International Journal of Radiation Oncology biology • physics

www.redjournal.org

Critical Review

Perineural Invasion and Perineural Tumor Spread in Head and Neck Cancer

Richard L. Bakst, MD,* Christine M. Glastonbury, MBBS,†,‡ Upendra Parvathaneni, MBBS, FRANZCR,§ Nora Katabi, MD,‖ Kenneth S. Hu, MD, FASTRO,¶ and Sue S. Yom, MD, PhD‡

**Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, New York; †Department of Radiology, University of California San Francisco, San Francisco, California; ‡Department of Radiation Oncology, University of California San Francisco, San Francisco, California; §Department of Radiation Oncology, University of Washington Medical Center, Seattle, Washington; ‖Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York; and ¶Department of Radiation Oncology, New York University Langone Medical Center, New York, New York*

Received Aug 30, 2018. Accepted for publication Dec 1, 2018.

Perineural invasion (PNI), the neoplastic invasion of nerves, is a common pathologic finding in head and neck cancer that is associated with poor clinical outcomes. PNI is a histologic finding of tumor cell infiltration and is distinct from perineural tumor spread (PNTS), which is macroscopic tumor involvement along a nerve extending from the primary tumor that is by definition more advanced, being radiologically or clinically apparent. Despite widespread acknowledgment of the prognostic significance of PNI and PNTS, the mechanisms underlying its pathogenesis remain largely unknown, and specific therapies targeting nerve invasion are lacking. The use of radiation therapy for PNI and PNTS can improve local control and reduce devastating failures at the skull base. However, the optimal volumes to be delineated with respect to targeting cranial nerve pathways are not well defined, and radiation can carry risks of major toxicity secondary to the location of adjacent critical structures. Here we examine the pathogenesis of these phenomena, analyze the role of radiation in PNI and PNTS, and propose guidelines for radiation treatment design based on the best available evidence and the authors' collective experience to advance understanding and therapy of this ominous cancer phenotype.

Pathology and Pathogenesis

Perineural invasion (PNI) is a common pathologic finding in many head and neck cancers, including squamous cell carcinoma (SCC) and adenoid cystic carcinoma (ACC; Table 1). Initial theories suggested that PNI was simply an extension of lymphatic metastasis, which was eventually disproven. Modern studies have demonstrated that PNI is a deliberate, molecularly mediated process that results from reciprocal interactions between cancer and nerve, challenging the historic notion that this is an event driven purely by the progress of cancer alone.[1,2] There is growing evidence that the supportive cells within peripheral nerves

Note—An online CME test for this article can be taken at https://academy.astro.org.

Reprint requests to: Richard L. Bakst, MD, Icahn School of Medicine at Mount Sinai, Department of Radiation Oncology, 1184 Fifth Ave, 1st Floor, Box 1236, New York, NY 10029. Tel: (212) 241-3545; E-mail: Richard.Bakst@mountsinai.org

Conflicts of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 103, No. 5, pp. 1109–1124, 2019
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2018.12.009

Table 1 Head and neck cancer types commonly associated with perineural invasion

Histology	Primary tumor site
Adenoid cystic carcinoma	Major or minor salivary glands
Salivary ductal carcinoma	Major or minor salivary glands
Mucoepidermoid carcinoma	Major or minor salivary glands
Squamous cell carcinoma	Cutaneous or mucosal site
Desmoplastic melanoma	Cutaneous

interact with the cancer and directly promote neoplastic invasion and dissemination along nerves.[3-5]

When reporting the pathology of head and neck cancer, the presence versus absence of PNI should be documented. Nevertheless, the histologic evaluation of PNI can be variable, and different patterns of tumor−nerve interaction are observed. Histologically, there are 3 connective tissue layers that comprise the nerve sheath: (1) the innermost endoneurium, which surrounds individual nerve fibers (axons and associated Schwann cells); (2) the perineurium, which surrounds individual nerve fascicles and is composed of endothelial cells vested by basal lamina; and (3) the outermost epineurium, which binds together several nerve fascicles to form larger nerves (Fig. 1).[6,7] PNI is a histologic finding of tumor cell infiltration and is distinct from perineural tumor spread (PNTS), which is macroscopic tumor extension along a nerve from the primary tumor that is radiologically or clinically apparent.

In 1985, Batsakis et al[8] defined PNI as tumor cell invasion in, around, and through peripheral nerves and this remains the most commonly used definition of PNI. Furthermore, Liebig has specified that the presence of tumor cells within any of the 3 nerve sheath layers represents PNI and has expanded the PNI definition to include 2 histologic patterns of nerve involvement.[7] The first pattern (type A) is identified when tumor cells are located within the peripheral nerve sheath and infiltration into the 3 nerve sheath layers can be distinguished. The second pattern (type B) is noted when tumor cells are seen in close proximity to the nerve and involve at least 33% of its circumference.[7] The term *intraneural invasion* is used when tumor cells are noted to involve the innermost endoneurium (Fig. 1). Some investigators have regarded intraneural invasion as a subset of PNI that should be specifically reported, but there is currently insufficient evidence to determine whether intraneural invasion shows more aggressive behavior compared with other types of PNI.[7-11] In addition, determination of the exact histologic pattern of PNI can be difficult in practice, and deeper sections or immunohistochemistry, or both (ie, S100 and keratin), are necessary for determination of PNI in equivocal cases.

Clinical Significance

PNI by head and neck cancers is a significant cause of morbidity and mortality, and it confers a poor prognosis.[12-14] PNI has been reported across many case series at varying prevalence rates of 25% to 80% of head and neck mucosal SCCs,[15-18] and it constitutes a pervasive feature present in at least half of ACCs.[19-22] Although PNI is rare in most skin cancers, it is seen in 36% to 50% of desmoplastic melanoma,[23-25] and the rare cutaneous SCCs (<5%) that manifest with PNTS are remarkably resistant to treatment. The local extension of cancer cells along nerves is an ominous clinical event that is associated with increased local recurrence and worsened survival.[7,13,22,26] PNI is considered an exacerbating feature that can worsen the prognosis of patients with surgical close margins,[21,27] and it has been associated with an increased risk of regional recurrence.[18,28-31]

Conversely, PNTS is not associated with greater risk of regional metastasis, but the locally mediated morbidity can

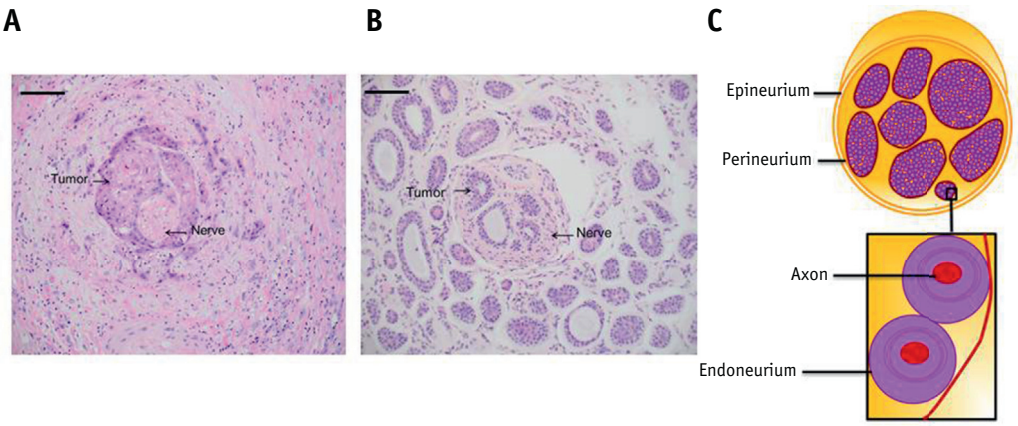

Fig. 1. Perineural invasion is a histologic finding. (A) Squamous cell carcinoma with perineural invasion in which tumor cells surround the nerve sheath. (B) Adenoid cystic carcinoma in which the tumor cells are noted to involve the endoneurium also referred to as *intraneural invasion*. Scale bar, 100 μm. (C) A peripheral nerve sheath is composed of 3 tissue layers consisting of the epineurium, perineurium, and endoneurium.

be severe. In cases of advanced uncontrolled PNTS, patients experience debilitating symptoms such as neuropathic pain, numbness or other sensory nerve dysfunction, paralysis, disfigurement, and injury from motor nerve dysfunction. In certain scenarios, major nerve invasion allows the tumor to track proximally from the distal branches of the nerve toward the central nervous system, potentially leading to tumor invasion into the skull base foramina, where major cranial nerves (CNs) are located.[32] Uncontrolled disease at the base of skull is difficult to treat, and it risks substantial intracranial morbidity.

Over aggregated case series, there are a number of characteristics of nerve invasion that have been reported to increase locoregional and nerve-pathway failure. These characteristics include extent of PNI involvement and number of foci (eg, focal versus extensive; anecdotally, $\geq$2 nerves on microscopic evaluation of tumor specimen or $\geq$4 foci), caliber of the largest involved nerve diameter (0.1- or 1-mm cut points have been proposed depending on the specific case series), presence of "skipping" involvement longitudinally along the nerve, intraneural invasion, intratumoral versus extratumoral location of PNI, and involvement of a large-caliber or "named" nerve.[13,18,28,33-40] There have been controversies regarding the independent impact of these histologic features, and further classificatory development is needed to assess their clinical effect precisely.[38,41]

Imaging and Anatomy

Magnetic resonance imaging (MRI) is the most sensitive imaging method for the detection of extratumoral extension along a large nerve, which is referred to as perineural tumor spread (PNTS). PNTS can be subtle on imaging, and it usually requires careful evaluation over multiple sequences.[42] It has been suggested that because of this and perhaps also because of inadequate training of radiologists to look for it, PNTS on MRI might be missed frequently.[43]

The T1-weighted sequence is often referred to as the *head and neck anatomic sequence* because it results in high signal intensity of fat-containing structures. Fat, being uniformly hyperintense, allows clear delineation of other soft tissue contours such that a mass or a thickened nerve can be recognized easily. The reliably bright signal intensity on T1-weighted images can obscure contrast enhancement; therefore, it is necessary to negate or null the fat signal on postcontrast T1-weighted images using fat-saturation pulses to increase conspicuity of subtle enhancement, particularly along nerves surrounded by fat. Although routine T1-weighted and post-gadolinium fat-saturated T1-weighted MRI sequences are the most useful for PNTS detection, different slice thicknesses are performed in different institutions and practices, and thus detection of PNTS might be obscured. At many institutions, 3-mm axial and coronal images through the skull base are routinely performed for all head and neck cancer indications. Thus, a clinical suspicion of PNTS should be conveyed when the MRI scan is ordered and the protocol is established to obtain the most ideal imaging parameters. Regardless of the MRI technique performed, clinical concern for PNTS should always be communicated because it will greatly increase the radiologist's degree of suspicion that this subtle finding might be present.

Recent studies have investigated the role of positron emission tomography (PET) in PNTS[44]; however, PET has limited spatial resolution and low sensitivity for small-volume disease, as is most often apparent with PNTS. In addition, because normal brain tissue has a high fluorodeoxyglucose uptake, it is extremely difficult to detect PNTS at the skull base or extending intracranially. MRI remains the gold standard to detect tumor spread and to follow patients with or at risk for nerve invasion.[45]

Rationale and Consensus Indications for Radiation

Radiation therapy is usually indicated after discovery of PNI in head and neck mucosal SCC,[13,18,28,33-37,40] cutaneous SCC,[39] or salivary gland malignancies[21] because of its association with local, regional, and nerve pathway recurrence. With the advent of highly conformal technologies, radiation given as definitive, adjuvant, or salvage treatment can simultaneously or selectively address all or some of these potential patterns of recurrence. The most common scenario in which radiation therapy is considered is after resection of a mucosal or skin SCC or salivary gland tumor in which PNI is reported in the pathologic specimen. One must determine whether radiation therapy is indicated in the context of other clinicopathologic factors and if so, how the radiation should be designed to address the various patterns of failure at risk in each particular case.

The authors recommend adjuvant radiation in the following settings:

- Cutaneous SCC of the head and neck with extensive microscopic PNI or involvement of large-caliber nerves
- Aggressive salivary gland cancers such as ACC or salivary duct carcinoma (SDC) containing microscopic PNI
- Mucosal SCC with extensive microscopic PNI
- Any primary tumor demonstrating clinical or radiographic PNTS

The extent of radiation target volumes and dose regimens are discussed in the following section. Radiation can also be used in the definitive setting for cases with unresectable PNTS. In patients with skin cancer with gross PNTS, radiation can effectively control disease in 50% to 57% of patients.[46-48] There are also limited reports of the use of primary radiation therapy in unresectable or subtotally resected salivary gland tumors, primarily ACC, in which definitive radiation therapy can control disease for some time in 36% to 93% using photon or particle therapies.[49-51]

Radiation Therapy Design

When designing target volumes in cases of PNI, it is essential to weigh the risk−benefit level in the decision to cover the relevant CN pathways electively in addition to the primary tumor bed (Table 2). The optimal radiation treatment volume with respect to tracing the CN back to the skull is not well defined and can carry a significant risk of toxicity. The decision to include elective CN pathways in addition to the primary tumor region depends on the extent of PNI, histology, margin status, and clinical presentation weighed against the additional morbidity of increasing the treatment volume. For cutaneous and mucosal SCC with microscopic PNI, a wide margin on the tumor bed should be treated given the enhanced potential for local recurrence, and the potentially increased risk to the regional lymphatics should be considered as well.[13,39] We consider electively covering the CN innervating the primary tumor site in high-grade salivary gland tumors, including ACC and SDC, and in cutaneous SCC of the face involving a named nerve.[49,52] In cases that warrant this elective neural coverage, one can consider covering additional CNs at risk secondary to anastomotic interconnections, such as those running between CNs V and VII.[53,54] These interconnections should be always covered in cases of PNTS or pathologically positive margins in immediately adjacent named nerve pathways. Coverage of CNs with or without their interconnected nerve pathways generally should extend toward the base of skull because malignant cells have a predilection to spread centripetally away from the tumor and toward the central nervous system.[55] However, if symptoms or imaging indicate gross involvement of CNs distal to the primary tumor, all areas of PNTS should be treated to tumoricidal dose. For this less typical situation, anterograde coverage of the involved CNs and proximate anastomotic interconnections at risk should be weighed against the risk of toxicity to adjacent critical structures.

We have selected 6 common clinical cases representing a variety of head and neck cases of PNI and PNTS. Cancers of the major and minor salivary glands, which include the parotid gland, submandibular gland, and minor glands located on the hard palate, can manifest with PNI and PNTS in >40% of operable cancers at the time of surgery.[56] Cutaneous lesions of the forehead are a frequent site of skin SCCs, which can feature rates of PNI and PNTS that are higher than usual.[57] The intimate relationship of the nasopharynx to nearby CNs poses a high risk of direct extension from the tumor into intracranial locations where CNs originate or pass through or, more rarely, true PNI/PNTS. Lastly, PNI is a relatively frequent finding in oral cavity SCC, and it correlates with poor clinical outcomes, especially if there is progression to PNTS.[29] The targeting of relevant CN pathways for such cases is based on previously published contouring guidelines,[58-63] the authors' collective experience, prediction of likely failure patterns,[60,64-66] and anatomic localization of neural interconnections (Table 3).

Submandibular gland

The submandibular gland receives parasympathetic innervation from branches of the lingual nerve, which is 1 of 2 major branches that arise from the mandibular nerve (V3). The mandibular nerve emerges from the skull base at foramen ovale. The submandibular gland also receives innervation from the facial nerve (VII) via the chorda tympani nerve, which eventually joins the lingual nerve (V3). The deep portion of the gland is in close anatomic proximity, although it is not innervated by the hypoglossal nerve (XII).

Table 2 Author recommendations for target volume design

	Target volume design	Recommended indications
Dose selection	50-60 Gy	Microscopic focal intratumoral PNI
	60-66 Gy	Positive margin along nerve; consider concurrent chemotherapy
	66-70 Gy	Gross disease or PNTS on imaging; consider concurrent chemotherapy
Extent of coverage	Tumor bed only	Microscopic focal intratumoral PNI
	Tumor bed plus elective cranial nerve pathways	Adenoid cystic carcinoma or salivary ductal carcinoma histology; extensive PNI noted on pathology; involvement of a large-caliber (>0.1 mm) or named nerve; close margin along nerve; positive margin along nerve; clinical or radiographic PNTS
Directionality of coverage	Retrograde coverage (toward base of skull)	Standard
	Anterograde coverage (away from base of skull)	Cover only if symptoms, operative report, or imaging suggest anterograde spread; cover in cases of clinical and radiographic PNTS
Elective neural coverage	Include communicating interconnections	Clinical or radiographic PNTS; consider in cases of adenoid cystic carcinoma or extensive PNI noted on pathology

Abbreviations: PNI = perineural invasion; PNTS = perineural tumor spread.

Table 3 Cranial nerves at risk based on primary tumor location

Primary tumor site	Cranial nerves at risk via anatomic proximity to primary lesion	Origin at base of skull	Relevant branches	Additional cranial nerves at risk via internerve connections (evaluate and treat if involved)
Submandibular gland	V_3 XII (for deep lobe tumors with extraparenchymal extension)	V_3: foramen ovale XII: hypoglossal canal	Lingual nerve	—
Parotid gland	VII	VII: stylomastoid foramen	Mastoid, tympanic, labyrinthine, and genu segments	V_3 via auriculotemporal nerve
Hard palate	V_2	V_2: foramen rotundum	Greater and lesser palatine nerves	VII via greater superficial petrosal nerve and vidian nerve V_1 and V_3 via cavernous sinus and Meckel cave
Forehead (skin)	V_1	Superior orbital fissure	Supraorbital and supratrochlear branches → cavernous sinus → Meckel cave	—
Nasopharynx	Direct extension from tumor: V_3 and XII Cavernous sinus involvement: V_1, V_2, III, IV, VI	V_3: foramen ovale XII: hypoglossal canal	—	VII via greater superficial petrosal nerve and vidian nerve

For high-grade tumors of the submandibular gland with extensive PNI or in cases of ACC, the authors suggest elective coverage of the mandibular nerve up to foramen ovale (Fig. 2). Although skull base recurrences for submandibular gland cancers are relatively uncommon,[67] failures near the cranial foramina can develop if coverage up to the base of the skull is not included.[21,52] If the tumor grossly or pathologically involves the hypoglossal nerve, the authors suggest covering the hypoglossal nerve up to the hypoglossal canal. Although there is a true anatomic connection between the submandibular gland and the facial nerve via the chorda tympani, failures of VII from these tumors are rare; therefore, the facial nerve is not typically part of the elective clinical target volume.[68]

Parotid gland

PNI is also notoriously associated with ACC, where tumor cells are known to infiltrate along the nerve tract beyond the main tumor mass. Some studies have suggested that there is a correlation between PNI and the histologic growth patterns of ACC, and tumors with cribriform and solid patterns have higher rates of PNI compared with those with a tubular pattern. It has also been proposed that ACCs with "pushing fronts" do not exhibit PNI compared with tumors with infiltrative borders and that the combination of an infiltrative front and PNI does behave aggressively in ACC. Nevertheless, other studies have shown no correlation between PNI and different patterns or histologic grade in ACC.[19] In a manner similar to ACC, PNI is a common feature of SDC, which is identified in 69% of cases and has been reported to be a negative prognostic factor for this high-grade aggressive tumor.[69] Other high-grade salivary gland histologies, such as high-grade mucoepidermoid carcinoma, are also associated with PNI.[70]

The superficial and deep lobes of the parotid are separated by the facial nerve (VII), which gives rise to the 5 terminal branches within the gland that then innervate the muscles of facial expression. It is not uncommon for an advanced case of ACC involving VII to be initially diagnosed as Bell's palsy, even for several years, until MRI is obtained. Similarly, SDC often involves the extracranial portion of the facial nerve and has a tendency to metastasize through the temporal bone via PNTS.[71] The facial nerve has a complex intratemporal course before emerging from the skull base through the stylomastoid foramen, surrounded by a small fat pad. The intratemporal course of the facial nerve starts in the anterior superior aspect of the internal auditory canal, where the first segment (the

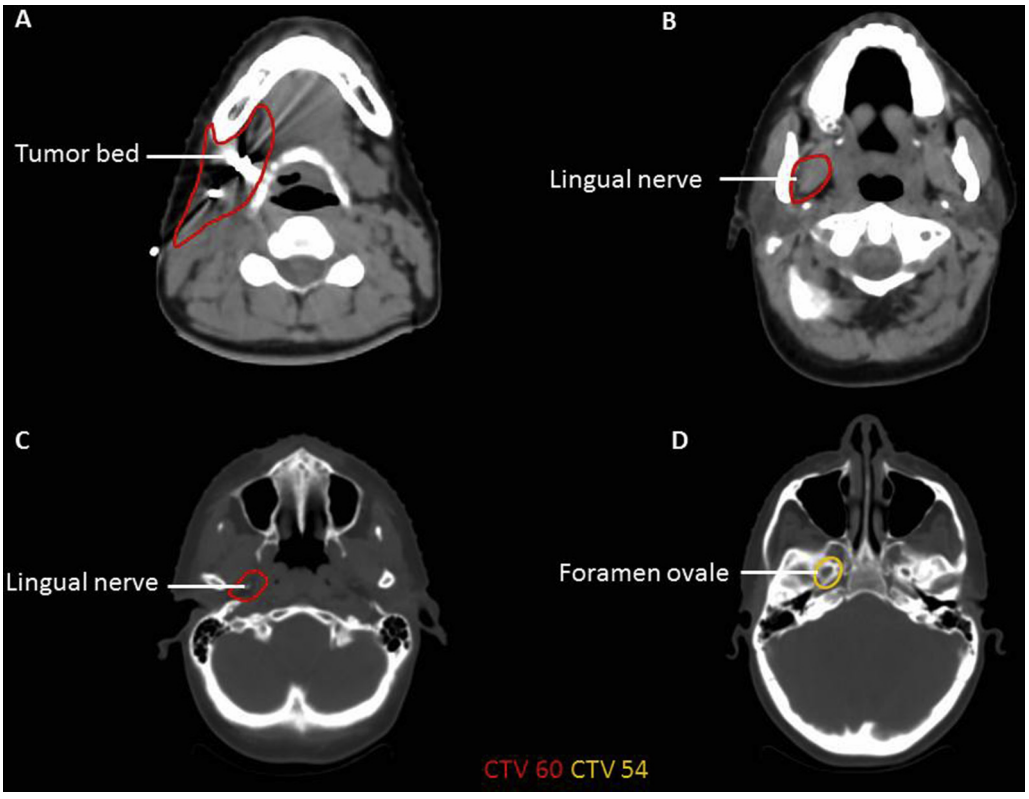

Fig. 2. Target volume delineation in a submandibular gland adenoid cystic carcinoma with extensive perineural invasion within the surgical specimen. The clinical target volume (CTV) includes the postoperative bed (A) and elective coverage of the lingual nerve (V3) pathway (B, C) to the foramen ovale (D). The dose is deintensified at the skull base to reduce the risk of toxicity.

labyrinthine segment) traverses superior to the cochlea to the geniculate ganglion. The greater superficial petrosal nerve (GSPN) branches from here, whereas the rest of the facial nerve does a near U-turn called the *anterior genu*. The tympanic segment then passes posteriorly and slightly laterally, beneath the horizontal semicircular canal to the posterior genu. The facial nerve innervates the stapedius muscle and descends as the mastoid segment to the stylomastoid foramen. It is from the mastoid segment that the chorda tympani arises.

The sensory and parasympathetic innervation of the parotid is through the auriculotemporal nerve (ATN), a branch of the mandibular division (V3) of the trigeminal nerve. The ATN also supplies the skin of the preauricular region and external ear, and its involvement can manifest as referred pain to the area in front of the ear. The ATN arises from V3 after its exit from the skull base through foramen ovale. V3 traverses between the lateral pterygoid muscle and tensor veli palatini initially, and it later runs between the lateral and medial pterygoid muscles and follows laterally along the pterygoid venous plexus. The ATN loops around the posterior aspect of the mandible (near the condyle) before connecting with the peripheral branches of CN VII in the retromandibular region.

For ACC, SDC, or high-grade tumor histologies involving the parotid gland with extensive PNI or PNTS along CN VII, electively targeting the stylomastoid foramen and the proximal course of CN VII within the temporal bone up to the geniculate ganglion and the labyrinthine segment is recommended by the authors (Fig. 3).[71,72] If the involvement of CN VII is grossly present at the geniculate ganglion, it may be necessary to radiate along the internal acoustic canal into the facial nerve nucleus of the brain stem; this decision must be weighed against a near-certain loss of hearing. If there is clear evidence or high concern for ATN involvement, it and V3 are electively treated up to the foramen ovale.[73] For focal microscopic PNI, one could consider sparing the cochlea and only targeting the stylomastoid foramen and the mastoid segments of CN VII.

Hard palate

The hard palate receives sensory innervation through the maxillary division (V2) of the trigeminal nerve. The most common path of PNTS from cancers arising in the palate is through the palatine nerve branches of V2, via the greater and lesser palatine foramina into the pterygopalatine fossa (PPF), and onward proximally through foramen rotundum and along the lateral wall of the cavernous sinus to the gasserian ganglion in the Meckel cave.[74,75] There is an interconnecting pathway that could be a potential route of

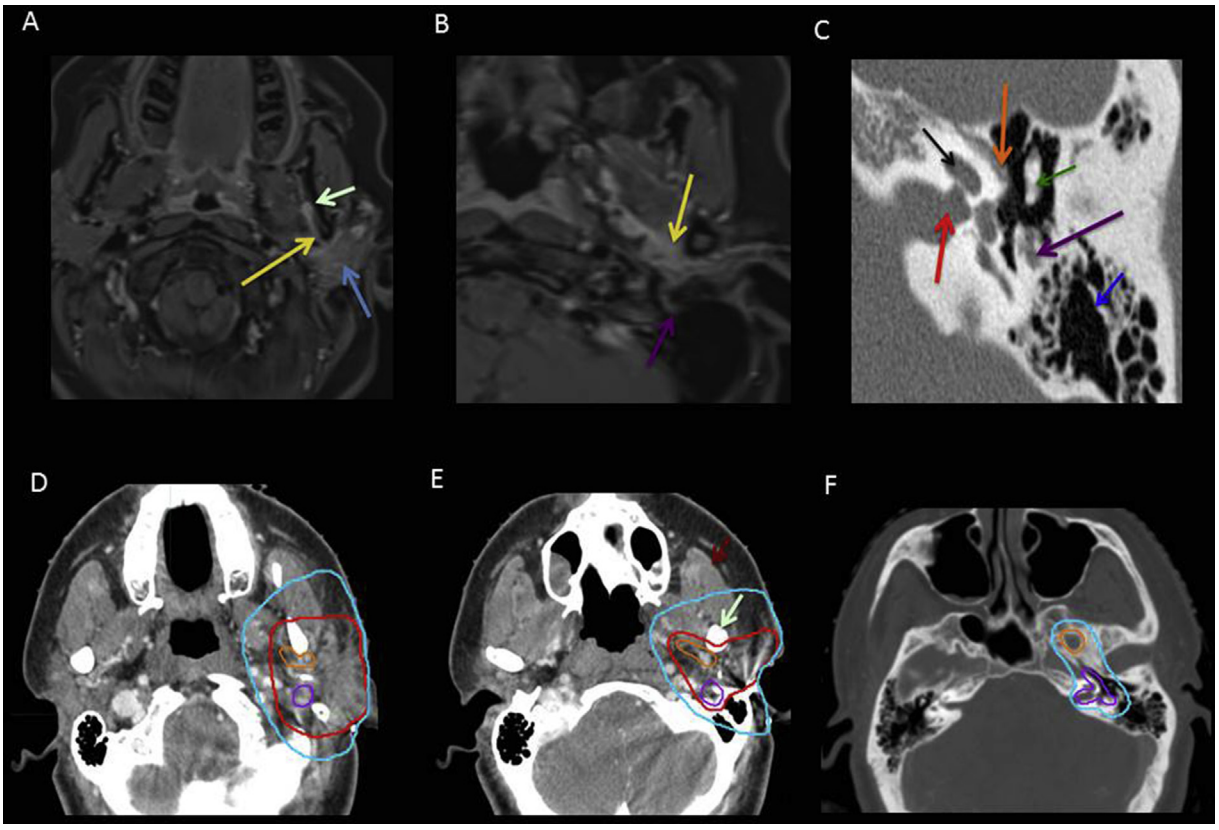

Fig. 3. Target volume delineation in a parotid gland malignancy with perineural tumor spread (PNTS). (A) Left parotid tumor (*blue arrow*) and PNTS along V3 auriculotemporal nerve (ATN; *yellow arrow*) on axial postcontrast T1 fat sat magnetic resonance imaging. Mandible (*light green arrow*). (B) PNTS along cranial nerve (CN) VII at the stylomastoid foramen (*purple arrow*) and ATN and V3 along the pterygoid plexus (*yellow arrow*). (C) Anatomy of VII nerve pathway within the temporal bone on axial computed tomographic scan: posterior genu (*purple arrow*) tucked between middle ear cavity (*green arrow*) and mastoid air cells (*blue arrow*), tympanic segment of VII (*orange arrow*) traversing between cochlea (*black arrow*) and middle ear cavity (*green arrow*), and canalicular segment (*red arrow*) within the internal auditory canal are demonstrated. (D) High-risk clinical target volume (70 Gy) in *red* encompassing gross disease in the parotid bed, facial nerve in the stylomastoid region (*purple*), and ATN (*orange*). Elective clinical target volume (*light blue*) covering masticator and parapharyngeal spaces. (E) Grossly involved ATN (*orange*) and CN VII (*purple*) treated to 70 Gy (*red*) in the retromandibular area. The masseter muscle (*dark red*) and mandibular condyle (*light green arrow*) are shown for reference. (F) Elective clinical target volume (*light blue*) covering foramen ovale (*orange*) and facial nerve in the temporal bone. For focal microscopic PNI, one could consider sparing the cochlea and only targeting the stylomastoid foramen and the mastoid segments of CN VII. The posterior genu, labyrinthine, and tympanic segments of the facial nerve are are outlined in *purple*. (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2018.12.009.)

spread between V2 and the facial nerve (CN VII) via the parasympathetic nerve fibers responsible for nasolacrimal secretions originating from the facial nerve as the GSPN at the geniculate ganglion (located at the anterior—proximal genu). From the geniculate ganglion, the GSPN travels along the petrous temporal bone immediately parallel to (and on the lateral aspect of) the petrous carotid artery before entering the PPF through the vidian or pterygoid canal. In addition, there are interconnections between the 3 divisions of the trigeminal nerve.

For ACC and SCC involving the palate with microscopic PNI, we recommend electively covering the palatine foramina and PPF proximally up to the foramen rotundum (Fig. 4). For PNTS and extensive PNI, we recommend further proximal coverage along V2, including the Meckel cave, cavernous sinus, and vidian nerve, and GSPN to the anterior genu. An advanced presentation with involvement of the Meckel cave would prompt inclusion of the cisternal segment of CN V heading into the brain stem nucleus and consideration of anterograde coverage of V1 and V3.

Cutaneous SCC of the face

In the presence of microscopic and extensive PNI, there is strong rationale supporting adjuvant radiation for cutaneous SCC.[39,47,76] In one study, the subset of patients with extensive PNI but not those with focal PNI benefited from radiation therapy with improved nerve-pathway control and

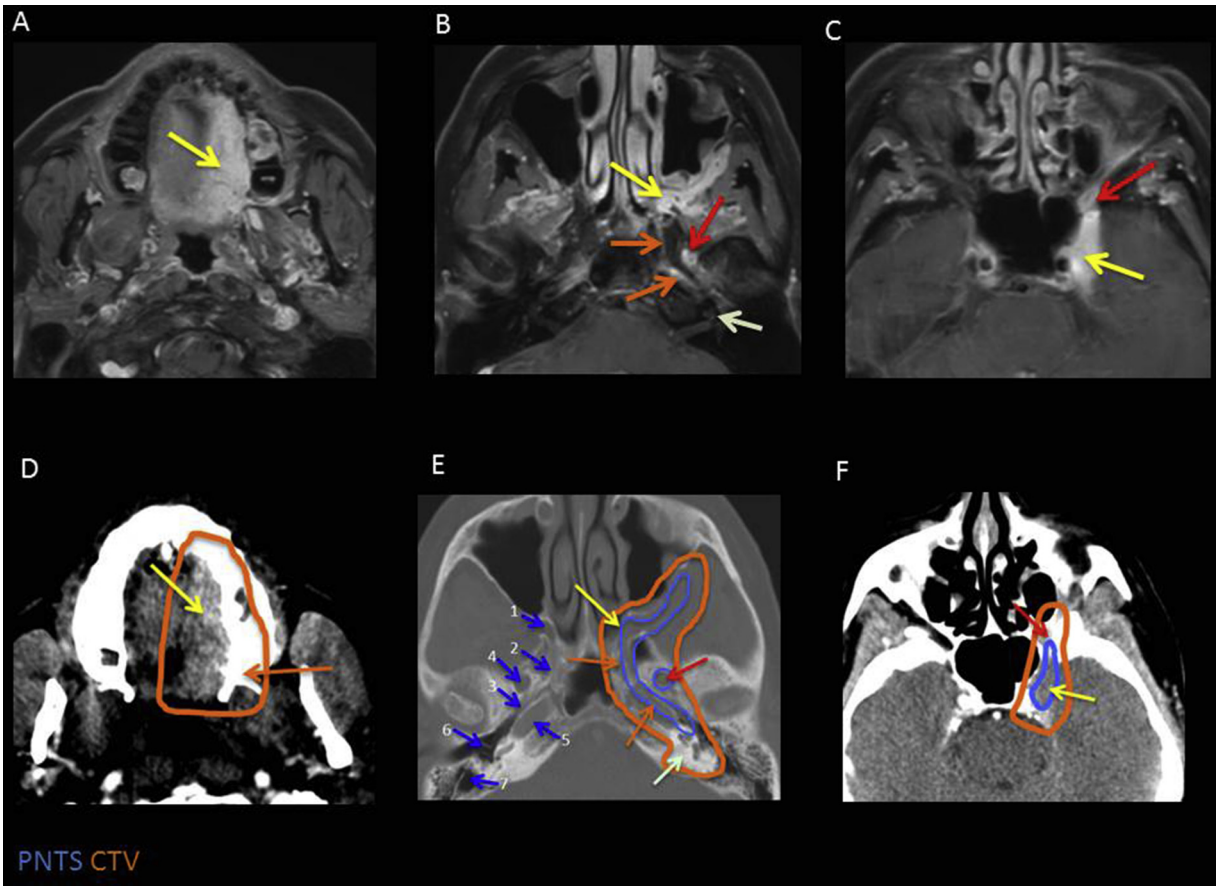

Fig. 4. Target volume delineation for an adenoid cystic carcinoma of hard palate with perineural tumor spread (PNTS) along V2. (A) Primary tumor involving left hard palate on axial postcontrast T1 fat sat magnetic resonance imaging. (B) PNTS along V2 in pterygopalatine fossa (PPF; *yellow arrow*) with lateral spread through the pterygomaxillary fissure into the retromaxillary masticator space. Interconnecting pathways (V2→VII) through the nerve of the vidian canal and greater superficial petrosal nerve (GSPN; *orange arrows*) with PNTS through the foramen ovale (*red arrow*). *Light green arrow* represents cochlea. (C) PNTS through the foramen rotundum (*red arrow*), involving the cavernous sinus and Meckel cave (*yellow arrow*). (D) Clinical target volume (CTV) covering tumor in the palate (*yellow arrow*) and greater and lesser palatine foraminae (*orange arrow*). (E) PNTS involving V2 in the PPF (*yellow arrow*) and interconnecting (V2→VII) pathways (*orange arrows*) along the vidian canal and GSPN. CTV includes PNTS along the foramen ovale (*red arrow*) and internal auditory meatus (*light green arrow*). Of note, for less advanced tumors with only microscopic PNI, we recommend electively covering the palatine foramina and PPF proximally up to the foramen rotundum only. The cochlea would be spared when this interconnecting pathway is not targeted. On the uninvolved right side, normal anatomic landmarks are shown: 1 = PPF; 2 = vidian canal; 3 = GSPN; 4 = foramen ovale; 5 = petrous carotid artery; 6 = middle ear cavity; 7 = mastoid air cells. (F) CTV covering PNTS through foramen rotundum (*red arrow*) and cavernous sinus (*yellow arrow*). (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2018.12.009.)

2-year disease-specific survival of 73% compared with the unirradiated patients who had DFS of 40%.[39] In another large study in which cutaneous SCC and basal cell carcinoma (BCC) were treated with adjuvant radiation for microscopic PNI, patients with focal PNI did better than those with extensive PNI, although no comparator patients with PNI were observed, precluding a quantification of the degree of benefit from therapy.[47]

PNI is identified in <5% of nonmelanomatous skin cancers and is more common in SCC than BCC, in recurrent than de novo disease, and exhibits tumors that are >2 cm or that have depth of invasion >1 cm.[57,77-79] A number of single-institution and national guidelines and consensus statements have generally agreed on the use of radiation in the presence of PNI, although specific technical recommendations are lacking.[48,80-82] For cutaneous SCC with focal PNI, a wide tumor bed margin should be irradiated given the enhanced potential for local recurrence.[39] In cases of extensive PNI or involvement of a large-caliber (>0.1 mm) or named nerve, the authors recommended elective coverage of the CN innervating the tumor site.

For forehead skin malignancies, branches of the ophthalmic nerve (V1) are commonly involved. Tumor can

enter the orbit through the supraorbital or supratrochlear foramina, traversing along the course of the frontal branch of V1, superior to the superior rectus and levator palpebrae superioris muscles. The frontal branch joins other smaller branches of V1 and exits the orbit through the superior orbital fissure. V1 courses along the superolateral wall of the cavernous sinus to the gasserian ganglion in the Meckel cave, along the cisternal segment of the trigeminal nerve, and then to the cistern to the lateral pons (Fig. 5).

Skin cancers originating in the midface along embryonal fusion planes of the "H-zone" involving the ear, nose, eyelid, and lip are associated with higher rates of local recurrence.[83] Skin cancers in the midface commonly involve branches of the maxillary nerve (V2), entering the deep face through the infraorbital foramen and coursing along the infraorbital nerve to the PPF. Here the nerve joins other branches of the maxillary nerve and courses through the foramen rotundum. It then traverses the cavernous sinus into the gasserian ganglion in the Meckel cave.

Skin cancers of the chin or lower lip can involve V3 and extend into the mental foramen into the inferior alveolar nerve and exit from the mandibular foramen into the foramen ovale into the Meckel cave. Skin cancers lateral to the eyebrow can involve various divisions of CN VII and extend into the stylomastoid foramen and the mastoid to the temporal bone and into the internal auditory canal. In patients with frank PNTS, anastomotic connections via the ATN, GSPN, and gasserian ganglion and into the cavernous sinus, orbital canal, and parotid need to be considered for elective coverage given that the risk for disease is significant.

Nasopharynx

CN involvement by nasopharyngeal carcinoma (NPC) can occur from direct extension of tumor compressing the nerves or from perineural spread along nerve connections at the skull base. CN palsy at diagnosis occurs in up to 10% to 36% of presenting patients, depending on the sensitivity of the method of detection.[84-86] CN palsies at presentation most commonly involve CNs V, VI, and XII[85] because

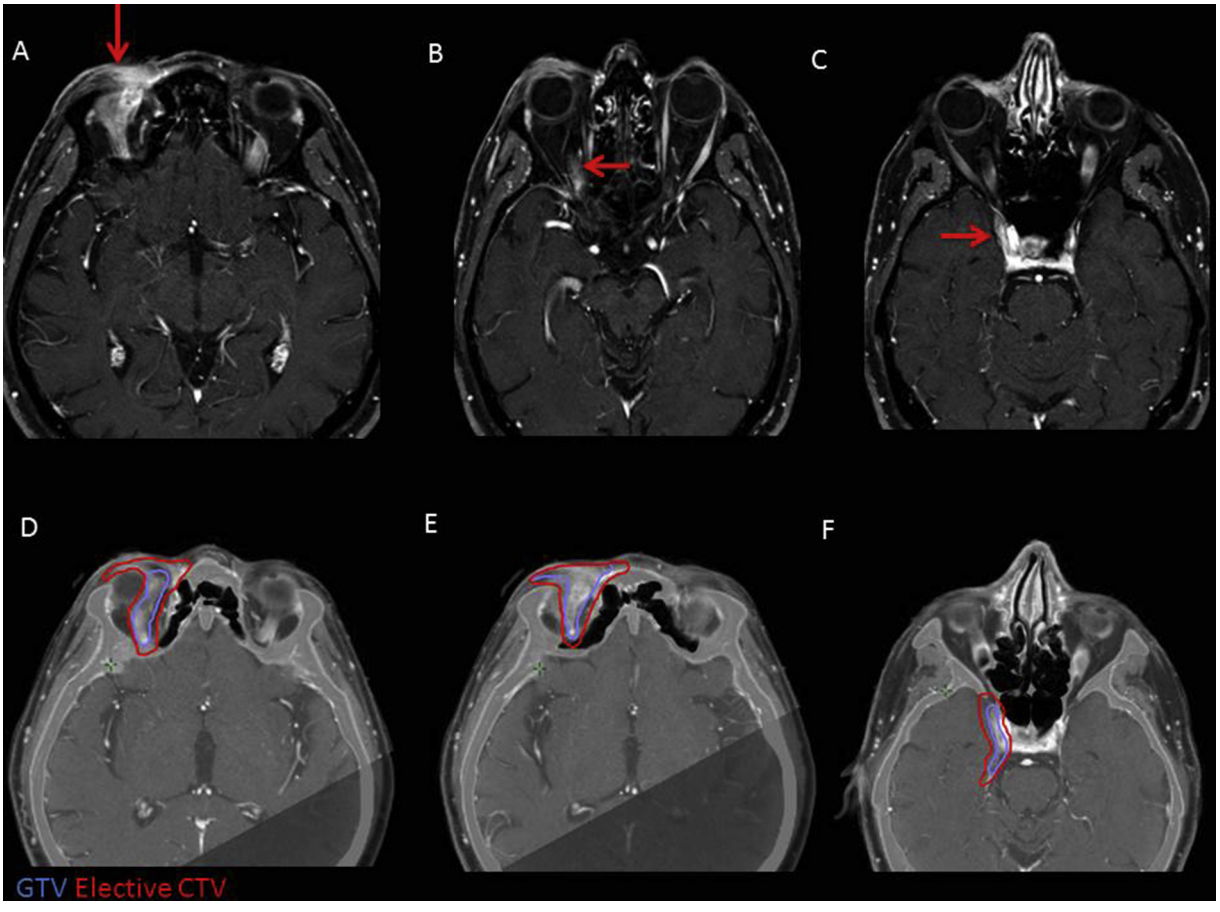

Fig. 5. Target volume delineation in a squamous cell carcinoma (SCC) of the right forehead with perineural tumor spread (PNTS). (A) Right supraorbital SCC of the skin (*red arrow*) on axial magnetic resonance (MR) imaging. (B) PNTS along the frontal branch of V1 to the superior orbital fissure (*red arrow*). (C) Intracranial PNTS from the superior orbital fissure to the cavernous sinus (*red arrow*). (D–F) The clinical target volume (CTV, *red*) is generated with MR fusion and includes gross disease (*blue*) and elective coverage of the cisternal segment of V1. (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2018.12.009.)

of the anatomic proximity of the nasopharynx to the cavernous sinus via the bilateral foramen ovale, lacerum, and hypoglossal canal. In patients with CN palsy, evaluation with MRI is associated with better 5-year local control and disease-specific survival.[86] Multiple palsies and lack of recovery from palsy are prognostic for worsened survival.[87]

Although there are published consensus guidelines regarding target volume delineation for NPC,[88] key anatomic pathways of PNTS serve as privileged routes for tumor infiltration deserving special attention. Most commonly, lateral spread of tumor to the parapharyngeal space can result in superior extension to the foramen ovale, the location of V3, resulting in access to the Meckel cave and the cavernous sinus—the location of V1, V2, III, IV, and VI.[89] Similarly, NPC can spread directly through the foramen lacerum to the cavernous sinus or can extend to the PPF through the sphenopalatine foramen and subsequently along V2 through the foramen rotundum. From the PPF, spread to the vidian nerve, GSPN, and geniculate ganglion (VII) is possible. Advanced primary tumors can extend posterolaterally to involve the hypoglossal canal or the jugular foramen, resulting in involvement of the "lower" CN passing through them.[90]

Elective CTV coverage for advanced T-stage (T3-4) NPC should therefore include at least 5 mm of coverage into the posterior maxillary sinuses and choanae, the bilateral PPF, bilateral foramen rotundum, ovale and lacerum, bilateral parapharyngeal spaces, ipsilateral or bilateral cavernous sinus, the sphenoid sinus, and a minimum of one third of the clivus (Fig. 6). In addition, spread along the vidian canal and GSPN should be assessed closely with MRI, and these regions must be covered when there is suspected involvement. Attempts to spare the uninvolved jugular foramen and hypoglossal canal can be made in the absence of posterolateral tumor extension or high jugular adenopathy because late radiation-induced CN palsies commonly develop in the lower CN after treatment.[91]

Oral cavity cancer

The oral tongue and buccal mucosa are richly innervated by motor and sensory nerves because of their role in speech, swallowing, and taste. The anterior two thirds of the tongue receives sensory innervation from the lingual nerve (V3) and taste via the chorda tympani (VII), whereas the posterior one third receives sensory innervation from the glossopharyngeal nerve (IX). The motor innervation of the tongue is derived predominately from the hypoglossal nerve (XII) with a contribution from the vagus nerve (X). Numerous branches of the buccal nerve, a sensory branch of the mandibular division of V3, densely innervate the entirety of the cheek and the skin of the perioral region.

PNI of these named CNs is rarely observed in SCC of the oral tongue or buccal mucosa. PNI more frequently develops in small, unnamed nerve fibers within the tumor specimen, at rates as high as 42% to 52%.[13,92] The presence of PNI in oral cavity cancer has been associated with worsened survival and regional nodal metastasis,[29-31] and the presence of PNI may be a factor warranting a neck dissection. PNI has also been demonstrated to be predictive of distant recurrences,[93] supporting its role as an adverse prognostic feature. However, the association of PNI with local failure is more controversial, with some studies demonstrating that it is an independent risk factor for local recurrence[12] and others not.[30] As such, the role of adjuvant radiation to the postoperative tumor bed in early-stage disease with PNI as the only adverse pathologic feature is not clear, with some studies demonstrating a benefit in regional control[12,] and others not.[35,94] Notably, the consensus definitions of PNI were not standardized across these studies, potentially accounting for these contradictory results.

The decision regarding the role of adjuvant radiation in oral cavity SCC should be made in the context of other clinical and pathologic variables. The finding of PNI generally warrants a neck dissection, and it is usually indicative of a more aggressive cancer phenotype. The authors suggest that the presence of extensive or large-caliber PNI should be considered a serious indication for radiation therapy in these cases. When adjuvant radiation is administered, the volumes should not routinely encompass CN pathways to the base of skull unless there is clinical, radiographic, or pathologic evidence of gross named nerve or CN involvement.

Dose Selection

Dose selection for cases of PNI balances disease burden and aggressiveness, risk of subsequent inoperable disease failure, and probabilities of toxicity to adjacent normal tissues. Although there is limited and mostly empirically derived clinical data to guide dose determination in these cases, general principles can be applied (Table 2).[16,43] The following recommendations are based largely on such principles in combination with our collective experience. Dose-painting techniques are highly recommended in anatomically complex cases to modulate doses to the tumor bed and along CN pathways.

In the adjuvant setting, we recommend that a tumor bed with microscopic PNI receive 60 Gy unless there is a close or positive margin, in which case the dose can be escalated to 64 to 66 Gy.[21] In cases that warrant elective neural coverage as discussed earlier, a dose range of 50 to 60 Gy to the relevant CN pathways is recommended.[95] Importantly, as the target volumes approach the base of skull, de-escalation toward a dose equivalent of 50 Gy[52] can be considered if there is difficulty sparing critical structures, such as the cochlea and brain stem. If there is intraoperative concern for extensive PNI or clinical or radiographic evidence of limited PNTS within the resection bed, the dose to the elective nerve pathways can be increased to up to 66 Gy in the proximate regions.

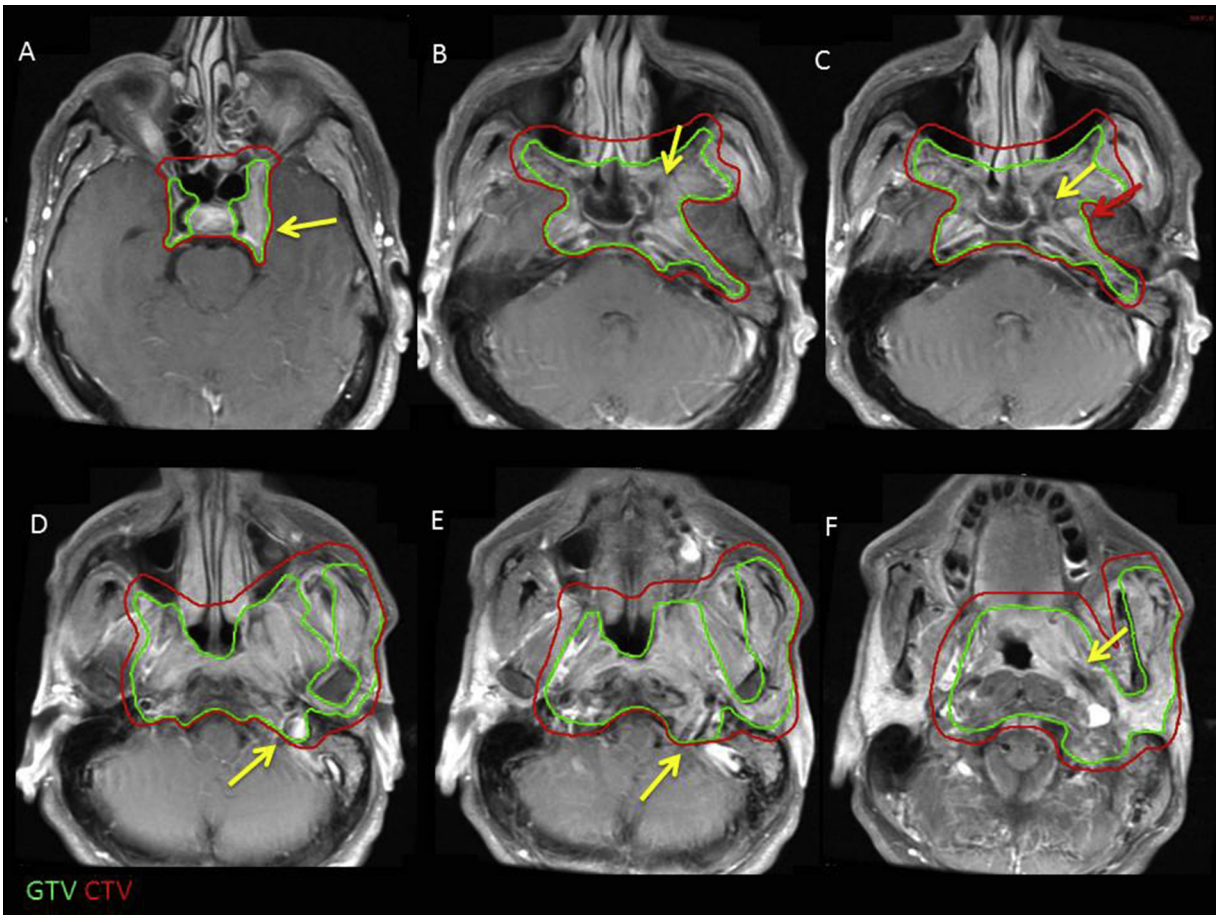

Fig. 6. Perineural tumor spread (PNTS) in nasopharyngeal cancer. *Green contour* represents gross tumor volume in this patient with extensive manifestation of PNTS requiring therapeutic doses to involved nerve pathways. *Red contour* represents high-dose clinical target volume (CTV) covering all gross disease. (A) Axial magnetic resonance imaging demonstrates involvement of the cavernous sinus (*yellow arrow*), which should always be treated, at least to elective dose, for T3-T4 primary tumors. The Meckel cave is posterolateral to the cavernous sinus. (B) PNTS involving the foramen rotundum (*yellow arrow*), which should always be covered at least in the elective clinical target volume and here is covered in high dose (*red contour*). (C) PNTS involving the vidian nerve (*yellow arrow*) and foramen ovale (*red arrow*). Although involvement of the vidian canal is rare, the foramen ovale should always be at least electively covered in cases of nasopharyngeal cancer. Of note, in this case there was gross disease that required coverage abutting the cochlea, but as a standard of care in less advanced cases, efforts would be made to spare the cochlea. (D) Large tumors can extend posterolaterally and involve the jugular foramen (*yellow arrow*) and (E) hypoglossal canal (*yellow arrow*). These structures can be relatively spared on a contralateral uninvolved side to reduce the risk of late cranial neuropathy. (F) Lateral spread to the parapharyngeal spaces (*yellow arrow*) can result in spread into the foramen ovale (V3), enabling access to the cavernous sinus. The bilateral parapharyngeal spaces should always be covered to at least an elective dose. (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2018.12.009.)

In the definitive inoperable setting, or where a complete resection of gross disease cannot be achieved, nerves demonstrating clinical or radiographic evidence of PNTS should be targeted to 70 Gy. This dose can be de-escalated beyond regions of PNTS where the nerve returns to normal caliber and appearance on imaging and clinical symptoms do not support specific involvement, but it should be noted that microscopic involvement of nerves interconnecting between areas of gross PNTS is highly likely. Elective doses may be more reasonable in areas of the nerve closer to the skull base thought to be at lower risk, which are more distant from the primary tumor or PNTS, but nerve pathways representing interconnections between nearby involved areas should be included in the higher-dose target volumes based on their proximity and likelihood of microscopic involvement. In the future, there may be opportunities to de-escalate radiation doses and further minimize treatment-associated toxicity with increasing sensitivity of imaging of PNI and PNTS and advances in the application of targeted therapy or immunotherapy.[96]

Systemic Therapy

Platinum-based compounds and biologic therapies targeting the epidermal growth factor receptor have been established in landmark head and neck cancer trials as radiosensitizers.[97-99] In the presence of PNI, the addition of systemic treatment combined with radiation is considered in selective situations depending on the extent of perineural disease (microscopic PNI versus PNTS), the tumor site (mucosal versus salivary gland versus primary skin cancer), and the histology (cutaneous versus mucosal SCC, salivary gland subtypes such as ACC/SDC and cutaneous SCC versus BCC). Other adverse clinicopathologic factors can be considered, such as T-stage, recurrent versus de novo presentation, pathologic margin status, and patient comorbidities.

In the setting of resected mucosal SCC, microscopic PNI alone is not an indication for adjuvant concurrent systemic therapy.[97] However, for patients with symptomatic nerve invasion, especially in cases of unresected gross PNTS, the poor outcomes justify consideration of a systemic agent concurrent with radiation. In patients with mucosal SCC, platinum compounds and cetuximab are most commonly used.[97-100] There has been early experience documenting the efficacy of checkpoint inhibition for mucosal SCC in the recurrent setting, but this therapy has not yet been established with concurrent radiation.[101]

For salivary gland malignancies, the Radiation Therapy Oncology Group clinical trial 1008 is currently testing whether improved survival can be achieved from addition of cisplatin to postoperative radiation for high-risk salivary gland cancers. Until these results are published, there are only limited retrospective series to support its use in select patients with adverse pathologic features.[102,103]

For patients with cutaneous SCC and BCC, the benefit of adding systemic therapy to radiation remains ill-defined and is primarily considered in patients with advanced PNTS.[104-107] Until additional trials confirm the benefit of adding systemic treatments to radiation, current guidelines remain neutral on this issue.[82] The Post-Operative Concurrent Chemo-Radiotherapy Versus Post-Operative Radiotherapy for Cancer of the Head and Neck trial (Trans Tasman Radiation Oncology Group 05.01) showed no disease-free or overall survival advantage from the addition of carboplatin to postoperative radiation therapy among patients with resected high-risk cutaneous SCC.[108] A number of series have documented the efficacy of checkpoint inhibition for recurrent and metastatic cutaneous SCC, and one trial reported a response rate of approximately 50%.[106,109-111] Numerous trials are underway to clarify the role of immunotherapy in the management of cutaneous SCC postoperatively and in the recurrent and metastatic settings. Case reports of the safety of hedgehog inhibitors with radiation for BCC have also been reported, and 2 such compounds are approved by the U.S. Food and Drug Administration for use in BCC that cannot be treated definitively.[110,112]

Treatment-Related Toxicities

Although radiation is effective and usually of only moderate localized risk in treating most cases of PNI, treatment of PNTS at the skull base and CN pathways may be exceptionally challenging and fraught with a risk of significant morbidity, including permanent blindness, hearing loss, temporal lobe necrosis, and cranial neuropathies. Radiation-induced cranial neuropathies can increase over time because of long latency, such as the incidence reported in 35% of nasopharyngeal cancer survivors at 15 years after treatment.[91] Although the incidence of these unrelenting deficits is likely lower with modern planning techniques, patients should be counseled on the probability of damage based on the anatomically identified extent of the PNTS and the known standard tolerance doses. In addition, radiosensitizing systemic therapy is often used for cases of unresected disease, and it can potentiate radiation toxicity.

Uncontrolled PNTS near the skull base poses high risk of morbidity from cancer progression; thus, high-dose radiation is advised despite these risks. Recurrences of PNTS are seldom resectable, and reirradiation is far less successful than initial treatment and has a far greater toxicity profile. An uncontrolled recurrence not only will result in fatality; it also subjects the patient to an extremely poor quality of life in the end stages from worsening, and often painful, cranial neuropathies.

Guidance on the normal structures encountered with well-recognized anatomic landmarks is provided in Table 4. Obviously, modern treatment technologies such as intensity-modulated radiation therapy (IMRT) combined with sound treatment planning principles must be used, including the techniques of avoiding "hot spots" and minimizing the "dose spill" into the uninvolved normal structures. In this regard, proton beam therapy (PBT) can have an advantage in certain circumstances. The main

Table 4 Normal tissues at risk based on cranial nerve coverage

Anatomic landmarks	Nerve pathway	Normal tissue at risk
Superior orbital fissure	V_1	Lacrimal gland, cornea, retina, optic nerve, optic chiasm, extraocular muscles
Foramen rotundum	V_2	Retina, optic nerve
Foramen ovale	V_3	Temporal lobe, cochlea, brain stem
Cavernous sinus	V_1, V_2	Temporal lobe, optic nerve, optic chiasm, pituitary
Meckel cave	V_1, V_2, V_3	Temporal lobe, brain stem, cochlea
Stylomastoid foramen Temporal bone	VII	Middle ear (effusions); cochlea, mastoiditis

advantage of using PBT compared with conformal photon-based planning techniques, such as IMRT, is to spare normal structures from dose spills in the intermediate- to low-dose range. This can help in reducing the dose bath to volume-sensitive structures at the skull base, such as the temporal lobe of the brain.[70] Dose escalation is also more easily achievable with PBT, and improved local control rates compared with historical data using photon-based techniques have been reported for skull base tumors such as chordomas, chondrosarcomas,[113] ACC,[51] and malignant sinonasal tumors,[114] which have anatomic and oncologic similarity to PNTS at the skull base. For skull base cases, it is strongly advisable to provide access to a multidisciplinary team including appropriate specialists from ophthalmology, otolaryngology, and neurology to assist in managing potential toxicities.

Future Directions

A growing understanding of the molecular basis for PNI opens the possibility of many novel therapeutic strategies. Preclinical data suggest that targeting neurotrophic factors or their receptors can directly inhibit nerve invasion.[2,5] Importantly, the irradiation of nerve pathways might act not only by inducing cancer cell death, but by also directly suppressing neurotrophic factor secretion critical to PNI pathogenesis. In an in vivo model of PNI, low doses of radiation to the nerve alone were sufficient to suppress nerve invasion through reduction in GDNF levels without radiating the cancer.[96] This finding suggests that target volumes encompassing the CN pathways also impair PNI through direct effects on the nerve microenvironment. Further investigation of how radiation affects PNI pathogenesis could enable refinement of radiation target volumes and dose strategies. To date, however, there are no active clinical trials focused on PNI. Clinical studies evaluating novel therapeutic targets and imaging approaches to detect smaller volumes of tumor along nerve pathways would enhance treatment possibilities for this aggressive cancer phenotype.

Conclusion

PNI is an ominous pathologic finding associated with poor clinical outcomes and morbidity. Appropriately targeted radiation therapy can improve local control and reduce the risk of unresectable failures in cases of PNI/PNTS. Designing target volumes requires careful attention to nerve-pathway anatomy and appropriate integration of clinical, radiographic, and pathologic information. Dose selection in cases of nerve invasion balances the issues of disease burden, risk of catastrophic failure, and probability of toxicity to nearby normal tissues. Although PNI/PNTS was traditionally viewed as a purely cancer-driven event, it is now appreciated that the nerve microenvironment and immune system are important mediators, which can be targeted independently from the cancer. Future treatments may incorporate a growing understanding of neurally mediated pathogenesis.

References

1. Bakst RL, Wong RJ. Mechanisms of perineural invasion. *J Neurol Surg B Skull Base* 2016;77:96-106.
2. Gil Z, Cavel O, Kelly K, et al. Paracrine regulation of pancreatic cancer cell invasion by peripheral nerves. *J Natl Cancer Inst* 2010;102:107-118.
3. Bakst RL, Xiong H, Chen CH, et al. Inflammatory monocytes promote perineural invasion via CCL2-mediated recruitment and cathepsin B expression. *Cancer Res* 2017;77:6400-6414.
4. Deborde S, Omelchenko T, Lyubchik A, et al. Schwann cells induce cancer cell dispersion and invasion. *J Clin Invest* 2016;126:1538-1554.
5. Demir IE, Boldis A, Pfitzinger PL, et al. Investigation of Schwann cells at neoplastic cell sites before the onset of cancer invasion. *J Natl Cancer Inst* 2014;106.
6. Akert K, Sandri C, Weibel ER, et al. The fine structure of the perineural endothelium. *Cell Tissue Res* 1976;165:281-295.
7. Liebig C, Ayala G, Wilks JA, et al. Perineural invasion in cancer: A review of the literature. *Cancer* 2009;115:3379-3391.
8. Batsakis JG. Nerves and neurotropic carcinomas. *Ann Otol Rhinol Laryngol* 1985;94:426-427.
9. Binmadi NO, Basile JR. Perineural invasion in oral squamous cell carcinoma: A discussion of significance and review of the literature. *Oral Oncol* 2011;47:1005-1010.
10. Dunn M, Morgan MB, Beer TW. Perineural invasion: Identification, significance, and a standardized definition. *Dermatol Surg* 2009;35:214-221.
11. Gil Z, Carlson DL, Gupta A, et al. Patterns and incidence of neural invasion in patients with cancers of the paranasal sinuses. *Arch Otolaryngol Head Neck Surg* 2009;135:173-179.
12. Chinn SB, Spector ME, Bellile EL, et al. Impact of perineural invasion in the pathologically n0 neck in oral cavity squamous cell carcinoma. *Otolaryngol Head Neck Surg* 2013;149:893-899.
13. Fagan JJ, Collins B, Barnes L, D'Amico F, Myers EN, Johnson JT. Perineural invasion in squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 1998;124:637-640.
14. Soo KC, Carter RL, O'Brien CJ, Barr L, Bliss JM, Shaw HJ. Prognostic implications of perineural spread in squamous carcinomas of the head and neck. *Laryngoscope* 1986;96:1145-1148.
15. Baumeister P, Welz C, Jacobi C, Reiter M. Is perineural invasion of head and neck squamous cell carcinomas linked to tobacco consumption? *Otolaryngol Head Neck Surg* 2018;158:878-881.
16. Hinerman RW, Mendenhall WM, Morris CG, Amdur RJ, Werning JW, Villaret DB. Postoperative irradiation for squamous cell carcinoma of the oral cavity: 35-year experience. *Head Neck* 2004;26:984-994.
17. Kurtz KA, Hoffman HT, Zimmerman MB, Robinson RA. Perineural and vascular invasion in oral cavity squamous carcinoma: Increased incidence on re-review of slides and by using immunohistochemical enhancement. *Arch Pathol Lab Med* 2005;129:354-359.
18. Rahima B, Shingaki S, Nagata M, Saito C. Prognostic significance of perineural invasion in oral and oropharyngeal carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004;97:423-431.
19. Barrett AW, Speight PM. Perineural invasion in adenoid cystic carcinoma of the salivary glands: A valid prognostic indicator? *Oral Oncol* 2009;45:936-940.
20. Dodd GD, Jing BS. Radiographic findings in adenoid cystic carcinoma of the head and neck. *Ann Otol Rhinology Laryngol* 1972;81:591-598.
21. Garden AS, Weber RS, Morrison WH, Ang KK, Peters LJ. The influence of positive margins and nerve invasion in adenoid cystic carcinoma of the head and neck treated with surgery and radiation. *Int J Radiat Oncol Biol Phys* 1995;32:619-626.

22. Stambuk HE. Perineural tumor spread involving the central skull base region. *Semin Ultrasound CT MR* 2013;34:445-458.
23. Anstey A, McKee P, Jones EW. Desmoplastic malignant melanoma: A clinicopathological study of 25 cases. *Br J Dermatol* 1993;129:359-371.
24. Carlson JA, Dickersin GR, Sober AJ, Barnhill RL. Desmoplastic neurotropic melanoma. A clinicopathologic analysis of 28 cases. *Cancer* 1995;75:478-494.
25. Rutten A, Hügel H, Kutzner H, Schirren CG, Küchler A, Groth W. Desmoplastic malignant melanoma. Clinical and histopathologic results of a study in 34 patients [in German]. *Hautarzt* 1996;47:447-453.
26. Goepfert H, Dichtel WJ, Medina JE, Lindberg RD, Luna MD. Perineural invasion in squamous cell skin carcinoma of the head and neck. *Am J Surg* 1984;148:542-547.
27. Ch'ng S, Corbett-Burns S, Stanton N, et al. Close margin alone does not warrant postoperative adjuvant radiotherapy in oral squamous cell carcinoma. *Cancer* 2013;119:2427-2437.
28. Lanzer M, Gander T, Kruse A, Luebbers HT, Reinisch S. Influence of histopathologic factors on pattern of metastasis in squamous cell carcinoma of the head and neck. *Laryngoscope* 2014;124:E160-E166.
29. Laske RD, Scholz I, Ikenberg K, et al. Perineural invasion in squamous cell carcinoma of the oral cavity: Histology, tumor stage, and outcome. *Laryngoscope Investig Otolaryngol* 2016;1:13-18.
30. Tai SK, Li WY, Chu PY, et al. Risks and clinical implications of perineural invasion in T1-2 oral tongue squamous cell carcinoma. *Head Neck* 2012;34:994-1001.
31. Yang X, Tian X, Wu K, et al. Prognostic impact of perineural invasion in early stage oral tongue squamous cell carcinoma: Results from a prospective randomized trial. *Surg Oncol* 2018;27:123-128.
32. Laine FJ, Braun IF, Jensen ME, Nadel L, Som PM. Perineural tumor extension through the foramen ovale: Evaluation with MR imaging. *Radiology* 1990;174:65-71.
33. Aivazian K, Ebrahimi A, Low TH, et al. Perineural invasion in oral squamous cell carcinoma: Quantitative subcategorisation of perineural invasion and prognostication. *J Surgical Oncol* 2015;111:352-358.
34. Brandwein-Gensler M, Smith RV, Wang B, et al. Validation of the histologic risk model in a new cohort of patients with head and neck squamous cell carcinoma. *Am J Surg Pathol* 2010;34:676-688.
35. Bur AM, Lin A, Weinstein GS. Adjuvant radiotherapy for early head and neck squamous cell carcinoma with perineural invasion: A systematic review. *Head Neck* 2016;38(suppl 1):E2350-E2357.
36. Carter JB, Johnson MM, Chua TL, Karia PS, Schmults CD. Outcomes of primary cutaneous squamous cell carcinoma with perineural invasion: An 11-year cohort study. *JAMA Dermatol* 2013;149:35-41.
37. Chatzistefanou I, Lubek J, Markou K, Ord RA. The role of perineural invasion in treatment decisions for oral cancer patients: A review of the literature. *J Craniomaxillofac Surg* 2017;45:821-825.
38. Miller ME, Palla B, Chen Q, et al. A novel classification system for perineural invasion in noncutaneous head and neck squamous cell carcinoma: Histologic subcategories and patient outcomes. *Am J Otolaryngol* 2012;33:212-215.
39. Sapir E, Tolpadi A, McHugh J, et al. Skin cancer of the head and neck with gross or microscopic perineural involvement: Patterns of failure. *Radiother Oncol* 2016;120:81-86.
40. Tai SK, Li WY, Yang MH, et al. Treatment for t1-2 oral squamous cell carcinoma with or without perineural invasion: Neck dissection and postoperative adjuvant therapy. *Ann Surg Oncol* 2012;19:1995-2002.
41. Chi AC, Katabi N, Chen HS, Cheng YL. Interobserver variation among pathologists in evaluating perineural invasion for oral squamous cell carcinoma. *Head Neck Pathol* 2016;10:451-464.
42. Moreira MCS, Dos Santos AC, Cintra MB. Perineural spread of malignant head and neck tumors: Review of the literature and analysis of cases treated at a teaching hospital. *Radiol Bras* 2017;50:323-327.
43. Ginsberg LE. Reinterpretation of head and neck scans: Massive can of worms or call to action? *AJNR Am J Neuroradiol* 2002;23:1617-1618.
44. Dercle L, Hartl D, Rozenblum-Beddok L, et al. Diagnostic and prognostic value of 18F-FDG PET, CT, and MRI in perineural spread of head and neck malignancies. *Eur Radiol* 2018;28:1761-1770.
45. Lee H, Lazor JW, Assadsangabi R, Shah J. An imager's guide to perineural tumor spread in head and neck cancers: Radiological footprints on (18)F-FDG PET with CT and MRI correlates [Epub ahead of print]. *J Nucl Med* 2018. Available at: https://doi.org/10.2967/jnumed.118.214312. Accessed October 16, 2018.
46. Balamucki CJ, Mancuso AA, Amdur RJ, et al. Skin carcinoma of the head and neck with perineural invasion. *Am J Otolaryngol* 2012;33:447-454.
47. Jackson JE, Dickie GJ, Wiltshire KL, et al. Radiotherapy for perineural invasion in cutaneous head and neck carcinomas: Toward a risk-adapted treatment approach. *Head Neck* 2009;31:604-610.
48. Moore BA, Weber RS, Prieto V, et al. Lymph node metastases from cutaneous squamous cell carcinoma of the head and neck. *Laryngoscope* 2005;115:1561-1567.
49. Balamucki CJ, Amdur RJ, Werning JW, et al. Adenoid cystic carcinoma of the head and neck. *Am J Otolaryngol* 2012;33:510-518.
50. Douglas JG, Laramore GE, Austin-Seymour M, Koh W, Stelzer K, Griffin TW. Treatment of locally advanced adenoid cystic carcinoma of the head and neck with neutron radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;46:551-557.
51. Pommier P, Liebsch NJ, Deschler DG, et al. Proton beam radiation therapy for skull base adenoid cystic carcinoma. *Arch Otolaryngol Head Neck Surg* 2006;132:1242-1249.
52. Chen AM, Garcia J, Granchi P, Bucci MK, Lee NY. Base of skull recurrences after treatment of salivary gland cancer with perineural invasion reduced by postoperative radiotherapy. *Clin Otolaryngol* 2009;34:539-545.
53. Catalano PJ, Sen C, Biller HF. Cranial neuropathy secondary to perineural spread of cutaneous malignancies. *Am J Otol* 1995;16:772-777.
54. Morris JG, Joffe R. Perineural spread of cutaneous basal and squamous cell carcinomas. The clinical appearance of spread into the trigeminal and facial nerves. *Arch Neurol* 1983;40:424-429.
55. Panizza BJ. An overview of head and neck malignancy with perineural spread. *J Neurol Surg B Skull Base* 2016;77:81-85.
56. Chen AM, Granchi PJ, Garcia J, Bucci MK, Fu KK, Eisele DW. Local-regional recurrence after surgery without postoperative irradiation for carcinomas of the major salivary glands: Implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys* 2007;67:982-987.
57. Ballantyne AJ. Perineural invasion by SCC. *J Dermatol Surg Oncol* 1984;10:502-504.
58. Anwar M, Yu Y, Glastonbury CM, El-Sayed IH, Yom SS. Delineation of radiation therapy target volumes for cutaneous malignancies involving the ophthalmic nerve (cranial nerve V-1) pathway. *Pract Radiat Oncol* 2016;6:e277-e281.
59. Biau J, Dunet V, Lapeyre M. Practical clinical guidelines for contouring the trigeminal nerve (V) and its branches in head and neck cancers [Epub ahead of print]. *Radiother Oncol* 2018. Available at: https://doi.org/10.1016/j.radonc.2018.08.020. Accessed October 17, 2018.
60. Gluck I, Ibrahim M, Popovtzer A, et al. Skin cancer of the head and neck with perineural invasion: Defining the clinical target volumes based on the pattern of failure. *Int J Radiat Oncol Biol Phys* 2009;74:38-46.
61. Ko HC, Gupta V, Mourad WF, et al. A contouring guide for head and neck cancers with perineural invasion. *Pract Radiat Oncol* 2014;4:e247-e258.
62. Mourad W, Hu KS, Harrison LB. Cranial nerves IX-XII contouring atlas for head and neck cancer, vol. 2017: RTOG. Available at: https://www.rtog.org/LinkClick.aspx?fileticket=B7fuSx-B1GU%3d&tabid=229

63. Mourad WF, Young BM, Young R, et al. Clinical validation and applications for ct-based atlas for contouring the lower cranial nerves for head and neck cancer radiation therapy. *Oral Oncol* 2013;49:956-963.
64. Dundar Y, Cannon RB, Monroe MM, Buchmann LO, Hunt JP. Skull base invasion patterns and survival outcomes of nonmelanoma skin cancers. *J Neurol Surg B Skull Base* 2017;78:164-172.
65. Moonis G, Cunnane MB, Emerick K, Curtin H. Patterns of perineural tumor spread in head and neck cancer. *Magn Reson Imaging Clin N Am* 2012;20:435-446.
66. Warren TA, Nagle CM, Bowman J, Panizza BJ. The natural history and treatment outcomes of perineural spread of malignancy within the head and neck. *J Neurol Surg B Skull Base* 2016;77:107-112.
67. Aro K, Tarkkanen J, Saat R, Saarilahti K, Mäkitie A, Atula T. Submandibular gland cancer: Specific features and treatment considerations. *Head Neck* 2018;40:154-162.
68. Ginsberg LE. MR imaging of perineural tumor spread. *Neuroimaging Clin N Am* 2004;14:663-677.
69. D'Heygere E, Meulemans J, Vander Poorten V. Salivary duct carcinoma. *Curr Opin Otolaryngol Head Neck Surg* 2018;26:142-151.
70. Holliday EB, Garden AS, Rosenthal DI, et al. Proton therapy reduces treatment-related toxicities for patients with nasopharyngeal cancer: A case-match control study of intensity-modulated proton therapy and intensity-modulated photon therapy. *Int J Particle Ther* 2015;2:19-28.
71. Huyett P, Duvvuri U, Ferris RL, Johnson JT, Schaitkin BM, Kim S. Perineural invasion in parotid gland malignancies. *Otolaryngol Head Neck Surg* 2018;158:1035-1041.
72. Leonetti JP, Marzo SJ, Agarwal N. Adenoid cystic carcinoma of the parotid gland with temporal bone invasion. *Otol Neurotol* 2008;29:545-548.
73. Singh FM, Mak SY, Bonington SC. Patterns of spread of head and neck adenoid cystic carcinoma. *Clin Radiol* 2015;70:644-653.
74. Ginsberg LE, DeMonte F. Imaging of perineural tumor spread from palatal carcinoma. *AJNR Am J Neuroradiol* 1998;19:1417-1422.
75. Ginsberg LE, Demonte F. Palatal adenoid cystic carcinoma presenting as perineural spread to the cavernous sinus. *Skull Base Surg* 1998;8:39-43.
76. Lin C, Tripcony L, Keller J, et al. Perineural infiltration of cutaneous squamous cell carcinoma and basal cell carcinoma without clinical features. *Int J Radiat Oncol Biol Phys* 2012;82:334-340.
77. Hassanein AM, Proper SA, Depcik-Smith ND, Flowers FP. Peritumoral fibrosis in basal cell and squamous cell carcinoma mimicking perineural invasion: Potential pitfall in Mohs micrographic surgery. *Dermatol Surg* 2005;31:1101-1106.
78. Leibovitch I, Huilgol SC, Selva D, Hill D, Richards S, Paver R. Cutaneous squamous cell carcinoma treated with mohs micrographic surgery in Australia II. Perineural invasion. *J Am Acad Dermatol* 2005;53:261-266.
79. Leibovitch I, Huilgol SC, Selva D, Richards S, Paver R. Basal cell carcinoma treated with Mohs surgery in Australia III. Perineural invasion. *J Am Acad Dermatol* 2005;53:458-463.
80. Expert Panel on Radiation Oncology-Head and Neck, Salama JK, Saba N, et al. ACR appropriateness criteria adjuvant therapy for resected squamous cell carcinoma of the head and neck. *Oral Oncol* 2011;47:554-559.
81. McCord MW, Mendenhall WM, Parsons JT, et al. Skin cancer of the head and neck with clinical perineural invasion. *Int J Radiat Oncol Biol Phys* 2000;47:89-93.
82. Stratigos A, Garbe C, Lebbe C, et al. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. *Eur J Cancer* 2015;51:1989-2007.
83. Strom TJ, Caudell JJ, Harrison LB. Management of BCC and SCC of the head and neck. *Cancer Control* 2016;23:220-227.
84. Chang JT, Lin CY, Chen TM, et al. Nasopharyngeal carcinoma with cranial nerve palsy: The importance of MRI for radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;63:1354-1360.
85. Li JC, Mayr NA, Yuh WT, Wang JZ, Jiang GL. Cranial nerve involvement in nasopharyngeal carcinoma: Response to radiotherapy and its clinical impact. *Ann Otol Rhinol Laryngol* 2006;115:340-345.
86. Liu L, Liang S, Li L, et al. Prognostic impact of magnetic resonance imaging-detected cranial nerve involvement in nasopharyngeal carcinoma. *Cancer* 2009;115:1995-2003.
87. Mo HY, Sun R, Sun J, et al. Prognostic value of pretreatment and recovery duration of cranial nerve palsy in nasopharyngeal carcinoma. *Radiat Oncol* 2012;7:149.
88. Lee AW, Ng WT, Pan JJ, et al. International guideline for the delineation of the clinical target volumes (CTV) for nasopharyngeal carcinoma. *Radiother Oncol* 2018;126:25-36.
89. Chong VF, Fan YF, Khoo JB. Nasopharyngeal carcinoma with intracranial spread: CT and MR characteristics. *J Comput Assist Tomogr* 1996;20:563-569.
90. King AD, Bhatia KS. Magnetic resonance imaging staging of nasopharyngeal carcinoma in the head and neck. *World J Radiol* 2010;2:159-165.
91. Kong L, Lu JJ, Liss AL, et al. Radiation-induced cranial nerve palsy: A cross-sectional study of nasopharyngeal cancer patients after definitive radiotherapy. *Int J Radiat Oncol Biol Phys* 2011;79:1421-1427.
92. Varsha BK, Radhika MB, Makarla S, et al. Perineural invasion in oral squamous cell carcinoma: Case series and review of literature. *J Oral Maxillofac Pathol* 2015;19:335-341.
93. Cracchiolo JR, Xu B, Migliacci JC, et al. Patterns of recurrence in oral tongue cancer with perineural invasion. *Head Neck* 2018;40:1287-1295.
94. Chatzistefanou I, Lubek J, Markou K, Ord RA. The role of neck dissection and postoperative adjuvant radiotherapy in CN0 patients with PNI-positive squamous cell carcinoma of the oral cavity. *Oral Oncol* 2014;50:753-758.
95. Amit M, Eran A, Billan S, et al. Perineural spread in noncutaneous head and neck cancer: New insights into an old problem. *J Neurol Surg B Skull Base* 2016;77:86-95.
96. Bakst RL, Lee N, He S, et al. Radiation impairs perineural invasion by modulating the nerve microenvironment. *PloS One* 2012;7:e39925.
97. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;350:1945-1952.
98. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;354:567-578.
99. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 2004;350:1937-1944.
100. Pignon JP, le Maître A, Maillard E, Bourhis J, and MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. *Radiother Oncol* 2009;92:4-14.
101. Ferris RL, Blumenschein G Jr., Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* 2016;375:1856-1867.
102. Sayan M, Vempati P, Miles B, et al. Adjuvant therapy for salivary gland carcinomas. *Anticancer Res* 2016;36:4165-4170.
103. Schoenfeld JD, Sher DJ, Norris CM Jr., et al. Salivary gland tumors treated with adjuvant intensity- modulated radiotherapy with or without concurrent chemotherapy. *Int J Radiat Oncol Biol Phys* 2012;82:308-314.
104. Apisarnthanarax S, Dhruva N, Ardeshirpour F, et al. Concomitant radiotherapy and chemotherapy for high-risk nonmelanoma skin carcinomas of the head and neck. *Int J Surg Oncol* 2011;2011:464829.
105. Maubec E, Petrow P, Scheer-Senyarich I, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. *J Clin Oncol* 2011;29:3419-3426.
106. Ribero S, Stucci LS, Daniels GA, Borradori L. Drug therapy of advanced cutaneous squamous cell carcinoma: Is there any evidence? *Curr Opin Oncol* 2017;29:129-135.
107. Tanvetyanon T, Padhya T, McCaffrey J, et al. Postoperative concurrent chemotherapy and radiotherapy for high-risk cutaneous squamous cell carcinoma of the head and neck. *Head Neck* 2015;37:840-845.

108. Porceddu SV, Bressel M, Poulsen MG, et al. Postoperative concurrent chemoradiotherapy versus postoperative radiotherapy in high-risk cutaneous squamous cell carcinoma of the head and neck: The randomized phase III TROG 05.01 trial. *J Clin Oncol* 2018;36:1275-1283.
109. Migden MR, Rischin D, Schmults CD, et al. Pd-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med* 2018;379:341-351.
110. Pollom EL, Bui TT, Chang AL, Colevas AD, Hara WY. Concurrent vismodegib and radiotherapy for recurrent, advanced basal cell carcinoma. *JAMA Dermatol* 2015;151:998-1001.
111. Ravulapati S, Leung C, Poddar N, Tu Y. Immunotherapy in squamous cell skin carcinoma: A game changer? *Am J Med* 2017;130:e207-e208.
112. Jacobsen AA, Aldahan AS, Hughes OB, Shah VV, Strasswimmer J. Hedgehog pathway inhibitor therapy for locally advanced and metastatic basal cell carcinoma: A systematic review and pooled analysis of interventional studies. *JAMA Dermatol* 2016;152:816-824.
113. Hug EB, Loredo LN, Slater JD, et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. *J Neurosurg* 1999;91:432-439.
114. Patel SH, Wang Z, Wong WW, et al. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: A systematic review and meta-analysis. *Lancet Oncol* 2014;15:1027-1038.