Postoperative iodine-125 interstitial brachytherapy for the early stages of minor salivary gland carcinomas of the lip and buccal mucosa with positive or close margins

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ABSTRACT: *Background.* The purpose of this study was to present our preliminary exploration of safety and efficacy of postoperative low-dose-rate brachytherapy for the early clinical stages of minor salivary gland carcinomas of the lip and buccal mucosa.

Methods. Twenty-seven patients with the early stages of minor salivary gland carcinomas of the lip and buccal mucosa received postoperative ^{125}I seed interstitial brachytherapy from March 2005 to May 2015. Actuarial likelihood estimates for local control, overall survival, and disease-free survival were calculated by Kaplan–Meier method.

Results. The actuarial 3-year, 5-year, and 10-year local control rates were 94.7%, 82.9%, and 82.9%, respectively. The actuarial 3-year, 5-year, and 10-year overall survival rates were 93.3%, 93.3%, and 77.8%, respectively. No patient experienced toxicity above grade 2.

Conclusion. Postoperative ^{125}I seed interstitial brachytherapy is an alternative to radical surgery for early stages of minor salivary gland carcinomas of the lip and buccal mucosa, which offers satisfactory cosmetic and functional outcomes. © 2017 Wiley Periodicals, Inc. *Head Neck* **39:** 572–577, 2017

KEY WORDS: lip, buccal, minor salivary gland, carcinoma, brachytherapy

INTRODUCTION

Minor salivary gland carcinomas of the lip and buccal mucosa are rare, accounting for only 2% to 3% of salivary gland tumors.[1] Several studies have shown that 21% to 84% of labial gland tumors and 42% to 100% of buccal gland tumors are malignant.[2–6] Despite the relatively low incidence, salivary gland carcinomas are diverse with as many as 24 different types recognized by the World Health Organization,[7] which bring about challenge on the management of salivary gland carcinomas. The mainstay treatment of minor salivary gland carcinoma is surgery. Under the premise of feasibility, resection should be performed with negative margins.[8] In addition, for patients with a positive margin, high histologic grade, tumors involving nerves, muscles, and bones, or high level of the T and N classification, postoperative radiotherapy is necessary.[8] As for cases of inoperable adenoid cystic carcinoma, the usage of neutron radiation was reported. A study performed by Huber et al[9] showed that the 5-year local control rate of neutron radiation in inoperable adenoid cystic carcinoma can reach 75%, which was significantly higher than photon radiotherapy and surgery plus radiotherapy. However, the subsequent side effects were more detrimental in neutron radiotherapy. Moreover, the efficacy of chemotherapy is limited on salivary gland tumors,[10] although certain chemotherapy drugs may provide alleviating effects for a subset of patients with advanced adenoid cystic carcinoma.[11] As another means of radiotherapy, brachytherapy has been widely applied to lip squamous cell carcinoma. However, few brachytherapy for minor salivary gland carcinomas of the lip and buccal mucosa have been reported.

The purpose of this study was to present our preliminary exploration of safety and efficacy of postoperative low-dose-rate brachytherapy for the early clinical stages of minor salivary gland carcinomas of the lip and buccal mucosa.

PATIENTS AND METHODS

This study was a retrospective analysis. Twenty-seven consecutive patients with minor salivary gland carcinomas of the lip and buccal mucosa received postoperative ^{125}I seed interstitial brachytherapy at Peking University School of Stomatology from March 2005 to May 2015. Table 1 describes the baseline information of patients. Ranging from 12 to 72 years old by the time of diagnosis, the patients had a median age of 45 years. Seventeen of 27 patients were women and 10 were men. The tumor site of 6 patients was the lip mucosa and the remaining 21 patients was the buccal mucosa. Until May 2015, the median follow-up time was 29 months (ranging from 4–122 months).

The histologic types of 27 patients are shown in Table 2. Adenoid cystic carcinoma was the most common type

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TABLE 1. Baseline characteristics.

Characteristics	No. of patients (%)
Sex	
Male	10 (37%)
Female	17 (63%)
Age, y	
Median	45
Range	12–72
Site	
Lip mucosa	6 (22%)
Buccal mucosa	21 (78%)
T classification	
T1	10 (37%)
T2	17 (63%)
T3	0
T4	0

(11/27), followed by mucoepidermoid carcinoma (7/27) and acinic cell carcinoma (3/27). There was 1 patient for each of the other 6 types: carcinoma in pleomorphic adenoma, cystadenocarcinoma, oncocytic carcinoma, adenocarcinoma not otherwise specified (NOS), polymorphous low-grade adenocarcinoma, and salivary duct carcinoma. Among the 7 cases of mucoepidermoid carcinoma, 4 were intermediate to high-grade and 3 were low grade.

According to the staging criteria of the Union for International Cancer Control seventh edition,[12] 10 of 27 patients were T1 classification and 17 were T2 classification. All patients were N0M0. Twenty-four patients were diagnosed on their first visit and the other 3 patients had a surgical history and incurred a recurrence. They all received surgical treatment in the institution. The surgical approaches were excisional biopsy or conservative tumor resection, whereas neck dissection was not performed on these patients with cN0 disease. Postoperative histologic examination showed salivary gland carcinomas and close ($<$1 mm) or positive margin status. All of these patients refused reoperation because of poor cosmetic and functional outcomes. With the informed consent of these 27 patients, they were treated with postoperative ^{125}I seed interstitial brachytherapy within 1 month after surgery. In addition, none of the 27 patients received external-beam radiotherapy or chemotherapy as an adjuvant treatment.

Low-dose-rate brachytherapy was performed with ^{125}I radioactive seeds (type 6711; Beijing Atom and High Technique Industries, Beijing, China), which had a half-life period of 59.4 days and a radioactivity of 22.2MBq to 29.6MBq per seed. Moreover, ^{125}I radioactive seeds emitted X-ray of 31.4 KeV and 27.4 KeV and γ-ray of 35.5 KeV. Permanent brachytherapy plan consists of preoperative planning and postoperative quality verification with preoperative and postoperative CT images in the brachytherapy treatment planning system (Beijing Atom and High Technique Industries), respectively. The clinical target volume was defined as gross tumor volume and its surrounding potential subclinical disease or microscopic residual tumor, which was 1 to 1.5 cm beyond the margins of the primary tumor. During the operation, hollow interstitial needles were inserted into the target area while the patient was under local or general anesthesia (Fig. 1), according to the plan with individual template made through rapid prototyping technique or combined with CT guidance. An applicator was then sequentially attached to the distal end of the needles and placed the ^{125}I seeds into the target area. ^{125}I radioactive seeds were implanted permanently 1-cm apart in a single layer of the lip and buccal. The parameters of actual implantation were inevitably different from those of the preplan. Consequently, postoperative quality verification was necessary. The median matched peripheral dose was 9000 cGy (range, 7000–12,000 cGy) based on the brachytherapy treatment planning system. The median D90 of quality verification was 9270 cGy (range, 7000–12,840 cGy) and the median V100 was 92.8% (90% to 93.8%), whereas V150 was $<$50% for all patients.

Toxicities associated with radiation were recorded and graded according to the Radiation Therapy Oncology Group grading system during the follow-up.

Actuarial likelihood estimates for local control, overall survival, and disease-free survival were calculated by the Kaplan–Meier method and outcomes between groups were compared by the log-rank test based on SPSS 13.0 for Windows. The p values $< .05$ was considered statistically significant. The tumor site (lip and buccal), T classification (T1 and T2), histologic grade (low grade and intermediate to high-grade), and recurrent tumor (primary and recurrent tumor) were considered to be risk factors and were divided into groups for the log-rank tests.

RESULTS

In the 27 cases, 2 patients experienced local recurrence. One patient had T1 classification adenoid cystic carcinoma and the other patient had T1 classification adenocarcinoma NOS. Local recurrence occurred 48 and 19 months after brachytherapy during the follow-up, respectively. After surgical resection, the 2 patients were currently under local control. The actuarial 3-year, 5-year, and 10-year local control rates were 94.7%, 82.9%, and 82.9%, respectively (Fig. 2A). All of the recurrent cases were in the group of T1 classification. As a result, the difference was statistically significant between T1 classification and T2 classification groups ($p = .003$; $p < .05$). In addition, all of the recurrent cases were in the group of buccal mucosas. Nevertheless, there was no statistically significant difference between groups of tumor site, histologic grade, or recurrent tumor, respectively.

TABLE 2. Histologic distribution.

Histology	Lip mucosa	Buccal mucosa	Total
ACC	3	8	11
Mucoepidermoid carcinoma	2	5	7
Acinic cell carcinoma	0	3	3
Carcinoma in pleomorphic adenoma	1	0	1
Cystadenocarcinoma	0	1	1
Oncocytic carcinoma	0	1	1
Adenocarcinoma NOS	0	1	1
Polymorphous low-grade adenocarcinoma	0	1	1
Salivary duct carcinoma	0	1	1
Total	6	21	27

Abbreviations: ACC, adenoid cystic carcinoma; NOS, not otherwise specified.

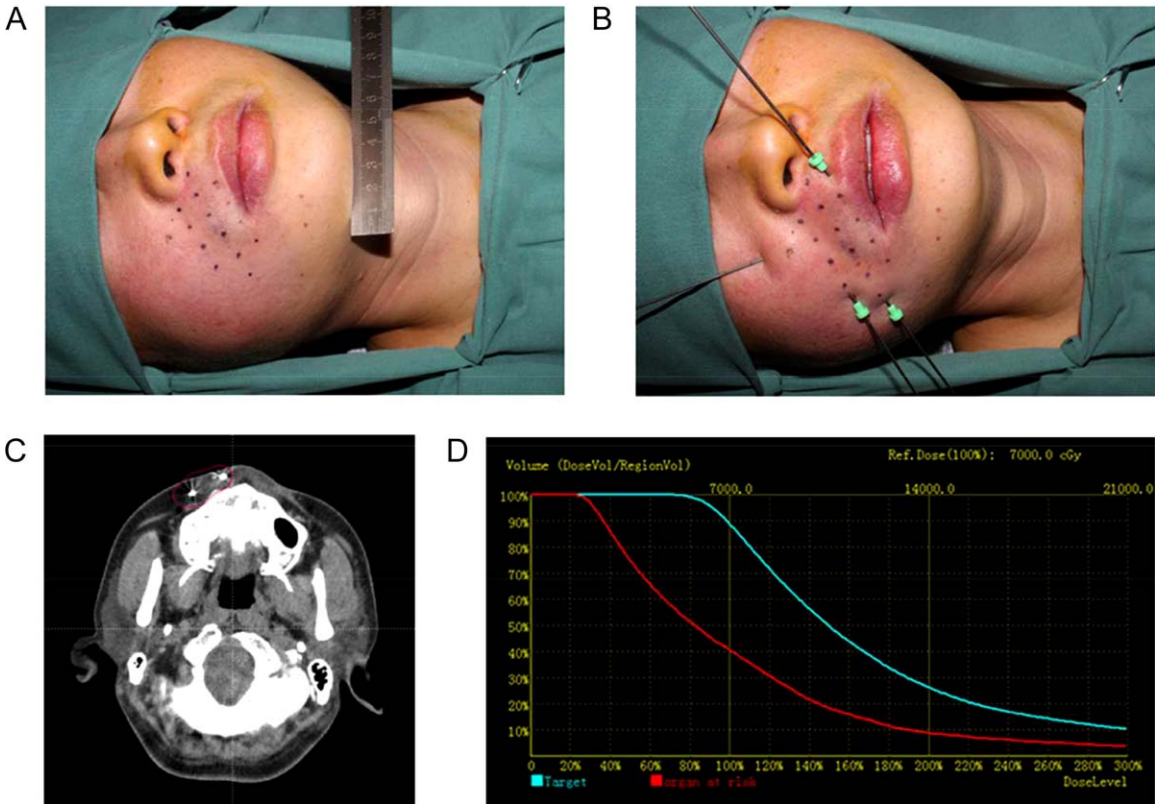

FIGURE 1. (A, B) Hollow interstitial needles were inserted into the target area and iodine-125 radioactive seeds were implanted permanently 1 cm apart in a single layer of lip and buccal according to the plan. (C) Postoperative CT images in the brachytherapy treatment planning system. (D) Dose-volume histogram of quality verification. [Color figure can be viewed at wileyonlinelibrary.com]

Two patients were deceased in the 27 cases. One patient had T2 classification cystadenocarcinoma and the other with T2 classification polymorphous low-grade adenocarcinoma died of systemic multiple metastases 26 and 68 months after brachytherapy, respectively. However, no local recurrence was observed for the 2 cases. In addition, 1 patient with T2 classification adenoid cystic carcinoma was detected with metastasis in the lung 113 months after brachytherapy. Currently, the patient is surviving with local control and lung metastasis. The actuarial 3-year, 5-year, and 10-year overall survival rates were 93.3%, 93.3%, and 77.8%, respectively (Fig. 2B). All of the failed cases were in the group of buccal mucosas. As a result, overall survival was significantly associated with tumor site ($p = 0$; $p < .05$). On the other hand, overall survival was not significantly associated with T classification, histologic grade, or recurrent tumor. Furthermore, the actuarial 3-year, 5-year, and 10-year disease-free survival rates were 88.4%, 77.4%, and 61.9%, respectively (Fig. 2C). The difference was statistically significant between the T1 and T2 groups (means for disease-free survival time; T1, 42.2 months; T2, 104.6 months; $p = .022$; $p < .05$). Nevertheless, there were no statistical differences between groups of tumor site, histologic grade, and recurrent tumor, respectively. There were no neck failures for the 27 cases during the follow-up.

Acute mucositis of grade 2 and acute dermatitis of grade 1 occurred in 3 patients simultaneously, whereas no late toxicities, including serious trismus and osteoradionecrosis, were observed. No patient experienced toxicity above grade 2. No patients presented any foreign body sensation.

DISCUSSION

Minor salivary gland carcinomas of the lip and buccal mucosa are rare. As a result of superficial tumor site, minor salivary gland carcinomas are often diagnosed as T1 or T2 classification. Usually, early-stage minor salivary gland carcinomas do not cause noticeable symptoms, such as pain or numbness. Clinically, it is difficult to distinguish between benign and malignant carcinomas. Imaging tools, such as CT, MRI, and positron emission tomography can considerably contribute to evaluating the tumor size and the violation of adjacent organs. In addition, because of the numerous histologic types of minor salivary gland carcinomas, preoperative fine-needle aspiration cytology is beneficial to determine the nature of the tumor. Similar to related studies,[2,4,5] cases in this study concentrate on adenoid cystic carcinoma (ACC) and mucoepidermoid carcinoma in terms of histologic types, accounting for 41% and 26%, respectively. Surgery was the mainstay treatment of minor salivary gland carcinomas, with radiotherapy as the most important adjuvant treatment. Because of the tumor site and T classification, the surgical procedure was usually excisional biopsy or conservative tumor resection. Consistent with the risk factors, such as high histologic grades and

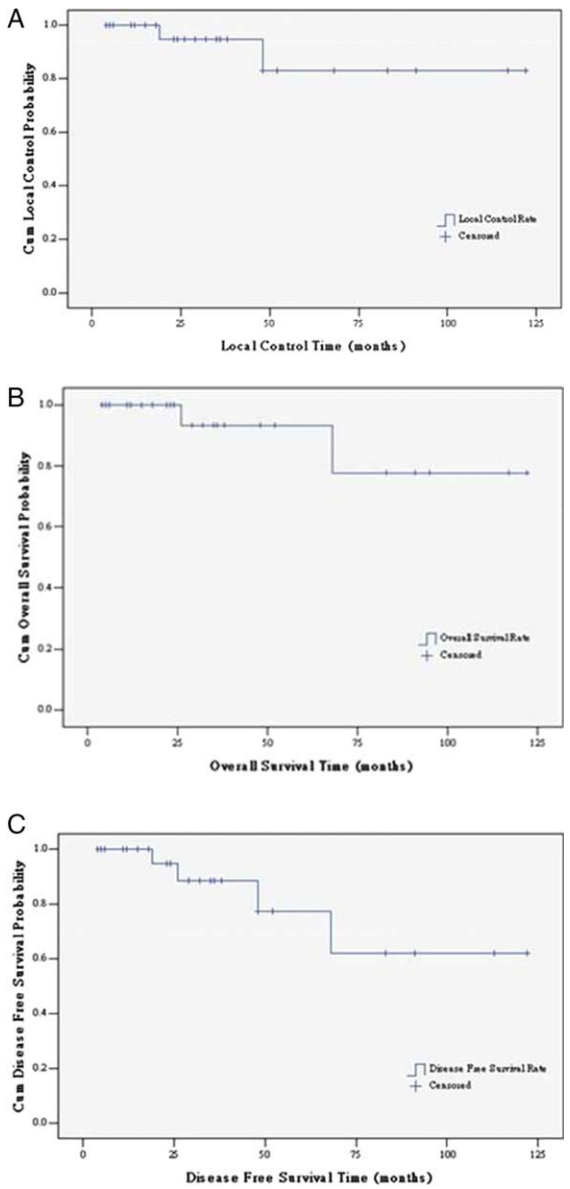

FIGURE 2. Kaplan–Meier curves for local control (A), overall survival (B), and disease-free survival (C). [Color figure can be viewed at wileyonlinelibrary.com]

positive margins, wide local resection or adjuvant radiotherapy can be subsequently carried out. However, the surgical resection often results in potential tissue defects of the lip vermilion or buccal mucosa, which could cause poor cosmetic outcomes and trismus.

Salivary gland carcinomas may relapse after many years, which are different from squamous cell carcinomas. Long-term local control rates of salivary gland carcinomas were often reported less than that of squamous cell carcinomas, even for early stages. Salgado et al[13] reported that with 1 to 246 months (median, 87 months) of follow-up, surgical treatment accompanied by adjuvant radiotherapy with a median dose of 63 Gy for 98 patients with minor salivary gland carcinomas can achieve an 87.9% 5-year local control rate and 83% 10-year local control rate. Parsons et al[14] reported that minor salivary gland carcinomas can relapse many years later, even 12 years in certain cases. Recurrence after years was more likely to occur in high-grade cases. However, polymorphous low-grade adenocarcinoma could also relapse as late as 15 years after the initial surgery.[15] Weber et al[5] reported a recurrence rate of 12% (6/50) in a large group of 50 patients with minor salivary gland tumors of lip and buccal mucosa treated by surgery (28 cases), radiotherapy (9 cases), or a combination (13 cases) with follow-up ranged from 1.5 years to 32.8 years. Cianchetti et al[16] reported a 10-year locoregional control rate of 85% in 76 patients with stages I to III minor salivary gland carcinomas after surgery and radiotherapy with median follow-up of 5.5 years. Similarly, the 3-year, 5-year, and 10-year local control rates in our study were 94.7%, 82.9%, and 82.9%, respectively. Two cases that relapsed were T1 classification ACC and adenocarcinoma NOS of buccal mucosa within 48 months and 19 months, respectively. After surgical resection, the 2 patients were under local control. The local control rates were usually close in cases of T1 and T2 classification. Because of the small sample size, T1 classification predicted for worse local control, which ought to be considered unreasonable. However, lip carcinomas usually have a better prognosis than buccal mucosa carcinomas. For patients who experienced recurrence after brachytherapy, surgery or brachytherapy was still an alternative method.

Whether to choose neck dissection for patients with cN0 disease with salivary gland carcinoma is controversial. Patients with high-grade carcinoma should receive elective neck dissection.[17] Nevertheless, for patients with cN0 disease refusing to receive radical surgery, it was reasonable to detect neck failure during the follow-up. In fact, there were no neck failures for the group. In our opinion, patients with early stages of minor salivary gland carcinomas of the lip and buccal mucosa can benefit from neck dissection.

Despite the long-term local recurrence, metastasis is the main factor affecting the survival of patients with early stages of salivary gland carcinomas, which results in lower long-term survival rates. As reported by Vander Poorten et al,[8] the 5-year overall survival rate was between 66% and 80% and the 10-year overall survival rate was between 56% and 70% for minor salivary gland carcinomas. As for early stages of minor salivary gland carcinomas, Cianchetti et al[16] reported a 10-year overall survival rate of 60% in 76 patients with stages I to III minor salivary gland carcinomas after surgery and radiotherapy with median follow-up of 5.5 years. On the other hand, Byers et al[18] stated that 12 patients with lip carcinomas only showed a 20% 5-year survival because of delay in diagnosis or inadequate treatment. In contrast, the actuarial 3-year, 5-year, and 10-year overall survival rates in our study were 93.3%, 93.3%, and 77.8%, respectively. Among the various factors that influenced the prognosis of minor salivary gland carcinomas, TNM staging has been attributed with the most importance.[14,16,19] Because patients in this study were diagnosed with T1/2 N0M0 classification, the overall survival rate was relatively higher. Two patients who were deceased in this study had died of distant metastases. The histologic types were cystadenocarcinoma and polymorphous low-grade adenocarcinoma. Theoretically, cystadenocarcinoma and polymorphous low-grade adenocarcinoma were low-grade carcinomas, with a lower distant metastasis rate and a better

prognosis.[15,20] On the other hand, Olusanya et al[21] reported a patient with a case of lip polymorphous low-grade adenocarcinoma with suspected lung metastasis who survived during the follow-up of 2 years. In our study, the patient had polymorphous low-grade adenocarcinoma and reflected no local recurrence after brachytherapy, but then died of systemic multiple metastases within 68 months, which was considered to be an outlier. Distinctly different from squamous cell carcinomas, salivary gland carcinomas are diverse with as many as 24 different types with different growth patterns and a range of biological behavior, which bring about challenge on the management and follow-up. Incidence of spread to regional lymph nodes and distant metastases are related to the histologic types. The distant metastasis rates can be as high as 50% in histologic types like adenoid cystic carcinoma, adenocarcinoma NOS, and carcinoma ex-pleomorphic adenoma.[22] Patients with salivary gland carcinomas ought to be followed up for at least 10 years and preferably even longer because of long-term recurrence and metastasis.

The resection of minor salivary gland carcinomas of the lip and buccal mucosa often involve the lip vermilion and skin resulting in poor quality of life of the patients. As a result, brachytherapy was applied to lip squamous cell carcinomas, but few cases regarding brachytherapy for minor salivary gland carcinomas of the lip and buccal mucosa have been reported. A study performed by Guinot et al[23] examined 54 and 33 patients with T1 and T2 lip carcinomas treated with high-dose-rate brachytherapy, respectively. With median follow-up of 45 months (range, 2–143 months), the T1 and T2 actuarial local control rates at 5 and 10 years were 100% and 93.2%, respectively. The T1 and T2 actuarial disease-free survival rates at 5 and 10 years were 91.1% and 76%, respectively. Local control rates can reach 90% to 95% at 5 years for early stages of lip squamous cell carcinomas treated by low-dose-rate brachytherapy and 80% to 90% for buccal mucosa carcinomas.[24] The half-life period of ^{125}I is 59.4 days, which is classified as low-dose-rate brachytherapy, exhibiting a favorable efficacy to slowly proliferating tumors.[25,26] The application of permanent ^{125}I seed interstitial brachytherapy for recurrent or locally advanced salivary gland carcinomas showed satisfactory efficacy.[27,28] According to Zhang et al,[29] surgery that preserved the facial nerves plus postoperative ^{125}I seed interstitial brachytherapy was successful in the treatment of parotid gland carcinomas and improving the subsequent quality of life in 12 patients. Stannard et al[30] reported that 9 patients with T1 or T2 salivary gland carcinomas of the hard and/or soft palate were treated with surgery with close or involved margins accompanied by postoperative brachytherapy. No recurrence was observed during the follow-up of 32 to 158 months (median, 50 months).

The tumor and involved lymph node bed are generally treated to 60 Gy in 30 fractions in postoperative external-beam radiotherapy.[10] On the other hand, the median matched peripheral dose was 9000 cGy based on the brachytherapy treatment planning system. Permanent ^{125}I seed interstitial brachytherapy had the advantage of being highly conformal and imposed less toxicities to normal tissues. The quality of life of patients with oral cancer is high even those being treated with low-dose-rate brachytherapy by another report.[31] Moreover, brachytherapy offers better functional and cosmetic results than surgery or external-beam radiotherapy alone in certain indications.[24]

CONCLUSIONS

Postoperative ^{125}I seed interstitial brachytherapy is an alternative to radical surgery for early stages of minor salivary gland carcinomas of the lip and buccal mucosa, which offers satisfactory cosmetic and functional outcomes. Because of the small sample size, the preliminary result needs more high levels of evidence to support. In addition, late local recurrence and metastasis were possible, and, thus, a long-term follow-up is recommended.

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