Microwave ablation versus liver resection for primary intrahepatic cholangiocarcinoma within Milan criteria: a long-term multicenter cohort study

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Summary

Background Ablation has been recommended by worldwide guidelines as first-line treatment for hepatocellular carcinoma (HCC), while evidence regarding its efficacy for primary intrahepatic cholangiocarcinoma (iCCA) is lacking. We aimed to study the efficacy of ablation in treating iCCA by comparing its prognosis with surgery.

Methods In this real-world multicenter cohort study from January 2009 to June 2022, 10,441 iCCA patients from ten tertiary hospitals were identified. Patients who underwent curative-intent microwave ablation (MWA) or liver resection (LR) for tumors within Milan criteria were included. One-to-many propensity score matching (PSM) at variable ratios (1:n ≤4) was used to balance baseline characteristics. Mediation analysis was applied to identify potential mediators of the survival difference.

Findings 944 patients were finally enrolled in this study, with 221 undergoing MWA and 723 undergoing LR. After PSM, 203 patients in the MWA group were matched with 588 patients in the LR group. The median follow-up time was 4.7 years. Compared with LR, MWA demonstrated similar overall survival (5-year 44.8% versus 40.4%; HR 0.96, 95% CI 0.71–1.29, $P = .761$). There was an improvement in the 5-year disease-free survival rate for MWA from 17.1% during the period of 2009–2016 to 37.3% during 2017–2022, becoming comparable to the 40.8% of LR ($P = .129$). The proportion of ablative margins ≥5 mm increased from 25% to 61% over the two periods, while this proportion of surgical margins was 62% and 77%, respectively. 34.5% of DFS disparity can be explained by the mediation effect of margins ($P < .0001$). Similar DFS was observed when both ablative and surgical margins exceeded 5 mm (HR 0.83, 95% CI 0.52–1.32, $P = .41$).

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Interpretation MWA may be considered as a viable alternative to LR for iCCA within Milan criteria when an adequate margin can be obtained.

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Keywords: Intrahepatic cholangiocarcinoma; Microwave ablation; Liver resection; Overall survival; Disease-free survival

Research in context

Evidence before this study
Ablation has been recommended by worldwide guidelines as first-line treatment in addition to surgery for early-stage hepatocellular carcinoma (HCC), while evidence regarding its efficacy and comparison with surgery in treating primary intrahepatic cholangiocarcinoma (iCCA) is lacking.

Added value of this study
This is the first study comparing ablation and resection for early-stage primary intrahepatic cholangiocarcinoma with a long-term follow-up and the largest sample size of ablation to date. Over the 12.5 years during this study, microwave ablation demonstrated an improvement of efficacy in treating iCCA and provided comparable overall survival and disease-free survival to liver resection in recent years. One potential mechanism is the improvement in ablative margin.

Implications of all the available evidence
This study provided support for the evidence-based selection of minimally invasive treatment for iCCA patients and supplemented the current situation where surgery is the only curative treatment option. Microwave ablation may be considered as a viable alternative to liver resection for early-stage iCCA patients when an adequate margin could be obtained.

Introduction
Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver cancer following hepatocellular carcinoma (HCC), with globally increasing incidence and mortality over recent decades.[1,2] While worldwide guidelines recommend both ablation and surgery as first-line curative therapies for early-stage HCC,[3–6] liver resection (LR) remains the sole recommended first-line option for early-stage primary iCCA due to limited evidence supporting alternative treatments with comparable efficacy.[7–9]

However, more than 60% of patients are not suitable for surgery or general anesthesia at diagnosis,[8] making it valuable to explore alternative treatment options that offer similar curative potential with surgery. A pooled analysis of 93 studies showed that among locoregional therapies for iCCA, ablation had the longest overall survival (OS).[10] Ablation has been proven to have comparable locoregional eradicating efficacy and prognosis to surgery for small HCCs,[11–13] but evidence lacks for iCCA. A meta-analysis reported a pooled 5-year overall survival rate of 40.6% after thermal ablation for primary iCCA,[14] which is comparable to that observed after LR (25–46%).[15] To date, only one study based on a limited sample size using the Surveillance, Epidemiology, and End Results (SEER) database, directly compared the survival outcomes between radiofrequency ablation (RFA) in 34 cases and LR in 150 cases for primary small T1 stage iCCA. The results indicated that LR provided a better prognosis than RFA. No study has yet compared another most used ablation modality, microwave ablation (MWA) with LR in treating primary iCCA.

MWA has higher thermal efficiency due to its primary active heating characteristics than RFA, making it probably a more suitable therapeutic candidate for iCCA.[16] A 10-year Italian multicenter study demonstrated that MWA was superior to RFA in treating unresectable iCCA.[17] Furthermore, recent advancements in equipment and technique have led to improved survival outcomes after MWA for HCC,[12,18,19] suggesting its promising potential as an alternative treatment option for primary iCCA.

Therefore, this real-world retrospective study aims to compare the prognostic difference between MWA and LR for primary iCCA in a large multicenter iCCA Chinese population with long-term follow-up and provide evidence for selecting alternative treatment.

Methods
Ethics statement
All research was conducted in accordance with both the Declarations of Helsinki and Istanbul. Ethical committee approval and written informed consent was obtained from patients at each hospital.

Study design and population

Ten tertiary medical centers participated in this multicenter real-world retrospective cohort study. From January 2009 to June 2022, a total of 10,441 patients diagnosed with iCCA were identified.

The inclusion criteria for this study were as follows: (1) pathologically diagnosed iCCA based on the WHO classifications[20]; (2) curative-intent liver resection or microwave ablation as the initial treatment; (3) tumor within Milan criteria, namely single tumor ≤5 cm in maximum diameter; multiple tumors ≤3 in number and each ≤3 cm; no evidence of major vascular/hilar invasion, extrahepatic/lymphatic metastasis or other malignancies; (4) age ≥18 years. Patients not meeting any one of these inclusion criteria were excluded.

Treatment modalities

Treatment decisions were made based on suggestions from multidisciplinary teams and patient preference and tolerance. All MWA procedures were performed percutaneously under ultrasound guidance (n = 163 [73.8%]) or computed tomography (CT) guidance (n = 58 [26.2%]). LRs were performed under open surgery [n = 629 (87.0%)], laparoscopic surgery (n = 88 [12.2%]) or robotic surgery (n = 6 [0.8%]). Both MWA and LR aimed to completely eradicate or remove visible tumors with adequate margins. Information regarding the specialists and details involved in the procedures can be found in Supplement Information 1–3 and our previous studies.[19,21]

Follow-up and outcomes

After the initial curative-intent treatments, patients underwent regular follow-up every 3–6 months for the first 2 years and annually thereafter. Prognostic information was obtained through various means including phone call, network contact, onsite visits, medical records, and death certificates. The start time for survival analysis is the date of initial treatment (ablation or surgery), and the end time is the last follow-up, recurrence or death time. The primary outcome was overall survival (OS), calculated from the date of ablation/surgery to death from any cause. The secondary outcome was disease-free survival (DFS), defined as the time interval between the first treatment and recurrence (including local, intrahepatic and extrahepatic recurrence) or death, whichever occurred earlier. Tumor status was determined by radiologic responses, including contrast-enhanced CT, magnetic resonance imaging (MRI) or ultrasound combined. Recurrence was defined when a newly developed lesion was detected at any site of the body. Evaluation of these outcomes followed the RECIST system guidelines.[22] Patients who were lost to follow-up were censored at last contact.

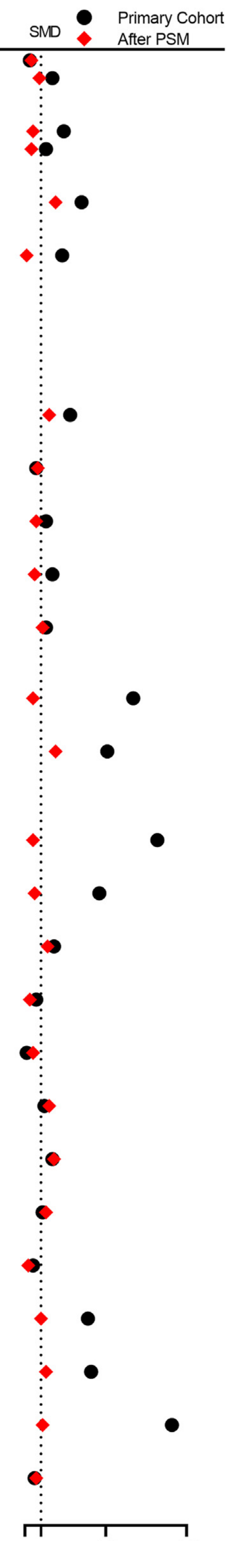
Study variables of interest included demographic characteristics, clinical characteristics, preoperative laboratory test results, perioperative characteristics and operative margin data. Detailed items and definitions of these variables can be found in Fig. 1 and Supplement Information 4. The operative margin was defined as the minimum distance from ablative or surgical margin to tumor border. The ablative margin was evaluated by contrast-enhanced CT or MR within 3–5 days after ablation based on the previous consensus.[23] The surgical margin was measured on the resected specimen.

Statistical analysis

Descriptive data are presented using numbers and percentages, mean and standard deviation for symmetrically distributed variables, and median and interquartile range for unsymmetrically distributed variables. Baseline variables were compared by Kruskal Wallis test for continuous variables, and Pearson χ^2 test, or Fisher's exact test for categorical variables. The prognostic roles of treatment and other confounders were evaluated by Cox proportional hazard regression model with backward stepwise selection. The proportional hazards assumption was assessed by Schoenfeld residuals and linearity assumption was verified by restricted cubic splines. The selection of confounding factors and mediators primarily considered the following aspects: (1) the inherent characteristics of patients known before treatment; (2) variables with statistically significant difference between the two groups at baseline selected as candidate variables (The alpha level was set to 0.2); (3) reported confounders by previous literature; (4) experts' consideration to be clinically significant; and (5) according to a causal directed acyclic graph (cDAG) (eFigure S1). In population before and after matching, risk differences were calculated by Cox regression, and Kaplan–Meier method was used to estimate cumulative rates of survival, utilizing log-rank test for survival comparison. The power of sample size was calculated using logrank test in PASS software v15.0.5 based on the hazard ratio (HR) of DFS between the two treatment groups.

To balance baseline characteristics between MWA and LR, one-to-many propensity score matching (PSM) by nearest neighbour method without replacement at variable ratios of 1:n (n ≤4) was applied. This can yield higher precision and thus smaller confidence intervals than simple 1:1 matching.[24,25] Logistic regression was used to estimate the propensity score. Confounders including age, gender, body mass index (BMI), smoking, drinking, etiology, Child class, cirrhosis, comorbidity, ECOG score, tumor size/number/location, clinical stage and preoperative laboratory test results were included in the propensity score model and the prediction probability was calculated as propensity score. A caliper distance of 0.2 times the SD of the logit of propensity score was used. The balance in these characteristics was examined by the standardized mean difference (SMD) with absolute values less than 0.1 considered acceptable. Propensity score matching

Variables	Primary Cohort MWA n=221	Primary Cohort LR n=723	Primary Cohort *P* value	PSM Cohort MWA n=203	PSM Cohort LR n=588	PSM Cohort *P* value
Age (y), mean (SD)	58.7 (11.1)	58.4 (10.4)	.75	58.7 (11.2)	58.3 (10.3)	.68
Gender, n (%)			.053			.33
Female	60 (27.2%)	255 (35.3%)		57 (28.3%)	192 (32.6%)	
Male	161 (72.8%)	468 (64.7%)		146 (71.7%)	396 (67.4%)	
BMI(kg/m^2), mean (SD)	23.2 (2.5)	23.8 (2.7)	.0071	23.2 (2.5)	23.3 (2.6)	.54
Smoking, n (%)			.12			.70
No	129 (58.2%)	468 (64.7%)		116 (57.2%)	347 (59.0%)	
Yes	92 (41.8%)	255 (35.3%)		87 (42.8%)	241 (41.0%)	
Drinking, n (%)			<.0001			.057
No	129 (58.4%)	539 (74.6%)		120 (59.3%)	405 (68.8%)	
Yes	92 (41.6%)	184 (25.4%)		83 (40.7%)	183 (31.2%)	
Etiology, n (%)			.59			.95
HBV	88 (39.9%)	305 (42.2%)		84 (41.4%)	284 (46.0%)	
Hepatolithiasis	21 (9.5%)	88 (12.2%)		20 (9.7%)	62 (10.5%)	
HCV	13 (5.7%)	36 (4.8%)		13 (6.2%)	34 (6.0%)	
HAV	3 (1.3%)	10 (1.4%)		3 (1.4%)	11 (1.9%)	
Schistosomiasis	3 (1.3%)	16 (2.2%)		3 (1.4%)	7 (1.2%)	
Alcoholic	1 (0.6%)	3 (0.4%)		1 (0.7%)	3 (0.5%)	
MAFLD	3 (1.3%)	3 (0.4%)		3 (1.4%)	3 (0.5%)	
Unknown	89 (40.5%)	262 (36.2%)		76 (37.9%)	184 (31.4%)	
Child class			.079			.19
A	204 (92.4%)	682 (94.3%)		189 (93.1%)	543 (92.4%)	
B	17 (7.6%)	41 (5.7%)		14 (6.9%)	45 (7.6%)	
Surgery history, n (%)			.42			.41
No	211 (95.6%)	679 (93.9%)		195 (95.9%)	553 (94.0%)	
Yes	10 (4.4%)	44 (6.1%)		8 (4.1%)	35 (6.0%)	
Cirrhosis, n (%)			.14			.45
No	155 (70.3%)	549 (75.9%)		143 (70.3%)	433 (73.6%)	
Yes	66 (29.7%)	174 (24.1%)		60 (29.7%)	155 (26.4%)	
Comorbidity score, n (%)			.038			.71
≤3	168 (75.9%)	600 (83.0%)		153 (75.2%)	440 (74.8%)	
>3	53 (24.1%)	123 (17.0%)		50 (24.8%)	148 (25.2%)	
ECOG score, n (%)			.25			.32
0	208 (94.3%)	701 (97.0%)		190 (93.8%)	569 (96.7%)	
1	10 (4.4%)	16 (2.2%)		10 (4.8%)	15 (2.6%)	
2	3 (1.3%)	6 (0.8%)		3 (1.4%)	4 (0.7%)	
Tumor size, n (%)			.0033			.66
≤3cm	137 (62.0%)	354 (49.0%)		123 (60.7%)	344 (58.6%)	
3-5cm	84 (38.0%)	369 (51.0%)		80 (39.3%)	244 (41.4%)	
Tumor location, n (%)			.032			.12
Left lobe	67 (30.3%)	278 (38.5%)		62 (30.5%)	183 (31.2%)	
Right lobe	106 (48.0%)	338 (46.8%)		98 (48.3%)	280 (47.6%)	
Both lobes	46 (20.8%)	76 (10.5%)		42 (20.7%)	111 (18.8%)	
Caudal lobe	2 (0.9%)	31 (4.3%)		1 (0.5%)	14 (2.4%)	
Tumor number, n (%)			<.0001			.51
Solitary	141 (63.9%)	621 (85.9%)		140 (69.0%)	417 (71.0%)	
Multiple	80 (36.1%)	102 (14.1%)		63 (31.0%)	171 (29.0%)	
Clinical stage, n (%)			<.0001			.61
I	122 (55.1%)	551 (76.2%)		120 (59.3%)	358 (61.0%)	
II	99 (44.9%)	172 (23.8%)		83 (40.7%)	230 (39.0%)	
CA199, n (%)			.043			.14
≤37U/ml	141 (63.9%)	398 (55.1%)		133 (65.5%)	344 (58.6%)	
>37U/ml	80 (36.1%)	325 (44.9%)		70 (34.5%)	244 (41.4%)	
CEA, n (%)			.63			.86
≤10ng/ml	206 (93.1%)	659 (91.2%)		188 (92.4%)	540 (91.9%)	
>10ng/ml	15 (6.9%)	64 (8.8%)		15 (7.6%)	48 (8.1%)	
ALT, n (%)			.99			.77
≤40U/L	154 (69.6%)	507 (70.1%)		137 (67.6%)	412 (70.0%)	
>40U/L	67 (30.4%)	216 (29.9%)		66 (32.4%)	176 (30.0%)	
GGT, n (%)			.24			.24
≤50U/L	134 (60.7%)	396 (54.8%)		119 (58.7%)	308 (52.3%)	
>50U/L	87 (39.3%)	327 (45.2%)		84 (41.3%)	280 (47.7%)	
ALB, n (%)			.036			.092
<35g/L	192 (86.7%)	664 (92.0%)		176 (86.9%)	528 (89.7%)	
≥35g/L	29 (13.3%)	59 (8.0%)		27 (13.1%)	60 (10.3%)	
TB, n (%)			.25			.23
≤34g/L	202 (91.1%)	678 (93.8%)		183 (90.3%)	549 (93.4%)	
>34g/L	19 (8.9%)	45 (6.2%)		20 (9.7%)	39 (6.6%)	
WBC, n (%)			.61			.85
≥4×10^9/L	206 (93.0%)	664 (91.8%)		188 (92.4%)	540 (91.9%)	
<4×10^9/L	15 (7.0%)	59 (8.2%)		15 (7.6%)	48 (8.1%)	
HGB, n (%)			.032			.20
≥110g/L	187 (85.0%)	678 (93.8%)		181 (89.2%)	556 (94.6%)	
<110g/L	34 (15.0%)	45 (6.2%)		22 (10.8%)	32 (5.4%)	
PLT, n (%)			<.0001			.091
≥100×10^9/L	176 (79.7%)	675 (93.4%)		167 (82.1%)	521 (88.6%)	
<100×10^9/L	45 (20.3%)	48 (6.6%)		36 (17.9%)	67 (11.4%)	
PT, n (%)			<.0001			.18
≤14s	165 (74.8%)	656 (90.7%)		161 (79.3%)	496 (84.3%)	
>14s	56 (25.2%)	67 (9.3%)		42 (20.7%)	92 (15.7%)	
Postoperative systematic therapy			.79			.68
Yes	35 (15.8%)	106 (14.7%)		32 (15.7%)	81 (13.8%)	
No	186 (84.2%)	617 (85.3)		171 (84.3%)	507 (86.2%)	



formed matched sets of subjects who share a similar value of the propensity score in the two treatment groups, then logrank and cox stratified on matched sets were used to test survival differences. Multiple imputation was employed for missing values using R's MI package with an imputation number of five. Predictors included BMI, serum carbohydrate antigen 199 (CA199), carcinoembryonic antigen (CEA), gamma-glutamyl transferase (GGT) and total bilirubin (TB) levels.

Stratification analysis was used to evaluate both treatments in different levels of variables. Causal mediation analysis quantified the mediation effect of operative margin within the association between treatment modalities and survival. The mediator of operative margin and its confounders was identified by the cDAG (eFigure S1). Natural direct and indirect effects were estimated.

All the analysis were performed and plotted using R 4.1.2 (https://www.R-project.org/) and GraphPad 9.5 (https://www.graphpad.com). The threshold of significance was set at two-tailed P value < 0.05.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Chuan Pang and Ping Liang had access to the dataset. All authors decided to publish the study findings.

Results

Baseline characteristics and PSM

944 out of 10,441 iCCA patients were included from January 2009 to June 2022 across 10 medical centers (mean 94.4 patients per center, range 51–230). Among them, 221 underwent microwave ablation (MWA) and 723 underwent liver resection (LR). The MWA cases were matched with LR cases at variable ratios as 109 versus 436 (1:4), 13 versus 39 (1:3), 32 versus 64 (1:2), 49 versus 49 (1:1), and 18 cases of ablation matched none of resection, resulting in a total of 203 MWA cases and 588 LR cases after PSM (eFigure S2). The calculated power was 0.996.

Patient baseline characteristics of the primary cohort showed that those who underwent MWA had higher rates of alcohol drinking, comorbidity score >3, tumor size ≤3 cm, multiple tumors, involvement of both left and right hepatic lobes and clinical stage II, as well as lower levels of carbohydrate antigen 199 (CA199), hemoglobin (HGB), platelet counts (PLT) and prothrombin time (PT). These baseline characteristics were well balanced after PSM with P values > 0.05 and SMD around 0.1 (Fig. 1).

Survival after MWA or LR in overall cohorts

The median follow-up time for all patients was 4.8 years (95% CI 4.4–5.4 years). The overall mortality rate was 40.7% (90 of 221) in the MWA group and 45.9% (332 of 723) in the LR group, with a median OS of 3.9 years after MWA and 4.2 years after LR. After PSM, the median follow-up time was 4.7 years (95% CI 4.6–5.4 years), with a mortality rate of 40.9% (83 of 203) in the MWA group and 46.9% (276 of 588) of the LR group. The median OS was 3.9 years after MWA and 4.0 years after LR. No significant difference in OS was observed between the two treatment groups before and after PSM (before PSM: HR 0.94, 95% CI 0.72–1.24, P = .677; after PSM: HR 0.96, 95% CI 0.71–1.29, P = .761) (Fig. 2A and B).

The overall recurrence rate was 55.7% (123 of 221) and 48.4% (350 of 723) in the MWA and LR groups. The median DFS was 1.7 years after MWA and 3.3 years after LR. After PSM, the recurrence rate was 57.1% (116 of 203) in the MWA group and 47.8% (281 of 588) in the LR group. The median DFS was 1.7 years after MWA and 3.6 years after LR. LR showed a better disease-free survival over MWA before and after PSM (before PSM: HR 0.71, 95% CI 0.55–0.92, P = .004; after PSM: HR 0.63, 95% CI 0.48–0.83, P = .0010) (Fig. 2C and D).

Detailed 1-year to 10-year OS and DFS rates were presented in eTable S1.

Survival between periods of 2009–2016 and 2017–2022

The treatment time was categorized into 2009–2016 and 2017–2022, because cases of MWA increased after 2017 and the sample size were comparable in these two periods. During these two periods, the OS between the MWA and LR groups remained consistently similar after matching (Fig. 3A and B). Nevertheless, the disparity in DFS between the two treatments remained statistically significant during 2009–2016 (5-year DFS 17.1% versus 44.4%, HR 0.51, 95% CI 0.34–0.76, P = .001; Fig. 3C), but became non-significant during 2017–2022 (5-year DFS 37.3% versus 40.8%, HR 0.74, 95% CI 0.49–1.12, P = .129; Fig. 3D). Further analysis revealed that DFS in the MWA group significantly improved after the year 2017 (Fig. 3E and F) but not in the LR group

Fig. 1: **Baseline characteristics of primary cohort and matched cohort**. Abbreviation: PSM, propensity score matching; MWA, microwave ablation; LR, liver resection; SMD, standardized mean difference; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; HAV, hepatitis A virus; MAFLD, nonalcoholic fatty liver disease; ECOG, Eastern Cooperative Oncology Group; CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ALB, albumin; TB, total bilirubin; WBC, white blood cell; HGB, hemoglobin; PLT, platelet counts; PT, prothrombin time.

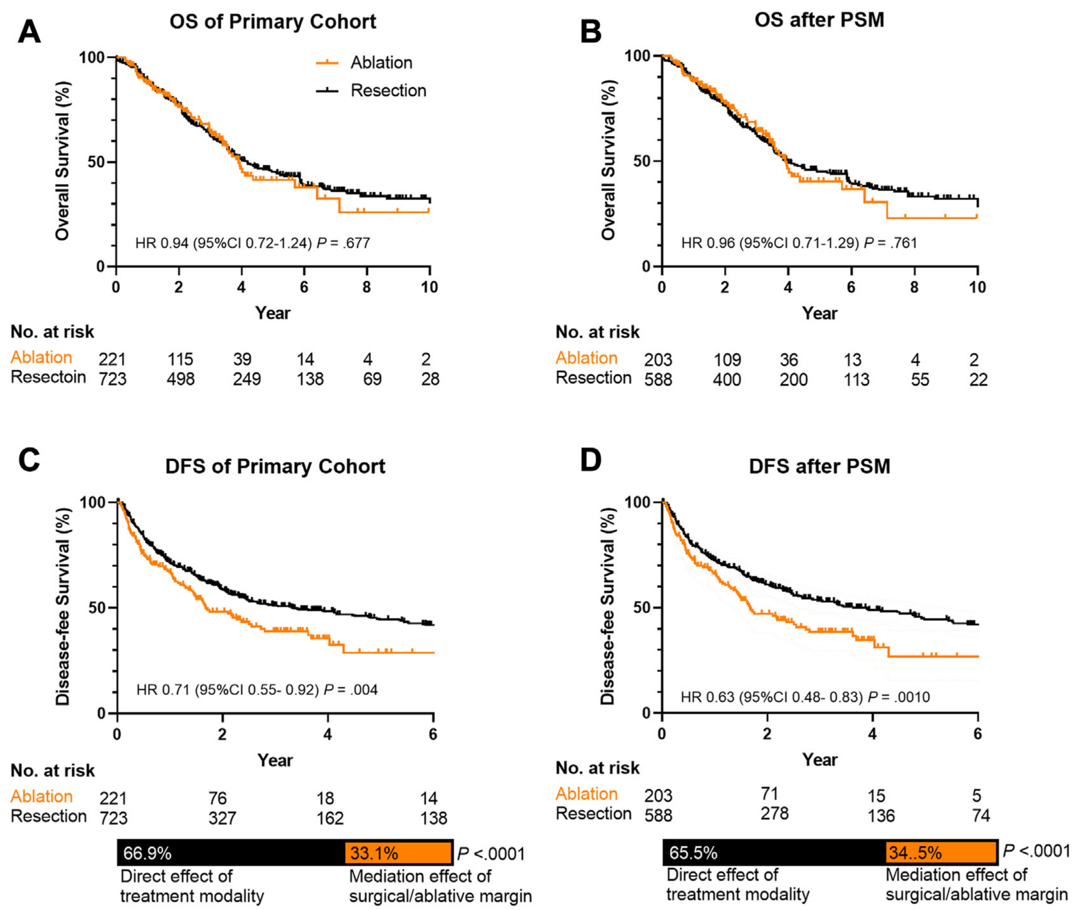


***Fig. 2:* Survival comparison between the two treatment modalities in overall cohorts**. A–D: Overall survival (OS) and disease-free survival (DFS) between the microwave ablation (MWA) and liver resection (LR) groups before and after propensity score matching (PSM), and the mediation analysis of operative margin on DFS (C, D).

(Fig. 3G and H). Survival comparison between the periods of 2009–2016 and 2017–2022 in primary cohorts was shown in eFigure S3. Baseline characteristics between the two periods before and after PSM was presented in eTable S2 and S3.

Effect of operative margin on recurrence

The univariate and multivariate analysis demonstrated that operative margin <5 mm is an independent risk factor for DFS in ablation cohort (HR 1.55, 95% CI 1.14–2.56, $P = .021$), resection cohort (HR 1.48, 95% CI 1.03–2.14, $P = .038$) and total cohort (HR 1.46, 95% CI 1.04–2.13, $P = .035$) (eTable S4 and S5). Mediation analysis revealed that the mediation effect of operative margin accounted for 34.5% of the difference in DFS between MWA and LR after PSM ($P < .0001$), while the remaining 65.5% represented the direct effects of different treatment techniques (Fig. 2D). From the years of 2009 to 2016, the mediation effect of operative margin accounted for 39.9% ($P < .0001$), but it became non-significance in 2017–2022 ($P = .126$) (Fig. 3C and D). eTable S6 provided detailed values regarding the mediation analysis.

Furthermore, there was an increase in the proportion of ablations with ≥5 mm margins from 25% in 2009–2016 to 61% in 2017–2022, with this proportion of surgical margins being 62% in 2009–2016 and 77% in 2017–2022 (Fig. 4E). When both ablation and resection achieved 5 mm margins, similar OS (HR 1.01, 95% CI 0.64–1.60, $P = .959$) and DFS (HR 0.83, 95% CI 0.52–1.32, $P = .410$) were observed. When both ablative and surgical margins were less than 5 mm but still negative, however, resection showed favorable DFS (HR 0.75, 95% CI 0.64–1.60, $P = .048$) (Fig. 4A–D).

Perioperative characteristics

MWA exhibited superior perioperative characteristics compared to LR, including shorter operation time (median 85 versus 165 min, $P < .001$), lower blood loss (median 50 versus 200 ml, $P = .03$), shorter hospital stay

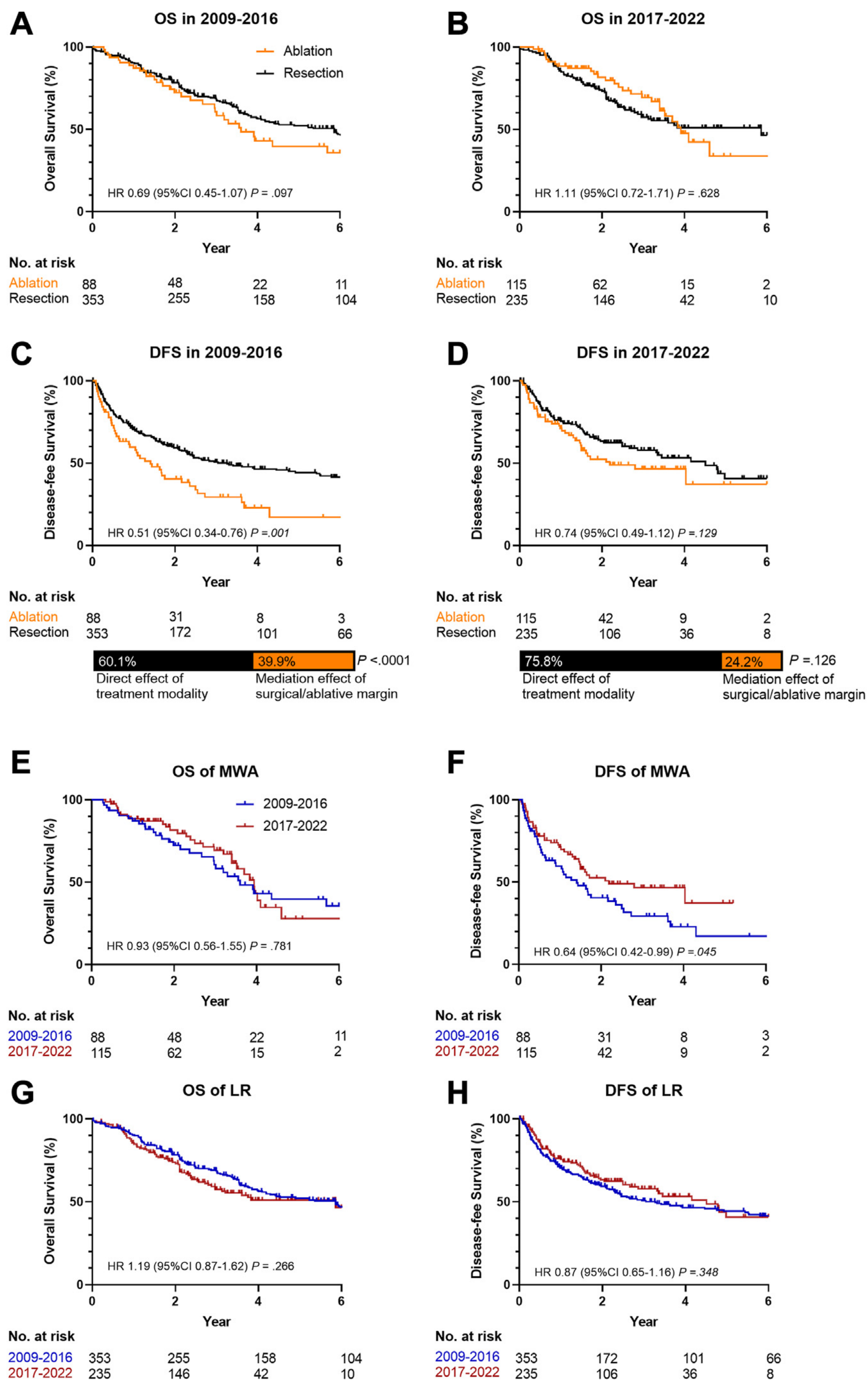


***Fig. 3:* Survival comparison between 2009–2016 and 2017–2022 periods**. A–D: Overall survival (OS) and disease-free survival (DFS) between the microwave ablation (MWA) and liver resection (LR) groups in 2009–2016 and 2017–2022 periods after propensity score matching (PSM), and the mediation analysis of operative margin on DFS (C, D); E–H: The OS and DFS between 2009–2016 and 2017–2022 periods in each treatment group after matched.

(median 12 versus 14 days, $P < .001$), lower cost [median 35,455 versus 48,253 yuan (Chinese renminbi), $P < .001$], lower rates of perioperative mortality (1.5% versus 2.4%, $P < .01$) and less complications above Clavien–Dindo grade II (7.6% versus 17.1%, $P < .001$) (Fig. 5A and B). But if laparoscopic surgery (including

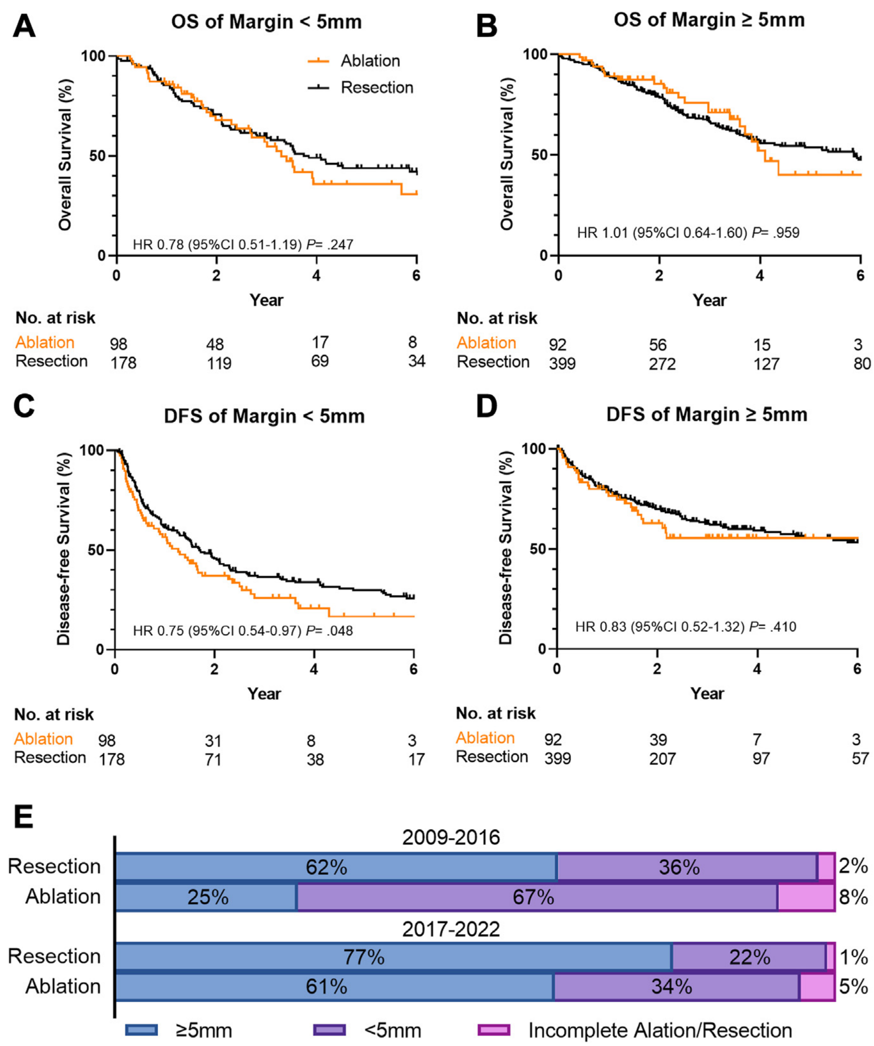


Fig. 4: **Survival comparison between different operative margins**. A and B: Overall survival (OS) between microwave ablation (MWA) and liver resection (LR) groups when both ablative and surgical margins were <5 mm or ≥5 mm in PSM cohorts; C and D: Disease-free survival (DFS) between MWA and LR when both ablative and surgical margins were <5 mm or ≥5 mm in PSM cohorts; E: The proportion of different margins between MWA and LR during 2009–2016 and 2017–2022 in PSM cohorts.

robotic surgery) was analysed separately from open surgery, it was better than open surgery in these perioperative aspects and approached ablation (eTable S9). Detailed information on perioperative characteristics and complications between periods of 2009–2016 and 2017–2022 before and after PSM were presented in eTable S7–S10.

Stratification analysis and risk factors

Stratification analysis demonstrated that LR outperformed MWA significantly both in OS and DFS among age less than 60 years, presence of hepatolithiasis, tumor located in left lobe and gamma-glutamyl transferase (GGT) >50U/L (eFigure S4). Multivariate analysis showed that the presence of hepatolithiasis and GGT >50U/L were also independent risk factors for DFS in the MWA cohort (eTable S5). Additionally, tumor size of 3–5 cm was identified as an independent risk factor for DFS specifically in the MWA group but not in the LR group. Detailed results of univariate and multivariate analyses for risk factors in each treatment and overall cohorts after PSM were provided in eTable S4 and S5.

Discussion

Both ablation and surgical resection are recommended as first-line curative treatments for early-stage hepatocellular carcinoma (HCC) by worldwide guidelines,[3–6] while surgical resection remains the only

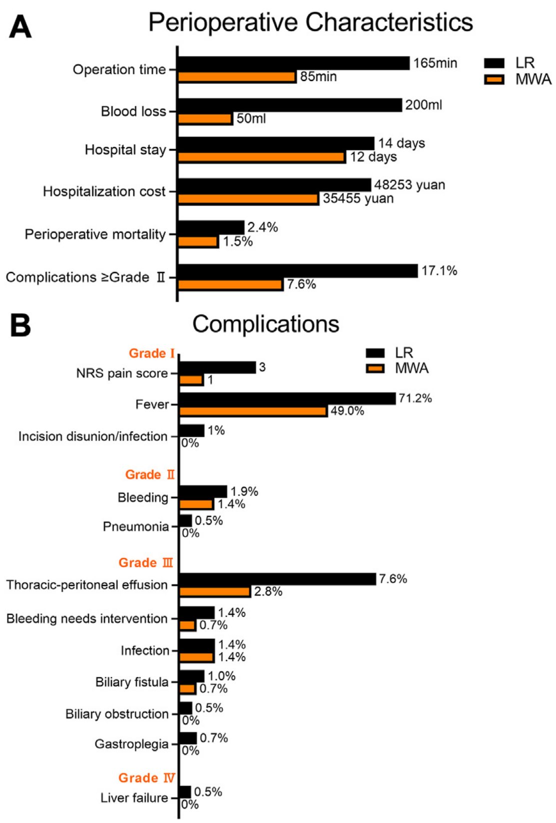


***Fig. 5:* Perioperative characteristics (A) and details of complications based on Clavien–Dindo grade (B) after PSM**. Values of operation time, blood loss, hospital stay and hospitalization cost are presented as median. Perioperative mortality: death within 30 days from surgery or ablation treatment. Other complications including cardiovascular and cerebrovascular events, mental disorders, urinary retention, portal thrombosis, acute pancreatitis, chylous leakage, severe fluid and electrolyte imbalance, gastrointestinal bleeding, hepatic lobe infarction, renal failure, surgical incision/needle tract implantation. Abbreviation: PSM, propensity score matching; MWA, microwave ablation; LR, liver resection; IQR, interquartile range; NRS, numeric rating scale.

recommended option for intrahepatic cholangiocarcinoma (iCCA).[7–9] There has been a lack of evidence for alternative treatments. This is the first study to investigate whether microwave ablation, a treatment candidate with curative potential, could provide comparable prognosis to liver resection in patients with early-stage primary iCCA based on a large Chinese real-world multicenter iCCA population with long-term follow-up. After balancing baseline characteristics through PSM, MWA demonstrated similar OS but unfavorable DFS compared to LR in the overall cohorts. Nevertheless, an improved DFS was observed in patients who underwent MWA after 2017 and became comparable to LR, suggesting that MWA may nowadays be considered as a more competent alternative treatment for primary iCCA than before. In recent years, advancements have been made in ablation techniques and its assistive technologies such as artificial fluid infusion, three-dimensional ablation planning systems, and multi-model image fusion navigation.[26–28] Several studies have reported improved efficacy of ablative therapy for HCC recently,[12,19] but there has been no previous literature regarding its efficacy improvement in treating intrahepatic cholangiocarcinoma (ICC) prior to this study. The only previous study comparing ablation and surgical resection for primary iCCA reported better overall and cancer-specific survival of surgical resection; however, that study included patients treated before 2014 and had only 34 patients who received radiofrequency ablation rather than microwave ablation.

Mediation analysis of this study revealed that one-third of the difference in DFS between MWA and LR was mediated through the effect of ablative and surgical margin. Previous studies and guidelines recommend a surgical margin of at least 5 mm.[9,29,30] Our results found that the proportion of MWAs that were able to reach 5 mm margins increased from 25% in 2009–2016 to 61% in 2017–2022, approaching the ratio seen with LRs (62%–77% from 2009–2016 to 2017–2022). This may partly explain the narrowed gap in recurrence between the two treatments after 2017. Also, we found that DFS was similar when both ablative and surgical margins reached this threshold, suggesting comparable local tumor eradication efficacy of MWA and LR when sufficient tumor coverage was achieved. This has been supported by studies on ablation treating other malignancies,[31–33] but also highlights the importance of achieving adequate margin if to choose ablation for iCCA.

Moreover, when both the ablative and surgical margins were less than 5 mm, DFS after surgery was superior to ablation. This is likely because beyond the minimum margin, the distance between the surgical margin and tumor was generally greater than that of the ablative margin. Therefore, it is crucial to carefully propose an adequate ablative margin before considering ablation as an initial radical option, even though surgical margins less than 5-mm were also found in 30–46% of cases in previous studies and our results.[29] MWA offers thermal efficiency advantage to ensure adequate ablative area, particularly for cases requiring larger tumor coverage.[11,13] Therefore, we consider MWA may be more suitable than RFA for iCCA treatment. An Italian 10-year multicenter study reported that MWA achieved better long-term survival outcomes than RFA in treating iCCA unfit for surgery.[17]

In comparison with surgical resection in this and previous studies, ablation as a minimally invasive procedure offers safety advantages while achieving similar prognosis, such as less trauma, faster recovery, shorter hospitalization, less costs, lower perioperative mortality and complication rate.[12] Importantly, ablation does not necessarily require general anesthesia and imposes fewer demands on patient conditions such as performance score, hepatic function and coagulation parameters; thus making it an appropriate alternative strategy particularly for patients who are unsuitable for surgery or general anesthesia and providing these patients hope for cure.

However, MWA also has its limitations. Stratification and multivariate analysis demonstrated that the presence of hepatolithiasis and gamma-glutamyl transferase more than 50U/L were associated with poorer survival after ablation, suggesting that ablation may not be suitable for patients with hepatolithiasis and potential biliary tract obstruction. This is probably because thermal alation cannot effectively address combined intrahepatic stones and cholangitis, thereby leaving these carcinogenic factors within the liver. Additionally, stratification results implied that patients younger than 60 years old and tumors located in the left lobe might be more appropriate candidates for liver resection. The left lobe is adjacent to the diaphragm, heart and gastrointestinal tract, making percutaneous ablation challenging, whereas surgical resection of the left lobe is relatively easier. In terms of tumor size, no significant difference between the two treatments was observed in the subgroup of tumors sized 3–5 cm, however, size of 3–5 cm is an independent risk factor for DFS after MWA rather than LR. This implies that caution should be exercised when performing ablation on tumors larger than 3 cm.

The present study does have several limitations. Firstly, although a large multicenter iCCA population was identified, given the limited proportion of patients receiving ablation treatment in real-world settings, the sample size of the MWA group is limited compared to that of the LR group. However, it still represents nearly three times the largest sample size of previous studies on primary iCCA treated with ablation (eTable S11) and has a power of 0.996. Secondly, different measurement methods were used for ablative margin and surgical margin assessment which may introduce potential bias. Nevertheless, the imaging-based and specimen-based methods employed in this study adhere to golden criteria for each treatment modality while providing optimal margin data currently available. Thirdly, due to the nature of retrospective design, potential selection bias may exist. Fourthly, the methodological limitations of the study design and analysis including unmeasured confounding and residual confounding due to measurement error in confounders. After matching, several variables with SMDs greater than 0.1 may also result in residual confounding. The stepwise selection used in Cox regression may subject to estimation bias. The HRs suffer from built-in selection bias.

In conclusion, MWA may offer comparable OS and DFS to LR for patients with iCCA within Milan criteria when an adequate margin of more than 5 mm can be achieved. Therefore, MWA could be considered as a viable alternative option for selected patients with primary iCCA, who may benefit from its minimally invasive nature and lower requirements for patient conditions, particularly those unsuitable for surgery or general anesthesia. However, for patients with hepatolithiasis, GGT >50U/L, tumors >3 cm or located in left lobe, ablation should be performed with caution.

Contributors

Ping Liang, Minghui Yang, Xiaoqing Jiang and Jie Yu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Chuan Pang, Jianming Li, Jianping Dou and Zhishuai Li are considered co–first authors.

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Data sharing statement

An anonymized dataset will be made available upon reasonable request, and after approvals have been obtained from relevant bodies.

Declaration of interests

None to report.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102336.

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