Clinical outcomes of percutaneous thermal ablation for pulmonary metastases from hepatocellular carcinoma: a retrospective study

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\textbf{ABSTRACT}

\textbf{Purpose:} To determine the effectiveness of ablation for pulmonary metastases (PM) from hepatocellular carcinoma (HCC).

\textbf{Methods:} Between 2010 and 2017, the study analyzed 39 patients who had a median age of 59 years. Primary HCC was under control and the number of PM was less than 5 (median: 2), with a maximum diameter of \(\leq 60\) mm (median: 15 mm). The primary endpoints were overall survival (OS) and local tumor progression-free survival (LTPFS). Secondary endpoints included technical success (TS), complication and tumor response. TS referred to PM treated using the treatment protocol. Multivariate analysis using the Cox proportional hazard model was conducted on the potential risk factors (univariate: \(p < 0.5\)) to determine the independent factors (multivariate: \(p < 0.05\)).

\textbf{Results:} The TS rate was 100\%. Major complications included pneumothorax (\(n = 3\)) requiring chest tube placement and pleural effusion requiring drainage (\(n = 2\)). Complete ablation was achieved in 32/38 patients (valid percent: 84.2\%) at 1 month after ablation. The 1-, 3- and 5-year OS rates were 79.8, 66.9 and 30.9\%, respectively. The 1-, 3- and 5-year LTPFS rates were 60.7, 34.2 and 22.8\%, respectively. The extent (unilateral vs. bilateral) of PM (hazard ratio (HR): 0.197, 95\% confidence interval (CI): 0.043–0.890, \(p = 0.035\)) and the number (\(\leq 2\) vs. \(> 2\)) of PM (HR: 0.555, 95\% CI: 0.311–0.991, \(p = 0.047\)) were found to be the independent risk factors for predicting OS.

\textbf{Conclusion:} Percutaneous thermal ablation is a safe and effective treatment for PM from HCC.

\section*{Introduction}

In hepatocellular carcinoma (HCC), the lung is the most common site of extrahepatic metastasis [1]. Systemic therapy and supportive care are recommended for HCC patients with extrahepatic metastasis [2]. However, the survival outcomes are still dismal. Sorafenib is associated with median overall survival (OS) of 5–7.13 months for HCC patients with pulmonary metastases (PM) [3,4]. Chemotherapy could provide a median OS of 2.8 months, and supportive care provides a 1-year OS rate of 20\% in patients with PM from HCC [5]. Moreover, several published studies demonstrated that surgical resection can provide a 5-year OS rate ranging from 10–66.9\% [6–9] in select candidates. However, the majority of patients are not eligible for surgical treatment due to the existence of multiple PM or if the target lesion diameter exceeds 3 cm [10].

Recently, percutaneous thermal ablation was proposed as a treatment option for patients with lung malignancies [11–13]. Inducing necrosis in lung malignancy has been demonstrated in an animal model [14]. In addition, clinical studies investigating the safety of thermal ablation in humans have found that the treatment could achieve high tumor response [15–17], with a 1-year OS rate and a 1-year progression-free survival (PFS) rate of 89–100\% and 49–53\%, respectively [18–24]. However, only a few small studies have examined the clinical outcomes of thermal ablation therapy for PM from HCC. Hence, we aimed to evaluate the safety and efficacy of thermal ablation for PM originating from HCC.

\section*{Patients and methods}

\textbf{Patients}

This retrospective study was performed at one single institution with approval from an institutional ethics committee, and written informed consent was obtained before treatment.

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From June 2010 to July 2017, a total of 39 HCC patients with PM were treated with percutaneous thermal ablation. (a) Patients aged ≥18 years and ≤80 years, (b) patients who did not receive other treatment for PM besides ablation, (c) patients whose intrahepatic disease was under control (no evidence of local residual disease or recurrence existed) at the time of ablation for the PM diagnosis, (d) patients who had less than 3 PM, (e) patients who had a metastatic lesion diameter of less than 60 mm and (f) patients who were treated with curative intent and had a follow-up period of ≥3 months were included. Treatment decisions were determined after discussions with a multidisciplinary team.

(a) Patients who had uncorrectable coagulopathy or sepsisemia, (b) patients who refused ablation therapy or received other therapies besides ablation for PM and (c) patients who had other extrahepatic metastasis were excluded. The patient enrollment flow chart is shown in Supplementary Appendix 1.

**Ablation procedures**

**Equipment**

All procedures were performed under the guidance of a 16-slice computed tomography (CT) scanner (Aquilion™, Canon Medical Co., Tokyo, Japan). A radiofrequency ablation (RFA) system (RITA Medical Systems, Mountain View, CA) coupled with an RF generator (Model 1500X, RITA Co., USA) and an RF electrode (StarBurst™XL, RITA Co., USA) was used. An RFA device was used, which provided a maximum output power of 200 W. For microwave ablation (MWA), an MWA system (FORSEA MTC-3CA, Qinghai Microwave Electronic Institute, Nanjing, China) was used in this study. The RF generator could provide a maximum output power of 120 W. For microwave ablation (MWA), an MWA was performed with a frequency of 2450 MHz and provided an output power of 0–120 W. For cryoablation, a cryoablation system (Cryo-HIT™, Galil Medical, Yokneam, Israel) was used.

The choice of ablation techniques depended on the tumor size and location [25,26]. MWA was the preferred method for target lesions larger than 3 cm and/or close to large vessels, or for patients who had an implantable cardiac device, while cryoablation was performed for lesions close to the heart, pericardium or large airways, as it preserves the collagen matrix or peripheral lesions. If a patient could derive advantages from RFA, MWA and cryoablation, the treatment modality was determined by the patient’s preference and the radiologist’s experience.

**Ablation procedure**

Patients were provided local anesthesia with 2% lidocaine and were placed in an appropriate position. All ablation procedures were performed under CT guidance. A 22-gauge Chiba needle was advanced into the target lesion to lead the antenna/electrode/cryoprobe to the target. For the cryoablation procedure, the cryoprobe was inserted into the target lesion, and 2 or 3 consecutive cycles of freeze (10 min) and thaw (5 min) were performed. For the RFA or MWA procedure, the ablation electrode/antenna was inserted into the target lesion, maintaining a power of 45 W for a total ablation time of 10 min.

Intraoperative CT scans helped determine the correct position of the antenna/electrode. At the end of the RFA or MWA procedure, the needle track was ablated in order to avoid bleeding along the electrode route. Repeat CT scans were immediately performed to evaluate the TS, ablation margin and complications. Up to 3 PM were ablated on the same side of the lung. The endpoint of each ablation session was marked by the creation of an ablation zone of a circumference of at least 5 mm around the target lesion. The remaining nodules were ablated in the following week in order to minimize the potential risk of ablation-related complications. The ablation procedures are shown in Figure 1.

**Assessment of treatment efficacy and follow-up**

Tumor response was evaluated per patient by CT at 1 month after ablation, and all assessable patients were followed up at 3-month intervals.

Complications were recorded and classified based on the Society of Interventional Radiology Classification System [27]. A minor complication was described as an event requiring no therapy or nominal therapy, and with no accompanied consequence. A major complication was defined as an event that required major therapy or prolonged hospitalization, or induced potential mortality or permanent adverse sequelae.

Pneumothorax exceeding 30% of a hemithorax, rapidly accumulating with mediastinal shift, or accompanied with respiratory or circulatory distress, was treated with chest tube placement. If the pneumothorax required chest tube placement for more than 72 h, or accorded with the definition of a major complication, it was considered as a major complication. Pleural effusion that exceeded 50% of a hemithorax or symptomatic pleural effusion was also treated with chest tube drainage [28]. Mild pleural effusion was defined as effusion exceeding no more than 50% of a hemithorax.

The primary endpoints were OS and local tumor progression-free survival (LTPFS). OS was defined as the interval from initial ablation to death or the latest date when the patient was still alive. LTPFS was defined as the interval from initial ablation to radiologic evidence of local tumor progression or the latest date of follow-up.

TS was defined as the target tumor treated with the predetermined treatment protocol and covered completely by the ablation zone [27]. Tumor coverage was assessed immediately after ablation. Local tumor response was evaluated using mRECIST at 1 month after ablation [25]. Unchanged morphologic features of the ablation zone or shrinkage without an enhancement at CT were considered as complete ablation. An increase in the overall size of the ablation zone without change in the enhanced zone was considered as incomplete ablation. Enlargement of the ablation zone to more than 10 mm due to the newly developed enhancement at CT was considered as local progression. If local progression or incomplete ablation was detected at 1 month after ablation, up to two ablation sessions were performed.
Statistical analysis

Data were analyzed using SPSS 20.0 for Windows (IBM Corp, Armonk, NY). The baseline and clinical characteristics were expressed as median±range or frequency (categorical variables). Survival data were depicted by the Kaplan–Meier method and compared using the log-rank test. Factors associated with OS were determined by performing univariate and multivariate analysis using the Cox proportional hazards model. Univariables with \(p<0.5\) were incorporated into the multivariate analysis. The final model was chosen based on those variables with \(p<0.05\) in the multivariate analysis. All the statistical tests were two-sided, and \(p<0.05\) was considered statistically significant.

Results

Demographic and clinical characteristics

Table 1 shows the baseline demographic characteristics of the patients. A total of 39 patients were included in this study. The sample included 33 (33/39, 84.6%) men and 6 (6/39, 15.4%) women. The median age of the patients was 59 years (range: 31–78 years). The median number of metastatic lesions per patient was 2 (range: 1–5). The median maximum diameter of the metastatic lesions was 15.0 mm (range: 6.00–52.00 mm). A total of 60 sessions were performed in 39 patients (23 patients had 1 session each, 11 patients had 2 sessions each and 5 patients had 3 sessions each).

Tumor response and local control rate

The TS rate was 100%. Thirty-three patients had ablation margins of \(\geq5\) mm: 29 of them were evaluated as having complete ablation, 1 of them was classified as having incomplete ablation, and 3 of them were evaluated as having local progression. Five patients had ablation margins of \(<5\) mm: 5 received salvage ablation at 1 month after ablation (3 were evaluated as having complete ablation, 2 were evaluated as having local progression). The remaining 1 did not have the images at 1 month after ablation, but the CT images at 4 months after ablation were evaluated as local progression.

Table 2 shows the tumor response at 1 month after ablation. A total of 32 patients (32/38, 84.2%) achieved complete ablation, 1 (1/38, 2.6%) was classified as having incomplete ablation, and 5 patients (5/38, 13.2%) had local progression.

Survival outcomes

The median follow-up period was 13.47 months (range: 4.5–67.09 months). Figure 2(A) shows the OS curves of the entire sample. The median OS rate was 45.14%. The 6-month and 1-, 2-, 3- and 5-year OS rates were 97.4, 79.8, 71.8, 58 and 30.9%, respectively. Twelve events occurred: six of them due to intrahepatic HCC, one of them due to hepatic failure, and five of them were out-of-hospital death with unknown cause.
Figure 2(B) shows the LTPFS curves. The 6-month and 1-, 2-, 3- and 5-year LTPFS rates were 80.4, 60.7, 45.5, 34.2 and 22.8, respectively. Twenty patients had local recurrence after ablation, of which 7 received ablation therapy. Twenty-seven patients had distant recurrence after ablation, and 12 of them received ablation.

Table 3 and Figure 3 show the OS rates and LTPFS rates in different subgroups divided by the number, laterality of metastases and ablation modalities. No significant difference was detected among all groups.

Univariate and multivariate cox proportional hazards regression analyses

Table 4 shows the results of the univariate and multivariate analyses. In the multivariate Cox regression analyses, adjusting for clinically significant univariate factors, the number of (≤2 vs. >2) PM (hazard ratio (HR): 0.555, 95% confidence interval (CI): 0.311–0.991, p = 0.047) and the extent (unilateral vs. bilateral) of PM (HR: 0.197, 95% CI: 0.043–0.890, p = 0.035) were determined as the independent prognostic factors for OS.

Complications

Major complications were observed in 5 (5/39, 12.8%) patients, including pneumothorax requiring chest tube placement (3 patients; 7.7%) and pleural effusion requiring chest tube drainage (2 patients; 5.1%). Minor complications included mild pneumothorax (18 patients), pneumonia (7 patients), mild hemorrhage (19 patients) and mild pleural effusion (22 patients). No ablation-related deaths were detected.

Discussion

Our study showed a high TS rate with the use of ablation for treatment of PM from HCC. The modality demonstrated an
acceptable safety profile, with no ablation-related deaths or life-threatening complications.

Percutaneous ablation therapy could provide promising survival outcomes. Hiraki et al. [29] reported 1- and 3-year OS rates of 87 and 57%, respectively, in 32 patients with PM from HCC after RFA treatment. Li et al. [30] retrospectively evaluated 29 HCC patients with PM who were treated with RFA, and reported 1- and 3-year OS rates of 73.4 and 30%, respectively, with a median OS of 21 months. The survival outcomes in the present study are promising and similar to those reported earlier. A possible reason for the promising survival outcome may be the repeatability of the ablation therapies. Previous studies have found that ablation therapy can be repeatedly performed in patients with recurrent lung tumors [24,31]. Yan et al. [16] demonstrated a 3-year OS rate of 92% in patients with recurrent lung tumors who underwent repeat RFA vs. 45% in those who did not undergo a repeat RFA. However, re-ablation was not the independent risk factor for OS. It is difficult to determine the accurate effect of repeat ablation on survival. Further randomized trials with larger sample sizes are needed to investigate the effect of the ablation session on survival.

Previous studies suggested using surgical resection to treat PM. The 5-year OS rates after resection for unilateral PM were reported to range from 28.2–66.9% [7–9,32,33]. Our findings are comparable to the results obtained using surgical resection. The 30-day mortality rates in patients undergoing lobectomy, segmentectomy and pneumonectomy were reported to be 0.26, 0.31 and 2.45%, respectively [34]. In comparison, the 30-day mortality rate after ablation therapy ranges from 0–0.35% in previous studies [18,21,35,36]. It seems that the mortality rates among ablation, lobectomy and segmentectomy are similar. Even though the rate after pneumonectomy was the highest, pneumonectomy is not a conventional therapy for PM. Thus, further randomized trials should be conducted to investigate whether these findings

### Table 3. Subgroup analysis for overall survival rate, local tumor progression-free survival rate and complete response rate.

| Subgroup               | Number | 3-year OS (%) | 5-year OS (%) | p Value | 3-year LTPFS (%) | 5-year LTPFS (%) | p Value | CR (1 month), % | p Value |
|------------------------|--------|---------------|---------------|---------|------------------|------------------|---------|-----------------|---------|
| ALL                    | 58     | 50.0          | 30.9          | 0.098   | 34.2             | 22.8             | 0.185   | 84.2           | 0.682   |
| Number of lesions ≤2   | 23     | 35.2          | 35.2          |         | 21.2             | NA               |         | 86.4           |         |
| Number of lesions >2   | 16     | 85.6          | 32.1          |         | 57.0             | 28.5             |         | 81.3           |         |
| Extent of lung metastases |       |               |               | 0.298   |                  |                  |         | 0.401          | 0.660   |
| Unilateral             | 20     | 65.8          | 65.8          |         | 39.7             | NA               |         | 89.5           |         |
| Bilateral              | 19     | 50.8          | 19.1          |         | 29.3             | 14.6             |         | 78.9           |         |
| Ablation technique     |        |               |               | 0.630   |                  |                  |         | 0.068          | 0.156   |
| RFA                    | 22     | 49.9          | NA            |         | 31.0             | NA               |         | 90.9           |         |
| MWA                    | 8      | NA            | NA            |         | NA               | NA               |         | 87.5           |         |
| Other                  |        |               |               |         |                  |                  |         |                 |         |
| RFA + MWA              | 2      | 100           | NA            |         | NA               | NA               |         | 66.7           |         |
| Cryoablation           | 7      | 75.0          | 50            |         | 30.0             | 33.3             |         | 50.0           |         |

NA: not available; RFA: radiofrequency ablation; MWA: microwave ablation; CR: complete ablation.

![Figure 2](image.png)

**Figure 2.** The Kaplan–Meier estimates of survival for all included patients. (A) The OS rates of all patients with pulmonary metastases (PM) from hepatocellular carcinoma (HCC) treated with thermal ablation. (B) The local progression-free survival rates of all patients with PM from HCC treated with thermal ablation.
Figure 3. The Kaplan–Meier estimates of survival for patients in different subgroups. (A) and (C): The overall survival (OS) rates and local progression-free survival (LTPFS) rates of patients with ≤2 or >2 PMs. (B) and (D): the OS rates and LTPFS rates of patients with unilateral or bilateral PM.

Table 4. Univariate and multivariate analysis of all included patients for overall survival in Cox proportional hazard model.

| Variation          | Univariate          | Multivariate         |
|--------------------|---------------------|----------------------|
|                    | HR (95%CI)          | p Value              | HR (95%CI)          | p Value              |
| Categorical variables |                    |                      |                      |                      |
| Gender             | 1.274 (0.272–5.963) | 0.758                | 2.277 (0.465–11.148) | 0.310                |
| Diabetes           | 1.042 (0.312–3.476) | 0.947                | 0.923 (0.390–1.445) | 0.727                |
| Hypertension       | 0.855 (0.185–3.966) | 0.842                | 0.769 (0.349–1.695) | 0.515                |
| Alcohol            | 0.570 (0.124–2.616) | 0.470                | 0.197 (0.043–0.890) | 0.035                |
| Smoking            | 0.814 (0.239–2.766) | 0.741                |                      |                      |
| Treatment for primary HCC | 0.751 (0.310–1.106) | 0.147                | 0.923 (0.390–1.445) | 0.727                |
| Ablation modality for PM | 0.740 (0.375–1.461) | 0.386                | 0.769 (0.349–1.695) | 0.515                |
| Extend of PM       | 1.893 (0.559–6.409) | 0.305                | 0.197 (0.043–0.890) | 0.035                |
| Liver cirrhosis    | 1.042 (0.312–3.476) | 0.947                |                      |                      |
| Age                | 0.996 (0.946–1.049) | 0.890                |                      |                      |
| Preoperative AFP   | 1.00006 (0.99997–1.0001) | 0.223            | 1.00007 (0.99995–1.0002) | 0.233            |
| Ablation session   | 0.892 (0.434–1.833) | 0.755                |                      |                      |
| Number of PM       | 0.802 (0.533–1.209) | 0.292                | 0.555 (0.311–0.991) | 0.047                |
| Maximum diameter of PM | 0.962 (0.883–1.047) | 0.367                | 0.979 (0.891–1.075) | 0.659                |
| Ablation margin    | 0.524 (0.110–2.494) | 0.417                | 0.838 (0.142–4.928) | 0.845                |

HCC: hepatocellular carcinoma; AFP: alpha-fetoprotein; PM: pulmonary metastases.
could indicate that a patient at high risk of death within 30
d of surgery would derive more advantages from abla-
tion therapy.

Tumor number is a significant element of complete abla-
tion. A previous study demonstrated that solitary tumors
have lower local recurrence rates compared with multiple
tumors [37]. Li et al. [30] investigated the prognostic factors
associated with survival rate after ablation therapy for PM,
and found that PM $\leq 3$ in number were associated with bet-
ter survival than PM exceeding 3 in number. In the current
study, patients with more than 2 metastases faced 0.555
times the risk of death compared to those with $\leq 2$ metasta-
ses. Moreover, the extent of PM was another independent
risk factor in the current study. However, not only TS, but
also the survival rate encouraged bilateral PM after ablation
treatment. In the present study, thermal ablation of bilateral
PM yielded a TS rate of 100% and the 5-year OS rate of
patients with bilateral PM cases after ablation was 19.1%.Ours
results are comparable to those of a previously reported
study about ablation efficacy for PM [38]. It should be noted
that the OS rate of bilateral PM patients treated with surgery
was only 8.3% [39]. Moreover, pulmonary function was not
significantly affected by RFA, whereas it has been shown to
reduce severely after bilateral pulmonary metastasectomy
[36,40]. Patients with more than 2 PM or patients with bilat-
eral metastases showed improved OS after ablation therapy,
albeit with a small magnitude of benefit; thus, these multi-
variate analysis results could be used to inform the conversa-
tion about risks and benefits with patients.

It should be noted that the TS rate was 100%, while the
complete ablation rate was only 84.2%. The distinction
between TS and complete ablation (or technique effective-
ness) should be clarified. Effectiveness should be demon-
strated with an appropriate time point, such as immediately
after the last course of the ablation protocol, or at 1 week or
1 month after treatment, at which complete ablation of the
macroscopic tumor (as evidenced at imaging follow-up) was
achieved. On the contrary, TS simply addresses whether the
tumor was treated according to protocol and was covered
completely, and it can be assessed either during or immedi-
ately after the procedure. TS highlights whether the protocol
could be effectively performed [41].

Whether different ablation techniques could induce differ-
ent clinically relevant outcomes, especially RFA and MWA, is
still under debate. Comparing the CR rate among different
ablation techniques showed no significant differences in the
current study. Previous studies indicated that MWA was
superior to RFA due to better survival for lung metastases
patients [42]. Moreover, a recent randomized, controlled,
phase 2 trial comparing the efficacy and safety of RFA and
MWA demonstrated that MWA was not superior to RFA in
terms of procedure time, local tumor progression, frequency
of complications, and OS [43]. Thus, further studies are
needed to clarify the difference between these ablation
techniques.

According to previous studies, the rate of pneumothorax
after thermal ablation ranges from 8.5–50% [21,35,36,44],
and the rate of major complications lies between 1.6 and
21% [28,45]. The rates of pneumothorax and pneumothorax
requiring chest tube placement in our study were consistent
with the findings of earlier studies. Previous research [44] has
reported that patients with PM located in the upper lobe are
more likely to require chest tube placement for pneumo-
thorax. Pleural effusion is one of the most commonly
reported complications for lung cancer, occurring in 1.3–60%
of ablation procedures [46]. The findings of our study are
similar to previous reports. The most likely cause of pleural
effusion is pleurisy induced by the conduction of ablation
energy to the pleura [47]. Further, multiple lesions ablated in
one ablation procedure, large-sized target lesions, lesions
abutting pleura (<10 mm), or procedures of long duration
may be associated with pleural effusion requiring treat-
ment [28].

This study has certain limitations. First, a selection bias
was unavoidable, given the retrospective nature of this
study. Second, the sample size was small, thus limiting the
statistical power of the current study. Third, because of the
complexity of the technique features (e.g., antenna design
and frequency of operation), comparison among MWA, RFA
cryoablation is difficult. Fourth, the patients included in
the study were in an advanced stage of HCC, and many
patients who reported recurrences after ablation may have
received other therapies, such as systemic therapy. However,
a detailed analysis of these patients is not possible. Fifth,
given the small sample size, the variation within the group
and the presence of interaction would affect the stability
and accuracy of the Cox proportional hazards model. Sixth,
information about other treatments for PM after ablation,
such as systemic treatment, and other treatments for local or
distant recurrence was insufficient. These aspects would
interfere with the analysis of the ablation efficacies.

In conclusion, percutaneous thermal ablation appears to
be safe and effective for patients with PM from HCC. Survival
outcomes are improved in patients with PM. However, multi-
center, randomized and controlled trials with larger sample
sizes are needed to confirm these findings.

Acknowledgments
The institutional review board of Ethics Committee has approved this
study. Informed consent was obtained from all individual participants
included in the study. Human experimentation guidelines of China were
followed in the conduct of this clinical research. The work described has
not been published or accepted elsewhere, in whole or in part. All the
authors listed have seen and approved the manuscript that is enclosed,
contributed significantly to the work.

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