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High-powered microwave ablation of larger hepatocellular carcinoma: evaluation of recurrence rate and factors related to recurrence

N.N. Zhang [a,b], W. Lu [a,b,*], X.J. Cheng [a,b], J.Y. Liu [a,b], Y.H. Zhou [a,b], F. Li [a,b]

[a] Tianjin Second People's Hospital, 7 Sudi Road, Tianjin 300192, China
[b] Tianjin Institute of Hepatology, 7 Sudi Road, Tianjin 300192, China

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AIM: To evaluate the safety and efficacy of high-powered (80–100 W) percutaneous microwave ablation (MWA) at a frequency of 2450±10 MHz for treating larger hepatocellular carcinoma (HCC) and to predict the risk factors of local recurrence after high-powered MWA.

MATERIALS AND METHODS: The study was approved by the Institutional Review Board, and informed consent was waived because of the retrospective study design. Forty-five patients with a total of 60 lesions received high-power (80–100 W) MWA at a frequency of 2450±10 MHz through a percutaneous approach that was guided by ultrasound. Of the 60 lesions with a maximum tumour measuring 3–8 cm, 46 lesions were 3–5 cm and 14 were 5–8 cm. The complete ablation rates, local recurrence rates, complications, and short-term survival were analysed. Ten possible risk factors for local recurrence were analysed.

RESULTS: The complete ablation rates were 82.61% for the first ablation and 100% for the second ablation for 3–5 cm lesions. The complete ablation rates were 64.29% (82.61% versus 64.29%, p=0.037) for the first ablation and 85.71% (100% versus 85.71%, p=0.055) for the second ablation for 5–8 cm lesions. Local recurrence was observed in 11 out of the 45 (24.44%) successfully treated patients. The 1-year and 2-year survival rates were 95.56% (43/45) and 86.67% (39/45), respectively. No procedure-related mortality was observed and no major bleeding, liver rupture, or liver abscesses occurred. Univariate analysis showed that a positive correlation existed between the number of lesions (p=0.022), proximity to the risk area (p=0.001), pre-ablation alpha-fetoprotein (AFP) levels (p=0.025), hepatitis B virus (HBV)-DNA replication (p=0.027) and local recurrence. Multivariate analysis identified HBV-DNA (p=0.031) and proximity to the risk area (p=0.039) as the independent prognosis factors causing postoperative HCC local recurrence.

CONCLUSION: High-powered MWA of larger hepatocellular carcinomas appears to be a safe and effective treatment. HBV-DNA and proximity to the risk area appear to be independent predictors of local tumour recurrence.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most frequently diagnosed cancer worldwide and is the second

* Guarantor and correspondent: W. Lu, Tianjin Second People's Hospital, Tianjin Institute of Hepatology, 7 Sudi Road, Tianjin 300192, China. Tel.: +86 22 27468102; fax: +86 22 27468023.
E-mail address: mail4luwei@163.com (W. Lu).

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most common cause of cancer-related death.[1] Surgical resection is recognised as a potentially curative treatment for patients with HCC. Unfortunately, the majority of primary HCCs are frequently considered to be unresectable because of the number of tumours, location of tumours, or poor hepatic functional reserve that is a result of underlying liver disease, thus making the resection of a large volume of the liver parenchyma unfeasible.[2] Thermal ablation, including radiofrequency ablation (RFA) and microwave ablation (MWA), are image-guided techniques that are used to treat tumours up to 3 cm in diameter.[3]

With improvements in devices and techniques, thermal ablation has displayed potential for treating HCC measuring >3 cm.[4] Meanwhile, RFA is the therapy of choice in very early and early HCC according to the Barcelona Clinic Liver Cancer (BCLC) classification when patients are not candidates for either liver resection or transplantation[5]; however, RFA has had limited success in treating larger tumours with high local recurrence rates.[6] MWA has some advantages over RFA with regard to energy delivery, such as larger ablation zones, higher treatment temperatures, and less susceptibility to heat-sink effects.[7] Recently, the advanced development of a cooled-shaft antenna has allowed MWA to be performed at much higher power outputs with longer ablation durations. This allows the lesion to be treated with a single application without severe skin burns or severe pain.[8] The present study was undertaken to evaluate the results of higher power output (80–100 W) MWA at a frequency of 2450±10 MHz in patients with larger HCC tumours measuring over 3 cm and to clarify the risk factors of recurrence after MWA.

Materials and methods

Patient enrolment

From January 2012 to June 2013, 45 HCC patients (38 men and seven women with a mean age of 58.41±7.67 years) with 60 lesions underwent percutaneous high-power (80–100 W) MWA at a frequency of 2450±10 MHz. All patients had chronic hepatitis B virus (HBV) infections. Of the 45 patients, 17 had tumours that were within 5 mm of risk areas (diaphragm, gall bladder, blood vessels, and gastrointestinal tract). Not all patients were amenable to surgical resection, and some declined surgical resection; treatment selections were made after a full multidisciplinary discussion. The MWA treatment procedure was explained to both the patient and his/her relatives. Final decisions were made by the patients and relatives, and consent for the ablation was signed by the patient or his/her relatives. The study was approved by the institutional review board. Because of the retrospective nature of this study, informed consent of the patients was waived.

HCC diagnosis was established based on histological evidence or typical findings with contrast-enhanced ultrasonography, contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI). The inclusion criteria for the study were no more than three lesions, no treatment undertaken for the lesions before MWA, tumour measuring >3 cm in diameter, and liver function Child–Pugh status score of A or B. Patients with extra-hepatic metastases or vascular invasion were excluded. The demographic characteristic data of these patients are listed in Table 1.

Ablation procedures

An ECO-100C microwave generator (ECO Microwave Electronic Institute, Nanjing, China) at a frequency of 2450±10 MHz and a power output of 0–100 W was used for MWA. The microwave antenna was a 15 cm 14 G water-cooled electrode needle. Ablation therapy was performed at 80–100 W output with one antenna. An overlapping ablative technique with antenna reinsertion was applied to treat tumours to ensure adequate coagulation necrosis. The ablation time was determined according to the ultrasound findings; the size and shape of the hyperechoic zone caused by gas microbubbles appearing in the ablation zone during the MWA procedure was monitored by ultrasound to assess the completion of therapy. Treatment was stopped when the entire target was completely hyperechoic and when the hyperechoic area overlapped the area of the tumour with a 1 cm safety margin.

Anaesthesia

Local anaesthesia with 2% lidocaine (Huibei Tianyao Pharmaceuticals, Huibei, China) and intravenous

Table 1
Demographic characteristics of hepatocellular carcinoma (HCC) patients.

Characteristic	No. of patients
Gender (male/female)	38/7
HBV e antigen	
Positive	6
Negative	39
HBV-DNA replication	
Positive	26
Negative	19
Child–Pugh classification	
Class A	31
Class B	14
Type of tumour	
Initial HCC	23
Recurrent HCC	22
Diameter of tumour (cm)	
3–5	46
5–8	14
No. of tumours	
Solitary	29
Multiple	16
Adjacent to risk area	
Diaphragm	6
Gall bladder	4
Blood vessels	5
Gastrointestinal tract	2
Serum alpha-fetoprotein level (ng/ml)	
≥400	11
<400	34

HBV, hepatitis B virus.

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anaesthesia with fentanyl (Yichang Renfu Pharmaceuticals, Huibei, China) was used for percutaneous MWA.

Ultrasound guidance system

The whole procedure was guided and constantly monitored by real-time ultrasound (EUB-2000, HITACHI Medical Systems, Tokyo, Japan) at a frequency of 1–5 MHz using a convex array probe. At the end of the procedure, the needle track was coagulated to prevent bleeding from the liver surface.

Assessment of technical success and follow-up

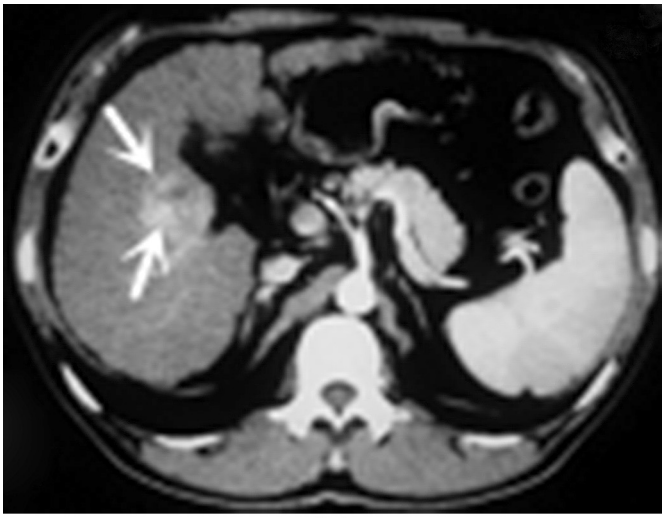
Technical success was evaluated by comparing contrast-enhanced ultrasonography or contrast-enhanced CT images performed 3 days after treatment. Complete ablation and technical success were considered to have been achieved if the ablation zone completely covered the tumour and if there was no irregular enhancement at the treatment margin. Incomplete ablation was defined as any irregular contrast enhancement that was found inside or next to the ablation zone. Additional MWA was performed for tumours with incomplete ablation within 1 week.

Contrast-enhanced ultrasound or contrast-enhanced CT of the abdomen was performed 1, 2, and 3 months after the procedure (Figs 1–2). All patients were monitored with contrast-enhanced ultrasound or contrast-enhanced CT of the abdomen every 3–6 months. A new lesion that appeared in or adjacent to the successfully treated lesion or an enlargement of the treated lesion was considered to be local recurrence. The presence of new intrahepatic or extrahepatic tumour nodules was defined as a distant recurrence. Patients with new lesions or a distant recurrence were considered for further treatment.

A major complication was defined as an event that led to substantial morbidity, disability, increase in level of care, hospital admission, or substantially lengthened hospital stay.[9] Major complications, such as skin burns, pneumothorax, haemorrhage, subcapsular haematoma, gall bladder perforation, gastrointestinal perforation, liver abscess, biliary leakage or stricture, and tumour dissemination, were documented.

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (SD). For qualitative variables, the chi-square test or Fisher's exact probability test was performed. For continuous variables, Student's *t*-test was applied. Cumulative recurrence-free survival was determined by using the Kaplan–Meier method with univariate comparisons between groups through the log-rank test. A two-tailed *p*-value of <0.05 was considered to be statistically significant. Statistical analyses were performed with the statistical package SPSS (version 16.0.01 for Windows, SPSS, 6 Chicago, IL, USA).



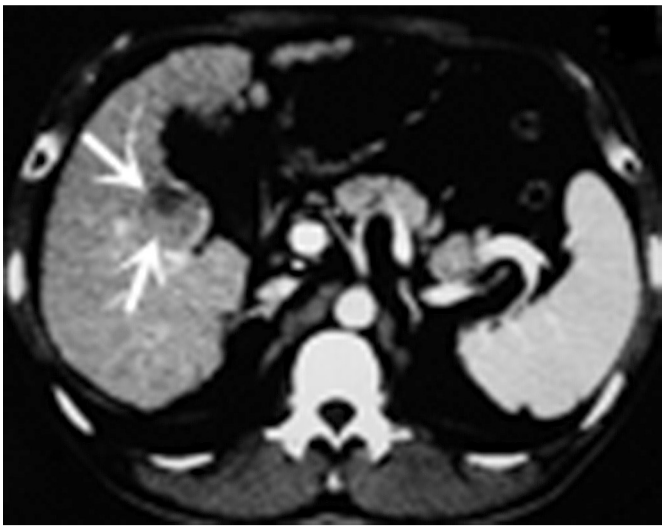


Figure 1 CT images of a 54-year-old man with a 4.1 cm diameter HCC lesion that is adjacent to the gall bladder and right portal vein. (a) Pretreatment CT image shows hyperattenuation of the lesion during the arterial phase (arrows). (b) One month after MWA treatment, contrast-enhanced CT shows uniform hypo-attenuation in the ablated area (arrows), which indicates complete ablation.

Results

Local tumour control

All patients were successfully treated with MWA. Thirty-eight of 46 lesions (82.61%) in the 3–5 cm group and nine of 14 lesions (64.29%) in the 5–8 cm group showed complete ablation after one treatment with MWA (p=0.037). Forty-six of 46 lesions (100%) in the 3–5 cm group and 12 of 14 lesions (85.71%) in the 5–8 cm group showed complete ablation after a second treatment with MWA (p=0.055; Table 2). Two of the 14 lesions in the 5–8 cm group were incompletely treated; these patients received additional MWA treatments.

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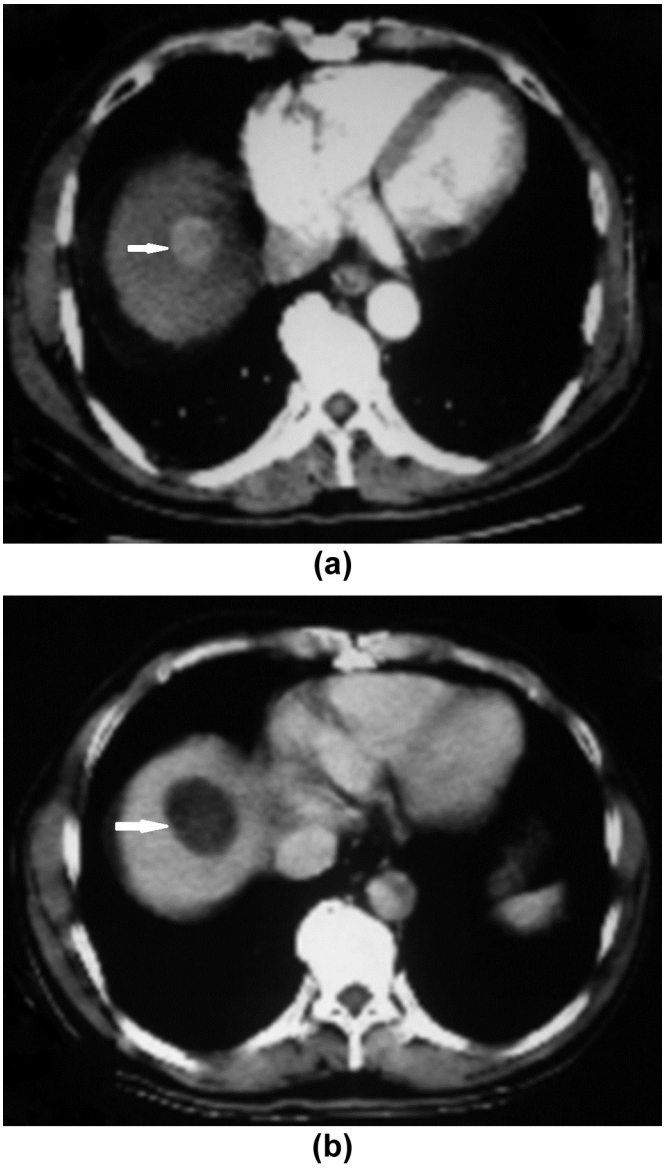

Figure 2 CT images of a 65-year-old man with a 3.5 cm diameter HCC lesion that is adjacent to the diaphragm. (a) Pretreatment CT image shows hyperattenuation of the lesion during the arterial phase (arrows). (b) One month after MWA treatment, CT shows uniform hypoattenuation in the ablated area (arrows), which indicates complete ablation.

Three days after the procedure, the ablation zone was measured with ultrasound. The average ablation zone of a tumour with a diameter of 3–5 cm was (4.71±0.6) cm × (5.48±0.7) cm. The average ablation zone of a tumour with a diameter of 5–8 cm was (5.57±0.6) cm × (8.46±0.5) cm.

Table 2
Complete ablation rate (n,%).

Complete ablation rate				
	3–5 cm (n=46)	5–8 cm (n=14)	Total (n=60)	p-Value
First ablation	38 (82.61)	9 (64.29)	47 (78.33)	0.037
Second ablation	46 (100)	12 (85.71)	58 (96.67)	0.055

Recurrence rate and analysis of postoperative recurrence factors

The mean follow-up period was 15 months (range 3–24 months). Local recurrence was observed in 11 of the 45 (24.44%) successfully treated patients. Seven of 45 patients (15.56%) developed a distant recurrence after the ablation. Of the 18 patients with 25 tumours in the recurrence group who underwent subsequent treatments, 10 tumours in the 3–5 cm group and three tumours in the 5–8 cm group underwent MWA and six tumours in the 3–5 cm group and six tumours in the 5–8 cm group underwent transcatheter arterial chemoembolisation (TACE) plus MWA. Univariate analysis (Table 3) showed that a positive correlation existed between the number of lesions (p=0.022), proximity to the risk area (p=0.001), pre-ablation alpha-fetoprotein (AFP) levels (p=0.025), HBV-DNA replication (p=0.027), and early recurrence. There was no significant correlation between recurrence and patient age, sex, diameter of tumour, tumour pathological grade, serum AFP after MWA, or Child–Pugh classification (Table 3).

Multivariate analysis (Table 4) identified that HBV-DNA (p=0.031) and proximity to the risk area (p=0.039) were

Table 3
Univariate analysis of factors associated with postoperative recurrence.

Factors	Recurrence group No. of patients	None recurrence group No. of patients	p-Value
Age (years)			
≤60	12	12	
>60	6	15	0.247
Gender (male/female)			
Female	3	4	
Male	15	23	0.591
No. of tumours			
Solitary	8	21	
Multiple	10	6	0.022
Diameter of tumour (cm)			
3–5 cm	16	30	
>5 cm	9	5	0.067
Tumour pathological grade			
High differentiation	4	12	
Low differentiation	14	15	0.204
Adjacent to risk area			
Yes	6	22	
No	12	5	0.001
Serum AFP before MWA (ng/ml)			
≤400	11	23	
>400	7	4	0.025
Serum AFP after MWA (ng/ml)			
≤400	14	24	
>400	4	3	0.412
Child–Pugh classification			
Class A	12	19	
Class B	6	8	0.793
HBV-DNA replication			
Positive	4	15	
Negative	14	12	0.027

AFP, alpha-fetoprotein; MWA, microwave ablation; HBV, hepatitis B virus.

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Table 4
Multivariate conditional logistic regression analyses of independent prognosis factor of postoperative hepatocellular carcinoma (HCC) recurrence.

	B	SE	Wals	Sig	OR
Adjacent to risk area	1.984	0.959	4.276	0.039	7.271
HBV-DNA replication	2.003	0.930	4.636	0.031	7.414
No. of tumours	0.949	0.908	1.092	0.296	2.583
Serum AFP before MWA	1.250	0.893	1.960	0.162	3.492

B, regression coefficient; SE, the standard error of regression coefficient; Wals, Wald chi-square value; Sig, *p*-value; OR, odds ratio.

independent prognosis factors causing postoperative HCC recurrence. The number of lesions and pre-ablation AFP levels ($p>0.05$) did not show a significant association. The rate of recurrence of patients with a tumour adjacent to the risk area was significantly higher than the rate of recurrence of patients with a tumour in the general area. The time until recurrence in patients with a tumour adjacent to the risk area was significantly shorter than the time until recurrence in patients with a tumour in the general area ($\chi^2 = 7.107$, $p=0.008$; Fig 3). The rate of recurrence of patients with positive HBV-DNA replication was significantly higher than the rate of recurrence of patients with negative HBV-DNA replication. The time until recurrence in patients with positive HBV-DNA replication was significantly shorter than the time until recurrence in patients with negative HBV-DNA replication ($\chi^2 = 5.263$, $p=0.022$; Fig 3).

Complications and survival

No procedure-related mortality was observed. No major haemorrhage, liver rupture, or liver abscess occurred. There were no significant changes in the full blood count, blood glucose levels or electrolytes. Twelve out of the 45 patients (26.67%) suffered from significant liver transaminase level increases, which usually reverted to normal levels within 1 week. Pain, fever, and asymptomatic pleural effusion were the most common minor complications after the treatment. Grade 1 pain (World Health Organisation criteria) in the upper abdomen was observed after the procedure in 15 patients (33.3%, 15/45). A low-grade fever was observed after treatment in 26 of the 45 (57.78%) patients. An asymptomatic pleural effusion was observed in four of the 45 (8.9%) patients. There were no episodes of skin burning or tumour seeding in the study. The frequency of procedure-related complications in the 3–5 cm group versus the 5–8 cm group is listed in Table 5. The 1-year and 2-year overall survival rates after the initial ablation were 95.56% (43/45) and 86.67% (39/45), respectively.

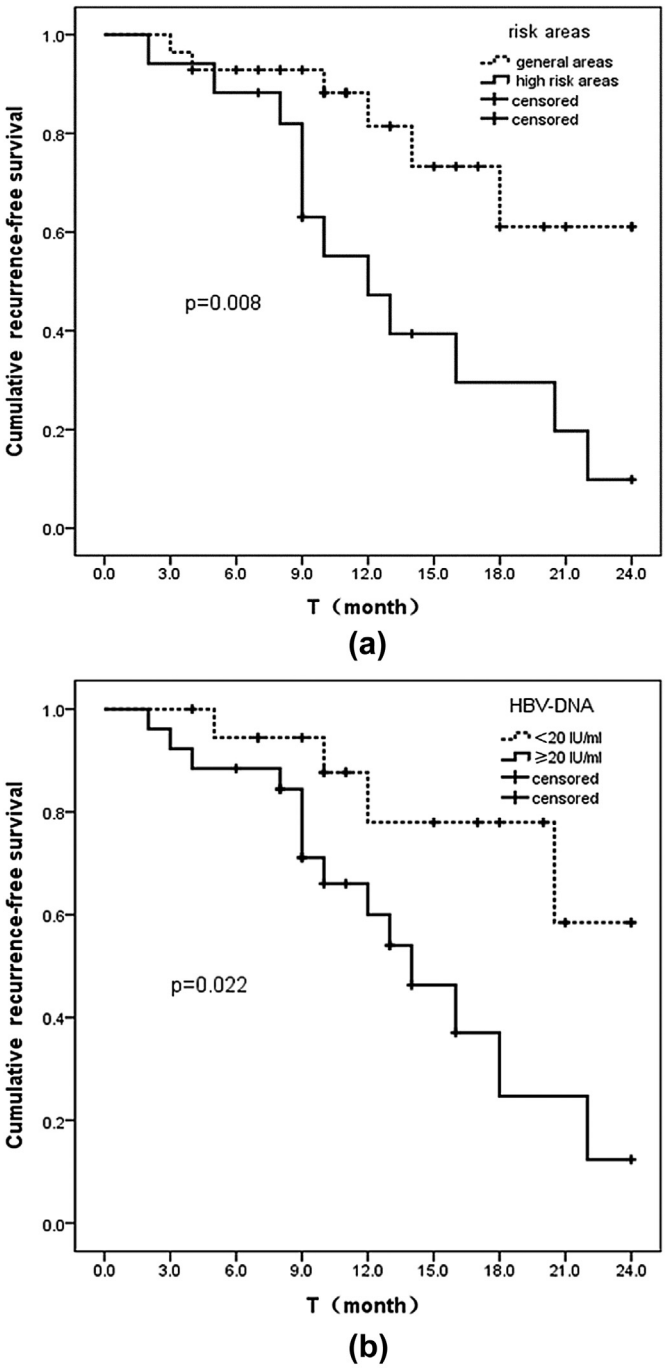

Figure 3 Cumulative recurrence-free survival in patients with/without a tumour that is adjacent to a risk area, and cumulative recurrence-free survival in patients with HBV-DNA replication. (a) Cumulative recurrence-free survival in patients with a tumour that is adjacent to a risk area and patients with a tumour in a general area after MCT (Kaplan–Meier method, $p<0.05$, log-rank test). (b) Cumulative recurrence-free survival in patients with positive HBV-DNA replication and patients with negative HBV-DNA replication after MCT (Kaplan–Meier method, $p<0.05$, log-rank test).

Discussion

Percutaneous MWA delivered using lower-powered devices (40–60 W) can successfully treat small tumours in patients with HCC[10]; however, the use of high-powered MWA to ablate larger tumours has been limited because this technique requires longer irradiation times that may induce skin burns. Microwave devices and antennas have been greatly improved; thus, ablating larger areas for shorter times may now be possible. Microwaves generate heat by oscillating dipole water molecules within tissues. Frequencies of 915 and 2450 MHz delivered with single, dual, or triple antennas are currently used for tissue

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Table 5
Procedure-related complications.

	3–5 cm group	5–8 cm group
Pleural effusion	2 (4.3%)	2 (14.3%)
Liver transaminase levels increase	5 (10.9%)	7 (50%)
Fever	15 (32.6%)	12 (85.7%)
Pain	7 (15.2%)	10 (71.4%)

ablation.[11] A study found that percutaneous MWA using these two frequencies achieves similar efficacy, but fewer antenna insertions were required at 915 MHz.[12]

In the present study, a 2450 MHz internally cooled shaft antenna with a high power output (80–100 W) was used. The antenna was equipped with two channels inside the shaft lumen that were filled with distilled water that was circulated using a peristaltic pump to provide continuous cooling. The low temperature of the antenna shaft allows for the delivery of more energy to the tissue without causing skin burns. Further, a low-temperature antenna shaft can reduce the temperature in the centre to decrease tissue charring and improve energy transfer, leading to a longer- and higher-output treatment.[13] These conditions made the remarkable expansion of the ablation zone possible. Specifically, the rate achieved for complete ablation of 3–5 cm lesions was significantly higher compared with that for 5–8 cm lesions (82.61% versus 64.29%, respectively, $p<0.05$). Similar results were obtained by others who found that the rate for complete ablation in patients (49 of 52) with 3–5 cm tumours is significantly higher compared with that in patients (21 of 28) with 5–8 cm tumours (94.2% versus 75%, respectively, $p=0.033$).[14]

Using MWA to achieve complete tumour ablation in patients with HCC may depend on factors such as the size, location, and boundary of tumours, as well as the adjacent structure. In the present study, the rates of local and distant recurrences were 24.44 and 15.56%, respectively. It is difficult to determine whether the development of a new HCC lesion is caused by intrahepatic metastasis associated with local recurrence or a multicentric origin. Therefore, it is important to determine the independent risk factors associated with the intrahepatic recurrence of HCC.

In the present study, multivariate analysis identified the area adjacent to the risk area as an independent prognostic factor of postoperative early recurrence. This is attributed to (1) difficulty to achieve a sufficient ablation margin to avoid injury for tumours adjacent to areas at risk, such as a major bile duct or blood vessel. The recurrence rate of tumours adjacent to risk areas increases because of insufficient ablation margins[15]; (2) an important inherent effect of the heat sink of tumours that are adjacent to blood vessels during thermal ablation may influence the effective temperature and cause incomplete ablation.[16] Therefore, the adjunctive use of dextrose solution,[17] carbon dioxide[18] or balloon interposition,[19] is suggested, which can separate and protect vital organs. The percutaneous technique allows for the safe and effective performance of the vast majority of ablations.

The combination of MWA with other non-invasive therapies, such as TACE and percutaneous ethyl injection (PEI), may prove to be effective for ablating lesions that are adjacent to risk areas. PEI has the advantage of allowing tumour treatment near organs and tissues at risk and avoids the problem of the heat-sink effect of adjacent vessels. One study performed PEI simultaneously with MWA therapy to treat tumours that were adjacent to both large vessels and bile ducts.[20] TACE followed by RF ablation was used to minimise heat loss because of perfusion-mediated tissue cooling and to increase the therapeutic effect of RFA.[21] Further research is required to determine the efficacy of combining TACE with MWA for lesions that are adjacent to risk areas.

Important unresolved clinical issues include predicting and preventing the extremely high rate of recurrence of HBV-related HCC even after curative treatment.[22] Several factors are associated with an increased risk of HCC recurrence after local ablation therapies, such as tumour multiplicity, size, and portal invasion as well as the levels of AFP and albumin and a patient's Child–Pugh class.[22] Furthermore, the present study identifies HBV-DNA replication as another independent prognostic factor for early postoperative recurrence of HCC. Similar results in other studies suggest that a high viral load is another risk factor for recurrence[23,24] and that antiviral therapy is associated with a lower risk of recurrence.[25] Given the strong association between the level of HBV-DNA and cancer recurrence, antiviral therapy may reduce the risk of HCC recurrence after MWA.

After undergoing MWA, four (8.9%) patients developed asymptomatic pleural effusion, which was gradually relieved after treatment within 1 week. These patients had lesions adjacent to the diaphragm; asymptomatic pleural effusion may be caused by the inflammatory effusion of the diaphragm after MWA. Therefore, adjunctively using a dextrose solution may reduce the possibility of damaging the diaphragm. In this study, high-powered MWA, which causes massive coagulation necrosis, may have led to the increase in liver transaminase levels that were detected in 10.99% of the tumours in the 3–5 cm group and 50% of the tumours in the 5–8 cm group. Therefore, it is important to protect liver function after administering high-powered MWA.

The limitations of the present study include its single-centre, retrospective design, and the relatively small number of patients. Therefore, multicentre, prospective randomised controlled studies with more patients are required to document the potential benefits of high-powered MWA therapy for HCC patients with large tumours.

In conclusion, high-powered MWA appears to be a safe and effective treatment for treating larger tumours in HCC patients. High levels of HBV DNA and the proximity of tumours to risk areas appear to be independent prognostic factors of postoperative recurrence. Thus, antiviral therapy and other non-invasive therapies combined with high-powered MWA may reduce the postoperative recurrence of HCC and improve long-term outcomes.

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