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ORIGINAL PAPER

Chemical ablation therapy of recurrent mediastinal nodal metastasis in post-radiotherapy cancer patients

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Abstract The aim of our study was to evaluate the treatment of post-radiotherapy recurrent mediastinal nodal metastasis. Post-radiotherapy esophageal cancer patients with mediastinal lymph node recurrence were enrolled in this study. Patients were randomized into the radiation (±chemotherapy) or the chemoablation group. Patients randomized to the chemoradiotherapy group received additional radiotherapy, second-line chemotherapy, or both. Patients randomized to the chemoablation group received CT-guided percutaneous chemical ablation. Clinical remission was assessed at 1 month by contrast CT. Reirradiation dose ranged from 2,200 to 3,600 cGy depending on dose-limiting constraints in consideration of prior radiotherapy dose. The RECIST criteria were used in the evaluation of response to therapy. The median length of follow-up is 6 months. Thirty-one patients were enrolled in the study. In the chemoradiation group, all patients underwent CT imaging at 1-month follow-up. Among these patients, seven had progressive disease, five had stable disease (SD), and four had partial response (PR). The 6-month survival rate was 12.5 %. In the chemoablation group at 1-month follow-up, 12 patients had SD and three patients had PR, and the 6-month survival rate was 46.6 %. Our results suggest that chemoablation therapy as salvage treatment after post-radiotherapy relapse is efficacious and safe.

Keywords Radiation therapy · Mediastinal nodal metastasis · Chemical ablation

Abbreviations

CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progressive disease

Introduction

Esophageal cancers are a common malignancy with high morbidity and mortality rates. Primary treatment modalities include surgery, radiotherapy, and chemotherapy. Even after radiotherapy or surgical adjuvant chemotherapy, the incidence of mediastinal lymph node metastasis and recurrence remain high. Enlarged mediastinal lymph nodes may compress the vena cava, trachea, and the recurrent laryngeal nerve, causing superior vena cava syndrome (SVCS), airway obstruction, and hoarseness, respectively. Due to the high sensitivity of the mediastinum to radiation injury, maximum radiotherapy dosage is often limited. Small volumes of undamaged tissue remain in the mediastinum for repeat irradiation and further remission is unlikely. Palliative chemotherapy is highly toxic and has relatively low efficacy. The management of recurrent mediastinal nodal malignancy is complicated and often involves poor prognosis.

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Chemical ablation is a well-tolerated and cost-effective procedure. It has been used in the treatment of various pathologies including hepatocellular carcinoma, polycystic liver disease, recurrent secondary hyperparathyroidism, and thyroid cancer metastases. In one study, the 5-year survival of PEI was shown to be no worse than that of radiofrequency ablation in the treatment of hepatocellular carcinoma [1]. It was also found to be associated with long-term survival [2]. When compared to surgical resection, the 5-year survival of PEI was not inferior to that of hepatocellular carcinoma [3]. Additionally, chemical ablation has also been found to improve overall survival with no increase in adverse events when combined with radiofrequency ablation [4]. In the treatment of papillary thyroid cancer, ultrasound-guided PEI was found to be a minimally invasive and efficacious alternative in the ablation of post-operative cervical lymph node metastases [5, 6]. CT-guided percutaneous chemical ablation is an important interventional tool in the treatment of tumors [7, 8]. It is especially efficacious in the treatment of liver tumors, GI tract tumors, and post-operative neck nodal metastases attributable to primary thyroid cancers [5].

Mediastinal nodal metastases have high morbidity and mortality. Patients with recurrent mediastinal nodal malignancies have poor prognoses. In patients initially treated with radiotherapy at or near the mediastinum for esophageal cancer, repeat radiotherapy is often limited by the radiation dosage and decreased efficacy. Surgical treatment in most of these patients is not viable due to radiation-induced mediastinal injury, fibrosis, or tissue friability. Most of these patients were not surgical candidates because of the stage of their tumors. For this reason, a minimally invasive approach to targeting and ablation of specific lymph nodes using image-guided chemoablation is here proposed for recurrent mediastinal nodal metastases.

Due to recent advances in real-time clinical imaging, chemical agents can be accurately and safely delivered to specific organs and tissues. Ultrasound-guided chemoablation has been found to be efficacious in the treatment recurrent cervical lymph node metastases due to primary papillary thyroid carcinoma [9]. However, the treatment of recurrent mediastinal nodal metastases with PEI has not been reported. The conventional approach to the treatment of recurrent nodal metastases is to repeat radiotherapy or chemotherapy, imaging-guided chemoablation may also be suitable and it may have better outcomes, less severe side effects, and less expense. In this study, 31 primary esophageal cancer patients with recurrent mediastinal lymph node metastases were treated. The efficacy and adverse effects of CT-guided chemoablation were compared to those of repeat chemoradiotherapy.

Table 1 Dosage of radiation therapy initial treatment

Patient group	5,000 cGy	6,000–6,600 cGy	Total
Chemoradiotherapy	6	10	16
Chemical ablation	4	11	15

Methods

Clinical information

This study was approved by the local ethics committee and Institutional Review Board (Pingyi branch of Qilu Hospital). Between July 12, 2009 and December 1, 2012, 31 esophageal cancer patients who had initially been treated for their primary malignancies at the oncology department of our institution were enrolled in this study. Patients were randomized 1:1 to either repeat chemoradiotherapy or chemoablation.

Patients included in this study were diagnosed with tumor progression secondary to esophageal with complications including superior vena cava syndrome (SVCS), dyspnea, and hoarseness. The dose of adjuvant radiotherapy was 5,000 cGy in 25 fractions. The radiation dosage for patients with post-surgery lymph node metastasis and for patients receiving radiotherapy with no surgical treatment was 6,000–6600 cGy in 30–33 fractions (Table 1). A total of 12 patients received two-dimensional radiotherapy and 19 patients received 3-dimensional conformal radiotherapy.

Chemical ablation

Materials

22G or 21G HAKKO PTC needle (made in Japan) was used in puncture procedure, chemical ablation agent, absolute ethanol, was obtained from Laiyang chemical plant (Laiyang Shandong, China), and Lipiodol was obtained from Guerbet Pharmaceuticals Co., Ltd (made in France).

CT guidance

Instruments A 16-slice spiral CT (Siemens SOMTOM Emotion, made in Germany) was used for imaging guidance. An outline of the positions of adjacent organs was made during conventional preoperative CT scanning. Based on the lesion location, its relationship with adjacent and vital structures, the optimal patient position, and instrument insertion sites were identified.

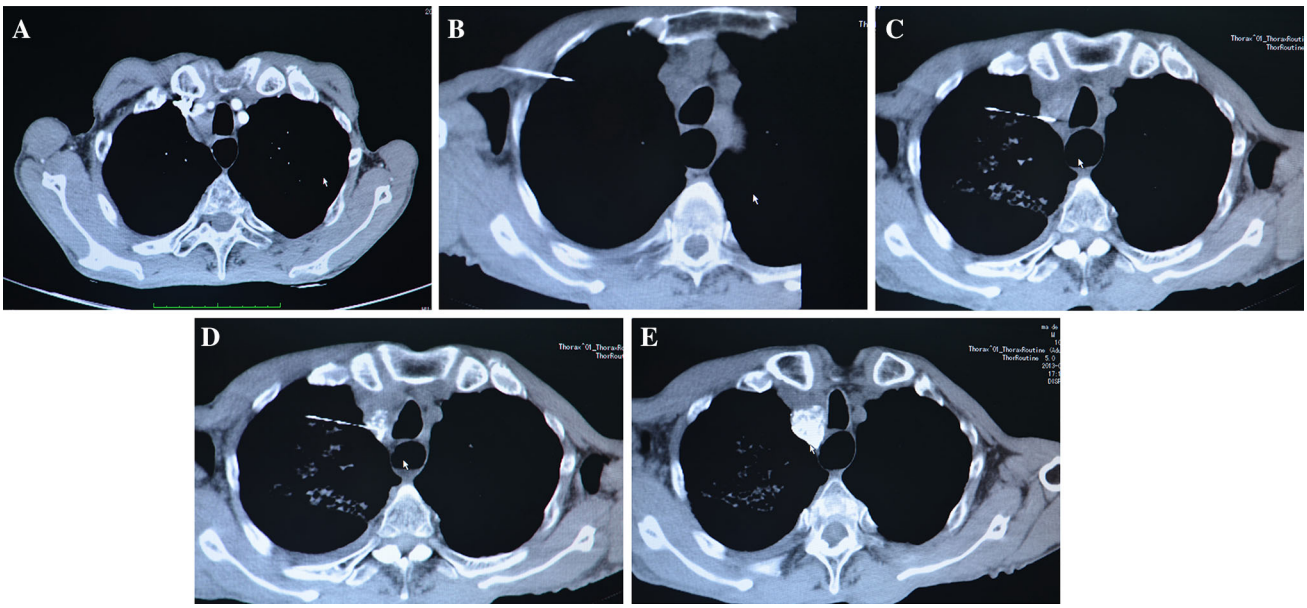

Fig. 1 **a.** Patient #1 (primary esophageal carcinoma), enhanced CT imaging of post-radiotherapy enlargement of mediastinal lymph node (station 2R) metastasis prior to chemical ablation. **b.** Patient #1 (primary esophageal carcinoma), thoracostomy needle insertion in the treatment of post-radiotherapy enlargement of mediastinal lymph node (station 2R) metastasis. **c**. Patient #1 (primary esophageal carcinoma), thoracostomy needle insertion in the treatment of post-radiotherapy enlargement of mediastinal lymph node (station 2R) metastasis. **d** Patient #1 (primary esophageal carcinoma), post-radiotherapy enlargement of mediastinal lymph node (station 2R) metastasis with successful lymph node penetration and injection. **e** Patient #1 (primary esophageal carcinoma), post-radiotherapy enlargement of mediastinal lymph node (station 2R) metastasis with successful lymph node penetration and injection

Chemoablation

Prior to the procedure, patients received respiratory therapy with rate and rhythm exercises. Pre-operative sedatives, analgesics, and anesthetics were administered. A conventional 22G needle was used for thoracostomy and mediastinostomy. Patients were instructed to inhale immediately after needle insertion (Fig. 1a). The needle was then advanced in a stepwise fashion while taking all vital mediastinal organs into consideration. This procedure usually requires three steps. During the first step, the needle is advanced under CT guidance to 50 % of the predetermined distance (Figs. 1b, 3b, c). During the second step, the angle of approach was adjusted. The needle was then advanced to the nearest lymph node while not traversing the level of large vessels. A scan was then performed to confirm the needle position. During step three, the needle was advanced into the predetermined coordinates within the lymph node for biopsy. This was followed by a confirmation scan. A solution (9:1) of ethiodol was then injected into the lymph node (Figs. 1c, 2c, 3d). Due to the irregularity in lymph node shape, which was caused by mediastinal metastasis, the injection volume could not be calculated using a spherical volume. Instead, an injection–validation–injection method was used. Here, a small volume was initially injected ($\approx$1 mL) followed by CT validation of the extent of ethiodol diffusion. Based on this initial trial, the direction of the needle and depth of penetration were adjusted, and then additional volumes were injected for complete and uniform dispersion of the chemical ablation agent.

Chemoradiotherapy

The instruments used in radiation therapy include accelerator linear (BJ6B, Beijing medical apparatus and instrument Institute) and treatment planning system (Topslane Venus). The dosage of radiation was based on the limitations imposed by vital structures such as the lung and spinal cord. The dosage of repeat radiotherapy was 2,200–3,600 cGy with a conventional fractionated dosage of 200 cGy/f. Chemotherapy administered included one course of gemcitabine (Haosen Pharmaceutical Group, Jiangshu, China) plus cisplatin (Haosen Pharmaceutical Group, Jiangshu, China) and one course of paclitaxel (Yangtz River Pharmaceutical Group, Jiangshu, China) plus cisplatin (Haosen Pharmaceutical Group, Jiangshu, China).

Statistical analysis

The statistical software SPSS version 13.0 was used for data analysis. Efficacy was compared using Fisher's exact

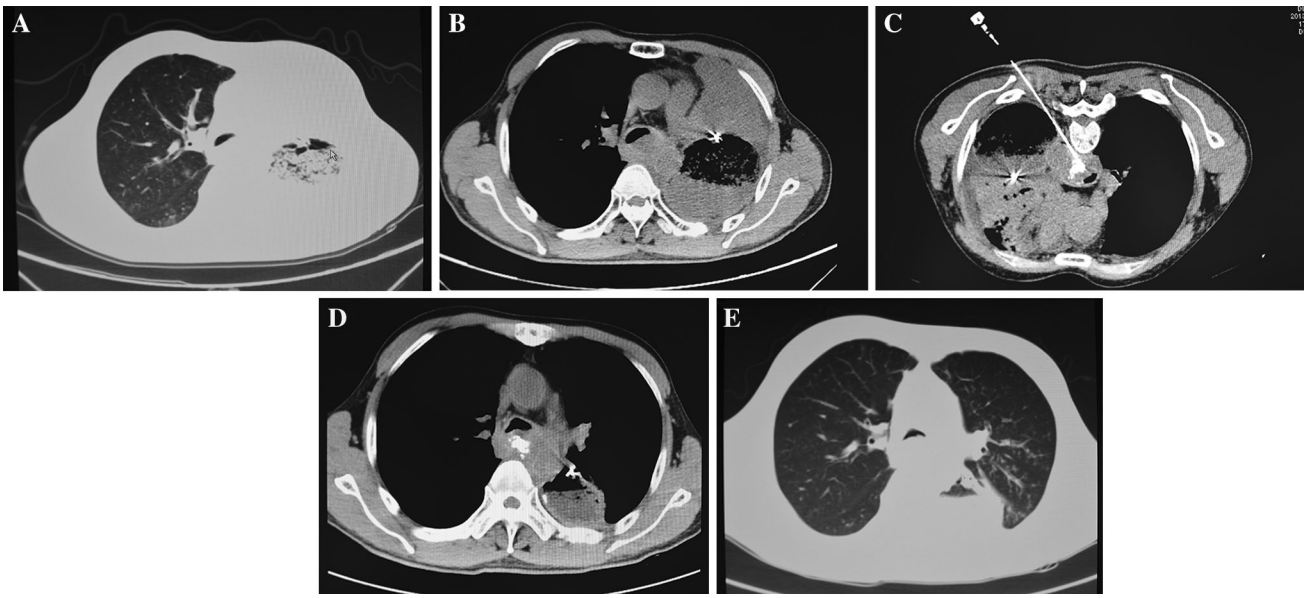

Fig. 2 **a** Patient #2 (primary esophageal carcinoma), post-surgical, post-radiotherapy mediastinal lymph node metastasis (region 7) with atelectasis of the left lung (lung window). **b** Patient #2 (primary esophageal carcinoma), post-surgical, post-radiotherapy mediastinal lymph node metastasis (region 7) with atelectasis of the left lung (mediastinal window). **c** Patient #2 (primary esophageal carcinoma), thoracostomy needle penetration in post-surgical, post-radiotherapy mediastinal lymph node metastasis (region 7) with atelectasis of the left lung. **d** Patient #2 (primary esophageal carcinoma), post-surgical, post-radiotherapy mediastinal lymph node metastasis (region 7) with atelectasis of the left lung. One week into follow-up, atelectasis showed significant improvement (mediastinal window). **e** Patient #2 (primary esophageal carcinoma), post-surgical, post-radiotherapy mediastinal lymph node metastasis (region 7) with atelectasis of the left lung. One week into follow-up, atelectasis showed significant improvement (lung window)

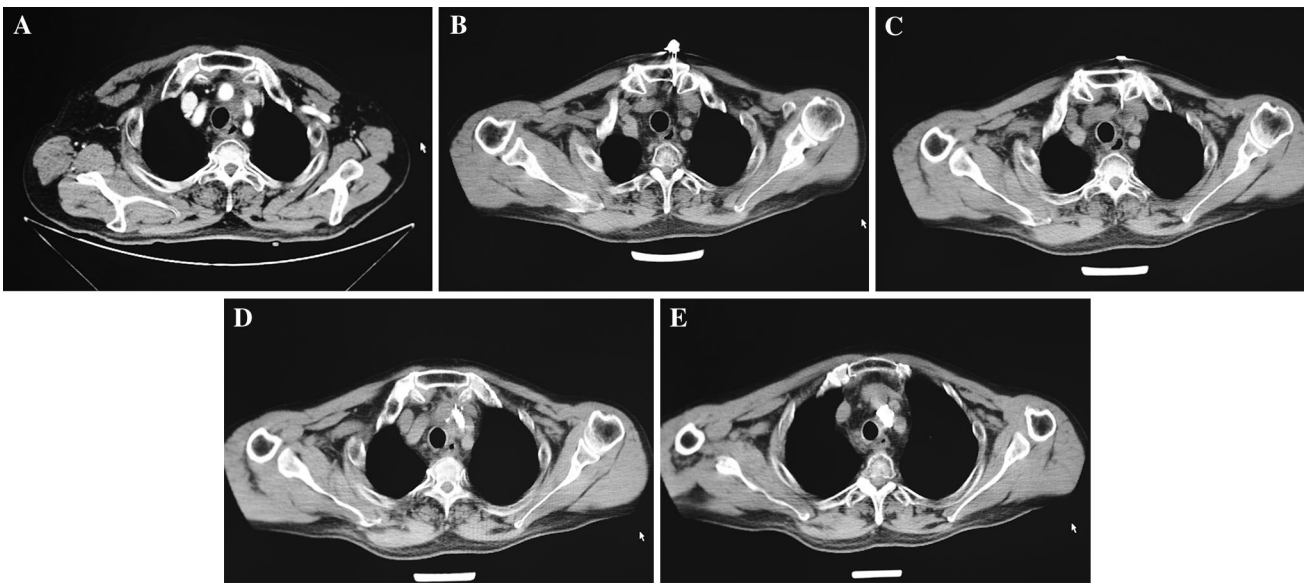

Fig. 3 **a** Patient #3 (primary esophageal carcinoma), enhanced CT scan of post-radiotherapy mediastinal lymph node metastasis (region 2L). **b** Patient #3 (primary esophageal carcinoma), post-radiotherapy mediastinal lymph node metastasis (region 2L) during thoracostomy needle penetration. **c** Patient #3 (primary esophageal carcinoma), post-radiotherapy mediastinal lymph node metastasis (region 2L) during thoracostomy needle penetration. **d** Patient #3 (primary esophageal carcinoma), post-radiotherapy mediastinal lymph node metastasis (region 2L) after chemical ablation. **e** Patient #3 (primary esophageal carcinoma), post-radiotherapy mediastinal lymph node metastasis (region 2L) after chemical ablation at 1-month follow-up

Table 2 CT imaging at 1 month after the procedure treatment

Patient group	CR	PR	SD	PD
Chemoradiotherapy	0	4	5	7
Chemical ablation	0	8	7	0

Table 3 Comparison of efficacy between chemoradiotherapy and chemoablation

Patient group	Efficacious	Non-efficacious
Chemoradiotherapy	9	7
Chemical ablation	15	0

Patients with CR, PR, and SD are classified as effective and patients with PD are classified as ineffective

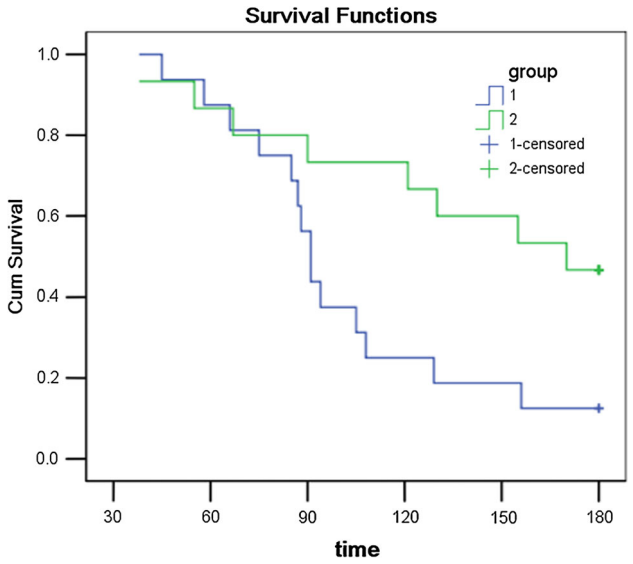

Fig. 4 Kaplan–Meier survival curve. Group 1: chemoradiotherapy group; Group 2: chemical ablation group

test, while survival was compared using the log-rank test. The threshold of statistical significant was $p < 0.05$.

Results

A total of 16 patients received chemoradiotherapy and 15 patients received chemoablation. In both treatment groups, CT imaging was performed prior to, immediately after, and at 1 month after treatment. CT imaging was also performed intraoperatively during chemoablation after each injection to verify the uniformity of the ablation agent dispersion. At 1 month, if the tumor size was found to be stable (SD) or reduced (CR or PR) in CT imaging accompanied by improvements in clinical symptoms, the outcome was described as efficacious. Patients with PD are considered non-efficacious.

Table 4 Survival rate at 6 months after treatment for recurrent mediastinal tumor

Patient group	Six months survival rate (%)
Chemoradiotherapy	12.5
Chemical ablation	46.6

Among 16 patients receiving chemoradiotherapy, 9 had efficacious responses (SD in five patients and PR in four patients,) at 1-month follow-up. However, among 15 patients receiving chemoablation, all had efficacious responses ($p = 0.007$, Fisher's exact test), demonstrating improved efficacy (Tables 2, 3). Additionally, the 6-month survival rate was significantly improved ($p = 0.024$, $\chi^2 = 5.064$, $df = 1$, log-rank test) among patients receiving chemoablation (46.6 %) compared to patients receiving chemoradiotherapy (12.5 %, Fig. 4; Table 4).

Among several patients who received chemoradiotherapy, tracheoesophageal fistulas in three patients and severe radiation esophagitis in five patients were diagnosed. In contrast, no significant complication was observed in chemoablation group.

Discussion

Primary esophageal carcinomas have high rates of mediastinal lymph node metastasis. Manifestations of metastatic disease include SVCS, compression of the trachea leading to airway obstruction, and hoarseness resulting from recurrent laryngeal nerve compression. Chemotherapy is the primary treatment modality for mediastinal lymph node metastasis. However, the treatment of post-radiotherapy tumor recurrence and tumor metastasis is often difficult. Because of multi-drug resistance, salvage chemotherapy often gets less curative effect. In theory, repeat radiotherapy may be used as treatment. However, the total advisable dose of radiation is limited by radiosensitive structures such as the spinal cord and lungs. This makes additional radiation treatments less efficient and may predispose the patient to complications such as tracheoesophageal fistulas. Lastly, palliative chemotherapy may also have limited use due to its high drug resistance and low efficacy.

In a complex body compartment such as the mediastinum, the treatment of mediastinal lymph node metastasis with radiofrequency and microwave ablation techniques has met with limited success. Procedures such as radioactive seed implantation carry a significant level of technical difficulty due to the risk of penetrating vital structures and limitations in achieving uniform distribution. Additionally,

highly radioactive particles increase the risks of injury to adjacent great vessels, the esophagus, and the trachea. These techniques are often limited by a fixed range of tissue volume or penetration depth [10]. The principal underlying chemical ablation is to penetrate tumor tissue under the imaging guidance followed by the injection of an ablation agent. This can lead to coagulation necrosis and tumor damage. One of the most widely used chemoablation agents is ethanol. It causes membrane disruption and protein denaturation, ultimately leading to tumor cell death [11–14]. In terms of real-time monitoring, chemical ablation can be guided with a variety of imaging techniques such as X-ray, ultrasound, CT, MRI, and DSA, which are cost-effective and have lower technical demands than other treatments [15].

In the current study, chemical ablation was not affected by the shape or position of the tumor. This is especially true in the presence of lymph node sinuses or an external fibrous envelope, which permits the uniform and complete dispersion of the ablation agent. Like repeat radiochemotherapy, chemoablation improved short term remission and survival. CT-guided percutaneous chemoablation may be a safe and efficacious alternative treatment for recurrent mediastinal lymph node metastases.

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