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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Safety and efficacy of ^{125}I brachytherapy for bilateral lung recurrences from hepatocellular carcinoma after resection or ablation

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Abstract

Purpose To evaluate the safety and efficacy of ^{125}I brachytherapy to treat bilateral lung recurrences from hepatocellular carcinoma (HCC) after resection or ablation.

Materials and methods We retrospectively recruited 95 patients with bilateral lung recurrences from hepatocellular carcinoma (HCC) after resection or ablation who had received 3–6-month sorafenib with or without stereotactic body radiotherapy (SBRT), from October 2011 to January 2015; patients were then randomly divided into two groups, 44 patients received computed tomography (CT)-guided ^{125}I brachytherapy (group A), and 51 patients were treated with supportive and symptomatic treatments (group B).

Results The median survival time was 19 months (range of 3–36 months). The local response rate (LRR) at 3, 6, 12, 18, 24, 30 and 36 months in group A was 81.8%, 65.9%, 59.1%, 45.0%, 38.6%, 22.7%, 11.4%, respectively, and 64.7%, 47.1%, 33.3%, 25.4%, 15.7%, 11.7%, 7.8%, respectively, in group B ($P < 0.05$). The mean progression-free survival time (PFST) and overall survival (OS) of group A were significantly longer than those of group B. Alpha fetoprotein (AFP) and tumor size were independent factors that affected the PFST and OS, normal AFP levels and less than 1-cm tumor diameter had better PFST and OS ($P < 0.05$). No massive bleeding or serious complications occurred.

Conclusion CT-guided ^{125}I brachytherapy is safe and effective for the treatment of bilateral lung recurrences from HCC after resection or ablation.

Keywords ^{125}I brachytherapy · Bilateral lung recurrences · Hepatocellular carcinoma · Safety · Efficacy

Introduction

Lung metastases (extrahepatic recurrence) from hepatocellular carcinoma (HCC) after radical treatment presented as systemic manifestation of the disease and its presence usually indicated a poor prognosis, especially in early metastases after treatment (Taketomi et al. 2010; Natsuizaka et al. 2005). Although it was less than 30% in all HCC patients after resection or ablation, metastatic lesions in the lung tended to be small and bilateral (Uchino et al. 2011). In fact, only a small number of patients with lung metastases were suitable for surgical resection or thermal ablation, and there were less for bilateral lung metastases (Chen et al. 2008; Chua and Morris 2012). In most patients, the sorafenib combined with radiotherapy was considered to be the standard treatment for bilateral lung metastases from HCC but not had durable remission and the long-term survival was disappointing (Bruix et al. 2012; Sun et al. 2016). Therefore, it was necessary and challenging for the treatment of bilateral lung metastases from HCC after resection or ablation.

Due to the unique radiobiological characteristics of ^{125}I seed, it effectively killed tumor cells without obvious damage to surrounding normal tissue. So, ^{125}I brachytherapy had been widely applied for the treatment of a variety of tumors with significant efficacy by providing a high local control rate (Zhang et al. 2008; Hu et al. 2012; Wang et al. 2013). Similarly, we also reviewed these reports and

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concluded that there were some studies for unilateral lung metastases from HCC following liver resection and these results were exciting (Hu et al. 2017). However, for bilateral lung recurrences from HCC after resection or ablation, there were few reports.

Thus, the purpose of this study was to investigate the safety and clinical value of computed tomography (CT)-guided ^{125}I brachytherapy for treatment of bilateral lung recurrences from HCC after resection or ablation.

Materials and methods

Patients selection

From October 2011 to January 2015, 95 patients who were diagnosed with bilateral lung recurrences from HCC after resection or ablation, and met the inclusion criteria, participated in this study (15 patients from Third affiliated hospital of Sun Yat-sen University, 80 patients from Sun Yat-sen University Cancer Center). This retrospective study was approved by the ethics committee of two hospitals. All patients previously experienced 3–6-month sorafenib (400 mg, twice daily) after the confirmation of lung recurrences. 13 patients in group A (brachytherapy) and 20 in group B (supportive and symptomatic treatments) previously received stereotactic body radiotherapy (dose range 50–70 Gy, 20–25 times, 3–4 weeks) for bilateral lung metastases. But all patients had recurrences at relatively short interval from the end of the initial treatment (group A: 14.6 ± 7.2 months; group B, 15.3 ± 6.8 months). Patients were then randomly divided into two groups. After being fully informed of the associated risks of brachytherapy, 44 patients received percutaneous ^{125}I seed implantation therapy for lung metastases (group A). 51 patients were given supportive and symptomatic treatments (group B). The characteristics of individual patients and tumors are summarized in Table 1.

The inclusion criteria were: (a) the primary liver lesion was treated by resection or ablation and pathologic analysis was HCC; (b)lung metastases confirmed by CT-guided fine-needle biopsy; (c) the metastatic lesions were bilateral in the lung and were also the only site of recurrence at enrolment; (d) not suitable or refuse to re-irradiation or surgery resection; (e) two–five lung lesions, single lesion with a diameter less than 5 cm; and (f) Eastern Cooperative Oncology Group performance status of 2 or less. The exclusion criteria were as follows: receiving additional treatment at another hospital; cachexia; systemic metastases; unable to tolerate percutaneous lung biopsy surgery; and severe cardiopulmonary dysfunction.

^{125}I seed

^{125}I seeds (Yunke Pharmaceutical Limited Liability Company, Chengdu, China) were included in 4.5-mm × 0.8-mm nickel–titanium tubes. The ^{125}I was adsorbed on the surface of a 3-mm × 0.5-mm silver rod. Each seed had an initial activity of $1.85–2.22 \times 10^{10}$ Bq and a half-life of 59.6 days, release of continuous low-dose γ-ray and soft X-ray (5% of 35 keV and 95% of 28 keV, respectively) after decaying into the organization. The average energy was 27–32 keV. The ^{125}I seeds had effective anti-tumor activity at a diameter of 1.7 cm. Within 8–10 months, 93–97% of the brachytherapy dose was delivered.

Radiation dosimetry

Before ^{125}I brachytherapy, to ensure the sufficient dose in lung lesions, a radiologist (Z.W.X or F.J.Z) and physicist (Z.H.Z) completed preoperative plan on the TPS planning system (Qilin Company, Beijing, China) together for all patients. GTV (gross tumor volume) referred to the range of lesion found in imaging. PTV (planning target volume) included the entire GTV plus the outer boundary of 0.5–1 cm. The dose was prescribed as the minimal peripheral dose (MPD) encompassing the PTV, The prescribed dose was an averaged 120 Gy (100–140 Gy). According to consensus by American Brachytherapy Society for prostate cancer (Nag 2000) and our previous ^{125}I brachytherapy study (Mo et al. 2018; Xiang et al. 2015; Yan et al. 2017). We designed a puncture path, calculated the required number of seeds, and generated a dose–volume histogram (DVH) with TPS (Fig. 1a–d). It was necessary to reduce the MPD at important organs and tissues by these following criteria: spinal cord 45–50 Gy, large vessels < 80 Gy, heart 45–50 Gy, esophagus < 60 Gy and so on.

^{125}I implantation

All ^{125}I brachytherapy seeds were implanted by the same two radiologists (F.J.Z and M.J.B), who had more than 10 years of experience in CT-guided ^{125}I brachytherapy. At the beginning of operation, appropriate positioning was achieved, and a wire was attached to the patient's body surface, marking the puncture position according to the preoperative plan made by TPS. After local infiltration anesthesia with 5–10 ml of 1% lidocaine (Yimin, Yichang, China), an 18-gauge spinal needle (Yunke Pharmaceutical Limited Liability Company, Chengdu, China) was inserted into a unilateral lung lesion, the direction of the needle adjusted under CT guidance and all of the needles reached

Table 1 Summary of patient and tumor characteristics

Characteristics	Value		Statistical analysis (*P*)
	Group A (*n* = 44, %)	Group B (*n* = 51, %)	
Age			0.597
Mean age (years)[a]	48.5 ± 11.5	49.4 ± 13.4	
≤ 60	34 (77.3)	37 (72.5)	
> 60	10 (22.7)	14 (27.6)	
Sex			0.562
Male	35 (79.5)	38 (74.5)	
Female	9 (20.5)	13 (25.5)	
ECOG performance status			0.885
0	28 (63.6)	31 (60.9)	
1	15 (34.1)	18 (35.3)	
2	1 (2.3)	2 (3.9)	
Previous treatment for HCC			0.956
Resection	33 (75.0)	38 (74.5)	
Ablation	11 (25.0)	13 (25.5)	
Vascular invasion in pathology (HCC)			0.631
Yes	11 (25.0)	15 (29.4)	
No	33 (75.0)	36 (70.6)	
No. of tumors			0.717
2	6 (13.6)	8 (15.7)	
3	13 (29.5)	20 (39.2)	
4	16 (36.4)	15 (29.4)	
5	9 (20.5)	8 (15.7)	
Tumor size			0.742
Largest tumor diameter (cm)[a]	1.6 ± 0.5	1.4 ± 0.6	
≤ 1	10 (22.7)	14 (27.5)	
> 1 to ≤ 2	31 (70.5)	35 (68.6)	
> 2 to ≤ 5	3 (6.8)	2 (3.9)	
Disease-free interval (months)			0.612
Mean no. of months	14.6 ± 7.2	15.3 ± 6.8	
≤15	21 (47.7)	27 (52.9)	
> 15	23 (52.3)	24 (47.1)	
Alpha fetoprotein			0.359
Elevated	29 (65.9)	38 (74.5)	
Within normal	15 (34.1)	13 (25.5)	

ECOG Eastern Cooperative Oncology Group, *HCC* hepatocellular carcinoma

[a]Data are mean ± standard deviation

the farthest boundary of tumor. From deep to shallow, the seeds were released while drawing back the needle and keeping adjacent seeds at a distance of 0.5–1 cm (Fig. 2a, b). The implantation was performed in one lung and then in the other lung. After confirmation of no pneumothorax or bleeding, the applicators were inserted into the contralateral lung lesions and the ^{125}I seeds were placed with the same method (Fig. 2c). The CT scan was performed again to exclude any postoperative complications and also imported in the TPS program to verify the location of the ^{125}I seed implantation and dose intensity (Fig. 2d, e).

Supportive and symptomatic treatments

In group B, symptomatic and supportive treatments included relieving related-clinical symptoms caused by metastases (such as cough, fatigue, pain, weight loss, etc), improving quality of life and prolonging survival time. These patients with cough were recommended to mucosolvan (Boehringer Ingelheim) 30-mg intravenous infusion in twice daily. A dose increase was considered if insufficient clinical improvement was observed after several weeks. One tablet daily that contained multivitamins and minerals (Centrum; Pfizer,

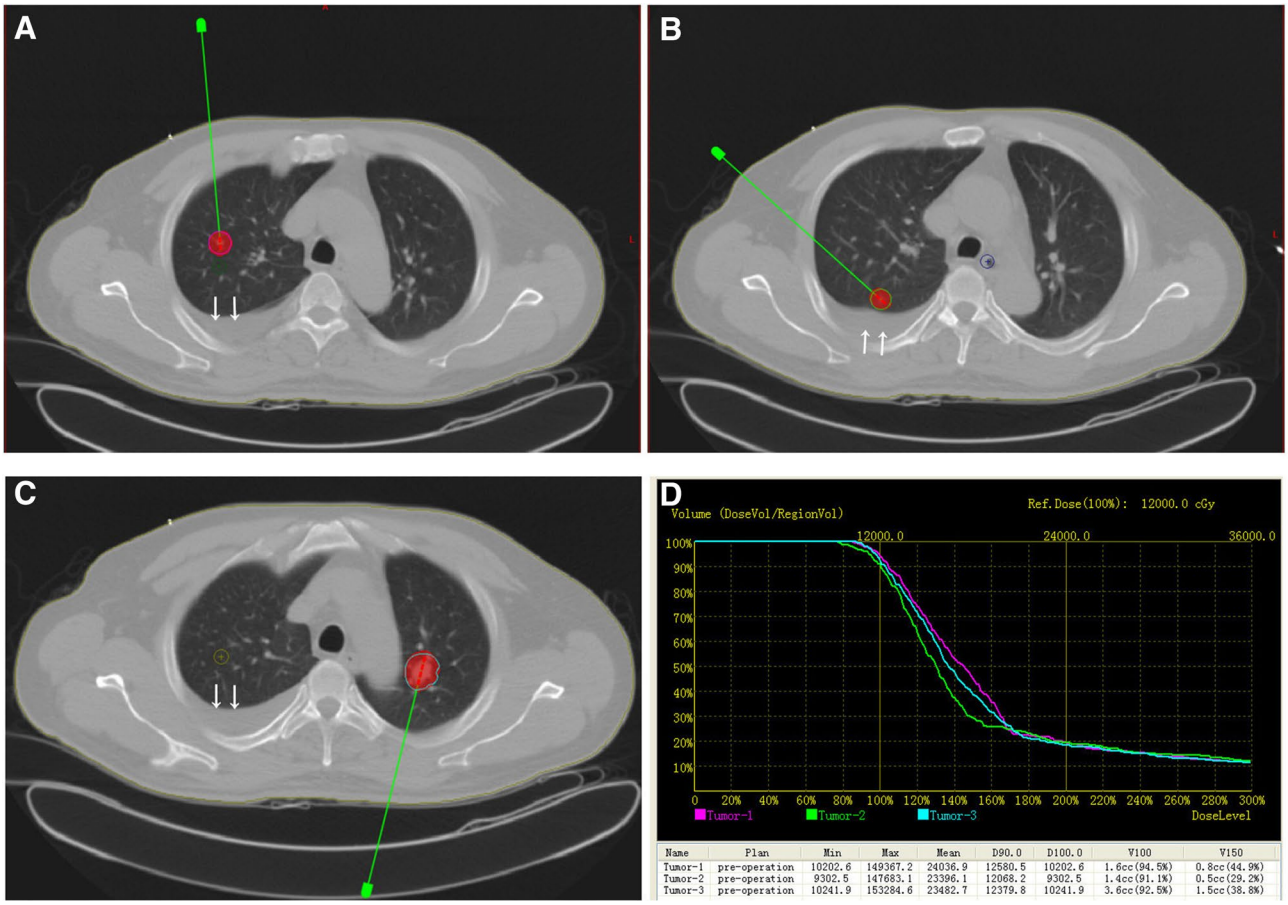

Fig. 1 A preoperative treatment planning system (TPS), there were three lesions in bilateral lung (two in the right, one in the left). **a–c** Red lines represented the tumor's contour; the planning target volume edge was covered by the isodose curve from 70 to 90%. Small amount of pleural effusion marked (arrows). **d** Preoperative dose–volume histograms (DVH). The prescription dose (PD) was 120 Gy, a total of 90% of the tumor target (D_{90}) received 125.8 Gy, 120.7 Gy, 123 Gy and 94.5%, 91.1%, 92.5% of the tumor received 100% of the prescribed dose (V_{100})

Kings Mountain, NC) was recommended for the patients with fatigue. For the patients with pain, 10 mg of OxyContin (Bard Pharmaceuticals Limited) was recommended to be taken up two times per day; the dose increase was considered if there was insufficient clinical improvement, 25–50% per day doses were administered and the maximum dose did not exceed 400 mg/day. The patients with weight loss were recommended to have a healthy diet, which included eating and drinking enough of the foods and liquids that had the important nutrients (vitamins, minerals, protein, carbohydrates, and fat).

Follow-up

The time interval between Sorafenib and ^{125}I brachytherapy or supportive care in two groups was no more than 2 weeks. According to the follow-up, those patients who accepted percutaneous ^{125}I implantation underwent electrocardio monitoring within the following 24 h; all postoperative symptoms were recorded. Contrast agent-enhanced chest CT images were obtained each month for the first 3 months, and then at once every 3 months. Follow-up imaging examinations were performed to evaluate the therapeutic effectiveness of ^{125}I brachytherapy. The major follow-up outcomes were LRR, PFST, OS, and brachytherapy-related complications.

Evaluation criteria

The effectiveness of ^{125}I brachytherapy was calculated according to the response evaluation criteria in solid tumors (RECIST): complete response (CR), partial response (PR), stable disease (SD), and progression disease (PD). Local response rate (LRR) was defined as the proportion of patients who received complete response and partial response. PFST was defined as the time from the date of study entry to the first documented disease progression, death, or end of the study. OS was defined as from the date of study entry to the date of death or last follow-up visit. Adverse effects of

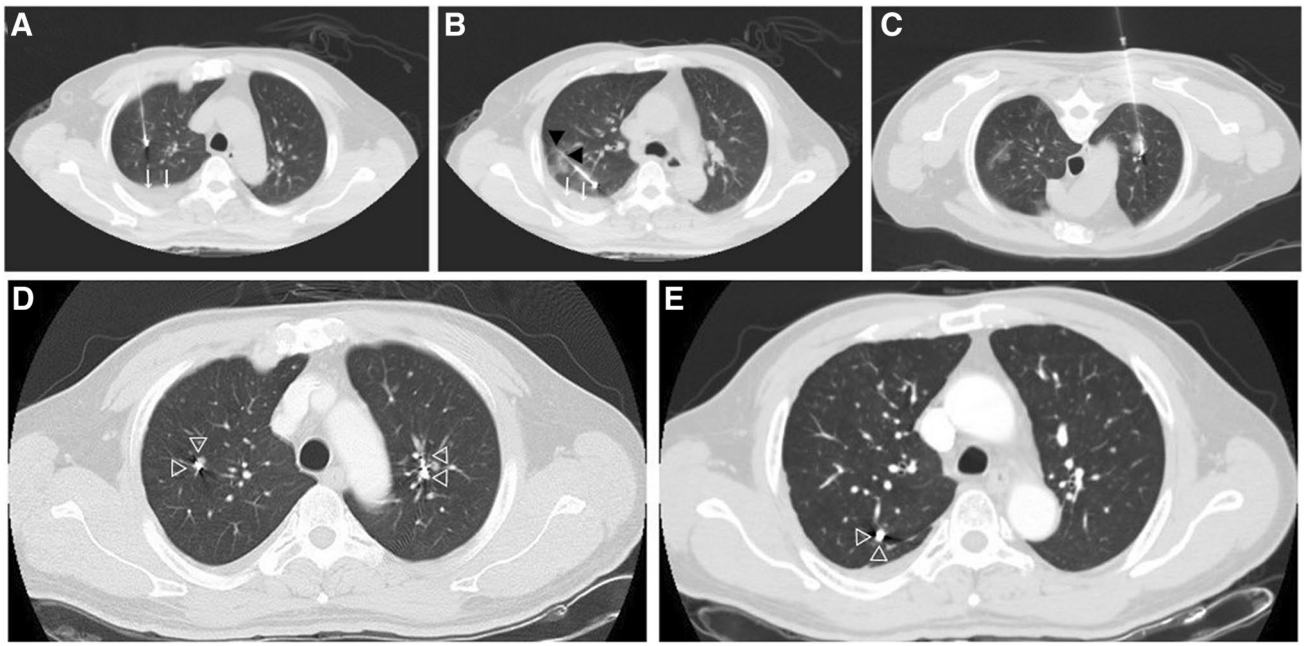

Fig. 2 Computed tomography (CT)-guided percutaneous ^{125}I seed implantation was performed. **a**, **b** Two applicators were inserted into the tumor in the right lung to implant ^{125}I seeds. A small amount of pulmonary hemorrhage (black arrows) and pleural effusion marked (white arrows). **c** After implantation in the right lung, one applicator was inserted into the other tumor in the left lung. **d**, **e** Three months after treatment, the tumors disappeared, with only seeds remaining (arrows)

irradiation were calculated by the Toxicity Criteria of the Radiation Therapy Oncology Group.

Statistical analyses

Statistical analysis was performed using SPSS version 20.0 (International Business Machines Corporation, New York, American), P values less than 0.05 were considered to indicate statistical significance. The characteristics of the patients in the two groups were compared by Pearson χ^2 test. Kaplan–Meier analysis (log-rank test) was used to compare OS and PFST in the two groups. A stratified Cox proportional hazards regression model was used to evaluate the association of study variables (age, sex, AFP, No. of tumors, tumor size, disease-free interval, etc.) with PFST and OS.

Results

The characteristics of individual patients and tumors are summarized in Table 1. The median survival time was 19 months (range of 3–36 months). 44 patients with 160 lesions in group A underwent CT-guided ^{125}I brachytherapy for bilateral lung metastases and 51 patients with 176 lesions were given symptomatic and supportive treatments in group B. In group A, 40 of the 44 (90.2%) met the postoperative TPS dose verification; four patients were re-implanted and eventually achieved the planned dose. The largest tumor diameter was 1.6 ± 0.5 cm and 1.4 ± 0.6 cm between two groups ($P = 0.742$). There were no statistically significant differences between patient characteristics in two groups.

Local response rate

The clinical efficacy of patients is summarized in Table 2. The LRR at 3, 6, 12, 18, 24, 30 and 36 months in group A was 81.8%, 65.9%, 59.1%, 45.0%, 38.6%, 22.7%, 11.4%, respectively, and was 64.7%, 47.1%, 33.3%, 25.4%, 15.7%, 11.7% and 7.8%, respectively, in group B ($P < 0.05$). ^{125}I brachytherapy had overall better local control efficacy and the difference was statistically significant.

Progression-free survival time

The median PFST was 20.4 ± 1.8 months (95% CI 16.8–24.0) in group A and 14.3 ± 1.2 months (95% CI 11.9–16.7) in group B. Cox proportional hazards regression model and log-rank (Mantel–Cox) tests showed that PFST was significantly higher in group A than in group B [$P = 0.026$, HR = 0.629, (95% CI 0.388–1.019), Fig. 3, Table 3]. Also, patients with normal AFP levels [$P < 0.01$, HR = 0.515, (95% CI 0.288–0.920), Fig. 4a] and ≤ 1 cm largest tumor diameter [≤ 1 cm vs > 1 to ≤ 5 cm: $P < 0.01$, HR = 0.657, (95% CI 0.348–1.238), Fig. 4b] had longer PFST, AFP and tumor size

Table 2 The clinical efficacy of treatment in two groups

Months	Local control efficacy									
	Group A					Group B				
	CR	PR	SD	PD	LRR (%)	CR	PR	SD	PD	LRR	*P*
3	20	16	5	3	36/44 (81.8)	8	25	9	9	33/51 (64.7)	0.017
6	16	13	7	8	29/44 (65.9)	5	19	14	13	24/51 (47.1)	0.039
12	14	12	5	13	26/44 (59.1)	5	12	9	25	17/51 (33.3)	0.033
18	12	10	4	18	22/44 (45.0)	4	9	8	30	13/51 (25.4)	0.048
24	10	7	2	25	17/44 (38.6)	3	5	6	37	8/51 (15.7)	0.047
30	7	3	0	34	10/44 (22.7)	2	4	4	41	6/51 (11.7)	0.036
36	3	2	0	39	5/44 (11.4)	2	2	1	46	4/51 (7.8)	0.021

Local response rate (LRR) defined as the proportion of patients with complete response and partial response

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, based on the Response Evaluation Criteria in Solid Tumors (RECIST)

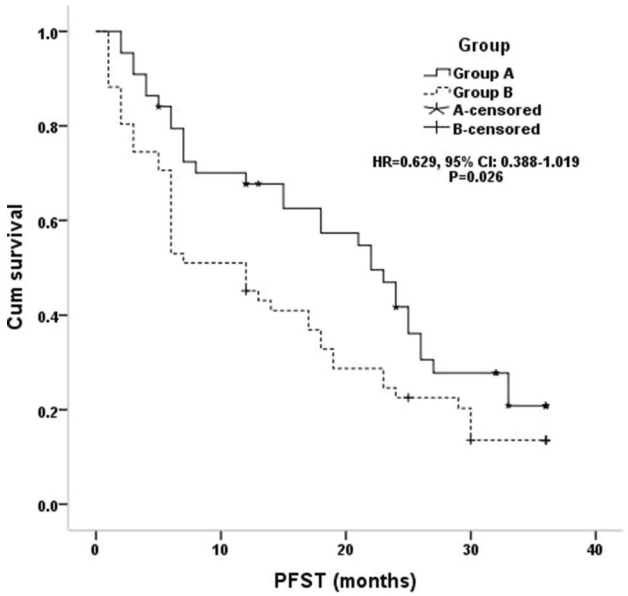

Fig. 3 Comparison of progression-free survival time (PFST) in group A and group B. *HR* hazard ratio

were independent factors that affected PFST (Table 3). There was no association between PFST and age, sex, ECOG performance status, previous treatment for HCC, No. of tumors, disease-free interval.

Overall survival

The 1-, 2-, and 3-year OS in group A was 74.7%, 54.8%, 21.8%, respectively, and 43.1%, 27.4%, 9.8% in group B respectively. The median OS time was 23.0 ± 1.8 months (95% CI 19.5–26.6) and 15.6 ± 1.2 months (95% CI 13.3–18.0) in two groups, respectively [$P < 0.01$, HR = 0.577, (95% CI 0.356–0.938), Fig. 5, Table 3]. Normal AFP levels [$P = 0.041$, HR = 0.545, (95% CI 0.305–0.974), Fig. 6a], ≤ 1 cm largest tumor diameter [≤ 1 cm vs > 1 to ≤ 5 cm: $P = 0.047$, HR = 0.632, (95% CI 0.334–1.193), Fig. 6b] had better OS, AFP and tumor size were independent factors that affected OS (Table 3). Age, sex, ECOG performance status, previous treatment for HCC, No. of tumors, disease-free interval had no association with OS.

Table 3 Stratified Cox proportional hazards regression analysis related PFST and OS

Variable	PFST			OS		
	P	HR	95% CI	*P*	HR	95% CI
Groups						
^{125}I brachytherapy	0.026	0.629	0.388, 1.019	< 0.01	0.577	0.356, 0.938
Supportive treatments						
Largest tumor diameter (cm)						
≤ 1	< 0.01	0.657	0.348, 0.920	0.047	0.623	0.334, 1.193
> 1 to ≤ 5						
Alpha fetoprotein						
Elevated	< 0.01	0.515	0.288, 0.920	0.041	0.545	0.305, 0.974
Within normal						

PFST Progression Free Survival Time, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval

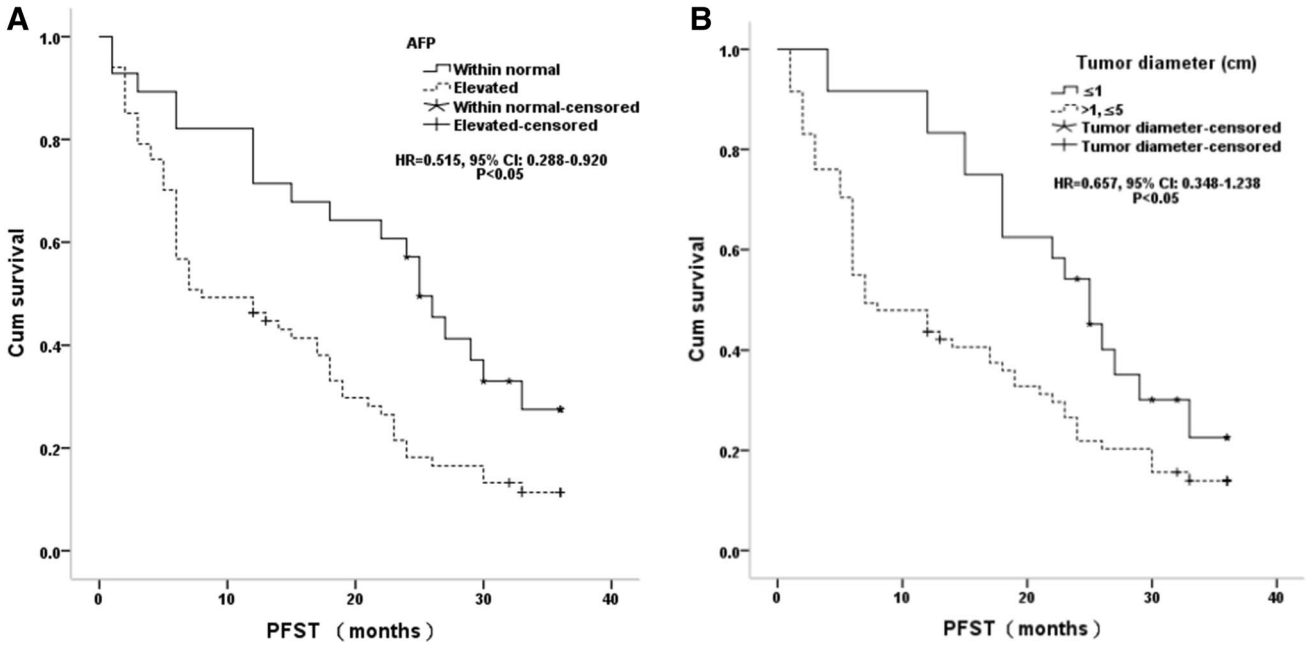

Fig. 4 Cox proportional hazards regression model explored these factors related with progression-free survival time (PFST). **a** AFP, **b** tumor diameter (cm). *HR* hazard ratio

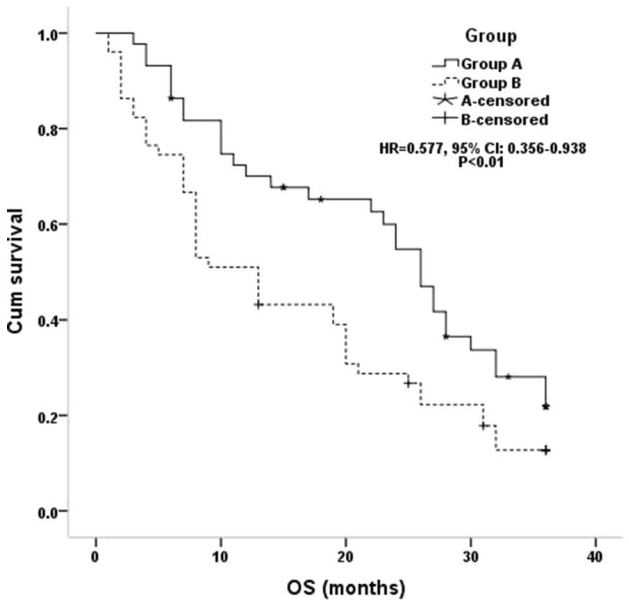

Fig. 5 Overall survival (OS) in group A and group B. *HR* hazard ratio

Complications

Several complications related to brachytherapy occurred in group A (Table 4). During the procedure, four patients in group A presented pneumothorax with pulmonary compression of more than 30% of the unilateral lung volume and recovered after drainage. The remaining nine patients had no apparent symptoms and did not undergo treatment. A small amount of local hematoma occurred in ten patients, and it involved applicator insertion through the lung, probably because of injury of small lung vessels. Two patients had minor displacement of radioactive seeds that did not cause clinical symptoms. Severe complications, such as massive bleeding and radioactive pneumonia were not observed.

Discussion

For bilateral pulmonary metastases from HCC after resection or ablation, ^{125}I implantation was a feasible treatment and solved many problems. As we all know, the surgery was unsuitable for multiple lung metastases secondary to HCC after resection or ablation, the efficacy was disappointing and many patients refused surgical treatment (Tomimaru et al. 2006). Also, sorafenib combined with radiotherapy is first treatment for these patients, but many patients had intolerable complications and the OS was not prolonged obviously (Abou-Alfa et al. 2006; Kitano et al. 2012). So, for progression disease of bilateral pulmonary metastases after sorafenib combined with radiotherapy treatment, ^{125}I brachytherapy provided an opportunity for remission in patients. As a low-dose rate brachytherapy, persistent low-dose irradiation of ^{125}I seed could affect the different stages of cell cycle, it could continue to kill tumor cells (Qu et al. 2014). When killing tumor cells, the γ-rays had lower oxygen dependence which can improve the killing effect on tumor cells (Zhou

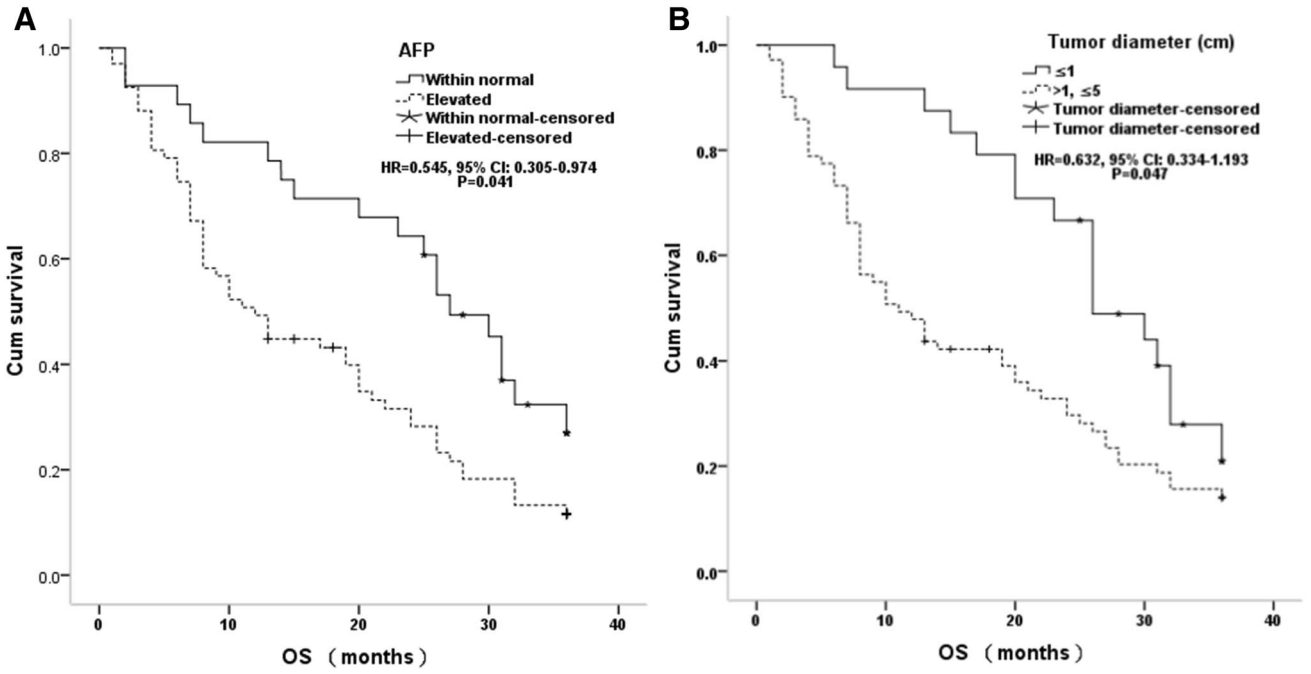

Fig. 6 Cox proportional hazards regression model explored these factors related with overall survival (OS). **a** AFP, **b** tumor diameter (cm). *HR* hazard ratio

Table 4 Complications of ^{125}I brachytherapy in group A

Complication (RTOG toxicity criteria)	No. of patients (%)				
	0	1	2	3	4
Pneumothorax	31 (70.5)	9 (20.5)	2 (4.5)	2 (4.5)	0
Local pulmonary hemorrhage	34 (77.3)	9 (20.5)	1 (2.3)	0	0
Bloody sputum	37 (84.1)	7 (15.9)	0	0	0
Chest pain	39 (88.6)	5 (11.4)	0	0	0
Displacement of seeds	42 (95.5)	2 (4.5)	0	0	0
Radioactive esophagitis	44 (100)	0	0	0	0
Radioactive pneumonia	44 (100)	0	0	0	0
Massive bleeding	44 (100)	0	0	0	0

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et al. 2014; Koritzinsky et al. 2001). Similarity, many studies had confirmed that ^{125}I radiation could inhibit the proliferation and promote the apoptosis of cells (Yang et al. 2014). So in spite of combination therapy failure, we considered that ^{125}I implantation might be an alternative treatment for bilateral lung recurrences from HCC after resection or ablation.

Another finding was that ^{125}I brachytherapy achieved better LRR, survival of these patients was significantly better in group A than in group B. Many previous studies for pulmonary metastases had also confirmed that ^{125}I brachytherapy was effective. Gao et al. reported that computed tomography-guided ^{125}I brachytherapy was safe and well local control rate for bilateral lung recurrences, the local control rate of 3, 6, 12, 24, and 36 months was 75.8%, 51.5%, 33.3%, 24.2%, and 9.1%, respectively (Wang et al. 2016). Zhang et al. also found that ^{125}I seed implantation for multiple pulmonary metastases of HCC had a high response rate (92.6%), the survival rates at 1 and 2 years were 67% and 30.8% (Zhang et al. 2014). Li et al. reported 8 patients with HCC who underwent liver transplantation and then were given to ^{125}I brachytherapy for lung metastases, the local control rates of multiple lung metastases after 4, 6, 12, 18 and 24 months were 92.2%, 82.4%, 76.2%, 73.3% and 72.2%, respectively, and the overall 1-, 2- and 3-year survival rates were 100%, 50% and 12.5%, respectively (Li et al. 2010). From these, we considered that the treatment of bilateral lung recurrences was valuable because the lung lesions were the only evidence of recurrence for HCC after

resection or ablation. For these patients, ^{125}I brachytherapy had so far been a radical treatment.

Cox proportional hazards regression model showed that AFP levels and tumor size were independent factors for OS and PFST. The median survival time of normal AFP level and metastases diameter (less than 1 cm) was better. Many previous studies had confirmed that AFP was the most specific and sensitive marker for predicting recurrence or metastasis of cured HCC (Ma et al. 2013; Cheng et al. 2014). As the primary lung tumor, tumor size directly reflected the invasiveness and metastatic ability of malignancy tumor (Loukeri et al. 2015). However, The result of this study showed that No. of metastases was not independent factor for survival time, this was inconsistent with previous reports, it could be explained by the inclusion criteria (bilateral lung recurrences in this study not just a single lesion) (Lee et al. 2010).

TPS plan was the key to ensuring the efficacy and reducing the related complications for bilateral lung metastases. In this study, the mean D_{90} was 120–130 Gy and V_{100} was 90–100%. Without damaging the surrounding organs, TPS plan could ensure that 95% of the tumor volume accepted 100% of the prescribed dose (PD), which was consistent with the American Brachytherapy Society's so-called dual 90 (90% of the tumor volume acquire 90% prescription dose) (Stewart et al. 2016). According to our own experience, CT scan could clearly show tumor location, boundary, important blood vessels and organs, which made applicators well controlled and reduced the possibility of pneumothorax and hemorrhage. There was no case of related death due to ^{125}I implantation in the study.

In fact, there were some limitations. First, although these patients were enrolled in two hospitals, the number of patients with ^{125}I brachytherapy was only 44; more cases and longer follow-up were desired for future survival analysis. Second, due to the limitation of described TPS, it was not always easy for brachytherapy applicators to determine the accurate position and location, especially when more lesions were treated. So, we recommended that less than 5 lesions can be suitable and the applicators must understand anatomy and three-dimensional structure of lung. Third, given seeds must be implanted into large lung metastases (more than 3 cm); we recommended that ^{125}I brachytherapy in combination with radiofrequency ablation might be adopted in which lesions were first inactivated by radiofrequency ablation and the residual lesions were then subjected to ^{125}I brachytherapy. Finally, we did not compare ^{125}I brachytherapy with sorafenib or radiotherapy, such a comparison will be of value and was desired for our future study.

In conclusion, CT-guided ^{125}I brachytherapy was safe and effective for the treatment of bilateral lung recurrences from HCC after resection or ablation, which would be an alternative to cancer therapy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All individual participants agreed the study and signed informed consent. This work was supported by the institutional review board (the Research Data Deposit Number is RDDA2018000894).

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