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

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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
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.

125I 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 125I radioactive seed implantation can produce a significant dose gradient between the tumor and adjacent normal tissues, thus protecting the organs at risk (OARs).125I 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 125I seeds can be used to treat cervical lymph node metastasis after radiotherapy of esophageal squamous cell cancer.26,27 In the past, interstitial 125I 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 125I brachytherapy for metastatic cervical lymph nodes with 3D printed coplanar template (3D-PCT). Our study retrospectively analyzed the clinical effect of CT-guided 125I 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 125I brachytherapy.

Materials and Methods

Patients

We retrospectively collected and analyzed the results of 32 patients with refractory cervical lymph node metastasis, who underwent interstitial 125I 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 125I 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 125I 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 125I 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 125I seed implantation.
**125I Radioactive Seed**

The 125I 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 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-125I 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.

**Interstial 125I Brachytherapy**

The 64-row spiral CT scanner (Siemens, Germany) was used during interstitial 125I 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, 125I 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 125I 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 125I 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 $\chi^2$ test and Fisher precision test were used to compare the classified variables and the $t$ test was used to
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.
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, 125I seed implantation has been widely used in tumor treatment. 125I 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 125I particles continuously release low dose rate x-rays and γ ray. The characteristics of 125I 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 125I seed implantation brachytherapy.38–40 Lin et al26 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 al41 reviewed 16 patients with lymph node recurrence of esophageal squamous cell carcinoma underwent 125I 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 125I 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 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 | | | |
| Male | 26 | 12 | 14 | .568 |
| Female | 6 | 2 | 4 |
| KPS | | | |
| 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 | | | |
| T1 | 2 | 2 | 0 |
| T2 | 7 | 2 | 5 |
| T3 | 18 | 7 | 11 |
| T4 | 5 | 3 | 2 |
| N stage | | | |
| N0 | 12 | 6 | 6 |
| N1 | 20 | 8 | 12 |
| M stage | | | |
| M0 | 31 | 13 | 18 |
| M1 | 1 | 1 | 0 |
| NPR | | | |
| 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.
| 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 |
| 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)
| 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.
Radiotherapy can affect the body’s immune microenvironment and immune system,\textsuperscript{44,45} which would induce immunomodulatory effects.\textsuperscript{36,47} 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.\textsuperscript{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\textsuperscript{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\textsuperscript{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.

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

| 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±6.72  | 104.64±7.21   | −0.484| .637 |
| HI (%)                      | 69.71±75.29  | 69.71±75.29   | 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.
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. 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. 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. 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 make the hot spots of dosimetry lead to obvious change of dose distribution. In this study, there was no significant differences in CI, EI, and HI between the preoperative and postoperative dosimetry, 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.

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 125I 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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