

# How many times $^{125}\text{I}$ seed implantation brachytherapy can be repeated for pulmonary metastases: clinical efficacy and complications

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## Abstract

**Purpose:** The aim of the study was to determine how many times iodine-125 ( $^{125}\text{I}$ ) seed brachytherapy (ISB) for recurrent pulmonary metastases (RPM) can be done, and the clinical efficacy and complications of repeated ISB in RPM treatment.

**Material and methods:** Between September 2013 and August 2018, 18 patients with RPM, after conventional chemotherapy, radiotherapy, and trans-arterial chemoembolization, received CT-guided repeated ISB. Patients were followed up, and local control, survival, and post-operative complications were analyzed retrospectively. The Kaplan-Meier method was used for survival analyses.

**Results:** Eighty-two metastases in 18 patients were treated with ISB, with 71 implantations (mean number of implantations per patient, 4; range, 3-8). The total number of implanted  $^{125}\text{I}$  seeds was 1,220 (mean number per patient, 68; minimum, 40; maximum, 110). The mean value of  $D_{90}$  for ISB was 138 Gy. Local control was 91.46%, 90.24%, and 89.02% at 1, 3, and 6 months after ISB, respectively. After repeated ISB, good local control was achieved, and all patients were discharged from hospital within 3 days. One month after, six metastases of large diameter were treated with ISB; computed tomography revealed level 1 radioactive injury to the lungs, but special treatment was not administered. Post-operative renal, hepatic, and vascular functions were normal.

**Conclusions:** ISB for RPM is safe and efficacious. RPM treatment seems not to be limited by number of times ISB could be repeated; at least up to 8 times for different sites of lung.

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**Key words:** lung neoplasms, iodine-125, brachytherapy, tomography, X-ray, computed, retrospective studies.

## Purpose

Relatively good long-term survival of patients with recurrent pulmonary metastases (RPM) may be due to good local control of pulmonary metastases, but unified guidelines for RPM treatment are lacking. Studies have demonstrated that implantation of iodine-125 ( $^{125}\text{I}$ ) seeds elicits good local control of pulmonary metastases [1,2,3]. Also, preliminary statistical studies and evaluations on the ability of lung tissue to tolerate  $^{125}\text{I}$ -seed brachytherapy (ISB) have been made [4].

In ongoing follow-up treatment undertaken by our research team, many patients were found to have RPM or multiple intra-pulmonary metastases. Previously, we showed that ISB can engender good local control, and

that patients can recover rapidly after brachytherapy [2,4]. The damage induced by radiation to adjacent lung tissue is minor, so we employ repeated ISB to control RPM.

We wished to establish if there is a limit to the number of treatments for repeated ISB that can be done for RPM. We reviewed clinical efficacy and complications of repeated ISB in patients with RPM.

## Material and methods

### *Ethical approval of the study protocol*

This study was approved by the ethics committee of the Affiliated Hospital of Jiangnan University. The retro-

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spective study and patients' information was approved by our institutional review board.

### **Inclusion and exclusion criteria for $^{125}\text{I}$ -seed brachytherapy**

Inclusion criteria for ISB of RPM included: 1. RPM  $\geq 3$  times and the patient was not a suitable candidate for resection; 2. Conventional methods such as radiotherapy, chemotherapy, and trans-arterial chemoembolization (TACE) could not control RPM effectively. Standard chemotherapy and TACE were administered during or after ISB to control the primary tumor or other types of metastases. Patients who had blood-coagulation dysfunction or a Karnofsky performance score of  $< 70$  were excluded.

### **Patients**

From September 2013 to August 2018, 18 patients (12 males and 6 females; mean age  $\pm$  standard deviation [SD], 60.28  $\pm$ 14.59 years; range, 18-78 years) with RPM (mean number of RPM, 4.556  $\pm$ 1.947; range, 3-9; total number, 82) and the largest diameter measuring 0.8-3.1 cm received computed tomography (CT)-guided ISB. The characteristics of patients and metastatic tumors are summarized in Table 1.

**Table 1.** Patient characteristics ( $n = 18$ )

	Patients (n)
Sex	
Male	12
Female	6
Age (years)	
$< 50$	4
50-70	10
$> 70$	4
Primary tumor	
Hepatocellular carcinoma	6
Colorectal adenocarcinoma	5
Gastric adenocarcinoma	1
Esophageal squamous cell carcinoma	1
Hypopharyngeal squamous cell carcinoma	2
Pancreatic adenocarcinoma	1
Ovarian cancer	1
Synovial sarcoma	1
Treatment history	
Local excision	18
Chemotherapy	11
Transcatheter arterial chemoembolization	13
Radiotherapy	3

In all cases, the primary cancer and metastases were confirmed by surgery or biopsy. Standard chemotherapy was administered to 11 patients, and three of them received radiotherapy. Each patient with hepatocellular carcinoma (HCC) had undergone TACE. In all, three patients with liver metastasis, two with bone metastasis, and three with metastasis of the adrenal glands underwent TACE. The primary tumor of all patients was well controlled, and RPM were recorded without chest pain, cough, or phlegm. However, the number of patients with pulmonary metastases continued to increase. RPM were seen on CT in 5 to 38 (12.44  $\pm$ 8.389) months after first implantation of  $^{125}\text{I}$  seeds.

### **Instrumentation**

Information regarding  $^{125}\text{I}$  seeds and implantation device has been described by our team previously [2,4]. The  $^{125}\text{I}$  seeds (Model 6711), implantation needle, and implantation device were provided by Atom Hitech. 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  $^{125}\text{I}$  radioactivity was 25.9 MBq, and half-life was 59.43 days.

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

### **$^{125}\text{I}$ -seed brachytherapy**

Information regarding the ISB procedure has been published previously [2,4]. 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 imaged with 3 mm thick slices with gridlines on the surface to measure the volume of metastases. Three-dimensional reconstruction was undertaken, and CT images were transferred to the TPS. The matched peripheral dose was calculated based on the target volume and number of  $^{125}\text{I}$  seeds. Gridlines from two CT scans were employed to identify the puncture point on the body surface. Local anesthesia (2% lidocaine) was administered to all patients preoperatively. 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. Extreme care was taken to ensure that the distribution of  $^{125}\text{I}$  seeds was three-dimensional and that damage to surrounding normal tissue was minimal. Dose verification (through the TPS) after implantation of  $^{125}\text{I}$  seeds ensured that the  $D_{90}$  value was attained; replanting of  $^{125}\text{I}$  seeds was carried out if necessary. Standard treatment to counteract bleeding and infection was initiated 24 hours after implantation of  $^{125}\text{I}$  seeds. 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. After puncture, the patient was bed rested and given oxygen support.

### Follow-up

Contrast-enhanced CT of the chest was done 1, 3, and 6 months after implantation of  $^{125}\text{I}$  seeds to ascertain changes in tumor diameter and assess new metastases. Local control was determined 6 months after implantation. Local control of lung metastases was calculated according to the modified response evaluation criteria in solid tumors [5]. Radioactive lung injury was evaluated according to the Common Terminology Criteria for Adverse Events v. 4.0 established by the National Cancer Institute [6].

### Statistical analyses

The duration of follow-up was from the date from implantation of  $^{125}\text{I}$  seeds. Prism v. 5 (GraphPad) was used for chart creation and statistical analyses. Data were the mean  $\pm$  SD. Kaplan–Meier analyses were used to evaluate overall local control and survival time.

## Results

### Implantation of $^{125}\text{I}$ seeds

Eighty-two metastases in 18 patients were treated with ISB, with 71 implantations (mean number of implantations per patient, 4; range, 3–8). The total number of

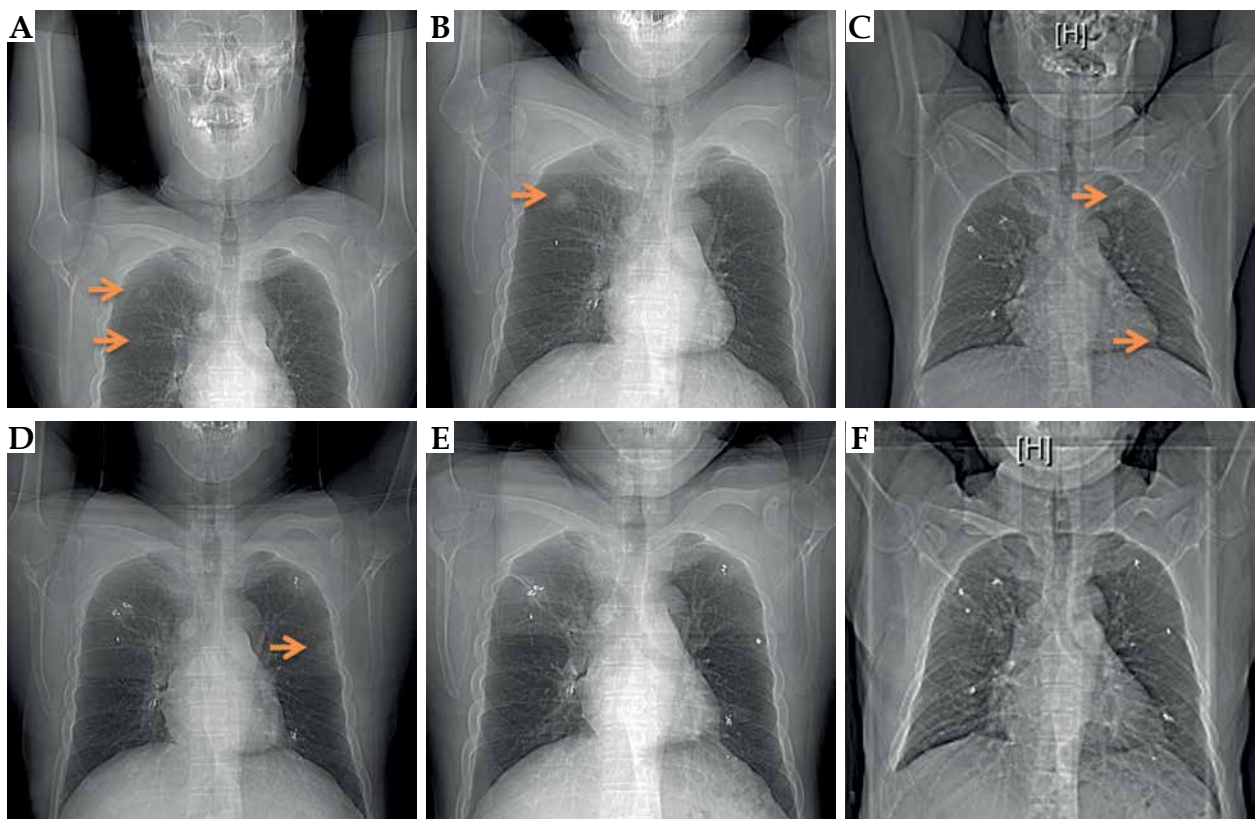
implanted  $^{125}\text{I}$  seeds was 1,220 (mean number per patient,  $68 \pm 20$ ; minimum, 40; maximum, 110). The mean value of  $D_{90}$  for ISB was 138 Gy.

### Adverse effects of treatment

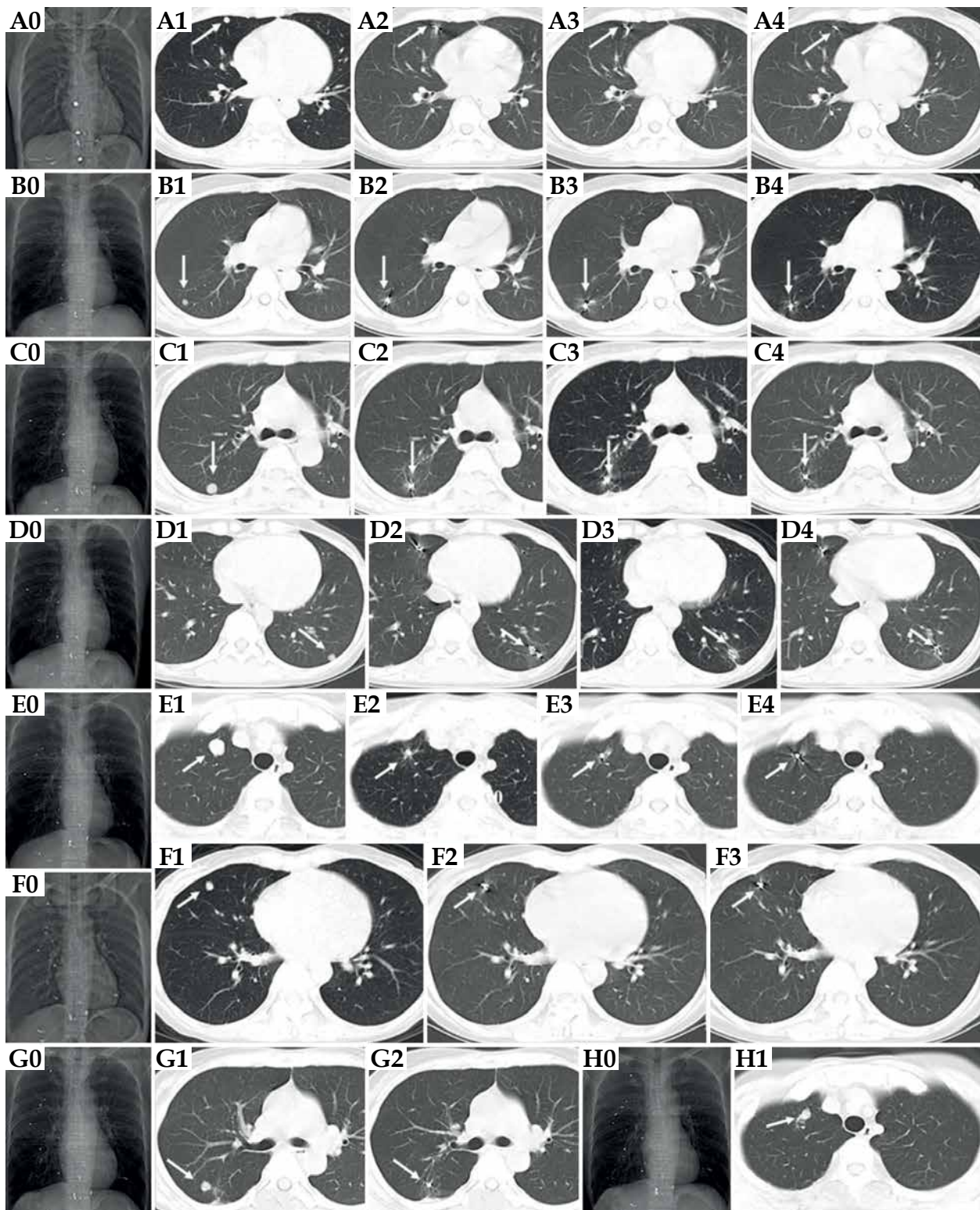
Significant pain or bleeding during ISB was not noticed. In 21 cases, we observed a small amount of pneumothorax, lung compression was  $< 30\%$ , and 34 cases of post-operative cough and phlegm were accompanied by mild hemoptysis, and these patients recovered without additional treatment. Two patients suffered displacement of  $^{125}\text{I}$  seeds to the heart; after long-term observation, these patients have no discomfort complaint. In one patient, subcutaneous metastases were found at the puncture site and, after implantation of  $^{125}\text{I}$  seeds, partial control was good, but was accompanied by mild skin damage. One month after six metastases of large diameter were treated with ISB, CT revealed a grade 1 radioactive injury to the lungs, but special treatment was not administered. Post-operative renal, hepatic, and vascular functions were normal.

### Treatment efficacy

All patients were treated with repeated ISB., and follow-up involved the use of contrast-enhanced CT. Treat-



**Fig. 1.** A 46-year-old male who underwent resection of synovial sarcoma in the right knee joint 1 year previously. CT images are shown. **A)** Preoperative image showing metastases in the right upper lung (arrows); **B)** 1 month after ISB: residual metastatic foci have progressed (arrow). Second implantation of  $^{125}\text{I}$  seeds was administered; **C)** 2 months after first ISB. Metastases in right upper lung have disappeared and only  $^{125}\text{I}$  seeds are visible, but the left lung has new metastasis (arrows). **D)** 5 months later. Left lung has new metastasis (arrow). **E)** 6 months later. Lung metastases disappeared and  $^{125}\text{I}$  seeds were gathered; **F)** 1 year later. New lung metastases not found and  $^{125}\text{I}$  seeds were gathered



**Fig. 2.** A 43-year-old female who underwent resection of pancreatic adenocarcinoma 1 year previously. Post-operative regular chemotherapy (gemcitabine 1000 mg; Day 1, Day 8) was done four times. Liver metastases appeared but were well controlled by TACE plus repeated ISB. CT images are shown. **A1-H1)** Preoperative. **A2-F2)** 3 months after ISB - metastases have disappeared; **A3-G2)** 6 months after ISB: few  $^{125}\text{I}$  seeds are left; **A4-E4)** 12 months after ISB:  $^{125}\text{I}$  seeds were gathered

ment characteristics and CT review based on changes in tumor diameter are shown in Table 1 and Figures 1 and 2. Local control of tumors 1, 3, and 6 months after implantation are shown in Table 2. Survival characteristics are shown in Figure 3.

Local control of tumors was 91.46%, 90.24% and 89.02% at 1, 3, and 6 months after ISB, respectively. Regular follow-up revealed that all patients had new RPM. However, after repeated ISB, good local control was achieved, and all patients were discharged from hospital within 3 days.

## Discussion

There is a potential survival benefit for patients who undergo pulmonary metastasectomy, even those with RPM [7,8]. Therefore, it is necessary to treat pulmonary metastases actively, but thoracotomy and video-assisted thoracoscopic surgery elicit considerable trauma [9].

The concept of minimally invasive treatment is accepted by most patients. Filippi *et al.* [10] suggested that stereotactic body radiation therapy (SBRT) of pulmonary metastases from colon cancer is superior to resection of pulmonary metastases, and that surgical treatment can be substituted by SBRT. Previously, we found that treatment using <sup>125</sup>I seeds was safer and more efficacious than SBRT for minimally invasive treatment of RPM. Significant differences were seen between the two ways in the incidence of radiation pneumonitis ( $p < 0.001$ ) as well as radiation-induced pulmonary fibrosis ( $p = 0.005$ ) [4]. Implantation of <sup>125</sup>I seeds in the present study was done under local anesthesia and patients did not complain of significant discomfort (CTCAE v.4.0, grade 1). Post-operative recovery was rapid, and patients were discharged within 3 days. Level 1 radioactive injury to peripheral lung tissue was noted at follow-up, and was likely related to the large diameter of metastases and high radiation dose.

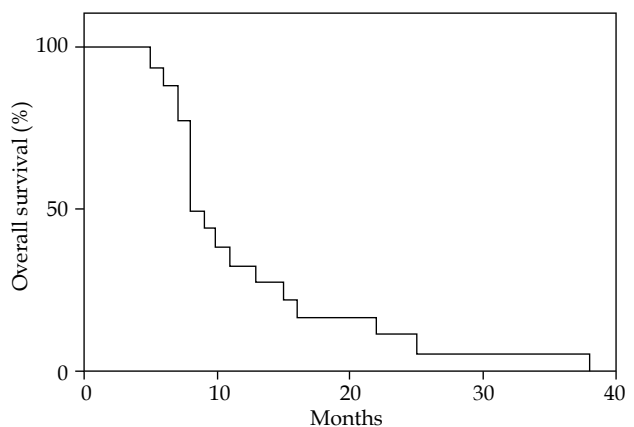
A combination of ISB and second-line chemotherapy is superior to chemotherapy alone, therefore is an efficacious and safe therapy [11]. ISB has been shown to be more effective in controlling inoperable large-cell lung cancer, and to improve overall survival and quality of life (QoL) compared with conventional radiotherapy and chemotherapy [12]. Compared with SBRT, brachytherapy can generate a comparable dose within the planning target volume (PTV D<sub>90</sub> [104.73 ± 2.10 Gy vs. 107.64 ± 2.29 Gy], mean volume receiving 100% of the prescription dose (V<sub>100%</sub>) [91.65% vs. 92.44%,  $p = 0.410$ ], while the organs at risk receive only a very low-dose. The mean lung doses (MLD) in brachytherapy were significantly lower than those in SBRT (1.952 ± 0.713 vs. 5.618 ± 2.009,  $p < 0.0001$ ) [13].

Radiofrequency ablation has been used to treat RPM, and local control has been achieved and survival prolonged [14,15]. Thermal ablation has minimal effects on pulmonary function or QoL, can be repeated, and may be considered more acceptable to patients because of the associated short stay in hospital and fast recovery [16]. Traiki and colleagues suggested that RPM in patients with colorectal cancer could be treated by percutaneous ra-

**Table 2.** Local control for 18 patients with 82 pulmonary metastases after <sup>125</sup>I seed brachytherapy

Duration of follow-up (months)	Local control				Local control (CR + PR/total)
	CR	PR	SD	PD	
1	64	11	5	2	91.46%
3	65	9	5	3	90.24%
6	67	6	6	3	89.02%

CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease



**Fig. 3.** Survival time of 18 patients with recurrent pulmonary metastases after ISB

diolofrequency/microwave ablation to provide good local control and potentially prolongation of overall survival; however, the incidence of pneumothorax was significantly higher (71%) than that of this group [17].

The detailed procedure and limitations of ISB have been described in detail previously [2,4,18]. In the present study, the prescription doses of ISB averaged 138 (range, 120-160) Gy, and the radiation doses were distributed within 1 cm of RPM by the TPS. Local control reached 90%, and the duration of local control was > 6 months.

Some studies have reported that repeated ISB for RPM treatment is safe and efficacious [19,20]. We found that repeated ISB (Figures 1, 2) did not affect lung function. This finding may have been due to our regular follow-up of patients, timely detection of RPM, and a relatively small diameter of RPM. We found that RPM treatment was not limited by the number of times ISB was done.

The present study had two main limitations. Firstly, it was a retrospective, single-center, small-sample study, and secondly, patients had a different primary tumor and other types of distant metastasis. Hence, we focused on local control of RPM. We found that minimally invasive therapy could achieve a good therapeutic effect, and that lung injury was insignificant even after repeated ISB.

## Conclusions

ISB for RPM is safe and efficacious. RPM treatment seems not to be limited by the number of times ISB is repeated, at least up to 8 times for different sites of lung.

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## Disclosure

Authors report no conflict of interest.

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