Imaging of Perineural Spread in Head and Neck Cancer

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KEYWORDS

• Perineural spread • Perineural invasion • Head and neck cancer • Skull base imaging

KEY POINTS

- Perineural spread (PNS) of tumor is a recognized pattern of metastasis occurring in the head and neck.
- Imaging plays a critical role in identifying PNS for adequate staging and treatment planning.
- Understanding the major branches and pathways of cranial nerves V and VII, key anatomic landmarks, interconnections between these nerves, and pearls and pitfalls of PNS imaging can aid in early detection, appropriate therapy, and the best possible chance for cure.

INTRODUCTION

Perineural tumor growth is a recognized pattern of malignant tumor metastasis occurring along the potential space between the nerve and the surrounding sheath. It is important to differentiate between perineural tumor spread (PNS) and perineural tumor invasion (PNI) whenever possible, as they are frequently used interchangeably in the literature and clinical practice. This interchange leads to ambiguity regarding their implications, although such differentiation may not always be feasible or accurate. We define PNS as the macroscopic tumor extension away from the primary tumor site detectable by imaging and PNI as a diagnosis made on histology, typically in a specimen including the primary tumor. Much of what is known about the prognosis and incidence of perineural tumor growth comes from pathologic studies investigating PNI, which we apply to PNS because this is done broadly in the literature and at some point they exist on the same spectrum.

The overall frequency of PNI in head and neck cancers has been reported in the range of 2.5% to 5.0%,[1] with PNS suspected to be lower. Such nerve involvement can be seen in all head and neck cancers, but certain tumors demonstrate a particular proclivity for this method of metastasis and should prompt the careful attention of the radiologist. The most commonly encountered histology is mucosal (5%) or cutaneous (5%–14%) squamous cell carcinoma (SCC), given that it is by far the most common head and neck malignancy, accounting for up to 95% of the approximately 650,000 head and neck cancers diagnosed each year worldwide.[2] The most common sites of mucosal SCC are the larynx, oral cavity, and the tonsils.[3] Adenoid cystic carcinoma (ACC) of the minor or major salivary glands is probably the most notorious offender, with reported rates of PNI in up to 50% of cases, although it comprises only 1% to 3% of all head and neck malignancies.[4] Basal cell carcinoma (BCC), melanoma, especially the desmoplastic type (1%–2%), mucoepidermoid carcinoma, and lymphoma round out the list of additional culprits.[5]

Only 30% to 40% of patients with PNI are symptomatic at presentation,[2] but the percentage is likely higher in clinical PNS, as noted in a series

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of patients with skin cancer in which 59 of 62 patients with PNS were symptomatic.[6] Symptoms include pain, paresthesias, dysesthesias, weakness, or paralysis. Symptoms attributed to multiple nerve distributions suggest more central involvement, such as the cavernous sinus, spread from one cranial nerve (CN) to another, or leptomeningeal disease.[7,8] As in most cases, the clinical history is important to guide a careful search pattern for PNS. The clinical scenarios with which PNS presents include the following:

1. At the time of diagnosis of a primary head and neck malignancy. In this setting, PNS-specific symptoms are often absent or overshadowed by symptoms related to the primary tumor.
2. Recurrence of a previously treated tumor. In this setting, symptoms usually precede imaging diagnosis, although occasionally PNS demonstrated on imaging may be the only manifestation of recurrent disease.
3. Symptoms such as pain, paresthesia, or diplopia with no known primary tumor. Because this presentation is rare and the primary tumors are often occult, patients are frequently misdiagnosed as having, for example, trigeminal neuralgia.

The risk of developing PNI in skin cancer is higher in poorly differentiated tumors, larger primary tumor size, male gender, history of recurrence after treatment, and midface location.[9] PNI is also associated with the increased risk of local recurrence and portends a poor overall outcome with the likelihood of residual disease proportionate to the proximal extent of the tumor[6] and the diameter of the involved nerves.[10] The 5-year local control rate in one series was 25% in patients with skin carcinoma with PNI.[6] Thus, the identification of PNS has important therapeutic and prognostic implications and is critical for adequate staging and treatment planning. Changes in planned treatment may include expansion of the radiation field and/or the surgical resection; for example, the need for mastoidectomy and/or temporal bone resection in case of a parotid tumor with PNS extending into the facial canal. Failure to identify early perineural disease may delay or prevent potentially curative treatment. Knowledge of the commonly involved nerve pathways and vigilance in assessing key landmarks can allow for accurate assessment of disease extent and allow for the best chance of obtaining durable control of the disease.

GROWTH PATTERN AND PATHOPHYSIOLOGY

The pattern of growth in PNS most commonly occurs in a contiguous retrograde fashion from the primary tumor or resection site toward the intracranial cavity, although it may spread in an antegrade direction as well. Early tumor growth is described as preferentially spreading along the axis of the nerve greater than concentric growth.[1] This may explain why some patients with PNS are initially asymptomatic, as concentric growth results in compression of the nerve fibers and the previously described symptomatology. Nerve enlargement may eventually expand or erode the skull base canals and foramina. In addition, "skip" or "resurfacing" lesions with sites of tumor separated by uninvolved nerve may be present, although this pattern has been questioned in a recent study by Panizza and Warren,[11] in which they examined 50 cases of SCC and found no skip lesions. Regardless, evaluation of key landmarks distal from the tumor site remain important from an imaging standpoint.

The pathophysiology of PNS is not well understood. Previous theories suggesting spread occurring passively along paths of least resistance or via epineural lymphatics have been rejected.[12] The most recent theories describe complex interactions in the nerve environment that promote perineural tumor growth. Tumor cells have been shown to upregulate genes that increase cell proliferation and decrease rates of apoptosis in the nerve mileu.[2] Proinvasive signals, such as brain-derived neurotrophic factor, nerve growth factor, neurotrophin-3 and neurotrophin-4, glial cell line–derived neurotrophic factor, substance P, and various chemokines,[2] have been shown to facilitate tumor growth along the nerve. Neural cell adhesion molecule, which mediates cell-to-cell adhesion in neuroectodermal tissues, was found to be expressed in 93% of patients with ACC with PNS.[13] The desmoplastic type of melanoma, a variant with increased incidence of PNS, stains for high levels of p75 neurotrophin receptors mediating PNS.[14]

PNS in the head and neck most commonly involves branches of the trigeminal and facial nerves, as these are the 2 nerves responsible for most of the sensory (**Fig. 1**) and motor innervation of the face. The trigeminal nerve provides sensory information from the face and motor innervation to the muscles of mastication. Understanding the CN anatomy is critical to identifying PNS. Our goal here is to review the major branches and pathways of CNs V and VII, key anatomic landmarks, interconnections between these nerves, and pearls and pitfalls of PNS imaging.

CRANIAL NERVE V1

PNS involving the ophthalmic branch of the trigeminal nerve is uncommon compared with involvement of the maxillary and mandibular

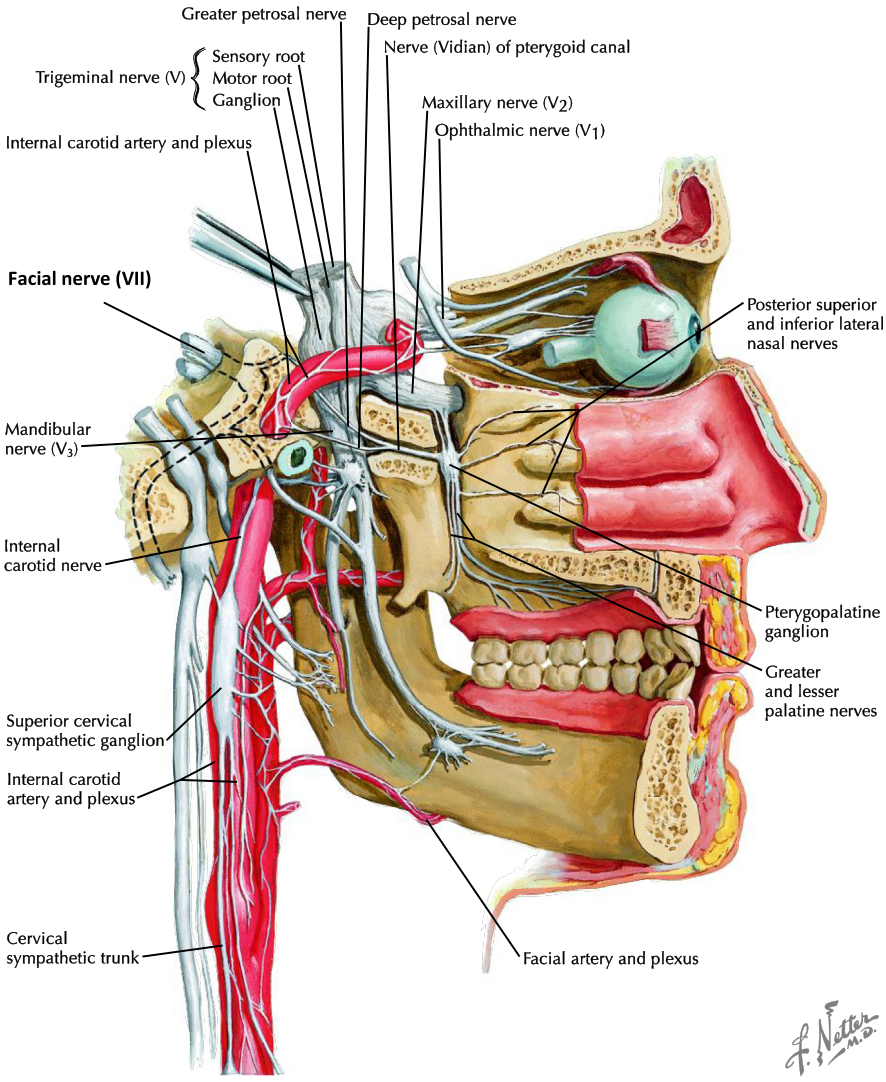

Fig. 1. Anatomic depiction of the course and major branches of the trigeminal nerve (V); ophthalmic (V1), maxillary (V2), and mandibular (V3) divisons; facial nerve (VII); and geniculate and pterygopalatine ganglia.

branches. The ophthalmic nerve branches to form the nasociliary, lacrimal, and frontal nerves. Most of the tumors are cutaneous in origin (SCC, BCC, melanoma), involving the terminal branches of the frontal nerve (supraorbital and supratrochlear nerve) which supply a large region of sun-exposed skin (forehead and eyebrow are the most common sites) (**Fig. 2**). Although less common, PNS arising from ACC of the lacrimal gland[15,16] can involve the same distribution. Shah and colleagues[17] described cases of PNS involving the nasociliary branch in medial canthus SCC and melanoma of the nasal ala. Symptoms or clinical evidence of ophthalmic branch involvement could be sinus pain or absence of the corneal blink reflex (nasociliary branch).

CRANIAL NERVE V2

The maxillary branch of the trigeminal nerve (V2) provides sensory innervation to the midfacial structures with main branches including the zygomatic, superior alveolar, and infraorbital nerves. It courses anteriorly from the cavernous sinus through the foramen rotundum and on to the pterygopalatine fossa (PPF), 3 key landmarks to assess for PNS involving V2. The PPF is located between the posterior wall of the maxillary sinus and the base of the pterygoid process with the perpendicular plate of the palatine bone at its anteromedial margin (**Fig. 3**). It serves as an important "crossroads" for PNS, connecting the masticator space laterally via the pterygomaxillary

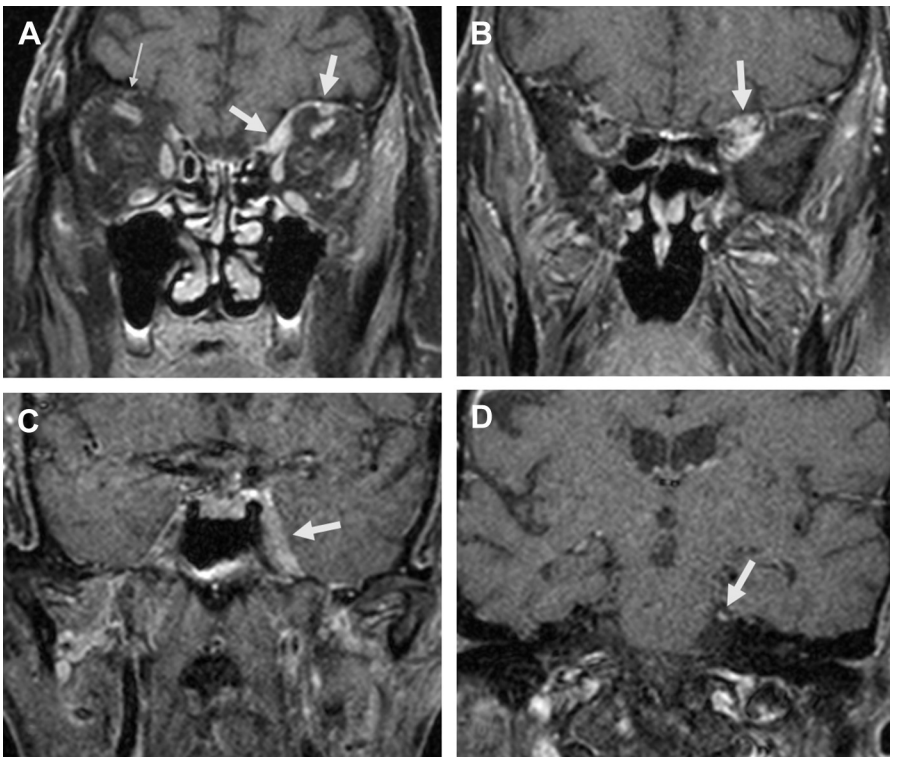

Fig. 2. A 74-year-old man with previous history of SCC of the forehead skin presents with diplopia and facial numbness. Coronal fat-suppressed contrast-enhanced image (*A*) shows enhancing tumor in the medial aspect of the orbit surrounding the superior rectus muscle compatible with PNS involving the supratrochlear nerve (ST in *A*), which extends to the frontal nerve (*F*). The normal right orbital nerve is barely visible (*thin arrow*). The orbital apex (*arrow* in *B*) and the cavernous sinus (*arrow* in *C*) are filled with tumor (presumably along the ophthalmic nerve [V1]) that reaches the cisternal segment of the trigeminal nerve (CN5) (*arrow* in *D*).

fissure, the face anteriorly via the infraorbital canal, the orbit and face superiorly via the inferior orbital fissure, the nasopharynx inferiorly via the pharyngeal (palatovaginal) canal, the palate inferiorly via the greater and lesser palatine foramina, the nasal cavity medially via the sphenopalatine foramen, and the middle cranial fossa via the foramen rotundum and vidian canal. On reaching the PPF, tumor may continue on through the foramen rotundum to the cavernous sinus and Meckel cave or anterograde along any of the previously described routes (**Fig. 4**). On reaching the Gasserian ganglion in the Meckel cave, it may spread via CN V3 through the foramen ovale. Tubular enhancement, widening of the canals, obliteration of the fat in the PPF, and denervation edema or atrophy of the masticator muscles are all characteristic imaging features of PPF involvement. PNS arising from nasopharyngeal carcinoma can involve the PPF by direct extension, via the sphenopalatine foramen or via the palatovaginal canal. Cutaneous melanoma or SCC in the V2 distribution can access the PPF via the zygomatic or infraorbital nerves (**Fig. 5**). Mucosal or minor salivary gland tumors of the palate and maxillary sinus may develop PNS via palatine, and superior alveolar branches, respectively. It bears repeating that the first sign of maxillary nerve infiltration may be discovered at a more central site such as the cavernous sinus, which should prompt careful search for a midface head or neck primary.[18]

CRANIAL NERVE V3

The mandibular branch of the trigeminal nerve (V3) carries sensory innervation from the chin, lower lip, floor of the mouth, tongue, and lateral-most side of the face. It also provides motor innervation to the muscles of mastication, tensor tympani muscle, tensor veli palatini, mylohyoid muscle, and anterior belly of the digastric muscles. The major branches are the auriculotemporal, lingual, inferior alveolar, and mental nerves. PNS of cutaneous cancers, such as melanoma or SCC of the lower lip or chin, occur along the mental nerve and follow its retrograde course through the mental

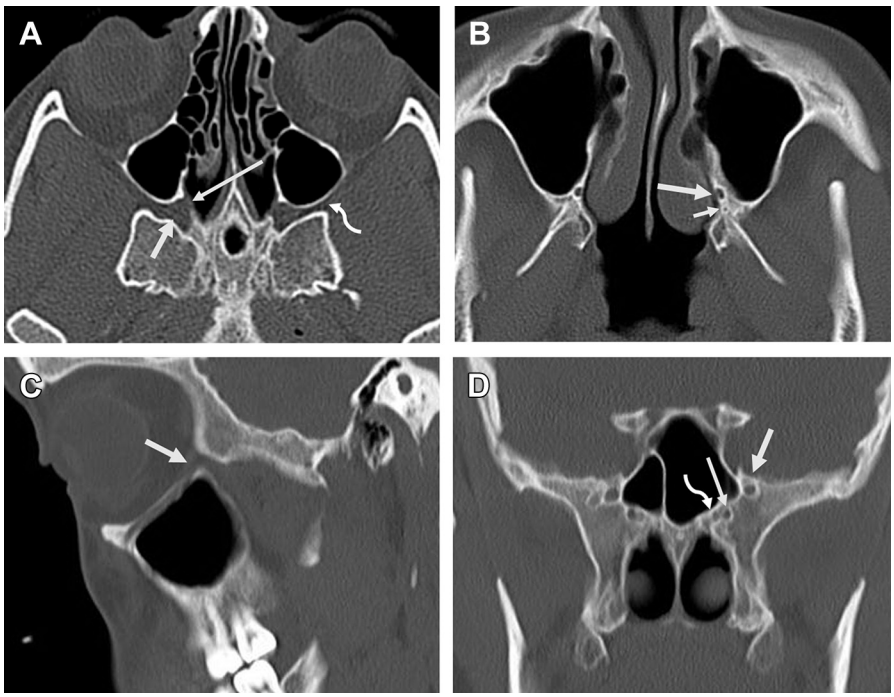

Fig. 3. Pterygopalatine fossa (PPF) (*short arrow* in *A*) is a cleft between the posterior wall of the maxillary sinus and anterior aspect of the pterygoid process containing the pterygopalatine ganglion, maxillary artery branches, and fat. Medially, it opens to the nasal cavity via the sphenopalatine foramen (*long arrow* in *A*). Laterally, PPF opens to the infratemporal fossa via the pterygomaxillary fissure, which transmits the posterior superior alveolar nerve (*curved arrow* in *A*). (*B*) Inferiorly, PPF is bound by the palatine bone and communicates with the palate through the greater (*large arrow*) and lesser palatine (*small arrow*) foramina, which house the palatine nerves. The inferior orbital fissure, which connects the PPF to the orbit, forms the superior limit of the PPF and it contains the zygomatic branch of the V2. The infraorbital nerve runs through the superior and lateral aspect of the PPF after it leaves the infraorbital nerve canal (*arrow* in *C*). Three openings are identified on the posterior wall of the PPF; from lateral to medial foramen rotundum transmitting the maxillary nerve (*thick arrow* in *D*), the vidian (pterygoid) canal (*thin arrow* in *D*), and the pharyngeal (palatovaginal) canal (*curved arrow* in *D*).

canal to involve the inferior alveolar branch along the medial aspect of the mandible to the main trunk of V3 and on to the foramen ovale. On reaching the foramen ovale, it may then involve the cavernous sinus and Meckel cave, gaining access to the trigeminal (Gasserian) ganglion (**Fig. 6**). Cancers arising from the parotid gland or skin involving the lateral-most aspect of the face that develop PNS may do so via the auriculotemporal branch of V3, which courses through the stylomandibular tunnel before arriving at the main mandibular nerve trunk (**Fig. 7**). Temporomandibular joint pain or dysfunction can occur with auriculotemporal nerve involvement. PNS may occur from any tumor arising from the masticator space or adjacent structures, such as the buccal mucosa, retromolar trigone, maxillary sinus, or nasopharynx. Denervation atrophy of the muscles of mastication may reflect perineural involvement and should be differentiated from actual muscle involvement or postradiation changes. Acute muscle denervation is T2 hyperintense without atrophy. Subacute denervation has T2 hyperintensity with some fatty replacement/loss of muscle bulk (hyperintensity may last up to a year). Chronic changes of muscle denervation show extensive fatty replacement and loss of bulk without T2 abnormality.

CRANIAL NERVE VII

The facial nerve (CN VII) provides motor innervation to the muscles of facial expression, the stylohyoid muscle, the posterior belly of the digastric muscle, and the stapedius muscles. It provides sensory innervation to the skin on and adjacent to the ear as well as taste to the anterior two-thirds of the tongue. Most cases of PNS involving CN VII occur with parotid malignancies or skin cancers invading the parotid gland. Once tumor gains access to the intraparotid segment of the facial nerve, it may spread through the

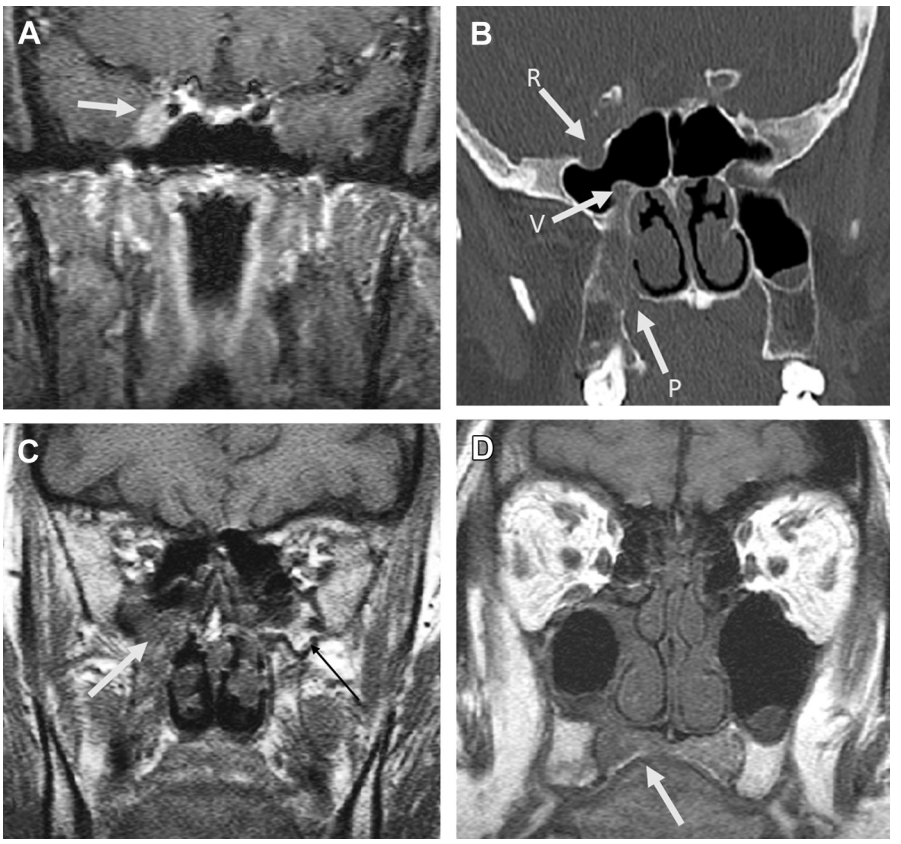

Fig. 4. A 56-year-old woman presented with diplopia. Coronal T1W image (*A*) shows a right cavernous sinus mass (*arrow*). Coronal CT (*B*) shows enlarged foramen rotundum (R), vidian canal (V), and greater palatine nerve canal (P) indicating PNS. Coronal unenhanced T1W MR image (*C*) shows effacement of the fat signal in the right PPF (*white arrow*) with preservation of fat signal in the left PPF (*black arrow*). A clinically occult tumor is seen in the right hard palate (*arrow* in *D*) which was shown to be adenocystic carcinoma arising from minor salivary gland.

stylomastoid foramen into the temporal bone, working its way through the mastoid and inner ear (**Fig. 8**).

Among salivary gland malignancies, PNS is most common in ACC (50%), followed by adenocarcinoma not otherwise specified (42%), SCC (22%), undifferentiated carcinoma (22%), mucoepidermoid carcinoma (20%), acinic cell carcinoma (11%), and carcinoma ex pleomorphic adenoma (9%).[19] Facial paralysis occurring as a result of PNS from parotid malignancy is often gradual, occurring over weeks to months, and should not be confused with the acute onset of idiopathic facial paralysis (Bell palsy).

INTERCONNECTIONS

Sites of spread that occur from one CN to another are important to be aware of when evaluating PNS, as they have clinical implications. On the most superficial level, tumors may spread between the cutaneous branches of CN V and VII, which is under the resolution of radiologic imaging. The most common route between the facial nerve and the mandibular nerve (V3) is the auriculotemporal nerve, which runs just posterior to the angle of the mandible. This allows parotid malignancies or cutaneous neoplasms access to the mandibular nerve and eventually the cavernous sinus. Less frequently, the greater superficial petrosal nerve in the vidian canal allows spread of tumor between the geniculate ganglion of the facial nerve and the pterygopalatine ganglion. The cavernous sinus (V1 and V2) and Meckel cave (V1, V2, and V3) are additional hubs for potential PNS communication involving branches of the trigeminal nerve.

IMAGING PEARLS

The most important factor in making a diagnosis of PNS is a radiologist who is aware of the clinical

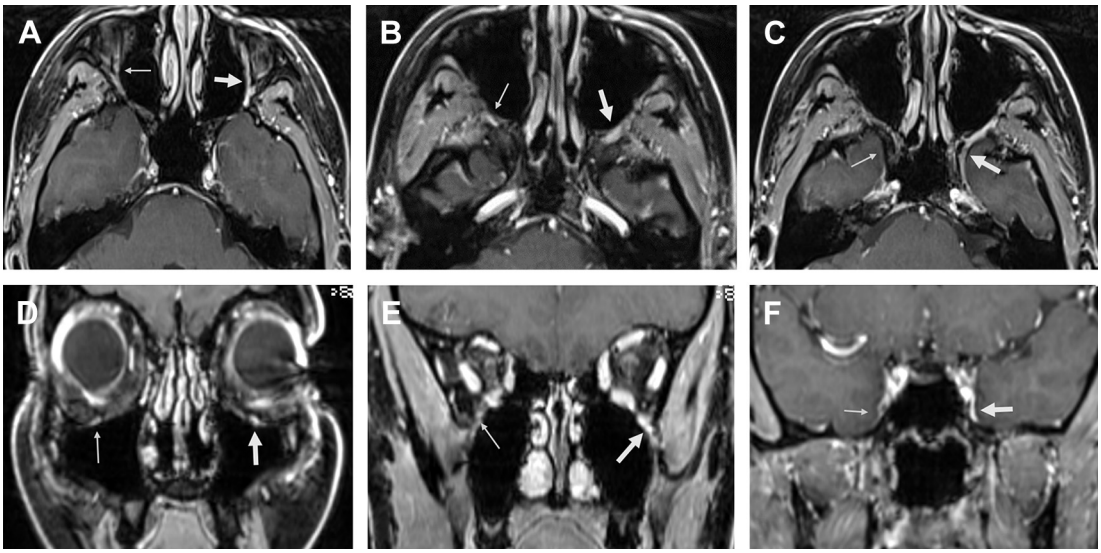

Fig. 5. A 56-year-old woman with history of facial pain refractory to medical therapy and trigeminal rhizotomy. Axial (*A–C*) and coronal (*D–F*) high-resolution postcontrast T1W images show slight thickening and abnormal enhancement of the left infraorbital nerve (*thick arrow*; *A*, *D*), extending through the infraorbital fissure into the PPF (*thick arrow*; *B*, *E*) and through the foramen rotundum and maxillary nerve into the cavernous sinus (*thick arrow*; *C*, *F*) compared with the normal nerve on the right side (*thin arrows*). The patient's remote history of a "minor dermatologic procedure" and skin SCC of the dorsum of the nose was discovered after imaging diagnosis of PNS.

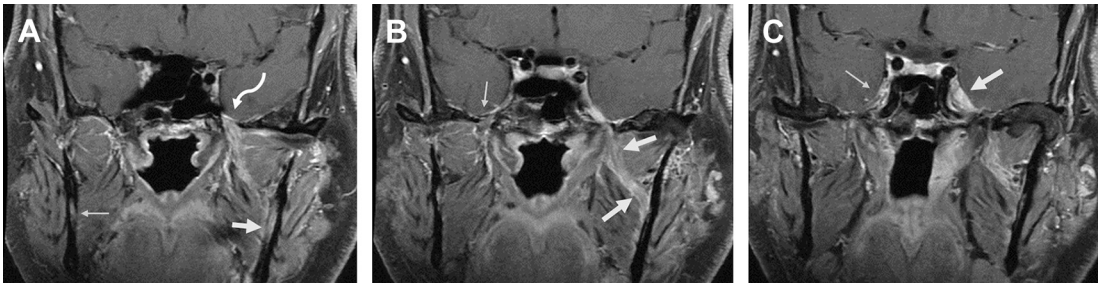

Fig. 6. Gingival SCC extending along the inferior alveolar nerve within the mandibular canal (*thick arrow* in *A*) then into the masticator (infratemporal) space (*arrows* in *B*) before reaching the foramen ovale (*curved arrow* in *A*). There is tumor extension to the Meckel cave and cavernous sinus (*thick arrow* in *C*). Thin arrows point to the normal mandibular canal (*A*), foramen ovale (*B*), and cavernous sinus (*C*).

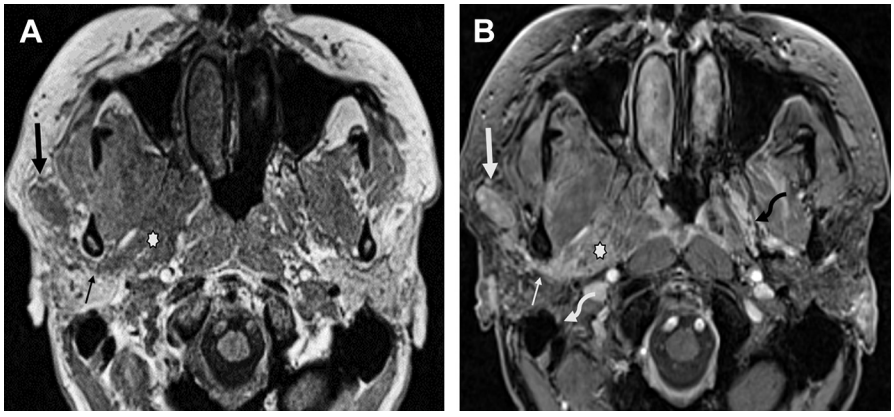

Fig. 7. PNS via the auriculotemporal nerve. Unenhanced (*A*) and contrast-enhanced fat-suppressed (*B*) T1W images show a right parotid primary malignant tumor (*thick arrows*) extending through the auriculotemporal nerve behind the mandibular angle (*thin arrows*). Bulky tumor is seen involving the mandibular nerve (V3) in the infratemporal fossa (*star*). The normal mandibular nerve (*black curved arrow* in *B*). Note that the right facial nerve (*curved white arrow*) is normal in the stylomastoid foramen.

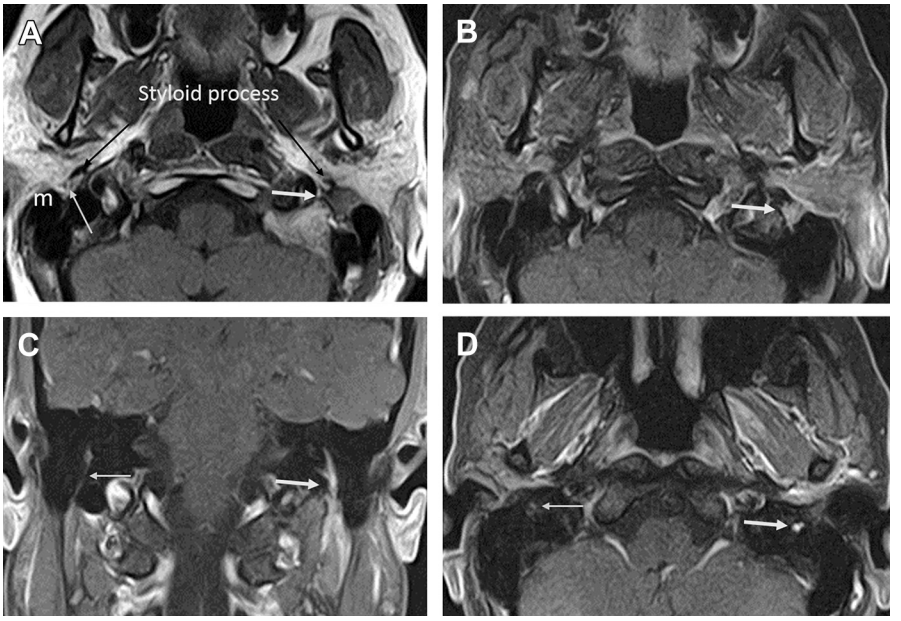

Fig. 8. PNS along the left facial nerve from high-grade parotid mucoepidermoid carcinoma. Axial T1W image through the stylomastoid foramen (*A*) shows an intermediate signal mass (*white thick arrow*). The normal right facial nerve can be seen as a tiny round structure (*white thin arrow*) surrounded by fat within the stylomastoid foramen, which is delimited by the mastoid tip (m) and the styloid process (*black arrow*). Axial fat-suppressed contrast-enhanced T1W (*B*) image shows enhancement of the mass filling the stylomastoid foramen. Coronal (*C*) and axial (*D*) fat-suppressed contrast-enhanced T1W images show extension of tumor along the mastoid segment of the facial nerve (*white thick arrows*). White thin arrows point to the normal right facial nerve.

symptoms, equipped with the anatomic knowledge, and prepared to carefully scrutinize the relevant CNs and their branches.

Knowing where the primary tumor is (or was) and the neural networks that serve that location is the most important first step to diagnosing PNS. Careful examination of the entire course of the nerve then should ensue. As a practical approach, critical examination of the PPF, stylomastoid foramen, and infratemporal fossa just below the foramen ovale would allow diagnosis of most PNS cases (**Box 1**).

A high-quality computed tomography (CT) scan, in the hands of an experienced radiologist, affords detection of most cases of PNS. Effacement of fat surrounding the CNs can readily be appreciated if proper attention to detail is given (**Fig. 9**). Findings observed on bone algorithm CT reconstructions such as foraminal destruction, erosion, or asymmetric widening, are frequently present in advanced cases and should alert radiologists to the presence of PNS (**Fig. 10**). CT is usually limited, however, in determining the extent of disease.

MR imaging is the method of choice for evaluation of PNS given its superior soft tissue contrast resolution. Many radiologists prefer high-resolution fat-saturated postcontrast images, although PNS may be identified on unenhanced T1-weighted (T1W) images as effacement of the fat pad present around each of these nerves. Some argue that non–fat-suppressed images may have better diagnostic utility because commonly present susceptibility artifacts at the skull base may obscure important foramina on fat-suppressed images.[20] Multiplanar reformations are also important in evaluation of the skull base foramina, as many are shown to better advantage in the coronal, sagittal, or oblique planes. Linear or curvilinear enhancement in a nerve distribution, infiltration of the PPF, lateral bowing of the cavernous sinus, or replacement of

Box 1
Key landmarks and contents for PNS

Key Landmarks	Nerve(s)
Pterygopalatine fossa	V2 and its branches
Stylomastoid foramen	Facial nerve
Foramen ovale	V3 and its branches
Foramen rotundum	V2 (maxillary nerve)
Cavernous sinus and Meckel cave	Cranial nerve V and its branches

Fig. 9. Most PNS extending to the skull base will involve 1 of the 3 sites shown. Because most nerves are surrounded by fat, which can be easily identified on CT, a careful scrutiny of common locations of PNS at the skull base will allow identification of PNS in most cases. Relatively subtle nerve enlargement and effacement of surrounding fat in the right PPF (*A*), left stylomastoid foramen (*B*), and right infratemporal fossa just below the foramen ovale (*C*) indicate PNS in these patients with palate adenocystic carcinoma, parotid mucoepidermoid carcinoma and oral tongue SCC, respectively (*thick arrows*). Thin arrows point to the normal contralateral nerves.

the normally cerebrospinal fluid–filled Meckel cave can also be seen with PNS. PET CT, which is more sensitive than MR imaging and CT in detection of primary tumors and nodal metastases, is often inferior to MR imaging in diagnosis of PNS. This is related to the small volume of disease in PNS combined with limited spatial resolution of PET. Utility of diffusion-weighted imaging (DWI) is also

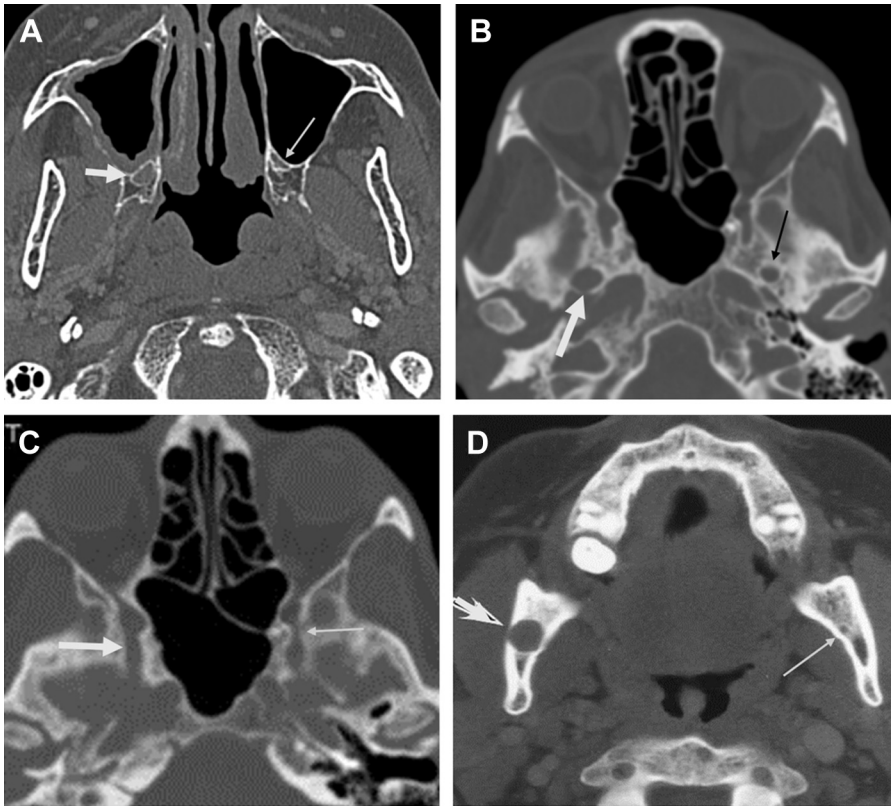

Fig. 10. Asymmetric enlargement of a nerve canal is a reliable CT finding of PNS in the proper clinical setting, although this is usually seen in advanced stages of disease. Axial CT images demonstrate enlargement of the right palatine nerve foramen (*A*), the right foramen ovale (*B*), the right foramen rotundum (*C*), and the right mandibular canal (*D*) (*thick arrows*) in separate patients with palatine nerve, mandibular nerve, maxillary nerve, inferior alveolar nerve PNS, respectively. Thin arrows point to the corresponding normal left sided nerves.

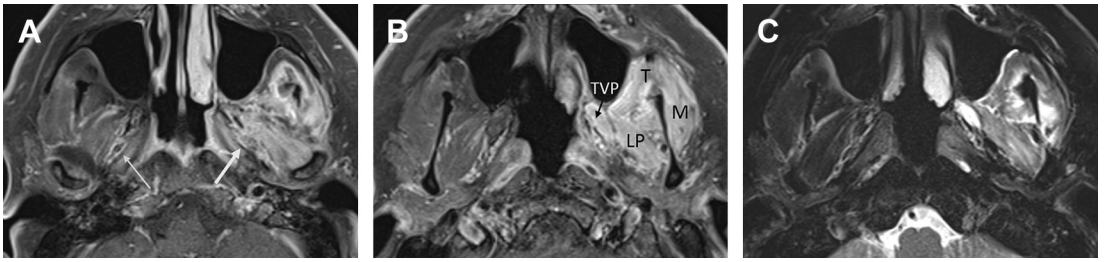

Fig. 11. Muscle denervation. Axial fat-suppressed contrast-enhanced T1W (*A*, *B*) and axial fat-suppressed T2W (*C*) images show enlarged and abnormally enhancing left mandibular nerve (V3) in the infratemporal fossa (*thick arrow* in *A*) compared with the normal right V3 (*thin arrow* in *A*) secondary to PNS from skin SCC. The muscles of mastication innervated by V3 show abnormal enhancement (*B*) and increased T2 signal (*C*). Other muscles innervated by the V3, not shown here, include medial pterygoid and tensor tympani muscles. LP, lateral pterygoid muscle; M, masseter muscle; T, temporalis muscle; TVP, tensor veli palatini muscle.

limited in diagnosis of PNS due to the common susceptibility artifacts at the skull base that create marked image distortion on DWI.

PITFALLS

Contrast enhancement is often seen in the perineural venous plexus surrounding the normal CNs and may mimic abnormal nerve enhancement, hence PNS. This is particularly problematic for small nerves and low-quality MR image studies that do not allow resolution of nerves from veins. The proximal greater superficial petrosal nerve, the geniculate ganglion, and the tympanic and mastoid segments of the facial nerve are common sites that may pose this problem. Comparison to the opposite site may be helpful, although venous plexus enhancement is often asymmetric as well. The perineural venous plexus may contribute to the enhancement seen involving the trigeminal ganglion and proximal portions of V1, V2, and V3. Crescent-shaped enhancement along the inferior aspect of the Meckel cave is routinely seen in the normal Gasserian ganglion on high-resolution MR imaging and should not be mistaken for PNS, which is usually larger and more rounded. Disruption of the blood-brain barrier secondary to ischemia, infarction, inflammation, trauma, or demyelination may result in segmental intracranial nerve enhancement, which should not be confused with PNS.[21] Last, as was mentioned before, understanding the imaging appearance of denervated muscles is important to avoid misinterpreting muscle enhancement seen in subacute denervation for tumor infiltration (**Fig. 11**). Other enhancing lesions besides PNS may involve the skull base foramina, such as meningiomas, schwannomas, or granulomatous diseases. Enlargement and enhancement of CNs also can be seen in rare demyelinating conditions and fungal or viral infections. Consideration of the clinical context is always key to the correct diagnosis.

SUMMARY

Identification of PNS has important therapeutic and prognostic implications and is critical for adequate staging and treatment planning. Careful attention to the neural pathways of the head and neck with routine evaluation of key landmarks can aid in early detection, appropriate therapy, and the best possible chance for cure.

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