



Efficacy and safety of radiofrequency ablation versus minimally invasive liver surgery for small hepatocellular carcinoma: a systematic review and meta-analysis

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Abstract

Background The aim of this study was to compare radiofrequency ablation (RFA) with minimally invasive liver surgery (MIS) in the treatment of small hepatocellular carcinoma (SHCC) and to assess short-term and long-term clinical outcomes. **Methods** PubMed, Embase, Cochrane Library, Web of science, and CBM were systematically searched for articles from inception to July 2018, comparing RFA and MIS in SHCC treatment. We evaluated overall survival (OS), disease-free survival (DFS), local recurrence, and complication rates, as well as hospitalization duration and operation times.

Results Six retrospective studies were analyzed, including a total of 597 patients, 313 treated with RFA and 284 treated with MIS. OS rates were significantly higher in patients treated with MIS at 3 years, when compared to RFA (OR 0.55; 95% CI 0.36 to 0.84). The 3-year DFS MIS rates were also superior to RFA (OR 0.63; 95% CI 0.41 to 0.98). In contrast, when compared to MIS, RFA demonstrated a significantly higher rate of local intrahepatic recurrences, (OR 2.24; 95% CI 1.47 to 3.42), and a lower incidence of postoperative complications (OR 0.34; 95% CI 0.22 to 0.53), as well as shorter operation times (OR – 145.31, 95% CI – 200.24 to – 90.38) and hospitalization duration (OR – 4.02, 95% CI – 4.94 to – 3.10).

Conclusions We found that MIS led to higher OS, DFS, and lower local recurrences in SHCC patients. Meanwhile, RFA treatments led to significantly lower complication rates, shorter operation times, and hospitalization duration. Considering long-term outcomes, MIS was found to be superior to RFA. However, RFA may be an alternative treatment for patients presenting a single SHCC nodule (≤ 3 cm), given its minimally invasive nature and its comparable long-term efficacy with MIS. Nevertheless, our findings should be explained with caution due to the low level of evidence obtained.

Keywords Small hepatocellular carcinoma · Radiofrequency ablation · Minimally invasive liver surgery · Laparoscopic hepatectomy · Robotic-assisted hepatectomy

According to the World Health Organization (WHO), liver cancer is now the fourth leading cause of cancer-related deaths worldwide, accounting for approximately 782,000

deaths and approximately 841,080 new cases in 2018 [1]. Hepatocellular carcinoma (HCC) accounts for about 75% to 85% of primary liver cancer, which is mainly caused by chronic infection with the hepatitis B virus (HBV) or hepatitis C virus (HCV) [2]. Advances in image diagnosis technology and widespread application of screening programs in high-risk populations have paved the way for the promptly detection of small hepatocellular carcinoma (SHCC) [3], creating conditions for early clinical intervention and means for a better prognosis of SHCC patients [4]. Although liver transplantation is still the ideal treatment for SHCC, as it can increase 5-year survival rates up to 75% to 92% [5], only a minority of patients can receive this treatment, limited by its high cost and donor shortage [6]. Therefore, liver resection and radiofrequency ablation (RFA) are both recognized as

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curative treatments for SHCC [7, 8]. Recently, due to refinement of the laparoscopic technique and the robotics platform approved for clinical use [9], the minimally invasive liver surgery (MIS) has been gradually regarded as a safe and effective approach to the liver resection option [10, 11]. In addition, compared to open surgery, MIS shows significant advantages in terms of short-term efficacy and has similar long-term efficacy [12]. Meanwhile, RFA has shown its own advantages, which include safety, cost-effectiveness, minimal invasiveness, and the fact that it can be operated repeatedly [7, 13]. Nonetheless, precisely which approach to take when treating SHCC patients still remains highly controversial in terms of treatment modality efficacy and safety [14–16].

To the best of our knowledge, this is the first meta-analysis to compare the RFA treatment with the MIS treatment in the clinical management of SHCC patients. Therefore, our study aimed to assess the long-term and short-term clinical outcomes of these two SHCC treatment approaches, in order to provide better informed clinical decisions for surgical oncologists and SHCC patients.

Materials and methods

Search strategy

Two independent reviewers (Si and Yan) comprehensively searched PubMed, Embase, Web of science, Cochrane Library, and the China Biomedical Literature Database (CBM) for relevant articles published from the inception dates to July 2018, comparing the use of RFA and MIS treatments in SHCC patients. We then used database-specific subject headings, known as Medical Subject Headings (MeSH) terms, and free text terms to search for potentially eligible studies (Online Appendix 1). In order to cover all the relevant studies, a reference list of retrieved articles was also crosschecked manually for additional studies. The searches were limited to human subjects, and in addition, no language or regional state restrictions were applied.

Study selection

Inclusion criteria

The inclusion criteria for our study were as follows: (1) definitive diagnosis of primary liver cancer. Patients diagnosed with HCC based on cytohistological evidence from liver biopsy specimens or in the absence of biopsy evidence, based on radiological imaging techniques including contrast-enhanced ultrasonography (CEUS), computed tomography (CT), and magnetic resonance imaging (MRI); (2) HCC meets the Milan criteria for HCC (single HCC

nodule smaller than 5 cm in diameter or up to 3 nodules that are each smaller than 3 cm in diameter) [5] or the University of California, San Francisco (UCSF) criteria (a single tumor smaller than 6.5 cm in diameter or up to 3 nodules that were each smaller than 4.5 cm in diameter and 8 cm in total diameter) [17], with liver function Child–Pugh class A or B (the number of patients with Child–Pugh C constitutes less than 10% of HCC patients); (3) no radiologic evidence of invasion into the major portal/hepatic vein branches and extrahepatic metastasis; (4) no previous treatment using transcatheter arterial chemoembolization (TACE), conventional surgery, chemotherapy, or other anti-tumor treatment; (5) clearly documented indications for RFA and MIS and all patients should be suitable for treatment with either RFA or MIS; and (6) included studies must report at least one of the outcomes mentioned below.

Exclusion criteria

The exclusion criteria for this study were as follows: (1) severe portal hypertension (past history of gastric and esophageal variceal bleeding, serious hypersplenism, or decompensated liver cirrhosis with ascites); and (2) pathologically confirmed cholangiocarcinoma, mixed liver cell cancer, or liver metastases. Additionally, the literature screening was done independently by two reviewers.

Data extraction and quality assessment

The data were strictly extracted by two independent reviewers using the inclusion and exclusion criteria described above. The extracted data included first author, publication year, country, type of study, gender, age, cases of patients, number of nodules, size of tumors, HCC Child–Pugh class, mean follow-up duration, and patient clinical outcomes. Any discrepancies between the two reviewers were resolved by discussion and to reach the agreement or by a third person (Hao). The long-term clinical outcomes included were 1- and 3-year overall survival (OS) rates, 1- and 3-year disease-free survival (DFS) rates, and local recurrence rate. The short-term outcomes included postoperative complication rates, operative time, and hospitalization duration.

The Newcastle–Ottawa Scale (NOS) for case–control studies was used to evaluate the quality of the methodology used in each included article [18, 19]. In total, six studies were assessed with regard to case selection, comparability, and outcomes. The results of this assessment are shown in Table 1.

Statistical analysis

All analyses were performed using the Review Manager, version 7.8 (Nordic Cochrane Centre; Oxford, England) and

Table 1 General information and quality score of the included studies

Author	Year	Country	Age (Mean±SD)	Sex m/f	Sample size			HBV and (or) HCV infection (%)	Liver cirrhosis (%)	Child (A %)	Tumor amount (number)			Tumor size (cm)	Follow-up duration (m) (Mean±SD)	NOS score
					RFA	MIS	Total				1	1–3				
Casaccia [22]	2015	Italy	61.48±7.75	37/13	24	26	50	74.00	NA	72.00	27	23	≤6.5	NA	8	
Song [23]	2015	China	48.00±9.63	140/16	78	78	156	94.23	78.85	98.72	156	0	≤4	31.20±21.04	9	
Vitali [24]	2015	Switzerland	67.30±26.67	82/23	60	45	105	59.00	NA	81.00	105	0	≤3	26.00±94.07	8	
Song [7]	2017	China	48.00±11.85	151/24	94	81	175	97.41	87.43	96.00	162	13	≤5	39.5±8.52	8	
Casaccia [14]	2017	Italy	60.82±7.25	34/21	22	24	46	71.74	NA	73.91	26	20	≤6.5	44.74±21.30	8	
Xu [8]	2017	China	57.06±12.66	52/13	35	30	65	87.69	NA	93.85	65	0	≤3	28.10±16.44	8	

RFA radiofrequency ablation, MIS minimally invasive liver surgery, m male, f female, HBV hepatitis B virus, HCV hepatitis C virus, Child Child–Pugh, NOS Newcastle–Ottawa Scale, NA not available

the Stata 14.0 (StataCorp; College Station, TX, USA) statistical software. For data evaluation, patients were divided in two groups, the RFA-treated group and the MIS-treated group. We then calculated the odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous outcomes and the mean difference (MD) for continuous outcomes. Meanwhile, we explored heterogeneity among trials using the Chi-squared (χ^2) test that included the inconsistency factor (I^2). Heterogeneity was defined as a P value of less than 0.05 or an I^2 greater than 50%. We then applied a fixed-effect model, when there was an absence or low heterogeneity ($I^2 < 50\%$) and a random-effect model, when there was moderate or high heterogeneity ($I^2 > 50\%$) [20].

A sensitive analysis was subsequently conducted by eliminating each study in the analysis at each turn. A potential publication bias was assessed by visually inspecting the Begg's funnel plots in which the log OR is plotted against the standard error (SE). A P value of less than ($<$) 0.05 was considered statistically significant [21].

Subgroup analysis

It is now well accepted that the tumor size, lesion number, location, liver function, the presence of portal vein invasion or vascular invasion, and the resection margin during surgical excision are independent prognostic factors affecting the survival of HCC patients. To this end, Kim et al. have suggested that tumor size is the only independent predictor that is positively correlated with local cancer progression after RFA treatment [15]. Notably, RFA of the liver can be performed by percutaneous, laparoscopic, or open approaches [13]. In our study, we have included among the approaches to RFA, percutaneous and laparoscopic RFA. Thus, we performed subgroup analysis based on detailed data regarding OS and DFS rates in patients with different tumor sizes (i.e., single HCC nodules ≤ 3 cm or ≤ 4 cm) and who had been treated with different approaches to RFA. Importantly, based on the current primary studies evaluated, it is difficult to apply individual subgroup analyses for other factors.

Because this study is a systematic review and meta-analysis, Institutional Review Board (IRB) approval was not needed.

Results

Description of study selection

A total of 1943 studies were initially identified by the search strategy previously established and one study was identified via reference and review. Subsequently, thirty-two studies were excluded for duplication using Endnote 7X (Clarivate Analytics; Philadelphia, PA, USA). The titles and abstracts

of 1912 records were then screened for inclusion. The full texts of 27 records were read and, finally, we identified six non-randomized controlled trial (NRCT) studies that met our meta-analysis criteria [7, 8, 14, 22–24]. The PRISMA flow diagram of the literature for meta-analysis is shown in Fig. 1 [25].

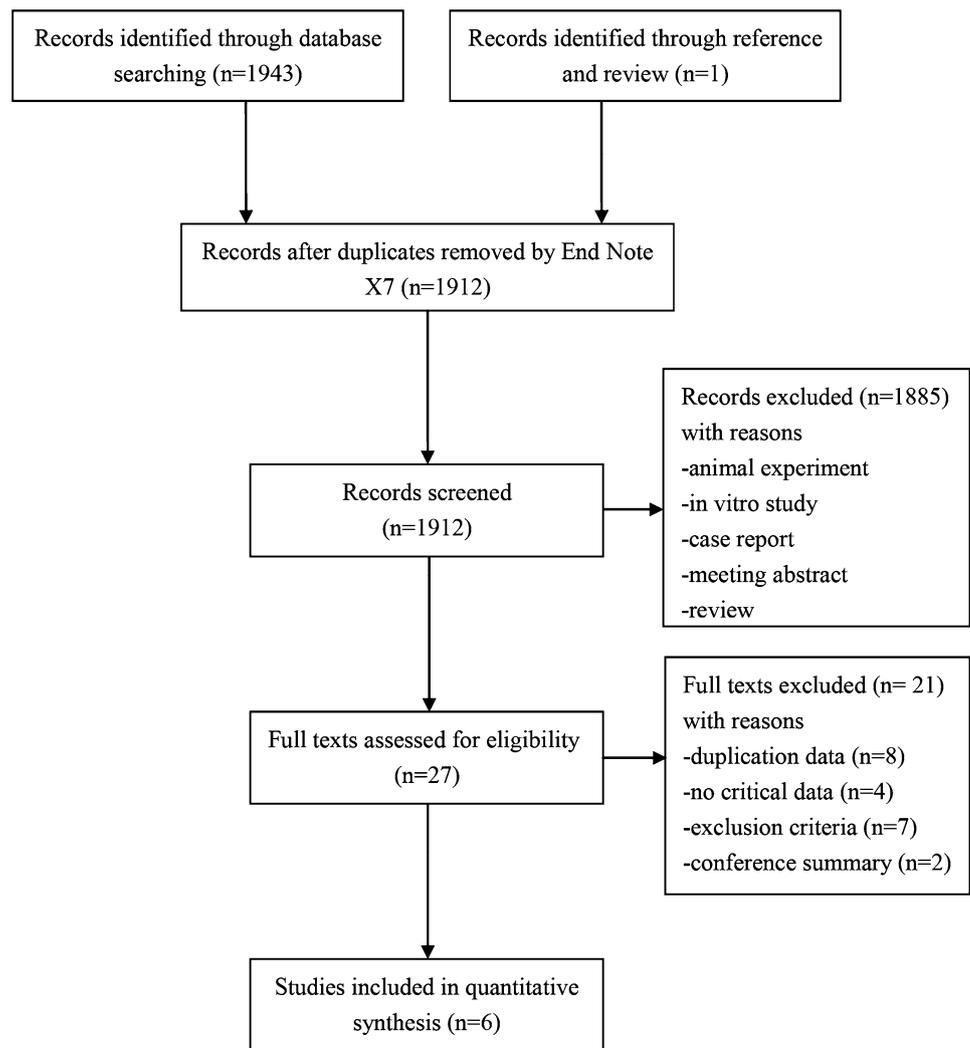
In our analysis, four studies used percutaneous RFA treatments [7, 8, 23, 24] and the remaining two studies used laparoscopic RFA [14, 22]. In addition, three studies were performed in China [7, 8, 23], one in Switzerland [24], and two in Italy [14, 22]. Out of the 597 patients from the six selected studies, 313 were classified into the RFA-treated group, and 284 into the MIS-treated group. These groups were evaluated for their therapeutic efficacy in treating SHCC patients. The details of the studies included in our meta-analysis are listed in Table 1.

Long-term clinical outcomes

Overall survival

Five of the studies selected reported 1- and 3-year OS rates [7, 8, 14, 23, 24]. However, no statistical differences were found between the two comparative groups for the 1-year OS rate (OR 0.76; 95% CI 0.35 to 1.63; $P = 0.48$). However, patients in the MIS-treated group presented higher OS rates, when compared to the RFA-treated group when evaluated for 3-year OS rates (OR 0.55; 95% CI 0.36 to 0.84; $P = 0.005$). Significant heterogeneity was not observed when the 1- and 3-year OS rates were evaluated ($\chi^2 = 1.82$, $I^2 = 0\%$; $\chi^2 = 1.88$, $I^2 = 0\%$, respectively), and a fixed-effect model was used (Fig. 2).

Fig. 1 The PRISMA flow diagram of the literature



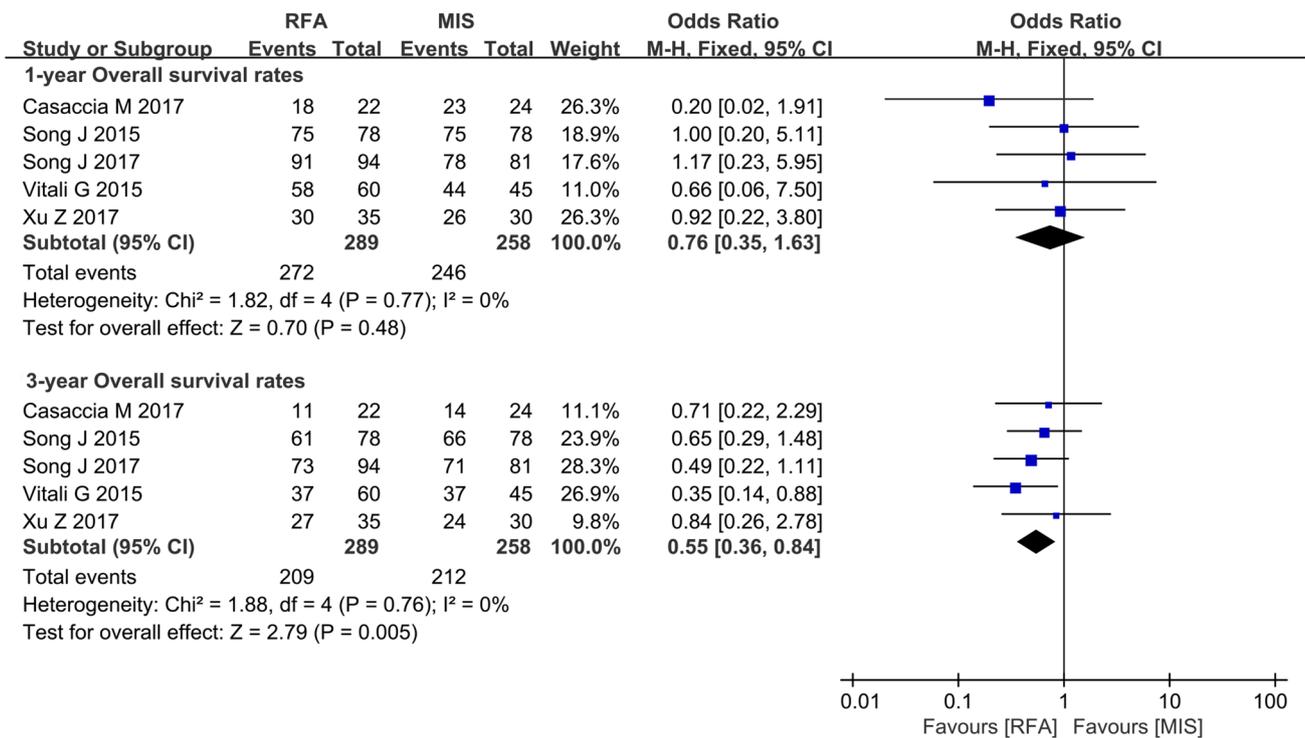


Fig. 2 The forest plot of postoperative 1-year and 3-year overall survival rates between RFA group and MIS group

Disease-free survival

Four of the studies selected reported 1- and 3-year DFS rates [7, 8, 14, 23]. The MIS-treated group presented a relatively higher DFS rate than the RFA-treated group for 1-year DFS rates (OR 0.63; 95% CI 0.41 to 0.98; $P=0.04$) and 3-year DFS rates (OR 0.51; 95% CI 0.34 to 0.74; $P=0.0005$). Notably, no significant heterogeneity was found in our analysis of DFS rates ($\chi^2=4.79$, $I^2=37\%$; $\chi^2=1.98$, $I^2=0\%$, respectively), and a fixed-effect model was used (Fig. 3).

Local recurrence rates

Five out of the six studies evaluated here reported local recurrence rates during median follow-up times [7, 8, 14, 23, 24]. However, there was no significant statistical heterogeneity data among the analyses performed ($\chi^2=1.66$, $I^2=0\%$). Markedly, the meta-analysis of these five studies using a fixed-effect model demonstrated that the MIS-treated group had relatively lower local recurrence rates than the RFA-treated group (OR 2.24; 95% CI 1.47 to 3.42; $P=0.0002$) (Fig. 4).

Short-term outcomes

Complications

Five out of the six studies evaluated here reported treatment-related complications, which included pleural effusions, lung infections, liver section effusion and infection, and postoperative bleeding [7, 8, 22–24]. The pooled meta-analysis showed that there were significant differences and favorable to the RFA-treated group (OR 0.34; 95% CI 0.22 to 0.53; $P<0.00001$), which suggested that RFA-treated patients presented a lower incidence of HCC treatment-related complications, when compared with MIS-treated patients. Of note, no statistical heterogeneity was found ($\chi^2=4.67$, $I^2=14\%$) among them, and a fixed-effect model was used (Fig. 5).

Operation times

Furthermore, five studies analyzed here reported operation times [7, 8, 22–24]. Our pooled results showed that the

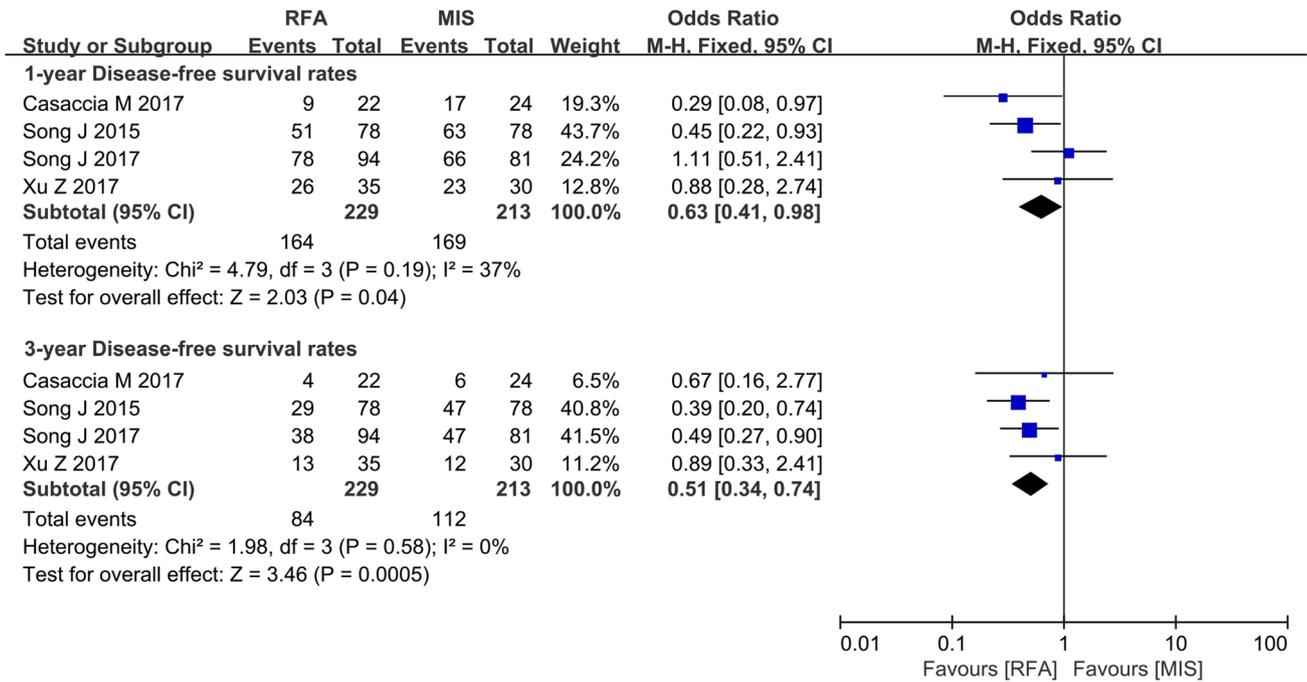


Fig. 3 The forest plot of postoperative 1-year and 3-year disease-free survival rates between RFA group and MIS group

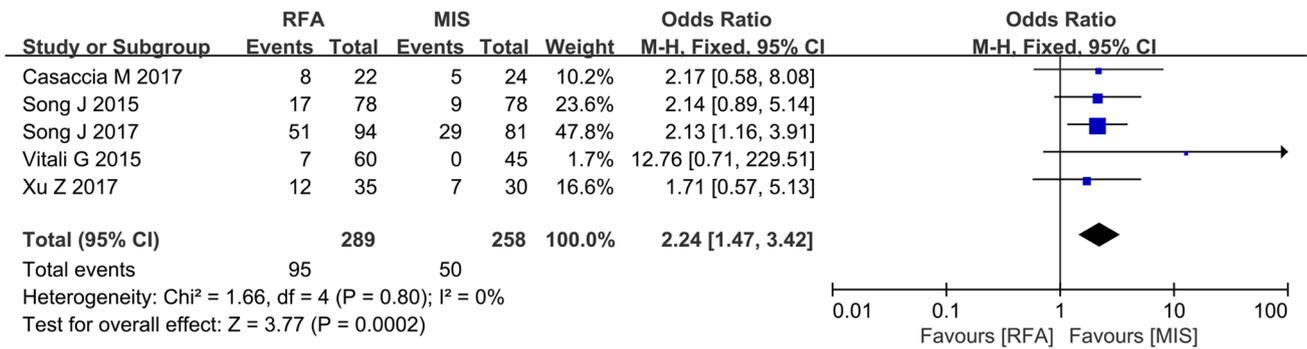


Fig. 4 The forest plot of postoperative local recurrence rates between RFA group and MIS group

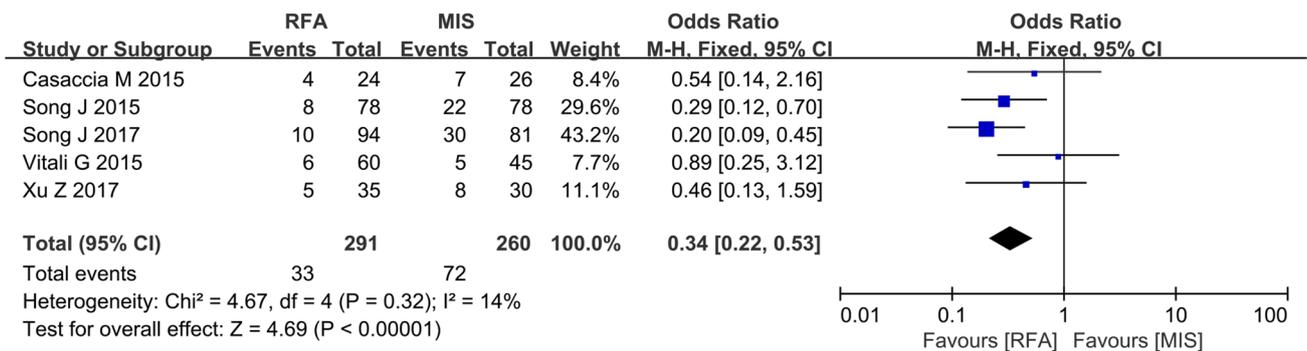


Fig. 5 The forest plot of incidence of postoperative complications between RFA group and MIS group

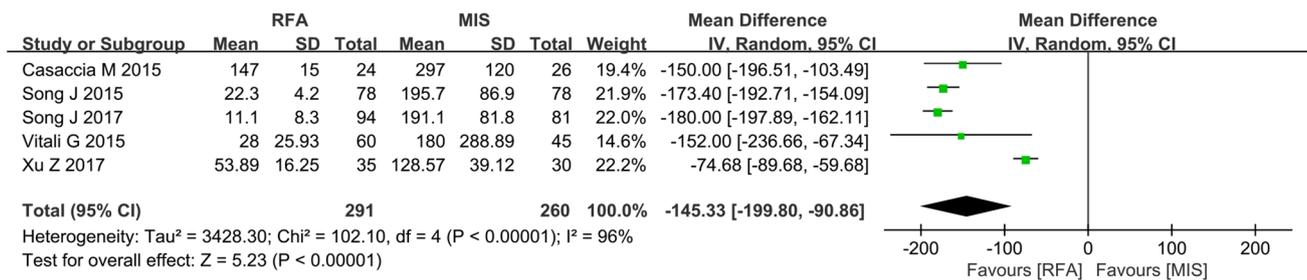


Fig. 6 The forest plot of operation times between RFA group and MIS group

MIS-treated group had significantly longer operative times than the RFA-treated group (OR – 145.33; 95% CI – 199.80 to – 90.86; $P < 0.00001$). In addition, there was a certain statistical heterogeneity ($\chi^2 = 102.10$, $I^2 = 96\%$) among them, and a random-effect model was used (Fig. 6).

Hospitalization duration

In our analysis, five studies reported hospitalization duration [7, 8, 22–24]. Our pooled results showed that the MIS-treated group had significantly longer hospitalization stays than the RFA-treated group (OR – 4.02; 95% CI – 4.94 to – 3.10; $P < 0.00001$). Moreover, according to our analysis, significant heterogeneity ($\chi^2 = 8.30$, $I^2 = 52\%$) was found among them, and a random-effect model was used (Fig. 7).

Subgroup analysis

Furthermore, three selected studies were included in our subgroup analysis according to the size of single SHCC nodules [8, 23, 24]. Our results showed that for bigger single SHCC nodules (≤ 4 cm), the RFA- or MIS-treated groups presented a similar effect on OS and DFS in 1-year rates. However, the MIS-treated group presented higher OS and DFS in 3-year rates. For smaller single nodules (≤ 3 cm), there was no significant observed differences in the 1- and 3-year OS and DFS rates, between the RFA- and MIS-treated groups (Table 2).

Moreover, five of the studies selected were included in the subgroup analysis based on the approach of RFA treatments [7, 8, 14, 23, 24]. Generally, our results suggested that there were no observable differences between the two groups, using laparoscopic-based RFA treatments in 1- and 3-year OS, and 3-year DFS rates. However, the MIS-treated group presented higher 1-year DFS rates. Similarly, when percutaneous-based RFA treatments were used between the two groups, no significant differences were found in 1-year OS and DFS rates; however, the MIS-treated group presented higher OS and DFS in 3-year rates (Table 2).

Sensitivity analysis and publication bias

In our study, we performed sensitivity analysis by investigating the influence of a single study on the overall pooled estimates by eliminating one study in each turn. Our results suggested that the influence of each individual data set on the pooled OR and MD was not statistically significant.

On account of only six studies currently available and included in this meta-analysis, the publication bias phenomenon was not evaluated for the clinical outcomes obtained [26].

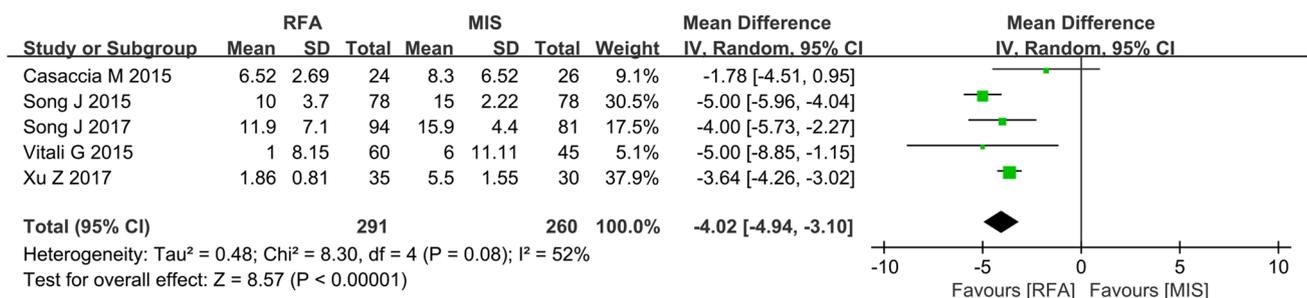


Fig. 7 The forest plot of hospitalization duration between RFA group and MIS group

Table 2 Subgroup analyses based on tumor sizes and approaches to RFA

Variables	Duration (year)		Overall survival		Disease-free survival		P value
	S/P	S/P	Statistical method	Effect estimate	Statistical method	Effect estimate	
Single nodule							
≤ 4 cm	3/326	2/221	OR (M–H, Fixed, 95% CI)	0.90 (0.34, 2.38)	OR (M–H, Fixed, 95% CI)	0.55 (0.30, 1.01)	0.05
3–year	3/326	2/221	OR (M–H, Fixed, 95% CI)	0.55 (0.32, 0.94)	OR (M–H, Fixed, 95% CI)	0.50 (0.29, 0.85)	0.01
≤ 3 cm	2/170	1/65	OR (M–H, Fixed, 95% CI)	0.85 (0.25, 2.86)	OR (M–H, Fixed, 95% CI)	0.88 (0.28, 2.74)	0.82
3–year	2/170	1/65	OR (M–H, Fixed, 95% CI)	0.48 (0.23, 0.99)	OR (M–H, Fixed, 95% CI)	0.89 (0.33, 2.41)	0.81
RFA approach							
Laparoscopic	1/46	1/46	OR (M–H, Fixed, 95% CI)	0.20 (0.02, 1.91)	OR (M–H, Fixed, 95% CI)	0.29 (0.08, 0.97)	0.04
3–year	1/46	1/46	OR (M–H, Fixed, 95% CI)	0.71 (0.22, 2.29)	OR (M–H, Fixed, 95% CI)	0.67 (0.16, 2.77)	0.58
Percutaneous	4/501	3/396	OR (M–H, Fixed, 95% CI)	0.96 (0.42, 2.22)	OR (M–H, Fixed, 95% CI)	0.73 (0.40, 1.32)	0.30
3–year	4/501	3/396	OR (M–H, Fixed, 95% CI)	0.53 (0.34, 0.83)	OR (M–H, Fixed, 95% CI)	0.49 (0.33, 0.74)	0.0006

S Study, P patients, OR odds ratio, M–H Mantel–Haenszel, Fixed Fixed-effect model, CI confidence interval

Discussion

The main findings obtained from our meta-analysis showed that there were no significant differences in 1-year OS rates between the two groups. However, the MIS-treated group presented a significant better survival rate in terms of OS at 3 years, and DFS at 1 to 3 years. Simultaneously, during the mean follow-up duration, the RFA-treated group showed a higher local recurrence rate. In addition, our meta-analysis showed that the RFA-treated group was associated with less postoperative complications, shorter operation times, and hospital duration, when compared to the MIS-treated group.

On the one hand, under normal conditions, patients with SHCC rarely succumb to their disease within a year of diagnosis and the recurrence of the disease has usually, a slow gradual impact on the OS of SHCC patients [27]. Notably, recurrences could be treated by repeated RFA therapy, hepatectomy, or TACE, all of which could affect OS [28]. In our current study, local recurrences were found to be more frequent after RFA treatments, when compared to MIS treatments. Furthermore, according to Rhim et al., the RFA technology in hepatic ablation is limited by the following factors: (1) limitation of ablation volume; (2) technically infeasibility in some tumors due to conspicuity and dangerous location; and (3) the heat sink effect which means the convected heat from the adjacent large vessel could affect the negative effect on the ablation [29]. Therefore, our observations could be due to an insufficient ablation of the primary SHCC tumor, the heat sink effect, and/or the presence of venous invasion in the adjacent liver of the tumor. Additionally, the safety margin of the RFA treatment was narrower than that of the MIS treatment, as in MIS, the entire Couinaud segment containing tumors is usually removed, so that a throughout elimination of the primary tumors can be conducted. With this, any potential sites of microscopic lesions and cancer embolus are more likely to be completely removed in these patients [30]. Therefore, this may explain the relative lower local recurrence rates seen in SHCC patients treated with MIS.

Our subgroup analysis according to approaches taken in RFA treatments should be treated with caution, as only one trial concerning 46 patients was evaluated in the laparoscopic RFA-treated group. Our results indicate that significantly higher survival outcomes at 3-year rates were observed in the MIS-treated group, when compared with the percutaneous RFA-treated group. Nevertheless, the laparoscopic RFA-treated group presented similar survival outcomes, but lower 1-year DFS rates, in comparison with the MIS-treated group. The main reason for this may be the laparoscopic approaches used, which can increase the probability of preexisting microscopic tumor foci

detection, given the fact that they allow complete abdominal exploration and intraoperative ultrasound assessments. Moreover, these laparoscopic approaches could also place the electrodes at accurate locations and possibly treat tumors in percutaneously inaccessible areas of the liver and also tumors that are in close proximity or invading adjacent organs [31]. At the same time, the laparoscopic approach to RFA treatment has proven to be superior to the percutaneous approach in lesions that are difficult or impossible to be treated in such a way or in severe liver disease [32]. In other words, it may extend the indications of RFA treatments.

Further, our subgroup analysis results according to tumor sizes indicate that RFA treatments seem to be a reasonable alternative choice for patients with single SHCC nodules (≤ 3 cm), who on account of RFA treatment can achieve equivalent OS and DFS rates at 1 and 3 years and have less tissue damage compared with MIS treatments. This is consistent with the National Comprehensive Cancer Network (NCCN) guidelines stating that RFA treatment alone may be curative in treating smaller SHCC tumors (≤ 3 cm) [33]. This may be due to the fact that vascular invasion is less frequent in smaller tumors (≤ 3 cm) [34], which helps explain the equivalent survival outcomes observed between the two groups. However, the fact that we were only able to analyze two studies containing 170 patients makes the interpretation of this result insufficient, and in practice, the location of the SHCC tumor is a key element when choosing between RFA and MIS treatments. The MIS treatment approach should be favored in patients with HCC tumors that are located in the left and inferior segments of the liver [35]. On the contrary, central lesions would require a larger surgical parenchymal sacrifice, increasing the risk of postoperative liver failure and thus are better treated with RFA therapy [24].

On the other hand, as minimally invasive therapy, RFA induces deep thermal injury by generating high-frequency alternative currents, which cause ionic agitation and conversion to heat in hepatic tissue while sparing the normal parenchyma [3]. In clinical practice terms, this procedure could be performed without general anesthesia. Most patients undergoing percutaneous RFA treatment only require a 2–3-day hospital stay or can even leave on the same day without hospitalization [36]. Therefore, it is not surprising that RFA treatment was found to be associated with less postoperative complications, shorter operation times, and shorter hospital duration.

Moreover, we considered that our meta-analysis adds several key insights, as follows: (1) As far as we know, this is the first meta-analysis that compares the RFA treatment with hepatic resection performed through a laparoscopic- or robot-assisted approach; (2) low heterogeneity between the two groups were observed on long-term outcomes; (3) we implemented two subgroup analyses to reduce the potential

bias due to patient selection in several series in terms of patient demographics and tumor characteristics.

Nonetheless, the results of this meta-analysis should be interpreted with caution for the following reasons: (1) All the data obtained in the present study come from non-randomized clinical trials (NRCTs), which means that the unpredictable confounding factors may affect our data analysis, even in the well-analyzed case–control studies. Therefore, the overall level of clinical evidence obtained here is relatively low; (2) the cumulative OS and DFS are time-to-event outcomes. In addition, HRs (hazard rates) are the most appropriate parameters to measure time-dependent outcomes [37]. However, in our analysis we extracted the OR, but not the HRs, in order to compare OS and DFS rates after RFA and MIS treatments for SHCC patients; (3) the different indications for RFA and MIS treatments are responsible for the slightly different patient characteristics of the two groups. In fact, patients with better liver function, higher albumin levels, lower bilirubin serum levels, and larger tumors tended to be resected, whereas patients with liver dysfunction, multiple tumors, and portal hypertension were ablated [22, 24]; (4) we calculated the recurrence and complication rates in the trials included in our analysis. However, the time interval of disease recurrence and the severity of complications in these studies were not completely uniform, which may lead to a high level of clinical heterogeneity; (5) RFA treatments can be performed using percutaneous, laparoscopic, or open approaches. In addition, several different RFA systems were used in the treatment centers, such as the RITA Medical System (Mountain View, CA, USA), Radionics (Burlington, MA, USA), and Valleylab (Boulder, CO, USA). Different approaches and RFA systems can also impact the data pooling and interpretation of results [38]; (6) in the selected studies, only VG et al. compared robotic-assisted laparoscopic hepatectomy with RFA treatments [24]. Although robotic-assisted laparoscopic hepatectomy shows similar safety, feasibility, and effectiveness to laparoscopic hepatectomy, there were no final conclusions in terms of anti-tumor results [9, 39].

Therefore, in future studies, we will include HRs in order to measure time-dependent outcomes and will also focus on the characteristics of the patient population, for instance age, alpha-fetoprotein levels, serum albumin levels, among others. Importantly, it will be necessary to define a standard time separation for local disease recurrences and a standard definition for treatment complication severity [28].

Conclusions

Based on the current available evidence, compared with MIS-treated patients, the RFA treatment for SHCC resulted in lower survival clinical outcomes and higher local

recurrence rates, although with fewer complications, shorter operation times, and hospitalization duration. Namely, our results show that MIS treatments may provide better long-term outcomes for SHCC patients, whereas RFA treatments were found to be associated with better short-term outcomes. Therefore, RFA treatments may have an advantage in relation to minimal invasiveness, while MIS treatments may have advantages regarding tumor removal [7]. Taking into consideration long-term survival data, the MIS treatment appears to be superior to RFA in treating SHCC patients; however, according to our subanalysis results evaluating single nodules, a RFA approach seems to be a better treatment for patients with single SHCC nodules (≤ 3 cm), given that it leads to equivalent OS and DFS in 1- and 3-year rates and can lead to less tissue damage compared with MIS treatment approaches, especially for patients who are eligible for tumor resection. Nevertheless, based on our analysis, we were not able to precisely identify a preferred primary treatment for these patients.

Furthermore, the laparoscopic approach to RFA has proven to be superior to the percutaneous approach in our current study, thereby extending the indications of RFA treatments. In conclusion, we suggest that higher quality randomized control clinical trials (RCTs) or future retrospective studies should focus on the efficacy and safety of RFA treatments in comparison with MIS treatments for SHCC patients in order to provide much needed credible evidence for better treatment options in SHCC.

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