Surgery combined with ^{125}I brachytherapy for treatment of carcinoma ex pleomorphic adenoma of the parotid gland

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Objective. The aim of this study was to investigate the effectiveness and safety of surgery combined with ^{125}I seed brachytherapy for treatment of carcinoma ex pleomorphic adenoma (CXPA) of the parotid gland and to identify the factors associated with prognosis.

Study Design. We conducted a retrospective analysis of data of patients with CXPA of the parotid gland treated with surgery plus ^{125}I seed brachytherapy at the Peking University School of Stomatology Hospital between December 2003 and July 2018.

Results. Fifty-five patients (median age, 51 years) were included in the study. Median follow-up was 50.5 months. The 3-, 5-, and 10-year overall survival rates were 91.1%, 91.1%, and 81.5%, respectively. The 3-, 5-, and 10-year local control rates were all 85.2%. Grades 1-3 adverse effects occurred in 22 patients; no grade 4 reactions occurred. T stage, N stage, tumor invasiveness, perineural invasion, and surgical margins significantly affected local control rates. Lymph node metastasis and perineural invasion were independent predictors of poor local control. Lymph node metastasis was an independent predictor of poor survival.

Conclusions. Surgery plus ^{125}I seed brachytherapy appears to be an effective and safe treatment for CXPA of the parotid gland. T stage, N stage, tumor invasiveness, and perineural invasion are factors influencing prognosis. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:395−404)

Carcinoma ex pleomorphic adenoma (CXPA), which is a subtype of malignant pleomorphic adenoma (also known as "malignant mixed tumor")[1] accounts for 5%-15% of salivary gland malignancies.[2-4] It occurs most commonly in the parotid gland (67%), followed by the submandibular gland (14%).[5] Histologically, CXPA contains both benign pleomorphic adenoma components and malignant components. Misdiagnosis is common because the proportion of benign pleomorphic adenoma components may be quite small. The malignant component of CXPA may include almost any subtype of salivary gland carcinoma; the most commonly reported types are adenocarcinoma not otherwise specified (NOS), salivary ductal carcinoma, adenoid cystic carcinoma, and myoepithelial carcinoma.[4,6-8] According to the 2005 World Health Organization (WHO) criteria, CXPA can be divided into 3 subtypes based on the degree of extracapsular invasion: noninvasive CXPA, minimally invasive CXPA, and frankly invasive CXPA.

CXPA is a highly malignant tumor with a high likelihood of metastasis and disease-related death,[4,5,9] but, because it is rare, there is still no standard treatment approach. As with most other salivary gland malignancies, surgery is the main treatment choice, supplemented with radiotherapy in patients having advanced-stage disease with positive or close surgical margins or with systemic therapy in patients diagnosed with regional and/or distant metastasis.[10,11] Chemotherapy alone is not generally advocated for CXPA. Postoperative radiotherapy significantly improves the local control rate (LCR),[12,13] but it does not appear to improve survival. Radiotherapy-related adverse reactions also have to be taken into account.

^{125}I seed brachytherapy has advantages for head and neck malignancies because of the complex anatomy of the region. It ensures continuous high-dose radiation to the target area, with relative sparing of the surrounding normal tissues. ^{125}I brachytherapy has been used in combination with surgery for treatment of salivary malignancies for decades, but there has been little research on the application of this treatment for parotid gland CXPAs. The aim of this retrospective study therefore was to evaluate the effectiveness and safety of surgery plus ^{125}I brachytherapy for treatment of parotid gland CXPA and to identify the factors influencing outcomes.

PATIENTS AND METHODS

Patients

The study sample was selected from among the 150 patients with parotid gland CXPAs who were treated at Peking University School of Stomatology Hospital between December 2003 and July 2018. Patients treated with surgery alone or surgery plus external radiotherapy were excluded. The remaining 55 patients who were treated with surgery plus ^{125}I brachytherapy were included in this retrospective study. The clinical data of these patients were retrieved from the hospital

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records. Two experienced pathologists reviewed the pathology slides to confirm the diagnosis and determine the degree of extracapsular tumor invasion, the histologic subtype (i.e., the major malignant component), the surgical margin status, and the presence of perineural invasion. Tumors were staged according to the 2017 American Joint Committee on Cancer classification. Due to the retrospective nature of the study, the need for institutional review board approval was exempt.

Surgery

All patients underwent complete tumor excision. The extent of resection varied. The operations included extracapsular dissection, partial parotidectomy, superficial parotidectomy, total parotidectomy, and en bloc resection of the parotid gland with adjacent invaded tissue. During surgery, the facial nerves were preserved as much as possible, and damaged nerve was rebuilt as synchronously as possible. Neck dissection was performed in patients with clinically positive neck nodes.

Brachytherapy

Patients underwent ^{125}I seed implantation at 4-12 weeks after surgery. The treatment plan was designed according to the tumor volume and location on the basis of postoperative multislice computed tomography (MSCT) and the pathologic diagnosis. A brachytherapy treatment-planning system (Beijing Atom and High Technique Industries Inc, Beijing, China) was used to design the treatment plan. The planning target volume (PTV) included a 0.5- to 1.5-cm margin around the gross tumor volume (GTV). In this series, there were 6 patients with pathologically confirmed lymph node metastasis after neck dissection. For all these 6 patients, the neck nodal basins were not covered with ^{125}I. The matched peripheral dose (MPD) ranged from 60 Gy to 120 Gy, varying according to T stage, tumor invasiveness, histologic subtype, and the adjacent structures. Generally, the dose was 60-80 Gy for early-stage disease with noninvasive or minimally invasive CXPA and 90-120 Gy for advanced-stage disease with frankly invasive CXPA. Seed implantation was performed using computed tomography (CT) or a customized template for guidance. Hollow interstitial needles (18-gauge, 150 mm) were inserted into the target area, and ^{125}I seeds (model 6711; Beijing Atom and High Technique Industries Inc, Beijing, China) with a half-life of 59.6 days, energy level of 27.4-31.4 keV, and activity of 18.5-25.9 MBq (0.5-0.7 mCi) were implanted. Dosimetric validation was performed within 48 hours of implantation.

Follow-up

Patients were followed up from the date of brachytherapy to the end of the study (December 31, 2018). Follow-up was conducted every 2 months for the first 6 months, then every 3 months until the end of the third year, then every 6 months until the end of the fifth year, and then once annually until the end of the study. Clinical and imaging examinations (head and neck MSCT/magnetic resonance imaging, chest radiography or CT, positron emission tomography/CT) were performed regularly to identify tumor recurrence or metastasis. The 3-, 5-, and 10-year overall survival (OS) rates, disease-free survival (DFS) rates, and LCRs were calculated. OS was defined as the percentage of patients who survived from the date of brachytherapy to the end of the study. DFS was defined as the percentage of patients who survived without local failure and/or distant metastasis from the date of brachytherapy to the end of the study. LCR was defined as the percentage of patients without recurrence at the treated site until the end of the study.

Statistical analysis

The demographic, clinical, and pathologic characteristics of our patients were described with summary statistics. Lymph node and distant metastasis rates and incidence of complications were evaluated using descriptive statistics. Survival analysis was performed using the Kaplan-Meier method; the log-rank test was applied to determine statistically significant differences between groups. Independent predictors of outcomes were identified using a Cox proportional hazards model. Data analysis was performed using PASW Statistics 18.0 software (SPSS, Chicago, IL, USA). All tests were 2-tailed, and $P \leq .05$ was considered statistically significant.

RESULTS

Characteristics

A total of 55 patients (31 men and 24 women; sex ratio, 1.29:1) with a histologic diagnosis of CXPA of the parotid gland were included in our study. Table I shows the demographic, clinical, and pathologic characteristics of the patients. The median age of the patients was 51 years (range, 8-84 years). Among the 55 patients, 14 had undergone previous surgery for benign pleomorphic adenoma. T classification was T1 in 4 patients, T2 in 13 patients, T3 in 14 patients, and T4 in 24 patients. Extracapsular dissection was performed for 18 patients, partial parotidectomy for 12 patients, superficial parotidectomy for 17 patients, total parotidectomy for 6 patients, and en bloc resection of parotid gland and involved adjacent structures for 2 patients. Neck dissection was performed for 6 patients with suspected lymph node metastasis during preoperative examination; postoperative pathology confirmed lymph node metastasis in all 6 patients. Among these 6 patients, 2 had 1 positive lymph node, and the other 4 had multiple positive lymph nodes. The

Table I. Patient and tumor characteristics

Characteristic	*n (%)*
Sex	
Male	31 (56.4%)
Female	24 (43.6%)
Previous surgery for pleomorphic adenoma	
No	41 (74.5%)
Yes	14 (25.5%)
T stage	
T1	4 (7.3%)
T2	13 (23.6%)
T3	14 (25.5%)
T4	24 (43.6%)
Lymph node involvement	
Negative	49 (89.1%)
Positive	6 (10.9%)
Surgery type	
ECD	18 (32.7%)
PP	12 (21.8%)
SP	17 (30.9%)
TP	6 (10.9%)
En bloc resection of parotid gland with involved adjacent structures	2 (3.6%)
Surgical margins	
Clear	24 (43.6%)
Close	15 (27.3%)
Positive	16 (29.1%)
Perineural invasion	
Negative	35 (63.6%)
Positive	20 (36.4%)
Tumor invasion	
Non-invasive CXPA	23 (41.8%)
Minimally invasive CXPA	2 (3.6%)
Frankly invasive CXPA	30 (54.5%)

CXPA, carcinoma ex pleomorphic adenoma; *ECD*, extracapsular dissection; *PP*, partial parotidectomy; *SP*, superficial parotidectomy; *TP*, total parotidectomy.

surgical margins were clear in 24 patients, close in 15 patients, and positive in 16 patients. Perineural invasion was identified during surgery in 20 patients. Among these 20 patients, 10 had facial paralysis before surgery; the other 10 developed facial paralysis after surgery. During surgery, for 5 patients with a facial nerve branch traversing the tumor, nerve anastomosis was performed immediately after the nerve was cut. For 1 patient, great auricular nerve transplant was performed after the facial nerve branch was removed. For another 2 patients, no nerve transplant was performed after the facial nerve trunk was cut. For the remaining 12 patients, the facial nerve was carefully separated from the gross tumor and preserved, although this was at the risk of leaving a small part of the tumor in situ. On pathologic review, 23 CXPAs were graded as noninvasive, 2 as minimally invasive, and 30 as frankly invasive.

Table II shows the histologic subtypes. The most common subtypes were adenocarcinoma NOS (12 of 55 [21.8%]), myoepithelial carcinoma (11 of 55 [20.0%]), and ductal carcinoma (8 of 55 [14.5%]).

Table II. Distribution of the histologic subtypes

Histologic subtype	*n (%)*
Adenocarcinoma, NOS	12 (21.8%)
Myoepithelial carcinoma	11 (20.0%)
Ductal carcinoma	8 (14.5%)
Mucoepidermoid carcinoma	4 (7.3%)
Oncocytic carcinoma	4 (7.3%)
Adenoid cystic carcinoma	4 (7.3%)
Polymorphous low-grade adenocarcinoma	2 (3.6%)
Squamous cell carcinoma	1 (1.8%)
Papillary cystadenocarcinoma	1 (1.8%)
Basal cell adenocarcinoma	1 (1.8%)

NOS, not otherwise specified.

Table III shows the characteristic of postoperative ^{125}I seed implantation brachytherapy. The MPD was 60 Gy for 5 patients, 80 Gy for 1 patient, 100 Gy for 5 patients, 110 Gy for 22 patients, and 120 Gy for 22 patients. Nine to 97 ^{125}I seeds (mean, 46.18; median, 46) were implanted. The actuarial D90 (0 ranged from 48 to 145 Gy, the V100 was at least 89.4%, and the V150 was less than 59.7%.

Local Control

Median follow-up was 50.5 months (range, 2-168 months). The 3-, 5-, and 10-year LCRs were all 85.2% (Figure 1). Local tumor recurrence occurred in 7 patients (Table IV), 6 of whom developed recurrence within 1 year of brachytherapy. The median time to local recurrence was 9 months (range, 2-15 months). All 7 patients had frankly invasive CXPAs, with the T stage being T3 in 3 patients and T4 in 4 patients. The histologic subtypes included adenocarcinoma NOS (2 patients), ductal carcinoma (2 patients), myoepithelial carcinoma (2 patients), and mucoepidermoid carcinoma (1 patient). Although 3 patients had positive surgical margins, 2 had close surgical margins, and 2 had

Table III. Characteristics of 125I seed implantation

Characteristic	*Value*
Matched peripheral dose of 125I seed implantation	n
60 Gy	5
80 Gy	1
100 Gy	5
110 Gy	22
120 Gy	22
Number of ^{125}I seeds	
Median	46
Range	9-97
Activity of ^{125}I seeds	
Range	0.5-0.7 mCi
Dosimetry validation	
D_{90}	48-145 Gy
V_{100}	≥89.4%
V_{150}	≤59.7%

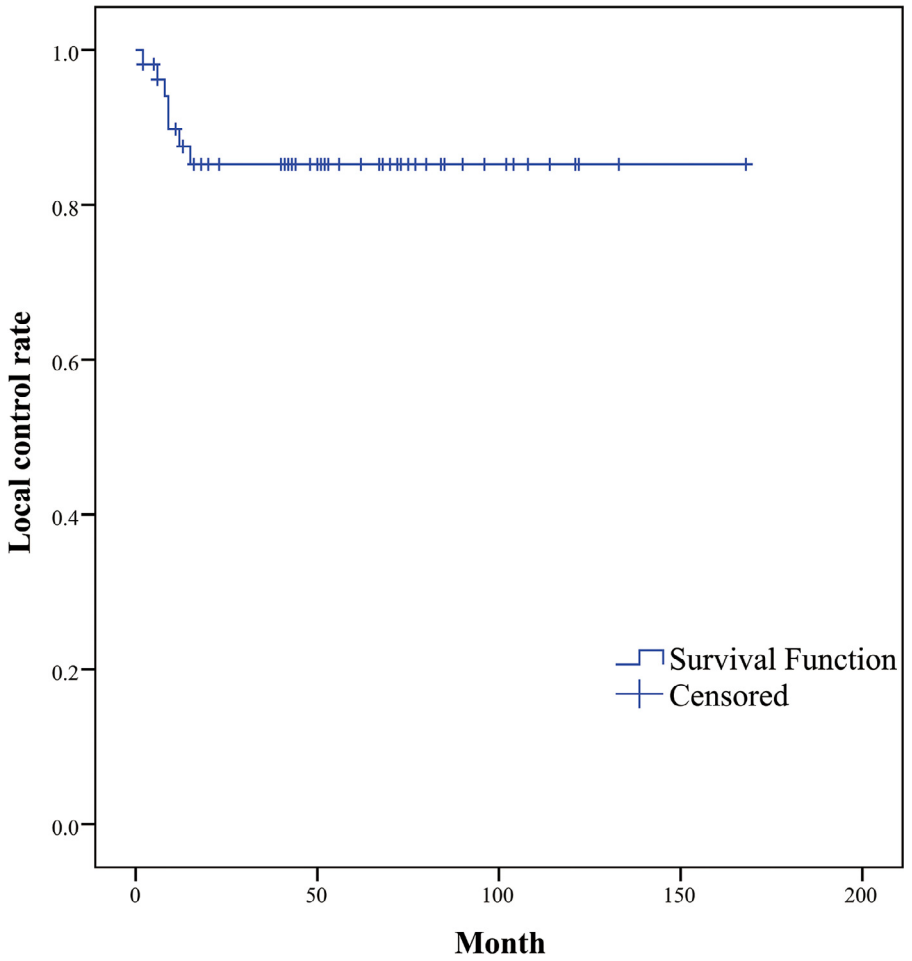

Fig. 1. Local control rate for all patients.

negative margins. The MPD was 100 Gy for 1 patient, 110 Gy for 3 patients, and 120 Gy for 3 patients. The recurrence sites were within 2 cm around the GTV for all patients.

In univariate analysis, T stage, N stage, tumor invasiveness, perineural invasion, and surgical margin status were significantly associated with LCR (Table V). The 3-, 5-, and 10-year LCRs were all 100% for T1/T2 tumors, whereas they were all 77.2% for T3/T4 tumors (P = .041; hazard ratio [HR], 42.88). The 3-, 5-, and 10-year LCRs were all 20.8% for patients with positive neck nodes, whereas they were all 92.9% for patients with negative neck nodes (P < .001; HR, 15.84). The 3-, 5-, and 10-year LCRs were all 100% for patients with noninvasive/minimally invasive CXPAs, whereas they were all 71.7% for patients with frankly invasive CXPAs (P = .008; HR, 66.99). The 3-, 5-, and 10-year LCRs were all 66.3% for patients with perineural invasion, whereas they were all 96.4% for patients without perineural invasion (P = .003; HR, 12.55). The 3-, 5-, and 10-year LCRs were all 62.6% for patients with positive/close surgical margins, whereas they were all 93.9% for patients with clear surgical margins (P = .004; HR, 7.84).

In multivariate analysis, the independent predictors of poor LCR were lymph node metastasis (HR, 17.20; 95% confidence interval [CI], 2.66-111.16) and perineural invasion (HR, 9.64, 95% CI, 1.02-91.39). Figure 2 shows the LCR for patients according to lymph node involvement and tumor invasiveness.

Survival

OS rates at 3, 5, and 10 years were 91.1%, 91.1%, and 81.5%, respectively (Figure 3). DFS rates at 3, 5, and 10 years were 89.0%, 86.5%, and 81.1%, respectively (Figure 3). Table VI shows the clinical and pathologic characteristics of the 6 patients who died during follow-up. The median time to death was 29 months (range, 5-75 months) from the day of brachytherapy. Although 5 patients with frankly invasive CXPAs died of local progression and distant metastasis, the other patient with noninvasive CXPA died of acute myocardial infarction at 67 months after treatment. All 6 patients had T4 stage disease. The most common

Table IV. Characteristics of the 7 patients who had recurrence

Patient	*Age (y)*	*Sex*	*T stage*	*Lymph node*	*Tumor invasion*	*Histologic subtype*	*Surgical margin*	*Matched peripheral dose (Gy)*	*Time to relapse (mo)*	*Site of recurrence*
1	38	M	4	Positive	Invasive	Ductal carcinoma	Close	100	9	Edge of GTV
2	52	M	3	Positive	Invasive	Ductal carcinoma	Clear	120	15	GTV + 2 cm
3	63	M	4	Positive	Invasive	Adenocarcinoma, NOS	Positive	120	2	Inside GTV
4	42	F	4	Negative	Invasive	Myoepithelial carcinoma	Clear	110	8	GTV + 1 cm
5	72	F	3	Negative	Invasive	Adenocarcinoma, NOS	Positive	110	6	GTV + 1 cm
6	55	M	3	Negative	Invasive	Mucoepidermoid carcinoma	Close	110	12	GTV + 1 cm
7	83	M	4	Positive	Invasive	Myoepithelial carcinoma	Positive	120	9	Inside GTV

Gross tumor volume (GTV) refers to clinically visible or accessible tumor sites and tumor areas that can be verified by means of examination.
GTV + 1 cm, 1 cm outside GTV; *GTV + 2 cm*, 2 cm outside GTV; *NOS*, not otherwise specified.

histologic subtype was myoepithelial carcinoma. Two patients had positive surgical margins. The MPD was 100 Gy for 1 patient, 110 Gy for 2 patients, and 120 Gy for 3 patients.

In univariate analysis (Table V), T stage ($P = .003$) and N stage ($P < .001$) were significantly associated with OS. The 3-, 5-, and 10-year OS rates were 77.5%, 69.8%, and 59.8%, respectively, for patients with T4 tumors, whereas they were all 100% for patients with T1-T3 tumors. The 3-year OS of patients with positive neck nodes was 62.5%, and the 5- and 10-year OS rates were both 0%. For patients with negative neck nodes, the 3-year OS was 94.9%, and the 5- and 10-year OS rates were both 90.2%. The OS rates at 3, 5, and 10 years of patients with T1/T2 tumors were higher than those of patients with T3/T4 tumors, but the differences were not significant (100%, 100%, 100% vs 86.4%, 86.4%, 70.9%, respectively; $P = .057$). In multivariate analysis, only lymph node metastasis was an independent predictor of poor OS (HR, 7.14; 95% CI, 1.41-36.14). Figure 4 shows the OS for all patients according to T stage and N stage.

Facial Nerve Function

The facial nerve function of all patients with intact facial nerve or with nerve transplant recovered gradually within 1 year after treatment. Table VII shows the facial nerve function according to the House-Brackmann grading system.

Lymph Node or Distant Metastasis

A total of 3 of 55 (5.5%) patients developed lymph node metastasis (at 2, 6, and 34 months after brachytherapy). T classification was T3 in 2 patients and T4 in 1 patient. All had invasive CXPAs. The histologic subtypes were adenocarcinoma NOS (2 patients) and ductal carcinoma (1 patient). The margin was positive in 2 patients.

Lung metastasis was diagnosed during follow-up in 5 of 55 (9.1%) patients. Among them, 1 patient developed systemic metastasis at 37 months after seed implantation. The median time to distant metastasis was 28 months. All of these patients had frankly invasive CXPAs. The histologic subtypes included myoepithelial carcinoma (2 patients), adenocarcinoma NOS (1 patient), ductal carcinoma (1 patient), and mucoepidermoid carcinoma (1 patient).

Adverse Reactions

No adverse reactions occurred in 33 of 55 (60%) patients. Grade 1-2 acute skin reactions (skin desquamation or mild edema) occurred in 20 of 55 (36.4%) patients, and grade 3 reaction (serous otitis media) occurred in 2 of 55 (3.6%) patients. No grade 4 acute toxicities were noted. All acute reactions resolved

Table V. Results of univariate analysis showing factors associated with local control rate and overall survival

Variables	*LCR*		*OS*	
	P value	*HR*	*P value*	*HR*
Age >60 y	.349	–	.309	–
Sex	.450	–	.434	–
Pleomorphic adenoma operation history	.852	–	.305	–
T stage	.041 (T1-2 & T3-4)	42.88	.057 (T1-2 & T3-4)	–
			.003 (T1-3 &T4)	107.12
Lymph node involvement	<.001	15.84	<.001	10.45
Tumor invasiveness (frankly invasive CXPA vs noninvasive/minimally invasive CXPA)	.008	66.99	.063	–
Perineural invasion	.003	12.55	.073	–
Surgical margins (positive/close vs clear)	.004	7.84	.168	–

CXPA, carcinoma ex pleomorphic adenoma; *HR*, hazard ratio; *LCR*, local control rate; *OS*, overall survival.

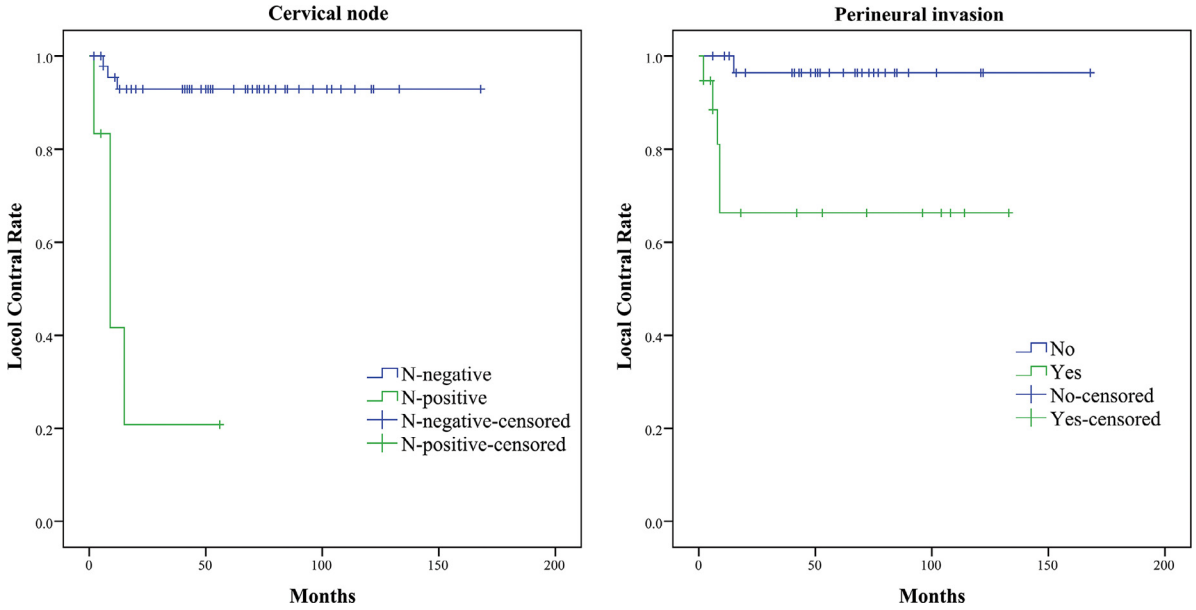

Fig. 2. Local control rate according to lymph node involvement and perineural invasion.

within 6 months. Late toxicity (moderate restriction of mouth opening) was detected in 2 of 55 (3.6%) patients. There were no serious late toxicities.

DISCUSSION

CXPA is considered a rare disease, but its true incidence may actually be underestimated because often overgrowth of the malignant component may mask the presence of the benign parotid adenoma component.[3] There has been a slow increase in the incidence of CXPA in the past decades.[9,12] A safe and effective treatment strategy is needed because regional or distant metastasis and disease-related death are common in patients with CXPA. In this study, we examined the effectiveness and safety of surgery combined with ^{125}I brachytherapy for treatment of CXPA and the factors affecting prognosis.

Radical surgical resection of the tumor is key to the treatment of CXPA. Superficial or total parotidectomy with sacrifice of the facial nerve involved by tumor adversely affects the patient's quality of life by causing facial depression and facial paralysis. Neck dissection is recommended for patients with invasive and high-grade CXPA because there is high possibility (≥50%) of cervical lymph node metastases.[13] In the present study, all patients underwent resection of tumor, with retention of as much glandular tissue and facial nerve as possible. More than half (54.5%) of the patients underwent extracapsular dissection and partial parotidectomy; the others needed superficial or total parotidectomy because of the large diameter of their neoplasms. Of the 20 of 55 (36.4%) patients who were found to have perineural invasion during operation, 12 underwent facial nerve dissection instead of neurectomy. Neck dissection was only performed in 6 patients

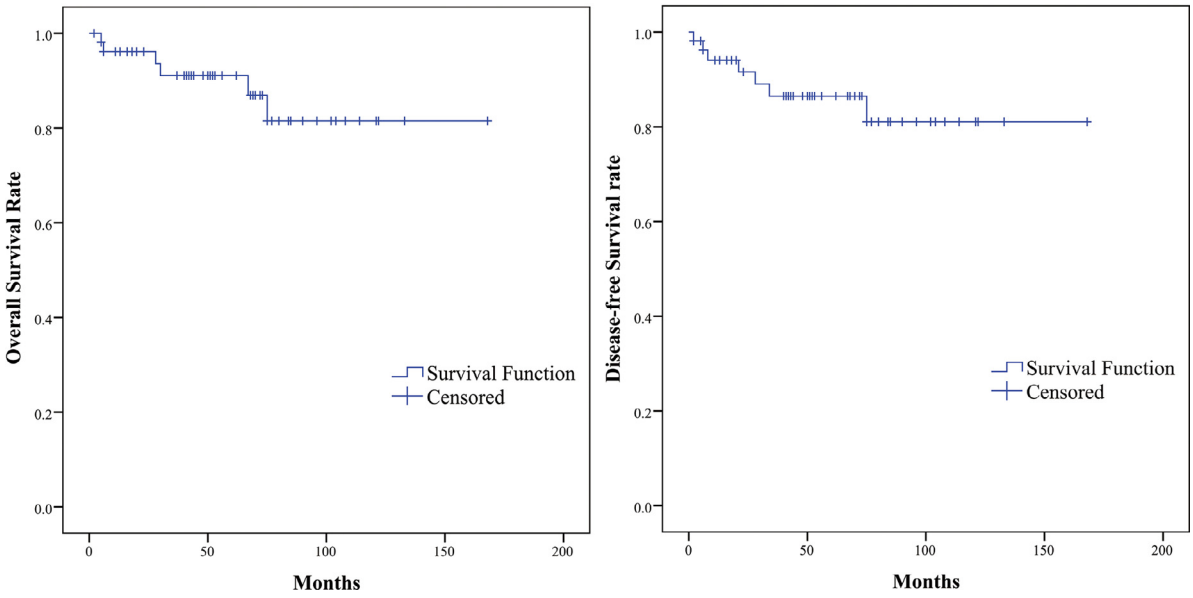

Fig. 3. Overall survival and disease-free survival for all patients.

with suspected positive lymph nodes. Thus, in general, surgery in our patient cohort was relatively conservative, which is also the reason why all patients received postoperative ^{125}I brachytherapy.

Survival rates and LCRs for patients with CXPA vary in previous studies. In an early review, Gnepp et al. found that the 5-year survival rate ranged from 25% to 65%.[2] A recent review showed the 5-year survival of CXPA to range from 25% to 75%.[6] In a 2001 study of 66 patients with CXPA, 48% of whom were treated with postoperative radiotherapy, the 3-year and 5-year OS rates were 39% and 30%, respectively.[4] In an another report, in which all patients (n = 66) received surgery and 21 (31.8%) patients with T3-T4 tumors received adjuvant radiotherapy, the 3-year and 5-year OS rates were 62.7% and 50.3%, respectively.[14] In a recent study of 619 patients with CXPA, of whom 97.2% received tumor resection, 61.2% received external beam radiation, and 11.3% received chemotherapy, the OS rates at 2 and 5 years were 84.6% and 68.5%, respectively.[12] The differences between these studies might be due to differences in tumor stage or invasiveness between the patient cohorts.

The role of radiotherapy in CXPA remains controversial. In a study of 28 patients with CXPA in which 26 patients received surgery and adjuvant external beam irradiation of 63 Gy, the 5-year locoregional control rate was 66% and the 5-year DFS rate was 44%.[15] Chen et al. found lower 3- and 5-year OS in patients treated with surgery plus postoperative radiotherapy than in patients treated with only surgery (59% and 44%, respectively, vs 70% and 57%, respectively); however, the 5-year LCR was much better in patients receiving postoperative radiation therapy (75% vs 49%).[16] In a study performed in 2012, Shinohara et al. found that radiation therapy improved OS in patients with high-grade disease and in those with positive lymph nodes.[17] In 2014, Chen et al. also noted that adjuvant radiation therapy improved the survival of patients with 2 or more positive lymph nodes.[9] These findings indicate that postoperative radiotherapy provides definite benefits for patients with CXPA. In our institution, we therefore recommend external radiotherapy for all patients with lymphatic metastasis. However, among the 6 patients with lymph node metastasis in this study, 3 refused radiotherapy because of cost considerations and the other 3 preferred a wait-and-watch approach.

In the present study, the LCR and OS at 3, 5, and 10 years were encouraging: OS rates were 91.1%, 91.1%, and 81.5%, respectively, and the LCRs were 85.2% at all 3 time points. In a retrospective study performed by Rito et al.[18] in which all patients underwent surgical excision and 70.7% received adjunctive radiation therapy, the 5-year OS was 81%, which is close to our result; however, the 10-year OS of 69% was much lower than ours. Overall, our OS and LCR data for patients with parotid gland CXPA is a dramatic improvement compared with previous reports, given that most of our patients underwent conservative resection. However, there is a large proportion (41.8%) of patients with noninvasive CXPA in our study, so the selection bias cannot be ignored.

Zhao et al.[14] found that the rate of locoregional failure for patients without lymph node involvement was significantly less than that of those with lymph node involvement (26.5% and 64.7%; P = .008). Locoregional recurrence rates in the T3-T4 groups was

Table VI. Characteristics of the 6 patients who died

Patient	Age (y)	Sex	T stage	Lymph node	Tumor invasion	Histologic subtype	Surgical margin	Matched peripheral dose (Gy)	Time to death (mo)	Cause of death
1	66	M	4	Negative	Non-invasive	Adenocarcinoma, NOS	Clear	120	67	Acute myocardial infarction
2	38	M	4	Positive	Invasive	Ductal carcinoma	Close	100	28	Lung metastasis
3	63	F	4	Positive	Invasive	Adenocarcinoma, NOS	Positive	120	5	Regional & lung metastasis
4	42	F	4	Negative	Invasive	Myoepithelial carcinoma	Clear	110	30	Tumor progression & lung metastasis
5	83	M	4	Positive	Invasive	Myoepithelial carcinoma	Positive	120	75	Tumor progression & lung metastasis
6	61	M	4	Negative	Invasive	Myoepithelial carcinoma	Clear	110	6	Tumor progression & lung metastasis

NOS, not otherwise specified.

significantly higher than in the T1-T2 groups (66.7% and 8.3%; $P < .001$).[14] These results were in line with ours. On univariate analysis, we found that T stage and N stage were significant factors affecting the LCR. Additionally, perineural invasion was identified as a risk factor for poor LCR; this may have been because the facial nerve was preserved in most of our patients, which inevitably resulted in some tumor around the nerve being left behind. In multivariate analysis, we found lymph node metastasis and perineural invasion to be independent predictors of poor LCR.

T stage and presence of lymph node metastasis were significantly associated with OS in our study. Lymph node metastasis (HR, 7.14; 95% CI, 1.41-36.14) was also an independent predictor of poor OS. In previous studies, the factors significantly associated with OS in patients with CXPA included age, T stage, lymph node involvement, histologic grade, tumor invasiveness, histologic grade, perineural invasion, histologic subtype, surgical margin, and proportion of malignant component ≥50%.[5,9,14,15,17-20] Zhao et al. demonstrated that T stage ($P = .004$) and lymph node involvement ($P < .001$) significantly influenced the OS of patients with major salivary gland CXPA.[14] Chen et al. investigated 55 patients with parotid gland CXPA, of whom 63% received postoperative radiation, and found significantly higher 3- and 5-year OS rates for patients with T1-T2 disease than for patients with T3-T4 disease ($P = .03$) and also for patients with pathologically negative lymph nodes than for those with pathologically negative lymph nodes ($P = .001$). In their study, pathologically confirmed lymph node metastasis was the only independent predictor of OS.[16] Our finding was a little different; we found significant difference in OS between patients with T1-T3 and those with T4 disease. No patient with T3 disease in our sample died.

In line with previous studies, we found tumor invasiveness to be a prognostic factor for LCR in patients with parotid gland CXPA. With regard to the prognostic significance of depth of invasion beyond the capsule, the previous literature is not consistent. In the study by Tortoledo et al., no patient with invasion depth <6 mm died of disease-related causes.[21] Olsen et al. noted that tumors with invasion depth ≤5 mm showed a benign clinical behavior.[4] According to Rito et al., tumor progression was unlikely when the depth of invasion was <2.5 mm.[18] Ye et al. proved that tumor invasion >1.5 mm was strongly related to higher mortality in patients with CXPA of major salivary glands.[20] In our study, we used the 2005 WHO criteria to classify parotid CXPA as (1) noninvasive CXPA (malignancy confined by the tumor capsule), (2) minimally invasive CXPA (malignant components invade tissue no more than 1.5 mm beyond the capsule), or (3) frankly invasive CXPA (tumor component invasion more than

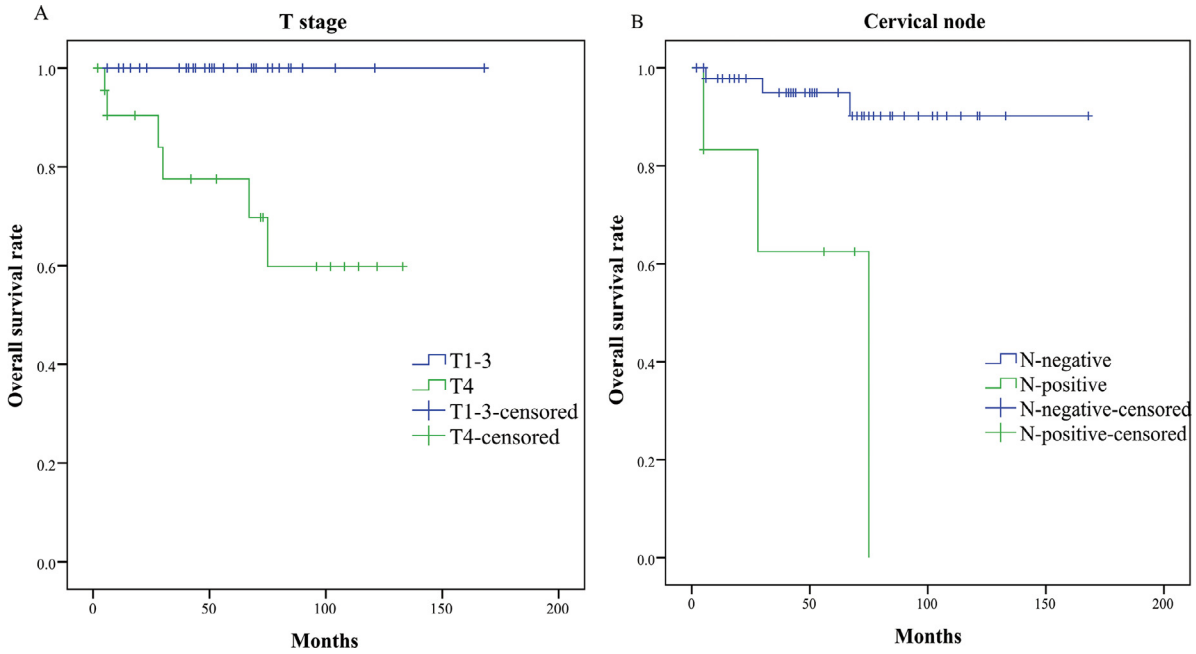

Fig. 4. Overall survival for all patients according to T stage (A) and cervical lymph node involvement (B).

Table VII. Facial nerve function according to the House-Brackmann grading system

Time	*n*				
	Grade I	*Grade II*	*Grade III*	*Grade IV*	*Grade V*
Before surgery	45	7	3	0	0
Before brachytherapy	35	13	4	1	2
6 mo after brachytherapy	42	8	1	0	2
1 y after brachytherapy	51	0	0	0	2

1.5 mm beyond the capsule). We found LCR to be significantly higher for patients with noninvasive or minimally invasive CXPA than for patients with frankly invasive CXPA. This finding is concordant with most previous studies. Zhao et al. reported that tumor invasiveness was significantly associated with local recurrence (P = .01) and DFS (P < .001).[14] Hu et al. reported 5-year OS rates of 100% and 98% for patients with noninvasive and minimally invasive disease, respectively, versus 59% for patients with frankly invasive disease.[5]

In general, T stage, N stage, tumor invasiveness, perineural invasion, and surgical margin status were significantly associated with LCR in our study, and, in univariate analysis, HRs of these factors were higher than common values previously reported. The reason for the high HRs was that T stage, lymph node metastasis, tumor invasiveness, and surgical margin status were high risk factors of LCR, but the patient number limitation of this study might affect the precision of HRs. Multivariate analysis showed that lymph node metastasis and perineural invasion were independent predictors of poor LCR. As for OS rate, T stage and N stage were significant risk factors. Lymph node metastasis was an independent predictor of poor OS.

In this study, 7 patients had local recurrences, all occurring within 3 years of brachytherapy, and most (6 of 7) occurring in the first year. All patients who had local recurrence, regional lymph nodes, or distant metastasis, as well as those who died during follow-up, had invasive CXPAs, with the malignant component being mostly high-grade malignancy such as ductal carcinoma, adenocarcinoma NOS, and myoepithelial carcinoma. No recurrence, metastasis, or death occurred in patients with noninvasive and minimally invasive CXPA; this is consistent with most previous reports. This finding suggests that, in clinical practice, close follow-up is essential during the first year after treatment, especially for patients with invasive CXPAs and CXPAs containing high-grade malignant subtypes. Patients with LCR failure in this study received radiation doses of 100-120 Gy, and their recurrence sites were all within 2 cm around the GTV. The T stage, tumor invasiveness, histologic subtypes, and surgical margin status of these cases, seem to remind us to prescribe higher peripheral doses or extend PTV for those patients with advanced-stage disease with invasive

CXPA, CXPA containing high-grade malignant subtypes, and positive or close surgical margins. Conversely, there were no LCR failures in patients who were prescribed lower peripheral doses, presumably indicating that the dose was sufficient for those patients with early tumors. However, given the patient number limitation of this study, this finding needs to be verified by further research with more patients.

In the head and neck region, radiotherapy can sometimes cause severe acute or late adverse reactions such as extensive oral ulceration, severe xerostomia, severe restriction of mouth opening, and even osteoradionecrosis of the jaws. In our cohort, however, most patients (96.4%) had no adverse reactions or only transient skin reactions; moreover, all acute reactions resolved within 6 months. Only 2 (3.6%) patients developed moderate restriction of mouth opening. No other late toxicities occurred. This is consistent with previous studies.[22-24]

CONCLUSION

In conclusion, surgery plus ^{125}I brachytherapy appears to be an effective and safe modality for treatment of parotid CXPA. The LCRs and OS rates are encouraging, and adverse reactions after brachytherapy are mild and self-limiting. T stage, lymph node metastasis, tumor invasiveness, and perineural invasion are the main factors affecting prognosis.

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