Radiation Therapy for Adenoid Cystic Carcinoma

Subjects: Allergy

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Adenoid cystic carcinoma (ACC) of the head and neck region, which accounts for 1–2% of all head and neck cancers, is a challenging clinical entity to treat due to its unique clinical and pathologic features and the lack of prospective data guiding ideal treatment approach. This disease is often characterized by a deceivingly indolent presentation followed by perineural invasion (PNI), local recurrence, and metastatic spread. In many cases with nerve invasion, tumor spread along nerve branches can lead to failure at the base of skull—a dreaded complication that is difficult to treat in a salvage setting. This article aims to summarize the current state of radiation treatment for ACC of the head and neck as relevant to the radiation oncologist.

adenoid cystic carcinoma radiotherapy perineural invasion

1. Radiologic Evaluation of Perineural Tumor Spread (PNTS)

Preoperative and pretreatment imaging is important to evaluate for PNTS, defined as the macroscopic tumor extension detectable by imaging along the nerve. Identification of PNTS is important for staging and treatment planning as it may affect the radiation field or tumor resection. However, PNTS evaluation can be challenging due to its intricate anatomy, challenging imaging technique for subtle findings, and the interpreting radiologist's level of suspicion and knowledge. Additionally, up to 40% of patients with PNTS are asymptomatic [1].

2. Imaging Techniques

Magnetic resonance imaging (MRI) is the modality of choice to evaluate soft tissue and perineural disease. It has high contrast resolution and allows for superior soft tissue evaluation. MRI has up to 95% sensitivity in detecting PNTS [2].

To evaluate PNTS, it is important to have an optimal imaging protocol that includes the entire course of the nerve with an appropriate field-of-view (FOV). Although 1.5 Tesla (T) is sufficient for evaluation of large cranial nerves, 3T is better at assessing for smaller nerve branches around the ear and parotid regions [3][4]. When imaging for PNTS, images should be thin slices, 3 mm or less, with 3-dimensional acquisition. A FOV should be 16–18 cm, but a smaller FOV may be needed to assess for peripheral and smaller branches.

There are certain imaging sequences that are particularly important for PNTS evaluation. T1-weighted pre-contrast images without fat saturation are useful to look for the loss of T1 hyperintense fat that accompanies the T1

hypointense nerves (**Figure 1**A). This sequence is particularly crucial for evaluation of extracranial cranial nerves [5][6]. Postcontrast T1 should be accompanied by fat suppression. Fat suppression accentuates the abnormal nerve enhancement by eliminating intrinsically bright T1 fat signal that surrounds the nerve (**Figure 1**B). T2 sequences are important in assessing for edema; this sequence should also have fat suppression to visualize abnormalities.

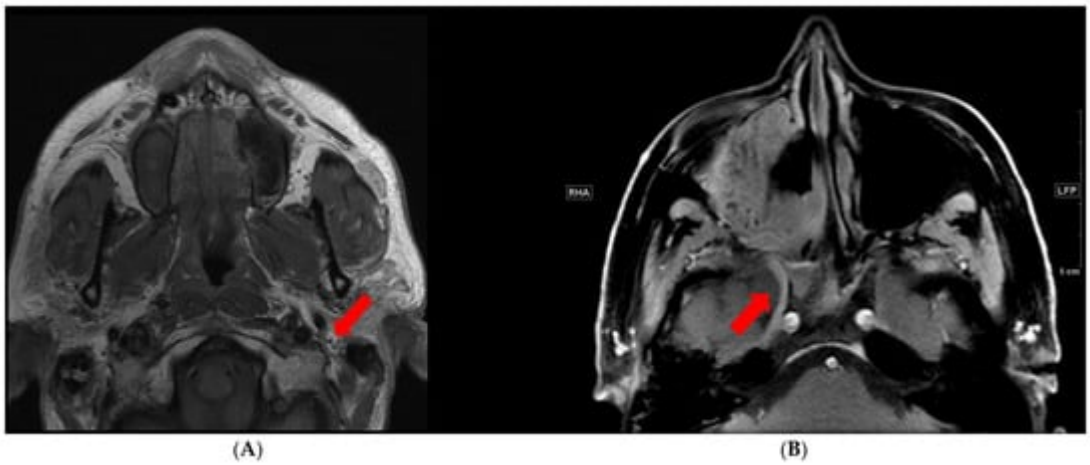

Figure 1. PNTS as seen on MRI. (**A**) Normal T1 hyperintense triangular fat around the facial nerve (arrow). (**B**) Postcontrast fat suppressed T1 image shows abnormally enhancing right V2 (arrow) and the pterygopalatine fossa.

More advanced imaging techniques can be utilized to assess nerves, such as MR Neurography. It utilizes special techniques to accentuate the nerves, such as reverse fast imaging with steady state precession, 3D-cranial nerve imaging, high-resolution high-contrast magnetic resonance neurography, and 3D double-echo steady-state with water excitation [7][8]. Specifically, targeted 3T MRI of the nerves has up to 95% sensitivity in detecting PNTS [9].

PNTS can be suspected by several imaging features. These include asymmetric enlargement of the nerve, asymmetric enhancement along the nerve, obliteration of the perineural fat planes, and destruction or widening of the neural foramina. Additionally, muscular denervation as a secondary sign can be a clue to suggest a search for PNTS.

3. Imaging Pitfalls

There are several technical considerations to keep in mind when assessing for perineural spread. Incomplete fat suppression can occur, especially at the air–bone interface, which can falsely suggest perineural enhancement. It is also important to note that there are parts of the cranial nerves that normally enhance due to perineural venous plexus accompanying the nerves, including the geniculate ganglion, proximal greater superficial petrosal nerve (namely the tympanic and mastoid segments [10]), and the proximal segments of the trigeminal nerves. Denervated muscles demonstrate enhancement and edema, which can have a mass-like appearance and may falsely suggest a mass in that region (**Figure 2**). Additionally, other entities can mimic PNTS, including infection, inflammation, ischemia, trauma, and demyelinating processes [11].

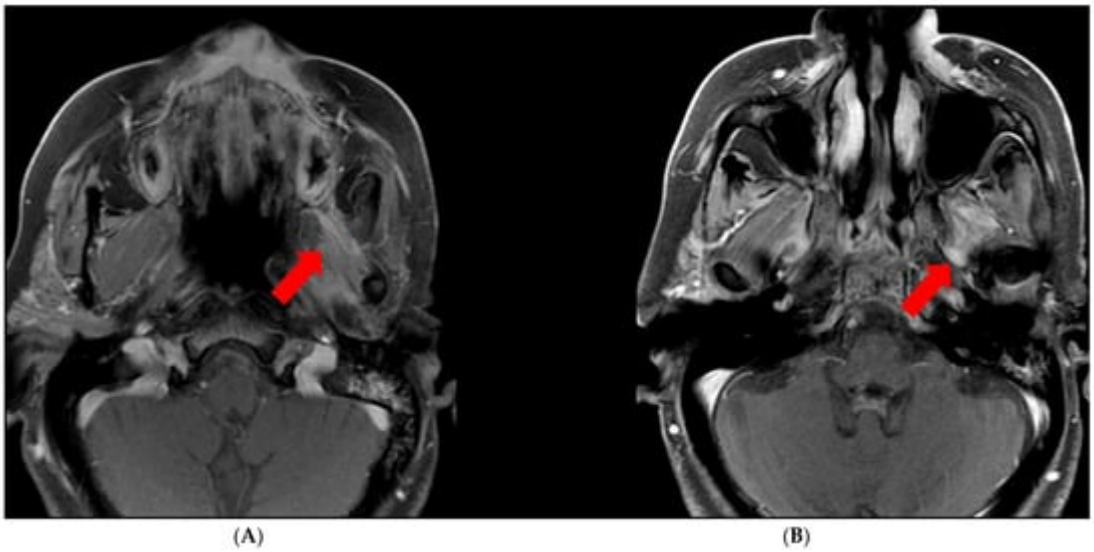

Figure 2. Muscle denervation edema/enhancement. (**A**) Asymmetric enhancement of the left muscles of mastication due to denervation (arrow). (**B**) PNTS along the left V3 (arrow).

4. Rationale for Radiation

Postoperative radiotherapy is nearly always indicated for patients with ACC due to its propensity for local relapse. Traditional indications for postoperative RT include incomplete surgical resection, positive or close margins, and presence of PNI [12][13][14][15][16][17][18][19][20]. In primarily retrospective studies, radiation has demonstrated locoregional control of 36–93% for unresectable or incompletely resected salivary gland tumors, including ACC [21][22][23][24]. Retrospective data on overall survival benefit with postoperative RT is mixed, with one study [25] showing a survival benefit for postoperative RT versus surgery alone (5-year overall survival 82.4% versus 72.5%), while others have shown no survival benefit despite a benefit in locoregional control [21][26][27]. Although radiation is indicated for the vast majority of patients with ACC due to the disease's propensity for early and late locoregional recurrence and association with perineural invasion, the omission of adjuvant radiotherapy can be considered for highly selected patients with early-stage disease, widely negative surgical margins, and no pathologic evidence of perineural invasion or lymphovascular invasion. Patients electing for observation should be counselled regarding the continued need for careful, long-term clinical follow up to assess for recurrence.

5. Radiation Therapy Design

In all surgically resected cases of ACC in which adjuvant radiation therapy is warranted, the primary tumor bed should be covered. The decision of when to electively treat at-risk cranial nerve pathways is more complex. Tracing the CNs back to the base if skull is clinically challenging and can result in increased toxicity; thus it is prudent to consider the balance of potential benefit of elective CN pathway coverage against the toxicity of volume expansion. ACC usually warrants serious consideration of elective coverage of at-risk CN pathways innervating the primary tumor site due to its propensity for PNTS [28][29]. In rare cases of early stage (T1 or T2) ACC of a major salivary gland in which PNI is not observed, treatment of the primary tumor bed alone with margin should be considered.

ACC rarely involves the lymphatics [30] and therefore the neck should not routinely be treated unless there is histologically confirmed disease in the neck or a high suspicion based on imaging. Advanced T-stage is associated with an increased risk of nodal involvement, and treatment of the neck can be considered in more advanced cases of this subtype [31]. It was outlined that common clinical ACC cases representing a variety of head and neck cases with PNI/PNTS (**Table 1**). There are previously published contouring guidelines [32][33][34][35][36][37][38] to aid in the target delineation of relevant CN pathways. For ACC arising from the parotid gland with extensive PNI or frank tumor involvement along CN VII, it recommend electively covering the stylomastoid foramen and the proximal course of VII in the temporal bone (**Figure 3**A) [39][40]. By contrast, in cases of microscopic PNI in early-stage disease of the parotid gland, coverage should only include the stylomastoid foramen and the mastoid segments of VII with the cochlea spared. If there is concern for involvement of the auriculotemporal nerve, it and V_3 are electively treated up to the foramen ovale (**Figure 3**B) [41].

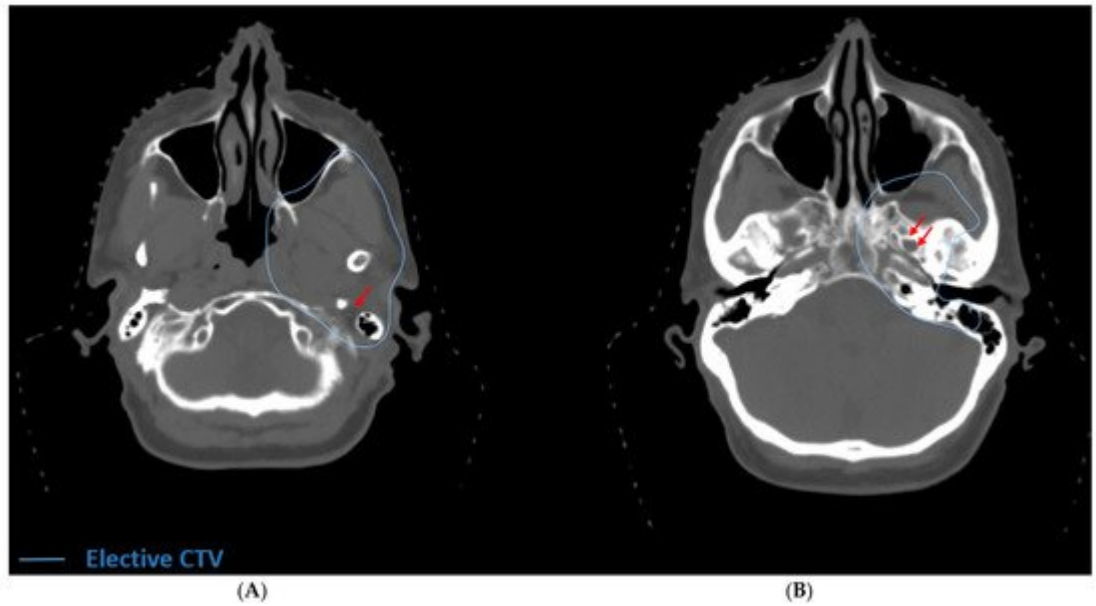

Figure 3. Definitive radiation for unresectable ACC of the deep lobe of the parotid with PNTS. (**A**) The elective volume includes the stylomastoid foramen (red arrow). In this case, there was extension into the parapharyngeal space and infratemporal fossa. (**B**) The elective volume includes the foramen ovale (double red arrows) because of radiographic involvement of V_3. In this case the elective volume was treated to 56 Gy.

Table 1. Cranial nerves at risk based on ACC primary site.

Primary ACC Tumor Site	Cranial Nerves at Risk	Origin at Base of Skull	Additional Cranial Nerves at Risk via Inter-Nerve Connections
Submandibular Gland	V_3	Foramen ovale	VII, via chorda tympani (rarely included in elective volumes as involvement is rare)
	XII (deep lobe involvement)	Hypoglossal canal	
Parotid Gland	VII	Stylomastoid foramen	V_3, via auriculotemporal nerve

Primary ACC Tumor Site	Cranial Nerves at Risk	Origin at Base of Skull	Additional Cranial Nerves at Risk via Inter-Nerve Connections
Hard Palate	V_2	V_2: foramen rotundum	VII, via greater superficial petrosal nerve and vidian nerve

6. Particle Therapy

Particle therapies, including proton, neutron, and carbon ion therapies, have been studied within ACC and may allow for further reductions in dose to normal structures compared to conformal photon-based planning. Since treatment of the base of skull is often included in cases of ACC, protons have demonstrated a reduction in the dose to critical structures such as the cochlea, brainstem, and temporal lobe [42]. Protons and other particle therapies should be given extra consideration for unresectable disease where dose escalation is critical [23]. Definitive radiotherapy with particle therapies for unresectable disease has demonstrated a 5-year locoregional control rate of 24–57%, with overall survival of 26.5–87% [43]. The rationale for particle therapy applies even more in the recurrent setting, where it may not be feasible to adequately respect normal tissue constraints using photons. Carbon ion radiotherapy may also hold promise within ACC. Relative to photons, Carbon ion radiotherapy has a relative biologic effectiveness (RBE) of approximately 3, and has demonstrated efficacy and tolerability with a number of centers around the world reporting promising retrospective outcomes in ACC; at least one prospective trial protocol is under recruitment [44][45][46][47]. Neutron therapy has also been utilized within ACC, with promising outcomes in retrospective studies [48][49]. Particle therapy may offer benefits in cases of re-irradiation, discussed below.

7. Re-Irradiation

The management of recurrent ACC cancers originating in an irradiated region is complex. Initial surgery of recurrence is ideal and may improve outcomes [50], but unfortunately recurrences related to PNTS are seldom resectable. Re-irradiation may be an option for selected patients, but the therapeutic window of re-irradiation is narrow. Re-irradiation for head and neck cancers in general is far less successful than initial treatment and has a far greater toxicity profile [51]. Given the complexity of the target volumes in upfront treatment, it is not uncommon for such areas of recurrence to have been either omitted or partially treated, allowing for potentially more room for re-irradiation. Obtaining prior radiation records including the target volumes is critical in such cases. Additionally, the patients should receive clinical work up to ensure that there is no distant disease which may change the risk of toxicity the patient is willing to accept. Securing locoregional control with re-irradiation may confer improved long-term quality-of-life compared to uncontrolled locoregional cancer progression, especially when there is PNTS. Irradiation of the involved nerves and elective targeting of adjacent pathways of spread similar to de novo cases is recommended, particularly if these areas were omitted or partially treated in the initial course. Since ACC is often associated with a prolonged natural history, late treatment effects need to be considered and the patient appropriately counseled. Patient selection is the single most important step in obtaining a beneficial outcome following re-irradiation and often requires a multi-disciplinary team to assist in managing potential toxicities. Time

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from initial course of radiation to local failure is an important variable to consider when selecting patients for re-irradiation, with longer intervals being more favorable. When available, particle therapy as discussed above can be considered in these instances due to its physical characteristics, which allow for greater sparing of tissues distal to the radiation target [52]. Re-irradiation with particle therapies has demonstrated a locoregional control of 41–70% with limited follow up in retrospective studies, with overall survival at 2 years of over 60% [53][54][55].

8. Concurrent Chemo-Radiotherapy

The role of concurrent chemo-radiation in adenoid cystic carcinoma is the subject of ongoing clinical investigation. For salivary gland malignancies, the clinical trial RTOG 1008 is currently testing whether the addition of cisplatin to standard postoperative radiation for high-risk salivary gland cancers involving the major salivary glands improves survival. High risk factors include pathologic stage T3-4, N1-3 or T1-2, N0 with a close or positive surgical margin. Notably, this randomized phase II/III trial includes high grade ACC (defined as >30% solid component). While it await these results, there are some limited retrospective series that support the use of concurrent chemo-radiotherapy in select patients with adverse pathologic features in salivary gland malignancies [56][57]. In the definitive setting, it is reasonable to extrapolate from other head and neck cancers and consider a concurrent radiosensitizing chemotherapy regimen to maximize tumor control [58]. Multidisciplinary discussion with medical oncology is recommended in such cases.

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