

# Iodine-125 brachytherapy alone for advanced primary parotid gland carcinoma

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C. Zhou, J. Zhang, J.-G. Zhang, S.-M. Liu, L. Zheng, M.-W. Huang, Y. Shi, X.-M. Lv: Iodine-125 brachytherapy alone for advanced primary parotid gland carcinoma. *Int. J. Oral Maxillofac. Surg.* 2018; 47: 561–567. © 2017 Published by Elsevier Ltd on behalf of International Association of Oral and Maxillofacial Surgeons.

**Abstract.** This study aimed to evaluate the efficacy of iodine-125 (<sup>125</sup>I) brachytherapy alone for the treatment of advanced parotid gland carcinoma and to identify predictors of tumour control and patient survival. Primary parotid gland carcinoma patients ( $n = 23$ ) treated with <sup>125</sup>I brachytherapy alone between 1 October 2005 and 31 July 2013 at Peking University Stomatology Hospital were enrolled in this retrospective study. All had clinical stage IV disease. The prescribed dose was 60–160 Gy. The local control rate, survival rate, and predictors of the prognosis were evaluated. Adverse events related to treatment were also noted. The average follow-up time was 29 months (range 9–74 months). Among the 23 patients, six had local failure and 11 died during the follow-up period. The 1-, 3-, and 5-year overall survival rates were 87.0%, 55.4%, and 47.5%, respectively. The 1-, 3-, and 5-year progression-free survival rates were 73.9%, 47.0%, and 39.2%, respectively. The 1-, 3-, and 5-year local control rates were 82.1%, 73.9%, and 73.9%, respectively. Age and distant metastasis were independent predictors of survival, while the preoperative duration of the disease was an independent predictor of local control. The use of <sup>125</sup>I seed brachytherapy alone for the treatment of primary parotid gland carcinoma can provide good short-term results without causing any severe side effects.

Key words: parotid gland carcinoma; <sup>125</sup>I seed; brachytherapy.

Accepted for publication 14 March 2017  
Available online 28 September 2017

Parotid gland carcinoma is relatively uncommon, accounting for only about 5% of all head and neck cancers. The annual incidence rate is 1.0/100,000<sup>1</sup>. Surgical excision forms the mainstay of treatment, with postoperative radiotherapy used to supplement surgery. Some oncologists recommend the use of radiotherapy alone for the treatment of inoperable tumours.

The 2005 World Health Organization classification recognizes 24 subtypes of salivary gland cancer. Different pathological types have different biological behaviour. Low-grade malignant tumours are characterized by slow progression, a low metastasis rate, and good prognosis, while high-grade tumours show invasive growth, relatively high local recurrence

rates, a high metastasis rate, and poor prognosis.

The clinical stage of disease is also related to the prognosis. However, the outcomes observed in some studies may have been influenced by imbalances in the proportions of patients at different stages of disease. The prognosis is generally poor in patients with advanced disease.

Radiotherapy is recommended for some advanced tumours when radical surgery cannot be performed due to the proximity of the tumour to vital structures, medical contraindications to surgery, or refusal of patient consent. However, due to poor normal-tissue sparing, the side effects of radiotherapy can be severe.

Iodine-125 ( $^{125}\text{I}$ ) seed brachytherapy is a treatment strategy in which radionuclide particles wrapped in titanium shells are implanted into the tumour target region according to preoperative treatment planning, enabling a high dose of radiation to be delivered directly to the tumour. Brachytherapy has been shown to be highly conformal and minimally invasive, with the ability to provide good local control and to cause few side effects<sup>2,3</sup>.

The purpose of this retrospective study was to evaluate the short-term effects, survival rate, side effects, and predictors of the prognosis following the use of radioactive  $^{125}\text{I}$  brachytherapy alone for the treatment of inoperable malignant primary parotid tumours.

## Methods

The study was approved by the Ethics Committee of Peking University School and Hospital of Stomatology.

This retrospective study included 23 patients with primary parotid gland carcinoma (12 males and 11 females) who were treated with  $^{125}\text{I}$  brachytherapy alone at Peking University School and Hospital of Stomatology between 1 October 2005 and 31 July 2013. The patients ranged in age from 2 months to 76 years (median age 47 years). The characteristics of the study patients are shown in Table 1. All patients had primary parotid gland carcinoma classified as clinical stage IV according to the Union for International Cancer Control (UICC) 2010 classification. The histological diagnosis was established in all cases by incisional biopsy or core needle biopsy before brachytherapy. None of the patients had undergone resection of the tumour before radiotherapy.

### $^{125}\text{I}$ seed implantation

A treatment planning system was used for pre-treatment planning (TPS; Beijing Atom and High Technique Industries Inc., Beijing, China). Planning was based on computed tomography (CT) images and took the pathological grade of the tumour into consideration. The planning target volume (PTV) was defined to cover the lesion with a 1–1.5 cm margin beyond the tumour. TPS displayed the dose distribu-

Table 1. Patient characteristics.

Characteristics	Number of patients (%)
Age, years	
Median (range)	47 (0.17–76)
≤40 years	5 (21.7)
40–60 years	14 (60.9)
>60 years	4 (17.4)
Sex	
Male	12 (52.2)
Female	11 (47.8)
Histological subtype	
High-grade	17 (73.9)
Adenoid cystic carcinoma	12
Adenocarcinoma	2
Salivary duct carcinoma	2
Oncocytic adenocarcinoma	1
Intermediate-grade	3 (13.0)
Intermediate-grade mucoepidermoid carcinoma	1
Papillary cystadenocarcinoma	1
Mucinous adenocarcinoma	1
Low-grade	3 (13.0)
Low-grade mucoepidermoid carcinoma	1
Cribriform cystadenocarcinoma	1
Sialoblastoma	1
T stage	
T1	0
T2	1 (4.3)
T3	0
T4	22 (95.7)
N stage	
N0	23 (100)
M stage	
M0	22 (95.7)
M1	1 (4.3)
Clinical stage	
I, II, III	0
IV	23 (100)
Facial nerve paralysis	
Yes	12 (52.2)
No	11 (47.8)
Prescription dose (Gy)	
60–80	1 (4.3)
80–120	16 (69.6)
120–160	6 (26.1)

tion curves and determined whether the prescription dose covered all target areas and whether the dose distribution in the target region was uniform.

$^{125}\text{I}$  seeds (model 6711) were obtained from Beijing Atom and High Technique Industries Inc. The seeds had a half-life of 59.4 days and energy level of 27.4–31.4 KeV; the activity was 25.9–29.6 MBq (0.7–0.8 mCi). Implantation was performed under general anaesthesia and with CT guidance according to the preoperative treatment plan. Hollow interstitial needles (18-gauge, 150 mm) were inserted into the target area, making sure that the direction and depth of the needle insertion followed the treatment plan. An applicator was then sequentially attached to the distal ends of the needles to place the  $^{125}\text{I}$  seeds into the target area; the injector was stepped back 1–1.5 cm each time, thus

the  $^{125}\text{I}$  seeds were distributed three-dimensionally in the gross tumour volume.

### Follow-up

Patients were followed up at 2, 4, and 6 months after treatment, and every 6 months thereafter. Each follow-up examination included the following: (1) a search for local and regional recurrence of the tumour: a physical examination was performed at each visit, including a visual examination and palpation, and a CT scan was performed at 2 months, 6 months, and 1 year after treatment, and annually thereafter. (2) A search for distant metastasis: routine chest radiography was performed every year, with positron emission tomography (PET)–CT when distant organ metastasis was suspected. (3) A search for radiation-induced damage: complications

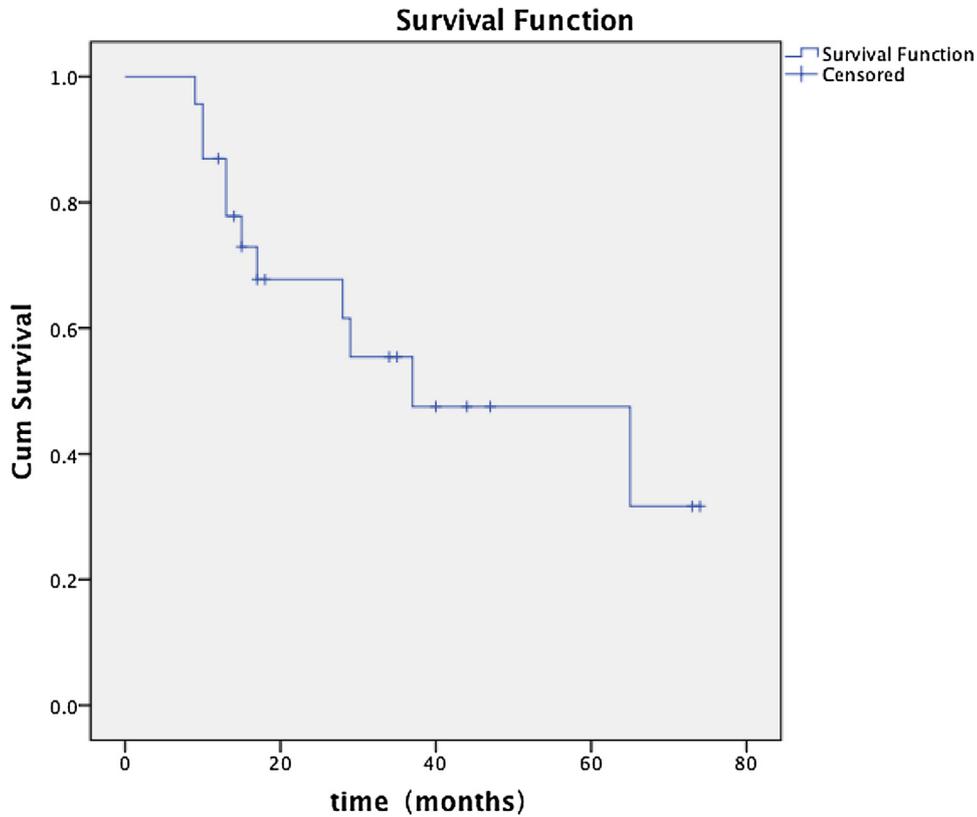


Fig. 1. Overall survival rate; Kaplan–Meier analysis.

were evaluated according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) grading system.

### Statistical analysis

All data were analyzed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). The log-rank test was used to analyze the effect on survival of single prognostic factors, including age, sex, histological grade, TNM stage, facial nerve involvement, and the prescription dose. Survival and local control rates were estimated by Kaplan–Meier analysis.

### Results

#### Overall survival rate and progression-free survival rate

The average follow-up time was 29.1 months (range 9–74 months). The overall survival rate was 52.2% (12/23). The 1-, 3-, and 5-year survival rates were 87.0%, 55.4%, and 47.5%, respectively (Fig. 1). The average survival time was 44.2 months (95% confidence interval (CI) 32.0–56.4 months). The progression-free survival rate was 43.5% (10/23). The 1-, 3-

, and 5-year progression-free survival rates were 73.9%, 47.0%, and 39.2%, respectively (Fig. 2). The average progression-free survival time was 37.9 months (95% CI 25.4–50.5 months).

On univariate analysis there was a significant difference in the survival rates between the different age-groups (i.e., ≤40 years, 40–60 years, and >60 years), with survival rates being lower in older patients ( $P = 0.003$ ). Patients with cervical lymph node metastasis and distant metastasis before and after treatment had significantly lower survival rates ( $P = 0.01$  and  $P = 0.001$ , respectively).

Sex, preoperative duration of disease, and local control were not significantly related to the survival rate ( $P = 0.469$ ,  $P = 0.38$ , and  $P = 0.587$ , respectively). High-degree histology, tumour diameter >2 cm, and presence of facial palsy were related to poor survival, although the relationships were not statistically significant ( $P = 0.082$ ,  $P = 0.142$ , and  $P = 0.140$ , respectively).

#### Local control rate

Six months after treatment, 14 patients (60.9%) had a complete response (CR), five (21.7%) had a partial response (PR),

one (4.4%) had stable disease (SD), and three (13.0%) had progressive disease (PD) (Table 2); thus, the efficacy of brachytherapy was 87.0% (CR + PR + SD). The 1-, 3-, and 5-year local control rates for the 23 patients were 82.1%, 73.9%, and 73.9%, respectively (Fig. 3), and the average duration of local control was 55.4 months (95% CI 42.7–68.1 months).

On univariate analysis, preoperative duration of disease (≤4 years, 4–8 years, >8 years) was significantly associated with the local control rate ( $P = 0.001$ ). The local control rate was inversely related to the preoperative duration of disease. The local control rate of patients with cervical lymph node metastasis was also significantly lower ( $P < 0.001$ ).

#### Lymph node metastasis and distant metastasis

Among the 23 patients with primary parotid gland carcinoma, two developed lymph node metastases after <sup>125</sup>I seed brachytherapy. No lymph node metastases were observed in the other 21 patients.

Distant metastasis was seen in nine patients (Table 3); one of these patients had intracranial metastasis prior to <sup>125</sup>I

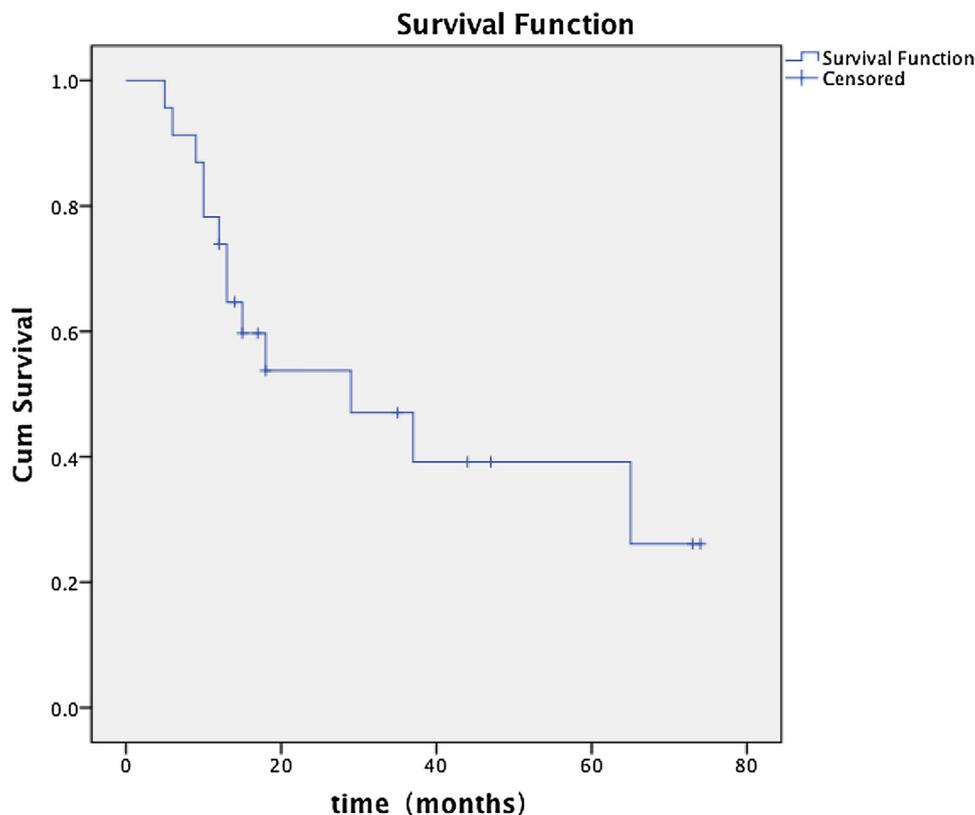


Fig. 2. Progression-free survival rate; Kaplan–Meier analysis.

Table 2. Local control of disease in patients with primary parotid gland carcinoma.

Local control	Number	Percentage
Complete response (CR)	14	60.9%
Partial response (PR)	5	21.7%
Stable disease (SD)	1	4.4%
Progression of disease (PD)	3	13.0%
Total	23	100%

treatment, while the other eight patients developed distant metastases at 3–65 months (average 21.5 months) after treatment. Among the nine patients with distant metastasis, two had failure of local control. All nine of these patients died within 2 years of developing distant metastasis. In all cases the cause of death was multiple organ failure or whole-body failure caused by distant metastasis. The 1-, 3- and 5-year survival rates of patients with distant metastasis were 66.7%, 22.2%, and 11.1%, respectively, and the average survival time was 24.4 months (95% CI 12.6–36.3 months).

### Complications

No RTOG/EORTC grade 3 or worse radiation injury (acute or late) was seen in any patient. All patients, however, had grade 1–2 skin reactions, such as skin hyperae-

mia, pigmentation, or depigmentation, but these improved within 6 months of completion of treatment. One patient developed a hemifacial spasm and moderate trismus 6 months after treatment.

## Discussion

### Local control rate

Surgery with postoperative radiotherapy is the strategy commonly adopted for the management of early-stage salivary gland carcinoma. The local control rate with this approach is about 50–54.5%<sup>4,5</sup>. Douglas et al. used fast neutron radiotherapy after surgery and reported a 6-year local control rate of 59%<sup>6</sup>. With the application of fast neutron irradiation in the treatment of adenoid cystic carcinoma, the local control rate has been reported to be in the range of 65–75%<sup>7,8</sup>.

Some institutions have reported the use of radiotherapy alone for the treatment of patients in whom surgery is contraindicated. In the early literature, the local control rate in patients with parotid gland carcinoma treated with gamma rays or X-ray alone was never more than 25%<sup>9,10</sup>. With the development of radiotherapy technology, the local control rate with radiotherapy alone has gradually increased. Chen AM, et al., in a retrospective study of 45 patients with salivary gland carcinoma treated with radiotherapy alone, reported that the 5- and 10-year local control rates were 70% and 57%, respectively, and that the response to treatment was dose-dependent<sup>11</sup>. Huber et al. analyzed 75 patients with inoperable, recurrent, or incompletely resected adenoid cystic carcinoma of the head and neck who received photon beam or neutron beam radiotherapy alone, and reported local control rates of 32% and 75% for photons and neutrons, respectively<sup>12</sup>. However, neutron beam radiotherapy failed to increase the survival rate, and serious long-term side effects limited its application. Only patients with advanced disease were included in the present study, but the local control rate was generally superior to the rates given in other reports.

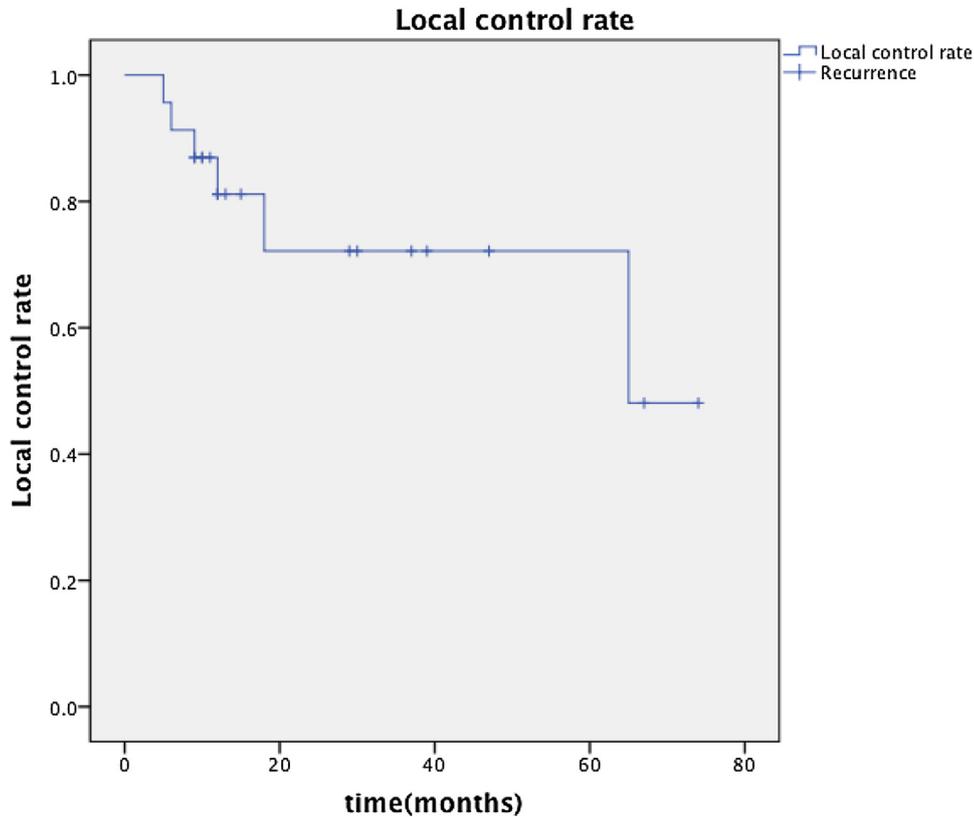


Fig. 3. Local control rate; Kaplan–Meier analysis.

Table 3. Distant metastasis in patients with primary parotid gland carcinoma.

Site	Number	Time/month	Time from metastasis to death (months)
Lung	4	65	0
		16	21
		3	7
		16	1
Skull and intracranial	2	Preoperative	15
		7	2
Lung, liver, bone	1	29	0
Intracranial, liver, bone	1	17	11
Liver	1	19	0

**Overall survival rate and progression-free survival rate**

For parotid gland carcinoma, the 5-year survival rate is closely related to tumour stage, with the rates in patients with stage I, II, III, and IV disease being 65%, 50%, 21%, and 9%, respectively<sup>13</sup>. The 5-year survival of patients with parotid gland carcinoma reported in the literature ranges from 46% to 71%, and the progression-free survival from 47% to 60%<sup>14–18</sup>. In patients with advanced carcinoma of the parotid gland, the 5-year survival rate has been only 9–37%<sup>13,19,20</sup>. In the series presented herein, the overall survival rate was 52.2% (12/23), and the 1-, 3-, and 5-year

survival rates were 87.0%, 55.4%, and 47.5%, respectively. The 1-, 3-, and 5-year progression-free survival rates were 73.9%, 47.0%, and 39.2%, respectively.

**Prognostic factors**

The survival analysis showed that the preoperative duration of disease, cervical lymph node metastasis, and distant metastasis were all predictors of local control failure. As all patients in this study had advanced carcinoma, the duration of disease was relatively long, ranging from 1 month to 30 years (average 52 months).

Age, cervical lymph node metastasis, and distant metastasis were shown to be predictors of survival in this study. Earlier

studies have shown age, sex, pathological grade, tumour stage, facial nerve involvement, surgical margin, postoperative adjuvant radiotherapy, and concurrent systemic diseases to be prognostic factors<sup>21–24</sup>. Some researchers have used weighted values for age, pain, tumour size, lymph node metastasis, skin infiltration, and facial nerve dysfunction in a formula to predict the prognosis in patients. Preliminary reports have shown that the method provides reliable results<sup>25</sup>. In the present study, sex was not significantly associated with survival. Surgical margin and postoperative adjuvant radiotherapy were not factors considered in this study.

Survival was found to be inversely (and significantly) related to age in this study; the survival rate in patients >60 years of age was significantly lower than that of patients <60 years of age. In the study by Cederblad et al., investigating 144 patients with parotid gland carcinoma, the 5-year survival rate was 58% in patients <65 years vs. 23% in patients >65 years, leading the authors to state that age was a predictor of survival<sup>26</sup>. In the study by van Weert et al. involving patients with head and neck adenoid cystic carcinoma, age was shown to be a prognostic factor<sup>20</sup>. However, Chen et al. did not find any

obvious effect of age on the prognosis in 45 patients with salivary gland carcinoma treated with radiotherapy alone<sup>11</sup>. The youngest patient in the present study was only 2 months old and was the only child included. This child suffered a sialoblastoma and underwent <sup>125</sup>I brachytherapy, but the disease progressed after 5 months. A second treatment was performed and a complete response was finally reached. This patient has now been followed up for 40 months.

One study reported that the 5-year survival of patients with malignant parotid tumours without lymph node metastasis was 75%, but that survival decreased to 15% when lymph node metastasis was present<sup>20</sup>. van Weert et al. supported this finding that lymph node metastasis was a predictor of a poor prognosis<sup>20</sup>. The findings of the present study are also consistent with these previous reports, with the survival rate of patients with lymph node metastasis being lower than that of patients without lymph node metastasis. In the present series, no patient had lymph node metastasis before treatment; however, two patients developed lymph node metastasis after treatment and died of distant metastasis 9 and 17 months after brachytherapy.

Among the 23 patients, one was diagnosed with intracranial metastasis before treatment and died 15 months after treatment. A total of eight patients developed distant metastasis after treatment. The time to detection of metastasis ranged from 3 months to 5 years (median 16 months) post brachytherapy. Distant metastasis occurred within 2 years after treatment in 75% (6/8) of these patients, suggesting that close follow-up for 2 years after brachytherapy may aid in the early detection of most metastasis.

A survival analysis was conducted after separating the patients into those with high-grade disease and those with low-to moderate-grade disease; the analysis showed that the survival rate of the patients with high-grade carcinoma was lower than that of patients with low-to moderate-grade carcinoma. Although not significant, a trend towards significance was seen ( $P = 0.082$ ). Harbo et al. examined the prognosis of 136 patients with malignant parotid tumours and found that the survival rate of patients with high-grade malignant tumours was significantly lower than that of patients with low-grade malignant tumours<sup>13</sup>. However, Cederblad et al., in their retrospective analysis of 144 cases of malignant parotid tumours, found no significant difference in the prognosis of patients with different pathological grades<sup>26</sup>.

In the present study, the 5-year survival rate of patients with facial paralysis was lower than that of patients without facial paralysis (33.8% vs. 68.2%), although the difference was not statistically significant ( $P = 0.140$ ). The studies of Cederblad et al. and Al-Mamgani et al. showed that the survival rate of patients with facial paralysis was significantly lower than that of patients without facial paralysis<sup>26,27</sup>.

A limitation of this study was the small sample size of only 23 patients. This report will be updated in the future as more patients are enrolled.

In conclusion, the cases of 23 patients with malignant primary parotid gland tumours who were treated with <sup>125</sup>I brachytherapy alone from 1 October 2005 to 31 July 2013 were analyzed retrospectively and the short-term effects of treatment, the predictors of the prognosis, and the side effects of treatment were evaluated. The short-term outcome was good, the local control rate was high, and there were no severe side effects. Age, lymph node metastasis, and distant metastasis were found to be independent predictors of survival, while the preoperative duration of disease and lymph node metastasis were independent predictors of local control.

#### Funding

None.

#### Competing interests

None.

#### Ethical approval

Not required.

#### Patient consent

Not required.

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