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Original Article

Practical clinical guidelines for contouring the trigeminal nerve (V) and its branches in head and neck cancers

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ABSTRACT

Purpose: The trigeminal nerve (V) is a major route of tumor spread in several head and neck cancers. However, only limited data are currently available for its precise contouring, although this is absolutely necessary in the era of intensity-modulated radiation therapy (IMRT). The purpose of this article is to present practical clinical guidelines for contouring the trigeminal nerve (V) in head and neck cancers at risk of spread along this nerve.

Method: The main types of head and neck cancers associated with risks of spread along the trigeminal nerve (V) and its branches were comprehensively reviewed based on clinical experience, literature-based patterns of failure, anatomy and radio-anatomy. A consensus for contouring was proposed based on a multidisciplinary approach among head and neck oncology experts including radiation oncologists (JBi, ML, MO, VG and JB), a radiologist (VD) and a surgeon (CS). These practical clinical guidelines have been endorsed by the GORTEC (Head and Neck Radiation Oncology Group).

Results: We provided contouring and treatment guidelines, supported by detailed figures and tables to help, for the trigeminal nerve and its branches: the ophthalmic nerve (V1), the maxillary nerve (V2) and the manidibular nerve (V3). A CT- and MRI-based atlas was proposed to illustrate the whole trigeminal nerve pathway with its main branches.

Conclusion: Trigeminal nerve (V) invasion is an important component of the natural history of various head and neck cancers. Recognizing the radio-anatomy and potential routes of invasion is essential for optimal contouring, as presented in these guidelines.

Perineural invasion (PNI) is a well-recognized characteristics in head and neck cancers. It has been associated with poor prognosis, i.e. increased loco-regional recurrence and decreased survival [1–6]. PNI can present from either cutaneous, mucosal, or salivary gland head and neck malignancies [7]. Adenoid cystic carcinoma (ACC) and squamous-cell carcinomas (SCC) are the most frequent neoplasms to exhibit this behavior. PNI is a clinicopathological entity generally defined as tumor-cell invasion in, around, and through the nerves [8,9]. There are two distinct PNI categories [9]. The most common is "microscopic PNI" when PNI is identified in a resection specimen as a histological finding of small, microscopically identified peripheral nerves in the immediate proximity of the neoplasm. In that case, the extent of microscopic PNI may vary from focal to multiple (extensive). The second category is "macroscopic PNI", a clinical and/or radiological finding of larger nerves.

Macroscopic PNI has a wide variety of clinical manifestations: paresthesia, hypoesthesia, pain, burning, numbness or formication in a specific territory. However, up to 40% of patients with radiographic macroscopic PNI are completely asymptomatic [7,10] emphasizing the need for appropriate imaging interpretation in the management of head and neck cancers [11].

Because of its extensive and intricate network of nerve fibers, the trigeminal nerve (V), and especially the maxillary (V2), the mandibular nerves (V3), and in a lesser extent the ophthalmic nerve (V1) are commonly affected nerves. In addition, these nerves have various interconnections that serve as a mechanism for widespread dissemination. Tumors can propagate both anterograde and retrograde along these nerves. Retrograde PNI toward the skull base occurs more often [10].

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Intensity-modulated radiation therapy (IMRT) is the standard method of radiotherapy (RT) of head and neck cancers [12–15]. IMRT is a technique that allows precise anatomical targeting of the target volumes to be irradiated while protecting healthy tissues. Because of its precision, this technique requires that each volume must be strictly and rigorously defined, as inadequate IMRT of PNI could result in failures especially at the base of skull as cancer can spread along cranial nerves. The delineation of these volumes is complex, and requires a solid learning curve.

Presently, there are limited data to guide radiation oncologists with the management of these microscopic and macroscopic PNI regarding simultaneously the indications, delineation, and dose prescription in the field of IMRT [10,16,17]. The purpose of this article is to present practical clinical guidelines for the delineation of the trigeminal nerve (V) in the treatment of head and neck cancers using IMRT. These practical clinical guidelines have been endorsed by GORTEC (Head and Neck Radiation Oncology Group – *Groupe d'Oncologie Radiothérapie Tête et Cou*).

Main types of head and neck cancer associated with risks of spread along the trigeminal nerve (V) and its branches, and respective anatomy

A CT- and MRI-based delineation atlas of the trigeminal nerve (V) and its main branches potentially involved in the dissemination of head and neck cancers is provided in the Supplementary material. The trigeminal nerve (V) is the largest cranial nerve, and emerges from the lateral aspect of the pons and then runs anteriorly to the Meckel cave located laterally and inferiorly to the cavernous sinus containing the trigeminal ganglion (also named Gasserian ganglion). From the trigeminal ganglion, three major branches emerge and have singular pathways: the ophthalmic (V1), the maxillary (V2), and the mandibular (V3) nerves [18]. Head and neck cancer localizations associated with potential risk of PNI of these branches are presented in Table 1.

Epidemiology

The incidence of PNI in head and neck cancer varies according to the histopathology and the localization of the primary cancer site. It has been reported in 27–82% of head and neck SCC [19–22] and 31–96% of ACC [23]. Considerable variation in the rates of PNI may be attributed to different detection methods for both the pathological diagnosis of PNI [19] and radiological interpretation of macroscopic PNI [24]. Some sites are less likely to present or recur with macroscopic PNI, although histologically the tumor specimen may display microscopic PNI. These include tongue, floor of mouth, tonsil, or larynx [24]. On the contrary, cutaneous, skull base, paranasal sinuses, or nasopharyngeal tumors are more likely to present with macroscopic PNI.

ACC is a relatively uncommon malignancy in the head and neck region but has a well-documented propensity for PNI [25]. ACC is a slow-growing epithelial tumor of salivary glands that can arise anywhere within the upper respiratory tract. It generally has a very slow growing, indolent course with frequent recurrences and late metastases. It is found approximatively in 60% in minor salivary glands, with the hard palate as the first site; and in 40% in major salivary glands, with the parotid gland as the first site.

Anatomy of the trigeminal nerve branches and associated tumors at risk

Ophthalmic nerve (V1)

From the trigeminal ganglion, the ophthalmic nerve (V1) continues forward within the lower part of the cavernous sinus. The main branch penetrates the orbit via the superior orbital fissure and then splits into three branches (frontal, lacrimal, and nasociliary) that subsequently run in the roof of the orbit.

The frontal branch divides into the supraorbital and supratrochlear nerves overall innervating the skin of the forehead and scalp, the mucosa of the frontal sinus, the upper eyelid and its conjunctiva. Therefore, cutaneous malignancies of the upper third of the face (upper eyelid and forehead especially) (Fig. 1) and tumors originating from the frontal sinuses are at risk.

The lacrimal branch provides the sensory supply to the lacrimal gland (making tumors from the lacrimal gland, are at risk) while the nasociliary branch is responsible for the sensory innervation of the cornea, the skin of the nose, and part of the nasal and paranasal sinus mucosa.

Maxillary nerve (V2)

From the trigeminal ganglion, the second division of the trigeminal nerve, the maxillary nerve (V2) travels within the wall of the cavernous sinus just below the ophthalmic nerve (V1). It, then, goes through the skull base via the foramen rotundum, and joins the pterygopalatine ganglion in the pterygopalatine fossa (PPF) where it gives off several branches, making of the PPF a hub for PNI spread (Figs. 2 and 3).

From the PPF, the infraorbital nerve goes anteriorly in the infraorbital canal, along the orbital floor, and emerges into the face via the infraorbital foramen. It provides three alveolar nerves innervating the upper teeth and gingival in the maxilla, and three

Table 1
Ophthalmic (V1), maxillary (V2), and mandibular (V3) nerves involved in head and neck cancers' perineural invasion and associated tumors at risk.

Cranial nerve	Main branch path	Specific branch	Tumors potentially associated
Ophthalmic nerve – V1	Brainstem → Trigeminal ganglion → Cavernous sinus → Superior orbital fissure → Roof of orbit	Frontal nerve	Skin: upper third of face Fontal sinus
		Lacrimal nerve	Lacrimal gland
Maxillary nerve – V2	Brainstem → Trigeminal ganglion → Cavernous sinus → Foramen rotundum → Pterygopalatine fossa	Sensory branches	Skin: middle third of face
		Posterior superior alveolar nerve	Maxillary sinus
		Pterygopalatine ganglion	Nasopharyngeal Oropharyngeal Maxillary sinus and ethmoïd sinus
		Greater and lesser palatine nerves	Hard palate
Mandibular nerve – V3	Brainstem → Trigeminal ganglion → Floor of Meckel cave → Foramen ovale → Masticator space	Inferior alveolar nerve	Skin: lower third of face If invading the mandible If invading the floor of mouth
		Main branch	If invading the masticator space or parapharyngeal space
		Lingual nerve	Floor of mouth, tongue, submandibular gland
		Auriculotemporal nerve	Parotid gland Skin: external ear

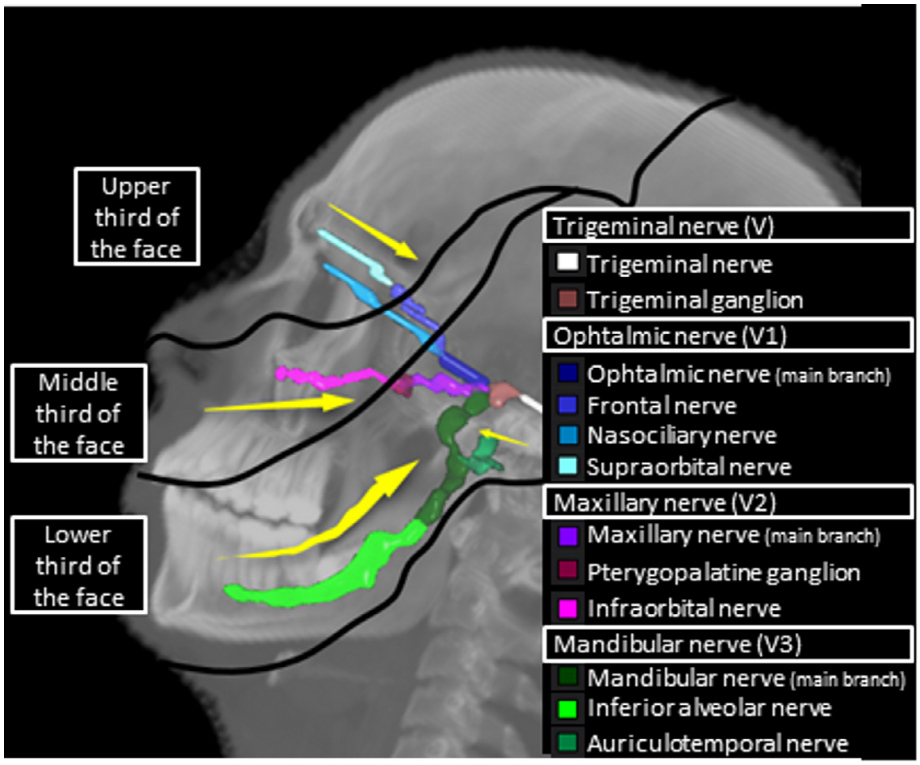

Fig. 1. Cutaneous malignancies potential extension pathways (yellow arrows) along the branches of the trigeminal nerve (V). The upper third of the face may spread along branches of the ophthalmic nerve (V1), the middle third along branches of the maxillary nerve (V2) and the lower third along branches of the mandibular nerve (V3).

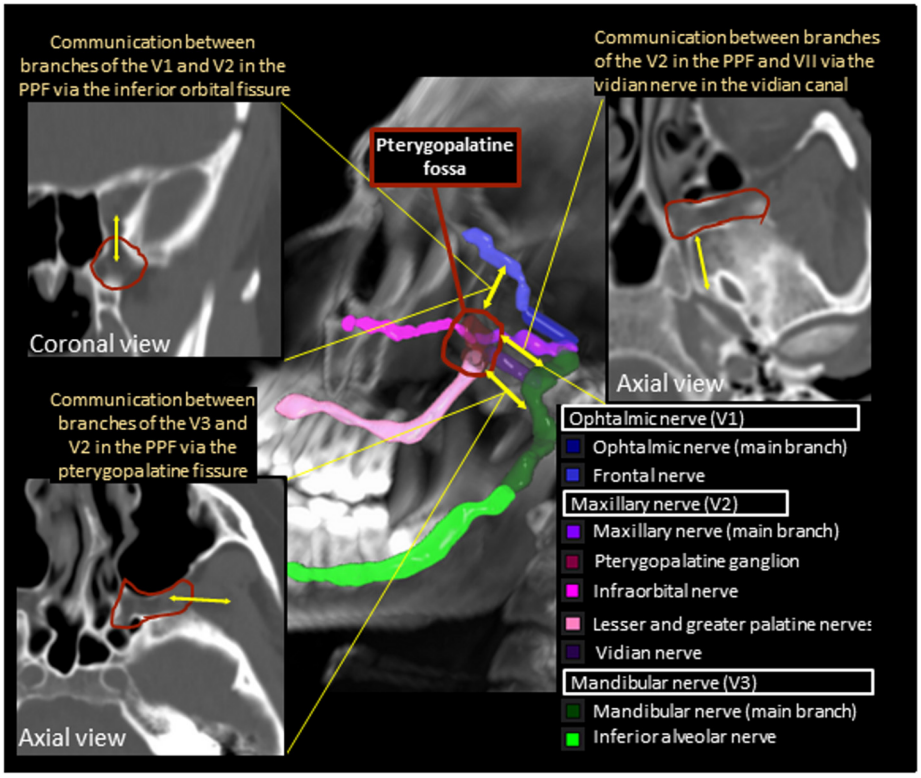

Fig. 2. The pterygopalatine fossa (PPF) as a hub for PNI spread and communication between the different branches of the trigeminal nerve (V) and the facial nerve (VII).

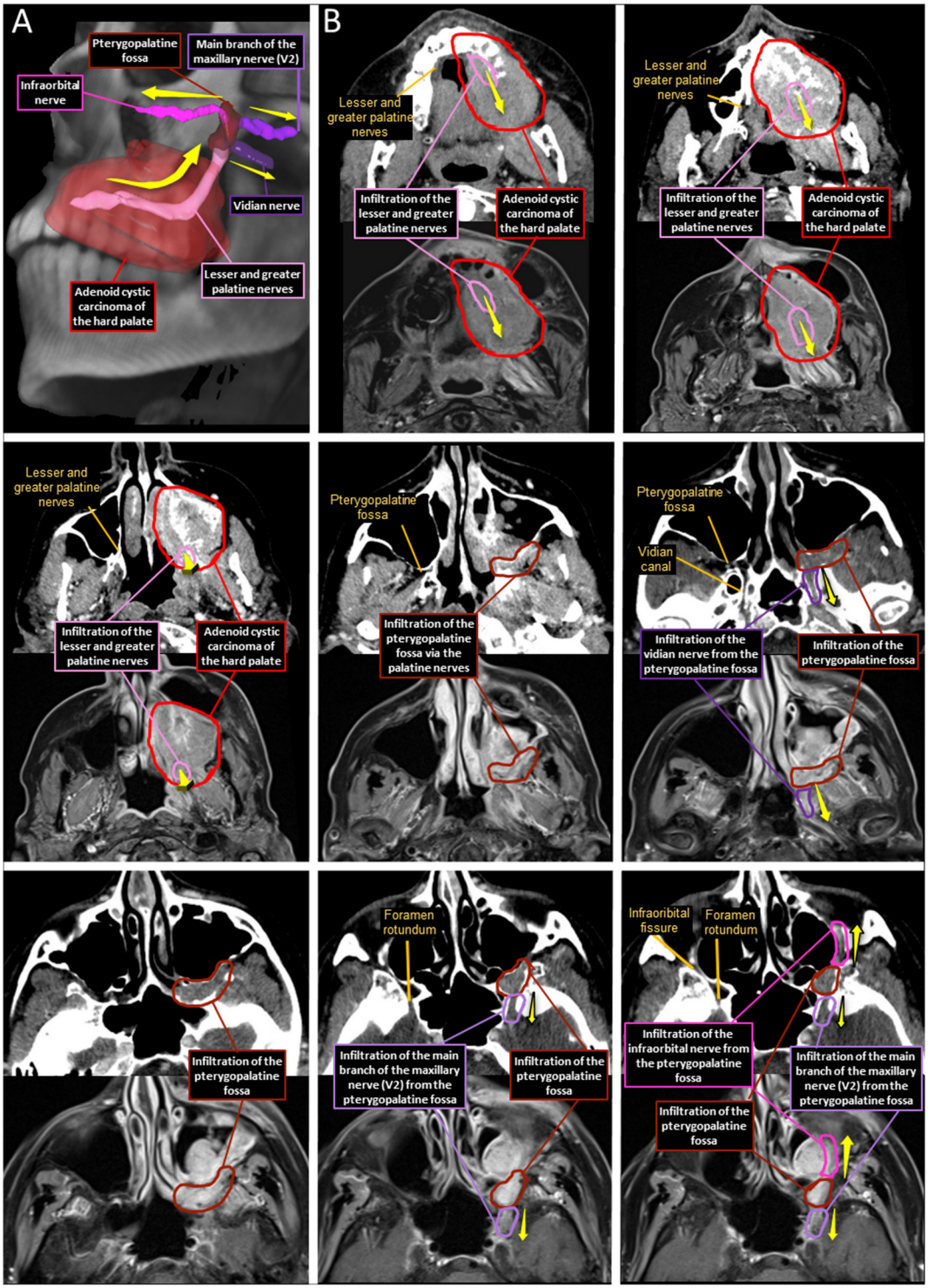

Fig. 3. Adenoid cystic carcinoma of the hard palate with macroscopic PNI of branches of the maxillary nerve (V2). (A) 3D overview of the extension pathways (yellow arrows) along the lesser and greater palatine nerves, infiltrating in a retrograde manner the pterygopalatine fossa and then infiltrating the Vidian nerve (in the Vidian canal) and the main branch of the maxillary nerve (through the foramen rotundum) and in an anterograde manner the infraorbital nerve (through the infraorbital fissure). (B) Axial views of both CT-scan and corresponding post Gado T1-weigthed MRI of the different nerve extension pathways from the bottom-up. Abbreviations. PNI: perineural invasion; CT: computed tomography; Gado: gadolinium; MRI (magnetic resonance imaging).

cutaneous nerves of the face innervating the inferior eyelid, conjunctiva, lateral nose and superior lip. Therefore, cutaneous malignancies of the middle third of the face (the lower eyelid, malar cheeks, nasal cavity and lateral nose, upper lip especially) are at risk of PNI via the infraorbital nerve (Fig. 1).

Tumors of the maxillary sinus have multiple routes that allow cancers to spread to the PPF. Invasion of the lateral walls allows access to the superior alveolar nerve, which originates from the PPF. The most direct route would be penetration of the posterior wall, which would place the cancer directly within the PPF. In

addition, tumor from the maxillary sinus can exit via various draining ostia into the nasal cavity, and spread to the nasopharynx, as nasopharyngeal tumors can also spread via the maxillary nerve (V2) [26]. Nasopharyngeal tumors can access the sphenopalatine foramen (located posterior to the nasal cavity near the roof of the nasopharynx) and spread to the PPF. Advanced oropharyngeal tumors can also spread in the superficial mucosal space to the nasopharynx, or access directly to the PPF.

From the PPF emerge the lesser and greater palatine nerves, which traverse similarly named foramen, and the nasal and nasopalatine nerves exit via the sphenopalatine foramen. Tumors of the hard palate can access the greater and lesser palatine nerves, and can ascend to the PPF (Fig. 3).

Mandibular nerve (V3)

The third division of the trigeminal nerve, the mandibular nerve (V3), runs laterally from the floor of the Meckel cave, and exits the skull base via the foramen ovale into the masticator space. Therefore, all tumors invading the masticator space (such as advanced nasopharyngeal or oropharyngeal tumors, rhabdomyosarcoma, lymphoma, and metastatic tumor) are at risk of PNI via the mandibular nerve (V3) (Fig. 4). The mandibular nerve (V3) divides into an anterior and a posterior trunk. The anterior trunk gives several motor branches to the masticator muscles and one sensory branch, the buccal nerve, which gives sensation to the skin over the cheek and the second and third molars.

The posterior trunk divides into three branches: the auriculotemporal nerve, the lingual nerve, and the inferior alveolar nerve. The auriculotemporal nerve passes through the parotid gland to supply sensation to the temporal scalp, making of cutaneous malignancies of this region (Fig. 1) as well as parotid gland tumors at risk (Fig. 5) [39,40]. The lingual nerve innerves the tongue to supply sensation to the floor of mouth and the anterior two-thirds of the tongue, making tumors of these regions at risk. The lingual nerve also gives a branch for the parasympathetic innervation of submandibular and submental glands, making tumors of this region at risk. The inferior alveolar nerve enters the mandibular canal via the mandibular foramen, finally exits the mandibular canal via the mental foramen, and divides into several terminal branches that innervate the skin of the chin and the lower lip, making cutaneous malignancies of this region at risk (Fig. 1). Moreover, all tumors invading the mandible can be at risk of PNI via the inferior alveolar nerve.

Communicating interconnections between the nerves

Between branches of the trigeminal nerve (V)

The branches of the trigeminal nerve communicate and allow spread of neoplasm from one division of the trigeminal nerve to another (Fig. 2). Potential communication exists between the ophthalmic nerve (V1) and maxillary nerve (V2) at the orbital apex, where they are in close proximity to each other after passing through the superior orbital fissure. The inferior orbital fissure joins the PPF and allows potential spread of tumor from the ophthalmic nerve (V1) in the orbit to the maxillary nerve (V2). The orbit also communicates with the masticator space through the inferior orbital fissure. Thus, a lesion from the ophthalmic nerve (V1) or the maxillary nerve (V2) may spread directly to the mandibular nerve (V3). The direct lateral communication of the PPF to the masticator space allows potential spread of neoplasm between the maxillary (V2) and mandibular (V3) nerves.

Between trigeminal (V) and facial (VII) nerves

Additionally, the trigeminal (V) and facial (VII) nerves directly communicate in three locations. First, the PPF forms a junction between the Vidian nerve and branches of the maxillary nerve (V2) (Figs. 2 and 3). Another branch of the facial nerve (VII), the chorda tympani, directly joins the lingual nerve, a division of the mandibular nerve (V3). Third, the auriculotemporal branch of the mandibular nerve (V3) crosses through the body of the parotid gland at right angles to the facial nerve and, here, usually has direct communications with the facial nerve (VII). Therefore, if macroscopic PNI involving the trigeminal nerve is observed, careful examination of the facial nerve should be performed for signs of tumor spread.

Imaging approaches for the evaluation of macroscopic PNI

PNI is often asymptomatic, heralding the importance of careful radiologic evaluation when it is suspected [27]. CT-scan and MRI play complementary roles in the evaluation of macroscopic PNI, but MRI has become the modality of choice due to better soft-tissue contrast, reduced dental artifacts, and a more accurate

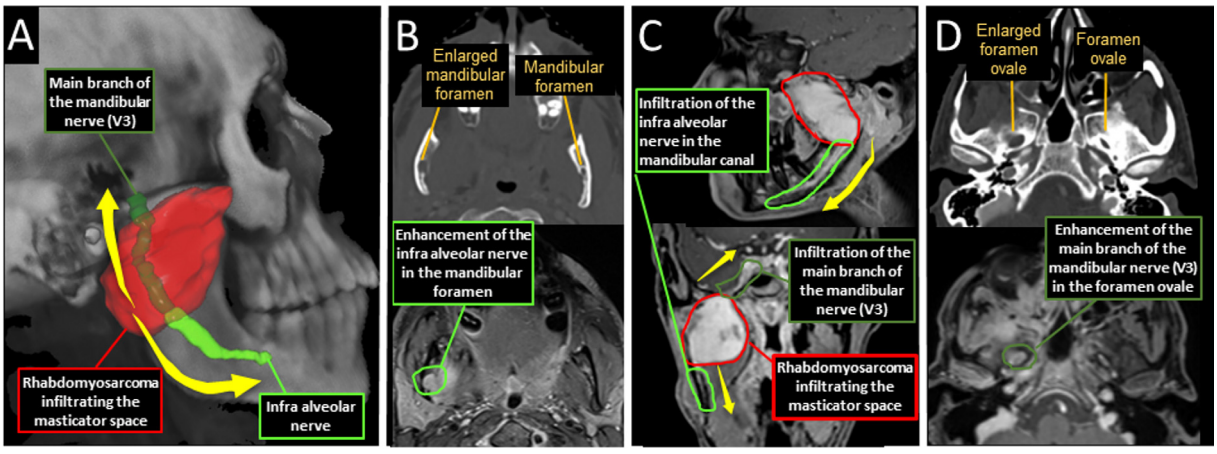

Fig. 4. Rhabdomyosarcoma infiltrating the masticator space with macroscopic PNI of branches of the mandibular nerve (V3). (A) 3D overview of the extension pathways (yellow arrows) along the main branch of the mandibular nerve (through the foramen ovale) in a retrograde manner, and along the inferior alveolar (in the mandibular canal) in an anterograde manner. (B) Note enlargement of the mandibular foramen on CT-scan, and corresponding enhancing lesion on post Gado T1-weigthed MRI. (C) Sagittal and coronal views of post Gado T1-weigthed MRI of the different nerve extension pathways. (D) Note enlargement of the foramen ovale on CT-scan, and corresponding enhancing lesion on post Gado T1-weigthed MRI. Abbreviations. PNI: perineural invasion; CT: computed tomography; Gado: gadolinium; MRI (magnetic resonance imaging).

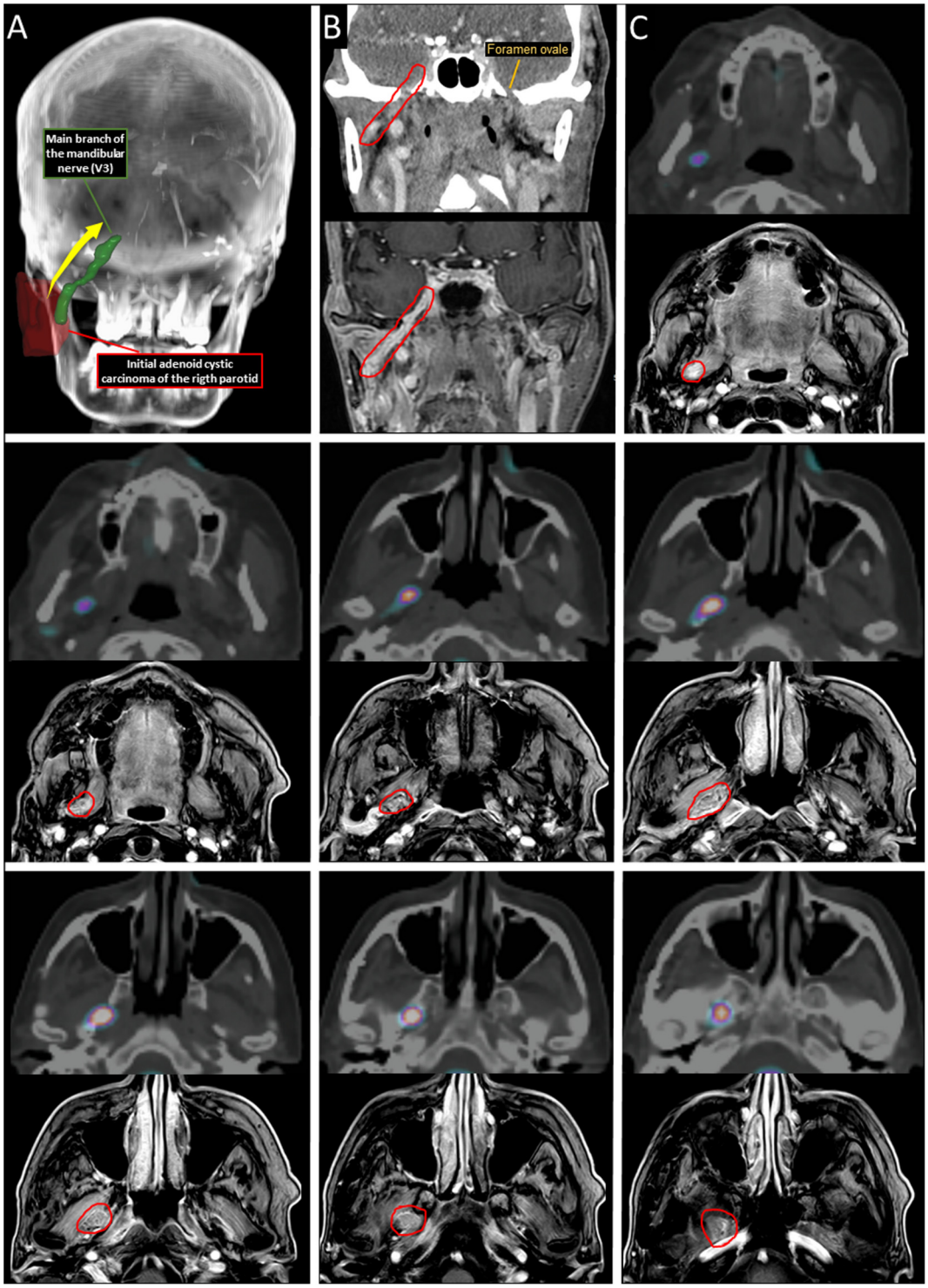

Fig. 5. Recurrence of an adenoid cystic carcinoma of the right parotid as a macroscopic PNI of the main branch of the mandibular nerve (V3). (A) 3D overview of the extension retrograde pathway (yellow arrow) along the main branch of the mandibular nerve (V3). (B) Coronal views and (C). Axial views of both ^{18}FDG-PET-CT and corresponding post Gado T1-weigthed MRI of the nerve extension pathway from the bottom-up. Enhancement along the main branch of the mandibular nerve is delineated in red on MRI images. Abbreviations. PNI: perineural invasion; CT: computed tomography; Gado: gadolinium; MRI (magnetic resonance imaging).

assessment of intracranial spread [11,27–30]. This poses a challenge for radiation oncologists as all CT-based delineation of radiation targets are currently performed only on serial axial CT slices. Close collaboration between radiation oncology and diagnostic radiology is required during the radiotherapy planning process. MRI has a sensitivity of 95–100% for detection of macroscopic PNI [31–33]. However, in 2011, Gandhi et al. [31] reviewed a series of 30 operated macroscopic PNI cases, and correlated histology with diagnostic MRI imaging. They found that MRI did not correctly define the extent of the PNI in 5 of the 30 cases (17%). In 2015, Baulch et al. [32] underwent a similar study with 38 cases. They found that MRI did not detect the macroscopic PNI in 2 of the 38 cases (5%). Of the 36 detected macroscopic PNI, MRI did not correctly define the extent of the PNI in 4 of the 36 cases

(11%). Multiplanar reformations are also important in evaluation of the skull base foramina, as many are shown to better advantage in coronal, sagittal, or oblique planes. As an example, foramen ovale or involvement of the Meckel cave, may be best visualized on coronal images [28].

On T1-weighted MRI, fat is generally present, and is normally hyperintense just after a nerve exits a foramen and in the pterygopalatine fossa. Obliteration of these fat pads is a key element in detecting macroscopic PNI [11,24]. Direct evidence of macroscopic PNI spread on MRI would be enlargement and enhancement along the course of a cranial nerve on post contrast T1-weighted images (Figs. 3, 4 and 5). Many radiologists prefer high-resolution fat-saturated postcontrast images. There is controversy regarding the use of fat-suppression sequences, as associated artifact may occur with this sequence, and the nerve may be better visualized without fat suppression [34].

Although MRI has become the gold standard for evaluation of PNI, CT-scan can play a role as well. CT-scan is superior to MRI for evaluating bony changes, which is important because a substantial portion of the trigeminal and facial nerves are surrounded by, or contained within, bony structures. Evaluation of certain foramen and areas should be routine in evaluating head and neck malignancies. These include the supraorbital foramen, superior and inferior orbital fissures, pterygopalatine fossa, foramen rotundum, Vidian canal, palatine foramen, foramen ovale, and mandibular foramen. Convexity of the cavernous sinus wall, and the presence of soft tissue or enhancement within the Meckel cave can also be signs of macroscopic PNI [24,28,29]. Masticator muscle atrophy occurring with chronic mandibular nerve (V3) denervation can be appreciated on both MRI and CT-scan. In such cases, increased intensity on T2-weighted images and abnormal enhancement in the muscle after acute or subacute denervation is present [30].

^{18}FDG-PET-CT is often inferior to MRI in diagnosis of macroscopic PNI. This is related to the small volume of disease in macroscopic PNI combined with limited spatial resolution of ^{18}FDG-PET-CT [35].

So-called "skip lesions" may occur radiologically, such that the abnormalities of the nerve may appear discontinuous on imaging (Fig. 2B) [29,33]. Pathologically, macroscopic PNI is usually found to be continuous [28,33]. This discrepancy is probably related to the fact that imaging may not detect abnormal regions of the nerve where there is low tumor burden, and thus will underestimate the full extent of nerve involvement.

Treatment considerations and radiotherapy planning – Table 2

General management

Microscopic PNI

Concerning head and neck SCC, the diagnosis of microscopic PNI is typically the result of biopsy and/or surgical excision of the primary tumor with histological sectioning. For patients undergoing surgery, few studies have attempted to assess the benefit of adjuvant RT in patients with head and neck SCC with PNI as their only indication for adjuvant therapy, making firm conclusions difficult [36–38]. We can suggest that focal microscopic PNI in the absence of other high-risk features to be a relative indication for adjuvant RT, discussed on a case-by-case. Extensive PNI is generally considered as more systematic indication for adjuvant RT. Concerning concurrent chemotherapy, patients whose cancers were found to have PNI were included in the phase III EORTC 22931 trial comparing postoperative RT to postoperative RT and concurrent cisplatin [39]. The addition of concurrent cisplatin improved locoregional control in comparison with postoperative RT alone. However, in a subsequent combined analysis of the EORTC and a similar phase III RTOG 9501/Intergroup trial, the beneficial effect of concurrent cisplatin was more pronounced for patients with positive margins and/or nodal extracapsular extension [37,40]. The use of concurrent chemotherapy is usually not recommended on the only basis of PNI but can be considered on case-by-case, especially in case of extensive PNI and/or other high-risk features.

Concerning ACC and other salivary gland tumors, controversy exists with the prognostic significance of microscopic PNI as an independent factor [25]. In a retrospective analysis, Chen et al. reported that postoperative RT was associated with reduced risk of skull-base recurrences in 140 patients with salivary gland cancers and PNI. The probability of skull-base recurrence was 5 and 15% ($p = 0.03$) with or without postoperative RT, respectively [41], consistent with the findings of other authors [42,43]. The retrospective nature of these trials, the heterogeneity of pathologies included in many of the series of salivary gland tumors, and lack of routine use of pretreatment MRI, which could have identified the presence of macroscopic PNI, are limits to the interpretation of these studies. The management of salivary gland cancers and PNI is complex. Histopathology and tumor grade must be taken into account. Polymorphous low-grade adenocarcinomas (PLGAs) demonstrate a propensity for PNI, but PLGAs can have an indolent natural history with risk of late local recurrences [44–46]. These cancers may be managed by surgery alone if surgical margins are clear, whereas salivary duct carcinomas and ACC [47] have higher risk of local and skull-base recurrences. Postoperative RT is a standard recommendation for the latter two cancers.

Macroscopic PNI

Treatment guidelines for patients with macroscopic PNI have not been established. However, different series report surgical resection followed by postoperative RT leads to improved patient outcomes [48–50]. The surgical management of macroscopic PNI requires careful preoperative assessment. Consistent with the usual oncologic principles of surgical management, the involved nerve must be resected with the intent of obtaining clear surgical margins. Care must be taken as there is a risk of underestimation of PNI extent on preoperative imaging [28]. Most patients with macroscopic PNI require postoperative RT with or without chemotherapy. Histopathology is a significant determinant of the role of primary surgery. For SCC and particularly nasopharyngeal carcinoma, where RT with or without chemotherapy is used definitively as standard treatment, extensive skull-base surgery might not be indicated.

For inoperable and macroscopically residual ACC, definitive RT is the standard treatment [51–53]. Despite the relatively low rate of tumor cure in this setting, definitive RT can result in long progression-free intervals. Also, particle therapies with protons, neutrons or carbon ions have been advocated as potentially providing better disease control [54–56]; however, the data supporting these approaches are limited, and these techniques are not widely available.

Recommendations for radiotherapy

Prerequisite

IMRT is the standard method of RT for head and neck cancers [12–15]. For the management of PNI with IMRT, the collection and interpretation of all necessary elements are required:

- Clinical examination: signs of potential PNI should be searched and the specific territory noted. Clinical history can also reveal discrete perineural invasion that could otherwise remain undetected.

Table 2
Recommendations for treatment volumes for radiotherapy in head and neck cancers with perineural invasion. Abbreviations: ACC = adenoid cystic carcinoma; PNI = perineural invasion; SCC = squamous cell carcinoma; CTV = clinical target volume; Gy = Gray; GTV = Gross tumor volume.

Nerve paths to be included in the high-risk CTV (CTV-P1)				Nerve paths to be included in the low-risk CTV (CTV-P2)	
Primary radiotherapy		Post-operative radiotherapy		For both primary and post-operative radiotherapy according to indication	
GTV = Post-contrast enhancement along the nerve	CTV-P1 = GTV + 5 mm[a] along the nerve path	In case of positive R1 margin, CTV-P1 includes Positive margin + 5 mm[a] along the nerve path	CTV-P1 Includes PNI in Tumor bed	Adenoid cystic carcinoma[b] Macroscopic PNI	Nerve paths[c] for at least 30 mm and discussed up to skull base (often recommended)[d] Consider nerve interconnections In case of skull base or intracranial involvement, consider nerve paths to the brainstem
				SCC with multiple microscopic PNI	Nerve paths[c] for at least 30 mm and discussed up to skull base (often recommended)[d]
				SCC with focal microscopic PNI	Nerve paths in the GTV/tumor bed

[a] This margin can be increased in case of MRI imaging extent doubt.
[b] Despite the lack of randomized evidence, particles RT might be considered, when available, for inoperable or macroscopically residual ACC.
[c] Standard coverage of cranial nerve pathways retrograde toward base of skull. Nerve pathways are chosen according to primary tumor localization. Consider antegrade coverage if symptoms, operative report or imaging suggesting.
[d] For non well-lateralized tumors, bilateral nerve path coverage for at least 20–30 mm and discussed up to skull base has to be considered.

- Analysis of imaging: diagnostic radio-anatomy of macroscopic PNI is discussed in the specific paragraph above. In the cases of high risk of macroscopic PNI according to tumor histopathology and/or tumor localization, it is crucial to assess the full extent of the nerve back to brainstem.
- In case of post-operative IMRT: operative and anatomopathological reports with exact histology, identification of the level of microscopic PNI (from focal to extensive) and identification and quality of resection of affected nerves in case of macroscopic PNI.

Before target volume delineation, a particular attention has to be paid on the co-registration of MRI sequences and planning CT as both modalities are of interest (see paragraph *Imaging Approaches for the Evaluation of macroscopic PNI* above). MRI imaging performed in the treatment position might improve the accuracy of the IMRT planning and thus is recommended whenever possible [57]. The personalized thermoplastic masks used for head and neck cancers can be made compatible with MRI machines, however they aren't most of the time [58]. As trigeminal nerve (V) issues are nearby the skull base, rigid co-registration, with high quality assurance all along the process, is usually recommended [58,59].

Treatment volumes

Primary radiotherapy. For non-resected macroscopic PNI, the gross tumor volume (GTV) should include the entire post-contrast enhancement along the nerve path. An additional 5 mm margin along the nerve path should be added to the GTV to create the high-risk clinical target volume (CTV-P1). This margin can be increased in case of MRI imaging extent doubt. Zukauskaite et al. [60] recently published a series of 1576 patients treated with primary RT for head and neck SCC. They found that the vast majority of recurrences occurred in the GTV. However, this study only included SCC and not histology as ACC, and excluded locations as nasopharynx, paranasal sinuses or skin which are at particular risk of PNI spread. The low-risk CTV (CTV-P2) should include an additional margin along the nerve path for at least 30 mm and a potential additional margin up to the skull base should be discussed and is often recommended [47,61]. In case of skull base involvement, the CTV-P2 should be prolonged in skull to the brainstem. Also, antegrade CN involvement should be considered to reduce risks of recurrence and failure. Consideration should also be given to treating closely adjacent nerves or branches in the event of involvement at a neural junction.

Post-operative radiotherapy. For resected macroscopic PNI with positive R1 margins, the CTV-P1 should include the close margin + 5 mm along the nerve path. This margin can be increased in case of MRI diagnostic imaging extent doubt. The CTV-P1 should include PNI in the entire tumor bed.

For both primary and post-operative radiotherapy. For cases with high-risk of tumor spread along the nerve according to tumor histology (i.e., cutaneous or non-cutaneous head and neck SCC with extensive PNI or ACC) or tumor localization (i.e., pterygopalatine fossa or masticator space invasion, nasopharyngeal or maxillary sinuses tumors), CTV-P2 should include the potentially-involved nerve path according to primary tumor localization for at least 30 mm and a potential additional margin up to the skull base should be discussed and is often recommended. For non-lateralized tumors, bilateral potentially involved nerve path should also be considered.

As target volumes might encompass usual organs at risk (such as brainstem, brain, optic pathway; especially in case of skull base involvement), individual compromises have to be considered on case-by-case based on the risk of undercoverage of PTV (and thus potential risk of recurrence) *versus* risk of toxicities.

In conclusion, trigeminal nerve (V) invasion is an important component of the natural history of various head and neck cancers. Recognizing the radio-anatomy and potential routes of invasion is essential for optimal contouring and IMRT planning, as presented in this manuscript.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2018.08.020.

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