Microwave versus Radiofrequency Ablation Treatment for Hepatocellular Carcinoma: A Comparison of Efficacy at a Single Center

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ABSTRACT

Purpose: To compare efficacy and major complication rates of radiofrequency (RF) and microwave (MW) ablation for treatment of hepatocellular carcinoma (HCC).

Materials and Methods: This retrospective single-center study included 69 tumors in 55 patients treated by RF ablation and 136 tumors in 99 patients treated by MW ablation between 2001 and 2013. RF and MW ablation devices included straight 17-gauge applicators. Overall survival and rates of local tumor progression (LTP) were evaluated using Kaplan-Meier techniques with Cox proportional hazard ratio (HR) models and competing risk regression of LTP.

Results: RF and MW cohorts were similar in age ($P = .22$), Model for End-Stage Liver Disease score ($P = .24$), and tumor size (mean 2.4 cm [range, 0.6–4.5 cm] and 2.2 cm [0.5–4.2 cm], $P = .09$). Median length of follow-up was 31 months for RF and 24 months for MW. Rate of LTP was 17.7% with RF and 8.8% with MW. Corresponding HR from Cox and competing risk models was 2.17 (95% confidence interval [CI], 1.04–4.50; $P = 0.04$) and 2.01 (95% CI, 0.95–4.26; $P = .07$), respectively. There was improved survival for patients treated with MW ablation, although this was not statistically significant (Cox HR, 1.59 [95% CI, 0.91–2.77; $P = .103$]). There were few major (≥ grade C) complications (2 for RF, 1 for MW; $P = .28$).

Conclusions: Treating HCC percutaneously with RF or MW ablation was associated with high primary efficacy and durable response, with lower rates of LTP after MW ablation.

ABBREVIATIONS

CI = confidence interval, HCC = hepatocellular carcinoma, HR = hazard ratio, LTP = local tumor progression, MW = microwave

Thermal ablation is currently used in two predominant ways to treat hepatocellular carcinoma (HCC): as a bridge to transplantation and as definitive therapy in patients who are unable or unwilling to undergo surgical resection or transplantation (1,2). In patients undergoing definitive therapy for HCC, there is increasing evidence to support ablation as first-line therapy, including several randomized controlled trials in which ablation compares favorably to surgical resection (3–5). As a result, the Barcelona Clinic for Liver Cancer guidelines, which are widely accepted in Europe and North America, now recommend ablation for treatment of very early

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or early HCC in patients who are not surgical candidates (2,6).

Radiofrequency (RF) ablation has the longest history among thermal ablation methods, and most of the larger HCC trials were performed with RF (7,8). However, in recent years, there has been increasing interest in microwave (MW) ablation because of potential physical advantages that are increasingly realized with modern high-powered devices. Whether the physical differences between RF ablation and MW ablation translate into better clinical outcomes remains an open question. Although a few RF versus MW ablation case-series comparison studies are available, they are limited in general applicability, as the MW equipment was either early first-generation equipment (and may no longer be used) or is unavailable in Europe or the United States (9–11). The choice of equipment is an important factor to consider because of important technical variables that distinguish MW systems. Therefore, despite evidence suggesting equivalent outcomes with RF ablation and MW ablation for treatment of HCC, a comparison using modern MW ablation equipment currently available in the United States and Europe is necessary to guide future clinical practice. The purpose of this study is to compare the local treatment efficacy and major complication rate of a 17-gauge RF ablation system and a 17-gauge MW ablation system for the treatment of HCC.

MATERIALS AND METHODS

Patient Selection

This study was conducted under a waiver of informed consent from the institutional review board and complied with the Health Insurance Portability and Accountability Act. All subjects who underwent percutaneous RF ablation or MW ablation for HCC at a hepatic transplant center during the period 2001–2013 were identified for potential analysis. Patients were excluded if they had undergone combination treatment with transarterial chemoembolization before ablation. At our institution, transarterial chemoembolization is performed in combination with thermal ablation for those outside of the Milan criteria or when a solitary tumor > 3 cm is ill-defined on imaging. No patient with prior chemotherapy for HCC was included in the cohort. The study group included 55 patients with 69 tumors treated by RF ablation and 99 patients with 136 tumors treated by MW ablation. RF ablation was used in all patients treated before 2011. In January 2011, we began using MW ablation routinely. During 2011, RF ablation was used by the physician's choice in three cases in which the tumor was abutting the diaphragm or critical structures; otherwise, all patients were treated with MW ablation in the years 2011–2013. All patients were referred for ablation after an interdisciplinary discussion with hepatologists, hepatobiliary surgeons, transplant surgeons, oncologists, and radiologists. Liver dysfunction was categorized using the standard Model for End-Stage Liver Disease (12).

Ablation Procedures

All treatments were performed at a single center by one of seven board-certified abdominal radiologists with 1–16 years of ablation experience. Each case was performed via a percutaneous approach with the patient under general anesthesia in a dedicated computed tomography (CT) suite. Image guidance for electrode and antenna placement was provided by real-time ultrasound (ACUSON Sequoia; Siemens Medical Solutions, Mountain View, California, or LOGIQ E9; GE Medical Systems, Waukesha, Wisconsin) with CT used to confirm needle placement when necessary (LightSpeed Plus or LightSpeed XTRA; GE Medical Systems).

RF ablation was performed using an internally water-cooled electrode and generator with an impedance-based pulsing algorithm (Cool-tip; Covidien, Boulder, Colorado) RF technology using a single electrode, a cluster electrode, or multiple electrodes in switched mode (Cool-tip Switching Controller; Covidien). MW ablation was performed using a high-powered gas-cooled system with continuous in-phase output to up to three antennas (Certus 140; NeuWave Medical, Inc., Madison, Wisconsin).

Immediately after ablation, all patients underwent a CT scan (LightSpeed Plus or LightSpeed XTRA) including late arterial and portal venous phases that was performed with 80–150 mL of intravenous contrast material if there were no contraindications. The ablation endpoint was identification of complete coverage of the tumor and a 5-mm circumferential margin. Achieving the ablation endpoint was defined as technical success (13,14). Patients were monitored for complications after the procedure during an overnight hospital admission and by nursing telephone contact 5–7 days after the procedure; any adverse events reported by the patient were documented in the medical record. Complications were classified according to the Society of Interventional Radiology (SIR) classification of complications by outcome (15).

Patient Follow-up

Patients were evaluated every 3 months for 1 year and then at least every 6 months thereafter with contrast-enhanced CT or contrast-enhanced magnetic resonance imaging to evaluate for local tumor progression (LTP) at the ablation site and for signs of delayed complications. LTP was determined according to standard reporting parameters (13). Follow-up imaging was interpreted by abdominal imagers with subspecialty training. For the 18 patients (32.7%) who underwent RF ablation and 20 patients (20.2%) who underwent MW ablation who subsequently underwent liver transplantation, the latest available study before transplant was considered the final follow-up imaging study after ablation. Date of death was determined by medical record review and search of public records for patients lost to follow-up.

Statistical Analysis

Time-to-event outcomes were computed in months, based on differences between each event (LTP, overall survival) and ablation date. Kaplan-Meier actuarial survival estimates were obtained separately for each group and compared with a log-rank test. Because RF ablation had been available for approximately 14 years, whereas MW ablation had been available for only approximately 5 years at our institution, we used log-rank tests truncated at 48 months of follow-up. In patients with multiple ablation sessions, survival was determined from time of initial ablation, and LTP was considered only on a per-ablation basis. That is, the two subjects whose LTP was treated with repeat ablation alone had their LTP count "reset" to zero at the time of their next ablation.

To better assess the differences in risk of experiencing an event (LTP) between groups, a Cox proportional hazard model with event type as a stratum and patients as a cluster was fitted to obtain hazard ratio (HR) and 95% confidence interval (CI) values. LTP was obtained on a per tumor basis; all other outcomes were obtained on a per subject basis. Six patients received both kinds of ablations on separate tumors during separate sessions and are included in both the RF and MW ablation data sets and considered as independent cases. Similarly, patients receiving the same kind of ablation (RF or MW) on multiple occasions were also considered as independent cases. There were 16 patients who underwent multiple RF ablations or MW ablations, all for new tumor distant from the initially treated tumor. As an additional comparison of LTP between groups, Fine and Gray competing risk survival estimates were calculated with transplant and death as the other competing risk events to obtain HR and 95% CI. A P value $< .05$ (two-sided) was the criterion for statistical significance. There was no adjustment of P values for multiple testing. All statistical graphics and computations were obtained in R 3.1.0 (R Core Team, 2014, R Foundation for Statistical Computing, Vienna, Austria; available at: http://www.R-project.org/).

RESULTS

Patient Population

The study population comprised 154 patients (55 in the RF cohort, 99 in the MW cohort) with 205 tumors targeted for treatment with either RF ablation ($n = 69$) or MW ablation ($n = 136$) between December 2001 and March 2014. The population was predominantly male (121 men vs 33 women) with a mean age of 62 years. Patients receiving MW ablation had a slightly higher mean Model for End-Stage Liver Disease score than patients receiving RF ablation (9.6 vs 8.8), but this difference was not statistically significant ($P = .39$). Patient data are summarized in **Table 1**.

Tumors and Follow-up

Mean tumor size was 2.2 cm (range, 0.6–4.5 cm) in the RF group and 2.1 cm (range, 0.5–4.2 cm) in the MW

Table 1. Patient Demographics and Tumor Size

Characteristic	RF	MW	*P* Value
Total patients	55	99	—
Total tumors treated	69	136	—
Sex (M/F)	40/15	81/18	.22
Mean age, y (range)	62 (23–88)	61 (44–82)	.24
MELD	8.8	9.6	.39
BCLC stage			.37
0	6	16	
A	49	83	
Etiology of liver disease			.01
Hepatitis C	28	56	
Hepatitis B	4	4	
Alcohol abuse	9	15	
Nonalcoholic steatohepatitis	2	3	
Hepatitis C and alcohol abuse	4	9	
Unknown or other	8	12	
Mean tumor size, cm (95% CI)	2.4 (2.2–2.6)	2.2 (2.0–2.3)	.09
$<$ 3 cm	53/69 (76.8%)	118/136 (86.8%)	.08
$\geq$ 3 cm	16/69 (23.2%)	18/136 (13.2%)	

BCLC = Barcelona Clinic for Liver Cancer; CI = confidence interval; MELD = Model for End-Stage Liver Disease; M/F = male/female; MW = microwave; RF = radiofrequency.

group. When controlling for multiple tumors within a patient, this was not statistically significant (P = .09). Most tumors in both groups were < 3 cm (76.5% in RF group and 86.8% in MW group). The follow-up period was longer for patients receiving RF ablation because of the earlier introduction of RF ablation into our practice (median follow-up 31 months vs 24 months).

Local Tumor Control

All ablations achieved technical success at the completion of the ablation procedure. The Cox HR for LTP after RF ablation was 2.17 (95% CI, 1.04–4.50; P = .04), while the Fine and Gray HR was 2.07 (95% CI, 0.95–4.26; P = .07) (Figs 1, 2). The Fine and Gray HR of 6.00 for progression of tumors > 3 cm treated with RF ablation was notable, although not statistically significant (P = .08). Progression data are listed in Table 2.

Overall Survival

There was decreased survival for patients treated with RF ablation compared with MW ablation with HR of 1.59 (95% CI, 0.91–2.77; P = .090) (Fig 3).

Complications

There were no intraprocedural deaths or deaths immediately after the procedure. There were few major (≥ grade C) complications in either group. In the RF cohort, there were two complications (n = 2 of 55; 3.6%) requiring specific interventions: a single small hemothorax requiring thoracentesis and a single intraperitoneal hemorrhage requiring transfusions and urgent exploratory laparotomy at the direction of the referring surgeon. The patient who underwent thoracentesis recovered without sequelae; the patient with intraperitoneal hemorrhage is discussed further later on. In the MW cohort, there was a single intraprocedural pneumothorax (n = 1 of 99; 1.0%; P = .27 RF vs MW) requiring aspiration and a pleural blood patch. A chest tube was not required in this case, and the patient was discharged per standard protocol without long-term sequelae.

There was one death within 30 days in each group. The patient in the RF cohort had intraperitoneal hemorrhage following the procedure that required transfusion and ultimately exploratory laparotomy to control. The patient's recovery from the procedure and laparotomy

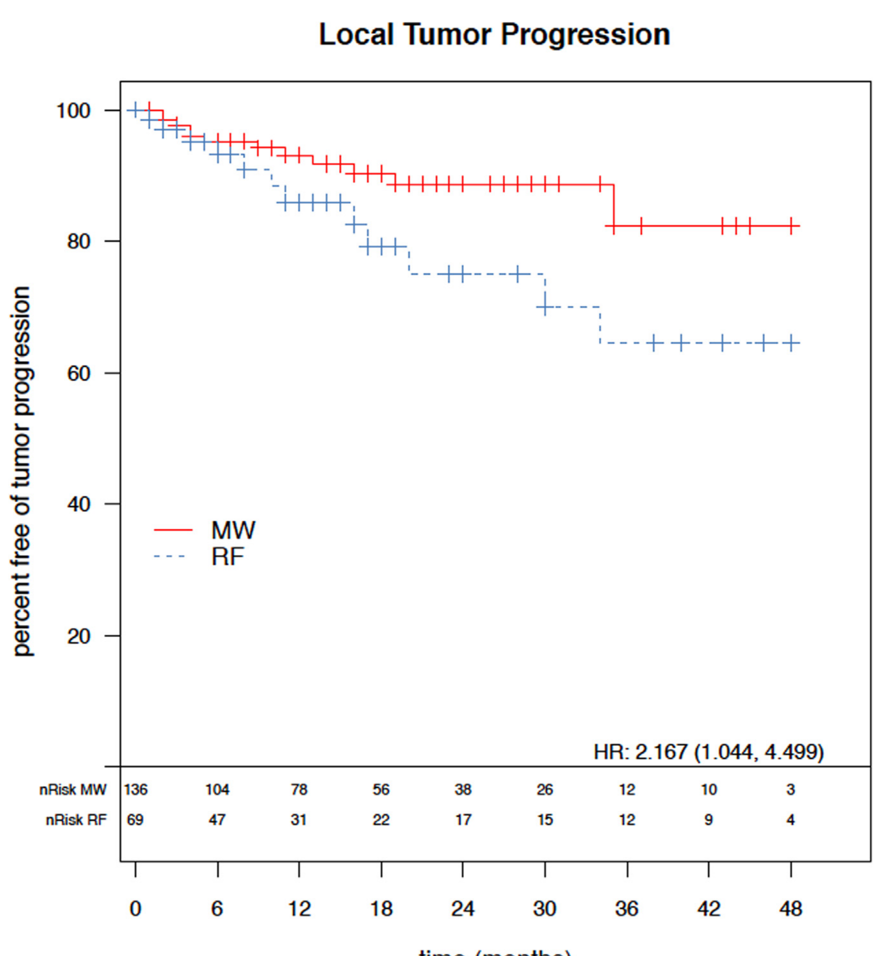

Figure 1. Kaplan-Meier curves of LTP for MW ablation (red) and RF ablation (blue) demonstrating fraction of tumors free of LTP by time in months.

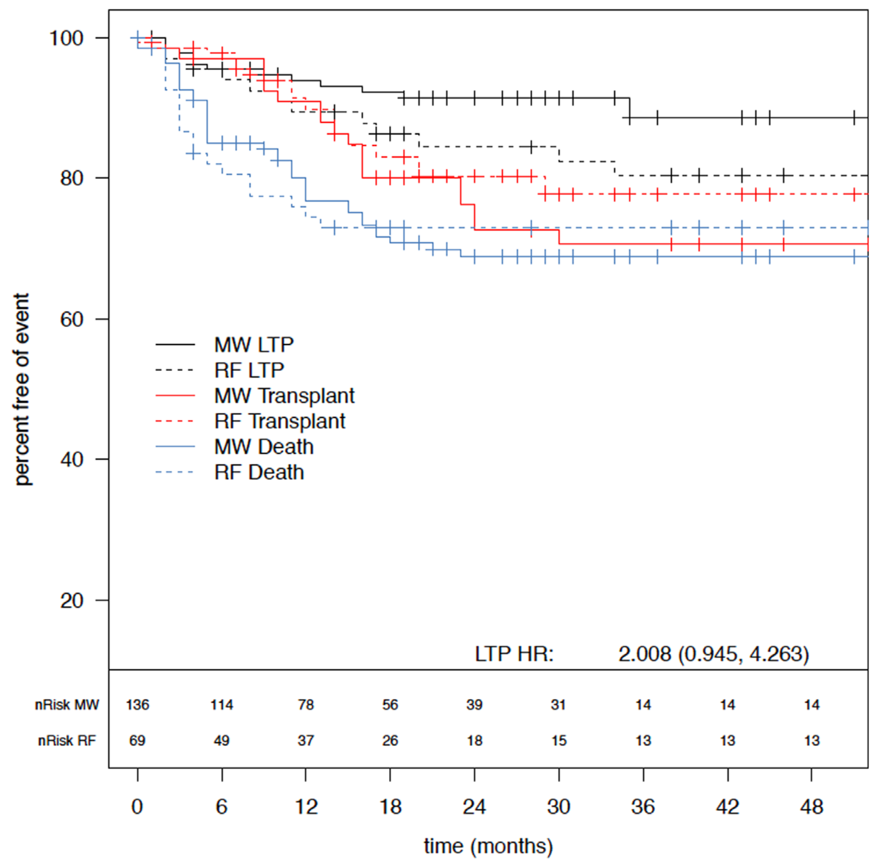

Figure 2. Fine and Gray curves of LTP, transplant, and death for tumors treated by MW ablation and RF ablation demonstrating fraction of tumors free of event by time in months.

Table 2. Follow-up Including Progression Data

Follow-up Time and LTP	RF	MW	Fine and Gray HR (95% CI, *P* Value)	Cox HR (95% CI, *P* Value)
Median follow-up, mo (range)	31 (1–148)	24 (1–57)	—	—
LTP	12/69 (17.4%)	12/136 (8.8%)	2.07 (0.95–4.26, $P = .07$)	2.17 (1.04–4.50, $P = .04$)
LTP for tumors $<$ 3 cm	7/53 (13.2%)	11/118 (9.3%)	1.63 (0.69–3.85, $P = .27$)	1.82 (0.78–4.26, $P = .11$)
LTP for tumors $\geq$ 3 cm	5/16 (31.3%)	1/18 (5.6%)	6.00 (0.80–44.9, $P = .08$)	6.29 (0.68–58.0, $P = .17$)

CI = confidence interval; HR = hazard ratio; LTP = local tumor progression; MW = microwave; RF = radiofrequency.

was complicated by a delayed transfusion reaction and subsequent hepatic failure leading to death approximately 30 days after the procedure. A patient in the MW cohort developed pneumonia; the patient refused treatment, resulting in sepsis and death approximately 1 week after the procedure.

DISCUSSION

In this study, patients with HCC with closely matched tumor sizes had an increased risk of LTP when treated with RF ablation compared with MW ablation. This finding has important implications for interventional oncologists when choosing a modality for treating patients who are referred for and deemed appropriate to undergo thermal ablation. In addition, there was improved overall survival in the MW cohort, although the patient populations were heterogeneous.

Published rates of LTP for RF ablation and MW ablation vary widely by institution, tumor size, type of device, experience of the operators, and other variables. However, a finding that supports the generalizable nature of our results is that the LTP rate in each separate limb of this study appears to track closely with the largest published experience for both RF ablation and MW ablation. A study by Kim et al (16) of RF ablation for the treatment of 1,502-early stage HCC tumors with a mean size of 2.2 cm and mean follow-up of 33 months (virtually identical to the 2.4-cm size and 31-month median follow-up in this study) demonstrated a LTP rate of 19.4%—very similar to the rate of 17.4% found in this study. The largest study to date of MW ablation for treatment of HCC (17) included 1,363

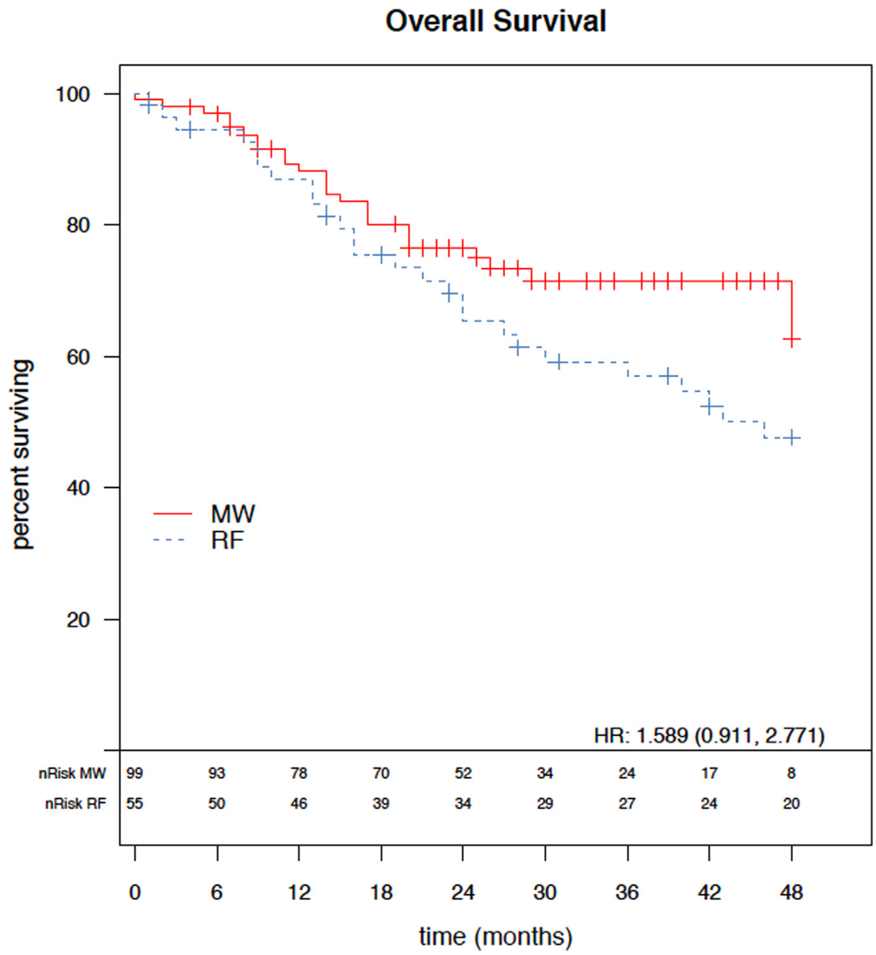

Figure 3. Kaplan-Meier curves of overall survival (death) for MW ablation (red) and RF ablation (blue) demonstrating fraction of patients alive by time in months.

tumors with a mean size of 2.9 cm and mean follow-up of 17.3 months (vs 2.2-cm size and 24-month median follow-up in this study) and demonstrated an overall LTP rate of 5.9%, slightly better than the 8.8% rate in this study, possibly related to shorter follow-up. However, neither of these single-modality studies had a comparison arm with any other ablation technology.

Only a few studies comparing RF ablation and MW ablation for the treatment of HCC have been published, and no large randomized controlled trials have been published. Previous studies described the use of MW ablation equipment that is unavailable in Europe or the United States. Patients accrued before 2007 were likely treated by early devices that were associated with low power, short treatment times, and relatively small ablation zones compared with more recent devices and may not be exactly applicable to the current suite of MW tools (9,10,18,19). Only one small randomized study comparing RF ablation and MW ablation has been published (11). That study was limited to small HCCs with very short follow-up (42 patients with 5.1 months of follow-up) and used MW technology available only in China. The results demonstrated larger MW ablation zones compared with RF ablation but no difference in LTP rates. Sample size was too small and follow-up interval was too short to make conclusions about survival (11). In contrast, our study used a higher power, third-generation MW ablation system and a multiple-applicator approach for RF and MW ablations when necessary (20). The current study also is the largest series to date comparing systems available in North America and Europe.

There are several potential reasons for the lower LTP detected with MW ablation compared with RF ablation in our study. Prior authors demonstrated that modern MW ablation devices are able to heat continuously at a faster rate to generate greater temperatures than RF ablation systems (21). Increased heating rates and internal temperatures overcome vascular perfusion more effectively. Water vaporization also leads to contraction of the treated tissue, resulting in a larger effective margin than may be evident from imaging alone (22). In addition, multiple antenna systems more efficiently distribute the applied energy throughout the tumor and margins (23–25). These properties of MW ablation are particularly important for tumors > 3 cm and for tumors adjacent to large blood vessels (26,27).

Concerns about increased complications resulting from higher power MW systems creating larger ablation zones appear unfounded based on the results of this and prior studies (28,29). There were very few major complications overall, with no difference between groups. This finding is concordant with a large multicenter study of complications after MW ablation in which the authors found that complications were not increased with MW ablation despite large ablation zones—perhaps as a result of "lessons learned" from the earlier RF era (28). In addition, the use of intraprocedural monitoring and adjunctive strategies such as hydrodissection may allow for more aggressive ablations and have become commonly applied (30).

This study has some limitations. As with any retrospective study, there are limitations related to heterogeneity of patient populations between the two groups. In this study, we used both the conventional Cox proportional hazard model that censors transplant and death and the competing risk analysis of Fine and Gray, in which transplant and death are categorized separately. Slight differences between the outcomes of these analyses are likely due to factors such as underlying liver disease and the associated length of time to transplant or death.

The most important limitation to this study is that it is not a prospective randomized controlled trial and because of the retrospective nature lacks a power analysis. However, a well-recruited randomized controlled trial comparing RF ablation and MW ablation is unlikely because of logistical constraints, and a single-center retrospective case series with comparable patient populations may be the most realistic option. Another limitation to the present study is the fact that most patients who underwent RF ablation were accrued before the patients who underwent MW ablation; this could bias the results, as the operators could have benefited from the earlier experience with RF ablation. The longer follow-up time after RF ablation may also have contributed to some bias. Although both of these limitations are important, the operators for the RF arm of the study had prior experience with cryoablation and RF ablation, whereas the physicians in the MW arm included three new faculty members who had no prior ablation experience outside of residency/fellowship training. Both Kaplan-Meier and Fine and Gray analyses controlled for differences in follow-up intervals. Finally, this study is also limited in that only major complications were recorded, and a full analysis of safety, particularly minor complications, could not be performed.

In conclusion, the results of this single-center study demonstrate high primary efficacy and a durable response for both RF ablation and MW ablation of HCC, with lower rates of LTP noted after MW ablation. Major complications were low with both techniques. These results support consideration for the addition of MW ablation to the guidelines for treatment of very early and early HCC.

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