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 pronouncability 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 125I 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 125I 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.

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 125I implant was 100–160 Gy, which was adjusted according to the dose of prior radiation and the adjacent struc-
Table 1: Patient characteristics

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

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Overall survival (%)</th>
<th>Local control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miglianico et al. [31]</td>
<td>1987</td>
<td>21</td>
<td>79, –</td>
<td>66, –</td>
</tr>
<tr>
<td>Mendenhall et al. [30]</td>
<td>2004</td>
<td>40</td>
<td>57, 42</td>
<td>56, 43</td>
</tr>
</tbody>
</table>

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

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 125I 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 125I implantation; 8 patients developed distant metastases after 125I implant. Distant metastases oc-

M.-W. Huang · L. Zheng · S.-M. Liu · Y. Shi · J. Zhang · G.-Y. Yu · J.-G. Zhang

125I 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 125I 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 125I 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. 125I 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
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 $^{125}\text{I}$ brachytherapy

**Fig. 1**

- a. The administration of iodine-125 seeds brachytherapy.
- b. The isodose curve in the implant plan from CT scan.
- c. The implantation of needles.
- d. The isodose curve after seed implantation from CT scan.
- e. 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 $^{125}\text{I}$ 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 $^{192}\text{Ir}$,
198Au, and 125I [1, 10, 11, 18, 26, 34, 37, 42, 44, 45]. 192Ir 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 198Au implant brachytherapy, 198Au 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]. 125I 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% 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 125I brachytherapy. Jiang et al. [17] treated recurrent head and neck cancer with 125I 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 125I 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 125I 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 125I implants alone. Considering the stage of the tumors in the series, the LC and OS results are encouraging, and suggest that 125I brachytherapy is a feasible and effective modality for the treatment of unresectable or recurrent ACC after primary 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.
References