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FULL PAPER

Efficacy and safety of percutaneous microwave ablation for hepatocellular carcinomas <4 cm in difficult location

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Objective: Tumor location is a critical factor for determining technical success and local recurrence following percutaneous ablation of hepatocellular carcinomas (HCC). The purpose of this retrospective study was to evaluate the safety and outcome measures of percutaneous microwave ablation (pMWA) for HCCs <4 cm in difficult locations.

Methods: Retrospective review included 81 patients who underwent pMWA for HCCs <4 cm. Forty-three patients (30 males and 13 females; mean age, 61 years) with 53 HCCs located near the diaphragm, heart, gallbladder, kidney, gastrointestinal tract, large vessel and exophytic location were included under difficult location group. Thirty-eight patients (29 males and nine females; mean age, 60 years) with 48 HCCs in other locations were included under control group. Baseline demographics were recorded. Technical efficacy, local tumor progression (LTP), and complication rates were evaluated.

Results: Mean follow-up period was 3.4 months (range 1–7). There was no major complication in both the groups; two patients had a mild perihepatic hemorrhage in the difficult location group which was managed conservatively. There was no difference between the groups in the overall technical efficacy rate (84.9% vs 91.7%, $p = 0.294$), LTP rate (4.4% vs 2.2%, $p = 0.57$) or complication rate (4.6% vs 0%, $p = 0.177$).

Conclusion: Our data suggest that there is no significant difference in technical efficacy, LTP or complication rates for MWA in both difficult and normal locations.

Advances in knowledge: With proper patient selection, pre-procedural planning and appropriate technique, pMWA is feasible, safe, and effective for small HCCs in difficult location with an acceptable range of complications.

INTRODUCTION

Hepatocellular carcinoma (HCC) has been recognized as a leading cause of death among patients with chronic liver disease (CLD). Based on Barcelona Clinic Liver Cancer (BCLC) staging system, patients with very early-stage (BCLC 0) and early-stage (BCLC A) HCC can benefit from resection, transplantation or ablation.¹ Ablation techniques play an increasingly vital role in the management of very early-stage (BCLC 0) and early-stage (BCLC A) HCCs and provides excellent 5-year survival of >50%.

Liver being a solid vascular organ with abundant blood vessels, it is more likely to be affected by heat-sink effects. Based on this phenomenon, microwave ablation (MWA) is considered superior to radio-frequency ablation (RFA)

in treating HCCs <4 cm as it is less prone for heat-sink effects.^{2,3} Combined TACE and ablation seems to provide better results than ablation and TACE alone for the treatment of large HCC exceeding 4 cm in size, significantly improving the efficacy, quality of life, and long-term survival of patients.⁴

HCC location is a critical factor for local recurrence following percutaneous ablation.⁵ HCCs located near the diaphragm, heart, gastrointestinal tract, gallbladder, kidneys are more difficult to treat by ablation technique as they carry a serious threat of damaging vital organs. Exophytic and subcapsular HCC is another challenging location with high risk of tumor rupture. HCCs in these locations are more prone for residual disease or local

Figure 1. Workflow of the study.

nP – Number of patients; nT – Number of tumors

progression owing to creation of suboptimal ablation volume.⁶ Conservative strategy in these locations leads to under treatment in an attempt to avoid complications arising from direct penetrating or thermal injuries. However, careful pre-procedure planning and appropriate access site selection could result in improved clinical outcomes with low complication rates.

Previous studies evaluating the safety and efficacy of microwave ablation showed that percutaneous MWA was safe and effective in treatment of HCC located near the diaphragm,^{7,8} heart,⁹ gallbladder,¹⁰ gastrointestinal tract,¹¹ large vessels,¹² and subcapsular exophytic locations.¹³ But all these studies were focused on specific location. The purpose of this single center retrospective study was to evaluate the safety and outcome measures of percutaneous microwave ablation for small HCCs in all these difficult locations.

METHODS AND MATERIALS

Patient selection

This retrospective study was conducted according to the standards of the declaration of Helsinki and approved by institutional scientific review board and ethical committee. Informed consent was waived off considered the retrospective nature of the study.

Clinical records of all patients who underwent MWA for HCCs < 4 cm between January to September 2019 were analyzed (Figure 1). Of total 89 patients who underwent MWA during this period, 43 patients with 53 HCCs were included in difficult location group. Criteria for difficult location include subcapsular/exophytic HCCs, HCCs ≤ 5 mm from the diaphragm, heart, gallbladder,

kidney, gastrointestinal tract, and < 10 mm from large vessels with caliber of ≥ 3 mm. Thirty-eight patients with 48 HCCs in locations other than the difficult location criteria were included in the control group. Patients who were lost to follow-up ($n = 7$) and those with incomplete medical records ($n = 1$) were excluded from the study. HCC was diagnosed according to the AASLD guidelines using contrast-enhancing CT/MR imaging for typical lesions and ultrasound (USG) guided biopsy/fine-needle aspiration cytology for atypical lesions. As per AASLD guidelines, non-invasive criteria to diagnose HCC include the LI-RADS five lesion, which shows arterial phase hyper enhancement with one or more of the following: non-peripheral washout, enhancing capsule, or threshold growth.¹⁴ Eight HCCs in the difficult location group and four HCCs in control group were histologically proven HCC, while rest of the HCCs was diagnosed with non-invasive criteria. The maximum diameter was recorded for all HCCs from pre-procedure planning ultrasonography. Management decisions were taken by consensus with Hepatology, Interventional radiology and Hepato-pancreatico-biliary surgery teams.

MWA procedure

A written informed consent was obtained from all patients before MWA. All MWA were performed percutaneously under ultrasound guidance or in combination with CT scan for tumors not discernible or difficult to locate by ultrasound. All MWA procedures in both difficult location and control groups were performed by a single interventional radiologist with more than 12 years of experience in percutaneous ablation. The procedure was performed under deep sedation and local anesthesia along

Table 1. Strategies for needle placement depending on tumor location.

Tumor Location	Approach
Subdiaphragmatic tumors	Transhepatic access with angled intercostal approach
Near large vessels	Needle path parallel to the blood vessel as possible avoiding direct puncture.
Exophytic tumors	Indirect approach with intervening normal hepatic parenchyma.
Adjacent to Gall bladder, Heart, Kidney and Gastrointestinal tract	Needle path either parallel or away from the visceral organs and maximizing the distance as much as possible

with monitoring of heart rate, blood pressure, and oxygen saturation in interventional radiology suite. Deep sedation was given by using IV injections of midazolam, propofol, and fentanyl in appropriate doses by anaesthesiologist. We used 19 cm length MWA SOLERO applicator, (Single applicator with 15G stainless steel shaft, dielectric antenna with optimized ceramic tip, coolant channel with thermocouple and 2.86 m flexible, fully cooled cable) and the SOLERO microwave generator with operating frequency of 2.45 GHz and powers of up to 140 W (AngioDynamics, Amsterdam, Netherlands). The region from the skin to the liver capsule was infiltrated with local anesthesia using 5–10 ml of 2% lidocaine. Through percutaneous approach, MWA applicator is then directed toward the tumor under real-time ultrasound guidance except for one tumor where CT guidance was additionally used for accurate localization. Different strategies were followed for needle placement depending on the tumor location as shown in Table 1 and Figures 2–4. Once the applicator was positioned within the HCC, appropriate power and time was selected based on the manufacturer prescribed guidelines and ablation was performed. Ablation zone was monitored continuously under real time ultrasound guidance to screen for immediate complications. Ablation was considered complete if gaseous

cloud produced while ablating covered the entire HCC volume with with additional coverage of at least 5–15 mm of adjoining normal liver parenchyma as visualized by ultrasound or plain CT. In case the ablation zone was found to be inadequate, the needle was repositioned to complete the ablation. Ablation power and duration of ablation were recorded during all procedures. Tract ablation was performed during needle removal to avoid tumoral seeding. Hydro-dissection was not required for any MWA in the present study as none were exophytically indenting over bowel or diaphragm. Most exophytic lesion had adequate visceral fat adjacent to it and for some of the dome/surface/paracardiac lesion the needle was off centered to avoid any direct injury to the adjoining structure. After ablation, patients were monitored in the hospital for 1–3 days to look for any immediate procedure-related complications and post-ablation syndrome. Procedure-related complications were classified into mild, moderate, severe, or life-threatening adverse event based on new proposed adverse event classification by Society of Interventional Radiology (SIR).¹⁵

Treatment outcome and follow-up

Follow-up was done 1, 3, and 6 months after MWA with contrast-enhanced triple Phase CT/MRI scan of the abdomen,

Figure 2. 59-year-old male with hepatocellular carcinoma. A, Ultrasound image shows well-defined mixed echogenic tumor (indicated by small arrow) located just beneath the diaphragm (large arrows); B, Ultrasound image shows MWA needle (arrowhead) placed centrally within the tumor through angled intercostals approach; C, Post-ablation ultrasound image shows air cloud completely covering the tumor (arrow); D, Pre-procedure contrast-enhanced CT image shows arterial phase enhancing tumor (arrow) adjacent to the diaphragm (arrow heads); E, Follow-up CT after 1 month shows no arterial phase enhancement within the tumor bed (arrow) consistent with complete response.

Figure 3. 64-year-old female with hepatocellular carcinoma. A, Ultrasound image shows well-defined iso-hypoechogenic tumor adjacent (indicated by arrowheads) to gallbladder; B, Ultrasound image shows MWA needle (arrowheads) placed parallel and away from the gallbladder; C, Post-ablation ultrasound image shows air cloud completely covering the tumor; D, Pre-procedure fat-saturated T1 contrast-enhanced MRI image shows an arterial phase enhancing tumor (arrow) adjacent to the gallbladder (arrowhead); E, Follow-up CT after 1 month shows no arterial phase enhancement within the tumor bed (arrow) consistent with complete response.

Figure 4. 53-year-old male with hepatocellular carcinoma. A, Ultrasound image shows well-defined iso-hypoechoic tumor (indicated by small arrow) adjacent to right hepatic vein (large arrow); B, Ultrasound image shows MWA needle (arrowheads) placed parallel to large vessel avoiding direct injury; C, Post-ablation ultrasound image shows complete ablation of the tumor (small arrow) as well as the needle tract (arrowheads); D, Pre-procedure contrast-enhanced CT image shows faint arterial phase-enhancing tumor (arrowhead) adjacent to the right hepatic vein (arrow); E, Follow-up CT after 1 month shows residual arterial phase-enhancing nodule along the medial aspect of the tumor bed (arrowhead) consistent with partial response.

liver function test, and serum Alpha-fetoprotein (AFP) levels. The imaging evaluation was done using mRECIST (response evaluation criteria in solid tumors) criteria.¹⁶ Complete response was indicated by absence of any enhancing area in HCC bed and incomplete if the nodular-enhancing component is still visualized at HCC site. HCCs with incomplete response were treated with repeat microwave ablation, TACE, stereotactic body radiation therapy (SBRT) or surgery. Primary technical efficacy, overall technical efficacy, and local tumor progression rates were defined according to the image-guided tumor ablation: standardization of terminology and reporting criteria.¹⁷ Primary technical efficacy rate (PTR) was defined as percentage of HCCs showing complete response following single session of MWA. Overall technical efficacy rate was defined as percentage of HCCs showing complete response following single or multiple sessions of MWA. Local tumor progression (LTP) was defined as the appearance of enhancing foci at the edge of ablation zone during follow-up after a technically successful complete ablation. New intrahepatic lesions treated with MWA were considered as another index lesion and followed from that point of time for local tumor progression.

Statistical analysis

Data analysis was performed by a secondary operator who assisted the primary operator for all MWA procedures. Statistical analysis was performed using SPSS v.22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were denoted as mean $\pm$ standard deviation or median with range and compared using independent t-test or the Mann-Whitney U-test. Categorical variables were expressed as proportions and compared

using the Pearson's chi-square test or Fisher's exact probability test; a p-value of < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics

Of total 81 patients included in our study, 43 patients with 53 HCCs were in difficult location group and 38 patients with 48 HCCs were in control group. Most common difficult locations of the HCCs were adjacent to the diaphragm (17/53, 32%) and large vessels (17/53, 32%) followed by gallbladder (6/53%, 11%), exophytic locations (6/53%, 11%), adjacent to kidney (3/53%, 6%), gastrointestinal tract (2/53%, 4%), and heart (2/53%, 4%). All the patients had underlying CLD. Commonest causes of CLD were hepatitis B virus, hepatitis C virus, ethanol intoxication and non-alcoholic steatohepatitis. Majority of patients were under BCLC stage A (55/81, 68%) and few under BCLC stage 0 (7/81, 9%), and stage B (19/81, 23%). ECOG performance status score was either 0 or one for all patients. As per Child-Pugh scoring system, 37/81 (45.7%) patients were classified as class A and 44/81 (54.3%) under class B, with CTP scores ranging between 5 and 9. Model for End-stage Liver Disease (MELD) Na score ranged from 8 to 27. HCC size ranged between 1.1 and 3.9 cm in difficult location group and 1.0–3.7 cm in the control group. There was no statistical significance between the groups in the baseline characteristics of patient's age, Child-Pugh score, MELD Na score, BCLC staging, serum bilirubin, AST, ALT levels, tumor size, and duration of ablation as outlined in [Tables 2 and 3](#).

Technical success

Forty-four out of 53 HCCs in difficult location group and 44 out of 48 HCCs in control group showed complete response at first follow-up imaging study with primary technical efficacy rates of 83 and 91.7%, respectively. Among the difficult location group, 7/53 (13.2%) HCCs showed a partial response, three of which were in the segment VIII abutting the diaphragm, three in the segment V abutting the large vessel and one in the segment II abutting the stomach. Repeat ablation was performed in one of this incompletely treated HCC abutting the diaphragm which showed complete response in the next follow-up imaging. The rest of these HCCs were treated with TACE ($n = 4$), surgical resection ($n = 1$), or liver transplantation ($n = 1$). Two out of 53 HCCs (3.7%) in the difficult location group showed stable disease due to technical failure and were treated subsequently with TACE. Both of these HCCs with stable disease were located just beneath the dome of diaphragm in the segment VII and VIII. Four out of 48 (8.3%) HCCs in the control group showed partial response and were further treated with TACE ($n = 2$) or alcohol ablation ($n = 2$). Overall technical efficacy rate for difficult location group was 84.9% (45/53) vs 91.7% (44/48) for the control group. There was no significant statistical difference in the overall technical efficacy rate between the difficult location group and control between the groups ($p = 0.294$). Further technical efficacy rate for subgroups was 76.5% for HCCs near the diaphragm (13/17), 82.4% for HCCs near the large vessels (14/17), 50% for HCCs near the gastrointestinal tract (1/2) and 100% each for HCCs near gallbladder (6/6), kidney (3/3), heart (2/2), and exophytic locations (6/6). On subgroup analysis, even the overall technical

Table 2. Baseline characteristics of study population.

Characteristics		Difficult location group(<i>n</i> = 43)	Control group(<i>n</i> = 38)	<i>p</i> value
Age (Years)	Mean ± SD	61 ± 7.5 (44–76)	60 ± 7.6 (46–72)	0.554
Child score	Mean ± SD	7.4 ± 0.9 (5–9)	7.2 ± 0.8 (5–9)	0.296
MELD Na score	Mean ± SD	15.7 ± 5.1 (8–27)	14.5 ± 4.4 (9–25)	0.263
S. Alpha-fetoprotein (ng/mL)	Median ± IQR	7.6 ± 94.5 (7.5–2432)	14.2 ± 63.9 (4.9–605)	0.132
S. Bilirubin (mg/dL)	Mean ± SD	1.5 ± 0.6 (0.5–2.9)	1.4 ± 0.6 (0.6–3.3)	0.456
S. Aspartate Transaminase (IU/L)	Mean ± SD	57.5 ± 24.8 (28–138)	47.6 ± 29.1 (18–292)	0.102
S. Alanine Transaminase (IU/L)	Mean ± SD	41.1 ± 17.2 (19–95)	42.2 ± 27.6 (13–138)	0.828

efficacy rate for HCCs abutting the diaphragm was not significantly different from those in the control group ($p = 0.101$).

Local Tumor Progression (LTP)

The mean follow-up period was 3.4 months (range 1–7 months). Among the 45 HCCs, which showed complete response in the difficult location group, two HCCs (4.4%) developed LTP in the follow-up period with one located adjacent to the stomach and other one in subdiaphragmatic location. Similarly, LTP was seen in one (2.2%) of 44 completely ablated HCCs in the control group. The difference in LTP rates was not statistically significant between the groups (4.4% vs 2.2%. $p = 0.57$). The overall LTP rate was 3.3%.

Complications

There was no major complication in both the difficult location group as well as the control group. Two patients in the difficult location group developed a mild perihepatic hemorrhagic collection following the procedure which were classified as a mild adverse event and managed conservatively. The overall complication rate for the difficult location group was 4.6% (2/43) vs 0% (0/38) for the control group. This difference was not statistically significant ($p = 0.177$). There were no reports of burns at the needle insertion site, tumor seeding, pneumothorax, pleural effusion, diaphragmatic hernia or palsy, liver abscess formation, liver failure or procedure-related death after MWA.

DISCUSSION

Microwave ablation is one of the commonly used ablative modality to treat small HCCs. Our study showed that microwave ablation can be safely performed for HCCs in difficult location and was also effective with satisfactory outcomes.

Anatomical location of HCC is an important contributing factor for local recurrence following percutaneous ablation. In the recent years, focus is shifted toward assessing the efficacy and safety of

pMWA for HCCs located in difficult locations. With the advancement of high-powered generators and internal cooling system, microwave ablation has become both safe and effective in treating HCCs even in difficult locations.⁷ Our study showed no significant difference in overall technical efficacy rate, local tumor progression rate, or in the complication rate between HCCs in difficult location and those located elsewhere suggesting that MWA is both safe and effective for HCCs in difficult locations. Overall technical efficacy rate for HCCs in difficult location group was 84.9 vs 91.7% for the control group ($p = 0.294$).

Even for HCCs in subdiaphragmatic location, the overall technical efficacy rate was not significantly different from the control group except for the fact that there were two reports of technical failure. Reason behind the technical failure can be explained due to poor localization of HCC by ultrasound secondary to lung interference and difficulty in positioning antennas with more inclined approaches once the patient is deeply sedated. Similarly, off-center placement of the antenna may also lead to incomplete ablation at periphery. These factors ultimately increase the incidence of local tumor progression due to poor monitoring of the ablation zone. In such cases, additional CT guidance/combination with TACE or contrast enhanced ultrasound guidance¹⁸ can improve both HCC localization and antenna placement with higher chance of clinical success.

Overall local tumor progression rate (3.3%) in our study was low, which is well within the range of LTP reported for both RF and MW ablation.^{4,19 20} The difference in LTP rate was not statistically significant between difficult location and control groups (4.4% vs 2.2%. $p = 0.57$). The cases which had LTP in difficult location group were performed early in our experience with microwave ablation, and reason for LTP in these cases might be due to cautious ablation of these HCCs with a concern to avoid damage to adjacent diaphragm and stomach which ultimately resulted in inadequate ablation.

Table 3. Baseline tumor characteristics.

Characteristics		Difficult location group(<i>n</i> = 53)	Control group(<i>n</i> = 48)	<i>p</i> value
Tumor size (cm)	Mean ± SD	2.5 ± 0.9 (1.1–3.9)	2.2 ± 0.7 (1.0–3.7)	0.066
Duration of ablation (mins)	Mean ± SD	3.6 ± 1.6 (2.0–6.0)	3.5 ± 1.8 (2.0–6.0)	0.768
Power (Watts)	Mean ± SD	95 ± 24.7 (60–140)	90 ± 16.5 (60–100)	0.240

In the present study, two patients had HCC rupture with mild perihepatic hemorrhagic collection in the difficult location group while no complication was recorded in the control group. Both the patients were managed conservatively and were considered as minor complication based on SIR new adverse event classification system.¹⁶ Partial exophytic nature added to the subdiaphragmatic location might be the possible cause for HCC rupture in both these cases. No major complication was reported both in the difficult location or control group. Complication rate obtained in our study is also well within those reported by previous investigators.²¹

Adjuvant technique was used only for one HCC where percutaneous ethanol was used to ablate the HCC margins as the tumor was seen protruding toward the gallbladder lumen. Risk of complication increases when HCC is both exophytic and located adjacent to vital structure. Ethanol in such cases acts both as coolant as well produces chemical ablation of HCC margins, thereby producing synergistic necrotizing effects with larger ablation volumes than those achieved by MWA alone.^{12,22,23} Hydro-dissection and balloon interposition can also be used to prevent thermal injury to adjacent organs by its insulation and convection effects secondary to increased distance and fluid interposition between the ablation zone and surrounding organ.²⁴ But in all our patients with exophytic HCCs, either there was fat surrounding the shrunken liver preventing any direct injury to the adjoining organ(s) or we off-centered the needle position to reduce any risk of injury. Other ways of avoiding complications include: positioning needle as parallel to the vessels as possible, use of ultrasound guidance for real-time placement of needle for avoiding any vital structure and

combined ultrasound and CT guidance for subdiaphragmatic/paracardiac lesions, efforts not to directly puncture the lesion and take some normal liver parenchyma using oblique approach for entering the subcapsular lesions. Despite the use of minimal adjuvant techniques, complication rates were low and was not statistically significant between difficult location and control groups.

This study had some limitations. First all the ablations were performed by a single interventional radiologist with more than 12 years of experience in ablation techniques. Similar results might not be possible with a beginner. However, a recent study by Takai TR, et al²⁵ showed that a well-supervised ablation training program produced similar clinical outcomes and complication rates with no significant difference between the trainees and expertise group. Second is the retrospective nature and smaller sample size, especially for HCCs adjacent to gallbladder, kidney, heart, and gastrointestinal tract. Third, survival rates could not be estimated due to short duration of follow-up. Finally, all the MWA were performed with single system operating at a specific frequency, and results may vary across systems.²⁶

CONCLUSION

Percutaneous microwave ablation is feasible, safe, and effective for HCCs <4 cm in difficult location, although the combination of these difficult locations might increase the complication risk. With proper patient selection, pre-procedural planning and appropriate technique, MWA would be an ideal option to treat small HCCs located adjacent to vital structures with an acceptable range of complications.

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