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ORIGINAL ARTICLE

Combination therapy by transarterial injection of miriplatin-iodized oil suspension with radiofrequency ablation (RFA) versus microwave ablation (MWA) for small hepatocellular carcinoma: a comparison of therapeutic efficacy

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Abstract

Purpose To compare the technical efficacy and complications of the transarterial injection of a miriplatin-iodized oil suspension combined with radiofrequency ablation (RFA) or microwave ablation (MWA) in the treatment of small hepatocellular carcinomas (HCCs).

Materials and methods This retrospective study included 123 HCCs in 101 patients treated with the transarterial injection of a miriplatin-iodized oil suspension and RFA (MPT-RFA) (maximum diameter: 1.5 ± 0.5 cm, range: 0.6–3.0 cm) and 68 HCCs in 49 patients treated with the transarterial injection of a miriplatin-iodized oil suspension and MWA (MPT-MWA) (maximum diameter: 1.6 ± 0.7 cm, range: 0.5–3.0 cm). Technical success was defined as the achievement of an ablative margin of at least 5 mm for each tumor. Technical success, complications, and local tumor progression were compared between the two groups.

Results The initial technical success rate was significantly higher with MPT-MWA (94.1%) than with MPT-RFA (76.4%; $P=0.003$). The number of treatment sessions per nodule was significantly lower with MPT-MWA (1.1) than with MPT-RFA (1.3) ($P=0.004$). The major complication rates were similar with MPT-RFA (5.8%) and MPT-MWA (2.7%) ($P=0.391$). The one-year local tumor progression rate was similar between MPT-RFA (0%) and MPT-MWA (0%) ($P=0.73$).

Conclusion MPT-MWA may have improved therapeutic efficiency in the treatment of small HCCs.

Keywords Microwave ablation (MWA) · Hepatocellular carcinoma · Ablative margin · Radiofrequency ablation (RFA) · Miriplatin

Introduction

Hepatocellular carcinoma (HCC) ranks sixth in terms of prevalence and fourth in terms of mortality among malignant neoplasms worldwide [1]. Radiofrequency ablation (RFA) is the standard reference technique for percutaneous ablation; however, even in small HCCs measuring 3 cm or smaller, the local tumor progression rate with RFA monotherapy is as high as 41.0% [2, 3]. Local tumor control is very important because the presence of the local tumor progression significantly decreases survival in patients with HCC who have undergone curative RFA [4]. Several studies have shown that RFA following transcatheter arterial chemoembolization (TACE) (TACE-RFA) expands the ablative zone and is useful in preventing local tumor progression [5, 6]. The local tumor progression rate in small HCCs measuring 3 cm or smaller treated by TACE-RFA is 3.9–16.0% [2, 6, 7]. However, when performing TACE-RFA in one session, liver infarction is a potential risk [8, 9]. Compared with conventional TACE-RFA, the simultaneous combination of the transarterial injection of a miriplatin-iodized oil suspension and RFA (MPT-RFA) expands the ablative area without causing liver infarction and has similar therapeutic efficacy to that of TACE-RFA [10].

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Microwave ablation (MWA) has gained increased attention because it provides thermal energy more rapidly and larger ablative volumes than RFA, particularly in the new MWA using the Emprint system (Covidien, Boulder, CO). No study has compared the transarterial injection of a miriplatin-iodized oil suspension and MWA using the Emprint system (MPT-MWA) with conventional MPT-RFA in terms of the therapeutic efficacy and complications, particularly for the treatment of small HCCs. This study attempted to compare the therapeutic efficacy and complication rates of MPT-RFA and MPT-MWA in the treatment of small HCCs.

Materials and methods

Patient selection

This was a retrospective study of patients with HCC who had undergone combination therapy with MPT-RFA or MPT-MWA between January 2016 and December 2019. This retrospective study was approved by the hospital's institutional review board. The requirement for informed consent for the use of data was waived. The inclusion criteria for this study were as follows: (a) ineligible for surgical intervention; (b) Child–Pugh class A or B; (c) three or fewer tumors ≤ 3 cm in diameter; (d) no vascular invasion; and (e) no extrahepatic metastasis. The exclusion criteria were as follows: (a) total bilirubin ≥ 3.0 mg/dl; (b) platelet count < 40,000/μl or prothrombin activity < 40%; (c) presence of refractory ascites; (d) presence of other uncontrollable malignancies.

Concerning the ablation modality, RFA was utilized in all the patients treated before August 2018. In Starting in August 2018, we began using MWA routinely. The study population comprised 150 patients (101 MPT-RFA, 49 MPT-MWA) with 191 HCCs targeted for treatment with either MPT-RFA ($n = 123$) or MPT-MWA ($n = 68$) between January 2016 and December 2019. The incidence of des-γ-carboxy-prothrombin (DCP) > 40 (mAU/ml) was significantly higher in the MPT-MWA group than in the MPT-RFA group ($P = 0.005$). The tumor size was 1.5 ± 0.5 cm in the MPT-RFA group (range 0.6–3.0 cm) and 1.6 ± 0.7 cm in the MPT-MWA group (range 0.5–3.0 cm), with no significant difference ($P = 0.203$). Tumor location (subphrenic location, subcapsular location) was assessed by preoperative CT and MR imaging. When the HCC was in the liver dome and adjacent to the diaphragm, the lesion was defined as a subphrenic lesion. When the HCC was superficially located, abutting the liver capsule, the lesion was defined as a subcapsular location. The subcapsular location comprised 47 lesions (38.2%) in the MPT-RFA group and 31 lesions (45.6%) in the MPT-MWA group, with no significant difference ($P = 0.322$). The subphrenic location comprised 33 lesions (26.8%) in the MPT-RFA group and 18 lesions (26.5%) in the MPT-MWA group, with no significant difference ($P = 0.957$). The baseline characteristics are summarized in Tables 1 and 2.

Combination therapy

All the procedures were performed in an angiographic suite [Artis Q TA (SIEMENS AG, Germany), SOMATOM Definition AS20: (SIEMENS AG, Germany)]. Ablation was performed immediately after the transcatheter arterial miriplatin injection and percutaneously using local anaesthesia [1% lidocaine hydrochloride with epinephrine bitartrate (1% xylocaine E; Aspen Pharma, Tokyo, Japan)] with moderate sedation (fentanyl citrate (Janssen–Kyowa Co., Ltd., Tokyo, Japan), midazolam (Astellas, Tokyo, Japan), and hydroxyzine hydrochloride (Pfizer, Tokyo, Japan)).

Transarterial injection of miriplatin-iodized oil suspension

Common femoral arterial access was achieved using a 4-F vascular sheath. Celiac arteriography was performed to assess the tumour blood supply. A 1.9-F microcatheter (Tellus; ASAHI INTECC, Seto, Japan) was used to select the arteries that fed the tumors. The miriplatin-iodized oil suspension (MPT) was prepared by dissolving 70 mg of miriplatin (MIRIPLA: Dainippon Sumitomo Pharma, Osaka, Japan) in 3.5 ml of iodized oil (MIRIPLA suspension vehicle: Dainippon Sumitomo Pharma,). In this study, the maximum doses of miriplatin and iodized oil were 120 mg and 6 ml, respectively. The MPT was warmed to 40 °C because we intended to increase the accumulation of the MPT [11, 12]. MPT was injected at one or several catheter positions where the tumor staining was visualized clearly. If the tumor staining was faint, the injection site was determined by CT during hepatic arteriography. In the MPT-RFA group, the most of the MPT was injected into the right or left hepatic artery in 15 lesions (12.1%, 15/123), a segmental artery in 17 lesions (13.8%, 17/123), and a subsegmental artery in 91 lesions (73.9%, 91/123). In the MPT-MWA group, the most of the MPT was injected into the right or left hepatic artery in 7 lesions (10.0%, 7/68), a segmental artery in 14 lesions (20.6%, 14/68), and a subsegmental artery in 47 lesions (69.1%, 47/68). The MPT was administered under continuous fluoroscopic guidance until visible stasis of flow to the selected hepatic artery was noted. In the MPT-RFA group, the mean [± standard deviation (SD)] doses of miriplatin and iodized oil per lesion were 36.1 ± 20.5 mg and 2.1 ± 1.3 ml, respectively. In the MPT-MWA group, the mean (± SD) doses of miriplatin and iodized oil per lesion were 35.3 ± 21.7 mg and 2.3 ± 1.6 ml, respectively. No significant difference was found in the dose of miriplatin ($P = 0.858$) and iodized oil ($P = 0.705$) between the groups.

Table 1 Baseline patients characteristics of the two groups

Variable	MPT + RFA, *N* (%)	MPT + MWA, *N* (%)	*P*
Patient characteristics			
No. of patients	101	49	
Age (years, mean ± SD)	72.3 ± 9.0	71.8 ± 8.6	0.911
Age range	45–92	52–87	
Sex			
Men	84(83.2)	38(77.5)	0.408
Women	17(16.8)	11(22.5)	
History of HCC			
Naïve HCC	17 (16.8)	13 (26.5)	0.161
Recurrent HCC	84 (83.2)	36 (73.5)	
No. of tumors			
1	83 (82.1)	33 (67.3)	0.203
2	14 (13.9)	13 (26.5)	
3	4 (4.0)	3 (6.2)	
Cause of liver disease			
HBV	37 (36.6)	17 (34.6)	0.861
HCV	36 (35.6)	16 (32.7)	
Other	28 (28.8)	16 (32.7)	
Child–Pugh class			
A	91 (89.1)	45 (91.8)	0.729
B	10 (10.9)	4 (8.2)	
AFP (ng/mL)			
≤ 20	82 (81.2)	34 (69.4)	0.171
> 20	19 (18.8)	15 (30.6)	
DCP (mAU/ml)[a]			
≤ 40	76 (77.5)	25 (54.3)	0.005
> 40	22 (23.5)	21 (46.7)	

Values in parentheses are percentages

RFA, radiofrequency ablation; MWA, microwave ablation; MPT + RFA, transarterial injection of a miriplatin-iodized oil suspension and RFA; MPT + MWA, transarterial injection of a miriplatin-iodized oil suspension and MWA; SD, standard deviation; HCV, hepatitis C virus; AFP, α-fetoprotein; DCP, des-γ-carboxy-prothrombin; HCC, hepatocellular carcinoma. [a]The serum DCP level could not be measured in 3 MPT-RFA patients and 3 MPT-MWA patients because they were being administered warfarin

Ablation

To avoid nontarget organ thermal injury, organ displacement using a hyaluronic acid gel [13] before ablation was performed for 20 HCCs (17%, 20/123) in the MPT-RFA group and 8 HCCs (19%, 12/68) in the MPT-MWA group. During this period, the transhepatic approach was first chosen to place the radiofrequency electrode or microwave antenna even if the tumor was located in the subphrenic region. When a transhepatic approach was judged to be too difficult, a transpulmonary approach was chosen to place the radiofrequency electrode or microwave antenna [14]. For RFA, we used the VIVA RF ablation system (STARmed Gyeonggi-Do, Korea) with a 17-gauge internally cooled electrode. The exposed tip length of the cooled electrode was selected based on the tumor size. For MWA, we used a 2.45-GHz MWA system (Emprint ablation system; Covidien, Boulder, Colorado) with a 13-gauge antenna and an internally cooled tip surrounded by saline irrigation channels. Placement of the needle (RFA electrode, MWA antenna) into the tumor was performed under CT fluoroscopy (SOMATOM Definition AS20). Positioning of the needle was confirmed by CT (Figs. 1a, 2a). Before the start of the initial ablation, the depth of the tumor was measured as the distance from the needle entry site of the skin to the deepest portion of the tumor on the CT (Figs. 1a, 2a). Ablation was performed according to the manufacturer's protocol to create an ablative margin larger than 5 mm around the tumor. For initial ablation of MWA, preheat ablation (45 W for 1 min and 75 W for 1 min) was routinely performed to avoid steam popping, which may increase the risk of peritoneal seeding [15]. To achieve a sufficient margin, as much additional overlapping ablation as possible was performed by repositioning the needle. Ablation was repeated until the ablative area estimated

Table 2 Baseline tumor characteristics of the two groups

Variable	MPT + RFA, *N* (%)	MPT + MWA, *N* (%)	*P*
No. of tumors	123	68	
Maximum tumor size (cm)			
Mean ± SD	1.5 ± 0.5	1.6 ± 0.7	0.203
Range	0.6–3.0	0.5–3.0	
Maximum tumor size (cm) 2.1–3.0	31(25.2)	20(29.0)	0.472
Tumor location			
Subcapsular location	47(38.2)	31(45.6)	0.322
Subphrenic location	33(26.8)	18(26.5)	0.957
Tumor segment			
Segment 1	1(0.8)	2(2.9)	0.257
Segment 2	11(8.9)	6(8.8)	0.978
Segment 3	13(10.6)	7(10.3)	0.953
Segment 4	13(10.6)	5(7.3)	0.466
Segment 5	19(15.4)	9(13.2)	0.679
Segment 6	18(14.6)	15(22.0)	0.194
Segment 7	11(8.9)	2(2.9)	0.118
Segment 8	37(30.2)	22(32.6)	0.260

Values in parentheses are percentages

RFA, radiofrequency ablation; MWA, microwave ablation; MPT + RFA, transarterial injection of a miriplatin-iodized oil suspension and RFA; MPT + MWA, transarterial injection of a miriplatin-iodized oil suspension and MWA; SD, standard deviation

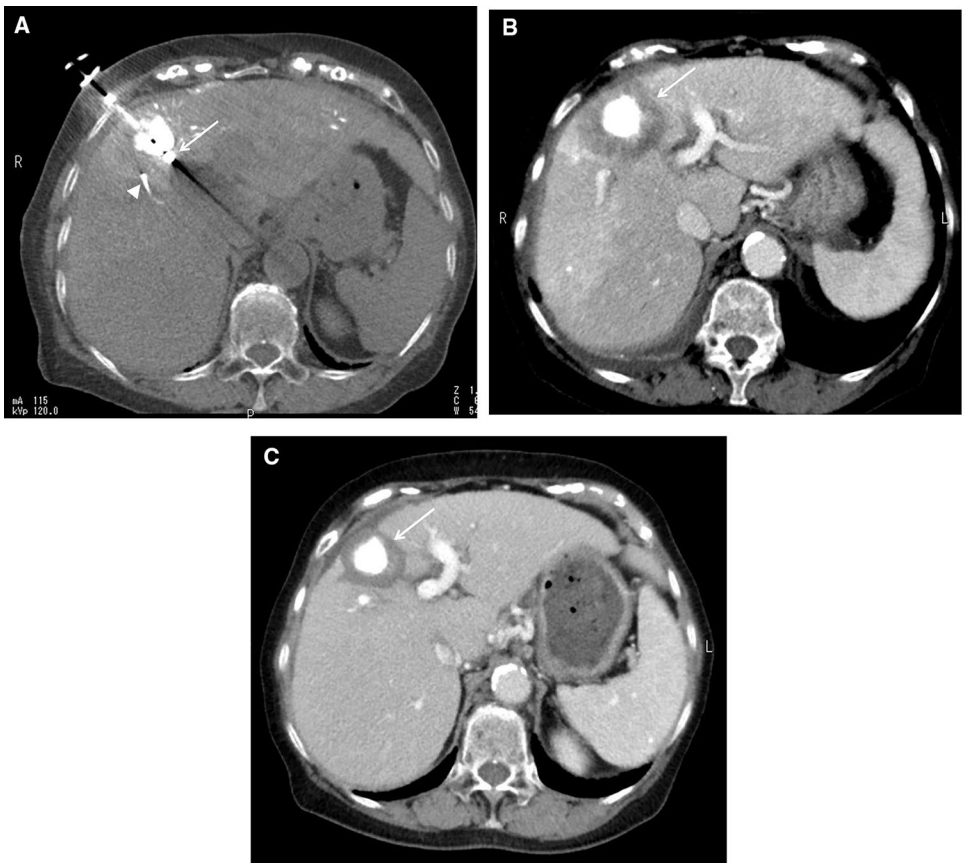

Fig. 1 **a**–**c** A 77-year-old woman with HCC measuring 2.4 cm in the medial segment. **a** Microwave ablation (MWA) was performed on the same day after the transarterial injection of a miriplatin-iodized oil suspension under real-time CT fluoroscopic guidance. The antenna was placed at the centre of the tumor (arrow). The depth of the tumor was 5.8 cm. The microcatheter was placed near the tumor (arrowhead). The lesion was ablated for 2 min under preheating ablation (45 W for 1 min and 75 W for 1 min) and 8.5 min at 100 W. **b** Axial contrast-enhanced CT image obtained one day after MWA. The tumor enhancement disappeared, and the tumor was surrounded by hypoattenuated nonenhanced areas (ablative margin) (arrow). **c** Axial contrast-enhanced CT image obtained 6 months after MWA showing no local tumor progression (arrow)

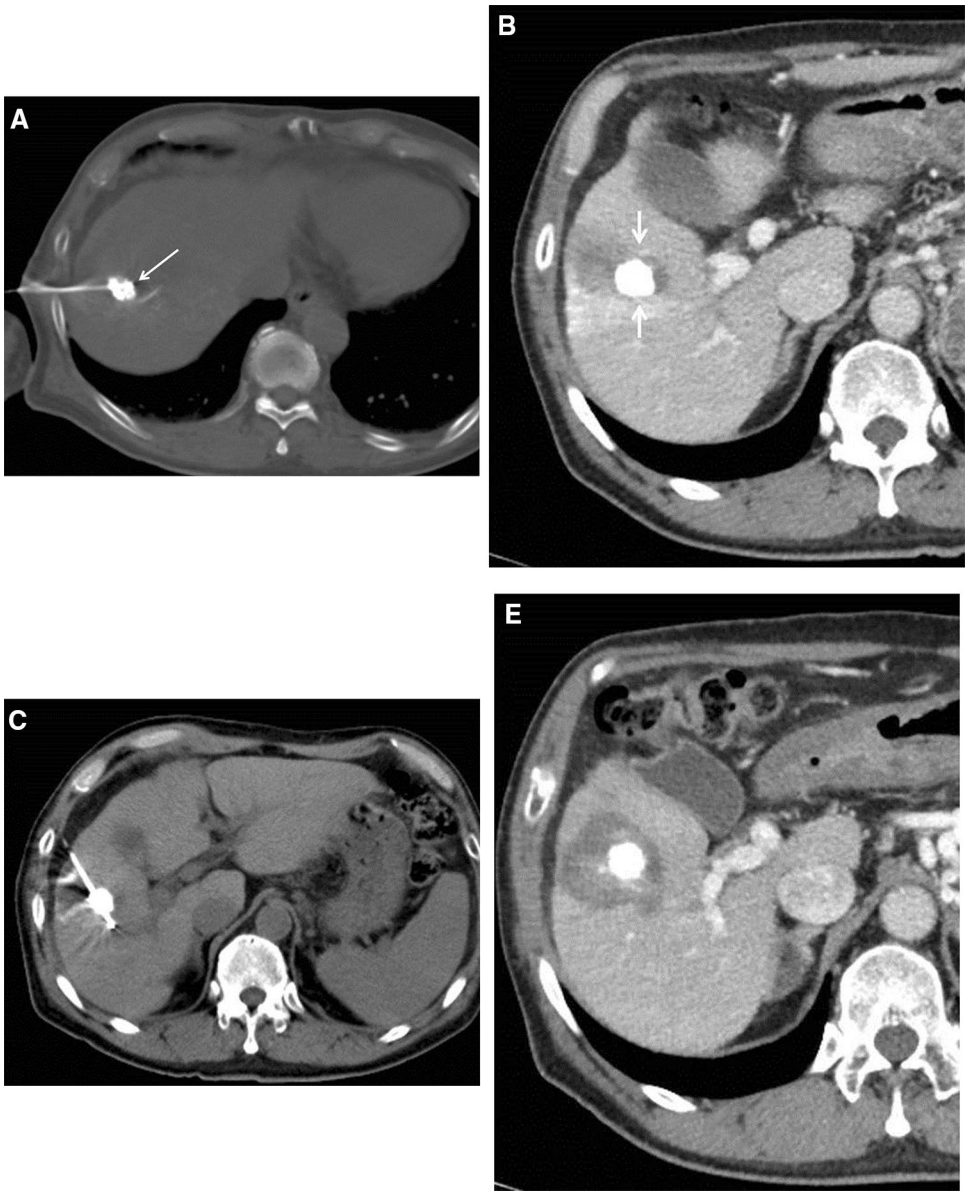

Fig. 2 **a–d** A 69-year-old man with HCC measuring 1.8 cm in the posterior segment. **a** Radiofrequency ablation (RFA) was performed on the same day after the transarterial injection of a miriplatin-iodized oil suspension under real-time CT fluoroscopic guidance. The RFA electrode (3-cm tip exposure) was placed at the tumor (arrow). The depth of the tumor was 9.5 cm. One ablation was performed for 12 min. **b** Axial contrast-enhanced CT image obtained one day after the first RFA session. The ventral and dorsal sides of the ablative margin were insufficient (arrow). **c** A second RFA session was performed to establish a sufficient ablative margin. An RFA electrode (3-cm tip exposure) was placed in a different direction from the initial RFA. One ablation was performed for 12 min. **d** Axial contrast-enhanced CT image obtained one day after the second RFA session. The tumor was surrounded by a sufficient ablative margin (arrow)

by CT covered the index tumor with an ablative margin larger than 5 mm. For RFA, tract ablation was performed, while maintaining the electrode temperature > 80 °C ℃ without circulating saline within the electrode. For MWA, tract ablation was performed at 75 W while retracting the antenna and ablating every centimetre of the needle track for 10 s. Immediately after ablation, hepatic arteriography and plain CT were performed to identify for serious complications, such as massive bleeding and pneumothorax.

Treatment endpoint

The ablation endpoint was the identification of complete tumor coverage and a 5-mm circumferential margin on contrast-enhanced three-phase CT one day after ablation (Figs. 1b, 2b). Additional ablation was performed within the same hospital stay if the ablative margin was insufficient (< 5 mm) (Fig. 2c). Additional ablation was performed for the areas in which the initial ablative margin was insufficient. Additional ablation was performed without additional transarterial MPT injection after liver function had recovered from the previous ablation session.

Assessment

Technical success was defined as the attainment of more than a 5-mm ablative margin and was evaluated using contrast-enhanced three-phase CT one day after ablation (Figs. 1b, 2d). The initial technical success rate was defined as the percentage of tumors managed successfully

after the initial ablation session. The secondary technical success rate was defined as the percentage of tumors managed successfully with repeated ablation [14]. Complications were classified as minor (requiring no therapy) and major (requiring therapy and hospitalization) according to the Society of Interventional Radiology guidelines [16]. Complications were assessed based on the number of ablation sessions. The hospital stay was defined as the interval from the date of initial treatment to discharge.

Follow-up

The follow-up protocol included a routine physical examination and the performance of laboratory tests every month and three-phase contrast-enhanced CT or gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI every 3 months to monitor tumor recurrence and delayed complications (Fig. 1c). Local tumor progression was defined as the appearance of nodular enhancement around or within the ablative area. Intrahepatic distant recurrence was defined as the appearance of new tumors in the untreated liver parenchyma. Recurrence was defined according to the standard reporting parameters [16]. Follow-up visits were closed at the time of death or the last visit of the patient until June 30, 2020.

Statistical analysis

Comparisons of the two groups were conducted using Wilcoxon's rank-sum test for continuous variables and Fisher's exact test for categorical variables. Tumor segments were compared using chi-squared test result. The time-to-event outcomes (local tumor progression, intrahepatic distant recurrence, extrahepatic metastases, overall survival) were computed in months based on the difference between each event and ablation date. The Kaplan–Meier method was used for each group and compared with the log-rank test. Local tumor progression was obtained on a per tumor basis. Intrahepatic distant recurrence, extrahepatic metastases, and overall survival were obtained on a patient basis. Seventeen patients received both kinds of ablations on separate tumors during separate sessions; thus, they were included in both the MPT-RFA and MPT-MWA datasets and considered as independent. Similarly, patients receiving the same kind of ablation (RFA or MWA) on multiple occasions were also considered as independent. Twenty-six patients had undergone multiple RFA or MWA, all for new tumor distant from the initially treated tumor. Differences with a P value < 0.05 were regarded as statistically significant. The data were analysed using JMP 10.0 software (SAS, Cary, NC).

Results

Treatment procedures and outcomes

The depth of the tumor in the MPT-RFA group was 9.3 ± 2.3 cm (median 9.3 cm; range 3.0–14.5 cm) and that in the MPT-MWA group was 9.5 ± 2.6 cm (median 9.9 cm; range 4.0–14.0 cm), with no significant difference ($P = 0.578$). In the MPT-RFA group, technical success was achieved after one RFA session in 94 HCCs (76.4%), after two RFA sessions in 26 HCCs (21.1%), and after three RFA sessions in 3 HCCs (2.5%). In the MPT-MWA group, technical success was achieved after one MWA session in 64 HCCs (94.1%) and after two MWA sessions in 4 HCCs (5.9%). Thus, the secondary technical success was 100% in both groups. The initial technical success rate in the MPT-MWA group (94.1%) was significantly higher than that in the MPT-RFA group (76.4%) ($P = 0.003$). In total, 155 and 72 ablation sessions were required in the MPT-RFA and MPT-MWA groups, respectively. The number of treatment sessions per nodule was 1.3 ± 0.5 in the MPT-RFA group (range 1–3) and 1.1 ± 0.2 in the MPT-MWA group (range 1–2). The MPT-MWA group required significantly fewer treatment sessions than the MPT-RFA group ($P = 0.004$). The total ablation time per nodule was also significantly shorter in the MPT-MWA group (10.0 ± 6.3 min; range 3–28 min) than in the MPT-RFA group (17.8 ± 11.8 min: range 4–72 min) ($P < 0.001$). The transpulmonary approach was applied in 22 sessions in the MPT-RFA group (14.2%, 22/155) and in 4 sessions in the MPT-MWA group (5.6%, 4/72), with no significant difference ($P = 0.056$). The lung parenchymal penetration distance in the MPT-RFA group was 14.7 ± 8.9 mm (median 12.3 mm; range 4.3–38.2 mm) and that in the MPT-MWA group was 8.2 ± 4.3 mm (median 6.6 mm; range 5.4–16.7 mm), with a statistically significant difference ($P = 0.043$). In the MPT-RFA group, the additional ablation was performed at 4.9 ± 2.0 days (median 5 days; range 2–10 days) after initial ablation. In the MPT-MWA group, the additional ablation was performed at 5.6 ± 1.3 days (median 5 days; range 4–10 days) after initial ablation, with no significant difference ($P = 0.369$). Additional ablation was performed during the initial hospital stay. The posttreatment hospital stay was also significantly shorter in the MPT-MWA group (5.4 ± 2.4 days; median 5 days; range 2–12 days) than in the MPT-RFA group (7.0 ± 3.6 days; median 7 days; range 2–20 days) ($P = 0.016$). The treatment procedure and outcomes are shown in Table 3.

Table 3 Ablation procedures in the two groups

Variable	MPT + RFA, *N* (%)	MPT + MWA, *N* (%)	*P*
No. of HCC lesions	123	68	–
Total no. of ablation sessions	155	72	–
No. of ablation sessions			
Mean ± SD	1.3 ± 0.5	1.1 ± 0.2	0.004
Range	1–3	1–2	
No. of ablation sessions			
1	94(76.4)	64(94.1)	0.002
2	26(21.1)	4(5.9)	
3	3(2.5)		
Initial technical success	94 (76.4)	64 (94.1)	0.003
Secondary technical success	123 (100)	68 (100)	–
Total ablation time (min)			
Mean ± SD	17.8 ± 11.8	10.0 ± 6.3	< 0.001
Range	4–72	3–28	
Total no. of ablations			
Mean ± SD	1.8 ± 1.0	2.1 ± 1.3	0.367
Range	1–6	1–7	
Transpulmonary approach	22 (14.2)	4 (5.6)	0.056
Lung parenchymal penetration distance (mm)			
Mean ± SD	14.7 ± 8.9	8.2 ± 4.3	0.043
Median, range	12.3, 4.3–38.2	6.6, 5.4–16.7	
Hospital stay (days)			0.016
Mean ± SD	7.0 ± 3.6	5.4 ± 2.4	
Median, range	7, 2–20	5, 2–12	

Values in parentheses are percentages

RFA, radiofrequency ablation; MWA, microwave ablation; MPT + RFA, transarterial injection of a miriplatin-iodized oil suspension and RFA; MPT + MWA, transarterial injection of a miriplatin-iodized oil suspension and MWA; SD, standard deviation

Complications

No procedure-related deaths occurred. The major complication rates in the two groups were similar (MPT-RFA, 5.8%, 9/155; MPT-MWA, 2.7%, 2/72, $P = 0.391$). In the MPT-RFA group, there were nine major complications required specific interventions: seven cases of pneumothorax requiring chest tube drainage (4.5%) and two cases of intraperitoneal hemorrhage requiring transcatheter arterial embolization (1.3%). In the MPT-MWA group, there were two cases of intraperitoneal hemorrhage requiring transcatheter arterial embolization (2.7%). Intraperitoneal hemorrhage requiring transcatheter arterial embolization in both groups was found by hepatic arteriography immediately after ablation. In hepatic arteriography, all hemorrhage were located at the liver capsule which was punctured. No major complications led to any sequelae due to the additional interventions. The minor complication rate was 3.2% (5/155) in the MPT-RFA group and 2.7% (2/72) in the MPT-MWA group. No significant difference was found in the incidence of minor complications between the two groups ($P = 0.848$). All the minor complications were self-limiting pneumothorax, which occurred in the patients who had undergone treatment with a transpulmonary approach. Lung parenchymal penetration distance in the patients with pneumothorax requiring drainage was significantly longer (mean 21.1 ± 12.6 mm; range 7.7–38.2 mm) than those in the patients with a self-limiting pneumothorax or no pneumothorax (mean 11.4 ± 6.0 mm; range 4.3–26.2 mm) ($P = 0.048$). There were no liver infarctions or bilomas in any patients during the follow-up periods. The complications are summarized in Table 4.

Recurrence and overall survival

The follow-up period was 23.0 months±11.3 in the MPT-RFA group (range 3–47 months) and 10.1 months ±4.5 in the MPT-MWA group (range 6–23 months). The follow-up period was significantly longer for patients who had undergone MPT-RFA due to the earlier introduction of RFA into our practice ($P < 0.001$). Local tumor progression was found for two of 123 HCCs (1.6%) treated with MPT-RFA. No

Table 4 Complications in the two groups

Variable	MPT + RFA, *N* (%)	MPT + MWA, *N* (%)	*P*
Total no. of ablation sessions	155	72	
Major complications	9 (5.8)	2 (2.7)	0.391
Pneumothorax requiring drainage	7 (4.5)	0	0.019
Intraperitoneal hemorrhage	2 (1.3)	2 (2.7)	0.448
Minor complications	5 (3.2)	2 (2.7)	0.848
Self-limiting Pneumothorax	5 (3.2)	2 (2.7)	0.848

Values in parentheses are percentages

RFA, radiofrequency ablation; MWA, microwave ablation; MPT + RFA, transarterial injection of a miriplatin-iodized oil suspension and RFA; MPT + MWA, transarterial injection of a miriplatin-iodized oil suspension and MWA

local tumor progression was found after treatment with MPT-MWA. The one-year cumulative local tumor progression rate was 0% in the MPT-RFA group and 0% in the MPT-MWA group (Fig. 3). No significant difference was found in the local tumor progression rate between the patient groups ($P = 0.736$). Intrahepatic distant recurrence was found for 57 of 101 patients (56.4%) treated with MPT-RFA, and 5 of 49 patients (10.2%) treated with MPT-MWA. Extrahepatic metastases were not found in either group. The one-year cumulative intrahepatic distant recurrence rate was 43.5% [95% confidence interval (CI) 33.6–53.9%] in the MPT-RFA group and 29.3% (95% CI 9.6–61.8%) in the MPT-MWA group. No significant difference was found in the intrahepatic distant recurrence rate between the two patient groups ($P = 0.322$) (Fig. 4). In the MPT-RFA group, of the 20 patients (19.5%; 20 of 101) who died, the cause of death was liver failure (90%; 18 of 20), gastric cancer (5%; 1 of 20), and brain haemorrhage (5%; 1 of 20). In the MPT-MWA group, 2 patients died (4.1%; 2 of 49): The causes of death in the MPT-MWA group were liver failure (50%; 1 of 2) and heart failure (50%; 1 of 2). The overall survival rates were 93.7% (95% CI 86.7–97.1%) at 1 year and 80.1% (95% CI 70.1–88.0%) at 2 years in the MPT-RFA group. In the MPT-MWA group, the survival rates were 100% at 1 year and 75% (95% CI 37.7–93.7%) at 2 years. No significant difference was found in the survival rates between two groups ($P = 0.819$) (Fig. 5).

Discussion

The initial technical success rate (76.4%), number of the treatment sessions (1.3 per lesion), and local tumor progression rate (2.7%) in the MPT-RFA group of our study were similar to those in previous RFA studies that employed a combination of TACE or transarterial injection therapy with the same treatment endpoint as our study [3, 7, 10, 17]. In this study, the MPT-MWA group showed superior therapeutic efficacy (initial technical success rate, 94.1%; number of treatment sessions, 1.1) compared to MPT-RFA for small HCCs, and the hospital stay was significantly shorter in the MPT-MWA group (5.4 days) than in the MPT-RFA group (7.0 days). Shorter ablation times, fewer treatment

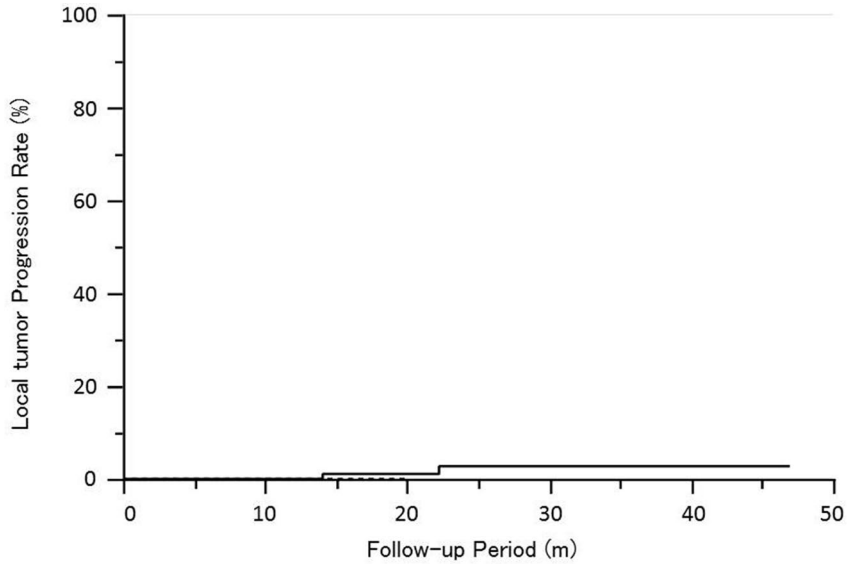

Fig. 3 Graph showing the local tumor progression rate in the transarterial injection of a miriplatin-iodized oil suspension and radiofrequency ablation (MPT-RFA) group (solid line) and the transarterial injection of a miriplatin-iodized oil suspension and microwave ablation (MPT-MWA) group (dashed line). No significant difference was found in the local tumour progression rate ($P = 0.736$). The one-year cumulative local tumor progression rate was 0% in the MPT-RFA group and 0% in the MPT-MWA group. The two-year local tumor progression rate in the MPT-RFA group was 2.7% [95% confidence interval (CI) 0.6–10.4%]

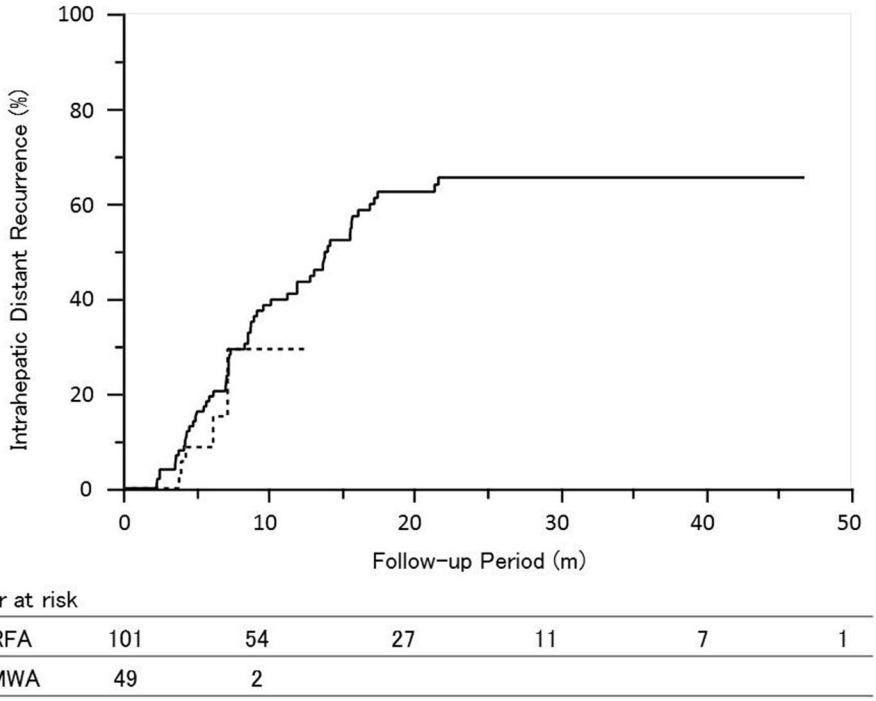

Fig. 4 Graph showing the intrahepatic distant recurrence rate in the transarterial injection of a miriplatin-iodized oil suspension and radiofrequency ablation (MPT-RFA) group (solid line) and the transarterial injection of a miriplatin-iodized oil suspension and microwave ablation (MPT-MWA) group (dashed line). No significant difference was found in the local tumour progression rate ($P = 0.322$). The intrahepatic distant recurrence rates were 43.5% [95% confidence interval (CI) 33.6–59.3%] and 29.3% (95% CI 9.6–61.8%) in 101 MPT-RFA patients and 49 MPT-MWA patients, respectively

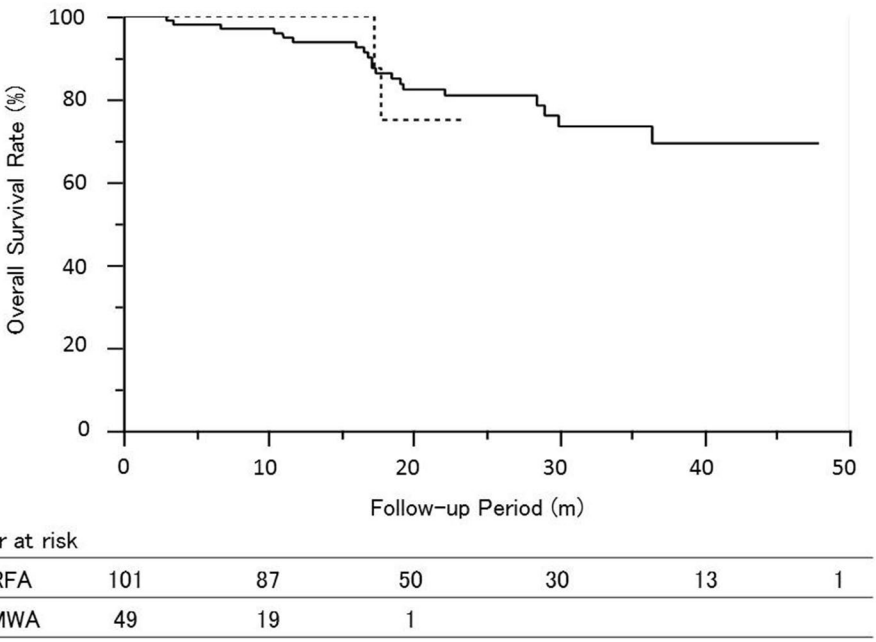

Fig. 5 Overall survival rates in the transarterial injection of a miriplatin-iodized oil suspension and radiofrequency ablation (MPT-RFA) group (solid line) and the transarterial injection of a miriplatin-iodized oil suspension and microwave ablation (MPT-MWA) group (dashed line). No significant difference was found in the local tumour progression rate ($P = 0.819$). The overall survival rates were 93.7% [95% confidence interval (CI) 86.7–97.1%] and 100% at 1 year and 80.1% (95% CI 70.1–88.0%) and 75% (95% CI 37.7–93.7%) in 101 MPT-RFA patients and 49 MPT-MWA patients, respectively

sessions, and shorter hospital stays are considered to reduce the burden on patients. Regarding the therapeutic efficacy, we believe that MPT-MWA should be favoured rather than MPT-RFA in the treatment of small HCCs. We believe that the high therapeutic efficacy of MWA is due to Emprint's new technology called "Thermosphere™ technology''. It provides three kinds of spatial energy control—thermal, field and wavelength control. These control types maintain a predictable, spherical ablation zone throughout a procedure [18]. Ierardi et al. [19] documented one of the earliest in vivo series of ten liver tumors treated using the Emprint system. In this study, the technical success rate was 100%, with a mean ablation time of 3.85 min. The roundness index traverse was 0.94, indicating that a spherical zone of ablation was consistently achieved [19]. However, the ablative area produced by RFA is sometimes unpredictable due to tissue boiling and charring, leading to the tissue acting as an electrical insulator and limiting the effect of RFA through

increased impedance [20, 21]. Compared with RFA, the consistent ablative area is the most valuable characteristic of MWA using the Emprint system, leading to an improvement in technical efficacy. Overall, the local tumor control rate was good in both the MPT-RFA and MPT-MWA groups. The cause is likely due to the margin of 5 mm was achieved in both groups. The transarterial injection of MPT before ablation makes assessing the ablative margin simpler and more feasible on posttreatment CT [10, 22]. Because MWA alone provides a wider ablative area than RFA, the role of MPT injection before MWA is to facilitate accurate tumor targeting and precise ablative margin assessment rather than expanding the ablative area.

The major complication rate was 5.8% in the MPT-MWA group and 2.7% in the MPT-MWA group, with no significant difference. Pneumothorax, the most frequently found major complication in the MPT-RFA group, occurred more frequently (4.5%) than that reported in previous studies (0.2–0.4%) [23, 24]. In this study, 26 subphrenic tumors that were difficult to puncture using a transhepatic approach were treated with a transpulmonary approach. A transpulmonary approach is an important factor affecting pneumothorax. In this study, the incidence of pneumothorax requiring chest tube drainage was more frequent in MPT-RFA than in MPT-MWA. The high incidence of pneumothorax requiring drainage in MPT-RFA might be explained by the fact that the needle passes significantly longer distance of lung parenchyma in MPT-RFA (mean 14.7 ± 8.9 mm) more than in MPT-MWA (mean 8.2 ± 4.3 mm) ($P = 0.043$). However, a transpulmonary approach with a larger MWA needle appears to be associated with a risk of pneumothorax. Therefore, a transpulmonary approach should be avoided to prevent pneumothorax. If a transhepatic approach is difficult, artificial pneumothorax [25] should be considered. Intraperitoneal hemorrhage requiring embolization was found to be a major complication in both groups. In the MPT-RFA group, the rate of intraperitoneal hemorrhage (1.3%) was comparable to that in previous reports [23, 24, 26]. We believe that the frequency of intraperitoneal hemorrhage after MWA in this study (2.7%) was high considering the major complication rates from previous studies (2–3%) [27–29]. Previous MWA articles used several devices other than Emprint; however, a large dataset using Emprint is lacking. Emprint requires a larger needle size (13 gauge) than other MWA devices (14–17 gauge). The larger needle size might account for the hemorrhage. A recent Emprint MWA article reported that one hemorrhage requiring embolization was occurred in 44 MWA-treated patients (ratio 2.3%) [30]. Another reason for the high hemorrhagic rate might be the method of hemorrhage detection. In many papers, active bleeding is preceded by clinical symptoms and is confirmed following CT. In our study, because hepatic arteriography was routinely performed in all cases immediately after removal of the needle, the detection of hemorrhage may have been more sensitive. MWA can produce more uniform and larger tumor necrosis. However, it should be noted that these characteristics, in turn, may be associated with a theoretically increased risk of damaging neighboring organs, particularly vascular and biliary structures [29].

This study has some limitations. First, the bias of the learning curve cannot be avoided because MPT-MWA was introduced after MPT-RFA. A prospective, randomized controlled trial is needed. Second, the follow-up period in the MPT-MWA group was very short, limiting the assessment of overall local tumor progression and survival. Further research with a long follow-up period is needed. Third, the effect of MPT injection before MWA on the volume of the ablative area is unknown. Basic experimental studies are also necessary. Furthermore, the reference ablation dimensions for MWA are determined according to ex vivo data. Establish optimal ablation protocols for clinical practice is warranted.

In conclusion, MPT-MWA has better therapeutic efficacy than MPT-RFA for small HCCs and may be a safe and useful therapeutic option. These results require confirmation in prospective, randomized trials.

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Compliance with ethical standards

Conflict of interest We have no conflicts of interest.

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