

A novel 125I seeds fixed on gastric tube for treatment of inoperable esophageal carcinoma

A case report

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Abstract

To explore the treatment benefit of 125I seeds fixed on a gastric tube in the early inoperable esophageal carcinoma (EC).

Three senile patients with early inoperable EC who were treated with brachytherapy between October 2017 and February 2019 were included in this study. 125I seeds were fixed on the gastric tube, which was then inserted on the surface of the EC. One patient suffered from severe pulmonary insufficiency; 1 patient underwent colon cancer surgery one week before treatment and suffered from liver dysfunction and esophageal varices; 1 patient suffered from venous embolism of lower extremities and pulmonary artery embolism.

All three patients were successfully operated and completed treatment. During the operation, no displacement and shedding of 125I seed gastric tube occurred. After surgery, the discomfort while swallowing and pain after eating were significantly improved. Moreover, dysphagia was relieved in patient 3. In addition, no complications, such as perforation or bleeding, occurred. Local lesions were effectively controlled.

Gastric tube with 125I seeds provides a new treatment protocol for inoperable EC and malignant obstruction of esophageal carcinoma.

Abbreviation: EC = esophageal carcinoma.

Keywords: 125I seeds, brachytherapy, early esophageal carcinoma, seed- gastric tube

1. Introduction

Esophageal carcinoma (EC) is the 7th most commonly occurring cancer in men and the thirteenth most frequently occurring

cancer in women. Surgery is still considered the best treatment approach for EC, followed by chemotherapy and radiotherapy. Yet, elderly patients with inoperable EC may not always benefit from these treatments due to poor lung function, age, and combination with other diseases. Thus, there is an urgent need to explore new, safe, and effective therapies for inoperable EC.

Brachytherapy is a relatively new and safe approach. Seed-gastric tube belongs to brachytherapy intracavitary irradiation method. Conventional intraesophageal irradiation can easily cause damage to the surrounding organs and patients intolerance due to radiation. It is not often used clinically. Seed-gastric tube can avoid these two disadvantages well, which uses low dose or high dose radiation (emitted by iodine-125 seeds) to kill the tumor without affecting the surrounding tissue. So far, several studies have shown that brachytherapy, combined with external beam radiation treatment, has the highest success rate in intermediate-risk patients compared to all other treatments. Besides, this approach is particularly useful for treating patients with unresectable cancer.^[1,2] In this study, we explored the treatment benefit of a novel 125I seeds gastric tube in three patients with early inoperable EC. Briefly, the 125I seeds were placed in the gastric tube using a three-dimensional treatment planning system (Fig. 1), which was then inserted on the surface of the EC through interventional guidance, and was fixed at the outlet of the nasal cavity.

2. Materials and methods

2.1. Patients

Three senile patients (65 – 85 years; the average age of 76.8 ± 0.7 years) with early inoperable EC who were treated with 125I seeds gastric tube at The First Affiliated Hospital of Chengdu Medical

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JJ and YY contributed equally to this work.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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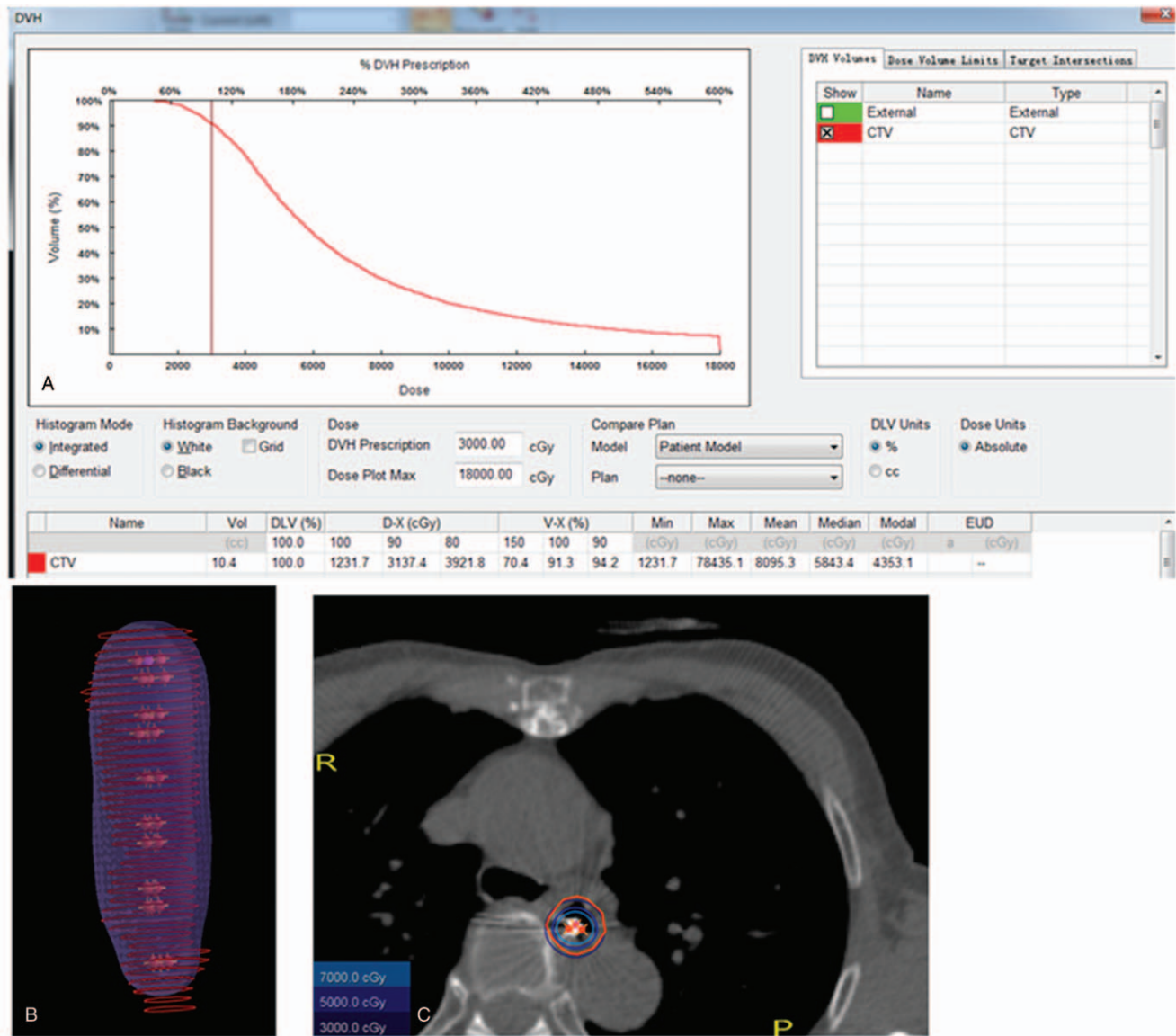


Figure 1. Placement of the seed catheter. (A) 30Gy isodose curve. (B) 3D display dose coverage (C)DVH (dose volume histogram).

College between October 2017 and February 2019 were included in this study. Two patients had lesions confined to the mucosa and submucosa (T1N0M0), and one patient had intralesional growth (T2N0M0). FRALL frailty score increased resistance/ decreased endurance, declined free motion, disease conditions, and weight loss, revealed a score of 3 to 4 points, which indicated a high probability of complications after surgical treatment. The clinical data of patients are shown in Table 1.

The present study was approved by the Ethics Committee of the Affiliated Hospital of Shandong Academy of Medical Science (approval No. FY2012001), and all patients signed informed consent.

2.2. Materials and equipment

¹²⁵I seeds (6711 type) were produced by China Isotope & Radiation Corporation. The tube containing ¹²⁵I seeds was used

as a seed catheter, which was patented by Professor NiuHongxin of the The First Affiliated Hospital of Chengdu Medical College, who invented the seed-gastric tube (patent number medical seed catheter: ZL201410343856.9). The lengths of the three chains (referred to as triple chains) were 4cm (27 grains), 8cm (54 grains), and 12cm (81 grains), respectively, and the angle between the three chains was 120° (Fig. 2).

2.3. Dosimetry of seed catheter

Dosimetry is of essential importance for the seed-gastric tube. The dose field of the ¹²⁵I seed chain is cylindrical. The dose of the seed chain is mainly affected by the change of seed activity and radial distance from the center and is weakly affected by the length of the seed chain. When the dose is > 1 cm from the center, the dose quickly drops. The regression equation of the radial cumulative dose (dose, Gy) with respect to the activity of the

Table 1
Patients' clinical data.

Cases	Gender/ age	Follow-up time (mo)	Symptoms	Cause of inoperability	Lesion location	Number of seed implantation (0.8mCi particle number)	Underlying disease	FRAIL Score
Case 1	M/76	32	Swallowing discomfort with pain	Severe mixed ventilation dysfunction, FEV1 36%, Vital capacity VT (0.43,0.92)	30–35 cm from incisors, rough mucous membrane, uneven surface, nodular changes	3 (24,12,10)	14 d (22–40GY) 10 d (16–30GY) 7 d (12–20GY)	3
Case 2	M/67	12	Discomfort when eating	One wk after colon cancer surgery, liver cirrhosis, esophageal varices	A 1.0 cm × 0.8cm mass in a place 27 cm from incisors	1 (18)	12 d (18–36GY)	3
Case 3	M/75	11	Swallowing obstruction, short of breath	Pulmonary embolism, lower extremity venous thrombosis, severe pulmonary insufficiency	32–38 cm from the incisor, grows in the esophageal lumen	2 (40, 24)	12 d (18–30GY) 7 d(13–24GY)	4

The therapeutic dose is only a range because the seed gastric tube is not fixed, and the dose difference between 0.5cm-1 cm is nearly doubled. What's more, to prevent local hot spots from causing perforation of the esophagus and leading to treatment failure, we should pay attention to individualization and adjust the treatment dose according to the patient's symptoms in the course of treatment. Generally after 7 days, the patient cannot tolerate it. If pain occurs, it indicates normal mucosal damage and the tube can be pulled out. Generally, normal mucosal injury can recover within 1–2 weeks. Recheck will be performed after one month and the treatment plan was adjusted based on the results of the recheck.
FEV = Forced Expiratory Volume, FRA = Fall Risk Assessment, VT = Tidal Volume.

radioactive seeds (mCi) and the distance of the measurement point from the center (cm)^[3] is measured using the following formula: $\ln \text{dose} = 138.0 \text{ activity} - 79.8 \text{ distance} + 160.5$.
Internal irradiation: The seed plane is 5 mm away from the cell plane, and the initial dose rate is 6.083cGy/h.

The empirical formula developed by the American Academy of Medical Physics^[4] was adopted to calculate the required irradiation time in different experimental groups: $D_c = D_0 (1.44T_{1/2})(1 - e^{-0.693t/T_{1/2}})$, where D_0 represents the initial dose rate, t represents the elapsed time, D_c the cumulative dose, $T_{1/2}$ represents the half-life period of the seed source (59.4d), and e is a constant 2.718. The results showed that irradiation for 33 hours, 66.9 hours, 101 hours, and 136 hours were required to obtain cumulative doses of 2Gy, 4Gy, 6Gy, and 8Gy, respectively; these doses were average doses of radiation to the tissue. In practice, the maximum dose of the local hotspot should be taken into account, and the irradiation should be employed several times.

2.4. Operation procedure

The patient was placed in a supine position. After local anesthesia with 2% lidocaine (or Tetracaine Hydrochloride Jelly) in the left or right nasal cavity, the super smooth guidewire and COBRA catheter were inserted under X-ray fluoroscopy. Then the super smooth guidewire was replaced, and the COBRA catheter was inserted to the esophageal lesion under the guidance of the guidewire. The contrast agent was then injected to mark the lower end of the tumor. Subsequently, the guidewire was sent to the stomach cavity and fixed, and the COBRA catheter was removed. After that, the triple-chain seed catheter was inserted along the guidewire, and was hung on the surface of the corresponding esophageal lesion in the esophageal cavity with the guidance of a gastroscop, and was fixed at the outlet of the nasal cavity. The seed-gastric tube itself has a thickness of 0.5 cm. Considering that the seed gastric tube is suspended, the distance from the lesion is between 0.5 to 1 cm. The distance is between 0.5cm and 1cm, but the dose difference is 4 times higher.

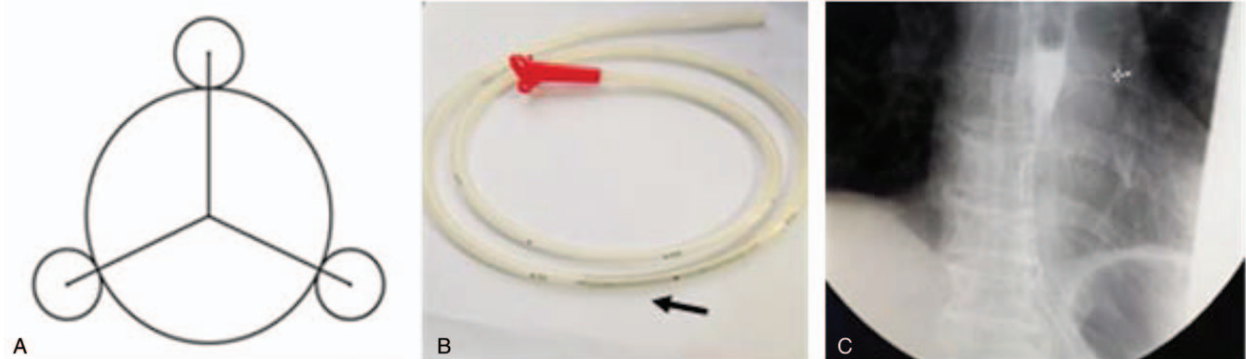


Figure 2. Diagram of seed-gastric tube. (A) Cross-section of the three-chains by simulation. (B) The arrow at the seed-gastric tube refers to the seed chain. (C) Barium meal shows seed-gastric tube.

Therefore, seed-gastric tube therapy emphasizes the individualization of treatment, and the therapeutic dose calculated according to the local seed gastric tube adherence dose to prevent perforation caused by local hot spots and treatment failure.

Consequently, 0.8mci 125I seeds were placed into the particle catheter for brachytherapy in the esophageal cavity. The distal end of the radioactive 125I seed gastric tube was extended to the stomach cavity. The seed-gastric tube was adjusted so that the part carrying the seeds crossed the tumor site of the esophagus, with the upper and lower ends exceeding approximately 1 to 2 cm (according to the standards for external radiotherapy, the length of tumor invasion may be 3 cm above and below the target area).

Comparing the NBI staining range on the images taken preoperatively and at 2 months postoperatively, it can be clearly seen that after the first treatment, the lesion range was reduced from 5 cm to 3 cm. For the second treatment, the seeds-gastric tube dose was adjusted. Since the external radiation is often limited by the tolerance of surrounding normal tissues, the local dose is often lower than the local dose of 125I seeds is much higher than that of external radiotherapy (Fig. 3).

2.5. Treatment method

Patients fasted for 12 hour before surgery. The length of the gastric tube was determined according to the location and length of the esophageal lesions; Figure 2 shows the implantation procedure of a seed-gastric tube, represented by the black arrow.

Besides, the therapeutic dose was affected by the size and position of the esophageal lesions, and the distance between the seed catheter and the lesions.

The treatment was not expected to succeed after only one therapy. The seed catheter was taken out 7 to 10 days after the first insertion, with a local dose of 30 Gy. One month later, all patients underwent gastroscopy to observe the size of the lesions and the conditions of the residual parts. If the lesion had a length of 5 cm, intraesophageal brachytherapy was performed by inserting 0.8mci 125I seeds into the triple chains without intervals, with a chain length of 5.5 cm, which was 0.5 cm longer than the lesion length, followed by CT review one month after the operation.

Each patient was followed up for more than half a year, with a maximum follow-up of 28 months. All three patients survived, and the local lesions were significantly controlled. With the seed-gastric tube, special attention needs to be paid to individualizing the seed-gastric tube.

3. Results

All three patients were successfully operated and completed treatment. During the operation, no displacement and shedding of 125I seed gastric tube occurred. After surgery, the swallowed discomfort and pain after eating were significantly improved. Moreover, dysphagia was relieved in case 3. All three patients were treated with a seed-gastric tube twice. No complications, such as perforation or bleeding, occurred. Local lesions were effectively controlled.

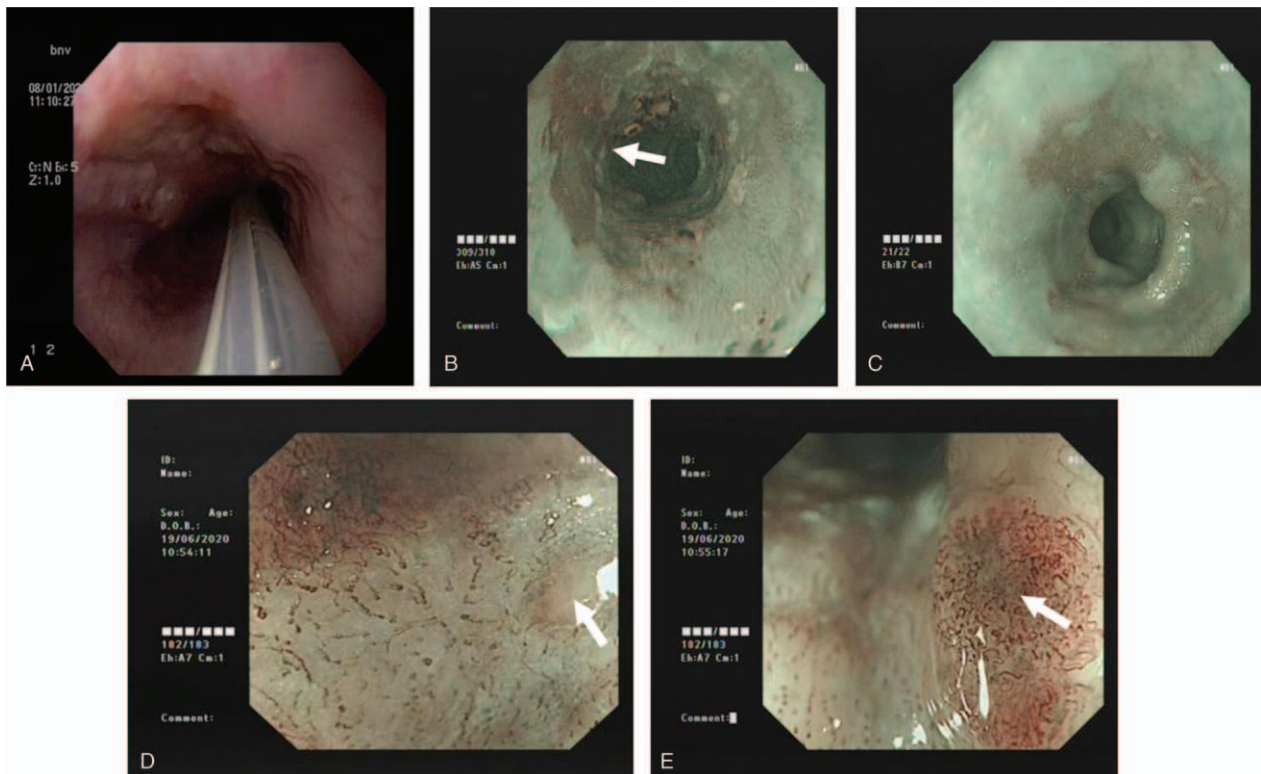


Figure 3. Changes in lesions before and two months after treatment (A) Gastroscope photo of particle gastric tube and lesion. (B) NBI staining range before lesion treatment. (C) NBI staining range 2 months after treatment. Lesions observed from seed-gastric tube graphics. (D) 28 months after treatment, the arrow points to avascular area. (E) 28 months after treatment, the arrow showed Type B3 angiogenesis. B, C showed obvious reduction of the esophageal lesion area seen by NBI staining before and two months after the operation. Second treatment was performed according to the reduced lesion site.

3.1. Case 1

The patient was re-examined at 1, 6, and 24 months after brachytherapy. Clinical data showed that the esophageal mucosal lesions were significantly alleviated; the nodules gradually disappeared; the esophageal wall was smooth, and esophageal scars were present. Also, the NBI lesion area and the B2 B3-type blood vessels were significantly reduced (Fig. 4). Moreover, tumor cells were more consistent in size and had

smaller atypia; pathological data of the EC cells before surgery and 2 years after surgery, as shown in Figure 5.

3.2. Case 2

CT and gastroscopy showed that the mass in the cavity was significantly reduced, and the patient’s obstructive symptoms improved significantly. A: the enhanced CT showed pulmonary



Figure 4. Gastroscopy review of Case 1, two years after treatment. (A) Before treatment; (B) 1 month after treatment; (C) 1 year after treatment; (D) 2 years after treatment. 1: general structure under a microscope. 2: NBI stained areas. 3: vascular morphology of JES classification.

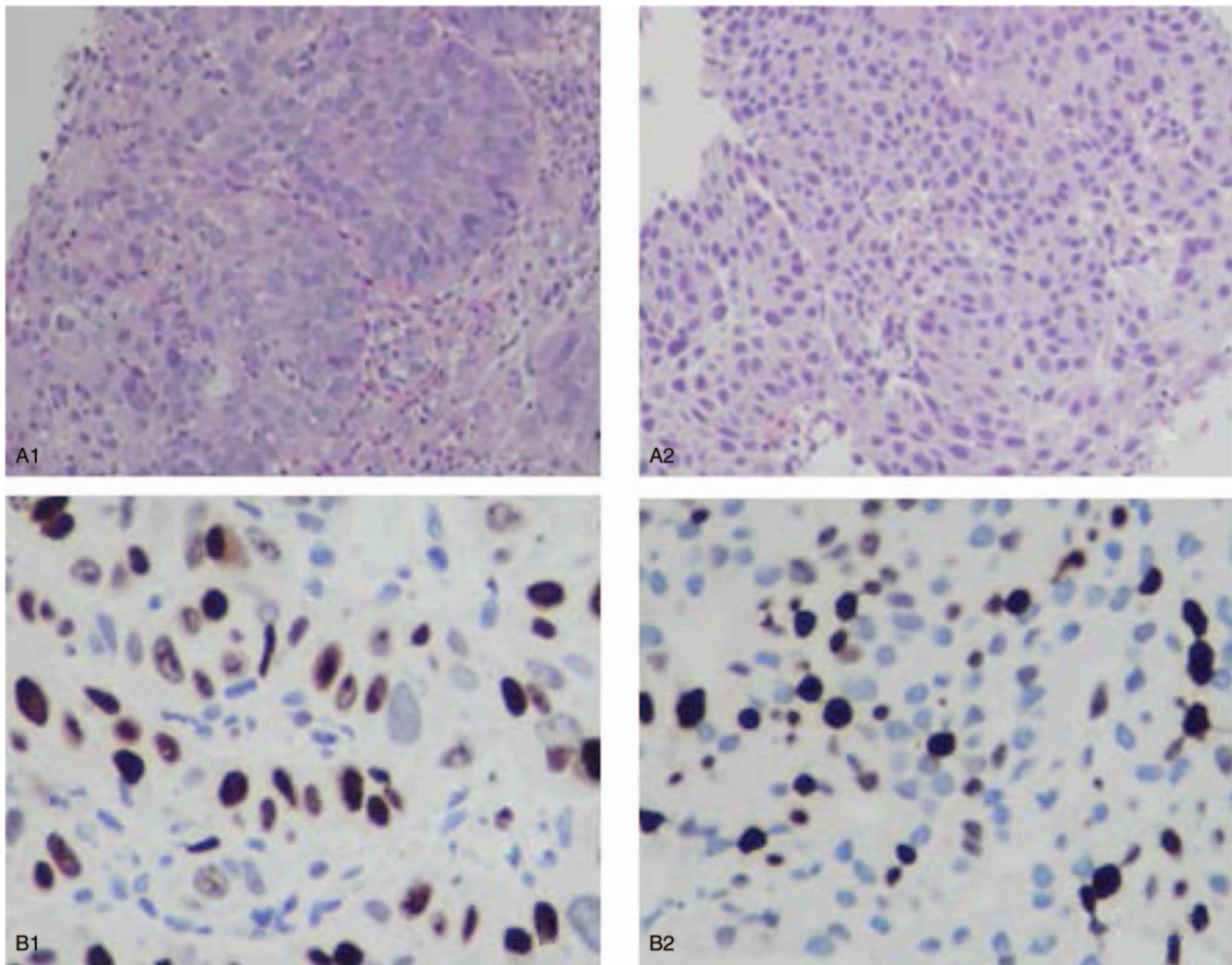


Figure 5. Pathological results of Case 1. (A) HE staining $\times 400$. A1: Before treatment, tumor cells were abundant and active, with large atypia and large volume. A2: Two years after treatment, tumor cells were more consistent in size and had smaller atypia. (B) Apoptosis. B1: Ki-67 positive rate was about 50%; B2: Ki-67 positive rate was about 40%.

artery embolization and ^{125}I seeds filter in the inferior vena cava. B: Preoperative and postoperative intraluminal masses, which were significantly reduced, and obstruction was alleviated. C: Preoperative, intraoperative and postoperative CT images, which showed the esophageal lesions were shrunk (Fig. 6).

3.3. Case 3

A: The seed-gastric tube was suspended at the lesion, and review at postoperative 2 months showed scarring of the lesion. B: Preoperative and postoperative varicose vein plexus at lower esophagus, which was also significantly reduced (Fig. 7).

4. Discussion

In this study, three senile patients with early inoperable EC were treated with brachytherapy between October 2017 and February 2019. The total prescriptive dose of 60 to 80 Gy given to the diseased esophagus was calculated using a Prowess 4.71 planning system, which was the average dose. However, the individualized

dose is particularly important when selecting treatment. Since the esophagus is a hollow viscus, radiation can often lead to complications, such as wall perforation. To solve this, we adopted a 3-chain seed catheter. Since the dose distribution around ^{125}I radioactive seeds follows the inverse square law, that is, the dose is inversely proportional to the square of the distance between the measurement point and the seeds, the dose gradient around the seeds is very steep. Its release is not only related to the activity of seeds and time, but also to the distance of the esophageal lesions. Also, because the seed-gastric tube cannot be completely fixed on the esophageal wall, a distance difference of 0.5 cm and 1 cm can lead to a dose difference.^[4] Therefore, in this study, the dose was given using multiple exposures. During each exposure, the dose did not exceed 40 Gy at a local 0.5 cm to ensure the safety of local dose, and to avoid local hot spots and perforation. One month later, patients were reviewed by a gastroscopy, and the seed chain length and dose were redesigned based on the conditions. Generally, 2 to 3 courses of treatment were given to avoid the emergence of hot spots and local perforation. After the first treatment, patients were reviewed (one

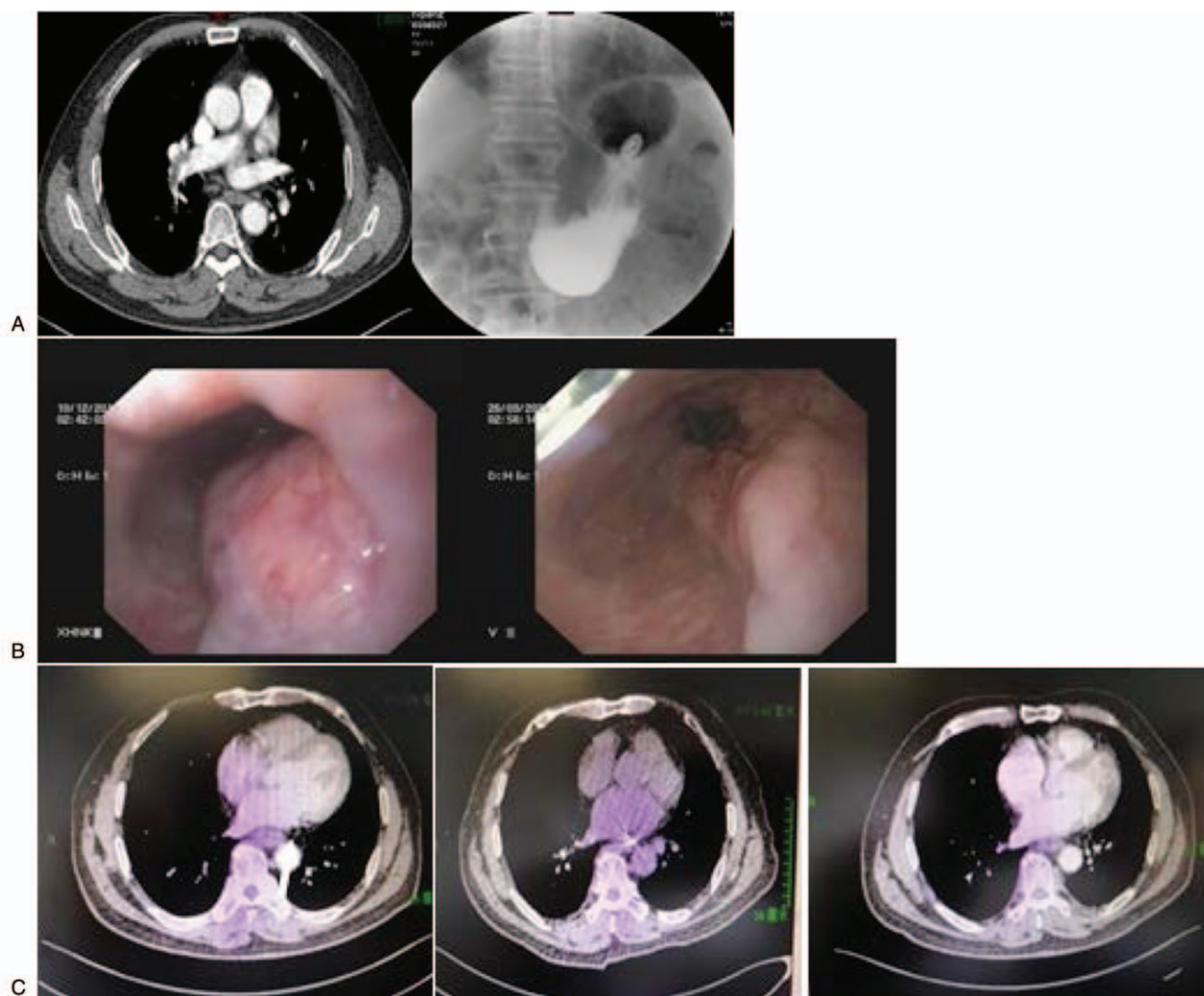


Figure 6. CT and gastroscopy imaging in Case 2, before and after treatment. (A) CT showed pulmonary artery thrombosis; barium meal showed the implanted seed gastric tube and filter of veins of lower extremities. (B) Gastroscopy showed smaller esophageal lesions. (C) CT images before surgery, 2 months post-operation, and at the time of implantation. The arrow showed that the esophageal mass was significantly reduced, and the symptoms of dysphagia were significantly improved, which indicated a satisfactory curative effect and provided opportunities for subsequent treatment for improving lung function.

month later). The lesion area of the esophagus was shrunk, based on which the length and treatment range of the seed-gastric tube were adjusted.

Inoperable cancer is often seen in elderly patients. Pulmonary function testing is an important basis for evaluating the indications of surgical treatment and selecting surgical protocols. For case 1, pulmonary function testing prompted severe mixed ventilation dysfunction. The lesion was 5 cm long, and the patient's pulmonary function was severely damaged. The patient was treated with a seed-gastric tube two times (each dose was 40Gy). During the pathology review after two years of follow-up, the examination of samples collected from scars in the esophageal bed showed that the atypical cells in the tumor bed were reduced, and nuclear heterogeneity was decreased. Besides, histochemistry indicated that the cell apoptosis and tumor cell atypia were significantly decreased. Local recurrence is the main reason for the failure of external radiation treatment for EC. Increasing the dose of external radiation is undoubtedly worse for patients with severely impaired pulmonary function. Radiative pneumonia and pulmonary fibrosis may further aggravate the lung damage of

patients, while radiative pneumonia rarely occurs during radioactive seed treatment.^[5]

For patients with inoperable EC, malignant obstruction is often the main symptom in the late stage. For these patients, stent treatment is commonly recommended. The seed-gastric tube doesn't involve the inherent defects of the stent; the aorta pulsation and the tension of the esophageal stent may lead to rupture of the diseased esophagus, aortic abrasion, and massive bleeding death. Furthermore, the stent may lead to obstruction due to the proliferation and migration of EC. Due to the limited tolerance of surrounding tissues, it is difficult to treat EC using general external radiation. In the present study, patient 2 suffered from intraluminal obstruction, significant dysphagia, and short of breath. In addition, he had embolism of veins in the right lower extremity and in the pulmonary artery. Undergoing surgery within two weeks of embolism can lead to thrombus shedding. Thus, the patient underwent thrombolytic therapy, in which a filter was used to control the embolism in the lower extremity. The patient's local lesion was controlled after two courses of seed gastric tube treatment; also, the intraluminal obstruction was

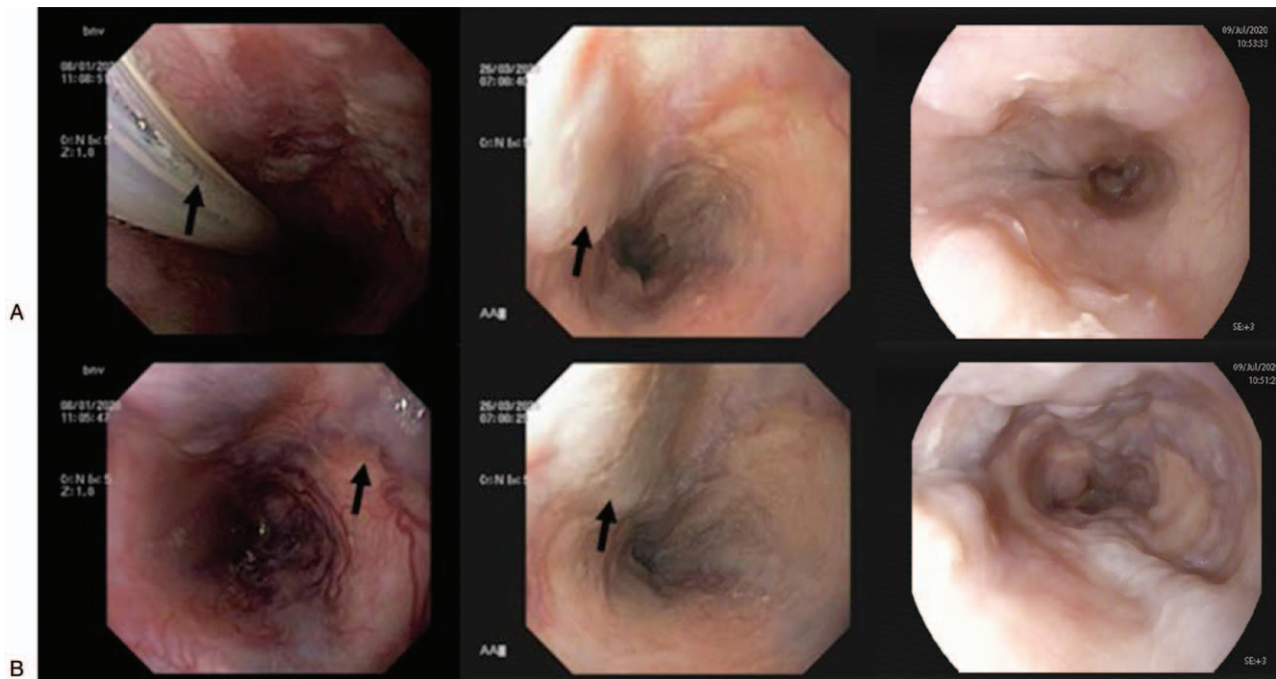


Figure 7. Case 3. (A) The seed-gastric tube and the lesion 27 cm away from the incisors showed scar-like change, which was significantly alleviated. (B) Esophageal varices before and after treatment, which were relieved, and the lower esophageal varices were also improved.

significantly alleviated. Although the treatment has no significant effect on the survival rate in advanced patients, the main purpose of our treatment is to relieve malignant obstruction and improve the patient's quality of life. After treatment, the patient was able to eat normally; his quality of life improved, and the treatment cost was reduced.

Patient 3 underwent colon cancer surgery one week before treatment. The lesion was in the early stage, but he suffered from hepatic sclerosis, which resulted in a great risk of colon surgery, esophageal surgery, and radical radiotherapy. Besides, he suffered from varicose veins in the lower esophagus and thus had an increased risk of bleeding in surgery, endoscopic mucosal resection, or dissection. Furthermore, since the mucosa is sensitive to radiotherapy, the patient's pain symptoms indicated that the normal mucosa was damaged, which is one of the signals of removing the seed catheter. Normally, the damaged oesophageal mucosa can recover after 1 to 2 weeks. After one month of treatment, the patient underwent gastroscopy. The 3DTPS plan was redesigned based on the reduced lesions, and the seed gastric tube dose was re-determined based on the lesion range, which allowed for the better control of the lesions and achievement of safe and effective treatment.

This study has a few limitations:

- (1) A seed-gastric tube was used to place 125I radiative seeds on the surface of the EC, and the radiation started after radiation dose increased from the minimum to 30 to 40Gy. The radiation dose needs to be calculated more specifically and accurately.
- (2) Early lesions are located in a shallower layer, but there is an inconsistent gap between the gastric tube and the tumor tissue on the esophageal wall. If the radiation source is biased towards either side, an uneven radiation dose will be

generated, which may cause an excessive large radiation dose on one side and an insufficient radiation dose on the other side. For this reason, it is necessary to individualize the treatment for each patient, to divide the treatment into several stages, and to redesign the treatment plan according to the size of the lesions after gastroscopy review.

- (3) Since the normal mucosa of the esophagus is most susceptible to radiation damage, it will cause pain and a burning heat sensation when eating, which requires timely removal of the seed catheter. After a week, the mucosal injury recovered quickly. We then re-developed a new treatment plan based on the range of lesions after treatment, so as to avoid the occurrence of serious complications. As the number of cases increases, the seed-gastric tube should be further improved to treat inoperable EC. In particular, we intend to introduce a seed balloon gastric tube to expand the malignant obstruction.

The seed balloon gastric tube is intended to be retained for 1 week, during which it should exert triple function:

- (1) prevents the seeds from adhering to the wall;
- (2) treats the obstructive segment, in which its continuous expansion can prevent tumor re-occlusion.
- (3) can support gastrointestinal nutrition.

In summary, 125I seeds fixed on a gastric tube provides a new treatment approach for patients who are unable to undergo surgery and conventional radiotherapy and chemotherapy. The method is minimally invasive and can achieve satisfactory local lesion control and improve patients' quality of life. Its safety can be ensured by the staged and individualized design of the implantation time and dose, and it has realistic application prospects in clinical practice.

Author contributions

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Writing – review & editing: Weikun Jia, Wei Li.

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