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Original Article

Safety and Efficacy of Physical Thermal Ablation Combined Sorafenib for Hepatocellular Carcinoma: A Meta-analysis

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Abstract

Background and Aims: To compare the efficacy and safety of physical thermal ablation (PTA), including radiofrequency ablation (RFA) and microwave ablation (MWA), combined with sorafenib and physical thermal ablation alone for the control and treatment of hepatocellular carcinoma (HCC) according to the available literature. ***Methods:*** Comprehensive searches were performed on PubMed, Embase, CNKI, the Cochrane Library, China Biomedical Literature Database (known as CBM), Weipu Journal, and Wanfang Database. Meta-analysis was performed using Revman 5.3 software. ***Results:*** A total of 15 studies, consisting of 2,227 HCC patients, were selected and included in this meta-analysis. Compared with the RFA-alone group, the patients in the RFA+sorafenib group had longer 1-, 2-, and 3-year overall survival (all $p<0.05$), better overall efficacy ($p<0.0001$), longer radiofrequency interval ($p<0.001$), and lower 2-year recurrence rate ($p=0.02$). The 1-year overall survival ($p=0.003$) and overall efficacy ($p=0.002$) of the MWA+sorafenib group were also higher than those of the MWA-alone group. The incidences of adverse reactions in the RFA+sorafenib group, such as hand-foot skin reactions ($p<0.001$), diarrhea and constipation ($p=0.0001$), hypertension ($p=0.009$), and alopecia ($p<0.001$), were significantly higher than those in the RFA-alone group. ***Conclusions:*** RFA or MWA combined with sorafenib has produced a better therapeutic effect on HCC than physical thermal ablation alone; however, adverse reactions have been obvious. It is necessary to evaluate the safety of combination therapy, and pay close attention to the adverse reactions that develop in patients.

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Keywords: Physical thermal ablation; Radiofrequency ablation; Microwave ablation; Sorafenib; Hepatocellular carcinoma; Meta-analysis.

Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; HFSR, hand-foot skin reaction; MWA, microwave ablation; OR, odds ratio; OS, overall survival; PEI, percutaneous ethanol injection; PTA, physical thermal ablation; RCT, randomized controlled trial; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor in the world. About 700,000 people die of HCC worldwide each year, with nearly half of those cases being from China.[1,2] Currently, the main treatments include liver transplantation, surgical resection, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), transarterial chemoembolization (TACE), and sorafenib.[3] Following development of medical technology and establishment of different prognosis scoring systems, like the Italian Liver Cancer tumor staging system and the Barcelona clinical liver cancer staging system, there are more therapy options for HCC patients.[4]

Surgical resection is considered to be the first-line treatment for HCC, but surgery is not always feasible due to factors such as multiple lesions, poor position, and patient status.[5] The early symptoms of liver cancer are not obvious, resulting in many patients having advanced liver cancer when they are diagnosed and missing the optimal window for surgery. The scarcity of liver sources and high costs also limit the widespread application of liver transplantation. Therefore, an effective and less invasive alternative therapy, physical thermal ablation (PTA), has been developed. PTA of the liver includes RFA and microwave ablation (MWA). Although the physical mechanisms of the two are different, they both target the tumor through imaging technology and insert the electrode into the tumor precisely. When the temperature of the tumor tissue reaches a certain level, the protein will be denatured to shrink the tumor.

A meta-analysis on the effects of RFA and hepatic resection in the treatment of liver cancer conducted by Xu *et al*.[6] showed that, compared with the hepatic resection group, the RFA group had similar 1-year overall survival (OS), lower 5-year OS, higher incidence of overall recurrence, shorter hospitalization duration and lower complication rate. Which means, compared with surgery, thermal ablation has the advantages of short duration and less complications. However, HCC patients treated with thermal ablation alone have a high recurrence rate and an unsatisfactory long-term prognosis.[7]

Sorafenib is a multi-targeted kinase inhibitor that inhibits the proliferation and differentiation of tumor cells by inhibiting the activity of B-Raf, Raf-1 and kinases in the Ras/Raf/MEK/ERK signaling pathway;[8] it can also reduce angiogenesis by inhibiting hepatocyte cytokine receptor (such as c-Kit), vascular endothelial growth factor receptors (such as the vascular endothelial growth factor receptors VEGFR-2,

VEGFR-3), platelet-derived growth factor receptors (such as the platelet-derived growth factor receptor PDGFR-β), etc.[9] A meta-analysis of 1,462 patients with unresectable HCC showed that compared with placebo, sorafenib improved disease control rate and reduced the risk of tumor progression and mortality.[10] A number of studies also pointed out that sorafenib alone or in combination with other therapies can prolong the survival of HCC patients.[11–13] However, sorafenib might delay the tissue repair after thermal ablation and adversely affect normal liver tissue. Therefore, the overall advantage of sorafenib in combination with PTA needs to be balanced, after considering its clinical efficacy effects and adverse effects.

Meta-analysis can provide a higher level of evidence for clinical decision-making by combining disaggregated data.[14] This study summarized the literature on the efficacy of PTA combined with sorafenib in the treatment of HCC, to explore the safety and efficacy of this combination therapy objectively.

Methods

Search strategy

A comprehensive literature search was conducted by two searchers on the PubMed, Embase, CNKI, Cochrane Library, China Biomedical Literature (known as CBM), Weipu Journal, and Wanfang databases on October 25–26, 2020 to identify articles published before September 2020. We collected randomized controlled trials (RCTs), controlled clinical trials, and cohort studies comparing RFA or MWA with sorafenib and PTA alone in the treatment of HCC, and reviewed the references to supplement with any missing studies. The search strategy was on the basis of the following terms: (physical thermal ablation) OR ((radiofrequency ablation OR (RFA) OR (RF ablation)) OR ((microwave ablation) OR (MWA) OR (MW ablation)) AND (sorafenib) AND ((Carcinoma, Hepatocellular) OR (HCC) OR (liver cancer) OR (liver tumor)).

Eligibility criteria

Inclusion criteria were: (1) English or Chinese language; (2) RCTs or high-quality cohort studies, quality score Jadad ≥3, Newcastle-Ottawa scale ≥5; (3) observation group treated with RFA/MWA combined with sorafenib, and control group treated with RFA/MWA alone; (4) participant Child-Pugh A/B; and (5) with data for at least one efficacy indicator (recurrence rate, survival rate, complications, radio frequency interval, etc.). Exclusion criteria were: (1) systematic review, meta-analysis, animal experiments, case reports, comments or letters; or (2) lack of required data in the results.

Quality evaluation and data extraction

Two researchers respectively scored the RCTs and non-RCTs according to the Jadad scale and the Newcastle-Ottowa scale, and independently extracted the original data according to the PICO principle (patient, intervention, comparison, and outcome), including basic information, safety indicators and effectiveness indicators.

The basic information included the first author, publication time, nationality of the patients, patient number of each group, sex ratio, age, type of study, and Child-Pugh classification. The safety indicators are the incidence of major adverse reactions, which included hand-foot skin reaction (referred to as HFSR), diarrhea and constipation, hypertension, alopecia, pyrexia, and fatigue. The effectiveness evaluation indicators included OS, recurrence rate, and overall efficacy. According to the World Health Organization solid tumor efficacy criteria, the treatment effect can be divided into four levels, namely complete remission, partial remission, the progression of the disease, and stable disease. The overall efficacy was defined as (complete remission+partial remission)/total number×100%. Different opinions on a controversial issue were solved through consultation with the third investigator.

Statistical methods

Meta-analysis and sensitivity analysis were performed using Revman 5.3 software. The categorical variables were described by odds ratio (OR) and the corresponding 95% confidence interval (CI). The continuous variables were described by mean difference and the corresponding 95% CI. The χ^2 test was used to assess heterogeneity. A fixed-effects model was applied when there was no or low heterogeneity (I^2<50%, p>0.1) and a random-effects model was applied when there was moderate or high heterogeneity (I^2≥50%, p≤0.1). The publication bias was evaluated by funnel plot analysis and Egger's test, using Stata software. A p-value of <0.05 (two-tailed) was considered statistically significant.

Results

Search results and basic information of the original literature

The process of literature screening is shown in Fig. 1. According to the criteria, this meta-analysis finally included 15 studies (3 RCTs, 5 controlled clinical trials, and 7 retrospective cohort studies).[15–29] Among these, 14 studies were high-quality and one was medium quality. A total of 2,227 patients were enrolled, of whom 1,100 were treated with PTA plus sorafenib and 1,127 were treated with PTA alone. The basic information of the studies is summarized in Table 1.

OS of HCC patients in the PTA+sorafenib group and the PTA-alone group

Seven studies, involving 1,634 individuals, reported the OS rate. The random-effects model was used because of the low grade of heterogeneity in the literature reporting OS rates at 1, 2, and 3 years OS rates (I^2=58%, 55%, and 76%, respectively). Overall, the 1- , 2- and 3-year OS rates of HCC patients in the RFA+sorafenib group were significantly higher than those of the RFA-alone group (1-year OS: OR=2.45, 95% CI: 1.25–4.79, p=0.009; 2-year OS: OR=1.87, 95% CI: 1.17–3.01, p=0.009; 3-year OS: OR=2.25, 95% CI: 1.34–4.85, p=0.004) (see Fig. 2).

MWA is another major category of physical thermal ablation, and we performed a subgroup analysis to summarize the overall survival rates of the two ablation methods. The result showed that MWA combined with sorafenib also significantly increased HCC patients' 1-year OS, with an OR of 2.74 (95% CI=1.42–5.29, p=0.009). Coupled with the results of RFA, it can be considered that HCC patients treated with PTA and sorafenib had a higher 1-year OS than those treated with PTA-alone (OR=2.43, 95% CI=1.50–3.95,

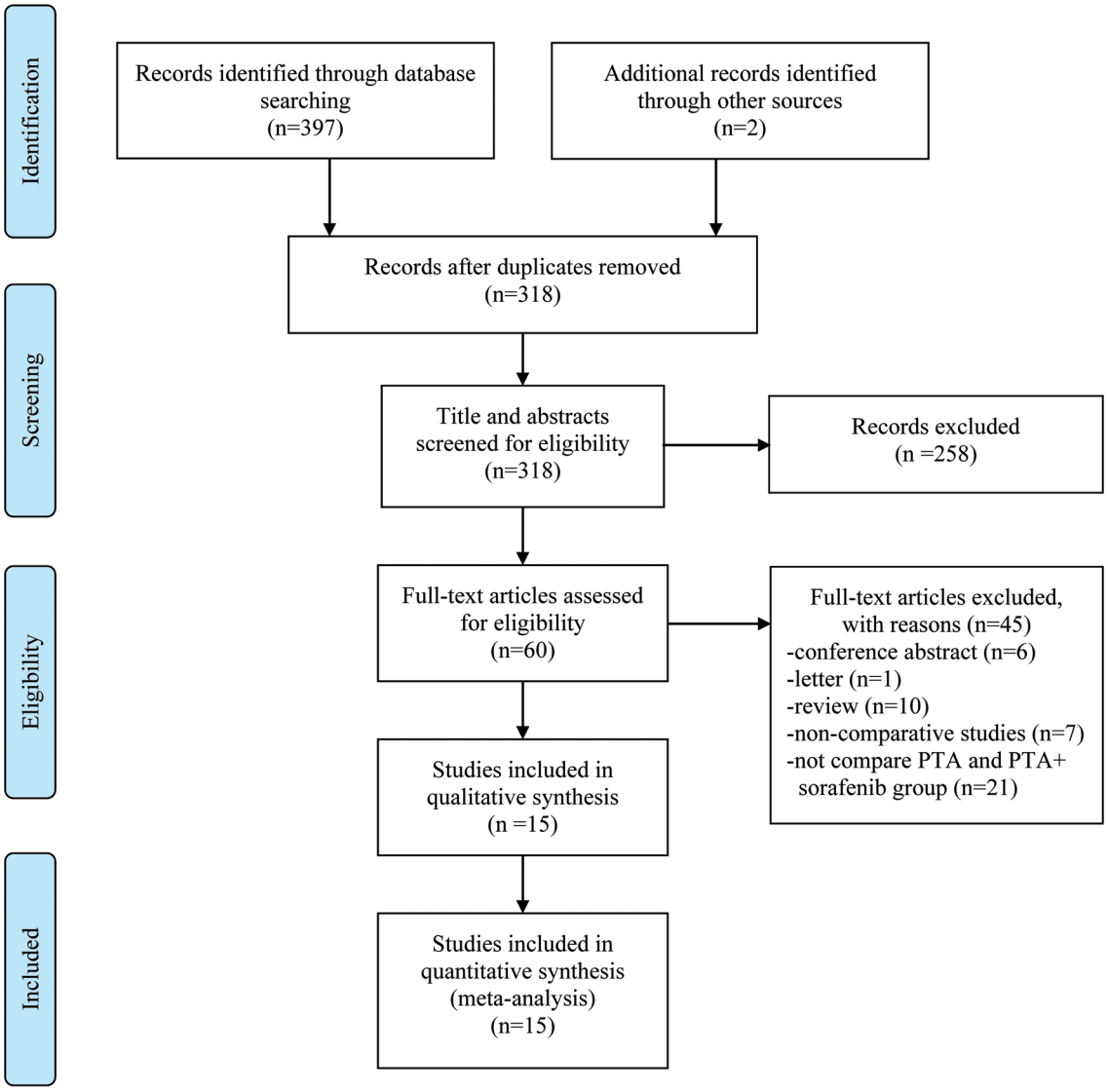

Fig. 1. Inclusion procession.

p=0.003) (see Fig. 3).

Recurrence rates of HCC patients in the RFA+sorafenib group and RFA-alone group

A total of four articles with 1,394 individuals provided information on recurrence rates. After merging them with a random-effects model, the OR of the 2-year recurrence rate was 0.40 (95% CI=0.18–0.87, p=0.02), indicating that the 2-year recurrence rate of HCC patients in the RFA+sorafenib group was lower than that of the RFA-alone group (see Fig. 4).

Overall efficacy of physical thermal ablation of HCC patients

Eight of the studies, involving 562 individuals, mentioned overall efficacy and were divided into two subgroups, according to different thermal ablation methods, four of which used RFA and three of which used MWA. A fixed-effects model was applied, as the studies were homogeneous (I^2=0%, p>0.10). Subgroup analysis showed that the overall efficacy of RFA combined with sorafenib for HCC patients was better than that of RFA alone (OR=2.72, 95% CI: 1.69–4.38, p<0.0001). The efficacy of MWA combined with sorafenib was also better than that of MWA alone (OR=2.18, 95% CI: 1.33–3.57, p=0.002). Overall, 312 patients were treated with PTA and sorafenib and 350 patients were treated with PTA alone; the total OR was 2.45 (95% CI=1.73–3.45, p<0.001), indicating that the overall efficacy of PTA combined with sorafenib was significantly better than that of PTA alone (see Fig. 5).

The radiofrequency interval of patients also indirectly reflects the effect of treatment. Three studies with 200 individuals documented the patient's radiofrequency interval, and a fixed-effects model was used since the heterogeneity test yielded results of p=0.21 and I^2=36%. The radiofrequency interval of HCC patients treated with RFA and sorafenib was longer than that of RFA alone (95% CI: 1.28–1.94, p <0.001), and the effect of combination therapy can be considered to be superior (see Supplementary Fig. 1.).

Table 1. Basic characteristics of the studies

Study	Nation	Type	No. of patients		Age in years[a]	Gender, male/female	Child-Pugh A, *n*	Quality score[b]
Bruix 2015[15]	Spain, China, Japan	RCT	RFA+so	556	58 (24–85)	451/105	541	5
			RFA	558	60 (19–83)	461/97	538	
Yu 2018[16]	China	RCT	RFA+so	23	58.19±4.34	17/6	13	3
			RFA	23	58.25±4.31	16/7	14	
Fu 2020[17]	China	RCT	RFA+so	51	57.4±3.8	34/17	32	4
			RFA	51	57.6±3.9	35/16	30	
Kan 2015[18]	China	CCT	RFA+so	30	53.7±9.6	24/6	12	6
			RFA	32	52.4±8.9	25/7	18	
Zhang 2015[19]	China	CCT	RFA+so	52	28–65 (51.2±13.4)	28/24	22	6
			RFA	68		31/37	43	
Wu 2016[20]	China	CCT	RFA+so	45	48±11	28/17	–	6
			RFA	45	50±9	30/15		
Gong 2017[21]	China	CCT	RFA+so	40	55.7±13.6	23/17	–	7
			RFA	50	53.9±12.4	28/22		
Sun 2011[22]	China	cohort	RFA+so	15	59.5 (35–80)	11/4	7	6
			RFA	15		12/3	9	
Feng 2014[23]	China	cohort	RFA+so	64	49.7±11.2	59/5	64	6
			RFA	64	50.9±10.9	59/5	64	
Fukuda 2014[24]	Japan	cohort	RFA+so	15	72.8±7.9	6/9	15	7
			RFA	30	72.1±8.0	8/22	25	
Li 2014[25]	China	cohort	RFA+so	8	53±6.8	5/3	–	5
			RFA	12	48±11.1	8/4		
Zhu 2018[26]	China	cohort	RFA+so	40	55.5±10.9	3/37	33	6
			RFA	66	54.1±10.1	5/61	48	
Hua 2012[27]	China	cohort	MWA+so	42	57.2 (38–74)	28/14	32	5
			MWA	48	54.7 (39–72)	32/16	37	
Zheng 2013[28]	China	CCT	MWA+so	44	56.2 (38–74)	30/14	34	5
			MWA	50	55.7 (39–72)	33/17	38	
Sun 2018[29]	China	cohort	MWA+so	45	48.5±7.2	31/14	41	6
			MWA	45	47.6±7.1	30/15	40	

[a]Age recorded with mean±standard deviation or median (interquartile range).
[b]Jadad score and Newcastle-Ottawa scale were used for RCTs and non-RCTs respectively.
Abbreviations: CCT, control clinical trial; MWA, microwave ablation; RCT, randomized clinical trial; RFA, radiofrequency ablation; so, sorafenib.

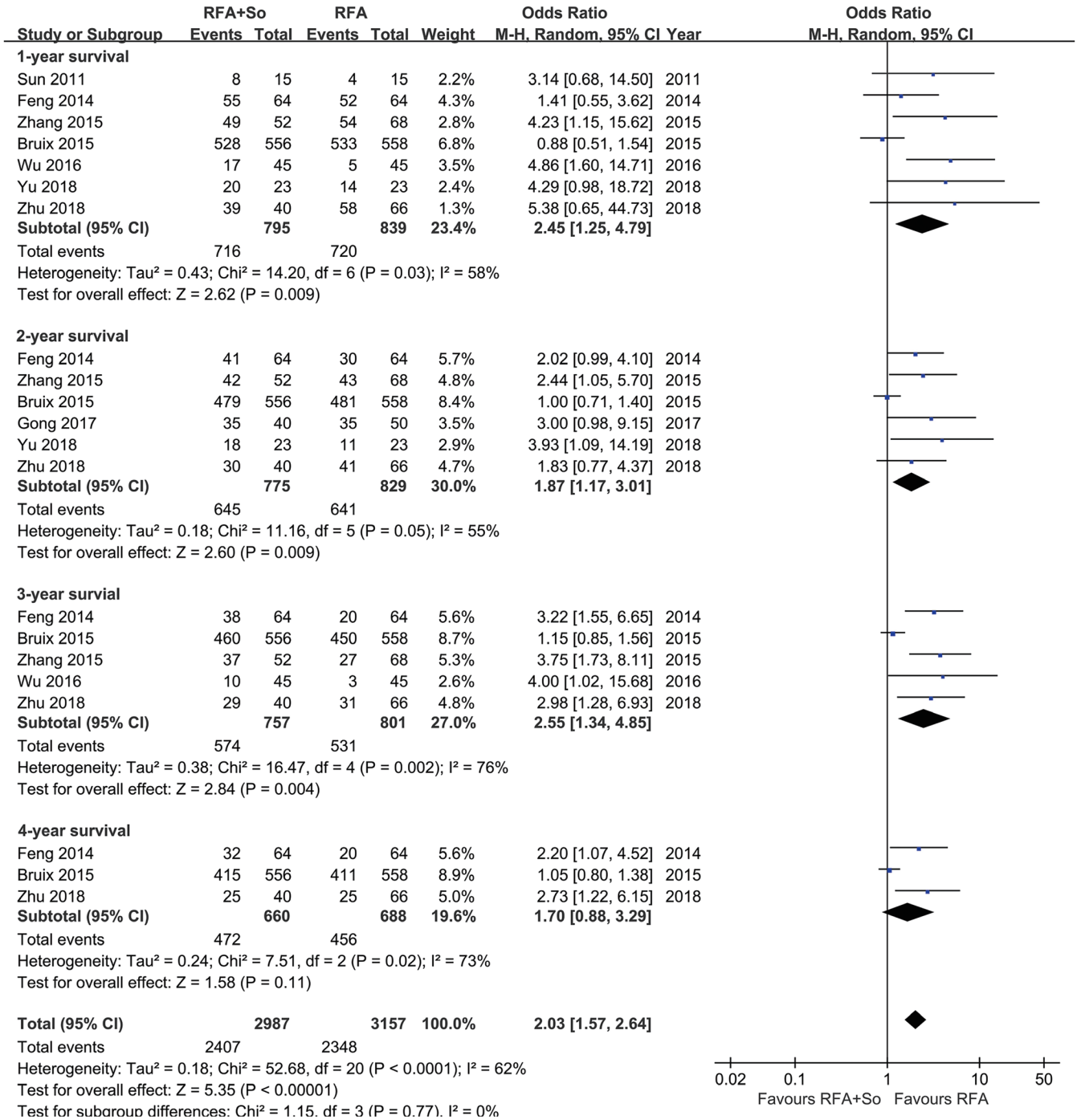

Fig. 2. OS in the RFA+sorafenib group and the RFA-alone group.

Adverse effects in the RFA+sorafenib group and the RFA-alone group

A total of nine studies, involving 1,561 individuals, reported adverse effects after treatment. The incidences of adverse reactions, such as HFSR (OR=47.57, 95% CI: 17.54–129.04, $p<0.01$), diarrhea and constipation (OR=7.01, 95% CI: 2.57–19.08, $p=0.005$), hypertension (OR=8.52, 95% CI: 1.70–42.73, $p=0.009$), and alopecia (OR=15.26, 95%CI: 9.43–24.71, $p<0.01$), in the combination therapy group were significantly higher than those in the PTA-alone group (see Fig. 6).

Sensitivity analysis and publication bias

The sensitivity analysis showed that the study conducted by Bruix *et al*.[15] significantly affected the calculated ORs of OS

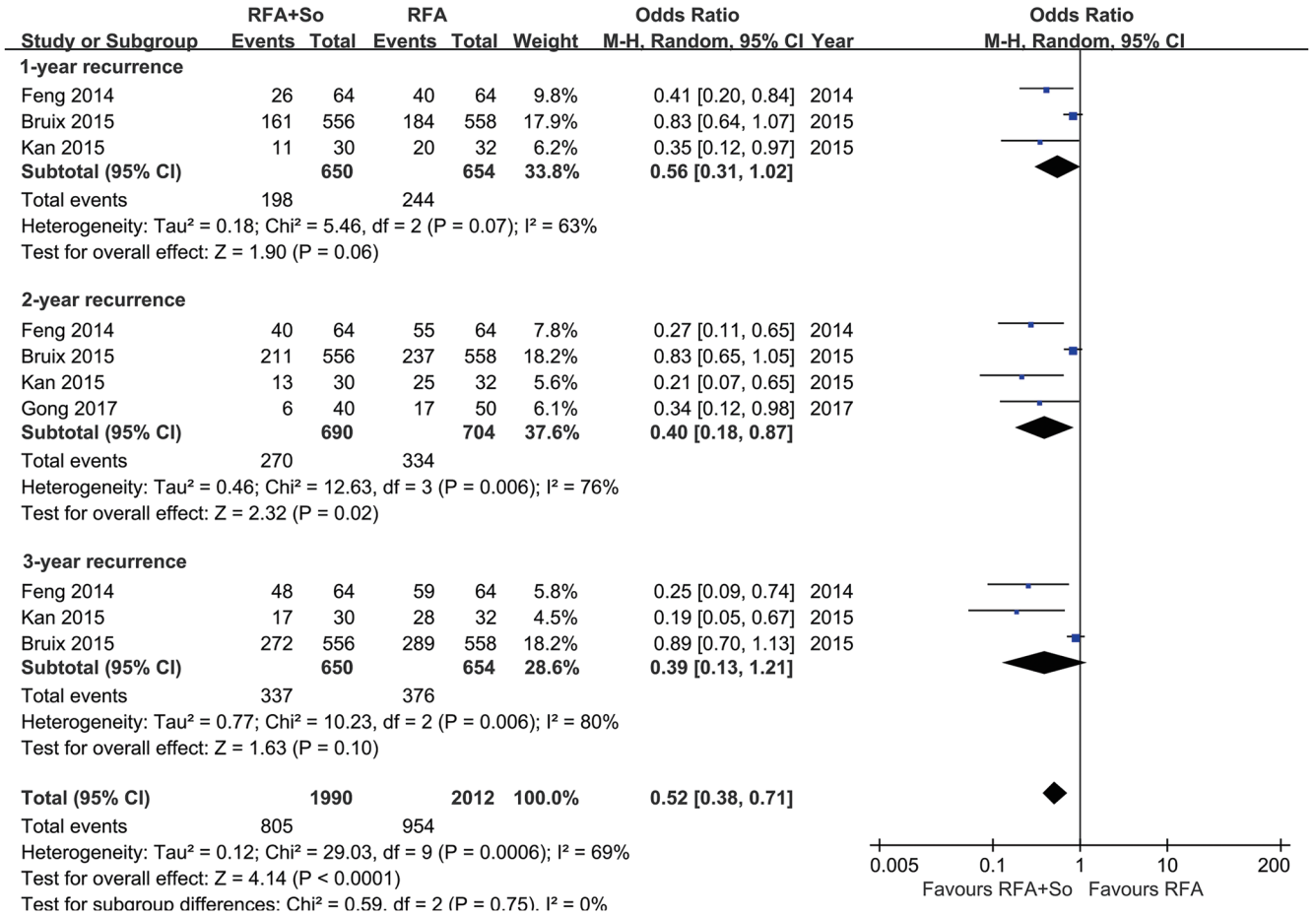

Fig. 3. Subgroup analysis of 1-year OS in the RFA and MWA treatment groups.

and recurrence rate. After excluding this trial, the I^2 value declined to 0%. The funnel plot of the 1-year OS revealed asymmetry; however, after excluding the Bruix 2015[15] study, the Egger's test results yielded p=0.107, indicating that there was no substantial publication bias (see Fig. 7). Further reading and evaluation found that this study was a high-quality RCT, recorded a number of indicators, provided results that were credible, and had application value. The reason why the results were different from others might be due to the variety of ethnicity (Spain, China, and Japan) and large sample size (n=1,114). In summary, we retained this high-quality study.

Discussion

Ablation combined with chemotherapy has been widely used in cancer treatment, such as for small cell lung cancer, advanced renal cell carcinoma, etc.[30,31] In the treatment of HCC, PTA has the advantages of little trauma and quick recovery, and can be applied as treatment of multiple times. However, the size of the lesion and the existence of heat dissipation make it difficult to ablate completely, resulting in a higher risk of local recurrence. When the diameter of the tumor is more than 3.0 cm, it is more likely to recur.[32,33] Therefore, reducing the recurrence rate of tumors after thermal ablation has become the focus of treatment improvement.

RFA+sorafenib: Higher survival rate and efficiency, longer radiofrequency interval and lower recurrence rate

Sorafenib, a kinase inhibitor, has been shown to have a synergistic effect in combination with RFA. It has the function of inhibiting angiogenesis in tumors, thereby reducing heat loss and indirectly enhancing ablation. Sorafenib itself also inhibits tumor cell proliferation and differentiation. From the perspective of evidence-based medicine, in order to explore whether the therapeutic effect of RFA combined with sorafenib is better than using RFA alone, a total of 15 studies were included in the meta-analysis, 12 of which were about RFA and included 939 patients treated with RFA plus sorafenib and 1,014 patients treated with RFA alone. We summarized the original literature and found that the RFA+sorafenib group had higher 1-, 2-, and 3-year OS and lower 2-year recurrence rate compared with the RFA-alone group; RFA combined with sorafenib also significantly extended the RF interval, which indirectly reduced the RFA-related adverse effect, and also reduced the pain and financial burden of patients.

However, the survival and recurrence indicators of the RFA+sorafenib group were not always better than the RFA-alone group. The 4-year survival rate and the 1- and 3-year recurrence rates were not significantly different between the two groups. Probably due to (1) a large-sample-size study,[15] there was no difference in the 1- and 3 recurrence

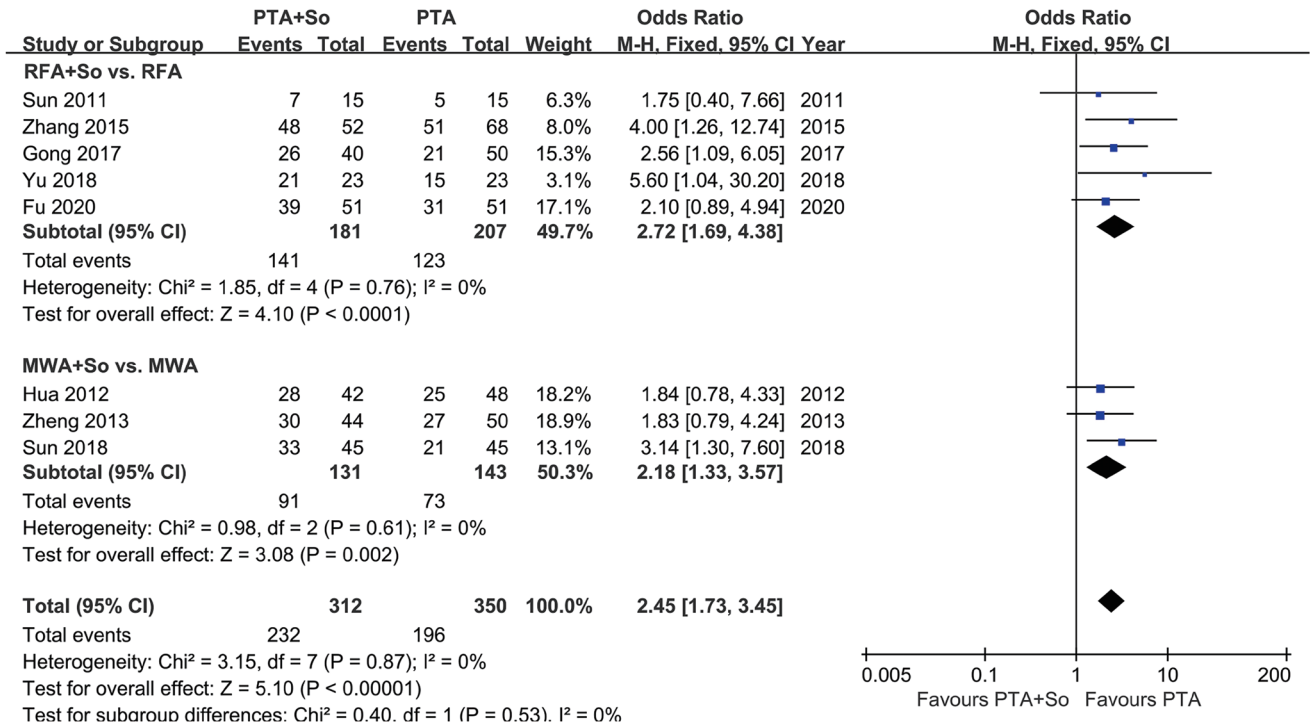

Fig. 4. Recurrence rates in the RFA+sorafenib group and the RFA-alone group.

rates between the two groups, since that study had a large weight in the meta-analysis, and (2) few studies reported the 4-year OS and, the 1- and 3-year recurrence rates and the heterogeneity was significant.

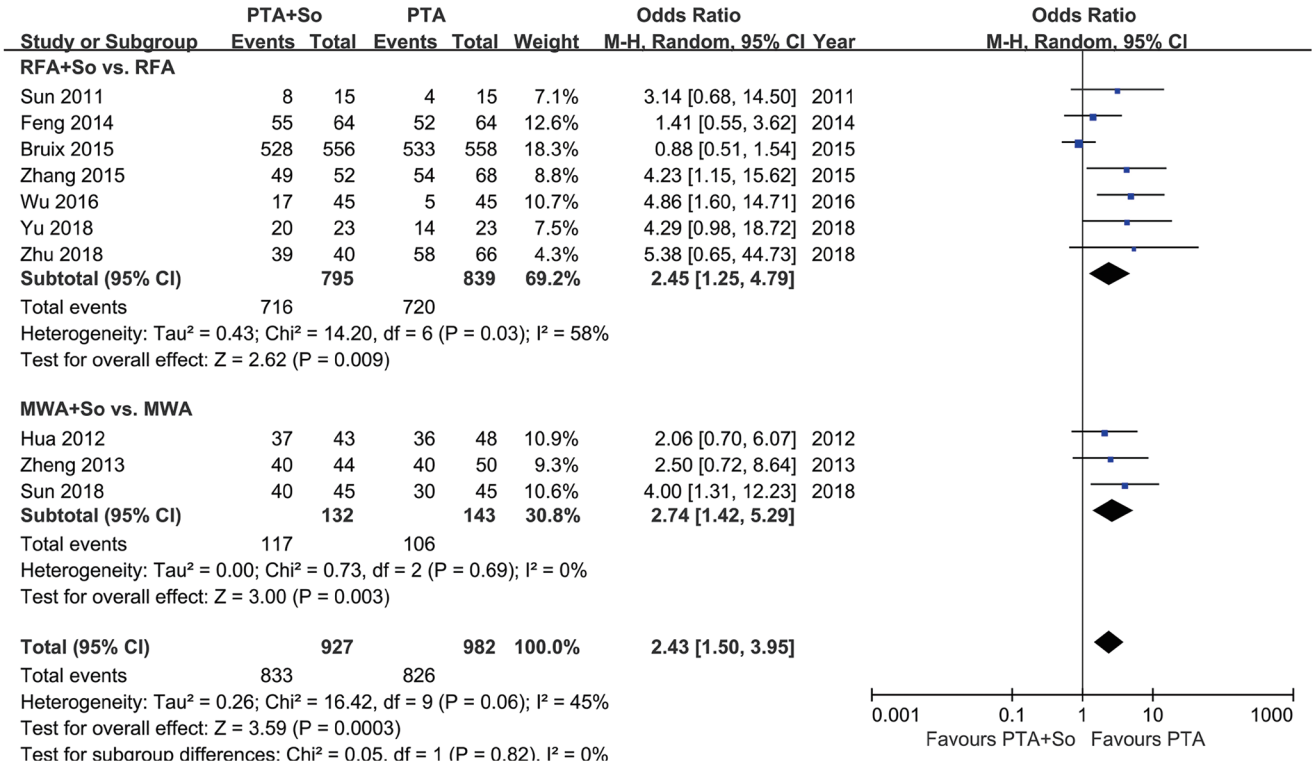

Fig. 5. Subgroup analysis of overall efficacy of RFA and MWA in HCC patients.

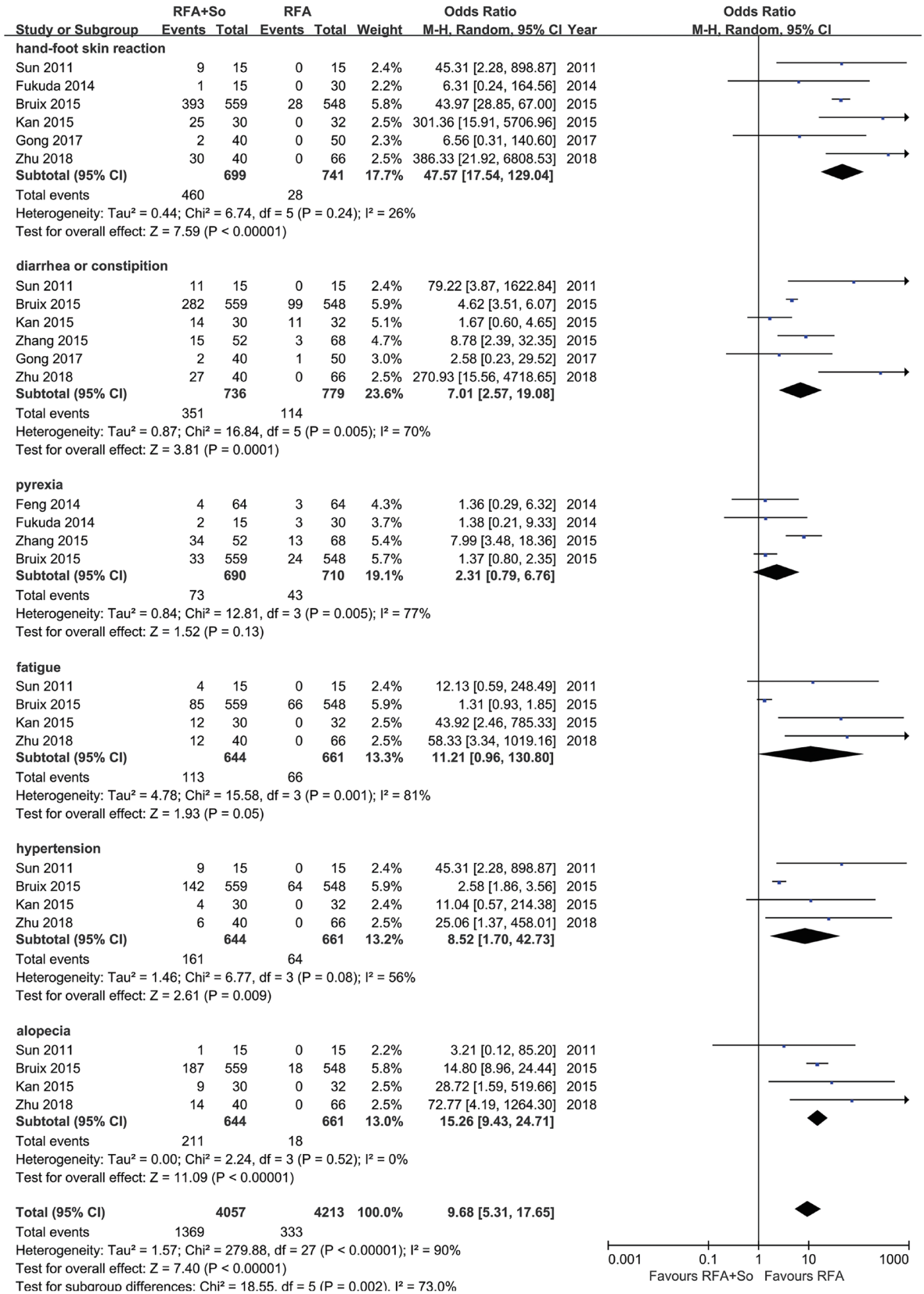

Fig. 6. Adverse effects of HCC patients in the RFA+sorafenib group and the RFA-alone group.

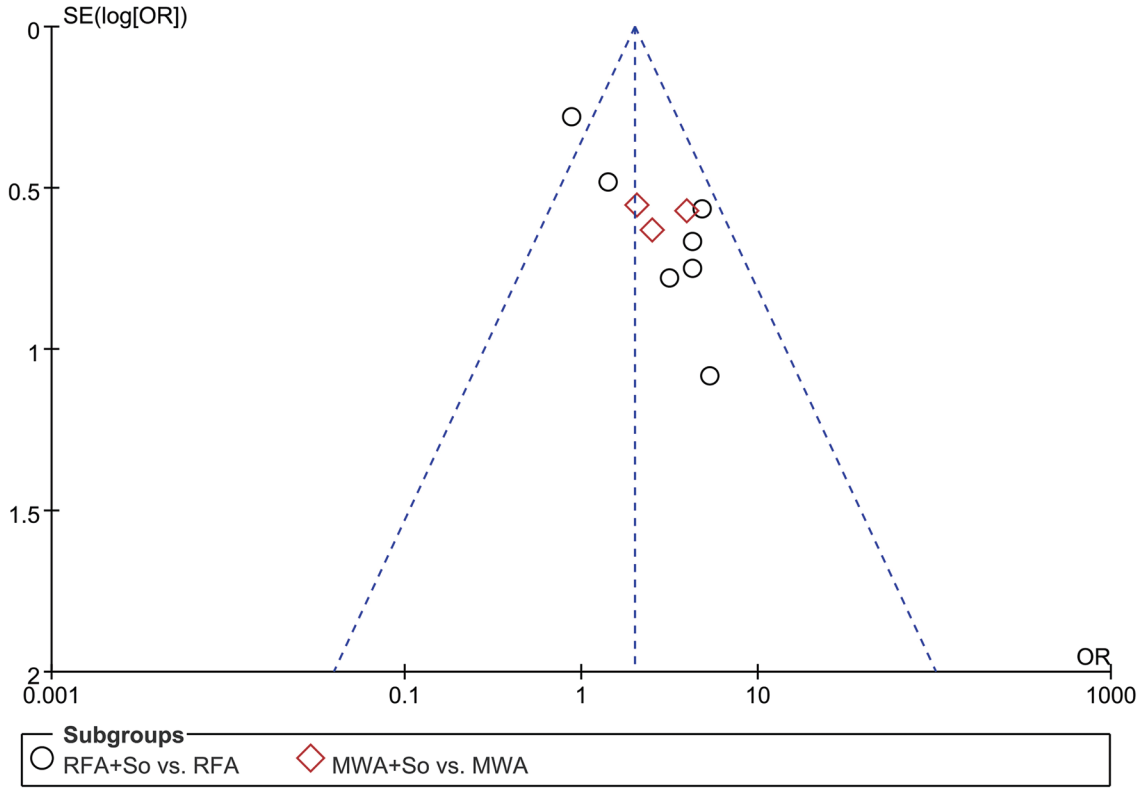

Fig. 7. Funnel plot of 1-year OS with 95% CI to assess publication bias.

Sorafenib brings significant adverse reactions

Sorafenib is a tyrosine kinase inhibitor that inhibits various receptors, such as RAF-1, VEGFR-2, and FLT-3, and has been used for first-line treatment of liver cancer, with millions of patients benefiting from it.[11] Our meta-analysis showed that combined use with sorafenib can significantly improve the effect of RFA, but the incidence of adverse reactions was significantly higher. Studies have suggested that the mechanism of HFSR may be that sorafenib can inhibit VEGF and PDGF, and damage the capillaries. When the hands and feet are subjected to direct pressure, the vessels are again mechanically damaged, thus prompting an inflammatory response and blister formation.[34] As we know, severe adverse effects may lead to the suspension of treatment and ultimately affect the patient's survival. There were also studies suggesting that diarrhea in HCC patients treated with sorafenib predicts better OS.[35,36] Reig *et al*.[37] believed that the development of dermatological adverse events within 60 days after the start of sorafenib was associated with better survival. Regardless of whether the adverse reaction can directly affect survival, it may affect the quality of life and cause a dose change or interruption of sorafenib, which may limit the anti-tumor effect. Therefore, standardized treatment and dose adjustment of sorafenib are necessary to improve the survival and life-quality of HCC patients.

RFA and MWA

Both RFA and MWA are PTA techniques. The mechanism of RFA is that the polar molecules in the tumor will run at high speed under the influence of high-voltage, generating heat to kill tumor cells. The MWA electrode emits microwaves, and the polarity of the water molecules in the tumor is changed by the voltage to form an alternating electric field to generate heat. MWA has higher thermal efficiency, faster heating speed, better heat dissipation resistance,[38] the ablation range is larger, the operation time is also shorter, and the MWA consumables are relatively inexpensive, which can reduce the economic burden on patients. Compared with RFA, the development of MWA was relatively late, first put into clinical application in China and Japan. Therefore, there were few MWA studies and limited survival index in this meta-analysis.

From the subgroup analysis of the existing literature, the total effective rate and 1-year survival rate of the combination group were higher than in the control group. There have been studies comparing the efficacy and safety of RFA and MWA, but the findings are still inconclusive. After summarizing the high-quality RCTs, this can serve as a topic of our next evaluation.

Limitations and summary

The studies selected for this meta-analysis were not all RCTs. Retrospective cohort studies have selection and recall biases, and the number of original articles was limited. In addition, the entire study cohort for this meta-analysis was incomprehensive in regards to race, and most of the research population was Chinese, with some Japanese and Spanish. The 2015 epidemiological survey report showed that nearly 27% of the world's cancer deaths are from China, and HCC is the second most common cause of cancer-related mortality in China, after lung cancer.[39] Due to hepatitis B virus infection, aflatoxin exposure, alcohol abuse and environmental pollution, China has become the country

with the highest incidence of liver cancer (about 55% of the world's full rate) and with the largest number of deaths.[40] China has a long way to go to control the incidence and mortality of liver cancer, which may be one of the important reasons why most of the research population in this meta-analysis was Chinese. Except for overall efficacy and radiofrequency interval, the heterogeneity of other indicators was remarkable. This may be due to differences in sample size, tumor size and number, patient age, and previous treatment history.

Chen *et al*.[41] have also conducted a meta-analysis of the efficacy of RFA combined with sorafenib in patients with HCC. Their results showed no significant difference in OS and recurrence rates, but only included five articles of RFA+sorafenib vs. RFA alone. In addition, their meta-analysis also included literature that did not only use RFA as a control group, which might affect the overall reliability. Our study strictly screened out 15 original studies, and our conclusions are different from theirs.

Nowadays, the ideal therapy for HCC is still being explored. A comprehensive comparative analysis of the scoring system for HCC published in the *World Journal of Hepatology* told us that an appropriate scoring system should be selected according to the patient's situation and a personalized strategy for HCC patients should be developed.[4] The characteristics and liver function of the patients determine whether the treatment is curative or only palliative, or a combination of the two, as mentioned in this study (RFA+sorafenib). Therefore, the formulation of HCC treatment strategy needs the combination of multiple disciplines, such as hepatobiliary surgery, interventional radiology, and oncology. Personalized settings and adjustments would be needed at any time, according to the patient's progression, adverse reactions and complications.

According to the current meta-analysis, PTA combined with sorafenib in the treatment of HCC is better than RFA or MWA alone. Patients who undergo the combination therapy should be closely observed for changes in skin, blood pressure, body temperature, gastrointestinal reactions, etc., to reduce the dose or discontinue the drug if necessary, and actively initiate symptomatic treatment. Although the subgroup analysis and random-effects models were applied in this study, the heterogeneity between studies may still affect the reliability of the results. The superiority of PTA plus sorafenib over PTA-alone still needs to be confirmed by more high-quality studies.

Conclusions

RFA or MWA combined with sorafenib has better efficacy than PTA alone; however, the adverse reactions are obvious. It is necessary to evaluate the safety of combination therapy and pay close attention to the adverse reactions of patients.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (BJ, QY), acquisition of data (YL, MJ), analysis and interpretation of data (MJ, BJ), drafting of the manuscript (MJ), critical revision of the manuscript for important intellectual content (XF, WX), administrative, technical, or material support, study supervision (QY).

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