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Effectiveness and Safety of CT-Guided ^{125}I Brachytherapy for Lung Metastasis from Hepatocellular Carcinoma

Yongxin Chen[1,2], Fei Gao[1,2*], Lin Chen[1,2], Sheng Peng[1,2], Yingjie Huang[1,2], Yao Wang [1,2]
[1]Department of Interventional Radiology, Sun Yat-sen University Cancer, Guangzhou, China
[2]State Key Laboratory of Oncology in South China, Guangzhou, China
Email: *sysugaofei@163.com

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ABSTRACT

To retrospectively evaluate effectiveness and safety of CT-guided ^{125}I brachytherapy in patients with lung metastasis from hepatocellular carcinoma, sixty lung metastatic lesions in 29 patients were percutaneously treated in 34 ^{125}I brachytherapy sessions. Each metastatic lesion was treated with computed tomographic (CT) guidance. Follow-up contrast material-enhanced CT scans were reviewed and the efficacy of treatment was evaluated. Months are counted from the first time of ^{125}I brachytherapy and the median duration of follow-up was 11 months (ranging from 6 - 17 months). The local control rates after 3, 6, 10 and 15 months were 86.2, 71.4, 60.9 and 50.0% respectively. At the time of writing, ten patients are alive without evidence of recurrence at 11 - 15 months. The 10 patients presented good control of local tumor and no systemic recurrence, and survived throughout the follow-up period. Other 11 patients died of multiple hematogenous metastases 5 - 15 months after brachytherapy. A small amount of local hematoma occurred in 5 patients that involved applicator insertion through the lung. Four patients presented pneumothorax with pulmonary compression of 30% - 40% after the procedure and recovered after drainage. Two patients had minor displacement of radioactive seeds. Severe complications such as massive bleeding and radiation pneumonitis did not occur. So CT-guided ^{125}I brachytherapy is effective and may be safely applied to lung metastasis from hepatocellular carcinoma.

Keywords: ^{125}Iodine; Brachytherapy; Lung Metastasis; Hepatocellular Carcinoma

1. Introduction

Hepatocellular carcinoma (HCC) is a very highly invasive tumor that metastasizes hematogenously and lymphogenously to distant sites. Most frequently affected sites are the lungs, regional lymph nodes, bones, and adrenal glands [1,2]. Since lung is the most common metastatic organ for hepatocellular carcinoma, lung metastasis is thus considered as a major prognostic factor for these metastatic patients. However, treatment of lung metastasis from hepatocellular carcinoma is usually challenging because the previous therapies (including surgery, chemoembolization, radiofrequency ablation, and various combinations of these treatments) limit the options available for subsequent treatment. ^{125}I brachytherapy has been widely applied for tumor treatment in clinic with significant efficacy providing promising results for local control of solid tumors such as prostate carcinoma, lung cancer, HCC, liver metastasis and pancreatic cancer [3-10]. When permanently implanted into the tumor, ^{125}I seeds send out continuous low-dose X-ray and γ-ray, leading to a dose of 160 - 180 Gy within the local tissue during the half-life of ^{125}I. The killing radius of ^{125}I seeds is 1.7 cm, with minimal effects on normal tissues since the radioactive energy is inversely correlated with the square of the radius [4]. The specific effect of ^{125}I radiation on tumor cells can efficiently inhibit the proliferation and repair of tumor cells, while the surrounding normal tissue only receives less than 25% of the doses received by the tumor cells [8]. The slow emission of radiation from the ^{125}I seeds also allows the surrounding normal tissue that receives sub-lethal or potentially lethal dose of radiation to have sufficient time for repair and recover [10].

However, there are few reports about the effects of lung metastasis with the methods of ^{125}I brachytherapy. We considered the possibility that it might be an alternative treatment for lung metastasis. Especially for patients whose condition is unsuitable for surgical resection, ^{125}I brachytherapy may provide an opportunity to achieve remission. This research retrospectively evaluated the cli-

*Corresponding author.

nical value of ^{125}I brachytherapy for lung metastasis from hepatocellular carcinoma.

2. Materials and Methods

2.1. Ethics

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved ethically by Sun Yat-sen University Cancer Center. All patients provided informed written consent.

2.2. Patients

From March 2005 to March 2012, twenty-nine patients underwent ^{125}I brachytherapy of lung metastasis from hepatocellular carcinoma. Twenty-two men and seven women (mean age, 59 years; range, 35 - 76 years) were enrolled in our study. All patients were pathologically proved as hepatocellular carcinoma. Treatment of the primary cancer were surgical resection in 16 patients, surgical resection combined with chemoembolization in 5 patients, radiofrequency ablation in 3 patients, and radiofrequency ablation combined with chemoembolization in 5 patients. The lung metastatic lesions was seen on computed tomographic (CT) images 6 - 13 months (mean, 9 months) after the first treatment of the primary cancer.

Our diagnosis was confirmed with pathologic proof at CT-guided needle biopsy before ^{125}I brachytherapy in all patients. The mean size of the lung metastatic lesions was 1.3 cm ± 0.7 (standard deviation) (range, 0.8 - 2.9 cm) in largest diameter. Our indication criteria for ^{125}I brachytherapy of lung metastatic lesions were as follows: 1) the metastatic lesion was solitary in the lung and the patient was not a candidate for surgical resection; 2) the number of lung metastatic lesions was not more than 3; and 3) the lung metastasis was the only evidence of recurrence.

2.3. Methods

The ^{125}I seed (Beijing Atom High Tech) in this study was shaped as cylindrical titanium package body with length of 4.5 mm, diameter of 0.8 mm and 3.0 mm × 0.5 mm inside the silver column (adsorption of ^{125}I, radioactivity: 0.8 mci, the average energy: 27 - 35 keV, half-life: 59.6 days, half layer: 0.025 mm of lead; anti-tumor activity: 1.7 cm, the initial dose rate: 7 cGy/h), and 0.05 mm wall thickness of titanium in its external shell.

Before ^{125}I brachytherapy, CT images with 5 mm section thickness were obtained for targeting the area of interest. A treatment plan was made for each patient using a computerized treatment planning system (TPS) (BT-RSI model TPS, YuanBo, Beijing, China) to determine the dose of radioactive seeds implanted and the placed site. A careful delineation of the tumor target volume was performed in every CT slice. Based on the three perpendicular diameters within the target tumor and a prescribed matched peripheral dose (MPD) of 100 - 140 Gy, TPS generated a dose-volume histogram (DVH), isodose curves of different percentages, and calculated the position (coordinates) of brachytherapy applicator, dose and number of implanted seeds. Planning target volume (PTV) is defined as a 1.5 cm of expansion external to the gross tumor volume. PTV edge was covered by isodose curve from 70% to 90% (**Figure 1**). The entry site and path of the needle were determined to avoid vital structures such as large vessels.

With CT (Siemens, Germeny) fluoroscopic guidance, a 18G brachytherapy applicator (Beijing Atom High Tech) was inserted into a lesion and positioned against its deepest margin after local anesthesia. A turntable or clip implant gun (Beijing Atom High Tech) was then attached to the applicator for implantation. Every ^{125}I seed was placed at a distance of 0.5 - 1.0 cm from each other (**Figures 2** and **3**). Within one month, a CT scan was per-

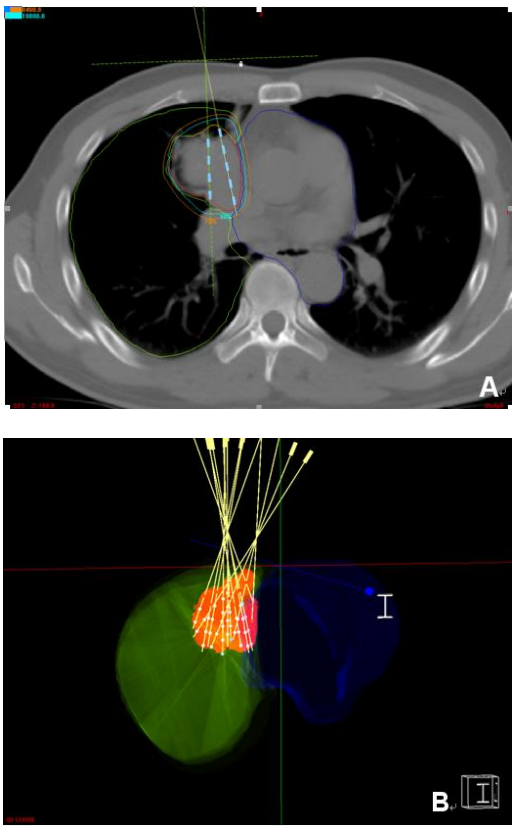

Figure 1. Pre-planning of ^{125}I brachytherapy. (A) Two-dimensional image of tumor on computerized radioactive treatment planning system (TPS), the PTV edge was cov- ered by isodose curve from 70% to 90%. (B) Three-dimen- sional graph of planar implantation and dose distribution on TPS.

formed to verify the position and intensity of ^{125}I seeds according to TPS (**Figure 4**). For tumors showing insufficient radioactivity, more ^{125}I seeds were implanted.

2.4. Follow-Up

According to our follow-up protocol, chest CT images were obtained each month before and after intravenous administration of contrast medium for up to 6 months and then at 2- to 3- month intervals (**Figures 2**, **3**). The efficacy of ^{125}I brachytherapy was assessed according to World Health Organization (WHO) response evaluation criteria for solid tumor as follows. 1) Complete response (CR) was defined as complete disappearance of tumor,

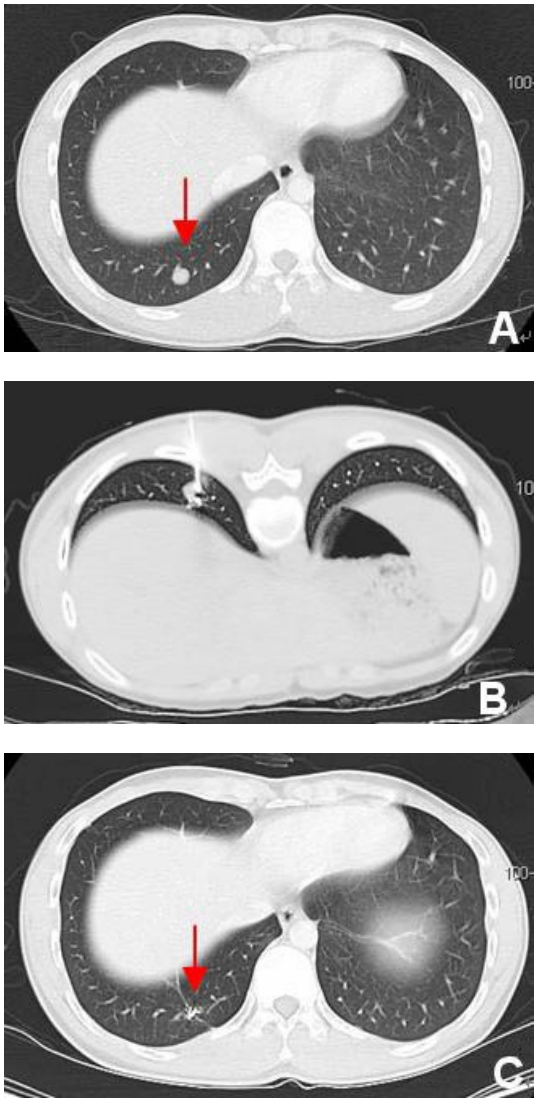

Figure 2. Case 1. (A) Lung metastasis from hepatocellular carcinoma, as indicated by the arrowhead. (B) During brachytherapy, an applicator accurately inserted into the tumor to implant ^{125}I seeds. (C) Three months after brachytherapy, tumor disappeared, with well distributed radioactive seeds remaining only, as indicated by the arrowhead.

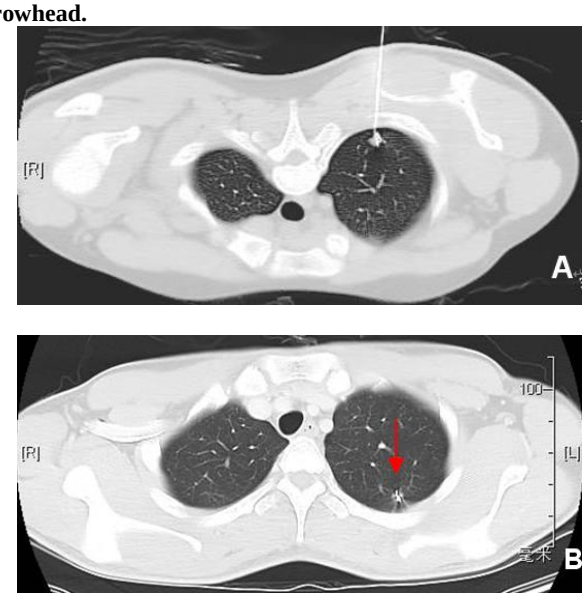

Figure 3. Case 2. (A) During brachytherapy, an applicator accurately inserted into the tumor to implant ^{125}I seeds. (C) Three months after brachytherapy, tumor disappeared, with well distributed radioactive seeds remaining only, as indicated by the arrowhead.

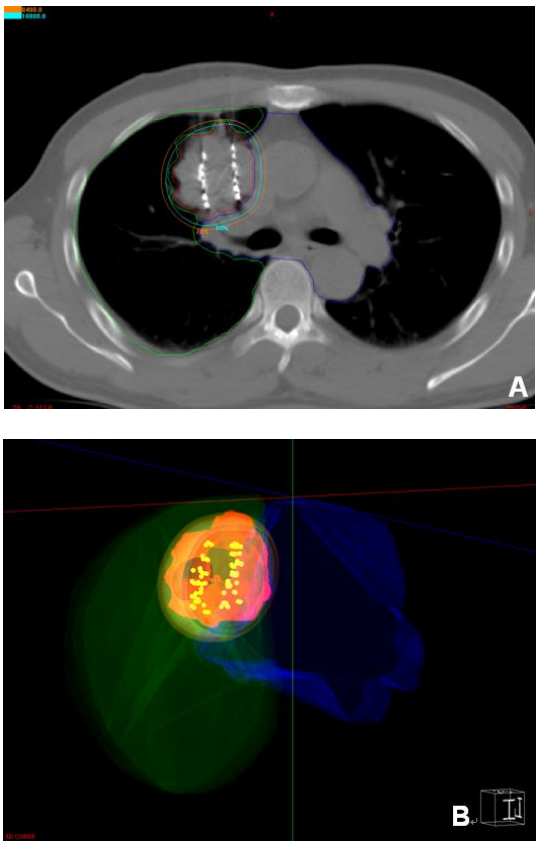

Figure 4. Verification of post-^{125}I brachytherapy. (A) Two-dimensional image of tumor on TPS, the PTV edge was covered by isodose curve from 70% to 90%. (B) Three-

dimensional graph of planar implantation and dose distribution on TPS.

no tumor or only accumulative metal granule shadow detectable by imaging analysis. 2) Partial response (PR) was defined as the shrinkage of tumor with the P value decreasing by ≥50% compared to the pre-procedure value. 3) No change (NC) was defined as a P value decrease of <50% or increase of <25% compared to the pre-procedure value. 4) Progression of disease (PD) was defined as a P value increase of ≥25% or the appearance of new tumor foci. Local control rate (LCR) was calculated as cases of (CR + PR)/total × 100%. We compared the products (P) of two largest and perpendicular diameters within the tumor under CT examination before and after the procedure.

3. Results

3.1. Implantation of 125I Radioactive Seeds

A total of 34 brachytherapies and 60 lung metastatic lesions were performed on the 29 patients, among which, 29 were successful at the first time, achieving the TPS criteria, and 5 didn't reach the TPS criteria, followed by additional implantations. The total number of implanted seeds was 493, with an average of 8.2 per tumor. The satisfactory rate of seed implantation was 94.1% (32/34).

3.2. Treatment Efficacy

Months are counted from the first time of ^{125}I brachytherapy and the median duration of follow-up was 11 months (range, 6 - 17 months). The local control rates after 3, 6, 10 and 15 month were 86.2, 71.4, 60.9 and 50.0% respectively. The 15-month survival rate of our study is 48.3% (14/29) excluding 4 patients who were alive without evidence of recurrence at 11, 11, 12 and 14 months. At the time of writing, ten patients are alive without evidence of recurrence at 11 - 15 months. The 10 patients presented good control of local tumor and no systemic recurrence and survived throughout the follow-up period. Eleven patients died of multiple hematogenous metastases 5 - 15 months after brachytherapy. Among the 29 patients, ^{125}I brachytherapy was repeated in 6 patients because of local residue or local progression of the lymph node. The clinical responses of patients to brachytherapy were summarized in **Table 1**.

3.3. Side Effects

Several complications related to the procedure occurred during or after brachytherapy. A small amount of local hematoma occurred in 5 patients that involved applicator insertion through the lung, probably because of injury of small lung vessels. Four patients presented pneumothorax with pulmonary compression of 30% - 40% after the procedure and recovered after drainage. During the follow-up, two patients had minor displacement of radioactive seeds. Severe complications such as massive bleeding and radiation pneumonitis did not occur.

4. Discussion

Extrahepatic metastases of HCC have been reported in 25 to 65 percent of autopsy series, with lung, bones, and regional lymph nodes as the most commonly involved sites and the most common site of metastasis is lung [2]. The prognosis of patients with extrahepatic metastases remains poor. In two studies, the median survival time was less than 7 months and the 1-year survival rate was as low as 25% [11,12]. Although we recognize that our study was small and had limited follow-up periods, the survival rates seem promising. The 15-month survival rate of our study is higher than the 1-year survival rate of the above two studies. The results of our study seem better compared with the above reports. At the time of this writing, particularly encouraging is the outcome of 10 patients who are alive without evidence of recurrence for 11 - 15 months after ^{125}I brachytherapy. For these patients, ^{125}I brachytherapy has been curable treatment so far. However, eleven patients died during follow-up. All the 11 patients had multiple hematogenous metastases at the time of follow-up, which resulted in death.

In our study, ^{125}I brachytherapy for lung metastases is not indicated if any uncontrollable recurrent foci are recognized at the primary site. In these cases of HCC, however, intrahepatic recurrences often occur and are not regarded to be well controllable by re-resections or other local treatments. In this series, we excluded patients with a history of intrahepatic recurrences as candidates for ^{125}I brachytherapy when the intrahepatic recurrent tumors could not be well controlled.

The success of ^{125}I brachytherapy depends on the accurate placement of radioactive seeds within a known volume of tumor [13]. Using CT guidance, an image of the implant volume can be seen and the position of each implant needle can be adjusted to ensure proper placement. In our study, the positions of the seeds are determined to provide a good dose distribution including a

Table 1. Clinical effectiveness of ^{125}I brachytherapy on lung metastasis.

Follow-up time (months)	No. of patients	Local control efficacy				Local control rate (%) (CR + PR)/Total %
		CR	PR	NC	PD	
3	29	20	5	2	2	86.2%
6	28	16	4	3	5	71.4%
10	23	12	2	4	5	60.9%
15	14	6	1	1	6	50.0%

Note—Months are counted from the time of ablation session. Four patients who were alive without evidence of recurrence at 11, 11, 12 and 14 months at the time of writing were excluded at 15 months of follow-up time.

minimum peripheral dose coverage, a uniform dose distribution, and the protection of surrounding tissues since methods for calculating optimal seed locations are available [14,15]. The relative coordinates of the seeds are then used for seed implantation within the lesions. Seeds and spacers are ejected from the needle when the depth of the needle specified by the plan is reached. Achieving this desired seed placement is left to the surgeon, who must take into account tissue deformations during the implant process [16,17]. Also inserting and retracting a needle in soft tissues cause the tissues to move, stretch and deform. This displacement and distortion of the tumor during the implantation result in misplaced seeds [17].

During the procedure, with the guidance of CT, the vital blood vessels and organs surrounding the tumor can be clearly displayed, allowing better control of implanting applicator and reducing the risk of damaging important blood vessels. No severe complications such as massive bleeding occurred during procedure, suggesting it is a safe procedure. To avoid radioactive damage on important organs such as vital blood vessels, the distance between implanted seeds should not be less than 10 mm to prevent accumulative radioactivity as a result of two closely positioned seeds. A route with minimal invasion into the lung tissue should be selected to reduce the risk of inducing pneumothorax. After procedure, it is better to keep patient hospitalized for 3 - 5 days and prospectively prescribe antibiotics and hemostatics to reduce the incidence of bleeding and infection.

Our study also had limitations that we only included 29 patients and followed them up for a maximum of 17 months. More cases and longer follow-up are desired for future survival analysis. We also expect to carry out further study on combining this local approach with systemic approach for tumor treatment.

In summary, the application of ^{125}I brachytherapy in treating lung metastasis from hepatocellular carcinoma is still in the developing stage. In this study, we found that ^{125}I brachytherapy has satisfactory short- to mid-term effect on controlling local lung metastasis, without severe complications such as massive bleeding or other complications associated with routine radiotherapy such as bone marrow arrest, radiation pneumonitis, digestive response or hair loss. Our study indicates that ^{125}I brachytherapy is a promising treatment for lung metastasis from hepato- cellular carcinoma.

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Abbreviations:

Hepatocellular carcinoma (HCC)
Computed tomographic (CT)
Treatment planning system (TPS)
Matched peripheral dose (MPD)
Dose-volume histogram (DVH)
Planning target volume (PTV)
World Health Organization (WHO)
Complete response (CR)
Partial response (PR)
No change (NC)
Progression of disease (PD)
Local control rate (LCR)
Products (P)

