologists must be diligent in their search for perineural spread when reviewing imaging studies of head and neck cancer patients.

REFERENCES


