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BRACHYTHERAPY

Brachytherapy 20 (2021) 383–392

Head and Neck

# Surgery combined with iodine-125 interstitial brachytherapy for treatment of parotid adenoid cystic carcinoma: A single-institution experience

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**ABSTRACT**

**PURPOSE:** The purpose of this study was to analyze the effectiveness and safety of the combination of surgery plus postoperative iodine-125 interstitial brachytherapy for treatment of adenoid cystic carcinoma (ACC) of the parotid.

**METHODS AND MATERIALS:** This study included a retrospective analysis of the data of patients who underwent postoperative iodine-125 interstitial brachytherapy for histology-confirmed ACC of the parotid between January 2002 and November 2018 in Peking University Hospital of Stomatology. Acute and long-term radiation-related toxicities were assessed by the criteria of the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer. Multivariate analysis was used to identify the factors affecting overall survival, disease-free survival (DFS), and distant metastasis–free survival (DMFS).

**RESULTS:** A total of 86 patients (53 women; median age 50 years, SD = 13.1) were included. Median followup was for 45.5 months. About half the patients (44/86, 51.3%) had clinical stage IV disease. Local recurrence occurred in 11 of 86 (12.8%) patients. No patient had nodal metastases in the followup period. The five- and 10-year DFS rates were 74.8% and 66.6%, respectively. The mean DMFS was 60.6 months. On multivariate analysis, preoperative facial palsy, type of surgery, perineural spread (PNS), and distant metastases were independent prognostic factors for DFS; preoperative facial palsy, nodal metastases, and PNS were independent prognostic factors for overall survival; and preoperative facial palsy, type of surgery, PNS, and pathological type were independent prognostic factor for DMFS.

**CONCLUSIONS:** The combination of surgery and iodine-125 interstitial brachytherapy appears to be an effective and safe treatment for primary ACC of the parotid. 

*Keywords:* Adenoid cystic carcinoma; Parotidectomy; Iodine-125 interstitial brachytherapy; Distant metastases; Multivariate analyses

## Introduction

Adenoid cystic carcinoma (ACC) of the salivary gland is a malignant tumor with higher risk of local recurrence (LR) and distant metastases than other pathological types. Perineural spread (PNS) is common, and consequent invasion of the skull base (1,2) may result in nerve paralysis and intractable pain; these patients have very high risk of LR after surgery and bad prognosis (3,4). Adjuvant radiotherapy after surgery can improve local control rate drastically, but extent of surgery, volumetric modulation, and radiation fields are important determinants of prognosis (5). Iodine-125 interstitial brachytherapy, an important modality with ionizing radiation, has the advantage of being highly conformal and can therefore improve local control in parotid gland carcinoma (6). Postoperative interstitial brachytherapy has been previously shown to be effective for management of parotid malignant carcinoma (7).

Received 11 January 2020; received in revised form 31 July 2020; accepted 30 September 2020.

This article was proofread by a native English professional with science background at Elixigen Corporation.

Disclosures: The authors declare that there are no conflicts of interest.

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1538-4721/$ - see front matter 
https://doi.org/10.1016/j.brachy.2020.09.017

The aim of this retrospective study was to review all cases of parotid ACC treated with surgery plus postoperative brachytherapy at our center and analyze the effectiveness and safety of this treatment approach and also to identify the factors influencing outcomes.

## Methods and materials

### *Patients*

A total of 86 consecutive patients with parotid ACC who were treated with surgery plus iodine-125 brachytherapy at the Peking University Hospital of Stomatology between January 2002 and November 2018 were included in this retrospective study. The characteristics of the tumors (including American Joint Committee on Cancer TNM stage (8)), histopathology results, treatment details (type of tumor surgery, whether neck dissection performed, and parameters of brachytherapy), and followup findings were analyzed.

The preoperative evaluation consisted of history taking, physical examination, and imaging examination. MRI is preferred because of its superior soft tissue difference (9). Contrast-enhanced CT (CECT, Siemens, AG, Forchheim, Germany; at 120 kV and 150 mA, with a slice thickness of 2 mm) scan was performed. The images were reviewed by an experienced radiologist, and the following imaging features were noted: (*1*) size of the tumor, (*2*) distinct or ill-defined demarcation from normal parotid tissue, (*3*) presence of enlarged (>1 cm) lymph nodes, (*4*) the relation of the tumor to the facial nerve (FN) (based on the location of the retromandibular vein (10)).

Patients were considered to have PNS if (*1*) the primary tumor had presented with ipsilateral facial palsy, (*2*) imaging showed the tumor surrounding the retromandibular region (FN pathway) or located adjacent to the stylomastoid foramen (FN trunk), and (*3*) intraoperative and histopathological examination showed close association of the tumor with the FN.

### *Surgery*

Patients were classified into four groups in accordance with the surgery performed:

- Group I patients underwent only local excision of tumor; the tumor was not related to the FN in these patients.
- Group II patients received FN dissection and complete excision of tumor; the tumor was attached to the FN in these patients.
- Group III patients received partial excision of the tumor, with preservation of the FN; the tumor showed an infiltrative pattern in these patients.
- Group IV patients received extended excision of the tumor along with removal of the trunk or major branches of the FN; the tumor showed infiltrative pattern, and the nerve (the trunk or the brunches) passed through the tumor in these patients.

Neck dissection was performed for patients with clinically positive nodes.

### *Iodine-125 seed implantation*

CECT was performed 1 month after surgery. The CECT data set was imported into a brachytherapy treatment planning system (BTPS; Beijing Atom and High Technique Industries, Beijing, China) to obtain the treatment plan. The iodine-125 seeds (model 6711; Jaco Pharmaceuticals Co. Ltd., Zhejiang, China) had activity of 18.5–29.6 MBq and half-life of 59.41 days. The prophylactic irradiation dose was 12,000 cGy in all cases. The clinical target volume (CTV) was delineated in accordance with the preoperative and postoperative imaging and the intraoperative and histopathological findings. For tumors which did not invade the FN, the organs at risk included the lacrimal gland, the optic nerve, the skull base, the middle ear, and the superficial skin. While for tumors which manifested as different extent of FN invasion, we delineated the course of the FN and the skull base area, the CTV included pharyngeal space, temporal fossa, and skin scar if the superficial skin was invaded, and the organs at risk also included the former cranial fossa slope and peripheral foramen.

Seed implantation was performed under general anesthesia and with the guidance of individualized three-dimensional printed templates. The templates—with 0.3-cm thickness to ensure adequate strength—were constructed from light-cured resin using the rapid forming machine Eden250 (Objet Company, Israel) and were individualized in accordance with the needle path orientation and depth in the BTPS (11,12). Forty-8 h after brachytherapy, plain CT was performed to check the number, position, and spatial distribution of the implanted seeds (also known as verification scan), and then the dose–volume histogram was generated.

This study was approved by Peking University Hospital of Stomatology Institutional Review Board.

### *Followup visits and evaluation*

After seed implantation, patients were evaluated every 2 months for the first 6 months, every 3 months until the end of the third year, and then every 6 months until the end of the fifth year (13). Local control condition, neck nodal metastases, distant metastases, and radiotherapy-related toxicities were checked at each followup. Head and neck CECT imaging was used to evaluate local control and neck condition at each followup, and chest radiograph or chest CT scan was used for inspecting distant metastases every half year; pathological examination (either at local or distant sites) was performed when necessary. Tumor recurrence was classified as local, regional, or distant. Local failure was defined as tumor progression or LR; regional

failure was defined as newly discovered ipsilateral metastatic lymph nodes; and distant metastases (to the lung, liver, bone, brain, and so on) were categorized on the basis of periodic positron emission tomography or computed tomography examination. Acute and long-term radiation-related toxicities were assessed by the criteria of the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (14).

### *Statistical analysis*

Overall survival (OS), disease-free survival (DFS), LR, regional recurrence, and distant metastasis–free survival (DMFS) were calculated from the date of surgery to the date of the events of interest. Categorical data were compared using the Pearson $\chi^2$ test. Survival curves were plotted using the Kaplan–Meier method, and subgroups were compared using the log-rank test. Univariate analysis was used to identify the factors associated with prognosis, and the multivariate logistic proportional hazards regression model was used to identify the factors with independent prognostic significance. Hazard ratios (HRs) and 95% confidence intervals were calculated. Two-sided $p \leq 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 22.0 (IBM Corp., Armonk, NY).

## Results

### *Patients' characteristics*

A total of 86 patients (median age, 50 years) were included in this study. The mean and median followup was for 56 months and 45.5 months, respectively. The most common presenting symptoms were palpable mass with pain (33/86, 38.4%) and ipsilateral facial palsy (10/86, 11.6%). About half of the patients (44/86, 51.3%) had clinical stage IV disease at presentation. Table 1 presents the demographic and tumor characteristics of the patients.

The histological sections were re-examined. In 45 cases, the specimen quality was inadequate for accurate diagnosis. In the remaining, four traditional types were identified: 19 of 86 (22.1%) cribriform type, 11 of 86 (12.8%) tubular type, 10 (11.6%) solid type, and 1 of 86 (1.2%) high-grade transformation (HGT). A total of 64 of 86 showed PNS status, with 32 of 86 (37.2%) patients showing pathological evidence of perineural invasion (PNI); among these, 3 patients had peripheral blood vessel invasion and 16 patients had intraneural invasion. Ten of 86 (11.6%) patients had unilateral facial palsy and 43 of 86 (50.0%) patients had tumors located close to the retromandibular region or the stylomastoid foramen radioscopically.

Table 1
Characteristics of the patients with adenoid cystic carcinoma

| Characteristics | Values |
|---|---|
| Patients (n) | 86 |
| Age, years, median ± SD | 50 ± 13.1 |
| Sex, n (%) | |
| Male | 33 (38.4%) |
| Female | 53 (61.6%) |
| Chief complaint, n (%) | |
| Palpable mass | |
| Painful | 33 (38.4%) |
| Painless | 53 (61.6%) |
| Facial palsy | |
| Yes | 10 (11.6%) |
| No | 76 (88.4%) |
| Tumor stage, n (%) | |
| T1 | 10 (11.6%) |
| T2 | 22 (25.6%) |
| T3 | 10 (11.6%) |
| T4 | 44 (51.2%) |
| Nodal stage, n (%) | |
| N0 | 79 (91.9%) |
| N1 | 5 (5.81%) |
| N2 | 2 (2.30%) |
| Followup period, months, median ± SD | 45.5 ± 14.2 |
| Followup period, range | 12–148 |
| Surgical margin, n (%) | |
| Negative | 21 (24.4%) |
| Close | 33 (38.4%) |
| Positive | 32 (37.2%) |
| Histopathological type, n (%) | |
| Cribriform | 19 (22.1%) |
| Solid | 10 (11.6%) |
| Tubular | 11 (12.8%) |
| HGT | 1 (1.16%) |
| Uncategorized | 45 (52.3%) |
| Clinical tumor volume | |
| Total | 67 (77.9%) |
| Partial | 19 (22.1%) |

HGT = high-grade transformation.

### *Surgery type and brachytherapy*

Group I patients (22/86, 25.6%) received local excision of the mass with negative margin. Group II patients (23/86, 26.7%) received local excision of the tumor with clinically close margins after dissection of the nerve from the tumor. Group III patients (8/86, 9.3%) received partial tumor excision with positive margins. Group IV patients (33/86, 38.4%) received extensive tumor resection with close margins. The patients were divided into three groups in accordance with the intraoperative condition and margin status (positive margin, close margin, negative margin). Figures 1a and 1b presents the Kaplan–Meier survival analysis of OS and DFS on different surgical modalities. Preoperative clinical examination and imaging revealed ipsilateral nodal metastases in 7 patients; they received elective neck dissection, and metastasis to level I–III nodes was confirmed pathologically.

The CTV was the complete parotid area for 67 of 86 (77.9%) patients and the primary tumor for the remaining 19 of 86 (22.1%) patients. The CTV was comparable between different margin status groups ($p = 0.088$). Figures 2a and 2b shows the Kaplan–Meier survival

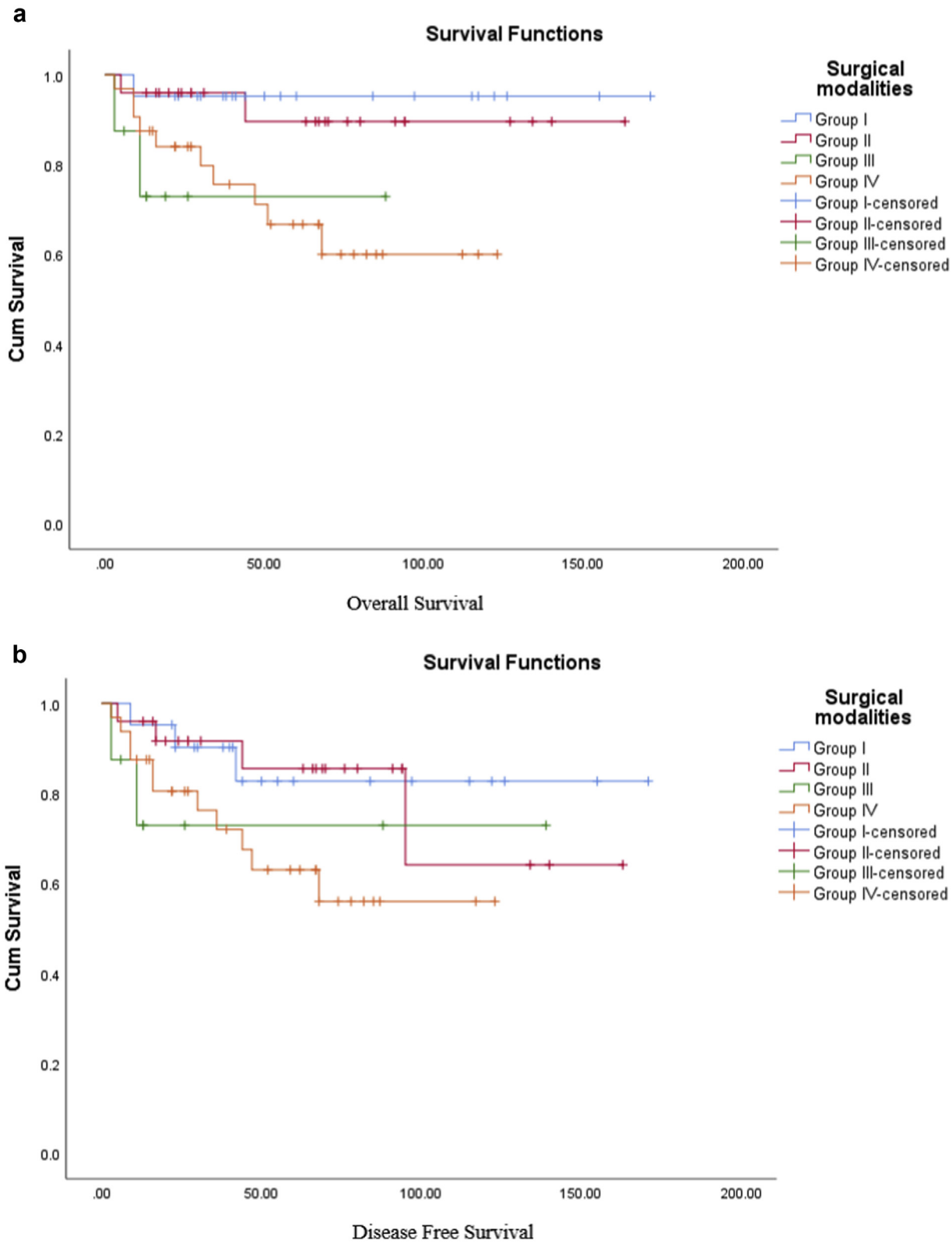


Fig. 1. Kaplan–Meier survival analysis of overall survival (a) and disease-free survival (b) on different surgical modalities.

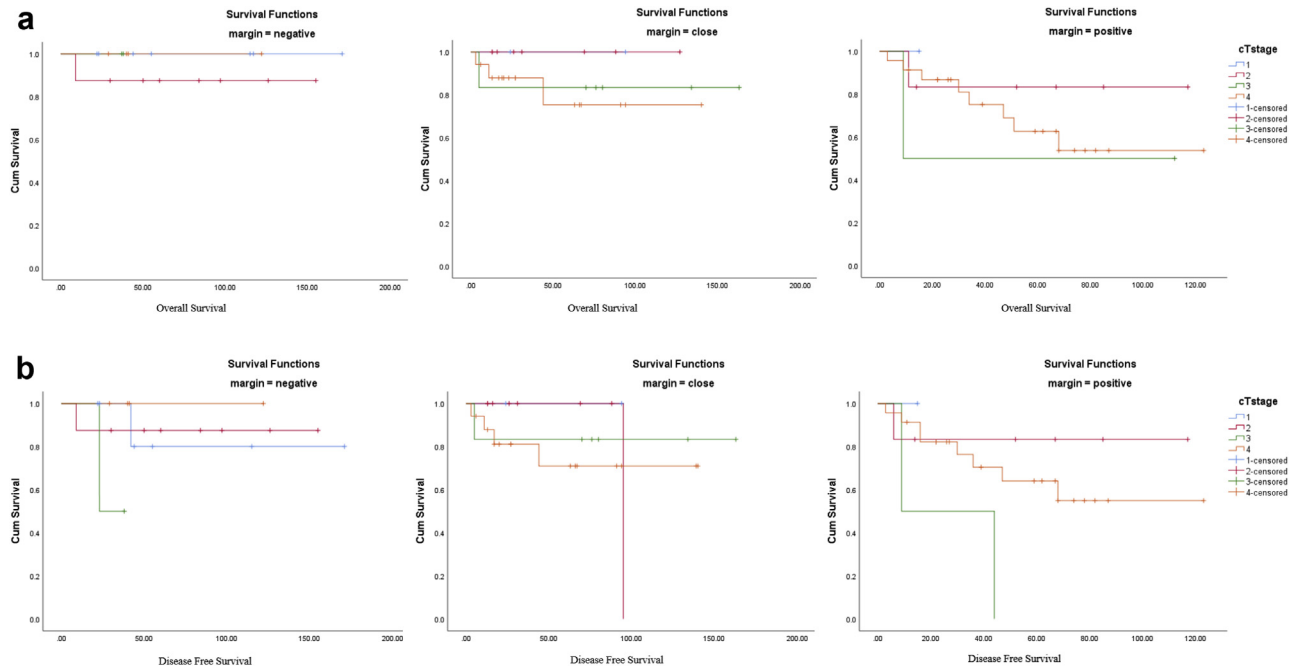


Fig. 2. Kaplan–Meier survival curves for overall survival (a) and disease-free survival (b) in different subgroups of margin status (negative, close, positive) and surgery type.

analysis of OS and DFS on prognostic factors including different margin status (negative, close, positive) and surgical modalities.

### *Locoregional recurrence*

LR was observed in 11 of 86 (12.8%) patients during followup. The 5-year and 10-year DFS rates were 74.8% and 66.6%, respectively. Table 2 shows the pattern of recurrence. The sites of recurrence were mainly around the external auditory canal, the skull base, and the parotid area (Figs. 3a-3f). Three patients developed blurred vision and disorder of ocular movement, which were probably because of intracranial metastases as needle biopsies did not confirm either orbital muscle infiltration or periosteal infiltration of the maxilla. Progressive trismus was observed in 3 patients; open biopsy confirmed LR in the pterygomandibular region in 2 patients and a second primary carcinoma of the mandibular ramus in the other patient. In the patients with LRs, six (6/11, 54.5%) were Group IV, who died of disease, whereas the other five were well controlled. Four patients (three recurrent sites located in the intraparotid and one located in the temporal bone) received local excision of the mass combined with brachytherapy. One patient (recurrent site located intraparotid) who had biopsy, which was proven to be squamous cell carcinoma, received extensive surgery and postoperative external beam radiotherapy. The 1- and 2-year actuarial LR control rates were 81.8% and 45.4%, respectively.

The DFS ranged from 5 months to 95 months. The mean recurrence-free survival was significantly lower for patients with LR than for those without LR (32.8 months vs. 57.84 months; $p = 0.001$). No patient had new-onset neck nodal metastases during followup, and none of the 7 patients who received neck dissection had neck recurrence.

On univariate analyses, the factors significantly associated with DFS included regional recurrence (HR = 13.7; $p = 0.001$) and distant metastases (HR = 8.1; $p = 0.001$). Sex ($p = 0.605$), histopathological type ($p = 0.162$), PNI ($p = 0.545$), PNS ($p = 0.547$), clinical tumor stage ($p = 0.746$), margin status ($p = 0.145$), preoperative facial palsy ($p = 0.293$), and preoperative distant metastases ($p = 0.236$) were not associated with DFS.

Table 2
Characteristics of metastases

| Metastases | Total | Site | n | Median survival (months) |
|---|---|---|---|---|
| Preoperative distant metastases | 1 | Pulmonary | 1 | 23 (survived with tumor) |
| Distant metastases | 12 | Pulmonary | 7 | 74 (2 DOD, 5 survived with tumor) |
| | | Brain | 1 | 34 (DOD) |
| | | Bone | 2 | 10 (DOD) |
| | | Hepatic | 1 | 30 (DOD) |
| | | Multiorgan | 1 | 23 (DOD) |

DOD = died of disease.

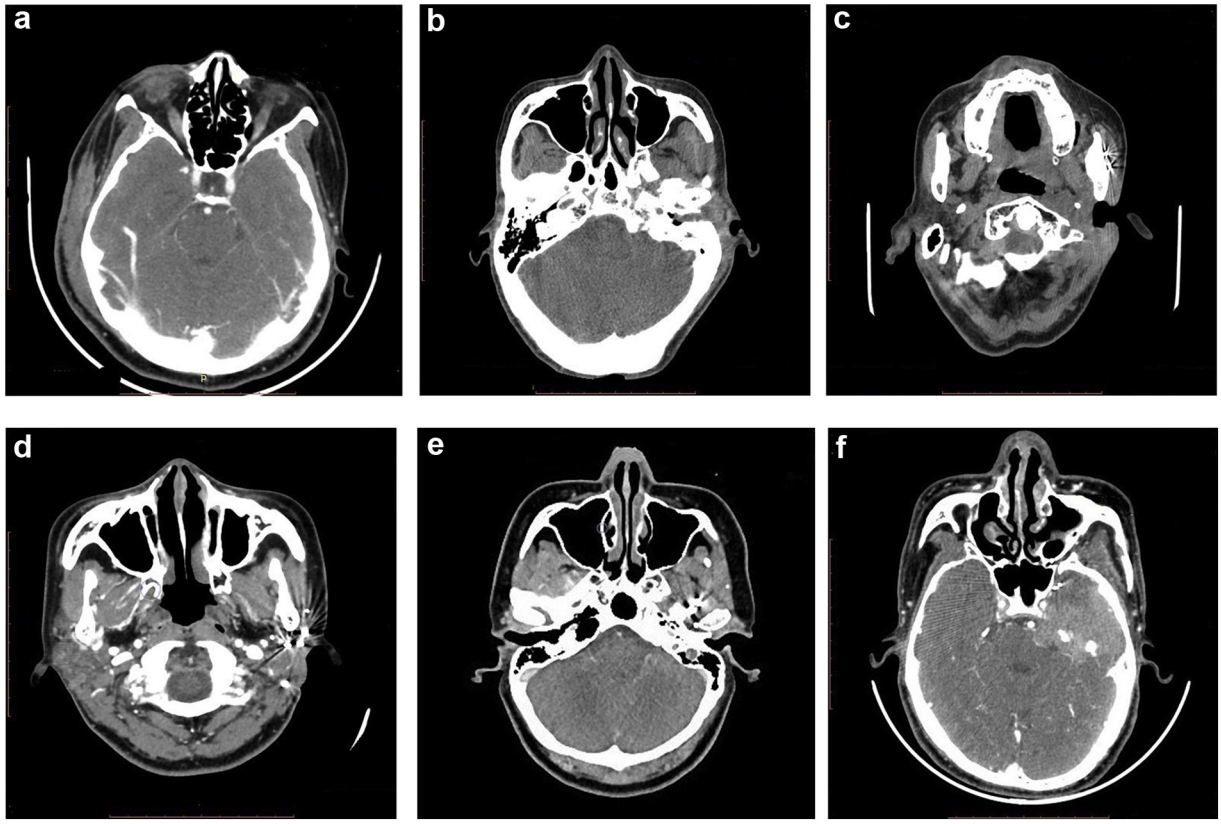


Fig. 3. Sites of recurrence of parotid adenoid cystic carcinoma. (a) temporalis muscle infiltrated by tumor; (b) external auditory canal recurrence manifesting as a palpable mass; (c) recurrence in the mandibular ramus, accompanying severe radiological toxicity; (d) recurrent tumor in the parotid gland; (e) skull base invasion; (f) intracranial involvement.

*Distant metastases*

A total of 13 patients were diagnosed with distant metastasis; among them, nine had pulmonary metastasis. Although 1 patient had pulmonary metastasis preoperatively, the other eight developed metastasis during follow-up. Tables 2 and 3 describe the location and pattern of distant metastasis. The mean DMFS was 50.1 months (SD = 12.3). One patient had distant multiorgan metastases without locoregional recurrence, 7 patients died, whereas other six survived with stable disease. All 13 patients with distant metastases had PNS. On univariate analysis, pathological type was significantly associated with DMFS (HR = 14.0, $p = 0.002$), and pulmonary metastasis (vs. nonpulmonary metastases) was significantly associated with OS (HR = 24; $p = 0.023$). Clinical tumor stage (HR = 6.25, $p = 0.026$), Sex ($p = 0.524$), PNI ($p = 0.350$), margin status ($p = 0.105$), preoperative facial palsy ($p = 0.305$), and neck nodal metastases ($p = 0.251$) were not associated with DMFS.

*Overall survival and local control*

The 5-year and 10-year OS rates were 80.1% and 77.4%, respectively, see in Table 4. Death was due to locoregional recurrence or distant metastasis in 15 of 86 (17.4%) patients. Age >60 years at diagnosis was associated with OS ($p = 0.012$) but not with DFS ($p = 0.167$) or DMFS ($p = 0.338$). Margin status was significantly associated with 5-year OS ($p = 0.046$), but not with DFS ($p = 0.145$). Multivariate analyses showed preoperative facial palsy (HR = 25; $p = 0.001$), clinical tumor stage (HR = 3.4, $p = 0.046$), and distant metastases (HR = 4.6; $p = 0.017$) to be independent prognostic factors for OS. Sex ($p = 0.190$), histopathological type ($p = 0.309$), PNI ($p = 0.353$), PNS ($p = 0.065$), neck nodal metastases ($p = 0.418$), and preoperative distant metastases were not associated with OS (Table 5). Group IV patients had worse OS and DFS than the other groups, with mean OS of only 22 months. Intergroup analyses showed clinical advanced stage ($p = 0.003$) and PNS ($p = 0.001$) to be indicators of worse prognosis.

*Multivariate analyses*

In multivariate logistic regression analysis, preoperative facial palsy, type of surgery, PNS, and distant metastasis were independent prognostic factors for DFS (Table 5); preoperative facial palsy, nodal metastasis, and PNS were independent prognostic factors for OS; and preoperative facial palsy, type of surgery, PNS, and pathological type were independent prognostic factors for DMFS.

Table 3
Characteristics of recurrences

| Recurrences | Total | 11 |
|---|---|---|
| Sex | Male | 5 |
| | Female | 6 |
| cT stage | T2 | 3 |
| | T3 | 3 |
| | T4 | 5 |
| Facial palsy | Yes | 2 |
| | No | 9 |
| Surgical group | I | 2 |
| | II | 3 |
| | III | 0 |
| | IV | 6 |
| Neck dissection | Yes | 4 |
| | No | 7 |
| Histopathological type | Unknown | 5 |
| | Solid | 2 |
| | Cribriform | 1 |
| | Tubular | 3 |
| PNI | Yes | 5 |
| | No | 6 |
| PNS | Yes | 9 |
| | No | 2 |
| Results | Alive | 5 |
| | Dead | 6 |
| Local recurrence | Auditory | 1 |
| | Parotid | 3 |
| | Mandibular ramus | 2 |
| | Skull base | 3 |
| | Temporal | 1 |
| | Second carcinoma | 1 |
| Distant metastasis | Yes | 5 |
| | No | 6 |
| Seed migration | Yes | 1 |
| | No | 10 |

PNI = perineural invasion; PNS = perineural spread.

*Radiotherapy-related toxicity*

Five patients experienced Grade 2 acute skin toxicity (tender or bright red erythema, patchy moist desquamation, moderate edema). Most patients experienced Grade 1 long-term skin toxicities (follicular, faint or dull erythema, epilation, dry desquamation, decreased sweating). Seven patients experienced Grade 3 toxicities (ear discharge with diminished hearing, formication). Two patients experience Grade 4 toxicities: manifesting as skin ulceration and hoarseness at the sixth month in 1 patient and a second primary tumor in the other patient.

Table 4
Survival outcomes in the different surgical groups

| Groups | I | II | III | IV |
|---|---|---|---|---|
| 5-year OS | 95.5% | 92.9% | 72.9% | 64.7% |
| 10-year OS | 95.5% | 92.9% | 72.9% | 58.2% |
| 5-year DFS | 83.7% | 88.4% | 72.9% | 61.1% |
| 10-year DFS | 83.7% | 66.3% | 72.9% | 54.3% |

OS = overall survival; DFS = disease-free survival.

*Seed migration*

Seed migration to the chest was observed in 1 patient in the third year. However, no adverse dosimetric consequences or pulmonary symptoms occurred.

## Discussion

As one type of indolent malignant tumors, complete tumor resection followed by postoperative radiotherapy can achieve satisfactory survival for head and neck ACCs, as the National Comprehensive Cancer Network clinical practice guidelines recommend. However, there is still some uncertainty regarding the surgical margin (15) and how residual tumor influences radiotherapy target volume or survival. Our study elucidated multiple prognostic factors and analyzed the effectiveness and safety of the combination of surgery plus postoperative iodine-125 interstitial brachytherapy for treatment of parotid ACCs. Some studies show that microscopic positive margin status is associated with worse survival and significantly higher rates of LR and distant metastases, but it does not affect regional recurrence–free survival (15,16).

In accordance with the National Comprehensive Cancer Network guideline recommendations, complete excision of ACC of the parotid, with preservation of the FN if possible (17), increases the possibility of local control rate, albeit at the cost of causing facial palsy. In our study, margin status had no significant effect on OS and DFS, indicating that preservation of the FN is feasible even when the tumor shows an infiltrative pattern. Patients with positive margins had relatively shorter OS and DFS. Most of these patients (23/33, 69.7%) were at advanced stage, and analysis showed advanced stage and PNS status to be significantly associated with poorer survival. "The OS and DFS of positive margin in minor salivary gland ACC are 63–68.8% and 40.2–69%, respectively (15,18). In this study, the 5-year OS and DFS of positive margin in early-stage parotid ACC (cT1-2) are 85.7% and 85.7%, respectively, whereas the 5-year OS and DFS in cT4 parotid ACC are 62.6% and 64%, respectively. The result showed that the margin status is an adverse prognostic factor of OS (HR = 6.177, $p = 0.046$) using this technique."

The postoperative prescribed dose to tumor bed for ACCs with nerve involvement and positive margin is 56–60 Gy, and those which invade the skull base had worse prognosis (17,19,20). However, the utility of radiotherapy for different margin or nerve status has not been elucidated further. The recurrence of ACC located mostly inside the target area in conventional external beam radiotherapy, proton beam therapy, and carbon-ion radiotherapy. In Koto's and Takagi's studies, patients had in-field (IF) and extending outside the field (EOF) recurrences (21,22). In the present study, there was no significant difference in CTV between different groups ($p = 0.088$). Out-of-field recurrence (the skull base,

Table 5
Prognostic factors for overall survival and disease-free survival

| | Overall survival | | | | Disease-free survival | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate analyses | | Multivariate analyses | | Univariate analyses | | Multivariate analyses | |
| Variables | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* |
| Sex | 0.476 (0.154–1.465) | 0.190 | 1.797 (0.129–24.972) | 0.662 | 0.715 (0.200–2.560) | 0.605 | 2.228 (0.148–35.324) | 0.553 |
| cT4 | 3.371 (0.977–11.635) | 0.046* | – | – | 0.811 (0.227–2.894) | 0.746 | – | – |
| cN positive | 2.031 (0.355–11.620) | 0.418 | – | – | 13.714 (2.540–74.036) | 0.001* | 8.799 (0.463–167.386) | 0.148 |
| Facial palsy | 25 (2.380–262.653) | 0.001* | 25 (2.38–262.653) | 0.007* | 3 (0.361–24.919) | 0.293 | 7.914 (1.130–55.411) | 0.037* |
| PNI | 0.558 (0.162–1.929) | 0.353 | – | – | 1.481 (0.413–5.313) | 0.545 | – | – |
| PNS | 5.880 (0.726–47.625) | 0.065 | – | – | 1.636 (0.325–8.231) | 0.547 | – | – |
| Preoperative metastases | 0.875 (0.673–1.137) | 0.708 | – | – | 1.333 (0.757–2.348) | 0.236 | – | – |
| Distant metastases | 4.571 (1.213–17.235) | 0.017* | – | – | 8.095 (1.959–33.460) | 0.001* | 16.89 (1.111–256.758) | 0.042* |

CI = confidence interval; HR = hazard ratio; PNI = perineural invasion; PNS = perineural spread.
* significant difference ($P < 0.05$).

external auditory canal, and intraparotid) was the most common pattern in our sample. The infiltrative and progressive characteristics of ACC may result in periosteal infiltration of the maxilla and mandible and muscle infiltration of the adjacent temporalis and masseter; these cases have much poorer survival. Patients had IF recurrences (N = 7) located around the auditory canal, the skull base, or inside the parotid, also EOF recurrences (N = 4) located in the mandibular ramus and temporal bone. The results showed high local control rate generally (5-year LCR: 79.3%, 10-year LCR: 70.6%), and the five- and 10-year LCR of Group IV (extensive tumor resection with close margins) were 80.2% and 54.9%, respectively.

Long-term followup has shown that distant metastasis is the main cause of treatment failure. The mean recurrence-free survival is 31.5–46 months, and the median survival time after metastasis to the bone, liver, or brain is only 8 months, and the 1-, 3-, and 5-year survival rates are 36%, 28%, and 28%, respectively (23). Although the association between tumor size and metastatic risk is unclear, some authors report that the possibility of intravasation increases sharply after a critical tumor size is reached (24). In the present study, adverse prognostic factors included clinical tumor stage, pathological type, and PNS status. We found PNI and advanced stage to be independent risk factors for OS and DFS; however, pulmonary metastases were relatively less common in our sample than in previous studies. The mean survival with distant metastases was for 60.6 months. Patients emerged with fewer distant metastases, and most patients survived with tumor (7/12, 58.3%).

Protons and charged particles have relatively low entrance doses, and the monoenergetic beam occurs at a specified depth; this makes precise dose delivery possible and decreases the risk of radiotherapy-related complications (25–27). Irradiation of the parotid can induce toxicities in adjacent critical structures, such as the external auditory canal, skin, and oral mucosa (28). In 257 patients with recurrent head and neck cancer, Riaz *et al.* (29) achieved locoregional control in 47% of patients with intensity-modulated radiotherapy. The incidence of severe radiotherapy-related toxicities (dermatitis, dysphagia, vascular injury) was 31%. In our study, most patients experienced relatively mild toxicities; only 9 patients experienced toxicities that impacted their quality of life.

Microscopic prognostic factors also include the presence and percentage of solid pattern, HGT, vascular invasion, and elevated mitotic index (30). Histopathological features of neural invasion include PNI (defined as the presence of tumor cells in the perineural space), perineural inflammation (cancer cell invasion into perineural space, with lymphocytic infiltration), and intraneural invasion (characterized by invasion and irregular destruction of the axons) (31). In head and neck squamous cell carcinoma, close or positive margin and PNI are adverse prognostic factors. In ACC, negative margin is unusual because of the infiltrative nature of the tumor. In our limited sample, microscopic PNI was common, but it was not a prognostic factor for OS or DFS. Histopathological type and surgical margin were also not prognostic factors in our sample. PNS, however, was a significant prognostic factor for OS and DFS.

Treatment modalities vary in ACCs; the 5-year OS ranges from 70% to 89%. In a collaborative study, 73.6% (1313/1784) of salivary gland ACCs received postoperative radiotherapy; the prescribed dose was 50–70.2 Gy, and the 5-year OS of early-stage and advanced stage ACCs was 78.4% and 79.3%, respectively (32). In the groups of our study, the 5-year OS of cT4 was 77.3%, and the 5-year OS of cT1-2 was 93.3%. In margin-positive cases, the 5-year OS of cT1-2 and cT3-4 was 85.7% and 62.6%, respectively. Generally, our results showed clinical tumor stage is an adverse prognostic factor influencing OS when the residual tumor is remained and should remove as much as possible. In Koto's and Takagi's studies, patients had IF and EOF recurrences in proton therapy and carbon-ion radiotherapy (21,22). Our study drew the similar conclusion that seven were IF recurrences and four were EOF, which showed that the design of CTV is closely linked to local recurrent sites and IF recurrence was more common in ACCs.

This study had limitations. First, selection bias was inevitable because this study was retrospective, whereas as one kind of rare malignant tumor in the whole body, the case number of ACC was relatively high in a tertiary hospital of Peking, China. We may carry out intrahospital collaboration in the future and explore a proper technique for parotid ACCs. Second, part of pathological sections met obstacles in further classification, constrained by technical limitations. We could not distinguish whether neurovascular infiltration or nerve invasion was existed in pathological sections, or differs HGT from the common solid type. In addition, as genetic diagnosis is developing, how to take advantage of small pieces of existed specimens may gradually become a research direction.

## Conclusion

This retrospective study showed that surgery combined with postoperative interstitial brachytherapy may be an effective and safe treatment for early-stage ACC of the parotid. The rates of nodal metastases, distant metastases, and radiological toxicities were low. The design of the CTV of target area and the dosimetry distribution of parotid brachytherapy needs further study, and our next step would be making efforts on improving local control rate in advanced stage ACC.

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