Original paper

Percutaneous computed tomography-guided permanent ^{125}I implantation as therapy for pulmonary metastasis

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Abstract

Purpose: To evaluate intermediate-term outcomes after computed tomography (CT)-guided radioactive ^{125}I seed implantation (CTRISI), and to determine prognostic variables associated with outcomes in patients with pulmonary metastases.

Material and methods: Thoracic surgeons evaluated and performed implantation of ^{125}I radioactive seeds under CT guidance or combined with surgical resection. Patients were monitored in the thoracic surgery clinic for recurrence and survival.

Results: Fifty patients (31 men, 19 women; median age, 59 years; range, 16-85) underwent CTRISI. The primary cancer was colorectal in 10 (20%), malignant fibrous histiocytoma in 8 (16%), sarcoma in 5 (10%), renal in 4 (8%), and other in 22 (44%) patients. CTRISI was the sole treatment in 45 patients (90%) and was combined with surgical resection in 5 patients (10%). The actuarial D_{90} of implanted ^{125}I seeds ranged from 90 to 160 Gy (median, 120 Gy). No procedurally related deaths occurred. At a median follow-up of 41.5 months (range, 7-74 months), 6 patients were alive. The median survival time was 42.1 months (95% confidence interval: 26.5-53.4), and the estimated 1-, 3-, and 5-year overall survival rates were 88.0%, 58.0%, and 26.7%, respectively. Lesion size was an important prognostic variable associated with overall and progression-free survival ($p < 0.05$).

Conclusions: CTRISI is safe in this group of patients with pulmonary metastases and provides reasonable results. Surgical resection remains the standard for resectable cases, but CTRISI offers an alternative for selected patients or may be used as a feasible approach in combination with surgical resection for selected patients.

Purpose

It is easier for malignant tumors to metastasize to the lungs than to many other organs. Autopsy studies of patients who died of cancer have shown the lungs to be the sole site of metastasis in about 20% of cases [1]. Effective treatment methods for pulmonary metastases are rather limited. Treatments for pulmonary metastases mainly include thoracotomy, radiotherapy, and chemotherapy. Surgical resection (i.e. metastasectomy) is now a standard therapeutic procedure for properly selected cases, and is routinely performed in many departments of thoracic surgery [2]. In particular, patients who have a single metastasis, a prolonged disease-free interval (> 36 months), complete primary tumor control, and no evidence of extrathoracic disease are good candidates for resection, which leads to good outcomes for these patients [2]. Surgical thoracotomy benefits certain patients with single or regional lesions. However, it is not suitable for patients with multiple lesions [3].

Several studies have demonstrated the potential benefits of metastasectomy for selected patients [2,4,5,6]. However, limitations to surgical approaches

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have prompted researchers to develop innovative and non-invasive options for treating pulmonary metastasis from primary cancers. Many patients with such limitations are treated with chemotherapy, and their long-term survival is not encouraging [7]. Selection of the appropriate treatment for inoperable patients is a cause of concern at present.

Computed tomography (CT)-guided radioactive ¹²⁵I seed implantation (CTRISI) could potentially be applicable in high-risk patients or patients who require repeated thoracotomies. Several studies have shown that CTRISI is a safe, feasible, and promising treatment for patients with malignant tumors after surgical excision of primary lesions and repeated chemotherapy, but few long-term outcomes have been reported [8,9,10]. CTRISI may also be used as an adjuvant to parenchyma-sparing surgery, in order to treat all lesions more completely, but data on intermediate-term results for these cases are also lacking.

The primary objectives of this study were: 1. to evaluate patient outcomes after CTRISI either alone or as an adjuvant to surgical resection in selected patients with pulmonary metastases, and 2. to evaluate prognostic variables associated with both overall survival (OS) and progression-free survival (PFS).

Material and methods

Patients

All patients provided informed consent for the medical procedures described in this report and for the use of their data in medical research. This study received institutional review board approval and was performed in accordance with the Declaration of Helsinki. We retrospectively reviewed patients who underwent CTRISI treatment for pulmonary metastases in the Department of Thoracic Surgery at the Second Hospital of Tianjin Medical University during the 6-year period from 2003 to 2009. This study was approved by the Second Hospital of Tianjin Medical University Ethics Committee. Patients with metastatic lung cancer who underwent CTRISI were identified. All patients underwent chest computed tomography (CT), and 10 patients (20%) also underwent positron emission tomography (PET/CT). The patients included in this study were those: 1. who were considered medically inoperable because of poor pulmonary function (predicted post-operative forced expiratory volume in 1 second or carbon monoxide lung diffusion capacity of less than 40%), high cardiac risk, or other comorbidities; 2. in whom prior treatments had failed; or 3. patients who refused surgery. We excluded patients who had recurrent or metastatic primary non-small cell lung cancer. Exclusion criteria included central tumors, cachexia, and coagulation disorders. In some patients who underwent operations, CTRISI was used as an adjuvant therapy. All patients were evaluated by a thoracic surgeon to determine suitability for CTRISI either as a sole treatment or as an adjuvant to surgical resection.

Patient characteristics

During the 6-year period, 50 patients (31 men and 19 women) underwent CTRISI for pulmonary metastases.

The patients had been diagnosed with primary colorectal cancer (10 patients, 20%), malignant fibrous histiocytoma (8 patients, 16%), sarcoma (5 patients, 10%), renal cancer (5 patients, 10%), and other cancers (22 patients, 44%). CTRISI was the sole treatment for 45 patients (90%), and it was combined with surgical resection for 5 patients (10%). The mean of the largest lesion diameter was 4.0 cm (range, 1-6 cm). Patient characteristics are summarized in Tables 1 and 2. The mean disease-free interval from treatment of the primary lesion to first metastasis at any site was 49.4 months. The mean interval to lung metastases, specifically, was 35 months. Seven patients had received prior treatment for intrathoracic metastatic disease. A median 2.0 lesions (range, 1-4 lesions) were treated with CTRISI per patient in each setting. Bilateral lesions were present in 15 patients. Among the patients with contralateral lesions, 2 patients were treated with surgical resection and adjuvant CTRISI, 10 patients were

Table 1. Summary of patient characteristics

Characteristic	Value
Sex, No. (%)	
Male	31 (62)
Female	19 (38)
Age mean (range), y	59(16-85)
Primary cancer, No. (%)	
Colon	10 (20)
Malignant fibrous histiocytoma	8 (16)
Sarcoma	5 (10)
Renal	5 (10)
Other	22 (44)
Breast	4 (8)
Head and neck	6 (12)
Urinary bladder	3 (6)
Stomach	2 (4)
Ovary	2 (4)
Melanoma	2 (4)
Oesophageal	1 (4)
Cervical	1 (4)
Myeloma	1 (4)
Lesion size (cm)	
Mean	4.2
Median	4.0
Site of first metastases, No. (%)	
Lung	38 (76)
Other	12 (24)

Table 2. Modified response evaluation criteria in solid tumors

Response	CT – mass size	CT – mass quality	PET[a]
Complete	Lesion disappearance (scar) or < 25% original size	Cyst cavity formation Low density	SUV < 2.5
Partial	> 30% decrease in the sum LD of target lesions	Mass central necrosis or central cavity with liquid density	Decreased SUV or area of FDG uptake
Stable lesion	< 30% decrease in the sum LD of target lesions	Mass solid appearance No central necrosis or cavity	Unchanged SUV or area of FDG uptake
Progression	Increase of > 20% in sum LD of target lesions	Solid mass, invasion adjacent structures	Higher SUV or larger area of FDG uptake

[a]PET performed selectively
CT – computed tomography, FDG – fluorodeoxyglucose, LD – lesion diameter, PET – positron-emission tomography, SUV – standardized uptake value

treated with CTRISI, and 3 patients who were receiving home oxygen declined further therapy. Extrathoracic disease was present in 5 patients and was under control. One patient underwent resection and CTRISI of liver metastases prior to CTRISI for the lung lesion.

Pre-treatment planning

Between 1 and 2 weeks prior to seed implantation, tumor volumes were measured using CT scans at 5 mm intervals. A radiation oncologist outlined the planning target volume (PTV) on each transverse image. The tumor volumes for all 50 patients varied from 1.18-212 cm^3 with a median of 47.8 cm^3. These tracings were digitized into a computer treatment planning system (TPS) (Prowess Panther 3D TPS, Chico, CA) and used to define the target volume for which the D_{90} (the dose delivered to 90% of the target volume defined by CT using a dose-volume histogram) irradiation value was prescribed. The total activity and the number of ^{125}I seeds implanted at the target site were determined using the TPS.

Seed implantation technique

Under adequate local anesthesia, 50 patients underwent seed implantation with CT guidance. After the target volume was determined, 18 gauge interstitial needles were inserted into the tumor using CT guidance. Precautions were taken to avoid large blood vessel punctures by placing the needles 1 cm apart and in a parallel array. ^{125}I seed implantation was performed such that the GTV and a 0.5 cm tumor margin were covered. ^{125}I seeds were implanted using a Mick applicator (Mick Radio-Nuclear Instruments, Inc.), and the distance between the centers of any two seeds was maintained at approximately 1.0 cm. All patients received perioperative prophylactic antibiotics.

Post-implant dosimetry evaluation

Post-operative dosimetry was routinely performed for all patients. The doses delivered by the implants were determined immediately or after 24 h of implantation using three-dimensional seed identification techniques and 5 mm thick CT scans. The CT-derived post-implant target volumes included the gross tumor volume and a 0.5 cm tumor margin. The contoured images and sources were entered into computerized treatment planning system software, and a redundancy check was performed to prevent seed duplication. The puncture needle interpolated the patient in the inspiratory phase. The actual D_{90} over the period of total decay was 90-160 Gy, with a median of 120 Gy. The median number of ^{125}I seeds implanted was 28 (range, 3-68). The specific activity of ^{125}I seeds ranged from 0.68-0.82 mCi per seed, with a median of 0.70 mCi. The seeds had a radioactive half-life of 59.6 days. The total amount of isotopes implanted ranged from 2.35-47.05 mCi, with a median of 16.45 mCi (Figure 1).
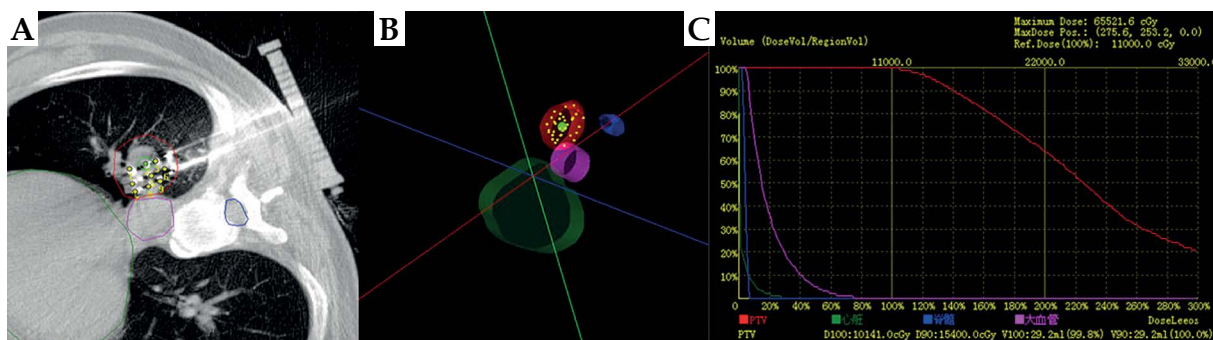
Fig. 1. Quality authentication, tumor imaging, and dose-volume histogram. **A)** Post-operative quality authentication: two-dimensional graph of the planar implantation and dose distribution on the treatment planning system. **B)** Three-dimensional image of the tumor on the computerized radioactive treatment planning system. **C)** A dose-volume histogram of the tumor and surrounding organs on the treatment planning system

Follow-up

Tumor response was evaluated after 4 weeks for the first time and every 2-3 months thereafter. Disease status was assessed by physical examinations, liver function tests, and complete blood and platelet counts. Disease progression was determined by imaging analyses, including CT scans and, for some patients, positron emission tomography/CT scans. The follow-up time was measured from the date of seed implantation. The median follow-up period was 41.5 months (range, 7-74 months). Complications were scored using the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORCT) Late Radiation Morbidity Score [11]. A modified Response Evaluation Criteria in Solid Tumors (RECIST) system was used to assess the initial response to treatment, as described previously [12,13] (Table 2). Patients were evaluated for initial response rate, time to progression, and overall survival.

Data collection and statistical analysis

This study aimed to determine the outcomes of CTRISI treatment for pulmonary metastases and to evaluate the prognostic variables that were predictive of outcomes. Information were collected on patient demographics, tumor characteristics, and treatment. The prognostic variables evaluated were cell type, approach (CTRISI alone or combined with surgical resection), metastasis size, metastasis number, disease-free interval from primary treatment to first metastasis at any site, disease-free interval from primary treatment to lung metastasis, age, and sex. The primary endpoints were clinical response rate, PFS, and OS. Overall survival was calculated as the time interval between the date of the operation and the date of death, and it was censored at the last follow-up date, if a patient was still alive. The PFS was calculated as the time interval between the date of the operation and the date of any progression or death. For patients who remained alive and progression-free, PFS was censored at the last follow-up date when the patient was known to be progression-free. OS and PFS were estimated by the Kaplan-Meier method using the Statistical Package for Social Sciences 16.0 software program for Windows (SPSS 16.0; IBM Corp., Armonk, NY, USA). The log-rank test was used to assess the associations between OS, PFS, and categorical variables, such as primary cancer cell type, approach, nodal disease, and site of first metastasis. A univariate Cox regression model was used to assess the association between OS, PFS, and continuous variables, such as age, the disease-free interval between the primary treatment and the date of first recurrence, the disease-free interval between the primary treatment and treatment of lung metastases, the size of the largest lesion, the site of first metastasis, and sex.

Results

Response

Initial responses were determined using the modified RECIST criteria. An initial complete response was observed in 5 patients (10%), a partial response was observed in 18 patients (36%), stable disease was observed in 15 patients (30%), and progression disease was observed in 10 patients (20%). Two patients (4%) were not evaluable. Early progression occurred in 5 patients (10%). Typical cases are shown in Figures 2-5.

Analysis of survival and progression

Six patients were alive after a median follow-up of 41.5 months (range, 7-74 months). The median OS for all patients was 42.1 months (95% confidence interval [CI], 26.6-53.4), and the estimated 1-, 3-, and 5-year OS rates were 88.0%, 58.0%, and 26.7%, respectively (Figure 6). During follow-up, 38 patients died in total, with 30 cancer-related deaths, 4 non-cancer-related deaths, and 4 undetermined causes of death. Progression to any site occurred in 72% of patients during follow-up, and the median PFS was 30.3 months (95% CI, 12.4-39.6 months). For the 2 patients whose treated lesions progressed locally, resections were performed.

Analysis of prognostic factors associated with survival and progression

We analyzed the following variables associated with OS and PFS: size, number of metastases, disease-free interval to first recurrence at any site and that to lung recurrence specifically, approach (CTRISI alone or CTRISI as an adjuvant to surgical resection), primary cell type, single or multiple lesions, site of first metastasis, age, and sex.

Size (≤ 3 cm vs. > 3 cm) was a significant predictive factor for both OS and PFS ($p < 0.05$). The median survival for patients with lesion diameters ≤ 3 cm was 60.0 months (95% CI: 47.9-72.1 months), compared with 32.0 months (95% CI: 16.0-47.8 months) for patients with lesion sizes > 3 cm ($p = 0.001$). Similarly, PFS was prolonged in patients with a lesion smaller than 3 cm. When considering all sites, the median overall PFS for patients for whom the largest lesion was ≤ 3 cm was 39.0 months (95% CI: 31.0-47.0 months), compared with 10.0 months (95% CI: 5.6-14.3 months) for patients with lesions > 3 cm ($p = 0.001$) (Figures 7 and 8).

Differences in OS and PFS were not significant when patients who were treated with CTRISI alone were compared with patients who were treated with surgery and adjuvant CTRISI. The median OS times were 39.0 months (95% CI: 25.4-52.6 months) and 46.0 months (95% CI: 25.6-66.4), respectively ($p = 0.334$). The median PFS times were 20.0 months (95% CI: 7.3-32.7 months) and 40.0 months (95% CI: 5.2-74.8 months), respectively ($p = 0.227$). No significant differences were noted when disease-free interval, approach, primary cell type, single vs. multiple lesions, site of first metastasis, age, or gender were analyzed. The analyses of associations between individual variables and OS or PFS are summarized in Table 3.

Complications

All approaches were shown to be safe and without serious complications, such as pneumothorax, hemothorax, displacement of 125I, fever, and leucopenia. Pneumotho-

rax occurred in 4 patients, with an incidence of 8%. Two of those patients required intraoperative suction, and the other 2 patients underwent closed-chest drainage. Hemothorax occurred in 2 patients, with an incidence of

4%. The symptoms disappeared after 3 days of hemostatic treatment. The ^{125}I radioactive seeds shifted and fell for 2 patients. In 1 patient, 2 seeds were removed due to hemoptysis, and in the other patient, seeds shifted to nor-
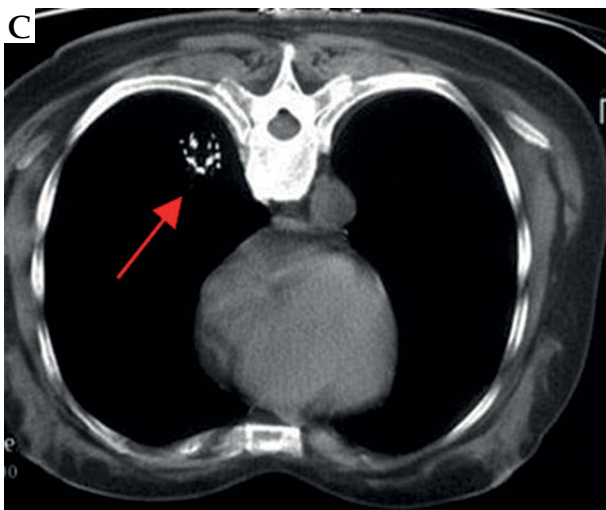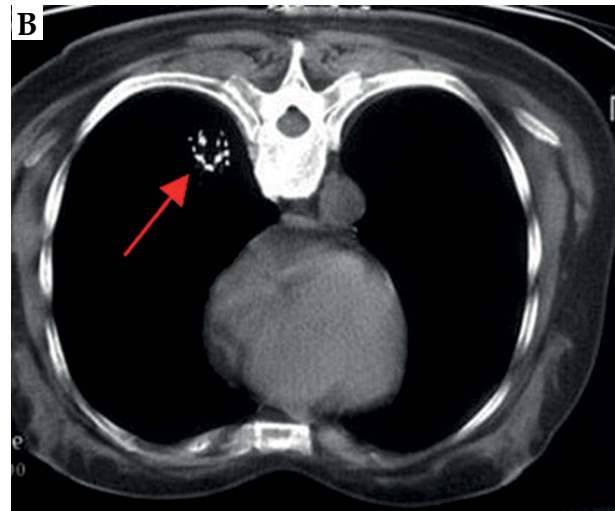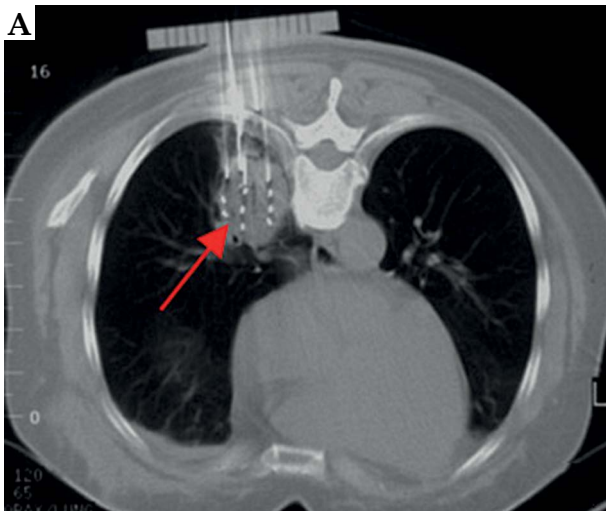
Fig. 2. Example case of post-operative ovarian cancer. A) Post-operative ovarian cancer 1 year after pulmonary metastasis, as indicated by the arrowhead. B) During brachytherapy, an applicator was accurately inserted into the tumor to implant ^{125}I seeds. C) Six months after brachytherapy, the tumor had disappeared, leaving only well-distributed radioactive seeds, as indicated by the arrowhead
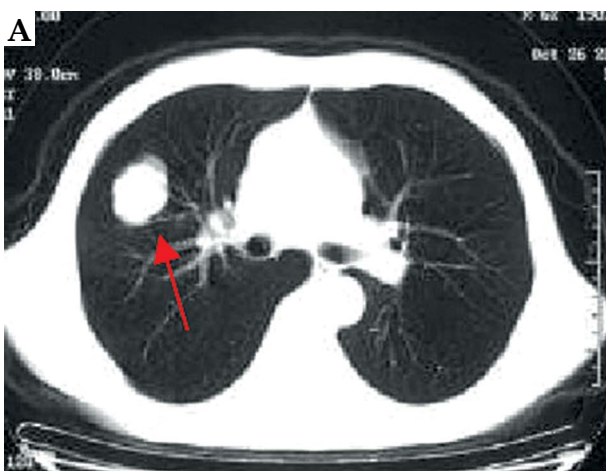
Fig. 3. Example case of post-operative gastric cancer. A) Post-operative gastric cancer 1 year after pulmonary metastases, as indicated by the arrowhead. B) Six months after brachytherapy, the tumor had disappeared, leaving only well-distributed radioactive seeds, as indicated by the arrowhead
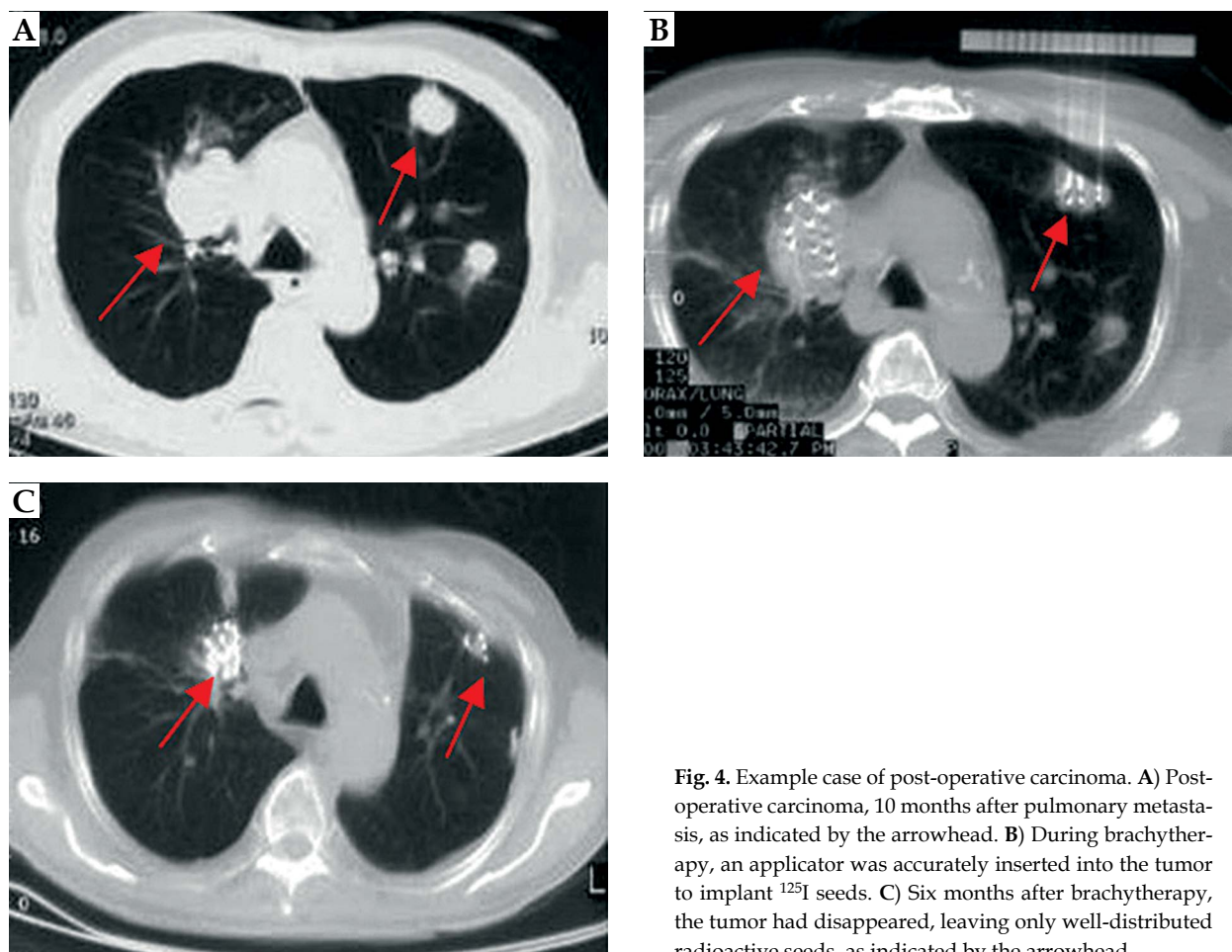
Fig. 4. Example case of post-operative carcinoma. **A**) Post-operative carcinoma, 10 months after pulmonary metastasis, as indicated by the arrowhead. **B**) During brachytherapy, an applicator was accurately inserted into the tumor to implant ^{125}I seeds. **C**) Six months after brachytherapy, the tumor had disappeared, leaving only well-distributed radioactive seeds, as indicated by the arrowhead

mal lung tissue or softer tissues during needle withdrawal, without symptoms and without clinical treatment. Fever occurred in 3 patients who all had temperatures below 38.5°C. Grade 1 toxicities occurred in 2 patients, and grade 2 toxicity occurred in the other patient, with symptoms disappearing after 1 day of treatment. Leucopenia occurred in 2 patients with grade 1 toxicities. No patients died of perioperative complications or late RTOG grade 4 or 5 complications (Table 4). One out of 50 patients was found to have a radioactive ^{125}I seed migrated to the right ventricle after one month.

Discussion

Pulmonary metastasis is common in the clinic. This is because negative pressure in the chest and the large numbers of capillary beds make the pulmonary circulation a low-voltage system, leading to a slower blood flow that allows tumor cells from other parts of the body to remain in the lungs. This makes the lungs the most common site of metastasis. Malignant tumors from many primary sites metastasize to the lungs via hematogenous spread, lymphatic spread, or direct invasion from adjacent organs.

CTRISI, stereotactic body radiation therapy (SBRT), microwave ablation, cryoablation, and radiofrequency ablation are minimally invasive treatments that are developing rapidly. Only patients with small and oligonodular pulmonary metastatic lesions that are favorably located without hilar or mediastinal nodal involvement or extrathoracic involvement are candidates for these methods [14]. SBRT is an emerging treatment modality that can potentially result in local control and long-term OS [15]. It allows the administration of a single large radiation dose to the tumor with better positioning precision, in comparison with conventional radiotherapy. However, the negative impact of breathing on precision is inevitable. In this respect, CTRISI is more precise than SBRT. Hence, many inoperable or reluctant patients become candidates for CTRISI.

CTRISI, a recently developed technology for the treatment of pulmonary metastases, has the following major benefits: direct delivery of high-dose radiation to the tumor (range, 140-180 Gy), with a very sharp fall off outside the implanted target area, continuous dose delivery, and a short overall treatment duration [16,17]. Permanent, low-energy radioactive seed implants offer three potential advantages: 1. high-dose gradients are available at tumor-normal tissue interfaces; 2. continuous radiation increases the probability of damaging malignant cells during a vulnerable phase of the cell cycle; and 3. continuous low-dose irradiation from low-energy sources is effective against the hypoxic components found in rapidly dividing cell populations [18,19].
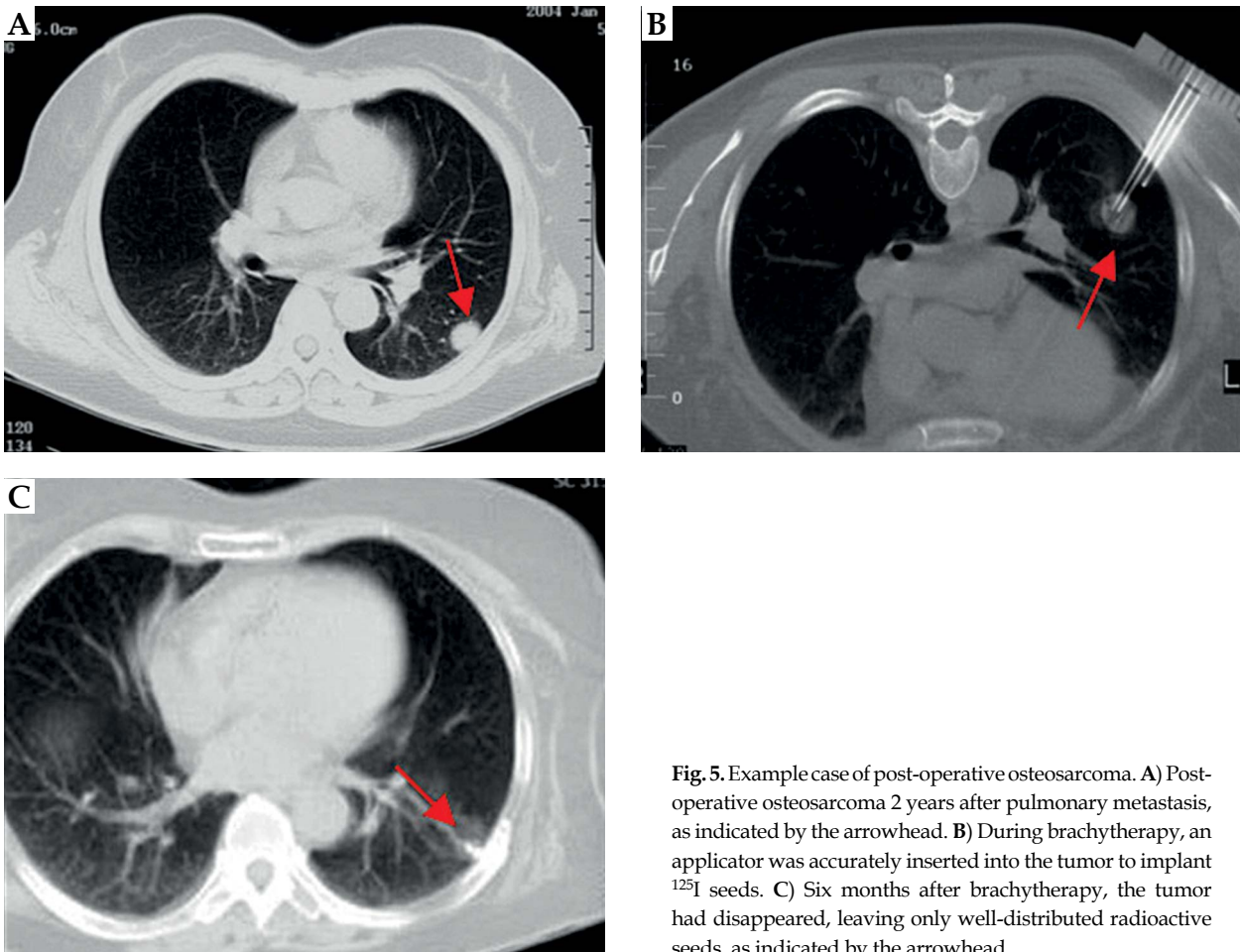
Fig. 5. Example case of post-operative osteosarcoma. **A)** Post-operative osteosarcoma 2 years after pulmonary metastasis, as indicated by the arrowhead. **B)** During brachytherapy, an applicator was accurately inserted into the tumor to implant ^{125}I seeds. **C)** Six months after brachytherapy, the tumor had disappeared, leaving only well-distributed radioactive seeds, as indicated by the arrowhead
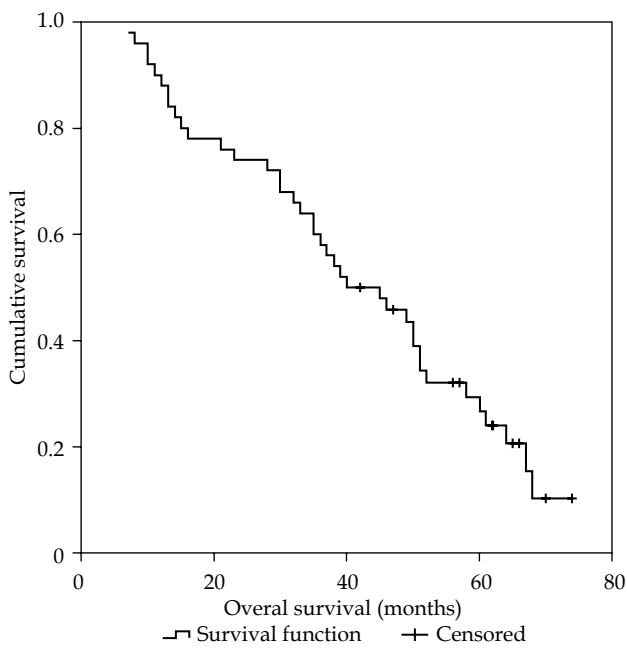
Fig. 6. Kaplan-Meier estimates of the overall survival of all patients after ^{125}I seed implantation
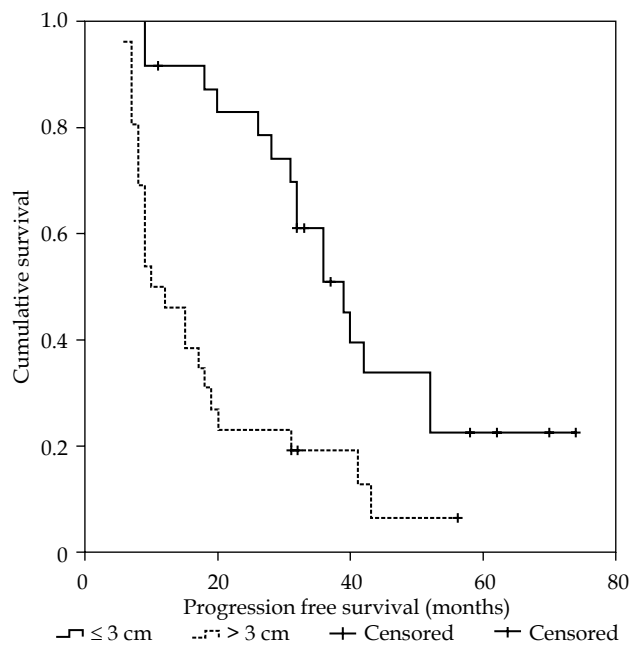
Fig. 7. Overall survival according to the size of the resected tumor

Complete resection is a good prognostic indicator for patients with pulmonary metastases [3]. However, it cannot be achieved in many patients. Therefore, CTRISI may be used in combination with surgical resection as a feasible approach for patients with lesions that are not resectable. In this study, 5 patients received CTRISI as an adjuvant to parenchyma-sparing surgical resection. This may be applicable for patients who have lesions located in both lungs or inside a single pulmonary lobe. CTRISI as an adjuvant may reduce tumor size and preserve normal lung tissue as much as possible. Furthermore, in the International Registry of Lung Metastases study, recurrence occurred in 53% of patients after a median duration of 10 months [2]. In about 22.5% of patients, metastatic lung recurrence was detected despite complete resection of pulmonary metastatic foci during the initial surgery [20]. The morbidity associated with multiple thoracotomies is higher, and about 22.5% of patients may present again with recurrent disease even after an additional thoracotomy [10]. Because many of the patients with recurrence are unable to tolerate an open thoracotomy again, CTRISI may offer an alternative treatment.

In the present study, the overall median survival was from 35 to 56 months after lung metastasectomy. The 5-year survival rates of patients were 29-94% [2,21,22,23]. Recently, Zhang *et al.* [9] reported results of 27 patients with hepatocellular carcinoma who underwent CTRISI treatment for pulmonary metastases. The patients were followed for 6-48 months (mean, 20.1 ± 2.2 months), and the OS rates 1 and 2 years after treatment were 67% and 30.8%, respectively, with a median survival of 13.5 months. Survival rates after pulmonary metastasectomy depend on the primary tumor type [24]. The range of OS times after SBRT was 12-40 months [9,25,26,27], and the median PFS time was 10 months [25]. The 1- and 3-year survival rates were 56-85% [9,25,26,27,28] and 40.8-63% [26,29], respectively. Our research showed that the median OS for all patients was 42.1 months (95% CI: 26.7-53.4 months), and the estimated 1-, 3-, and 5-year survival rates were 88.0%, 58.0%, and 26.7%, respectively, which were higher than those in other publications. Furthermore, the
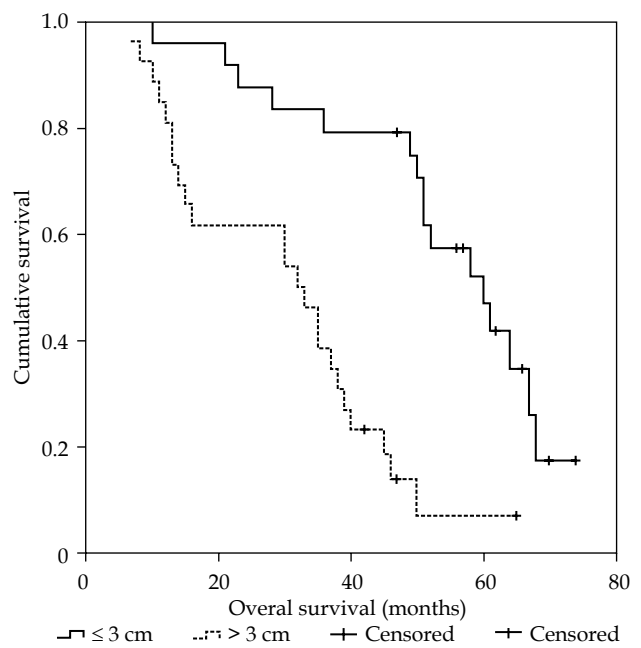

Fig. 8. Progression-free survival according to the size of the resected tumor

median PFS time was 30.3 months. Our results are better than those in the literature. External radiation therapy has been shown to cause radiation pneumonitis in 27% of patients [30]. However, our research showed that radiation therapy was safe without serious complications.

In addition to complete resection, other prognostic factors have been examined after surgical resection of pulmonary metastases [4,5]. Zabaleta *et al.* [22] reported the outcomes of 178 patients who underwent resections for lung metastases. Age, disease-free interval, nodule number, and nodule size were significant predictors of patient outcomes. Pennathur *et al.* [31] reported that lesion size was an important prognostic variable associated with overall and disease-free survival. This study showed that size was a significant predictor of both OS and disease-free survival. The median OS was 39 months for patients with

Table 3. Analysis of prognostic factors: association between overall survival and progression-free survival

Factor	Number of patients	*p* value	
		OS	PFS
Age (≤ 60 vs. > 60 y)	(16 vs. 34)	0.072	0.085
Sex (male vs. female)	(31 vs. 19)	0.139	0.109
Largest size of lesion* (≤ 3 vs. >3 cm)	(27 vs. 23)	0.000	0.000
Number of lesions (≤ 2 vs. > 2)	(22 vs. 28)	0.269	0.131
Number of treatment (≤ 1 vs. > 1)	(44 vs. 6)	0.097	0.292
Approach (CTRISI alone vs. CTRISI + thoracotomy)	(45 vs. 5)	0.334	0.227
Cancer type (colon vs. others)	(10 vs. 40)	0.095	0.092
Disease-free interval to metastases to the lung	(24 vs. 26)	0.056	0.036

Statistically significant (p < 0.05).
OS – overall survival, PFS – progression-free survival, CTRISI – computed tomography guided implantation of ^{125}I radioactive seeds

Table 4. Radiation-related acute and late complications

Grade	Grade 0	Grade 1	Grade 2
Acute complications			
Fever	47	2	1
Leucopenia	48	2	0
Late complications			
Lung	47	2	1
Subcutaneous tissue	48	2	0

lesions ≤ 3 cm, compared with 10 months for patients with lesions > 3 cm. There was no significant association between survival and primary focal pathologic types, site of first metastasis, disease-free interval, or number of metastases. However, the absence of significant associations may have been due to the small number of patients.

The combination of surgical resection and CTRISI as a therapeutic method is of interest to thoracic surgeons. Minimal data have been reported on the intermediate-term results of CTRISI combined with surgical resection. In addition, this study followed patients for one of the longest time periods (median, 41.5 months) to have been reported on CTRISI treatment of pulmonary metastases. This information may lead to better patient selection and prospective studies with the development of protocols for larger lesions, such as combining CTRISI with SBRT, microwave ablation, cryoablation, radiofrequency ablation or adjuvant therapy, or both, in these patients.

Our study, however, has limitations that are inherent to retrospective studies, such as selection bias. The patients with metastatic disease who were treated in this study had a variety of primary tumor types. An analysis of a larger sample is required to assess the time-to-event data more accurately. Several factors should be further examined, including optimal patient selection methods as well as the roles of combination therapy or adjuvant therapy.

Conclusion

Percutaneous interstitial permanent implantation of ^{125}I seeds is a feasible and promising minimally invasive salvage modality for patients with pulmonary metastases. This treatment has been proven to be safe and less time consuming. Our study included a limited number of cases and had a short follow-up time. Therefore, in order to reach definitive conclusions, it is necessary to perform further studies with large numbers of patients and long-term follow-up.

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Disclosure

The authors report no conflict of interests.

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