

## **Percutaneous CT-guided radiofrequency ablation for unresectable hepatocellular carcinoma pulmonary metastases**

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### ***Purpose***

To evaluate the outcomes of percutaneous CT-guided radiofrequency ablation (RFA) for unresectable hepatocellular carcinoma pulmonary metastases (HCCPM) and to identify the prognostic factors for survival.

### ***Materials and methods***

320 patients with pathologically or clinically confirmed HCCPM between January 2005 and January 2012 were reviewed. 29 unresectable candidates (26 men and 3 women) with 58 HCCPM were treated with 51 percutaneous CT-guided RFA sessions. The outcomes, including safety, local efficacy, survival and prognostic factors were evaluated.

### ***Results***

Pneumothorax requiring chest tube placement occurred in 2 (3.9%, 2/51) RFA sessions. During the median follow-up period after initial lung RFA of 62 months (range, 5-75 months), 18 (62%, 18/29) patients died of intrahepatic tumor progression and 11 (38%, 11/29) patients still alive. The 1-, 3- and 5-year overall survival rates from initial lung RFA were 71.6%, 27.9% and 9.3%, with the median survival time was 26.3 months (range, 3-66) in all patients. Univariate and multivariate analysis revealed serum AFP level small than 400ng/mL and complete response rate after initial lung RFA as better prognostic factors for overall survival.

### ***Conclusions***

As an alternative treatment procedure to pulmonary metastasectomy, percutaneous CT-guided RFA can be a safe and effective therapeutic option for unresectable HCCPM patients.

### ***Introduction***

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumors worldwide and the third contributor to cancer-related death. With the advancements of the multidisciplinary application of the surgical resection, transplantation, radiofrequency ablation (RFA), and transcatheter arterial chemoembolization (TACE), the intrahepatic tumor has been well controlled and the survival has been gradually improved, however, the prognosis of patients with extrahepatic metastases remains poor with the median natural survival time after diagnosis of extrahepatic metastasis was only 7-8.1 months. The lung is a prime metastatic target organ with approximately 20-30% of advanced HCC experienced pulmonary metastasis synchronously or metachronously. Lung metastasectomy has been validated as the curative therapeutic option to solitary pulmonary metastatic patients. However, only 25-30% of highly selective HCCPM patients benefit from surgical resection because of the association of multiple lung metastases or extrapulmonary disease. In addition, a trend of early recurrence and/or new metastatic lesions after lung metastasectomy also limits the second lung surgical indication.

Other alternatives palliative therapies in unresectable HCCPM are radiation therapy, alone or combined with systemic chemotherapy, but these therapeutic options have not greatly improved patient prognosis. New targeted agents such as sorafenib have been shown to extend survival in selected advanced HCC patients, however, a recently prospective phase II trial indicated that the presence of lung metastasis predicted poor response to sorafenib in advanced HCC patients.

Therefore, a novel therapeutic strategy is required to improve the survival of patients with unresectable HCCPM.

RFA has been accepted as a relatively safe and useful therapeutic option in the treatment of selected primary and metastatic lung tumors. The advantages of satisfied local control rate, repeatability, minimal invasion with short hospital stay and gain in quality of life, suggesting that RFA might be an alternative option for HCCPM patients where lung metastasectomy is unfeasible. Moreover, some studies have shown clinical outcomes of lung RFA in controlling HCCPM, however, the survival benefit of RFA as an either additional or substitutive local treatment method is still lacking in the pursuing of treatment in HCCPM and it remains to be determined whether survival data were a simple reflection of natural history in such a population. So in this study, we presented our experience on unresectable HCCPM patients characterized by adequately controlled intrahepatic lesions and no extrathoracic metastases, treated exclusively with lung RFA. The complications, local efficacy, survival and prognostic factors were evaluated which may be useful in cumulating evidence of this practice in HCCPM. The time interval between diagnoses of the HCC and lung metastases, number of tumors, and size of the largest tumor, hepatic virus infection, ZPS, serum AFP level before initial lung RFA, the response after initial lung RFA were assessed for its effect on survival.

### ***Materials and methods***

The retrospective study was approved by our institutional review board, and all patients provided written informed consent before CT-guided RFA for HCCPM.

### ***Patient selection***

Between January 2005 and January 2012, 320 consecutive patients without any evidence of distant metastases other than lung were reviewed. 29 unresectable candidates with 58 HCCPM were treated with 51 percutaneous CT-guided RFA sessions. There were 26 men and 3 women with a mean age of 49.6 years (range, 24-72 years). All patients treated with RFA had lesions proven to be pulmonary-only metastases from HCC based on typical radiological features of HCCPM on CT/MRI or PET-CT with the history of HCC, except for 3 patients who underwent CT-guided lung biopsy before RFA as the presentation is atypical.

The intrahepatic tumor was controlled by hepatectomy+TACE+RFA (n=10), liver transplantation+TACE+RFA (n=9), RFA (n=3), TACE+RFA (n=7), and the results were evaluated by CT scans with a contrast medium after one month later. The mean number of lung metastases was 2 (range, 1-8) and the maximum diameter was 17.5 mm (range, 5-50 mm) at the time of initial lung RFA. The mean disease-free interval between the time of the diagnosis of HCC and development of lung metastases was 17.7 months (range, 1-85 months). The mean duration between appearance of lung metastases and RFA was 6 months (range, 0-38 months). The last day of follow-up ended on the date of death or January 31 th, 2012, and the median follow-up period was 62 months (range, 5-7 months).

### ***Preablation evaluation***

The evaluation of intrahepatic tumor being "controlled" was based on radiological images without intrahepatic enhanced lesion lasting for more than one month after the curable treatment or along with the normalization of serum AFP for asynchronous metastases. For patients with synchronous lung metastases, the preferred treatment of intrahepatic lesions with curable intent was performed.

The judgment of lung metastases being "unresectable" and the indication for RFA were made by an interdisciplinary tumor board consist of thoracic surgeons, hepatobiliary surgeons, medical oncologists, radiation oncologists, and interventional radiologist taking the number and distribution of the lung metastatic lesions and co-morbidities and the risk of lung metastasectomy or the patient's refusal to accept lung metastasectomy into consideration. The choice of RFA is then an individual decision, based on the patient's risk-benefit relation. Once the decision was made, the interventional radiologist informed the patient of the risks and the possible complications and benefits of the procedure.

Indications for CT-guided RFA of HCCPM with curative intent were  $\leq 5$  cm diameter in size; five or fewer in number; no definite suspicious lesion other than lung metastasis on imaging studies at the time of HCCPM diagnosis; a distance between the lesion and the pulmonary hilum vessel, main bronchus, or organ belonging to mediastinum of 1 cm or more with possibility of safely complete ablation (except for one patient with lesion distance of  $<1$ cm; no contraindications for RFA such as coagulopathy (prothrombin time greater than 1.5s, platelet count less than  $100 \times 10^9/L$ ) and not previously received other treatment, such as chemotherapy and/or radiation therapy for HCCPM.

Pretreatment workup included a complete history, physical examination, and imaging modalities including lung, abdomen, and pelvic CT scans with contrast medium, brain MRI, and electrocardiogram, and laboratory examinations, including complete blood cell counts, blood chemistry, viral titers (such as hepatitis B virus, hepatitis C virus, and human immunodeficiency virus), and coagulation profile examinations.

### ***RFA Procedure***

Before the procedure, all the patients fasted for 12 hours. The RFA procedure was performed in a hospital CT room by two experienced interventional radiologists, a technician, an anesthetist, and a nurse. All procedures were performed under real-time CT-fluoroscopic guidance (CTi; GE Medical Systems, Milwaukee, Wis) with 5-mm collimation and 10-50 mA. The patient was placed in the appropriate position according to the location of the tumor with electrocardiograms, blood pressure, and saturation of blood oxygen monitored throughout the procedure. Intraprocedural pain was treated by using a combination of local anesthesia (subcutaneous 1% lidocaine) and conscious sedation (propofol, 1-2mg/kg/h), or general anesthesia (enflurane/isoflurane). General anesthesia (15 sessions, 15 patients) was administered when the tumor was close to the pleura or when the patient requested for it.

After thoracic CT scanning was performed, the precise location of the target lesion was identified and the puncture angles and depths of electrode insertion were thereby confirmed. Local anaesthesia (subcutaneous 1% lidocaine) was administrated at the selected puncture points, and then a 0.5-cm surgical incision (subcostal or intercostal) was made. Two grounding pads were placed on the proximal thighs. The RF electrode was carefully inserted into the center of the tumor at a predetermined angle in a stepwise manner under CT scan guidance.

A monopolar internally cooled electrode (Cool-tip; Valleylab, MA, USA) was used for all lung RFA procedures. The procedures were performed according to the manufacturer recommended protocol. Specifically, a 17-gauge single internally cooled electrode was applied for 12 minutes per ablation with one or two session for each site in the tumor using an impedance-controlled algorithm for the Cool-tip system. Each patient underwent 1~3 sessions of ablation and the tumors larger than 3 cm received multiple overlapping ablations to obtain the ablative margin. A maximum of 3 lung tumors were treated on the same side of the lung. The remaining tumors were treated by RFA on the following week to minimize the possible procedure-related complications, especially for pneumothorax. At the end of each ablation session, the electrode track was ablated to avoid possible bleeding and the risk of puncture-related implantation metastases. The technique successes and possible complications were evaluated by an additional CT scan immediately after

the procedure; and ablation was considered successful with the presence of ground-glass opacity diameter 0.5 to 1.0 cm in diameter greater than the lesion. Patients were discharged usually 1 to 3 days after the procedure.

### ***Postablation evaluation and Follow-up***

Postablation follow-up evaluations were performed at 1, 3, 6, 9 and 12 months; at 6-month intervals thereafter with clinical and radiological examinations. Local efficacy was assessed according to the modified RECIST criteria together with the level of serum AFP one month after the RFA procedure. A serum AFP response was defined as a value  $<20\mu\text{g/L}$ , or a  $\geq 50\%$  reduction. The time to local tumor progression (TTP) was the interval from the completion of all treatments to the re-emergence of targeted lesions, or the detection of new metastatic lesions. The OS period (including the median survival time and 1-, 3-, and 5-year OS rates) for each patient was defined as the date of entry into the treatment to the date of the last visit before January 31, 2012 or death from any cause.

### ***Statistical analysis***

Survival outcome was calculated by Kaplan-Meier survival analysis. Prognostic factors for long-term survival were identified by univariate survival analysis, according to Cox proportional hazards regression methodology. Factors with a p-value of  $<0.05$  in univariate analysis were included in multivariate analysis. Statistical significance with a p-value of less than 0.05 was considered significant. All statistical analyses were performed using the Statistical Package for the Social Sciences program (SPSS v16.0, SPSS Inc., Chicago, IL, USA).

In order to evaluate the local control of HCCPM and OS, univariate and multivariate analyses were performed using the time interval between diagnoses of the HCC and lung metastases, number of tumors, and size of the largest tumor, hepatic virus infection, ZPS, serum AFP level before initial lung RFA, the response after initial lung RFA. Multilevel analysis was used to adjust for the potential correlation of multiple tumors in a single patient. The hazard ratio (HR) and 95% confidence interval (CI) for each variable were estimated.

### ***Results***

No death was related to the RFA procedure. The major complication was symptomatic hemothorax (3.9%, 2/51) treated with drainage. Minor complications (19.6%, 10/51) included self-limited minor hemothorax, a low-grade fever ( $< 37.5^{\circ}\text{C}$ ), which were easily controlled and well tolerated. A total of 51 RFA sessions (mean per patient: 1.76; range, 1-5) were successfully performed on 58 HCCPM lesions with CT guided RFA for 29 patients. One month after initial RFA procedure, complete ablation after initial lung RFA was achieved in 61.5% (13/29) of the patients. 18.8% of the patients with residual tumor revealed by enhanced CT scan and additional RFA were performed in all these 16 patients. Serum AFP level response rate was 80.6%.

The mean TTP was 15.6 months (range, 0-55 months). During follow up, 61.5% (13/29) of patients experienced only one recurrence of targeted lesions, 27.6% (8/29) experienced new non-targeted lung lesions progression and treated with additional lung RFA.

During the mean follow-up period of 62 months (range, 5 to 75), 38% (11/29) patients are still being followed up, while 62% (18/29) patients have died resulting from the progression of hepatic lesions. From the entry into the treatment for HCCPM, the median survival time after initial lung RFA was 18.9 months (range, 2 to 66). The 1-, 3-, and 5-year OS rates were 71.6%, 27.9%, and 9.3%, respectively. For the CR cases, the median survival time and OS were 21 months and 87.5%, 50.0%, and 25.0%, respectively, and for PR were 16 months and 62.5%, 11.7%, and 0%,

respectively. Prognostic factors of overall survival were analyzed and reported, serum AFP level before lung RFA (HR = 1.4, 95% CI 1.2-5.9; P = 0.028) and response to initial lung RFA (HR = 2.5, 95% CI 1.4-4.5; P = 0.002) were significant predictors for overall survival.

## ***Discussion***

Advances in surgical techniques and locoregional therapy for HCC have resulted in better surgical outcomes and long-term survival in recent years. However, the recurrence rate after curative resection of HCC is high, with distant metastasis most frequently found in the lung. Because local control of intrahepatic recurrence has been undertaken in a more proper and safe manner, there has been an increase in the number of deaths resulting from respiratory failure from pulmonary metastasis. Hence, active treatment for pulmonary metastasis from HCC has received landmark clinical attention. RFA is gaining increasing acceptance as a safe and effective therapeutic modality for primary and second lung tumors. In the present study the 5-year overall survival for HCCPM was 71.6 % with a mean survival after initial lung RFA of 18.9 months. The reported data revealed that the median overall survival after surgical metastasectomy for solitary lesion was 16-52 months and a median 5-year survival was 0-75%. Compared with these data, lung RFA in selected unresectable patients might provide a relevant survival benefit. Besides, the survival outcomes of the present study are comparable with previously published reports. Median overall survival in the literature for HCCPM patients ranges between 15 and 63 months and 5 year overall survival between 21 and 80%.

Our study has shown that lung RFA is a relatively safe and useful therapeutic option for selected patients with unresectable HCCPM. It showed the TTP of 15.6 months in overall cases which is similar to the figures of PFS in HCCPM with metastasectomy, however, median OS of 18.9 months in our report using RFA procedure is lower than that of pulmonary metastasectomy with a median OS of 29 (range, 16-52) months, median progress-free survival of 19 (range, 7-38) months and a median 5-year survival rate of 28% (range, 0-58%) in several studies. The results might be explained that the difference study population in terms of more lung metastatic lesions in bilateral lungs or being multiplies in our study in comparison with metastasectomy cases with solitary metastatic nodules. It is noteworthy that the subgroup of patients with CR after RFA showed a median survival rate (21 months, OS of 87.5%, 50.0%, and 25.0% at 1-,3-,5- years, respectively) that was similar to the figures of on pulmonary metastasectomy in recent studies. Given that all our patients were not surgical candidates, lung RFA seems to provide survival benefit.

The CR rates we obtained are also similar to the previous studies of lung metastasis tumors treated with RFA procedure, but it is significantly higher than that obtained on primary lung cancer with RFA procedure. The reason are: 1) More infiltrative tumor would be predicted to have a higher risk of tumor progression associated with the RFA procedure; since metastatic lesions are spherical in shape with a smooth margin which is easier to obtain cleaner regions with the RFA procedure. Closer follow-up surveillance of our patients, who had been enrolled into our clinical studies, facilitates early detection of HCCPM and prompt treatment. 2) Increasing concentration of serum AFP is associated with diagnosis of HCC in 70% of Asian patients. Correspondingly, serum AFP level is a sensitive marker to monitor the response assistant with follow-up.

In univariate and multivariate analyses, the maximum tumor diameter and number were not found to be significant prognostic factors. Serum AFP level before lung RFA and complete response to initial lung RFA were found as significant predictors for overall survival, while the number and size of the lung metastases were not prognosis for survival. That may be explained that HCCPM treated with RFA in our study was limited as no more than 5 and less than 5 cm in diameter, the CR rate and OS of the patients with 1, 2 lesions and lesions diameter less than 3 cm were similar with the reports of pulmonary metastasectomy with one site of extrahepatic lesion. The patients with more than 3 lesions were treated with more than one session of RFA to reduce the incidence of pneumothorax. Besides, patients with bilateral lung metastases are poor candidates for surgical intervention. In the present study, tumor distribution was not a prognostic factor, which suggests

an advantage of lung RFA over surgical intervention. The lesser invasiveness of the former appears to support the indication of lung RF ablation. In addition, RFA can also ablate with multiple lesions with synchronous or metachronous presentation of HCCPM patient to reach the relatively long OS, but, the contribution to prolong survival of metastasectomy has hindered for number of lesions, metachronous metastasis and undetected micrometastatic lesions present at the time of surgery. Prognostic factors identified in our study will help to stratify those patients who may benefit from lung RFA.

In our study the profile of procedure-related complications are infrequent and the most frequent complication was pneumothorax in ablating multi-metastatic lung lesions and the incidence was no more than those reported in previous studies to be associated with RFA in treating solitary tumors, which was mainly due to the minimum puncture numbers during the insertion of electrode into the target tumor under CT guidance by experienced interventional radiologists, as studies had shown that the number of insertions of the radiofrequency electrode was a significant risk factor causing pneumothorax. Besides, symptomatic pneumothorax can be controlled easily by using chest tube placement. Other complications such as haemorrhage, pneumonia, tumor seeding along the needle tract and subcutaneous emphysema were not observed in the present study.

As patients with unresectable liver cancer or who are not surgical candidates generally have significant comorbidities, together with low mortality and morbidity, repetitive application of RFA is a feasible treatment alternative, which is especially benefit for metastatic tumors with the nature of multiple origins.

There were some limitations which may affect clinical value of the study. Firstly, this was a retrospective study with a small sample size possibly resulting in insufficient statistical power. Besides, the diagnosis of HCCPM was mainly confirmed by the enhancement pattern observed on contrast-enhanced CT studies together with the level of AFP. Lastly, the use of two different probes for performing the RFA could have introduced some additional variability in the outcomes.

## ***Conclusion***

Our study showed the CT-guided RFA is a safe and effective treatment option with curative pursuits or prolong survival for unresectable HCCPM patients with well-controlled intrahepatic lesions. Further larger prospective studies or randomized controlled trials are needed to confirm the safety and efficacy of RFA for unresectable HCCPM.

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## ***Declaration of Interest***

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