



Efficacy and safety of B-ultrasound-guided radiofrequency ablation in the treatment of primary liver cancer: Systematic review and meta-analysis

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Abstract

BACKGROUND

Primary liver cancer is one of the most lethal malignancies in the world. Traditional treatment methods have limitations in terms of efficacy and safety. Radiofrequency ablation (RFA) guided by B-ultrasound, as a minimally invasive treatment, has attracted increasing attention in the treatment of primary liver cancer in recent years.

AIM

To study the efficacy and safety of RFA were compared with those of traditional surgery (TS) for treating small liver cancer.

METHODS

At least 2 people were required to search domestic and foreign public databases, including foreign databases such as EMBASE, PubMed and the Cochrane Library, and Chinese databases such as the China National Knowledge Infrastructure database, China Biomedical Literature database, Wanfang database and VIP database. Controlled trials of RFA *vs* conventional surgery for small liver cancer were retrieved from January 2008 to January 2023. They were screened and evaluated according to the quality evaluation criteria in the Cochrane Handbook of Systematic Reviews. The meta-analysis was performed using RevMan 5.3 software.

RESULTS

A total of 10 studies were included in this study, including 1503 patients in the RFA group and 1657 patients in the surgery group. The results of the meta-analysis showed that there was no significant difference in 1-year overall survival

between the two groups ($P > 0.05$), while the 3-year and 5-year overall survival rates and 1-year, 3-year and 5-year tumor-free survival rates in the surgery group were greater than those in the RFA group ($P < 0.05$). In terms of complications, the incidence of complications in the RFA group was lower than that in the surgery group ($P < 0.05$).

CONCLUSION

In terms of long-term survival, TS is better than RFA for small liver cancer patients. However, RFA has fewer complications and is safer.

Key Words: Survival prognosis; Small liver cancer; Radiofrequency ablation; Traditional surgical resection; Meta-analysis

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Core Tip: To evaluate the efficacy and safety of B-ultrasound-guided radiofrequency ablation (RFA) in the treatment of primary liver cancer by meta-analysis. This study systematically searched a variety of medical databases, screened out clinical trials and observational studies that met the criteria, extracted relevant data, and used statistical methods for comprehensive analysis. The key indicators of RFA, such as tumor ablation success rate, patient survival rate, complication rate and postoperative recurrence rate, were mainly concerned. Through comparison and analysis, the aim is to provide more powerful evidence support for clinical practice, optimize the treatment strategy of primary liver cancer, and improve the quality of life and prognostic effect of patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC), one of the most common tumors of the digestive system, is very common in China, and the mortality rate is gradually increasing[1]. With the rapid development of medical technology, the diagnosis, treatment and prognosis of HCC, as well as small liver cancer, which is a common type of HCC, have significantly improved[2-4]. However, due to the strong compensatory capacity of the liver, most patients have no obvious clinical manifestations in the early stage, and most of them have lost the opportunity for surgery after discovery; therefore, early detection and early treatment are particularly important for the treatment of early small liver cancer. In the past, traditional surgical resection was the main treatment for small liver cancer, but the operation may be affected by the location of the tumor, the patient's heart, liver, kidney function and the patient's own factors[5]. Subsequently, liver arterial embolization, anhydrous ethanol injection and other treatment methods have gradually appeared, and studies have shown that the efficacy of these methods for small liver cancer patients is similar to that of traditional surgery (TS). In recent years, with the rapid development of thermal ablation technology, radiofrequency ablation (RFA), which is noninvasive and can cause complete necrosis of tumor tissue, has been gradually used for the treatment of early small liver cancer. However, whether it can be used as the best treatment for small liver cancer is currently controversial[6].

The incidence and mortality of liver cancer, a major cancer worldwide, remain high. Small liver cancer (HCC no larger than 5 cm in diameter) offers more treatment options and a better treatment prognosis due to its potential for early diagnosis. Traditional surgical treatment is regarded as the preferred treatment for small liver cancer because of its high rate of radical treatment. However, surgical treatment is often associated with greater trauma and an associated risk of postoperative complications[7]. With the advancement of medical technology, RFA has gained increasing attention as a minimally invasive treatment due to its less invasive nature, lower risk of complications, and shorter recovery time. This study evaluated the efficacy and safety of RFA *vs* conventional surgery for small liver cancer through a systematic review and meta-analysis of the literature. We will collect and analyze randomized controlled trials (RCTs) and large cohort studies to evaluate the short- and long-term effects of the two treatments on multiple dimensions, including key clinical measures such as overall survival, disease-free survival, local recurrence rate, and complication rate. Although RFA has been used clinically as an alternative strategy for the treatment of small liver cancer, there is a lack of clear conclusions supported by large-scale clinical data regarding its relative efficacy and safety compared to conventional surgery. In the current context of increasingly tight medical resources and rising medical costs, it is of great value to provide clinicians with an evidence-based treatment selection reference for patient treatment planning, improving quality of life and controlling medical costs[8].

Through this study, we expect to provide a more solid scientific basis for treatment decisions in patients with small cell lung cancer. We will systematically integrate existing studies to compare the advantages and limitations of RFA with those of conventional surgery to provide a comprehensive evaluation and recommendation of treatment strategies for small liver cancer patients. In addition, our findings may also provide directions for future clinical practice and guideline formulation and have important guiding significance for improving the treatment of small liver cancer patients, ensuring

patient safety and improving treatment quality.

MATERIALS AND METHODS

Retrieval method

The following public databases were used: EMBASE, PubMed, the Cochrane Library, the China National Knowledge Network database, the China Biomedical Literature database, the Wanfang database, and the VIP database. The search period was from January 2008 to January 2023. The main search terms were "hepatocellular carcinoma", "hepatectomy", and "radiofrequency ablation".

Inclusion and exclusion criteria

The inclusion criteria for patients were as follows: (1) Diagnosed with small liver cancer and were newly diagnosed; (2) No distant metastasis; and (3) Not receive treatment other than TS or RFA.

The exclusion criteria were as follows: (1) Not meet the diagnostic criteria for small liver cancer; (2) Not newly diagnosed; (3) Had distant transfers; and (4) Had too few observation indicators, too small of a sample size, or too short of a follow-up time.

Related literature evaluation and literature data analysis

Two researchers selected and evaluated the studies according to the quality evaluation criteria in the Cochrane Evaluation Manual and checked the results with each other.

Statistical analysis

For the included subjects, a meta-analysis was performed using RevMan 5.3. For the binary variables, the odds ratio (OR) and 95%CI were used, and the χ^2 test was used to assess heterogeneity among studies. When $I^2 < 50\%$ and $P > 0.1$, the heterogeneity among studies was low or nonexistent, and the fixed effects model was used in the meta-analysis. When $I^2 \geq 50\%$ and $P \leq 0.1$, the heterogeneity was high. At this time, the random effects model was adopted in the meta-analysis, the relevant factors that might affect the heterogeneity were excluded, and a funnel plot was used to evaluate the bias.

RESULTS

Literature search results and basic information

According to the retrieval method, a total of 1477 studies were retrieved, and 785 studies were included after all the duplicated studies, conference minutes, systematic reviews and reviews were excluded. Then, 10 studies were ultimately included after the title, abstract and full text of the article[9-12]. There were 1503 patients in the RFA group and 1657 patients in the TS group[13-15]. Two studies were RCTs, and the other 8 were non-RCTs[16-18]. The quality of 2 studies was grade B, and that of the other 8 studies was grade C. The literature retrieval process is shown in Figure 1, and the basic information of each study is shown in Table 1.

Meta-analysis of overall survival at 1 years, 3 years and 5 years

Overall 1-year survival rate: Heterogeneity between the RFA group and the TS group was detected ($I^2 = 54\%$, $P = 0.02$). A random effects model was used for the meta-analysis, and the results showed that the OR was 0.76 (95%CI: 0.45-1.31, $P = 0.33$), and the difference between the two groups was not statistically significant, as shown in Figure 2A.

Overall survival at 3 years: Heterogeneity was detected between the RFA group and the TS group ($I^2 = 71\%$, $P = 0.00003$). A random effects model was used for the meta-analysis, and the results showed that the OR was 0.63 (95%CI: 0.43-0.91, $P = 0.01$), and the differences between the two groups were statistically significant, as shown in Figure 2B.

The 5-year overall survival rate: Heterogeneity between the RFA group and the TS group was detected as $I^2 = 47\%$, $P = 0.06$, with no heterogeneity or slight heterogeneity. Meta-analysis was performed using the fixed effect model, and the results showed that the OR was 0.46 (95%CI: 0.39-0.54, $P < 0.00001$). The results showed that there was no heterogeneity among the RFA groups. The difference between the two groups was statistically significant, as shown in Figure 2C.

Meta-analysis of 1-year, 3-year and 5-year tumor-free survival rates

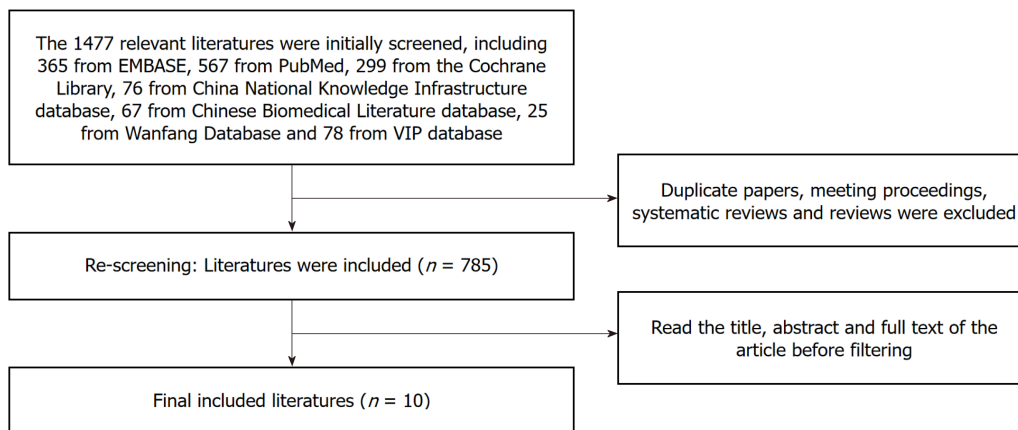
The 1-year tumor-free survival rate: Heterogeneity between the RFA group and the TS group was detected ($I^2 = 39\%$, $P = 0.11$), and no heterogeneity was found. A meta-analysis using the fixed effect model showed that the OR was 0.76 (95%CI: 0.62-0.92, $P = 0.004$), and the differences between the two groups were statistically significant, as shown in Figure 3A.

The 3-year tumor-free survival rate: Heterogeneity between the RFA group and the TS group was detected ($I^2 = 51\%$, $P = 0.04$). A random effects model was used for the meta-analysis, and the results showed that the OR was 0.52 (95%CI: 0.39-0.69; $P < 0.00001$), with a statistically significant difference between the two groups. For details, see Figure 3B.

Table 1 Basic information of patients

Ref.	Group	Cases	Average age (years)	Liver function A/B/C	Follow up time (months)	Complications
Feng <i>et al</i> [9]	RFA group	84	47 (18-76)	43/41/0	36	Unknown
	TS group	84	51 (24-83)	39/45/0	36	Unknown
Gory <i>et al</i> [10]	RFA group	96	65.1 ± 10	75/21/0	26 ± 14	Unknown
	TS group	52	59.3 ± 10.7	46/6/0	42 ± 12	Unknown
Guo <i>et al</i> [11]	RFA group	94	56 (19-75)	63/31/0	28 ± 13	32
	TS group	102	51.5 (18-75)	95/7/0	32 ± 14	42
Guo <i>et al</i> [12]	RFA group	86	52.5	84/2/0	27	7
	TS group	73	50	71/2/0	30	14
Huang <i>et al</i> [13]	RFA group	115	56.6 ± 14.3	110/5/0	37.2	33
	TS group	115	55.9 ± 12.6	106/9/0	46.4	59
Huang <i>et al</i> [14]	RFA group	413	54.67 ± 12.18	413/0/0	36.1 ± 12.4	19
	TS group	648	46.13 ± 16.89	648/0/0	33.7 ± 17.4	71
Lai <i>et al</i> [15]	RFA group	31	63.1 ± 12.8	Unknown	35 ± 17	12
	TS group	80	60.8 ± 9.9	Unknown	30 ± 20	48
Lee <i>et al</i> [16]	RFA group	369	66 ± 11	306/51/0	Unknown	Unknown
	TS group	330	61 ± 12	317/13/0	Unknown	Unknown
Tohme <i>et al</i> [17]	RFA group	60	65.6 ± 12	44/16/0	29	17
	TS group	50	66.3 ± 1	44/6/0	29	17
Ueno <i>et al</i> [18]	RFA group	155	66 (40-79)	52/91/0	36.1	31
	TS group	123	67 (28-85)	91/31/0	36.1	46

RFA: Radiofrequency ablation; TS: Traditional surgery.

**Figure 1** Literatures screening analysis flow chart.

The 5-year tumor-free survival rate: Heterogeneity between the RFA group and the TS group was detected ($I^2 = 9\%$, $P = 0.36$), and there was no heterogeneity. A fixed effect model was used for the meta-analysis, and the results showed that the OR was 0.51 (95%CI: 0.43-0.62, $P < 0.00001$), and the differences between the two groups were statistically significant, as shown in [Figure 3C](#).

Meta-analysis of complications: Heterogeneity between the RFA group and the TS group was detected ($I^2 = 0$, $P = 0.52$), and there was no heterogeneity. A meta-analysis was performed using the fixed-effects model, and the results showed an OR of 0.47, 95%CI: 0.37-0.59; $P < 0.00001$, indicating statistically significant differences between the two groups. For details, see [Figure 4](#).

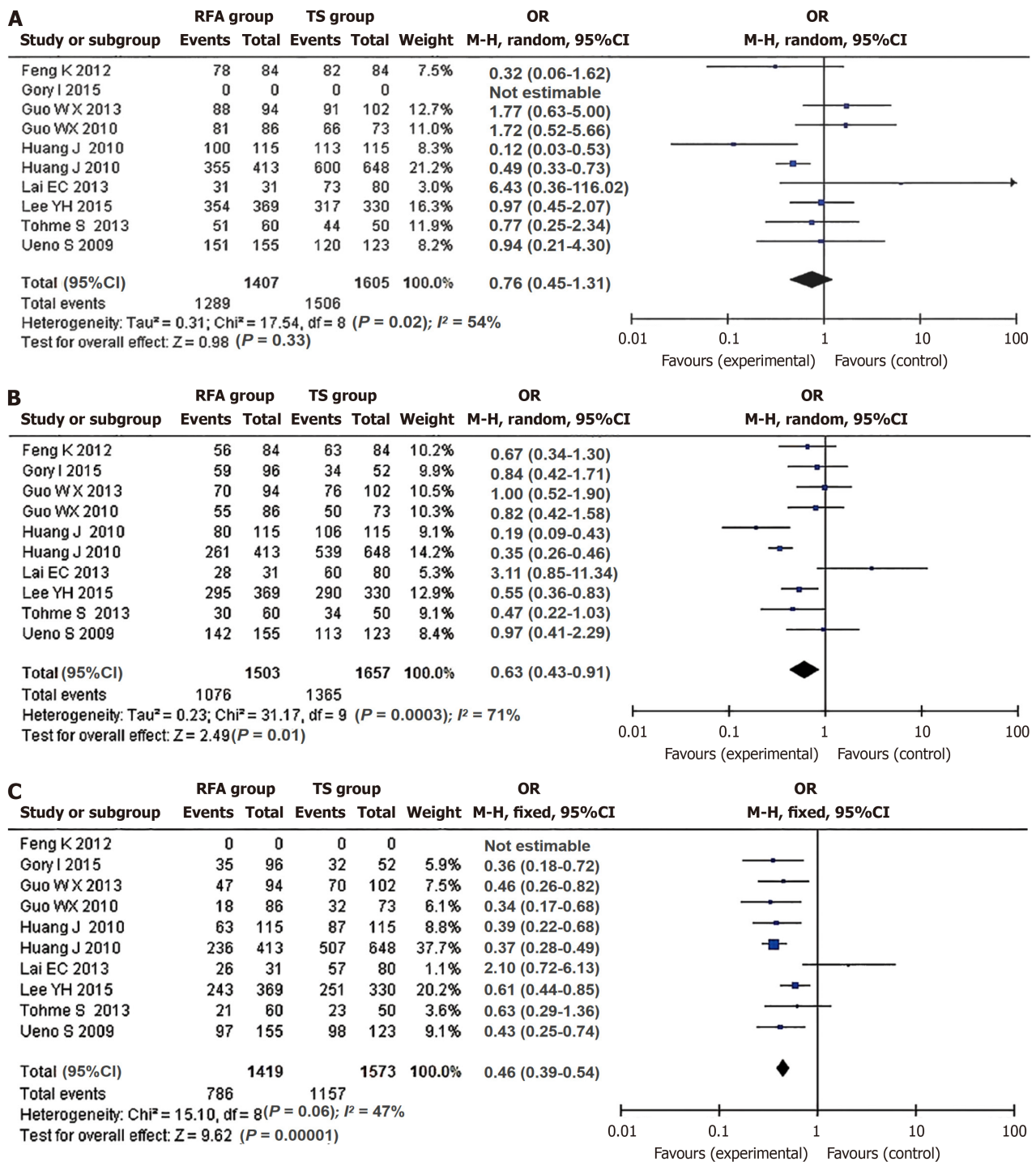


Figure 2 Meta-analysis of overall survival at 1 year, 3 years and 5 years. A: Overall survival at 1 year; B: Overall survival at 3 years; C: Overall survival at 5 years. RFA: Radiofrequency ablation; TS: Traditional surgery; OR: Odds ratio.

Assessment of publication bias: The funnel plot of each study indicated that the scatter points were basically symmetrical and distributed in an inverted funnel shape, so the funnel plot indicated no publication bias, as shown in Figure 5.

DISCUSSION

Small liver cancer is a common type of liver cancer, and because it is in the early stage of liver cancer, its clinical manifestations are often not obvious; therefore, the diagnosis and treatment of small liver cancer are particularly important[19-21]. Surgical resection and RFA can be used as first-line treatments for liver cancer patients who are less than 3 cm in diameter[22]. When the diameter of small liver tumors is ≥ 3 cm, RFA is less effective than surgical resection. To systematically understand the efficacy of RFA and TS in the treatment of small liver cancer, this study conducted a meta-analysis

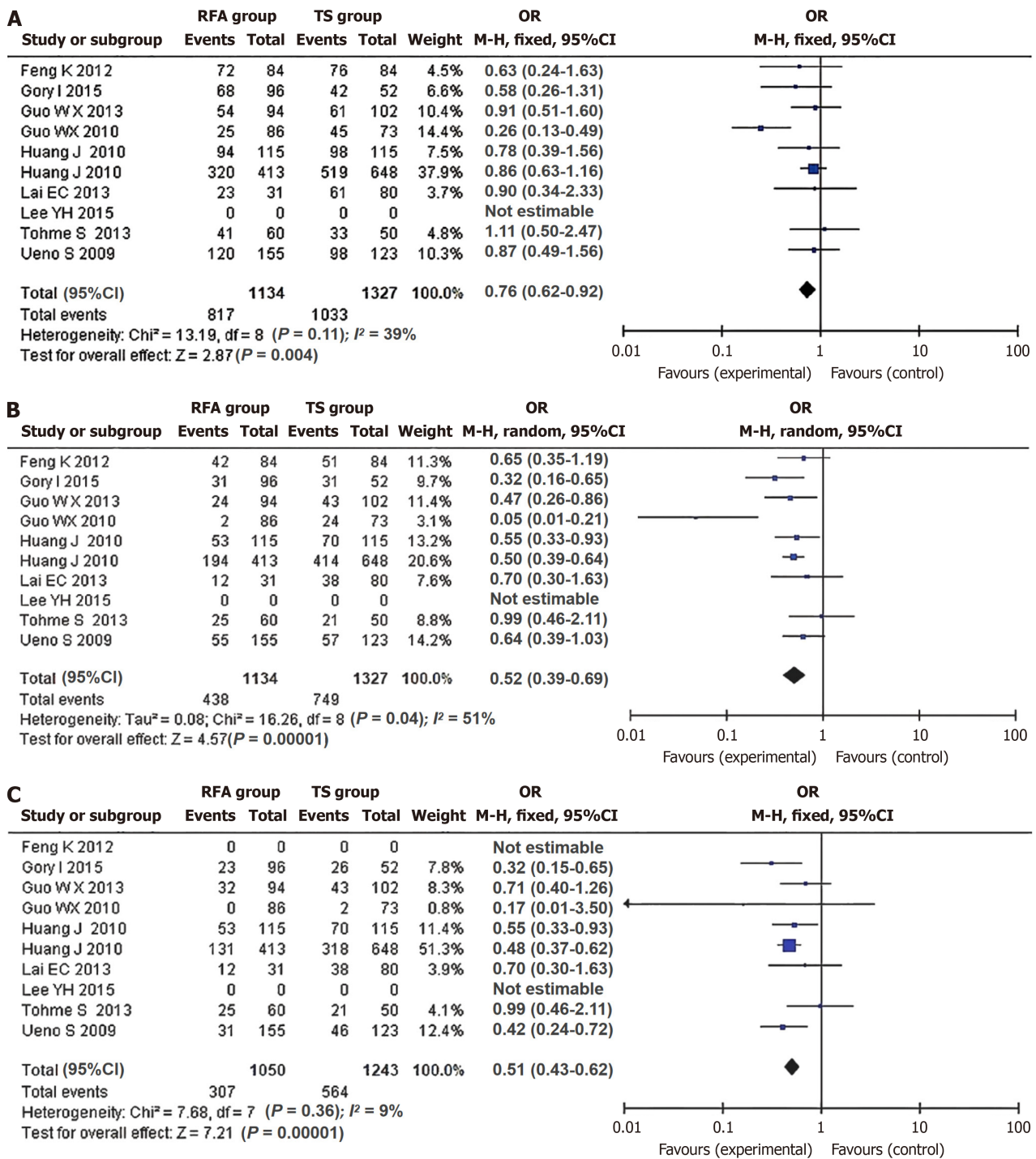


Figure 3 Meta-analysis of 1-year, 3-year and 5-year tumor-free survival rates. A: The 1-year tumor-free survival rates; B: The 3-year tumor-free survival rates; C: The 5-year tumor-free survival rates. RFA: Radiofrequency ablation; TS: Traditional surgery; OR: Odds ratio.

on the efficacy and safety of RFA and TS based on a number of domestic and foreign studies[23-25]. The advantage of TS is that the doctor can accurately locate the tumor during the process of laparotomy, and observation is more intuitive so that the tumor lesions can be completely removed[26]. The principle of RFA is to insert electrodes into the tumor and use the principle of electric heating to increase the temperature of the tumor cells to achieve denaturation, coagulation, and necrosis[27]. Its main advantages are less trauma, fewer complications, and strong repeatability, which can significantly shorten the length of hospitalization, reduce hospitalization costs, and significantly improve the quality of life of patients [28-30].

A total of 10 studies were included in this study, including 1503 subjects in the RFA group and 1657 subjects in the TS group. The results of the meta-analysis showed that, in terms of the 1-year overall survival rate, there was no significant difference between the two groups ($P > 0.05$), while in terms of the 3-year and 5-year overall survival rates and the 1-year, 3-year and 5-year cancer-free survival rates, the survival rate of the TS group was significantly greater than that of the RFA group ($P < 0.05$)[31-34]. This may be because the liver is an organ with multiple blood supplies and multiple branches, and the internal temperature of its tissues is very susceptible to the influence of multiple blood supplies and various

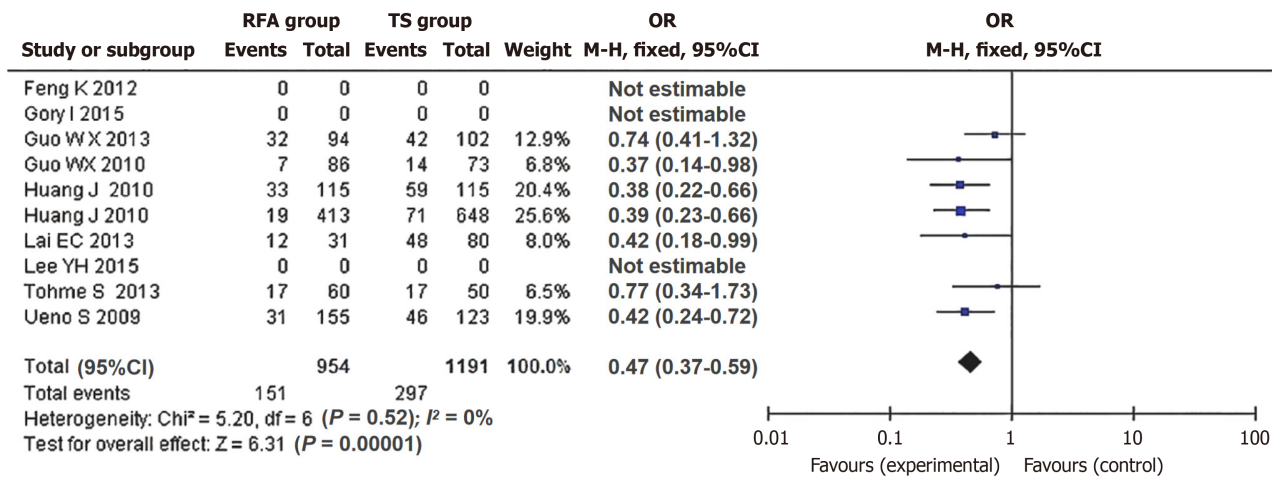


Figure 4 Meta-analysis of complications. RFA: Radiofrequency ablation; TS: Traditional surgery; OR: Odds ratio.

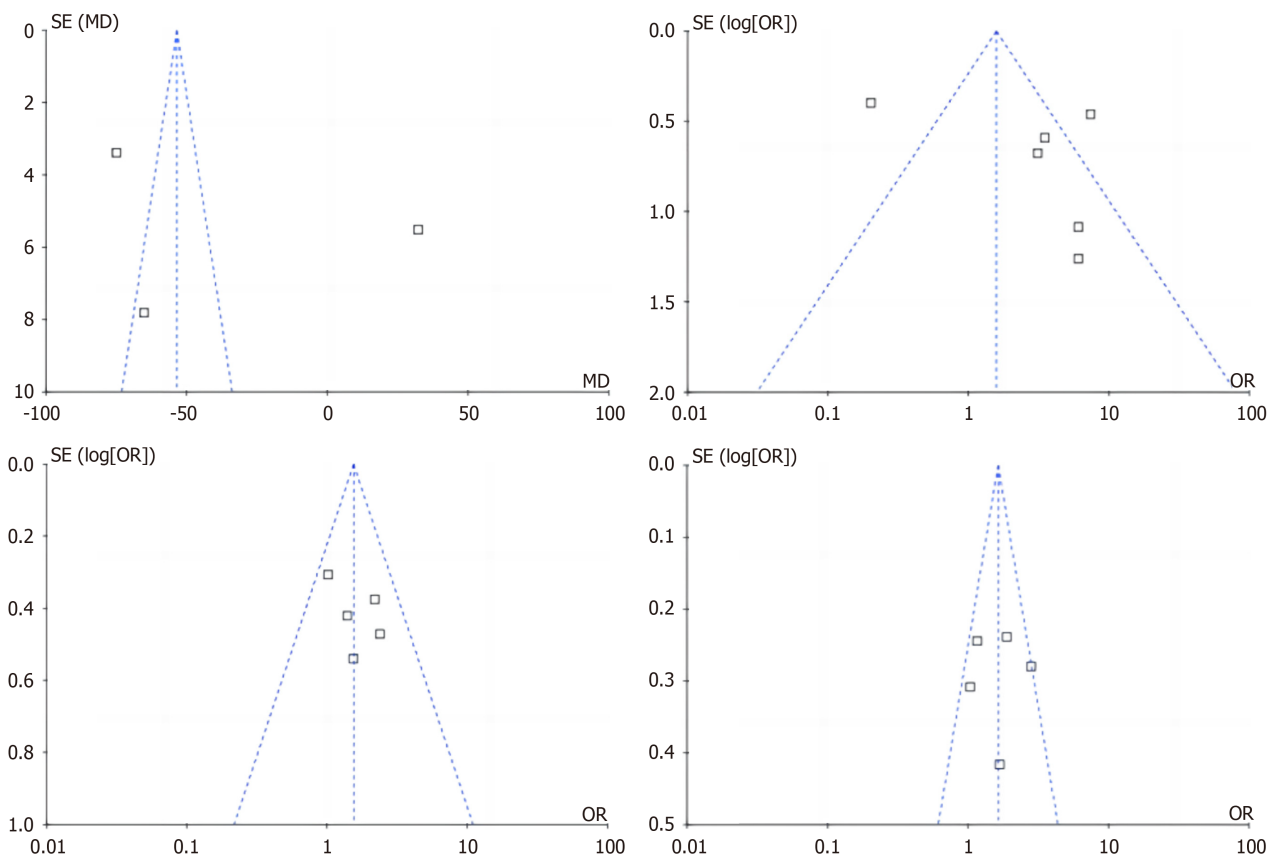


Figure 5 Published offset funnel plot analysis. OR: Odds ratio.

branches[35-37]. This may also be related to the fact that RFA itself cannot observe the whole liver tissue, which is likely to cause the tissues around the tumor itself to remain. In terms of complications, RFA mainly involves direct injury related to heat and puncture, and TS mainly involves fever, bleeding, infection, and aggravated liver function injury[38-40]. The results of this study showed that the incidence of complications in the RFA group was significantly lower than that in the TS group ($P < 0.05$).

However, this study also has the following shortcomings: (1) Due to the small number of studies included in this study and the small total sample size, the results may be biased; (2) The included literature is mainly from Asia; (3) Precise data were not available for each patient in each study included; and (4) There was considerable heterogeneity in some studies.

CONCLUSION

In summary, in terms of the long-term survival rate, TS is more effective than RFA for small liver cancer and can still be used as the first-line therapy for small liver cancer patients. However, RFA has fewer complications and is safer. It should be noted that the number of studies included in this meta-analysis was small, the quality of most studies was Grade C, and it was not possible to conduct further subgroup analysis of each study. Therefore, more double-blind, multicenter, randomized and large-sample controlled experiments should be conducted in the future to provide better guidance for clinicians in the diagnosis and treatment of small liver cancer.

FOOTNOTES

Author contributions: Zhang X wrote the manuscript; Zhu HY collected the data; Yuan M guided the study; all authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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PRISMA 2009 Checklist statement: This study strictly followed PRISMA 2009 inventory guidelines to ensure transparency and reproducibility of the systematic review and meta-analysis process. We follow PRISMA standards in literature screening, data extraction and analysis to improve the quality and credibility of research and provide readers with clear and comprehensive findings and conclusions.

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