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Seminars in
ROENTGENOLOGY

Perineural Tumor Spread in Head and Neck Malignancies

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Introduction

The network of nerves supplying the facial region is fascinating and innervates a complex variety of functions, including: movement of the facial and masticatory muscles; perception of skin sensation and taste; and secretomotor action of the salivary and lacrimal glands. Most of these functions are achieved by the facial and trigeminal nerves, with additional contributions from the glossopharyngeal and vagus nerves. The camaraderie of the trigeminal and facial nerves is spectacular in that at several locations, the trigeminal nerve allows its branches to be used as conduit for special facial nerve fibers to reach their destination. The assimilation of the chorda tympani (branch of facial nerve) into the lingual nerve (branch of trigeminal nerve) to carry taste sensation from the anterior two-thirds of the tongue is one such example. However, as is true with any association, this integration can prove perilous at times. Perineural tumor that "hitchhikes" onto the branches of the facial nerve at these locations of intermingling with the trigeminal nerve and vice versa is a perfect instance of the hazards of this friendship.

Perineural tumor spread (PNTS) is a detrimental sequela of malignant tumors, in which there is malignant spread of tumor along the course of a nerve distant to an extracranial primary tumor or in the setting of lymphoma, and is a gross feature amenable to imaging. It must be differentiated from perineural invasion, the latter being a histological diagnosis characterized by the invasion of the perineurium on a microscopic specimen.[1] Both perineural invasion and PNTS are indicators of worse prognosis associated with increased incidence of recurrence.[2,3] Henceforth, in this chapter we will review the relevant nerve anatomy and characteristic imaging features of PNTS.

Many malignant tumors can cause PNTS, though certain tumors are more commonly incriminated than others. Squamous cell carcinomas are probably the most common and can arise in the skin and spread perineurally conforming to the dermatomal distribution; or can arise in the mucosal space and spread via the locoregional nerves. Adenoid cystic carcinomas are notorious for PNTS and in the parotid glands commonly involve the facial nerve while those in the submandibular and sublingual glands involve the lingual nerve. Adenoid cystic carcinomas of the minor salivary glands arising in the mucosal space follow a pattern similar to other tumors in those locations and involve the nerve innervating the region. Malignant desmoplastic melanoma, basal cell carcinoma, adenocarcinoma, and lymphoma are other culpable tumors.

Following the general theme of complexity of the human body and its disease processes, there are several questions pertaining to PNTS that defy complete explanation. Why certain tumors like adenoid cystic carcinoma have a greater prevalence of PNTS than others or why the trigeminal and facial nerves are more frequently affected than other cranial nerves, are 2 such questions. Research backed theories have been proposed about the "neurotrophic" nature of certain tumors and molecular factors including brain-derived neurotrophic factor, nerve growth factor, neurotrophins 3 and 4, etc. have been implicated.[4] The mere ubiquitous presence of the branches of the trigeminal and facial nerves in the head and neck region has been proposed to be enough reason for their overwhelming involvement.

Clinical Features

The absence of clinical symptoms should not discourage the interpreting radiologist from diagnosing PNTS, since 40% of patients are asymptomatic at the time of diagnosis.[5] When present, the symptoms can include muscle weakness, pain, numbness, and paresthesias in the distribution of the nerve. Trigeminal neuralgia can be a symptom of PNTS and may be the initial presentation of malignancy in a patient. The clinical diagnosis of "idiopathic" trigeminal neuralgia should only be made after imaging and clinical evaluation excludes other causes, including PNTS. Symptoms of trigeminal neuralgia in an individual with a prior history of cancer, especially of

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the head and neck, should prompt a thorough search for PNTS. PNTS involving CN VII can be clinically misdiagnosed as Bell's palsy. By definition, Bell's palsy should resolve within 6-8 weeks. In patients with a clinical diagnosis of Bell's palsy, an atypical clinical course of facial nerve palsy such as an unresolving or progressive facial nerve paralysis should alert the radiologist to scrutinize the facial nerve closely for PNTS. Stroke is another common knee-jerk diagnosis for facial weakness and should not always be presumed as such, particularly if there is a history of head and neck cancer. Clinical distinction of peripheral facial nerve palsy from central facial nerve palsy on the basis of a quality neurological exam can help avoid this pitfall. Patients with PNTS may also present to the dentist with pain and paresthesia along the jaw, if the alveolar nerve is involved, and may be misdiagnosed with an odontogenic infection. Symptoms in the distribution of more than one cranial nerve can be due to tumor extension to the orbital apex, skull base or the cavernous sinus, which houses cranial nerves III, IV, V1, V2, and VI.[6] Symptoms involving both the 5th and 7th cranial nerves can be an ominous sign of substantial PNTS and require a thorough assessment of the pathways of these nerves, particularly the course of the greater superficial petrosal nerve and auriculotemporal nerves which are clinically important interconnections between these nerves. PNTS from skin malignancies extending retrograde along distal cutaneous trigeminal and facial nerve branches represents an important cause of PNTS which can extend to the skull base. Treatment of the cutaneous malignancy may predate the presentation of PNTS by years and a skin lesion on exam may not be evident at the time of diagnosis of PNTS. Identification of PNTS by the radiologist is a critically important poor prognosticator as skull base or intracranial involvement may preclude curative surgical therapy, and impacts treatment, including accurate radiation therapy planning.

Imaging PNTS

Head and neck radiologists adore fat planes, especially when scrutinizing images for PNTS. Loss of the normal fat pad surrounding nerves at the site of transit through the skull base, calvarium or maxillofacial structures with abnormal enhancement and thickening along the course of the nerves is a useful sign to detect PNTS[5] (Figure 1). Examination of the superior orbital and supraorbital fat pad can help detect V1 disease. V2 disease can be uncovered by the survey of foramen rotundum and of the normal fat within the pterygopalatine fossa, retromaxillary fat, fat along the orbital floor, and the premaxillary regions. Inspection of foramen ovale and the fat pads within the masticator space, along the medial surface of the mandible at the entry site of mandibular nerve and at the lateral chin at the mental foramen are useful for detecting V3 PNTS. Attention to the fat pad at the stylomastoid foramen can divulge PNTS along the facial nerve.

MRI remains the preferred modality for early diagnosis and follow-up of PNTS. In many cases, attention is drawn to the presence of PNTS by replacement of the hyperintense fat signal by mass-like hypointensity on precontrast T1-weighted images at important foraminal and skull base locations including but not limited to the pterygopalatine fossa, premaxillary fat pad, and mental foramen. Linear enhancing soft tissue at the site of tumor and along the expected course of the cranial nerve branches should raise the suspicion of PNTS. Enlargement of and enhancement within the cranial nerve canals and foramina should alert the interpreting radiologist of the possibility of PNTS. Thin-section pre- and postcontrast T1-weighted images are typically the most useful in the detection of PNTS.[7] Use of fat suppression on postcontrast images is usually a matter of interpreter preference. A typical MR imaging protocol, where PNTS is of concern, includes a 3D FIESTA sequence through the skull base foramina, smaller FOV (16-18 mm) thin section (3-4 mm) STIR, precontrast T1W and postcontrast T1W images. Images are obtained in at least 2 planes with an optional third plane for the postcontrast sequence. At our institution, whole brain DWI and FLAIR sequences are also obtained to rule out potential brain pathology. The recent development of MR neurography holds promise for detection of early PNTS.[8,9] The CT features of PNTS include loss of perineural fat pads, widening and/or erosion of the neural foramina and enhancing soft tissue masses in the expected locations of the foramina. These features are important to recognize as CT may be the initial study ordered in patients not yet diagnosed with malignancy, particularly if they present initially to the emergency room. As would be expected, the sensitivity of CT for the diagnosis of PNTS is much lower than that of MRI. Figure 1 demonstrates many of the characteristic imaging features of perineural tumor spread on CT and MRI.

An interesting imaging finding of PNTS is denervation injury to the muscles. Muscle denervation can be seen in 2 forms on imaging, an acute/subacute form (Fig. 1) seen during the first year and a chronic form (Fig. 2) seen 1-1.5 years after. The acute/subacute form is seen as diffusely increased T2 intensity and enhancement on MR imaging, while in the chronic stage the muscles are atrophic and replaced by fat.

In the majority of cases, PNTS starts in the vicinity of the primary tumor, usually contiguous to it. The common pattern of progression is in a retrograde fashion toward the main trunk of the involved nerve. In some instances, the progression may be antegrade toward the ramifying portion of the nerve. The length of the nerve is affected earlier compared to the thickness of the nerve.[10] "Skip" lesions have been described where affected enlarged and enhancing portions of the nerve are punctuated by radiologically normal appearing nerve segments.[2,5,7,11] Consequently, it is imperative to examine the entire course of the nerve involved, to exclude the presence of tumor distant to the primary site. This has treatment implications as it determines the extent of the treatment field and is important for prognostication.[12,13] Table 1 summarizes the common imaging features of PNTS. Careful routine assessment of key landmarks listed in Table 2 is important in patients with maxillofacial symptoms or nerve palsies of cranial nerves 5 or 7 as

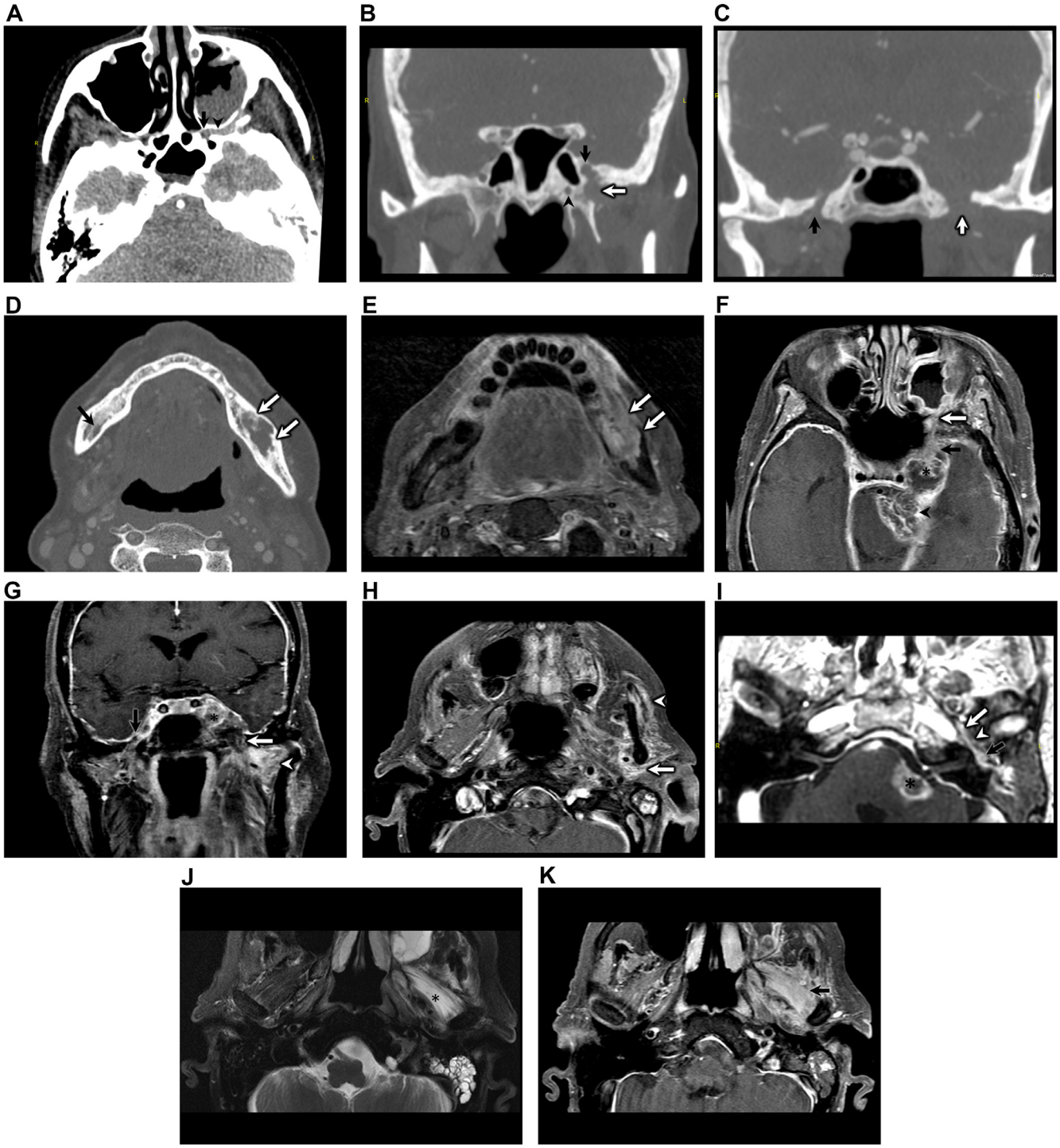

Figure 1 Characteristic imaging features of perineural tumor spread in a 77-year-old female presenting to the emergency room with new onset of left facial paralysis. (A) Axial contrast-enhanced CTA. Abnormal soft tissue density replaces the fat in the left pterygopalatine fossa (black arrow) and extends into the pterygomaxillary fissure (black arrowhead), an ominous sign. Adjacent left maxillary sinus opacification is incidental mucosal thickening. (B) and (C) Coronal reformat contrast-enhanced CTA in bone window. (B) Classic features of perineural tumor spread are seen including marked enlargement of the left foramen rotundum (black arrow), subtle enlargement of the left vidian canal (black arrowhead) and juxtaforaminal skull base erosion involving the left pterygoid process and greater sphenoid wing (white arrow) adjacent to the left foramen rotundum. Compare this to the normal contralateral right foramen rotundum and right vidian canal. (C) There is marked abnormal widening of the left foramen ovale (white arrow). Compare this to the normal right contralateral foramen ovale (black arrow). (D) Axial contrast-enhanced CTA in bone window. Extensive perineural tumor spread causes both widening and erosive changes seen along the left inferior alveolar nerve canal (white arrows). Compare this to the barely perceptible normal distal right inferior alveolar nerve canal (black arrow). (E) Corresponding axial T1-weighted postcontrast fat-saturated image confirms enhancing perineural tumor filling and eroding the left inferior alveolar nerve canal (white arrows). (F). Axial T1-weighted postcontrast fat-saturated

image demonstrates extensive perineural tumor spread along the course of left V2 from the superior left pterygopalatine fossa (white arrow) to the widened foramen rotundum (black arrow), and filling the left cavernous sinus (black asterisk) which has bulging margins. Tumor extends back to the left 5th nerve root entry zone (black arrowhead) where there is mass effect on the ventral pons. There is diffuse smooth dural enhancement seen. (G) Coronal T1-weighted postcontrast fat-saturated image demonstrates extensive perineural tumor widening the left foramen ovale (horizontal white arrow) and expanding the left cavernous sinus (black asterisk). Acute denervation enhancement is seen involving the left lateral pterygoid muscle (white arrowhead). Note the enhancement along the normal right foramen ovale (black arrow) that should not be mistaken for perineural tumor spread. There is diffuse thin dural enhancement. (H). Axial T1-weighted postcontrast fat-saturated image. Perineural tumor spread extends to involve the thickened, enhancing left auriculotemporal nerve (white arrow), and buccal branch of the left facial nerve (white arrowhead). (I) Axial T1-weighted postcontrast SPGR image. Enhancing perineural tumor spread along the left greater superficial petrosal nerve (white arrow) extending back to the geniculate fossa (white arrowhead) and thickened anterior tympanic left facial nerve (black arrow) is present. Perineural tumor spread at the ventral pons left fifth nerve root entry zone (black asterisk) is again seen. On the (J) axial T2-weighted fat-saturated and (K) axial T1-weighted postcontrast fat-saturated images, characteristic features of acute denervation injury are present including (J) T2 hyperintense edema (black asterisk) throughout the left lateral pterygoid muscle with (K) uniform enhancement (black arrow) and maintained muscle morphology. There is left mastoid opacification and left maxillary sinus mucosal thickening. This is extensive perineural spread from failed treatment of a known left alveolar ridge squamous cell carcinoma.

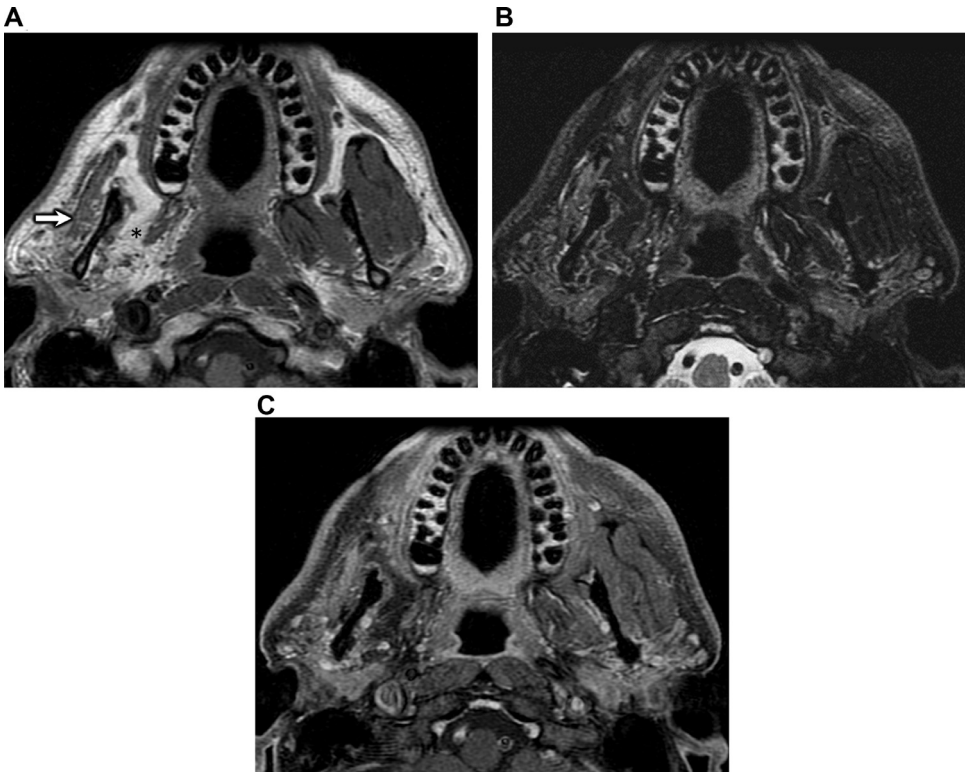

Figure 2 Chronic denervation injury. (A) Axial T1-weighted (B) axial T2-weighted and (C) axial T1-weighted postcontrast fat-saturated images demonstrate fatty atrophy (black asterisk) and volume loss (white arrow) of the right muscles of mastication with (B) lack of edema or (C) enhancement, indicating this is chronic in the patient previously treated with radiation for perineural tumor spread to the right V3.

patients with PNTS may present without a history of malignancy. A thorough knowledge of the normal anatomy of the 5th and 7th nerves is requisite for detecting and understanding the patterns of PNTS.

The Trigeminal Nerve (CN V)

The trigeminal nerve is the fifth and the largest of all the cranial nerves. The literal meaning of the word simply means triplets (http://www.merriam-webster.com/dictionary/trigeminal) and refers to the 3 large divisions of the nerve namely the

Table 1 Characteristic Imaging Features of Perineural Tumor Spread

Effacement of perineural, foraminal, and/or juxtaforaminal fat
Asymmetric nerve enlargement
Asymmetric nerve enhancement
Osseous foraminal enlargement and/or erosion
Features of denervation injury
Acute - edema, enhancement and enlargement of muscles supplied by affected nerve
Chronic - fatty atrophy and/or volume loss of muscles supplied by the affected nerve

Table 2 Key Anatomic Landmark Check List for Perineural Spread of Tumor Affecting Cranial Nerves V or VII

Landmark	Nerve (s) Relevant to Landmark	Typical Patterns of Involvement
Subcutaneous neural foramina		
Supraorbital foramen	Orbital and cutaneous V1 branches	Retrograde spread from primary cutaneous malignancy of face, frontal or ethmoid sinuses, or lacrimal gland along V1 branches
Infraorbital foramen	Infraorbital nerve and cutaneous V2 branches	Retrograde spread from (a) primary cutaneous malignancy of face, (b) mucosal malignancy of sinonasal cavity along V2 branches to PPF, V2 trunk Antegrade spread from perineural tumor that has involved PPF. See PPF landmark.
Mental Foramen	Inferior alveolar nerve and V3 branches	Retrograde spread from cutaneous malignancy of lower lip or chin or oral cavity mucosal neoplasm
Neural canals/fossae formed by facial bones		
Mandibular Foramen and inferior alveolar nerve canal	Inferior alveolar nerve and V3 branches	Retrograde spread from (a) cutaneous malignancy of lower lip and face (b) mucosal neoplasm of mandible/alveolar ridge or RMT
Stylomandibular tunnel	Auriculotemporal nerve	Retrograde spread from primary parotid tumor or facial cutaneous malignancy along intraparotid facial nerve branches to auriculotemporal nerve. Can spread to foramen ovale
Greater and Lesser Palatine Foramina	Greater and lesser palatine nerves	Retrograde spread from mucosal malignancy of palate Antegrade spread from perineural tumor that has reached PPF. See PPF landmark.
Pterygopalatine fossa	V2 trunk, V2 branches, vidian nerve	Retrograde spread from (a) primary cutaneous malignancy of face, (b) mucosal malignancy of sinonasal cavity or palate along V2 branches Antegrade spread from a primary parotid tumor or cutaneous malignancy along VII branches VII trunk to GSPN to vidian nerve to PPF
Superior orbital fissure	Orbital and cutaneous V1 branches	Retrograde spread from primary cutaneous malignancy of face, frontal or ethmoid sinuses, or lacrimal gland along V1 branches
Skull base foramina		
Foramen Rotundum	V2 branches, V2 trunk	Retrograde spread from (a) primary cutaneous malignancy of face, (b) mucosal malignancy of sinonasal cavity or palate along V2 branches Retrograde direct extension from nasopharyngeal malignancy through pharyngobasilar fascia to skull base
Vidian Canal	Vidian nerve, GSPN	Retrograde spread from perineural tumor that has reached PPF via V2 branches or antegrade spread from perineural tumor that has reached GSPN via VII branches. See PPF landmark Retrograde direct extension from nasopharyngeal malignancy through pharyngobasilar fascia to skull base vidian canal
Foramen Ovale	V3 trunk, V3 branches, Auriculotemporal nerve	Retrograde spread from (a) cutaneous malignancy of lower lip and face (b) mucosal neoplasm of FOM, mandible/alveolar ridge, RMT or nasopharynx along V3 branches to foramen ovale Retrograde spread from primary parotid tumor or facial cutaneous malignancy along intraparotid facial nerve branches to auriculotemporal nerve to foramen ovale

Table 2 (*Continued*)

Landmark	Nerve (s) Relevant to Landmark	Typical Patterns of Involvement
		Antegrade spread of perineural tumor involving the Gasserian ganglion. See Meckel's cave landmark.
Stylomastoid Foramen	Facial nerve and its branches	Retrograde spread from (a) primary parotid tumor along intraparotid branches of facial nerve b) primary facial/scalp/auricular, external auditory canal cutaneous malignancy along peripheral facial nerve branches to intraparotid facial nerve branches. PNS can extend to stylomastoid foramen with potential for intracranial PNS to involve the intratemporal facial nerve back to brainstem nucleus
Intracranial landmarks		
Cavernous sinus	V1 and V2	Retrograde spread from (a) primary cutaneous malignancy of face, (b) mucosal malignancy of sinonasal cavity or palate along V2 branches to V2 trunk PNS from primary cutaneous malignancy of face, frontal or ethmoid sinuses, or lacrimal gland along V1 branches to V1 trunk Antegrade spread from perineural tumor involving Gasserian ganglion. See Meckel's cave landmark.
Meckel's cave	Gasserian ganglion V1, V2, V3 trunks, and branches	Retrograde spread from (a) cutaneous malignancy of lower lip and face (b) mucosal neoplasm of FOM, mandible/alveolar ridge, RMT or nasopharynx along V3 branches to V3 trunk to Gasserian ganglion Retrograde spread from (a) primary cutaneous malignancy of face, (b) mucosal malignancy of sinonasal cavity or palate along V2 branches to V2 trunk to Gasserian Ganglion Retrograde spread from primary cutaneous malignancy of face, frontal or ethmoid sinuses along V1 branches to V1 trunk to Gasserian ganglion

Retrograde patterns or PNTS are more common than antegrade PNTS.

FOM, floor of mouth; GSPN, greater superficial petrosal nerve; PPF, pterygopalatine fossa; RMT, retromolar trigone; SOF, superior orbital fissure.

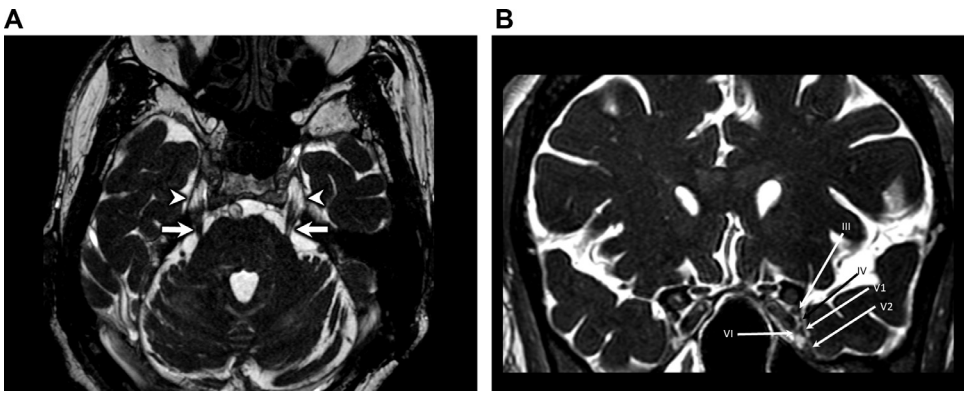

Figure 3 (A) Axial fast imaging employing steady-state acquisition shows normal appearing cisternal portions of trigeminal nerves (white arrows) and Gasserian ganglia in Meckel's caves (white arrowheads). (B) Coronal fast imaging employing steady-state acquisition postcontrast. The V1 and V2 divisions of the trigeminal nerve are sensory and transit the lateral wall of the cavernous sinus, along with cranial nerves III and IV. Cranial nerve VI is centrally located in the cavernous sinus.

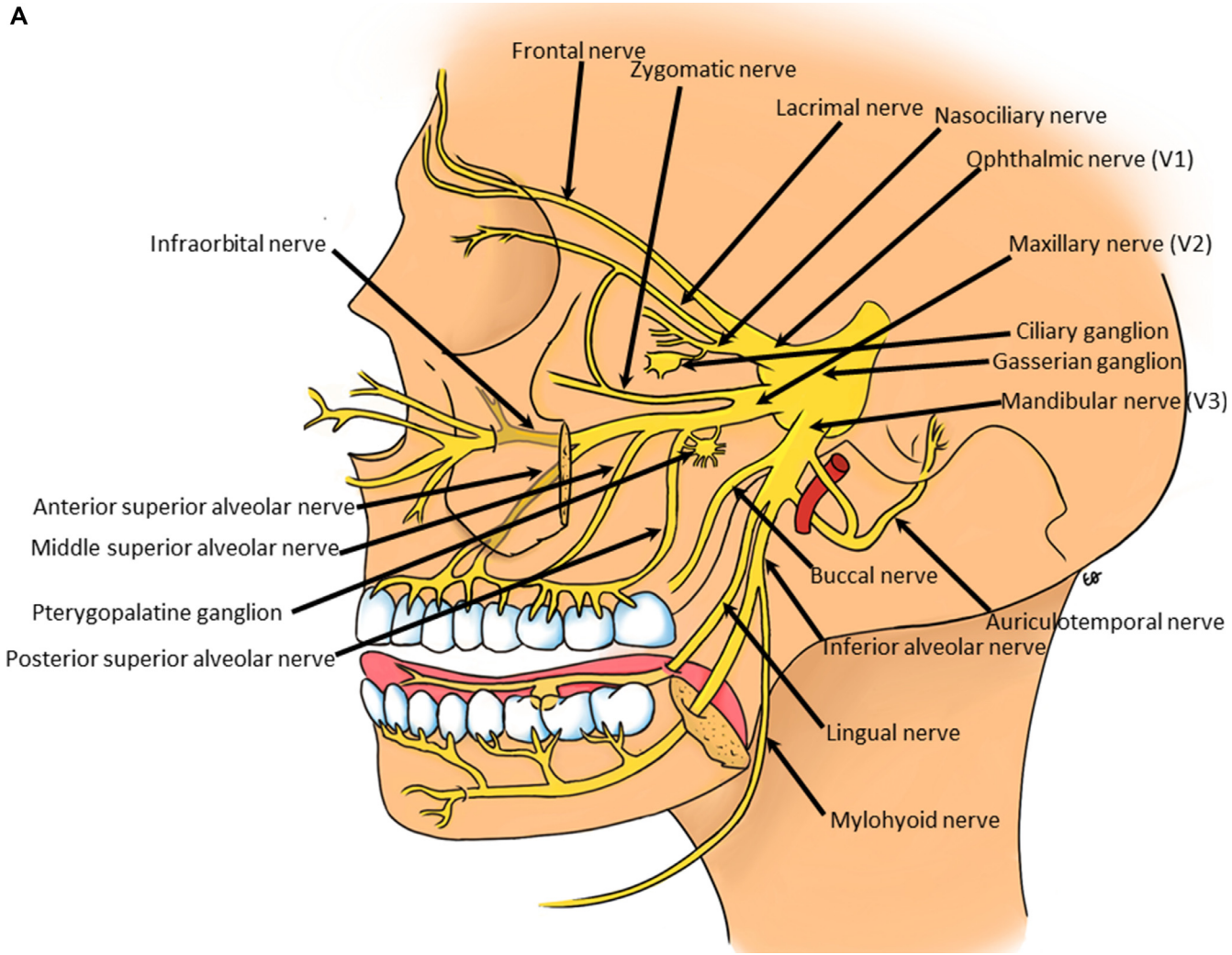

Figure 4 (A) The 3 divisions of the fifth nerve separate within the trigeminal cave. The V1 and V2 divisions are sensory and transit the lateral wall of the cavernous sinus. V1divides into the lacrimal, frontal and nasociliary branches before entering the orbit through the superior orbital fissure. V2 enters foramen rotundum then transits the pterygopalatine fossa where it gives off the zygomatic nerve, 2 sphenopalatine branches and superior alveolar branches. V3 has sensory and motor components and exits the skull base via foramen ovale, dividing into an anterior primarily motor trunk supplying the muscles of mastication. The dominant primarily sensory posterior trunk branches shown in the figure are more susceptible to perineural tumor spread and include the auriculotemporal, inferior alveolar, and lingual nerves. The auriculotemporal nerve is another area of communication between the trigeminal and facial nerves. (B) V2 or the maxillary nerve enters the pterygopalatine fossa and continues anteriorly as the infraorbital nerve. The greater and lesser palatine nerves extend caudally from the pterygopalatine fossa toward the palate. The greater superficial petrosal nerve exits the facial nerve near the geniculate fossa at the facial hiatus and joins the deep petrosal nerve to form the vidian nerve which enters the pterygopalatine fossa, serving as one of the key communications between the 5th and 7th nerves. (C) Coronal CT reformat without contrast. V2 exits the skull base through foramen rotundum (white arrow), seen as a round foramen just superior to the pterygoid process laterally. The vidian canal (black arrow) through which the vidian nerve transits is medial to foramen rotundum. These foramina should be routinely assessed as part of a search pattern when evaluating for perineural tumor spread. (D) and (E) axial CT without contrast. (D) The foramen rotundum (white arrow) is tubular in the axial plane and anteriorly extends to the superior margin of the pterygopalatine fossa (white asterisk), where V2 then courses anteriorly into the inferior orbital fissure (white arrowhead) as it courses toward the infraorbital nerve canal. (E) Foramen ovale (white arrowhead), through which V3 passes as it extends into the infratemporal fossa is oval shaped in the axial plane and seen parallel and lateral to foramen lacerum (black asterisk). The vidian canal (white arrow) is tubular in the axial plane, extending from the anterior margin of foramen lacerum to communicate with the pterygopalatine fossa (white asterisk). (F) Coronal CT reformat without contrast. In the coronal plane, foramen ovale (black asterisk) is normally seen as a discontinuity in the floor of the middle cranial fossa. (G) Axial and (H) coronal T1-weighted postcontrast fat-saturated image shows normal venous enhancement surrounding V3 within the foramen ovale (white arrows).

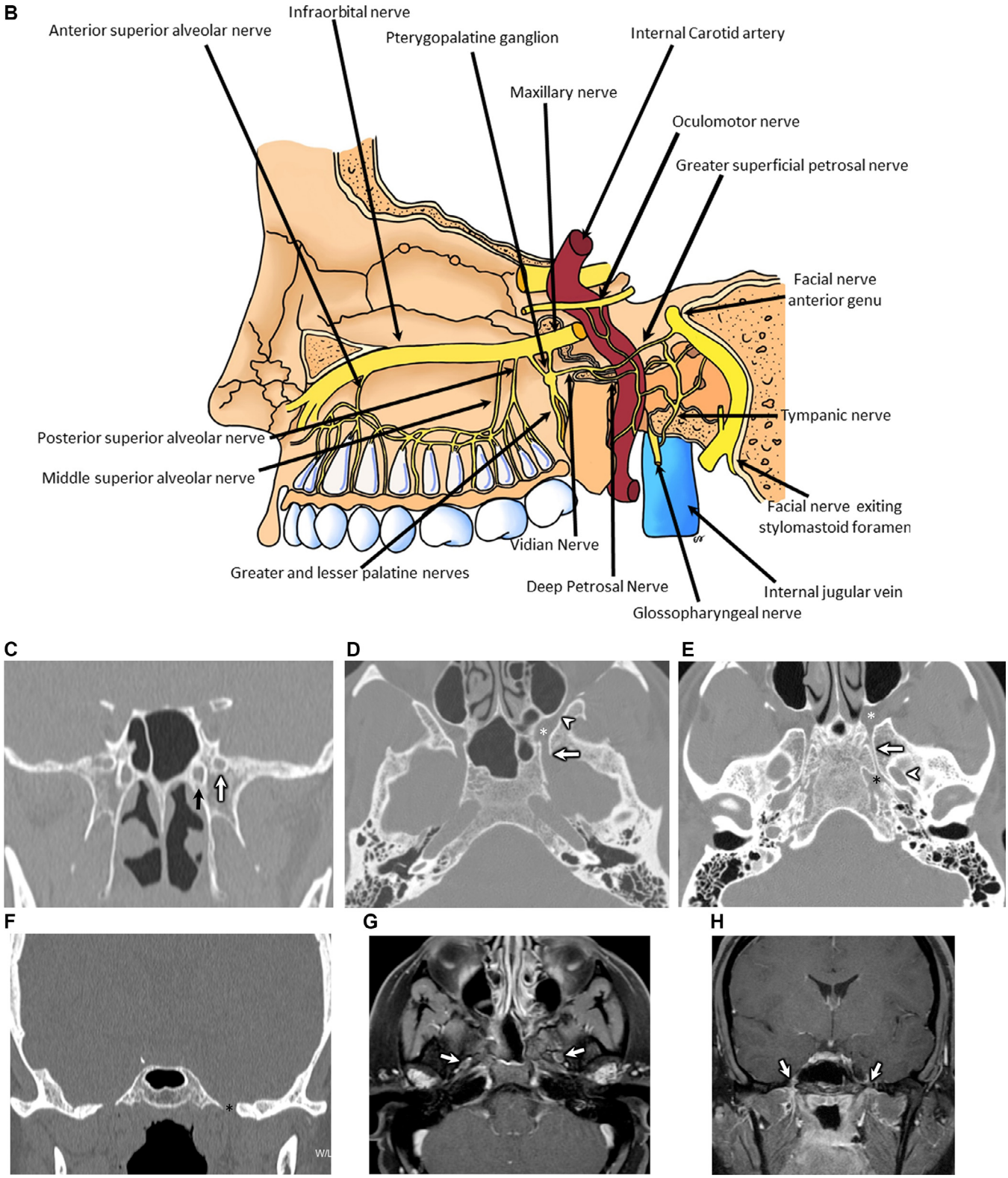

Figure 4 Continued.

ophthalmic (V1), maxillary (V2), and mandibular (V3). The nerve arises from the ventrolateral aspect of the pons and runs a short course within the prepontine cistern before it enters the trigeminal cave (named Meckel's cave after Johann Friedrich Meckel the Elder). Within this CSF filled meningeal cave/recess situated posterolateral to the cavernous sinus, is the large trigeminal ganglion (named Gasserian ganglion after Johann Lorenz Gasser). The 3 components (gems) of the fifth nerve separate within the trigeminal cave. The V1 and V2 divisions of the trigeminal nerve are purely sensory and transit the lateral wall of the cavernous sinus while the V3 division has both sensory and motor components and exits the skull base

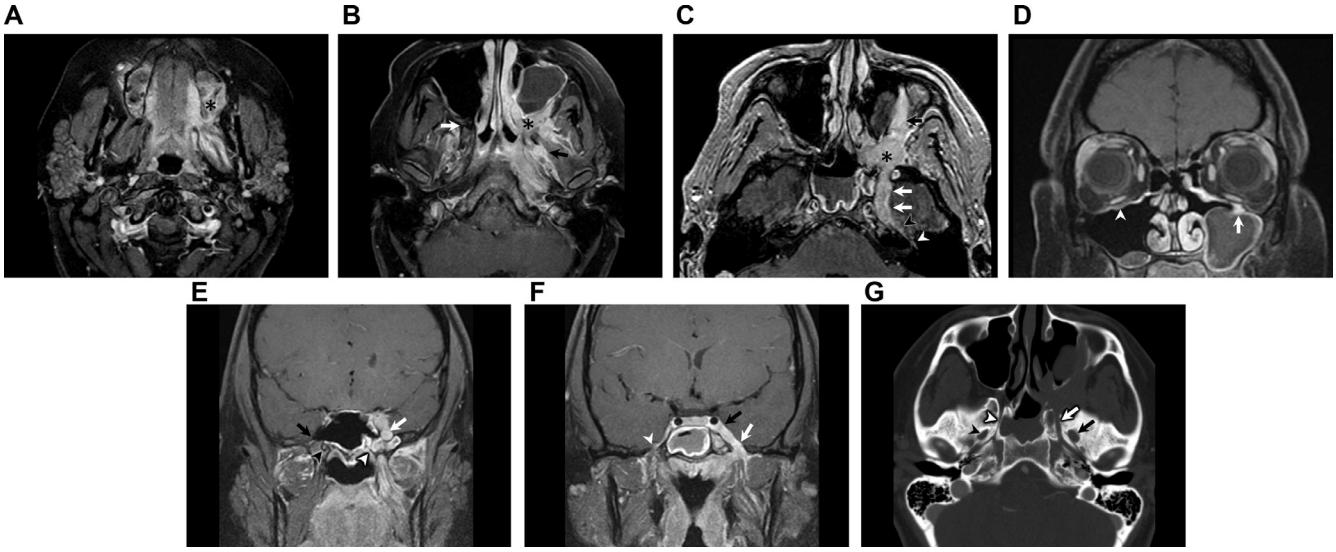

Figure 5 Surgically-proven adenoid cystic carcinoma of the left maxillary sinus with perineural tumor spread extending intracranially in a 22-year-old female with facial paresthesias. (A) Axial T1-weighted postcontrast fat-saturated image shows an infiltrative enhancing tumor within the eroded left superior alveolus and left hard palate (black asterisk). (B) Axial T1-weighted postcontrast fat-saturated image. Perineural spread of tumor extends into the left pterygopalatine fossa (black asterisk). There is also involvement of the left V3 (black arrow) which enhances abnormally just after exiting foramen ovale. Note the normal appearing right pterygopalatine fossa (white arrow). (C) Axial T1 weighted spoiled gradient fat-saturated image. There is extensive perineural spread of the tumor involving V2 branches from the left pterygopalatine fossa (black asterisk) including antegrade along the infraorbital nerve (black arrow) and retrograde to the left cavernous sinus and the Meckel's cave (white arrows). Perineural tumor spread from the 5th to 7th nerve branches is present with marked thickening of the left greater superficial petrosal nerve (black arrowhead) extending to the geniculate fossa (white arrowhead). D-F) Coronal T1-weighted postcontrast fat-saturated images. (D)There is perineural spread of tumor to the left CN V2 in the infraorbital groove (white arrow). Compare this to the normal-appearing nerve in the right infraorbital groove. (E) There is marked enlargement of left CN V2 in the foramen rotundum (white arrow) and the left vidian nerve within the vidian canal (white arrowhead). Compare these to the normal-appearing right foramen rotundum (black arrow) and right vidian canal (black arrowhead). (F). Perineural spread of tumor extends along the thickened left V3 in foramen ovale (white arrow). Perineural tumor spread expands the left cavernous sinus (black arrow). Compare this to the venous enhancement in the normal right foramen ovale (white arrowhead). (G) Axial contrast-enhanced CT in bone window shows abnormal widening of the left vidian canal (white arrow) and left foramen ovale (black arrow) secondary to perineural tumor spread. Compare these to the normal-appearing right vidian canal (white arrowhead) and right foramen ovale (black arrowhead).

via foramen ovale (Figs. 3 and 4). PNTS involving the cavernous sinus or Meckel's cave can extend antegrade along V1 and/or V2 as well as retrograde along the cisternal fifth nerve to the pons.

The Ophthalmic Nerve (V1)

The smallest division of the trigeminal nerve, the ophthalmic nerve, provides sensory innervation to the cornea, conjunctiva, lacrimal gland, part of the mucous membrane of the nasal cavity, skin of eyelids, eyebrow, forehead, and nose.[14] After its origin along the lateral wall of the trigeminal cave it runs anteriorly through the lateral wall of the cavernous sinus, below the third and fourth cranial nerves (Fig. 3B). Just before entering the orbit through the superior orbital fissure, it divides into the lacrimal, frontal, and nasociliary branches (Fig. 4A).

The lacrimal nerve deserves special mention since it participates in one of the several associations between the trigeminal and the facial nerves. The secretomotor fibers that innervate the lacrimal gland arise in the facial nerve and are carried in the greater superficial petrosal nerve (GSPN). The GSPN exits the facial nerve at the facial hiatus in the region of the geniculate fossa and joins the deep petrosal nerve to form the nerve of the pterygoid canal, which is commonly known as the vidian nerve. This nerve is contained in the vidian canal and enters the pterygopalatine fossa (PPF) (Fig. 4B-E). The secretomotor fibers relay in the pterygopalatine ganglion, where postganglionic fibers are carried in the zygomatic and zygomaticotemporal branches of V2. In order to reach their destination within the lacrimal gland, these fibers join the lacrimal nerve through a small interconnection. This interconnection therefore not only links the facial and trigeminal nerves but also physically joins V1 and V2. Tumors invading the PPF via direct contiguous spread or by PNTS involving the branches of CN V, can involve the vidian nerve and the GSPN with further retrograde spread to the facial nerve (Figs. 1 and 5).

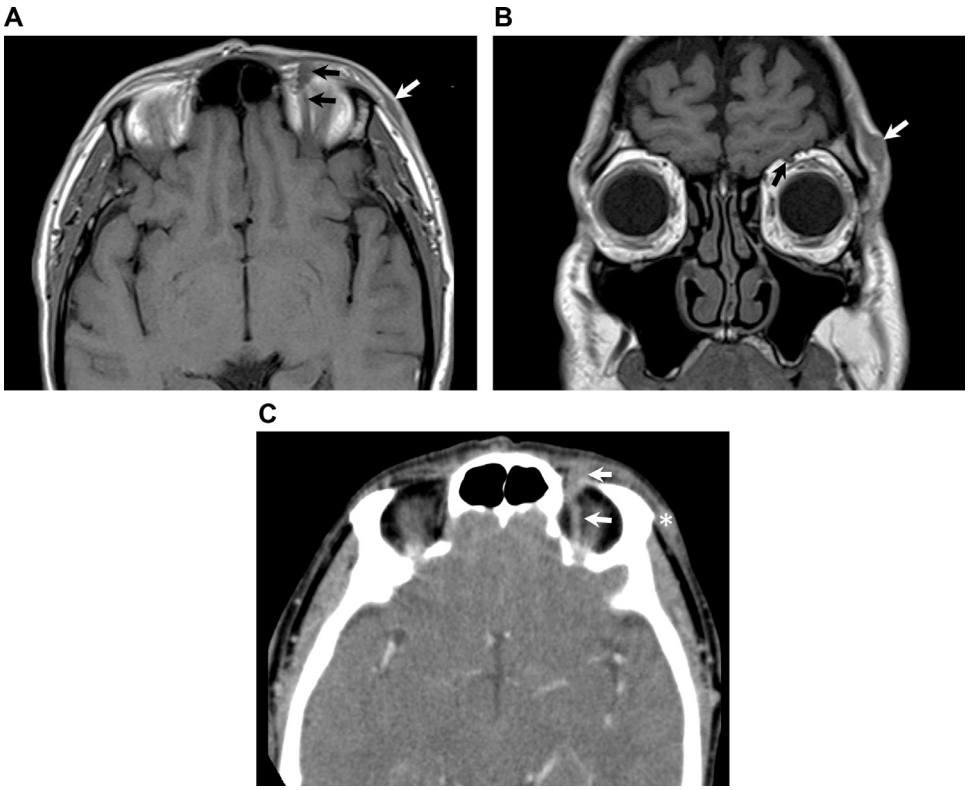

Figure 6 Perineural tumor spread from cutaneous squamous cell carcinoma along V1. (A) Axial T1 weighted image. There is a left temporal and upper eyelid cutaneous squamous cell carcinoma causing thickening of the left temporal subcutaneous tissue (white arrow) with perineural tumor spread to branches of V1 causing enlargement of the left supraorbital nerve (black arrows). (B) Coronal T1-weighted image without contrast. The ovoid left temporal cutaneous squamous cell carcinoma (white arrow) is well seen. Associate perineural tumor spread with an enlarged left supraorbital nerve (black arrow) is well seen against the background of T1 hyperintense normal orbital fat. (C) Axial contrast-enhanced CT. The left temporal subcutaneous thickening (white asterisk) from the cutaneous squamous cell carcinoma and the perineural tumor spread causing thickening of the left supraorbital nerve (white arrows) are also visible by CT.

The frontal nerve is more or less a continuation of V1 and divides into supratrochlear and supraorbital branches. The supraorbital nerve passes through the supraorbital foramen and terminates in medial and lateral branches. It provides sensory innervation to the skin of the forehead and scalp, as far back as the lambdoid suture. The supratrochlear nerve exits the orbit between the trochlear apparatus and the supraorbital foramen and innervates the skin of the lower forehead and the upper eyelid.[7]

The nasociliary nerve runs along the medial wall of the orbit and carries sensation from the mucosa of the anterior nasal septum, lateral nasal cavity, and skin of the ala and apex of the nose.

Skin cancers affecting the forehead, anterior scalp, and upper eyelid can involve the branches of V1 (Fig. 6). Lacrimal gland malignancies can potentially involve the lacrimal nerve. Tumors invading the PPF can involve V1 branches in an antegrade fashion.

The Maxillary Nerve (V2)

The second division of the trigeminal nerve is also a sensory nerve. It runs along the lateral wall of the cavernous sinus for a short distance (Fig. 3B) before it enters a bony canal at the skull base known as the foramen rotundum (Fig. 4C-D). Within the intracranial segment, it gives off the middle meningeal nerve which supplies the dura.

At the anterior end of the foramen rotundum, V2 enters the pterygopalatine fossa (PPF), where it gives off the zygomatic nerve, 2 sphenopalatine branches and multiple posterior superior alveolar branches (Fig. 4A-B). The zygomatic nerve enters the orbit through the inferior orbital fissure and divides into the zygomaticofacial and zygomaticotemporal branches. The latter innervates the skin of the side of the forehead and the temporal region; and contains postganglionic parasympathetic fibers which are carried to the lacrimal nerve, as has been described above. In some cases, where the lacrimal nerve is absent on a developmental basis, the zygomaticotemporal nerve innervates its territory including the lacrimal gland.[14] The zygomaticofacial nerve emerges on the face through a foramen in the zygomatic bone and innervates the skin of the prominence of the cheek. The sphenopalatine branches continue as palatine nerves and enter the greater and lesser palatine foramina to innervate the palate, tonsil, and the inferior nasal cavity. Tumors of the palate, gingiva, and sinonasal cavity can involve these branches and grow along the palatine nerves to the pterygopalatine fossa in a

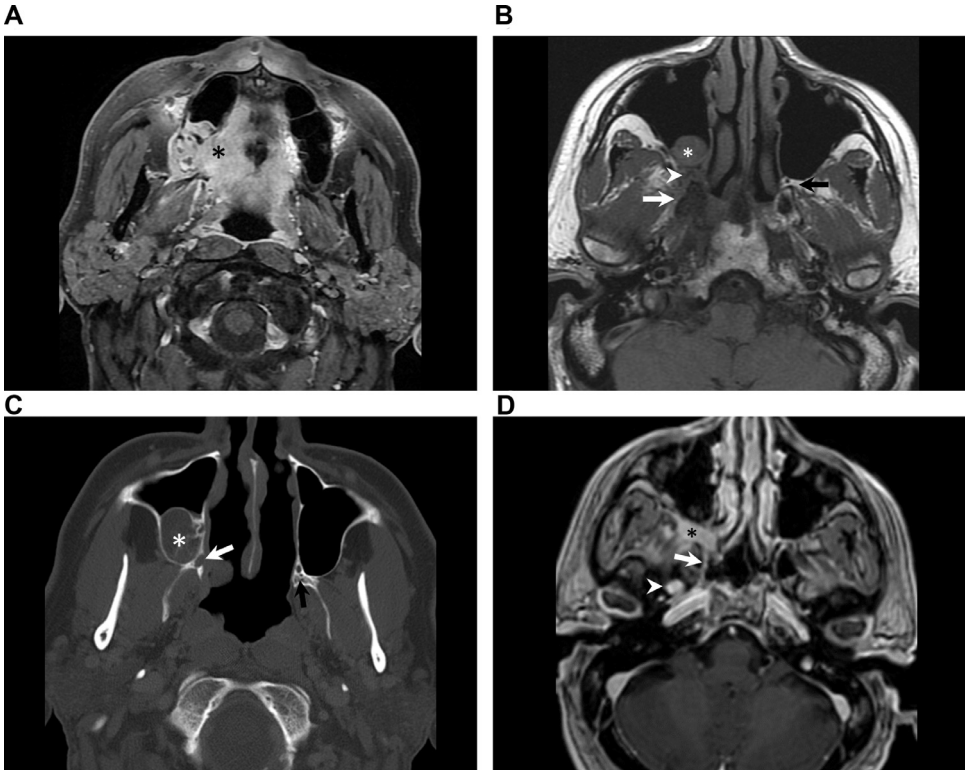

Figure 7 Right maxillary and hard palate adenoid cystic carcinoma with perineural spread along the palatine nerves to the pterygopalatine fossa and intracranially. (A) Axial T1-weighted postcontrast fat-saturated image. There is a large infiltrative enhancing biopsy proven adenoid cystic carcinoma arising from the right inferior maxillary sinus (black asterisk) and invading the hard palate and adjacent alveolus. (B) Axial T1 weighted image without contrast. Perineural tumor spread arising from the adenoid cystic carcinoma of the right inferior maxillary sinus (white asterisk) effaces the fat of the right pterygopalatine fossa (white arrowhead) via the palatine canals and infiltrates the right pterygoid plate (white arrow). Note normal T1 hyperintense fat signal in the left pterygopalatine fossa (black arrow). (C) Axial contrast-enhanced CT in bone window. The adenoid cystic carcinoma mass remodels the posterior right maxillary sinus (white asterisk). The right greater palatine canal (white arrow) is abnormally enlarged secondary to retrograde perineural tumor spread. Compare to this to normal sizes of the left greater and lesser palatine canals (black arrow). (D) Axial T1 weighted spoiled gradient fat-saturated image. There is extensive perineural tumor spread within the right pterygopalatine fossa (black asterisk), right vidian canal (white arrow), and right foramen ovale (white arrowhead).

retrograde fashion and extend intracranially (Fig. 7). The posterior superior alveolar branches innervate the maxillary molar teeth, the gingiva around the molars, the adjacent buccal mucosa, and parts of the maxillary sinus.

Anterior to the PPF, V2 enters the orbit through the inferior orbital fissure and traverses the infraorbital groove and canal. Within the infraorbital groove it gives off the anterior and middle superior alveolar nerves supplying the maxillary teeth and gingiva. The V2 exits the infraorbital foramen and terminates into branches that innervate the skin of the side of nose, lower eyelid, and upper lip. Cutaneous malignancies such as SCC and melanoma in these regions can thus involve the V2 branches (Fig. 8).

Infiltration of fat within the PPF (Figs 1, 5, 7 and 9) is an ominous sign, one that increases suspicion for PNTS manifold given the presence of many V2 branches within the PPF and its strategic location adjacent to the maxillary sinus, palate, orbit, and nasopharynx. Presence of tumor within the PPF creates the possibility of trans-spatial spread along multiple neural routes and also by direct invasion.

The Mandibular Nerve (V3)

V3 is the largest division of the trigeminal and has both sensory and motor components. Soon after its origin in the trigeminal cave, V3 exits the skull base through the foramen ovale and divides into an anterior (predominantly motor) and a posterior (predominantly sensory) trunk. The motor branches of the anterior trunk supply the muscles of mastication, with the exception of one branch, the buccinator nerve, which supplies the mucosa lining the inner surface of the buccinator muscle. The more widespread primarily sensory branches of the posterior trunk, make it more susceptible to PNTS. The posterior trunk divides into the auriculotemporal, inferior alveolar, and lingual nerves.

The auriculotemporal nerve is another area of communication between the trigeminal and facial nerves and forms this link in 2 forms (Fig. 4A). Firstly, it carries the postganglionic parasympathetic secretomotor fibers destined for the parotid gland, which merge into this nerve via branches of the otic ganglion, where preganglionic fibers arising from the VII and IX nerves relay. Secondly, the auriculotemporal

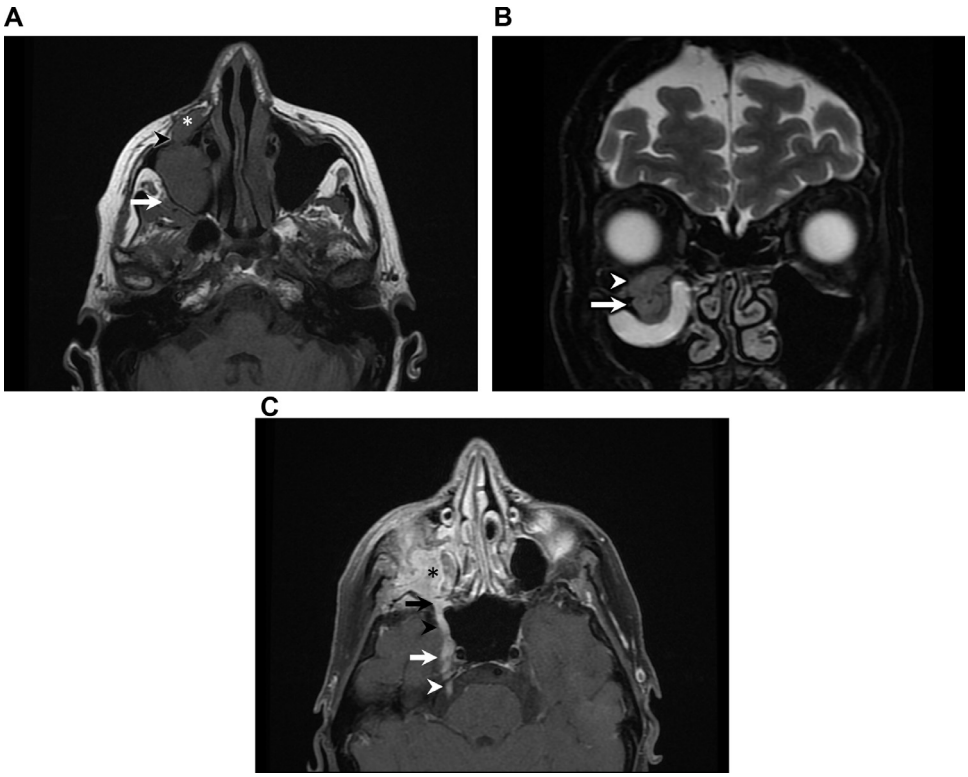

Figure 8 Extensive perineural spread of malignant melanoma in a patient with a palpable right facial mass. (A) Axial T1-weighted image demonstrates a mass in the right subcutaneous tissues (white asterisk) effacing the right infraorbital foramen (black arrowhead). Abnormal soft tissue replaces the right retroantral fat (white arrow) along the course of V2, raising suspicion for perineural spread of tumor. There is abnormal soft tissue opacifying the right maxillary sinus. (B) Coronal T2-weighted fat-saturated image. The tumor has T2 intermediate signal characteristics with extensive perineural spread of tumor along right V2, enlarging the right infraorbital nerve (arrow) and extending into the inferior right orbit (arrowhead). There is adjacent right maxillary sinus T2 hyperintense mucosal thickening. (C) Axial T1-weighted postcontrast fat-saturated image demonstrates enhancing tumor in the inferior right orbit (black asterisk) with perineural tumor spread involving right V2 in the right pterygopalatine fossa (black arrow), along widened foramen rotundum (black arrowhead) back to the Gasserian ganglion in Meckel's cave (white arrow) to the cisternal right fifth nerve (white arrowhead).

nerve gives branches to and traverses the parotid gland, the parenchyma of which also forms the bed of the *pes anserinus*, the neural web formed by the branching of the facial nerve. Radiologists are often trained to assess the facial nerve for PNTS in cases of adenoid cystic carcinoma. Remember to also evaluate the course of the auriculotemporal nerve which can be affected by PNTS from parotid and cutaneous malignancies. Involvement of this nerve may be seen in its course within the stylomandibular tunnel (Figs. 1, 10, and 11). Besides supplying the parotid gland, the auriculotemporal nerve innervates the skin of the temporal region, upper face, the pinna, and external acoustic meatus. The auriculotemporal nerve can be involved by adenoid cystic carcinomas of the parotid gland or by cutaneous malignancies of the upper face, pinna, and the external auditory meatus. Symptoms when present include periauricular discomfort, otalgia, and temporomandibular joint pain or dysfunction. Simultaneous V3 or VII symptoms can be an ominous sign of extensive PNTS.

The second branch of V3, the lingual nerve, is also a conduit for one of the branches of the facial nerve and forms another means of communication of the facial and trigeminal nerves. The special sensory gustatory fibers from the anterior two-thirds of the tongue, are first carried in the lingual nerve (V3) before they exit the lingual nerve and enter the chorda tympani (CN VII). The V3 component of the lingual nerve carries the general somatic sensation from the anterior two-thirds of the tongue mucosa. The nerve lies lateral to the tongue between the hyoglossus and mylohyoid muscles. Squamous cell carcinomas of the floor of mouth and submandibular gland can involve the lingual nerve.

The inferior alveolar nerve descends and courses laterally. Before entering the mandibular canal, it gives off a branch known as the mylohyoid nerve which provides motor innervation to the mylohyoid and anterior belly of digastric muscles. The nerve traverses the bony canal within the mandible (the mandibular or inferior alveolar nerve canal) and gives off several branches that supply the mandibular teeth and gingiva. The nerve exits the mandibular canal anteriorly at the mental foramen, where it terminates into incisive and mental nerves. The mental nerve supplies the skin of the chin, and the skin and mucosa of the lower lip. Squamous cell cancers of the mandibular

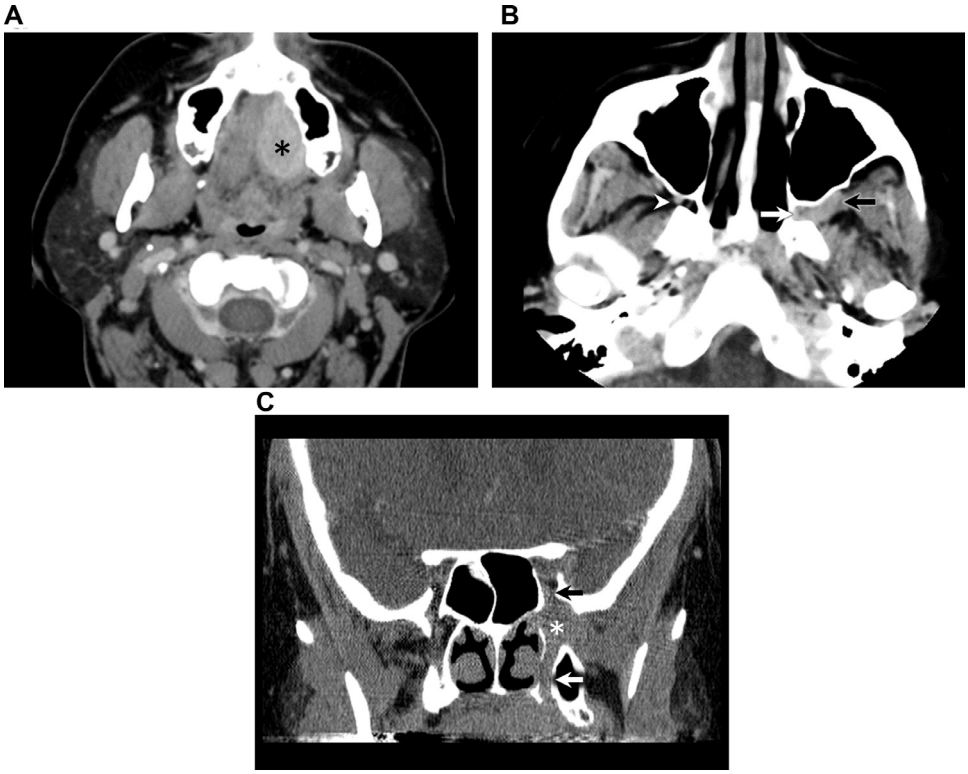

Figure 9 Perineural spread of tumor from hard palate adenoid cystic carcinoma infiltrates the pterygopalatine fossa. (A) Axial contrast-enhanced CT. There is an enhancing mass arising from the left hard palate (black asterisk). (B) Axial contrast-enhanced CT. Perineural tumor spread via the left greater palatine obliterates the fat of the left pterygopalatine fossa (white arrow), with extension through the left pterygomaxillary fissure effacing the adjacent left retromaxillary fat pad (black arrow). Compare this to the normal appearing right pterygopalatine fossa (white arrowhead). (C) Coronal reformat contrast-enhanced CT. Extensive perineural spread of tumor widens the left great palatine foramen (white arrow), fills the left pterygopalatine fossa (white asterisk) and extends superiorly into the left inferior orbital fissure (black arrow) where the fat planes are effaced on CT. Surgical pathology confirmed adenoid cystic carcinoma.

gingiva and retromolar trigone; and cutaneous malignancies of the lower lip and mandibular skin can involve the inferior alveolar nerve and the larger V3 stem in a retrograde manner (Figs. 1 and 11).

The Facial Nerve (CN VII)

The facial nerve arises from the pons and runs a cisternal course from its origin to its entry into the internal auditory canal (IAC) (Fig. 12). Following its root exit zone

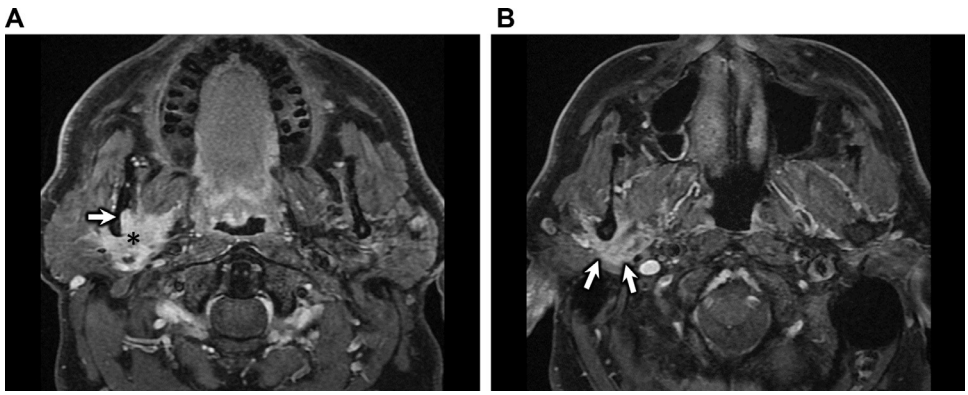

Figure 10 Perineural tumor spread involving the auriculotemporal nerve from deep parotid adenoid cystic carcinoma. (A) Axial T1-weighted postcontrast fat-saturated image shows an enhancing surgically-proven adenoid cystic carcinoma arising from the deep lobe of the right parotid gland (black asterisk). There is perineural tumor spread along the right inferior alveolar nerve widening the mandibular foramen (white arrow). (B) Axial T1-weighted postcontrast fat-saturated image shows perineural tumor spread along the characteristic course of the right auriculotemporal nerve (white arrows) which is abnormally enlarged and enhancing, extending through the right stylomandibular tunnel and coursing posteriorly to the right mandibular ramus.

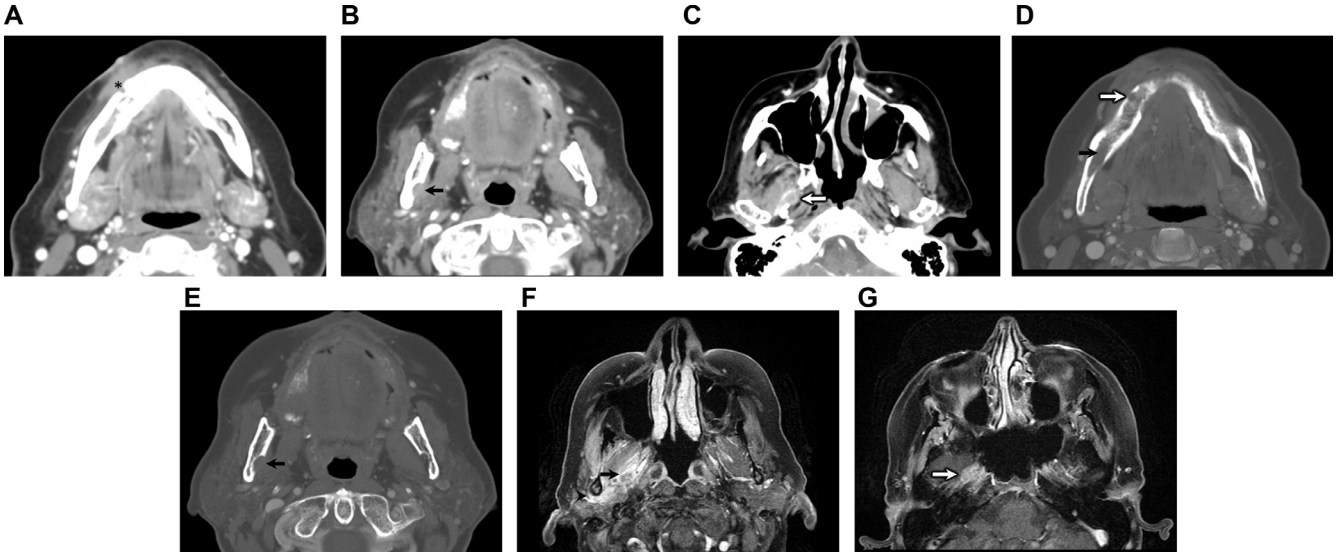

Figure 11 Intracranial perineural spread of tumor along V3 branches from a biopsy proven right mandibular alveolar squamous cell carcinoma. (A) Axial contrast-enhanced CT in soft tissue (A-C) and bone windows (D, E). There is abnormal soft tissue effacing the (A) right mental foramen fat pad (black asterisk), (B) the right mandibular foramen (black arrow) (C) and the juxtaforaminal fat pad surrounding right V3 (white arrow) just after it exits right foramen ovale, indicating extensive perineural spread of tumor. (D) On bone windows, associated abnormal widening of the (D) mental foramen (white arrow), inferior alveolar nerve canal (black arrow) and (E) right mandibular foramen (black arrow) is seen. (F, G) Axial T1-weighted postcontrast fat-saturated images demonstrate (F) enhancing perineural spread of tumor involving right V3 (black arrow) just after exiting foramen ovale with involvement of the thickened, enhancing right auriculotemporal nerve (black arrowhead) posterior to the right mandibular ramus. (G) Perineural spread of tumor abnormally enhances intracranially in the right foramen ovale (white arrow).

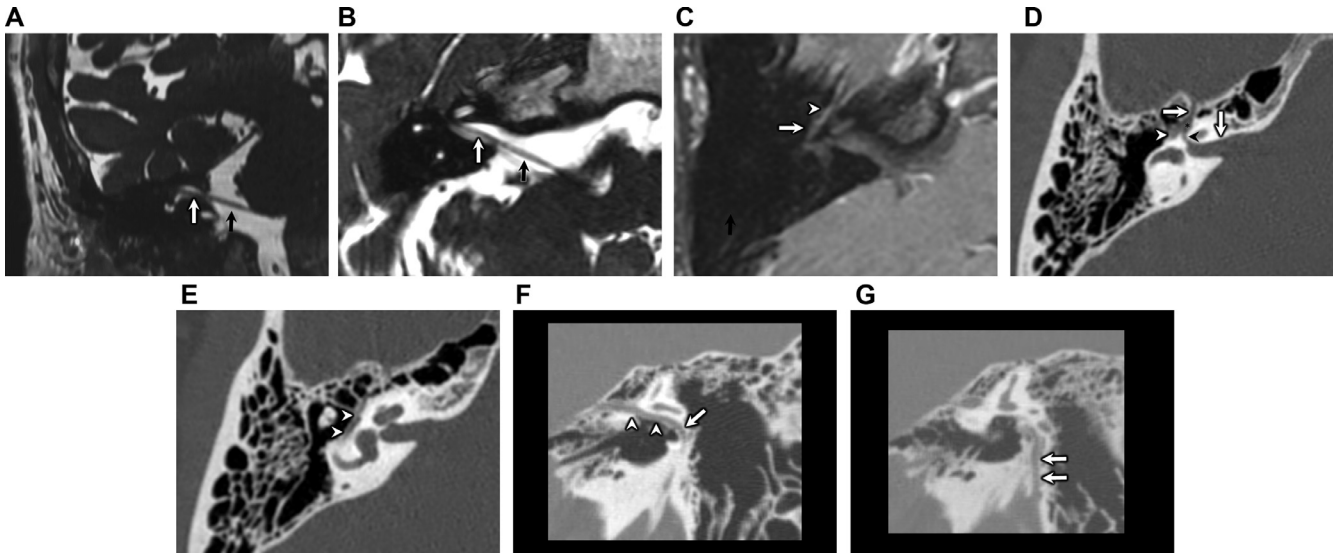

Figure 12 Normal facial nerve anatomy. Coronal (A) and axial (B) fast imaging employing steady-state acquisition images demonstrate the normal thickness and course of the cisternal (black arrows) and canalicular (white arrows) segments of the right facial nerve traversing the cerebellopontine angle. (C) Axial T1-weighted postcontrast fat-saturated image. Normal smooth enhancement of the right geniculate ganglion (white arrowhead) and tympanic segment (white arrow) of the facial nerve is typically seen and should not be mistaken as abnormal. The cisternal and canalicular segments of the facial nerve do not normally enhance. (D) and (E) Axial temporal CT without contrast. (D) The normal internal auditory canal is funnel shaped (vertical white arrow). The labyrinthine segment (black arrowhead) takes a sharp anterior turn toward the geniculate fossa (black asterisk) where the greater superficial petrosal nerve exits the facial hiatus (horizontal white arrow) and extends anteriorly toward the foramen lacerum. The facial nerve then makes a sharp turn posteriorly to form the tympanic segment (white arrowhead) that courses along the medial margin of the middle ear cavity. (E) The tympanic segment (white arrowheads) of the facial nerve courses along the medial margin of the middle ear cavity. (F) and (G) Sagittal oblique temporal bone CT reformat. (F) The tympanic segment (white arrowheads) of the facial nerve is seen coursing posteriorly, just inferior to the lateral semicircular canal along the along the medial margin of the middle ear cavity. At the posterior genu (white arrow), the facial nerve then turns inferiorly. (G) The vertical or mastoid segment (white arrows) then courses caudally and exits the stylomastoid foramen.

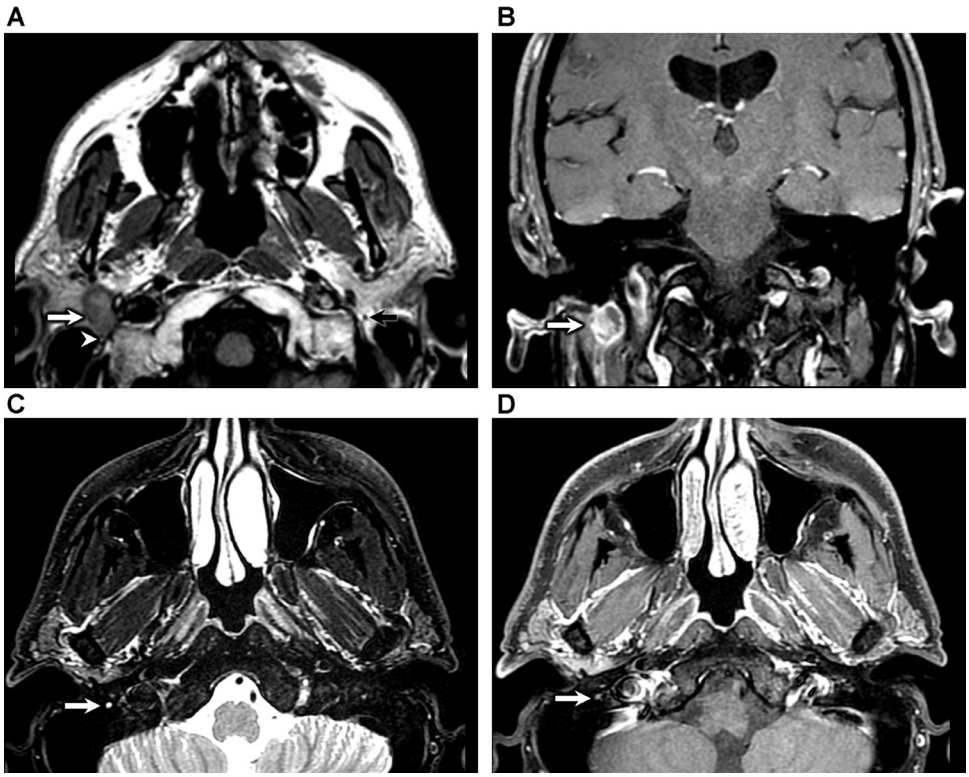

Figure 13 Malignant perineural tumor spread to the facial nerve from a parotid mass in a 55-year-old male with facial paralysis. (A) Axial T1 weighted image without contrast. There is a T1 hypointense round mass in the right parotid gland (white arrow) extending to the right stylomastoid foramen (white arrowhead), effacing the right facial nerve. Compare this to the normal left facial (black arrow) nerve seen surrounded by fat just after exiting left stylomastoid foramen. (B) Coronal T1-weighted postcontrast fat-saturated images confirms a solid enhancing mass (white arrow) in the deep right parotid gland just below the stylomastoid foramen. (C) The distal vertical segment of the right facial nerve (white arrow) is abnormally T2 hyperintense and enlarged with (D) asymmetric enhancement (white arrow) concerning for malignant perineural tumor spread, which was confirmed surgically, from a primary parotid mucoepidermoid carcinoma.

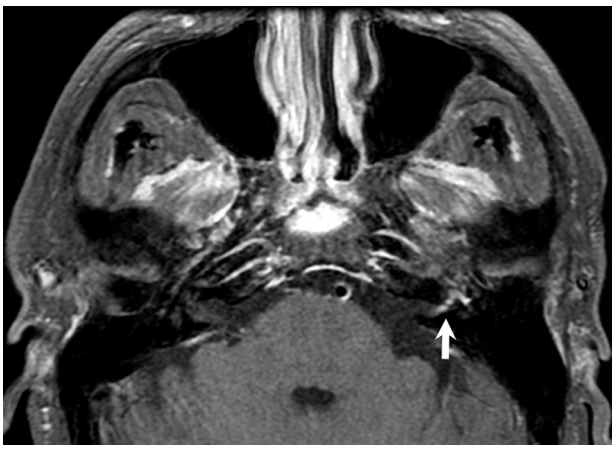

Figure 14 Bell's palsy with facial nerve neuritis in a 60-year-old male with new onset of facial nerve paralysis. Axial T1-weighted postcontrast fat-saturated image demonstrates smooth linear enhancement and enlargement of the distal intracanalicular, labyrinthine and anterior tympanic segments of the left facial nerve (white arrow) characteristic of neuritis. The patient's facial nerve palsy and the abnormal enhancement both resolved as is common in the normal course of Bell's palsy.

from the pontomedullary sulcus, the cisternal segment of the facial nerve can be divided into multiple segments (the attached segment, transitional segment, root detachment zone, and true cisternal segment) important in the pathophysiology of hemifacial spasm.[15] Within the IAC, i.e., the canalicular segment of the nerve lies in the anterosuperior quadrant. It courses anterolaterally within the petrous bone to form the labyrinthine segment. It then takes a sharp posterolateral turn, the angle thus formed called the anterior genu. The GSPN exits the facial nerve at the genu and courses anteriorly, inferior to the trigeminal cave. The posterolateral course of the facial nerve runs on the medial wall of the middle ear cavity and is therefore called the tympanic segment. The nerve then takes another turn (posterior genu) close to the pyramidal process (into which it sends its stapedial branch) and now travels inferiorly within the mastoid bone to form the mastoid segment. The nerve exits at the stylomastoid foramen and divides into its 5 terminal branches within the substance of the parotid gland (pes anserinus = goose foot — formed by the branching facial nerve).

PNTS to the facial nerve can occur by direct contiguous involvement complicating parotid malignancies, cutaneous

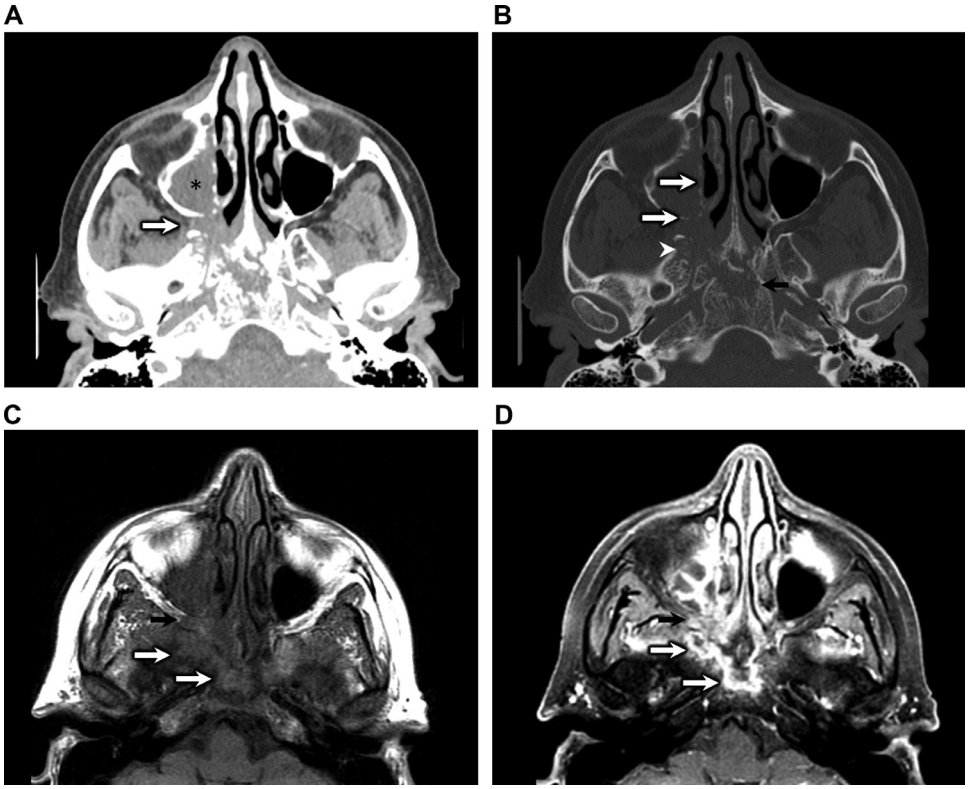

Figure 15 (A) Surgically proven mucormycosis involving the pterygopalatine fossa. (A,B) Axial CT without contrast. (A) There is abnormal soft tissue effacing the right pterygopalatine fossa (white arrow) with adjacent complete opacification of the right maxillary sinus (black asterisk). (B) Bone windows demonstrate areas of subtle erosion along the right maxillary sinus (white arrows), involving the right pterygoid process (white arrowhead) and the clivus (black arrow), indicating an aggressive process. (C) Axial T1-weighted image confirms abnormal central skull base T1-hypointense marrow (white arrows) and soft tissue in the right pterygopalatine fossa (black arrow) which on (D) axial T1-weighted postcontrast fat-saturated image demonstrates abnormal enhancement, respectively. Endoscopic surgery confirmed suspected invasive fungal sinusitis in this 60-year-old female acutely ill bone marrow transplant patient.

malignancies involving the parotid gland or can occur secondarily via its multiple connections to the trigeminal nerve that have been described previously, including the GSPN, the auriculotemporal nerve and the chorda tympani (Figs. 1, 5, and 13).

Aside from wispy enhancement at the anterior genu and the tympanic segments of the nerve due to vasa nervorum, enhancement elsewhere, or thick intense enhancement should be viewed with suspicion.[16] Loss of fat pad and enhancement at the stylomastoid foramen also raises suspicion for PNTS. Finally widening of the facial nerve canal and frank osseous erosion are more definitive signs.

The Spinal Nerves

The trigeminal and facial nerves dominate the discussion of PNTS. This however should not take our attention away from the fact that a large part of the sensory innervation of the skin of the head and neck is done by the branches of the superficial cervical plexus formed by the ventral divisions of the first 4 spinal nerves. Cutaneous malignancies of the head and neck can involve these nerve branches and have been described in case reports in the literature.[17] A mindfulness of this fact can save humiliation and potential litigation to the interpreting radiologist.

Why is It Important to Comment on PNTS?

Several reasons have been given for the importance of diagnosing PNTS. The following have stood out to us the most:

1. If PNTS is detected before surgery, it helps to plan surgery and ensure a tumor free margin.
2. If total tumor resection is unachievable, it helps to plan further treatment and widen the radiation field.
3. In either case, it helps in prognostication, as PNTS is associated with a worse prognosis.

Post-Treatment Assessment of PNTS

Following treatment for PNTS, pretreatment imaging features of PNTS including effacement of fat planes, foraminal

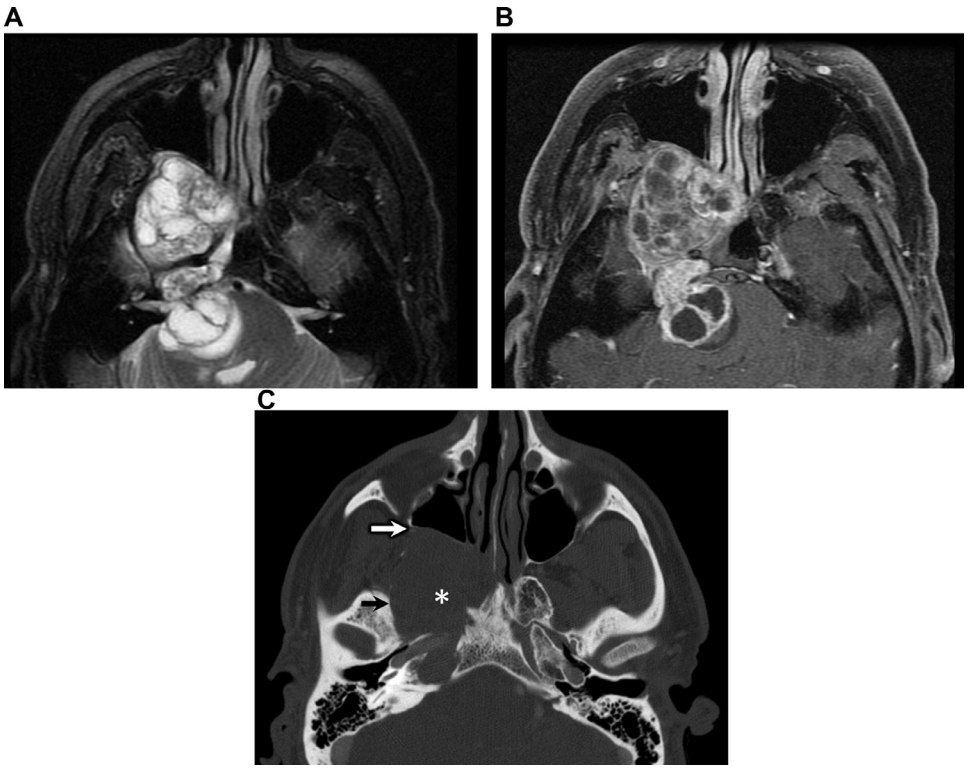

Figure 16 Surgically confirmed schwannoma of the right fifth nerve. (A) Axial T2-weighted fat-saturated and (B) axial T1-weighted postcontrast fat-saturated images demonstrate a large T2 hyperintense extra-axial heterogeneously enhancing fusiform mass with cystic change typical of a schwannoma extending from the right fifth nerve root entry zone along the course of V2 to the right pterygopalatine fossa. (C) Axial contrast-enhanced CT in bone window. There is associated benign-appearing pressure erosion and remodeling of the skull base (black arrow) and posterior wall of the right maxillary sinus (white arrow) due to long-standing slow growth of the schwannoma (white asterisk).

enlargement, nerve thickening, and enhancement often persist. Clinical features of progression or new progressive areas of PNTS are more reliable indicators of treatment failure in the post-treatment setting.

Differential Diagnosis

Mimics of malignant perineural spread of tumor that should be considered in the imaging differential include neuritis, nerve sheath tumor, meningioma, granulomatous disease, leptomeningeal tumor spread and rhinocerebral mucormycosis (Figs. 14-17). These diagnoses should be considered in the appropriate clinical context. Patients with neuritis frequently improve over a short interval (Fig. 14). Patients with rhinocerebral mucormycosis are usually acutely ill, may be diabetic or immunocompromised and have paranasal sinus inflammatory changes extending to adjacent perineural structures and/or the orbits (Fig. 15). Tell-tale signs of certain entities may help in arriving at a diagnosis. The usual fusiform appearance, T2W hyperintensity and occasional cystic change of nerve sheath tumors (Fig. 16); and dural tail, mineralization, vascular narrowing or adjacent hyperostosis of meningiomas may help in this regard (Fig. 17). Finally, a diligent search for an extracalvarial primary tumor as a source of PNTS may help to clinch the diagnosis.

Pitfalls

Normally, the cisternal segment of cranial nerves should not enhance and when enhancement of cranial nerve cisternal segments is present, this should be considered pathologic. However, vascular plexuses can surround and perfuse ganglia or nerves, particularly within skull base canals, foramina or after immediately exiting the skull base. Enhancement of the facial nerve at the geniculate fossa and commonly along the tympanic segment is an example of this (Fig. 12C). Venous enhancement surrounding V3 as it exits foramen ovale (Fig. 4G-H) is also normally common and can lead to an erroneous diagnosis of PNTS if misinterpreted as abnormal. This normal tram-track enhancement pattern can be more readily apparent on thin slice imaging and can lead to a false positive interpretation of PNTS. Thickening of the nerve, loss of fat plane, widening of foramina, and frank bone erosion are more definitive signs of disease spread.

Summary

Perineural tumor spread in head and neck cancers is associated with a worse prognosis. It is most common along the trigeminal and facial nerves and the most common causative neoplasm is squamous cell carcinoma, merely by prevalence. Other tumors commonly associated with PNTS are adenoid

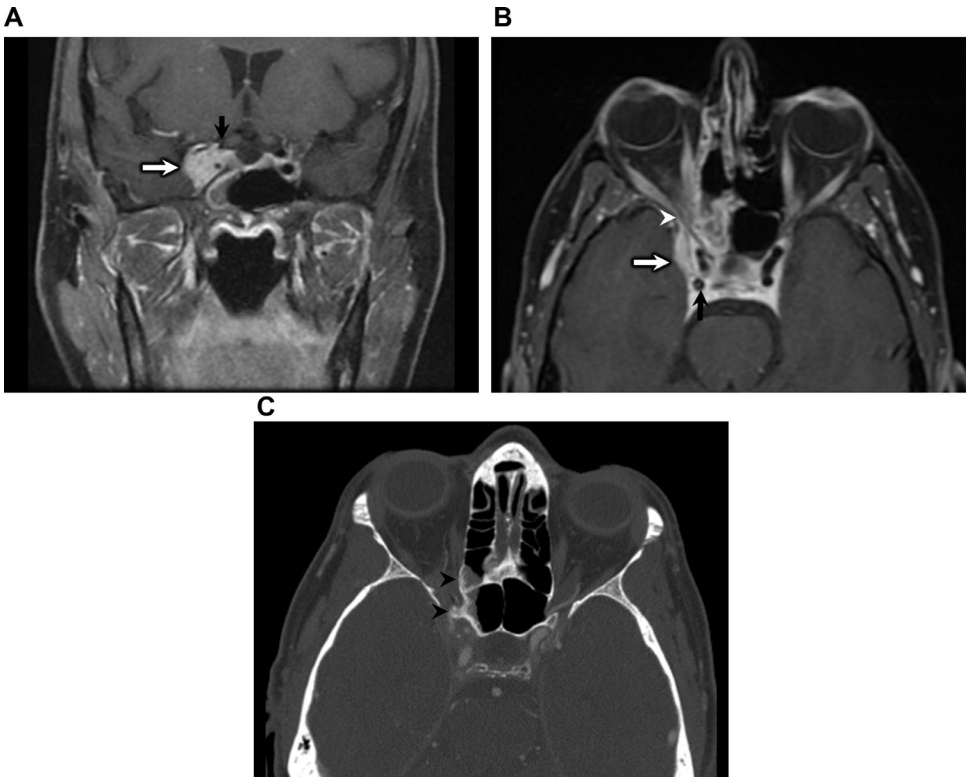

Figure 17 Meningioma of the right cavernous sinus and orbital apex. (A) Coronal and (B) axial T1-weighted postcontrast fat-saturated images demonstrate an avidly enhancing extra-axial mass (white arrows) in the right cavernous sinus with a dural tail extending into the right orbital apex (white arrowhead). There is associated marked narrowing of the cavernous right internal carotid artery (black arrows) and on (C) axial contrast-enhanced CT in bone window there is hyperostosis involving the adjacent sphenoid bone and posterior ethmoid air cells (black arrowheads), indicating this represents a meningioma, which was confirmed surgically.

cystic carcinoma, melanoma and lymphoma. Diagnosing PNTS may take "going the extra mile" on the part of the interpreting radiologist, as it may be subtle and requires an active search along critical landmarks in patients with maxillofacial symptoms or nerve palsies. Knowledge of the nerve anatomy therefore is of supreme importance.

Acknowledgment

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