Comparison of clinical efficacy and complications of $^{125}$I seed brachytherapy and stereotactic body radiation therapy for recurrent pulmonary metastases from colorectal carcinoma

Jie Li, MD, PhD*, Lijuan Zhang, MD, PhD†, Qigen Xie, MD, Weiguo Wang, MD, PhD, Yan Yan Hua, MD, Zongqiong Sun, MD, PhD*†

1Department of Interventional Radiology, the Affiliated Hospital of Jiangnan University (Wuxi 4th People’s Hospital), Jiangsu Province, Wuxi, China
2Department of Radiology, Wuxi People’s Hospital, Nanjing Medical University, China
3Department of Radiology, the Affiliated Hospital of Jiangnan University (Wuxi 4th People’s Hospital), Jiangsu Province, Wuxi, China
*The authors contributed equally to this work.

Abstract

Purpose: To evaluate the efficacies of $^{125}$I seed implantation and stereotactic body radiation therapy (SBRT) in treatment of recurrent lung metastases from colorectal cancer, to compare the tolerance of lung tissue to both forms of radiotherapy, and to analyze the factors that affect the prognosis.

Material and methods: According to treatment received, thirty colorectal cancer patients with post-operative lung metastases were separated into two groups: $^{125}$I seed implantation group (group A; $n = 16$) and SBRT group (group B; $n = 14$). Patients were followed up, and local control rate, survival, and post-operative complications were analyzed retrospectively. Kaplan-Meier method was used for survival analysis. Cox proportional hazards model was used to identify the independent predictors of poor prognosis.

Results: Survival was significantly different between group A and group B (median survival, 15 months and 11.5 months, respectively; $p = 0.015$). Local control rates at the first, third, sixth, and twelfth months after treatment were all $> 80\%$, with no significant difference between the two groups ($p = 0.829$). Significant differences were seen between the two groups in the number of treatments received ($p = 0.009$) and the incidence of radiation pneumonitis ($p < 0.001$) as well as radiation-induced pulmonary fibrosis ($p = 0.005$). On multivariate regression analysis radiation pneumonitis was an independent predictor of poor prognosis (HR = 3.356, 95% CI: 1.518-7.421; $p = 0.003$).

Conclusions: $^{125}$I seeds brachytherapy and SBRT are both effective for control of lung metastases but the former causes milder lung tissue damage. It can be repeated after short intervals, and appears to be a safe and efficient treatment for lung metastases.

J Contemp Brachytherapy 2018; 10, 4: 360–367
DOI: https://doi.org/10.5114/jcb.2018.77956

Key words: $^{125}$I seed, colorectal cancer, efficacy, lung metastasis, SBRT, survival analysis.

Purpose

Cancer is the second leading cause of death in China. According to the 2011 national statistics reported by the National Central Cancer Registry (NCCR), colorectal cancer is the fifth most common cause of cancer-related death [1]. At least 50% of patients with colorectal cancer will ultimately suffer distant metastases, and 5-25% of patients will have metastases to the lungs [2]. Metastasis to the lungs or its recurrence indicates failure of systemic control of the tumor and poor prognosis.

Recurrent lung metastasis of colorectal cancer has been treated with repeated resection with some degree of success [3,4]. With currently available minimally invasive treatments, it has now become possible to control recurrent lung metastases by local treatment and to delay the emergence of end-stage symptoms. In recent years, three-dimensional stereotactically guided local treatments such as radiofrequency ablation, stereotactic body radiation therapy (SBRT), and $^{125}$I seed implantation, have achieved good results in the treatment of pulmonary metastases [5,6,7,8,9,10,11,12].

Address for correspondence: Jie Li, MD, PhD, Department of Interventional Radiology, the Affiliated Hospital of Jiangnan University (Wuxi 4th People’s Hospital), Wuxi, China, phone: +86 0510 8868 2207, e-mail: lj1982020@126.com

Received: 15.03.2018
Accepted: 02.08.2018
Published: 31.08.2018
Classical SBRT is effective for local control of tumor but, when applied in the lung, it can cause radiation pneumonitis; SBRT is limited by the fact that the treatment cannot be repeated in the short term [13]. In comparison, \(^{125}\)I seeds implantation brachytherapy is a safe and efficient method for treatment of lung metastases. The radioactive seeds implanted into the lesion by precision puncture kill tumor cells by continuous irradiation but cause little radiation injury to adjacent lung tissue. Furthermore, the implantation can be repeated in short term, without adverse impact on lung function [14]. However, the clinical efficacies of \(^{125}\)I seeds brachytherapy and SBRT, and the prognosis following treatment with these methods, has not been fully studied.

The aim of this follow-up study was: 1. to compare the clinical efficacies of \(^{125}\)I seeds implantation and SBRT in the treatment of recurrent lung metastases from colorectal cancer; 2. to determine the incidence of radiation-induced lung injury in adjacent lung tissue; 3. to identify the factors affecting survival.

Material and methods

Patients

A total of 30 patients (20 men and 10 women; mean age, 61.80 ± 10.07 years) with recurrent lung metastases after resection of colorectal cancer, treated in our hospital from June 2013 to December 2016, were enrolled for this retrospective study. Patients were separated into two groups according to the treatment received: group A (n = 16) received \(^{125}\)I brachytherapy, and group B (n = 14) received SBRT.

Patients were eligible for inclusion in the study if they had biopsy-confirmed, recurrent simple pulmonary metastasis after colorectal cancer resection and had refused lung metastases surgery. Patients were excluded if they had: 1. metastasis to any other organ; 2. chronic empyema after resection of colorectal cancer; 3. Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 3; 4. Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 3.

The included patients were all diagnosed with pulmonary metastasis by computed tomography (CT) scan 7-19 months (mean, 11.80 ± 3.73 months) before the start of \(^{125}\)I brachytherapy or SBRT. In all cases, diagnosis was confirmed by CT-guided needle biopsy. All patients received 8-12 cycles of FOLFOX treatments before \(^{125}\)I seed implantation or SBRT treatment. Table 1 shows the baseline data of the two groups. Patients were followed up for a period of 8-23 months. Clinical and survival data were collected from the case records and by patient interview. The study protocol was approved by the ethics committee of our university.

Therapeutic protocol

\(^{125}\)I seeds implantation brachytherapy

Instruments and equipment

Gun-type \(^{125}\)I seed implants (Model-6711) were supplied by Atom-Hitech Limited (HTA Co. Ltd., China). The radioactive particle implantation treatment system (KL-SIRPS-3D) was provided by the Beijing Institute of Medical Science and Technology. The 18 G puncture needles were from Cook Medical, Bloomington, IN, USA. The 16-slice CT scanner was from Siemens, Germany. \(^{125}\)I seeds were tested for activity by the nuclear medicine specialist at the hospital, and then packaged into clips and sterilized by autoclaving. The Ag rod with \(^{125}\)I was mounted in the titanium tube and sealed at both ends. The length of the rod was 4.50 ± 0.3 mm and the external diameter was 0.80 ± 0.03 mm. The half-life of \(^{125}\)I seed was 59.6 days. Electron capture decay is accompanied by characteristic X-rays and internal conversion electrons. The electrons are absorbed by the titanium wall of the sealed \(^{125}\)I seed source. The predominant Te-KX characteristic X-rays are 27.4 and 31.4 keV, and γ-rays of 35.5 keV. The tissue penetration of \(^{125}\)I was only 1.7 cm.

Therapy process

Before the implantation, the CT data was inputted to the particle implantation treatment planning system (TTPS, BT-RSI; Yuan Bo, Beijing, China), which then delineated the target region, calculated the prescription dose and number of puncture needles, planned the puncture path, measured needle insertion depth, and calculated the total number of seeds that needed to be implanted. The treatment plan was implemented by a radiotherapy physician and a radiologist after they had first delineated the gross tumor volume (GTV), planning target volume (PTV), and adjacent vital organs (spinal cord, pulmonary artery, bronchus, etc.) on each CT image. A 5 mm margin was added to the GTV to create PTV, as has been recommended in earlier studies [12,14,15].

All seed implantations were performed by experienced radiologists. During seeds implantation, patient position was determined according to the location of the lung metastases. The patient was asked to breathe calmly during the procedure. According to the preoperative CT examination results, the body surface location was marked, and the patient was secured. A 3 mm thickness of the tumor target area was then scanned. The range of needle arrangement and the number of puncture points were determined after taking into consideration the CT scan positioning line and the body surface markers. The spacing between puncture points was set to 1 cm. After local anesthesia with 2% lidocaine, the 18 G puncture needles were inserted up to depths of 20 cm, according to the preoperative plan, until the tip was at the distal edge of the PTV. Depth of insertion and needle tip position were checked with CT and adjusted as needed. The seeds were implanted one at a time, with a distance of 0.5-0.8 cm between seeds. In principle, the implanted seeds should be equidistant from one another in order to achieve a uniform three-dimensional irradiation of the tumor. After implantation of the seeds, the CT images were transferred to the planning system for verifying the dosage, and assessing the dose distribution to the tumor area and the surrounding normal tissue. The aim was to ensure that the total activity of the implanted seeds reached the prescription dose of the treatment plan, giving an equal dose curve.
with a matched peripheral dose of 135 Gy (130-145 Gy). In terms of metrological requirements, a PTV of 90% ($D_{90}$) was 100-160 Gy for $^{125}$I seeds, with activity of 25.9 MBq. If the dose requirements were not met, additional seeds were implanted.

Our previous clinical experience has shown that the prescription dose for implantation therapy of intrapulmonary metastatic tumor is 135 Gy (120-150 Gy) on average. The 16 patients in group A had a total of 40 metastatic lesions, with a mean of 2.5 ± 0.63 (range, 2-4) lesions per patient. Implantation treatment was performed 36 times in all, which was 2.25 ± 0.45 times (range, 2-3 times) per patient. A total of 960 seeds were used, with an average of 24 (range, 10-50) seeds per lesion. Mean $D_{90}$ for $^{125}$I seeds implantation brachytherapy was 130 Gy.

### SBRT therapy

**Instruments and equipment**

The equipment used included medical linear accelerator (Synergy; Elekta, Sweden) equipped with CBCT, treatment planning system (XiO version 4.7; Elekta, Sweden), medical simulation positioning machine (LX-40A; Toshiba, Japan), two-dimensional ionization chamber.
Therapy process

The patient was positioned with arms raised above the shoulder and fixed with a chest grid membrane, and the three-dimensional activity of lung metastases was measured using a simulator. Subsequently, the activity of lung metastases was measured using the dual-energy subtraction technique. For example, in any one direction the thickness of the metastasis was > 5 mm, a gated breath-hold technique was used. CT of the tumor area was acquired with thickness of 2.5 mm and layer spacing of 2.5 mm, and the images were transferred to the TPS system through the local area network. For active metastasis, radiotherapy was administered to an extra 5 mm margin in the left-to-right direction and an extra 6 mm margin in the anteroposterior direction.

Radiotherapy was administered by one of two experienced radiotherapists. All the programs used five fields of static IMRT, DT 50 Gy/4 fx/2 W, 2-3 times/week. More than 95% of the PTV meeting the prescription dose, 90% prescription isodose lines completely cover PTV. The maximum dose point in the target area within 10%, strictly controlled lung $V_{5} \leq 55\%$, $V_{20} \leq 20\%$. The radiation exposure of important organs such as heart and spinal cord was controlled in the normal range. Fourteen patients in group B had a total of 33 metastatic lesions. SBRT was performed 23 times in all, which was $1.71 \pm 0.47$ times per patient (range, 1-2 times).

Follow-up and efficacy evaluation

Follow-up was for 8-23 months (mean, 13.03 ± 3.79 months). The study was terminated in February 2017. The survival time was calculated as the time from acceptance of pulmonary metastases treatment to last follow-up or death. Enhanced CT of the chest was performed at the end of the first, third, sixth, and twelfth months after start of treatment for evaluating the maximum diameter of the metastatic lung lesions, checking for new lesions, and assessing radiation-induced lung injury. The local control rate of lung metastases was calculated according to the modified response evaluation criteria in solid tumors (mRECIST) [16]. Radioactive lung injury was evaluated according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE 4.0) [17].

Statistical methods

Data were expressed as means ± standard deviation. The group $t$ test was used to compare the differences in age, metastatic tumor diameter, lung metastasis time, and the number of metastatic tumors. The Mann-Whitney U test was used to compare non-normally distributed continuous data. Kaplan-Meier method was used to analyze survival rates. Survival rates of the two groups were compared with the log-rank test. Cox regression model (proportional hazards model) was used for multivariate regression analysis of factors associated with survival. Variables that were found to be statistically significant on Kaplan-Meier analysis were entered into the Cox regression model. The screening for variables independently associated with survival was performed using multivariate analysis, based on the forward law of partial maximum likelihood estimation (forward: LR). All statistical tests were two sided, and $p \leq 0.05$ was considered statistically significant. GraphPad prism, version 5 (Graphpad Software Inc., San Diego, CA, USA) was used for graphing. SPSS for Windows, version 20 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Results

The study included 30 patients, age ranging 41-81 years (mean age, 61.80 ± 10.07 years). There were 20 men (mean age, 61.80 ± 8.13 years; range, 47-80 years) and 10 women (mean age, 61.80 ± 13.67 years; range 41-80 years). There were no significant differences between group A and group B patients in the baseline characteristics (Table 1). In group A, there were 3 patients with two lung metastases treated by single seeds implantation. In group B, there was 1 patient with two lung metastases located close to each other; this patient was treated with disposable SBRT.

The mean diameter of the pulmonary metastases was comparable in the two groups. In group A, all 40 pulmonary metastases were treated. In group B, there were 33 pulmonary metastases in all, of these 24 metastases were treated with 23 sessions of SBRT. Radiation-induced lung injury was associated with the size of the metastatic lesion. The risk of grade 3 radiation pneumonitis was significantly higher when lesion diameter was ≥ 2 cm (Figure 1).

Comparison of efficacy and tolerability

In group A, seeds implantation therapy was well tolerated by all patients. In group B, SBRT had to be discontinued after two sessions in all patients, because of radiation-induced lung injury. These patients subsequently received only symptomatic and supportive care (Figure 2). Local control rates at the first, third, sixth, and twelfth months were > 80% in both groups, without significant differences between the two groups ($p = 0.829$). In group A, some patients underwent seeds implantation up to four times, showing that the treatment with seed implantation can be repeated at short intervals. In group B, SBRT treatment could only be administered twice, due to the occurrence of radiation-induced lung injury. The incidence and severity of lung injury were both significantly higher in group B than in group A (Figure 3 and 4).

There were significant differences between the two groups in 1. the number of treatments received ($p = 0.009$); 2. the incidence of radiation-induced lung injury, including radiation pneumonitis ($p < 0.001$); and 3. the incidence of radiation-induced pulmonary fibrosis ($p = 0.005$).

Survival analysis and Cox regression analysis of factors influencing survival

Non-parametric Mann-Whitney test showed significant difference between group A and group B patients.
in survival time (median survival, 15 months and 11.5 months, respectively; \( p = 0.015 \); Figure 5) but not in the local control rate (\( p = 0.829 \)) (Table 2). The log-rank test showed significant difference in survival between group A and group B patients (\( p = 0.027 \)).

Kaplan-Meier analysis revealed that the number of repeat treatments and the occurrence of radiation pneumonitis and radiation-induced pulmonary fibrosis were significantly associated with survival (\( p < 0.05 \)). On multivariate regression analysis, radiation pneumonitis was an independent predictor of poor prognosis (HR = 3.356, 95% CI: 1.518-7.421; \( p = 0.003 \)).

Major post-operative complications

The treatments of all 30 patients were successfully completed. In group A, skin puncture for seeds implantation caused minor bleeding that was easily controlled. Four patients developed pneumothorax following seeds implantation but loss of lung volume was < 30%. These patients were successfully treated with bed rest and supplemental oxygen. Ten patients had cough and hemoptysis 3 days after the procedure; all improved after treatment with hemostatic drugs and antibiotics. No mediastinal, subcutaneous, or intravascular migration of seeds occurred.

Fig. 1. Graph showing the diameters of all 73 lung metastases. A) The mean diameters of the metastases in the two groups were not significantly different. B) The risk of radiation pneumonitis increases with the increase in lesion diameter; the risk of grade 3 radiation pneumonitis is significantly higher when lesion diameter is ≥ 2 cm.

Fig. 2. A 78-year-old woman had colon cancer resection. One year later, a metastatic lesion was found in the right upper lung. She was first treated with stereotactic body radiation therapy (SBRT). The top row shows the computed tomography (CT) images (a) before radiotherapy; (b) 4 months after SBRT; (c) 11 month after SBRT. Six months later, new lung metastatic nodules were found in the right lower lobe. SBRT could not be used because of radiation pneumonitis in the upper lobe of the right lung. Therefore, \( ^{125} \)I seeds implantation was applied. The lower row shows the CT images (A) before treatment, (B) 2 months after treatment, and (C) 6 months after treatment. \( ^{125} \)I seeds implantation and SBRT are both effective for control of lung metastases. However, the risk of radiation-induced lung injury is considerably lower with \( ^{125} \)I seed implantation.
seeds was observed. In group B, 11 patients developed cough with expectoration 3 months after radiotherapy. At 6 months after radiotherapy, the cough had subsided in 3 patients, but 8 patients had persistent cough and needed treatment with intravenous dexamethasone and antibiotics.

Discussion

Minimally invasive treatment is being increasingly accepted by patients. In addition, most doctors and patients favor the concept of retaining organs as far as possible. In this study, both $^{125}$I seed implantation brachytherapy and the SBRT were found to be effective for local control of lung metastases. However, $^{125}$I seed implantation treatment caused relatively slighter radiation-induced lung injury. Furthermore, it can be repeated at short intervals and is the better option for treatment of recurrent pulmonary metastases.

Filippi et al. [18] found that SBRT for lung metastases of colorectal cancer was better than surgical resection and indicated that it could replace surgical treatment. Trakul et al. [19] concluded that the occurrence of radiation pneumonitis could be reduced by decreasing the radiation dose but this would also decrease local control. Tochio et al. [20] and Crombe et al. [21] have reported that radiofrequency ablation is more effective than SBRT for local control of recurrent metastasis in the lungs.

In this study, earlier institution of treatment provided better control of metastases in both groups. When treatment is delayed, the tumor tends to be larger, and some amount of radiation lung injury is unavoidable irrespective of whether internal or external radiotherapy is used. Additionally, the larger the diameter, the more serious the radiation-induced lung injury. Owen et al. [22] treated patients with multiple or recurrent pulmonary metastases, and reported acute radiation pneumonitis and radiation-induced pulmonary fibrosis in 51% and 46% of patients, respectively. In the present study, patients treated with SBRT had different CTCAE 4.0 grades of radiation pneumonitis and radiation-induced pulmonary fibrosis. In addition, regression analysis showed that radiation pneumonitis is an independent risk-factor for poor prognosis.
Table 2. Treatment result

|                  | Radiation pneumonia (case) | Radiation-induced pulmonary fibrosis (case) | Local control rate of metastases |
|------------------|---------------------------|--------------------------------------------|---------------------------------|
|                  | Level 1 | Level 2 | Level 3 | Level 1 | Level 2 | Level 3 | 1 month | 3 months | 6 months | 12 months |
| Group A (\(^{125}\)I seed implantation) | 16 | 0 | 0 | 16 | 0 | 0 | 0.83 | 0.90 | 0.85 | 0.80 |
| Group B (stereotactic body radiation therapy) | 3 | 8 | 3 | 2 | 10 | 2 | 0.86 | 0.89 | 0.83 | 0.81 |
| \(p\) value     | < 0.0001 | 0.0051 | 0.83 |

The local control rate was calculated as complete response + partial response/total. The evaluation of local control was based on RECIST. The evaluation of radioactive lung injury was according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE4.0).

The process of seeds implantation and the precautions to be taken have been described in our earlier work. Larger and continuous dose of radiation is delivered with seeds implantation therapy. In this study, the prescription dose in group A was 135 Gy (120-150 Gy) and the matched peripheral dose of the implant was 135 Gy (130-145 Gy). In group B, the total dose of SBRT was 50 Gy, delivered in 4 sessions over 2 weeks. Thus, radiation is considerably lower with SBRT and additionally, radiation exposure is not continuous. No statistically significant difference was seen in the local control rates and the median survival times between the groups, but that may have been due to the small sample size and the short follow-up. Previous research has shown that lesions treated with seeds implantation are effectively controlled and will not recur within 6 months [14].

Fig. 4. A 60-year-old man had recurrent right upper lung metastatic nodules 9 months after colon cancer resection and was successfully treated with \(^{125}\)I seeds implantation radiotherapy. The scout images (A0/B0/C0) acquired after seeds implantation (arrows). Computed tomography (CT) images of the chest at different levels show the right lower lung metastatic nodules (with diameters of 15/12/9 mm) before implantation. CT images 6 months after seeds implantation (A2/B2/C2) show disappearance of the metastatic nodules; residual artifact of the seed can be seen. CT images 10 months after seed implantation (A3/B3/C3) show small blurred areas around the seeds. A3 shows a recurrent pleural metastatic nodule (arrow) near the original one. Seeds implantation brachytherapy is being considered again for this recurrent metastatic nodule.

Fig. 5. The survival rate of group A patients was significantly better than that of group B patients.
We found a high incidence of minor complications such as post-operative hemoptysis and pneumothorax. These complications can be reduced by minimizing the number of punctures, ensuring that they are as far as possible from large vessels and trachea. In addition, previous experience has shown that both lungs should not be treated at the same time because of the danger of inducing bilateral pneumothorax [14,15].

Our study has some limitations. The sample size was small and only attempted to assess local control. Further, the follow-up period was short. Implantation of \(^{125}\)I seeds was used as a palliative measure to control local metastases; it could not control the general progression of tumors and most patients died during the follow-up period.

Conclusions

\(^{125}\)I seed brachytherapy and SBRT are both effective for control of lung metastases. However, radiation-induced lung injury limits the use of SBRT for recurrent metastases in the lungs. In contrast, \(^{125}\)I seed brachytherapy can be repeated at short intervals as it causes milder lung tissue damage. It appears to be a safe and effective treatment for recurrent pulmonary metastasis.

Acknowledgments

We are very grateful to Dr. Zou Qin-Zhou, Dr. Zhou Le-Yuan, and Dr. Zhou Jia-Liang for their help in the collection and analysis of the data of patients undergoing SBRT. We thank our anonymous reviewers and the editor for their valuable comments. We are also grateful to Science and Technology Development Project of Wuxi Hospital Management Center (YGM1123 to Jie Li), the Jiangsu Provincial Commission of Health and Family Planning (Q201615 to Jie Li), and Dr. Hou Rong-Yuan, and Dr. Zhou Jia-Liang for their help in the collection and analysis of the data of patients undergoing SBRT.

Disclosure

The authors report no conflict of interest.

References

1. Chen W, Zheng R, Zeng H. Annual report on status of cancer in China, 2011. Chin J Cancer Res 2015; 27: 2-12.
2. Gonzalez M, Ris HB, Krueger T et al. Colorectal cancer and thoracic surgeons: close encounters of the third kind. Expert Rev Anticancer Ther 2012; 12: 495-503.
3. Chen F, Sakai H, Miyahara R et al. Repeat resection of pulmonary metastasis is beneficial for patients with colorectal carcinoma. World J Surg 2010; 34: 2373-2378.
4. Kanzaki R, Higashiyama M, Oda K et al. Outcome of surgical resection for recurrent pulmonary metastasis from colorectal carcinoma. Am J Surg 2011; 202: 419-426.
5. Ridge C, Solomon SB. Percutaneous ablation of colorectal lung metastases. J Gastrointest Oncol 2015; 6: 685-692.
6. Yan TD, King J, Sjarif A et al. Percutaneous Radiofrequency Ablation of Pulmonary Metastases from Colorectal Carcinoma: Prognostic Determinants for Survival. Ann Surg Oncol 2006; 13: 1529-1537.
7. Jung J, Song SY, Kim JH et al. Clinical efficacy of stereotactic ablative radiotherapy for lung metastases arising from colorectal cancer. Radiat Oncol 2015; 10: 238.