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^{125}I brachytherapy alone for recurrent or locally advanced adenoid cystic carcinoma of the oral and maxillofacial region

Adenoid cystic carcinoma (ACC) is a relatively rare tumor that accounts for approximately 1% of all oral and maxillofacial malignancies, 10% of all salivary gland neoplasms, and approximately 22% of all malignant tumors of the salivary glands [14, 20, 39]. Adenoid cystic carcinoma is the predominant histologic type among malignancies of the minor salivary glands [20, 29].

In general, ACC is characterized by slow progression, wide perineural invasion, a relatively low probability of regional lymph node metastases, and a pronounced ability to recur over a prolonged period [20, 27]. It has a tendency to develop distant metastases, and patients may live for a relatively long period with metastatic diseases [20, 27]. Therefore, it is important to control local diseases in order to prolong survival and improve quality of life [50].

Surgery is generally recommended for ACC [16, 19, 30, 32, 48]. However, the early and wide invasion associated with this tumor, as well as the complexity of the local anatomy, can make it difficult to obtain negative margins during surgery. Therefore, many oncologists recommend postoperative radiotherapy (RT) for advanced disease, a close or incomplete resection, bone invasion and perineural invasion in an attempt to improve local control [2, 15, 26, 48]. Postoperative RT is usually delivered as external beam RT. Reports suggest that the 5- and 10-year local control rates for head and neck ACC are 40–46 and 21–25%, respectively, when treated surgically alone, and increase to 64–95 and 68–83%, respectively, when treated with surgery and postoperative radiotherapy [20, 36].

However, the management of recurrent and/or locally advanced unresectable ACC, particularly for those who have previously had external beam RT, remains a challenge [9]. Radical surgery is difficult to perform, as it often involves adjacent vital structures. Although external beam RT alone is a modality for patients with unresectable tumors, the redelivery of effective doses is almost impossible because of the limited tolerance of adjacent normal critical structures [1]. A systematic review revealed that chemotherapy might have a palliative benefit for a small proportion of patients with recurrent ACC of salivary gland origin, though the effects of chemotherapy remain controversial [16, 25, 48].

Brachytherapy may resolve this issue by delivering a high dose of radiation directly to the tumor, while simultaneously sparing adjacent normal tissue [11, 46]. The benefits of brachytherapy for the treatment of malignant tumors have been demonstrated, and a variety of radioactive sources have been used [1, 3, 11, 12, 13, 26, 34, 37, 41, 49].

The purpose of this study was to evaluate the feasibility and effectiveness of using ^{125}I brachytherapy alone for the management of recurrent or locally advanced ACC of the oral and maxillofacial region.

Patients and methods

A total of 38 patients with recurrent or locally advanced ACC of the oral and maxillofacial region received ^{125}I brachytherapy alone at the Peking University School and Hospital of Stomatology between 2001 and 2010. The group included 18 males and 20 females, with a male:female ratio of 1:1.1. Their ages ranged from 7–82 years (median 54 years; mean 53.3 years). The study was approved by the Ethics Committee of Peking University School and Hospital of Stomatology.

The patient- and tumor-associated characteristics are shown in **Tab. 1**. The majority of the tumors were located in the paranasal/skull base region, followed by major or minor salivary glands. The tumor size varied from 1.5–8 cm. The histological diagnosis was obtained by incisional biopsy or needle aspiration biopsy before brachytherapy.

Inclusion criteria were as follows: patients with recurrent and locally advanced unresectable tumor after prior surgery and radiotherapy; patients with locally advanced tumor with inoperable disease who refused external RT. Eleven patients with obvious tumor-related pain before treatment were included in a pain control evaluation. Patients used the visual analogue scale (VAS) to grade pain during the 1-year follow-up period.

The brachytherapy treatment planning system (BTPS, Beijing Atom and High Technique Industries Inc., Beijing, China) was used to create implant plans based on patients' CT images (**Fig. 1a**). The prescribed dose target volume (PTV) was outlined by oncologists to cover the lesion with a 0.5–1 cm margin. The prescribed dose (PD, or matched peripheral dose) of the ^{125}I implant was 100–160 Gy, which was adjusted according to the dose of prior radiation and the adjacent struc-

Tab. 1 Patient characteristics

Characteristics	
Age (years), median (range)	54 (7–82)
Sex (n)	
Male	18
Female	20
Tumor site (No. of patients)	
Major salivary glands (parotid, submandibular, sublingual gland)	12
Minor salivary glands of oral cavity	12
Paranasal/skull base region (including nasal cavity)	14
Tumor size (No. of patients)	
<3 cm	8
3–6 cm	19
>6 cm	11
Distant metastasis at first visit (No. of patients)	9
Prior treatment for tumors (No. of patients)	
None	9
Surgery	3
Radiotherapy (conventional fractionation, 2 Gy/day)	1
Surgery and radiotherapy (conventional fractionation, 1.8–2 Gy/day)	25
Prior surgery times	
One	15
Two	9
Three or more	4
Prior radiotherapy times	
One	25
Two	1
Prior cumulative radiotherapy dose (No. of patients)	
<60 Gy	7
60–66 Gy	15
>66 Gy	4

Tab. 2 Results from the literature on adenoid cystic carcinoma of the head and neck treated with radiotherapy alone

Author	Year	n	Overall survival (%)	Local control (%)
			5-, 10-year	5-, 10-year
Balamucki et al. [4]	2011	46	56, 37	55, 36
Cowie and Pointon [7]	1984	41	–	37, –
Miglianico et al. [31]	1987	21	79, –	66, –
Mendenhall et al. [30]	2004	40	57, 42	56, 43

n number of patients, – the literature did not provide relevant data.

tures. Generally, for patients who had previously received external RT, the dose was 100–140 Gy, and it was 140–160 Gy for the others. Implantation was performed under CT and/or template guidance according to the plan ([35], **Fig. 1b**). A median of 62 ^{125}I seeds (model 6711, 4.5 mm long and 0.8 mm in diameter, China Institute of Atomic Energy) was implanted. The seeds had a half-life of 59.4 days and an activity of 18.5–33.3 MBq per seed. The evaluation of post plan was routinely obtained for each patient (**Fig. 1c, d**). The actuarial D_{90} (dose delivered to 90% of the target volume) was larger than PD in all patients and ranged from 109–202 Gy (median 152 Gy; mean 158 Gy). The V_{100} (the percentage of the target volume receiving at least 100% of the prescription dose) of each patient was more than 95%, and the V_{150} (the percentage of the target volume receiving at least 150% of the prescription dose) for all cases was less than 50%. The neck was not treated since all patients had clinically negative neck nodes.

Follow-up consisted of routine physical examinations and appropriate imaging examination. A CT or PET-CT scan was undertaken 6 and 12 months after implantation, or as necessary. Patients were typically seen at 2-month intervals for the first year, and at 4-month intervals thereafter. The presence of distant metastases was checked using X-rays, ultrasound, CT or PET-CT. Complications were evaluated according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORCT) grading system [8].

SPSS 13.0 for Windows (SPSS Inc., Chicago, IL) was used for data analysis. A two-sided $p<0.05$ was considered statistically significant. The survival time was calculated from the date of implantation to the final follow-up assessment or the date of death. Local control was defined as a lack of tumor progression either in or adjacent to the implanted volume. The probabilities of local control (LC), and overall survival (OS) were calculated using the Kaplan–Meier product-limit method. The size and site of tumors were analyzed for impact on OS, and on local control with univariate analyses using the classical log-rank test.

Results

Local control rate

The follow-up period was 12–122 months (median 51 months), and the 2-, 5-, and 10-year complete local tumor control rates were 86.3, 59, and 31.5%, respectively (**Fig. 2**). Patients with recurrent disease (n=29) had a 5-year LC rate of 57.3%, while those with primary disease (n=9) had a LC rate of 66.7%. However, this difference was not statistically significant (p=0.58).

In general, the tumor site did not significantly influence the LC rate (p=0.92). However, smaller tumors revealed a trend towards better LC (p=0.04). The 5-year LC rates for different sizes, <3, 3–6, and >6 cm, were 71.4, 66.9, and 21.9%, respectively. An ACC that involved the skull base and treated with ^{125}I implantation alone can be seen in **Fig. 3**.

Overall survival rate

The 2-, 5-, and 10-year OS rates were 92.1, 65, and 34.1%, respectively (**Fig. 4**). Tumor site did not significantly influence the OS rate (p=0.95). According to size, patients with tumors greater than 6 cm had a 5-year survival rate of 45.5%, which was significantly lower than that observed for tumors less than 6 cm, which had a 5-year survival rate of 71.5% (p=0.04).

Thirteen patients died during this study. Eleven died as a result of distant metastases, and two died of local brain involvement.

Distant metastases

Distant metastases were present in 9 patients prior to ^{125}I implantation; 8 patients developed distant metastases after ^{125}I implant. Distant metastases oc-

curred between 8 and 60 months (median 28 months, mean 32 months). The lungs were most frequently involved with distant metastases (n=16), followed by the liver (n=2), and bone (n=1).

Only 1 patient with a tumor in the oral cavity developed a neck metastasis 14 months after implantation, and subsequently underwent a neck dissection.

Pain control

The pain change scaled according the Visual Analogue Scale (VAS) system before and after ^{125}I implant occurred in 7 of the 11 patients between 1 and 8 months after brachytherapy. Pain disappeared in 1 patient who had a tumor in the parotid gland 2 months after implantation; partial or mild improvement in pain occurred in 6 patients 0.25–2 months after implantation; and no obvious changes were observed in 4 patients, all of who had tumors in the oral cavity.

Complications

No severe complications (RTOG grades 3–4) were observed. Five patients with oral cavity tumors experienced temporary mucositis in the irradiated area, which healed without treatment within 2–6 weeks. In all, 19 patients experienced temporary minor side effects (RTOG grades 1 and 2), including mild pain and cutaneous pigmentation.

Discussion

Surgery is generally recommended for resectable ACC [16, 48], and adjuvant external RT is usually administered if there are adverse risk factors, such as close or positive margins, perineural or vascular invasion, lymph node metastases, or if the tumor is in advanced stages [2, 6, 21, 24, 26]. Many oncologists believe that the optimal treatment for patients with adenoid cystic carcinoma is surgery with adjuvant RT [6, 30, 33]. In a study by Mendenhall et al. [30], a significant proportion of patients with incompletely resected disease were cured with RT alone. However, controversy remains regarding the role of RT for the adjuvant treatment of ACC [16, 23, 28], which claims that postoperative RT does not have any obvious benefits [23, 28].

Although ACC has been considered relatively radioresistant, external RT has been used alone in patients unfit for surgery or in those with inoperable disease [4, 7, 22, 29, 30, 31, 40, 47]. However, for recurrent and locally advanced ACC following previous surgery and external RT, an effective treatment strategy has not been confirmed to date [9]. Radical surgery is difficult to achieve following previous surgery or if vital tissue is involved. Considering the tolerance limit of normal tissue in areas of re-

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^{125}I brachytherapy alone for recurrent or locally advanced adenoid cystic carcinoma of the oral and maxillofacial region

Abstract

Background and purpose. This retrospective study was to evaluate the local control and survival of ^{125}I brachytherapy for recurrent and/or locally advanced adenoid cystic carcinoma (ACC) of the oral and maxillofacial region.

Patients and methods. A total of 38 patients with recurrent and/or locally advanced ACC of the oral and maxillofacial region received ^{125}I brachytherapy alone from 2001–2010. Twenty-nine were recurrent cases following previous surgery and radiation therapy. The other 9 cases involved primary tumors. Overall, 12 tumors were located in the major salivary glands, 12 in the minor salivary glands, and 14 in the paranasal region, the nasal cavity or the skull base. The prescribed dose was 100–160 Gy.

Results. Patients were followed for 12–122 months (median 51 months). The 2-, 5-, and 10-year local tumor control rates were 86.3, 59, and 31.5%, respectively. The 2-, 5-, and 10-year overall survival rates were 92.1, 65 and 34.1%, respectively. Tumors >6 cm had significantly lower local control and survival rates. No severe complications were observed during follow-up.

Conclusion. ^{125}I brachytherapy is a feasible and effective modality for the treatment of locally advanced unresectable or recurrent ACC.

Keywords

Brachytherapy · Adenoid cystic carcinoma · Oral and maxillofacial · Salivary gland neoplasms · Head and neck neoplasms

Alleinige ^{125}I Brachytherapie zur Behandlung rezidivierter oder lokal fortgeschrittener adenoid-zystischen Karzinome in Mund-, -Kiefer- und Gesichtsbereich

Zusammenfassung

Hintergrund und Ziel. Diese retrospektive Studie untersucht die lokale Kontrolle und Überlebensrate durch Brachytherapie mit ^{125}I für das rezidivierte und/oder lokal fortgeschrittene adenoid-zystische Karzinom (ACC) der oralen und maxillofazialen Region.

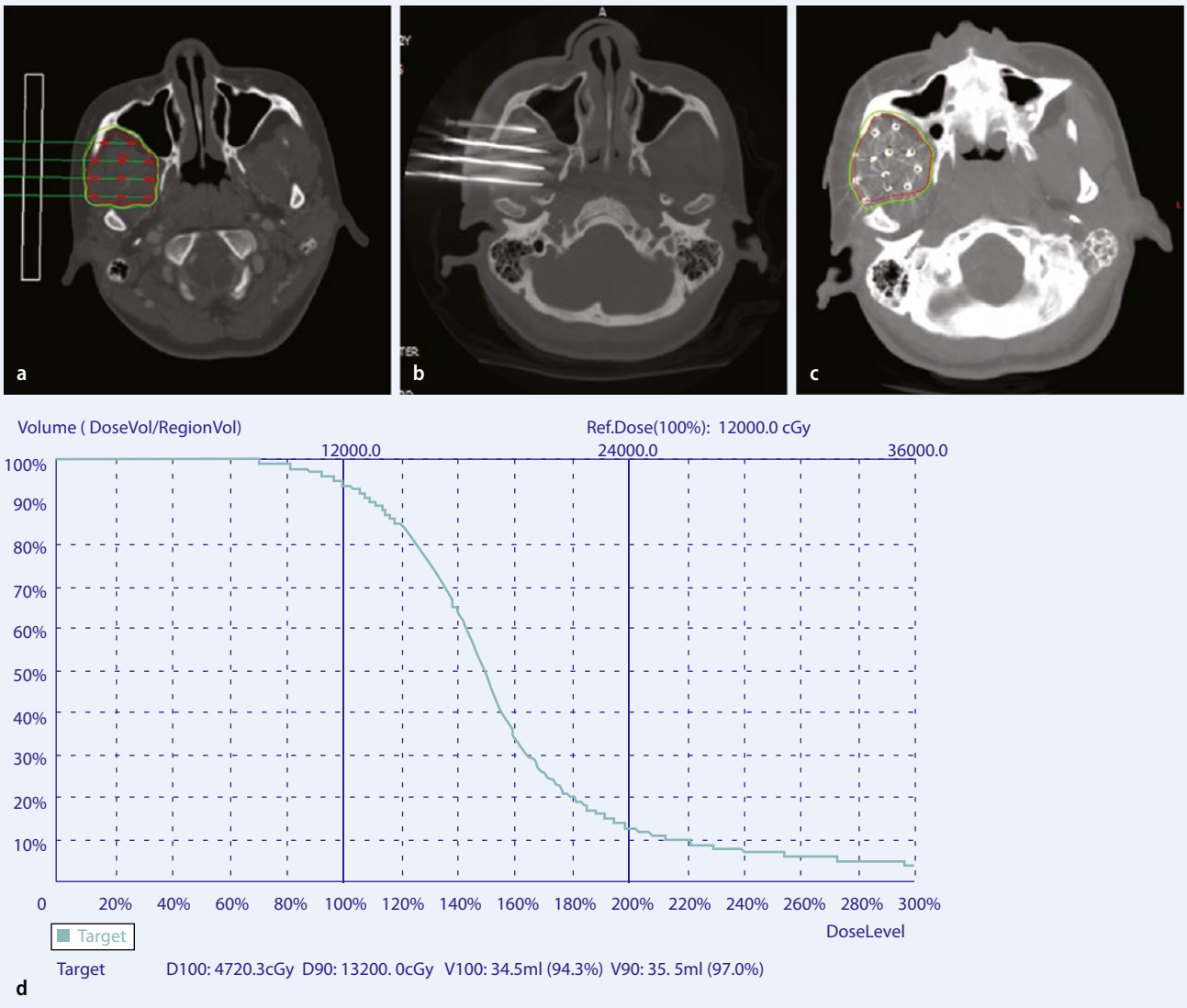
Patienten und Methoden. Von 2001 bis 2010 wurden 38 Patienten mit rezidiviertem und/oder lokal fortgeschrittenem ACC im Mund, -Kiefer- und Gesichtsbereich durch ^{125}I-Brachytherapie behandelt. Davon handelte es sich in 29 Fällen um Rezidive nach chirurgischer Tumorentfernung und Strahlentherapie. Die übrigen 9 Fälle waren primäre Tumormanifestationen. Bei 12 Patienten war die Tumorlokalisation in den großen Speicheldrüsen, bei weiteren 12 Patienten in den kleinen Speicheldrüsen und bei 14 Patienten in der paranasalen Region, der Nasenhöhle oder der Schädelbasis. Die applizierte Strahlendosis betrug zwischen 100 und 160 Gy. Der Beobachtungszeitraum lag zwischen 12 und 122 Monaten (Median 51 Monate).

Ergebnisse. Bei den lokalen Tumorkontrollen nach 2, 5 und 10 Jahren waren jeweils 86,3%, 59% und 31,5% tumorfrei. Die 2-, 5- und 10-Jahres-Überlebensraten betrugen 92,1%, 65% und 34,1%. Tumoren >6 cm zeigten signifikant niedrigere lokale Tumorfreiheit und niedrigere Überlebensraten. Während des Follow-up-Zeitraums wurden keine schweren Komplikationen beobachtet.

Fazit. Die ^{125}I-Brachytherapie ist praktikabel, wirksam und stellt eine Modalität in der Behandlung eines lokal fortgeschrittenem inoperablem oder rezidiviertem ACC dar.

Schlüsselwörter

Brachytherapie · Adenoid-zystisches Karzinom · Oral und maxillofazial · Speicheldrüsenneoplasien · Kopf- und Halsneoplasien



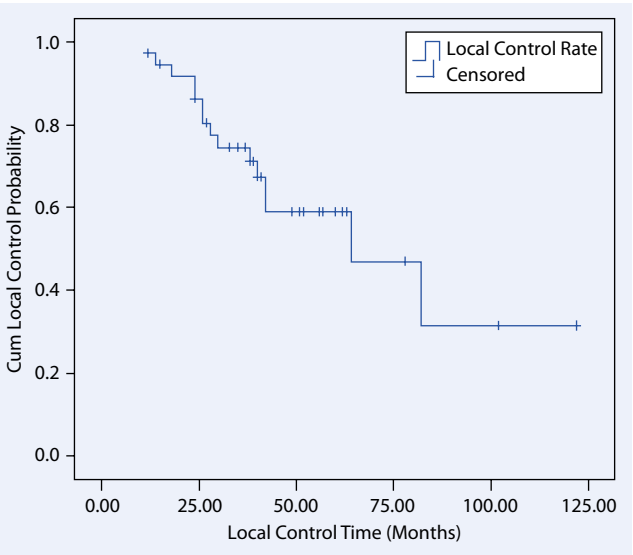


Fig. 1 ▲ The administration of iodine-125 seeds brachytherapy. **a** The isodose curve in the implant plan from CT scan. **b** The implantation of needles. **c** The isodose curve after seed implantation from CT scan. **d** The dose volume histograms of PTV after seed implantation.
The *inner red curve* represents PTV. The *yellow and green curves* are isodose lines of D100 (120 Gy) and D90 (108 Gy), respectively

Fig. 2 ◀ Local control probability after ^{125}I brachytherapy

current disease, the redelivery of external RT can be problematic in previously irradiated fields.

The advantages of brachytherapy are that it is minimally invasive and delivers higher radiation doses to target areas, while at the same time sparing surrounding normal tissue [11, 46]. Many radioisotopes have been used for brachytherapy, including ^{192}Ir,

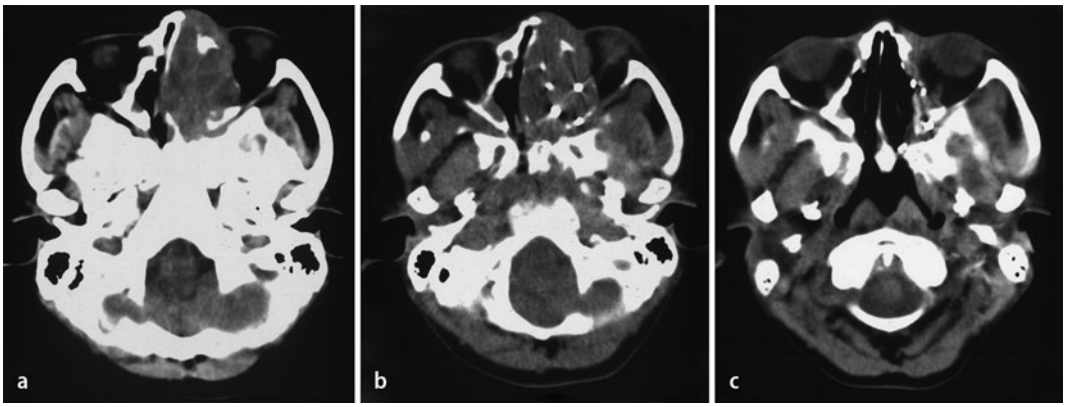


Fig. 3 ◀ **a** A patient with ACC involving the paranasal area and the skull base. **b** Treated with ^{125}I implantation alone. **c** Complete tumor regression 6 months later

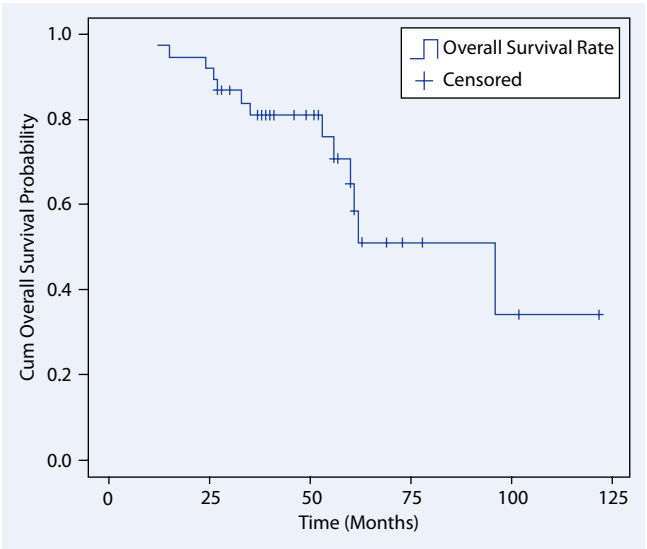


Fig. 4 ◀ Overall survival probability after ^{125}I brachytherapy

^{198}Au, and ^{125}I [1, 10, 11, 18, 26, 34, 37, 42, 44, 45]. ^{192}Ir brachytherapy has usually been used as a boost for large tumors, or for afterload brachytherapy [10, 41]. Although Ashamalla et al. [1] reported an average progression-free survival of 52 months in patients with recurrent palatal ACCs treated with ^{198}Au implant brachytherapy, ^{198}Au with its short half-life of 2.7 days has been used more frequently to treat squamous cell carcinomas and other tumors that proliferate rapidly [11, 43]. ^{125}I brachytherapy has increasingly been used for slowly progressive salivary gland malignant tumors, due to its long half-life (59.4 days), low photon energy (27–35 KeV) and to the fact that it can be easily screened, thus, protecting adjacent vital structures and attending staff [11, 51]. Stannard et al. [45] reported a 100% local control rate in 9 patients with malignant salivary gland tumors, with positive or close margins, treated with postoperative ^{125}I brachytherapy. Glaser et al. [11] reported disease-free survival for cases of head and neck cancer (8 of 18 patients were with ACC) of 89 and 53% at 2 and 5 years, respectively, following surgery and ^{125}I implants, which found that ^{125}I implants did not result in any additional complications. Zhang et al. [51] reported a 100% LC rate and no complications (follow-up 50–74 months, median 66 months) in patients with residual parotid malignant tumors post-surgery treated solely with ^{125}I brachytherapy. Jiang et al. [17] treated recurrent head and neck cancer with ^{125}I implants alone and reported a 5-year LC rate of 39%.

As a monotherapy for ACC, external radiotherapy has achieved 5- and 10-year LC rates of approximately 37–66 and 36–43%, respectively [4, 7, 30, 31], and 5- and 10-year OS rates of 56–79 and 37–42%, respectively [4, 7, 30, 31]. Both LC and OS rates from the literature of patients with ACC treated with RT alone can be seen in **Tab. 2**. In our series, we used ^{125}I implants alone to treat recurrent or locally advanced ACC, and the 5- and 10-year LC rates achieved were 59 and 31.5%, respectively. The 5-year LC rates were 57.3 and 66.7% for recurrent and primary tumors, respectively. The 5- and 10-year OS rates were 65 and 34.1%, respectively. For recurrent tumors, the 5-year overall survival rate was 61.8, and 75% for primary tumors (p=0.19).

Our findings consolidate the opinion that ACC size is an important predictor of treatment response and prognosis, and are consistent with results from other studies [1, 5, 32, 36]. In our series, patients with tumors >6 cm had significantly lower LC and survival rates (p=0.04). A further factor influencing survival is the presence of distant metastases (p<0.05) [38]. Overall, 17 of the 38 patients in our study had distant metastases. The distant metastases rate, and the interval from ^{125}I implantation to the occurrence of metastases observed in our study, is similar to that reported by other studies [5, 23].

In this study, we presented our experience of treating locally advanced or recurrent ACC with ^{125}I implants alone. Considering the stage of the tumors in the series, the LC and OS results are encouraging, and suggest that ^{125}I brachytherapy is a feasible and effective modality for the treatment of unresectable or recurrent ACC after prior surgery and radiotherapy, which seems better than external beam radiation. In addition, patients with tumors >6 cm had significantly lower LC and survival rates. Our study was a short-term retrospective analysis on a limited number of patients, and therefore a larger, prospective, long-term, randomized multicenter study is needed to confirm our findings.

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Conflict of interest. On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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