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Name of Journal: *World Journal of Gastrointestinal Surgery*

Manuscript NO: 80396

Manuscript Type: META-ANALYSIS

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

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

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

Abstract

BACKGROUND

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

AIM

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

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 of 0.96 (95%CI: 0.31-2.96). However, the RH subgroup had a better OS-3 and 5 years than the LT, RFA, and TACE subgroups. Hierarchic step diagram of different subgroups measured by Wald test yielded the same results as the forest plot analysis. The results were LT had the better in OS-1 year (OR = 1.04, 95%CI: 0.34-03.20) and LT had a probability to be inferior than RH in OS-3 years (OR = 10.61, 95%CI: 0.21-1.73) or 5 years (OR = 0.95, 95%CI: 0.39-2.34) respectively. According to the predictive p-score evaluation, LH subgroup had a better DFS but RH had the best OS. However, meta-regression analysis revealed that LT had a better DFS (P < 0.001) as well as OS-3 years (P = 0.881) and 5 years (P = 0.188). The differences in superiority between the 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

Chen JL, Chen YS, Ker CG. Network meta-analysis of the prognosis of curative treatment strategies for recurrent hepatocelluar carcinoma after hepatectomy. *World J Gastrointest Surg* 2022; In press

Core Tip: Network meta-analysis was used to compare the treatments including repeated hepatectomy, radiofrequency ablation, trans-arterial chemoembolization, and liver

transplantation (LT) for the patients of recurrent hepatocellular carcinoma from 30 articles published from 2012-2021. The I^2 values were obtained by Q test and random effect models were used for analysis. The favorability of disease-free survival (DFS), and overall survival (OS) based on forest plot analysis and hierarchic step diagram of subgroups by Wald test, forest plot analysis, and predictive *P* score for subgroup analysis. Repeated hepatectomy or LT had a domain of better DFS or OS than others based on the testing methods from this network meta-analysis.

INTRODUCTION

In Taiwan, hepatocellular carcinoma (HCC) is the most common cause of death among all cancers in 2019, ranking second in men and fourth in women[1]. Despite improvements in hepatitis control and care programs in Taiwan through anti-viral 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 or a major global health problem. According to Eastern and Western studies, the recurrence rates after primary hepatectomy are around 70% or higher within 5 years, usually after resection[2-6] are crucial for improved survival, but the option of a re-treatment method should be established where possible[7].

Till now, a precise treatment strategy for rHCC, including surgical or non-surgical methods, has remained 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 patient profile[13]. Therefore, a better treatment option for rHCC would be advantageous, but a practice 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 gains clinical decision-making insight 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 two-arm 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 the primary HCC[11,12,19,20]. However, these guidelines were useful of not for rHCC, they shared a relatively similar carcinogenesis with primary HCC.

Treatment options for rHCC include repeated hepatectomy (RH), RFA, trans-arterial chemoembolization (TACE), LT, radiation therapy, and systemic target or immunotherapy[21-24]. However, 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 last decade, many studies comparing different treatment options for rHCC have been published. Four curative re-treatment methods, including RH, RFA, TACE, and LT, are now routinely adopted in our current practices and are also coded globally[8,9,25-27]. Therefore, Therefore, we aimed to conduct an NMA to compare four curative re-treatment 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) included studies 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 re-treatment methods RH, RFA, TACE or LT. For each study arm's outcome, the title, first author, and publication year, as well as the intervention methods, outcomes, and associated risk factors, if available. 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.

Quality assessment

For quality assessment in the meta-analysis, two statistical models based on heterogeneity could be used: the fixed-effect and random-effect models. In the fixed-effect model, all studies in the meta-analysis shared the same true effect size, whereas, in the random-effect model, the true effect size varies from study to study. The heterogeneity among trials was assessed using the Q-test with I^2 values, which represents the proportion of total variation in studies based on estimated heterogeneity[28]. An I^2 statistic of more than 50% or a P value of less than 0.05 indicates significant heterogeneity among trials, and the random-effect model was used. The overall heterogeneity and publication bias of the effect 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 07631, 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 I^2 statistic of more than 50%, or P

value[28]. A frequentist analog to the surface under the cumulative ranking curve could be replaced by a *P* score, which measures whether a treatment is certainly better than the comparative treatments[14,16]. Another predictive *P* score would be 100% when a treatment is certain to be the best and 0% when it is 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 funnel plot analysis[31,32]. The statistically significant level was set at 0.05 for all treatment comparisons.

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 supplement table s1 and reference code number 3, 6, 9, 21-22, 24, 26-27 and 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 ± 8.3, 18.1 ± 6.5, 14.7 ± 6.6, and 19.4 ± 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.

Diseases free survival and overall survival of rHCC after re-treatment

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 ± 8.8%, 57.1 ± 13.3%, and 51.2 ± 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 ± 7.4%, and in the RH subgroup, with a 3-year OS of 71.9 ± 13.7% and a 5-year OS of 53.2 ± 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 methods in Figures 3A-C. In addition, the RH subgroup had a better OS-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 in Figure 3D. RH subgroup had a more favorable OS-3 years and OS-5 years than LT (OR: 1.64, 95%CI: 0.56-4.66 and OR: 1.05, 95%CI: 0.43-2.56), RFA, and TACE subgroups, respectively in Figures 3E and F.

Hierarchic step diagram for comparison with 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 expressed ranking probability with OR and 95%CI. LT had the better in OS-1 year (OR = 1.04, 95%CI: 0.34-03.20) and RH had a higher ranking probability based on OS-3 years (OR = 0.61, 95%CI: 0.21-1.73) or OS-5 years (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 DFS-1 year, 3 years, and 5 years in the 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 OS-1 year, 3 years, and 5 years 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 result than RH in DFS-1 year, 3 years and 5 years with $\beta = 0.93$ ($P = 0.001$). $\beta = 1.181$ ($P < 0.001$), and $\beta = 1.258$ ($P < 0.001$) respectively. LT compared with RH resulted in inferior in OS-1 year with $\beta = -0.036$ ($P = 0.913$), but superior in OS-3 years with $\beta = 0.04$ ($P = 0.881$), and OS-5 years with $\beta = 0.392$ ($P = 0.188$) respectively. From this study, LT had better result in DFS ($P < 0.001$) and OS-3 or 5 years ($P > 0.05$). RH had a better result in OS-1 year ($P > 0.05$) than others as shown in the Table 3.

Heterogeneity and publication bias

The heterogeneity among studies was estimated based on I^2 values using the Q-test. The I^2 values for DFS-1 year, 3 years, and 5 years were 86.65%, 94.86%, and 95.81%, respectively, and for OS-1 year, 3 years, and 5 years, they were 79.07%, 89.72%, and 93.43%, respectively in Table 4. Therefore, the random-effect models were used for analysis based on a P value of less than 0.05 obtained from the I^2 value among re-treatment 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 demonstrated in Supplementary Figures 1–6. The publication bias was assessed by Egger's regression test and resulted in OS-1 year, 3 years and 5 years of $P = 0.8459$, 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 OS-1 year, 3 years and 5 years were depicted in the Figure 5A-C.

DFS and OS summary of subgroups among all testing methods

The best-pooled outcomes of the four re-treatment 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 significant difference compared to other treatments.

DISCUSSION

NMA models are simple to implement in our clinical decision-making as a treatment strategy for patients with rHCC after primary liver resection[8,55]. The high recurrence rate has consistently undermined the patients' 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 LT, LH 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]. LT compared with RH, salvage LT group had a significantly higher 3- and 5-years DFS than the RH subgroup respectively with significant difference[57]. Although LT appears to have better survival, operative mortality still existed and ranged from 1.9% to 11%, which is higher than that in RH (ranging from 0% to 6%), with a significant difference[22,42,45,47]. Currently, LT is being considered as a treatment for rHCC, but it is challenging due to organ shortages. Therefore, the number of patients who met the transplantation criteria at the time of recurrence was low, 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 then LT was 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. If 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 EASL 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 re-treatment 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, Yamamoto *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 one year[35,65]. On the basis of ongoing hepato-carcinogenesis, late rHCC occurring more than one year after primary resection in the context of cirrhosis is regarded as a de novo tumor occurrence of different clonal origin[64,66,67]. The longer recurrence time would provide enough time to grow enough to be diagnosed again. In addition, before deciding on re-treatment 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 multi-centric occurrence pattern is associated with better long-term outcomes than the intrahepatic metastasis pattern. LT is the preferred option for intrahepatic rHCC, especially for multi-centric 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 LT and curative locoregional therapy (RFA or TACE) group regarding the 1- and 3-year OS. However, the 5-year OS and 1-, 3-, 5-year DFS were significantly higher after salvage LT than after locoregional therapy[57]. The feasibility of a re-treatment 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-to-large nodular tumors, impaired liver function, or were unable to receive surgical curative treatment. If rHCC patients treated by palliative approach (TACE or target therapy) or having a median size of the recurrent nodule > 5 cm would have a significant dismal 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 down staging, and then advised for curative LT, according to the treatment flowchart based on the BCLC staging and treatment strategy published in 2022[59].

rHCC can be caused by multi-centric carcinogenesis or inadequate initial treatment. Prevention of HCC recurrence 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 HCC recurrence. 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 way 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, and 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 comparable favorable DFS and OS. Currently, no solid algorithm can be expected to provide a guideline for our 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 multi-parametric evaluation should be in place for personalized patients with rHCC, and it should be integrated into multi-disciplinary tumor boards and partners in care programs at each institution.

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