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BRACHYTHERAPY

Brachytherapy 17 (2018) 244–249

Head and Neck

The role of ^{125}I interstitial brachytherapy for inoperable parotid gland carcinoma

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ABSTRACT

PURPOSE: The treatment of inoperable parotid gland carcinoma is challenging and controversial. The purpose of this paper was to present our experience in treating this malignancy using ^{125}I interstitial brachytherapy.

METHODS AND MATERIALS: Thirteen patients with advanced carcinomas of the parotid gland were included and treated with ^{125}I interstitial brachytherapy in Peking University School and Hospital of Stomatology from January 2003 to December 2015. All patients were treated with ^{125}I interstitial brachytherapy as a sole modality for the primary tumor. Furthermore, all of them were treated with neck dissection with/without adjunctive external beam radiotherapy for the neck, simultaneously. The prescription dose of interstitial brachytherapy was 140–160 Gy.

RESULTS: Median followup was 56 months (range: 8–105 months). The 2-year and 5-year local control rates were 91.7% and 58.2%, respectively. The 2-year and 5-year overall survival rates were 100% and 61%, respectively. No cervical lymph node metastasis was observed during the followup. No interstitial brachytherapy-related severe complications occurred. Facial nerve function was preserved well.

CONCLUSIONS: ^{125}I interstitial brachytherapy is a feasible and effective treatment for inoperable parotid gland carcinomas without severe complications. And neck dissection with/without external beam radiotherapy is necessary for patients with cervical metastasis or at high risk of cervical metastasis.

Keywords: Brachytherapy; Parotid gland; Carcinoma; Neck dissection; Inoperable

Introduction

Parotid gland carcinoma is relatively rare and represents about 3–6% of head and neck malignancies (1, 2). Surgery is the mainstay treatment for parotid gland carcinoma (2). Radiotherapy is commonly recommended as an adjunctive therapy for patients at high risk of local recurrence (3, 4).

Although external beam radiotherapy, neutron radiation, and chemotherapy have been reported as a usage for parotid gland carcinoma, optimal modalities for inoperable carcinomas of parotid gland (medically or surgically inoperable) have not yet been fully realized. Radiotherapy with dose equivalent to at least 66 Gy in 33 fractions for the primary tumor and involved nodes is recommended for patients with inoperable carcinomas of parotid gland (1, 5). Nevertheless, the clinical results are not satisfactory. For patients treated with radiotherapy alone, the locoregional control at 5 years was 4–50% (1, 5, 6). As for patients with high level of T classification or histologic grade, the prognosis was even worse.

As an alternative, ^{125}I interstitial brachytherapy had the advantage of being highly conformal, which resulted in a high local control (LC) in salivary gland carcinomas (7). In this study, ^{125}I interstitial brachytherapy for inoperable parotid carcinomas was reported. Furthermore, neck dissection with/without external beam radiotherapy for the neck was performed for these cases at high risk of cervical metastasis.

Received 1 June 2017; received in revised form 31 August 2017; accepted 27 September 2017.

Financial disclosure: This study was supported by the New Technology New Therapeutics Project of Peking University School and Hospital of Stomatology and partially supported by the National Natural Science Foundation of China (81502652).

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1538-4721/$ - see front matter
https://doi.org/10.1016/j.brachy.2017.09.017

Methods and materials

Patients' characteristics

In this study, 13 patients with advanced carcinomas of the parotid gland were treated with ^{125}I interstitial brachytherapy in our hospital from January 2003 to December 2015. Eight of these patients were female and five were male, ranging from 8 to 82 years old (median, 54 years) by the time of diagnosis.

Fine needle aspiration biopsy and/or incisional biopsy were performed for histologic diagnosis. The histologic types of the 13 patients were shown as follows: mucoepidermoid carcinoma (2/13, one intermediate grade, one high grade), oncocytic carcinoma (2/13), adenoid cystic carcinoma (2/13), epithelial-myoepithelial carcinoma (2/13), myoepithelial carcinoma (2/13), acinic cell carcinoma (1/13), salivary duct carcinoma (1/13), and adenocarcinoma not otherwise specified (1/13). According to the staging criteria of the Union for International Cancer Control seventh edition, the patients were staged. Distant metastasis at the very onset was observed in 2 patients with myoepithelial carcinoma and adenoid cystic carcinoma, respectively. Clinically positive cervical nodes were observed in 4 patients. The baseline characteristics of all patients were shown in Table 1.

Treatment strategy

The inclusion criteria of patients with locally advanced parotid gland carcinomas were as follows: tumors were inoperable; patients refused surgery which may result in facial palsy; and patients suffered from other diseases as surgery contraindication. All patients were treated with ^{125}I interstitial brachytherapy as a sole modality for the primary tumor in the parotid gland region. Furthermore, all of them were treated with neck dissection simultaneously.

Table 1
Characteristics of patients

Age (y): mean (range)	53 (8–82)
Gender (no. of patients)	
Male	5
Female	8
Tumor site (no. of patients)	
Skull base involved	4
Skull base not involved	9
Facial nerve function	
Facial nerve palsy	2
Facial nerve without palsy	11
Tumor size (no. of patients)	
≤6 cm	8
>6 cm	5
With distant metastasis at the very onset (no. of patients)	2
Primary tumor (no. of patients)	11
Recurrence tumor (no. of patients)	2
Prior treatment of recurrence tumors (no. of patients)	
Surgery	1
Surgery and radiotherapy	1
Grade (no. of patients)	
Low grade	4
High grade	9

The incision was designed as a large arc to keep away from the radiation target area, which may reduce the influence of radiation on the incision healing, especially for those patients who were treated with interstitial brachytherapy in the parotid region and external beam radiotherapy in the neck.

Seven patients with cervical metastasis in the pathologic examination were received external beam radiotherapy for the neck area.

Interstitial brachytherapy in the parotid gland region

The brachytherapy treatment planning system (Beijing Atom and High Technique Industries Inc., Beijing, China) was used to create preplans based on patients' CT images. The planning target volume was outlined to cover the tumor with a 0.5-cm margin. The planned dose (or matched peripheral dose) of the ^{125}I interstitial brachytherapy was 140–160 Gy, and the planned dose was 130 Gy for patients who received radiotherapy before. ^{125}I implantation was performed with individual template and/or CT guidance according to the preplan. The individual template made through rapid prototyping technique contained all the information of preplan including needle pathway and face features simultaneously. Hollow interstitial needles were inserted into the target area from different directions to avoid bone, major blood vessels, and vital organs, and ^{125}I radioactive seeds were implanted permanently with individual template and/or CT guidance. Quality verification was performed for all patients. The activity of ^{125}I (model 6711, China Institute of Atomic Energy; half-life 59.4 days) was ranging from 18.5 to 33.3 MBq per seed. The actuarial D_{90} (the dose delivered to 90% of the target volume) was 144.5–192.6 Gy (median 153.6 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 procedure of ^{125}I interstitial brachytherapy was described in detail in Fig. 1.

Seven patients with positive lymph nodes in the pathologic examination received adjunctive external beam radiotherapy for the neck area after neck dissection. The target area was away from the parotid tumor area treated with brachytherapy, which could avoid severe toxicities. The dose of external beam radiotherapy was 56–66 Gy (conventional fractionation; 2 Gy/d).

The patient with myoepithelial carcinoma observed lung distant metastases at the very onset received radiation to the lung lesion. The patient with multiple lung metastases of adenoid cystic carcinoma did not received any treatment to the lung lesions.

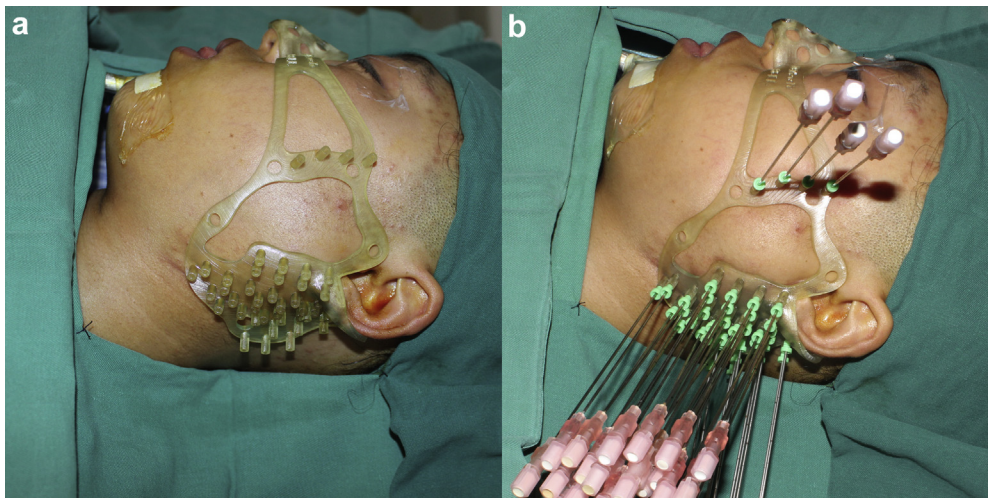

Fig. 1. The individual template made through rapid prototyping technique contained all the information of preplan including needle pathway and face features simultaneously (a). Hollow interstitial needles were inserted into the target area from different directions to avoid bone, major blood vessels, and vital organs, and ^{125}I radioactive seeds were implanted permanently according to the plan with individual template and CT guidance (b).

Patients were typically followed up at 2-month intervals for the first year and then at 4-month intervals thereafter. The followup consisted of routine physical examinations and appropriate imaging examination of the primary site and neck; CT or positron emission tomography/computed tomography (PET/CT) scans were performed if necessary (Fig. 2). Facial nerve function of patients was evaluated by the House–Brackman (H–B) grading system. Toxicities were evaluated according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer grading system.

Statistical analysis

The statistical analysis was carried out by SPSS 13.0 for windows (SPSS Inc, Chicago, IL). The likelihood estimates for LC and overall survival (OS) were calculated by the Kaplan–Meier method, and outcomes between groups were compared by the log-rank test. The p-values < 0.05 were considered statistically significant. The tumor size, histologic grade, facial function, cervical lymph node metastasis, and distant metastasis were considered to be risk factors for LC and OS.

Results

Overall survival

The followup time ranged from 8 to 105 months (median 56 months). Four patients died during the followup, 3 of which died of distant metastasis, and 1 died of local brain involvement. The 2-year and 5-year OS rates were 100% and 61%, respectively (Fig. 3a). Histologic grade, lymph node involvement, or facial nerve involvement did not significantly influence the OS rates. The 5-year OS for patients with low-grade tumors was 100%, and it was 41.7% for high-grade tumors. The 5-year OS for patients without lymph node involvement was 66.7%, and it was 60% for patients with lymph node involvement. However, low-grade tumor and no lymph node involvement had a trend toward better OS without significant difference ($p = 0.49$ and 0.326, respectively). Tumor size and distant metastasis showed a significant influence on the OS rate ($p < 0.05$). Tumors smaller than 6 cm had a 5-year OS rate of 75%, and it was 33.3% for patients with tumors larger than 6 cm ($p = 0.028$).

Local control

Four patients relapsed during the followup, 3 of them suffered carcinomas in high-grade (1 salivary duct carcinoma, 1 mucoepidermoid carcinoma, and 1 adenocarcinoma not otherwise specified). The other was adenoid cystic carcinoma with skull base involvement. The LC rates were 91.7% at 2 years and 58.2% at 5 years (Fig. 3b). Although it was not significant, carcinomas in low grade had a trend toward better LC with a 5-year LC rate of 100%, compared with 66.7% for carcinomas in high grade ($p = 0.574$). In general, cervical lymph node involvement, distant metastasis, or facial nerve involvement did not significantly influence the LC rate ($p > 0.05$). However, the larger tumor size was predictive of decreased survival ($p < 0.05$). Tumors smaller than 6 cm had a 5-year LC rate of 83.3%, and it was 26.7% for patients with tumors larger than 6 cm ($p = 0.013$).

Cervical lymph node and distant metastasis

Positive cervical lymph nodes were found in 4 patients in the pathologic examination. Moreover, 3 patients who had elective neck dissections showed occult neck metastasis. During the followup, distant metastasis occurred in 3 patients at 20, 40, and 44 months, respectively. Two of them were lung

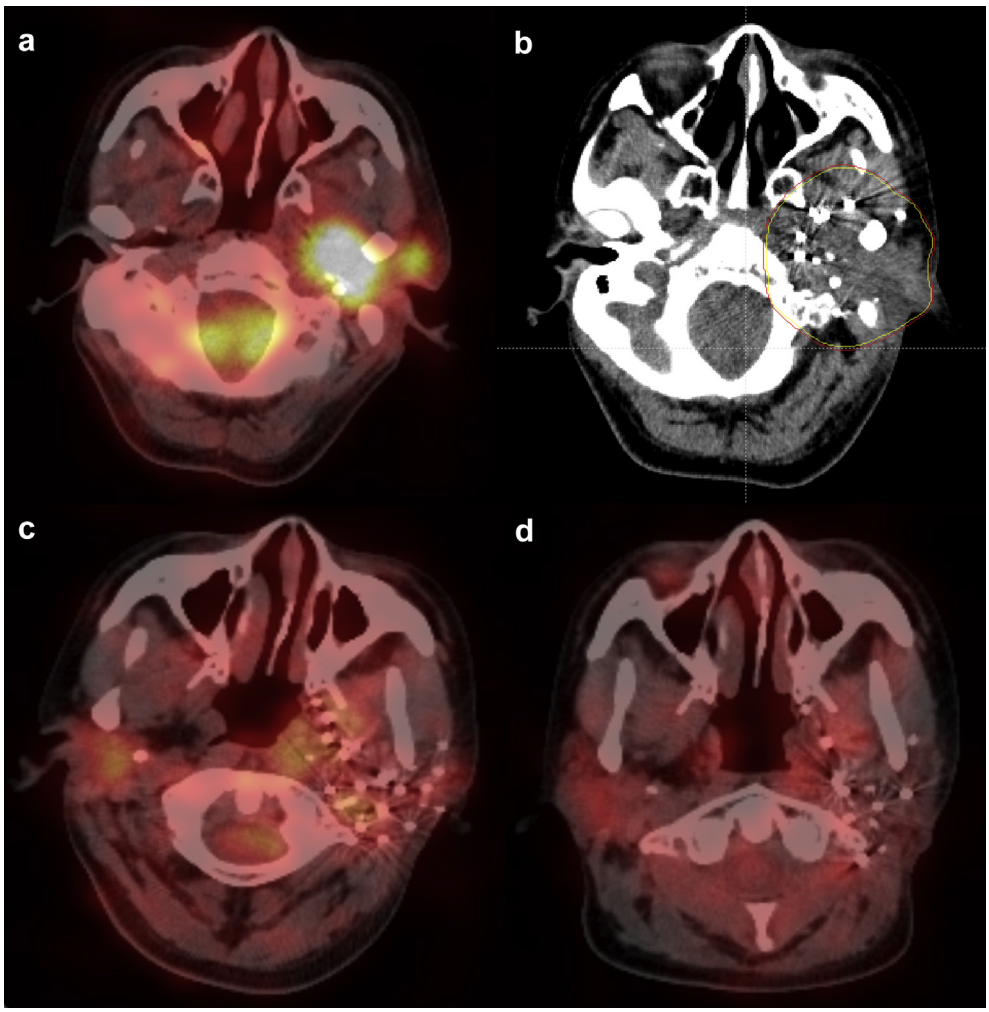

Fig. 2. Preoperative PET/CT showed an unresectable parotid gland carcinoma (a). Quality verification using postoperative CT images in the brachytherapy treatment planning system showed that D_{90} curve cover the tumor area (b). PET/CT showed that the area of hypermetabolism regressed and inflammatory changes occurred around the area 6 months after brachytherapy (c). PET/CT showed no sign of recurrence 2 years after brachytherapy (d). PET/CT = positron emission tomography/computed tomography.

metastasis. The other was multiple metastasis. Including the 2 patients with distant metastasis at the very onset, 3 patients died of distant metastasis during the followup.

Toxicities and complications

During the followup, trismus in Grade 2 was observed in 1 patient. Acute dermatitis (Grades 1–2) was observed in all the 13 patients. In another word, all the 13 patients experienced slight skin pigmentation change, whereas no late toxicities, including oral cavity mucositis, xerostomia, cataracts, and osteoradionecrosis, were observed. No necrosis and ulceration of skin developed. No facial nerve function damage was observed.

Discussion

Surgery is the mainstay treatment for resectable parotid gland carcinoma (8). And radiotherapy was mainly recommended as a postoperative adjuvant treatment. Indications of radiotherapy include T3–4 primary tumors, incomplete or close margins, high-grade tumors, recurrent disease, perineural invasion, and nodal involvement (1, 2). Combined with radiotherapy, OS rate of resectable parotid gland carcinomas was about 70% (8, 9). The LC and OS were influenced by the stage of tumors. High-stage parotid carcinomas usually had low LC and OS, and the mean 5-year survival rate was only 35% (10). Renehan *et al.* (9) reported 103 patients with parotid gland carcinomas treated by surgery with/without radiotherapy, and the 10-year survival rates for T1, T2, and T3–4 were 96%, 61%, and 17%, respectively. Tumor size (T classification) is the most significant risk factor for survival and LC of parotid gland carcinomas (1, 8, 10, 11). High T classification normally leads to poor prognosis. In this study, tumors were in T3 or T4 classification, and we still achieved good results. Moreover, histologic grade also showed an influence on the treatment results in this study.

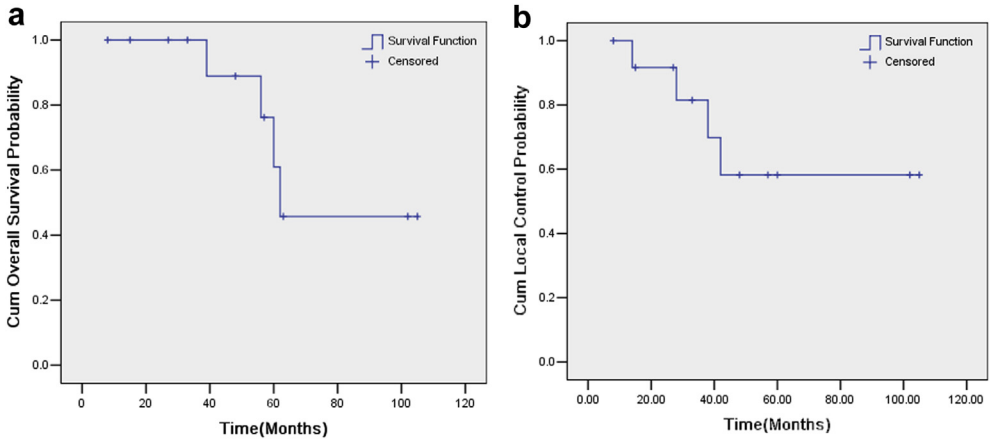

Fig. 3. Kaplan–Meier curves for overall survival (a) and local control (b).

Tumor in low grade showed a trend toward better results, which was consistent with other studies (9).

Fewer studies have considered the treatment for patients with inoperable parotid gland carcinomas. Most patients in this condition were in high T stage. Radiotherapy with a high dose of greater than 66 Gy is recommended in literatures (5, 12). However, the prognosis is poor (12–14). Matthiesen *et al.* (13) reported that 17 patients with parotid gland carcinoma were treated with radiotherapy and all the 3 patients in T4 classification in the study failed. Mendenhall *et al.* (15) treated salivary gland tumors in 64 patients using definitive RT, and only 20% of patients with Stage IV disease were cured with RT alone. Chen *et al.* (12) reported 45 patients with salivary gland carcinomas were treated with definitive radiation and the Stage T3–4 disease predicted decreased LC. The 10-year LC rate for patients with T4 tumors was just 30%. According to Bhide *et al.* (1), 11 patients were treated with radiotherapy alone and the 2-year and 5-year LC rates were 21%. Moreover, the disease-free survival was 29% at both 2 and 5 years, and the median OS was just 0.6 year.

Interstitial brachytherapy has the advantages of minimal invasive and delivering higher radiation dose to the target area. The low growth fraction and long doubling time of salivary gland tumors make them sensitive to ^{125}I interstitial brachytherapy because of long half-life of ^{125}I (59.4 days). Glaser *et al.* (7) reported 2 and 5-year disease-free survival rates for slowly proliferating salivary gland tumors in the head and neck region of 89% and 53%, respectively, following postoperative ^{125}I implants, which found that ^{125}I implants did not result in any additional complications. Zheng *et al.* (16) had 5-year LC and OS rates of 53.6% and 66.7%, respectively, in 15 patients with recurrent previously irradiated parotid gland carcinomas by postoperative ^{125}I interstitial brachytherapy without severe complications. In our prior study, we treated 38 patients with recurrent and/or locally advanced adenoid cystic carcinoma of head and neck with ^{125}I interstitial brachytherapy alone, and the 5-year LC and OS rate were 59% and 65%, respectively. In this study, the 5-year LC and OS were 58.2% and 61%, respectively (17). Few comparable reports are available in the literature. LC in head and neck tumors has a significant influence on patient's survival and quality of life (6, 18). In this study, the LC achieved was increased without increasing complications. Especially, facial nerve function was preserved effectively. Thus, interstitial brachytherapy could be an alternative modality to conventional treatment according to the study.

Because of the low incidence of parotid gland carcinomas, some issues about the treatment are still controversial, such as the necessity of neck dissection and the extent of a neck dissection. In this study, 7/13 patients were found cervical metastasis, and 3 in the 7 patients who had elective neck dissections showed occult neck metastasis. Based on these results, neck dissection would be recommended for advanced parotid gland carcinomas. And these results we observed in this study were supported by other studies. In literatures, tumors in high stage, high grade are risk factors of cervical metastasis, which indicate the necessity of neck dissection (19, 20). About 13–39% patients in advanced parotid carcinomas were found with cervical metastasis (8, 19, 21–23). Furthermore, parotid gland carcinomas have an occult metastasis rate of 12–45% (5, 23). Klussmann *et al.* (8) reported 142 patients treated with primary resectable parotid gland carcinoma, among which 21.8% patients had cervical lymph node metastasis and 17.6% patients presented with occult metastasis. Lima *et al.* (23) found an occult metastasis rate of 26% in 19 patients with parotid gland carcinomas. Lymph nodes metastasis can be found in all neck levels, and skip metastasis had been described (8). In brief, radical-modified neck dissection is recommended as a surgical modality for parotid carcinomas, especially for tumors in high stage and grade (8, 24). Moreover, postoperative radiotherapy significantly improved regional control in the pN + cases (5).

Conclusions

Preliminary results of ^{125}I interstitial brachytherapy for inoperable parotid gland carcinoma were presented in this study. ^{125}I interstitial brachytherapy offered satisfactory LC with no severe complications and toxicities. Neck dissection with/without adjunctive external beam radiotherapy was necessary for patients with cervical metastasis or at high risk of cervical metastasis. The combined treatment modality has yielded promising results for inoperable parotid gland carcinoma, which, nevertheless, needs more high levels of evidence to support.

Acknowledgments

The authors acknowledge Dan Zhao (Peking University School and Hospital of Stomatology) for their assistance in the preparation of this article.

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