

Ultrasound-guided percutaneous microwave ablation for small liver cancers adjacent to large vessels: long-term outcomes and strategies

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Abstract

Objective The aim of the study was to evaluate the long-term efficacy and safety of percutaneous microwave ablation (MWA) for small hepatic cancers adjacent to large vessels and to investigate the treatment strategies.

Methods From March 2009 to July 2015, a total of 86 patients with 94 tumors underwent ultrasound (US)-guided percutaneous MWA, with pathologically proven or clinically diagnosed liver cancers measuring ≤ 3 cm in diameter and located ≤ 10 mm from a major vessel ($n = 94$). Regular follow-up after MWA was performed to assess treatment efficacy and perioperative complications.

Results The complete ablation rate at 1 month after MWA was 93.3% (84/90). The 6-, 9-, 12-, 24-, 36-, 48-, 60-, 72-, and 84-month local recurrence rates were 2.4%, 2.4%, 3.7%, 6.6%, 8.4%, 8.4%, 8.4%, 8.4%, and 8.4%, respectively. There were no major complications. The perioperative special complication rate was 5.32% (5/94), including 3 cases of moderate liver function damage and 2 cases of limited sub-capsular hematoma.

Conclusion Percutaneous MWA for small hepatic cancers adjacent to large vessels is feasible, effective, and safe with an acceptable rate of complications. The key point is to strictly follow operative indications and adopt proper treatment strategies.

Key words: ultrasound (US); liver cancer; percutaneous microwave ablation (MWA)

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Hepatocellular carcinoma (HCC) is the sixth most common malignancy in the world in terms of numbers of cases (626 000 or 5.7% of new cancer cases) and causes more than 500 000 deaths every year^[1]. In addition, the liver is also a common site of metastasis from invasive solid tumors, such as colon cancer, breast cancer, neuroendocrine tumors, and sarcomas. The majority of patients with hepatic malignancies are not suitable for potentially curative resection due to inadequate hepatic reserve, advanced tumor stage, or other contraindications. The rate of surgical resection has been reported to be less than 30% of primary liver cancers and 10%–20% of liver metastasis^[2]. Recently, ultrasound (US)-guided percutaneous microwave ablation (MWA) as a minimally invasive therapy has been developed and has been widely

used in the clinical treatment of liver cancer.

Clinical evidence has confirmed the efficacy and safety of percutaneous MWA and radiofrequency ablation (RFA) for the treatment of HCC, especially for small HCCs measuring ≤ 3 cm^[3–4]. However, for cases in which the tumors are adjacent to large vessels, some previous studies have defined this as a treatment contraindication because of the higher rate of complications and incomplete necrosis^[5]. With the developments in technology and the accumulation of clinical experience, more studies have been published in this field. Some studies had shown that the rate of complete ablation and local tumor progression of local thermal ablation compared favorably with those far away from the large blood vessels^[6–7]. Other researchers express the opinion that a lesion located in

the area adjacent to large vessels is an independent risk factor that significantly affects the outcome of RFA [5].

Thus, researchers' viewpoints are variable on this issue and the most research has focused on percutaneous RFA, not MWA, which is also an important and popular modality for small liver cancers in eastern countries, such as China and Japan. Moreover, a fact we cannot ignore is that lesions are often found in this special area abutting large vessels and MWA is different from RFA in many ways. The long-term efficacy and safety of percutaneous MWA for small liver cancers adjacent to large vessels has not been studied sufficiently. More attention needs to be given to the liver lesions in this special and high-risk region.

In the authors' institution, we have successfully performed many cases of MWA for tumors located adjacent to large vessel. To confirm the feasibility, safety, and efficiency of our approach, we evaluated complete ablation, local tumor progression, and early complications as an indicator of treatment in 86 patients with 94 lesions treated with ultrasound-guided percutaneous MWA.

Patients and methods

Patient selection

From March 2009 to July 2015, a total of 86 patients (66 were men, 20 women; average age 51.27 years \pm 11.13 years; range 21–73 years) with 94 tumors (average diameter 2.01 cm \pm 0.63 cm; range 0.8–3.0 cm) underwent ultrasound-guided percutaneous MWA at the Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, and were enrolled in this retrospective study (Table 1).

Among these lesions, 85 lesions were diagnosed as primary HCC and 9 were liver metastasis from extrahepatic organs (2 stomach cancer, 3 colorectal carcinoma, 1 breast cancer, 1 glucagon cancer, 1 malignant interstitialoma, and 1 leiomyosarcoma). A total of 62 cases were recurrent

HCC after hepatic resection and 23 cases were of primary liver carcinoma. These patients underwent percutaneous MWA because they were not suitable for hepatic resection or preferred to undergo minimally invasive therapy. All patients met the inclusion criteria and were divided into two subgroups according to tumor location. Patients were closely followed up until March 2016. Written informed consent for this procedure was obtained from all of the enrolled patients.

Inclusion criteria

The inclusion criteria were: (1) Confirmed liver malignancy: (i) primary or metastatic liver cancer was confirmed by pathology through a tumor biopsy before ablation; (ii) HCC diagnosis: tumor markers [α -fetoprotein (AFP) \geq 200 μ g/L] and at least two of the following modalities confirmed the diagnosis of HCC: contrast-enhanced ultrasound (CEUS), contrast-enhanced computed tomography (CECT), or contrast-enhanced magnetic resonance imaging (CEMRI); (iii) liver metastasis diagnosis: tumors were identified on at least two modalities (CEUS, CECT, or CEMRI) that indicated liver cancer. (2) Tumors located adjacent to large vessels. (3) Accessibility of tumors via a percutaneous approach under ultrasound guidance. (4) The size of a single nodule of HCC or a metastasis was \leq 3 cm and the number of tumors was three or fewer. (5) No portal vein embolus or extrahepatic metastases. (6) The prothrombin time was less than 25 s, the prothrombin time activity percentage was higher than 40%, and the platelet count was \geq 40 cells \times 10⁹ /L. The maximum diameter of the nodules was measured by US in more than two planes.

Definition of the special locations

All of the lesions were located less than 5 mm from large vessels, which were defined as the main, first, or second branch of the portal vein (group A), the base of the hepatic veins, or the inferior vena cava (group B). There were 42 lesions in group A and 52 lesions in group B. The distance between the edge of the nodule and the large vessel was measured by scanning multiple planes on US, computed tomography (CT), or magnetic resonance imaging (MRI).

Treatment strategy

Percutaneous MWA was performed using an ECO-100c microwave system (Qinghai Microwave Electronic Research Institute, Nanjing, China) with a frequency of 2450 MHz and a power output of 0–100 W. All of the patients underwent ultrasound with a 3.5-MHz microconvex probe (Aloka, Tokyo, Japan) that was matched with a biopsy guide (Aloka, Tokyo) to confirm the range and relationship with its surrounding structures including the large vessels, main duct, and others and

Table 1 General condition of the patients (*n*)

Characteristics	No. of the patients
Patients (M/F)	86 (66/20)
Number of nodules	94
Tumor size (cm)	Range 0.8–3.0
	mean ($\bar{x} \pm s$) 2.01 \pm 0.63
Age (years, $\bar{x} \pm s$)	51.27 \pm 11.13
Hbs Ag (+)	65
AFP (μ g/L)	< 20 54
	20–400 22
	> 400 18
	mean ($\bar{x} \pm s$) 598.4 \pm 1868.6
Indication of treatment	Primary HCC 85
	Recurrence HCC 9

based on it, the puncture route, organ avoidance, and location of needle points should be well planned. First, pentazocine (50 mg; pethidine hydrochloride, Qinghai Pharmaceutical, Xining, Qinghai Province, China) was intra-muscularly injected, and then local anesthesia (10 mL of 2% lidocaine; Shanghai Fosun Industrial, Shanghai, China) was applied. After local anesthesia, a 14-gauge, 18-cm-long, internally-water-cooled MWA antenna (Qinghai Microwave Electronic Research Institute, Nanjing, China) was inserted into the center of the tumor under ultrasound guidance (Aloka ProSound α 7 or Philips EPIQ5) and the microwave system was set at 60 W output and at a 6-min ablation cycle. The entire procedure was continuously monitored using ultrasound. The coagulation necrosis area was carefully checked after the ablation to ensure it covered the lesions' edges by more than 5 mm in cases of ablation failure [8].

Follow up

All of the patients underwent CECT, CEUS, or CEMRI as well as blood chemistry tests, including AFP and liver function tests, at 1 month post-ablation, to evaluate the treatment results. The tumor was considered to have undergone completed necrosis on the basis of all the following findings: (1) the lack of enhancing tissue at the ablated tumor site; (2) the non-enhancing area extended beyond the tumors' borders; and (3) the margins of the ablation zone were smooth and sharp. The tumor was defined as having received incomplete ablation if enhancing tissue at the ablated tumor site was found, which needed additional treatment. US and blood chemistry was performed every month and enhanced imaging follow-up tests (CEUS, CECT, or CEMRI) were performed every 3–6 months after MWA for the first year after MWA and then every 3 months and 6–12 months during the next year.

During the follow-up period, all of the patients were observed for recurrence at the ablation zone and for new intra-hepatic distant recurrence (IDR). Local tumor progression (LTP) was defined as an enhancing nodule within or around the initial complete ablation zone, and IDR was indicated by an enhancing nodule distant from the complete ablation zone in the liver. These two different types of recurrence (LTP and IDR) were defined as intra-hepatic recurrence. LTP was described by the local tumor recurrence rate. Cases in which patients with intrahepatic multiple tumors in end-stage were excluded and the lesions ablated were covered. Major complications were defined as one that might threaten a patient's life, lead to substantial morbidity and disability, or result in a lengthy hospital stay if left untreated. Other complications were considered minor [9].

Statistical analysis

SPSS 19.0 statistical software was used to analyze the variables. For continuous variables such as liver function, a normal test was used. The appropriate normal transform method was chosen to meet the normal distribution, and then, a paired *t*-test was used. The general data of the patients, such as the hospitalization days after treatment, age, AFP levels, tumor size, and postoperative temperature, were described as $\bar{x} \pm s$. For qualitative variables such as ablation rate and local recurrence rate, the χ^2 -test was used. The total local recurrence rates were calculated using the Kaplan-Meier method. A *P* value < 0.05 was considered statistically significant.

Results

Patients' general condition post-treatment

All patients with local anesthesia felt uncomfortable during and after the treatment process, and the major toxicities included tenderness beneath the xiphoid process and shoulder pain, but they were tolerable and did not affect the success of treatment. Eight cases developed mild gastrointestinal symptoms after the operation, e.g., nausea, vomiting, and poor appetite.

The average temperature of the 94 cases was (36.93 \pm 0.51) °C, 1 day after the treatment and no patient had a marked fever. The average number of hospitalization days was (3.88 \pm 3.1) days after treatment. There was no significant difference between the groups considering the general condition of patients (Table 2).

Effectiveness of percutaneous MWA treatment

Eighty-four (93.3%) of the 90 tumors exhibited a complete ablation after the MWA by contrast-enhanced imaging (CEUS/CECT/CEMRI; Fig. 1 and 2). Six tumors were confirmed to be incompletely ablated 1 month after the treatment, of which 3 received a subsequent secondary ablation. One was treated with radiotherapy and 2 underwent conservative palliative treatment. Treatment success at 1 month after the initial and secondary ablations was observed in 87 of the 89 tumors. The complete ablation rate in group A (Fig. 1) and group B (Fig. 2) was 92.7% vs. 93.9% (*P* = 0.821) with no statistically significant difference. Moreover, 4 cases were lost to follow-up after discharge (Table 2).

Early complications

All of the 86 patients had transiently damaged liver function, which was measured by five indicators [serum glutamic-pyruvic transaminase (GPT/ALT), glutamic-oxaloacetic transaminase (GOT/AST), albumin (ALB), total bilirubin (TBIL), and prothrombin time (PT)]. The levels of ALT, AST, and TBIL in the pre-MWA group were higher than in the post-MWA group; in addition, the level

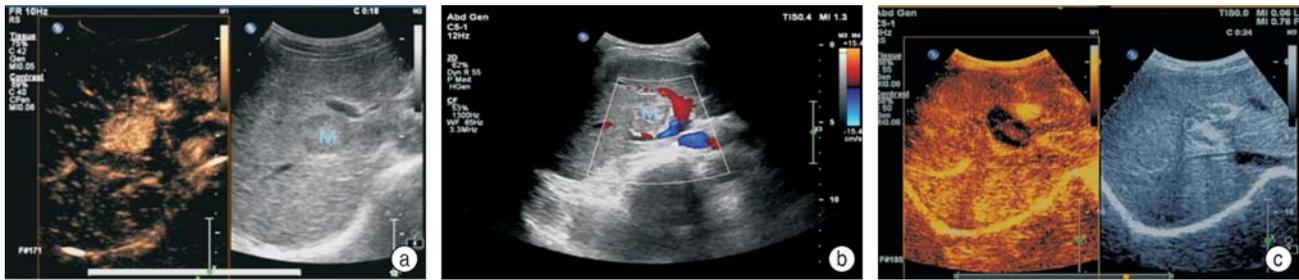


Fig. 1 MWA for a nodule located on the porta hepatis of group A. (a and b) This patient had hypervascular HCC in segment 8 (M), between the right anterior branch of the portal vein and the base of the right hepatic vein, and near the inferior vena cava. (c) After the treatment, the nodule was completely ablated. The patient had no complications such as hemorrhage or duct injury.

Table 3 Comparison of hepatic function before and after treatment

Hepatic function	Pre-treatment group	Post-treatment group	Paired numbers	<i>t</i>	<i>P</i>
ALT (U/L)	30.20 ± 18.9	123.9 ± 88.5	71	-13.074	< 0.001
AST (U/L)	31.84 ± 22.32	149.8 ± 114.3	69	-13.822	< 0.001
ALB (g/L)	40.72 ± 6.91	37.45 ± 6.02	70	4.485	< 0.001
TB (μmol/L)	14.09 ± 10.1	17.94 ± 7.72	66	-4.348	< 0.001
PT (s)	13.71 ± 1.56	13.92 ± 2.94	42	1.048	0.31

Note: All five indicators did not meet the normal distribution, and we chose the appropriate normal transformation method (extraction of root) to meet it; the *P* value of the K-S normal-tests were all greater than 0.05

of ALB was lower pre-treatment than post-treatment, and the differences were statistically significant (*P* < 0.001). There was no statistically significant difference between the groups before and after treatment for PT (*P* = 0.31; Table 3).

Moderate hepatic function damage was found in 3 cases after the operation (ALT ≥ 300 U/L, TBIL 34.2–51.3 μmol/L, PT prolonged by 3–5 s, moderate ascites, blood ammonia was higher than the normal level, or more than three of the five indicators listed occurred simultaneously [10]) and minor hepatic function damage occurred in the other 91 cases. For patients who had minor hepatic damage, their hepatic function level recovered to the pre-

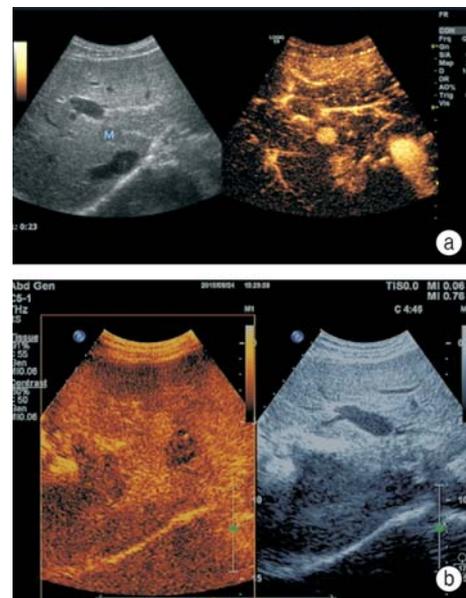


Fig. 2 MWA for a nodule located on the porta hepatis of group B. (a) This patient had hypervascular HCC close to the inferior vena cava, and the minimum distance was 4 mm measured by ultrasound scans. (b) After the treatment, the nodule was completely ablated with a well-defined perfusion defect in the late phase. The patient had no complications such as hemorrhage or duct injury.

Table 2 Effectiveness of MWA and patients' general condition

Variables	Group A	Group B	Total	<i>T</i> (χ ²)	<i>P</i>
<i>n</i>	41	49	90		
Hospitalization days (day, $\bar{x} \pm s$)	3.98 ± 3.33	3.8 ± 3.05	3.88 ± 3.1	0.555	0.237
Temperature (°C, $\bar{x} \pm s$)	36.96 ± 0.47	36.9 ± 0.55	36.93 ± 0.51	0.262	0.692
Effectiveness	Complete ablation	46	84	0.051	0.821
	Incomplete ablation	3	6		
Local recurrence	Ratio (%)	92.7	93.9	0.059	0.808
	N	35	43		
	Y	3	3		
	Ratio (%)	7.9	6.5		

Note: Four cases were missing in the follow-up period. Group A: lesions adjacent to the main, first, or second branch of the portal vein; group B: lesions adjacent to the base of hepatic veins or the inferior vena cava. The *T*-test was performed for comparing temperature and hospitalization days and the χ²-test was performed for comparing local recurrence rate and effectiveness.

peration level after being treated with hepatic protection agents and measures to reduce jaundice for 3 to 7 days and they returned to a normal level after 2 months.

There were 5 cases of special complications among the 94 cases of treatment for tumors adjacent to large vessels. Two patients encountered limited sub-capsular hematomas of the liver. Ninety-four cases had hepatic function damage, including 91 cases of mild liver function damage and 3 cases of moderate liver function damage. Liver function returned to the preoperative state after 3–7 days' symptomatic treatment in patients with mild liver function damage. There were no significant differences between the two groups.

In the 3 patients with moderate impairment of liver function, five blood chemistry indicators were measured on the postoperative first and 7th day. The average levels of ALT, AST, ALB, and TBIL returned from 419 U/L, 420 U/L, 36 g/L, and 24.7 $\mu\text{mol/L}$ to 134 U/L, 36.3 U/L, 32.7 g/L, and 13.3 $\mu\text{mol/L}$, respectively, and had returned to a normal level 2 months later.

Bleeding around the puncture site occurred in 2 cases, but the amount was limited. One patient was cured after 40 mL of dark red fluid was drawn off via ultrasound-guided percutaneous needle aspiration. The volume of sub-hepatic localized liquid in the other case was 3.9 cm \times 1.9 cm, but the patient recovered without needing treatment.

There were no major complications. Five cases had minor complications and the mean hospital stay was 7 days. The overall postoperative morbidity rate of minor complications was 5.32% (5/94), and no deaths were directly associated with complications of MWA ablation.

Long-term clinical outcomes

The mean follow-up period was (30.5 \pm 20.0) months, and the median follow-up period was 28.0 months (range, 6.0–84.0 months) after MWA for these 90 cases. The median time to local tumor recurrence was 7.0 months (range, 6.0–86.0 months). There were 6 of 84 tumors (7.7%) that developed a local recurrence, 7.9% vs. 6.5% in groups A and B with no statistically significant difference, i.e., 3 cases per group. Of the 84 tumors that had a complete ablation, LTP was observed during the follow-up period in 6 patients with 6 lesions (Fig. 3). The respective cumulative incidence of local recurrence using Kaplan-Meier methods at 3-, 6-, 12-, 24-, 36-, 48-, 60-, 72-, and 84-months was 2.4%, 2.4%, 3.7%, 6.6%, 8.4%, 8.4%, 8.4%, 8.4%, and 8.4%, respectively (Fig. 4).

The following therapies for LTP cases were administered to these patients: 1 patient with recurrence within 2 months after ablation was treated with traditional Chinese medicine; 1 patient with recurrence after 10 months died after local radionuclide therapy; 1 patient was cured after resection again after 8 months;

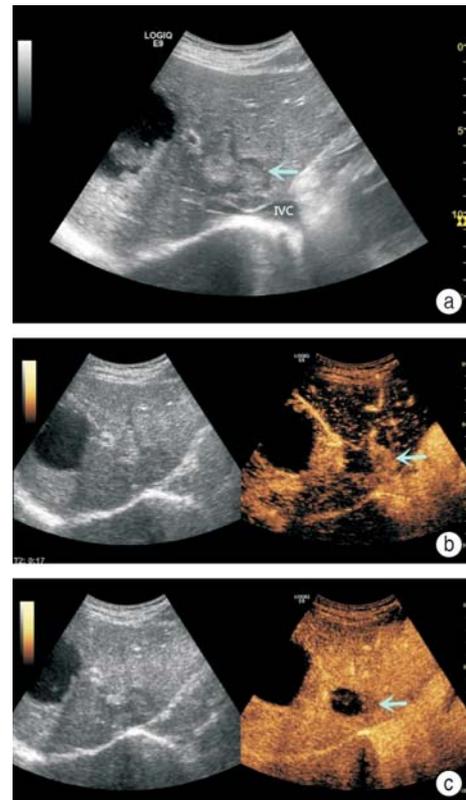


Fig. 3 MWA for a nodule located on the porta hepatis of group B. (a) This patient underwent percutaneous MWA for hypervascular HCC in segment 4, close to the inferior vena cava. (b and c) Six months after the first treatment, a lesion of local recurrence was found (arrowheads: b: arterial phase; c: late phase).

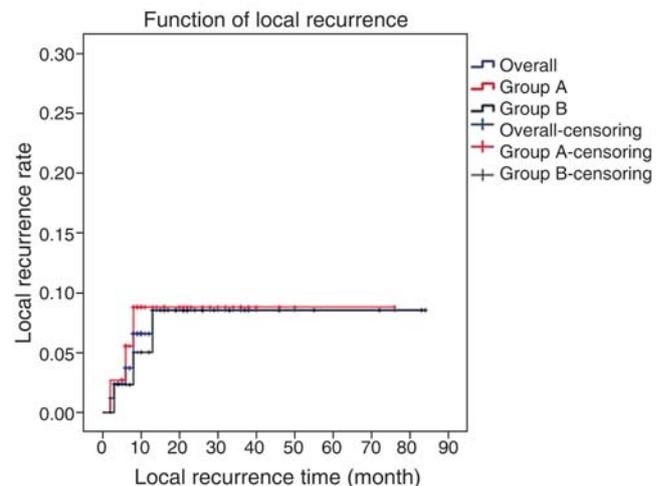


Fig. 4 Cumulative local tumor recurrence rates after percutaneous microwave ablation for nodules close to the large vessels. The red line represents the nodules in group A, the black line represents ones in group B, and the blue line represents the overall nodules.

and 3 patients were cured in 3 months, 6 months and 19 months, respectively, after ablation with a second completed ultrasound-guided percutaneous MWA. Six cases were excluded due to tumor progression.

Discussion

Percutaneous MWA for small liver cancers is effective and the results are comparable to surgical resection. Previous studies reported that the complete ablation rate of MWA for small HCC ranged from 95.64% to 97.6%^[11-12]. Shi *et al*^[13] enrolled 224 cases of primary HCC that met the standard of Milan and were divided into a surgical resection group and MWA group. The disease-free and cumulative survival was compared between the groups and the results showed that the 1-, 3-, and 5-year cumulative survival rates of the MWA group were 94.0%, 70.0%, and 52.0%, respectively, while those of the surgical resection group were 94.0%, 94.0%, and 72.0%, respectively ($P = 0.513$). The 1-, 3-, 5-years disease-free survival rates were 77%, 38%, and 18%, respectively, while those of the surgical resection group were 85%, 57%, and 31%, respectively ($P = 0.005$). For patients with a tumor diameter 3 cm or less, there were no obvious differences in cumulative survival ($P = 0.577$) or disease-free survival rates ($P = 0.140$) between the groups.

However, for patients with liver tumors adjacent to large vessels, some researchers consider them unsuitable for thermal ablation. Lu *et al*^[14] reported that the rate of incompletely treated or locally recurrent tumors was 5/74 (7%) in the non-perivascular group and 15/31 (48%) in the perivascular group ($P < 0.01$). Multivariate logistic regression analysis showed that the presence or absence of a large peritumoral vessel was an independent and dominant predictor of treatment outcome. Huang *et al*^[15] confirmed that the complete ablation rate was 96.3%, but local tumor progression was detected in 22 of 163 tumors (13.5%).

In the present study, the complete ablation of 90 tumors was 93.3% (84/90) and the 6-, 9-, 12-, 24-, 36-, 48-, 60-, 72-, and 84-month local recurrence rates were 2.4%, 2.4%, 3.7%, 6.6%, 8.4%, 8.4%, 8.4%, 8.4%, and 8.4%, respectively, which is in accordance with or even better than the results reported by published studies^[13-15]. The difference between the two groups for different locations is not statistically significant, which suggests they can be treated equally. Compared with laparoscopic surgery and open surgery, the hospital stay and treatment cost had considerable advantages in the present study.

The main difficulty with MWA of the lesions is how to ensure the patient's safety as well as complete ablation of the tumor. In this study, early complications were rare and generally not life-threatening. No serious complications occurred during or after the treatment.

Since the lesions selected for this research were located in the high-risk and special area of the liver for MWA, theoretical and operational feasibility is indispensable for obtaining satisfactory treatment and ensuring safety.

Theoretically, the wall of blood vessels is composed of smooth muscle and fibrous connective tissues in different proportions with certain elasticity and contractility. After fine needle aspiration is performed, the wall can close the pinhole through its elasticity. In addition, the liver is a parenchymatous organ and minimal bleeding may occur due to spontaneous hemostasis. In clinical practice, the following measures should be adopted to guarantee a good result: first, it is very important to strictly control the indications for patients being treated, who should have excellent hepatic and blood coagulation functions. In these cases, inner-hepatic or sub-hepatic bleeding is rare. Second, the needle insertion path should be as parallel to the blood vessel as possible, avoiding large vessels and the main bile duct and applying the principle of clinging to but not piercing the vessel wall. When the needle insertion cannot avoid all vessels along the path, the operator can choose to bypass the second order and smaller portal venous branches and distant part of the hepatic vein (distance to inferior vena cava ≥ 2 cm). In addition, for the main trunk of the portal vein and for first order branches, the inferior vena cava and near segment of the hepatic vein to the heart should definitely not be punctured because those large vessels are exposed or half-exposed outside the liver parenchyma in the area of the hepatic portal and it is difficult to control bleeding there. Third, the needle should be immediately readjusted to a location under the hepatic capsular or subcutaneous when the needle path is found to be inconsistent with the anticipated puncture path during the procedure. Then, the direction should be adjusted before inserting again. Changing the direction after the needle has pierced blood vessels or the inside of tumors is not acceptable; this can reduce potential damage to bile ducts and blood vessels and prevent seeding metastasis. Fourth, skilled and experience operators may improve the successful rate of first US-guided puncture and reduce the probability of injuries caused by repeated punctures. In our study, the treatments were done by two doctors with more than 10 years' experience in MWA (Kaiyan Li, and Hongchang Luo; see Fig. 5).

To date, many scholars have developed new technologies relying on platforms constructed by multiple disciplinary researchers. Jung *et al*^[16-17] have reconstructed 3D pictures showing the relationship between tumors and important structures surrounding the liver that enable surgeons to establish and find the most appropriate needle puncture pathways through the spatial conformation. Lonardo *et al*^[18] have applied a method of continuation perfusion of cold normal saline into the central bile duct of the hepatic

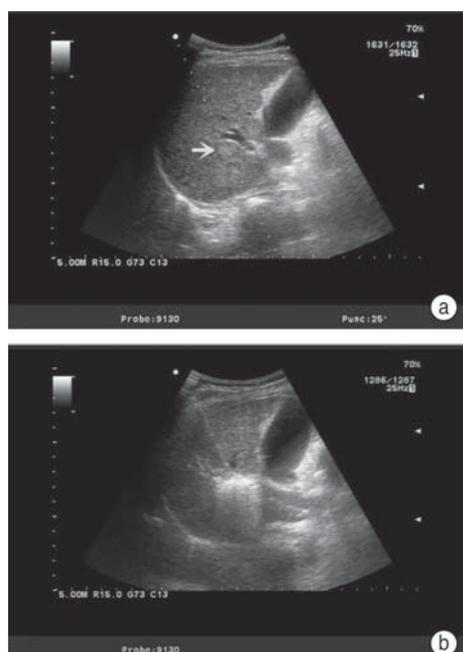


Fig. 5 (a) The lesion lies on the visceral side of the right anterior portal branch. The puncture path inserted through the portal branch. (b) The heat distribution completely covered the original lesion area.

portal to prevent injuries to the main bile duct during the process of treating tumors with RFA.

Among the cases in this group, 6 lesions had incomplete ablation. After a careful study of post-operation CEUS, CECT, CEMRI, 2 cases had residual tumor close to great vessels and that effect might be caused by the blood flow drawing away heat during the process of treatment. Two cases were located in the periphery or original surgical scars and their borders within the scars were unclear on 2-D ultrasound images, and incorrect judgment of the scope of the lesions resulted in incomplete ablation. Residual tumors in 2 cases were found tilted to one side, which was related to the deviated needlepoint positions that did not reach accurate positions. These cases indicate that heat loss and residual tumors in the periphery of blood vessels can be reduced through moderately prolonging the MWA ablation time and combining percutaneous absolute ethanol injection (PEI)^[19] and transhepatic arterial chemotherapy and embolization (TACE)^[20] in areas close to great vessels. Furthermore, intraoperative enhanced ultrasound can help tumors with unclear 2-D borders attain more definite borders and scope for treatment.

Conclusion

Percutaneous MWA for small hepatic cancers adjacent to large vessels is feasible, effective, and safe with an acceptable incidence of complications. The key point is

to follow indications strictly and adopt proper strategies.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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