

Computed tomography-guided implantation of ^{125}I seeds brachytherapy for recurrent multiple pulmonary oligometastases: initial experience and results

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Abstract

Purpose: To retrospectively evaluate the efficacy and safety of computed tomography (CT)-guided percutaneous interstitial brachytherapy using ^{125}I radioactive seeds for multiple pulmonary metastatic tumors.

Material and methods: Between September 2013 and December 2015, 22 patients with multiple pulmonary metastases, who after conventional chemotherapy and trans-arterial chemoembolization (TACE) therapy were considered unable to withstand stereotactic body radiation therapy (SBRT), received CT-guided ^{125}I brachytherapy. Clinical data were studied retrospectively. A planning target volume of 90% (D_{90}) was 120-160 Gy for ^{125}I seeds with an activity of 25.9 MBq. A CT-based evaluation performed 1, 2, and 6 months' post-implantation enabled review of local control of tumors.

Results: Twenty-two patients with 65 pulmonary metastases successfully completed treatment. The mean value for D_{90} for implantation for ^{125}I seeds was 132 Gy. Complete response (CR) + partial response (PR) was documented in 81.54%, 78.46%, and 78.46% of patients at 1, 2, and 6 months after implantation, respectively. Fourteen out of 22 patients had CR, 3 had PR, 2 had stable disease (SD), and 3 had progressive disease (PD). Most of the metastases (CR + PR + SD; 87.69% after 6 months) were controlled by implantation.

Conclusions: CT-guided ^{125}I brachytherapy is a safe and effective treatment for multiple pulmonary metastatic tumors, and can achieve good short-term local control, so long as the radiation dose is sufficient.

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Key words: brachytherapy, computed tomography, ^{125}I , pulmonary metastatic tumors.

Purpose

In China, lung cancer is the most common and leading cause of death [1]. Recurrent multiple pulmonary metastases (RMPM) usually predisposes to a poor prognosis. Understandably, the therapeutic efficacy of surgical treatment combined with external radiotherapy and/or chemotherapy is inadequate and unsatisfactory. Three-dimensional stereotactic radiotherapy using interstitial implantation of ^{125}I seeds is now considered a novel complement to surgery and external radiotherapy [2,3,4].

Because patients with lung metastases have a longer periods of progression-free survival (PFS) and overall sur-

vival (OS) than those with metastases in other organs [5], we consider that RMPM have intermediate states, in which the spread of disease is limited to the lungs and metastases is present in limited numbers [6]. ^{125}I has a relatively long half-life and can function in dividing tumor cells, thereby reducing their proliferation. The continuous rate of low-dose radiation of ^{125}I seeds was more efficient in inhibiting cell growth than external beam radiation [7].

Both seed implantation and stereotactic body radiotherapy (SBRT) can treat distant lung metastases. Evidence supporting the use of SBRT for lung metastases has expanded rapidly over the past decade, showing

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high rates of local control with low associated toxicity [8]. However, ¹²⁵I seeds can provide recurrent short-term treatment for RMPM (less than 1 week), while SBRT is typically associated with a variety of complications, and often unable to proceed to the second and third radiotherapy cycles in the same lobe in a short time (more than 2 months) [9,10]. Considering the treatment restrictions of SBRT for RMPM, we have summarized in our report a set of implantation treatments for recurrent multiple cases of lung metastases.

Material and methods

Patients

From September 2013 to December 2015, 22 patients (14 males and 8 females; mean age \pm standard deviation, 58.09 ± 3.562 years; range, 16-81 years) with RMPM (mean number, 3; range, 2-10; total number, 65) and the largest diameter measuring 1.2-3.6 cm received computed tomography (CT)-guided ¹²⁵I brachytherapy. Characteristics of patients and metastatic tumors are summarized in Table 1. In all cases, the primary cancer and metastases were confirmed by surgery or biopsied specimens. Standard chemotherapy was administered to 11 patients and 4 of them received radiation therapy. Every patient with hepatocellular carcinoma (HCC) had undergone transarterial chemoembolization (TACE). In all, 3 cases of liver metastasis, 2 of bone metastasis, and 3 of adrenal metastasis underwent TACE. All cases of the primary tumor were well controlled, and RMPM were recorded without chest pain, cough, and phlegm symptoms; however, cases of intrapulmonary metastases continued to increase. The study protocol was approved by the Ethics Committee of our university. All patients provided written informed consent to participate in the study.

Recurrent multiple pulmonary metastases were seen on CT 8-23 months (11.95 ± 0.78) months after the first ¹²⁵I implantation. The diagnosis was confirmed by CT-guided needle biopsy before ¹²⁵I brachytherapy in the enrolled patients. Inclusion criteria for ¹²⁵I brachytherapy of RMPM were as follows: 1) multiple metastases (number, ≥ 2) in the lungs, and the patient was not a suitable candidate for resection; 2) conventional methods such as chemotherapy and TACE could not effectively control the metastases; 3) patients with multiple tumor metastases of the lung who were unable to withstand radiation-related complications. Patients who had blood-coagulation dysfunction or a Karnofsky performance score of < 70 were excluded. Standard chemotherapy and TACE were administered during or after brachytherapy to control the primary tumor or other metastases.

Instrumentation

The ¹²⁵I seeds (Model-6711), implantation needle, and implantation gun were provided by Atom-Hitech Limited (HTA Co. LTD. [approval] H20045969 China). Each seed comprised a cylindrical titanium body (length, 4.5 mm; diameter, 0.8 mm). Dimensions within the silver column were 3.0 mm \times 0.5 mm, adsorption of ¹²⁵I radioactivity was 25.9 MBq, and the half-life was 59.43 days.

Preoperative evaluation of metastases with conventional CT (Siemens 16 row, Germany) enabled data transmission to a treatment-planning system (TPS) (BT-RSI; Yuan Bo, Beijing, China). This system enabled outlining the target lesion, calculation of gross tumor volume and clinical target volume, mapping of the needle's path and depth, and computation of the number of seeds and needles. The planning target volume of 90% (D_{90}) was 120-160 Gy for ¹²⁵I seeds with an activity of 25.9 MBq.

¹²⁵I seed brachytherapy

We ensured that each patient was calm with a steady respiratory rate as assessed by CT. All patients, in the supine or prone position, were scanned with 3-mm-thick slices with gridlines on the surface to measure the volume of metastases. Three-dimensional reconstruction was performed, and the CT images were transferred to a TPS. The matched peripheral dose was calculated based on the target volume and the number of ¹²⁵I seeds. We use gridlines joint CT scans to identify puncture point on the body surface. Local anesthesia (2% lidocaine) was administered to all patients before

Table 1. Patient characteristics ($n = 22$)

Factor	Patients, <i>n</i>
Gender	
Male	14
Female	8
Age (years)	
< 30	2
30-50	3
50-70	12
> 70	5
Median	61.5
Primary tumor	
Hepatocellular carcinoma	11
Colorectal adenocarcinoma	3
Gastric adenocarcinoma	3
Esophageal squamous cell carcinoma	1
Hypopharyngeal squamous cell carcinoma	1
Pancreatic adenocarcinoma	1
Malignant peripheral nerve sheath tumor	1
Synovial sarcoma	1
Tumor treatment	
Local excision	14
Chemotherapy	11
Transcatheter arterial chemoembolization	14
Radiation therapy	4

the surgery. The implantation needle was inserted into the area of metastases under CT guidance, and the spacing between seeds was kept at 0.5-0.8 cm. The implantation process is shown in detail in Figure 1. All care was taken to ensure that seed distribution was three-dimensional and the damage to surrounding normal tissue was minimal. Dose verification (through TPS) after implantation of ^{125}I seeds ensured that the D_{90} value was attained; replanting of ^{125}I seeds was carried out if necessary. Standard treatment to counteract bleeding and infection was initiated 24 h after

implantation. In order to minimize the risk of pneumothorax, we avoided puncturing both lungs in one treatment and carried out unilateral lung puncture for up to two metastases. Post puncture treatment, patients were required to rest in bed and were given proper oxygen inhalation.

Follow-up

Chest CT was performed 1, 2, and 6 months after implantation to ascertain changes in tumor size and review for

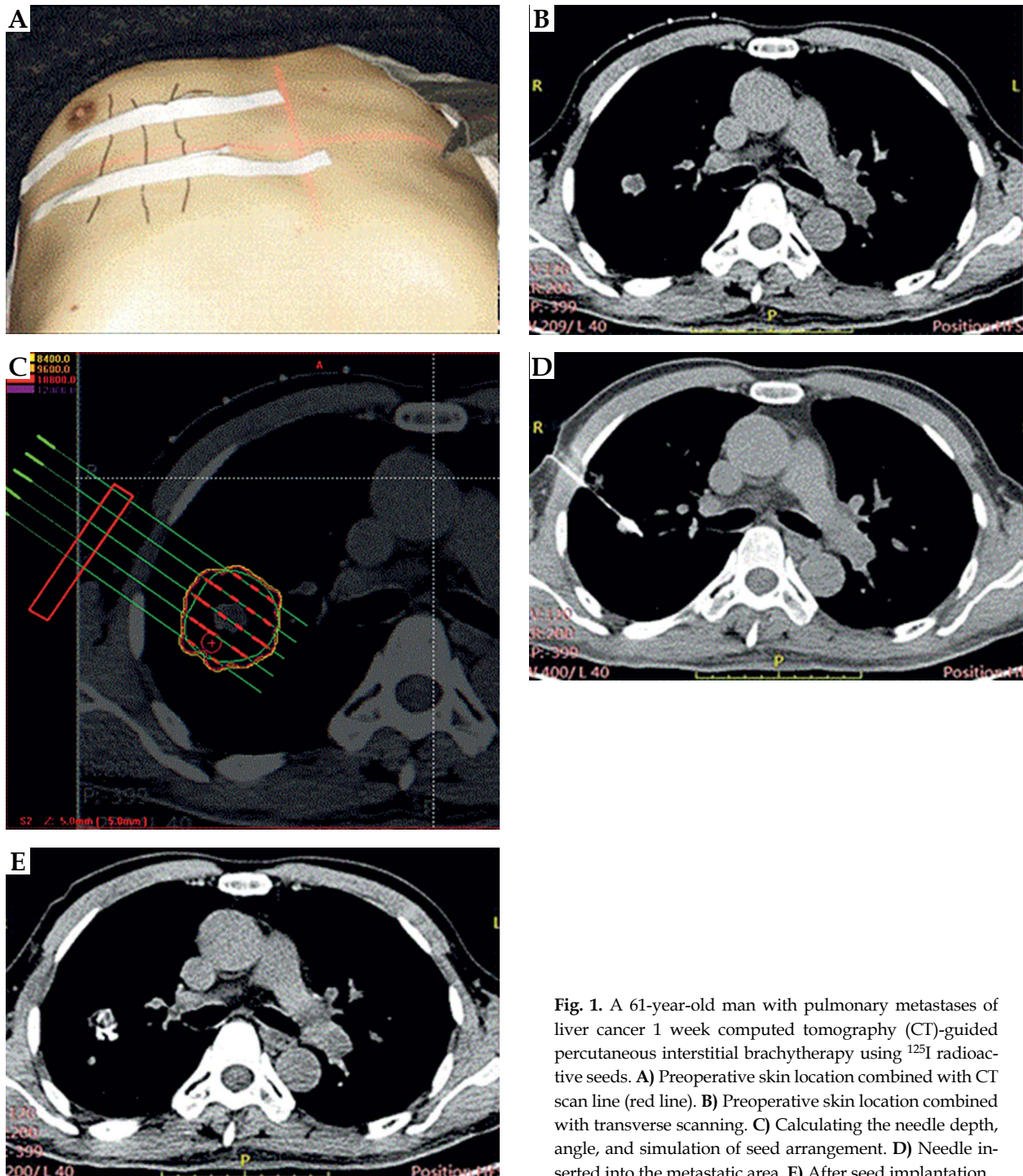


Fig. 1. A 61-year-old man with pulmonary metastases of liver cancer 1 week computed tomography (CT)-guided percutaneous interstitial brachytherapy using ^{125}I radioactive seeds. **A)** Preoperative skin location combined with CT scan line (red line). **B)** Preoperative skin location combined with transverse scanning. **C)** Calculating the needle depth, angle, and simulation of seed arrangement. **D)** Needle inserted into the metastatic area. **E)** After seed implantation

new metastases. Local control was determined 6 months after implantation. According to the Response Evaluation Criteria in Solid Tumors (2010 version) [11], we evaluated the following parameters: complete response (CR; disappearance of all target lesions for ≥ 1 month); partial response (PR; $\geq 30\%$ decrease in the sum of the largest diameter of target lesions with the baseline sum of the largest diameter as reference); progressive disease (PD; $\geq 20\%$ increase in the sum of the largest diameter of target lesions, taking as reference the smallest sum of the largest diameter recorded since the treatment started or the appearance of one or more new lesions); and stable disease (SD; neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, with the smallest sum of the largest diameter since the treatment started as reference).

Statistical analyses

Follow-up time was considered as the date from seed implantation. GraphPad Prism v5 (Avenida, CA, USA) was used for all charting and statistical analyses. Data are expressed as mean \pm SE. Kaplan-Meier analyses were used to evaluate overall local control and survival time.

Results

Implantation of ^{125}I seeds

In total, 65 cases of metastases in 22 patients were treated with ^{125}I seeds brachytherapy, with 44 implantations (mean number of implantations, 2; range, 1-5). The total number of implanted seeds was 1090 (mean, 50 ± 6 per patient; minimum: 20, maximum: 160). The mean value for D_{90} for ^{125}I implantation was 132 Gy.

Adverse effects of treatment

Twenty-two patients successfully completed the treatment. All needles were disposable, and five patients complained of pain at the puncture site, but these symptoms disappeared 24 hours after initiation of analgesic therapy. Lung puncture process typically results in a small amount of leakage, which can be reduced by minimizing the number of punctures. In our study, there were 4 cases of pneumothorax, where in the pulmonary compression was less than 30% with conservative treatment. Three days after the operation, 16 patients presented with cough, sputum, and hemoptysis. After 1 month

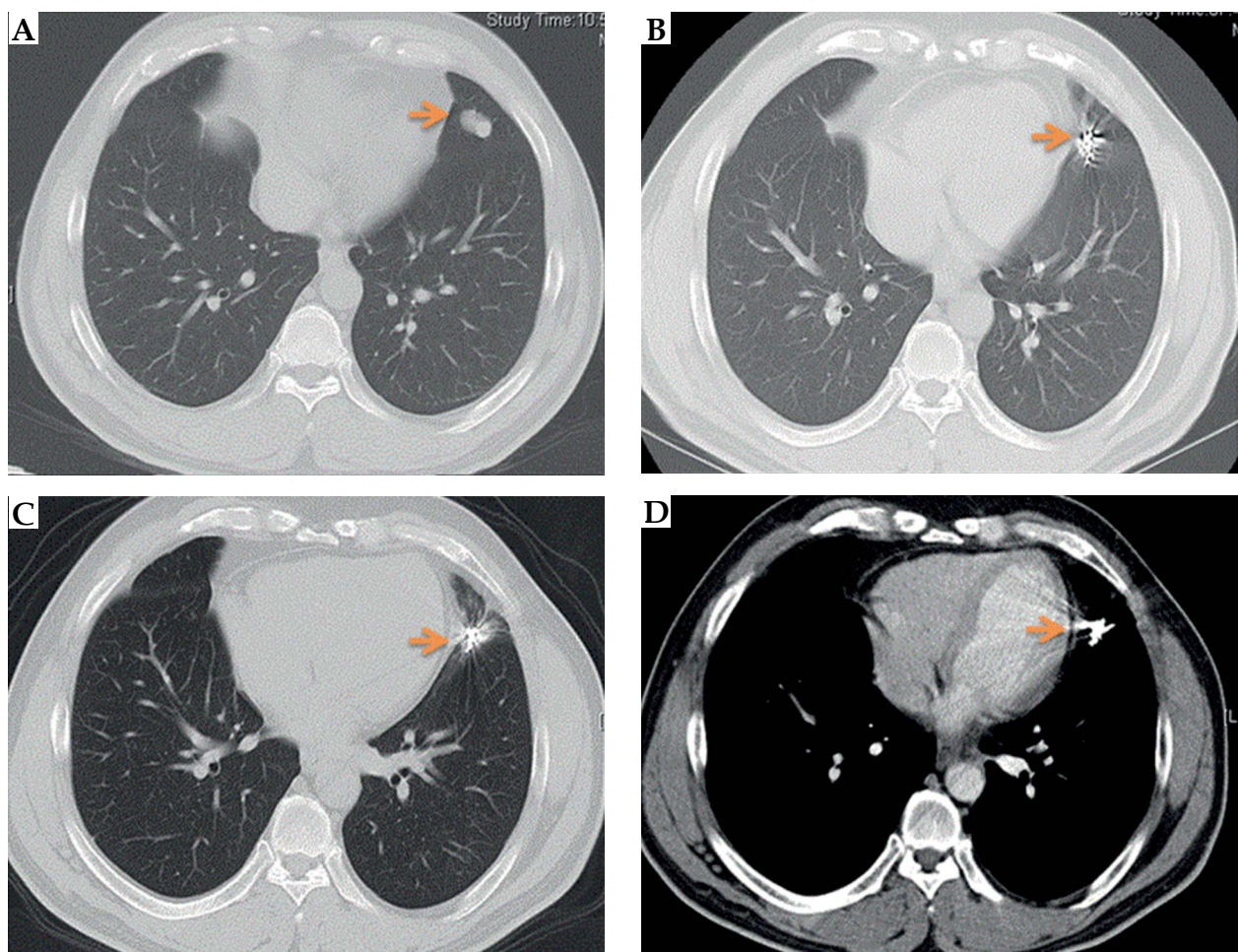


Fig. 2. A 40-year-old woman with resection of pancreatic cancer since 1 year and pulmonary metastases since 1 week underwent computed tomography (CT)-guided percutaneous interstitial brachytherapy using ^{125}I radioactive seeds. **A)** Preoperative upper lobe of left lung metastases. **B)** Metastases resolved 1 month after the operation. **C-D)** Mediastinal window: ^{125}I seeds gathered 6 months after the operation

Table 2. Local control for 22 patients with 65 pulmonary metastases after computed tomography-guided permanent implantation of ^{125}I seed brachytherapy

Follow up time	Local control efficacy				Local control rate % (complete response + partial response/total)
	Complete response	Partial response	Stable disease	Progressive disease	
1 month	41	12	8	4	81.54%
2 months	41	10	7	5	78.46%
6 months	41	10	6	6	78.46%

of operation, 1 case of puncture subcutaneous metastasis occurred; we have been closely monitoring this patient thus far. Minor radiation pneumonitis was observed in two lungs at follow-up CT. The post-surgical renal, hepatic, and vascular functions were normal. In this group, there was no particle movement.

Treatment efficacy

At the ≥ 8 -month follow-up, contrast-enhanced spiral CT was used to evaluate the efficacy of implantation. Treatment characteristics and CT review based on changes in tumor size are shown in Table 1 and Figure 2. Local control of tumors at 1, 2, and 6 months after implantation are shown in Table 2. Survival characteristics are shown in Figure 3.

CR + PR was documented in 81.54%, 78.46%, and 78.46% of patients at 1, 2, and 6 months after implantation, respectively. Fourteen out of 22 patients had CR, 3 had PR, 2 had SD, and 3 had PD. Two patients developed new metastases within a short time post implantation, and percutaneous implantation metastasis was observed in one patient. In some patients, owing to emerging newer pulmonary metastases, up to 5 implantations were required. Most of the metastases (CR + PR + SD; 87.69% after 6 months) were controlled by implantation.

Discussion

Currently, minimally invasive loco-regional approaches such as radiofrequency ablation (RFA)/microwave ab-

lation or SBRT have been introduced as an alternative to surgery [12,13,14,15,16]. Radiofrequency ablation is most effective when reserved for treating three or fewer lesions, < 3.5 cm in diameter, and that are not in close proximity to large blood vessels owing to the heat-sink effect [14]. Stereotactic body radiotherapy has shown promise in early-stage disease, and reported outcomes are impressive [15], but central tumors cannot be treated with SBRT because of the low tolerance of the great vessels, main bronchus, and heart to radiation [16]. Compared with conventional radiotherapy and chemotherapy, ^{125}I -implantation treatment was more effective to control inoperable, large lung cancers, and improved the overall survival and quality of life [17]. Computed tomographic and fluoroscopic-guided brachytherapy with ^{125}I seeds implantation is a safe, feasible, and effective modality for the treatment of inoperable early-stage non-small-cell lung cancer (NSCLC) [18]. ^{125}I implants for the treatment of lung cancer or malignant thoracic tumors showed local control rates ranging from 81% at 6 months to 75.3% at 3 years [19,20].

In this study, we showed that repeated implantation of ^{125}I seeds brachytherapy is a feasible method to treat RMPM. Being a minimally invasive procedure, this method has, to some extent, overcome the challenges associated with surgery and radiotherapy. Implanting radioactive seeds, in principle, should be delivered by the TPS. The arranged dose should be as uniform as possible: sources are typically arranged in a straight line, parallel to each other, and the radioactive source (particles) are equidistant. In this group, the total radiation dose was increased by 10-15% than the conventional prescription dose. With the increased dose, the local control effect and inflammatory response was increased. In fact, as per the plan of implantation, pulmonary metastases can be effectively controlled and will not recur within six months. We found a high incidence of blood in the sputum and postoperative pneumothorax, although this was not serious. While performing the puncture, if the needle runs along the vascular bundles carefully avoiding cutting the blood vessels and trachea, these complications can be reduced. In order to avoid pneumothorax of double-lung, treatment of unilateral multiple metastases of the lung and the same lobe requirements is recommended to minimize the number of puncture.

Pulmonary metastases are hematogenous metastasis, and are diagnosed late as they usually show no respiratory symptoms, and are rarely suitable for surgery. Like

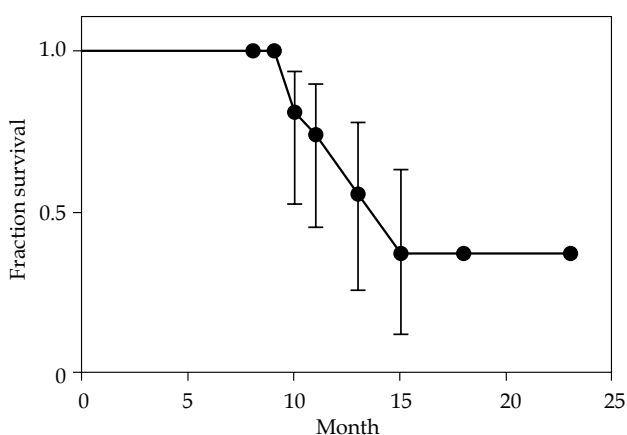


Fig. 3. Follow-up of survival time curve for the 22 patients with multiple pulmonary metastases after computed tomography (CT)-guided ^{125}I brachytherapy seed permanent implantation

our study, all had undergone various treatments such as chemotherapy and TACE. In our study, CR + PR was documented in 81.54%, 78.46%, and 78.46% of patients at 1, 2, and 6 months after implantation, respectively, which are satisfactory results. Zhang *et al.* [21] studied CT-guided radioactive ¹²⁵I seed implantation treatment of multiple pulmonary metastases of HCC (27 cases), wherein all patients had ≥ 2 metastases, and the survival rates at 1 and 2 years were 67% and 30.8%, respectively. Li *et al.* [22] studied feasibility of ¹²⁵I brachytherapy combined with sorafenib treatment in patients with multiple lung metastases after liver transplantation for HCC (8 cases): the local control rates of multiple lung metastases after orthotopic liver transplantation for HCC after 4, 6, 12, 18, and 24 months were 92.2, 82.4, 76.2, 73.3, and 72.2%, respectively. Both survival and local control rates were very similar to our study results. However, we started follow-up 1 month after implantation, and most metastases reduced after the 1-month of follow-up. Follow-up after 2 months showed that most metastases had disappeared and only ¹²⁵I seeds were remaining. For these multiple pulmonary metastases, ¹²⁵I seeds brachytherapy has so far been a curative treatment.

Our study has some limitations. The sample size was small and only used for evaluation of local control of pulmonary metastases. Further, most of the patients had undergone multiple treatments such as chemotherapy and TACE among others, with continued progression to multiple lung metastases, thereby causing loss of confidence in the patients. Under these circumstances, the high rate of local-control multiple pulmonary metastases with seeds implantation provided a confidence boost for affected patients. Although local implantation of ¹²⁵I seeds was a palliative treatment to control local metastases, it could not control the general progression of tumors, and most patients had died at the 23-month follow-up. Because of the continuing emergence of pulmonary metastases, implantation of ¹²⁵I seeds can be repeated. If lung function is favorable, implantation can be repeated within a short time. We hope that clinicians will be more actively involved in related research.

Conclusions

As a minimally invasive method, CT-guided ¹²⁵I brachytherapy is safe and effective for multiple pulmonary metastatic tumors and can achieve good short-term local control if the radiation dose is sufficient. CT-guided ¹²⁵I brachytherapy carries few complications, is simple, safe, and a good complement to conventional cancer treatment.

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Disclosure

Authors report no conflict of interest.

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