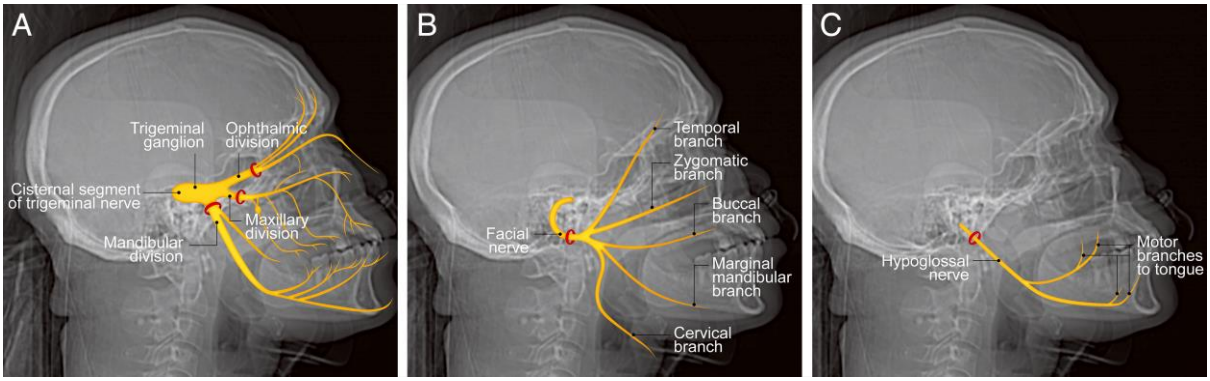
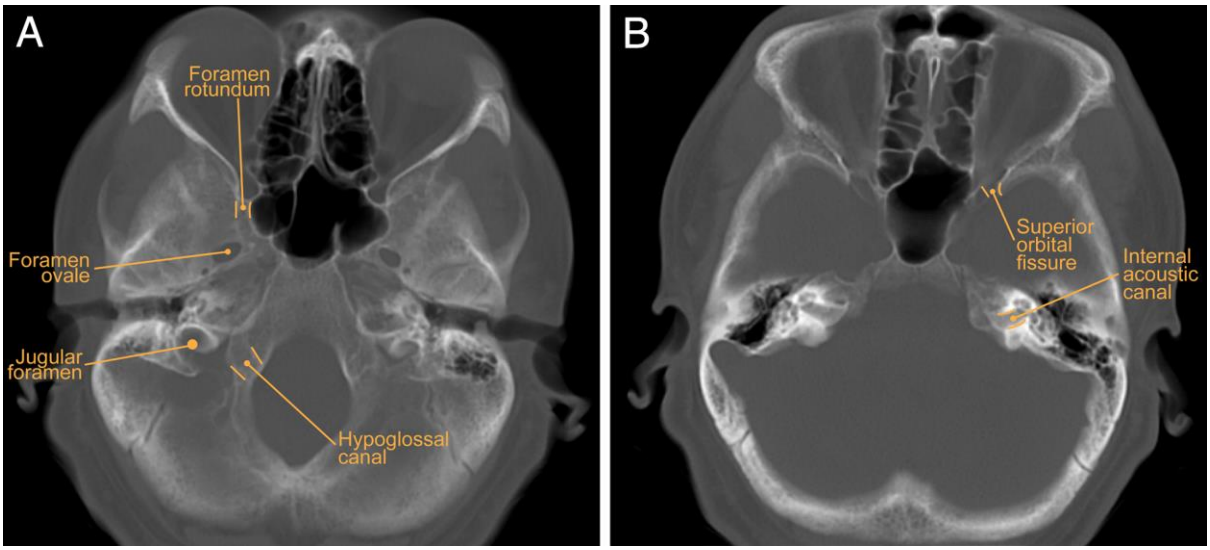
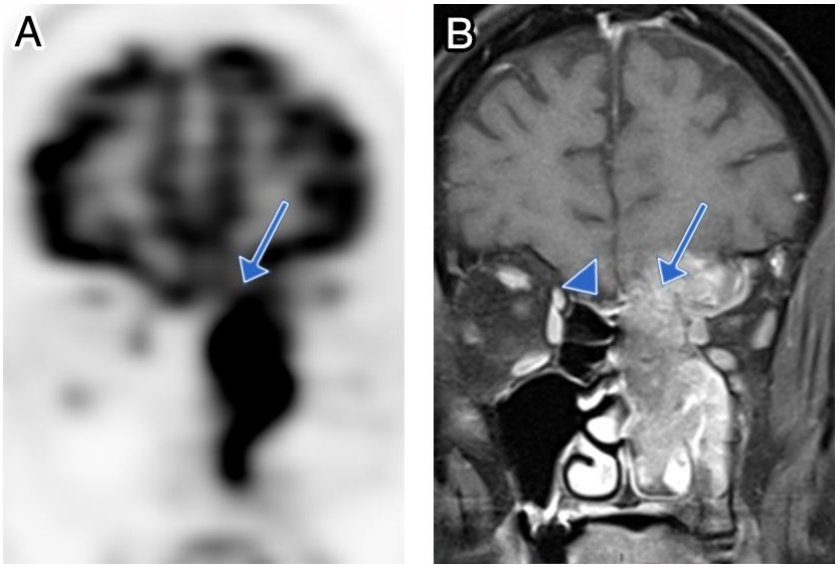


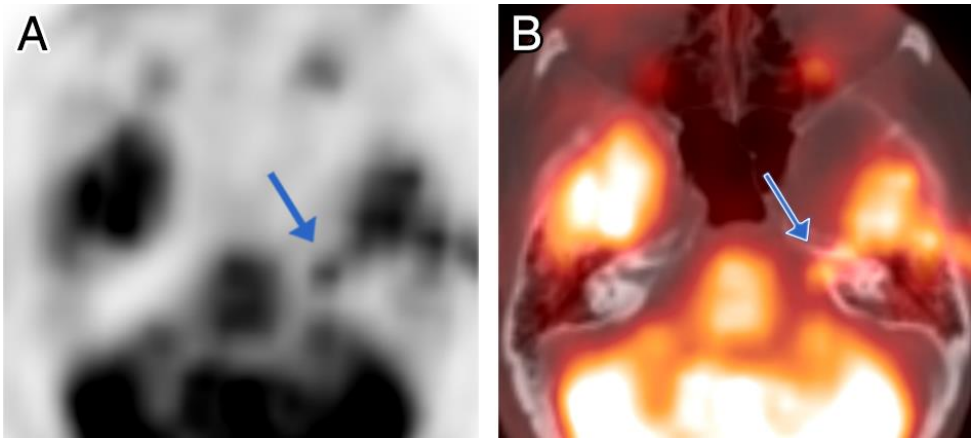
SUPPLEMENTAL FIGURE 1. Illustration of the nerves commonly involved in perineural spread. The trigeminal nerve and its three divisions **(A)**, the facial nerve and its five terminal motor branches **(B)**, and the hypoglossal nerve **(C)** are shown on a lateral skull radiograph.



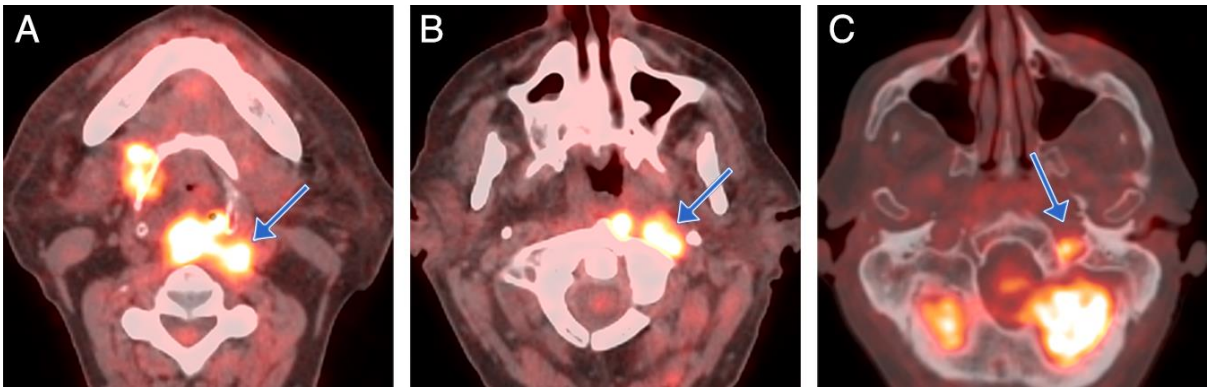
SUPPLEMENTAL FIGURE 2. Bony pathways used by the nerves commonly involved in perineural spread. The maxillary and mandibular divisions of the trigeminal nerve exit the skull through foramen rotundum and foramen ovale, respectively **(A)**. The facial nerve traverses the internal acoustic canal **(B)** before exiting the skull through the stylomastoid foramen. The ophthalmic division of the trigeminal nerve enters the orbit by via the superior orbital fissure **(B)**. The hypoglossal nerve travels through the hypoglossal canal **(A)** to enter the carotid space. The glossopharyngeal nerve, vagus nerve, and spinal accessory nerve enter the carotid space via the jugular foramen **(A)**.



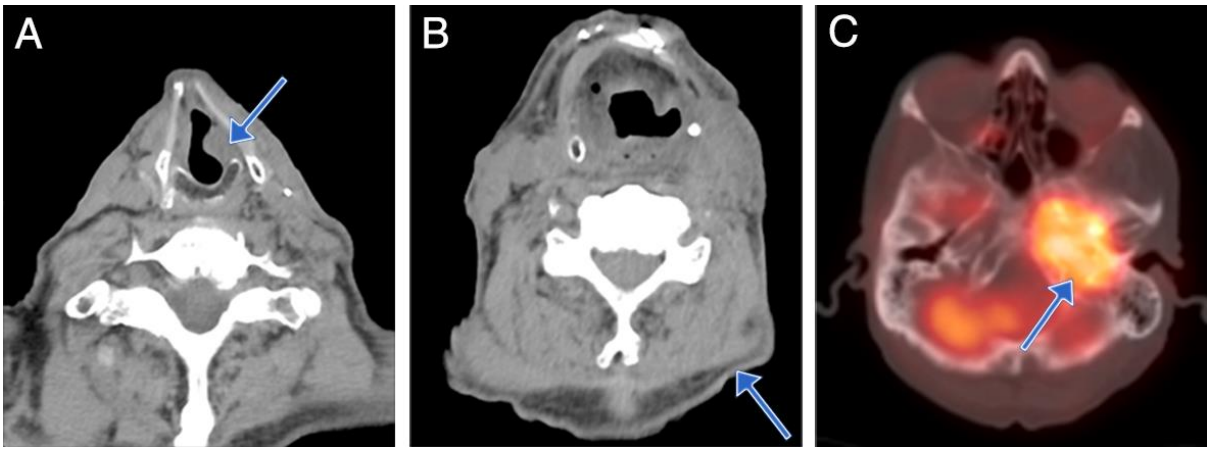
SUPPLEMENTAL FIGURE 3. Cranial nerve I involvement in a patient with poorly differentiated carcinoma of the left sinonasal cavity and hypermetabolic tumor spread through the left cribriform plate (arrow) on coronal 18F-FDG PET image **(A).** Enhancing mass in the left sinonasal cavity invading through the left cribriform plate is seen with left olfactory bulb involvement (arrow) with normal right olfactory bulb (arrowhead) on coronal T1-weighted fat-suppressed post-contrast MRI **(B)**. The tumor was inoperable due to its extensive invasion into the surrounding structures.



SUPPLEMENTAL FIGURE 4. Cranial nerve VIII involvement in a patient with high grade salivary duct carcinoma of the left parotid gland with perineural invasion into the left facial nerve and left facial weakness, status-post surgical excision and radiation therapy, now presenting with complete left-sided sensorineural hearing loss. Axial 18F-FDG PET **(A)** and axial fused PET/CT **(B)** images show abnormal focal radiotracer uptake in the left cerebellopontine angle extending into the left internal acoustic canal (arrow) representing tumor involvement along intracanalicular segment of CN VII. A presumed diagnosis of PNS along CN VIII was made with greater confidence given the location of abnormal FDG uptake and the sensorineural hearing loss.



SUPPLEMENTAL FIGURE 5. Cranial nerves IX, X and/or XI involvement in a patient with poorly differentiated, locally advanced squamous cell carcinoma of the base of tongue status-post chemoradiation therapy, with local recurrence and persistent left-sided neck pain. Axial fused 18F-FDG PET/CT images show an FDG-avid posterior oropharyngeal wall mass extending into the prevertebral space and left retropharyngeal region (arrow) **(A)**, extending superiorly along the left carotid space (arrow) **(B)** into the left jugular foramen (arrow) **(C)**. Given the site of tumor recurrence as well spread along the course of the cranial nerves IX, X and XI in the carotid space and jugular foramen, PNS along one or more of the cranial nerves IX, X, and XI was suspected. The patient had concurrent distant metastatic disease and received palliative care.



SUPPLEMENTAL FIGURE 6. Secondary signs/end-organ dysfunction from cranial nerve involvement by perineural spread of tumor on axial images taken from 18F-FDG PET/CT. A patient developed left vocal cord paresis (arrow) on axial CT **(A)** and left trapezius muscular atrophy (arrow) on axial CT **(B)** secondary to involvement of the left vagus (CN X) and spinal accessory nerves (CN XI), respectively, by a large FDG-avid tumor involving the left skull base including left jugular foramen on axial fused PET/CT (arrow) **(C)**. Asymmetric FDG uptake was not observed on the corresponding PET images due to the low physiologic uptake in these muscles in the resting state.

SUPPLEMENTAL TABLE 1.
Rates of perineural invasion in head and neck cancers by histologic type

	Histologic type	Rate of PNI	Incidence
Common neoplasms	Squamous cell carcinoma (mucosal)	14%-63% (*11*)	95% of non-cutaneous head and neck malignancies (*11*)
	oral cavity	63% (*11*)	25% of mucosal HNSCC (*12*)
	larynx & hypopharynx	36% (*13*)	34% of mucosal HNSCC (*12*)
	Squamous cell carcinoma (cutaneous)	2.5%-14% (*14*)	20% of non-melanoma skin cancers (*15*)
	Basal cell carcinoma	0.2%-3% (*16*)	80% of non-melanoma skin cancers (*15*)
	Mucoepidermoid carcinoma	29% (*17*)	30%-40% of salivary gland malignancies (*17*)
Neoplasms with high rates of PNI	Microcystic adnexal carcinoma	80% (*18*)	lifetime occurrence of less than one in a million (*19*)
	Desmoplastic melanoma	32% (*20*)	5% of melanoma cases (*20*)
	Adenoid cystic carcinoma	51%-56% (salivary) (*21*)	7.5%-10% of salivary gland malignancies (*21*)
		76% (cutaneous) (*22*)	0.23 case per one million person-years (*23*)

HNSCC: head and neck squamous cell cancer

SUPPLEMENTAL TABLE 2.
Primary tumor sites for cranial nerves commonly involved in perineural spread

	Cranial nerves	Tumor sites
Most commonly involved nerves	Facial (CN VII)	Parotid gland/adjacent skin, temporal bone/adjacent skin, external auditory canal, pterygopalatine ganglion
	Mandibular (CN V3)	Skin of lower lip and lower face, oral cavity, masticator space, oropharynx, nasopharynx, and parotid gland/adjacent skin
	Maxillary (CN V2)	Midfacial skin, upper lip, oral cavity, oropharynx, nasopharynx, nasal cavity, maxillary sinus, and palate
Less commonly involved nerves	Ophthalmic (CN V1)	Skin of upper face, orbit, lacrimal gland, frontal sinus, and ethmoid sinus
	Hypoglossal (CN XII)	Nasopharynx, tongue

SUPPLEMENTAL TABLE 3.
Clinical features and imaging findings of perineural spread along cranial nerves

Associated signs and symptoms	Involved cranial nerve (CN)	Imaging findings		
		Primary sign: abnormality along the nerve		Secondary sign: denervation injury
		Location of abnormality	Key skull base bony landmarks	
Anosmia, abnormal taste	Olfactory (CN I)	Roof of nose, cribriform plate, anterior cranial fossa	Cribriform plate of ethmoid	
Visual loss	Optic (CN II)	Retrobulbar orbit, optic canal, suprasellar cistern	Optic canal	
Diplopia, ptosis, anisocoria	Oculomotor (CN III)	Superior orbital fissure, cavernous sinus, interpeduncular cistern	Superior orbital fissure	Extraocular muscles (except superior oblique and lateral rectus)
Vertical diplopia	Trochlear (CN IV)	Superior orbital fissure, cavernous sinus, ambient cistern	Superior orbital fissure	Superior oblique muscle
Paresthesia over forehead and upper eyelid, abnormal corneal reflex	Ophthalmic (CN V1)	Superior extraconal orbit, superior orbital fissure, cavernous sinus, Meckel's cave, prepontine cistern	Superior orbital fissure	
Paresthesia over upper cheek, upper lip, and posterior portion of nose	Maxillary (CN V2)	Infraorbital foramen, infraorbital canal, inferior orbital fissure, pterygopalatine fossa, foramen rotundum, cavernous sinus, Meckel's cave, prepontine cistern	Inferior orbital fissure, Foramen rotundum	
Paresthesia over chin and lower lip, trismus, abnormal jaw jerk reflex	Mandibular (CN V3)	Mental foramen, mandibular canal, masticator space/infratemporal fossa, foramen ovale, cavernous sinus, Meckel's cave, prepontine cistern	Foramen ovale	Masseter, medial and lateral pterygoid muscles
Lateral gaze diplopia	Abducens (CN VI)	Superior orbital fissure, cavernous sinus, prepontine cistern	Superior orbital fissure	Lateral rectus muscle
Hemiparesis of the upper and lower face	Facial (CN VII)	Parotid space, stylomastoid foramen, temporal bone, internal acoustic canal, cerebellopontine angle	Stylomastoid foramen	Facial muscles
Hearing loss, imbalance	Vestibulo-cochlear (CN VIII)	Internal auditory canal, cerebellopontine angle	Internal acoustic canal	
Absent gag reflex, glossopharyngeal neuralgia	Glosso-pharyngeal (CN IX)	Base of tongue and pharynx; carotid space; jugular foramen; cerebellomedullary cistern	Jugular foramen	
Dysphagia, hoarseness, vocal cord paralysis	Vagus (CN X)	Tracheoesophageal groove, carotid space, jugular foramen, cerebellomedullary cistern	Jugular foramen	Vocal cord, palatogossus muscle
Shoulder girdle depression,	Accessory (CN XI)	Posterior triangle of the neck, carotid space, jugular foramen,	Jugular foramen	Trapezius and sternocleidomastoid

inability to rotate head		cerebellomedullary cistern, foramen magnum		muscle
Dysarthria, dysphagia, tongue deviation	Hypoglossal (CN XII)	Tongue/floor of mouth, carotid space, hypoglossal canal, cerebellomedullary cistern	Hypoglossal canal	Extrinsic and intrinsic muscles of the tongue