

Brachytherapy for recurrent malignant tumours of the parotid gland

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Abstract

To find out if brachytherapy with radioactive seeds was effective in patients with recurrent malignant tumours of the parotid gland we retrospectively studied 64 such patients, 24 of whom were treated with implantation of radioactive seeds alone, and 40 of whom had their recurrent tumours resected followed by implantation of radioactive seeds. Patients were followed up for a mean of 50 months (range 4 months to 12 years). The local control rate was 76.6%, and overall survival 79.7%. Of the 24 patients treated with brachytherapy alone, 22 achieved a complete response (91.7%). At 1, 3, and 5 years the local control rates were 81.5%, 67.2%, and 53.8%, respectively, and the overall survival 82.7%, 70%, and 61.2%, respectively. In the 40 patients whose tumours were resected before brachytherapy, the local control rates at 1, 3, and 5 years were 87.5%, 82.4%, and 78.6%, respectively, and the overall survival was 97.5%, 86.5%, and 86.5%, respectively. Sex, age, histopathological grade, size of tumour, history of radiotherapy, time of recurrence and method of treatment were not shown to have a significant effect on local control, but method of treatment had a significant impact on overall survival ($p=0.008$). We conclude that treatment of recurrent malignant tumours of the parotid efficacy can be successfully treated with brachytherapy with radioactive seeds, either alone or combined with resection.

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Keywords: Parotid gland; Recurrence; Radioactive seed

Introduction

The 5-year overall survival of malignant parotid tumours ranges from 55% to 87%, depending on the clinical stage, histopathological type, and treatment given. The local recurrence rate ranges from 11% to 37%.^{1–3} Tumours usually recur within the first 3 years after initial treatment.⁴ Post-operative radiotherapy can decrease the local recurrence rate

and increase survival in patients with tumours of the parotid gland.^{5–8}

We know of few studies that have investigated the treatment of recurrent malignant tumours of the parotid gland, even though the rate of recurrence is relatively high.^{9,10} Currently, the predominant treatment for such tumours is resection.⁹ However, scarring and infiltration often make resection difficult in these patients. If the involved area has previously been treated with radiotherapy operation is even more difficult, and a second course of radiotherapy is technically challenging. We treat these recurrent tumours by resection or brachytherapy with radioactive seeds, or both, which have so far shown promising results. The purpose of this study was to find out how effective brachytherapy with radioactive seeds is in patients with recurrent malignant parotid tumours.

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Patients and methods

We retrospectively evaluated 64 patients with recurrent malignant tumours of the parotid gland who were treated by brachytherapy with radioactive seeds. The study was approved by the Ethics Committee of Peking University School of Stomatology. The local recurrences were diagnosed by clinical examination, computed tomography (CT), and histopathological examination in Peking University School and Stomatology Hospital between 2001 and 2012. They included 21 men and 43 women, median age 45 (range 2–80) years. The diagnoses are shown in Table 1, and the mean (range) interval between the last treatment and recurrence was 2 years (3 months to 12 years).

Forty-five patients had developed recurrent tumours for the first time, 9 of whom had been treated with postoperative radiotherapy in addition to resection. Nineteen patients had two or more recurrences, and their primary treatment had been parotidectomy. Three had postoperative radiotherapy after the first operation, and further recurrence was treated by resection. Two of them were given postoperative radiotherapy. The dose given to the 14 patients who had previously had routine radiotherapy was 45–65 Gy. The largest diameter of the recurrent tumours was 1–7 cm (Table 1).

Table 1
Details of patients and tumours ($n=64$). Data are number of patients or tumours, unless otherwise stated.

Variable	Value
Sex:	
Male	21
Female	43
Median (range) age (years)	45 (2–80)
Histological type:	
Mucoepidermoid carcinoma	17
Adenoid cystic carcinoma	18
Acinic cell carcinoma	6
Malignant mixed tumour	7
Myoepithelial carcinoma	6
Adenocarcinoma	4
Basal cell adenocarcinoma	1
Sebaceous carcinoma	1
Lymphoepithelial carcinoma	1
Papillary cystadenocarcinoma	1
Oncocytic adenoma	1
Sialoblastoma	1
Recurrences:	
One	45
More than one	19
Size of tumour (cm):	
<2	6
2–4	30
4–6	23
>6	5
Treatment:	
Parotidectomy	50
Parotidectomy and radiotherapy	14

Surgical treatment

Of the 64 patients, 40 had their tumours resected followed by brachytherapy. In 36 of these the resection was complete but in the remaining 4 it was incomplete because the facial nerve was encased in tumour, and the patients requested that the nerve be preserved. The volume of residual tumour was 2–4 cm³. The facial nerves of the patients who did not have facial nerve palsy before the operation were preserved. Twenty-four were not operated on for various reasons and they were treated with implantation of radioactive seeds alone.

Brachytherapy

The CT DICOM data of the patients was put into a special treatment plan system (Beijing Atom and High Technique Industries Inc., Beijing, China). For the patients treated by resection followed by implantation, the planned target volume was defined as 10 mm beyond the preoperative gross tumour volume and the postoperative bed from CT scans, combined with the target area as recorded by intraoperative photographs. The matched peripheral dose was 80–100 Gy, which was adjusted according to the previous dose of radiation and the adjacent structures. The dose for the patients with residual tumour was 120 Gy. For the patients treated by brachytherapy alone, the planned tumour volume covered the lesion with a 10 mm margin, and the matched peripheral dose was 120 Gy. The dose was prescribed as the matched peripheral dose together with the planned target volume. Doses delivered to organs at risk were designed to be within acceptable limits of tolerance by the computerised treatment planning system.

The ¹²⁵I seed (Beijing Atom and High Technique Industries Inc., Beijing, Model 6711, $t_{1/2}$ 59.4 days, energy level 27.4–31.4 keV) activity was 0.8 mCi, and seeds were implanted under CT or template guidance, or both, according to the plan. A mean of 41 ¹²⁵I seeds (range 11–101) were implanted and the CT scan and treatment planning system of each patient were obtained immediately after implantation to detect the location and distribution of seeds (Table 2).

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

Statistical analysis

Local control and overall survival were calculated using Kaplan–Meier survival curves. Data on patients who had operation and brachytherapy compared with those who were treated by brachytherapy alone were analysed separately. The log rank test was used to compare the 2 groups. Univariate analyses were used to measure the effect of the following characteristics on outcome: sex, age, histopathological grade, size of tumour, history of radiotherapy, time of recurrence,

Table 2
Methods of treatment.

Variable	Number
Resection of tumour and brachytherapy with radioactive seeds	40
Brachytherapy with radioactive seeds alone	24
Resection of tumour:	
Complete	36
Incomplete	4
Brachytherapy with radioactive seeds:	
Activity of ¹²⁵ I seeds (mCi)	0.8
Mean (range) ¹²⁵ I seeds	41 (11–101)
Matched peripheral dose (Gy)	80–120

and method of treatment. We used SPSS (version 13, SPSS Inc., Chicago, IL) for analysis.

Results

Efficacy of treatment

Of the 24 patients treated by brachytherapy alone, 22 achieved complete response; the follow-up time was 4 months to 9 years, and the success rate was 91.7%. In the remaining two patients, the tumours were not controlled, and both patients died. In addition, four patients died of metastases. Five patients developed further local recurrence (after 12–36 months). These patients had their brachytherapy repeated; 3 had good outcomes but 2 died of metastases. The local control rates and overall survival are shown in Table 3 and Figs. 1 and 2.

Forty patients had their tumours resected followed by implantation of radioactive seeds. In 36 the resection was complete, and in 4 incomplete. The patients were followed up for 1–12 years, and 8 patients developed local recurrences. Two died of recurrence, and 3 died of metastases. In the 4 whose resection was only partial, the residual tumours disappeared after brachytherapy. After follow-up for 1–5 years,

Table 3
Efficacy of treatment.

Time	Brachytherapy with radioactive seeds alone	Resection of tumour and brachytherapy with radioactive seeds
Local control rate (%):		
1 year	81.5	87.5
3 years	67.2	82.4
5 years	53.8	78.6
Overall survival (%):		
1 year	82.7	97.5
3 years	70	86.5
5 years	61.2	86.5
Duration of follow up	4 months–9 years	1–12 years

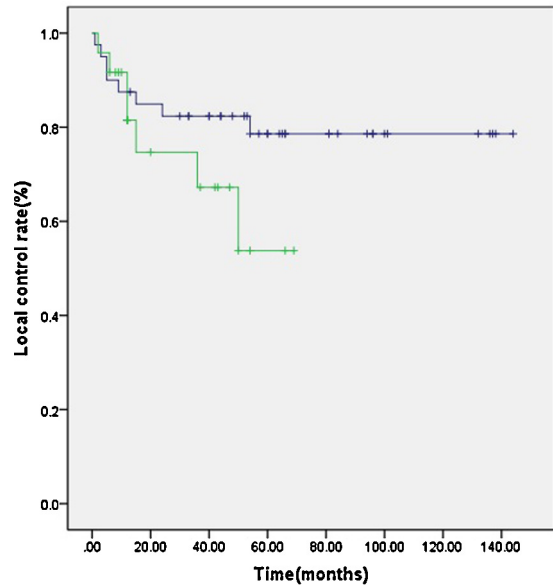


Fig. 1. Kaplan–Meier curve of local control for patients who had brachytherapy alone (green line) compared with those who had operation and brachytherapy (blue line).

only one of these patients developed a recurrence and died 2 years later. The local control rates and overall survival are shown in Table 3 and Figs. 1 and 2, and the difference between the group who had brachytherapy after partial resection was significant ($p = 0.008$) (Fig. 2).

The total group was followed up for a mean of 50 months (range 4 months to 12 years). The local control rate was 76.6% and the overall survival 79.7%. Twenty patients were disease-free for more than 5 years. In 15 patients, the tumour recurred locally or the first recurrence had not been controlled. Three

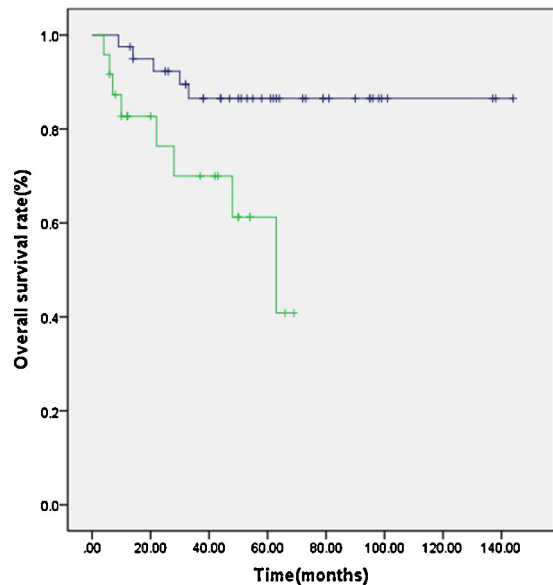


Fig. 2. Kaplan–Meier curve of overall survival for patients who had brachytherapy alone (green line) compared with those who had operation and brachytherapy (blue line).

patients had lymph node metastases in the neck (including 2 patients with local recurrence). Four patients died of their local recurrence, and 9 died of metastases to other organs.

The results of univariate analyses showed that none of the following characteristics differed significantly affected local control: sex (chi square = 0.38, $p = 0.54$), age (chi square = 0.04, $p = 0.83$), histopathological grade (chi square = 1.08, $p = 0.30$), size of tumour (chi square = 1.30, $p = 0.25$), radiotherapy history (chi square = 1.94, $p = 0.164$), recurrence times (chi square = 0.29, $p = 0.59$) and method of treatment (chi square = 1.86, $p = 0.17$). However, method of treatment had a significant impact on overall survival: sex (chi square = 0.06, $p = 0.81$), age (chi square = 0.26, $p = 0.61$), radiotherapy history (chi square = 0.05, $p = 0.83$), recurrence times (chi square = 0.10, $p = 0.76$), method of treatment (chi square = 6.99, $p = 0.008 < 0.01$), size of tumour (chi square = 2.73, $p = 0.098$), and histopathological grade (chi square = 0.20, $p = 0.65$) (Fig. 2).

Function of the facial nerve

Forty-two patients had no palsy of the facial nerve, and 28 of them were operated on. The facial nerves of 2 patients were damaged during dissection, one of whom had an immediate nerve graft. In the other patient, the proximal end of the nerve could not be found, and so it could not be reconstructed. Function of the facial nerve was good 6 months postoperatively in 27 patients (including the patient who had the nerve grafted).

Side effects of brachytherapy

Two patients who had been treated with radiotherapy previously developed ulceration of the skin wound (RTOG grade 4). The ulcer in one healed after 11 months, and in the other it had partially healed after 6 months. Other patients developed pigmentation of the skin (RTOG grade 1).

Discussion

The most common cause of failure of treatment in patients with malignant parotid tumours is local recurrence, and Koul et al. assessed 184 such patients including 34 (38%) with local recurrence.¹⁰ Recurrent malignant parotid tumours with indistinct borders and multifocal recurrent tumours have often been incompletely resected and are therefore at greater risk of local recurrence. Kobayashi et al. reviewed 20 patients with recurrent tumours of the parotid gland, and found that 9 patients developed secondary parotid cancer after the initial operation, and 11 developed multiple recurrences (mean 2.8).⁹ In our study, 19 patients (30%) developed 2 or more recurrences, and some developed up to 4. The mean (SD) interval between recurrence and the last treatment was 2 (range 8–72 months, MEAN 23 months, SD = 19.61) years, and the shortest interval was less than a year.

The treatment of recurrent malignant parotid gland tumours is difficult, as they usually adhere to the mastoid process, mandible, muscle, and facial nerve, which makes extensive resection difficult.¹¹ Postoperative radiotherapy is therefore required to reduce the rate of local recurrence. However, further irradiation can cause severe side effects in patients who have previously been treated with radiotherapy.^{12,13} Pederson et al. gave repeat radiotherapy to 14 patients with recurrent malignant salivary gland tumours. Ten patients developed grade 3 (or higher) mucositis, and 3 developed skin toxicity. Six patients had feeding tubes until the time of their last follow-up or death.¹⁴ Brachytherapy with radioactive seeds may be a good alternative to a repeat course of radiotherapy because it involves low energy, the dose reduces sharply with distance, and non-malignant tissues are given lower doses, which avoids severe side effects.^{15,16} Brachytherapy with radioactive seeds is also highly effective for malignant parotid gland tumours and other malignant tumours of the salivary glands.^{17,18} Of the 64 patients in our study, 14 had previously been treated with radiotherapy. Of these, 2 developed grade 4 skin toxicity, and none developed mucositis or ear toxicity.

Resection combined with postoperative radiotherapy is the mainstay of treatment in primary malignant parotid gland tumours, and has yielded 5-year local recurrence rates of 11%–37% and overall survival of 55%–87%.^{1,3,19,20} In our study, 40 patients with recurrent parotid gland tumours had their tumours resected followed by brachytherapy; the 5-year local control rate was 78.6%, and the 5-year overall survival was 86.5%. The overall survival in our study is better than the 5-year overall survival of 66.7% and the 3-year overall survival rate of 35.7% reported for recurrent salivary tumours treated with surgery alone and those treated with chemotherapy plus reirradiation, respectively.^{9,14} Resection combined with brachytherapy can therefore improve local control rates and survival in patients with recurrent parotid carcinomas and even equals the rates achieved in patients with primary tumours.

For patients who are unfit for surgery or who have unresectable tumours, radiotherapy is the primary treatment, and yields 5-year local control rates of 21%–28%.²¹ Fast neutron radiotherapy produces better control rates,²² but tends to cause severe side effects, and is not widely used because it requires expensive specialised equipment. Matthiesen et al. reported that of 17 patients with malignant parotid gland tumours treated with radiotherapy alone, 11 achieved a complete clinical response.²³ Magnano et al. identified relapse in 3/15 of patients whose tumours were treated with radiotherapy alone; the patients who relapsed responded poorly to operation, radiotherapy, and other treatments.²⁴ In our study, 22 of the 24 patients treated with brachytherapy alone achieved complete response, yielding an effective rate of 91.7% (Table 3). Brachytherapy with radioactive seeds is therefore a good treatment for patients with recurrent malignant tumours of the parotid gland, even though its

efficacy was poorer than that of resection combined with brachytherapy.

Some studies have shown that age, grade, stage, perineural invasion, and resection margins were prognostic factors. We have shown that no factor had a significant effect on local control, but the method of treatment was confirmed to have a significant impact on overall survival. Patients treated by resection and brachytherapy did better than those who had brachytherapy alone.

Recurrent tumours are not easily distinguishable from normal tissues and scars, and they usually adhere to the facial nerve, which cannot be dissected. For these patients, resection necessarily involves the sacrifice of some branches of the facial nerve or even of the main nerve stem. Our previous research has indicated that resections that preserve the facial nerve combined with implantation of radioactive seeds produced good local control rates in patients with malignant tumours of the parotid gland.²⁵ In the present study, 28 patients who did not have facial palsy preoperatively had resections in which the facial nerve was preserved, and the function and local control rate were not influenced in 27/28 of these patients. The facial nerve should therefore be preserved as far as possible.

In conclusion, brachytherapy with implantation of radioactive seeds, either alone or combined with resection, is a good alternative treatment for recurrent malignant parotid tumours.

Conflict of interest

We have no conflict of interest.

Ethics statement/confirmation of patients' permission

The study was approved by the Ethics Committee of the University. All patients gave informed consent for publication.

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