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ORIGINAL ARTICLE

Ultrasound-guided No Touch liver pedicle microwave ablation in hepatocellular carcinoma treatment*

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Abstract

Objective This study aimed to investigate the feasibility, safety, and clinical effect of No Touch liver pedicle microwave ablation (NTLP-MWA).
Methods The outcomes of 118 patients diagnosed with hepatocellular carcinoma (HCC) between 2014 and 2015 were retrospectively analyzed. Patients were divided into three groups. In group A, 35 patients underwent ultrasound-guided NTLP-MWA, 27 in Group B were treated with routine microwave ablation (RMWA), and 56 in group C underwent anatomic hepatectomy (AH). The preoperative basic data, intraoperative data, and postoperative data were analyzed among the three groups.
Results The treatment time, intraoperative blood loss, and postoperative liver function (alanine transaminase) in the NTLP-MWA and RMWA groups were significantly different from those in the AH group (all $P < 0.005$). There was no difference in the complete elimination rate and local recurrence within 1 year among the three groups. Treatment was not an independent risk factor for early postoperative recurrence. There was no significant difference in the 5-year overall survival rates among the three groups.
Conclusion NTLP-MWA is safe and reliable, in accordance with the principles of oncology treatment, and worth further promotion in clinical practice.
Key words: ultrasonic guidance; hepatocellular carcinoma; microwave ablation; liver pedicle

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Hepatocellular carcinoma (HCC) is one of the five most common malignancies in the world, ranking first in cancer incidence and mortality in China (Chen *et al.* 2014). In some parts of Asia, HCC is the most common cause of cancer-related deaths. The incidence of HCC is increasing significantly in European and American countries (Tan *et al.* 2018). Currently, more than 500,000 new cases are diagnosed each year. China has a high incidence of HCC. According to the World Cancer Report released by the World Health Organization in 2014, China accounts for half of the new cases of HCC and more than half of the total deaths globally (McGuire, 2015).

Therefore, the treatment of HCC has attracted increasing attention worldwide. Surgical treatment has always been considered the primary treatment for HCC. However, most patients cannot be treated surgically because of tumor anatomical location, tumor size, tumor number, insufficient liver residue, and extrahepatic metastasis. Meanwhile, non-surgical treatment is currently available for most patients with HCC. With the development of medical technology and equipment, it is necessary to regenerate therapeutic strategies for HCC.

In recent years, topical ablation has rapidly developed. Owing to the advantages of minimally invasive, repeatable, real-time monitoring, and high clinical compliance, ultrasound-guided ablation of HCC has

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become the third major treatment method for HCC after anatomic hepatectomy (AH) and interventional treatment (Feng *et al.* 2014; Abdelsalam *et al.* 2016; Xu *et al.* 2018). However, for lesions with a diameter between 2 and 5 cm, the conventional multi-antenna and multi-point acupuncture treatment in a polyhedral geometric model is likely to cause residual lesions, leading to incomplete ablation (Berber. 2016; Zaidi *et al.* 2016; Lee *et al.* 2017; Long *et al.*2016). No touch liver pedicle microwave ablation (NTLP-MWA) is a new method of topical ablation. Before the ablation of the lesion, the hepatic pedicle of the liver segment or subsegment, where the lesion was located, was first destroyed to prevent the metastasis of tumor cells along the portal system. This study aimed to investigate the feasibility, safety, and clinical applications of NTLP-MWA by comparing the outcomes of NTLP-MWA, routine microwave ablation (RMWA) and AH.

Materials and methods

Study population

This study was approved by the institutional review board of Tongji Hospital. Written informed consent was obtained from all the patients. Consecutive, unrelated adult patients (n =118, 97 for men; mean age, 56.77±11.08 years) who were treated in the Tongji hepatic surgery center between January 2014 and December 2015 were retrospectively studied if they fulfilled the standard diagnostic criteria for HCC.

Microwave ablation would be administered if the patients did not meet the surgical guidelines, or did not wish to undergo surgical treatment. NTLP-MWA was administered to patients with lesions located in one segment, and the liver pedicle was evident on preoperative ultrasound examination or CT scan. Patients were divided into three groups. In group A, 35 patients underwent ultrasound-guided NTLP-MWA, 27 in group B were treated with RMWA, and 56 in group C underwent AH.

All enrolled patients were required to meet the following conditions: (1) Preoperative diagnoses based on the guidelines of the American Association for the Study of Liver Diseases, and all lesions presented typical manifestations on contrast-enhanced ultrasound, contrast-enhanced CT scan, or magnetic resonance imaging: hyperenhancement in arterial phase, rapid wash-out in portal/late phase; (2) Patients had no vascular infiltration, liver function Child-Pugh class A, American Society of Anesthesiologists score of 2 or less, ICG-R15 less than 15%; (3) Preoperative imaging examination confirmed a single lesion with a diameter of 2–5 cm; (4) The lesion located in a certain liver segment or a sub-hepatic segment; and (5) All patients signed informed consent before treatment. The study was performed in accordance with the Declaration of Helsinki and the ethical guidelines for clinical studies of the local ethics committee. Patients were excluded if they had obvious portal vein tumor thrombus, distant metastasis, multiple lesions, or a lesion diameter less than 2 cm or greater than 5 cm.

In our study, the basic preoperative data (age, sex, lesion size, alpha-fetoprotein [AFP] level, etc.), operative materials (treatment time, intraoperative blood loss), and postoperative data (postoperative liver function indicators, complications, local recurrence rate, and overall survival rate) of the three groups of patients were observed.

Microwave ablation

Imaging was performed with an Esaote MyLab™ ClassC ultrasound machine (Esaote, Genova, Italy), using an IOT342 appleprobe in open hepatectomy and an LP323 probe in laparoscopic hepatectomy. The probe frequency was 4–10 MHz, and the LP323 probe angle could be up/down 90° and right/left 90° through the two adjustment rods at the tail. Ablation was performed with a model ECO-100A1 microwave tumor ablation system (ECO, Nanjing, China) with a frequency of 2450 MHz, an output power of 0–150 W, and an ECO-100AI8 disposable microwave ablation antenna.

NTLP-MWA

The patients in group A underwent ultrasound-guided NTLP-MWA. Preoperative imaging data of the patients were fully analyzed to assess the route of the hepatic segment or subsegmental pedicle where the lesion was located. During the ablation, conventional ultrasound or laparoscopic ultrasound was first used to insert the microwave antenna into the hepatic pedicle of the liver segment or subsegment where the lesion was located without touching the tumor through the skin, and then the hepatic pedicle was damaged. The power of the microwave tumor ablation system was 60 W, and the duration of single ablation was 4 min. The microwave antenna was then inserted into the lesion and placed in an appropriate position for ablation. The ablation range of the tumor was ensured to be covered by a single antenna multiple times or multiple-antenna single time. The microwave tumor ablation system had a power of 60 W and a single ablation time of 6 min. The actual total ablation time was based on the lesion size. After treatment, the microwave antenna was slowly removed. When approaching the liver capsule, the power was turned on again, and the antenna passage was cauterized to prevent tumor metastasis and bleeding in the antenna passage.

RMWA

RMWA was performed directly in group B. Before ablation, the position and size of the lesion were fully understood, and the position adjacent to the surrounding important blood vessels and pipelines was designed. Two or three ablation antennas were placed at a spacing of 1–1.5 cm simultaneously, or one ablation antenna was inserted in different positions of the lesion multiple times at intervals of 1–1.5 cm each until the lesion was completely damaged. The ablation range was superimposed on each other in geometric shapes to ensure that the overall ablation range covered the lesion and the surrounding normal liver tissues by approximately 1 cm, and the ablation time and power of each ablation were consistent with those of group A.

Anatomic hepatectomy

AH refers to the complete removal of the hepatic segments supplied by the portal vein and major branches of the hepatic artery surrounding the lesion. Surgery was classified according to Couinaud's conventional terminology from eight segments of the liver (Couinaud, 1986). Dissection of one or more segments: five segments, extended hepatectomy; Four segments, lobectomy (right hepatectomy); Three segments, left hepatectomy (lobectomy); central hepatectomy, two sections; left lateral segment resection, right anterior or posterior sector resection; and one segment, a wedge resection (Inoue. 2012; Liu *et al.* 2019). Intraoperative ultrasound was used to detect lesion size and location, ruling out any lesions undiscovered in preoperative image evaluation, information about hepatic vascular structures, and location of the lesion in the liver segment that was resected. The Glisson system of the corresponding liver segment or subsegment was selected after dissecting the first hilum or the liver parenchyma, and clipping and dissecting the liver parenchyma along the ischemic line on the liver surface, followed by the dissection of the corresponding liver segment. The Pringle method was used to block the first hilum during the liver parenchyma dissection procedure (Pringle. 1908).

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences ver. 25 software (IBM Corp., Armonk, NY, USA). Quantitative data are expressed as mean±standard error of the mean. Statistical analysis was performed using analysis of variance followed by the Tukey-Kramer multiple comparisons test or unpaired two-tailed Student's *t*-test. Percentages were compared using the chi-squared test or Fisher's exact test. Multivariate logistic regression analysis was performed on the clinical indicators with statistical differences in univariate analysis to calculate the OR value of each independent risk factor. Statistical significance was set at $P < 0.05$. The Kaplan-Meier method was used to establish the survival curves of the three groups.

A patient was considered lost to follow-up if the last information available was older than 3 months with a total follow-up duration of < 5 years. To estimate the time of OS, the last follow-up assessment or death was measured from the date of treatment.

Results

Patient characteristics and follow-up

Between January 2014 and December 2015, 118 patients were treated in the Tongji Hepatic Surgery Center were divided into 3 groups. The background demographic patient characteristics including sex, age, underlying diseases (history of hypertension, diabetes, or hepatitis), tumor size, cirrhosis, Child-Pugh score, AFP, and liver function, are listed in Table 1.

Table 1 Baseline characteristics

Variables	Variables				
	NTLP-MWA (*n*=35)	RMWA (*n*=27)	AH (*n*=56)	X^2/F	*P*
Gender					
Male	29	22	46	0.020	0.990
Female	6	5	10		
Age	59.80 ± 11.26	56.04 ± 13.11	55.77 ± 11.08	1.940	0.148
Diabetes	4	3	6	0.012	0.994
Hypertension	15	12	27	0.274	0.872
Cirrhosis	27	20	44	0.209	0.901
Tumor size	2.72 ± 0.58	2.78 ± 0.53	2.67 ± 0.44	1.447	0.240
AFP	638.26 ± 1356.76	218.91 ± 393.06	945.06 ± 5121.29	0.371	0.691
pre-ALT	36.91 ± 30.83	29.81 ± 12.17	32.95 ± 18.79	0.818	0.444

NTLP-MWA, No Touch liver pedicle microwave ablation; RMWA, routine microwave ablation; AH, anatomic hepatectomy; AFP, Alpha-fetoprotein; ALT, Alanine aminotransferase

Table 2 Comparison of treatment effect

Group	Patients	Operation time (min)	Intraoperative bleeding (mL)	post-ALT-1d	post-ALT-3d
NTLP-MWA	35	29.91 ± 5.71	15.86 ± 3.53	108.89 ± 92.97	44.49 ± 35.48
RMWA	27	21.00 ± 4.53	14.44 ± 3.49	132.15 ± 68.02	38.19 ± 16.42
AH	56	136.86 ± 9.24	213.13 ± 103.16	141.31 ± 92.70	65.52 ± 45.61
F		3291.869	713.000	4.512	4.383
P		0.000	0.000	0.013	0.015

NTLP-MWA, no Touch liver pedicle microwave ablation; RMWA, routine microwave ablation; AH, anatomic hepatectomy; ALT, Alanine aminotransferase

During the 5-year follow-up, seven patients (5.93%) were lost to follow-up: two in the NTLP-MWA group, five in the AH group, and none in the RMWA group.

Comparison of treatment characteristics

Comparing the 3 groups, the median treatment time in the NTLP-MWA group, RMWA group and AH group was 29.91 min (IQR: 24.20–35.62), 21.00 min (IQR: 16.47–25.52), 136.86 min (IQR: 127.62–146.10), respectively. The treatment time in the NTLP-MWA and RMWA groups was significantly shorter than that in the AH group. The intraoperative blood loss in the NTLP-MWA, RMWA, and AH group were 15.86 mL (IQR: 12.33–19.39), 14.44 mL (IQR: 10.95–17.93), 213.13 mL (IQR: 109.97–316.29), respectively. The blood loss in the AH group was significantly higher than that in the NTLP-MWA and RMWA groups. The levels of alanine transaminase in the NTLP-MWA and RMWA groups was lower than that in the AH group on the 1st and 3rd day after treatment (Table 2).

Comparison of postoperative recurrence and survival rate

Reexamination 1 month after the treatment showed no residual lesion in the NTLP-MWA and AH groups, and the complete ablation rate was 100%. In the RMWA group, one patient had residual lesions, with a complete ablation rate of 96.30%. However, the difference was not statistically significant ($P = 0.183$).

After 1 year of follow-up, a total of 5 patients were lost to follow-up, including two in the NTLP-MWA group and three in the AH group. Five patients relapsed, including 2/33 (6.61%) in the NTLP-WMA group, 2/27 (7.41%) in the RMWA group, and 1/53 (1.89%) in the AH group. No patient died in any of the groups. The local recurrence rate of the AH group was lower than that of the NTLPMWA and RMWA groups, but the difference was not statistically significant (P = 0.453). Univariate analysis showed that treatment was not a risk factor for early recurrence after surgery (Table 3). Logistic multivariate analysis showed that tumor lesions, differentiation degree, and AFP were closely related to early postoperative recurrence, but treatment was not an independent risk factor for early postoperative recurrence (Table 4).

At the end of the 5-year follow-up period, a total of seven patients were lost, including two in the NTLP-MWA group and five in the AH group. The 5-year overall survival rates of the NTLP-MWA, RMWA, and AH

Table 3 Comparison of local treatment and recurrence

Group	1 month		1 year	
	Local residual	Non-residue	Local residual	Non-residue
NTLP-MWA	0	33	2	31
RMWA	1	26	2	25
AH	0	56	1	52
X^2	3.399		1.584	
P	0.183		0.453	

NTLP-MWA, no Touch liver pedicle microwave ablation; RMWA, routine microwave ablation; AH, anatomic hepatectomy

Table 4 Multivariate analysis of risk factors for recurrence after 1 year

Group	*P*	HR (95%CI)
NTLP-MWA (*vs.* AH)	0.331	29.91 ± 5.71
RMWA (*vs.* AH)	0.254	21.00 ± 4.53
Tumor size < 3 cm (*vs.* ≥ 3 cm)	0.046	136.86 ± 9.24
Well tumor differentiation (*vs.* poor or moderate)	0.046	3291.869
AFP < 400 (*vs.* ≥ 400)	0.033	0.000

NTLP-MWA, no Touch liver pedicle microwave ablation; RMWA, routine microwave ablation; AH, anatomic hepatectomy; AFP, Alpha-fetoprotein

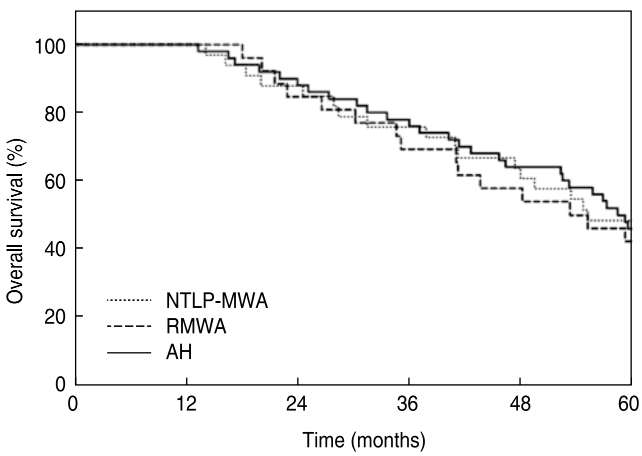

Fig. 1 Comparison of 5-year overall survival of three groups

groups were 48.48% (16/33), 44.44% (12/27), and 47.06% (24/51), respectively. The overall survival rate of the NTLP-MWA group was slightly higher than that of the other two groups, but the difference was not statistically significant ($P = 0.952$) (Fig. 1).

Adverse events

The incidence of complications in the NTLP-MWA and RMWA groups was lower than that in the AH group ($P < 0.05$). No serious complications were found in any of the patients in the two groups during and after treatment, whereas there were different degrees of subxiphoid process pain, right shoulder, and upper arm radial acid distension. In the NTPL-MWA group, two patients had a small amount of peritoneal effusion, and three had pleural effusion. Among them, one patient had pleural effusion and a small amount of peritoneal effusion due to the lesion's proximity to the top of the diaphragm. In the RMWA group, three patients developed pleural effusion, and the complication rate was 11.11% (3/27). In the AH group, all patients reported postoperative incision pain, two cases of liver limitation wound effusion, 12 cases of abdominal cavity effusion, and 15 cases of pleural effusion, including 10 patients simultaneously, appeared as pleural effusion and peritoneal effusion, two cases of hepatic limitations wound effusion, and five with pleural effusion puncture pumping liquid treatment, and the complication rate was 33. 93% (19/56).

Discussion

Hepatocellular carcinoma (HCC) is one of the most common digestive tract malignancies in China (Chen *et al.* 2016). With the widespread use of radiological techniques in HCC, an increasing number of HCC patients are now diagnosed at an early stage. Thermal ablation, mainly microwave ablation and radiofrequency ablation, has achieved satisfactory results in the treatment of HCC. Previous studies have shown that 70% of very early-stage HCC patients can achieve a similar 5-year survival rate with thermal ablation and hepatectomy. Several studies have compared the outcomes of radiofrequency ablation (RFA) and hepatectomy and have recommended that RFA be the preferred approach, even if HCC can be removed (Liu *et al.* 2016; Pompili *et al.* 2015; Xu *et al.* 2017). Microwave ablation has a higher ablation frequency, faster heat production, higher internal temperature of the tumor, larger ablation range, shorter ablation time, and easy control of the thermal field. Because it can directly lead to coagulation necrosis of the tumor, microwave ablation has the advantages of being minimally invasive, safe, and repeatable. It is one of the treatment options chosen by the majority of doctors and patients (Lee *et al.* 2014; Cavagnaro *et al.* 2019; Stauffer *et al.* 2003). When the diameter of the HCC was greater than 3 cm, the size of the tumor was irregular, the capsular can be interrupted, and the tumor tissue gasification during the ablation process is serious. Consequently, hyperechoic with fuzzy boundaries appear in the ablation foci and surrounding areas, which can easily cause ablation leakage and lead to residual lesions (Xu *et al.* 2017; Galanakis *et al.* 2018). Based on these shortcomings, for lesions of larger diameters, microwave ablation can be combined with multiple antennas to significantly expand the ablation volume (Violi *et al.* 2018; Facciorusso *et al.* 2016; Laeseke *et al.* 2009), so that microwave ablation has greater advantages. However, it should be noted that when the lesion volume is large, multi-antenna ablation is performed. The multi-point antenna placement method is susceptible to potential incomplete ablation due to the influence of the lesion location and the doctor's experience in antenna placement, which may lead to tumor recurrence or metastasis.

HCC cells form microinfiltration in the tumor-bearing segment of the liver in several ways: 1) invading the portal system and spreading to the distal end, 2) causing an arteriovenous short circuit to the central countercurrent of the portal vein; and 3) blocking the central countercurrent of the portal vein by tumor thrombus. AH is the first choice for the treatment of HCC by exposing the landmark vascular structure of the liver segment where the lesion is located, ligating the severed hepatic pedicle, and simultaneously removing the lesion and the liver segment to reduce the risk of recurrence of postoperative microfiltration and maximize the volume of the functional liver. The criterion for successful surgery is the treatment of the hepatic pedicle (Zhao *et el.* 2020; Shindoh *et al.* 2016; Li *et al.* 2016).

NTLP-MWA is a combination of routine microwave ablation and management of the hepatic pedicle, which is the key point in AH. First, we should find the hepatic pedicle of the liver segment where the lesion is located. To achieve the effect of ligation and dissociation of the hepatic pedicle in AH, to avoid the metastasis of tumor cells via the portal vein and adhere to the principles of oncology treatment, the first antenna was used to conduct thermal destruction of the hepatic pedicle without contact with the lesion, while the second antenna was used to conduct thermal ablation of the lesion (Fig. 2).

By comparing AH and RMWA, we analyzed the operation time, intraoperative bleeding volume, postoperative complications, postoperative liver function, 1-year local recurrence rate, and overall survival rate of the 118 patients in our study. The NTLP-MWA group and RMWA group compared with the AH group had significantly reduced blood loss, shortened the operation time, and had less influence on the patients, and patients recovered faster after treatment. Compared with the

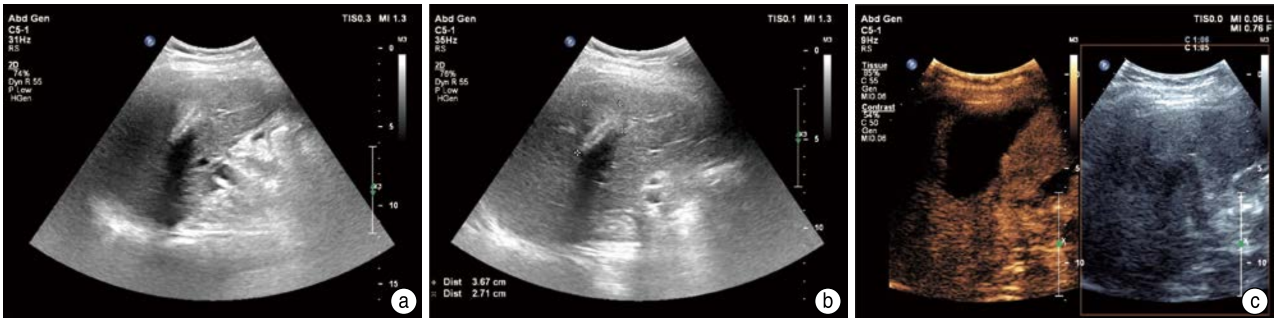

Fig. 2 (a) The lesion was located Segment III of the liver; (b) Two-dimensional sonogram of the lesion after No Touch hepatic pedicle microwave ablation; (c) Postoperative contrast-enhanced ultrasonography showed no contrast agent filling in Segment III of liver

RMWA group, the NTLP-MWA group exhibited less residual tumor tissue and more complete ablation. There were no statistically significant differences in the 1-year and overall survival rates among the three groups. However, it is worth mentioning that the absolute number of patients with local recurrence was higher in both the microwave ablation group and the conventional microwave ablation group than in the hepatectomy group. Our study shows that the NTLP-MWA is an effective and safe treatment. The complete ablation rate for HCC was 100%. There were no significant or serious complications, and a small amount of pleural effusion and peritoneal effusion were acceptable in some patients. In this study, there were two cases of local recurrence within 1 year in the NTPL-MWA group. The authors believe that there are the following reasons: (1) There may be multiple portal vessels supplying blood to the tumor-bearing hepatic segment; (2) In the early stage of the study, the injection accuracy was insufficient or the ablation time was short, and the ablation of the hepatic pedicle was incomplete. To achieve the best ablation effect, it is important to conduct a detailed preoperative imaging evaluation. By comparing the preoperative ultrasound, CT, and magnetic resonance imaging, the vessels in the liver segment where the lesion is located can be identified to avoid loss of the vessels in the hepatic pedicle or the retention of the pedicle during the operation. During the ablation, precise antenna insertion was needed, the optimal route was chosen to avoid the lesion, and the microwave antenna was inserted into the target liver pedicle precisely. In these ways, we could shorten the duration of the microwave ablation and reduce the damage range. When the power was increased to 60 W and microwave ablation was performed for 4 min, the insertion site of the microwave antenna was approximately 2 cm away from the bifurcation of the hepatic pedicle. The ablation achieved satisfactory results and avoided damage to adjacent important structures.

Limitations

A limitation of our study is its retrospective nature. Another limitation is that it was a single-center study without incorporating the results from other centers, and the results may not be comparable to those obtained from other centers. However, a single-center study can avoid such technical differences.

This study also has the following limitations: because hepatic pedicle microwave ablation is a new minimally invasive technique, the research time is shorter, and no touch technique cannot be used for ablation of some lesions in special sites, which are supplied by multiple branches of the hepatic pedicle. Moreover, the number of cases near the hepatic hilum, diaphragmatic roof, or adjacent large vessels was small. More cases will be included in future studies to extend the follow-up period to achieve more accurate comparative results.

Conclusions

To our knowledge, NTLP-MWA is a new local ablation technique. This new method has great potential in clinical applications, which can reduce the amount of surgical bleeding, shorten the operation time, have less influence on the liver function, and aid faster recovery after surgery. Further research is expected to contribute to its extensive clinical application.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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