

Primary Intracranial Adenoid Cystic Carcinoma: Report of Three Cases

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Abstract

Objective Nasal cavity and paranasal sinuses host a variety of malignant tumors with adenoid cystic carcinoma (ACC) being the most frequent cancer of salivary gland origin. The histological origin of such tumors virtually precludes primarily intracranial localization. The aim of this study is to report cases of primarily intracranial ACC without evidence of other primary lesions at the end of an exhaustive diagnostic workup.

Methods An electronic medical record search complemented by manual searching was conducted to identify prospective and retrospective cases of intracranial ACCs treated in Endoscopic Skull Base Centre Athens at the Hygeia Hospital, Athens from 2010 until 2021 with a mean follow-up time of at least 3 years. Patients were included if after complete diagnostic workup there was no evidence of a nasal or paranasal sinus primary lesion and extension of the ACC. All patients were treated with a combination of endoscopic surgeries performed by the senior author followed by radiotherapy (RT) and/or chemotherapy.

Results Three unique illustrative cases (ACC involving the clivus, cavernous sinus and pterygopalatine fossa, one orbital ACC with pterygopalatine fossa and cavernous sinus involvement and one involving cavernous sinus, and Meckel’s cave with extension to the foramen rotundum) were identified. All patients underwent subsequently proton or carbon-ion beam radiation therapy.

Conclusions Primary intracranial ACCs constitute an extremely rare clinical entity with atypical presentation, challenging diagnostic workup and management. The design of an international web-based database with a detailed report of these tumors would be extremely helpful.

Keywords

- adenoid cystic carcinoma
- endoscopic transnasal surgery
- intracranial ACC
- proton beam therapy

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Introduction

Adenoid cystic carcinoma (ACC) is a slow growing malignant tumor derived from minor or major salivary glands accounting for approximately 5% of sinonasal cancers.¹ Its tendency to recur locally, the potential to invade perineural structures, and its aggressive nature complicate its treatment.² Metastases often occur late, and although 5-year survival is relatively good, most patients present with recurrences many years after the initial diagnosis.³ ACC is the third most common salivary gland tumor and presents with three main histological growth patterns: solid, tubular, and cribriform. The solid pattern is associated with the worst prognosis. However, in most cases, those different patterns coexist.⁴

Nasal cavity and paranasal sinuses may host a variety of malignant tumors with ACC being the most common salivary gland tumor of the sinonasal tract. Nasal obstruction, rhinorrhea, facial pain, epistaxis, tingling, numbness, and burning sensation are the most common symptoms.⁵ Notoriously, ACC has the tendency to spread along the perineurium of small cranial nerve branches, usually those of the trigeminal nerve. In some patients, perineural invasion represents the only symptom and may be present prior to the detection of the primary carcinoma.^{2,6}

Ideally, complete surgical resection with negative margins will give the patient the best prognosis; however, this is rarely feasible. Complete macroscopic resection, with magnification and detail provided by extended endoscopic endonasal techniques, leads to the best oncologic outcomes and lower morbidity as compared with external approaches.⁷

Traditionally, and as expected by their origin, ACC tumors arise in areas covered by epithelium and containing minor or major salivary glands. Hence, there are only a few case reports of ACC tumors presenting as primarily endocranial tumors.^{8,9} We present three patients with ACC tumors which presented as primarily endocranial-skull base lesions. These cases are of interest due to their diagnostic and therapeutic challenges related to their unique anatomical and histological features.

Materials and Methods

A systematic retrospective review of electronic medical records complemented by manual searching was conducted with the aim of identifying cases of primary intracranial ACCs treated by the Endoscopic Skull Base Centre Athens, Hygeia Hospital, Athens from 2014 to 2021. The study was approved by the institutional review board. Patients presenting with intracranial ACC without evidence of other primary lesions following a complete diagnostic workup including computed tomography (CT) and magnetic resonance imaging (MRI) were included. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments and was approved by the ethical committee of the "Hygeia Hospital, Athens, Greece."

Results

In total, 79 patients treated for malignant tumors of the nose, paranasal sinus, and skull base were screened. Three cases were identified: one case of ACC of the clivus and pterygopalatine fossa, one orbital ACC with pterygopalatine fossa and cavernous sinus involvement, and one involving cavernous sinus, Meckel's cave extending to foramen rotundum. These three cases are presented in detail below.

Case 1

A 70-year-old male patient presented to our department with dizziness, vertigo, and diplopia of 6-month duration. He also complained of closed rhinolalia, numbness of the left facial region (trigeminal nerve V2 and V3), and tongue paresis ipsilateral. He was initially diagnosed by his family doctor as suffering from myopathy and treated with steroid medication but his symptoms kept deteriorating. His medical history included controlled blood hypertension and dyslipidemia.

His examination revealed left hemifacial hypoesthesia and paresis of the hypoglossal nerve, and his diagnostic nasal endoscopy was without the evident disease. The MRI showed gadolinium-enhancing tissue of the left pterygopalatine fossa, infratemporal fossa, nasopharynx, lateral cavernous sinus, and Meckel's cave involving the divisions of the trigeminal nerve, while CT scans revealed areas of hyperostosis of the left clivus, greater wing, and pterygoid process of the sphenoid. Surprisingly, there were many osteosclerotic areas without evidence of lytic lesions (→Fig. 1).

The patient was operated with an extended endoscopic approach. Endoscopic medial maxillectomy was performed to maximize lateral access. Following sphenopalatine and vidian artery ligation, the content of the pterygopalatine fossa was accessed. The foramen rotundum and medial and lateral pterygoid plates were identified. Large bony specimens from the pterygoid root and plates were removed for biopsy with the bone being extremely sclerotic (→Fig. 1). Removal was subtotal as clear margins could not have been achieved with such extended disease, without causing significant damage to important vascular and neural structures.

Histopathology showed a low-grade tubular ACC, with a Ki-67 marker ranging between 2 and 25%.

He received radiotherapy (RT) in the form of the proton beam therapy which was well tolerated. After 2 years, he sustained radiation necrosis of the superior alveolar process of the left maxilla with the loss of two molar teeth. He was subjected to debridement and wound closure with local flaps intraorally by maxillofacial surgeons and two courses of hyperbaric oxygen therapy, 15 each. Diplopia is still persistent, and he suffers from temporomandibular joint impairment but without evident disease seen on the MRI scan, 3 years after the initial diagnosis.

Case 2

A 47-year-old female patient was referred to our department with sudden onset lateral diplopia. She was also suffering from headaches, orbital pain, and right upper eyelid ptosis for 6 months but her symptoms had been misattributed to

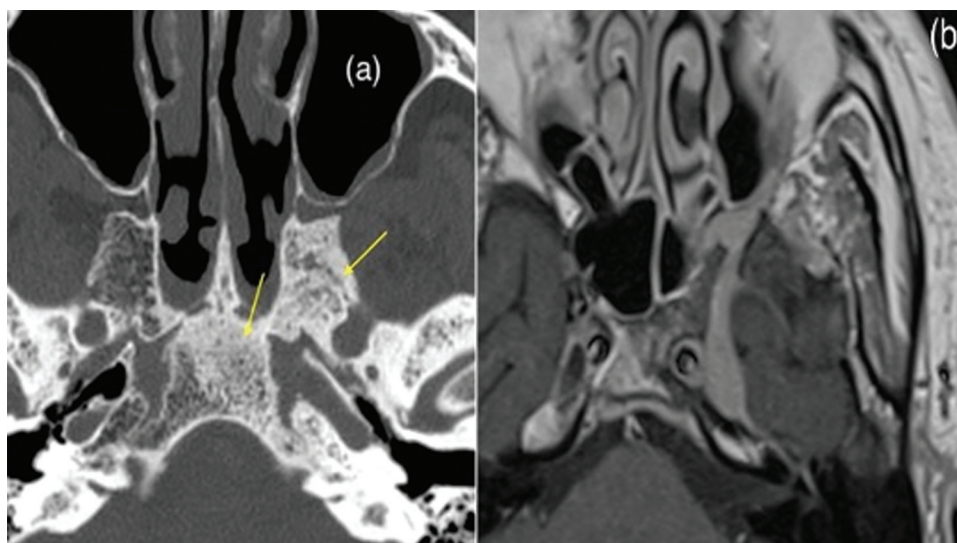


Fig. 1 Case 1: (a) Preoperative axial CT showing the osteosclerotic infiltration of the left greater wing and pterygoid root as well as the left part of the clivus (yellow arrows). (b) Preoperative axial T1-weighted MR scans showing gadolinium-enhanced ACC at the left trigeminal ganglion and the lateral cavernous and the pterygopalatine fossa, including the divisions of the trigeminal nerve. ACC, adenoid cystic carcinoma; CT, computed tomography; MR, magnetic resonance.

her previous history of four rhinoplasties. Nasal endoscopy was normal. Gadolinium-enhanced MRI scan showed a small tumor of the right orbit in contact with the medial rectus and superior oblique muscle and in close proximity to the anterior ethmoid artery. An extensive spread following the intraorbital branches of the trigeminal nerve was evident (► **Fig. 2**). The pterygopalatine fossa and cavernous sinus were also involved. An extension from the orbital lesion

directly to the ethmoid roof was noted with minor erosion of the lamina papyracea and the fovea ethmoidalis.

Biopsy via an endoscopic endonasal approach under general anesthesia from all three sites revealed the presence of ACC, which was confirmed after immunohistochemistry and a second opinion from an expert pathologist. The fluorescence in situ hybridization analysis did not show a *NTRK1* gene rearrangement.

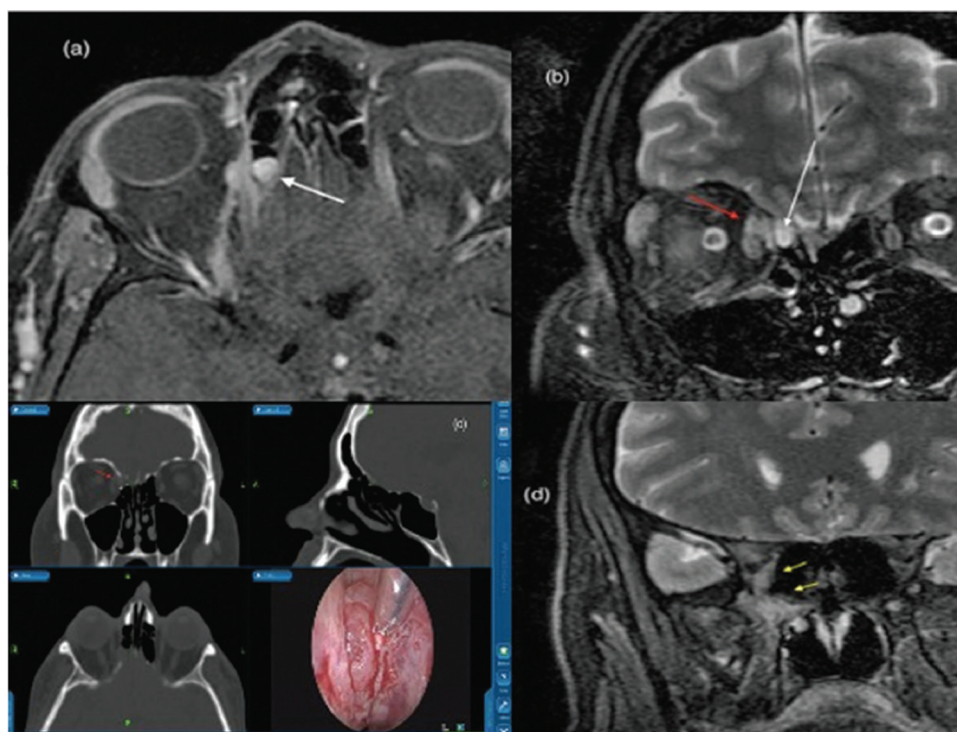


Fig. 2 Case 2: (a) Preoperative axial postgadolinium T1-weighted MRI and (b) coronal T2-MRI and (c) intraoperative neuronavigation multiplanar images demonstrating a tiny ethmoidal tumor (white arrow) that affects the orbit (red arrow) through an almost intact lamina papyracea (asterisk). (d) Linear intraorbital extension through nasociliary nerve to the apex area invading pterygopalatine fossa and extending to cavernous sinus. MRI, magnetic resonance imaging. Note: Yellow arrows indicate the intraorbital extension.

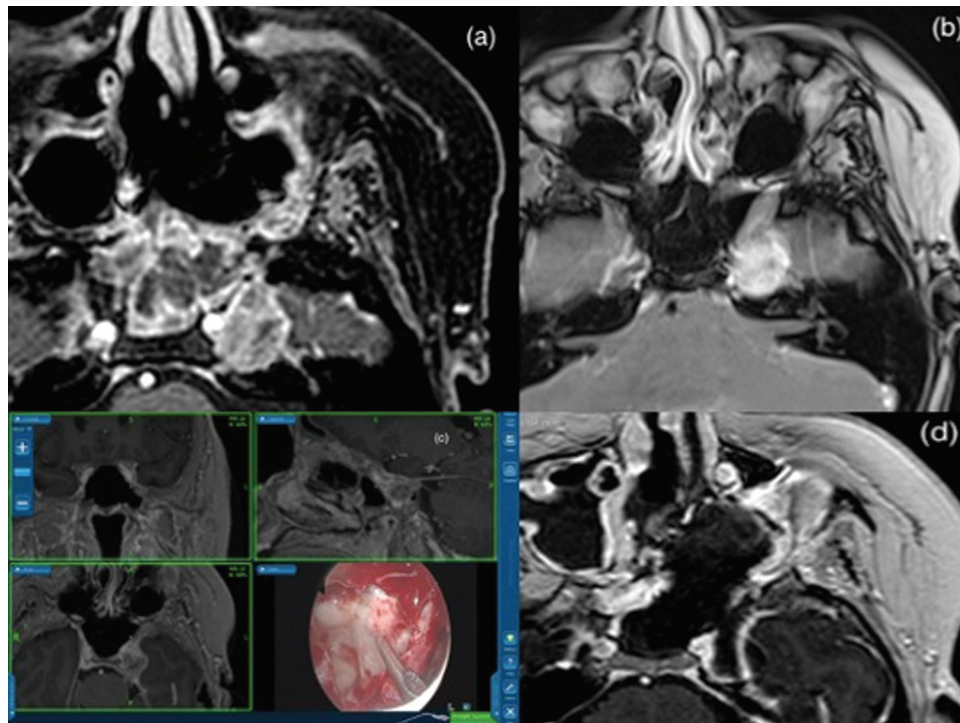


Fig. 3 Case 3: (a) and (b) Preoperative axial gadolinium-enhanced T1-weighted MRI showing an ACC infiltrating the left cavernous sinus and Meckel's cave with extension to the corresponding pterygopalatine fossa. (c) Intraoperative neuronavigation images of the endoscopic transsphenoidal approach. Suction tip points out the projection of the tumor to the lateral wall of the sphenoid sinus. (d) Postoperative image showing the near total removal of the tumor. ACC, adenoid cystic carcinoma; MRI, magnetic resonance imaging.

The best treatment after multidisciplinary discussion was that because of normal visual acuity of the patient and the low chance of gross total resection with negative margins even after orbital exenteration (due to extension in cavernous sinus and perineural spread), a subtotal resection with orbital preservation and adjuvant proton beam RT would be the best option.

The patient underwent proton beam RT (74 Gy in 37 sessions) which was tolerated well with normal visual acuity, albeit with affected orbital and eyelid mobility. After 36 months, the patient developed a local recurrence intra-orbitally with infiltration of fat and ocular muscles. The apex, cavernous sinus, and pterygopalatine fossa were free of disease on all MRIs. Following multidisciplinary discussion, it was decided that orbital exenteration would be the treatment option.

Case 3

A 39-year female patient was referred to us with progressive left oculomotor, trigeminal (maxillary branch), and abducens nerve palsies with severe orbital pain. Her symptoms started 2 years earlier with xerophthalmia, eyelid ptosis, and orbital pain. CT and MRI scans revealed a tumor involving Meckel's cave, lateral cavernous sinus with the minimal extension via foramen rotundum into the pterygopalatine fossa. Initially, it was diagnosed as a trigeminal schwannoma at another center, and the patient was treated with three sessions of radiosurgery (CyberKnife). After a transient improvement of symptoms, the patient's symptoms deteriorated and she was finally referred to our center for further

management. Biopsy of the lesion under general anesthesia via an endoscopic endonasal transsphenoidal approach was performed, which confirmed a low-differentiation (K_i-67 50%) ACC.

The multidisciplinary oncology board suggested surgical removal of the lesion followed by adjuvant RT. The patient was operated via an extended endonasal endoscopic transpterygoid approach to the lateral cavernous sinus and Meckel's cave (quadrangular space). The boundaries were the temporal lobe laterally, the cavernous sinus and paraclival and parasellar internal carotid artery (ICA) medially, the petrous part of the ICA inferiorly, and the V2 nerve superiorly. A gross total removal was achieved (→ Fig. 3). Postoperative RT with carbon ion was given, although the initial adjuvant treatment strategy was for proton beam RT.

The patient had an uncomplicated postoperative course with only mild pain in the late postoperative period. The postoperative MRI scans confirmed the gross total removal of the lesion. However, following carbon-ion treatment, the patient suffered from severe radiation necrosis of the brain stem and passed away 9 months after completion of treatment.

Discussion

ACC was first described in 1856 by Billroth and primarily named cylindroma.³ It accounts for approximately 1% of all malignant tumors of the oral and maxillofacial areas.¹⁰ It most commonly arises from the major and minor salivary glands, nasopharynx, and lacrimal glands although it may be found in the lung, trachea, mammary gland, and skin.⁸

Despite being a slow-growing tumor, ACC is characterized by locally aggressive invasion and high tendency to recur.^{8,9}

The incidence of intracranial extension of sinonasal ACC ranges from 4 to 22%.¹¹ This tumor may be primary or secondary as a result of direct invasion of the skull base, as well as hematogenous or perineural spreading. Three main routes of intracranial invasion of salivary gland ACCs have been identified: along the Eustachian tube (peritubal space), the mandibular and maxillary nerves, and the ICA.¹² The most common site of intracranial involvement is the Gasserian ganglion, with an estimated incidence of 35.8%, while cavernous sinus is involved in 15.1% of intracranial ACCs.¹³

Primary intracranial ACC is very rare. It is thought to arise from existing buccal cell rests in the absence of an extracranial primary tumor.⁹ Among the limited cases of primary intracranial ACCs reported in the literature, the Gasserian ganglion,¹⁴ the middle cranial fossa,^{8,15,16} the frontal lobe,^{17,18} the cavernous sinus,^{11,19} and the posterior fossa¹⁵ comprise the vast majority of locations. Additionally, a primary orbital neoplasm may be an ACC in 4.8% of the cases most commonly arising superolaterally from the lacrimal gland, and infrequently in the medial aspect of the orbit from the lacrimal apparatus. Primary orbital ACC from an extra lacrimal region is rare.²⁰

In our series, we present one case of ACC of the pterygopalatine region and clivus, one orbital ACC with pterygopalatine fossa and cavernous sinus involvement, and one involving the cavernous sinus, Meckel's cave with extension to the foramen rotundum, all three without evidence of other primary lesions. Two of our cases were primary intracranial ACC without evidence of extracranial involvement. The other case had only a very small lesion in the superior ethmoids in contact with the lamina papyracea and the fovea ethmoidalis but an extensive spread to the orbit, the pterygopalatine region, and the cavernous sinus via trigeminal branches.

Interestingly this particular lesion displayed a linear spreading tumor-infiltrating distinct (adjacent) anatomic areas without the typical bulky mass effect. This filamentous growth pattern inhibited the early recognition of the tumor in imaging studies even by experienced radiologists.

ACC has an insidious course. Symptoms of an intracranial ACC depend on its location and can be difficult to characterize. The presentation may be subtle, and neurologists will be in most cases the first to assess and treat the patient due to the involvement of the orbit, the cranial nerves, or the cavernous sinus.^{13,21} This was in line with our series where cranial nerve palsies were the main and first symptoms, leading to a delayed diagnosis. Symptoms are unspecific so the patient does not seek medical advice, and when that happens the first physician is usually not an experienced ENT or skull base surgeon.

Imaging these tumors is challenging even in the most experienced "eyes." The radiological features of ACCs are atypical and may mimic many other pathologies, either benign or malignant. Our team collaborates with dedicated head and neck radiologists when dealing with tumors. These

tumors are difficult to be distinguished in imaging studies (CT or MRI) from meningiomas or schwannomas as they mimic these lesions and present as well-demarcated, hyperdense extra-axial masses on the CT scan, with homogenous contrast enhancement following cranial nerves.⁹ On the MRI scan, intracranial ACCs are isointense on the T1-weighted image, slightly hyperintense on the T2-weighted images, and show tumor enhancement with a delayed increase of the thallium accumulation, which are characteristics similar to those of intracranial meningiomas.²² These can be regarded as the main contributing factors leading to significant delay until the symptoms become more intense and intracranial invasion of vital structures is suspected, something that necessitates more radical diagnostic steps like biopsies. In one of our cases, the ACC of Meckel's cave mimics a trigeminal schwannoma for which stereotactic RT was employed without prior biopsy. Failure of initial treatment, worsening of paresthesia, and additional cranial nerve palsies raised the need for histological diagnosis.

Biopsy is mandatory in these cases to obtain a histology-driven treatment. Managing patients based only on radiological criteria is dangerous as is clear in our second case. An extended endoscopic approach is optimal to obtain tissue samples with minimal morbidity without compromising oncological results or preventing possible future intervention. Given the rarity and aggressive biological behavior of these tumors, a second histopathological opinion by a dedicated pathologist is crucial as this can confirm or revise the diagnosis.²³

The mainstay treatment for ACCs is radical surgical resection.^{8,11,22} However, a free-margin surgical resection is extremely difficult to achieve for three main reasons: the critical relationship with vital structures, the presence and proximity of cranial nerves, and lastly, the initial "asymptomatic" course of the disease which delays the right diagnosis. An exhaustive preoperative planning with a CT scan and pre- and postgadolinium MRI defines the limits of the tumor and aids at choosing between an external, an endoscopic, or combined approach.¹ Advances in endonasal endoscopic surgery render many sinonasal and skull base tumors amenable to a purely endoscopic approach but in such cases as in our series this is difficult to achieve, due to extensive nerve infiltration and occurrence of metastasis. Endoscopic endonasal approach has the advantage of avoiding complications related to a skin incision, brain retraction, or dissection of the cranial nerves as compared with traditional external ones by providing a direct path to the tumor. Consequently, a potential decrease in surgical morbidity, with quick recovery, minimal postoperative discomfort, and reduced costs should be taken seriously into consideration when a histological diagnosis is needed.^{24,25} It has been reported that surgical margins can be evaluated intraoperatively with frozen sections, and the resection should be modified until total tumor removal is achieved or if further tumor resection is impossible to achieve irrespectively of the approach.¹ Such surgical techniques of course are irrelevant when the tumor is in contact with the ICA or infiltrates the cavernous sinus, as in our cases. Although the significant role

of surgery is well established, postoperative RT has been employed in certain cases, since this tumor is regarded as radiosensitive, but not radiocurable.⁸ It seems that radiation often produces tumor regression, relieves symptoms, and decreases local recurrence rates.^{13,26} Especially for orbital ACC, eye-sparing surgery and adjuvant RT have demonstrated favorable local control and long-term survival outcomes in patients with orbit-confined ACC.

However, RT is limited by the sensitivity to high-dose radiation of vital structures including the brainstem, optic structures, and cochlea.²⁷ Lastly, although there have been reports of tumor shrinkage and complete radiological resolution with chemotherapy and brachytherapy respectively, no definite conclusions can be drawn for the effectiveness of these treatment options.^{28,29} Biological markers as *NTRK1* genes seem to play a role in the development and metastatic occurrence of ACCs and may be used in the future as a potential therapeutic target.

Despite the recent significant advances of skull base surgery and the combination of postoperative RT, a remarkable number of patients will develop local tumor recurrence.³⁰ But even if local control is achieved, approximately 39% of cases will develop distant metastasis most commonly in the liver, bones, or lungs.³¹ Particle beams, such as proton beams have a larger radiation energy delivery than photon beams. By modulating the Bragg peak of protons in energy and time, a conformal radiation dose can be delivered to the tumor while sparing the surrounding healthy tissues.^{31,32} The effectiveness of proton beam therapy in patients with ACC of the skull base has been previously documented. Terasaki et al reported a local control rate of 93% at 5 years while freedom from distant metastasis at 5 years was proved to be 62%.³¹ Gentile et al presented a five-year overall survival of 59% when treating patients with unresectable ACC of the nasopharynx involving the skull base with definitive proton beam therapy.²⁷ However, one should keep in mind even proton beam therapy may cause a variety of acute or late toxicities such as dermatitis, mucositis, xerostomia, eye damage, tinnitus, serous otitis media, endocrine deficits, and most important radiation necrosis.^{27,31}

Choosing the optimum treatment for these patients can be very challenging as occasionally the extension of the tumor makes it impossible to achieve a radical excision. To obtain negative margins, we have to resort to procedures like orbital exenteration. But if a nerve skip metastasis already exists, we may dramatically impair the quality of life of the patient without changing their overall survival. Due to the lack of other effective treatment modalities, the best option sometimes for the patient is the achievement a near-total removal of the tumor and adjuvant RT. A significant complication of this treatment is radiation necrosis due to the close proximity of the target tissue to brain, cranial nerves, and arteries.

Lastly, the prognosis of ACC is poor, even after combined treatment with radical surgery and RT in most reported studies. Specifically, Gamel and Font reported a survival of 47% at 5 years and 20% at 10 years after surgery.³³ This could

be attributed to the delayed diagnosis and characteristic perineural invasive character of the ACC. The need for early diagnosis and radical tumor resection, if possible, coupled with postoperative radiation should be emphasized so that local disease control and better long-term survival will be achieved.²³

Conclusion

ACC is a slow-growing tumor characterized by locally aggressive invasion and high tendency of recurrence. Delayed diagnosis often occurs in ACCs with intracranial invasion, as patients are treated by a neurologist at first, their nasal endoscopy is normal, and their imaging scans (CT and MRI) lack specific findings or mimic low-grade tumors. Management consists of radical tumor resection followed by postoperative radiation, with proton beam therapy showing important results. We presented three unique cases of ACC with intracranial extension of pure intracranial ACC. One case of ACC of the pterygopalatine region, one orbital ACC with extension to the pterygopalatine fossa and cavernous sinus involvement, and one involving the cavernous sinus and Meckel's cave.

To avoid misdiagnoses of intracranial ACC, an international web-based database for these lesions would help recognize these tumors earlier.

Conflict of Interest

None declared.

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