ELSEVIER

Brachytherapy ■ (2020) ■

BRACHYTHERAPY

Comparison of outcomes using radiotherapy or brachytherapy after resection of primary adenoid cystic carcinoma in oral and maxillofacial regions

C. Li, S.M. Liu, L. Zheng, M.W. Huang, Y. Shi, X.M. Lv, J.G. Zhang, X. Peng, J. Zhang*

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

ABSTRACT We wished to investigate the outcome of surgery combined with external-beam radiotherapy (EBRT) or brachytherapy (^{125}I seeds) for the treatment of primary adenoid cystic carcinoma (ACC) of the oral and maxillofacial region. Data of patients with primary ACC were reviewed retrospectively. Patients were divided into EBRT and brachytherapy groups. Wide tumor excision was done to achieve negative margins. Standard radiotherapy in the EBRT group was 60 Gy. A treatment-planning system was used to create implantation plans with a prescribed dose of 60−120 Gy and ^{125}I seeds were implanted postoperatively. Kaplan−Meier method and log-rank tests were used to analyze local control and survival. The median duration of followup was 66.1 and 46.8 months for the EBRT group and brachytherapy group, respectively. There was no significant difference in local control, control of metastasis to regional lymph nodes, or control of distant metastasis between the two groups. There was no significant difference in overall survival, disease-specific survival, or disease-free survival in the two groups at 3 years and 5 years. The prevalence of complications in the brachytherapy group was lower than that in the EBRT group. Both methods elicited good treatment effects, but the prevalence of adverse events was lower in the brachytherapy group.

Keywords: Adenoid cystic carcinoma; ^{125}I seeds; Brachytherapy; External-beam radiotherapy; Oral and maxillofacial region

Introduction

Adenoid cystic carcinoma (ACC) is a malignant epithelial tumor that occurs most commonly in the salivary glands [1]. ACC accounts for 1% of all malignant tumors of the oral and maxillofacial region, and about 22%−30% of all malignant tumors of the salivary glands[2−4]. ACC is most common in the fifth and sixth decades of life and affects both sexes equally[2]. The minor salivary glands of the palate are the most common sites, followed by the parotid glands[5]. ACC is highly aggressive, with a proclivity for perineural invasion[1,2] and hematogenous metastasis, usually to the lung. Metastasis to the lymph nodes(LNs) is relatively rare.

A combination of radical surgery and postoperative radiotherapy is considered to be optimal therapy for ACC [6−11]. Intraoperatively, the aim is wide excision to achieve negative margins[12,13], but due to tumor location and the need for functional preservation, this is not always possible. Moreover, because of the infiltrative growth pattern and a tendency for perineural spread, the tumor margin is difficult to determine[2]. Thus, postoperative radiotherapy is usually employed to improve local control.

The purpose of this retrospective study was to investigate the outcome of surgery combined with external-beam radiotherapy (EBRT) or brachytherapy (using ^{125}I seeds) for primary ACC of the oral and maxillofacial region.

Received 8 May 2020; received in revised form 23 June 2020; accepted 19 August 2020.

Disclosures: The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

* Corresponding author. Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, Zhongguancun South Street 22, Haidian District, Beijing, China. Tel.: +86 01082195246.

E-mail address: zhangjie06@126.com (J. Zhang).

1538-4721/$ - see front matter
https://doi.org/10.1016/j.brachy.2020.08.013

Methods and materials

Ethical approval of the study protocol

The study protocol was approved by the Ethics Committee of Peking University School and Hospital of Stomatology (Beijing, China).

Patients

A total of 114 patients with primary ACC of the oral and maxillofacial region treated at the Stomatology Hospital of Peking University from 2001 to 2011 formed the study cohort. All patients were diagnosed by histopathology. Distant metastasis was not found in any patient upon the diagnosis. The clinical characteristics of patients are shown in Table 1.

Surgery

Patients underwent surgery after tumor histopathology had been defined. Multiple factors were taken into consideration: tumor site, tumor volume, the extent of disease, feasibility of reconstruction, and discretion of the surgeon. The type of surgical procedure ranged from simple excision to extensive composite resection. The aim of surgery was maximal excision of the tumor, and it was aided by examination of frozen sections (if appropriate).

For the tumors located at the base of the mouth, the base of the tongue, submandibular gland, parotid gland, and classified as T3 or above, selective neck dissection was performed. Patients with clinically positive LNs received therapeutic neck dissection.

Table 1
Characteristics of the 114 ACC patients

Characteristic	Brachytherapy	EBRT
Sex, n (%)		
Male	21 (28)	19 (49)
Female	54 (72)	20 (51)
Median age, years (range)	48.0 (18−74)	45 (26−76)
Median duration of follow up, months (range)	46.8 (0.4−111.0)	66.1 (2.8−134.6)
Tumor site, n (%)		
Parotid glands	24 (32.0)	10 (25.6)
Submandibular glands	13 (17.3)	5 (12.8)
Sublingual glands	7 (9.3)	6 (15.4)
Palate	11 (14.7)	10 (25.6)
Mouth floor	11 (14.7)	0 (0)
Cheek	2 (2.7)	1 (2.6)
Tongue	3 (4.0)	5 (12.8)
Parapharyngeal	1 (1.3)	0 (0)
Other	3 (4.0)	1 (2.6)
T stage, n (%)		
T_1	22 (29.3)	11 (28.2)
T_2	19 (25.3)	9 (23.1)
T_3	2 (2.7)	3 (7.7)
T_4	23 (30.7)	16 (41)
Not reported	9 (12.0)	0 (0)
N stage, n (%)		
N_0	64 (85.3)	36 (92.3)
N_1	3 (4.0)	1 (2.6)
Not reported	8 (10.7)	2 (5.1)
Perineural invasion, n (%)		
Yes	59 (78.7)	29 (74.4)
No	16 (21.3)	10 (25.6)
Surgical margin, n (%)		
Positive	14 (18.7)	2 (5.1)
Negative	61 (81.3)	33 (84.6)
Not reported	0 (0)	4 (10.3)

Implantation of ^{125}I seeds

Implantation plans were created on a treatment-planning system (Beijing Atom and High Technique Industries, Beijing, China) using postoperative computed tomography (CT) images (Fig. 1a−c, e). ^{125}I seeds (model 6711; half-life, 59.4 days; radioactivity, 0.6−0.8 mCi/seed) were implanted under guidance by CT and/or individual digital template (Fig. 2) using hollow needle interstitial needles (18G, 150 mm). Implantation of ^{125}I seeds was undertaken 2 weeks after surgery. The planning target volume included a margin around the tumor of 10−15 mm. The prescribed dose was 100 Gy for patients with a negative margin upon surgery and 120 Gy for patients with a positive margin. CT was carried out 1 week after implantation of ^{125}I seeds to verify the implementation of our plan (Fig. 1D, F). If necessary, supplementary implantation of ^{125}I seeds was undertaken.

EBRT

Patients received EBRT after healing of the surgical wound. Radiotherapy was undertaken in no more than 7 weeks after surgery. EBRT was delivered with 6-MV photons using a linear accelerator. The target volume included the primary tumor bed with 2-cm margins and pathologically involved regional lymph nodes (RLNs). The standard radiotherapy protocol was 60 Gy (2 Gy/daily) after surgery. If a positive margin and positive LN were present, the patient was given 66 Gy as the radiotherapy dose. Three-dimensional conventional radiotherapy or intensity-modulated radiotherapy were carried out.

Follow-up

Patients were followed up 2, 4, and 6 months after implantation of ^{125}I seeds, and then every 6 months. Control of the primary lesion, as well as the status of LNs and lungs, was monitored by physical examination and/or imaging. The Radiation Therapy Oncology Group (RTOG) toxicity scoring system was used to grade the side effects during the follow-up.

Statistical analyses

SPSS v20.0 (IBM, Armonk, NY) was used for statistical analyses. The Kaplan−Meier method was employed for survival analyses. The log-rank test was used to assess local

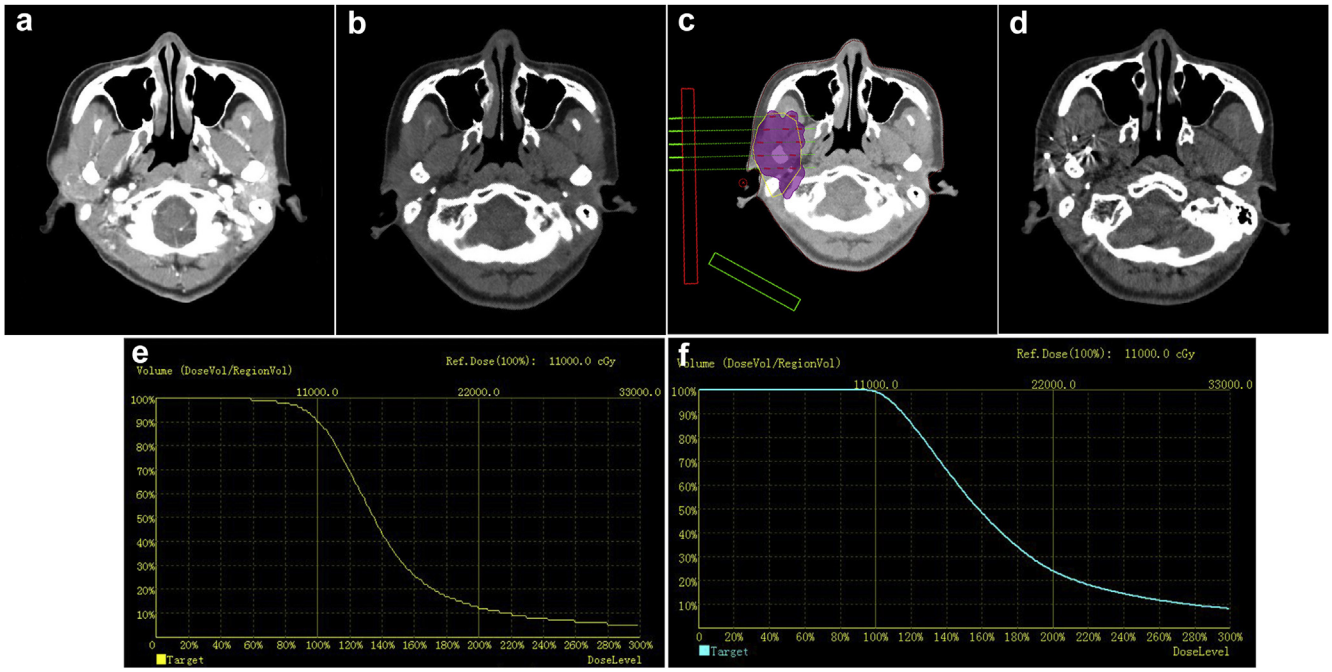

Fig. 1. Treatment plan and verification after implantation of 125I seeds. CT image of the tumor before surgery (a). CT image of tumor area after surgery (b). Planning target volume of brachytherapy (c). CT image for verification after implantation of 125I seeds (d). Dose−volume histogram of the plan for implantation of 125I seeds (e). Dose−volume histogram for verification (f).

control, control in LNs, overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) between the EBRT group and brachytherapy group.

Results

Local control

After 5−134 months of follow-up, 22 patients had local recurrence, and 92 did not. The prevalence of local control at 3 years and 5 years was 90.4% and 81.4%, respectively.

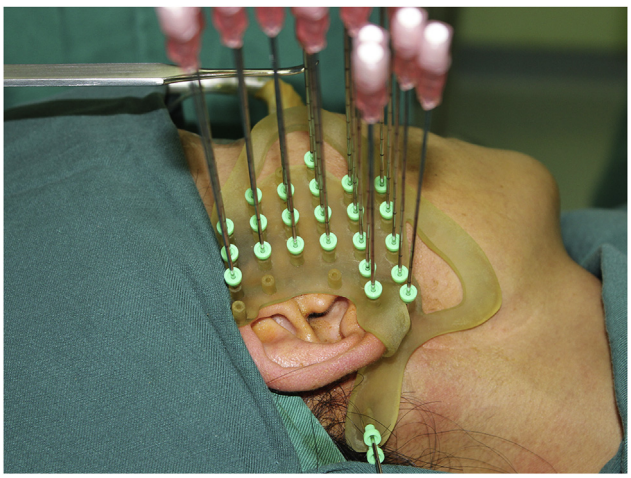

Fig. 2. Implantation of 125I seeds with the guidance of an individual digital template.

In the EBRT group, there were 39 patients, 31 of whom did not suffer recurrence. The prevalence of local control in the EBRT group at 3 years and 5 years was 91.5% and 84.8%, respectively.

Among the 75 patients in the brachytherapy group, 61 did not experience recurrence. The prevalence of local control in the brachytherapy group at 3 years and 5 years was 90.0% and 78.8%, respectively.

The log-rank test showed no significant difference in the prevalence of local control between the EBRT group and brachytherapy group ($p = 0.528$).

Control of RLN metastasis

Metastasis to RLNs was not observed in 105 of 114 patients. The prevalence of control of RLN metastasis at 3 years and 5 years was 94.3% and 91.3%, respectively. Metastasis to RLNs occurred in nine patients (7.9%).

Among the 75 patients in the brachytherapy group, 64 were N0, three were N1, and the N classification of eight patients was not known. Metastasis to RLNs occurred in seven patients during follow-up, and the prevalence of control of RLN metastasis at 3 years and 5yearswas 94.3% and 89.2%, respectively.

Among the 39 patients in the EBRT group, 36 were N0, one was N1, and two were N2. After treatment, metastasis to RLNs occurred in two cases. In one case of a tumor in the tongue, the cervical lymph node was covered by EBRT. The other tumor was located in the palatal region, and the

EBRT area did not cover the neck. The prevalence of control of RLN metastasis at 3 years and 5 years was 94.0%.

The log-rank test showed no significant difference in control of RLN metastasis between the EBRT group and brachytherapy group ($p = 0.193$).

Distant metastasis

At the end of follow-up, 36 patients (31.6%) were found to have distant metastasis, 15 patients (20%) were in the brachytherapy group, and 21(53.8%) in the ERBT group.

Among the 36 patients with distant metastasis, lung metastasis was the most common site in 29 patients (80.6%), followed by metastasis to bone (eight cases, 22.2%), brain (five cases, 13.9%), and liver (five cases, 11.1%). Multiple tumor metastases occurred in five patients, all of whom had lung metastases.

Among the 15 patients with distant metastasis in the brachytherapy group, 11 (73.3%) had lung metastasis only. Among the 21 patients with distant metastasis in the EBRT group, 13 (61.9%) had lung metastasis only.

Survival

Twenty-two patients died. OS at 3 years and 5 years was 85.2% and 77.9%, respectively.

There were 39 cases in the EBRT group, and 19 died; OS at 3 years and 5 years was 84.4% and 74.9%, respectively. There were 75 cases in the brachytherapy group, and 12 died. OS at 3 years and 5 years was 86.0% and 79.6%, respectively. There was no significant difference between the two groups with regard to OS ($p = 0.193$) (Fig. 3).

DSS at 3 years and 5 years in the brachytherapy group was 89.8% and 83.8%, respectively. DSS at 3 years and 5 years in the EBRT group was 91.6% and 88.6%, respectively. The log-rank test showed no significant difference in DSS between the brachytherapy group and EBRT group ($p = 0.685$) (Fig. 4).

In the brachytherapy group, 30 patients suffered a local recurrence, RLN metastasis, or distant metastasis, and DFS at 3 years and 5yearswas 74.9% and 54.3%, respectively. In the EBRT group, 24 patients presented with local recurrence, RLN metastasis, or distant metastasis, and DFS at 3 years and 5yearswas 66.5% and 47.0%, respectively. The log-rank test showed no significant difference in DFS between the brachytherapy group and the EBRT group ($p = 0.407$) (Fig. 5) The survival rates are shown in Table 2.

Adverse effects

According to the RTOG scoring system, no patients developed grade-4 toxicities or died as a result of EBRT. In the EBRT group, mucositis and dermatitis were the main side effects; 15 patients developed toxicity of grade ≥2. Four patients developed multiple late toxicities, including fibrosis, hypothyroidism, trismus, and xerostomia. In the brachytherapy group, three patients had slight dermatitis; grade-III adverse effects were not encountered.

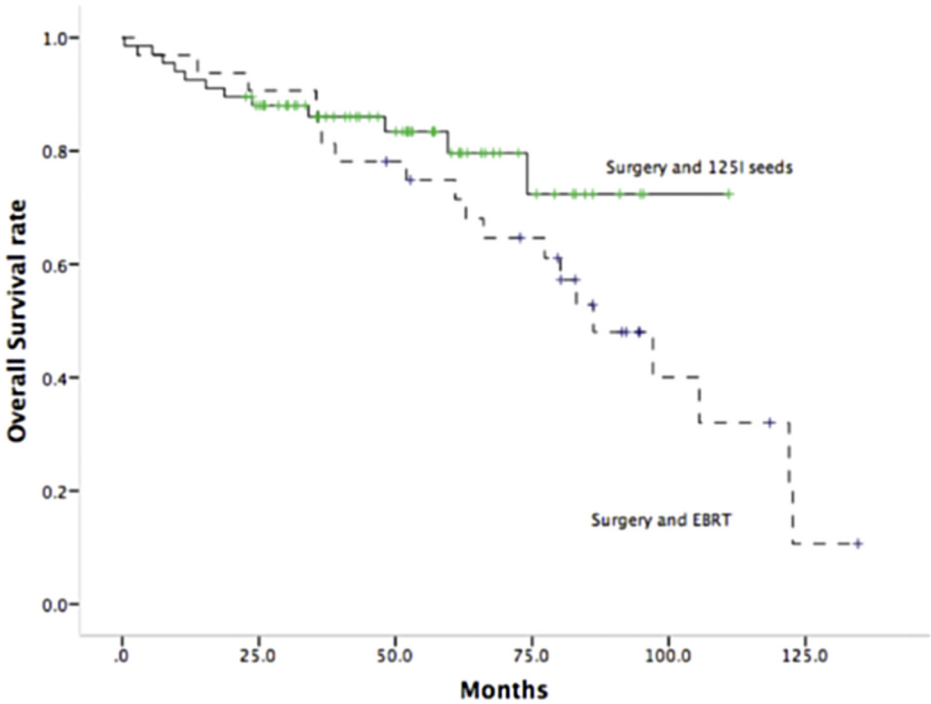

Fig. 3. Overall survival in each group.

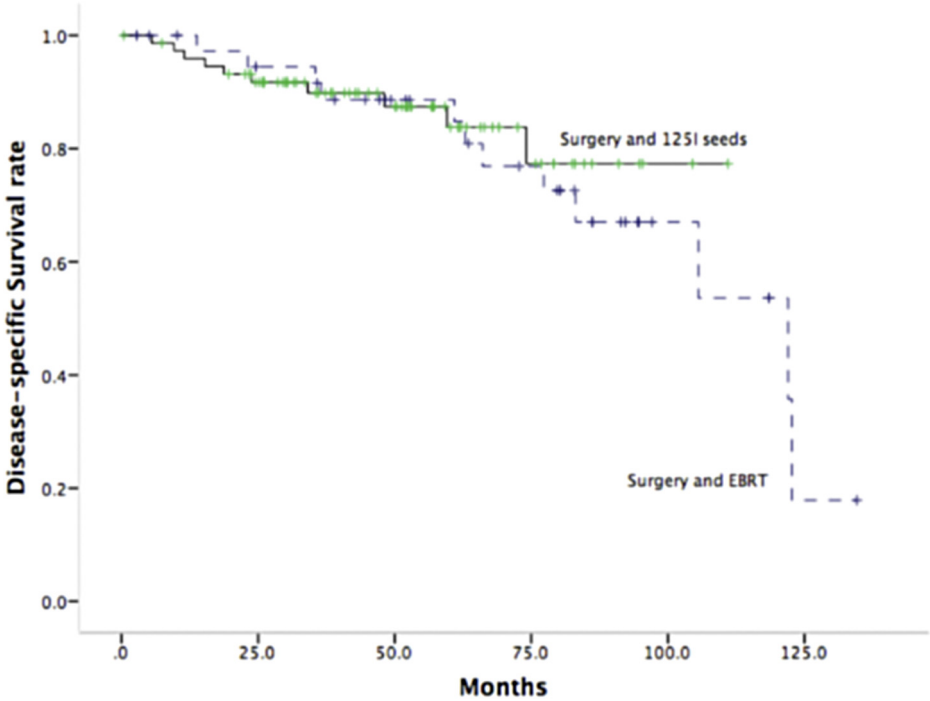

Fig. 4. Disease-specific survival in each group.

Discussion

The primary treatment of ACC is resection and postoperative radiotherapy. Al-Mamgani *et al.* showed that the prevalence of local control at 5 years and 8 years of ACC patients treated with resection and postoperative radiotherapy was 88%[9]. Iseli *et al.* showed that the prevalence of local control at 10 years in 95 patients with salivary ACC treated with resection and radiotherapy was 43.5%[14].

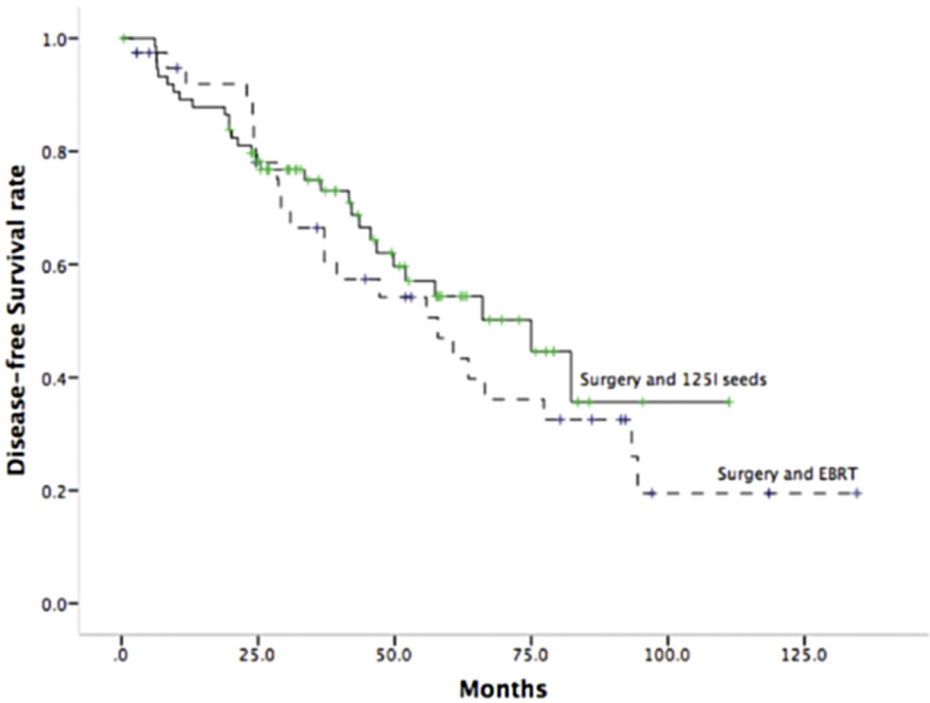

Fig. 5. Disease-free survival in each group.

Table 2
Survival in the two groups

	3 years (%)	5 years (%)	*P*
OS			
Brachytherapy	86.0	79.6	0.193
EBRT	84.4	74.9	
DSS			
Brachytherapy	89.8	83.8	0.685
EBRT	91.6	88.6	
DFS			
Brachytherapy	74.9	54.3	0.407
EBRT	66.5	47.0	

Mendenhall and colleagues revealed that the prevalence of local control at 5 years and 10 years was 94% and 91%, respectively[7]. Garden *et al.* reported the prevalence of local control at 5 years and 10 years to be 95% and 86%, respectively, in 198 patients treated with surgery and postoperative radiotherapy[6]. In a study in 140 ACC patients, Chen *et al.* reported the prevalence of local control at 5 years and 10 years to be92% and 84%, respectively, in patients treated with postoperative radiotherapy compared with 80% and 61%, respectively, for those treated with surgery alone[8]. The type of radiotherapy in the studies mentioned above was EBRT.

Implantation of ^{125}I seeds is brachytherapy, which is a type of radiotherapy. The advantages of brachytherapy are a high target area dose and a low dose of radiation to surrounding normal tissues. Studies have shown good efficacy for brachytherapy against malignant salivary tumors[15−21]. However, there are some limitations in brachytherapy, such as the limited range of radiation. The prevalence of local control in the two groups in our study is comparable with that obtained in previous studies. Brachytherapy or EBRT combined with surgery can be a feasible treatment option for ACC.

Van Weert *et al.* showed that OS at 5 years and 10 years in ACC patients treated with resection and radiotherapy was 68% and 52%, respectively[22]. Kokemueller and colleagues reported that OS and DFS at 5 years and 10 years in 74 patients with ACC treated with surgery and radiotherapy were 71% and 54%, and 57% and 45%, respectively[2]. Mendenhall and coworkers stated that, in 46 patients with ACC of the parotid glands treated by surgery and radiotherapy, OS and DFS at 5 years was 67% and 75%, respectively[7]. The survival of patients in our study showed only a slight difference with that reported in other studies.

Lloyd *et al.* reported metastasis to LNs after primary surgery in only 17% of their patients. They found that the involvement of isolated LNs, without distant metastasis, did not have a significant influence on survival, but was a risk factor for subsequent distant metastasis[23]. Other scholars have reported the prevalence of LN metastasis to be 5.4%−15%[2,4]. In our study, LN metastasis was 13.1%, and there was no significant difference between the brachytherapy group and the EBRT group.

Distant metastasis, which often occurs independent of local treatment outcomes, has been reported to be 16%−52% in ACC patients[2,4,9,11], and is the most common cause of death[1,2,4]. Zhang *et al.* found distant metastasis in 40.9% of their patients, with the lung being the most common site; the median time from treatment to distant metastasis was 32.6 months[4]. Kokemueller *et al.* reported that the lungs and bone were the most common sites of distant metastasis, with most metastasis occurring 5 years after surgery; the mean DFS in their study cohort was 14.4 years[2]. In the present study, distant metastasis was seen in 36 (31.6%) patients, and lung metastasis was the most prevalent.

The prevalence of side effects of EBRT in our study was acceptable. No patients developed grade-4 toxicities or died as a result of EBRT. However, the prevalence of complications in the brachytherapy group was lower than that in the ERBT group. Usually, the toxicity associated with the implantation of ^{125}I seeds is mild mucositis and dermatitis. On the other hand, one advantage of the implantation of ^{125}I seeds is the absence of late toxicity. ERBT can result in severe toxicity, including severe mucositis and dermatitis, fibrosis, hypothyroidism, trismus, and xerostomia.

This study has several limitations. First of all, this study is a retrospective study, and there will be selective bias in case selection in the brachytherapy treatment group and the EBRT group. Second, ACC involves many sites, including the parotid gland and other large salivary glands, as well as minor salivary glands, which have a certain influence on the research results. Finally, ACC requires longer follow-up.

Conclusions

Administration of EBRT or brachytherapy after resection in patients with ACC of the oral and maxillofacial region was efficacious, but patients treated by brachytherapy had fewer adverse events.

Acknowledgments

We would like to thank Dr. Peng X for the information on patients undergoing EBRT.

References

[1] Maciejewski A, Szymczyk C, Wierzgon J. Outcome of surgery for adenoid cystic carcinoma of head and neck region. *J Craniomaxillofac Surg* 2002;30:59−61.

[2] Kokemueller H, Eckardt A, Brachvogel P, *et al*. Adenoid cystic carcinoma of the head and neck–a 20 years experience. *Int J Oral Maxillofac Surg* 2004;33:25−31.

[3] Tian Z, Li L, Wang L, *et al*. Salivary gland neoplasms in oral and maxillofacial regions: a 23-year retrospective study of 6982 cases in an eastern Chinese population. *Int J Oral Maxillofac Surg* 2010;39:235−242.

[4] Zhang CY, Xia RH, Han J, *et al*. Adenoid cystic carcinoma of the head and neck: Clinicopathologic analysis of 218 cases in a Chinese population. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013;115:368−375.

[5] Yu SF. *Oral histology and pathology.* 1st ed. Beijing: Peking University Medical Press; 2005.
[6] Garden AS, Weber RS, Morrison WH, *et al*. The influence of positive margins and nerve invasion in adenoid cystic carcinoma of the head and neck treated with surgery and radiation. *Int J Radiat Oncol Biol Phys* 1995;32:619−626.
[7] 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* 2004;26:154−162.
[8] 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* 2006;66:152−159.
[9] 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* 2012;48:278−283.
[10] 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* 2013;189:502−507.
[11] Takagi M, Demizu Y, Hashimoto N, *et al*. Treatment outcomes of particle radiotherapy using protons or carbon ions as a single-modality therapy for adenoid cystic carcinoma of the head and neck. *Radiother Oncol* 2014;113:364−370.
[12] Stannard CE, Hering E, Hough J, *et al*. Post-operative treatment of malignant salivary gland tumours of the palate with iodine-125 brachytherapy. *Radiother Oncol* 2004;73:307−311.
[13] 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* 2015; 121:3001−3009.
[14] Iseli TA, Karnell LH, Graham SM, *et al*. Role of radiotherapy in adenoid cystic carcinoma of the head and neck. *J Laryngol Otol* 2009;123:1137−1144.
[15] Zhang J, Zhang JG, Song TL, *et al*. 125I seed implant brachytherapy-assisted surgery with preservation of the facial nerve for treatment of malignant parotid gland tumors. *Int J Oral Maxillofac Surg* 2008;37: 515−520.
[16] Zhang J, Zheng L, Liu SM, *et al*. Brachytherapy for recurrent malignant tumours of the parotid gland. *Br J Oral Maxillofac Surg* 2015; 53:58−62.
[17] Zheng L, Lv X, Shi Y, *et al*. (125)I interstitial brachytherapy for the treatment of myoepithelial carcinoma of the oral and maxillofacial region. *Brachytherapy* 2016;15:240−245.
[18] Huang MW, Wu WJ, Lv XM, *et al*. The role of (125)I interstitial brachytherapy for inoperable parotid gland carcinoma. *Brachytherapy* 2018;17:244−249.
[19] Zhou C, Zhang J, Zhang JG, *et al*. Iodine-125 brachytherapy alone for advanced primary parotid gland carcinoma. *Int J Oral Maxillofac Surg* 2018;47:561−567.
[20] Li C, Liu SM, Zheng L, *et al*. (Study of surgery combined with 125I brachytherapy for adenoid cystic carcinoma of oral and maxillofacial region). *Beijing Da Xue Xue Bao Yi Xue Ban* 2019;51:49−52.
[21] Wu ZY, Wu WJ, Zheng L, *et al*. Efficacy of combined surgery and (125) I seed brachytherapy for treatment of primary mucoepidermoid carcinoma of the parotid gland. *Head Neck* 2019;41:3219−3225.
[22] van Weert S, Bloemena E, van der Waal I, *et al*. Adenoid cystic carcinoma of the head and neck: A single-center analysis of 105 consecutive cases over a 30-year period. *Oral Oncol* 2013;49:824−829.
[23] Lloyd S, Yu JB, Wilson LD, *et al*. 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* 2011; 34:76−81.