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^{125}I seed implant brachytherapy-assisted surgery with preservation of the facial nerve for treatment of malignant parotid gland tumors

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Abstract. The surgical treatment of malignant parotid gland tumors combined with ^{125}I seed implant brachytherapy and preservation of the facial nerve is described. Tumor and parotid gland resection with preservation of the facial nerve was carried out in 12 patients with malignant parotid gland tumors. ^{125}I seeds were implanted into the target area intra- or postoperatively. The extent of regional control of the tumor was followed up, and facial nerve function was evaluated. None of the patients had tumor recurrence during the follow-up period of 50–74 months (median follow-up period, 66 months). Facial nerve function had recovered to normal by 6 months postoperatively in all patients. A limited surgical resection combined with ^{125}I seed implant brachytherapy is therefore considered to be an alternative treatment for local control of malignant parotid gland tumors with preservation of the facial nerve.

Keywords: radiotherapy; radioactive seeds; parotid gland; malignant tumor; facial nerve.

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Malignant salivary gland tumors account for approximately 1–3% of head and neck tumors and 7% of epithelial cancers[5,12,24]. Radical resection is currently the predominant treatment for malignant tumors of the parotid gland, despite a high local recurrence rate of 13–32% and distant metastasis rate of 13–26% postoperatively[14,31,34]. In advanced cases, the local recurrence rate could be up to 50–60%. Postoperative radiotherapy often needs to be prescribed to reduce tumor recurrence[6,15,17,19,30,33].

Preserving or sacrificing the facial nerve is an integrated part of treatment planning and depends on various factors, such as the clinical stage of the tumor, the biological differentiation of the tumor cells, and the extent of facial nerve invasion. Sacrificing the facial nerve can lead to aesthetic deficits and functional disability, causing emotional and psychological distress to the patient[4]. Preserving the facial nerve may compromise radical surgery, if the facial nerve has been invaded by the tumor. In such situations, postoperative radiotherapy of 40–60 Gy is routinely advised.

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External radiotherapy of the head and neck region is associated with some severe short- and long-term complications, such as extensive oral mucosal ulceration, and osteoradionecrosis of the upper or lower jaw[2,18,23,27]. A radiotherapy dose of 40–60 Gy is not considered sufficient to eliminate the residual tumor, since salivary tumors are less sensitive to radiotherapy. ^{125}I seed brachytherapy is a promising alternative method to external radiotherapy. It is easy and involves the use of low photon energy (27–35 keV). The seeds can be screened, and the dose reduced sharply with distance, thereby minimizing the risk of damage to the adjacent vital structures and to the staff; these properties make it an ideal isotope for application to this region[3,16,32].

The preliminary results of treating a group of patients with malignant parotid gland tumors by a combination of tumor resection and ^{125}I seed implantation with preservation of the facial nerve are described here.

Materials and Methods

Patients

Twelve patients (7 males and 5 females) aged between 14 and 48 years (median age 31 years) were included in this retrospective study. They were treated from 2001 to 2003 at Peking University School and Stomatology Hospital. To characterize the nature of the tumors, specimens were obtained intra- or postoperatively for pathological examination. Mucoepidermoid carcinoma was diagnosed in 6 patients (poorly differentiated in 2; moderately differentiated in 3; well differentiated in 1), adenoid cystic carcinoma in 3, and adenocarcinoma, papillary cystadenocarcinoma, and pleomorphic adenocacinoma in 1 patient each. The clinical staging of the tumors is shown in Table 1. Two patients (1 each with pleomorphic adenoma and adenocarcinoma) with facial nerve dysfunction were classified as T4a. Neck lymph node metastasis was not found in any patient. None of the patients had undergone radiotherapy previously. This study was approved by the Ethics Committee of Peking University. All patients provided written informed consent.

Surgical treatment

During surgery, the tumor with the entire parotid gland was dissected. Intraoperatively, the tumor was adherent to the main facial nerve trunk in 4 patients and to a few branches of the facial nerve in 6 patients, resulting in a fragile, thick and edematous appearance of the facial nerve (Fig. 1). The facial nerve was carefully separated from the surrounding tissue and the tumor mass. The main facial trunk and the temporal trunk were found to traverse the tumor mass in 1 patient each, thereby prohibiting direct separation from the tumor mass. In these situations, the tumor was grossly dissected first, and a small block (approximately 1.0 × 1.0 cm) of the tumor surrounding the nerve was left *in situ* (Fig. 2). A biopsy of the residual tumor was taken for immediate pathological examination and showed a positive result.

In all cases, pathological examination of intraoperative frozen sections was conducted at regular intervals. Of these, 9 cases had malignant tumors, and the ^{125}I seeds were implanted during surgery. Pathological examination of wax sections was required in 3 patients to establish a definitive diagnosis based on their tumor characteristics. After a definitive diagnosis was established, the seeds were implanted 2 weeks postoperatively.

Radical neck dissection was not performed because clinical examination and CT scanning did not show neck lymph node metastasis in any patient.

Table 1. Clinical stages of patients

Patient No.	Diagnosis	Tumor size(cm)	T	Stage
1	mucoepidermoid carcinoma(H)	2.0 × 1.5	T2	II
2	mucoepidermoid carcinoma(M)	2.5 × 1.8	T2	II
3	pleomorphic adenoma cancer	3.4 × 2.8	T4a	IVA
4	adnoid cystic carcinoma	3.0 × 2.7	T2	II
5	mucoepidermoid carcinoma(M)	3.8 × 3.5	T3	III
6	papillary cystadenocarcinoma	1.8 × 1.8	T1	I
7	mucoepidermoid carcinoma(M)	2.0 × 1.8	T2	II
8	adenocarcinoma	3.5 × 3.0	T4a	IVA
9	adnoid cystic carcinoma	2.2 × 1.9	T2	II
10	mucoepidermoid carcinoma(L)	3. × 2.0	T2	II
11	adnoid cystic carcinoma	2.4 × 22	T2	II
12	mucoepidermoid carcinoma(L)	3.5 × 2.8	T2	II

H, high grade; L low grade; M, medium grade

Placement of ^{125}I seed implants

The placement of ^{125}I seed implants was determined from CT scans in combination with the target area as recorded by intraoperative photographs. The ^{125}I seed activity was 0.7 mci. The matched peripheral dose (MPD) was 60 Gy. The reference point was located 0.5 cm outside the target area, and the reference point dose was 90% of the isodose line. The passage through which implantation was performed was 1 cm wide. Seed implantation was performed according to the Paris principles. Based on the scheme of implantation, the seeds were implanted at a depth of 10 mm. A CT scan and Treatment Plan System of each patient were obtained immediately after seed implantation to detect the location

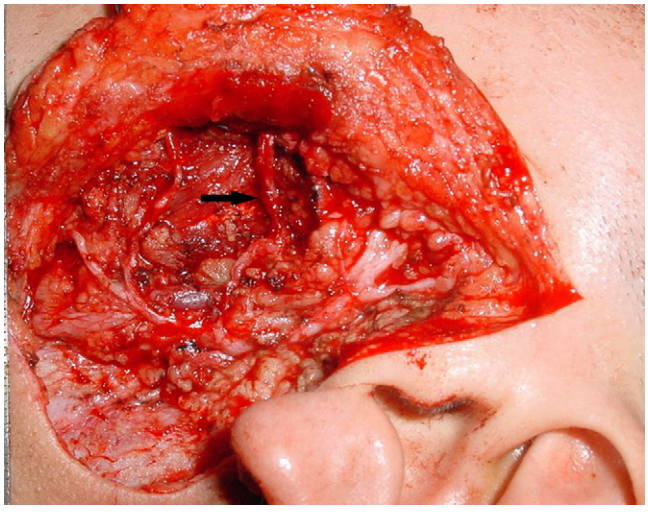

Fig. 1. Facial nerve (arrow) thickened and edematous.

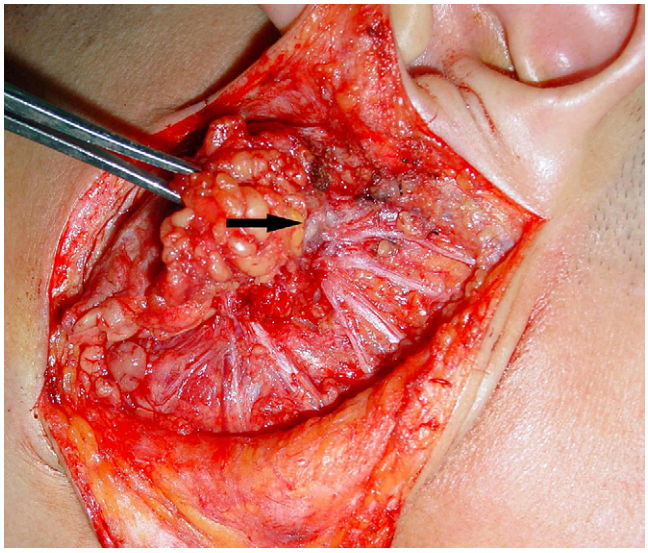

Fig. 2. Intraoperative view of the tumor tissue (arrow) adhering to the facial nerve.

and distribution of seeds. In cases where seeds were malpositioned in a way that could reduce the effect of radiotherapy, a group of new seeds was re-implanted. According to the scheme of implantation, 13–33 ^{125}I seeds (mean, 25) were implanted. The MPD was 60 Gy, D90 was >80 Gy, and V150 was <50%. In 9 patients, implantation was performed intraoperatively, and in the other 3, postoperatively. (Fig. 3a–c)

Follow-up and assessment of facial nerve function

During follow up, CT scans were performed every 2 months to examine for tumor recurrence, and TPS was used to analyze the dose at the target area and calculate the remaining dose.

Postoperatively, facial nerve function was evaluated regularly every 2 months according to 2 systems. The House-Brackman (H-B) system grades the extent of facial nerve disturbance into 6 levels (Table 2). Three observers independently analyze the photographs of each patient and the results of the photographic analysis are reported by an unbiased observer. Electroneurography (ENoG) was also carried out using a four-channel electroneurography instrument (OTE, Italy) with a frequency range of 20–50 Hz. Square wave stimulation was applied for 0.1 ms with a stimulation intensity of 15–20 mA. The inception electrode was a dipolar surface electrode with a diameter of 7 mm and was placed in front of the ear with the anode below the cathode. The recording electrodes were placed on the frontalis muscle (I), the upper eyelid orbicularis oculi muscle (II), the upper lip orbicularis oris muscle (III), and the quadrate muscle of the lower lip (IV). According to the Gantz method, the amplitude of the largest compound muscle action potential (CMAP) (i.e. Am) was recorded, and the nerve degeneration rate (DR) was calculated as DR (%) = affected side Am/healthy side Am × 100.

Results

Twelve patients were followed up for 50–74 months (average follow-up period, 66 months). During follow up, the residual tumors in 2 patients were found to have disappeared at 2 months after seed implantation. None of the patients had tumor recurrence or side-effects of radiotherapy, and none of them complained of dryness of the mouth, oral mucosal ulceration, or restriction of mouth opening.

Before treatment, facial nerve function was recorded in all patients according to the H-B system. Two were H-B grade III: weak and slight mouth opening with maximum effort was possible in one; and slight movement of the forehead was possible in the other. The remaining patients were H-B grade I. Postoperatively at 2 weeks, 5 patients were H-B grade V, and 7 were H-B grade IV. After 6 months, the function of the muscles of facial expression recovered completely in 10 H-B grade I patients. The 2 H-B grade III patients who had facial nerve dysfunction preoperatively recovered incompletely

Table 2. House–Brackman facial grading system

Grade	Characteristics
I. Normal	Normal facial function in all areas
II. Mild dysfunction	Gross Slight weakness noticeable on close inspection May have very slight synkinesis At rest, normal symmetry and tone Motion Forehead: moderate to good function Eye: complete closure with minimal effort Mouth: slight symmetry
III.Moderate dysfunction	Gross Obvious but not disfiguring difference between the two sides. Noticeable but not severe synkinesis, contracture, or hemifacial spasm At rest, normal symmetry and tone Motion Forehead: slight to moderate movement Eye: complete closure with effort Mouth: slightly weak with maximum effort
IV.Moderately severe dysfunction	Gross Obvious weakness and/or disfiguring asymmetry At rest, normal symmetry and tone Motion Forehead: none Eye: incomplete closure Mouth: asymmetric with maximum effort
V.Severe dysfunction	Gross Only barely perceptible motion At rest, asymmetry Motion Forehead: none Eye: incomplete closure Mouth: slight movement
VI. Total paralysis	No movement

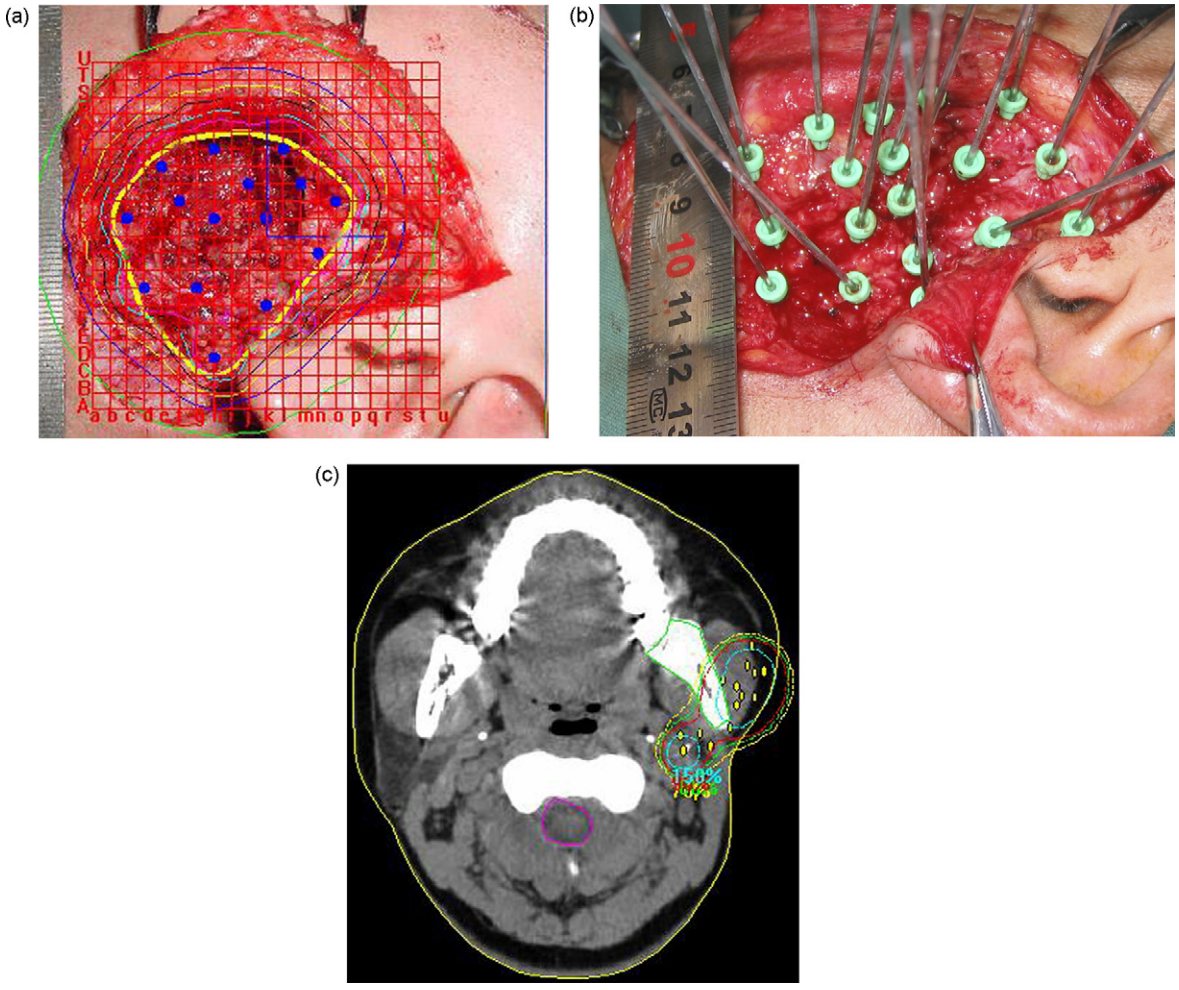

Fig. 3. (a) Implant plan for TPS seeds; blue dots indicate seed position, the yellow line is the target area. (b) Seeds implanted. (c) CT verification of the dose and seed position; the yellow dot shows the seed and the red line is the 90% dose isodose line.

with H-B grade II up to 36 and 40 months of follow up.

Before treatment, ENeG was used to record the extent of damage to the facial nerve as a result of tumor invasion. The DR of 4 involved facial nerve branches was 70–90% and that of 12 involved facial nerve branches was 40–70%. At 2 weeks after treatment, 18 facial nerve branches were found to have DR >70%. After 6 months, ENeG indicated that only 5 facial nerve branches had DR >70% (Tables 3 and 4).

Table 3. The facial nerve function of parotid gland malignant tumor evaluated before and after treatment using the House–Brackman grading system

Time	Grade				
	I	II	III	IV	V
Pretreatment	10	0	2		
Two weeks after treatment				7	5
Two months after treatment		6	6		
Four months after treatment	8	4			
Six months after treatment	10	2			

Table 4. The nerve degeneration rate of parotid gland malignant tumors before and after treatment

Degeneration rate	<10%	10–40%	40–70%	70–90%	>90%
Pretreatment	20	12	12	4	0
2 weeks post treatment	2	12	16	12	6
6 months post treatment	24	13	6	3	2

Discussion

Management of parotid malignant tumors and preservation of the facial nerve

The routine treatment of malignant parotid gland tumors is extensive excision of the tumor and the parotid gland. If the facial nerve is adherent to the tumor, it is always sacrificed[12,29]. Facial nerve resection results in drooping of the angle of the mouth and difficulty in closing the eye and raising the eyebrow, and has serious effects on the patient's quality of life[21]. In the present study, the facial nerve was carefully dissected during surgery and was preserved, thus allowing nerve function to be restored gradually after surgery. The residual tumor cells can be killed completely by ^{125}I seed brachtherapy. Spiro and Spiro indicated that sacrificing

the facial nerve does not improve the treatment outcome in patients with parotid cancer[28]. In the present study, pre- and postoperative ENeG showed that some facial nerve branches had been damaged heavily and could not recover completely; although other branches had recovered (DR >70%) after 6 months. According to the H-B system, facial nerve function had resumed up to grade I and grade II simultaneously, leading to slight facial asymmetry. Previously, routine nerve grafting sacrificed other provide nerves and led to slower recovery. Reddy et al. reported the results of nerve grafting after resection in 12 patients: all patients were less than H-B grade IV after 6 months and 9 resumed to H-B grade III after 2 years; most of these patients were <30 years old[26]. Recovery of the grafted nerve was slow, generally starting by the ninth month with clinically obvious improvement by 2 years[10,13]. ENeG shows the peak of the nerve reinnervation wave after 3–5 months, and clinical signs are evident by 6–10 months; however, nerve function does not improve further until over 1 year.

Radiotherapy in the management of parotid gland malignant tumor

The most common cause of failure of treatment of malignant parotid gland tumors is local recurrence[7]. Owing to the anatomical characteristics of the parotid gland, tumor resection is restricted by the facial nerve, and a safe margin of tumor resection is difficult to obtain; in particular, attempting to preserve the facial nerve in younger patients influences radical resection of the tumor. Postoperative radiotherapy is necessary to improve the local control rate of the tumor[9,20].

Previous studies have reported that radiotherapy can be used only for palliative therapy of malignant parotid gland tumors since these include epidermal or adenoid carcinomas that are not sensitive to radiotherapy[2]. An increasing number of studies have indicated that surgery combined with radiotherapy improves the local control rate of the tumor and patient survival[1,11]. The γ-ray irradiation distance of ^{125}I seeds is short (17–20 mm), which increases the dose to the target area and gives a very low dose of radiation to the surrounding normal tissue. Using ^{125}I seed implantation, the dose of radiation to the centre of the target area is double compared with routine external radiotherapy, thereby ensuring complete tumor treatment[25]. In addition, the seeds can be implanted in the defined area intraoperatively. Routine external radiotherapy has the disadvantages of low dose to the target area and a long duration of treatment, which can kill only the M-phase tumor cells, and can result in skin infection, oral mucosal ulceration, anorexia, nausea, restriction of mouth opening, and osteoradionecrosis of the mandible, necessitating discontinuation of treatment in some cases due to intolerable side-effects. Fast neutron radiotherapy has good efficacy for the treatment of some residual tumors, but its disadvantages are high cost and grade III/IV side-effects[8].

^{125}I seed implant brachytherapy for treatment of malignant tumors of the head, neck, breast, lung, prostrate and skin has many advantages, such as microsurgical technique, high effectiveness, fewer side-effects, and a treatment efficiency of 83–100%. ^{125}I seed treatment has been a standard treatment regimen for some prostate cancers[22]. The local recurrence rate of primary parotid carcinoma is 13–32%, and most cases have tumor recurrence within the first 3 years after initial treatment[33]. In this study, none of the 12 patients had tumor recurrence during the follow-up period of 50–74 months. Facial nerve function was restored at 6 months postoperatively. The follow-up period for some malignant parotid gland tumor is known to be as long as 10–15 years; therefore these patients are still being followed up.

In conclusion, ^{125}I seed implant brachytherapy may be an adjunctive method for the preservation of facial nerve during treatment of parotid gland malignant tumor. Considering the morphological heterogeneity and relative rarity of this type of tumor, arriving at a definite conclusion requires a large number of patients and long-term follow up.

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