



Laparoscopic hepatectomy versus microwave ablation for multifocal 3–5 cm hepatocellular carcinoma: a multi-centre, real-world study

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Background: Researches comparing laparoscopic liver resection (LLR) with microwave ablation (MWA) for 3–5 cm multifocal hepatocellular carcinoma (MFHCC) are rare.

Materials and methods: From 2008 to 2019, 666 intrahepatic tumours in 289 patients from 12 tertiary medical centres in China were included in this retrospective study. Propensity score matching (PSM) was performed to balance variables between the two treatment groups over time frames 2008–2019 and 2013–2019 to observe the potential impact of advancements in intervention techniques on overall survival (OS), disease-free progression (DFS) of patients. complications, hospitalization, and cost were compared.

Results: Among 289 patients, the median age was 59 years [interquartile range (IQR) 52–66]. 2008–2019, after PSM, the median OS was 97.4 months in the LLR group and 75.2 months (95% CI 47.8–102.6) in the MWA group during a follow-up period of 39.0 months. The 1-year, 3-year and 5-year OS rates in the two groups were 91.8%, 72.6%, 60.7% and 96.5%, 72.8%, 62.5% [hazard ratio (HR) 1.03, 95% CI 0.62–1.69, $P = 0.920$]; The corresponding DFS rates were 75.9%, 57.2%, 46.9%, and 53.1%, 17.5%, 6.2% (HR 0.35, 95% CI 0.23–0.54, $P < 0.001$). 2013–2019, the median OS time was not reached in either group during the 34.0 months of follow-up, the 1-year, 3-year and 5-year OS rates in the two groups were 90.2%, 67.6%, 56.7% and 96.5%, 76.7%, 69.7% (HR 1.54, 95% CI 0.79–3.01, $P = 0.210$); The corresponding DFS rates were 69.6%, 53.9%, 43.3%, and 70.4%, 32.1%, 16.5% (HR 0.68, 95% CI 0.41–1.11, $P = 0.120$). The incidence of major complications was similar in both groups (all $P > 0.05$). MWA had shorter intervention times, hospitalization, and lower costs.

Conclusions: For resectable MFHCC patients, LLR is preferable due to its lower recurrence rate. For patients who do not qualify for LLR, advances in ablation technology have promoted MWA as a promising alternative.

Keywords: disease-free survival, laparoscopic liver resection, microwave ablation, multifocal hepatocellular carcinoma, overall survival

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Introduction

Surgery is the first choice in the clinical treatment of hepatocellular carcinoma (HCC), but the characteristics of multifocal development make resection incurable in the majority of cases^[1,2]. Even though complete resection of multifocal hepatocellular carcinoma (MFHCC) is attainable with preoperative imaging evaluation, the prognosis of MFHCC is worse than that of a single tumour due to the high recurrence rate^[3]. It has been reported that ~41–75% of patients are identified with MFHCC at the time of diagnosis^[4–6], especially for multiple lesions with diffuse distribution, which is a ticklish question for any surgeon and represents a great fundamental challenge.

Clinical consensus has been reached on the treatment of 2–3 tumours within 3 cm^[7,8]. However, for 3–5 cm MFHCC, there are still no clear treatment recommendations due to lack of evidence^[9,10]. Theoretically, alternative treatment options for such MFHCC also include liver transplantation and transcatheter arterial chemoembolization (TACE)^[11]. However, the limited organ availability and high cost of the former discourage most patients; the efficacy of the latter is likely to be affected by cirrhosis^[12], the blood supply to the tumour, and vascular superselection techniques^[13,14]. Hence, alternative interventions are urgently needed in clinical to expand the treatment space for more patients with 3–5 cm MFHCC.

Studies have shown that patients with early-stage HCC (mainly located in superficial or anterolateral liver positions) treated with laparoscopic liver resection (LLR) suffer fewer complications and have shorter hospital stays compared to traditional open resection while achieving competitive oncologic outcomes in terms of ablation^[9,11,12]. Therefore, the European Association for the Study of the Liver (EASL) recommends that minimally invasive approaches, such as LLR, should be considered more often in well-trained centres^[7]. Microwave ablation (MWA) has shown possible superiority in larger HCC compared to other ablations^[13], the EASL described that this technique showed promising results in terms of local control and survival^[7]. We previously compared the clinical outcomes of two minimally invasive techniques for solitary 3–5 cm HCC^[14], but knowledge gaps remain in the comparison of multifocal tumours^[7,15].

Therefore, this study directly compares LLR and MWA in the treatment of HCC patients with 2 or 3 tumours at initial diagnosis to assist clinicians in making referable treatment decisions.

Material and methods

The study was approved by the ethical committees of the primary research centre and conformed to the 1975 Declaration of Helsinki, and had completed the clinical study registration. The work has been reported in line with the STROCSS criteria^[10], Supplemental Digital Content 1, <http://links.lww.com/JS9/C370>. Because the study was designed to be retrospective, the ethics committee waived the informed consent procedure. This is a retrospective part of a multicenter bidirectional cohort study in China. The efficacy of LLR and MWA was dynamically compared in the real world through two propensity score matching (PSM).

HIGHLIGHTS

- From 2008 to 2019, laparoscopic liver resection (LLR) and microwave ablation (MWA) had comparable overall survival rates before and after propensity score matching, while MWA was strongly linked to worse disease-free survival.
- Although we observed improved control of recurrence rates for MWA in matched analysis from 2013 to 2019 (hazard ratio 0.68, $P = 0.120$), the converging separated K–M curve suggested that there was still a gap in efficacy between MWA and LLR in clinical practice.
- The incidence of major complications rates was similar in both groups (all $P > 0.05$), MWA had shorter intervention times, hospitalization, and lower costs (all $P < 0.001$).

Study population and inclusion criteria

In this study, 296 cases were extracted from the database consisting of 3385 patients with 3–5 cm liver cancer admitted to 12 authoritative medical centres in China from January 2008 to October 2019. Inclusion criteria: (1) At least 18 years old; (2) Child–pugh A or B; (3) Imaging evaluation of 2 or 3 tumours within 1 month before treatment; (4) At least one tumour was histopathologically diagnosed as HCC; (5) No vascular invasion or distant metastasis. Seven patients were lost to follow-up (LLR: 5, MWA: 2), 666 tumours from 289 patients were eventually included in the analysis. (2 tumours in 201 patients; 88 patients with 3 tumours) (Fig. 1).

Variables and definitions

Demographic characteristics include age, sex, BMI, body surface area (BSA), smoking, drinking, health status (ECOG), liver cirrhosis, epidemiology, antiviral treatment, portal hypertension and splenomegaly, ascites, Child–pugh classification, comorbidities, laboratory examination, tumour size, tumour number, tumour burden score (TBS), period of intervention.

Age, ECOG, portal hypertension, Child–pugh classification, preoperative haemoglobin, preoperative serum albumin, size, number and TBS of the above parameters are used as matching variables of the two time cohorts (Supporting Table S1, S2, Supplemental Digital Content 2, <http://links.lww.com/JS9/C371>).

Definition of portal hypertension: For patients without previous gastroesophageal varices, we refer to the following criteria: (1) Alone or combined to platelets and spleen size (splenomegaly with a decreased platelet count ($100 \times 10^3/\mu\text{l}$ or less)); (2) Imaging showing collateral circulation^[16]. For patients with previous gastroesophageal varices, we defined portal hypertension directly based on their history of chronic liver disease^[17]. Tumour size was defined as the size of the largest tumour. TBS was defined as the distance from the origin of a Cartesian plane and comprised of maximum tumour size (x -axis) and number of tumours (y -axis) so that $\text{TBS}^2 = (\text{maximum tumour diameter})^2 + (\text{number of tumours})$ ^[2,18–20].

Treatment strategy

The concept of the multidisciplinary team (MDT) was introduced earlier in the 12 participating centres of the study, which ensured

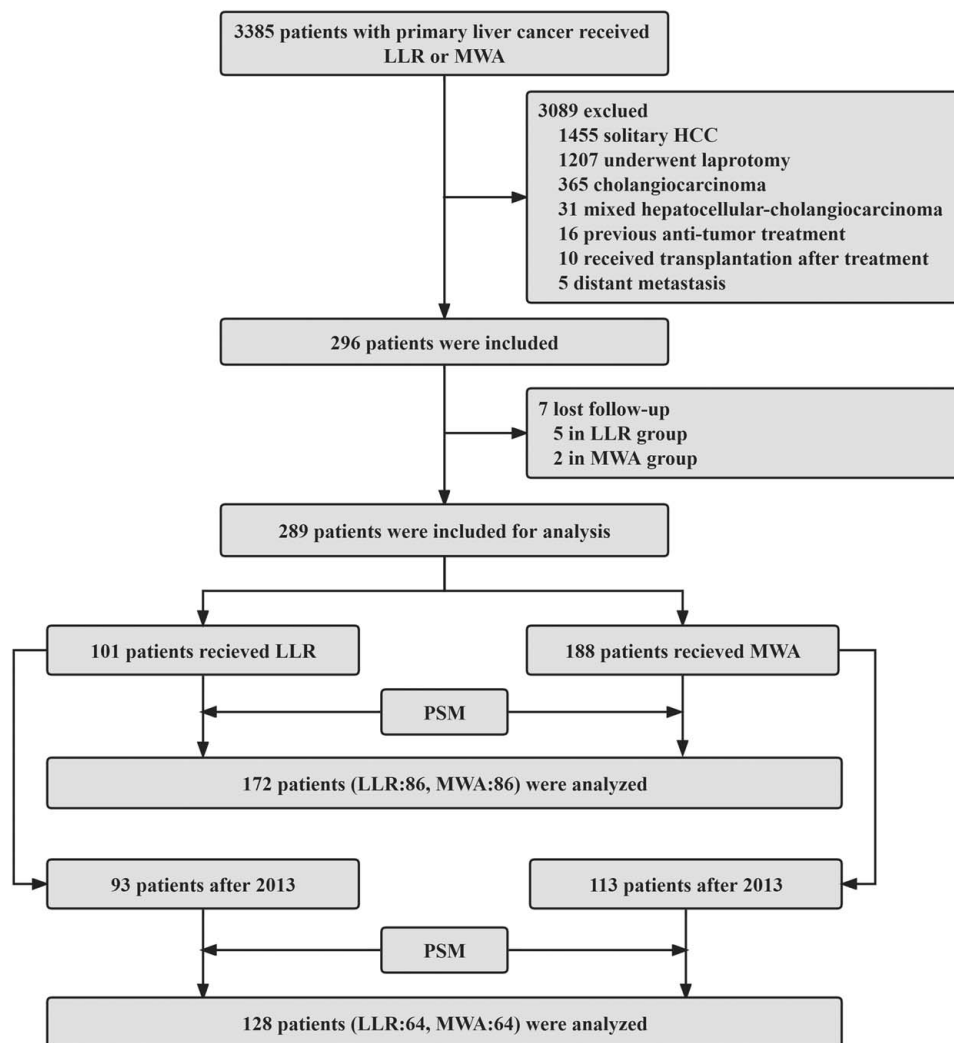


Figure 1. Study flow chart. HCC, hepatocellular carcinoma; LLR, laparoscopic liver resection; MWA, microwave ablation; PSM, propensity score matching.

that each newly diagnosed patient was given the best treatment strategy.

LLR: Based on the patient's preoperative images, the surgical team develops an individualized surgical plan, such as major resection, segmental resection, or anatomical hepatectomy. Details of the operation have been previously reported^[21]. All tumours can be completely resected. Preferred margins are greater than 1 cm; however, if margins are less than 1 cm to ensure that there are no residual tumour cells in the resected section. If more than 3 tumours are detected during the procedure, the surgeon stops the resection and advises the patient to consider TACE or radiation therapy^[22].

MWA: This procedure is performed by experienced radiologists, and ablation is performed in strict accordance with the preoperative plan. Since 2013, the widespread use of new technologies such as three-dimensional (3D) visualization and artificial hydrothorax and abdomen has greatly improved the accuracy and technical efficiency of the puncture^[23,24]. Supporting Appendix 2 shows the technical and equipment details, Supplemental Digital Content 2, <http://links.lww.com/JS9/C371>.

Study endpoints

The primary endpoint was overall survival (OS), defined as death from any cause, calculated from the date of intervention until the last exposure or death. The secondary endpoint was disease-free progression (DFS), defined as the time interval between the first treatment and recurrence or death. All complications were subgraded according to the Clavien–Dindo classification system^[25]. Other endpoints included length of stay and hospital costs. Specific follow-up management can be found in our previous references^[23].

Statistical analyses

The SPSS 22.0 and R 4.0.3 statistical packages were used to analyze the data. Multiple imputation was used to deal with missing data. The propensity score was generated by logistic regression analysis. Parameters that were selected or recommended by experts were used as independent variables (Age, ECOG, portal hypertension, Child–pugh classification, preoperative haemoglobin, preoperative serum albumin, size, number and TBS), and grouped variables were used as dependent

variable for model fitting. We used the same matching strategy (same inclusion variables and caliper) to process the data from 2008 to 2019 and 2013 to 2019. The sample size of the two time cohorts after matching was 172 and 128, respectively. The equilibrium before and after matching is tested and the standardized mean difference is calculated. Kaplan–Meier (K–M) survival curves method and Cox proportional-hazards model were used to analyze OS and DFS. Hazard ratio (HR) with 95% CI

were estimated using the Cox proportional-hazards model. Treatment effects were evaluated among subgroups by adding interaction terms to Cox proportional-hazards models, and to confirm our outcomes' robustness, we performed sensitivity analyses by multivariable Cox proportional-hazards models (the crude analysis, multivariable analysis, and inverse probability weighting). Continuous data were described by median and quartile according to whether they were normally distributed.

Table 1
Baseline comparison between LLR group and MWA group of total population before and after PSM.

Variables	Before PSM			After PSM		
	LLR (<i>n</i> = 101)	MWA (<i>n</i> = 188)	<i>P</i>	LLR (<i>n</i> = 86)	MWA (<i>n</i> = 86)	<i>P</i>
Mean age [SD], years	57.0 [8.9]	60.4 [10.8]	0.004	57.4 [8.5]	57.7 [9.9]	0.843
Sex, <i>n</i> (%)						
Male	76 (75.2)	157 (83.5)	0.090	64 (74.4)	70 (81.4)	0.270
Mean BMI [SD], kg/m ²	24.5 [3.1]	24.9 [3.1]	0.255	24.6 [3.1]	24.9 [3.0]	0.479
Mean BSA [SD], m ²	1.8 [0.1]	1.8 [0.2]	0.256	1.8 [0.1]	1.8 [0.2]	0.327
Smoking, <i>n</i> (%)						
Yes	56 (55.4)	106 (56.4)	0.878	48 (55.8)	50 (58.1)	0.758
Alcohol, <i>n</i> (%)						
Yes	50 (49.5)	105 (55.9)	0.302	42 (48.8)	46 (53.5)	0.542
ECOG PS, <i>n</i> (%)						
0	96 (95.0)	164 (87.2)	0.028	82 (95.3)	82 (95.3)	1.000
1	4 (4.0)	23 (12.2)		4 (4.7)	4 (4.7)	
2	1 (1.0)	1 (0.5)		0	0	
Liver cirrhosis, <i>n</i> (%)						
Yes	64 (63.4)	160 (85.1)	< 0.001	60 (65.9)	72 (79.1)	0.076
Epidemiology, <i>n</i> (%)						
HBV	55 (55.5)	136 (72.3)	0.002	46 (53.5)	56 (65.1)	0.105
HCV	9 (8.9)	27 (14.4)	0.181	8 (9.3)	11 (12.8)	0.466
Antiviral, <i>n</i> (%)						
Yes	28 (27.7)	76 (40.4)	0.032	24 (27.9)	34 (39.5)	0.107
Portal hypertension, <i>n</i> (%)						
Yes	12 (11.9)	28 (14.9)	0.480	9 (10.5)	11 (12.8)	0.634
Splenomegaly, <i>n</i> (%)						
Yes	16 (15.8)	32 (17.0)	0.797	11 (12.8)	14 (16.3)	0.516
Ascites, <i>n</i> (%)						
Yes	10 (9.9)	16 (8.5)	0.694	8 (9.3)	8 (9.3)	1.000
Child–pugh, <i>n</i> (%)						
A	97 (96.0)	180 (95.7)	1.000	83 (96.5)	83 (96.5)	1.000
B	4 (4.0)	8 (4.3)		3 (3.5)	3 (3.5)	
Comorbidity, <i>n</i> (%)						
Hypertension	21 (20.8)	64 (34.0)	0.018	26 (30.2)	18 (20.9)	0.162
Diabetes	9 (8.9)	45 (23.9)	0.002	13 (15.1)	9 (9.9)	0.235
Laboratory tests						
Mean Hb count [SD], (× 10 ⁹ /l)	144.2 [20.0]	134.4 [18.5]	< 0.001	141.4 [19.7]	140.1 [17.3]	0.636
Mean RBC count [SD], (× 10 ⁹ /l)	4.6 [0.6]	4.3 [0.7]	< 0.001	4.6 [0.6]	4.6 [0.6]	0.859
Mean ALT [SD], u/l	30.8 [17.5]	34.5 [25.9]	0.197	30.7 [18.2]	30.9 [18.2]	0.940
Mean AST [SD], u/l	30.4 [17.2]	35.4 [24.5]	0.068	31.2 [18.4]	32.4 [23.2]	0.704
Mean TP [SD], g/l	69.4 [6.3]	67.2 [6.9]	0.006	69.2 [6.4]	69.0 [6.7]	0.825
Mean ALB [SD], g/l	41.2 [4.6]	38.4 [4.9]	< 0.001	40.7 [4.3]	40.6 [4.1]	0.809
Mean TBil [SD], μmol/l	16.7 [24.1]	16.7 [9.0]	0.967	16.6 [25.9]	16.6 [8.6]	0.994
Mean DBil [SD], μmol/l	7.0 [18.2]	6.0 [4.6]	0.477	7.2 [19.8]	5.5 [3.8]	0.436
Tumour size (cm), <i>n</i> (%)						
4 < D ≤ 5	30 (29.7)	51 (27.1)	0.642	25 (29.1)	19 (22.1)	0.294
No. Tumour, <i>n</i> (%)						
2	72 (71.3)	129 (68.6)	0.638	59 (68.6)	55 (64.0)	0.519
3	29 (28.7)	59 (31.4)		27 (31.4)	31 (36.0)	
Mean TBS [SD],	4.5 [0.7]	4.4 [0.6]	0.051	4.5 [0.7]	4.5 [0.5]	0.739

ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; DBil, indirect bilirubin; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, haemoglobin; HBV, hepatitis b virus; HCV, hepatitis c virus; LLR, laparoscopic liver resection; MWA, microwave ablation; PSM, propensity score matching; RBC, red blood cell; TBil, total bilirubin; TBS, tumour burden score; TP, the total protein.

Frequency and percentage were calculated for count data. Statistical significance was defined as P less than 0.05 (two-sided).

Results

Baseline comparison

Among the 289 patients, 80.6% (233/289) were male, the median age was 59 years [interquartile range (IQR) 52–66], the HBV infection rate was 66.0% (191/289), and the incidence of 2 tumours was 69.6% (201/289) (LLR 71.3%, MWA 68.6%). Patients in the MWA group had HBV infection rate (72.3% vs. 55.5%, $P = 0.002$), more patients with cirrhosis (85.1% vs. 63.4%, $P < 0.001$), more patients on antiviral therapy (40.4% vs. 27.7%, $P = 0.032$), lower haemoglobin (mean 134.4 vs. 144.2 g/l, $P < 0.001$), total serum protein (mean 67.2 vs. 69.4 g/l, $P = 0.006$) and serum albumin (mean 38.4 vs. 41.2 g/l, $P < 0.001$). All matched variables were well balanced by PSM, and 86 cases in each group were included in the analysis (Table 1, Supporting Fig. S4, Supplemental Digital Content 2, <http://links.lww.com/JS9/C371>). Baseline comparisons between censored and enrolled cases were not performed because only 7 patients were reviewed. The baseline comparisons of patients before and

after matching from 2013 to 2019 are shown in Supporting Table S2, Supplemental Digital Content 2, <http://links.lww.com/JS9/C371>.

Comparison of OS and DFS between the two groups from 2008 to 2019

The median follow-up period before PSM from 2008 to 2019 was 40.1 months (IQR 23.3–70.4). The median OS was 90.1 months (95% CI 80.6–99.5) in the LLR group and 75.6 months (95% CI 57.1–94.1) in the MWA group, with an overall mortality rate of 35.6% (36/101) and 41.4% (78/188). The estimated OS rates at 1, 3, and 5 years were 92.0%, 74.2%, and 62.3% in the LLR group and 96.8%, 77.2%, and 62.8% in the MWA group (HR 1.05, 95% CI 0.70–1.57, $P = 0.830$) (Fig. 2A). The median DFS in the LLR group and MWA group were 62.2 (95% CI 35.1–89.4) months and 18.2 (95% CI 13.2–23.3) months, and the overall recurrence rates (including local recurrence, intrahepatic distant recurrence and extrahepatic distant metastatic recurrence) were 47.5% (48/101) and 71.2% (134/188) in the two groups, respectively. The corresponding 1-year, 3-year, and 5-year DFS rates were 75.7%, 56.4%, 48.1%, and 60.9%, 24.2%, 16.1%, respectively (HR 0.45, 95% CI 0.32–0.63, $P < 0.001$) (Fig. 2C).

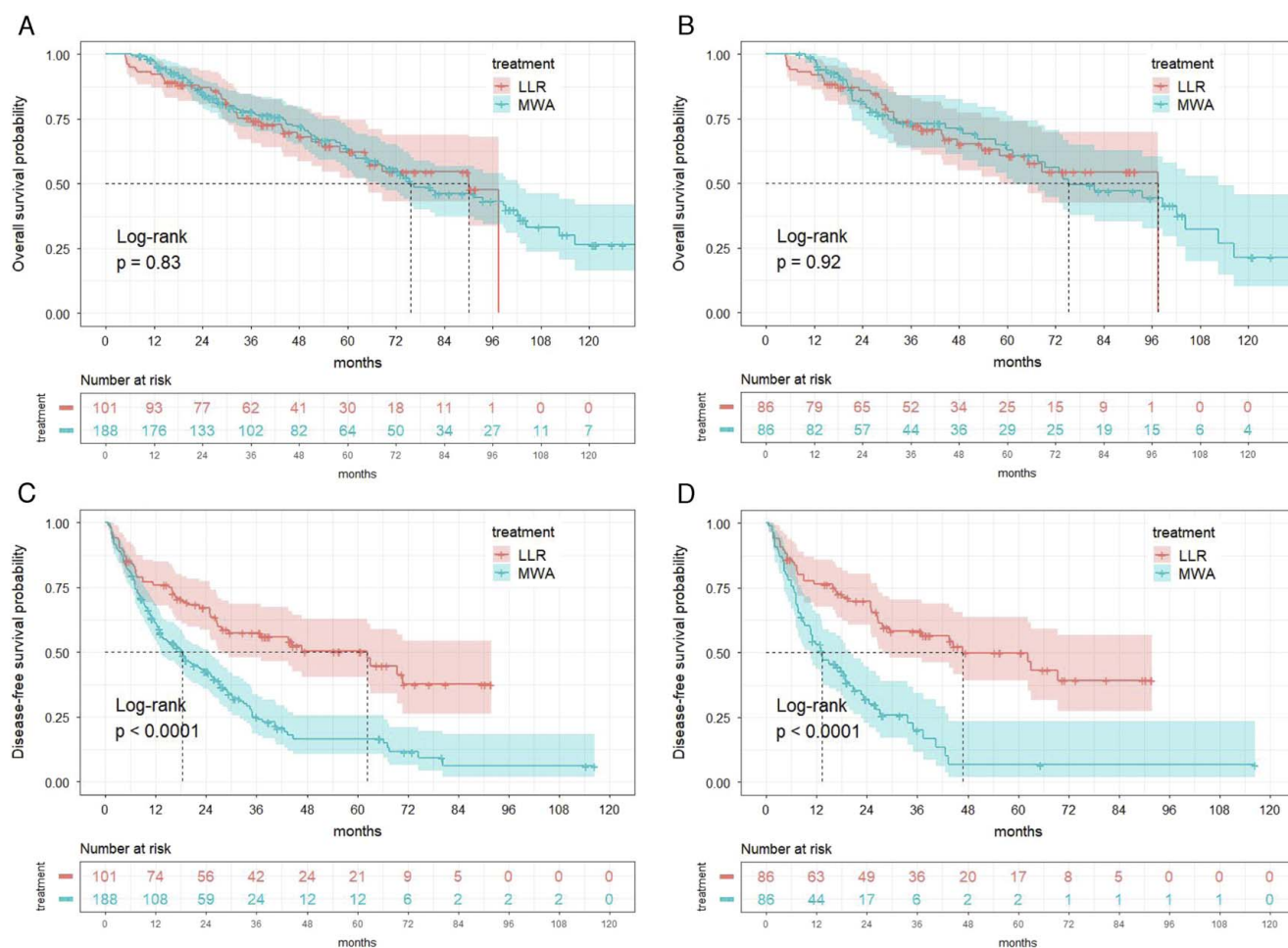


Figure 2. K–M curves of hepatocellular carcinoma patients before and after matching from 2008 to 2019. (A) overall survival (OS) before matching; (B) OS after matching; (C) disease-free survival (DFS) before matching; (D) DFS after matching. LLR, laparoscopic liver resection; MWA, microwave ablation.

After PSM, the median OS was 97.4 months in the LLR group and 75.2 months (95% CI 47.8–102.6) in the MWA group during a follow-up period of 39.0 months (IQR 21.3–69.2). Mortality rates were 36.0% (31/86) and 45.3% (39/86), respectively. The 1-year, 3-year, and 5-year OS rates were 91.8%, 72.6%, and 60.7% in the LLR group and 96.5%, 72.8%, and 62.5% in the MWA group (HR 1.03, 95% CI 0.62–1.69, $P = 0.920$) (Fig. 2B). The median DFS was 46.7 (95% CI 22.8–70.6) months and 13.2 (95% CI 7.8–18.6) months in the LLR and MWA groups, respectively, and the overall recurrence rates of two groups were 46.5% (40/86) and 74.4% (64/86) in the two groups, respectively. The 1-year, 3-year, and 5-year DFS rates were 75.9%, 57.2%, 46.9% and 53.1%, 17.5%, 6.2%, respectively (HR 0.35, 95% CI 0.23–0.54, $P < 0.001$) (Fig. 2D).

Comparison of OS and DFS between two groups from 2013 to 2019

Before PSM, the median follow-up was 36.0 months (IQR 21.4–58.7), and the median OS could not be estimated for either group. The overall mortality rates of the LLR group and MWA group were 30.1% (28/93) and 27.4% (31/113), respectively. The estimated OS rates at 1, 3, and 5 years were 92.1%, 75.5%,

and 65.3% in the LLR group and 97.5%, 74.7%, and 56.9% in the MWA group (HR 0.90, 95% CI 0.54–1.49, $P = 0.670$) (Fig. 3A). The median DFS was 62.2 (95% CI 40.1–84.4) months in LLR group and 27.2 (95% CI 20.7–33.8) months in MWA group, and the recurrence rates were 45.1% (42/93) and 53.9% (61/113) respectively. The corresponding 1-year, 3-year, and 5-year DFS rates were 75.7%, 58.6%, 50.4% and 70.7%, 36.1%, 20.5% (HR 0.60, 95% CI 0.40–0.89, $P = 0.011$), respectively (Fig. 3C).

After PSM, the median OS time was not reached in either group during the 34.0 months of follow-up (IQR 18.9–59.7). Mortality rates were 34.4% (22/64) and 21.9% (14/64), respectively. 1-year, 3-year, and 5-year OS rates were 90.2%, 67.6%, and 56.7% in the LLR group and 96.5%, 76.7%, and 69.7% in the MWA group (HR 1.54, 95% CI 0.79–3.01, $P = 0.210$) (Fig. 3B). The median DFS of LLR group and MWA group were 44.5 (95% CI 9.0–80.1) months and 24.8 (95% CI 16.1–33.5) months, and the overall recurrence rates were 48.4% (31/64) and 56.3% (36/64) in the two groups, respectively. The 1-year, 3-year, and 5-year DFS rates were 69.6%, 53.9%, 43.3% and 70.4%, 32.1%, 16.5% (HR 0.68, 95% CI 0.41–1.11, $P = 0.120$) (Fig. 3D).

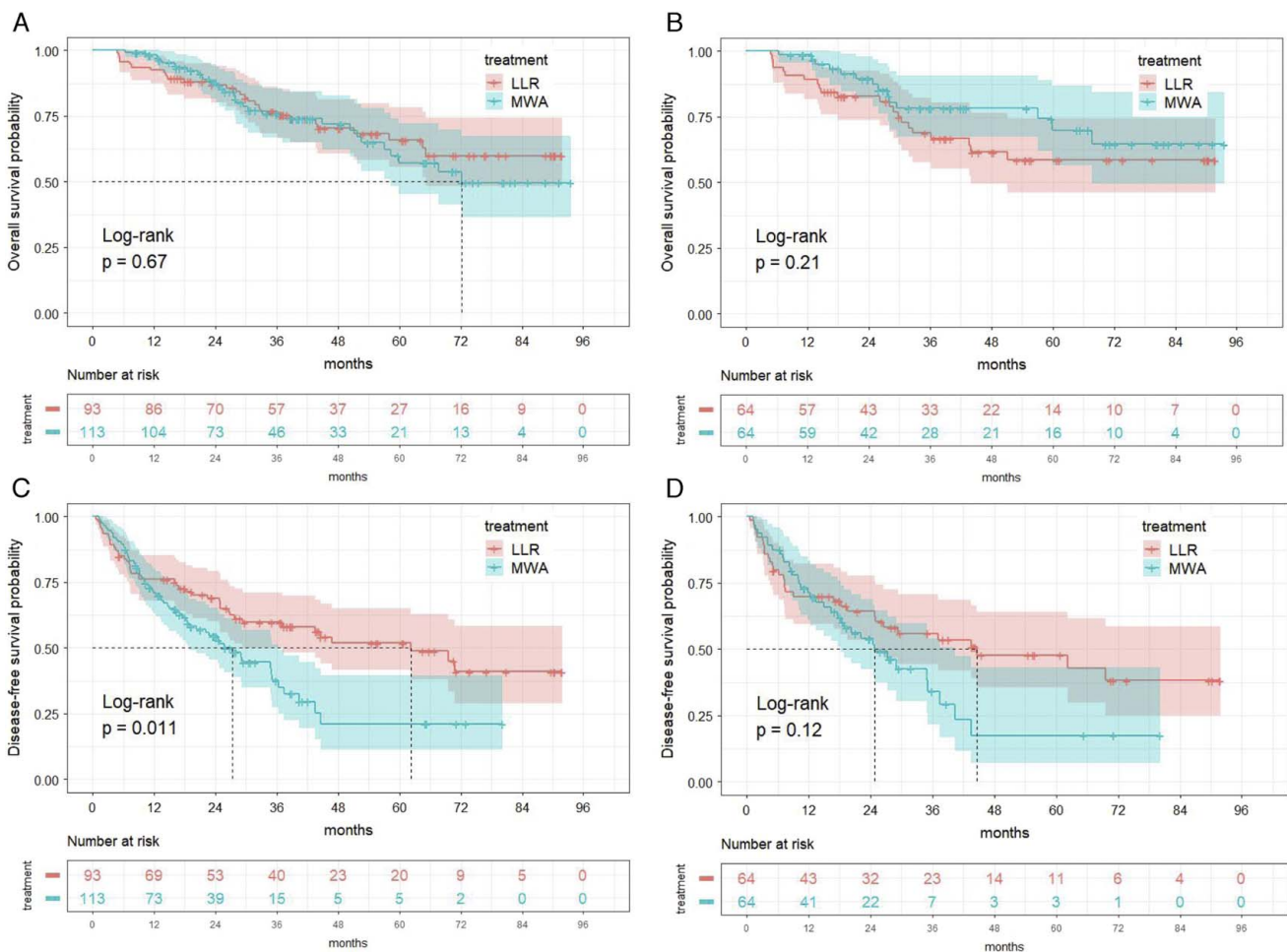


Figure 3. K-M curves of hepatocellular carcinoma patients before and after matching from 2013 to 2019. (A) overall survival (OS) before matching; (B) OS after matching; (C) disease-free survival (DFS) before matching; (D) DFS after matching. LLR, laparoscopic liver resection; MWA, microwave ablation.

The subgroup forest plots showed no significant interaction between the groups and the two treatment modalities after matching, with LLR significantly more favourable for DFS (Fig. 4).

Subgroup analysis for tumour number

Tumour numbers not only reflect the biological behaviour of HCC but also affect the prognosis of patients^[26,27]. Therefore, we further observed the efficacy of the two approaches from 2013 to 2019 in the presence of different tumour numbers.

Two tumours: there was no significant effect of LLR and MWA on OS (HR 1.00, 95% CI 0.46–2.20, $P = 1.000$), although the statistical difference in DFS disappeared (HR 1.50, 95% CI 0.81–2.75, $P = 0.190$), the curves remained significantly separated (Supporting Fig. S5A, S5C, Supplemental Digital Content 2, <http://links.lww.com/JS9/C371>).

Three tumours: although the K–M curves showed better survival in the MWA group (OS: HR 0.20, 95% CI 0.04–0.95, $P = 0.024$; DFS: HR 1.38, 95% CI 0.60–3.21, $P = 0.450$), some of the estimated effect sizes might be imprecise due to the relatively small sample size, and need to be verified by large sample studies (Supporting Fig. S5B, S5D, Supplemental Digital Content 2, <http://links.lww.com/JS9/C371>).

Safety, time, and cost analysis after PSM from 2008 to 2019 and 2013 to 2019

As shown in Table 2, there was no significant difference in the incidence of grade III–IV complications between the two cohorts (2008–2019: $P = 0.350$; 2013–2019: $P = 0.300$). Details are as follows (LLR vs. MWA): 2008–2019: thoracic and peritoneal

effusion (1.2% vs. 3.5%, $P = 0.312$), liver and kidney failure (0.0% vs.1.2%, $P = 0.316$), infection (0.0% vs.1.2%, $P = 0.316$), needle tract implantation metastasis (0.0% vs.1.2%, $P = 0.316$) and postoperative bleeding (3.5% vs. 1.2%, $P = 0.312$). 2013–2019: thoracic and peritoneal effusion (1.6% vs. 4.7%, $P = 0.310$), postoperative infection (0.0% vs. 1.6%, $P = 0.315$), postoperative bleeding (3.1% vs. 1.6%, $P = 0.559$) and liver and kidney failure (0.0% vs. 1.6%, $P = 0.315$). Notably that the rate of intraoperative blood transfusion was significantly higher in the LLR group than in the MWA group, but was associated with a lower postoperative fever rate. Table 3 briefly illustrates that compared to LLR, MWA had shorter operation time (2008–2019: mean 38 vs. 220 min; 2013–2019: mean time 43 vs. 230 min), shorter hospital stay (2008–2019: mean 11 vs. 17 days; 2013–2019: mean 11 vs. 18 days) and lower total costs (2008–2019: mean cost \$7637 vs. \$9889; 2013–2019: median cost \$6419 vs. \$10,244, all P less than 0.001).

Sensitivity analyses

To verify the stability of our results, we carried out sensitivity analyses by multivariable Cox proportional-hazards models, which mainly involved Crude analysis, Multivariate analysis and Propensity-score analysis. As can be clearly seen from Table 4, including the two time cohorts of 2008–2019 and 2013–2019, all the conclusions tend to be consistent after correction and processing by the included analysis methods.

Discussion

Approximately 906 000 new cases of cancer and 830 000 cancer-related deaths are caused by liver cancer, which is currently a

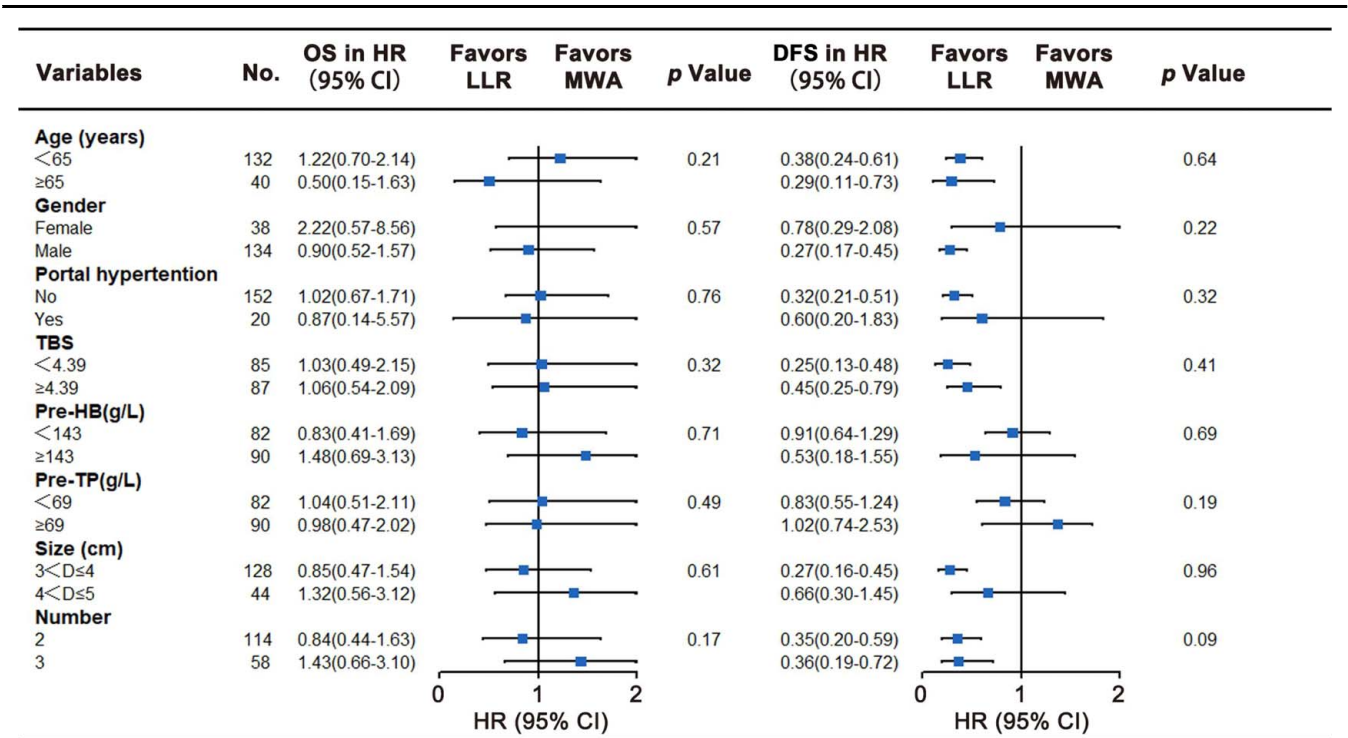


Figure 4. Subgroup forest plot after matching from 2008 to 2019. DFS, disease-free survival; HR, hazard ratio; LLR, laparoscopic liver resection; MWA, microwave ablation; OS, overall survival; Pre-HB, preoperative haemoglobin; Pre-TB, preoperative total protein; TBS, tumour burden score.

Table 2
Safety profile in 2008–2019 and 2013–2019 after PSM.

Complications	Grade	2008–2019			2013–2019		
		LLR (<i>n</i> = 86)	MWA (<i>n</i> = 86)	<i>P</i>	LLR (<i>n</i> = 64)	MWA (<i>n</i> = 64)	<i>P</i>
Mean NRS Pain score, [SD]	I	3.2 [1.2]	1.2 [1.7]	< 0.001	3.2 [1.2]	1.5 [1.9]	< 0.001
Fever, <i>n</i> (%)	I	24 (27.9)	42 (48.8)	0.005	21 (32.8)	37 (57.8)	0.004
Intraoperative blood transfusion, <i>n</i> (%)	—	28 (32.5)	0	< 0.001	22 (34.3)	0	< 0.001
Pneumonia, <i>n</i> (%)	II	0	0	—	0	0	—
Hypoproteinemia, <i>n</i> (%)	II	2 (2.3)	4 (4.7)	0.406	0	2 (3.1)	0.154
Postoperative bleeding, <i>n</i> (%)	II–III	3 (3.5)	1 (1.2)	0.312	2 (3.1)	1 (1.6)	0.559
Biliary leak, <i>n</i> (%)	III	2 (2.3)	0	0.155	1 (1.6)	0	0.315
Intestinal leak, <i>n</i> (%)	III	0	0	—	0	0	—
Thoraco-abdominal effusion, <i>n</i> (%)	III	1 (1.2)	3 (3.5)	0.312	1 (1.6)	3 (4.7)	0.310
Infection, <i>n</i> (%)	III	0	1 (1.2)	0.316	0	1 (1.6)	0.315
Needle tract implantation transfer, <i>n</i> (%)	III	0	1 (1.2)	0.316	0	0	—
Liver or kidney failure, <i>n</i> (%)	IV	0	1 (1.2)	0.316	0	1 (1.6)	0.315

LLR, laparoscopic liver resection; MWA, microwave ablation; NRS, numerical rating scale; PSM, propensity score matching.

global public health challenge^[28,29]. And according to earlier research, ~41–75% of patients had confirmed MFHCC at the time of diagnosis^[4–6]. The early stage of 2 or 3 HCC tumours less than or equal to 3 cm is widely established, and recommendations call for a variety of therapies for tumours in this category^[7,8]; however, there is no international consensus on resectable 3–5 cm HCC (up to 3 tumours) due to the lack of sufficient confirmatory medical evidence^[7,8]. Our previous study had gained some room for the treatment of patients with solitary 3–5 cm HCC^[23], and what was surprising was that we found similar outcomes in the comparison of treatments for 3–5 cm MFHCC: The OS of 3–5 cm HCC (2 or 3 tumours) after MWA was comparable to that of LLR, and since 2013, advances in ablation technology had improved the local control of MWA, thereby reducing the recurrence rate of tumours.

Studies have demonstrated that the minimally invasive hepatectomy procedure known as LLR can effectively reduce post-operative ascites, liver failure, and morbidity while ensuring oncological outcomes^[30]. Around the world, LLR was not widely used in properly trained medical centres until around 2015 due to a long learning curve^[31], which is comparable to the growth trajectory of MWA in the 12 medical centres being studied^[23]. We re-matched 2013–2019 as an independent cohort to assess whether technological advancements could somewhat improve patient prognosis given the successful spread of artificial fluid thorax, artificial ascites, 3D visualization, multimodal image fusion navigation, and contrast-enhanced ultrasound navigation technologies in the field of ablation after 2013.

The database's total number of eligible samples dropped to 296 when we concentrated on comparing the two minimally

invasive procedures. It is worth noting that there were 87 fewer patients in the LLR group than in the MWA group, although the sample size in the solitary tumour database was twice as large^[23]. Despite the superior performance of LLR in lowering the recurrence rate in HCC patients, the variation in sample size between the two treatment groups may hint at the technical limitations of LLR in the treatment of MFHCC. Liver transplantation is undoubtedly an optional treatment for this type of HCC, especially the proposal of Hangzhou Criteria^[32], which further expands the transplantation indication, but the limited supply of organs and the high cost deter most patients. According to the current study, patients who reject LLR or have difficulty tolerating LLR or diffuse tumour distribution may benefit from MWA as a potential therapeutic option. From 2008 to 2019, LLR and MWA had comparable overall survival rates before and after PSM, while MWA was strongly linked to worse DFS. Although we observed improved control of recurrence rates for MWA in our matched analysis from 2013 to 2019, the separated K–M curve suggested that there was still a gap in efficacy between MWA and LLR in clinical practice. To this end, we further carried out a sensitivity analysis for the overall survival of patients, and after the adjustment analysis of the crude analysis, multi-variable analysis, and propensity-score analyses, the final conclusions were still consistent with the original conclusion, which confirmed the reliability of our preliminary study to a large extent. The conclusion on OS is in line with the clinical and our research hypothesis because there are many factors affecting the final survival, all the existing therapies may have limited influence on OS for tumours with poor prognosis, such as HCC. However, factors such as microvascular invasion, surgical field exposure,

Table 3
Comparison of time and cost between two groups in 2008–2019 and 2013–2019 after PSM.

	2008–2019			2013–2019		
	LLR (<i>n</i> = 86)	MWA (<i>n</i> = 86)	<i>P</i>	LLR (<i>n</i> = 64)	MWA (<i>n</i> = 64)	<i>P</i>
Mean intervention time, min, [SD]	220 [83]	38 [13]	< 0.001	230 [89]	43 [19]	< 0.001
Mean length of stay, days, [SD]	17 [6]	11 [5]	< 0.001	18 [6]	11 [5]	< 0.001
Mean total cost, US\$, [SD]	9889 [4146]	7637 [1596]	< 0.001	10244 [3934]	6419 [1224]	< 0.001

LLR, laparoscopic liver resection; MWA, microwave ablation; PSM, propensity score matching; US\$, US dollar.

Table 4
Associations between treatment modalities and OS in the crude analysis, multivariable analysis, and propensity-score analyses.

	2008–2019	2013–2019
Crude analysis—hazard ratio (95% CI)	1.05 (0.70–1.57)	1.12 (0.67–1.87)
Multivariable analysis—hazard ratio (95% CI) ^a	1.27 (0.81–2.00)	1.42 (0.78–2.60)
Propensity-score analyses—hazard ratio (95% CI)		
With inverse probability weighting ^b	1.26 (0.79–2.00)	1.44 (0.76–2.74)
With matching ^c	1.03 (0.62–1.69)	1.54 (0.79–3.01)

ECOG, Eastern Cooperative Oncology Group; OS, overall survival; TBS, tumour burden score.

^aShown is the hazard ratio from the multivariable Cox proportional-hazards model, with stratification according to treatment and with additional adjustment for age, ECOG, portal hypertension, Child–pugh classification, preoperative haemoglobin, preoperative serum albumin, size, number and TBS on presentation.

^bShown is the primary analysis with a hazard ratio from the multivariable Cox proportional-hazards model with the same strata and covariates with inverse probability weighting according to the propensity score.

^cThe analytical process can be seen in the research methodology.

distance between incisional margin and tumour, and whether ablation has sufficient safety boundary can significantly affect DFS. Compared with MWA, LLR undoubtedly handles these aspects better and is further confirmed by postoperative pathology, which may be the potential reason for the higher recurrence rate associated with MWA. Therefore, in prospective studies, MWA may need to make efforts in the areas of identification of MVI, accurate localization, and scientific thermal field distribution.

Tumour number is a significant risk factor for early recurrence in patients with HCC after radical therapy^[27]. As demonstrated by Li, according to the Milan criteria classification, poorer DFS in patients with HCC following radical resection is highly related to the increased number of tumours, even if patients undergo R0 resection^[33]. Therefore, we further explored the efficacy of both treatment modalities in patients with 2 or 3 tumours. It's interesting to note that in patients with different tumour numbers, we observed results consistent with the primary findings, although the number of patients with 3 tumours might only reflect a certain trend. In this study, we also observed that, after grouping by tumour number, the prognosis of the three-tumour group was poorer than that of the two-tumour cohort (Supporting Fig. S3, Supplemental Digital Content 2, <http://links.lww.com/JS9/C371>).

The subgroup forest plots showed that there was no significant interaction between the two treatment modalities and sub-variables, indicating the stability and reliability of the data. In the safety analysis, we could see that there was no statistically significant difference between the two cohorts in terms of major complications after the intervention, but the NRS pain scores in the LLR group remained higher, and the number of intraoperative blood transfusions was higher even with the routine use of postoperative analgesia pumps, which deserves further attention. We also observed that the MWA group was associated with a higher proportion of postoperative fever, which may be related to the infiltration of necrotic tumour tissue into the blood after ablation. In the comparison of time and cost, MWA was associated with shorter hospital stays, treatment times, and total costs; however, we should also be aware that the cost comparison associated with a single treatment does not reflect the full course of a patient's disease, because MWA is highly reproducible.

Studies have shown that the imaging manifestations of HCC present as multiple anatomically independent tumours in an

individual liver, but this manifestation may represent a deep clonal mechanism and biological behaviour of each tumour nodule^[34]. It is known that MFHCC clones are mainly derived from two forms: intrahepatic metastatic HCC from a single tumour centre, that is IM-type HCC, and multicenter primary HCC from a polyclonal centre, that is MO-type HCC^[35]. The former tends to be associated with more microvascular infiltration and a poorer prognosis. The latter has a relatively good local treatment outcome because of its lower risk of minor metastasis^[36,37]. So, the visualization of K–M curves in 3 tumour patients may be due to the MWA group managing more MO-type HCC. In addition, it is worthwhile for surgeons and imaging experts to focus on the fact that the key to improving the efficacy of MFHCC is to continuously improve the local treatment measures and actively explore comprehensive treatment strategies combining local with systemic treatment.

We used multicenter data and PSM to minimize regional heterogeneity and inclusion bias, hoping to produce relatively robust findings that allow people to give an objective view of LLR and MWA. But there were still some limitations: First, as a retrospective study design, it was difficult to avoid selection bias even when PSM was applied, after all, the number of variables included in a match is limited, which made it difficult to balance potential influencing factors; Second, the 3D visualization technique did not cover all cases, so it was difficult to accurately balance the tumour burden between the two groups; Third, due to the limited sample size, it was difficult to conduct stratified analysis of tumour site, sex, age and other key variables; Fourth, although liver cirrhosis and portal hypertension lost statistical difference between the two groups after PSM, MWA group accounted for a larger proportion, which affected the technical implementation of MWA and even DFS to a certain extent; Fifth, there were variations in HCC epidemiology between China and the West, and whether the conclusions can be generalized needs to be confirmed by prospective studies.

Consistently, surgical operation was the primary treatment for clinical HCC patients, but in real-life clinical settings, a considerable number of patients refused surgery or could not tolerate surgery due to severe comorbidities. This status quo must arouse people's sufficient attention and then promote people to appreciate minimally invasive technology such as percutaneous MWA more objectively. Only in this way could we promote the implementation of large-scale randomized controlled trials (RCTs) and the development of diversified minimally invasive techniques for HCC.

Conclusions

In conclusion, LLR can provide better survival outcomes for suitable patients. With the advancement of technology, MWA is progressively demonstrating some potential value. It may be an effective alternative to LLR for patients who are not suitable for resection due to advanced age, multiple comorbidities, severe cirrhosis, or scattered tumour distribution.

Ethical approval

Ethical approval for this study (S2019-348-01) was provided by the Ethical Committee of the Chinese PLA general hospital, Beijing, China on 26 December 2019.

Consent

Informed consent was exempted due to the retrospective nature and the use of deidentified images.

Author contribution

Conception and design: P.L., J.Y. and S.W.; Administrative support: Z.W., C.P., Q.M.; Collection and assembly of data: Z.W.; Data analysis and interpretation: Z.W., C.P.; Provision of study materials or patients: all authors; Manuscript writing: all authors; Final approval of manuscript: all authors.

Conflicts of interest disclosure

All authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Research registration unique identifying number (UIN)

NCT 05796700 (<https://clinicaltrials.gov/>).

Guarantor

Ping Liang.

Data statement

For scientific reasons, raw data may be obtained with the permission of the corresponding author.

Provenance and peer review

No, thanks.

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