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Contents

Monthly Volume 15 Number 2 February 27, 2023

EDITORIAL

121 Hot topics in pancreatic cancer management

Caputo D

REVIEW

- 127 Minimum platelet count threshold before invasive procedures in cirrhosis: Evolution of the guidelines Biolato M, Vitale F, Galasso T, Gasbarrini A, Grieco A
- 142 Comprehensive multimodal management of borderline resectable pancreatic cancer: Current status and progress

Wu HY, Li JW, Li JZ, Zhai QL, Ye JY, Zheng SY, Fang K

MINIREVIEWS

- 163 Impact of endoscopic ultrasound-guided radiofrequency ablation in managing pancreatic malignancy Lesmana CRA
- Current management of concomitant cholelithiasis and common bile duct stones 169

Pavlidis ET, Pavlidis TE

177 Surveillance strategies following curative resection and non-operative approach of rectal cancer: How and how long? Review of current recommendations

Lauretta A, Montori G, Guerrini GP

ORIGINAL ARTICLE

Retrospective Study

193 Causes of epigastric pain and vomiting after laparoscopic-assisted radical right hemicolectomy - superior mesenteric artery syndrome

Xie J, Bai J, Zheng T, Shu J, Liu ML

201 Analysis of the impact of ERAS-based respiratory function training on older patients' ability to prevent pulmonary complications after abdominal surgery

Gu YX, Wang XY, Xu MX, Qian JJ, Wang Y

Prognostic value of preoperative immune-nutritional scoring systems in remnant gastric cancer patients 211 undergoing surgery

Zhang Y, Wang LJ, Li QY, Yuan Z, Zhang DC, Xu H, Yang L, Gu XH, Xu ZK

222 Efficacy and safety of preoperative immunotherapy in patients with mismatch repair-deficient or microsatellite instability-high gastrointestinal malignancies

Li YJ, Liu XZ, Yao YF, Chen N, Li ZW, Zhang XY, Lin XF, Wu AW



Contents

World Journal of Gastrointestinal Surgery

Monthly Volume 15 Number 2 February 27, 2023

Observational Study

234 Hepatobiliary manifestations following two-stages elective laparoscopic restorative proctocolectomy for patients with ulcerative colitis: A prospective observational study

Habeeb TAAM, Hussain A, Podda M, Cianci P, Ramshaw B, Safwat K, Amr WM, Wasefy T, Fiad AA, Mansour MI, Moursi AM, Osman G, Qasem A, Fawzy M, Alsaad MIA, Kalmoush AE, Nassar MS, Mustafa FM, Badawy MHM, Hamdy A, Elbelkasi H, Mousa B, Metwalli AEM, Mawla WA, Elaidy MM, Baghdadi MA, Raafat A

SYSTEMATIC REVIEWS

249 Hypophosphatemia as a prognostic tool for post-hepatectomy liver failure: A systematic review

Riauka R, Ignatavicius P, Barauskas G

META-ANALYSIS

258 Network meta-analysis of the prognosis of curative treatment strategies for recurrent hepatocellular carcinoma after hepatectomy

Chen JL, Chen YS, Ker CG

273 Does size matter for resection of giant versus non-giant hepatocellular carcinoma? A meta-analysis Lee AJ, Wu AG, Yew KC, Shelat VG

CASE REPORT

- Primary malignant melanoma of the esophagus combined with squamous cell carcinoma: A case report 287 Zhu ML, Wang LY, Bai XQ, Wu C, Liu XY
- 294 Mesh erosion into the colon following repair of parastomal hernia: A case report Zhang Y, Lin H, Liu JM, Wang X, Cui YF, Lu ZY

LETTER TO THE EDITOR

303 Fecal microbiota transplantation as potential first-line treatment for patients with Clostridioides difficile infection and prior appendectomy

Zhao JW, Chang B, Sang LX



Contents

Monthly Volume 15 Number 2 February 27, 2023

ABOUT COVER

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AIMS AND SCOPE

The primary aim of World Journal of Gastrointestinal Surgery (WJGS, World J Gastrointest Surg) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

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META-ANALYSIS

Network meta-analysis of the prognosis of curative treatment strategies for recurrent hepatocellular carcinoma after hepatectomy

Jen-Lung Chen, Yaw-Sen Chen, Chen-Guo Ker

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Abstract

BACKGROUND

Recurrent hepatocellular carcinoma (rHCC) is a common outcome after curative treatment. Retreatment for rHCC is recommended, but no guidelines exist.

AIM

To compare curative treatments such as repeated hepatectomy (RH), radiofrequency ablation (RFA), transarterial chemoembolization (TACE) and liver transplantation (LT) for patients with rHCC after primary hepatectomy by conducting a network meta-analysis (NMA).

METHODS

From 2011 to 2021, 30 articles involving patients with rHCC after primary liver resection were retrieved for this NMA. The Q test was used to assess heterogeneity among studies, and Egger's test was used to assess publication bias. The efficacy of rHCC treatment was assessed using disease-free survival (DFS) and overall survival (OS).

RESULTS

From 30 articles, a total of 17, 11, 8, and 12 arms of RH, RFA, TACE, and LT subgroups were collected for analysis. Forest plot analysis revealed that the LT subgroup had a better cumulative DFS and 1-year OS than the RH subgroup, with an odds ratio (OR) of 0.96 (95%CI: 0.31-2.96). However, the RH subgroup had a better 3-year and 5-year OS compared to the LT, RFA, and TACE subgroups. Hierarchic step diagram of different subgroups measured by the Wald test yielded the same results as the forest plot analysis. LT had a better 1-year OS (OR: 1.04, 95%CI: 0.34-03.20), and LT was inferior to RH in 3-year OS (OR: 10.61, 95%CI: 0.21-1.73) and 5-year OS (OR: 0.95, 95%CI: 0.39-2.34). According to the predictive P score evaluation, the LT subgroup had a better DFS, and RH had the



best OS. However, meta-regression analysis revealed that LT had a better DFS (P < 0.001) as well as 3-year OS (P = 0.881) and 5-year OS (P = 0.188). The differences in superiority between DFS and OS were due to the different testing methods used.

CONCLUSION

According to this NMA, RH and LT had better DFS and OS for rHCC than RFA and TACE. However, treatment strategies should be determined by the recurrent tumor characteristics, the patient's general health status, and the care program at each institution.

Key Words: Hepatocellular carcinoma; Recurrence; Network meta-analysis; Curative treatment; Outcome; Survival rate

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Core Tip: Network meta-analysis was used to compare treatments for recurrent hepatocellular carcinoma including repeated hepatectomy, radiofrequency ablation, transarterial chemoembolization, and liver transplantation. Thirty articles published from 2012-2021 were included in the analysis. Disease-free survival and overall survival were compared using forest plot analysis and hierarchic step diagram of subgroups by the Wald test, forest plot analysis, and predictive *P* score for subgroup analysis. Repeated hepatectomy or liver transplantation had better disease-free survival and overall survival compared to the others based on the testing methods from this network meta-analysis.

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INTRODUCTION

In Taiwan, hepatocellular carcinoma (HCC) was one of the most common causes of cancer-related deaths in 2019, ranking second in men and fourth in women[1]. Despite improvements in hepatitis control and care programs in Taiwan through antiviral therapy and vaccination projects, HCC remains a critical public health issue with a poor prognosis. Recurrent HCC (rHCC) after primary treatment is common in most patients, often resulting in a life-threatening situation and a major global health problem. According to Eastern and Western studies, the recurrence rates after primary hepatectomy are 70% or higher within 5 years[2-6]. Retreatment methods are crucial for improved survival, but the option of a retreatment method should be established where possible[7].

Currently, a precise treatment strategy for rHCC, including surgical or non-surgical methods, is controversial[8-10]. However, once an rHCC lesion is diagnosed during an imaging study, an effective treatment method should be implemented without delay. The therapeutic options for primary HCC are clearly dependent on the specified staging and international guidelines. Curative techniques such as liver transplantation (LT), hepatectomy, and radiofrequency ablation (RFA), among others, have been established[11-13]. Consequently, rHCC management necessitates specific guidance based on risk factors such as recurrence time, tumor nature, and the patient profile[13]. Therefore, a better treatment option for rHCC would be advantageous, but a guideline for clinical decision-making is still lacking.

In evidence-based medicine, network meta-analysis (NMA) of clinical studies is used to reach a conclusion based on multiple treatment comparisons[14]. It quickly garners insight for clinical decisionmaking by synthesizing both direct evidence from head-to-head trials and indirect evidence from indirect comparisons with treatment comparators[15-17]. The majority of studies are traditional twoarm meta-analyses, but NMA integrates multiple arms, including surgical and non-surgical arms, and provides a useful ranking of intervention methods for patients with rHCC[18]. Many institutions have adopted the consensus guidelines for primary HCC[11,12,19,20]. However, these guidelines are not useful for rHCC.

Treatment options for rHCC include repeated hepatectomy (RH), RFA, transarterial chemoembolization (TACE), LT, radiation therapy, and systemic target or immunotherapy[21-24]. When compared with other treatments, LT resulted in better overall survival (OS) in rHCC, whereas TACE was significantly worse than LT, RH, and RFA[8]. Accordingly, treatment strategies should be chosen based on the tumor characteristics and the patient profile at the time of recurrence.

In the recent decade, many studies comparing different treatment options for rHCC have been published. Four curative retreatment methods, including RH, RFA, TACE, and LT, are now routinely adopted in current practice and are coded globally[8,9,25-27]. Therefore, we aimed to conduct an NMA to compare four curative retreatment methods for patients with rHCC after primary hepatectomy.

MATERIALS AND METHODS

Search strategy and data extraction

A systematic search for rHCC treatment on PubMed, EMBASE, and the Cochrane Library Databases from 2012 to 2021 was conducted, and all relevant clinical cohorts or observational studies were identified. The keywords of article searching were HCC, recurrent hepatocellular carcinoma, liver cancer, recurrence, liver resection, hepatectomy, repeated hepatectomy, repeated liver resection, radio-frequency ablation, RFA, trans-arterial chemo-embolization, TACE, chemotherapy, chemoembolization, or liver transplantation. In this NMA, articles included should meet the following criteria: (1) Patients had an intrahepatic rHCC after initial liver resection; (2) Randomized controlled or observational clinical studies; (3) Must compare one of the four curative rHCC treatments, including RH, RFA, TACE, and LT; and (4) Have prognosis or outcome results. The exclusion criteria were as follows: (1) Conference abstracts, commentaries, case reports, reviews, or meta-analyses; and (2) Insufficient main outcome data for data extraction. If there were more than two studies from the same institution, the data were extracted from the most recent one. After reviewing the retrieved full articles, a final decision on eligibility for analysis was made.

The topics of each article were appropriately categorized in order to select the articles concerned with the retreatment methods of RH, RFA, TACE, or LT. For each study arm's outcome, the title, first author, publication year, intervention methods, outcomes, and associated risk factors, if available, were extracted. The study's endpoints were the disease-free survival (DFS) and OS rates for each subgroup. In addition, data for DFS were collected from 49 arms pooled for comparison in all studies, including recurrence-free survival in one arm of RH and RFA and two arms of LT, progression-free survival in one arm of TACE, and tumor-free survival in one arm of LT.

In addition, we conducted a relevant search by Reference Citation Analysis (https://www.referencecitationanalysis.com/) to supplement the latest cutting-edge research results.

Quality assessment

For quality assessment in the meta-analysis, two statistical models based on heterogeneity could be used: the fixed effects and random effects models. In the fixed effects model, all studies in the meta-analysis shared the same true effect size, whereas in the random effects model the true effect size varies from study to study. The heterogeneity among trials was assessed using the Q test with l^2 values, which represents the proportion of total variation in studies based on estimated heterogeneity[28]. An l^2 statistic of more than 50% or a *P* value of less than 0.05 indicated significant heterogeneity among trials, and the random effects model was used. The overall heterogeneity and publication bias of the effects model were used to assess the size deviation of the inconsistency in the variance parameter. After comparing each subgroup, ranking diagrams of presumed therapeutic effects were created based on the probability of superiority.

Statistical analysis

In this NMA, the data were analyzed using R software (version 3.0.2; R Foundation, Vienna, Austria) and comprehensive meta-analysis (Biostat Inc., 4 North Dean Street, Englewood, NJ, United States). The Q test is the sum of a heterogeneity measurement, which represents the variability of treatment effect between direct and indirect comparisons in a meta-analysis based on an *P* statistic of more than 50% or *P* value[28]. A frequent analog to the surface under the cumulative ranking curve could be replaced by a P score, which measured whether a treatment was better than the comparative treatments[14,16]. Another predictive P score was 100% when a treatment was certain to be the best and 0% when it was certain to be the worst[16,29]. The forest plot displayed a summary of the overall estimation and was compared by treatment method subgroup. A hierarchic step diagram of the cumulative comparative efficacy of treatment methods based on effect size was displayed with odds ratios (OR) and 95%CI, which were used to measure superiority in decision-making with the Wald test[30]. For each arm, publication bias was assessed using Egger's test and illustrated with a funnel plot analysis[31,32]. The statistically significant level was set at 0.05 for all treatment comparisons.

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Figure 1 Network graph of study number. Numbers appeared on the line of paired studies, and numbers with parenthesis at the angles of connected line were the cumulative number of subgroup of treatment methods in all studies. A: One-year and three-year overall survival (OS); B: Five-year OS. LT: Liver transplantation; RFA: Radiofrequency ablation; RH: Repeat hepatectomy; TACE: Transarterial chemoembolization.



Figure 2 Pooled mean survival rates of disease-free and overall survival of the patients treated by repeated hepatectomy, radiofrequency ablation, transarterial chemoembolization, or liver transplantation in recurrent hepatocellular carcinoma from all studies. A and B: The results of transarterial chemoembolization (TACE) disclosed the inferiority to other treatment options in disease-free survival (DFS) (A) or overall survival (B). The data of DFS were recorded and pooled together from recurrent-free survival in one arm of repeated hepatectomy and radiofrequency ablation and two arms of liver transplantation (LT), progression-free survival in one arm of TACE, and tumor-free rate in one arm of LT. DFS: Disease-free survival; LT: Liver transplantation; OS: Overall survival; RH: Repeated hepatectomy; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization.

RESULTS

Profiles of eligible articles of treatment methods in all studies

After the initial search, a total of 2671 published articles relating to rHCC treatment from 2012 to 2021 were retrieved. After duplicate removal and initial screening, 157 relevant articles were selected based on the selection criteria. Finally, 30 articles involving patients with intrahepatic rHCC after primary liver resection were included. Data were extracted from these studies and pooled for analysis. There were 4, 10, and 16 studies, with three, two, and one arm, respectively. These 30 articles were assembled and divided into 17, 11, 8, and 12 subgroups with the interventions RH, RFA, TACE, and LT, respectively, as shown in Figure 1. The basic characteristics of all studies are listed in Supplementary Table 1[3,6,9,21-22, 24,26-27,33-54]. There were 14, 4, 4, 5, 2, and 1 articles from China, Taiwan, Korea, Japan, France, and Germany, respectively. The patients' characteristics and the cumulative mean value of the subgroups are summarized in Table 1. The total numbers of patients were 1405, 1013, 1123, and 1484 in the RH, RFA, TACE, and LT subgroups, respectively. Males were dominant in all groups, with prevalence ranging from 79.9% to 89.1%. The mean recurrence times after primary liver resection were 26.0 \pm 8.3, 18.1 \pm 6.5, 14.7 \pm 6.6, and 19.4 \pm 10.4 mo in the RH, RFA, TACE, and LT subgroups, respectively. The other relative factors of patients in each subgroup are listed in Table 1.

Table 1 Cumulative mean value of 49 arms of studies and patient profiles from 30 articles of curative treatment of recurrent hepatocellular carcinoma after primary liver resection

Arm in study, <i>n</i>	Patient, <i>n</i>	Male %	Age in yr	HBV (+) %	HCV (+) %	Cirrhosis %	MVI (+) %	rChild A %	Time to recurrence in mo	rTumor size in mm	rTumor (<i>n</i> = 1) %
RH = 17	1405	79.9	56.5 ± 6.8	68.6	33.3	55.8	29.8	78.7	26.0 ± 8.3	25.3 ± 6.8	76.2
RFA = 11	1013	83.2	56.4 ± 5.5	78.5	12.4	59.0	26.6	94.9	18.1 ± 6.5	21.5 ± 4.0	78.6
TACE = 8	1123	86.5	54.6 ± 8.7	73.4	21.7	49.3	30.7	91.7	14.7 ± 6.6	32.2 ± 16.1	62.3
LT = 12	1484	89.1	53.6 ± 5.3	81.7	9.3	68.4	31.6	76.9	19.4 ± 10.4	27.1 ± 8.0	62.2

¹Patients *n*, cumulated number of patients in subgroup from all studies.

Details of each study are listed in Supplementary Table 1. RH: Repeated hepatectomy; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization; LT: Liver transplantation; r: Recurrent; HBV: Hepatitis B virus; HCV: Hepatitis C virus; MVI: Microvascular invasion.

DFS and OS of rHCC after retreatment

The cumulative means of DFS and OS rates were assessed using the Wilcoxon rank sum test, as illustrated in Figure 2. The pooled 1-year, 3-year, and 5-year DFS in patients with rHCC were found to be the best in the LT subgroup, with 76.3 \pm 8.8%, 57.1 \pm 13.3%, and 51.2 \pm 16.0%, respectively (Figure 2A). The pooled OS rates were found to be better in the RFA subgroup, with a 1-year OS of 91.1 \pm 7.4%, and in the RH subgroup, with a 3-year OS of 71.9 \pm 13.7% and a 5-year OS of 53.2 \pm 17.6% (Figure 2B), with a significant difference in the 5-year OS between the RH and LT subgroups (P = 0.019). However, TACE was found to be inferior in both DFS and OS rates.

Comparison favorability of pooled outcome displayed with forest plot

The forest plot analysis revealed that LT had a higher DFS than other treatment methods (Figure 3A-C). In addition, the RH subgroup had a better 1-year OS than the LT (OR: 0.96, 95% CI: 0.31-2.96), RFA (OR: 1.19, 95% CI: 2.71-2.00), and TACE (OR: 2.56, 95% CI: 1.26-5.20) subgroups (Figure 3D). RH subgroup had a more favorable 3-year and 5-year OS than the LT (OR: 1.64, 95% CI: 0.56-4.66 and OR: 1.05, 95% CI: 0.43-2.56), RFA, and TACE subgroups (Figure 3E and F).

Hierarchic step diagram for comparison with the Wald test

The Wald test was used to compare the OS between the four interventional arms: RH, RFA, TACE, and LT. The results of cumulative comparisons between each treatment were displayed using a hierarchical step diagram in Figure 4. Compared to other treatments, RH had an expressed ranking probability with OR and 95%CI. LT had the better in 1-year OS (OR: 1.04, 95%CI: 0.34-03.20), and RH had a higher ranking probability based on 3-year OS (OR: 0.61, 95% CI: 0.21-1.73) or 5-year OS (OR: 0.95, 95% CI: 0.39-2.34), while TACE had the lowest probability of the better OS.

Predictive P score

Based on the predictive P score evaluation, the LT group had the best 1-year, 3-year, and 5-year DFS (Table 2). TACE data were insufficient for DFS analysis. In terms of OS, RH had the highest P scores of 0.739, 0.932, and 0.8331 for 1-year, 3-year, and 5-year OS, respectively. TACE had the lowest P scores for OS.

Meta-regression analysis

Meta-regression analysis provided a sensitivity analysis for model specification [29]. Compared to other treatments, LT had better results than RH in 1-year, 3-year, and 5-year DFS with β = 0.93 (*P* = 0.001), β = 1.181 (P < 0.001), and $\beta = 1.258$ (P < 0.001) respectively. LT compared with RH was inferior for 1-year OS with β = -0.036 (*P* = 0.913) but superior for 3-year OS with β = 0.04 (*P* = 0.881) and 5-year OS with β = 0.392 (P = 0.188), respectively. From this study, LT had better results for DFS (P < 0.001) and 3-year and 5-year overall survival (P > 0.05). RH had a better result for 1-year OS (P > 0.05) than other treatment options (Table 3).

Heterogeneity and publication bias

The heterogeneity among studies was estimated based on l^2 values using the Q test. The l^2 values for 1year, 3-year, and 5-year DFS were 86.65%, 94.86%, and 95.81%, respectively, and for 1-year, 3-year, and 5-year OS, they were 79.07%, 89.72%, and 93.43%, respectively (Table 4). Therefore, the random effects



Table 2 Predictive P score for each treatment method for recurrent hepatocellular carcinoma								
P score/subgroup	1-yr DFS	3-yr DFS	5-yr DFS	1-yr OS	3-yr OS	5-yr OS		
RH	0.6470	0.4999	0.5100	0.7390 ¹	0.9320 ¹	0.8331 ¹		
LT	0.9986 ¹	0.9998 ¹	0.9820^{1}	0.6980	0.5470	0.7505		
RFA	0.3531	0.0003	0.0080	0.5340	0.5090	0.4159		
TACE	0.0012	NA	NA	0.0300	0.0130	0.0500		

¹Best treatment option.

DFS: Disease-free survival; NA: Not available; LT: Liver transplantation; OS: Overall survival; RFA: Radio-frequency ablation; RH: Repeated hepatectomy; TACE: Transarterial chemoembolization.



Figure 3 Forest plot analysis demonstrated the odds ratio (95%CI) of 1-year, 3-year, and 5-year disease-free survival in the liver transplantation subgroup compared with repeated hepatectomy, radiofrequency ablation, and transarterial chemoembolization and 1-year, 3-year, and 5-year overall survivalin the repeated hepatectomy subgroup compared with liver transplantation, radiofrequency ablation, and transarterial chemoembolization with the random effects model. A: One-year disease-free survival (DFS); B: Three-year DFS; C: Five-year OS; F: Five-year OS; F: Five-year OS. RFA: Radiofrequency ablation; RH: Repeated hepatectomy; LT: Liver transplantation; OR: Odds ratio; TACE: Transarterial chemoembolization.

models were used for analysis based on a *P* value of less than 0.05 obtained from the *I*² value among retreatment methods. The Z value indicated the pooled effect size of all subgroups, and further details are listed in Supplementary Table 2. A detailed analysis of heterogeneity using a forest plot for DFS and OS is available in Supplementary Figures 1-6. The publication bias was assessed by Egger's regression test and resulted in 1-year, 3-year, and 5-year OS *P* values of 0.8459, 0.0562, and 0.3574, respectively. Funnel plot graphs were used for displaying publication bias among all studies. The number of potential missing studies for the association between analysis of treatment methods of 1-year, 3-year, and 5-year OS were depicted in the Figure 5A-C.

DFS and OS summary of subgroups among all testing methods

The best-pooled outcomes of the four retreatment methods analyzed by multiple testing methods are summarized in Table 5. In general, the LT subgroup had superior DFS (P < 0.001), whereas the RH subgroup had superior OS without a significant difference compared to other treatments.

Chen JL et al. Network meta-analysis of recurrent HCC

Table 3 Meta-regression analysis for comparison of subgroups							
	_	SE	95%CI		_ .		
Subgroup	β		Lower limit	Upper limit	Zvalue	P value	
1-yr DFS							
Intercept	0.658	0.177	0.311	1.005	3.720	< 0.001	
LT vs RH	0.930 ¹	0.283	0.376	1.485	3.290	0.001	
RFA vs RH	-0.315	0.272	-0.848	0.217	-1.160	0.246	
TACE vs RH	-1.823	0.447	-2.699	-0.946	-4.080	< 0.001	
3-yr DFS							
Intercept	-0.353	0.212	-0.769	0.063	-1.660	0.096	
RFA vs RH	-0.609	0.335	-1.266	0.049	-1.810	0.070	
TACE vs RH	-2.235	0.751	-3.707	-0.763	-2.980	0.003	
LT vs RH	1.181 ¹	0.322	0.550	1.812	3.670	< 0.001	
5-yr DFS							
Intercept	-0.748	0.216	-1.171	-0.325	-3.460	0.001	
RFA vs RH	-0.834	0.366	-1.552	-0.116	-2.280	0.023	
TACE vs RH	-0.762	0.577	-1.893	0.369	-1.320	0.186	
LT vs RH	1.258 ¹	0.324	0.623	1.893	3.880	< 0.001	
1-yr OS							
Intercept	2.185	0.208	1.777	2.594	10.480	< 0.001	
LT vs RH	-0.036 ¹	0.332	-0.687	0.614	-0.110	0.913	
RFA vs RH	-0.041	0.325	-0.677	0.596	-0.130	0.900	
TACE vs RH	-0.614	0.332	-1.264	0.036	-1.850	0.064	
3-yr OS							
Intercept	0.996	0.162	0.679	1.313	6.150	< 0.001	
RFA vs RH	-0.394	0.251	-0.885	0.098	-1.570	0.116	
TACE vs RH	-1.114	0.287	-1.676	-0.551	-3.880	< 0.001	
LT vs RH	0.040 ¹	0.265	-0.479	0.558	0.150	0.881	
5-yr OS							
Intercept	0.204	0.185	-0.158	0.565	1.100	0.270	
RFA vs RH	-0.317	0.293	-0.890	0.257	-1.080	0.279	
TACE vs RH	-0.917	0.328	-1.559	-0.275	-2.800	0.005	
LT vs RH	0.392 ¹	0.298	-0.192	0.975	1.320	0.188	

¹Best treatment option.

DFS: Disease-free survival; LT: Liver transplantation; OS: Overall survival; RFA: Radiofrequency ablation; RH: Repeated hepatectomy; SE: Standard error; TACE: Transarterial chemoembolization.

DISCUSSION

NMA models are simple to implement in clinical decision-making as a treatment strategy for patients with rHCC after primary liver resection [8,55]. The high recurrence rate has consistently undermined patient survival, making rHCC a major global healthcare problem. In terms of the optimal strategy for rHCC, LT had the best OS, followed by RH and RFA, while TACE had the worst[8]. Compared to RH and RFA, the LT subgroup had a superior DFS but not OS[42,45,47,56]. However, patients with rHCC treated with RH had a better OS, with no significant difference between the testing methods in our study, which is consistent with other studies[9]. The salvage LT group had a significantly higher 3-year and 5-year DFS than the RH subgroup with significant difference[57]. Although LT appears to have



Table 4 Overall heterogeneity of outcome measured by Q test with random effects model and pooled effect size of each subgroup

Outcome	Heterogeneity			Pooled effect (overall)			
	Q value	df (Q)	P value	ľ	Z value	95%CI	P value
1-yr DFS	224.670	30	< 0.001	86.65	0.672	0.625-0.716	P < 0.001
3-yr DFS	583.665	30	< 0.001	94.86	0.414	0.370-0.46	P < 0.001
5-yr DFS	764.476	32	< 0.001	95.81	0.315	0.276-0.357	P < 0.001
1-yr OS	219.820	46	< 0.001	79.07	0.874	0.850-0.895	P < 0.001
3-yr OS	437.662	45	0.002	89.72	0.642	0.642-0.714	P < 0.001
5-yr OS	730.285	48	< 0.001	93.43	0.546	0.497-0.594	P = 0.068

DFS: Disease-free survival; OS: Overall survival.

Table 5 Summary of the better pooled outcome of treatments depended on the analysis method								
Test method	1-yr DFS	3-yr DFS	5-yr DFS	1-yr OS	3-yr OS	5-yr OS		
Wilcoxon rank sum test	LT	LT	LT	RFA	RH	RH		
Forest plot analysis	LT	LT	LT	LT	RH	RH		
Wald test	LT	LT	LT	LT	RH	RH		
<i>P</i> score	LT	LT	LT	RH	RH	RH		
Meta-regression analysis	LT	LT	LT	RH	LT	LT		

DFS: Disease-free survival; LT: Liver transplantation; RFA: Radio-frequency ablation; RH: Repeated hepatectomy; OS: Overall survival.

OS-1 yr RH		_	
1.0404 (0.3376; 3.2066)	LI		
0.8387 (0.5008; 1.4046)	0.8061 (0.2435; 2.6686)	RFA	
0.3911 (0.1922; 0.7956)	0.3759 (0.1016; 1.3908)	0.4663 (0.2378; 0.9143)	TACE
OS-3 yr RH			
0.6107 (0.2146; 1.7382)	LT		
0.6110 (0.3690; 1.0119)	1.0005 (0.3276; 3.0559)	RFA	
0.1897 (0.0864; 0.4166)	0.3107 (0.0859; 1.1242)	0.3105 (0.1450; 0.6650)	TACE
OS-5 yr RH			
0.9527 (0.3880; 2.3390)	LT		
0.6256 (0.3665; 1.0679)	0.6566 (0.2412; 1.7875)	RFA	
0.1434 (0.0610; 0.3370)	0.1505 (0.0445; 0.5089)	0.2292 (0.1004; 0.5232)	TACE

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Figure 4 Hierarchic step diagram of cumulative comparative efficacy of treatment methods based on the effect size displayed with the odds ratio and corresponding 95% confidence interval of the 1-year, 3-year, and 5-year overall survival. All results were presented as the ratio of the x-axis over the y-axis with the Wald test. The better option had an underline and TextTitle letter. LT: Liver transplantation; OS: Overall survival; RFA: Radiofrequency ablation; RH: Repeated hepatectomy; TACE: Transarterial chemoembolization.

> better survival, operative mortality still existed and ranged from 1.9% to 11.0%, which is higher than that in the RH group (ranging from 0% to 6.0%), with a significant difference[22,42,45,47].

> Currently, LT is considered the best treatment for rHCC, but it is challenging due to organ shortages. Therefore, the number of patients who meet the transplantation criteria at the time of recurrence is low,





Figure 5 Publication bias measured by the comparison of the specific effect for 1-year, 3-year, and 5-year overall survival. P > 0.05 were obtained among all studies after Egger's regression test. A: One-year overall survival (OS); B: Three-year OS; C: Five-year OS. LT: Liver transplantation; RFA: Radiofrequency ablation; RH: Repeated hepatectomy; TACE: Transarterial chemoembolization.

particularly in Asian countries[40,42,45,58]. There was no significant difference in DFS or OS between the patients who underwent primary LT and those who underwent primary resection and LT performed after recurrence from primary resection[27]. Surgical resection has been shown to be a viable procedure in the treatment of primary HCC or rHCC, with better survival than non-surgical methods in general[9,52,53].

The patients with rHCC who were treated again with a curative RH or LT approach had evident survival advantages. When the Japan Society of Hepatology guideline for primary HCC is applied to rHCC, either RFA or TACE are generally indicated in Child-Pugh Class A or B patients with 2-3 tumors of 3 cm or less in diameter or 4 tumors or more, and TACE may be indicated in some patients even with minor vascular invasion[12]. According to the European Association for the Study of the Liver guideline for primary HCC, most patients with rHCC had a similar recurrent tumor burden, favoring non-surgical treatment^[59]. In this study, the cumulative means of recurrent tumor size and the percentage of single nodules were 21.5-32.2 mm and 62.2%-78.6%, respectively. Recurrent tumor size is one of the most significant prognostic factors associated with survival [6,9,60]. Currently, surgical resection is the first option in both primary and rHCC. An NMA revealed that RH is the most feasible intervention for recurrence after primary resection and is widely used to compare other treatments^[8]. Nevertheless, RFA or TACE are less invasive and have fewer complications but have a lower survival rate.

Tumor recurrence after HCC resection has been proven to be unpreventable^[13]. Based on the retreatment methods, the recurrence time after primary resection had a strong impact on survival. There is no universal definition of early and late recurrence after resection, and recurrence time ranges from 8 to 24 mo[13,61-64]. According to an international study, curative procedures mostly benefited patients who relapsed after 8 mo [61]. However, Yamashita *et al* [42] reported that the recurrence time may effectively identify patients with a poor prognosis who relapse before 17 mo. Because intrahepatic recurrence is often associated with aggressive cancer cell biological behavior and a poor prognosis[62, 64], the potential effect of curative procedures such as RH, LT, or RFA may be considered, especially when the recurrence is within 1 year[35,65].

On the basis of ongoing hepatocarcinogenesis, late rHCC occurring more than 1 year after primary resection in the context of cirrhosis is regarded as a de novo tumor occurrence of different clonal origin [64,66,67]. In addition, before deciding on retreatment methods, it is possible to overlook de novo



minute nodules. In this situation, TACE will have unexpected benefits for the simultaneous treatment of ignored minute nodules alongside the main recurrent tumor. Therefore, the 5-year OS is significantly lower in patients with early recurrence and ranges from 4.5%-15.4% to 27.1%-36.3% compared to late recurrence, according to previous studies[64,68,69].

For patients with intrahepatic rHCC, a multicentric occurrence pattern is associated with better longterm outcomes than the intrahepatic metastasis pattern. LT is the preferred option for intrahepatic rHCC, especially for multicentric occurrence patients[70]. Appropriate rHCC management strategies are important for improving long-term survival if available data can be used to aid clinical decision-making [7]. Nevertheless, in most institutions, treatment strategy with RH and RFA could be the first-line treatment for rHCC. There is no difference between the LT and curative locoregional therapy (RFA or TACE) groups regarding 1-year and 3-year OS. However, the 5-year OS and 1-year, 3-year, and 5-year DFS were significantly higher after salvage LT than after locoregional therapy[57]. The feasibility of a retreatment method is determined by the number and location of the recurrent tumor, liver function, remnant liver volume, and the patient's general health status at the time of recurrence.

In this study, about one-third of the patients at the time of recurrence had multiple or moderate-tolarge nodular tumors, impaired liver function, or were unable to receive surgical curative treatment. rHCC patients treated by a palliative approach (TACE or target therapy) or having a median size of the recurrent nodule > 5 cm have a significantly decreased OS compared with curative treatment methods [58]. Non-surgical methods such as RFA or TACE were effective as non-radical treatments for these patients. TACE, while not as effective as other curative treatments, significantly improves survival in patients with unresectable rHCC[41,49,54]. TACE was also recommended in rHCC as a treatment for downstaging before curative LT, according to the treatment flowchart based on the Barcelona Clinic Liver Cancer staging and treatment strategy published in 2022[59].

rHCC can be caused by multicentric carcinogenesis or inadequate initial treatment. Prevention of rHCC necessitates early diagnosis and complete anatomic resection of primary HCC lesions with a safety margin[71]. Currently, there are no solid and effective chemotherapeutic agents available to prevent rHCC. However, molecularly targeted drugs and anti-hepatitis B/C virus oral nucleoside/ nucleotide analogs agents are recommended, but they are expensive and not promising. Therefore, the only option is to detect tumors as early as possible, and tumors can be treated based on the facilities at each institution.

The most common limitation of NMA is unexplained heterogeneity for available pairwise comparisons, which random effects meta-analysis models can accommodate[72]. In NMA studies, we should place more emphasis on treatment effects and consider the possibility of uncertainty with less emphasis on the probabilities of an NMA output. Clinical decision-making highlights the complexities of recommending a treatment method at the individual level based on tumor burden and patient condition.

CONCLUSION

In conclusion, patients with rHCC treated with RH or LT had comparably favorable DFS and OS. Currently, no solid algorithm can be expected to provide a guideline for patients with rHCC. Treatment strategies with RH, LT, RFA, or TACE are determined by factors such as liver function, tumor burden, metastasis, vascular invasion, and others. A multiparametric evaluation should be in place for personalized treatment of patients with rHCC, and it should be integrated into multidisciplinary tumor boards and partners in care programs at each institution.

ARTICLE HIGHLIGHTS

Research background

Recurrent hepatocellular carcinoma (rHCC) is a common outcome after curative treatment. Retreatment for rHCC is controversial, and no guidelines are currently available.

Research motivation

Acceptable decision making for treatment of rHCC patients is a priority.

Research objectives

Our objectives were to conduct a network meta-analysis (NMA) to compare curative treatments including repeated hepatectomy (RH), radiofrequency ablation, transarterial chemoembolization (TACE), and liver transplantation (LT) for patients with rHCC after primary hepatectomy.

Research methods

There were 30 articles involving patients with rHCC after primary liver resection from 2011 to 2021 that were retrieved for this NMA.

Research results

The best-pooled outcomes of four retreatment methods were analyzed by multiple testing methods. In general, the LT subgroup had superior disease-free survival (DFS) (P < 0.001), whereas the RH subgroup had superior overall survival (OS) without significant differences compared to other treatments.

Research conclusions

RH and LT had better DFS and OS for rHCC than radiofrequency ablation and TACE. However, treatment strategies should be determined by the recurrent tumor characteristics, the patient's general health status, and the care program of each institution.

Research perspectives

Retreatment with RH, LT, radiofrequency ablation, or TACE are determined by factors such as liver function, tumor burden, metastasis, vascular invasion, and others. A multiparametric evaluation should be in place for personalized treatment of patients with rHCC and re-evaluated in the future.

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FOOTNOTES

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