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CT-guided iodine-125 seed permanent implantation for recurrent head and neck cancers

Yu L Jiang¹, Na Meng¹, Jun J Wang^{1*†}, Ping Jiang¹, Hui SH Yuan^{2†}, Chen Liu², Ang Qu¹, Rui J Yang¹

Abstract

Background: To investigate the feasibility, and safety of ¹²⁵I seed permanent implantation for recurrent head and neck carcinoma under CT-guidance.

Results: A retrospective study on 14 patients with recurrent head and neck cancers undergone ¹²⁵I seed implantation with different seed activities. The post-plan showed that the actuarial D90 of ¹²⁵I seeds ranged from 90 to 218 Gy (median, 157.5 Gy). The follow-up was 3 to 60 months (median, 13 months). The median local control was 18 months (95% CI, 6.1-29.9 months), and the 1-, 2-, 3-, and 5- year local controls were 52%, 39%, 39%, and 39%, respectively. The 1-, 2-, 3-, and 5- survival rates were 65%, 39%, 39% and 39%, respectively, with a median survival time of 20 months (95% CI, 8.7-31.3 months). Of all patients, 28.6% (4/14) died of local recurrence, 7.1% (1/14) died of metastases, one patient died of hepatocirrhosis, and 8 patients are still alive to the date of data analysis.

Conclusion: CT-guided ¹²⁵I seed implantation is feasible and safe as a salvage or palliative treatment for patients with recurrent head and neck cancers.

Background

Most patients who have ever undergone surgery for head and neck cancer or those local advanced or regional recurrence cancer patients received surgery combined with adjuvant external-beam radiotherapy (EBRT) [1,2]. Management of patients with recurrent head and neck cancers after surgery, EBRT, and adjuvant chemotherapy is a challenge for clinical oncologists. Salvage surgery is often technically feasible after the patients treated with full doses of EBRT, but the curative potential of surgery alone is low; further, the morbidity is high [3]. Redelivery of effective doses of EBRT is difficult because of the limited tolerance of adjacent normal tissues. Therefore, there has been a growing interest in combining salvage surgery with intraoperative interstitial brachytherapy [4].

Temporary intraoperative interstitial brachytherapy has its advantage in this aspect, in which a high dose of radiation is delivered directly to the cancer, while ensuring that a much lower dose is delivered to the adjacent

normal structures [5-7]. The use of high-dose rate (HDR) and low-dose rate (LDR) brachytherapy in previously irradiated regions is often safe because the use of implants ensures the delivery of the dose to very specific and limited volumes of tissue. A variety of isotopes are available for use as HDR or LDR temporary interstitial brachytherapy, but the most commonly used isotope is Iridium-192, Co-60 or Cs-137 et al, especially for treating recurrent solid cancers [8-10]. However, the use of those isotopes for intraoperative HDR brachytherapy requires very complicated shielding [11].

Computed tomography (CT)-guided permanent brachytherapy was initially used for treating liver malignancies [12,13]. This novel technique ensures protracted cell killing over a period of several months through targeted delivery of high-dose radiation. The advantages of this technique are as follows: (1) it is minimally invasive, (2) dose distribution can be accurately predicted, (3) continuous irradiation increases the likelihood of damaging malignant cells in a vulnerable phase of the cell cycle, and (4) the incidence rate of acute adverse effects is low.

We have gained significant experience in using permanent ¹²⁵I seed implantation for treating recurrent rectal

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cancer and spinal metastases [14,15]. The theoretical benefit of seed permanent implantation as a salvage treatment is enhanced disease control in the region of recurrence through precise and continuous LDR irradiation, which, in turn, minimizes injury to the overlying skin and surrounding neurovascular structures.

In this study, we investigated the efficacy and feasibility of percutaneous CT-guided ¹²⁵I seed permanent implantation for recurrent head and neck cancers and analyzed the local control, survival and complications of this modality.

Patients and methods

We conducted a retrospective analysis of 14 patients (median age, 40 years; range, 19-74 years) who had been treated for recurrent head and neck cancers with CT-guided ¹²⁵I seed permanent implantation at Peking University Third Hospital between Feb 2003 and November 2009. The study population included 9 male and 5 female patients. The criteria for eligibility were as follows: histologically proven recurrent head and neck cancer after surgery and radiotherapy, without any evidence of distant metastasis; a Karnofsky Performance Status (KPS) score ≥ 60 ; and no severe impairment of kidney, liver, or bone marrow function. The diameter of recurrent tumor was less than 7 cm. All patients had ever been reviewed by the surgeons and radiation oncologists, and were considered not suitable for salvage surgery and EBRT again or the patients refused to receive surgery and EBRT further.

Before the operation, we evaluated the history and physical condition of all the patients, hematological and chemical tests, and obtained CT images of the head and neck and radiographs of the chest. Patient characteristics are shown in Table 1.

Of the 14 patients, 2 had undergone radical surgery alone, 6 had received EBRT alone, and 6 had undergone surgery and EBRT. Two patients had undergone surgery twice and the other two patients had undergone surgery three times. Among the patients who underwent EBRT, 1, 5, and 6 patients received it 4 times, twice, and once, respectively. The total dose delivered to PTV ranged from 48.5 to 250 Gy (median, 70 Gy). Six patients had been administered chemotherapy (3-13 cycles; median, 4 cycles). Five patients had regional recurrence in the lymph nodes and 9 patients had recurrence in the primary lesions.

A detailed CT-aided tumor-volume study was also performed for all the patients 1-2 weeks before seed implantation. We obtained transverse images of the targets at 5-mm intervals. The images were transferred to a computerized treatment planning system (TPS, Pro-ess, version 3.02, SSGI, USA). The radiation oncologist outlined the planning target volume (PTV) on each

Table 1 Patient characteristics (n = 14)

	No. of patients	Percentage (%)
Median age	40(range,19-74)	
Gender		
Male	9	64
Female	5	36
KPS		
60	1	7
70	4	29
80	6	43
90	2	14
100	1	7
Primary tumor stage		
Stage I	1	7
Stage II	3	21
Stage III	4	29
Stage IV	5	36
Unclear	1	7
Primary tumor		
Sinus paranasal	5	36
Nasopharynx carcinoma	3	21
Larynx	2	14.3
Hypopharyngeal carcinoma	1	7
Nasal cavity	1	7
Mandible	1	7
Infratemporal fossa	1	7
Previous surgery	8	57
Previous chemotherapy	6	43
Previous radiotherapy	12	86
One	7	50
Two	4	29
Four	1	7
Previous cumulative dose(Gy)		
≤ 50 Gy	2	14
50 ~ 100 Gy	5	36
>100 Gy	5	36
Median dose(Gy)	70(range,50-250)	

transverse image, to which the prescribed D90 (the doses delivered to 90% of the target volume) was prescribed. The PTV included the gross tumor volume (GTV) with a 0.5-1 cm margin. A radiation dose of 90-160 Gy was prescribed to the PTV and calculated through computerized treatment planning system.

We had previously reported the implant technique used in this study [14]. Seed implantation was performed in all the 14 patients under local anesthesia in the CT room. After determining the target volume, 18-gauge interstitial needles were inserted into the tumor through the skin surface with PTV under CT supervision. Most of the 18-gauge needles were placed 1.0 cm apart in a parallel array in the PTV. Precautions were taken to avoid puncturing the large vascular and neural

structures and the bronchus. The median number of needles is 14 (range, 5-42). After placing the needles, ^{125}I seeds (Model 6711; Beijing Atom and High Technique Industries Inc., Beijing) were implanted using a Mick applicator; the seeds were implanted 1.0 cm apart. All the patients received perioperative prophylactic antibiotics.

Postoperative dosimetric measurements were routinely obtained for all the patients. The implant dosimetry was determined using three-dimensional seed identification, and axial CT images (slice thickness, 5 mm) of the implanted area were obtained immediately or 24 h after seed implantation. The CT-derived postimplant target volumes were defined to encompass the GTV with a 0.5-1 cm margin. The ^{125}I seeds were identified on the CT images by using a combination of manual selection and an automated redundancy check feature available on the Prowess treatment planning system. We generated isodose curves for each slice (Fig. 1) and dose-volume histograms of the target (Fig. 2). The actuarial median number of the implanted ^{125}I seeds was 48 (range, 21-158). The specific activity of ^{125}I seeds ranged from 0.40 to 0.80 mCi/seed (median, 0.65 mCi). The total activity of the implanted seeds ranged from 8.8 to 113.6 mCi (median, 24.9 mCi). The evaluation of post plan shown the actuarial D90 ranged from 90 to 218 Gy (median, 157.5 Gy). The seed implanted volume ranged from 9.1 to 290.4 cm³ (median, 32 cm³).

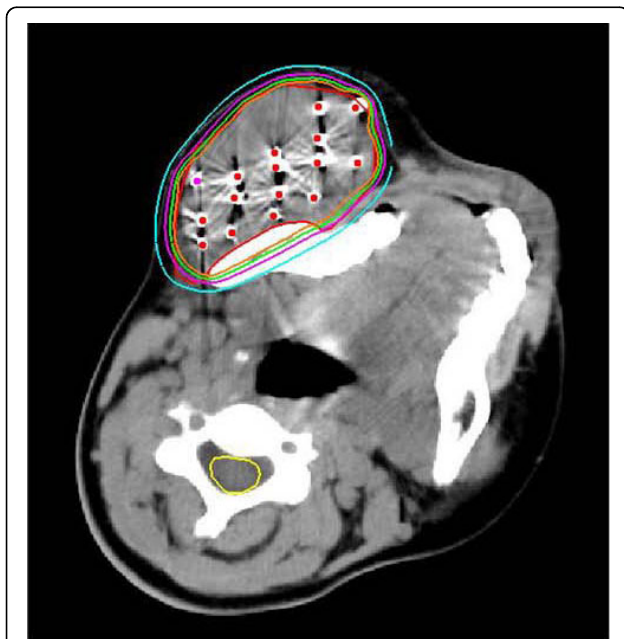


Figure 1 The isodose curve after seed implantation from CT scan. The inner red curve represents GTV. The ellipses are iso-dose lines of 160, 140, 120, 90 Gy from inside, respectively.

Tumor response was first evaluated at 4 weeks after implantation. Subsequent evaluations were performed at 2-3-month interval for the next 2 years and 6-month interval, thereafter. The disease status was assessed by physical examinations, liver function tests, and complete blood and platelet counts. Disease progression was determined by means of imaging studies, including CT scans and ultrasonography. The follow-up time was calculated from the date of seed implantation. The median follow-up period was 13 months (range, 3-60 months).

The complications were scored using the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) late radiation morbidity score [16].

The survival time was calculated from the date of implantation to the last date of follow-up or date of death. In these calculations, deaths due to any reason were scored as events. Local control was defined as the lack of tumor progression either in or adjacent to the implanted volume. Tumor responses were assessed using CT and ultrasound according to the World Health Organization (WHO) criteria [17]. The overall local control and survival times were determined using the Kaplan-Meier method by using SPSS 10.0 for Windows (SPSS, Chicago, IL).

Results

Local control

The follow-up period ranged from 3 to 60 months (median, 12 months). The median local control was 18 months (95% CI, 6.1-29.9 months), and the 1-, 2-, 3- and 5-year local controls were 52%, 39%, 39%, and 39%, respectively. Of all patients, 28.6% (4/14) died of local recurrence, 7.1% (1/14) died of metastases, and 1 died of hepatocirrhosis 20 months after seed implantation and 8 still survive to the date of this analysis (Fig. 3).

Survival

The median survival time was 20 months (95% CI, 8.7-31.3 months), and the 1-, 2-, 3- and 5-year survival rates were 65%, 39%, 39%, and 39%, respectively (Fig. 4).

Complications

One patient had grade one skin reaction, one experienced grade 1 mucosal reaction, and one developed ulceration with tumor progression after 11 months. We did not observe blood vessel damage and neuropathy in the patients.

Discussion

The treatment of patients with recurrent head and neck cancer in a previously irradiated area is particularly challenging for both surgery and EBRT. In such circumstances, redelivery of EBRT is not possible because of

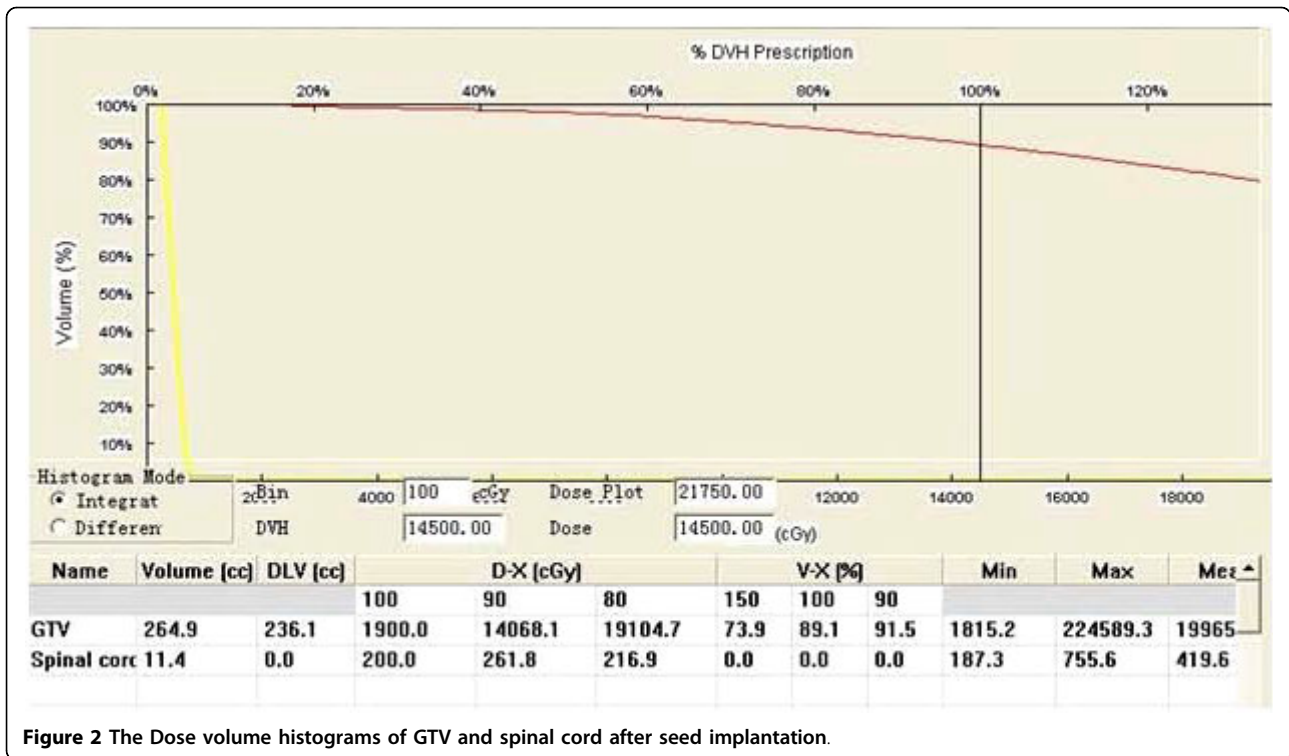


Figure 2 The Dose volume histograms of GTV and spinal cord after seed implantation.

the high radiation dosage previously applied and the tolerance of adjacent normal tissue. However, local control rates of up to 50% and a 5-year survival rate of 20% have been reported after redelivery of EBRT [18-20]. The use of re-irradiation combined with chemotherapy for recurrent head and neck carcinomas, after previous full-dose radiotherapy, has shown encouraging median survivals [21-23]. However, this approach has sometimes met some trouble for patients who have ever received

EBRT and worry about the normal tissue damages. The re-irradiation possibility is small for patients who have ever received twice EBRT, even IMRT or IGRT.

Surgery combined with intraoperative HDR interstitial brachytherapy has become a modality of salvage treatment for managing patients with locally advanced or recurrent head and neck cancer, with a local control rate of 40-60% and a 5-year survival rate of 14% [24,25]. Salvage surgery or surgery combined with intraoperative

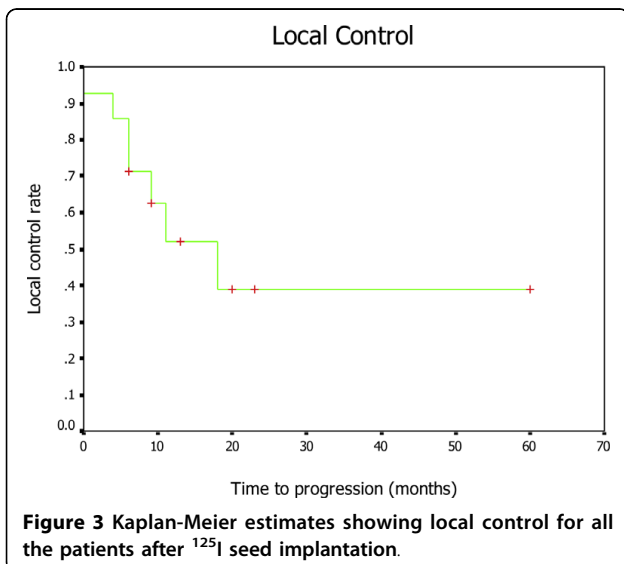


Figure 3 Kaplan-Meier estimates showing local control for all the patients after ¹²⁵I seed implantation.

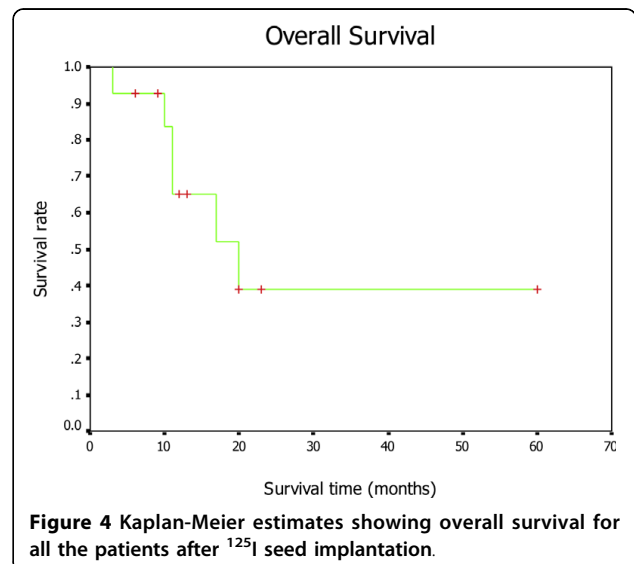


Figure 4 Kaplan-Meier estimates showing overall survival for all the patients after ¹²⁵I seed implantation.

HDR is often technically feasible, but its curative potential is low, and local failure rate is $\geq 40\%$ [26].

Intraoperative pulsed-dose-rate (PDR) brachytherapy is an alternative reirradiation strategy that lowers the risk of severe morbidity [27]. The use of this technique resulted in excellent local control rates of up to 80% with minimal side effects when performed in carefully selected patients [28]. Intraoperation PDR imposed some practical limitations, the tumor size and location of most recurrences inhibited its application. Normal tissue fibrosis after EBRT can impair bimanual palpation of recurrent tumors during the needle implantation, the organ at risk is often in the vicinity of the tumor. The patient treatment usually lasted several days. Radium-226 and iridium-192 have been used for T1 and T2 patients with oral cavity and oropharynx carcinomas and produced excellent control rates and functional results [29-33]. Vikram et al reported 124 patients with advanced recurrent head and neck cancer who were treated using ^{125}I implants [34]; 71% of these patients showed complete regression, 18% showed $>50\%$ regression, and 11% showed no response. Overall, local control was achieved in 64% of the patients until their deaths. Only 9% of the patients survived for 2 years and 5.5% survived for 5 years. Goffinet et al reported using permanent ^{125}I seed implants as a surgical adjuvant in the management of patients with advanced recurrent head and neck cancer; most of the patients in this study had received prior treatment. Management involved a salvage operation combined with permanent ^{125}I seed implants, and a local control rate of 70% had been achieved [35]. Park et al reported 35 patients with advanced recurrent squamous cell cancers of the head and neck that were treated with surgical resection followed by adjuvant ^{125}I seed implantation. The 5-year disease-free survival rate was 41% [36]. The use of concomitant intraoperative HDR or LDR brachytherapy has been shown to enhance actuarial survival and local control rates, but the occurrence of local complications have also been reported in 11-56% of cases [37]. Martinez et al reported an overall complication rate of 11% [37], and Goffinet et al reported an overall complication rate of approximately 50% [35]. The main complications were skin ulceration and wound breakdown; however, carotid rupture, which is a fatal complication, has also been occasionally reported.

Catheters are inserted during intraoperative HDR or PDR brachytherapy on the basis of preoperative images and intraoperative presentation. Planning of intraoperative HDR or PDR brachytherapy has a number of potential disadvantages: (1) the target volume and shape may change between the time of pre-plan and real time implant insertion; (2) the dose calculation is depended on pre-plan, and did not realized real time and post-

plan in operation or after operation. However, image-guided seed permanent implantation overcomes these disadvantages in some selected patients. We observed a very low rate of complications, one patient had grade one skin reaction, one experienced grade one mucosal reaction, and one developed ulceration with tumor progression after 11 months, and no adverse events were attributable to seed implantation itself. One patient had ulceration because of tumor progression after seed implantation. We did not observe the occurrence of bone and soft tissue necrosis, carotid rupture, or other grade 4 or 5 toxicity.

Image-guided HDR brachytherapy for non-small-cell lung cancer and other malignancies has recently been reported by other groups [38-41]. This enables the use of circumscribed high-dose radiotherapy for the tumor target as well as the safety margin. CT-guided ^{125}I permanent seed implantation has the following advantages: (1) the implantation technique is supervised real timely on CT scan and can be performed easily under local anesthesia; (2) the possibility of target geographical miss is reduced; (3) radiation dose to the surrounding tissues is minimized due to the sharp dose fall-off outside the implanted volume, thereby lowering the morbidity; and (4) it has a shorter treatment time than re-irradiation or surgery combined with HDR. Krempien et al have reported that frameless image-guided interstitial needle implantation was feasible and accurate for 14 patients with locally recurrent head and neck cancers [42]. The 1- and 2-year local control rates were 78% and 57%, respectively, and the actuarial 1- and 2-year survival rates were 83% and 64%, respectively. Image guidance allows virtual planning and navigated needle implantation, which, in turn, facilitates optimized dose distribution and reduces adjacent tissue damage.

We elaborated this technique for routine use in a large number of recurrent cancer patients by using CT-guidance and routinely obtained a standard postoperative dosimetry for all patients using the 3D-CT dataset. This demonstrated that a good tumor control rate and low complication rate could be achieved using percutaneous CT-guided ^{125}I seed permanent implantation while treating recurrent carcinomas [14,15]. Our results showed that the 1-, 2-, 3-, and 5-year control rates were 52%, 39%, 39%, and 39%, respectively, with a median local control of 18 months. The 1-, 2-, 3-, and 5-year actuarial overall survival rates were 65%, 39%, 39%, and 39%, respectively, with a median survival of 20 months.

In conclusion, CT-guided ^{125}I seed permanent implantation is an effective salvage modality of radiotherapy for recurrent head and neck carcinoma after previous surgery or EBRT. It eliminates the need for further surgery or EBRT, improves the outcome, and low side effects. Considering the limited number of patients involved in

this study, arriving at a definite conclusion requires a large number of patients and long-term follow-up.

Abbreviations

The abbreviations used are: ¹²⁵I: iodine-125; LDR: low-dose rate; HDR: high-dose rate; SLD: sublethal damage; TPS: treatment planning system; EBRT: external beam radiotherapy; GTV: gross tumor volume; PTV: planning target volume; LR: local recurrence; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; TTP: time to progression; OS: overall survival.

Conflict of interests statement

We disclose to Radiation Oncology the following potential conflicts of interest: this study is supported by the Fund of Capital Medical Development and Research, item NO. 2009-2024.

Authors' contributions

YLJ, NM, AQ and PJ participated in the data collection and performed the statistical analysis, HSY and CL carried out the needle penetration, RJY carried the dose calculation of seed implantation, JJW participated in the design of the study and seed implantation. All authors read and approved the final manuscript.

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