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ORIGINAL ARTICLE

Sorafenib combined with radiofrequency ablation as treatment for patients with hepatocellular carcinoma: a systematic review and meta-analysis

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Summary

Purpose: *To evaluate the safety and efficacy of a combination of sorafenib and radiofrequency ablation (RFA) in patients with hepatocellular carcinoma (HCC).*

Methods: *A systematic literature search was conducted using PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBMdisc), WanFang Database, for all years up to January 2017. Pooled analyses of overall survival (OS), tumor-free survival, recurrence rates and adverse events were performed.*

Results: *IA total of 7 case control studies consisting of 1765 HCC patients were selected and included in this meta-analysis. Patients treated with sorafenib-RFA and sorafenib alone, RFA alone and surgery had no significant differences in 1-year OS (p=0.310), 2-year OS (p=0.262), 3-year OS (p=0.179), 4-year OS (p=0.238) and 5-year OS (p=0.933); 1-year recurrence rate (p=0.653), 2-year recurrence rate (p=0.416), 3-year recurrence rate (p=0.304), and 5-year recurrence rate (p=0.807); 1-year tumor-free survival rate (p=0.943), 3-year tumor-free survival rate (p=0.825), 5-year tumor-free survival rate (p=0.893) and overall adverse events (p=0.097).*

Conclusion: *RFA-sorafenib combination may not be a better approach for patients with HCC. More well-designed randomized clinical trials (RCTs) should be performed before we finally arrive at a rational comprehension about the therapeutic value of the discussed options.*

Key words: *hepatocellular carcinoma, meta-analysis, radiofrequency ablation, sorafenib*

Introduction

Hepatocelluar carcinoma (HCC) is the sixth most lethal malignancy and a prevalent liver cancer wordwide [1]. Treatment of this malignancy should be carefully selected based on its stages. Currently, hepatic resection (HR), liver transplantation (LT), RFA, transhepatic arterial chemoembolization (TACE) and sorafenib are recommended as the main therapeutic modalities [2]. Among these therapeutic approaches, RFA is recognized as the main ablative method for patients with HCC, which also functions as a bridge to liver transplantation [3]. According to the Barcelona Clinic Liver Cancer (BCLC) system, patients with HCC diagnosed at a BCLC 0 should be considered for surgery only if a transplant is available; if not, RFA should be the first-line option [4]. However, the long-term prognosis for HCC patients treated with RFA is not satisfactory owing to the high incidence of recurrence, including multicentric carcinogenesis and local tumor recurrence [5]. Therefore, multimodality treatments for HCC patients are needed to prevent recurrences.

Sorafenib is a multikinase inhibitor with a broad spectrum of anticancer activities on tumor cell proliferation and angiogenesis, which targets endothelial growth factor receptors (VEGFR) 1, 2,

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and 3; Raf kinase; platelet-derived growth factor receptor β (PDGFR β); RET-receptor tyrosine kinase; c-KIT; and FMS-like tyrosine kinase 3 (FLT-3). Compared with placebo, sorafenib can prolong OS in patients with metastatic renal-cell carcinoma (RCC) [6-8]. In a multifocal tumor model of HCC, sorafenib and RFA alone resulted in a significant volume reduction of non-RFA-targeted tumors, but this effect was enhanced when both modalities were combined [9]. Sorafenib can initially promote necrosis and delay tissue repair after RFA, which also can adversely affect the normal liver tissue and increase RFA toxicity. Thus, the overall advantages of sorafenib-RFA need to be weighed against its clinical effects and adverse effects.

Therefore, we did a systematic review to evaluate the safety and efficacy of a combination of sorafenib and RFA approach in patients with HCC. This may provide additional information regarding the efficacy of sorafenib.

Methods

Literature search

Related studies were searched in PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBMdisc), and WanFang Database up to January 2017. The search was conducted using MeSH terms, keywords, and combined words, which included hepatocellular carcinoma, hepatocellular neoplasm, liver cancer, liver carcinoma, liver neoplasm, liver tumor, sorafenib, nexavar, radiofrequency ablation, RF ablation and RFA.

Inclusion criteria

Eligible studies for this meta-analysis should meet the following criteria: (1) patients should have pathological or histological confirmation of HCC; (2) the studies should compare the clinical outcomes of sorafenib-RFA and sorafenib alone, RFA alone, or other treatments; (3) the studies should report at least 1-, 2-, 3-, 5-year, OS, tumor-free survival, recurrence rates and adverse events.

Exclusion criteria

The following studies were excluded from the meta-analysis: (1) original articles which did not report comparative outcomes about the therapeutic value of sorafenib-RFA and other treatments; (2) review articles, case reports, abstracts, editorials, letters and meta-analyses; (3) articles without sufficient data to analyze after contacting the authors of the study; (4) duplicate publications.

Data extraction

Two reviewers independently extracted the relevant data from the selected studies by using a predesigned data form. Any disagreements were solved by discussion. Data retrieved from each publication included: (1) basic characteristics of each study such as the first author, year of publication, country, sample size, treatment regimens, research duration and the time of follow up; (2) clinical outcomes: 1-, 2-, 3-, 5-year OS, tumor-free survival, recurrence rates and adverse events.

Quality assessment

Quality assessment for each eligible study was carried out by the same two reviewers who independently read and scored each publication, according to Newcastle-Ottawa Scale (NOS) [10]. When discrepancy occurred, a third author was consulted. Studies with NOS≥6 were considered to be of high quality.

Statistics

All statistical analyses were done using the STATA 12.0 software. Heterogeneity was evaluated with x^2-based Q-test: if the p value was higher than 0.1 or I^2 was lower than 50%, this demonstrated that all included studies were lacking heterogeneity, and the Mantel-Haenszel method (fixed effect model) was used to merge the studies. Otherwise the random effect model was adopted. Calculation for dichotomous variables was carried out using odds ratios (OR) and their 95% confidence interval (95%CI) as the summary statistic. Two-sided $p<0.05$ was considered statistically significant. Sensitivity analysis was performed to evaluate the stability of the results. Publication bias was evaluated by using the Begg's and Egger's test.

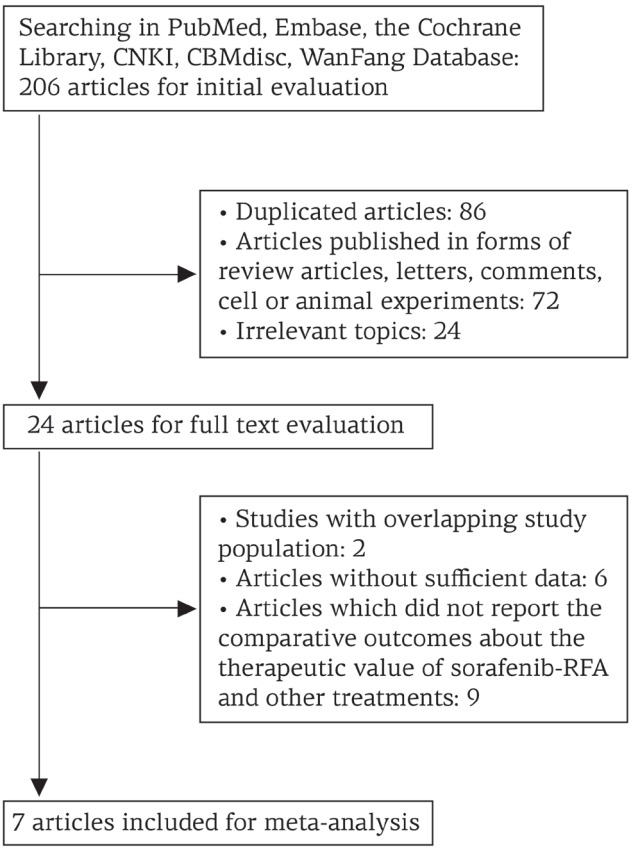

Figure 1. Flow chart of study selection process.

Results

Baseline characteristics of included studies

According to the search strategy, our search yielded a total of 206 studies on RFA-sorafenib combination treatment from published works. Following the inclusion and exclusion criteria, 7 case-control studies [8,11-16] consisting of 1765 HCC patients were selected and included in this meta-analysis. Detailed information about the flow chart of study selection process is shown in Figure 1.

The baseline characteristics of the included publications are presented in Table 1. Regarding the geographical distribution, 3 studies were conducted in China, 1 in Japan and 1 in Italy. 820 patients underwent RFA-sorafenib combination and 945 patients underwent RFA-alone, sorafenib-alone or surgery. NOS scores were more than 6 in all studies. The detailed information of the included studies are summarized in Table 1.

Overall survival

Comparing patients in the RFA-alone, sorafenib-alone or surgery therapeutic approach groups, patients in the RFA-sorafenib combination group did not have inferior 1-year OS

Table 1. Baseline characteristics of included studies

Study	*Country*	*Treatment*		*Treatment regimens*	*Sample (n)*		*Mean age, years (range)*		*Child-Pugh A (n, %)*		*HBV (n, %)*		*Follow up (mos)*	*NOS*
		Arm 1	*Arm 2*		*Arm 1*	*Arm 2*	*Arm 1*	*Arm 2*	*Arm 1*	*Arm 2*	*Arm 1*	*Arm 2*		
Giorgio et al. 2016	Italy	RFA+So	So-alone	RF, 80-100 Watt for 5-8 minutes. Sorafenib, 800mg/day, Oral(either in the combination or sorafenib alone groups.	49	50	71 (69-75)	72 (70-76)	49	50	16 (32.65)	17 (34.00)	36	7
Kan et al. 2015	China	RFA+So	RFA-alone	RF,10-15 mintunes, area was 0.5cm wider than the tumor. Sorafenib, 400mg twice daily on Day4-7 after the1st RFA.	30	32	53.7±9.6	52.4±8.9	12 (40.00)	14 (43.75)	30	32	40	6
Yan et al. 2016	China	RFA+So	Surgery	RF, 30-50W. Sorafenib, 400mg, twice daily, orally 2h after a meal,for 4 weeks.	60	60	62.6±2.5		-		-		60	6
Fukuda et al. 2014	Japan	RFA+So	RFA-alone	RF, 40-60W for 12 minutes. Sorafenib, 400-800mg, twice per day for 7 days.	16	136	72.8±7.9	72.1±8.0	16 (100)	120 (88.20)	2 (12.50)	13 (9.56)	30	7
Feng et al. 2014	China	RFA+So	RFA-alone	RF, at the highest energy setting for 5 minutes. Sorafenib, orally at a dosage of 400mg twice daily.	64	64	49.7±11.2	50.9±10.9	-		-		36	6
Wu et al. 2016	China	RFA+So	RFA-alone	RF, performed by RITA RF-1500. Sorafenib, 800mg, twice per day after a meal.	45	45	50±9	48±11	-		-		36	6
Bruix et al 2015	Spain, Japan and China	RFA+So	RFA-alone	RF, local ablation. Sorafenib, first to 400mg once a day and then to 400mg every other day.	556	558	58 (24-85)	60 (19-83)	541 (97.30)	538 (96.42)	282 (50.72)	264 (47.31)	60	7

RFA: radiofrequency ablation, So: sorafenib, NOS: Newcastle-Ottawa Scale

(OR=1.08, 95%CI: 0.93-1.25, p=0.310), 2-year OS (OR=1.10, 95%CI: 0.93-1.31, p=0.262), 3-year OS (OR=1.12, 95%CI: 0.95-1.33, p=0.179), 4-year OS (OR=1.18, 95%CI: 0.90-1.54, p=0.238) and 5-year OS (OR=0.98, 95%CI: 0.57-1.67, p=0.933). More details and heterogeneity tests are displayed in Figure 2.

Recurrence rate

With observable interstudy heterogeneity, there were no significant differences in 1-year recurrence rate (OR=0.89, 95%CI: 0.54-1.47, p=0.653), 2-year recurrence rate (OR=0.82, 95%CI: 0.51-1.33, p=0.416), 3-year recurrence rate (OR=0.78, 95%CI: 0.49-1.25, p=0.304), and 5-year recurrence rate (OR=0.78, 95%CI: 0.11-5.52, p=0.807), between RFA-sorafenib combination group and control group (sorafenib alone, RFA alone, or surgery). Heterogeneity tests are depicted in Figure 3.

Tumor-free survival rates

There was only one study which reported tumor-free survival rates. The results of meta-analysis showed that patients in the RFA-sorafenib combination group did not gain significantly shorter 1-year tumor-free survival rate (OR=1.02, 95%CI: 0.60-1.72, p=0.943), 3-year tumor-free survival rate (OR=0.93, 95%CI: 0.50-1.75, p=0.825), and 5-year tumor-free survival rate (OR=0.95, 95%CI: 0.47-1.94, p=0.893).

Subgroup analysis of overall survival and recurrence rate

Subgroup analysis by treatment method indicated that RFA+sorafenib vs sorafenib-alone, RFA+sorafenib vs RFA-alone, neither RFA+sorafenib vs surgery did not show significant difference in 1-, 3-, and 5-year survival rates. However, compared with patients in the RFA-alone group, patients in the RFA-sorafenib

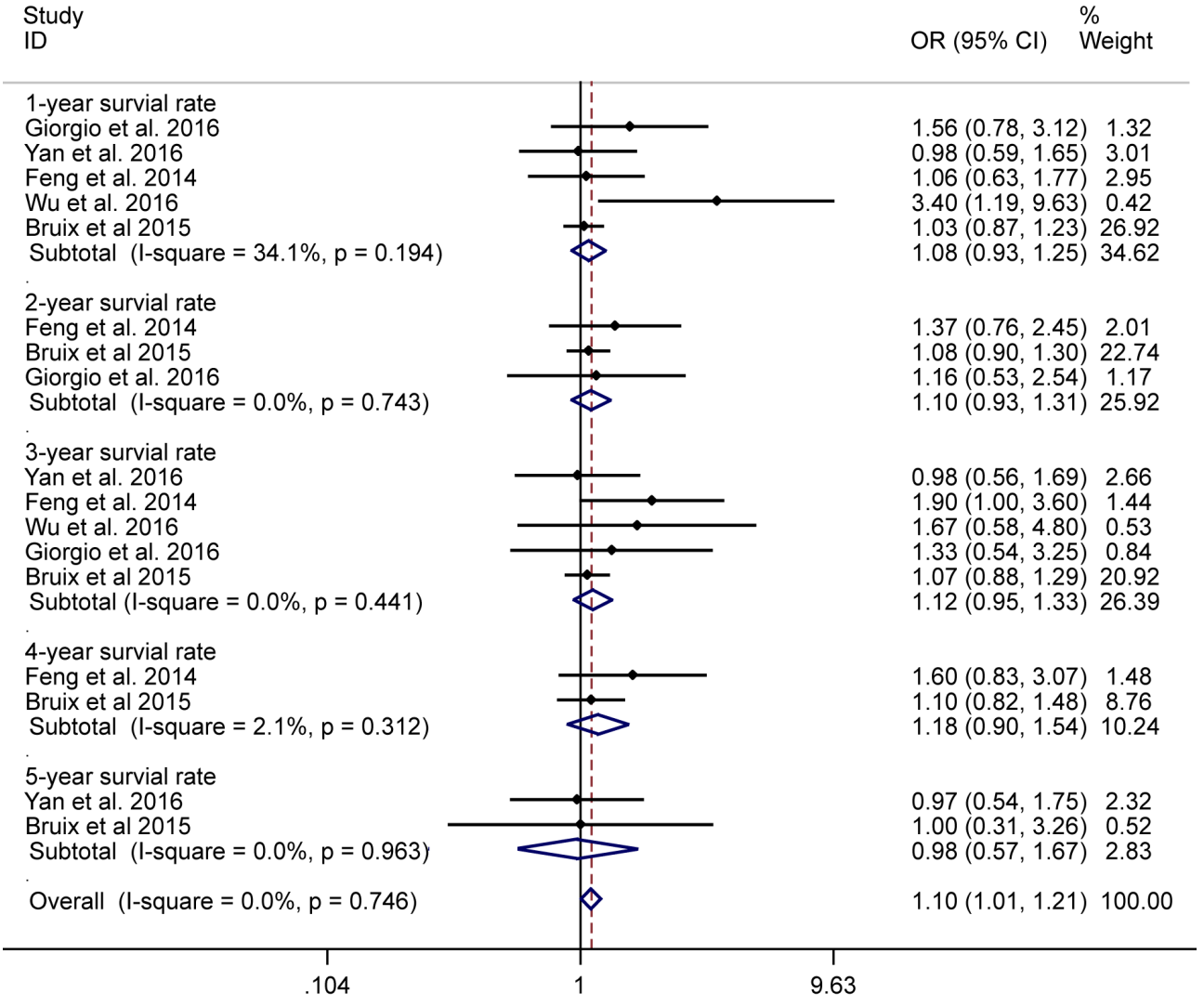

Figure 2. Meta-analysis of overall survival.

combination group had a lower 5-year recurrence rate (OR=0.29, 95%CI: 0.12-0.70, p=0.004). More details are shown in Table 2.

Adverse events

The results of meta-analysis based on the random effects model revealed that there were no significant differences in the overall adverse events (OR=1.51, 95%CI: 0.928-2.452, p=0.097), fever (OR=1.36, 95%CI:1.36, 0.43-4.29, p=0.604), abdominal bleeding (OR=1.89, 95%CI: 0.32-11.26, p=0.487), abdominal pain (OR=0.75, 95%CI: 0.35-1.62, p=0.463), hand-foot skin reaction (OR=4.77, 95%CI: 0.79-28.80, p=0.089), diarrhea (OR=2.16, 95%CI: 0.68-6.79, p=0.189), weight loss (OR=2.47, 95%CI: 0.78-7.84, p=0.124), asthenia (OR=1.40, 95%CI: 0.52-3.78, p=0.504), increased ALT (OR=1.27, 95%CI: 0.82-1.96, p=0.292), increased AST (OR=1.26, 95%CI: 0.80-1.98, p=0.313), excempting infection (OR=0.06, 95%CI: 0.01-0.43, p=0.006).

Publication bias

Funnel plots of OS and recurrence rate did not show significant asymmetry (Figure 4a and 4b).

Discussion

HCC is a primary malignant disease derived from liver cells, and is considered as one of the most common digestive system cancers worldwide [17]. The treatment options for HCC include hepatectomy, liver transplantation, chemotherapy, ablative therapy and molecular targeted therapies [18]. Moreover, hepatectomy and liver transplantation are considered to be curative methods [19]. However, in fact, HCC is usually diagnosed at advanced stages when the application of curative treatments seems to be of little value [20]. For intermediate HCC indentified by the BCLC, the local-regional therapies including RFA, TACE, and percutaneous ethanol injection (PEI) are suggested

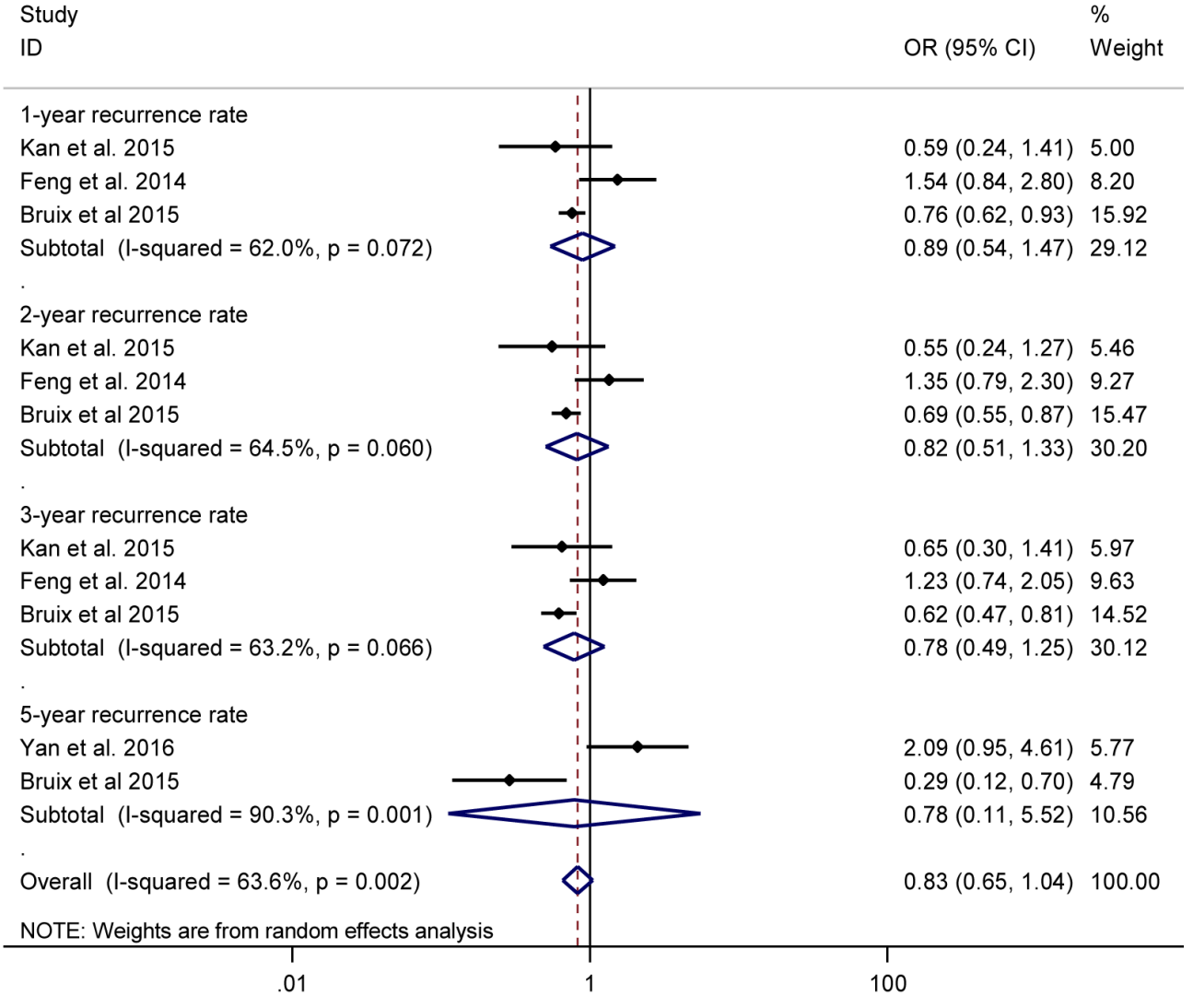

Figure 3. Meta-analysis of recurrence rate.

as the optimal treatments [21]. These methods have been shown to prolong survival and treatment response of patients, particularly RFA and TACE [22].

Among the numerous molecular targeted drugs, sorafenib (nexavar), an oral multi-target kinase inhibitor, has been clinically approved for the treatment of advanced renal cell carcinoma and HCC, and studies with sorafenib as potential therapeutic strategy are now ongoing [23]. Being a multi-target kinase inhibitor, sorafenib can block tumor cell proliferation by inhibiting the activity of B-Raf, Raf-1 and kinases in the Ras/Raf/MEK/ERK signaling pathway [24]. Additionally, sorafenib can inhibit angiogenesis through targeting of the hepatocyte factor receptor (c-Kit),

Table 2. Subgroup analysis of overall survival and recurrence rate

Subgroups	*Overall survival*				*Recurrence rate*			
	n	*OR*	*95%CI*	*p*	*n*	*OR*	*95%CI*	*p*
1-year	5	1.08	0.93~1.25	0.310	3	0.89	0.54~1.47	0.653
RFA+So *vs.* So-alone	1	1.56	0.78~3.12	0.215			-	
RFA+So *vs.* RFA-alone	3	0.98	0.59~1.65	0.411	3	0.89	0.54~1.47	0.653
RFA+So *vs.* Surgery	1	1.07	0.91~1.25	0.945			-	
3-year	5	1.12	0.95~1.33	0.179	3	0.78	0.49~1.25	0.304
RFA+So *vs.* So-alone	1	1.33	0.53~3.31	0.935			-	
RFA+So *vs.* RFA-alone	3	1.13	0.94~1.36	0.179	3	0.78	0.49~1.25	0.304
RFA+So *vs.* Surgery	1	0.98	0.56~1.70	0.545	-			
5-year	2	0.98	0.57~1.67	0.933	2	0.78	0.11~5.52	0.807
RFA+So *vs.* So-alone			-				-	
RFA+So *vs.* RFA-alone	1	1.00	0.31~3.26	0.995	1	0.29	0.12~0.70	0.004
RFA+So *vs.* Surgery	1	0.97	0.54~1.75	0.924	1	2.09	0.95~4.61	0.069

RFA: radiofrequency ablation, So: sorafenib

Table 3. Meta-analysis of adverse events

Adverse events	*n*	*OR*	*95%CI*	*I²*	*Ph*	*p*
Fever	4	1.36	0.43~4.29	77.50%	0.004	0.604
Abdominal bleeding	4	1.89	0.32~11.26	70.80%	0.016	0.487
Abdominal pain	3	0.75	0.35~1.62	72.10%	0.028	0.463
Hand-foot skin reaction	3	4.77	0.79~28.80	80.10%	0.007	0.089
Diarrhoea	2	2.16	0.68~6.79	72.70%	0.056	0.189
Weight loss	2	2.47	0.78~7.84	74.20%	0.049	0.124
Asthenia	1	1.40	0.52~3.78	-	-	0.504
Infection	1	0.06	0.01~0.43	-	-	0.006
Increased ALT	1	1.27	0.82~1.96	-	-	0.292
Increased AST	1	1.28	0.80~1.98	-	-	0.313
Overall		1.51	0.928~2.452	88.40%	0.0001	0.097

Ph: p value of Q test for heterogeneity test

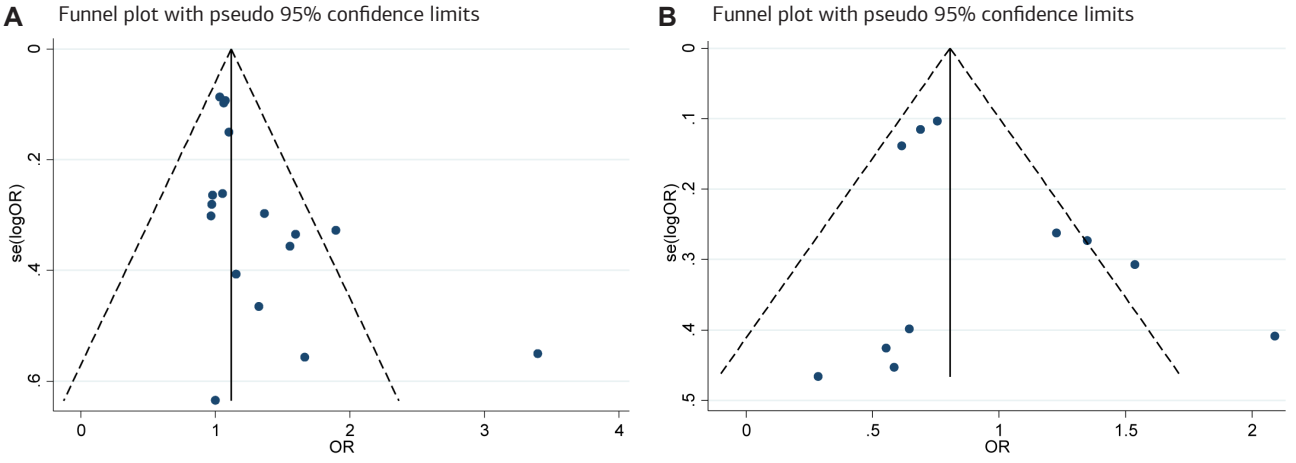

Figure 4. (A) Funnel plot of overall survival; **(B)** Funnel plot of recurrence rate.

vascular endothelial growth factor receptor (VEGFR)-2, VEGFR-3, Fms-like tyrosine, platelet-derived growth factor receptor (PDGFR-β) and other tyrosine kinases [25]. Although sorafenib has opened a window of hope after decades of searching for effective agents to treat HCC, the overall outcomes are far from satisfactory [26].

In the present meta-analysis we found that patients with HCC who were treated with RFA-sorafenib combination had the same survival outcomes with patients who were treated with RFA alone, sorafenib alone, and sugery. Surgical resection is considered to be the first-line treatment for HCC [27]. However, hepatectomy is not always possible due to large tumor size, poor health status, and anatomic location [28]. RFA, which has the advantage of minimal invasiveness, might be favorable for HCC. Besides, with the advances in imaging-guided location, artificial hydrothorax, and the probes, the indications for RFA have been greatly expanded [29]. Nevertheless, there has been no consensus on whether RFA can get similar therapeutic value as surgery.

Admittedly, there are several limitations in our meta-analysis. First of all, the majority of the enrolled studies were retrospectively performed, which were susceptible to several biases. Second, heterogeneity was remarkable in our meta-analysis, which might be attributed to the sample size, age, tumor size, study region, liver function and history of previous treatments of the patients. Third, the clinicopathological features of patients in the RFA-sofafenib combination group might not be comparable to that of patients in the other treatment groups. We hope that future randomized controlled studies may resolve this problem and provide us with much more sound clinical evidence.

In conclusion, several therapeutic methods are available for the treatment of HCC, but the prognosis for HCC is still dismal. Different therapeutic methods have their own advantages and disadvantages, and the ideal treatment approach for HCC has not yet been identified, since our meta-analysis indicated no significant difference between RFA-sorafenib combination and other treatments. In future studies, more well-designed RCTs should be performed before we finally arrive at a rational comprehension about the therapeutic value of the discussed options.

Authors' contributions

Lin Chen and Xingming Ma were responsible for literature search, data gathering and quality control; Xin Liu and XiaoMeng Cui were responsible for data analysis and preparation of the manuscript.

Conflict of interests

The authors declare no conflict of interests.

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