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Review

Ablative Treatments and Surgery for Early-Stage Hepatocellular Carcinoma: A Network Meta-Analysis

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ABSTRACT

Background: We compared overall survival (OS) and disease-free survival (DFS) for hepatocellular carcinoma (HCC) following radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, and liver resection (LR), with the aim of evaluating treatment plans for early-stage HCC.

Methods: Studies in PubMed, Web of Science, and Cochrane databases from April 1, 2004, to April 1, 2024, were searched. Articles were evaluated for quality using the randomized controlled trials tool. Two tool and the Newcastle–Ottawa Scale. Data obtained from the literature were netted using Stata 15.0 and r 4.2.3. The assessed primary outcomes were OS and DFS at 1 and 3 y.

Results: A total of 25 publications with 4548 patients were included, including 13 studies in mainland China and 12 in other regions. For 1-y DFS, the hazard ratio (HR) was 0.54 (95% credible interval (CrI): 0.38–0.76) for LR compared with RFA and 0.57 (95% CrI: 0.3–-0.82) for LR compared with MWA. For 3-y DFS, the HR was 0.52 (95% CrI: 0.38-0.72) for LR compared with RFA and 0.53 (95% CrI: 0.37–0.76). In the Chinese mainland, LR may have a better 1- and 3-y DFS than MWA, but similar survival to RFA. In the other regions, LR had a better DFS than MWA and RFA patients. The rest of the comparisons were not statistically significant.

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Conclusions: For early-stage HCC, LR may be more effective in reducing tumor recurrence than ablative treatments. Cryoablation may be a potential treatment for HCC. The differences in treatment effectiveness in different regions are worth further study.

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Introduction

Primary liver cancer is the sixth most common cancer globally and the third leading cause of death.[1] Hepatocellular carcinoma (HCC) is the most common form of liver cancer and is mainly caused by viral hepatitis.[2] Early diagnosis and timely intervention can reduce the mortality and increase the life expectancy of HCC patients. There are increasingly diverse treatments available, especially for early-stage HCC with Barcelona Clinic Liver Cancer (BCLC) grade 0 and BCLC stage A, including radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation (CA), and liver resection (LR). Recently, ablation techniques have been significantly improved, and RFA is recommended over percutaneous anhydrous ethanol infusion as the preferred modality for percutaneous treatment of HCC by the American Association for the Study of Liver Diseases.[3] Nevertheless, reports on the comparison of prognosis between LR and ablative treatments in early-stage HCC, especially small HCC (<2–3 cm), have been inconsistent. For example, a randomized controlled trial (RCT) reported that the tumor recurrence rates were not different between LR and RFA for early-to-mid stage HCC.[4] In contrast, a prospective study showed a higher rate of intrahepatic recurrence and a lower medium-to-long-term disease-free survival (DFS) in RFA than LR.[5]

Several meta-analyses have compared the prognosis of LR with those of specific ablation treatments. One meta-analysis found that overall survival (OS) and DFS rates were higher in the LR group than in RFA group,[6] whereas another meta-analysis suggested a higher DFS rate for LR than RFA, with no difference in OS.[7] One meta-analysis suggested no difference in OS and DFS between MWA and LR in the short term but a better OS for MWA than LR in the medium-to-long term.[8] Moreover, there is a lack of evidence comparing the prognosis of LR, CA, MWA, and RFA for early-stage HCC. Clarifying the differences in the outcomes of these treatments may shed light on effective HCC treatment. To address this gap, we conducted a net meta-analysis comparing the prognosis of LR and ablation treatments (RFA, MWA, and CA) in early-stage HCC.

Materials and Methods

The current network meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-NMA extension statements for network meta-analysis.[9] The protocol was registered with PROSPERO (registration number: CRD42023415742).

Search strategy

We searched PubMed, Web of Science, and Cochrane databases for literature published from April 1, 2004, to April 1, 2024. Some relevant literature was supplemented by independent review. We used "RFA," "MWA," "cryosurgery," "carcinoma, hepatocellular," and "hepatectomy" as the subject terms; combinations of subject terms and free terms in groups of two or three were used to search the databases. The types of studies were RCTs or cohort studies, and the language of the studies was limited to English. The search strategy for PubMed is shown in the Supplementary Material, and the same search strategy is applied to other databases.

Selection criteria

Two reviewers (Min and Tong) independently screened the titles and abstracts of potential publications and reviewed the full text of the eligible articles.

The study's inclusion criteria were as follows: (1) randomized controlled study or cohort study design, (2) comparison of surgical treatment of partial LR with ablative treatments, (3) participants with very early or had early-stage HCC following the BCLC classification, specifically a single node ≤2 cm as very early-stage HCC and a single node ≤5 cm or up to three nodes ≤3 cm as early-stage HCC[3], and (4) publication language was English.

The exclusion criteria were as follows: (1) no definitive survival data, (2) duplicate publications of multiple abstracts and/or papers by the same author team, (3) studies of subjects with vascular invasion and intermediate to advanced HCC, and (4) case reports, case series, narrative studies, systematic reviews, or commentaries.

Data extraction

Two researchers (Min and Tong) independently screened the literature, and any discrepancies were resolved by discussion by the senior investigators (Li). The extracted data were entered directly into a preconstructed table.

Study outcomes

Hazard ratio (HR) was determined by comparing OS and DFS rates for different groups after one and 3 y. The calculated risk ratios for OS and DFS rates were based on relevant statistical methods.[10]

Construction of network diagrams

Stata 15.0 software was used to evaluate the treatment network by the generation of network diagrams in which circles represent interventions and the thickness of the line connecting the circles is proportional to the number of studies between interventions. Network diagrams of closed triangles were also evaluated.

Assessment of risk of bias

The Cochrane revised tool (randomized controlled trials tool [ROB] 2.0) was used for the evaluation of the risk of bias in prospective cohort studies.[11] The Newcastle–Ottawa Scale was used to assess bias in retrospective cohort studies. The risk of publication bias was assessed using funnel plots.

Statistical analysis

Stata 15 and *r* 4.0.3 software were used for statistical analysis. A network relationship diagram was drawn by Stata 15 to represent the network relationships between the interventions. In this study, inconsistency model tests and node-splitting were used to assess the overall network inconsistency and local inconsistency. Bayesian models were built using the 'rjags' package and the 'gemtc' *r* packages to perform a net meta-analysis of the outcome indicators of the four interventions. Stata 15 software was also used to plot the probability ranking graph and the funnel graph reflecting publication bias.

Results

Characteristics of the included studies

The study screening process is shown in Figure 1. A total of 1430 relevant papers were retrieved from PubMed, Web of Science, and Cochrane databases after removing duplicates, and another 21 papers were obtained from other relevant references. After the titles and abstracts were reviewed, 59 papers were initially selected as meeting the study criteria. After careful reading of the studies, 25 papers were selected. The basic information and underlying data were extracted and are presented in Table 1. The 25 papers include 5 RCT studies and 20 cohort studies; all were two-arm studies. The studies were published from 2005 to 2023 and included 4548 patients.

Assessment of networks

A complete triangular relationship existed between RFA, MWA, and CA, which was the same as that for RFA, MWA, and

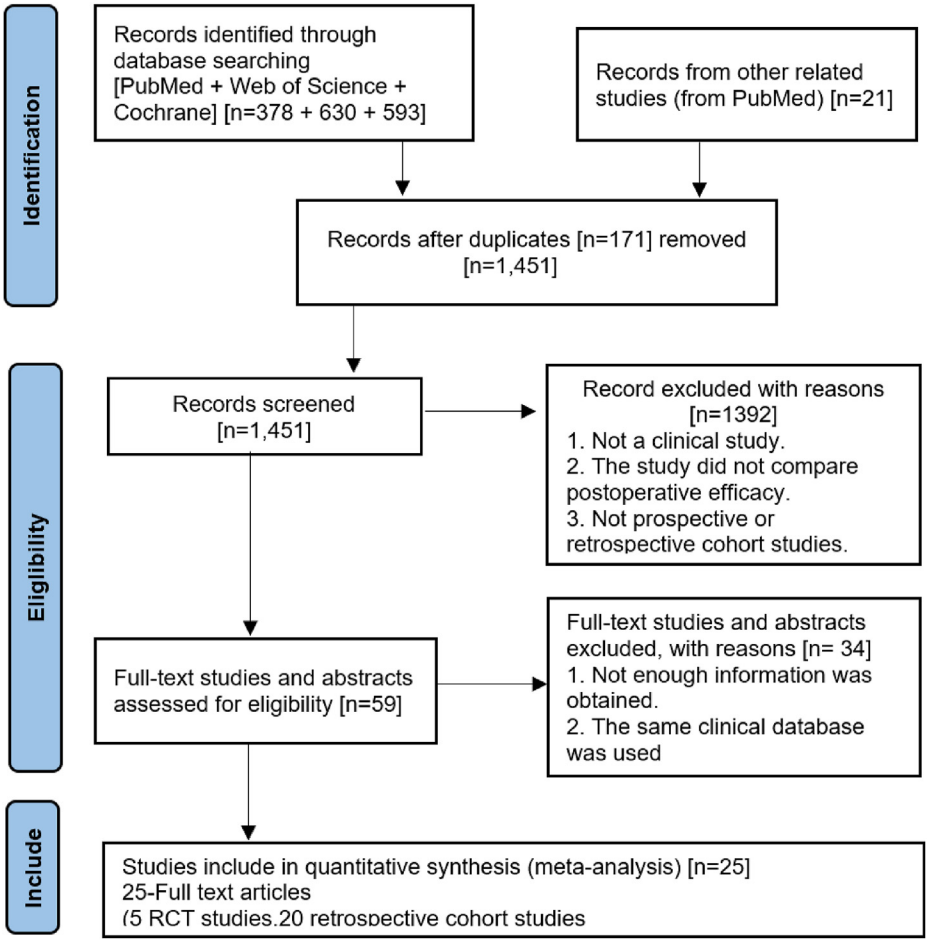

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart for selection of the studies.

Table 1 – Basic information of the included studies.

Author, year	Region	Participants, *n*	Patient age, years	OS rates (%)		DFS rates (%)	
				1 y	3 y	1 y	3 y
Ng, 2017[4]	Other regions	RFA: 109	57.0 (23.0–78.0)	95.4	82.3	70.6	46.6
		LR: 109	55.0 (31.0–82.0)	94.5	80.6	74.1	50.9
Lee, 2018[5]	Other regions	RFA: 34	56.1 ± 7.4	100	97.1	-	44.1
		LR: 29	55.6 ± 7.9	96.6	96.6	-	66.7
Chong, 2020[12]	Other regions	RFA: 46	64.5 (42.0–85.0)	93.5	72.7	58.7	22.7
		MWA: 47	63.0 (50.0–80.0)	97.9	67.1	51.1	24.1
Feng, 2012[13]	Chinese mainland	RFA: 84	51.0 (24.0–83.0)	96	74.8	90.6	61.1
		LR: 84	47.0 (18.0–76.0)	93.1	67.2	86.2	49.6
Wang, 2015[14]	Chinese mainland	RFA: 180	53.34 ± 8.91	97	66	84	50
		CA: 180	53.87 ± 9.59	97	67	89	54
Ohmoto, 2008[15]	Other regions	RFA: 34	67.0 (44.0–78.0)	100	70	63	26
		MWA: 49	64.0 (38.0 – 75.0)	89	49	52	15
Theodora, 2016[16]	Other regions	RFA: 55	62.0 (23.0–88.0)	83.6	49.1	-	-
		MWA: 99	61.0 (44.0–82.0)	78.8	24	-	-
Lu, 2005[17]	Chinese mainland	RFA: 53	54.5 ± 11.7	71.7	37.6	37.2	15.5
		MWA: 49	50.1 ± 13.7	81.6	50.5	45.9	26.9
Liu, 2018[18]	Chinese mainland	RFA: 436	56.0 (46.0–65.0)	96.4	80.7	60.4	22.8
		MWA: 126	54.0 (45.3–60.0)	99	94.6	78.9	46.9
Zhang, 2013[19]	Chinese mainland	RFA: 47/31	54.0 ± 10.5	93.6/87.1	66/61.3	68.1/74.2	34/54.8
		MWA: 36/41	54.0 ± 9.5	100/85.4	80.6/36.6	72.2/53.3	41.7/26.8
Thomas, 2015[20]	Other regions	RFA: 25	57.0 ± 4.2	100	72	96.9	90.6
		MWA: 28	60.0 ± 4.2	100	79	97.2	91.7
Ding, 2013[21]	Chinese mainland	RFA: 85	58.64 ± 8.52	98.7	82.7	80.3	39.5
		MWA: 113	59.06 ± 11.68	98	77.6	75	32.1
Xu, 2017[22]	Chinese mainland	RFA: 159	54.0 ± 11.0	98.7	86.8	89.9	67.3
		MWA: 301	54.2 ± 11.0	99.3	90.4	94.4	71.8
Casaccia, 2017[23]	Other regions	RFA: 22	60.82 ± 7.25	81.8	50	40.9	18.2
		LR: 24	63.58 ± 9.55	95.8	58.3	70.8	25
Chong, 2018[24]	Other regions	RFA: 59	59.3 ± 11.0	96.6	78.7	59.3	25.3
		LR: 59	57.7 ± 10.5	94.9	88.2	86.3	68
Lai, 2013[25]	Other regions	RFA: 31	63.1 ± 12.8	100	92	76	40
		LR: 80	60.8 ± 9.9	92	75	76	60
Roberto, 2009[26]	Other regions	RFA: 74	68.0 ± 7.0	88	66	-	-
		LR: 78	68.0 ± 8.0	93	85	-	-
Shi, 2014[27]	Chinese mainland	MWA: 40/56	56.6 ± 9.2	98/95	78/72	85/73	54/34
		LR: 37/54	54.5 ± 9.9	97/94	82/71	89/83	66/57
Sun, 2020[28]	Chinese mainland	MWA: 51/64	57.5 ± 9.6	97.4/90.9	76.9/65.5	82.1/68.4	51.1/41.1
		LR: 41/73	54.5 ± 10.4	100/93.5	83.3/74.2	88.6/83.6	72.7/58.8
Zheng, 2020[29]	Chinese mainland	MWA: 93	58.0 (49.0–66.0)	90.1	82.9	66.3	46.1
		LR: 300	57.0 (50.0–62.0)	95.5	86.1	71.8	44.3
Hu, 2019[30]	Chinese mainland	MWA: 64	55.2 ± 7.2	85.8	63.5	77.8	49
		CA: 56	54.9 ± 11.3	92	87.4	81.4	58.5
Zhang, 2022[31]	Chinese mainland	RFA: 67	57.78 ± 10.97	98.5	85	79.1	47
		LR: 67	57.51 ± 8.37	98.5	90	88.1	65.6
Cheng, 2022[32]	Other regions	RFA: 31	65.48 ± 11.73	96	79.2	60.6	37.9
		LR: 99	63.60 ± 9.86	97.9	96.2	91.2	66.7
Li, 2021[33]	Other regions	RFA: 58	61 (34–80)	91.4	77.2	91.2	62
		LR: 58	61 (35–82)	98.2	88.8	93	71.7

(continued)

Table 1 – (*continued*)

Author, year	Region	Participants, *n*	Patient age, years	OS rates (%)		DFS rates (%)	
				1 y	3 y	1 y	3 y
Feng, 2022[34]	Chinese mainland	MWA: 121	57.1 ± 9.7	98.3	84.7	81.8	54.4
		LR: 121	57.0 ± 8.4	96.5	81.8	85.4	67.8

Patient age is shown as mean (range) or ± standard deviation.

LR (Fig. 2), allowing for computational consistency and inconsistency analysis. OS and DFS outcomes for LR, RFA, MWA, and CA combined are presented in tables and forest plots (Table 2, Fig. 3). Surface under the cumulative ranking curve plots reflected the different treatment modalities with different outcome rankings (Fig. 4). The largest number of studies was studies evaluating RFA and MWA. Only one study addressed all outcomes between MWA and CA, and one study addressed all outcomes between RFA and CA; there was no direct study evidence between LR and CA (Table 1).

The 1-y and 3-y OS of the four treatment modalities were not significantly different. Regarding 1-y DFS, LR was significantly better than RFA (HR 0.54, 95% credible interval (CrI): 0.38–0.76) and MWA (HR 0.57, 95% CrI: 0.39–0.82), but similar to CA. LR also had a better DFS than RFA (HR 0.52, 95% CrI: 0.38–0.72) and MWA (HR 0.53, 95% CrI: 0.37–0.76) at 3 y after the procedure. There was no significant difference in the 3-y DFS between LR and CA.

Rank probability of treatment regimen

The ranked probability ranking of the effect of all four treatment modalities was reflected by the surface under the cumulative ranking curve graph (Fig. 4). Regarding 1-y survival, CA ranked first with the highest probability (0.621), followed by LR (0.316), then MWA and RFA; for 1-y DFS, LR ranked first (0.72), followed by CA (0.28), and RFA and MWA ranked last. For 3-y survival, CA ranked first with the highest probability (0.773), followed by LR (0.206), then RFA (0.04) and MWA (0.01)

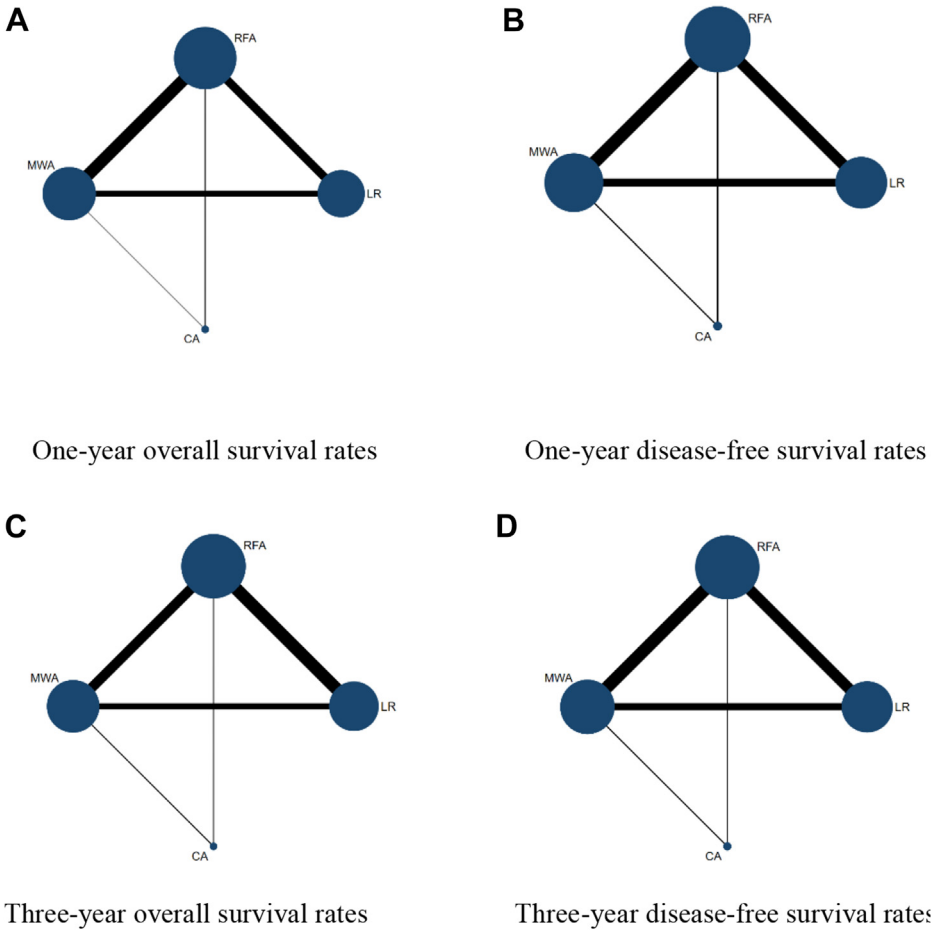

Fig. 2 – Net relationship diagram of LR, RFA, MWA, and CA in the study. (A). 1-y overall survival rates. (B). 1-y disease-free survival rates. (C). 3-y overall survival rates. (D). 3-y disease-free survival rates.

Table 2 – League table demonstrating the hazard ratio and 95% credible interval for OS rates at 1 y and 3 y and DFS rates at 1 y and 3 y for different treatments.

	Treatment	LR	RFA	MWA	CA
OS rates at 1 y	LR vs	NA	0.71 (0.45, 1.13)	0.81 (0.49, 1.35)	1.22 (0.41, 3.64)
	RFA vs	1.40 (0.88, 2.22)	NA	1.14 (0.74, 1.76)	1.71 (0.60, 4.87)
	MWA vs	1.23 (0.74, 2.04)	0.88 (0.57, 1.36)	NA	1.50 (0.55, 4.13)
	CA vs	0.82 (0.27, 2.44)	0.58 (0.21, 1.66)	0.67 (0.24, 1.83)	NA
DFS rates at 1 y	LR vs	NA	0.54 (0.38, 0.76)	0.57 (0.39, 0.82)	0.76 (0.31, 1.87)
	RFA vs	1.85 (1.31, 2.61)	NA	1.05 (0.76, 1.46)	1.41 (0.60, 3.33)
	MWA vs	1.76 (1.22, 2.54)	0.95 (0.69, 1.32)	NA	1.35 (0.57, 3.16)
	CA vs	1.31 (0.53, 3.21)	0.71 (0.30, 1.67)	0.74 (0.32, 1.74)	NA
OS rates at 3 y	LR vs	NA	0.79 (0.53, 1.17)	0.74 (0.48, 1.14)	1.52 (0.53, 4.34)
	RFA vs	1.27 (0.86, 1.89)	NA	0.95 (0.65, 1.38)	1.52 (0.53, 4.34)
	MWA vs	1.35 (0.88, 2.07)	1.06 (0.73, 1.54)	NA	2.04 (0.75, 5.58)
	CA vs	0.66 (0.23, 1.89)	0.52 (0.19, 1.41)	0.49 (0.18, 1.34)	NA
DFS rates at 3 y	LR vs	NA	0.52 (0.38, 0.72)	0.53 (0.37, 0.76)	0.59 (0.25, 1.40)
	RFA vs	1.92 (1.38, 2.66)	NA	1.02 (0.74, 1.42)	1.13 (0.49, 2.58)
	MWA vs	1.88 (1.31, 2.68)	0.98 (0.70, 1.36)	NA	1.11 (0.48, 2.53)
	CA vs	1.70 (0.71, 4.03)	0.89 (0.39, 2.02)	0.90 (0.40, 2.07)	NA

with little difference; for 3-y DFS, HR ranked first (0.882), followed by CA (0.118), with RFA and MWA ranking last.

Consistency and inconsistency analyses

To develop the final model with all resulting parameters, the adaptation iterations were kept at 20,000, thus removing the initial simulation results of the Markov Chain Monte Carlo analysis from the model. The number of simulation iterations was kept at 100,000. The sparsity factor was kept at 10, and the number of chains was kept at 4. For all four outcome parameters, the assessment of the adequacy of convergence of the Gelman Rubin diagnosis was below 1.05 (Fig. 5). The *P*-value of inconsistency in node-splitting was not significant for all the outcomes in all the comparisons (Table 3).

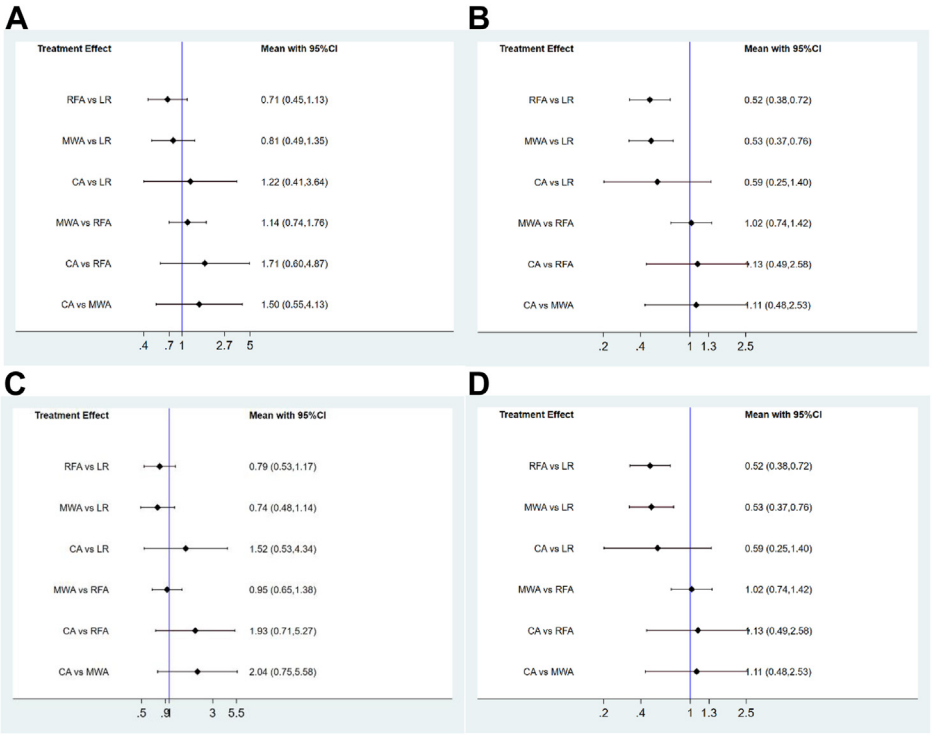

Fig. 3 – Forest plot of 1-y OS rates (A), 1-y DFS rates (B), 3-y OS rates (C), and 3-y DFS rates (D).

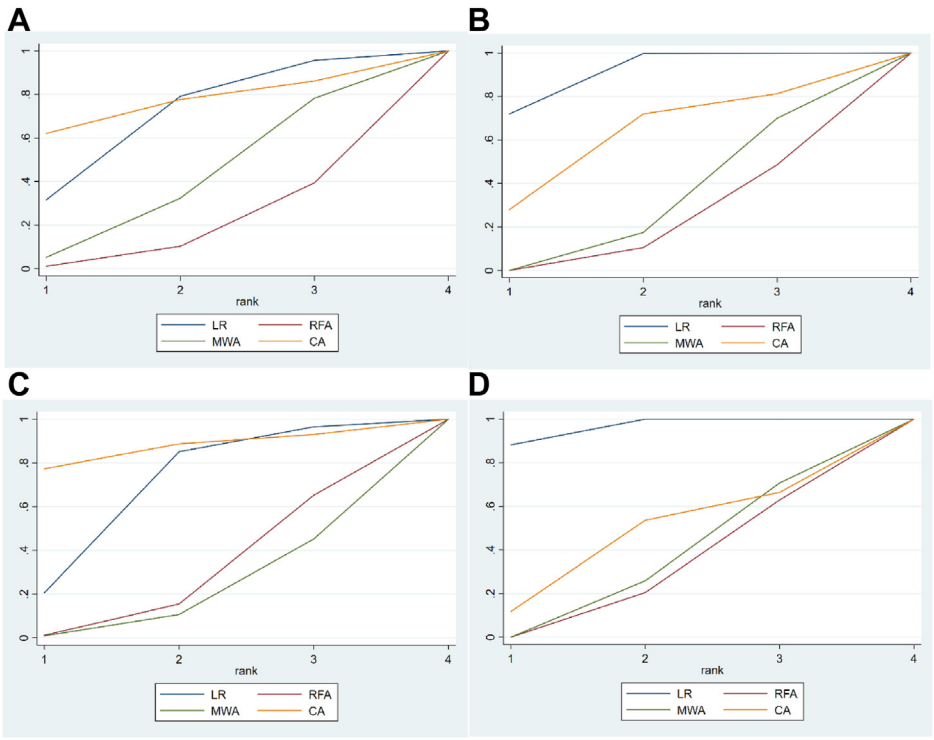

Fig. 4 – Rank probability of LR, RFA, MWA, and CA based on each outcome criteria evaluated in the study. 1-y OS rates (A), 1-y DFS rates (B), 3-y OS rates (C), and 3-y DFS rates (D).

Subgroup analysis

We divided the studies according to the location where the study was conducted: the Chinese mainland[13,14,17-19,21,22,27-31,34] and other regions.[4,5,12,15,16,20,23-26,32,33] The efficacy of CA was only analyzed in studies in the Chinese mainland, so the Chinese mainland subgroup included four different treatment modalities, while the subgroup of the other regions included only three treatment modalities (LR, RFA, and MWA). In the Chinese mainland group, patients with LR showed a better 1-y and 3-y DFS compared with patients with MWA, but the rates were similar to those of patients with RFA (Table 4). In the other regions group, LR had a better DFS than MWA and RFA (Table 5).

Table 3 – Consistency inspection and nodal analysis.

Statistical approach	Inconsistent model	Nodal difference method
	P-value	Minimum *P*-value
One-year OS rates	0.48	0.480
One-year DFS rates	0.36	0.537
Three-y OS rates	0.39	0.188
Three-y DFS rates	0.79	0.491

Risk assessment

For the five RCT studies, we used the ROB two tool to assess the risk of bias; the results are shown in Table 6. For the non-RCT studies, we used the Newcastle–Ottawa Scale scale for scoring; the final assessment scores were above 6 (Table 7), suggesting less bias. Analysis of the data using Stata revealed a symmetrical funnel plot distribution (Fig. 6), suggesting a small and acceptable publication bias.

Discussion

The current network meta-analysis compared the prognosis of three common ablative treatment modalities (RFA, MWA, and CA), with conventional LR for early-stage HCC. The results showed that LR had significant advantages over RFA and MWA for 1-y and 3-y DFS. There was no statistically significant difference in 1-y and 3-y OS among the four treatment modalities and no significant difference in OS or DFS for CA compared with other treatment modalities. Unlike the previous network meta-analysis, we examined LR, a traditional treatment modality and included the most recent studies for comparison.[35,36]

We did not find a significant difference in OS between RFA and LR, indicating that RFA, which avoids the postoperative trauma and medical costs associated with LR, showed an excellent early to mid-term prognosis in the treatment of HCC.

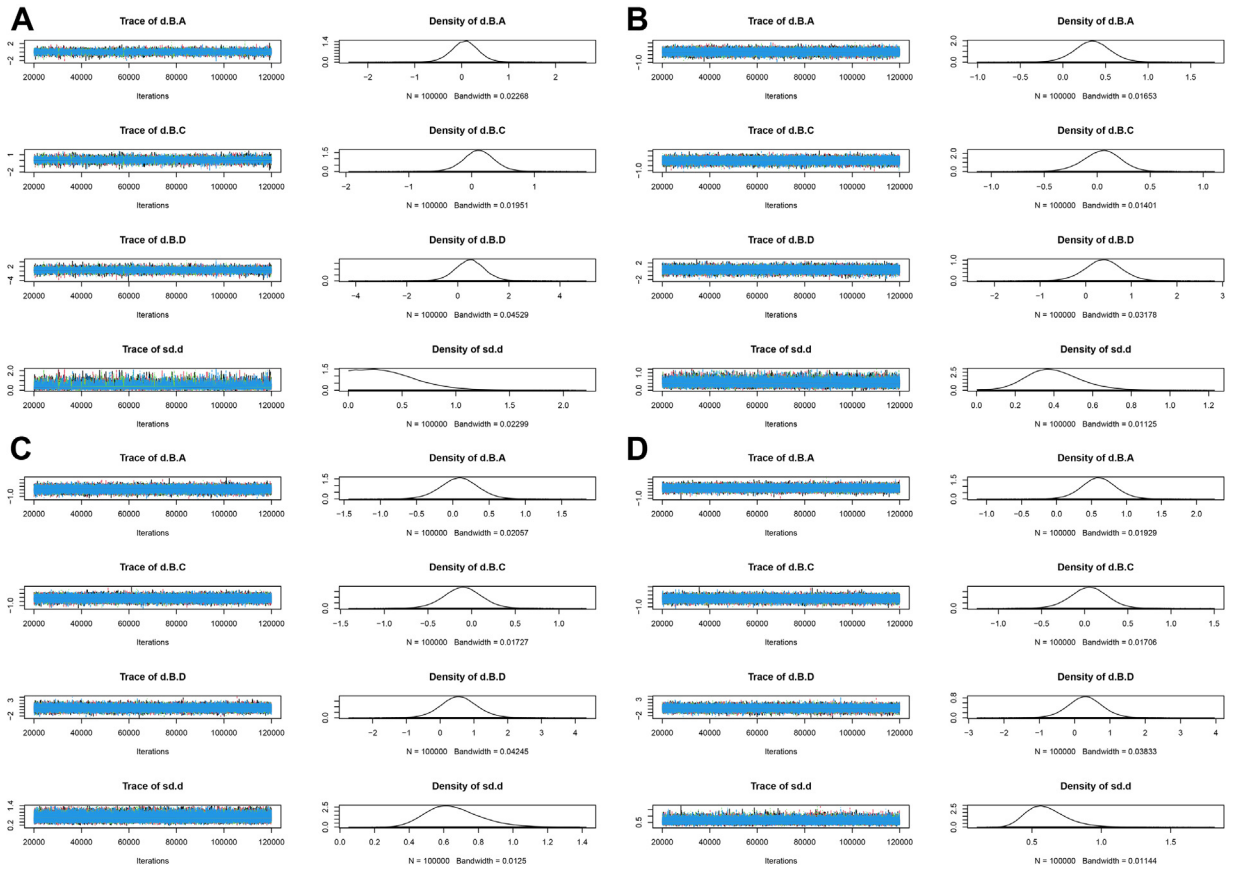

Fig. 5 – The model diagnostics of the developed model. 1-y OS rates (A), 1-y DFS rates (B), 3-y OS rates (C), and 3-y DFS rates (D).

Table 4 – League table of results from the Chinese mainland studies.

	Treatment	LR	RFA	MWA	CA
OS rates at 1 y	LR vs	NA	0.80 (0.42, 1.55)	0.95 (0.56, 1.64)	1.47 (0.54, 4.01)
	RFA vs	1.24 (0.65, 2.40)	NA	1.19 (0.74, 1.91)	1.83 (0.72, 4.65)
	MWA vs	1.05 (0.61, 1.80)	0.84 (0.52, 1.36)	NA	1.54 (0.65, 3.65)
	CA vs	0.68 (0.25, 1.86)	0.55 (0.22, 1.39)	0.65 (0.27, 1.54)	NA
DFS rates at 1 y	LR vs	NA	0.65 (0.41, 1.03)	0.67 (0.46, 0.98)	0.91 (0.39, 2.09)
	RFA vs	1.55 (0.97, 2.46)	NA	1.04 (0.73, 1.49)	1.41 (0.65, 3.04)
	MWA vs	1.49 (1.02, 2.17)	0.96 (0.67, 1.37)	NA	1.35 (0.63, 2.89)
	CA vs	1.10 (0.48, 2.54)	0.71 (0.33, 1.54)	0.74 (0.35, 1.59)	NA
OS rates at 3 y	LR vs	NA	0.84 (0.48, 1.47)	0.88 (0.56, 1.40)	1.69 (0.63, 4.55)
	RFA vs	1.19 (0.68, 2.08)	NA	1.05 (0.67, 1.65)	2.01 (0.82, 4.95)
	MWA vs	1.13 (0.72, 1.79)	0.95 (0.61, 1.49)	NA	1.92 (0.78, 4.73)
	CA vs	0.59 (0.22, 1.59)	0.50 (0.20, 1.22)	0.52 (0.21, 1.29)	NA
DFS rates at 3 y	LR vs	NA	0.63 (0.36, 1.09)	0.61 (0.39, 0.96)	0.69 (0.26, 1.84)
	RFA vs	1.59 (0.92, 2.75)	NA	0.97 (0.63, 1.51)	1.10 (0.45, 2.70)
	MWA vs	1.63 (1.04, 2.56)	1.03 (0.66, 1.60)	NA	1.13 (0.46, 2.77)
	CA vs	1.44 (0.54, 3.83)	0.91 (0.37, 2.22)	0.88 (0.36, 2.16)	NA

Table 5 – League table of results from studies of the other regions.

	Treatment	LR	RFA	MWA
OS rates at 1 y	LR vs	NA	0.67 (0.27, 1.63)	0.50 (0.10, 2.40)
	RFA vs	1.50 (0.61, 3.67)	NA	0.75 (0.20, 2.82)
	MWA vs	1.99 (0.42, 9.52)	1.33 (0.35, 4.95)	NA
DFS rates at 1 y	LR vs	NA	0.43 (0.25, 0.75)	0.32 (0.12, 0.86)
	RFA vs	2.33 (1.34, 4.06)	NA	0.74 (0.33, 1.70)
	MWA vs	3.14 (1.16, 8.49)	1.35 (0.59, 3.08)	NA
OS rates at 3 y	LR vs	NA	0.75 (0.41, 1.36)	0.47 (0.18, 1.19)
	RFA vs	1.33 (0.74, 2.41)	NA	0.62 (0.30, 1.29)
	MWA vs	2.15 (0.84, 5.51)	1.61 (0.77, 3.35)	NA
DFS rates at 3 y	LR vs	NA	0.44 (0.29, 0.65)	0.37 (0.17, 0.80)
	RFA vs	2.28 (1.54, 3.39)	NA	0.83 (0.43, 1.63)
	MWA vs	2.74 (1.26, 5.95)	1.20 (0.61, 2.34)	NA

The results of LR compared with MWA were similar to those of LF and RFA. There was no statistically significant difference in prognostic outcomes between MWA and RFA, and the two showed an almost identical OS and DFS in the latest RCT.[12] Because of the heat sink effect, RFA has limitations for paravalvular lesions, mainly because blood flow takes away the high energy of radio frequency.[37] Some studies have shown that MWA can better treat tumors located in the paravalvular area and cope with larger tumors.[38] Therefore, theoretically, MWA could be an alternative to RFA for early-stage HCC; however, the data in the current analysis did not indicate a significant difference between the two.

In terms of DFS, LR showed an advantage over RFA and MWA, which implies that there may be local tumor progression after ablation, which is mainly related to the tumor site, ablation radius, the presence of repeated punctures, and the presence of satellite lesions and microvascular invasion.[38] In addition to the heat sink effect, when tumors are adjacent to blood vessels, most operators may prefer a more conservative and safe scope of ablation, so the probability of recurrence increases. In contrast, when the tumor is located far from the intrahepatic vessels under the liver envelope, treatment with ablation is not entirely suitable. Some studies have shown that when ablating tumors are located under the pericardium, the high-energy vapor generated during ablation may spread tumor fragments to the needle tract or even the abdominal cavity, resulting in tumor recurrence after ablation.[39] When the tumor size is $> 2–3$ cm, the high-energy coverage area of RFA may be insufficient, and the postoperative recurrence rate is elevated,[40] which is also related to the operator's judgment on whether high-energy coverage is achieved. This network meta-analysis does not specify the exact tumor location and therefore, LR could be considered in those who can tolerate surgery or have high-risk locations.

CA is an effective technology because of its ability for ablation visualization and induces an immune response to suppress tumor cells.[37,41,42] Compared with the antigenic denaturation caused by thermal ablation, CA preserves the integrity of tumor antigens, promotes the infiltration of immune cells into the tumor microenvironment, and improves the body's ability to generate specific immune responses to tumors.[43] Recent animal studies showed that CA modulates the tumor microenvironment and that incomplete CA combined with systemic matrix metalloproteinase inhibitors promotes the infiltration of cytotoxic CD8+ T cells within the residual tumor.[43] While our study showed no significant difference between CA and other ablative treatments for patients with early-stage HCC, CA was not worse than LR in terms of

Table 6 – Assessment of the RCTs included in the meta-analysis.

SI. No.	RoB 2 parameters	Ng et al.[4]	Lee et al.[5]	Chong et al.[12]	Feng et al.[13]	Wang et al.[14]
1	Randomization process	LR	LR	LR	LR	LR
2	Concealment of allocation	LR	LR	LR	SC	LR
3	Assignment to intervention	LR	LR	LR	LR	LR
4	Adhering to intervention	LR	LR	LR	LR	LR
5	Missing of outcome data	LR	LR	LR	LR	LR
6	Measurements of outcome	LR	LR	LR	LR	LR
7	Selection of reported results	SC	SC	LR	LR	LR
8	Overall bias	SC	SC	LR	SC	LR

LR low risk, RR high risk, SC some concern.

Table 7 – Assessment of the non-RCTs included in the meta-analysis.

Study	Selection		Selection (non-exposed cohort)	Ascertainment (exposure)	No outcome events before study	Comparability	Exposure	Adequacy of follow-up	Completeness of follow-up	Scores
	Representativeness (expressed cohort)					Control for important	Assessment of outcome events			
Ohmoto et al.[15]	1		1	1	0	2	1	1	1	8
Theodora et al.[16]	1		1	1	0	1	1	1	1	7
Lu et al.[17]	1		1	1	0	1	1	1	1	7
Liu et al.[18]	1		1	1	0	1	1	1	1	7
Zhang et al.[19]	1		1	1	0	1	1	1	1	7
Thomas et al.[20]	1		1	1	0	2	1	1	1	8
Ding et al.[21]	1		1	1	0	2	1	1	1	8
Xu et al.[22]	1		1	1	0	2	1	1	1	8
Casaccia et al.[23]	1		1	1	0	2	1	1	1	8
Chong et al.[24]	1		1	1	0	2	1	1	1	8
Lai et al.[25]	1		1	1	0	2	1	1	1	8
Roberto et al.[26]	1		1	1	0	1	1	1	1	7
Shi et al.[27]	1		1	1	0	2	1	1	1	8
Sun et al.[28]	1		1	1	0	1	1	1	1	7
Zheng et al.[29]	1		1	1	0	2	1	1	1	8
Hu et al.[30]	1		1	1	0	1	1	1	1	7
Zhang et al.[31]	1		1	1	0	2	1	1	1	8
Cheng et al.[32]	1		1	1	0	2	1	1	1	8
Li et al.[33]	1		1	1	0	2	1	1	1	8
Feng et al.[34]	1		1	1	0	2	1	1	1	8

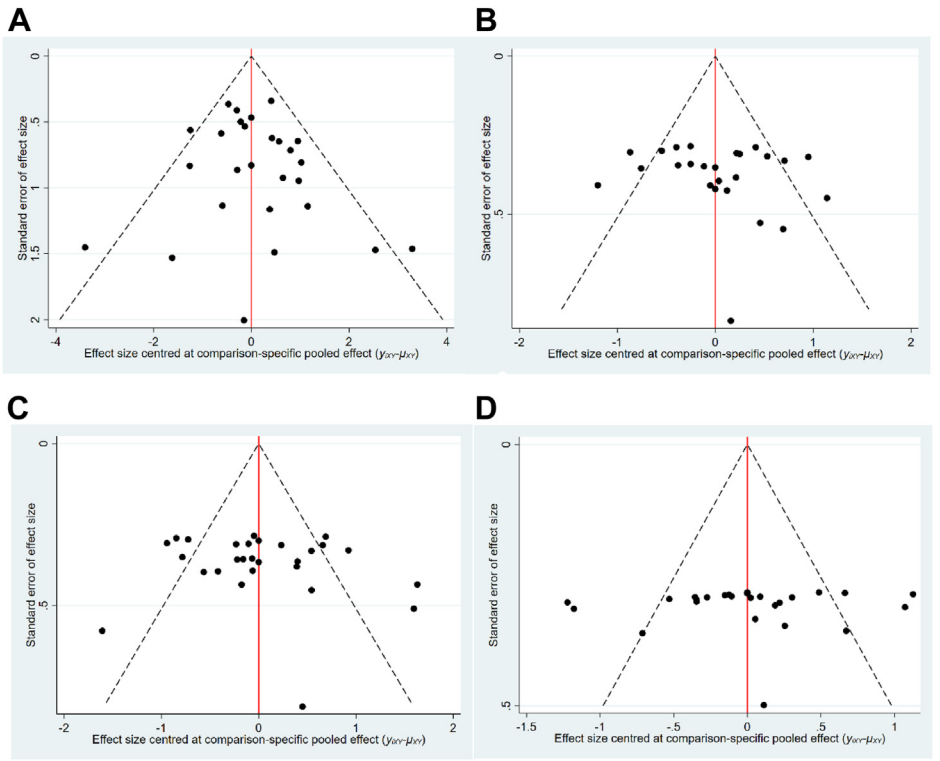

Fig. 6 – Funnel plots showing publication bias. (A). 1-y overall survival rates. (B). 1-y disease-free survival rates. (C).3-y overall survival rates. (D). 3-y disease-free survival rates.

OS and DFS, which suggests some priority for CA among several ablative treatments. The ranking of probability of therapeutic effect was first in both OS aspects of CA, which demonstrates its potential. A cohort study demonstrated the advantage of CA over RFA for lesions that are paravascular.[44] A multicenter RCT by Wang et al. demonstrated that CA is more conducive to local tumor control than RFA, although there was no significant difference between CA and RFA in terms of OS and DFS.[14] However, CA is not widely used in treating HCC, and few studies have been conducted worldwide, with most conducted in China. There are no clinical studies directly comparing CA with hepatectomy, so we indirectly compared the efficacy of the two approaches using a network meta-analysis. However, it is undisputed that CA has good research prospects. There is an urgent need for large cohort studies or RCTs on CA. The immune response induced by CA is also worth future attention, and the mechanism needs to be further explored. In the future, CA combined with immune checkpoint inhibitors may be the mainstream treatment for advanced HCC.

The results of subgroup analysis based on the country region showed that within the nonmainland China studies, LR showed a significant advantage in DFS over RFA and MWA, consistent with our overall findings. In contrast, within the mainland China group, the four treatment modalities showed no statistical differences in OS and DFS rates. As surgical resection for early-stage HCC is considered effective, this result may indirectly suggest that the recurrence rates of RFA and MWA differ between subgroups. We speculate that this correlation may stem from the distinct epidemiological profiles of HCC prevalent in mainland China and the operation of ablation procedures.

We conducted a comparative analysis of the descriptions of ablation procedures by examining studies on RFA and MWA from various regions.[13,16,31,45,46] The equipment used in most studies was sourced from different manufacturers, leading to variations in ablation power and duration as reported. Notably, the extent and principles of ablation procedures showed some divergence between mainland China and other regions. In mainland China, the ablation boundary is typically extended to 1 cm beyond the tumor edge, in contrast to the 0.5 cm margin commonly practiced in other regions of China. When the ablation margin is greater than 0.5 cm, the residual tumor is often invisible on imaging, that is, “imaging complete ablation” but not “pathological complete ablation”.[31] When addressing slightly larger tumors exceeding 4 cm, mainland China favors augmenting the ablation power to encompass the tumor, thus circumventing the need for repeated punctures and emphasizing the ablation of the needle tract. Conversely, in other regions of China, a consistent power setting is used across multiple punctures to cover the tumor, which may introduce the risk of needle tract metastasis. Some studies in these regions did not explicitly address needle tract ablation in their operative descriptions, potentially contributing to the observed discrepancies between the mainland China subgroup and the subgroup of other regions.

Epidemiologically, China bears the highest burden of HCC, with 65% of cases attributed to hepatitis B virus infection,

followed by hepatitis C virus infection and alcoholic liver disease.[47] In contrast, the main causes of HCC in Western countries are hepatitis C virus, alcoholic liver disease, and nonalcoholic fatty liver disease.[47] The difference in disease spectrum between Chinese and Western countries may have contributed to the differences in the subgroup analyses.

In clinical practice, tumor size is the main influencing factor for surgical or ablative treatment choice. Most studies investigated the correlation between tumor size and prognosis. In all the included studies, the subjects were very early or had early-stage HCC under BCLC classification, defined as a single node ≤5 cm or a maximum of three nodes ≤3 cm. In the study data, only data on the average size of tumors were available, which did not reflect the relationship between tumor size and the number of tumors, so no subgroup analysis was performed. Further investigation is warranted on the choice of treatment modalities for single or multiple HCC to fill this gap.

Conclusion

We systematically compared the prognostic indicators of four modalities for early-stage HCC and found that LR had a significant advantage over RFA and MWA for DFS, particularly in nonmainland China regions, but not in mainland China. RFA and MWA showed a higher local recurrence risk compared with surgical treatment of early-stage HCC. CA showed comparable efficacy to LR, suggesting that CA might be the future trend in percutaneous ablation therapy for early-stage HCC. These findings may contribute to the clinical management of early-stage HCC.

Supplementary Materials

Supplementary data related to this article can be found at doi: 10.1016/j.jss.2024.09.046.

Disclosure

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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CRediT authorship contribution statement

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