

Combination Therapy by Transarterial Injection of Miriplatin-iodized Oil Suspension with Microwave Ablation for Medium-Sized Hepatocellular Carcinoma: the Preliminary Experience

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Abstract

Purpose: To evaluate the feasibility and safety of transarterial injection of a miriplatin-iodized oil suspension combined with Emprint miriplatin-iodized oil suspension-microwave ablation in patients with medium-sized (3-5 cm) hepatocellular carcinomas.

Materials and Methods: This retrospective study included a total of 11 patients with 12 hepatocellular carcinomas (mean size, 3.6 ± 0.6 cm) underwent miriplatin-iodized oil suspension-microwave ablation. Microwave ablation was performed under the guidance of computed tomography fluoroscopy following transarterial miriplatin-iodized oil suspension injection on the same day. Technical success, complications, and local tumor progression were assessed.

Results: The primary and secondary technical success rates were 75.0% and 100%, respectively. The number of treatment sessions per nodule was 1.25 ± 0.45 . A total 15 sessions were required to achieve technical success (one session in nine lesions, two sessions in three lesions). Two major complications (pneumothorax [n = 1] and hemorrhage [n = 1]) occurred (2/15, 13.3%). No local tumor progression was observed during the follow-up period (mean 12.0 ± 2.0 months, range 2.7-23.9 months).

Conclusions: Miriplatin-iodized oil suspension-microwave ablation for medium-sized hepatocellular carcinomas can be safely performed with good local control.

Key words: Microwave ablation, Hepatocellular carcinoma, Medium-sized, Transarterial injection, Miriplatin

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Introduction

Hepatocellular carcinoma (HCC) has the sixth highest incidence and fourth highest mortality rate among all malignant neoplasms worldwide [1]. To treat an HCC that is larger than 3 cm, several transarterial procedures (balloon occlusion, transcatheter arterial chemoembolization [TACE], and transcatheter arterial infusion chemotherapy [TAI]) have been combined with RFA to expand the ablation zone [2-4].

Microwave ablation (MWA) has emerged as a valuable alternative to RFA. It has the potential to improve treatment efficacy and expand the ablation zones with less heat sink effects [5]. Emprint is the latest MWA device available in Japan; it produces a 4.2-cm ablation zone with a single ablation. Emprint MWA is expected to effectively treat HCCs that are larger than 3 cm, and several studies have reported that the TACE-MWA combination therapy using various MWA devices other than Emprint is effective for HCC lesions that are larger than 3 cm [6, 7]. On the other hand,

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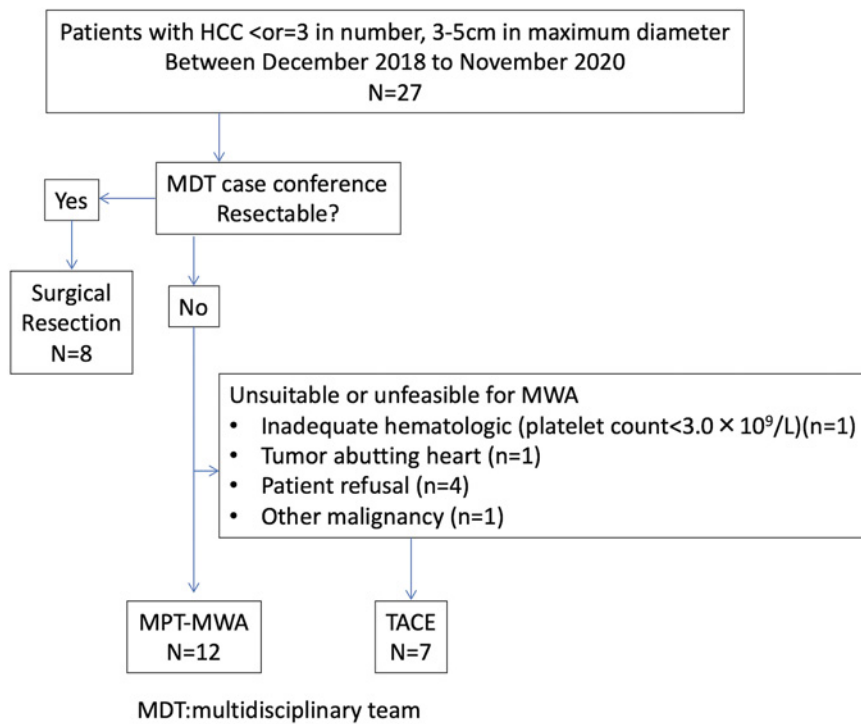


Figure 1. The treatment options of each case were decided by the liver tumor board consisting of a hepatologist, hepatobiliary surgeon, and interventional radiologist. Imaging, liver function, treatment history, comorbidity, age, patient's request, etc. were considered in the selection of treatment options. Such treatment options include curative approaches (surgical resection, orthotopic liver transplant, and microwave ablation) and noncurative approaches (transarterial chemoembolization, stereotactic body radiation therapy, and systemic therapy) to prolong survival by slowing down tumor progression.

transarterial MPT injection combined with MWA for the treatment of small HCCs has recently been reported to be a safe therapeutic option that yields favorable therapeutic results [8]. Unlike intraarterial iodized oil injection, transarterial MPT injection is expected to exert an anticancer effect [9].

However, for medium-sized HCC, there is no report about the clinical effectiveness of MWA combined with intraarterial MPT injection.

Thus, the clinical outcomes of transarterial MPT injection combined with Emprint MWA (MPT-MWA) for the treatment of HCCs that are larger than 3 cm, with curative intent, were retrospectively assessed.

Materials and Methods

Patient selection

This was a retrospective study of patients with medium-sized (3-5 cm) HCCs who underwent MPT-MWA between December 2018 and November 2020. This retrospective study was approved by the institutional review board of the hospital. The requirement for informed consent for the use of the data was waived. In our institute, the treatment option of the patients with medium-sized HCC was determined by liver tumor board consisting of a hepatologist, hepatobiliary

surgeon, and interventional radiologist (multidisciplinary team: MDT). The patient inclusion flowchart is presented in **Fig. 1**. The reasons why liver resection could not be performed were poor hepatic reserve (n = 8), comorbidity (n = 2), and patient's refusal of general surgery or surgical resection (n = 2). Hepatic reserve was totally assessed using several modalities, such as liver scintigraphy using technetium 99m-labeled asialoglycoprotein analog (TcGSA), indocyanine green retention at 15 min (ICGR15 test), and computed tomography (CT) volumetry (estimated future liver remnant, total liver volume). Tumor size and location (subphrenic and subcapsular locations) were assessed via preoperative CT and magnetic resonance imaging. When the HCC was in the liver dome and adjacent to the diaphragm, the lesion was defined as subphrenic; when it was superficially located abutting the liver capsule, the lesion was defined as subcapsular. If the HCC was adjacent to the vessels (portal vein, hepatic vein), the lesion was defined as perivascular. The subcapsular location comprised 7/12 lesions (58.3%). The subphrenic location comprised 5/12 lesions (41.7%). The baseline characteristics are presented in **Table 1** and **2**.

Combination therapy

MWA was immediately performed percutaneously after transcatheter arterial MPT injection. Local anesthesia (1% lidocaine hydrochloride with epinephrine bitartrate 1% xylo-

Table 1. Patient Characteristics.

Case	Age	Sex	History of HCC	Etiology of liver diseases	Child–Pugh class	Number of tumor	ALBI grade	AFP (ng/mL)	DCP (mAU/mL)
1	80	M	Naïve	NBNC	A	1	1	3.2	20
2	72	F	Naïve	HBV	A	1	1	522	744
3	84	M	Recurrent	HCV	B	1	3	11.6	N/A
4	69	M	Recurrent	HBV	B	1	2b	2	Warfarin used
5	52	M	Naïve	NBNC	A	1	1	922.2	298
6	45	M	Recurrent	NBNC	B	1	2b	3	21
7	75	M	Naïve	NBNC	A	1	2a	16.1	68
8	82	M	Naïve	HBV	A	1	1	N/A	745
9	79	M	Naïve	NBNC	A	1	1	6.3	26
10	74	M	Naïve	HCV	A	1	1	N/A	32
11	84	F	Naïve	NBNC	B	2	1	17.4	98

M, male; F, female; HBV, hepatitis B; HCV, hepatitis C; NBNC, nonhepatitis B and nonhepatitis C; ALBI, albumin–bilirubin; AFP, α -fetoprotein; DCP, des- γ -carboxy prothrombin; N/A, not assessed

Table 2. Tumor Characteristics.

Tumor number	Segment	Size (mm)	Macroscopic classification	Tumor location		
				Subphrenic	Subcapsular	Perivascular
1	S8	37	cm	No	No	No
2	S8	38	cm	Yes	Yes	Yes (RHV, MHV)
3	S6	37	cm	Yes	Yes	No
4	S3	50	cm	No	Yes	Yes (P3)
5	S8	31	cm	Yes	Yes	No
6	S8	42	cm	Yes	Yes	Yes (MHV, RHV)
7	S2	38	cm	No	Yes	Yes (P2)
8	S8	30	sn	Yes	Yes	Yes (MHV)
9	S8	32	sn	No	No	Yes (P8)
10	S8	32	sn	No	No	Yes (P8, MHV)
11	S8	38	cm	No	No	Yes (P8)
12	S3	32	cm	No	No	Yes (P3)

cm, confluent multinodular; sn, simple nodular; RHV, right hepatic vein; MHV, middle hepatic vein; P, portal vein

caine E; Aspen Pharma, Tokyo, Japan) was employed with moderate sedation [fentanyl citrate (Janssen-Kyowa Co., Ltd., Tokyo, Japan), midazolam (Astellas, Tokyo, Japan), and hydroxyzine hydrochloride (Pfizer Japan Inc., Tokyo, Japan)].

Transarterial MPT injection

Common femoral arterial access was achieved using a 4-F vascular sheath. Celiac arteriography was performed to assess tumor blood supply. A 1.9-F microcatheter (Tellus; ASAHI INTECC, Seto, Japan) was used to select the arteries that fed the tumors. The 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 8 mL, respectively. The MPT was warmed to 40°C to increase its accumulation [4, 10, 11] and was injected via the feeding artery as selectively as possible. MPT was administered until accumulation was confirmed via

fluoroscopy and CT (**Fig. 2a**). If there was weak accumulation in the tumor despite the MPT injection, ethiodized oil (Lipiodol 480; Guerbet Japan, Tokyo, Japan) alone was injected until accumulation was achieved. The mean doses of miriplatin and iodized oil per lesion were 61.2 ± 31.6 mg and 4.0 ± 2.3 mL, respectively.

MWA

For MWA, a 2.45-GHz MWA system (Emprint ablation system; Covidien, Boulder, Colorado) was used with a 13-gauge antenna and an internally cooled tip surrounded by saline irrigation channels. Placement of the needle (MWA antenna) into the tumor was performed using CT fluoroscopy (SOMATOM Definition AS20, SIEMENS AG, Germany). The positioning of the needle was confirmed by CT (**Fig. 2b-d**). Ablation was performed according to the manufacturer's protocol to create an ablative margin larger than 5 mm around the tumor. For the initial MWA ablation, pre-heating ablation (45 W for 1 min and 75 W for 1 min) was routinely performed to avoid steam popping, which could

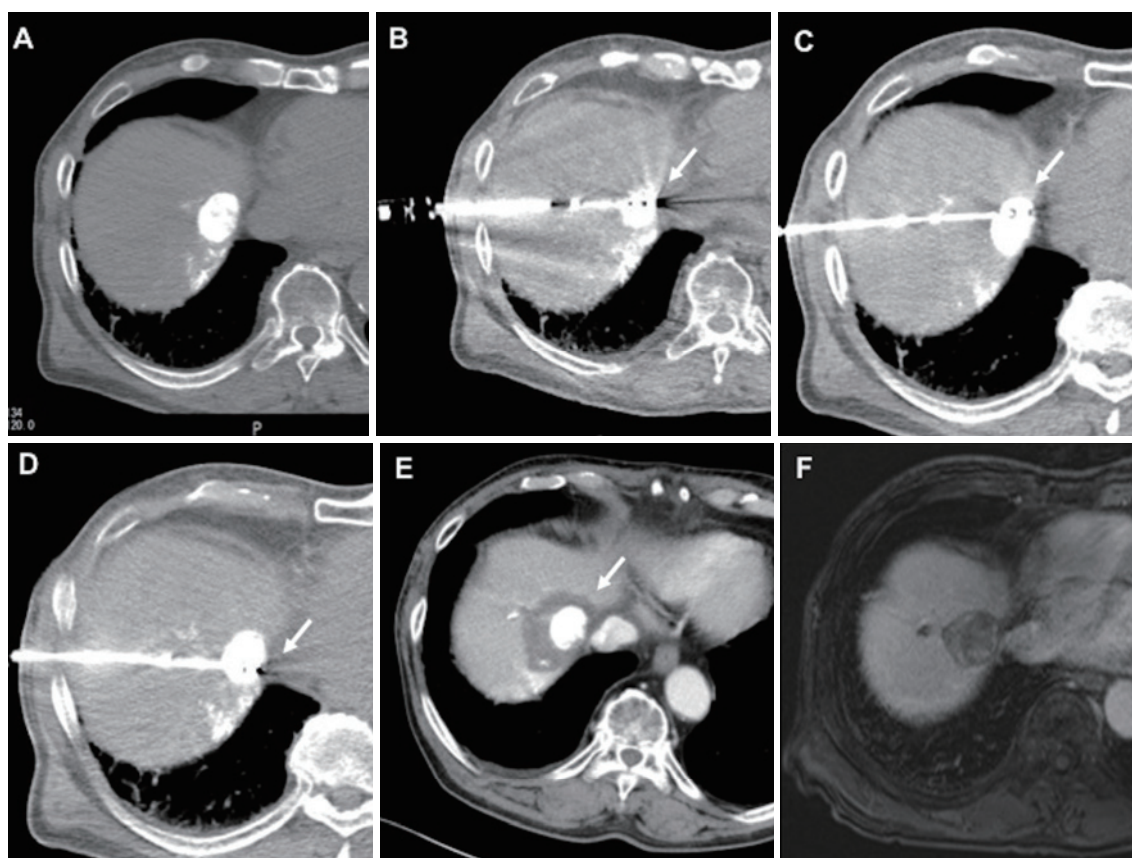


Figure 2. a–f An 82-year-old man with hepatocellular carcinoma (HCC) measuring 3.0 cm in segment 8. Microwave ablation (MWA) was performed on the same day after transarterial injection of miriplatin-iodized oil suspension (MPT) under real-time computed tomography (CT) fluoroscopic guidance. a MPT was injected *via* A8 and accumulated in HCC (*arrow*). b–d MWA was performed using CT fluoroscopy guidance. While confirming the needle position *via* IVR-CT, three overlapping ablations were performed to achieve a sufficient ablative margin covering the entire tumor (*arrow*). The needle position was as follows: b. cranial side of the tumor, c. medial side of the tumor, and d. caudal side of the tumor. The total ablation time was 19.5 min, including the preheating ablation (45 W 2 min + 75 W 2 min + 100 W 15.5 min). e. Axial contrast-enhanced CT image obtained 1 d after MWA. Tumor enhancement disappeared, and the tumor was surrounded by hypoattenuated nonenhanced areas (ablative margin) (*arrow*). f. Axial gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid magnetic resonance image obtained 6 months after MWA showing no local tumor progression.

increase the risk of peritoneal seeding [12]. To achieve a sufficient margin, as much additional overlapping ablation as possible was performed by repositioning the needle. For each ablation, the ablation zone was simulated using SYNAPSE VINCENT® (Fujifilm Medical Co., Tokyo, Japan) based on the CT images taken after the needle positioning. Ablation was repeated until the ablation zone estimated by CT covered the index tumor with an ablative margin larger than 5 mm. Tract ablation was performed at 75 W while retracting the antenna and ablating every centimeter of the needle track for 10 s. Immediately after ablation, hepatic arteriography and plain CT were performed to identify serious complications, such as massive bleeding and pneumothorax. One lesion was ablated using the hydrodissection technique [13] to displace the stomach. Other lesions were more than 1 cm away from vital intraabdominal organs. During this

period, the transhepatic approach was first selected to place the microwave antenna even if the tumor was located in the subphrenic region. When the transhepatic approach was judged to be too difficult, the transpulmonary approach was employed [14].

Technical success is defined as the identification of complete tumor coverage and a 5-mm circumferential margin on contrast-enhanced three-phase CT 1 day following ablation (Fig. 2e). Additional ablation was performed within the same hospital stay if the ablative margin was insufficient (<5 mm). Additional ablation was performed without additional transarterial MPT injection after the liver function had recovered from the previous ablation session.

Follow-up

The follow-up protocol included a routine physical exami-

nation and the conduct of laboratory tests every month and three-phase contrast-enhanced CT or gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced MRI every 3 months to monitor tumor recurrence and delayed complications (**Fig. 2f**). Local tumor progression was defined as the development of nodular enhancement around or within the ablation zone. 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 [15]. Follow-up visits were closed at the time of death or the last visit of the patient until November 30, 2020.

Assessment

The primary technical success rate was defined as the percentage of tumors that were successfully managed after the initial ablation session. The secondary technical success rate was defined as the percentage of tumors successfully managed with repeated ablations [14]. Complications were classified as minor (requiring no therapy) and major (requiring therapy and hospitalization) according to the Society of Interventional Radiology guidelines [15]. Complications were identified as predictable (i.e., pneumothorax, when the transpulmonary approach was used) or unpredictable. Hospital stay was defined as the interval from the date of the initial treatment to discharge. Technical success and complication were evaluated on a session basis, whereas local tumor progression was evaluated on a lesion basis. Survival and distant recurrence were evaluated based on each patient.

Statistical analysis

The time-to-event outcomes (local tumor progression, intrahepatic distant recurrence, extrahepatic metastases, and overall survival) were computed in months based on the difference between each event and ablation date. Local tumor progression was observed on a per-tumor basis. Intrahepatic distant recurrence, extrahepatic metastases, and overall survival were obtained on a patient basis. The relationship between initial success and tumor location was analyzed using Fisher's exact test. Differences with a P value < 0.05 were regarded as statistically significant. The data were analyzed using the EZR 1.53 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [16].

Results

Technical success

Technical success was achieved in 12 HCCs: after one session in nine HCCs (75.0%) and after two sessions in three HCCs (25.0%). Therefore, the primary success rate was 75%, and the secondary technical success rate was 100%. The number of treatment sessions per nodule was 1.25 ± 0.45 (range 1-2). The number of ablation per nodule was 3.8 ± 1.9 (range 1-8). The total ablation time per nodule was 25.7 ± 7.3 min (range 12-34.5 min). The transpul-

monary approach was applied in only one session in the tumor located in segment 8 (1/15, 6.7%). Three tumors (3/12, 25%) required an additional ablation session, which was performed 6.7 ± 2.1 days (range 5-9 days) after the initial ablation. The tumors that required additional ablation were No. 4, No. 6, and No. 9. No. 4 was subcapsular and in contact with P3. No. 6 was subphrenic and in contact with the middle and right hepatic veins. No. 9 was not subcapsular but was in contact with P8. Tumor location (perivascular, subphrenic, and subcapsular) did not affect the primary technical success: primary technical success rate of the perivascular tumor (6/9, 66.7%) vs. nonperivascular tumor (3/3, 100%) ($p = 0.509$), that of subphrenic tumor (4/5, 80%) vs. nonsubphrenic tumor (5/7, 71.4%) ($p = 1$), and that of subcapsular tumor (5/7, 71.4%) vs. nonsubphrenic tumor (4/5, 80%) ($p = 1$).

The post treatment hospital stay was 7.3 ± 3.1 days (range 3-12 days). The treatment procedures and outcomes are presented in **Table 3** and **4**.

Complications

No procedure-related deaths were reported. There were two major complication requiring specific interventions (2/15, 13.3%): one case of pneumothorax, which was considered to be a predictable complication of the transpulmonary approach, and one case of intraperitoneal hemorrhage, which was considered to be unpredictable. Thus, the major complication rate was 13.3% (2/15), and the unpredictable complication rate was 6.7% (1/15). The pneumothorax was found on CT immediately after MWA using the transpulmonary approach, which improved with 1-day chest tube drainage. Intraperitoneal hemorrhage was observed on hepatic angiography immediately after MWA and bleeding from the liver puncture site, which subsided after transcatheter arterial embolization. No major complications led to any sequelae due to the additional interventions. No minor complications were noted. We have encountered six self-limited fever after the ablation session (fever duration mean 2.5 days; range 1-4 days), which is regarded as post ablation syndrome. In this study, no hepatic reserve deterioration was observed based on the Child-Pugh score 1 month after ablation. No miriplatin-related adverse events or development of ascites was observed. The complications are presented in **Table 3**.

Recurrence and overall survival

The follow-up period was 12.0 ± 2.0 months (median 13.0 months; range 2.7-23.9 months). No local tumor progression was observed after treatment with MPT-MWA. Intrahepatic distant recurrence was noted in five patients (5/11, 45.4%). For the treatment of intrahepatic distant recurrence, four patients underwent MPT-MWA, and one patient underwent MPT-RFA. The time to intrahepatic distant recurrence after initial treatment was 8.9 ± 6.6 months (range 4.3-20.5 months). No extrahepatic metastases were observed. One patient died of liver failure. The overall survival rate was 87.5% (95% CI, 38.7%-98.1%) at 1 year. The recurrence

Table 3. Treatment Procedure and Outcome.

Tumor number	Session number	MPT injection site	No. of injected artery	MPT (mg)	Iodized Oil (mL)	Ablation n	Ablation Time (min)	Transpulmonary approach	Minor complication	Major complication	Hospital days
1	1	A8	1	28	2.4	3	28.5	No	No	No	6
2	2	A8	1	70	4	8	24.5	Yes	No	Yes (Pneumothorax)	4
3	3	A6 + 7	1	17.5	1.6	4	28	No	No	No	9
4	4	LHA	1	35	2	1	19	No	No	No	12
	5					2	4	No	No	No	
5	6	RHA	1	70	8	4	27	No	No	No	7
6	7	A8	1	70	4	4	28	No	No	Yes (Bleeding)	11
	8					2	6.5	No	No	No	
7	9	A2	1	70	4	4	36	No	No	No	8
8	10	A8	1	25	1.4	3	19.5	No	No	No	3
9	11	A8	1	49	2.8	1	9.5	No	No	No	10
	12					1	10.5	No	No	No	
10	13	A5 + 8	1	70	4	1	12	No	No	No	3
11	14	A5 + 8	1	120	8	5	35	No	No	No	9
12	15	A2 + 3	1	120	8	2	20	No	No	No	5

Additional session was performed without additional MPT injection.

MPT, miriplatin; RHA, right hepatic artery; LHA, left hepatic artery

Table 4. Recurrence and Survival.

Case	Tumor number	Local tumor progression	IDR	Location and size of IDR	Treatment for IDR	Time to IDR (month)	Extrahepatic metastasis	Survival	Follow-up month
1	1	No	No				No	Alive	23.9
2	2	No	Yes	S8 10 mm,	MPT-RFA	8.5	No	Alive	21.4
3	3	No	Yes	S3 15 mm, S6 14 mm	MPT-MWA	5.3	No	Alive	18.9
4	4	No	Yes	S6 15 mm, S6 15 mm	MPT-MWA	20.5	No	Alive	17.0
5	5	No	Yes	S4 10 mm	MPT-MWA	6	No	Alive	16.3
6	6	No	No				No	Dead (liver failure)	5.5
7	7	No	Yes	S8 24 mm	MPT-MWA	4.3	No	Alive	13.0
8	8	No	No				No	Alive	6.7
9	9	No	No				No	Alive	4.1
10	10	No	No				No	Alive	2.7
11	11	No	No				No	Alive	2.7
	12	No	No				No	Alive	2.7

IDR, intrahepatic distant recurrence; MPT, miriplatin; RFA, radiofrequency ablation; MWA, microwave ablation

and survival are summarized in **Table 4**.

Discussion

This study demonstrated that the primary technical success rate of MPT-MWA was 75% with a mean treatment session of 1.25 session per lesion for HCCs that are larger than 3 cm. These results were comparable to those of RFA or TACE-RFA [3, 17]. The average ablation time per lesion was 25.7 min, which applied a mean 3.8 ablation. The ablation time may be shorter than that of RFA, because 3.8 ablation costs more ablation time in RFA. The duration of hospital stay was short (7.3 ± 3.1 days). In most reports of TACE-RFA for HCC, RFA was performed 2-4 weeks after TACE [3, 18, 19]. Thus, our MPT-MWA can be performed in a relatively short treatment period. High treatment effi-

cacy (shorter ablation times, fewer treatment sessions, and shorter hospital stay) is considered to reduce patient burden.

The high technical efficacy of Emprint MWA is due to the new Emprint technology called "Thermosphere™ technology." It provides three types of spatial energy control: thermal, field, and wavelength. These control types maintain a predictable spherical ablation zone throughout the procedure [20]. Emprint MWA can provide a maximum of 4.2 cm spherical ablation zone in one ablation. On the other hand, the ablation zone produced by RFA is sometimes unpredictable due to thermal sink or electrical shunt caused by the blood vessels adjacent to the tumor [21, 22]. Compared with RFA, the consistent predictable ablation zone is the most valuable merit of MWA using the Emprint system and cause an improvement technical efficacy.

To obtain a sufficient margin, it is often necessary to

change the position of the needle and perform multiple ablations (so-called overlapping ablation). Intraarterial injection of MPT is very useful for ablation planning as it can demarcate the tumor location. However, three lesions (3/12, 25%) require additional treatment session. In future study, we should investigate any factor influencing the primary technical success, such as tumor location (subphrenic, subcapsular, and perivascular). Moreover, MPT has an anticancer effect and may be effective for microsatellite lesions [23].

The treatment options for unresectable HCCs that are larger than 3 cm include TACE, TACE-RFA, and MWA [24]. Although TACE is widely used for large HCCs, recurrence is frequent. Chu et al. reported that for medium-sized HCCs, the local tumor progression rate was significantly higher in the TACE-alone group than in the TACE-RFA or RFA-alone groups (45.2% vs 28.4%, 27.8% $p = 0.003$) [25]. TACE-RFA is generally considered to be more effective than RFA alone for the treatment of HCCs that are larger than 3 cm [24]. However, the size of the ablation zone of RFA expanded by TACE and the shape of the ablation zone of RFA could not be predicted [5]. The use of TACE-MWA has been increasingly reported in HCCs larger than 3 cm, but many reports have focused on tumor volume reduction and palliative therapy, and few reports have focused on cure of tumor [6, 7]. In addition, these reports did not demonstrate any detailed ablation technical factors, such as ablation time, number, and ablation endpoint (ablation margin).

According to the recent review of MWA for the treatment of liver tumor, major complications have been reported with figures between 2.6% and 4.6% [26]. Our major complication rate was 13.5%, including predictable complication in one case (6.7%). Considering that our study was an early initial study of the MPT-MWA combination therapy with a small sample size, our major complication rate seems to be high. Intraperitoneal hemorrhage was observed in one patient (6.7%). Emprint uses a larger needle (13 G) than other MWA devices (15-17 G). However, we could not find any studies that reported the needle size of ablation device as the risk factor of hemorrhage incidence. We rather think that bleeding is caused by the shape of the Emprint needle. Emprint needles have a blunt tip, and they may be more resistant to puncture liver capsule than sharp-tipped needles. Resistance during liver capsule puncture may cause laceration of the liver capsule, which then leads to bleeding. Care must be taken when puncturing liver capsule using Emprint. Pneumothorax requiring drainage occurred in one case (6.7%), which was considered to be a predictable complication due to the use of the transpulmonary approach. Transpulmonary puncture is a factor of pneumothorax [14], and since Emprint needles are larger, transpulmonary puncture should be avoided by using artificial pneumothorax [27] as much as possible. The combined use of intraarterial MPT injection appeared to be relatively safe in MWA as in RFA [11], since there were no serious complications, such as liver infarction, in this study. Miyamoto et al. reported that MPT combined with MWA in the same session for HCCs

that are smaller than 3 cm was safe [8].

This study has several limitations. First, this was a retrospective study with a small sample size and short follow-up period. Further research with a large sample size and long follow-up period and a prospective study compared MPT-MWA with other therapies, such as RFA and hepatectomy, are needed. Second, the effect of MPT injection before MWA on ablative volume is unknown. In particular, a basic study on the obtainment of larger ablation zones is necessary. In addition, which arterial procedures combined with MWA is better should be investigated. Third, the ablation protocol was based on *ex vivo* data. The optimal ablation protocol should be established in future studies.

In conclusion, MPT-MWA may be curative and effective for the treatment of patients with medium-sized HCCs.

Conflict of interest: None

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