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Interstitial ^{125}I Brachytherapy as a Salvage Treatment for Refractory Cervical Lymph Node Metastasis of Thoracic Esophageal Squamous Cell Carcinoma After External Irradiation With a CT-Guided Coplanar Template-Assisted Technique: A Retrospective Study

Peishun Li, PhD[1], Jing Fan, PhD[1,*], Kaixian Zhang, PhD[1], Junjie Wang, MD[2], Miaomiao Hu, PhD[1], Sen Yang, PhD[1], Chao Xing, PhD[1], and Qianqian Yuan, PhD[1]

Abstract

Purpose: To analyze the outcome and prognosis of patients with refractory cervical lymph node metastasis of thoracic esophageal squamous cell carcinoma after external irradiation, who underwent interstitial ^{125}I brachytherapy as a salvage treatment with a CT-guided coplanar template-assisted technique. We also want to compare the dosimetry of 3D printed coplanar template-assisted interstitial ^{125}I brachytherapy preoperative and postoperative, and to explore the accuracy of this technology.
Material and methods: We retrospectively collected and analyzed the results of 32 patients with refractory cervical lymph node metastasis of thoracic esophageal squamous cell carcinoma after external irradiation, who underwent interstitial ^{125}I brachytherapy as a salvage treatment with a CT-guided coplanar template-assisted technique from January 2012 to December 2017.
Results: The actual D90 were 114 to 240 Gy, and the median postoperative dosimetry assessment was 177.5 Gy. The local control rates at 3, 6, 9, and 12 months were 87.5%, 59.38%, 40.63%, and 31.25%, respectively. The median local control time was 7.5 months. The median overall survival time was 10.5 months (95% CI, 8.9-13.4), and the survival rates of 1- and 2-year, respectively, were 43.75% and 9.38%. There were 36 lesions in 32 patients. By performing a paired *t*-test analysis, there was no significant difference in D90, D100, V100, V150, V200, GTV volume, CI, EI, and HI between preoperative and postoperative ($P > .05$).
Conclusions: Interstitial ^{125}I brachytherapy can be used as a salvage treatment for patients with refractory cervical lymph node metastasis of thoracic esophageal squamous cell carcinoma after external irradiation. With the auxiliary function of 3D printed coplanar template, the main dosimetry parameters verified after the operation can meet the requirements of the preoperative plan with good treatment accuracy.

Keywords

^{125}I, cervical lymph node, thoracic esophageal cancer, CT-guided, coplanar template

[1] Department of Oncology, Tengzhou Central People's Hospital, Shandong, China
[2] Department of Radiation Oncology, Peking University 3rd Hospital, Beijing, P. R. China
*Co-first author.

Corresponding Authors:
Kaixian Zhang, Department of Oncology, Tengzhou Central People's Hospital, Tengzhou, Shandong 277599, China.
Email: kaixianzhangtz@163.com
Junjie Wang, Department of Radiation Oncology, Peking University 3rd Hospital, Beijing 100191, P. R. China.
Email: junjiewang_edu@sina.cn

Abbreviations

3D-PCT, 3D printed coplanar template; CI, conformal index; D90, the dose delivered to 90% CTV; D100, the dose delivered to 100% CTV; EI, external volume index of target area; GTV, gross tumor volume; HI, homogeneity index; KPS, karnofsky performance status; LCR, local control rate; OARs organs at risk; OS, overall survival; PTV planning target volume; TPS, treatment planning system; V100, the volume to withstand 100% of the prescribed dose; V150, the volume to withstand 150% of the prescribed dose; V200, the volume to withstand 200% of the prescribed dose.

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Introduction

Esophageal carcinoma is the sixth leading cause of cancer-related death around the world, with a dismal prognosis.[1] Although chemoradiotherapy is one of the effective treatments for esophageal cancer,[2–4] the most patients who undergo radical chemoradiotherapy suffer the recurrence or metastasis within 2 years.[5–7] The overall survival (OS) has been improved by advances in treatment,[8,9] but one of the most common treatment failures is lymph node metastasis.[10] Based on the research of 3-field lymph node dissection, cervical lymph node metastasis rate is around 20%.[11–13] It is difficult to retreat cervical lymph node metastasis of esophageal cancer. And the overall remission rate of cervical lymph node is only 34%.[14] However, there is no standard treatment for recurrent cervical lymph nodes due to previous treatments. The second-course radiotherapy has been used clinically, but the target dose is difficult to reach the radical dose because of the dose tolerance of adjacent organs. The efficacy is not promising and there is an increased risk of damage to normal tissue during the second-course radiotherapy.[15] For cervical lymph node metastasis after external beam radiotherapy, local tissue fibrosis and poor blood circulation increase the difficulty of surgical treatment.

^{125}I seeds are commonly used as permanent implanted radioactive sources in clinical practice. And the low-dose radiation is continuously released by the decay of radionuclide, which damages the DNA of tumor cells and induces apoptosis of tumor cells.[16] Interstitial permanent ^{125}I radioactive seed implantation can produce a significant dose gradient between the tumor and adjacent normal tissues, thus protecting the organs at risk (OARs). ^{125}I seed implantation has been widely used in the treatment of head and neck tumor, lung cancer, locally advanced pancreatic tumor, recurrent rectal tumor, prostate tumor, and malignant luminal obstruction.[17–25] It has been reported that ^{125}I seeds can be used to treat cervical lymph node metastasis after radiotherapy of esophageal squamous cell cancer.[26,27] In the past, interstitial ^{125}I brachytherapy was completed by freehand, which seriously depended on the experience of the performer. In recent years, some scholars have used Computer Aided Design and Rapid Prototyping technology to design and manufacture 3D printing template to assist particle implantation.[28] There are few researches about the effects of ^{125}I brachytherapy for metastatic cervical lymph nodes with 3D printed coplanar template (3D-PCT). Our study retrospectively analyzed the clinical effect of CT-guided ^{125}I seed implantation by 3D-coplanar template in the treatment of recurrent cervical lymph nodes of thoracic esophageal squamous cell carcinoma after external beam radiotherapy. The purpose of this study is also to compare the dosimetry of this therapy before and after surgery, and to explore the accuracy of this technology in ^{125}I brachytherapy.

Materials and Methods

Patients

We retrospectively collected and analyzed the results of 32 patients with refractory cervical lymph node metastasis, who underwent interstitial ^{125}I brachytherapy as a salvage treatment with a CT-guided coplanar template-assisted technique from January 2012 to December 2017. These patients had previously received external beam radiation for thoracic esophageal squamous cell carcinoma. All patients were discussed by a Multidisciplinary Team minimum consisting of surgeons, oncologists, and radiologists before deciding on a course of treatment. All patients had signed an informed consent form for ^{125}I brachytherapy, which stated the advantages and disadvantages of radioactive seed implantation. This study was approved by the local Institutional Review Board (Ethics number: 2020-Ethics Review-37), conducted in accordance with the Declaration of Helsinki. This study did not require informed consent from participants. The reporting of this study conforms to STROBE guidelines.[29]

Selection of the Patients

The indication for interstitial ^{125}I brachytherapy in our study was as follows: (1) all cases were pathologically diagnosed as esophageal squamous cell carcinoma; (2) maximum diameter of lesion ≤ 7 cm; (3) the metastatic cervical lymph nodes were pathologically confirmed to be consistent with the primary tumor; (4) inability to tolerate surgery or refuse surgical resection; (5) karnofsky performance status (KPS) ≥ 70, and expected survival≥ 3 months.

The exclusion for ^{125}I seed implantation was as follows: (1) severe organ dysfunction; (2) coagulation dysfunction, anticoagulant therapy should be stopped at least 5 to 7 days before implantation; (3) poor general condition or cachexia; (4) the interval from last radiotherapy was less than 3 months; (5) no CT and other imaging data at 3 months after ^{125}I seed implantation.

^{125}I Radioactive Seed

The ^{125}I radioactive seeds used in our study have a length of 4.5 mm and diameter of 0.8 mm (activity: 0.5-0.8 mCi; half-life: 59.4 days), which are cylindrical and provided by Beijing Atomic Technology Co., Ltd (China). The maximum radiation radius of emulated particles is 17 mm, and they emit X rays and γ rays with energy of 27.4 to 31.5 keV. It is a kind of low dose rate irradiation material.

Preoperative Plan

Preoperative plan was delineated by clinicians, radiologist, and physicians together. The patients underwent enhanced CT scan (thickness, 5 mm) of the area of interest less than 7 days before the treatment, who were fixed by vacuum negative pressure pad. The patients took the same position throughout the course of treatment, with the head toward to the side of the non-^{125}I seed implantation. CT images were transmitted to computer-assisted treatment planning system (TPS) to evaluate the feasibility of treatment and to design preoperative planning. A radiation oncologist outlined the gross tumor volume (GTV) and the OARs with a computer-assisted TPS (3D TPS, Beijing Hang Tian Kelin Science and Technology Development Co). GTV was defined as metastatic lymph nodes measured 1 cm in the long axis. Planning target volume (PTV) was defined as a 1.0 cm of expansion external to the GTV. PTV edge was covered by 90% isodose curve. The entry site and path of the needles were determined to avoid vital structures. The coplanar template was made of corn resin, template thickness 2.0 cm, with the specifications of 8 cm × 8 cm × 2 cm or 10 cm × 10 cm × 2 cm, provided by Beijing Atomic Technology Co., Ltd.

Interstitial ^{125}I Brachytherapy

The 64-row spiral CT scanner (Siemens, Germany) was used during interstitial ^{125}I brachytherapy. The supporting structure, which was used to fix 3D-PCT, was connected to the CT bed. The patient lied on the CT bed with the same position and was fixed with a vacuum negative-pressure pad. Then, the CT images were acquired at 5 mm slice thicknesses with contrast materials. The predetermined puncture site was marked on the skin. 2% lidocaine was used for local anesthesia. The 3D-PCT was placed on the patient skin. Turned on the CT laser light and made the *x*-axis and *y*-axis laser line to coincide with the positioning cross line of the 3D-PCT, further calibrate the template position to ensure the accuracy. The 18-G implantation needles were inserted into the lesions through the puncture holes on the coplanar template. The CT images were acquired after all the needles were punctured to 1/3 of the expected depth to observe the difference between the actual position and the preoperative plan. If it was completely consistent with the preoperative plan, the needles were punctured to the expected depth. If not, the needles should be reoriented.

When all the needles had been inserted into the lesion, ^{125}I seeds were then implanted according to the preoperative plan, which were released every 0.5 to 1 cm apart, with gradual withdrawal of the needles. Puncture sites were bandaged and compressed for hemostasis after the implantation. The number of particles should be counted throughout the operation in order to prevent the loss of particles. If a particle falls, it should be picked up by the radiation monitor and put into a lead can. During the operation, radioactive particles should not be exposed in the air to avoid unnecessary radiation to the surrounding people. After the operation, the instruments and the surrounding environment were detected by radiation monitors.

Postoperative Dosimetry Evaluation

CT scan was performed 3 days after operation to reduce the error of tumor volume due to tissue edema. And images were transmitted to TPS for dose verification (Figure 1). Dose parameters were calculated to evaluate the dose distribution, which include D90 (prescribed doses delivered to 90% of the GTV), D100, V100, V150, V200, GTV volume, CI (conformal index), EI (external index), and HI (homogeneity index). The patients received a course of antibiotics and hemostasis to prevent the occurrence of infection and bleeding after surgery.

Assessments and follow-up

The investigators evaluated the tumor response in patients every 3 months by means of spiral computed tomography, with the use of RECIST, version 1.1. Safety was monitored by means of an assessment by the investigators of treatment-related adverse events and serious adverse events. Patients, who were lost during the follow-up period, were analyzed assuming there was a disease progression on the last visit date or death.

Study End Points and Subgroup Analysis

The primary endpoint of this study was the local control rate (LCR). The secondary outcomes were OS (time from the day of radioactive ^{125}I seed implantation to death from any cause), preoperative and postoperative dosimetry evaluation, duration of response, safety, tolerability, and to identify special factors related to prognosis. LCR was defined as CR + PR + SD [LCR = (CR + PR + SD)/total × 100%], and short-term (3 months after implantation) efficacy was divided into CR + PR and SD + PD according to RECIST 1.1. OS was defined as the time between the date of ^{125}I seed implantation and the last follow-up or death. Treatment-related adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 and were coded and summarized according to the preferred terms in the Medical Dictionary for Regulatory Activities, version 15.0.

Statistical Analysis

All statistical analyses were conducted using SPSS version 23.0. The x^2 test and Fisher precision test were used to compare the classified variables and the *t* test was used to

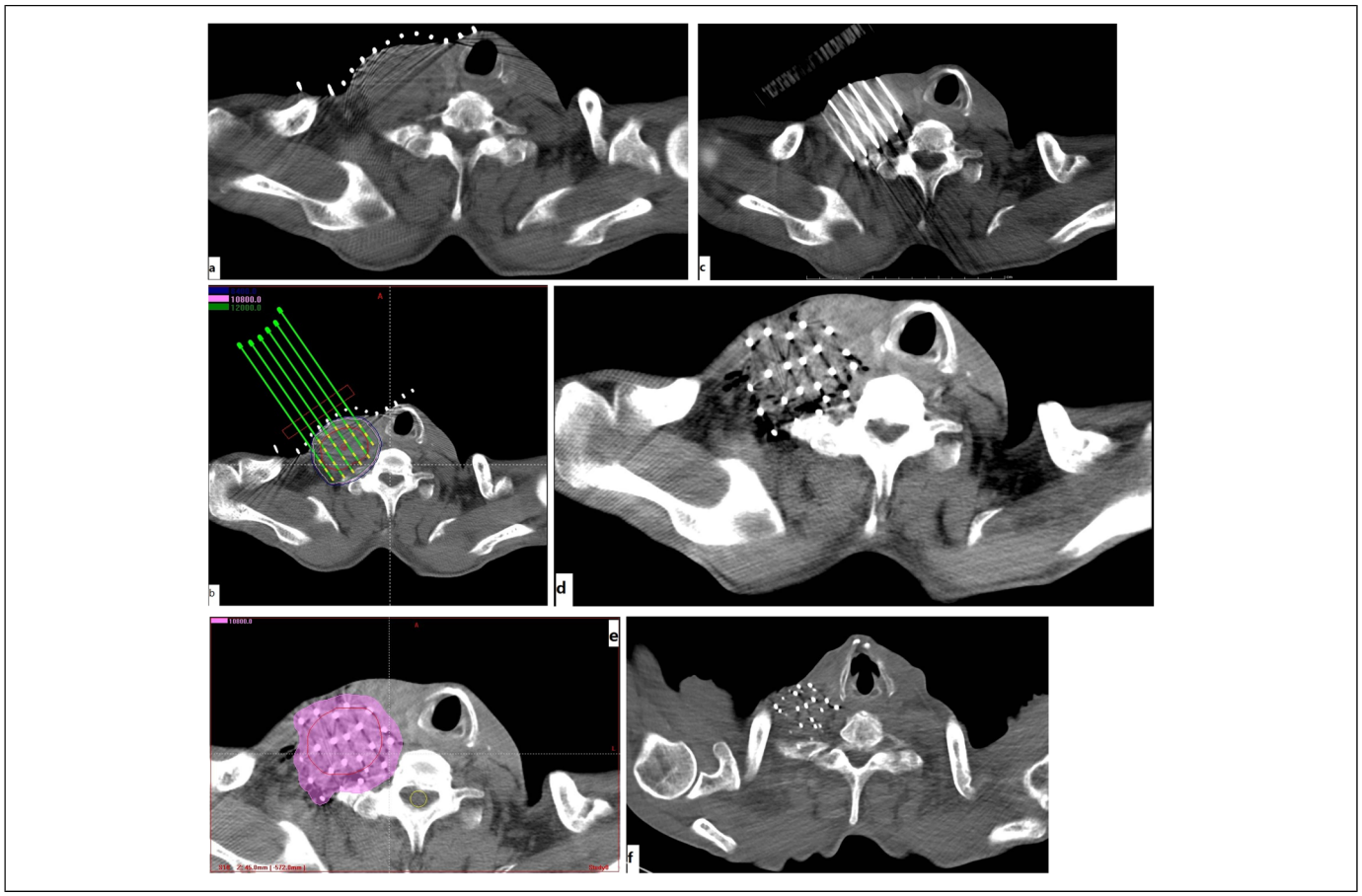

Figure 1. Representative CT scans of a patient during the whole treatment process. (a) Preoperative image. (b) Preoperative plan. (c) Operation process. (d) Postoperative image. (e) Postoperative dosimetry evaluation. (d) Three months after ^{125}I seed implantation.

compare the measurement data of normal distribution. $P < .05$ was considered statistically significant.

Results

Patients' Characteristics

We performed a retrospective analysis of 32 patients with 36 recurrent cervical lymph nodes of thoracic esophageal squamous cell carcinoma after external beam radiotherapy, who underwent interstitial ^{125}I brachytherapy as a salvage treatment with a CT-guided coplanar template-assisted technique at Tengzhou Central People's Hospital from January 2012 to December 2017. All the patients underwent interstitial ^{125}I brachytherapy because they either refused (14/32, 43.75%), or their performance status did not allow patients to undergo surgical resection or chemoradiotherapy (18/32, 56.25%). The characteristics of the patients were summarized in Table 1. Twenty-six males and 6 females, aged from 43 to 76 years (median, 68 years), with KPS scores from 70 to 90 (median, 80), and previous cumulative radiation doses from 50 to 66 Gy (median, 60 Gy). The recurrent cervical lymph node was identified 4 to 32 months (mean, 10.5 months) after the first treatment. In all 32 cases, 18 (18/32, 56.25%) showed moderate pain or severe pain. Twenty-one patients (21/32, 65.63%) received postoperative treatment (Chemotherapy 5, Immunotherapy 3, Target therapy 3, Chemotherapy plus Immunotherapy 4, Immunotherapy plus Target therapy 2, Chemotherapy plus Target therapy 4), and 11 patients (11/32, 34.37%) received best supportive care.

Outcome of ^{125}I Seed Implantation

All patients were followed up to the expiration date, with a median follow-up time of 10.5 months (range 4-26 months). All patients were successfully performed implantation at the first time. Median number of ^{125}I seeds implanted was 51.5 (range, 10-94). The specific activity of seeds ranged from 0.5 to 0.8 mCi/seed, with a median of 0.67 mCi/seed. Actual D90 were 114 to 240 Gy, with a median of 177.5 Gy in postoperative dosimetry evaluation. The clinical characteristics of patients performed implantation were summarized in Table 2.

Effectiveness of ^{125}I Seed Implantation

The local pain grades greatly relieved 1 to 3 months after implantation. Before implantation the scores of pain were 4 to 9, and after implantation the scores of pain were 0 to 3.

Table 1. Characteristics of Patients (n = 32).

	Total	≥1-year	<1-year	*P* value
Median age	68 (43-76)	62 (43-76)	66 (46-73)	
Gender				.568
Male	26	12	14	
Female	6	2	4	
KPS				.025
70	4	1	3	
80	15	6	9	
90	13	7	6	
Median tumor size(cm)	4.15(1.6-6.7)	3.9(1.6-6.0)	4.2(1.8-6.7)	.827
Primary tumor stage				
T Stage				.268
T1	2	2	0	
T2	7	2	5	
T3	18	7	11	
T4	5	3	2	
N stage				.581
N0	12	6	6	
N1	20	8	12	
M stage				.249
M0	31	13	18	
M1	1	1	0	
NPR				.116
1-3(mild pain)	14	9	5	
4-6(moderate pain)	10	3	7	
7-10(severe pain)	8	2	6	

Abbreviation: KPS, Karnofsky performance status; NPR, numerical pain rating; ≥1-year, OS≥1-year; <1-year, OS<1-year.

The LCRs after 3, 6, 9, and 12 months were 87.5%, 59.38%, 40.63%, and 31.25%, respectively. The median local control time was 7.5 months.

The median OS time was 10.5 months (95% CI, 8.9-13.4), and 1- and 2-year survival rates were 43.75% and 9.38%, respectively.

Differences Between Pretreatment Planning and Postoperative Dosimetry Evaluation

There were 36 lesions in 32 patients. The dosimetric comparison before and after implantation is shown in Table 3. There was no significant difference between preoperative and postoperative parameters, including D90, D100, V100, V150, V200, GTV volume, CI, EI, and HI, which were compared by paired *t*-test ($P > .05$).

Side Effects

Three patients (3/32, 9.37%) presented fever with 37.9 °C, 38.1 °C, and 38.4 °C, respectively, the day after implantation and alleviated by oneself without special processing in a couple of days. One patient (1/32, 3.12%) presented grade IV skin toxic effect, which was improved after symptomatic treatment (Figure 2). No fatal complications such as massive bleeding happened.

Discussion

Lymph node recurrence is the main mode of treatment failure in esophageal cancer, and lymph node status is closely related to survival in patients with esophageal cancer. And it suggests that even patients receiving multimodal treatment still have a short survival time.[30–33] If recurrent lymph nodes are effectively treated, long-term survival can be ensured.[34] However, at present, there is no clear optimal treatment for patients with cervical lymph node recurrence of thoracic esophageal squamous cell carcinoma after external radiation radiotherapy.

In recent years, with the emergence of computer 3-dimensional TPS and the development of modern imaging technology, ^{125}I seed implantation has been widely used in tumor treatment. ^{125}I seed implantation has the advantages of its efficacy, safety, and feasibility, which can reduce the damage to the surrounding tissue and protect the medical staff and patients more easily.[35,36] ^{125}I particles continuously release low dose rate x-rays and γ ray. The characteristics of ^{125}I particles help to inhibit the proliferation and repair of cancer cells, while the adjacent normal tissues will not be affected and the dose ≥ 25% will be delivered to the tumor target.[37]

In China, the predominant histological type of esophageal cancer is squamous cell carcinoma.[1] More and more animal experiments and clinical studies have confirmed that squamous cell carcinoma is very sensitive to ^{125}I seed implantation brachytherapy.[38–40] Lin et al[26] reviewed 19 patients with recurrent cervical lymph nodes of esophageal cancer patients with radioactive seed implantation, who found that the LCRs after 3, 6, 12, and 24 months were 84.2%, 63.2%, 32.0%, and 26.0%, respectively, with a median of 10 months. The 1- and 2-year survival rates were 31.6% and 10.5%, respectively. Gao et al[41] reviewed 16 patients with lymph node recurrence of esophageal squamous cell carcinoma underwent ^{125}I seed implantation, who found that the LCRs after 3, 6, 10, and 15 months were 75.0%, 50.0%, 42.9%, and 33.3%. The patients in our study who received ^{125}I implantation demonstrated a promised local control and survival rates. The LCRs after 3, 6, 9, and 12 months were 87.5%, 59.38%, 40.63%, and 31.25%, respectively. The median local control time was 7.5 months. The median OS time was 10.5 months, and 1- and 2-year survival rates were 43.75% and 9.38%, respectively.

Fifty-seven patients were included in a randomized phase III trial, which investigated the potential benefit of concurrent re-irradiation, fluorouracil, and hydroxyurea versus methotrexate for patients treated with palliative intent for recurrent or second primary head and neck squamous cell carcinoma in previously irradiated area.[42] Although 4 complete responses were achieved in R-RT arm (none in Ch-T arm), re-irradiation did not improve OS compared with methotrexate (23% vs 22% at 1

Table 2. Treatment Characteristics Prior to ^{125}I Seed Implantation (n = 32).

NO.	Gender	Age	Lesion location	Number of metastatic nodes	Stage	Position of implant seeds	Recurrent time (months)	Seed activity (mCi)	Seeds number	D90 (Gy)	LCT (months)	Previous cumulative dose (Gy)	OS (months)	Cause of death
1	M	52	Middle thoracic esophagus	1	pT3N1M0	Left neck metastatic LN	6	0.7	20	135	5	60	10	Progression of tumor
2	M	60	Lower thoracic esophagus	1	pT3N0M0	Right neck metastatic LN	10	0.6	16	196	10	64	15	Progression of tumor
3	M	52	Middle thoracic esophagus	2	pT2N1M0	Right neck metastatic LN	6	0.8	65	177	2	66	4	Progression of tumor
4	M	59	Lower thoracic esophagus	1	pT3N1M1	Right neck metastatic LN	12	0.7	18	160	7	60	13	Trauma
5	M	61	Middle thoracic esophagus	1	pT2N1M0	Right neck metastatic LN	32	0.6	10	168	4	60	5	Progression of tumor
6	M	69	Upper thoracic esophagus	1	pT3N1M0	Right neck metastatic LN	8	0.67	40	188	2	60	7	Progression of tumor
7	F	43	Upper thoracic esophagus	1	pT4N0M0	Right neck metastatic LN	4	0.72	30	158	5	60	6	Progression of tumor
8	F	43	Upper thoracic esophagus	2	pT1N1M0	Right neck metastatic LN	8	0.5	41	207	13	60	25	Progression of tumor
9	F	62	Upper thoracic esophagus	1	pT3N1M0	Right neck metastatic LN	6	0.7	40	189	2	60	5	Progression of tumor
10	M	56	Middle thoracic esophagus	1	pT3N0M0	Right neck metastatic LN	21	0.8	20	218	4	60	6	Progression of tumor
11	F	48	Upper thoracic esophagus	1	pT3N1M0	Left neck metastatic LN	8	0.75	30	171	5	64	6	Progression of tumor
12	M	60	Middle thoracic esophagus	1	pT2N1M0	Right neck metastatic LN	7	0.67	55	141	4	50	4	Progression of tumor
13	M	50	Middle thoracic esophagus	1	pT3N1M0	Right neck metastatic LN	4	0.76	37	124	12	60	14	Progression of tumor
14	M	64	Lower thoracic esophagus	1	pT3N0M0	Right neck metastatic LN	15	0.6	80	157	10	60	12	Progression of tumor

(continued)

Table 2. (continued)

NO.	Gender	Age	Lesion location	Number of metastatic nodes	Stage	Position of implant seeds	Recurrent time (months)	Seed activity (mCi)	Seeds number	D90 (Gy)	LCT (months)	Previous cumulative dose (Gy)	OS (months)	Cause of death
15	M	58	Lower thoracic esophagus	1	pT3N1M0	Right neck metastatic LN	27	0.6	79	114	15	60	15	Progression of tumor
16	M	47	Middle thoracic esophagus	1	pT2N1M0	Left neck metastatic LN	16	0.8	73	196	2	58	4	Pneumonia
17	M	61	Upper thoracic esophagus	1	pT3N1M0	Right neck metastatic LN	14	0.5	61	182	12	64	12	Progression of tumor
18	M	51	Middle thoracic esophagus	1	pT4N1M0	Right neck metastatic LN	11	0.6	90	176	17	60	17	Progression of tumor
19	M	67	Lower thoracic esophagus	1	pT3N0M0	Left neck metastatic LN	31	0.7	65	233	8	60	8	Progression of tumor
20	M	70	Upper thoracic esophagus	1	pT4N0M0	Left neck metastatic LN	6	0.6	53	177	22	64	25	Progression of tumor
21	F	66	Middle thoracic esophagus	1	pT3N1M0	Right neck metastatic LN	12	0.8	58	178	15	60	17	Progression of tumor
22	M	73	Middle thoracic esophagus	1	pT2N1M0	Right neck metastatic LN	7	0.67	66	129	4	60	11	Pneumonia
23	M	66	Upper thoracic esophagus	1	pT3N0M0	Right neck metastatic LN	10	0.78	75	232	3	64	9	Progression of tumor
24	M	75	Middle thoracic esophagus	1	pT3N1M0	Right neck metastatic LN	18	0.6	67	160	7	60	7	Pneumonia
25	M	71	Middle thoracic esophagus	1	pT4N0M0	Left neck metastatic LN	11	0.6	39	168	18	60	18	Pneumonia
26	M	71	Lower thoracic esophagus	1	pT2N0M0	Left neck metastatic LN	9	0.7	35	184	9	60	12	Pneumonia
27	M	54	Lower thoracic esophagus	2	pT3N1M0	Right neck metastatic LN	5	0.7	93	163	8	60	8	Progression of tumor
28	M	71	Middle thoracic esophagus	2	pT3N0M0	Right neck metastatic LN	14	0.6	60	197	6	60	10	Progression of tumor

(continued)

Table 2. (continued)

NO.	Gender	Age	Lesion location	Number of metastatic nodes	Stage	Position of implant seeds	Recurrent time (months)	Seed activity (mCi)	Seeds number	D90 (Gy)	LCT (months)	Previous cumulative dose (Gy)	OS (months)	Cause of death
29	M	58	Lower thoracic esophagus	1	pT4N1M0	Left neck metastatic LN	9	0.7	54	204	3	60	4	Pneumonia
30	M	75	Upper thoracic esophagus	1	pT2N0M0	Right neck metastatic LN	11	0.6	50	188	13	62	13	Heart disease
31	F	76	Middle thoracic esophagus	1	pT3N0M0	Right neck metastatic LN	12	0.6	25	193	8	60	11	Progression of tumor
32	M	64	Upper thoracic esophagus	1	pT1N1M0	Left neck metastatic LN	20	0.6	11	240	22	60	26	Pneumonia

Abbreviations: F, female; M, male; MPD, minimal peripheral dose; PFS, progression-free survival; OS, overall survival.

year, NS). Compared with the historical data of irradiation, ^{125}I brachytherapy may be promising as a salvage therapy for refractory cervical lymph node metastasis of thoracic esophageal squamous cell carcinoma after external irradiation.

In this study, 21 patients (21/32, 65.63%) died of disease progression. In a careful review of the data of all enrolled patients, 11 patients (11/32, 34.37%) did not receive postoperative treatment, and ^{125}I brachytherapy is a local mode of treatment that does not completely replace systemic therapy. Zhang W et al[43] found that ^{125}I brachytherapy combined with chemotherapy can significantly enhance the clinical efficacy of patients with advanced non-small cell lung cancer without increasing the incidence of complications of chemotherapy through a meta-study. Concurrent or sequential systemic therapy should be applied to improve patients' outcomes.

Table 3. Comparison of Preoperative and Postoperative Dosimetry Parameters in 36 Lesions From 32 Patients ($\overline{x} \pm s$).

Parameters	Preoperative	Postoperative	*t*	*P*
D90 (Gy)	178.40 ± 30.28	178.21 ± 30.64	0.501	.62
D100 (Gy)	85.88 ± 22.51	76.36 ± 18.89	1.042	.318
V100 (%)	98.03 ± 1.96	97.58 ± 2.35	0.537	.601
V150 (%)	87.33 ± 7.21	87.02 ± 6.72	1.011	.332
V200 (%)	69.73 ± 18.29	68.29 ± 17.06	1.435	.177
GTV volume (cm^3)	52.36 ± 31.21	52.42 ± 31.19	−0.843	.416
Seeds number	48.56 ± 23.44	48.68 ± 23.45	−1.679	.103
CI	0.58 ± 0.11	0.53 ± 0.13	1.394	.189
EI (%)	101.00 ± 69.71	104.64 ± 75.29	−0.484	.637
HI (%)	14.38 ± 9.24	14.02 ± 11.64	0.211	.836

Abbreviations: D90, the dose delivered to 90% CTV; D100, the dose delivered to 100% CTV; V100, the volume to withstand 100% of the prescribed dose; V150, the volume to withstand 150% of the prescribed dose; V200, the volume to withstand 200% of the prescribed dose; GTV, tumor target volume; CI, conformal index; EI, external volume index of target area; HI, homogeneity index

Radiotherapy can affect the body's immune microenvironment and immune system,[44,45] which would induce immunomodulatory effects.[46,47] Checkpoint blockade immunotherapy has shown significant and long-lasting clinical effects in some tumors. In theory, the combination of radiotherapy and immunotherapy can improve LCR and OS. However, more prospective clinical studies are needed to confirm this idea. Wenjing Song et al reported a patient who had refractory left cervical lymph node metastasis of esophageal squamous cell carcinoma after surgical resection and external irradiation, found that the combination of radioactive particle implantation and immune checkpoint inhibitor obtained good curative effect.[48]

CT scanning has the characteristics of high spatial resolution and is not disturbed by structures such as gas and bone. Particularly, CT scan images can be synchronously compared and browsed between preoperative enhanced images and intraoperative images. Meanwhile, it is more accurate and safer to distinguish vascular, mucous membrane, gland, and other structures that can be clearly displayed only with enhanced CT scan. Due to the complex anatomical structure of the neck and the rich peripheral blood vessels and nerves, it is difficult to puncture with conventional seed implantation. And it is easy to damage the blood vessels and other organs. At the same time, because there is no standard operation, most doctors still use unarmed experience to implant radioactive particles, which leads to inconsistent preoperative and postoperative dose, unable to repeat, uncontrollable dose, and difficult to promote technical means. Our research retrospectively evaluated the clinical outcome of CT-guided ^{125}I seed implantation by coplanar template for cervical metastatic lymph nodes recurrence of esophageal squamous cell carcinoma after external beam radiotherapy.

The key to affect the curative effect of ^{125}I brachytherapy is how to implant particles accurately, and the rationality of particle spatial distribution is the premise of accurate dose. Using image guidance, details of needles and seeds in the volume can be seen and the position of each needle and seed can be adjusted to ensure proper placement according to the pretreatment planning during implantation. In the past, except for prostate cancer, most of the tumors were punctured with bare hands.

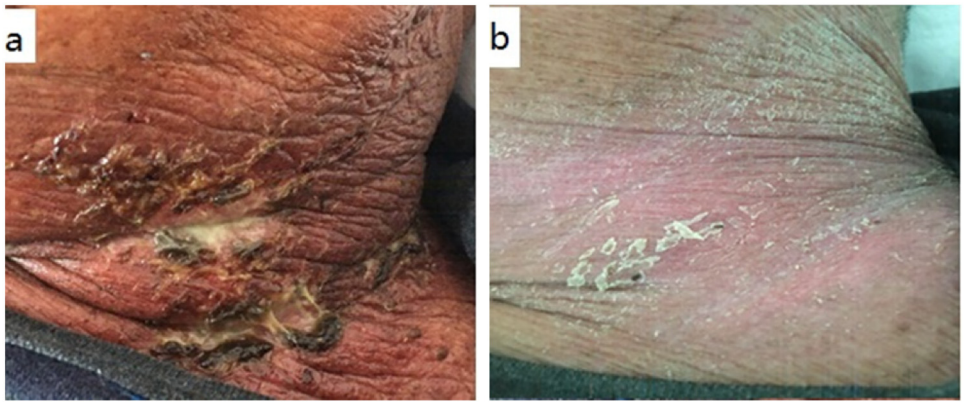

Figure 2. Grade IV skin toxic effect. (a) One month after ^{125}I seed implantation. (b) Three months after ^{125}I seed implantation.

Although there was imaging guidance, it was highly dependent on personal experience and had strong randomness. It was difficult to accurately arrange the needles according to the preoperative plan, to ensure that multiple puncture needles at the same level were parallel and equidistant, and to ensure that multiple puncture needles at different levels were parallel and equidistant. There is a large difference between the postoperative and preoperative dose, which is easy to occur the cold and hot spots of dosimetry lead to insufficient local dose of tumor or excessive dose of adjacent normal tissue, which makes it difficult to achieve homogeneity and standardization.

Recently, some scholars have conducted a comparative study on the dosimetry of 3D printing non-coplanar template guided particle implantation, and found that there is no difference between the preoperative and postoperative dosimetry, which may become a standard operation with good repeatability.[33–36] But this kind of non-coplanar template also has the following disadvantages: the needle path is prefabricated on the template, once the patient's tumor position and body surface have relative displacement during the operation, the template needle path direction cannot be adjusted, which will lead to the template cannot be used.

3D PCT is a coplanar puncture template with coordinate system and positioning identification system printed by 3D printing technology. In fact, it is improved from the parallel matrix template used in prostate cancer particle implantation.[49] The center of 3D PCT has a cross axis to calibrate the template position accurately. And pinholes are perfectly compatible with puncture needles. In our previous study, 3D PCT assisted particle implantation was used. There was no significant difference between preoperative and postoperative dosimetric parameters, showing good consistency.[50] In this study, there was no significant differences in D90, D100, V100, V150, V200, and other dosimetric parameters before and after implantation of 36 lesions, indicating the accuracy and consistency of this treatment. CI, EI, and HI are important dosimetric evaluation indexes of radioactive particles. Because the dose attenuation of particles follows the law of inverse square of distance and exponential attenuation, a little change of particle spacing can lead to obvious change of dose distribution.[36] In this study, there was no significant differences in CI, EI, and HI between postoperative and preoperative. The results of this study show that the application of 3D printing templates can make the particle implantation have a high accuracy in the conformity of the dose distribution, the distribution outside the target area, and the uniformity.

The method of 3D-PCT guided particle implantation also has some disadvantages. Because the needle path cannot be changed flexibly, it is mainly used for lesions with regular shape, single puncture direction, and no obstruction to the needle path. It is not suitable for the multi-angle non-coplanar implantation of the lesion.

Precautions for 3D-PCT guided particle implantation: (1) adequate preoperative preparation is the key to reduce surgical complications; (2) the template should be as close as possible to the skin to prevent the template displacement from affecting the accuracy of needle insertion; (3) the template should be calibrated with a 3D movable laser lamp, and the angle and direction of the template should be adjusted with a digital goniometer; (4) if the needle tip is beveled, it should be noted that the bevel of each needle should be consistent; (5) the puncture needle should avoid passing through the blood vessel.

Fever occurred in 3 patients the day after ^{125}I brachytherapy, with 37.9 °C, 38.1 °C, and 38.4 °C, respectively, which was alleviated by oneself without special treatment in a few of days. A patient appeared with grade IV skin toxic effect, which was improved after symptomatic treatment. In this report, there were no fatal complications, including massive hemorrhage and radiation injury to important organs. The main side effects of ^{125}I seed implantation include intraoperative puncture-related injury and postoperative radiation damage to the adjacent skin and mucous membranes. The ^{125}I particles are pushed to the lesion through an implanted needle with a diameter of about 1.2 to 1.7 mm, and the damage to the skin on the body surface is minimal. In the preoperative planning, the dose to the skin and mucous OARs can be controlled by TPS.

We acknowledge the following limitations in our study. It was a retrospective study with a single arm. There was no control group with the current standard treatment of salvage surgery or repeat EBRT. More randomized controlled prospective multicenter studies in more patients are needed, in order to further demonstrate the effectiveness of this technique as a therapeutic option for neck lymph node recurrent after external beam radiotherapy for thoracic esophageal squamous cell carcinoma.

In conclusion, the interstitial implantation of ^{125}I seeds has the advantage of safety, reliability, satisfactory, and less side-effect, which can be used to treat cervical lymph node recurrence of thoracic esophageal squamous cell carcinoma after external beam radiotherapy. And with the assist of 3D-PCT, the treatment could be even more accurate.

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Ethics Statement

All patients signed an informed consent approved by the institutional review board.

Declaration of Conflicting Interests

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ORCID iD

Peishun Li https://orcid.org/0000-0002-1009-3453

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