JHEP|Reports

Microwave ablation *vs.* single-needle radiofrequency ablation for the treatment of HCC up to 4 cm: A randomized-controlled trial

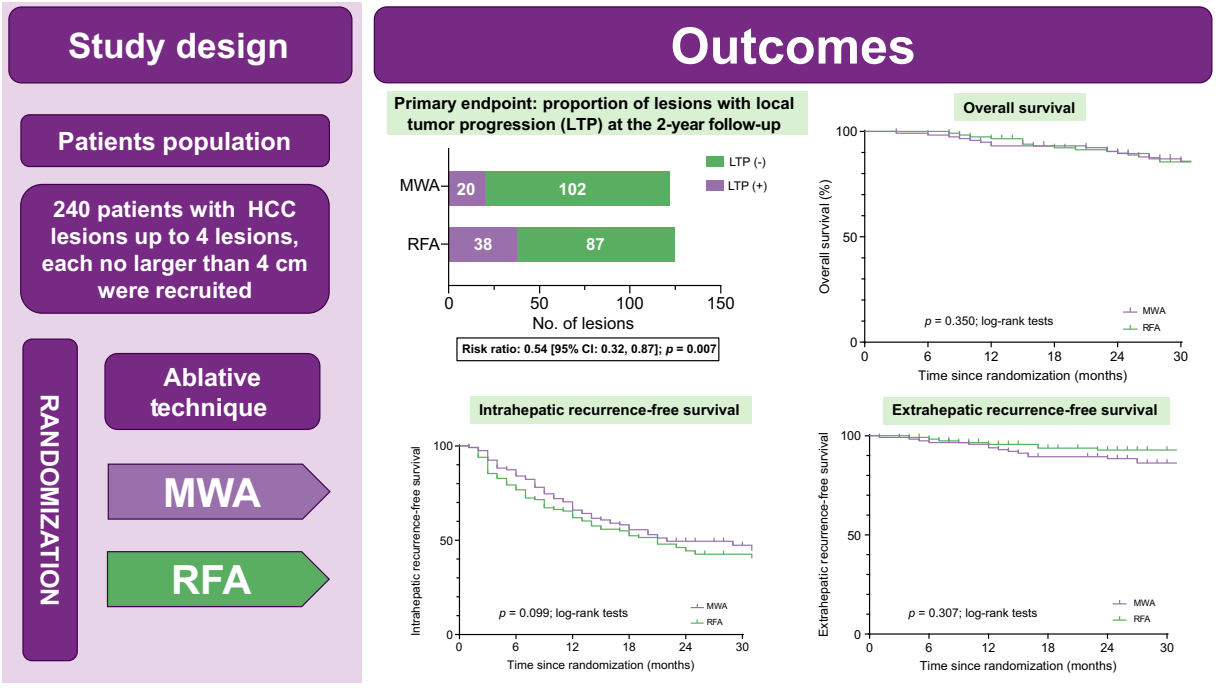
Authors

Katsutoshi Sugimoto, Kento Imajo, Hidekatsu Kuroda, …, Atsushi Nakajima, Shigehiro Kokubu, Takao Itoi

Correspondence

sugimoto@tokyo-med.ac.jp (K. Sugimoto).

Graphical abstract



Highlights:

- The proportion of lesions with LTP after 2 years was lower with MWA than with RFA.
- Ablation margin (<3 mm) was an independent predisposing factor for LTP.
- DCP was an independent predisposing factor for intra- and extrahepatic recurrence.
- Both techniques appeared safe, with only two severe complications reported.

Impact and implications:

While some randomized control trials (RCTs) have compared the efficacy of microwave ablation (MWA) and radiofrequency ablation (RFA) for small hepatocellular carcinoma (HCC), the superiority of MWA over RFA remains unverified despite its theoretical benefit. This study is the first to demonstrate the utility of MWA over single-needle RFA for patients with HCC, with a significant difference between the two groups in the proportion of lesions with local tumor progression after a 2-year follow up. Moreover, the two techniques were safe, with only two severe complications reported in the entire study cohort. Given that an RCT differs slightly from daily clinical situations, practical and anatomical criteria for selecting the optimal technique on a lesion-by-lesion basis are required.

https://doi.org/10.1016/j.jhepr.2024.101269

Research article

JHEP|Reports

Microwave ablation *vs.* single-needle radiofrequency ablation for the treatment of HCC up to 4 cm: A randomized-controlled trial

Katsutoshi Sugimoto[1,*,†], **Kento Imajo**[2,3,†], Hidekatsu Kuroda[4], Go Murohisa[5], Kazue Shiozawa[6], Kentaro Sakamaki[7], Takuya Wada[1], Hirohito Takeuchi[1], Kei Endo[4], Tamami Abe[4], Takashi Matsui[6], Takahiro Murakami[6], Masato Yoneda[3], Atsushi Nakajima[3], Shigehiro Kokubu[2], Takao Itoi[1]

JHEP Reports **2025**. vol. 7 | 1–8

Background & Aims: Radiofrequency ablation (RFA) is the standard treatment for small hepatocellular carcinoma (HCC), specifically for tumors <3 cm in size and numbering fewer than three, excluding surgical candidates. Microwave ablation (MWA) is an innovative approach believed to have theoretical benefits over RFA; however, these advantages are yet to be empirically verified. Therefore, we evaluated and compared the effectiveness of MWA and RFA in managing HCC tumors up to 4 cm in size.

Methods: In this multicenter randomized controlled trial conducted across five centers in Japan, eligible participants had up to 4 tumors, each up to 4 cm in size, and were not considered for surgery. Patients were randomly assigned to undergo MWA or RFA. The primary outcome was the rate of local tumor progression (LTP), whereas secondary outcomes included overall survival (OS) and intra- and extrahepatic recurrence-free survival (RFS) at the end of the 2-year follow up.

Results: In total, 240 participants were screened from July 12, 2018, to December 7, 2021. Four participants were excluded: three did not meet inclusion criteria, and one died from an unknown cause during treatment. Consequently, 119 (130 lesions) and 117 (136 lesions) participants were treated with MWA and RFA, respectively. The proportion of lesions with LTP at the 2-year follow up was significantly lower in the MWA group (20 [16.4%] lesions) than in the RFA group (38 [30.4%] lesions) (risk ratio, 0.54; p = 0.007). OS and both intra- and extrahepatic RFS did not significantly differ between groups.

Conclusions: MWA is more effective than RFA in reducing local tumor progression for HCC tumors up to 4 cm. However, no differences were observed in OS and RFS.

Introduction

Percutaneous local ablation therapies for hepatocellular carcinoma (HCC) began during the 1980s with the advent of percutaneous ethanol injection (PEI).[1] PEI is a safe, cost-effective, and efficacious treatment for small HCCs; however, as the tumor size increases, the efficacy of this treatment is limited by the presence of fibrous septa and tumor capsules, which inhibit ethanol diffusion.[2] During the 1990s, percutaneous first-generation microwave coagulation therapy (PMCT) was developed using Microtaze (Nippon Syouji Kaisya, Osaka, Japan). Although originally designed for hemostasis in liver resections[3] and later adapted for tumor ablation by Seki *et al.*,[4] PMCT reportedly has local tumor control superior to PEI. However, PMCT requires multiple sessions for larger tumors owing to its small ablation area, leading to its replacement by radiofrequency ablation (RFA) during the late 1990s.[5] RFA is currently considered a first-line treatment among percutaneous local ablation therapies for HCC. On an individual basis, RFA can be appropriate for patients with larger tumors (3–5 cm), multiple tumors (up to three nodules), and advanced liver disease (Child-Pugh score B), even when surgical treatment is not feasible.[6]

Next-generation microwave ablation (MWA) has recently been developed and widely adopted globally because of theoretical advantages over single-needle RFA. This technique results in shorter ablation times, higher ablation temperatures, and larger ablation zones compared with single-needle RFA. In addition, it reportedly reduces the heat sink effect near large blood vessels. Recently, two large-scale randomized controlled trials (RCTs) were published that focused on the use of MWA. In the RCT by Vietti *et al.*,[7] involving 152 patients with HCC treated by a cooled-shaft MWA system (Acculis Sulis VpMTA) or clustered internally cooled electrode (Covidien E series), no statistically significant difference was observed between the two methods in local recurrence rates 2 years post treatment, although a slightly higher tendency was noted with RFA (odds ratio: 1.62, 95% CI: 0.66–3.94, p = 0.27), and no difference was

* Corresponding author. Address: Department of Gastroenterology and Hepatology, Tokyo Medical University, 6-7-1 Nishi-shinjuku, Shinjuku, Tokyo 160-0023, Japan. Tel.: +81-3-3342-6111; Fax: +81-3-5381-6654.
E-mail address: sugimoto@tokyo-med.ac.jp (K. Sugimoto).
† These co-first authors contributed equally to this work.
https://doi.org/10.1016/j.jhepr.2024.101269

observed in complication rates. Similarly, an RCT by Yu *et al.*,[8] involving 203 patients with HCC treated by a cooled-shaft MWA system (KY-2000) or multipolar RFA system (CelonLab Power), reported no significant differences in local recurrence or complication rates. To date, no solid evidence exists regarding the effectiveness of MWA over RFA, including single-needle, clustered, and multipolar systems.

New microwave systems have been introduced to produce more spherical ablations and address issues of unpredictability. The Emprint Ablation System (Medtronic, Minneapolis, MN, USA) is a new-generation microwave system that uses thermosphere technology to control the microwave field and length. This technique combines thermal control using a cooling system that extends to the tip of the antenna with field shape and wavelength control, allowing for more spherical and predictable ablations.[9] This device was approved for use by the FDA in April 2014 and by its Japanese counterpart in July 2017.

Therefore, the current RCT compared the efficacy of next-generation MWA *vs.* single-needle RFA, which is the most popular RFA system in Japan, in patients with HCC (≤4 cm in size with up to four nodules).

Patients and methods

We conducted an RCT at five tertiary centers in Japan (Tokyo Medical University Hospital [Site 1], Yokohama City University Hospital [Site 2], Iwate Medical University Hospital [Site 3], Seirei Hamamatsu Hospital [Site 4], and Toho University Ohashi Medical Center [Site 5]). The study was approved by the Ethics Committee of each institution, and written informed consent was obtained from all participants. It was registered with the University Hospital Medical Information Network (UMIN No. 000033297). The study protocol is provided in Supplementary file S1.

The inclusion criteria were: (1) age ≥20 years; (2) an HCC lesion diagnosed based on typical findings of HCC on contrast-enhanced computed tomography (CT) (CECT) or gadoxetic acid (Primovist; Bayer Health Care, Osaka, Japan)-enhanced magnetic resonance imaging (MRI) (EOB-MRI) within 4 weeks before enrollment, using the non-invasive criteria recommended by the Japan Society of Hepatology;[10] (3) an HCC lesion measuring ≤4 cm in size with up to four nodules; (4) no extrahepatic manifestation or vascular invasion; (5) Child-Pugh score ≤9; (6) a HCC lesion treatable using both MWA and RFA at each center; (7) Eastern Cooperative Oncology Group[11] performance status of 0–2; (8) white blood cell count of 2,000–10,000/mm^3, platelet count ≥50,000/mm^3, hemoglobin level ≥8.0 g/dl, prothrombin time ≥50%, serum creatinine level ≤1.5 mg/dl, and blood urea nitrogen level ≤35 mg/dl; and (9) patients who were ineligible for, or did not anticipate undergoing, surgery. The exclusion criteria were: (1) concurrent cancer in other organs or a history of different cancers within 5 years before enrollment, except for basal cell carcinoma; (2) severe respiratory symptoms; (3) contrast media hypersensitivity reactions; and (4) pregnancy.

The following parameters were recorded at baseline: patient demographics (age and sex); etiology of the liver disease (HCV, HBV, and others); naïve or non-naïve status of HCC treatment; Child-Pugh score; tumor markers, such as α-fetoprotein (AFP), AFP-L3, and des-γ-carboxy prothrombin (DCP); number and maximum diameter of the lesions; tumor form (simple nodular type or others); Couinaud classification; and detailed tumor location (adjacent to [<3 mm] liver surface [hump], portal vein [major or minor branch], hepatic duct, hepatic vein, inferior vena cava, gall bladder, colon, heart, stomach, duodenum, diaphragm, and kidney). In this study, the portal vein was classified into its major and minor branches. The major branches included the main trunk and the first- or second-order branches of the portal vein, whereas the minor branches were the vessels distal to the third-order branch of the portal vein.

Randomization and masking

The patients were randomly categorized into the MWA (experimental) and RFA (control) groups. Randomization was centralized and performed using a fixed-block method (block size, 8) to reduce bias and achieve balance in patient allocation. The adjusted factors for allocation were tumor diameter (≤3 or >3 cm), patients who were naïve or non-naïve of HCC treatment, and serum AFP level (≤200 or >200 ng/ml). If at least one HCC was >3 cm in size, the patient was considered to have a large tumor diameter. Patient allocation and assignment were performed by a non-clinician who was not involved in patient care. Although the patients were blinded to the treatment, the physicians were not, owing to the different devices used.

Procedures

Eight expert hepatologists (KS and HT from Site 1; KI from Site 2; HK and KE from Site 3; GM from Site 4; and KSh and MT from Site 5) with 9–24 years of expertise in ablation therapy performed the MWA and RFA procedures. All MWAs were performed using a 13-gauge antenna of a 2.4-GHz system (Emprint Ablation System; Medtronic). RFAs were performed using a 17-gauge internally cooled electrode applicator (Cool-tip RF Ablation System E Series; Medtronic) or a 17-gauge internally cooled length-adjustable applicator (VIVA RF System; STARmed, Gyeonggi-do, Republic of Korea). All interventions were conducted percutaneously with patients under conscious sedation with ultrasound (US) guidance using a dedicated US system. We aimed for a 5-mm margin around the ablated tumors. Contrast-enhanced US (CEUS) using Sonazoid, CT/MRI fusion, and a needle-tracking system (Smart Navigation; Canon Medical Systems) were used as necessary to identify tumors and ensure precise needle placement. Ancillary procedures, such as artificial pleural effusion or ascites, were used in selected cases to detect tumors that were adjacent to the diaphragm or those obscured by lung artifacts, and to minimize the risk of thermal injury to adjacent anatomical structures. Overlapping ablation was allowed in both procedures, depending on the tumor size. The technical details of MWA and RFA were not specified. The detailed procedures for both techniques at each center are described in Supplementary file S2.

Assessment of treatment efficacy and follow-up

CECT (section thickness: 5 mm) was performed 1–3 days after MWA or RFA to evaluate treatment efficacy. Assessments were conducted at each center. The radicality of MWA and RFA was classified into 4 grades (R grades: A, B, C, and D) as previously reported by Nishikwa *et al.*,[12] based on the extent of the resected tumor margin. Grade A (absolutely curative) was defined as an ablative margin of ≥5 mm around the entire tumor.

Grade B (relatively curative) was defined as an ablative margin that extended around the entire tumor with a margin of <5 mm in some places. Grade C (relative noncurative) was defined as an incomplete ablative margin despite no apparent residual tumor. Grade D (absolutely noncurative) was defined as apparent incomplete tumor ablation. Additional ablation was performed within 2 weeks if the safety margin was deemed insufficient (*i.e.* grades C and D). The assessment was based on not only axial images, but also sagittal and coronal images, and the ablative margin was similarly assessed to determine whether it was <3 mm. However, ablation was not mandatory if achieving a circumferential ablative margin was difficult owing to the tumor location (*i.e.* adjacent to the bold vessels and heart-sensitive structures). Follow-up for these patients started only when the tumor was completely ablated (*i.e.* grades A and B).

Follow-up surveillance CECT or EOB-MRI was performed at 4-month intervals, and blood tests, including tumor markers (such as AFP, AFP-L3, and DCP), were conducted every 2 months for up to 24 months of follow up. An additional CECT or EOB-MRI was performed if at least one tumor marker was elevated. Intrahepatic HCC recurrence was classified as either recurrence at a site distant from the primary tumor or recurrence adjacent to (in contact with) the treated site (local tumor progression: LTP). LTP should fulfil one of the following criteria: (1) typical HCC observed adjacent to the edge of the ablation zone; (2) lesions present in the vein, including the ablation zone; or (3) lesions appear adjacent to the ablation zone with re-elevation of tumor markers. Distant metastases were defined as extrahepatic lesions. The date of tumor progression was recorded to ascertain LTP-free and recurrence-free survival (RFS). The diagnosis was made by two or more physicians (*e.g.* one radiologist and one attending physician) and, in case of difference of opinion, a decision was made through consensus.

Outcomes

The primary endpoint was the proportion of lesions with LTP at the end of the 2-year radiological follow-up. The secondary endpoints included overall survival (OS), intrahepatic and extrahepatic RFS at the end of the 2-year follow up, and safety. OS was defined as the proportion of patients alive at the end of the 2-year radiological follow up. Intrahepatic and extrahepatic RFSs were those patients alive without the appearance of new hepatic lesions with typical features of HCC and those patients alive without the appearance of extrahepatic lesions with typical features of HCC at the end of the 2-year radiological follow up, respectively. Safety represented treatment-related complications, which were classified according to the Clavien–Dindo classification system.[13]

Statistical analyses

This study was designed to assess whether MWA was more effective than RFA, based on the hypothesis that MWA was superior to RFA in terms of LTP after the ablation of HCC lesions ≤4 cm in size within four lesions. Lu *et al.*[14] compared the efficacies of MWA and RFA in HCC and reported LTP rates of 11.8% and 20.9%, respectively. The mean observation periods were 25.1 and 24.8 months for MWA and RFA, respectively. Assuming a 2-year nodal complete response (CR) rate of 90% for MWA and 80% for RFA, a total of 220 lesions would be required per group to statistically prove this 10% difference as significant (α = 2.5%, power = 80%, one-sided test). The current trial included four lesions, which corresponded to 110 patients per group, assuming each patient had an average of two lesions. Considering the few cases excluded from the analysis (*e.g.* those registered but untreated), the target number of participants was set at 120 per group, with an overall total of 240 in the study as a whole.

Normally distributed continuous variables are expressed as means ± SDs; skewed continuous variables are presented as the median (IQR); and categorical variables are expressed as counts and percentages to summarize the data background. The LTP rate was analyzed on a lesion-by-lesion basis. Conversely, OS, intrahepatic RFS, extrahepatic RFS, and complication rates were analyzed on a patient-to-patient basis. The proportion of lesions with LTP at the 2-year follow up was compared using a one-sided Fisher exact test. Overall, intrahepatic RFS and extrahepatic RFS were estimated and compared using Kaplan-Meier curves and log-rank tests. In those RFS analyses, the earliest occurrence of recurrence, death attributable to the original disease, or death caused by another disease, were considered an event. All time estimates were obtained from the date of randomization, and all patients were followed up until death. In a *post hoc* analysis, the clinical variables associated with LTP, intrahepatic recurrence, and extrahepatic recurrence between the two groups were estimated using a multivariate Cox proportional hazards model. In the analysis, only hazard ratios (HRs) and unadjusted CIs were presented because these outcomes were not definitive and should be interpreted as exploratory. Deviations are presented using SDs, IQRs, or 95% CIs. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary,

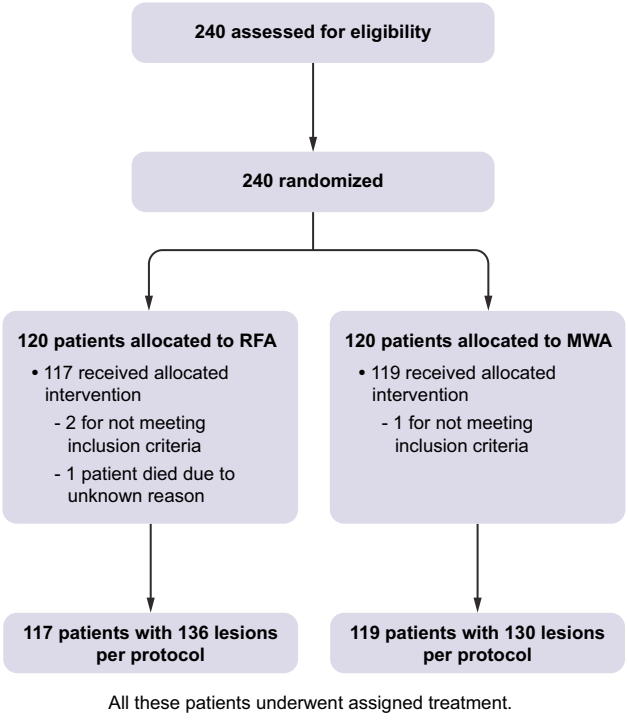


Fig. 1. CONSORT flowchart showing the study profile and patient disposition. MWA, microwave ablation; RFA, radiofrequency ablation.

NC, USA) or GraphPad Prism version 9.0.1 (GraphPad Software, San Diego, CA, USA). A one-sided p <0.025 and two-sided p <0.05 for the primary and secondary endpoints, respectively, were considered statistically significant.

Results

Patients

Overall, 240 patients were randomized between July 12, 2018, and December 7, 2021. Of these, four (1.7%) patients did not receive their allocated treatment: one died of unknown causes, and the others experienced tumor extension beyond the inclusion criteria during the allocated treatment. Ultimately, the study population comprised 236 patients: 119 (with 130 lesions) and 117 (with 136 lesions) treated with MWA and RFA, respectively (Fig. 1). All patients underwent the assigned treatment, and no additional ablation therapy was performed within 2 weeks in both groups after ablation therapy.

Comparison of clinical factors between each modality group

The baseline characteristics of the patients, including sex, mean age, etiology of the liver disease, naïve or non-naïve of HCC, Child-Pugh score, blood tests (including tumor markers), and the number of lesions, did not significantly differ between the two groups (Table 1). Additionally, the characteristics of the lesions, including tumor size, form (simple nodular type or others), location, and adjacent structures, did not significantly differ between the two groups (Table 2).

The frequency of CEUS and CT/MRI fusion did not significantly differ between the groups. By contrast, the needle-tracking system was more frequently used for MWA (12.6% [15/119]) than for RFA (2.6% [3/117]) (p = 0.006). The frequency of ancillary procedures, such as artificial pleural effusion or ascites, did not significantly differ between the two groups (Table S1).

During this analysis, the median follow-up durations were 33 (IQR, 27–42) and 37 (IQR, 27–44) months in the MWA and RFA groups, respectively (p = 0.337). Nine patients (3.8%) with 19 lesions (7.1%) were lost to follow up until the time point of the primary endpoint analysis. Therefore, we omitted these cases and calculated the primary endpoint. The proportion of lesions with LTP at the 2-year follow-up was significantly lower in the MWA group (20 [16.4%] lesions) than in the RFA group (38 [30.4%] lesions) (risk ratio [RR]: 0.54 [95% CI: 0.33, 0.87]; p = 0.007) (absolute risk difference: 0.14 [95% CI: 0.04–0.24]; p = 0.007). For the secondary endpoints, the Kaplan-Meier analysis of overall survival at the 2-year follow-up did not

Table 1. Patient characteristics according to different ablation therapies.

Patient characteristics	RFA (n = 117)	MWA (n = 119)
Sex (male/female) (%)	77 (32.6)/40 (17.0)	81 (34.3)/38 (16.1)
Mean age (yr)	74.1 ± 9.0	74.0 ± 9.9
Etiology (HCV/HBV/HCV + HBV/other) (%)	43 (18.2)/19 (8.1)/0 (0.0)/55 (23.3)	40 (17.0)/17 (7.2)/1 (0.4)/61 (25.9)
Treatment naïve/non-naïve (%)	43 (18.2)/74 (31.4)	42 (17.8)/77 (32.6)
Child-Pugh score (5/6/7/8/9) (%)	89 (37.7)/22 (9.3)/5 (2.1)/1 (0.4)/0 (0.0)	94 (39.8)/18 (7.6)/31.3)/2 (0.9)/2 (0.9)
T-Bil (mg/dl)	0.7 (0.52–0.9)	0.7 (0.5–0.9)
Alb (g/dl)	3.9 (3.6–4.2)	4 (3.6–4.2)
PT-INR	1.08 (1.03–1.15)	1.05 (1.00–1.13)
Plt (× 10 [4])	13.1 (10.0–16.4)	13.6 (10.7–17.0)
AFP (ng/ml)	5 (2.9–13.1)	5 (2.1–11.7)
AFP-L3 (%)	0.5 (0.5–6.1)	0.5 (0.5–7.6)
DCP (mAU/ml)	28.0 (17.5–82.5)	32.5 (18.3–68.3)
Number of lesions (1/2/3/4) (%)	101 (42.8)/13 (5.5)/3 (1.3)/0 (0.0)	110 (46.6)/7 (3.0)/2 (0.9)/0 (0.0)

Variables are expressed as mean ± SD or median (IQR). AFP, α-fetoprotein; Alb, albumin; DCP, des-γ-carboxy prothrombin; MWA, microwave ablation; Plt, platelet; PT-INR, prothrombin time-international normalized ratio; RFA, radiofrequency ablation; T-Bil, total bilirubin.

Table 2. Tumor characteristics according to different ablation therapies.

Tumor characteristics	RFA (n = 136)	MWA (n = 130)
Maximum tumor diameter (cm)	1.9 ± 0.7	1.9 ± 0.7
Tumor form (simple nodular type/others) (%)	119 (44.7)/17 (6.4)	110 (41.4)/20 (7.5)
Couinaud classification: S1/S2/S3/S4/S5/S6/S7/S8 (%)	2 (0.8)/11 (4.1)/10 (3.8)/10 (3.8)/13 (4.9)/24 (9.0)/21 (7.9)/45 (16.9)	1 (0.4)/7 (2.6)/11 (4.1)/16 (6.0)/10 (3.8)/29 (10.9)/23 (8.7)/33 (12.4)
Tumor location (adjacent to)		
Liver surface (hump) (%)	27.2% (37/136)	29.2% (38/130)
Portal vein (major branch) (%)	2.9% (4/136)	3.1% (4/130)
Portal vein (minor branch) (%)	24.3% (33/136)	18.5% (24/130)
Hepatic duct (%)	4.4% (6/136)	3.1% (4/130)
Hepatic vein (%)	14.0% 19/136)	7.7% (10/130)
Inferior vena cava (%)	1.5% (2/136)	2.3% (3/130)
Gall bladder (%)	2.2% (3/136)	2.3% (3/130)
Colon (%)	0.7% (1/136)	2.3% (3/130)
Heart (%)	0.7% (1/136)	2.3% (3/130)
Stomach (%)	2.2% (3/136)	3.1% (4/130)
Duodenum (%)	1.5% (2/136)	1.5% (2/130)
Diaphragm (%)	16.2% (22/136)	22.3% (29/130)
Kidney (%)	2.9% 4/136)	4.6% (6/130)

Variables are expressed as mean ± SD. Abbreviations: MWA, microwave ablation; RFA, radiofrequency ablation.

significantly differ between the two groups (MWA group: 0.90 [95% CI: 0.83, 0.94] *vs.* RFA group: 0.90 [95% CI: 0.82, 0.94], $p = 0.350$; Fig. 2A); intrahepatic recurrence-free survival at the 2-year follow up was not significantly longer in the MWA group (0.50 [95% CI: 0.40–0.58]) than in the RFA group (0.44 [95% CI: 0.35–0.53], $p = 0.099$; Fig. 2B); and extrahepatic RFS at the 2-year follow-up did not significantly differ between the two groups (MWA group: 0.89 [95% CI: 0.81–0.93] *vs.* RFA group: 0.93 [95% CI: 0.86–0.96], $p = 0.307$; Fig. 2C).

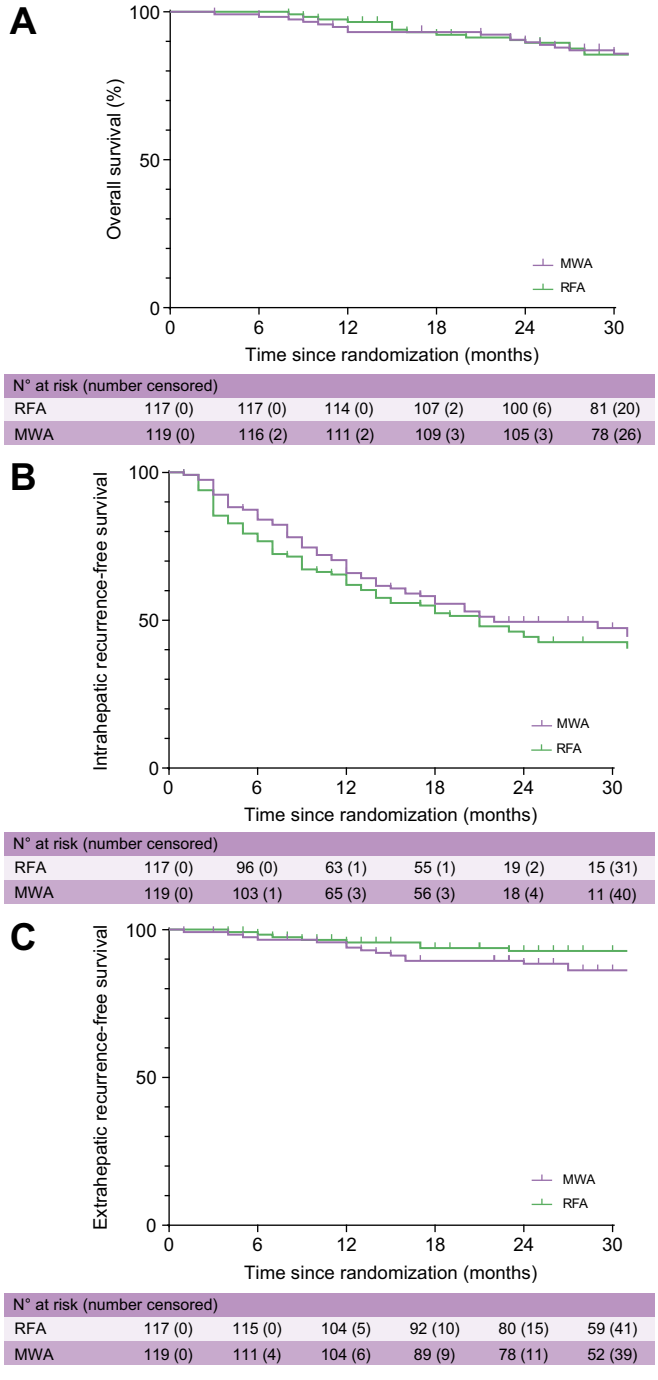


Fig. 2. Overall survival and intra- and extrahepatic recurrence-free survival. Kaplan–Meier curve of (A) overall survival, (B) intrahepatic recurrence-free survival, and (C) extrahepatic recurrence-free survival in each group. No significant difference was observed between the two techniques ($p = 0.350$, $p = 0.099$, and $p = 0.307$, respectively; log-rank tests). MWA, microwave ablation; RFA, radiofrequency ablation.

Factors contributing to recurrence after ablation

The *post hoc* analysis revealed that the maximum diameter (HR: 1.51 [95% CI: 1.06–2.17]), ablation device (MWA group, HR: 0.53 [95% CI: 0.31–0.91]), and ablation margin (<3 mm, HR: 2.14 [95% CI: 1.22–3.77]) were independent predisposing factors for LTP (Table 3). Etiology (non-viral: HR: 1.39 [95% CI: 1.13–1.71), non-naïve nodule (HR: 1.86 [95% CI: 1.24–2.77]), the number of nodules (1/2/3) (HR: 2.00 [95% CI: 1.34–2.97]), and DCP (HR: 1.001 [95% CI: 1.000–1.002]) were independent predisposing factors for intrahepatic recurrence (Table 4). Furthermore, DCP (HR: 1.003 [(95% CI: 1.000–1.04]) was an independent predisposing factor for extrahepatic recurrence (Table 5).

Table 3. Predisposing factors for local tumor progression after ablation.

	Hazard ratio (95% CI)
Variable	**Multivariate**
Maximum diameter	1.51 (1.06–2.17)*
Tumor form (non-simple nodular type)	1.63 (0.86–3.09)
Non-naïve nodule	1.40 (0.81–2.41)
Tumor location (adjacent to)	
Portal vein (major + minor)	1.09 (0.62–1.93)
Hepatic vein + inferior vena cava	0.95 (0.43–2.08)
Ablation device (MWA)	0.53 (0.31–0.91)*
Ablation margin (<3 mm)	2.14 (1.22–3.77)*

*p <0.05 (multivariate Cox proportional hazards model). MWA, microwave ablation.

Table 4. Predisposing factors to intrahepatic recurrence of HCC after ablation.

	Hazard ratio (95% CI)
Variable	**Multivariate**
Sex (female)	1.00 (1.00–1.00)
Mean age (yr)	1.00 (0.98–1.02)
Etiology (non-viral)	1.39 (1.13–1.71)*
Non-naïve nodule	1.86 (1.24–2.77)*
Child–Pugh score (5/6/7/8/9)	0.80 (0.59–1.08)
AFP	1.000 (0.999–1.001)
AFP-L3	1.010 (0.999–1.021)
DCP (mAU/ml)	1.001 (1.000–1.002)*
Number of nodules (1/2/3)	2.00 (1.34–2.97)*
Ablation device (MWA)	0.82 (0.58–1.16)

*p <0.05 (multivariate Cox proportional hazards model). AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; MWA, microwave ablation.

Table 5. Predisposing factors to extrahepatic recurrence of HCC after ablation.

	Hazard ratio (95% CI)
Variable	**Multivariate**
Etiology (non-viral)	0.86 (0.56–1.32)
DCP (mAU/ml)	1.002 (1.000–1.003)*
Number of nodules (1/2/3)	0.91 (0.31–2.64)

*p <0.05 (multivariate Cox proportional hazards model). DCP, des-γ-carboxy prothrombin.

Table 6. Complications based on the Clavien–Dindo classification.

Modality	RFA (n = 117)	MWA (n = 119)	*p* value
Grade I	44.4% (52/117)	44.5% (53/119)	n.s.
Grade II–V	1.7% (2/117)	1.7% (2/119)	n.s.
Details of ≥Grade II			
Hepatic infarction	NA	1 (II)	NA
Pleural effusion requiring drainage	1 (III)	1 (III)	NA
Arterial bleeding requiring embolization	1 (III)	NA	NA

MWA, microwave ablation; NA, not applicable; n.s., not significant (X^2 test); RFA, radiofrequency ablation.

Comparison of complications in each modality group

Table 6 presents a comparison of the complication profiles in each ablation group. No significant differences were found in grade I (MWA group: 44.5% [53/119] *vs.* RFA group: 44.4% [52/117]) or grade II complications (MWA group: 1.7% [2/119] *vs.* RFA group: 1.7% [2/117]). In addition, no treatment-related deaths occurred.

Discussion

This RCT demonstrated that next-generation MWA was more effective compared with single-needle RFA for treating HCC lesions ≤4 cm in size. A significant difference was observed between the two groups in terms of the proportion of lesions with LTP after the 2-year follow up, which was the primary endpoint. Regarding the secondary endpoints, no significant difference was found between the two groups in OS, intrahepatic RFS, and extrahepatic RFS at the end of the 2-year follow up. Moreover, the safety profiles did not differ significantly between the two treatment groups. Although some RCTs[7,8,15,16] have compared the efficacy of next-generation MWA and RFA for HCC, to our knowledge, this is the first RCT to demonstrate the superiority of next-generation MWA over RFA for HCC.

In this study, maximum diameter, ablation device, and ablation margin were independent predisposing factors for LTP. A previous pathological study showed that 19% of HCCs ≤3.0 cm in diameter had satellite lesions that were undetected during pretreatment evaluation.[17] Therefore, obtaining an entire circumference with a 5-mm margin is recommended for ablation therapy to prevent LTP,[18] and MWA is more suitable for this purpose compared with RFA. However, obtaining an entire circumference with a 5-mm margin is sometimes difficult in clinical practice when lesions are adjacent to blood vessels, such as the portal and hepatic veins. An *et al.*[19] reported that, for patients with periportal HCC, the LTP rate was significantly higher in the RFA group than in the MWA group. This was because rapid heating and higher intratumoral temperature associated with MWA can restrict blood supply to the tumor-bearing portal tributaries, thereby reducing the heat sink effect. However, HCCs adjacent to blood vessels, such as the portal vein, were not predisposing factors for LTP in this study. This could be because, although An *et al.*[19] defined perivascular HCC as a tumor nodule abutting the first- or second-grade branches of the portal veins, the proportion of HCCs adjacent to such major portal veins in the current study was only 2.9% (4/136) and 3.1% (4/130) in the RFA and MWA groups, respectively, resulting in statistical power impairment. Although An *et al.* recommended MWA for HCCs adjacent to such major portal veins, external beam radiation therapy, including proton beam therapy[20] and stereotactic body radiation therapy,[21] should be recommended to prevent LTP and bile duct injury. In addition, irreversible electroporation can be useful for this purpose.[22]

Non-viral etiology was identified as an independent predisposing factor for intrahepatic recurrence. Previous studies suggested that antiviral therapy for chronic HBV[23] and HCV[24] significantly reduces the risk of HCC. Almost all participants in this study had already received antiviral therapy (*i.e.* nucleoside analogs or direct-acting antivirals). By contrast, the incidence and mortality of alcohol- and metabolic dysfunction-associated steatotic liver disease-related HCCs have increased in both[25] because there are no effective drugs or public policies targeting these emerging risk factors. DCP was also a significant predisposing factor for both intrahepatic and extrahepatic recurrences because distant recurrence depends on the carcinogenic potential of non-cancerous tissues. The IMbrave 050 phase III RCT recently demonstrated superior RFS using atezolizumab plus bevacizumab in the adjuvant setting for patients with HCC at high risk of recurrence after surgical resection or local ablation (tumor size >2 cm but ≤5 cm and multifocal HCC).[26] Although the updated analysis of the study showed that initial RFS benefit with atezolizumab plus bevacizumab *vs.* active surveillance was not sustained, some adjuvant therapies might be necessary when performing ablation therapy for patients with high tumor marker levels.

Although MWA has some advantages over RFA, it also has some disadvantages. First, the MWA needle tip is difficult to observe using US, particularly for deep-seated lesions. Therefore, to overcome this challenge, we used a virtual needle-tracking system that tracks the position of the needle tip using a small sensor on the shaft, which could be a useful method for achieving more precise monitoring of the MWA needle tip during puncture and ablation (Fig. S1). Second, the MWA needle (13-gauge) was thicker than the RFA needle (17-gauge), which might have caused bleeding. However, no significant difference was observed in the frequency and severity of complications between MWA and RFA.

This study has some limitations. First, although all MWAs were performed using the same device (Emprint Ablation System), RFAs were performed using two different devices (Cool-tip RF ablation System E Series and VIVA RF System). This variation makes it difficult to assess and compare MWA and RFA accurately. However, the two radiofrequency (RF) electrodes were both 17-gauge, monopolar, and internally cooled applicators. The only difference is that the VIVA RF System is a length-adjustable applicator. Therefore, almost no bias appears to exist among the RF applicators. Other types of RF electrode, such as bipolar[27] and separable clustered[28] electrodes, should be compared with the MWA system. Second, although treatment allocation was strictly maintained in all cases, and patients were blinded to the treatment they received, the

physicians were not blinded when performing ablation therapy because the devices used differed, causing a positive bias for MWA. Third, although LTP was improved with MWA, there was no observed trend toward decreased global recurrence or improvements in RFS or OS. This raises concerns about the reliability of LTP as a surrogate marker for treatment efficacy. Although the surrogate value of LTP might be appropriate for solitary tumors, it appears to be inadequate in cases of multifocal disease. Consequently, alternative endpoints other than LTP might be necessary for accurately evaluating local ablation therapies. Finally, although the RCT demonstrated the superiority of MWA on the LTP rate at the 2-year follow up over RFA, the MWA needle (13-gauge) was slightly thicker than the RFA needle (17-gauge), and needle-tip visibility on MWA was worse than that on RFA. Therefore, we believe that RFA might be more suitable than MWA for the US-guided treatment of small and deep-seated lesions (*i.e.* located in S1), particularly in daily clinical practice. However, this study included only three S1 lesions (RFA, two lesions; MWA, one lesion), and a detailed analysis of these lesions was not possible.

Conclusions

This RCT demonstrates the superiority of MWA (Emprint Ablation System) over single-needle RFA (17-gauge, monopolar, and internally cooled electrodes) in terms of LTP at the end of a 2-year follow up in patients with up to 4 HCCs ≤4 cm in size.

Affiliations

[1]*Department of Gastroenterology and Hepatology, Tokyo Medical University, Tokyo, Japan;* [2]*Department of Gastroenterology, Yokohama City University Graduate School of Medicine, Yokohama, Japan;* [3]*Department of Gastroenterology, Shin-yurigaoka General Hospital, Kawasaki, Japan;* [4]*Division of Gastroenterology and Hepatology, Department of Internal Medicine, Iwate Medical University School of Medicine, Iwate, Japan;* [5]*Department of Gastroenterology, Seirei Hamamatsu General Hospital, Shizuoka, Japan;* [6]*Division of Gastroenterology and Hepatology, Department of Internal Medicine, Toho University Ohashi Medical Center, Tokyo, Japan;* [7]*Faculty of Health Data Science, Juntendo University, Tokyo, Japan*

Abbreviations

AFP, α-fetoprotein; Alb, albumin; CECT, contrast-enhanced computed tomography; CEUS, contrast-enhanced ultrasound; CR, complete response; CT, computed tomography; DCP, des-γ-carboxy prothrombin; EOB-MRI, gadoxetic acid-enhanced magnetic resonance imaging; HCC, hepatocellular carcinoma; HR, hazard ratio; LTP, local tumor progression; MRI, magnetic resonance imaging; MWA, microwave ablation; n.s.: not significant; NA, not applicable; OS, overall survival; PEI, percutaneous ethanol injection; Plt, platelet; PMCT, microwave coagulation therapy; PT-INR, prothrombin time-international normalized ratio; RCT, randomized controlled trial; RF, radiofrequency; RFA, radiofrequency ablation; RFS, recurrence-free survival; T-Bil, total bilirubin; US, ultrasound.

Financial support

This study received funding from Tokyo Medical University.

Conflicts of interest

None declared by authors.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: KS, KI. Acquisition of data: KS, KI, HK, GM, KSh, TW, HT, KE, TA, TMa, TMu, MY. Statistical analysis: KSa. Interpretation of data: KS, KI. Drafting manuscript: KS, KI. Critical revisions of the manuscript for important intellectual content: KS, KI, HK, GM, KSh. Funding and administrative support: SK, AN, TI.

Data availability statement

All the data in this study are available from the corresponding author upon request. This clinical trial was registered in the University Hospital Medical Information Network (UMIN No.: 000033297).

Acknowledgements

We thank Kanako Yoshida (Department of Gastroenterology and Hepatology, Tokyo Medical University Hospital) for conducting the randomization, Ryoko Soya (Department of Gastroenterology and Hepatology, Tokyo Medical University Hospital) for translating the study protocols, and Yoshinari Kikuchi (Japan Lifeline Co., Ltd.) for providing valuable MWA and RFA data.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101269.

References

[1] Seki T, Nonaka T, Kubota Y, et al. Ultrasonically guided percutaneous ethanol injection therapy for hepatocellular carcinoma. Am J Gastroenterol 1989;84:1400–1407.

[2] Shiina S, Teratani T, Obi S, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology 2005;129:122–130.

[3] Tabuse K, Katsumi M, Kobayashi Y, et al. Microwave surgery: hepatectomy using a microwave tissue coagulator. World J Surg 1985;9:136–143.

[4] Seki T, Wakabayashi M, Nakagawa T, et al. Percutaneous microwave coagulation therapy for patients with small hepatocellular carcinoma: comparison with percutaneous ethanol injection therapy. Cancer 1999;85:1694–1702.

[5] Shibata T, Limuro Y, Yamamoto Y, et al. Small hepatocellular carcinoma: comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. Radiology 2002;223:331–337.

[6] European Association for The Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908–943.

[7] Vietti Violi N, Duran R, Guiu B, et al. Efficacy of microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma in patients with chronic liver disease: a randomized controlled phase 2 trial. Lancet Gastroenterol Hepatol 2018;3:317–325.

[8] Yu J, Yu XL, Han ZY, et al. Percutaneous cooled-probe microwave versus radiofrequency ablation in early-stage hepatocellular carcinoma: a phase III randomized controlled trial. Gut 2017;66:1172–1173.

[9] Alonzo M, Bos A, Bennett S, et al. The Emprint™ ablation System with Thermosphere™ Technology: one of the newer next-generation microwave ablation technologies. Semin Intervent Radiol 2015;32:335–338.

[10] Kudo M, Kawamura Y, Hasegawa K, et al. Management of hepatocellular carcinoma in Japan: JSH consensus statements and recommendations 2021 update. Liver Cancer 2021;10:181–223.

[11] Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the eastern cooperative Oncology group. Am J Clin Oncol 1982;5:649–655.

[12] Nishikawa H, Inuzuka T, Takeda H, et al. Percutaneous radiofrequency ablation therapy for hepatocellular carcinoma: a proposed new grading system for the ablative margin and prediction of local tumor progression and its validation. J Gastroenterol 2011;46:14181426.

[13] Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187–196.

[14] Lu MD, Xu HX, Xie XY, et al. Percutaneous microwave and radiofrequency ablation for hepatocellular carcinoma: a retrospective comparative study. J Gastroenterol 2005;40:1054–1060.

[15] Kamal A, Elmoety AAA, Rostom YAM, et al. Percutaneous radiofrequency versus microwave ablation for management of hepatocellular carcinoma: a randomized controlled trial. J Gastrointest Oncol 2019;10:562–571.

[16] Vogl TJ, Martin SS, Gruber-Rouh T, et al. Comparison of microwave and radiofrequency ablation for the treatment of small- and medium-sized hepatocellular carcinomas in a prospective randomized trial. RöFo 2024;196:482–490.

[17] Okusaka T, Okada S, Ueno H, et al. Satellite lesions in patients with small hepatocellular carcinoma with reference to clinicopathologic features. Cancer 2002;95:1931–1937.
[18] Nakazawa T, Kokubu S, Shibuya A, et al. Radiofrequency ablation of hepatocellular carcinoma: correlation between local tumor progression after ablation and ablative margin. AJR Am J Roentgenol 2007;188:480–488.
[19] An C, Li WZ, Huang ZM, et al. Small single perivascular hepatocellular carcinoma: comparisons of radiofrequency ablation and microwave ablation by using propensity score analysis. Eur Radiol 2021;31:4764–4773.
[20] Mizumoto M, Ogino H, Okumura T, et al. Proton beam therapy for hepatocellular carcinoma: multicenter Prospective Registry Study in Japan. Int J Radiat Oncol Biol Phys 2024;118:725–733.
[21] Moon AM, Kim HP, Singal AG, et al. Thermal ablation compared to stereotactic body radiation therapy for hepatocellular carcinoma: a multicenter retrospective comparative study. Hepatol Commun 2023;7:e00184.
[22] Wada T, Sugimoto K, Sakamaki K, et al. Comparisons of radiofrequency ablation, microwave ablation, and irreversible electroporation by using propensity score analysis for early stage hepatocellular carcinoma. Cancers (Basel) 2023;15:732.
[23] Jeng WJ, Chien RN, Chen YC, et al. Hepatocellular carcinoma reduced, HBsAg loss increased, and survival improved after finite therapy in hepatitis B patients with cirrhosis. Hepatology 2024;79:690–703.
[24] Chen YJ, Huang JY, Baskaran R, et al. Long-term survival and cancer risk in the hepatitis C virus-infected patients after antiviral treatment: a nationwide cohort study. J Cancer 2024;15:113–125.
[25] Kim DY. Changing etiology and epidemiology of hepatocellular carcinoma: asia and worldwide. J Liver Cancer 2024;24:62–70.
[26] Qin S, Chen M, Cheng AL, et al. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomized, open-label, multicenter, phase 3 trial. Lancet 2023;402:1835–1847.
[27] Hocquelet A, Aubé C, Rode A, et al. Comparison of no-touch multi-bipolar vs. monopolar radiofrequency ablation for small HCC. J Hepatol 2017;66:67–74.
[28] Choi JW, Lee JM, Lee DH, et al. Radiofrequency ablation using a separable clustered electrode for the treatment of hepatocellular carcinomas: a randomized controlled trial of a dual-switching monopolar mode versus a single-switching monopolar mode. Korean J Radiol 2021;22:179–188.

Keywords: Ablation technique; Cancer; Local tumor progression; Randomized controlled trial.
Received 26 June 2024; received in revised form 25 October 2024; accepted 4 November 2024; Available online 13 November 2024