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^{125}I Seed implant brachytherapy for the treatment of parotid gland cancers in children and adolescents

Salivary gland neoplasms are rare in children and adolescents and less than 5% of all salivary gland tumors are found in patients ≤16 years of age [1]. The frequency of individual salivary neoplasms is most common in the parotid gland and most parotid gland tumors in children and adolescents are malignant [2, 3, 4, 5, 6]. As a result of their rarity, optimal treatment strategies to manage these diseases are lacking. Radiation, when recommended in children, has similar indications to those for adult patients [2, 7, 8].

^{125}I seed brachytherapy remains an attractive option for radiating limited volumes with higher doses to improve local control in malignant parotid gland tumors [9]. This paper presents our experience with 12 cases of parotid cancers occurring in children who were treated with ^{125}I seed implant brachytherapy.

Patients and methods

Patients

Between October 2003 and November 2008, 12 patients (7 boys and 5 girls) aged between 1 and 15 years were included in this retrospective study. In all patients the tumors were pathologically examined prior to ^{125}I seed implant brachytherapy. Myoepithelial carcinoma was diagnosed in 7 patients, acinar cell carcinoma in 2, sebaceous carcinoma in 1, adenocarcinoma in 1, and sialoblastoma in 1 patient. Details of tumor characteristics are given in **Tab. 1**. No patient had neck lymph node metastases or distant metastases. The tumor classification for 8 patients was T2 (**Fig. 1a**), and for 4 patients was T4b (**Fig. 3a, b**). Treatment was approved in all cases by the Ethical Committee of Peking University School and Hospital of Stomatology. All patients' guardians provided written informed consent prior to their inclusion in the study.

Treatment

Eight patients with T2 underwent conservative surgical resection followed by ^{125}I seed brachytherapy. The tumor was dissected with the entire parotid gland during surgery. Intraoperatively, the tumor was close to a few branches of a facial nerve in 3 patients and adherent to a few branches of facial nerve in 4 patients (**Fig. 1b**). The facial nerve was carefully separated from the surrounding tissue and the tumor mass in 7 patients. The temporal branch was found to traverse the tumor mass in 1 patient. The branch was cut and nerve was anastomosed. Four patients with T4b underwent biopsy and no tumor resection was performed. All patients had malignant tumors as determined by pathological examination of wax sections.

No patient had neck dissection because no evidence showed neck lymph node metastasis in clinical examination and CT scan.

Seed implantation treatment planning

Treatment planning for all patients was designed by a computerized treatment planning system (RT-RSI; Beijing Atom and High Technique Industries Inc., Beijing, China). The planning target volume (PTV) was defined at 10–15 mm beyond the preoperative gross tumor volume (GTV) and the postoperative bed from computerized tomography (CT) scans in combination with target area as recorded by intraoperative photographs. The ^{125}I seed activity was 0.7–0.8 mCi. The matched peripheral dose (MPD) was 60 Gy for 8 patients with T2 and 120 Gy for 4 patients with T4b. The dose was prescribed as the MPD encompassing the PTV. Dosages delivered to organs at risk were designed within acceptable limits of tolerance by the computerized treatment planning system.

^{125}I seed implantation

The implantation of radioactive seeds was performed at approximately 2 weeks postoperatively in all patients after wound healing had been achieved. The distribution of ^{125}I seeds (Beijing Atom and High Technique Industries Inc., Beijing, Model 6711, $t_{1/2}$ 59.4 days, energy level 27.4–31.4 KeV) was determined from CT scans in combination with the target area as recorded by intraoperative photographs. The interstitial needles (18-gauge, stainless steel, hollow needles) were inserted into the target area (with a 0.5 cm margin), 1 cm apart. An applicator was then sequentially attached to the distal end of the needles to place the ^{125}I seeds into the target area. According to the scheme of implantation, 11–97 ^{125}I seeds (mean 35) were implanted (**Tab. 2**). The space between seeds (center to center) was maintained at 10 mm. A CT scan and treatment plan system for each patient were obtained immediately after seed implantation to detect seed location and dose distribution (**Fig. 1d**). Dosages to organs at risk were within acceptable limits of tolerance after treatment.

Tab. 1 Patient and tumor characteristics

Characteristics	Value
Sex (n)	
Male	7
Female	5
Age (years)	
Median	13
Range	1–15
Histology	
Mucoepidermoid carcinoma (high grade)	2
Mucoepidermoid carcinoma (low grade)	5
Acinar cell carcinoma	2
Sebaceous carcinoma	1
Adenocarcinoma	1
Sialoblastoma	1
Primary or recurrent tumor	
Primary tumor	9
Recurrent tumor	3
Tumor size	
2.0–3.0 cm	6
3.0–4.0 cm	2
Over 6 cm	4
Tumor location relative to the facial nerve	
Close to the facial nerve	3
Adherent to the facial nerve	4
Surrounding the facial nerve	5
Facial nerve function before surgery (H-B system)	
Grade I	6
Grade II	5
Not available	1
Facial nerve function before brachytherapy (H-B system)	
Grade II	6
Grade III	3
Grade IV	1
Grade V	1

H-B House-Brackman facial grading system.

Tab. 2 Characteristics of ^{125}I seed implantation and outcome

	Value
Surgery type (n)	
Conservative surgery with preservation of the facial nerve	7
Conservative surgery with sacrifice of the facial nerve trunk	1
Incisional biopsy	4
Matched peripheral dose of ^{125}I seed implantation (Gy)	
For T2	60
For T4b	120
^{125}I seed activity (mCi)	0.7–0.8
Number of ^{125}I seeds	
Median	35
Range	11–97
Follow-up (months)	
Median	72
Range	41–104
Status	
Distant metastases	1
Related death	1
No evidence of disease	11
Facial nerve function 6 months after brachytherapy (H-B system)	
Grade I	10
Grade III	1
Toxicities after ^{125}I seed implantation	
Temporary skin redness	6
Temporary skin pigmentation	2
Permanent skin pigmentation	4
Slight restriction of mouth opening	1

H-B House-Brackman facial grading system.

Assessment of facial nerve function

Eight patients with T2 and 3 patients with T4b had facial nerve function evaluated before seed implantation (**Fig. 1c**) and regularly every 2 months after seed implantation according to the House-Brackman (H-B) facial grading system (**Fig. 2, 3**).

The H-B system classifies the extent of facial nerve disturbance into six levels. Three observers independently analyzed the photographs of each patient and an unbiased observer reported the results of the photographic analyses.

Follow-up and assessment of toxicity

All patients had a follow-up assessment every 2 months or earlier, if a new clinical sign or symptom appeared, with a complete history and physical examination and a CT scan. Local control was defined as lack of tumor recurrence either in or adjacent to the implanted volume on physical and radiographic examination. A computerized treatment planning system was used to analyze the dose at the target area and to calculate the remaining dose. Toxicity was graded according to the Radiation Therapy Oncology Group (RTOG) grading system and the National Cancer Institute common toxicity criteria (version 3.0; [10]).

Statistical methods

Descriptive statistics were calculated for patient and tumor characteristics, treatment features, and toxicities. Overall survival was calculated from the date of implantation to the last follow-up date or death. Disease-free survival was calculated from the date of implantation to the time of locoregional recurrence, distant metastasis, or death. Overall and disease-free survival rates were calculated using the Kaplan–Meier method.

Results

Eight patients with T2 were followed up for 47–104 months (average follow-up period 81 months). During this period, there was no evidence of locoregional recurrence or distant metastasis. These patients were alive at the final follow-up assessment. Four patients with T4b were followed up for 41–59 months (average follow-up period 50 months). Three pa-

tients with T4b had complete remission and no recurrence or distant metastasis (Fig. 3d, e). One patient with T4b had partial remission and died of pulmonary metastasis 41 months after seed implantation. The other 3 patients with T4b were alive at the final follow-up assessment. The 3-year and 5-year disease-free survival rates were both 91.7%, the 3-year overall survival was 100%, and the 5-year overall survival was 91.7% using the Kaplan–Meier method.

Temporary redness of skin was observed in 2 patients with T2 and 4 patients with T4b, and a further 2 patients with T2 developed temporary skin pigmentation within 2 months of seed implantation (Fig. 2b). Skin effects in all the patients with T2 had recovered within 12 months of seed implantation (Fig. 2d), and all the patients with T4b had developed permanent skin pigmentation. One patient with T4b had slight restriction of mouth opening. None of the patients experienced serious radiotherapy side effects, and none complained of dryness of the mouth or oral mucosal ulceration. No radiation-induced tumor or effects on facial growth and development were observed. No keloid scarring was observed in the field of the operation.

Before treatment, facial nerve function was recorded in all patients with T2 and 3 patients with T4b according to the H-B system. Two patients with T2 and 3 patients with T4b had weakness only of the marginal branch of the facial nerve, corresponding to H-B grade II paresis. The remaining patients were H-B grade I. One week postoperatively, facial nerve function was recorded again in all patients. One patient with temporal branch anastomoses had no movement of the forehead, corresponding to an H-B grade V paresis. One had incomplete eye closure, corresponding to an H-B grade IV paresis. Three were H-B grade III, with slight movement of the forehead possible in two, and slight and weak mouth opening with maximum effort possible in the third. Six were H-B grade II and slight symmetry of mouth opening was possible. After 6 months, function in all muscles of facial expression had completely recovered in 10 patients (Fig. 2a, c, Fig. 3f), and the patient with temporal branch anastomoses recovered to H-B grade III.

Discussion

Parotid gland malignant tumors are rare in children, and as a result, there is a lack of optimal treatment strategies for the management of this condition. The routine treatment of malignant parotid gland tumors in adults involves extensive excision, and if the facial nerve is adherent to the tumor, it is always sacrificed [11, 12]. Surgery needs to ensure preservation of the facial nerve in children unless the nerve is directly invaded or the intact nerve limits resection [7, 13, 14]. In the present study, the facial nerve was carefully dissected during surgery in 8 patients with T2, in 1 case the temporal branch was cut and required nerve anastomosis. Thus, facial nerve function may recover gradually postoperatively. According to the H-B

Abstract · Zusammenfassung

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Abstract

Background and purpose. There is a lack of optimal treatment strategies for managing salivary gland cancers in children and adolescents. This study is aimed at assessing the effect of ^{125}I seed implantation for the treatment of parotid cancers in children and adolescents.

Patients and methods. A total of 12 patients younger than 16 years with parotid gland malignant tumors underwent ^{125}I seed implant brachytherapy between October 2003 and November 2008. All patients were assessed after treatment and at the local tumor control appointments. Facial nerve function, maxillofacial development, and radioactive side-effects were assessed.

Results. The follow-up period ranged from 41–104 months. One patient with T4b died of pulmonary metastasis. The other patients were alive during the follow-up period. There were no serious radiation-related complications. The treatment did not affect facial nerve function and dentofacial growth in any of the children.

Conclusion. For parotid gland cancers in children, ^{125}I seed implant brachytherapy may be an acceptable treatment without serious complications and with satisfactory short-term effects.

Keywords
Brachytherapy · Parotid gland · Neoplasms · Children · Adolescents

Brachytherapie mit ^{125}I-Seed-Implantation zur Behandlung von Parotiskarzinomen bei Kindern und Jugendlichen

Zusammenfassung

Hintergrund und Ziel. Es gibt einen Mangel an optimalen Strategien für die Behandlung von Speicheldrüsenkrebs bei Kindern und Jugendlichen. Das Ziel dieser Studie ist die Beurteilung der Wirkung einer ^{125}I-Seed-Implantation bei der Behandlung von Parotiskarzinomen bei Kindern und Jugendlichen.

Patienten und Methoden. Insgesamt 12 Patienten unter 16 Jahren mit bösartigen Tumoren der Ohrspeicheldrüse unterzogen sich von Oktober 2003 bis November 2008 einer Brachytherapie mit ^{125}I-Seed-Implantation. Alle Patienten wurden nach der Behandlung und lokaler Tumorkontrolle nachverfolgt. Fazialisfunktion, Kieferentwicklung und radioaktive Nebenwirkungen wurden beurteilt.

Ergebnisse. Die Nachbeobachtungszeit betrug 41–104 Monate. Ein Patient mit T4b verstarb aufgrund von Lungenmetastasen. Die anderen Patienten überlebten die Follow-up-Periode. Es gab keine schwerwiegenden strahlenbedingten Komplikationen. Bei keinem der Kinder hatte die Behandlung einen Einfluss auf die Fazialisfunktion und das dentofaziale Wachstum.

Schlussfolgerung. Für Krebserkrankungen der Ohrspeicheldrüse bei Kindern kann eine Brachytherapie mit einer ^{125}I-Seed-Implantation eine akzeptable Behandlung ohne schwerwiegende Komplikationen und mit zufriedenstellender kurzfristiger Wirkung sein.

Schlüsselwörter
Brachytherapie · Ohrspeicheldrüse · Neoplasien · Kinder · Jugendliche

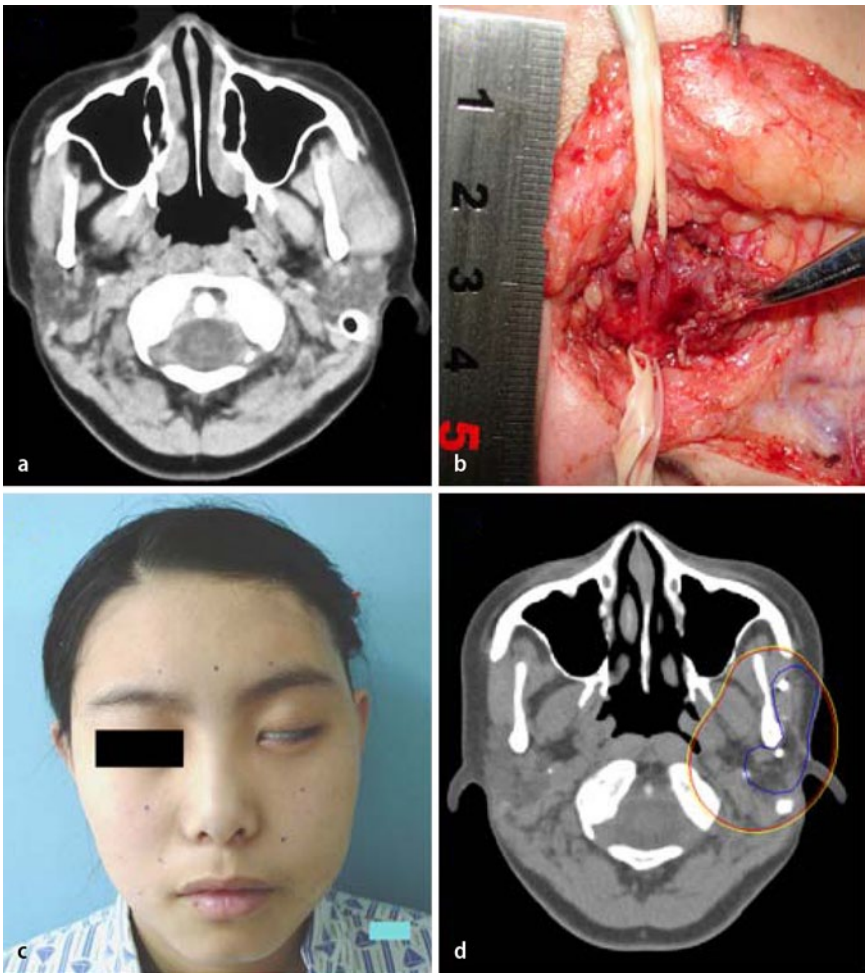

Fig. 1 ▲ **a** CT shows the tumor in the *left* parotid gland. **b** The buccal branches of facial nerve are adherent to the tumor. **c** This patient had incomplete eye closure 1 week postoperatively. **d** A typical transverse slice shows the distributions of the ^{125}I seeds and isodose curves of the patient underwent postoperative ^{125}I seed implant brachytherapy

system, facial nerve function had recovered to the level of grade III.

Radiotherapy is often used in case of residual disease, high-grade tumors, perineural and vascular invasion, soft tissue extension, large lesions, and multiple level nodal metastases [7, 15]. It is reported that a case with recurrent high grade mucoepidermoid carcinoma was successfully treated by reirradiation in combination with cetuximab and that accelerated radiotherapy using the concomitant boost technique is feasible in patients with locally advanced head and neck cancer [16, 17]. Some studies have indicated that surgery combined with radiotherapy improves local tumor control and patient survival [18, 19]. However, postoperative radiotherapy in children needs to be used with caution because of radiation-induced sequelae. There is a lack of optimal treatment strategies for managing these T4b diseases. In one series, postradiation sequelae were noted in 60% of cases, which included dental caries, delayed dental development, and trismus [7]. In the current study, 8 patients with T2 required postoperative radiotherapy as a result of perineural invasion and 4 patients with T4b needed radiotherapy. There are few reports in the literature on the use of interstitial brachytherapy in the treatment of parotid cancer. ^{125}I seed brachytherapy remains an attractive option for radiating limited volumes with higher doses to improve local control in malignant parotid gland tumors [9]. Its main advantage over external radiotherapy derives from its enhanced conformality and rapid dose fall off, thus, delivering biologically higher doses to the tumor while at the same time reducing the dose to adjacent normal structures at a very low dose rate (0.07–0.09 Gy/h initial dose rate, $t_{1/2}$=60 days) [20, 21]. This allows repair of sublethal damage that protects healthy organs from late tissue damage. Theoretically, the very low dose rate of ^{125}I, an advantage in terms of late tissue damage, may be adequate to control slow growing tumors. In two different rat prostate tumor models (Dunning-PAP and Nb AI-1), Nag et al. [22, 23] have shown that the low dose rates achieved by ^{125}I (0.07–0.09 Gy/h) produced less tumor growth delay than that produced by the higher dose rates achieved by Pd-103 (0.17–0.20 Gy/h). Most parotid gland cancers are slow growing tumors. Thus, theoretically ^{125}I seed implantation is more appropriate for children with parotid gland cancers than other types of brachytherapy. These properties make it an ideal isotope for application to parotid gland cancers in children. ^{125}I seed implant brachytherapy did not affect recovery of the injured facial nerve in our study. Facial nerve function of 10 patients was restored within 6 months of surgery. During follow-up, all patients who had received seed implantation brachytherapy had no long-term trismus, dentofacial deformity, osteoradionecrosis, or secondary malignant changes.

The local recurrence rate of primary parotid carcinoma is 13–32%, and most cases have tumor recurrence within 3 years of the initial treatment [24]. In this study, all patients underwent seed implantation because of residual disease, perineural invasion, soft tissue extension, and close margins. None of the 8 patients with T2 or 3 patients with T4b had tumor recurrence during the follow-up period, and only 1 patient with T4b died of pulmonary metastasis 41 months after the seed implantation. Although this follow-up period is relatively short, good control was achieved in all patients.

There are some reports in the literature that 5–10% of children treated for first malignancy have developed subsequent second tumors with long follow-up time [25, 26]. The important radiation-induced second malignant tumors are central nervous system tumors, thyroid tumors, osteosarcoma, soft tissue sarcomas, and non-melanoma skin cancer [27]. In this

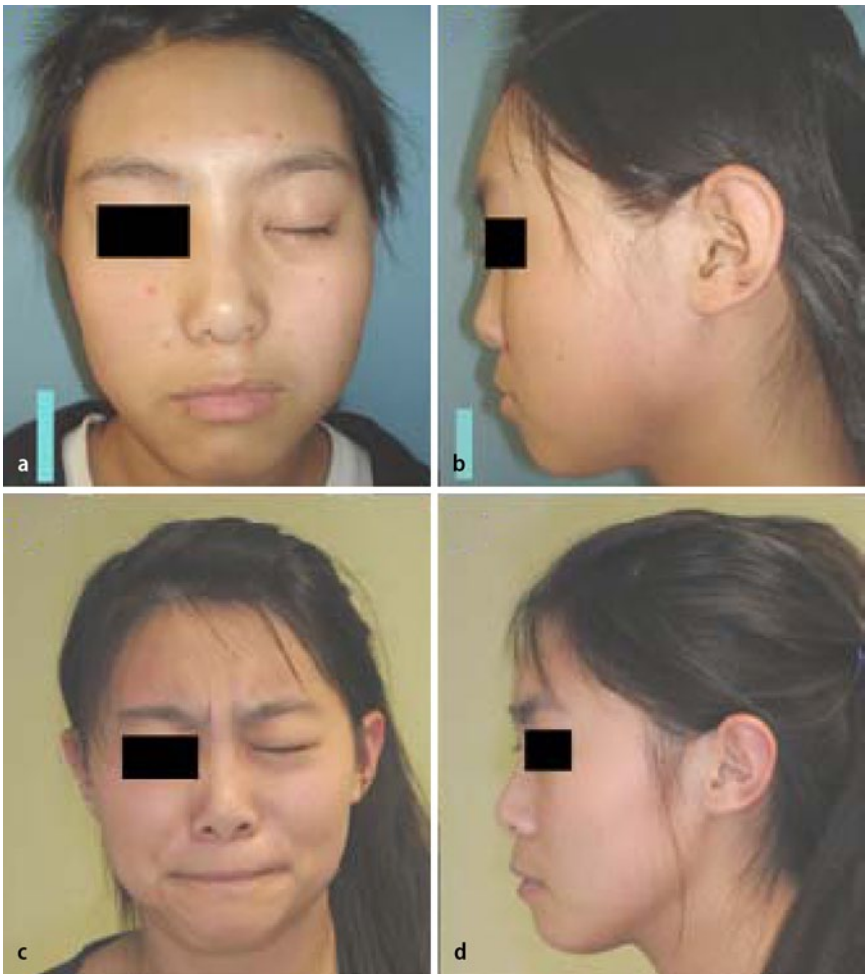

Fig. 2 ▲ **a** After 6 months, the patient who underwent postoperative ^{125}I seed implant brachytherapy recovered with H-B grade I. **b** Temporary skin pigmentation in the left parotid gland region. **c**, **d** After 36 months, there were no serious complications in the local region and the skin of the *left* parotid gland recovered

study, there were no radiation-induced second malignant tumors during the follow-up. Radiation-induced tumors tend to have a longer latency. Thus, these children in the study need life-long follow-up.

Conclusion

This study of children and adolescents with parotid gland cancer treated with ^{125}I seed implantation brachytherapy demonstrates good local control and overall survival rates with few complications. ^{125}I seed implantation brachytherapy may be an alternative method for the treatment of parotid gland cancers in this population; however, further studies are needed with larger numbers of patients and a longer follow-up assessment.

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Conflict of interest. On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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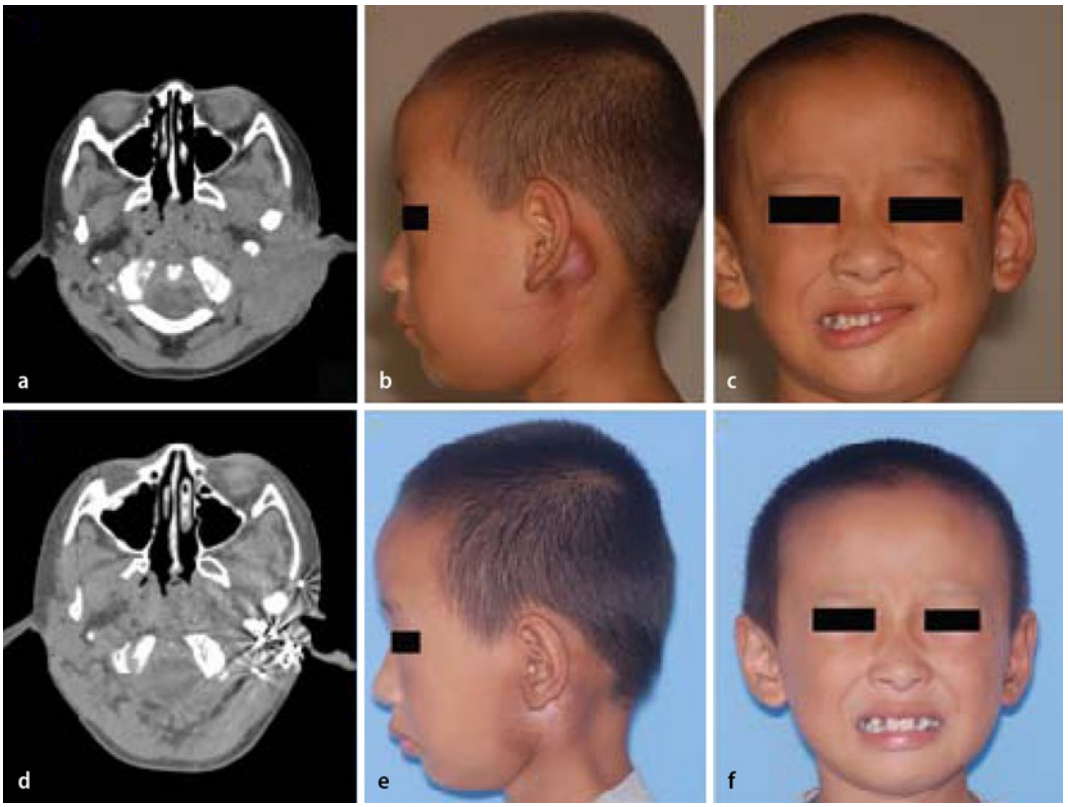

Fig. 3 ◀ **a** CT shows the tumor in the *left* parotid gland. **b** The profile shows the tumor has invaded the skin. **c** The picture shows this patient had weakness of the marginal branch of the facial nerve, corresponding to a H-B grade II paresis. **d** A typical transverse slice shows the distributions of the ^{125}I seeds of the patient underwent ^{125}I seed implant brachytherapy. **e** After 12 months, there were no serious complications in the local region and the skin of the *left* parotid gland recovered. **f** After 12 months, the patient who underwent ^{125}I seed implant brachytherapy recovered with H-B grade I

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