Definitive ^{125}I Brachytherapy of Locally Advanced Adenoid Cystic Carcinoma Involving the Skull Base With Satisfying Efficacy and Safety

Ning Xu, DDS, * *Lei Zheng, DDS, MD,* † *Wen-Jie Wu, DDS, MD,* ‡
Ming-Wei Huang, DDS, MD, § *Jie Zhang, DDS, MD,* ‖ *and Jian-Guo Zhang, DDS, BSMeD* ¶

Purpose: Adenoid cystic carcinoma (ACC) involving the skull base is difficult to treat and sometimes unresectable. The purpose of this study was to evaluate the efficacy and safety of ^{125}I radioactive seed interstitial brachytherapy for treatment of these patients.

Materials and Methods: Patients with ACC involving the skull base treated by definitive ^{125}I brachytherapy from March 2008 through December 2018 at the Peking University Hospital of Stomatology (Beijing, China) were retrospectively identified. Overall survival (OS), as the primary efficacy indicator, and progression-free survival (PFS) and distant metastasis-free survival (DFS), as the secondary efficacy indicators, were analyzed by Kaplan-Meier survival analysis and Cox regression analysis. Adverse radiotherapy (RT) reactions, as safety indicators, were recorded.

Results: Thirty-two patients with (r)T4b locally advanced disease were enrolled. The prescription dose (PD) was 60 to 120 Gy. The dose delivered to 90% of the target volume was 99.1 to 145.2 Gy, the percentage of the target volume receiving at least 100% of the PD was at least 88.2%, and the percentage of the target volume receiving at least 150% of the PD was smaller than 74.0%. Mean follow-up was 32 months (median, 21 months; range, 3 to 95 months). The 1- and 3-year OS rates were 93.3 and 62.6%, the 1- and 3-year PFS rates were 90.0 and 46.4%, and the 1- and 3-year DFS rates were 91.7 and 61.1%, respectively. Survival was significantly associated with local recurrence ($P = .04$) and distant metastasis except in the lung ($P = .05$). The rate of severe chronic adverse RT reactions was 3.1%; no severe acute adverse RT reactions were observed.

Conclusion: ^{125}I brachytherapy appears to be an effective and safe treatment in the short-term for ACC involving the skull base and could be the preferred treatment for patients with prior RT. Local control with brachytherapy could provide survival benefit even in patients with lung metastasis.

J Oral Maxillofac Surg 77:2143-2153, 2019

Adenoid cystic carcinoma (ACC) is a rare highly malignant tumor that is characterized by slow and invasive growth, skip lesions, neurologic invasion, and distant metastasis.[1-5] Because of the biological characteristics of the tumor and the complex anatomy of the skull base, many atypical presentations are possible, which

Received from Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, Beijing, China.

*Resident.

†Associate Professor.

‡Resident.

§Associate Professor.

‖Professor and Department Head.

¶Professor.

Conflict of Interest Disclosures: None of the authors have any relevant financial relationship(s) with a commercial interest.

Address correspondence and reprint requests to Dr Zhang: Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, No 22 Zhongguancun South Avenue, Haidian District, Beijing 100081, People's Republic of China; e-mail: rszhang@126.com

Received January 17 2019

Accepted March 24 2019

0278-2391/19/30357-X

https://doi.org/10.1016/j.joms.2019.03.031

can lead to delayed diagnosis. Thus, the disease is often detected only at a locally advanced stage, when treatment can be challenging.[6-10]

The anatomy of the skull base and the presence of many important structures in the region make surgery very difficult and risky, especially for patients with locally advanced recurrent tumor.[11] When reoperation is contraindicated because of locally advanced tumor, radiotherapy (RT) can provide relief. Intensity-modulated RT, fractionated stereotactic RT, neutron RT, proton RT, and heavy ion RT are the available options.[9,12-17] In addition, because of the complex shape of the skull, the attenuation of x-rays by the dense bone, and the depth at which the target area is located, the prescription dose (PD) is often difficult to achieve. Moreover, use of an excessive dose to achieve the planned PD could result in severe adverse RT reactions. With ^{125}I radioactive seed interstitial implantation brachytherapy, by careful selection of the location of the radioactive seeds, it is possible to precisely irradiate the target area and minimize the dose to adjacent normal tissue. This is a definite advantage in the treatment of tumor involving the skull base. Although several groups have reported favorable results with the use of ^{125}I brachytherapy for the treatment of ACC in the head and neck region,[8,18,19] there has not been any systematic analysis.

The purpose of this study was to evaluate the effectiveness and safety of ^{125}I interstitial implantation brachytherapy for ACC involving the skull base. The authors hypothesized that, because of its high conformability and ability to spare adjacent normal tissues, ^{125}I brachytherapy would provide favorable survival outcomes and low incidence of adverse RT reactions in patients with ACC involving the skull base.

Materials and Methods

STUDY POPULATION

Patients with ACC involving the skull base treated with definitive ^{125}I brachytherapy from March 2008

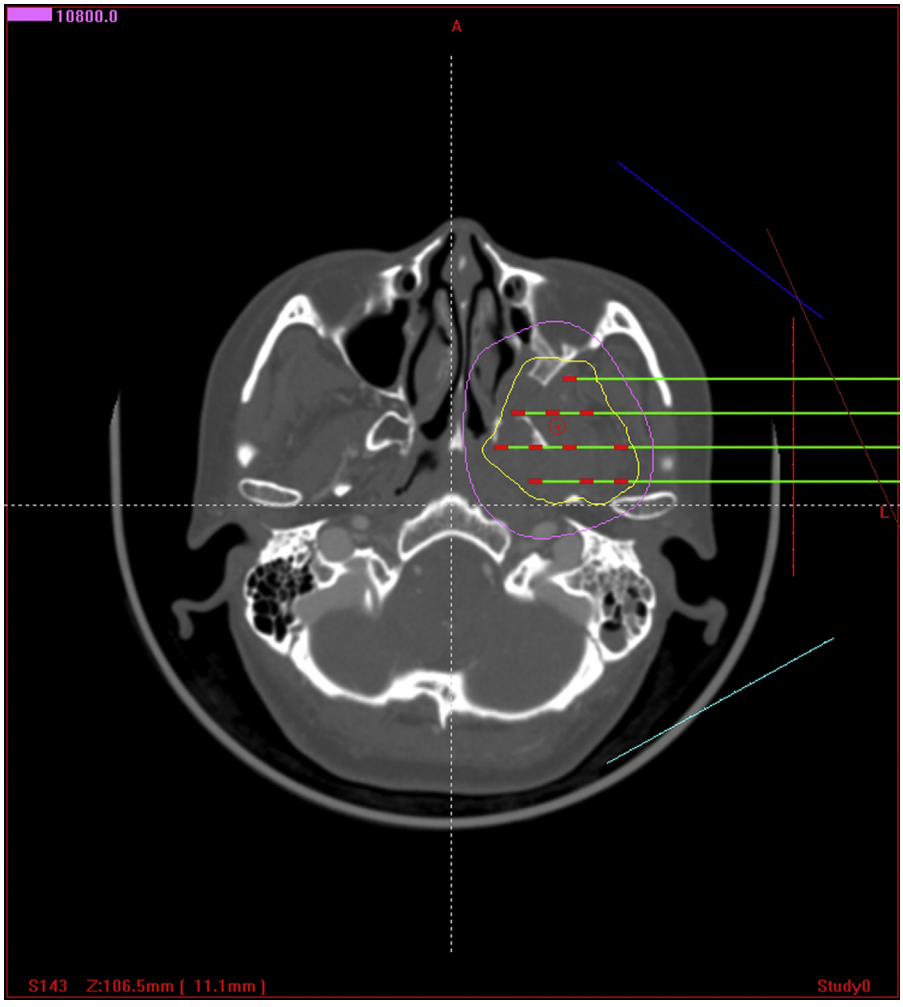

FIGURE 1. Delineation of planning target volume and arrangement of ^{125}I radioactive seeds.

Xu et al. ^{125}I Brachytherapy of Adenoid Cystic Carcinoma. J Oral Maxillofac Surg 2019.

FIGURE 2. Three-dimensional individual template positioned after general anesthesia.

Xu et al. [125]I Brachytherapy of Adenoid Cystic Carcinoma. J Oral Maxillofac Surg 2019.

through December 2018 were retrospectively identified. Patients were eligible for inclusion if they had *1)* locally advanced ACC involving the skull base; *2)* histologic diagnosis confirmed by incisional or needle aspiration biopsy examination, and *3)* a Karnofsky Performance Score of at least 70. Those with any severe systemic disease or malignant tumor of other organs were excluded.

This study was conducted in accordance with international ethical standards and was approved by the institutional review board of the Peking University School of Stomatology (Beijing, China). Informed consents were obtained from all patients before treatment.

^{125}I BRACHYTHERAPY PROCEDURE

Patients' computed tomography (CT), magnetic resonance imaging, or positron emission tomography (PET) with CT (PET-CT) images in Digital Imaging

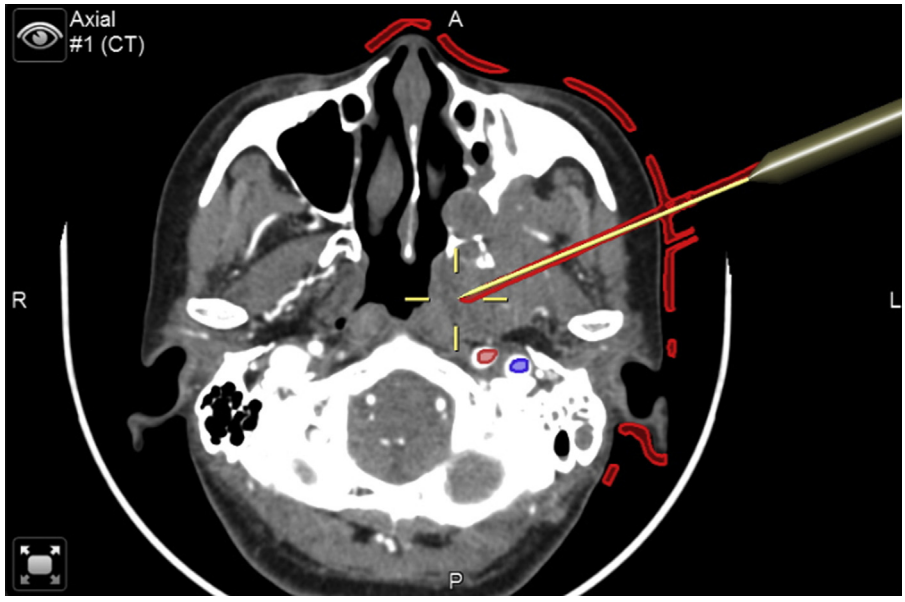

FIGURE 3. Needle tip location verified by navigation system using computed tomography.

Xu et al. [125]I Brachytherapy of Adenoid Cystic Carcinoma. J Oral Maxillofac Surg 2019.

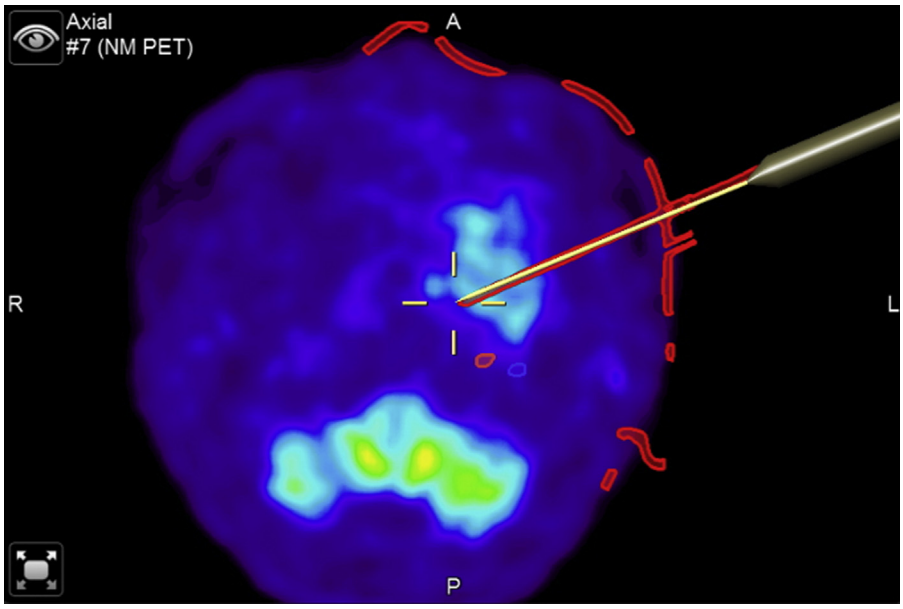

FIGURE 4. Needle tip location verified by navigation system using positron emission tomography with computed tomography.

Xu et al. ^{125}I Brachytherapy of Adenoid Cystic Carcinoma. J Oral Maxillofac Surg 2019.

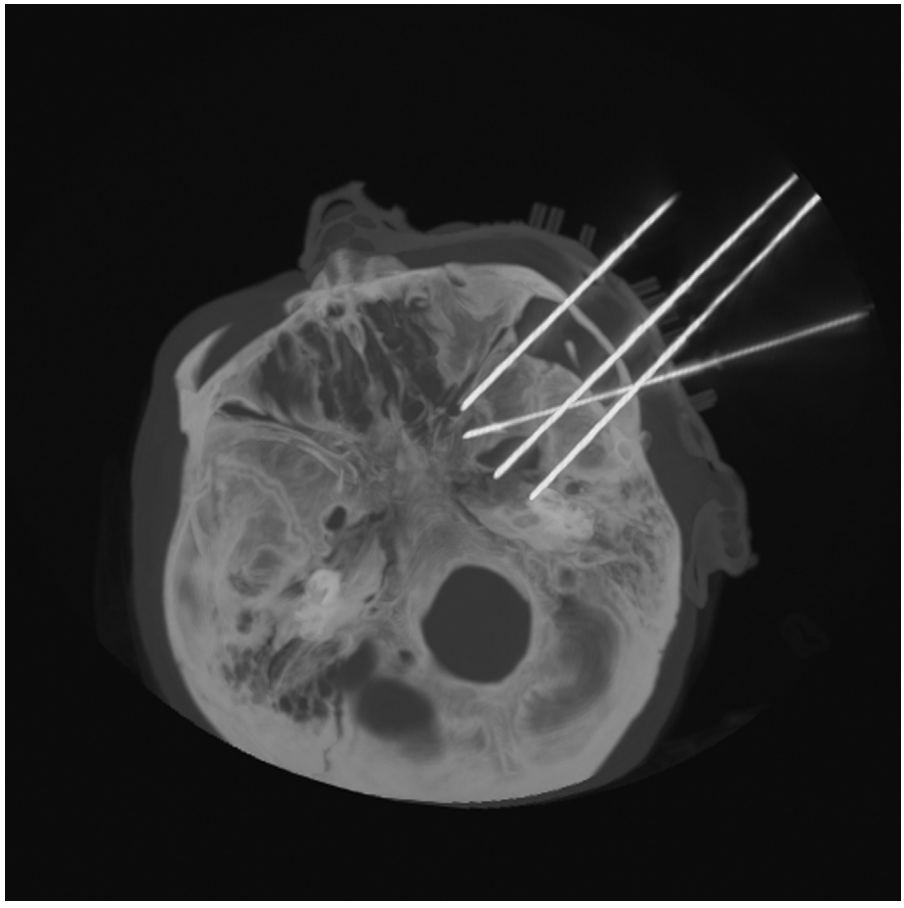

FIGURE 5. Computed tomogram after needle puncture.

Xu et al. ^{125}I Brachytherapy of Adenoid Cystic Carcinoma. J Oral Maxillofac Surg 2019.

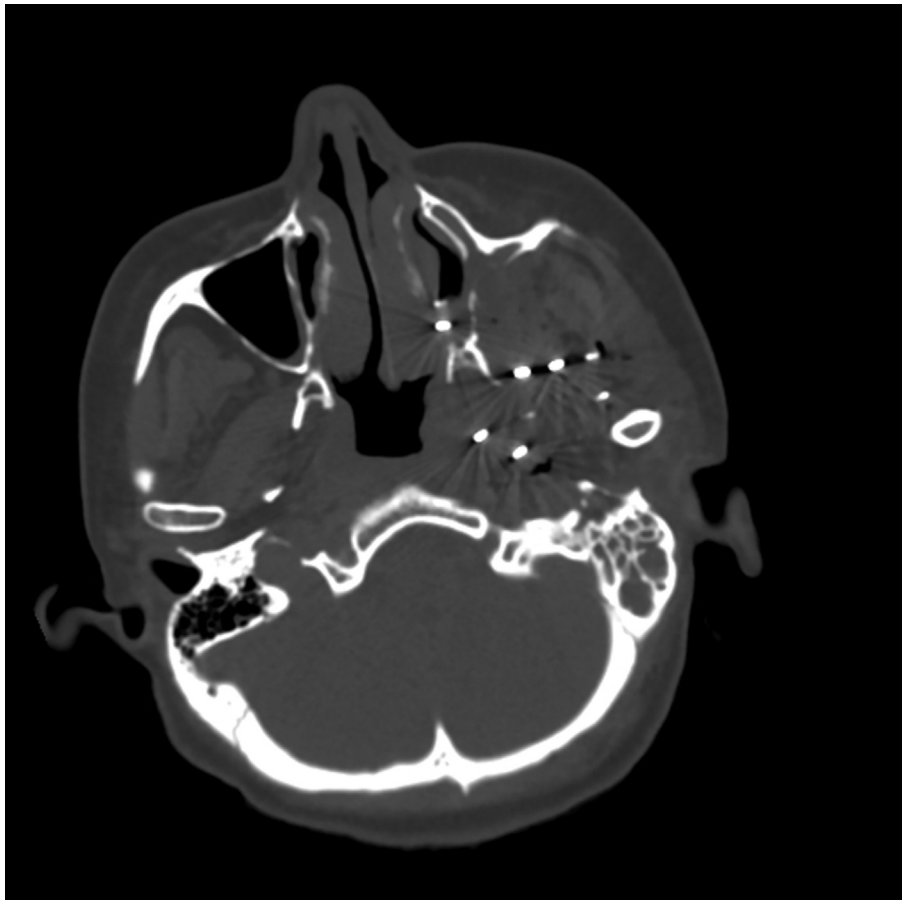

FIGURE 6. Computed tomogram immediately after implantation.

Xu et al. ^{125}I Brachytherapy of Adenoid Cystic Carcinoma. J Oral Maxillofac Surg 2019.

and Communications in Medicine (DICOM) format were imported into the treatment plan system (Beijing Astro Technology Co, Ltd, Beijing, China) for the brachytherapy treatment plan design. The PD ranged from 60 Gy to 120 Gy; the PD was 60 to 80 Gy for patients with prior RT and 100 to 120 Gy for other patients. The planning target volume (PTV) was outlined to cover a 0.5- to 1-cm margin around the tumor (Fig 1). Radioactivity of the ^{125}I radioactive seed was 2.2 to 2.7 $\times$ 10^8 Bq per seed with a half-life of 59.4 days (4.5 mm long and 0.8 mm in diameter; model 6711; China Institute of Atomic Energy, Beijing, China). Radioactive seed implantation was performed under general anesthesia. Implantation guide techniques, including 3-dimensional printed individual templates, a navigation system, and intraoperative CT, were used to ensure the accuracy of radioactive seed implantation (Figs 2-6). After percutaneous puncture, the needle was advanced into the PTV area under guidance. Radioactive seeds were implanted only after confirming correct positioning of the needle tip.[20] Accuracy of seed implantation was verified with CT 1 to 2 days after implantation.

DATA COLLECTION

All patients were required to attend follow-up every 2 months for the first 6 months and every 4 to 6 months thereafter. Those with follow-up shorter than 6 months were recorded as lost to follow-up. At each visit, patients underwent physical examination for evaluation of local tumor condition and presence of distant metastasis. CT was performed every 6 months and chest radiography was performed every 12 months; PET-CT and bone scanning were performed when indicated (Fig 7). Acute and chronic adverse RT reactions were recorded.

STATISTICAL ANALYSIS

Overall survival (OS) was used as the primary efficacy indicator, and progression-free survival (PFS) and distant metastasis-free survival (DFS) were the secondary efficacy indicators. The Kaplan-Meier (KM) method was used for survival analysis, and Cox regression analysis was used for correlation analysis. Associations between OS and local control and distant metastasis were analyzed.

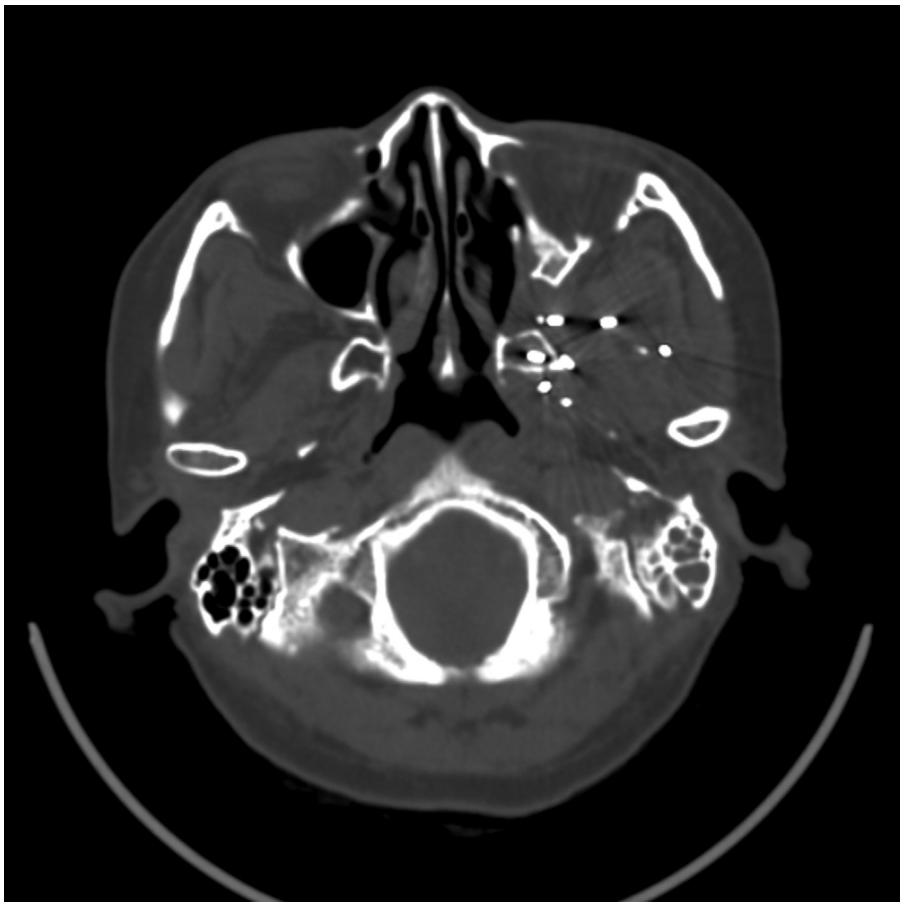

FIGURE 7. Computed tomogram 16 months after treatment shows complete tumor response and no evidence of recurrence.

Xu et al. ^{125}I Brachytherapy of Adenoid Cystic Carcinoma. J Oral Maxillofac Surg 2019.

Acute and chronic adverse RT reactions were scored by the Common Terminology Criteria for Adverse Events 4.0 (US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Bethesda, MD). SPSS 20.0 (IBM Corp, Armonk, NY) was used for statistical analysis. A *P* value less than or equal to .05 was considered statistically significant. Variables with *P* values less than or equal to .10 were entered into the multivariate analysis using the Cox proportional hazards model.

Results

PATIENTS' CHARACTERISTICS

This retrospective study enrolled 32 patients (9 men, 23 women) with ACC involving the skull base who were treated with ^{125}I brachytherapy in the Peking University Hospital of Stomatology from March 2008 through December 2018 (Table 1). The patients' median age was 50 years (range, 25 to 81 years). Most patients (29 of 32; 90.6%) had recurrent tumor. All were evaluated as having (r)T4b (ie, very advanced local disease). Of the 32 patients, 15 (46.9%) had lung metastasis before treatment was started, 2 patients also had bone metastasis, and 1 patient had bone and liver metastasis.

The most common symptom was local pain (12 of 32; 37.5%). Two patients (6.3%) had facial paralysis at presentation. The most common primary tumor sites were the palatine small salivary glands (15 of 32; 46.9%) and the maxillary sinuses (10 of 32; 31.2%).

TUMOR CHARACTERISTICS

Table 2 lists the tumor characteristics of the 32 patients. All patients had a pathologically and radiographically confirmed diagnosis of (r)T4b locally advanced ACC with skull base involvement by the eighth edition of the American Joint Committee on Cancer staging manual. This stage is classified as unresectable in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology.

Imaging findings showed that the pterygoid process and pterygopalatine fossa were the most frequently involved structures in the skull base (65.6 and 46.9%, respectively), followed by the ethmoid sinus (25%).

Table 1. PATIENT CHARACTERISTICS

Patient Characteristics	
Sample size, n	32
Gender ratio (men/women)	39.1% (9/23)
Age (yr), median (range)	50 (25-81)
Presenting symptom, n (%)	
Pain	12 (37.5)
Swelling	8 (25.0)
Paresthesia	5 (15.6)
Limitation of mouth opening	3 (9.4)
Facial paralysis	2 (6.3)
No symptoms	2 (6.3)
Tumor origin, n (%)	
Palatine gland	15 (46.9)
Maxillary sinus	10 (31.3)
Parotid gland	4 (12.5)
Buccal small salivary gland	1 (3.1)
Sublingual gland	1 (3.1)
Submandibular gland	1 (3.1)
RT history, n (%)	11 (34.4)
Distant metastasis, n (%)	
No	17 (53.1)
Lung	12 (37.5)
Lung and other organs	3 (9.4)
Local recurrence, n (%)	9 (28.1)

Abbreviation: RT, radiotherapy.

Xu et al. ^{125}I Brachytherapy of Adenoid Cystic Carcinoma. J Oral Maxillofac Surg 2019.

In 2 patients, the tumor involved the extraocular muscles and the soft tissue around the optic nerve. In addition, 2 patients had intracranial tumor invasion before treatment.

HISTORY OF TREATMENT

Twenty-nine patients (90.6%) had undergone surgery (complete or partial resection of tumor) in the past 1.5 to 22 years. Of these 29 patients, 11 also received postoperative RT during the past 10 months to 16 years (neutron RT, 1 patient; external RT, 10 =patients), with 6 patients undergoing RT within the preceding 3 years. The mean radiation dose of external RT was 57.6 Gy (range, 54 to 60 Gy), and the radiation dose of the patient who received neutron RT was 16.6 nGy (equivalent to 55 to 65 Gy of external RT).

Table 2. TUMOR CHARACTERISTICS

Tumor Characteristics	n (%)
Tumor stage (r)T4b	32 (100)
Structure involved	
Pterygoid process	21 (65.6)
Pterygopalatine fossa	15 (46.9)
Ethmoid sinus	8 (25.0)
Stylomastoid foramen	4 (12.5)
Orbit	2 (6.3)
Intracranial extension	2 (6.3)

Xu et al. ^{125}I Brachytherapy of Adenoid Cystic Carcinoma. J Oral Maxillofac Surg 2019.

^{125}I BRACHYTHERAPY

In this group of patients, the dose delivered to 90% of the target volume was 99.1 to 145.2 Gy, the percentage of the target volume receiving at least 100% of the PD was at least 88.2%, and the percentage of the target volume receiving at least 150% of the PD was smaller than 74.0%. Mean follow-up was 32 months (median, 21 months; range, 3 to 95 months); 13 patients were followed for longer than 24 months, 8 patients were followed for longer 36 months, and 6 patients were followed for longer than 60 months. Two patients (6.3%) had follow-up shorter than 6 months and therefore were classified as lost to follow-up.

SURVIVAL ANALYSIS

Of the 32 patients, 9 had died by the end of the study: 5 of local progression and 4 of distant metastasis. Median time from seed implantation to death was 16 months (range, 3 to 77 months). The 1- and 3-year OS rates were 93.3 and 62.6%, the 1- and 3-year PFS rates were 90.0 and 46.4%, and the 1- and 3-year DFS rates were 91.7 and 61.1%, respectively.

Of the 32 patients, 2 had progressive disease and died of local progression (at 3 and 4 months after treatment). Nine patients had local recurrence; time from treatment to local recurrence was 9 to 61 months. Of these 9 patients, 3 died during the study period (at 4, 7, and 13 months after tumor recurrence). Distant metastases were detected in 3 patients during the follow-up period: 2 patients had lung metastases and 1 patient had vertebral bone metastasis. No patient had cervical lymph node metastasis.

Table 3 lists the results of correlation analysis between survival and various variables. Analysis of the results showed a significant association between local recurrence and survival (P = .04; adjusted hazard ratio = 1.2; Fig 8). There was a significant difference in survival rates between patients with and without distant metastasis except in the lung (3-year survival rate, 76.4 vs 0%; P = .05; adjusted hazard ratio = 10.0; Fig 9). However, there was no relevant difference in survival rates between patients with and without lung metastasis. Age, gender, presenting symptom, and tumor origin were not statistically associated with survival.

Table 3. COX REGRESSION ANALYSIS OF VARIABLES AND SURVIVAL

Variables	n	Univariate *P* Value	Unadjusted HR (95% CI)	Multivariate *P* Value	Adjusted HR (95% CI)
Local recurrence		.05	1.8 (1.3-8.4)	.04	1.2 (1.2-7.5)
Yes	9				
No	21				
Distant metastasis except for lung		.02	16.8 (1.7-163.0)	.05	10.0 (1.0-96.1)
Yes	4				
No	26				
Pterygoid process involvement		.03	10.9 (1.3-91.1)	.12	6.76 (0.6-73.4)
Yes	21				
No	9				
Lung metastasis		.56	1.7 (0.3-9.2)	—	—
Yes	12				
No	15				
Age (yr), mean ± SD	53 ± 28	.37	1.0 (0.9-1.0)	—	—
Presenting symptom		.97	1.0 (0.2-4.9)	—	—
Pain or swelling	20				
Others	10				
Tumor origin		.33	0.5 (0.1-2.1)	—	—
Palatine or maxillary sinus	23				
Others	7				
Gender		.52	1.6 (0.4-6.7)	—	—
Male	8				
Female	22				
RT history		.84	1.2 (0.2-5.9)	—	—
Yes	11				
No	19				
Pterygopalatine fossa involvement		.42	1.8 (0.4-7.6)	—	—
Yes	15				
No	15				

Abbreviations: CI, confidence interval; HR, hazard ratio; RT, radiotherapy; SD, standard deviation.

Xu et al. ^{125}I Brachytherapy of Adenoid Cystic Carcinoma. J Oral Maxillofac Surg 2019.

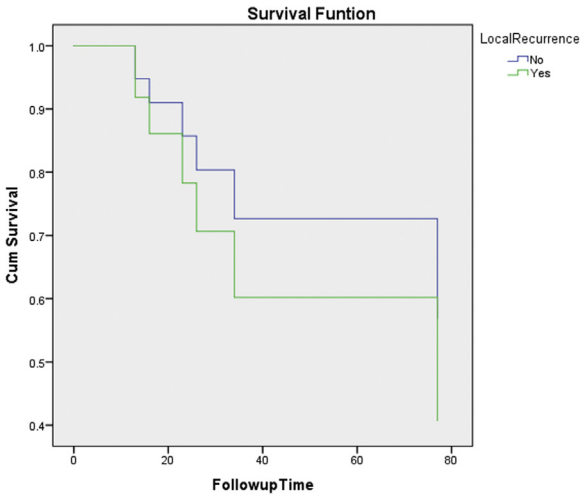

FIGURE 8. Survival curves for local recurrence.

Xu et al. ^{125}I Brachytherapy of Adenoid Cystic Carcinoma. J Oral Maxillofac Surg 2019.

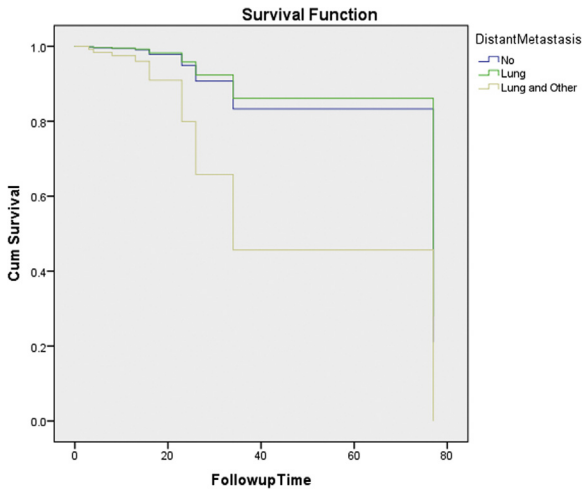

FIGURE 9. Survival curves for distant metastasis.

Xu et al. ^{125}I Brachytherapy of Adenoid Cystic Carcinoma. J Oral Maxillofac Surg 2019.

No statistical association was seen between survival and history of RT. A significant association was seen in univariate analysis between survival and pterygoid process involvement ($P = .03$), but not in multivariate analysis ($P = .12$). There was no statistical association between survival and pterygopalatine fossa involvement. Pterygoid process involvement and pterygopalatine fossa involvement were not significantly associated with local recurrence ($P = .51$ and .95, respectively).

ADVERSE RT REACTIONS

During follow-up, 4 of 32 patients (12.5%) developed local pain or oral mucosal erosions (classified as grade 2 to 3 acute adverse RT reaction), which subsided with symptomatic treatment.

Chronic adverse RT reactions were seen in 8 of 32 patients (25.0%). One patient had diminution of vision in the right eye and a painful palatal fistula (grade 5 chronic adverse RT reaction). The tumor had invaded the orbital floor and the soft tissue around the optic nerve. The PTV of this patient covered the optic nerve, with a PD of 120 Gy and radioactive seed activity of 2.59×10^8 Bq per seed. Grade 2 to 3 chronic adverse RT reactions were seen in another 7 patients: 2 patients had skin hyperpigmentation, 4 patients had local pain, and 1 patient had facial numbness and limited mouth opening. No serious RT reactions, such as osteoradionecrosis or a second primary cancer, occurred during follow-up.

Of the 11 patients who had received prior RT treatment, 1 patient had a grade 3 acute adverse RT reaction (local pain) and 3 patients developed grade 2 to 3 chronic adverse RT reactions (local pain and skin hyperpigmentation). Cox regression analysis showed no significant correlation between previous RT and adverse RT reaction ($P = .97$).

Discussion

Because of biological characteristics such as slow and invasive growth and a tendency for perineural invasion, ACC often presents with pain. Lung metastasis also is common.[1,3,21] ACC originating in the palatine glands or maxillary sinus might not be accompanied by any symptoms until nerve invasion and bone destruction occur. At this time, the tumor is staged as T3 or even T4, and treatment is difficult. Cranial nerves, such as facial nerves and trigeminal nerves, extend downward from the skull base; ACC originating near these nerves can grow along these nerves to reach the skull base.[6,22] According to the NCCN Clinical Practice Guidelines in Oncology, these tumors are considered unresectable. Therefore, alternative treatments need to be applied. In recent years, various RT modalities, including neutron RT and proton RT, have been used for the treatment of ACC.

This study showed that ^{125}I brachytherapy could provide favorable outcomes in ACC involving the skull base and cause relatively few adverse RT reactions. Because of the slow growth pattern of ACC, patients with lung metastasis can survive for a relatively long time.[1,2,4,23-25] One patient in the present sample had survived for 89 months with lung metastasis and was still alive at the end of the study. However, 4 patients with local progression died within 3 to 9 months. KM survival analysis showed that the survival rate of patients with distant metastasis except for the lung was considerably worse than for other patients. Local progression also was associated with considerably worse survival. However, there was no

Table 4. SUMMARY OF PREVIOUS STUDIES ON ADENOID CYSTIC CARCINOMA INVOLVING THE SKULL BASE

Study	Year	Patients, n	RT Type	Tumor Stage	Median Dose (Gy)	Median Follow-Up Time (mo)	3-yr Survival Rate, %	4-yr Survival Rate, %	5-yr Survival Rate, %
Mendenhall et al[14]	2004	29	Photon RT	T4	72.4	79	—	—	50
Schulz-Ertner et al[9]	2005	29/34	Photon RT/carbon ion boost	T4b	72/66	16/24	—	75.8/77.9	—
Pommier et al[15]	2006	23	Proton RT	T4b	75.9 CGE	64	—	—	77
Morimoto et al[16]	2014	22	Proton	T4b	65	—	80	—	—
Jensen et al[17]	2015	58	IMRT with ^{12}C boost	T4 90%	66	74	89.6	—	76.5
Gentile et al[7]	2017	14	Proton RT	T4 93%	73.8	69	—	—	59

Abbreviations: —, study did not provide relevant data; CGE, cobalt gray equivalent; IMRT, intensity-modulated radiotherapy; RT, radiotherapy.

relevant difference in survival between patients with and without lung metastasis during the study period. These findings suggest that local control is crucial in the treatment of ACC involving the skull base. Even in the presence of lung metastasis, local treatment can improve short-term survival outcomes. However, in patients with bone and liver metastasis, the need for local treatment must be carefully evaluated in each case.

For those patients with previous RT, re-irradiation could cause severe adverse RT reactions, and this is especially true in the skull base area.[26,27] However, in the present study, adverse RT reactions were few and mild in the 11 patients who had previous RT, indicating the relative safety of ^{125}I brachytherapy.

No serious acute adverse RT reactions were observed in the present study. A grade 5 chronic adverse RT reaction was observed in 1 of 32 patients. Grade 2 to 3 adverse RT reactions are relatively mild and are related to the low-dose radioactivity of the radioactive seeds and the depth of the PTV.

From 2004 through 2018, 6 studies were published on the use of different RT modalities for treatment of ACC involving the skull base (Table 4). The sample size ranged from 14 to 58, and median follow-up was 16 to 79 months. The 5-year OS in these studies ranged from 50 to 77%. None of these studies included patients with prior RT. The highest 5-year survival rate was reported by Pommier et al[15] in a study published in 2006. They used proton RT to treat 23 patients with ACC extending to skull base and reported a 5-year OS of 77% and a 5-year DFS of 56%. All but 3 of their patients had gross tumor before the initiation of radiation, 1 patient had suspicious lung metastasis at presentation, and no patient had received previous radiation to the primary site.

The outcomes in the present study are not as good as those in the studies cited earlier. There could be several reasons for this difference. First, all patients in the present sample had T4b locally advanced disease, with 2 patients also having intracranial extension before treatment. Second, nearly half the patients had distant metastasis before treatment, including 2 patients with bone metastasis and 1 with liver metastasis; this would have had an impact on prognosis. Third, 11 patients had a history of RT, and the PD had to be restricted to avoid adverse RT reactions.

Because of the relatively short follow-up in this study, the long-term outcome could not be assessed precisely. The true incidence of chronic adverse RT reactions after ^{125}I brachytherapy can be established only after longer follow-up.

^{125}I radioactive seed interstitial implantation brachytherapy appears to be an effective treatment for ACC involving the skull base, with a relatively low incidence of adverse RT reactions in the short-term. Local control with ^{125}I brachytherapy can improve survival even in patients with lung metastasis, although this effect was not seen in patients with bone and liver metastasis before treatment. ^{125}I brachytherapy could be the preferred treatment for patients with previous RT. Larger studies with long-term follow-up are necessary to establish the optimal technique for ^{125}I brachytherapy in the skull base area.

References

1. Spiro RH: Distant metastasis in adenoid cystic carcinoma of salivary origin. Am J Surg 174:495, 1997
2. Jang S, Patel PN, Kimple RJ, McCulloch TM: Clinical outcomes and prognostic factors of adenoid cystic carcinoma of the head and neck. Anticancer Res 37:3045, 2017
3. Chen AM, Bucci MK, Weinberg V, et al: Adenoid cystic carcinoma of the head and neck treated by surgery with or without postoperative radiation therapy: Prognostic features of recurrence. Int J Radiat Oncol Biol Phys 66:152, 2006
4. Al-Mamgani A, van Rooij P, Sewnaik A, et al: Adenoid cystic carcinoma of parotid gland treated with surgery and radiotherapy: Long-term outcomes, QoL assessment and review of the literature. Oral Oncol 48:278, 2012
5. Lloyd S, Yu JB, Wilson LD, Decker RH: Determinants and patterns of survival in adenoid cystic carcinoma of the head and neck, including an analysis of adjuvant radiation therapy. Am J Clin Oncol 34:76, 2011
6. Barrera-Flores FJ, Villarreal-Del Bosque N, Diaz Gonzalez-Colmenero A, et al: Perineural spread-susceptible structures: A non-pathological evaluation of the skull base. Eur Arch Otorhinolaryngol 274:2899, 2017
7. Gentile MS, Yip D, Liebsch NJ, et al: Definitive proton beam therapy for adenoid cystic carcinoma of the nasopharynx involving the base of skull. Oral Oncol 65:38, 2017
8. Huang MW, Zheng L, Liu SM, et al: 125I brachytherapy alone for recurrent or locally advanced adenoid cystic carcinoma of the oral and maxillofacial region. Strahlenther Onkol 189: 502, 2013
9. Schulz-Ertner D, Nikoghosyan A, Didinger B, et al: Therapy strategies for locally advanced adenoid cystic carcinomas using modern radiation therapy techniques. Cancer 104:338, 2005
10. da Cruz Perez DE, Pires FR, Lopes MA, et al: Adenoid cystic carcinoma and mucoepidermoid carcinoma of the maxillary sinus: Report of a 44-year experience of 25 cases from a single institution. J Oral Maxillofac Surg 64:1592, 2006
11. Ramakrishna R, Raza SM, Kupferman M, et al: Adenoid cystic carcinoma of the skull base: Results with an aggressive multidisciplinary approach. J Neurosurg 124:115, 2016
12. Iseli TA, Karnell LH, Graham SM, et al: Role of radiotherapy in adenoid cystic carcinoma of the head and neck. J Laryngol Otol 123:1137, 2009
13. Douglas JG, Laramore GE, Austin-Seymour M, et al: Treatment of locally advanced adenoid cystic carcinoma of the head and neck with neutron radiotherapy. Int J Radiat Oncol Biol Phys 46:551, 2000
14. Mendenhall WM, Morris CG, Amdur RJ, et al: Radiotherapy alone or combined with surgery for adenoid cystic carcinoma of the head and neck. Head Neck 26:154, 2004
15. Pommier P, Liebsch NJ, Deschler DG, et al: Proton beam radiation therapy for skull base adenoid cystic carcinoma. Arch Otolaryngol Head Neck Surg 132:1242, 2006
16. Morimoto K, Demizu Y, Hashimoto N, et al: Particle radiotherapy using protons or carbon ions for unresectable locally advanced head and neck cancers with skull base invasion. Jpn J Clin Oncol 44:428, 2014
17. Jensen AD, Nikoghosyan AV, Poulakis M, et al: Combined intensity-modulated radiotherapy plus raster-scanned carbon ion boost for advanced adenoid cystic carcinoma of the head and neck results in superior locoregional control and overall survival. Cancer 121:3001, 2015

18. Zhang J, Zheng L, Liu SM, et al: Brachytherapy for recurrent malignant tumours of the parotid gland. Br J Oral Maxillofac Surg 53:58, 2015
19. Huang MW, Wu WJ, Lv XM, et al: The role of (125)I interstitial brachytherapy for inoperable parotid gland carcinoma. Brachytherapy 17:244, 2018
20. Huang MW, Liu SM, Zheng L, et al: A digital model individual template and CT-guided 125I seed implants for malignant tumors of the head and neck. J Radiat Res 53:973, 2012
21. He S, Li P, Zhong Q, et al: Clinicopathologic and prognostic factors in adenoid cystic carcinoma of head and neck minor salivary glands: A clinical analysis of 130 cases. Am J Otolaryngol 38:157, 2017
22. Ableman TB, Newman SA: Perineural spread of head and neck cancer: Ophthalmic considerations. J Neurol Surg B Skull Base 77:131, 2016
23. Ali S, Palmer FL, Katabi N, et al: Long-term local control rates of patients with adenoid cystic carcinoma of the head and neck managed by surgery and postoperative radiation. Laryngoscope 127:2265, 2017
24. Ellington CL, Goodman M, Kono SA, et al: Adenoid cystic carcinoma of the head and neck: Incidence and survival trends based on 1973-2007 Surveillance, Epidemiology, and End Results data. Cancer 118:4444, 2012
25. Girelli L, Locati L, Galeone C, et al: Lung metastasectomy in adenoid cystic cancer: Is it worth it? Oral Oncol 65:114, 2017
26. Jensen AD, Poulakis M, Nikoghosyan AV, et al: Re-irradiation of adenoid cystic carcinoma: analysis and evaluation of outcome in 52 consecutive patients treated with raster-scanned carbon ion therapy. Radiother Oncol 114:182, 2015
27. McDonald MW, Zolali-Meybodi O, Lehnert SJ, et al: Reirradiation of recurrent and second primary head and neck cancer with proton therapy. Int J Radiat Oncol Biol Phys 96:808, 2016