Original paper

Five-year outcome of ultrasound-guided interstitial permanent ^{125}I seeds implantation for local head and neck recurrent tumors: a single center retrospective study

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Abstract

Purpose: The aim of this study was to evaluate the efficacy and safety of interstitial permanent low-dose-rate ultrasound-guided ^{125}I seeds implantation of local head and neck recurrent tumors.

Material and methods: Sixty-four consecutive patients, with 81 lesions in total, underwent permanent implantation of ^{125}I seeds under ultrasound guidance. Post-operative dosimetry was performed for all patients. Follow-up period ranged 103.5 months (median, 14 months).

Results: Among the 81 lesions, the totally response rate was 80.2%, and 22 (27%) and 43 (53%) lesions showed complete and partial remission. The 1-, 3-, and 5-year tumor control rates were 75.2%, 73.0%, and 69.1%, respectively. The results for cervical lymph node recurrence were better than those for recurrence or residual disease of primary head and neck neoplasms, with 5-year local control rates of 72.7% and 39.9%, respectively. D_{90} was an independent prognostic factor of the tumor control, and lesion recurrence location and time to tumor progression were prognostic factors of survival. As of the date of follow-up, 22 of 64 patients were still alive. The 1-, 3-, and 5-year overall survival rates were 57.4%, 31%, and 26.6%, respectively, with a median survival of 20 months. Grade 4 skin ulceration was seen in two patients; grade 1 or 2 skin reactions were seen in 11 patients (17%) who had received external beam radiotherapy before. Other severe complications were absent.

Conclusions: Interstitial permanent implantation of ^{125}I seeds under ultrasound guidance is feasible, efficacious, and safe for refractory head and neck metastasis or recurrence.

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Key words: head and neck cancer, recurrence, cervical lymph node metastasis, ultrasound-guided, brachytherapy.

Purpose

Head and neck malignant neoplasms are common carcinomas worldwide. Among them, head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide [1]. Surgery, radiotherapy, and/or chemotherapy are the standard management for these patients. Despite progression in techniques of surgery and radiotherapy, locoregional relapses account for approximately 80% of treatment failure [2]. Second surgery and re-irradiation are rarely selected because of unacceptable morbidity and mortality; furthermore, there are no consensus guidelines for local recurrent tumors of head and neck.

Interstitial permanent low-dose-rate ^{125}I seeds implantation, which is one of the most promising modalities of brachytherapy, has been successfully performed in many different malignant tumors in the past 15 years in China. We have previously reported results regarding ^{125}I seeds implantation for recurrent head and neck carcinoma [3,4] under computed tomography (CT) or ultrasound guidance, in which the initial beneficial seed implantation was reported.

Ultrasound has higher sensitivity (96.8%) than palpation (73.3%) for detection of cervical lymph nodes [5]. It has gained recent popularity in maxillofacial imaging and to transcervically visualize the base of tongue tumors [6], as it is non-ionizing, non-invasive, and cost effective [7]. This study investigates the efficacy and feasibility of ^{125}I seeds implantation under ultrasonography guidance of recurrent head and neck carcinomas and reports long-term results of local control rates, survival rates, and complications.

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Material and methods

Patients

A total of 70 patients (median age, 60 years; range, 4-94 years) with a malignant mass in head and neck region were admitted between January 2004 and December 2014 at Peking University 3rd Hospital. Six patients were lost to follow-up and 64 met the inclusion criteria. In a total of 81 lesions of the head and neck, ^{125}I seeds implantation was evaluated. Of the 81 lesions, 54 were cervical lymph node recurrence, and another 27 were local recurrence of primary or residual disease. Patient inclusion criteria were as follows: 1. Recurrent tumor confirmed by pathologic diagnosis; 2. External radiotherapy or surgery history; 3. Karnofsky performance status score ≥ 60; and 4. Complete follow-up data. Patients with intracranial tumors were excluded. Local recurrence, regional recurrence, or both were all defined as recurrence. The characteristics of patients are shown in Table 1.

Treatment process

The tumor volumes (mean volume, 8 cc; range, 2.5-320 cc) and maximum diameter (mean, 2.5 cm; range, 1-10 cm) were measured using CT scans at 5 mm intervals or ultrasound. 70 of 81 lesions had a pre-plan. The clinical target volume (CTV) included gross tumor volume (GTV) and extended margin of 0.5 cm. These tracings were digitized into a computer treatment planning system (TPS 3D-TPS treatment planning system; Beijing Fei Tian Industries, Inc.) and used to calculate the D_{90} (the doses delivered to 90% of the target volume defined by CT or ultrasonography [US] dose volume histogram's [DVH]). The pre-plan showed D_{90} of 110-160 Gy (median, 130 Gy).

All patients underwent ^{125}I seed implantation guided by ultrasonography (color doppler ultrasound with high frequency probe and guiding stabilization devices, Alokaα-10; Figure 1 shows different types of probe and guiding stabilization devices). The procedure was done under local anesthesia. Then, interstitial needles (18-gauge) attached to ultrasound probe stabilization devices were inserted into the tumor with US real-time guidance; the needles exceeded 0.5 cm of GTV and kept each other in a parallel array of 0.5 cm apart. Precautions were taken to avoid puncture of large blood vessels. After all needles were inserted into the tumor, ^{125}I seeds (Beijing Atom and High Technique Industries, Inc., Model 6711,T1/2: 59.4 days, energy level: 27.4-31.4 keV) were implanted using Mick applicator. The seeds were placed at 0.5 cm to 1 cm interval in the PTV (not GTV) and after implantation, each needle was removed. The median number of ^{125}I seeds implanted was 20 (range, 3-89). The specific activity of ^{125}I seeds ranged from 0.35 to 0.80 mCi per seed (median, 0.70 mCi).

Post-operative dosimetry was performed for all patients 24 hours later using 3-5 mm thick CT scans. The contoured images and sources were entered into TPS software. Isodose curves for each slice and DVH of the target were generated. The post-plan evaluation showed that D_{90} range was 90-160 Gy, with a median of 130 Gy.

Tumor response was firstly evaluated at 4 weeks, and then every 2-3 months for the first 2 years and every 6 months thereafter. The follow-up time was measured from the date of seed implantation. The median follow-up period was 14 months (range, 1-103.5 months). Complications were scored using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Score. Tumor responses were documented according to the World Health Organization criteria.

All statistical analyses were conducted using SPSS version 19.0 (SPSS, Chicago, IL, USA). Survival time was defined from the start of implantation to death, and time to tumor progression (TTP) was defined from the start of

Table 1. Characteristics of patients (n = 64)

	No.	Percentage (%)
Median age (years)	60	(4～94)
Gender		
Male	42	66
Female	22	34
Position	81	
Cervical lymph node recurrence	54	67
Local recurrence or residual	27	33
Primary tumor stage		
Stage I	4	6
Stage II	12	18
Stage III	23	36
Stage IV	24	37
Undetermined	1	3
Primary cancer		
Nasopharyngeal cancer	12	19
Laryngocarcinoma	12	19
Buccal cavity carcinoma	12	19
Thymic carcinoma	5	8
Oropharyngeal cancer	5	8
Hypopharyngeal carcinoma	5	8
Soft tissue sarcoma	4	6
Paranasal sinus carcinoma	3	4
Unknown	2	3
Others	4	6
Previous radiotherapy	61	95
Previous operation	29	45
Previous cumulative dose (Gy)		
Median dose (Gy)	60 (40-74)	

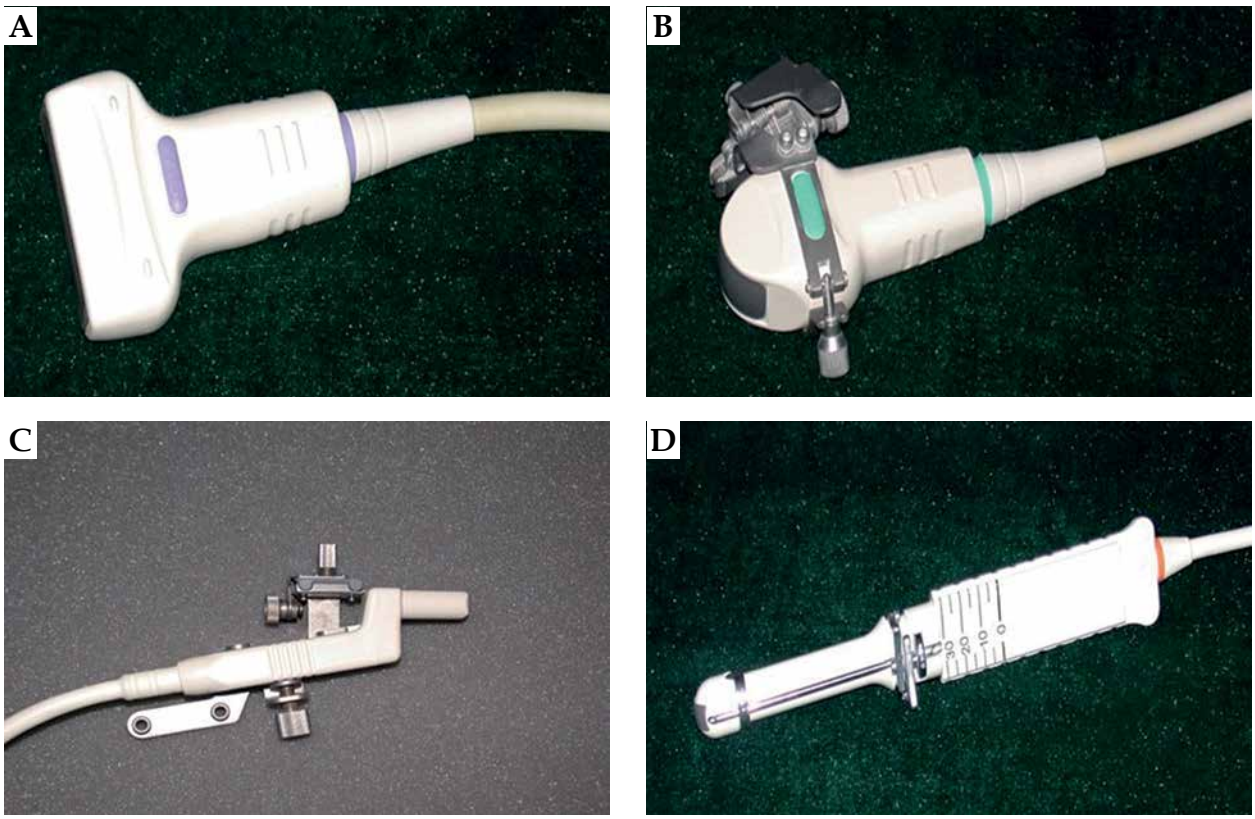

Fig. 1. Different types of probe and guiding stabilization devices, Alokaα-10. **A**) High frequency probe; **B**) Altotrequent convex lens probe; **C, D**) Special probe

implantation to clinical or radiological progression of the disease. The Kaplan-Meier method was applied to survival, and local control probabilities calculation and Cox regression was applied to univariate and multivariate analysis. A p value of < 0.05 was considered statistically significant.

Results

Among the 81 lesions, total response rate was 80.2%; 22 lesions showed complete remission (27%) and 43 showed partial remission (53%). The 1-, 3-, and 5-year tumor control rates were 75.2%, 73%, and 69.1%, respectively (Figure 2A). The results for cervical lymph node recurrence were better than those for local recurrence or residual disease of primary head and neck neoplasm. The 5-year local control rates were 72.7% and 39.9%, respectively (Figures 2B, C). As of the date of the last follow-up, 22 of 64 patients were still alive, the 1-, 3-, and 5-year overall survival rates were 57.4%, 31%, and 26.6%, respectively, with a median survival of 20 months. The 1-, 3-, and 5-year cancer specific survival rates were 67%, 42.7%, and 36.6%, respectively (Figure 2D), with a median survival of 20.8 months. The results of local control were better if $D_{90} \geq 130$ Gy ($p = 0.03$; Figure 2E).

Grade 4 side effects of skin ulceration were seen in two patients with cervical lymph node recurrence. One lesion was a progression of the disease and the patient died of pneumonia 8 months later; other patient had a partial response and died of local recurrence 8 months later. Grade 1 or 2 skin reactions were seen in 11 patients (17%) who had received external beam radiation. No bleeding and continuous pain were recorded, and none of the patients showed bone or soft tissue necrosis. There was a good cosmetic outcome in some patients (Figure 3).

We analyzed factors including age, gender, stage, lesions location, tumor size, D_{90}, and recurrence interval time (Table 2). In univariate analysis, gender, lesion location, and D_{90} were prognostic factors of tumor local control ($p = 0.004$, 0.017, and 0.03, respectively). Multivariate analysis demonstrated that D_{90} is an independent prognostic factor for tumor local control ($p = 0.015$), and lesions recurrence location and time to tumor progression (TTP) were prognostic factors for survival ($p = 0.0001$ and 0.0001, respectively; Table 3).

Discussion

In a retrospective analysis, we investigated the treatment results of 64 patients (81 lesions) with recurrent tumors of the head and neck who underwent permanent implantation of ^{125}I seeds (from January 2004 to October 2014). The aim of our study was to evaluate the efficacy and safety of interstitial permanent low-dose-rate ^{125}I seeds implantation under ultrasound guidance, and to report long-term treatment outcomes. We have, therefore, explored an alternative way to treat patients with local and regional recurrent head and neck malignant tumors.

Salvage surgery serves as the first therapeutic option for local or regional recurrence of head and neck carci-

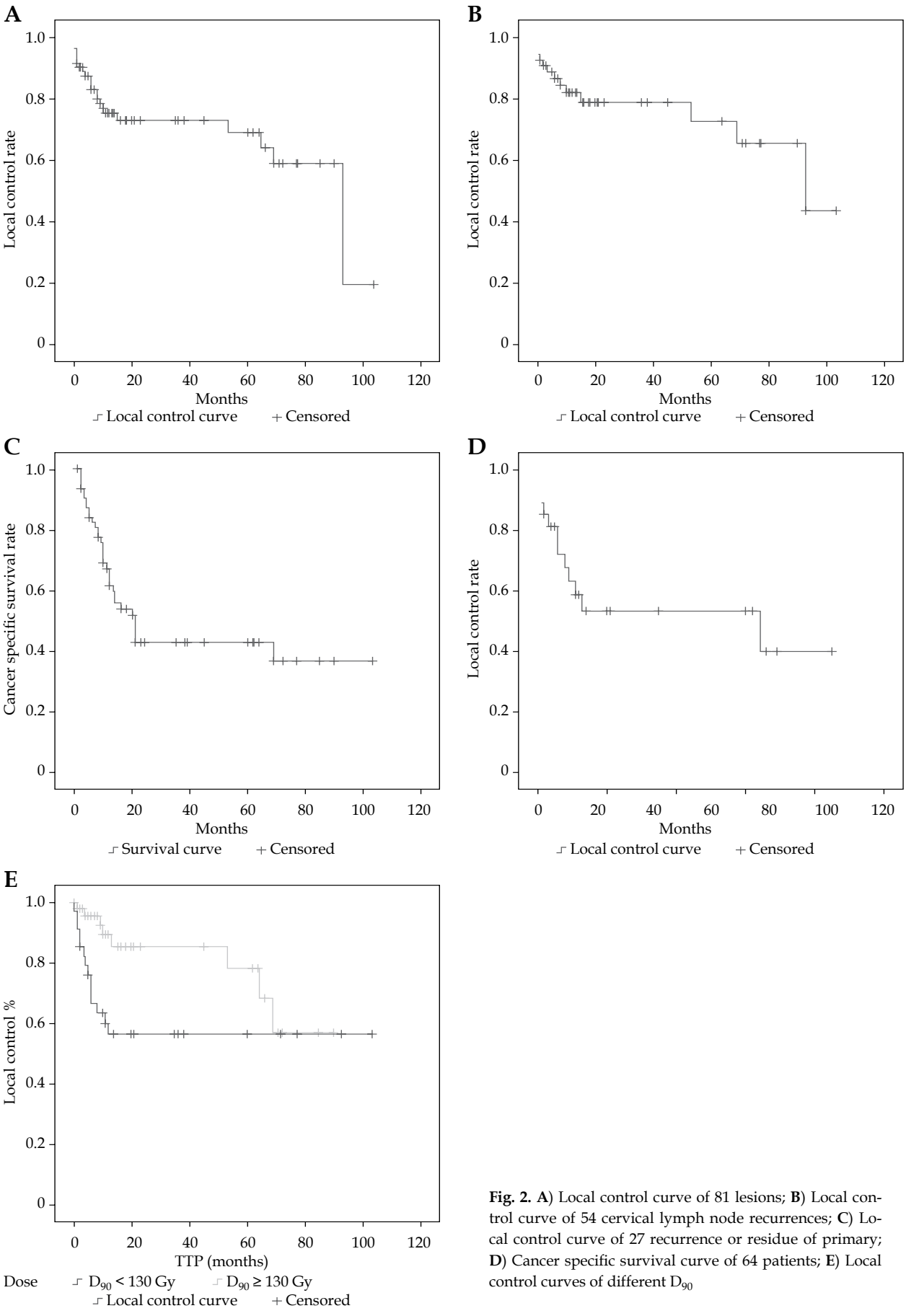

Fig. 2. A) Local control curve of 81 lesions; **B**) Local control curve of 54 cervical lymph node recurrences; **C**) Local control curve of 27 recurrence or residue of primary; **D**) Cancer specific survival curve of 64 patients; **E**) Local control curves of different D_{90}

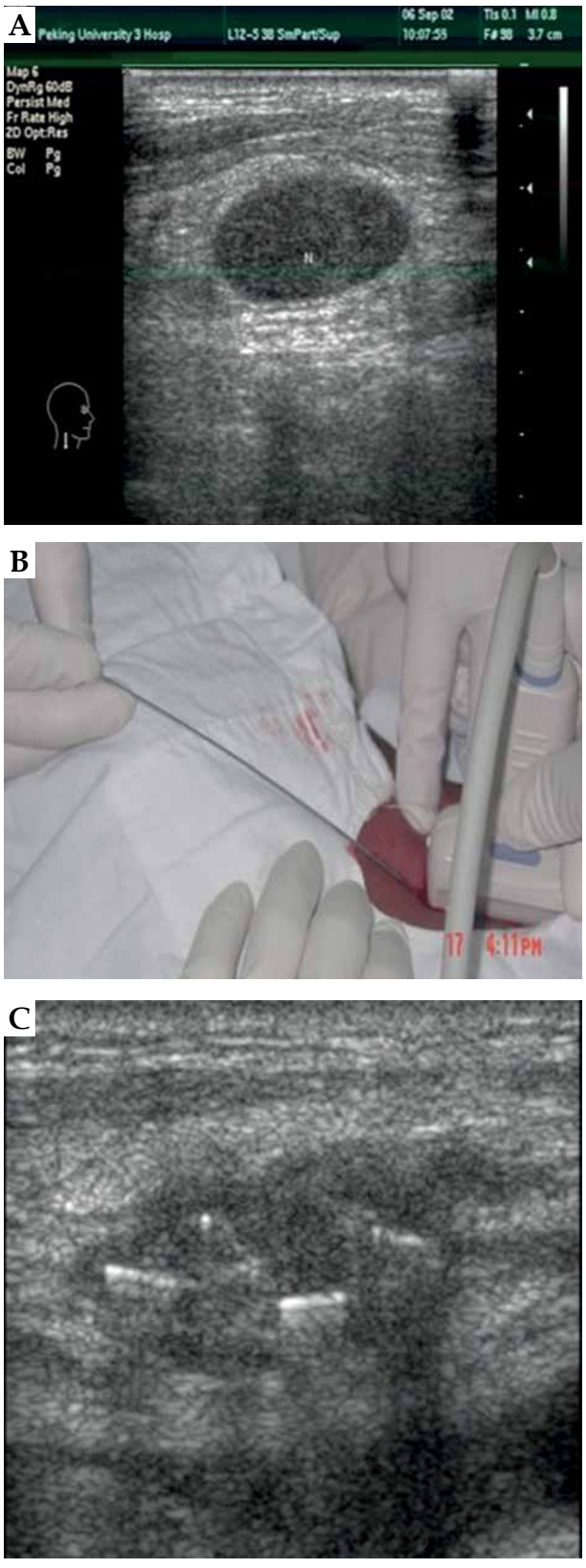

Fig. 3. Patient with cervical lymph node recurrence of hypopharyngeal cancer. **A**) Ultrasound image of lymph node before ^{125}I seeds implantation; **B**) High frequency probe applied during seeds implantation; **C**) Seeds in ultrasound image after seeds implantation 1 months later

Table 2. Univariate analysis of impact factors for local control

Factors	*n*	Local control (5 y)	χ^2	*p*
Age				
≤ 60 y	40	60.7%	0.001	0.974
> 60 y	41	66.8%		
Gender				
Female	26	90.4%	8.084	0.004
Male	55	56.6%		
Stage				
I	5	–	2.73	0.433
II	19	80.2%		
III	27	65.3%		
IV	30	37.2%		
Diameter				
< 3 cm	50	69	1.481	0.224
≥ 3 cm	31	53.7		
Position				
Primary	27	39.9%	5.692	0.017
Cervical lymph node	53	72.7%		
D_{90}				
< 130 Gy	34	56.6%	4.699	0.03
≥ 130 Gy	47	78.1%		
Recurrence interval time				
≤ 12 m	47	64.1%	1.492	0.474
12-24 m	9	88.9%		
≥ 24 m	24	46.3%		

TNM stage – according to AJCC Cancer Staging Manual (2002); Diameter – tumor diameter; Position – tumor location; D_{90} – the doses delivered to 90% of the target volume; Recurrence interval time – interval between seed implantation and last treatment

noma. It is particularly challenging based on the tissue impairment caused by the previous therapies and therefore has a high complication rate of > 90% [8], including fistulas and skin necrosis. Survival rates after salvage surgery vary from 20-45% in oropharyngeal and hypopharyngeal cancers, and up to 82% in laryngeal cancers [8,9] but post-operative quality of life is reduced. Furthermore, few patients are suitable candidates for curative resection. In such cases, chemotherapy alone with a poor response rate (yielding a median survival between 5 and 9 months) has traditionally been considered, and the addition of cetuximab to platinum-based chemotherapy improves median survival to 11 months [10]. Re-irradiation is a potentially curative option for some patients. How-

Table 3. Multivariate analysis of impact factors by Cox regression

Local control					Overall survival				
Factors	β	SE	χ^2	*p*	Factors	β	SE	χ^2	*p*
D_{90}	1.090	0.448	6.248	0.012	Position	–2.135	0.438	30.462	0.0001
					TTP	–0.230	0.034	49.231	0.0001

D_{90} – doses delivered to 90% of the target volume; Position – tumor location; TTP – time to progression

ever, re-irradiation-induced toxicity is high, and patients must be cautiously selected, taking into account performance status, location and extension of recurrent disease, co-morbidities, current speech and swallowing function, the interval from the initial radiation therapy to recurrence, previously received doses to critical structures, and prior treatment toxicity. Nevertheless, several questions remain unanswered and long-term survival is infrequent [11]. Two phase II trials (RTOG96-10 and RTOG99-11) of re-irradiation concurrent chemotherapy reported a median survival of 8.5 and 12.1 months, respectively, and a 2-year survival rate of 25.9% but accompanied by high acute toxicity in both studies [12,13]. Our retrospective study showed promising results for 1-, 3-, and 5-year overall survival (57.4%, 31%, and 26.6%, respectively), with a median survival of 20 months and acceptable complications. We speculated that ^{125}I seed implantation is an effective modality for this group of patients.

As a well-accepted option for re-irradiation, brachytherapy plays an important role in the treatment of recurrent HNSCC [14]. Either low-dose-rate (LDR) or high-dose-rate (HDR) techniques can be applied as monotherapy or in combination with external beam radiotherapy in nasopharynx, oral cavity, oropharynx, and lymph node recurrences [15,16]. A 5-year local control rate of 57-69% and a 5-year overall survival rate of 14-40% have previously been reported [17,18,19]. Brachytherapy has been used less often in recent years, as more studies investigated improved local control with concurrent chemoradiation. In this study, interstitial permanent low-dose-rate ^{125}I seeds implantation as monotherapy was selected for local or regional recurrent tumors of the head and neck. The results showed totally response rate of 80.2%, and the 5-year local control of cervical lymph node recurrence of 72.7%. It was better than that of the primary head and neck local tumor recurrence or residual disease (39.9%). Of 81 lesions, eight lesions had progressive disease, and five of these eight lesions were cervical lymph node recurrences, whereas three lesions were residual disease of the primary after the first surgery. There is limited published literature regarding the relationship between prognosis and recurrent patterns of primary disease and cervical recurrence. In this study, we found that lesions recurrence location and TTP were prognostic factors for survival. Multivariate analysis demonstrated that D_{90} is an independent prognostic factors of local tumor control. Thus, we suggest that a prescription dose (D_{90}) of ≥ 130 Gy may be associated with better local control, and patients with cervical recurrence may have improved survival.

Ultrasound-guided biopsy is routinely used in diagnosis or treatment for superficial lesions of the head and neck, and it can detect nodes even less than 2 mm in diameter, while CT and magnetic resonance imaging are less sensitive than ultrasound in detecting nodes of < 5 mm in diameter [20]. Owing to the challenging anatomical complex of the oropharynx such as the base of tongue, ultrasound offers significant advantages regardless of artifact and soft tissue definition compared with CT [6]. In this study, we performed seeds implantation by color Doppler ultrasound with a high frequency probe and guiding stabilization devices. Our local results are promising and had good cosmetic outcomes. Two cases of grade 4 side effects of skin ulceration were seen in the cervical lymph node position. Both patients had had previous radiation and the recurrence lesion had invaded the subcutaneous tissues before seeds implantation. We summarized the merits of ultrasound-guided seeds implantation as follows: 1) real-time-guided; 2) no extra radiation dose exposure; 3) convenient and quick; 4) reproducible. The disadvantages include low image resolution and the fact that only two-dimensional images are available.

Conclusions

Interstitial permanent implantation of ^{125}I seeds under ultrasound guidance is feasible, efficacious, and safe for refractory head and neck recurrences. It is a preferable option for patients with cervical lymph node recurrences or metastases from the head and neck, superficial maxillofacial region, and base of the tongue carcinomas. Tumor invading skin is a contraindication.

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Disclosure

Authors report no conflict of interest.

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