A comparison between radiofrequency ablation combined with transarterial chemoembolization and surgical resection in hepatic carcinoma: A meta-analysis

ABSTRACT

Objective: This study determined whether the effect of combination therapy for hepatic carcinoma (HCC) is comparable to surgical resection (SR). According to the guidelines of the American Association for the Study of Liver Disease, radiofrequency ablation (RFA) and SR are recommended for early HCC. However, patients treated with RFA had worse long-term survival than those who received SR. Many studies utilizing the combination therapy with RFA and transarterial chemoembolization (TACE) have reported better prognosis as compared to RFA alone.

Materials and Methods: A comprehensive search in databases was conducted. Six retrospective studies and one cohort were enrolled in this meta-analysis. The overall survival (OS), disease-free survival (DFS), and major complications were compared between RFA plus TACE and SR. The pooled hazard ratio and 95% confidence interval (CI) were calculated and analyzed.

Results: After comparison, no significant difference in the OS and DFS at 1 and 3 years between the combination therapy and SR was observed (OS1: pooled relative risk [RR]: 0.82, 95% CI [0.56, 1.21]; OS3: pooled RR: 1.07, 95% CI [0.82, 1.39]; DFS1: pooled RR: 0.92, 95% CI [0.58, 1.45]; DFS3: pooled RR: 1.18, 95% CI [1.00, 1.40]). SR had better clinical outcomes than combination therapy with respect to long-term survival and disease progression (OS5: pooled RR: 1.12, 95% CI [1.03, 1.23]; DFS5: pooled RR: 1.15, 95% CI [1.03, 1.28]). Major complications were reduced with combination therapy (pooled RR: 0.46, 95% CI [0.25, 0.85]).

Conclusion: SR should remain as the first-line therapy for early HCC.

KEY WORDS: Hepatectomy, hepatocellular carcinoma, radiofrequency ablation, transarterial chemoembolization

INTRODUCTION

Hepatic carcinoma (HCC) remains one of the leading causes of cancer-related death globally. HCC has been ranked as the second cause of mortality and as the fifth cause for mobility impairment of all cancer cases.[1] In the United States, there has been a rapid growth in the incidence rate of HCC over the past 20 years.[2] The curative therapies include tumor ablation, hepatic resection, and liver transplantation, while some other options such as transarterial chemoembolization (TACE) and sorafenib are considered as palliative treatments.[3] Despite the fast advancement in this field over the past decades, the overall long-term survival of HCC is still poor.

Surgical resection (SR) is considered as the first therapeutic strategy for HCC when liver transplantation is not available due to shortage of donors.[4] However, the application of hepatic resection requires the patient to still have good liver function and early-stage HCC. According to the suggestion by the Barcelona Clinical Liver Cancer (BCLC) group, the criteria for hepatic resection include one tumor, no cirrhosis, no portal hypertension, and BCLC Stage A.[5] Nowadays, radiofrequency ablation (RFA) has become a routine choice for patients with early-stage HCC. The heat can destroy necrosis in tumor and activate the host immune system.[6] Some randomized controlled studies have provided support for RFA. However, the application of SR should remain as the first-line therapy for early HCC.
trials have reported a comparable survival rate between SR and RFA in patients with Child-Pugh A plus early-stage HCC, thus challenging the traditional method of SR.\cite{7,9} TACE functions by blocking the blood supply to starve the tumor. Usually, TACE is applied as a palliative treatment for intermediate HCC. More than half of the receivers have benefited from the therapy, showing extensive tumor necrosis.\cite{10} The efficiency of RFA plus TACE has been tested in many clinical trials, in which improved short- and long-term survival outcomes can be achieved in medium-sized HCC (3–5 cm) but not in HCC (<3 cm), compared to RFA.\cite{11,12} The decrease in heat loss after TACE may contribute to the success of RFA plus TACE.\cite{13,14}

Over the past few years, many studies have compared the efficiency between RFA combined with TACE and SR. A randomized controlled trial reported better clinical outcomes using SR rather than RFA plus TACE, while some other studies reported no significant differences in overall survival (OS) and disease-free survival (DFS) between these two therapies. No consensus has been reached for this topic. In this systematic review, the efficiency of RFA plus TACE and SR for HCC is summarized and compared.

MATERIALS AND METHODS

Literature search strategy
This systemic meta-analysis followed the review protocols and guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) group. Four electronic databases including PubMed, Web of Science, EMBASE, and Cochrane were utilized. A total of 639 relevant studies were included in this study using the following keywords: “radiofrequency,” “transarterial chemoembolization,” “hepatectomy,” and “liver cancer.” A comprehensive literature search was independently conducted by three researchers (Wang Hongye, Shu Yimei, and Cao Cheng).

Selection criteria
After the preliminary review of titles and abstracts, 639 papers were excluded. The inclusion criteria were as follows: (1) a focus on the relationship between the combination of RFA plus TACE and SR in HCC, (2) the full-text articles were restricted to English, and (3) high-quality studies evaluated by Newcastle–Ottawa scale (NOS). The exclusion criteria for this analysis were as follows: (1) case report, meta-analysis, and treatment guidelines and (2) absence of the required data in the results. One randomized controlled trial and six cohorts were finally included. The concrete information including reference, country, type, number of patients, time, and quality score of each study is summarized in Table 1. The major complications were liver failure, bleeding, and ascites. All disagreements were discussed and resolved by Hongye Wang and co-author Yihai Liu.

Data extraction
The OS and DFS were analyzed in this study as the main outcomes, as well as therapeutic complications. After strict selection of studies from the literature, the data involving OS and DFS at 1, 3, and 5 years, as well as complications were carefully recorded and analyzed. Source of data, control, number of patients, age, tumor diameter, concentration of alpha-fetoprotein, CTP A/B, hepatitis B virus/hepatitis C virus (HBV/HCV), characteristics of population, and time of publication were also included.

Statistical analysis
The relative risks (RRs) and 95% confidence intervals were used to analyze statistics using binary variables. The RR corresponding to each outcome was pooled using a fixed model (Mantel–Haenszel method) or random model (DerSimonian and Laird method) when heterogeneity exists across studies. The heterogeneity of the included trials was assessed using Cochran’s Q test and Higgins I² statistic. A P < 0.10 or I² >50% suggested significant heterogeneity. When significant heterogeneity was confirmed, a sensitivity analysis was applied to explore the origin of heterogeneity. Publication bias was evaluated by Beggs’s test, and a P < 0.05 was considered statistically significant, which indicated publication bias. All the statistical analyses were carried out using the STATA version 12.0 (STATA Corporation, College Station, TX, USA) software.

Table 1: Characteristics of the included studies

| References | Country | Years | Type     | Sex (male/female) | NP | Age (years) | Tumor diameter (cm) | AFP (µg/L) (<100 µg/L) | CTP A/B (%) | HBV/HCV (%) |
|------------|---------|-------|----------|-----------------|----|-------------|---------------------|------------------------|--------------|-------------|
| Yamakado K | Japan   | 2008  | Retrospective | 130/36 | 166 | 65.8±9.0 | 2.6±0.9 | 142/24 | 166/0 | 20/124 |
| Kagawa     | Japan   | 2010  | Retrospective | 79/38 | 117 | 66.8±8.4 | 2.6 (0.9–5) | No | 117/0 | 17/84 |
| Takuma Y   | Japan   | 2013  | Retrospective | 235/96 | 330 | 68.9±5.0 | 2.3±0.5 | No | 283/47 | 38/135 |
| Kim J      | Korea   | 2013  | Retrospective | 67/17 | 84 | 60.1±10.9 | 2.6±0.7 | 63/21 | 82/2 | 46/19 |
| Liu H      | China   | 2016  | Cohort    | 180/20 | 200 | 50.5±16.0 | 2.9±1.5 | No | 194/6 | 177/ NR |
| Bholee A   | China   | 2017  | Retrospective | 204/18 | 222 | 53.1±11.0 | 3.0±1.1 | 147/74 | 214/8 | 205/6 |
| Peng Z     | China   | 2018  | Retrospective | 91/11 | 186 | 56.2 (18.6–75.0) | 2.6±0.9 | 71/31 | 173/13 | 170/ NR |

NP=Number of patients, NR=No report, HBV=Hepatitis B virus, HCV=Hepatitis C virus, AFP=Alpha-fetoprotein, CTP=Child-Turcotte-Pugh
RESULTS

Identification of included studies
After the strict selection of studies, seven studies were included in this meta-analysis. The search process is presented in the flowchart in Figure 1, and the criteria were recorded as follows: authors, time of publication, country, study design, number of patients, median age, tumor diameter, Child-Pugh level, and HBV/HCV [Figure 2] according to the PRISMA guidelines [15]. All studies were retrospective, and most of the studies were from East Asia (3, 3, and 1 from Japan, China, and South Korea, respectively). The studies were conducted between 1995 and 2015. A total of 1305 patients were enrolled in the seven studies. The quality test was conducted by two authors (Hongye Wang and Yihai Liu) independently, and the NOS analysis revealed that the studies included were of high quality.

Results of meta-analysis
The main results in our systemic review included the OS and DFS in 1, 3, and 5 years, respectively, as well as major complications after treatment. As indicated in Figure 2, there was no significant difference in OS at 1 and 3 years between the RFA plus TACE group and the SR group. However, the SR group had a better long-term survival in 5 years [Figure 2]. Moreover, the comparison of DFS in these two groups showed no significant differences at 1 and 3 years, while the SR group had better DFS at 5 years [Figure 3]. Therefore, it was concluded that RFA plus TACE treatment had comparable efficiency as SR in the short-term survival and disease progression; however, patients seem to benefit more from SR from a long-term perspective. Finally, the RFA plus TACE treatment method resulted in a slightly higher rate of major complications [Figure 4].

Begg’s funnel plot was generated to evaluate publication bias. Publication bias was detected for OS at 1, 3, and 5 years ($P = 1.0, 1.0, \text{ and } 0.707, \text{ respectively}$); DFS at 1, 3, and 5 years ($P = 0.764, 0.548, \text{ and } 1.0, \text{ respectively}$); and major complications ($P = 0.806$); respectively [Figure 5].

A sensitivity analysis was conducted to detect the effects of each included study by repeating the meta-analysis while dislodging one study at a time. As shown in Figure 6, no study had influenced the pooled hazard ratio; thus, our results can be considered to be reliable.
DISCUSSION

RFA plus TACE has become an important alternative strategy for HCC. In our study, no significance was found for OS at 1 and 3 years as well as DFS at 1 year when comparing RFA plus TACE and traditional SR. However, the SR had a better DFS and long-term OS than the combination therapy. In addition, RFA plus TACE treatment might result in slightly higher rate of major complications.

RFA is now considered as an effective technique for local or regional HCC with diameter <5 cm. Considering high morbidity of HCC in the elderly and increase onset in the younger group, RFA exerts several advantages over SR, such as lower risks, cheaper expense, less lesions in healthy tissues, and shorter duration of hospitalization. However, incomplete ablation may give rise to recurrence. When utilizing thermal ablation, RFA eliminates tumors both directly and indirectly. This causes coagulative necrosis of the tumor and the influx of cellular content, such as RNA, DNA, and high mobility group protein B1, which can activate the innate immunity. Moreover, with greater amounts of infiltration by APC and T-cells in the ablated zone, RFA can result in better activation of adaptive immunity. Compared to SR, some studies and meta-analyses have found that RFA resulted in lower OS and DFS. In the meantime, HCC receives nutrition from the hepatic arteries. TACE can be used to block the blood flow and potentially reduce the heat loss during the ablation, thus improving the efficiency theoretically. Since satellite tumor foci cannot be detected by computed tomography or magnetic resonance imaging, TACE increases the therapeutic area, which partly accounts for the higher OS in the combination therapy. Furthermore, some studies have confirmed that patients benefited more from RFA plus TACE than a single therapy.

Hepatic resection is the treatment of choice for patients with HCC who do not have hepatic cirrhosis. As for the surgical group with hepatic cirrhosis, some complications may be life-threatening, such as liver failure. Because of the invasiveness after incision, some surgical-related complications cannot be avoided. Several cohort studies have compared the complications between RFA and SR and concluded that RFA was safer than SR. Consistent with our data, the combination strategy had little side effects. Hepatic resection showed better OS and DFS than monotherapy. Meanwhile, some studies have also reported a higher efficiency when combining SR and RFA or TACE than RFA or TACE alone.

A former systemic study has compared the OS and DFS between these two treatment strategies. However, only a limited number of studies were included in the study. Thus, more studies were collected systematically for further analysis. Guo found no significant difference between 1- and 3-year OS and 1-year DFS but a disparity between 5-year OS and 5-year
DFS, which was consistent with our analysis.\textsuperscript{[31]} However, our results demonstrated that no important significant difference of 3-year DFS existed in these two methods. While only one randomized controlled trial was available, more randomized controlled trials were implemented to test the influence of RFA plus TACE on the medium survival rate and DFS. In fact, microwave ablation, which is another ablation technique, exhibited better clinical outcomes when combined with TACE than SR.\textsuperscript{[32,33]} Furthermore, in some other tumors, RFA plus transarterial embolization showed comparable clinical outcomes as SR.\textsuperscript{[34]}

Our study has some limitations. Initially, there was a large time span for the document selection, so the studies included might adopt diverse ablation devices. Along with the development of ablation technology, the experience for the operators accumulated over these years, thus resulting in increased efficiency, which likely affected the results. Second, many retrospective studies were included in our analysis; hence, the inherent defects, such as selection bias and poor reliability of the pooled results, could not be neglected. Moreover, the histological examination for RFA plus TACE groups was limited, while that in the SR, section was almost completed. Although the consensus for noninvasive diagnosis of HCC has been reached for many years by the American Association for the Study of Liver Disease, some false-positive cases may still exist following these criteria, which can interfere with the authenticity by inflating the survival rate for patients treated by RFA plus TACE. In addition, patients with Child-Pugh A score tend to receive SR in most cases, while the patients with Child-Pugh B group usually miss the choice for surgery and adopt RFA as an alternative. Therefore, the worse prognosis for the RFA group may be attributed to their poorer liver conditions, which subsequently increases the bias. Finally, the small sample of studies might alter the results.

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Figure 5: Begg's funnel plot of overall survival, disease-free survival, and major complications
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Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
2. Petrick JL, Braunlin M, Laversanne M, Valery PC, Bray F, McGlynn KA. International trends in liver cancer incidence, overall and by histologic subtype. 1978-2007. Int J Cancer 2016;139:1534‑45.
3. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358‑80.
4. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907‑17.
5. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012;379:1245‑55.
6. Chu KF, Dupuy DE. Thermal ablation of tumours: Biological mechanisms and advances in therapy. Nat Rev Cancer 2014;14:199-208.
7. Lencioni R. Loco-regional treatment of hepatocellular carcinoma. Hepatology 2010;52:762‑73.
8. Germani G, Pleguezuelo M, Gurusamy K, Meyer T, Isgro G, Burroughs AK. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocellular carcinoma: A meta-analysis. J Hepatol 2010;52:380‑8.
9. Tateishi R, Shima S, Teratani T, Ohi S, Sato S, Koike Y, et al. Percutaneous radiofrequency ablation for hepatocellular carcinoma. An analysis of 1000 cases. Cancer 2005;103:1201-9.
10. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 2003;37:429-42.
11. Peng ZW, Chen MS, Liang HH, Gao HJ, Zhang YJ, Li JQ, et al. A case-control study comparing percutaneous radiofrequency ablation alone or combined with transcatheter arterial chemoembolization for hepatocellular carcinoma. Eur J Surg Oncol 2010;36:237-63.
12. Shibata T, Isoda H, Hirokawa Y, Arizono S, Shimada K, Togashi K. Small hepatocellular carcinoma: Is radiofrequency ablation combined with transcatheter arterial chemoembolization more effective than radiofrequency ablation alone for treatment? Radiology 2009;252:905-13.
13. Peng ZW, Zhang YJ, Chen MS, Xu L, Liang HH, Lin XJ, et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: A prospective randomized trial. J Clin Oncol 2013;31:426-32.
14. Morimoto M, Numata K, Kondou M, Nozaki A, Morita S, Tanaka K. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: A randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. Cancer 2010;116:5452-60.
15. Díaz-González A, Sanduzzi-Zamparelli M, Sapena V, Torres E, Llarch N, Iserte G, et al. Systematic review with meta-analysis: The critical role of dermatological events in patients with hepatocellular carcinoma treated with sorafenib. Aliment Pharmacol Ther 2019;49:482-91.
16. Pereira PL. Actual role of radiofrequency ablation of liver metastases. Eur Radiol 2007;17:2062-70.
17. den Brok MH, Sutmuller RP, van der Voort R, Bennink EJ, Fidgord CG, Ruers TJ, et al. In situ tumor ablation creates an antigen source for the generation of antitumor immunity. Cancer Res 2004;64:4024-9.
18. Wissniowski TT, Hänsler J, Neureiter D, Frieser M, Schaber S, Esslinger B, et al. Activation of tumor-specific T lymphocytes by radio-frequency ablation of the VX2 hepatoma in rabbits. Cancer Res 2003;63:6496-500.
19. Dromi SA, Walsh MP, Herby S, Traughber B, Xie J, Sharma KV, et al. Radiofrequency ablation induces antigen-presenting cell infiltration and amplification of weak tumor-induced immunity. Radiology 2009;251:58-66.
20. Li L, Zhang J, Liu X, Li X, Jiao B, Kang T. Clinical outcomes
of radiofrequency ablation and surgical resection for small hepatocellular carcinoma: A meta-analysis. J Gastroenterol Hepatol 2012;27:51-8.

21. Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg 2010;252:903-12.

22. Chen QW, Ying HF, Gao S, Shen YH, Meng ZQ, Chen H, et al. Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2016;40:309-14.

23. Hyun D, Cho SK, Shin SW, Park KB, Lee SY, Park HS, et al. Combined transarterial chemoembolization and radiofrequency ablation for small treatment-naive hepatocellular carcinoma infeasible for ultrasound-guided radiofrequency ablation: Long-term outcomes. Acta Radiol 2018;59:773-81.

24. Kasugai H, Osaki Y, Oka H, Kudo M, Seki T, Osaka Liver Cancer Study Group. Severe complications of radiofrequency ablation therapy for hepatocellular carcinoma: An analysis of 3,891 ablations in 2,614 patients. Oncology 2007;72 Suppl 1:72-5.

25. Koda M, Murawaki Y, Hirooka Y, Kitamoto M, Ono M, Sakaeda H, et al. Complications of radiofrequency ablation for hepatocellular carcinoma in a multicenter study: An analysis of 16,346 treated nodules in 13,283 patients. Hepatol Res 2012;42:1058-64.

26. Kong WT, Zhang WW, Qiu YD, Zhou T, Qiu JL, Zhang W, et al. Major complications after radiofrequency ablation for liver tumors: Analysis of 255 patients. World J Gastroenterol 2009;15:2651-6.

27. Hyun MH, Lee YS, Kim JH, Lee CU, Jung YK, Seo YS, et al. Hepatic resection compared to chemoembolization in intermediate- to advanced-stage hepatocellular carcinoma: A meta-analysis of high-quality studies. Hepatology 2018;68:977-93.

28. Zheng N, Wei X, Zhang D, Chai W, Che M, Wang J, et al. Hepatic resection or transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus. Medicine (Baltimore) 2016;95:e9599.

29. Chen J, Lai L, Lin Q, Huang W, Cai M, Zhu K, et al. Hepatic resection after transarterial chemoembolization increases overall survival in large/multifocal hepatocellular carcinoma: A retrospective cohort study Oncotarget 2017;8:408-17.

30. Qi X, Liu L, Wang D, Li H, Su C, Guo X. Hepatic resection alone versus in combination with pre- and post-operative transarterial chemoembolization for the treatment of hepatocellular carcinoma: A systematic review and meta-analysis. Oncotarget 2015;6:36838-59.

31. Guo W, He X, Li Z, Li Y. Combination of transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) vs. surgical resection (SR) on survival outcome of early hepatocellular carcinoma: A Meta-Analysis. Hepatogastroenterology 2015;62:710-4.

32. Li S, Zhang L, Huang ZM, Wu PH. Transcatheter arterial chemoembolization combined with CT-guided percutaneous thermal ablation versus hepatectomy in the treatment of hepatocellular carcinoma. Chin J Cancer 2015;34:254-63.

33. Wu M, Gao S, Song H, Zhang Z, Wang J, Liu R, et al. Percutaneous thermal ablation combined with simultaneous transarterial chemoembolization for hepatocellular carcinoma ≤5 cm. J Cancer Res Ther 2019;15:766-72.

34. Sommer CM, Pallwein-Prettner L, Vollherbst DF, Seidel R, Rieder C, Radeleff BA, et al. Transarterial embolization (TAE) as add-on to percutaneous radiofrequency ablation (RFA) for the treatment of renal tumors: Review of the literature, overview of state-of-the-art embolization materials and further perspective of advanced image-guided tumor ablation. Eur J Radiol 2017;86:143-62.