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CT-guided ^{125}I brachytherapy for mediastinal metastatic lymph nodes recurrence from esophageal carcinoma: Effectiveness and safety in 16 patients

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ABSTRACT

Objectives: To retrospectively evaluate effectiveness and safety of CT-guided ^{125}I brachytherapy in 16 patients with mediastinal metastatic lymph nodes recurrence from esophageal carcinoma.
Materials and methods: Sixteen metastatic lymph nodes in 16 patients were percutaneously treated in 19 ^{125}I brachytherapy sessions. Each metastatic lymph node was treated with computed tomographic (CT) guidance. Follow-up contrast material-enhanced CT or positron emission tomographic (PET) scans were reviewed and the treatment's effectiveness was evaluated.
Results: Months are counted from the first time of ^{125}I brachytherapy and the median duration of follow-up was 11 months (range, 5–16 months). The local control rates after 3, 6, 10 and 15 months were 75.0, 50.0, 42.9 and 33.3% respectively. At the time of writing, four patients are alive without evidence of recurrence at 16, 9, 16 and 9 months. The 4 patients presented good control of local tumor and no systemic recurrence, and survived throughout the follow-up period. The other 12 patients died of multiple hematogenous metastases 5–15 months after brachytherapy. A small amount of local hematoma occurred in 2 patients that involved applicator insertion through the lung. Two patients presented pneumothorax with pulmonary compression of 30 and 40% after the procedure and recovered after drainage. One patient had minor displacement of radioactive seeds. Severe complications such as massive bleeding and radiation pneumonitis did not occur.
Conclusion: ^{125}I radioactive seed implantation is effective and may be safely applied to mediastinal metastatic lymph nodes recurrence from esophageal carcinoma.
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1. Introduction

Recurrence is the most common cause of death for patients who undergo surgery for esophageal cancer and is thus considered a major prognostic factor [1,2]. If lymph node recurrence is treated effectively, relatively long survival may be possible for selected patients [3–5]. However, treatment of recurrent esophageal cancer is usually challenging because the previous therapies (including surgery, radiation, chemotherapy, and various combinations of these treatments) limit the options available for subsequent treatment. ^{125}I seed implantation has been accepted as a useful minimally invasive therapy for tumors in a variety of organs [6–8]. However, there are few reports about the effects of tumor metastatic lymph nodes with the methods of ^{125}I brachytherapy. This research retrospectively evaluated the clinical value of ^{125}I brachytherapy for mediastinal metastatic lymph nodes recurrence from esophageal carcinoma, although to our knowledge it had not yet been investigated in the mediastinum.

2. Materials and methods

2.1. Ethics

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved ethically by Sun Yat-sen University Cancer Center (the number of Ethics Committee approval was GWLHJJ2003-03). All patients provided informed written consent.

2.2. Patients

From March 2003 to March 2009, sixteen patients underwent ^{125}I brachytherapy of a mediastinal metastatic lymph node. The characteristics of the patients and lymph nodes are summarized in

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Table 1
Characteristics of 16 patients with mediastinal lymph node recurrence from esophageal carcinoma.

Patient no./age (years)/sex	Treatment of primary cancer	Time to diagnosis of metastatic lymph node (months)[a]	Metastatic lymph node	
			Largest diameter (cm)	Shortest diameter (cm)
1/53/M	Surgery and chemotherapy	11	1.3	1.2
2/70/M	Surgery and chemotherapy	12	1.7	1.3
3/51/M	Radiotherapy and chemotherapy	8	2.6	2.5
4/49/M	Surgery and chemotherapy	7	1.7	1.6
5/46/M	Surgery and chemotherapy	10	1.9	1.5
6/45/F	Radiotherapy and chemotherapy	12	2.2	1.2
7/60/M	Surgery and chemotherapy	13	1.8	1.8
8/55/M	Radiotherapy and chemotherapy	7	2.2	1.5
9/38/M	Radiotherapy and chemotherapy	9	3.2	1.8
10/73/M	Radiotherapy and chemotherapy	12	1.7	1.2
11/66/M	Surgery and chemotherapy	10	1.9	1.5
12/53/F	Radiotherapy and chemotherapy	12	2.2	2.0
13/37/M	Surgery and chemotherapy	9	3.2	3.1
14/54/F	Radiotherapy and chemotherapy	12	2.2	1.4
15/65/M	Surgery and chemotherapy	10	1.9	1.7
16/56/F	Radiotherapy and chemotherapy	12	2.2	2.0

[a] Time is counted from the first treatment of primary cancer to diagnosis of the metastatic lymph node on routine follow-up CT images.

Table 1. 16 patients, 12 men and 4 women (mean age, 54 years; range, 37–73 years), were enrolled in our study. All patients were pathologically proved as esophageal carcinoma. Treatment of the primary cancer was surgical resection combined with chemotherapy in 8 patients, and radiotherapy combined with chemotherapy in 8 patients. The metastatic mediastinal lymph node was seen on computed tomographic (CT) images 7–13 months (mean, 10 months) after the first treatment of the primary cancer. In addition, one patient showed slight superior vena cava syndrome, and other patients showed no relative symptoms. According to our diagnostic criteria, lymph nodes are considered to be metastatic when they are larger than 1.0 cm in short-axis diameter.

Our diagnosis was confirmed with pathologic proof at CT-guided needle biopsy before ^{125}I brachytherapy in twelve patients. Needle biopsies were performed twice when the first results were negative. The other 4 cases were treated based on the CT criteria because they refused biopsy. The mean size of the lymph nodes was 1.7cm ± 0.6 (standard deviation) (range, 1.3–3.2 cm) in largest diameter. Our indication criteria for ^{125}I brachytherapy of metastatic lymph nodes were as follows: (a) the metastatic lymph node was solitary in the mediastinum and the patient was not a candidate for surgical lymph node resection or (b) the metastatic mediastinal lymph node was the only evidence of recurrence. Patients who had extra-mediastinal lymph nodes metastasis, hematogenous metastases, or Karnofsky performance score < 70 were excluded. No other esophageal cancer therapies were the patients received during brachytherapy because most of the patients received the previous therapies (including surgery, radiation, chemotherapy, and various combinations of these treatments).

2.3. Methods

The ^{125}I seed (Beijing Atom High Tech) in this study was shaped as cylindrical titanium package body with length of 4.5 mm, diameter of 0.8 mm and 3.0 mm × 0.5 mm inside the silver column (adsorption of ^{125}I, radioactivity: 0.8 mCi, the average energy: 27–35 keV, half-life: 59.6 days, half layer: 0.025 mm of lead; antitumor activity: 1.7 cm, the initial dose rate: 7 cGy/h), and 0.05 mm wall thickness of titanium in its external shell. The operation cost of one patient was about $2000–$3000 and the cost of each ^{125}I seed was $62.

Before ^{125}I brachytherapy, CT images with 5 mm section thickness were obtained for targeting the area of interest. A treatment plan was made for each patient using a computerized treatment planning system (TPS) (BT-RSI model TPS, YuanBo, Beijing, China) to determine the dose of radioactive seeds implanted and the placed site. A careful delineation of the tumor target volume was performed in every CT slice. Based on the three perpendicular diameters within the target tumor and a prescribed matched peripheral dose (MPD) of 100–140 Gy, TPS generated a dose–volume histogram (DVH), isodose curves of different percentages, and calculated the position (coordinates) of brachytherapy applicator, dose and number of implanted seeds. Planning target volume (PTV) is defined as a 1.5 cm of expansion external to the gross tumor volume. PTV edge was covered by isodose curve from 80% to 90% (Fig. 1). The entry site and path of the needle were determined to avoid vital structures such as large vessels.

With CT (Siemens, Germany) fluoroscopic guidance, a 18G brachytherapy applicator (Beijing Atom High Tech) was inserted into a lymph node and positioned against its deepest margin after local anesthesia. A turntable or clip implant gun (Beijing Atom High Tech) was then attached to the applicator for implantation. Every ^{125}I seed was placed at a distance of 0.5–1.0 cm from each other (Fig. 2). Within one month, a CT scan was performed to verify the position and intensity of ^{125}I seeds according to TPS. For tumors showing insufficient radioactivity, more ^{125}I seeds were implanted.

2.4. Follow-up

According to our follow-up protocol, chest CT images were obtained each month before and after intravenous administration of contrast medium for up to 6 months and then at 2–3-month intervals. The effectiveness of ^{125}I brachytherapy was assessed according to World Health Organization (WHO) response evaluation criteria for solid tumor as follows. (1) Complete response (CR) was defined as complete disappearance of tumor, no tumor or only accumulative metal granule shadow detectable by imaging analysis. (2) Partial response (PR) was defined as the shrinkage of tumor with the p value decreasing by ≥50% compared to the pre-procedure value. (3) No change (NC) was defined as a p value decrease of <50% or increase of <25% compared to the pre-procedure value. (4) Progression of disease (PD) was defined as a p value increase of ≥25% or the appearance of new tumor foci. Local control rate (LCR) was calculated as (CR + PR)/total no. of cases × 100%. We compared the products (p value) of two largest and perpendicular diameters within the tumor under CT examination before and after the procedure.

Fig. 1. Pre-planning of ^{125}I brachytherapy. (A) Three-dimensional image of tumor on computerized radioactive treatment planning system (TPS). (B) Two-dimensional graph of planar implantation and dose distribution on TPS. (C) A dose–volume histogram (DVH) of tumor and surrounding organs on TPS.

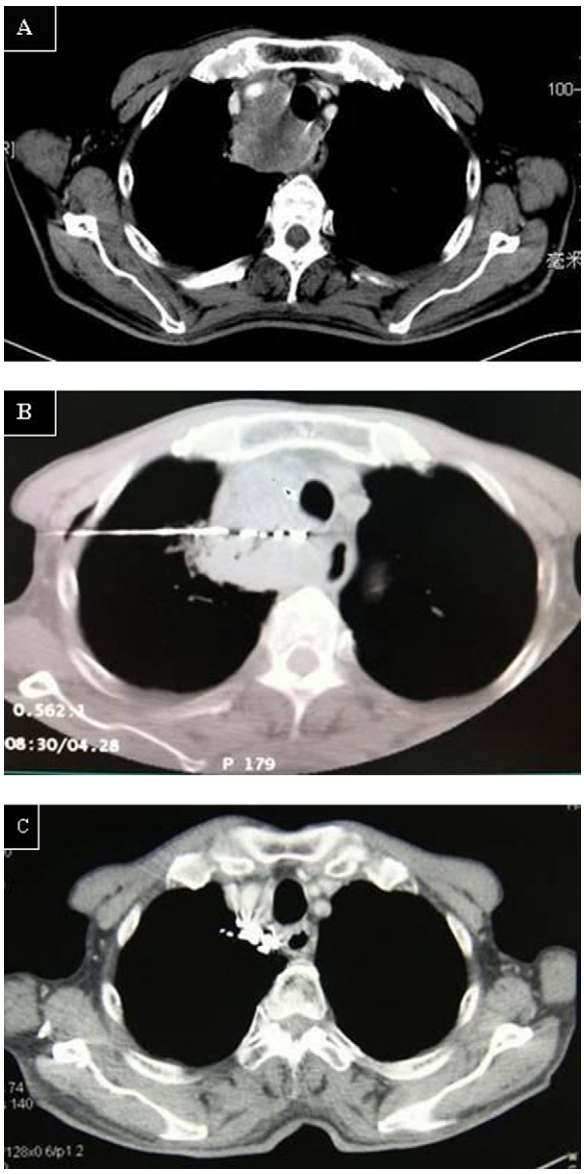

Fig. 2. Case 1. (A) Mediastinal metastatic lymph nodes recurrence from esophageal cancer after surgery. (B) During brachytherapy, an applicator accurately inserted into the tumor to implant ^{125}I seeds. (C) Four months after brachytherapy, tumor disappeared, with well distributed radioactive seeds remaining only.

3. Results

3.1. Implantation of ^{125}I radioactive seeds

A total of 19 brachytherapies were performed on the 16 patients, among which, 16 were successful at the first time, achieving the TPS criteria, and 3 did not reach the TPS criteria, followed by additional implantations. The total number of implanted seeds was 206, with an average of 10.8 per tumor. The satisfactory rate of seed implantation was 89.5% (17/19).

3.2. Treatment effectiveness

Months are counted from the first time of ^{125}I brachytherapy and the median duration of follow-up was 11 months (range, 5–16 months). The local control rates after 3, 6, 10 and 15 months were 75.0, 50.0, 42.9 and 33.3% respectively. At the time of writing, four patients are alive without evidence of recurrence at 16, 9,

Table 2
Clinical effectiveness of ^{125}I brachytherapy on mediastinal metastatic lymph node.

Follow-up time (months)	No. of patients	Local control efficacy				Local control rate (%) (CR + PR)/total %
		CR	PR	NC	PD	
3	16	2	10	1	3	75%
6	12	4	2	1	4	50%
10	7	2	1	2	2	42.9%
15	3	1	0	1	1	33.3%

Note: Months are counted from the time of ablation session. Two patients who were alive without evidence of recurrence at 9 and 9 months at the time of writing were excluded at 10 and 15 months of follow-up time.

16 and 9 months. The 4 patients presented good control of local tumor and no systemic recurrence and survived throughout the follow-up period (Figs. 2 and 3). The other 12 patients died of multiple hematogenous metastases 5–15 months after brachytherapy. Among the 12 patients, ^{125}I brachytherapy was repeated in 3 patients because of local residue or local progression of the lymph node. The clinical responses of patients to brachytherapy are summarized in Table 2.

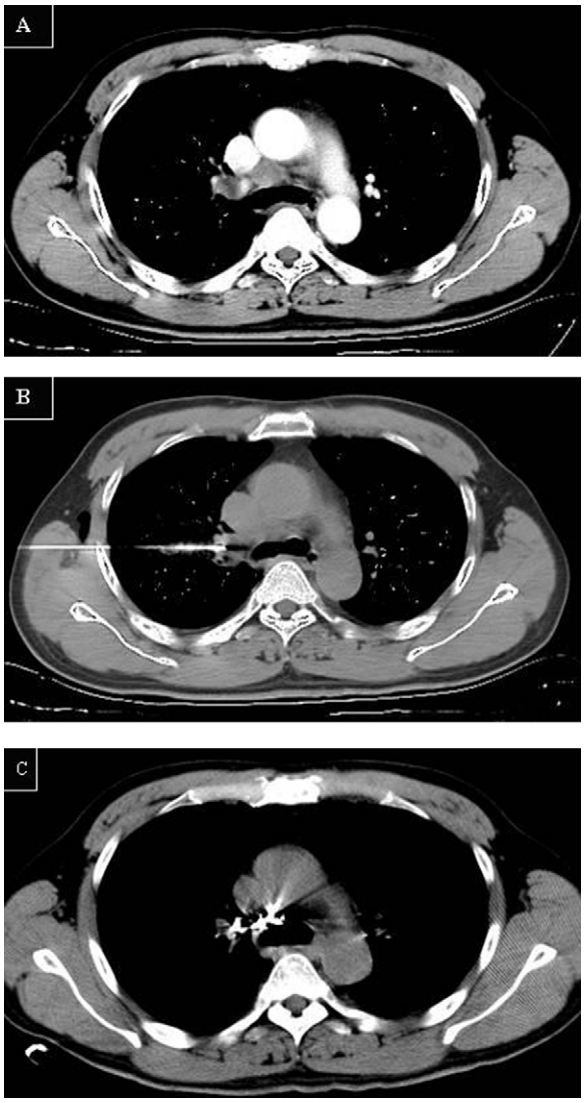

Fig. 3. Case 2. (A) Mediastinal metastatic lymph nodes recurrence from esophageal cancer after radiotherapy and chemotherapy. (B) During brachytherapy, an applicator accurately inserted into the tumor to implant ^{125}I seeds. (C) Six months after brachytherapy, tumor disappeared, with well distributed radioactive seeds remaining only.

3.3. Side effects

Several complications (Table 3) related to the procedure occurred during or after brachytherapy. A small amount of local hematoma occurred in 2 patients that involved applicator insertion through the lung, probably because of injury of small lung vessels. Two patients presented pneumothorax with pulmonary compression of 30 and 40% after the procedure and recovered after drainage. During the follow-up, one patient had minor displacement of radioactive seeds. Severe complications such as massive bleeding and radiation pneumonitis did not occur.

4. Discussion

^{125}I brachytherapy has been widely applied for tumor treatment in clinic with significant efficacy providing promising results for local control of solid tumors such as prostate carcinoma, lung cancer, lung metastasis, hepatocellular carcinoma, liver metastasis and pancreatic cancer [6–12]. When permanently implanted into the tumor, ^{125}I seeds send out continuous low-dose X-ray and γ-ray, leading to a dose of 160–180 Gy within the local tissue during the half-life of ^{125}I. The killing radius of ^{125}I seeds is 1.7 cm, with minimal effects on normal tissues since the radioactive energy is inversely correlated with the square of the radius [7]. The specific effect of ^{125}I radiation on tumor cells can efficiently inhibit the proliferation and repair of tumor cells, while the surrounding normal tissue only receive less than 25% of the doses received by the tumor cells [11]. The slow emission of radiation from the ^{125}I seeds also allows the surrounding normal tissue that receives sublethal or potentially lethal dose of radiation to have sufficient time for repair and recover [13]. We considered the possibility that it might be an alternative treatment for metastatic mediastinal lymph nodes. Especially for patients whose condition is unsuitable for surgical resection, ^{125}I brachytherapy may provide an opportunity to achieve remission even after administration of chemoradiation therapy.

The outcomes of patients with lymph node recurrence of esophageal cancer are poor. The following survival rates have been reported: a 1-year survival rate of 35% after recurrence in patients who underwent treatment of lymph node recurrence [4] and of less than 40% after recurrence among patients who underwent treatment of local regional recurrence that mostly involved the lymph node [3], a median survival of 7 months after recurrence in patients with regional recurrence that mostly involved the lymph node [2], and a 10 month survival rate of 0% in patients with intramediastinal recurrence that mostly involved the lymph node [14]. Although we recognize that our study was small and had limited follow-up periods, the survival rates seem promising. At the time of this writing, particularly encouraging is the outcome of four patients who are alive without evidence of recurrence for 16, 9, 16 and 9 months after ^{125}I brachytherapy. For these patients, ^{125}I brachytherapy has been a curative treatment so far. However, twelve of sixteen patients died during follow-up. All the twelve patients had multiple

Table 3
Results of ^{125}I brachytherapy.

Patient no.	Complications	Patient's outcome
1	A small amount of local hematoma	Died of multiple hematogenous metastases at 10 months
2	None	Alive without evidence of recurrence at 16 months
3	None	Died of multiple hematogenous metastases at 5 months
4	None	Died of multiple hematogenous metastases at 6 months
5	A small amount of local hematoma	Alive without evidence of recurrence at 9 months
6	Pneumothorax	Died of multiple hematogenous metastases at 14 months
7	None	Died of multiple hematogenous metastases at 14 months
8	None	Died of multiple hematogenous metastases at 16 months
9	None	Died of multiple hematogenous metastases at 15 months
10	Pneumothorax	Died of multiple hematogenous metastases at 13 months
11	None	Alive without evidence of recurrence at 16 months
12	None	Died of multiple hematogenous metastases at 6 months
13	None	Died of multiple hematogenous metastases at 5 months
14	None	Alive without evidence of recurrence at 9 months
15	Displacement of radioactive seeds	Died of multiple hematogenous metastases at 7 months
16	None	Died of multiple hematogenous metastases at 10 months

Note: Months are counted from the first time of ^{125}I brachytherapy.

hematogenous metastases at the time of follow-up, which resulted in death.

The success of ^{125}I brachytherapy depends on the accurate placement of radioactive seeds within a known volume of tumor [15]. Using CT guidance, an image of the implant volume can be seen and the position of each implant needle can be adjusted to ensure proper placement. In our study, the positions of the seeds are determined to provide a good dose distribution including a minimum peripheral dose coverage, a uniform dose distribution, and the protection of surrounding tissues since methods for calculating optimal seed locations are available [16,17]. The relative coordinates of the seeds are then used for seed implantation within the lymph nodes. Seeds and spacers are ejected from the needle when the depth of the needle specified by the plan is reached. Achieving this desired seed placement is left to the surgeon, who must take into account tissue deformations during the implant process [18,19]. Also inserting and retracting a needle in soft tissues cause the tissues to move, stretch and deform. This displacement and distortion of the tumor during the implantation results in misplaced seeds [19].

During the procedure, with the guidance of CT, the vital blood vessels and organs surrounding the tumor can be clearly displayed, allowing better control of implanting applicator and reducing the risk of damaging important blood vessels. No severe complications such as massive bleeding occurred during procedure, suggesting it as a safe procedure. To avoid radioactive damage on important organs such as vital blood vessels, the distance between implanted seeds should not be less than 10 mm to prevent accumulative radioactivity as a result of two closely positioned seeds. When implanting radioactive seeds into lung, a route with minimal invasion into the lung tissue should be selected to reduce the risk of inducing pneumothorax. After procedure, it is better to keep patient hospitalized for 3–5 days and prospectively prescribe antibiotics and hemostatics to reduce the incidence of bleeding and infection.

Our study also had limitations with regard to interpretation of CT images of metastatic lymph nodes. Small lymph nodes without pathologic confirmation can be benignly reactive. However, the criteria we used offered 95% specificity in diagnosis of metastatic lymph nodes from esophageal cancer [20]. In addition, we only included sixteen patients and followed them up for a maximum of 16 months. More cases and longer follow-up are desired for future survival analysis. We also expect to carry out further study on combining this local approach with systemic approach for tumor treatment.

In summary, the application of ^{125}I brachytherapy in treating lymph node recurrence of esophageal cancer is still in the developing stage. In this study, we found ^{125}I brachytherapy has satisfactory short- to mid-term effect in controlling local metastatic lymph nodes, without severe complications such as massive bleeding or other complications associated with routine chemo- and radiotherapy such as bone marrow arrest, digestive response or hair loss. Our study indicates that ^{125}I brachytherapy is a promising treatment for lymph node recurrence of esophageal cancer.

Conflicts of interest

None declared.

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