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Review Article

Radiofrequency Ablation versus Surgical Resection for Management of Colorectal Liver Metastasis: Systematic Review and Meta-Analysis

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Abstract

Background: Radiofrequency ablation [RFA] has a different outcome than hepatic resection [HR] for treating colorectal liver metastases. The size of the tumor, number of tumors, age, presence of primary node, and metachronous metastasis were independent risk factors influencing the results. Therefore, this study aims to review the previous studies comparing radiofrequency ablation [RFA] over surgical resection in treating colorectal liver metastases.

Methods: Twenty Three [23] observational studies were eligible for analysis. Of the 23 observational studies, four compare 1 year of OS between HR and RFA, 14 compare three years of OS, and nine compare five years of OS. Three studies compare 1-year DFS between HR and RFA, 6 studies compare three years of DFS, and eight studies compare 5 years of DFS. 15 studies compare the recurrence rates between HR and RFA, nine studies compare the complications rates between HR and RFA, and six studies compare the duration of hospital stay between HR and RFA.

Results: 3092 patients enrolled in 23 studies were identified. There were no significant differences between RFA and HR in 1, 5 years OS with pooled RR of 1.26 {95% CI: [1.58, 2.74]} and 1.11 {95% CI: [0.99, 1.26]} respectively; however, three years OS showed lower OS in RFA than HR with pooled RR of 1.25{95% CI: [1.04, 1.51]}. Also, CRLM patients experienced significantly higher incidences of total, intrahepatic, and local recurrence rates in RFA than HR with pooled RR of 2.06 {95% CI: [1.42, 3.00]}, 1.67{95% CI: [1.21, 2.33]}and 3.76 {95% CI: [2.25, 6.30]} respectively.

Conclusion: RFA revealed a lower long-term survival rate and a greater recurrence rate in CRLM patients. Independent survival predictors included age, number of tumors, primary node positivity, and metachronous metastasis.

Keywords: Ablation; Colorectal; Liver Metastasis; Radiofrequency; Surgical Resection.

INTRODUCTION

Presently, colorectal cancer is among the most prevalent cancers in humans, affecting one million people annually worldwide [1,2] . Up to 50% of patients with colorectal cancer experienced colorectal metastases at the time of diagnosis [CRLM] [3]. Overall survival [OS], which has emerged as the primary cause of cancer-related death in patients with colorectal cancer, is significantly impacted by colorectal liver metastasis; the median OS for patients with untreated CRLM is 4–12 months [4, 5] .

The mainstay of treatment for liver metastases of colorectal cancer is surgery. Individuals who have liver metastases from colorectal cancer can significantly extend their life expectancy. Achieving a 50% five-year survival rate and a 25% cure rate for patients is possible [6].

Although the primary treatment is liver resection, patients' chances of survival are significantly impacted by the metastasis's postoperative recurrence. As the main course of treatment following surgery, adjuvant chemotherapy can lower the chance of metastatic recurrence [7,8]. Surgery is not appropriate for all patients with liver metastases from rectal tumors, however. Because of physical conditions, scattered distribution, extra hepatic metastases, or liver metastasis, some individuals cannot undergo surgery [9].

Currently, in addition to surgery, chemotherapy, radiation therapy, and Hong and Georgiades are used to treat liver metastases [10]. RFA is increasingly being used to treat individuals with CRLM, and local therapy approaches are crucial to the care of these patients. RFA is a minimally invasive procedure often guided by MRI, CT, or ultrasound. It offers reasonable local control for tiny tumors and could be used as a substitute for incurable CRLM treatment [11]. The electrode is inserted straight into the intended tissue to eradicate the cancer. It is the most utilized type of thermal ablation [12]. RFA uses various technical techniques to provide energy to the tumor site, raise the surrounding temperature, and destroy tissue cells [13].

Guidelines or databases primarily inform clinical decision-making. There are differences in the clinical therapies for liver metastases of colorectal cancer. Through a comprehensive review and meta-analysis, we hope to establish a foundation for clinical decision-making for treating colon cancer liver metastases, elucidating the effects of surgical resection and RFA.

METHODS

1. Develop the targeted research question of the meta-analyses:

After conducting a literature search, we discovered that colorectal cancer [CRC] is a common disease globally, with over 50% of patients experiencing liver metastases. Patients with metastatic colorectal cancer [mCRC] treated with standard therapy have a poor five-year overall survival rate. However, liver transplantation can enhance clinical outcomes in a well-chosen cohort with an excellent 5-year overall survival rate of 83%. Surgery for liver metastases can increase survival and potentially lead to a cure, with 5- and 10-year survival rates of 42% and 25%, respectively, being possible. Radiofrequency ablation [RFA] may have an alternate role in treating old and vulnerable individuals with different organ dysfunctions. Over the past ten years, RFA has surpassed other ablative therapies because of its low morbidity rates [8.9%], mortality [0.5%], safety, and patient acceptability.

There have been reports of data on long-term survival [5-year OS] following various RFA techniques, ranging from 22% to 30%. Minor [≤4 cm] single CRLM has increased by 40% over five years. Numerous investigations have contrasted the effectiveness of RFA and HR concerning survival, efficacy, safety, and other variables that could affect patients with CRLMs. Their findings and conclusions, meanwhile, continued to be contradictory.

***Null hypothesis*:** the effect of radiofrequency ablation is the same as surgical resection for managing colorectal liver metastasis.

***Alternative hypothesis*:** For the treatment of colorectal liver metastases, radiofrequency ablation had a different outcome than surgical excision. The size of the tumor, number of tumors, age, presence of central node, and metachronous metastasis were independent survival factors that influenced both results.

2. Determination of search terms and search strategy

2. 1. Electronic search engines/libraries

We began an electronic systematic search with PubMed [which includes Medline] in March 2023. The National Center for Biotechnology Information and the American National Library of Medicine are the sources of this database. We broadened our search to include additional databases, including Web of Science, Scopus, Google Scholar, and Cochrane Library websites, because relying solely on the PubMed database can overlook 30% to 80% of pertinent studies. Furthermore, we performed a manual review by reviewing the citations in the included articles and the relevant references listed in PubMed and associated journals.

2. 2. Search terms:

Search terms included: "colorectal liver metastasis" OR "colorectal liver secondaries" OR "CRLM" OR "colorectal cancer" OR "CRC" OR "colon cancer" OR "rectal cancer" OR "liver cancer" OR "liver metastases" AND "radiofrequency ablation" OR "RFA" OR "thermal ablation" AND "liver resection" OR "hepatic resection" AND "survival" OR "recurrence" OR "outcome."

2. 3. Eligibility of studies for inclusion

We imported all the citation abstracts and bibliographic information the database had gathered into Mendeley [reference management]. Before the first pass, screening, duplicate citations were eliminated. The inclusion and exclusion criteria were used to determine the eligibility of citations [titles and abstracts]. All Studies deemed eligible upon title and abstract screening were screened in full text according to inclusion and exclusion criteria **[Table 1].**

Table [1]: Specification of population, intervention, comparison, and outcomes [PICO].

Population	Inclusion criteria	Exclusion criteria
	• Adults diagnosed with CRLM who received RFA or HR.	• Patients suffered other tumors or metastasis that may influence our outcomes. • Experimental trials on animals or non-human studies. • Studies not conducted in the adult population. • Abstracts, letters, editorials, expert opinions, reviews, case reports. • Without sufficient data or did not meet our including criteria.
Intervention	• Patients receiving RFA as intervention group.	Patients are receiving other modalities of management.
Comparison	• Patients receiving HR as a comparison group.	
Outcome	• Disease-free survival rate. • Recurrence rate • Overall survival rate. • The occurrence of complications [hemorrhage from liver resection, infection]	Other outcomes are needed to meet our inclusion criteria.
Language restrictions	• English language only	Studies published in languages other than English are excluded.
Date Range	• There is no date range	

3. Outcome measures:

We considered the fact that patient outcomes compare the effectiveness of radiofrequency ablation versus surgical resection in managing colorectal liver metastasis, considering factors such as overall survival rate, recurrence rate, disease-free survival rate, and the incidence of complications [infection, bleeding after liver resection].

4. Data extraction:

Data gathering is essential to a systematic review. It fills in the gaps between a meta-analysis and a review. For the data analyst/reviewer, making this as simple, clear, and precise as possible greatly expedites the data cleaning and checking process. Inadequate collaboration between analysts and reviewers may result in mistakes that propagate and yield inaccurate findings and conclusions in systematic reviews. Reviewers putting more and more pressure on data to be extracted consistently and methodically as more sophisticated meta-analysis approaches are employed. The number of surviving patients for OS and DFS was calculated by multiplying the percentage of survivors by the initial sample size for the treatment arm, or the treatment group minus the excluded patients.

***4. 1. Data Extraction Planning*:**

As part of our data extraction planning, we created and tested a form to ensure we included a prompt to extract the data we needed for data synthesis/analysis and explain the research.

4.2. Data Extraction Elements:

Our research question components [PICO], eligibility [inclusion/exclusion criteria], and study characteristics such as the study name, year of publication, first author, total sample size, type of treatment, tumor size, follow-up period, primary outcome, 1,3,5 years overall survival, 1,3,5 years disease free survival, recurrence rate, number of metastases, complications, and hospital stay were all taken into consideration as we extracted information from each included article.

5. Quality assessment:

We used the Newcastle-Ottawa scale to evaluate the quality of each study independently. There are three components to it: selection, comparability, and outcome. study can receive up to one star for every numbered item in the Selection and Outcome categories. A comparative rating of no more than two stars is possible. Cohort studies are eligible for a maximum of nine [9] stars, while cross-sectional studies are only eligible for six [6] stars. Three or four stars in selection, one or two stars in comparability, and two or three stars in outcomes were needed for a "good" quality score. Two stars in selection, one or two stars in comparability, and two or three stars in outcomes were required to receive a ―fair‖ quality score. A ―poor quality score reflected 0 or 1 star[s] in selection, 0 stars in comparability, or 0 or 1 star[s] in outcomes.

6. *Data Synthesis and Statistical Methods*

Since we selected effect size for dichotomous outcomes, the data were shown as relative risk [RR] with 95% confidence intervals [CI]. The effect size was weighted with generic inverse variance. The heterogeneity between studies is then assessed using the chi-square-based Q statistical test after the effect size has been weighted by inverse variance. Additionally, I^2 statistics were used to quantify heterogeneity, with cut-offs of 25%, 50%, and 75% to suggest low heterogeneity [25–50%], moderate heterogeneity [50–75%], and high heterogeneity [>75%]. $P \leq 0.05$ was considered to represent significant heterogeneity.

Pooled RR was estimated using a random effects model. Begg's test was employed to evaluate publication bias, in turn. We concluded that there was no evident publication bias if the funnel plot shapes showed no apparent signs of asymmetry.

All statistical analyses were carried out using the usual statistical techniques offered by RevMan 5.2. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] standards were adhered to in this systematic review and meta-analysis **[Figure 1].**

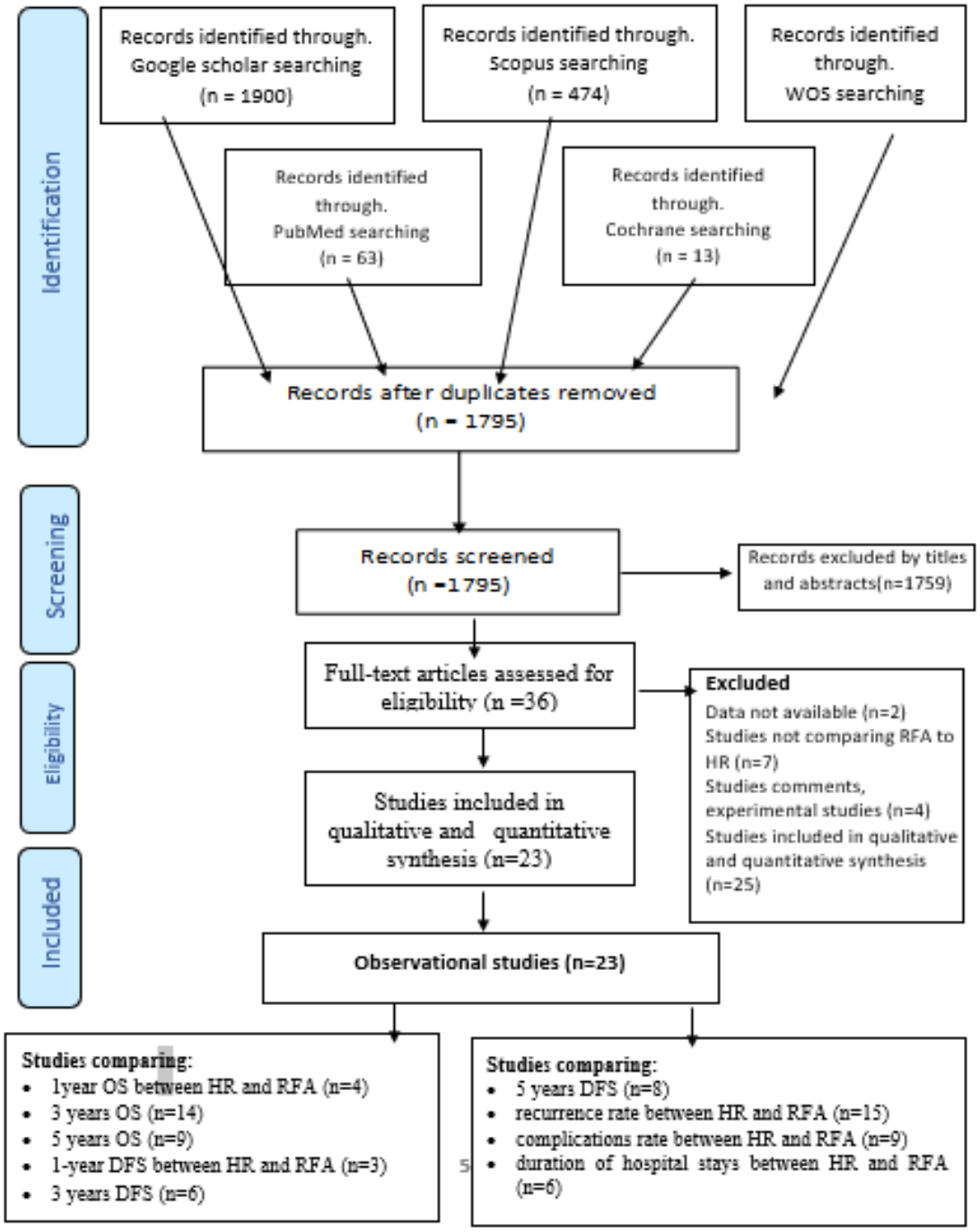

Figure [1]: PRISMA flow diagram explaining the cascade of searching several databases, removing duplicates, screening steps, and meta-analysis processes.

RESULTS

Study characteristics

The database search results and the selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses format**.** Twenty-three observational studies were deemed suitable for analysis based on the search technique previously outlined. Of the twenty-three observational studies, nine compare five years' OS, fourteen compare three years' OS, and four compare one year's OS between HR and RFA. Eight studies compare five-year DFS, six three-year DFS, and three compare one-year DFS between HR and RFA. Fifteen research have compared the rates of recurrence, nine studies have compared the rates of complications, and six studies have compared the length of hospital stay between RFA and HR **[Table 2].**

Quality assessment:

The average score in the NOS quality assessment was 7.3 out of a total score of 9. Quality assessment analysis indicates that, of 23 observational studies, 14 had an NOS score of 7, followed by five studies with a score of 8 and four studies with a score of 6. According to our definition of good quality, approximately 82.6% and fair quality by 17.4% [Table 3, figure 2, 3]. The risk of bias for each included study is displayed in Figure [2], with most studies indicating generally

good methodological quality, especially in the selection, including ' representativeness of the exposed cohort' and 'selection of the non-exposed cohort', also a low risk of bias in 'comparability' and 'assessment of outcome.' A high risk of bias was observed in 'was follow up long enough for an outcome to occur.' In contrast, an unclear risk of bias was observed in the ascertainment of exposure,' demonstrating that the outcome of interest was absent at the start of the study and the ' adequacy of follow-up of the cohort.'

Outcomes

Overall survival rate [OS]

1-Year OS: 364 patients enrolled in four studies reported 1-year OS for RFA versus HR. The overall effect showed a non-significant risk ratio between RFA and HR. [RR = 1.26; 95% CI: [0.58, 2.74], with no heterogeneity between studies I2=0.0, P = 0.55] [14, 15, 16, 34] Figure [4].

3-Year OS: Fourteen studies included 1901 patients and reported 3-year OS for RFA versus HR. The overall effect showed a significant risk ratio between RFA compared to HR [RR = 1.25; 95% CI: [1.04, 1.51]], indicating a lower 3-year overall survival **rate in** RFA patients than in HR patients. there is moderate heterogeneity [cut off=50-75%] among the studies [I2=68%, P =0.02] [14 ,15 , 16 , 17, 18 ,19 ,20, 21 ,22, 23, 24, 28, 34, 35] Figure[5].

5-Year OS: 1232 patients enrolled in nine studies reported 5-year OS for RFA versus HR. The overall effect showed a non-significant risk ratio between RFA and HR. [RR = 1.11; 95% CI: [0.99, 1.26]] with low heterogeneity among the studies [I2=24%, P=0.08], [14, 15, 19, 20, 22, 25, 26, 30, 34], Figure [6].

Disease-free survival rate [DFS]

1-Year DFS: a total of 226 patients included in three studies reported 1-year DFS for RFA versus HR. The overall effect showed a significant risk ratio between RFA compared to HR. [RR = 1.62; 95% CI: [1.10, 2.37], indicating a higher 1-year DFS rate in HR patients than RFA patients, there is no heterogeneity between studies [I^2= 0%, P = 0.01], [14, 15, 34], Figure [7].

3-Year DFS: Six studies included 642 patients who reported DFS for 3 years for RFA versus HR. The overall effect showed a significant risk ratio between RFA compared to HR. [RR = 1.29; 95% CI: [1.07, 1.55]] indicating a lower 3-year DFS rate in RFA patients than in HR patients. There is low heterogeneity [cut off= 25-50%] among the six studies [I2=43%, p=0.007], [14, 15, 22, 23, 30, 34], Figure [8].

5-Year DFS: Eight studies consisted of 1036 patients who reported DFS 5 years for RFA versus HR. The overall effect showed a significant risk ratio between RFA compared to HR. [RR = 1.10; 95% CI: [1.02, 1.18], indication higher 5 years DFS rate in RFA patients than HR patients, there is no heterogeneity between studies [I^2=0%, P = 0.02], [14, 15, 22, 25, 26, 30, 33, 34], Figure [9].

Complications

Nine studies included 836 patients who reported complications for RFA versus HR. The overall effect showed a significant risk ratio between RFA compared to HR with a higher complication rate in HR as compared with RFA with [RR = 0.71; 95% CI: [0.52, 0.98], P = 0.04], [15, 17, 24, 25, 26, 31, 32, 34, 36]. The pooled studies show mild heterogeneity [cut off= 25-50%] with [I2 = 46, P < 0.07] thus the random model was using [Figure 10].

Total recurrence

Fifteen studies with 2155 patients reported total recurrence for RFA versus HR. The overall effect showed a significant risk ratio between RFA compared to HR with a higher incidence of recurrence rate in RFA patients than in HR patients [RR = 2.06; 95% CI: [1.42, 3.00]], there is high heterogeneity [cut off>75%] among the fifteen studies [I2=88%, P = 0.0001], [16, 18, 19, 20, 21, 23, 24, 25, 26, 27, 28, 29, 30, 32, 34], Figure [11] .

Extrahepatic recurrence: Seven studies included 680 patients who reported extrahepatic recurrence for RFA versus HR. The overall effect showed a non-significant risk ratio between RFA and HR. [RR = 0.97; 95% CI: [0.75, 1.26], there is no heterogeneity between the studies [I^2= 0% P = 0.83], [20, 24, 25, 28, 29, 31, 32], Figure [12].

Intrahepatic recurrence: 976 patients in nine studies reported intrahepatic recurrence for RFA versus HR. The overall effect showed a significant risk ratio between RFA and HR. [RR = 1.67; 95% CI: [1.21, 2.33]] indicating a lower intrahepatic recurrence rate in HR patients than in RFA patients; there is moderate heterogeneity [cut off= 50-75%] among the nine studies [I2=56%, P = 0.02] [16, 19, 20, 24, 25, 28, 29, 31, 32], Figure [13].

Local recurrence: Seven studies included 819 patients who reported local recurrence for RFA versus HR. The overall effect showed a significant risk ratio between RFA and HR. [RR=3.76; 95% CI: [2.25, 6.30]] indicating a higher local recurrence rate in RFA patients than HR patients, there is no heterogeneity among the seven studies [I2=3%, P=0.0001], [16, 19, 20, 24, 25, 31, 32], Figure [14].

Publication bias

Begg's funnel plot was used to assess the publication bias of the included literature, and we could roughly evaluate the publication bias by seeing whether their ships were of any evident assembly. The funnel plot of the overall 3-year OS showed asymmetric distribution, indicating some publication bias in the analysis [I2=68%, P =0.02]. In this concern, the funnel plot of the total recurrence showed asymmetric distribution, indicating some publication bias in the analysis [I2=88%, P =0.0001].

Table [2]: Summary of included studies for systematic review and meta-analysis.

Authors	Country	Sample size	Groups	Age [Mean±SD]	Sex [Female, male]		Treatment	Tumor size	Follow up time	main outcome
Lee et al. [2015]	Korea	153	RFA [51]	60 years in HR group [30-79 years and 58.5 years [35-75 years]	16 [31%] female.	35 [69%] male.	RFA intraoperatively and hepatectomy	1.8 cm [1 cm-3 cm]	45 months [12 - 58 months]	DFS, OS, complication
			HR [102]		29 [28%] female	73[71.6%] male		1.7 cm [0.2 - 3 cm]		
Kim et al. [2011]	Korea	455	RFA [177]	[60.4 ± 10.7 years]	56 [31.6%] female	121 [68.4] male	RFA [intraoperatively or percutaneous] and hepatectomy with chemotherapy postoperative in 92.7% in RFA group and 88.8% in HR group	2.1 cm [0.5-6.2 cm]	every 3-6 months by CEA, CT, MRI or PET	OS, DFS
			HR [278]	[57.1±10.9 years]	110 [39.6%] female	168 [60.4] male		2.6 cm [0.5-13 cm]		
Ko at al. [2014]	Korea	29	RFA [17]	61.35 ± 8.33 years	10 [58.8%] females	7 [41.2%] males	RFA and HR	2.02 +-1.17 cm	every 4 months in initial 2 years and every 6 months thereafter	OS, DFS,recurrence rate
			HR [12]	67.5± 7.44 years	4 [33.3%] females	8 [66.7%] males		3.59±.81 cm		
Lee et al. [2008]		153	RFA [37]	59 [28-75] years	11 [29.7%] females	26 [70.3%] males	RFA [intraoperatively or percutaneous] and HR	2.25 cm [0.8- 5 cm]	48.2 months and 39.2 months after treatment	recurrence rate, OS, DFS
			HR [116]	58 [26-79] years	40 [34.5%] females	76 [65.5%] males		3.29 cm [0.5-18 cm]		
Oshowo at al. [2003]	UK	45	RFA [20]	57 [34-80 years]	14 [70%] females	6 [30.0%] males	RFA [percutanously] and liver resection	3 cm [1-10 cm]		OS, complication
			HR [25]	63 [52-77 years]	10 [40%] females	15 [60%] males		4 cm [2-7 cm]		
Gleisner et al. [2008]	USA	203	RFA [11]	60 years	3 [27.2%] females	8 [72.7%] males	RFA [intraoperatively] and HR	2.5 cm		DFS, OS, recurrence rate
			HR [192]	61 years	71 [37%] females	121 [63%] males		3.5cm [2-5 cm]		
Hur et al. [2009]	Korea	67	RFA [25]	62.6 [33-82 years]	10 [40%] females	15 [60%] males	RFA [intraoperatively or percutaneous] and HR	2.5 cm [0.8-3.6cm]	42 months [13-120 months]	OS, complications, recurrence rate
			HR [42]	58 [42.75 years]	15 [35.7%] females	27 [64.3] males		2.8cm [0.68cm]		
Mckay et al. [2009]	Canada	101	RFA [43]	67 [37-83 years]	18 [41.9%] female	25 [58.1] male	RFA [intraoperatively] and HR	3 cm [1-7.5 cm]	38 months and 30 months	OS, DFS , complications and recurrence rate
			HR [58]	67 [28-83 years]	29 [50%] females	29 [50%] males		4.1cm [1.5-14.5cm]		
Lee et al. [2011]	Korea	53	RFA [28]	61[32 -82 years]	5 [17.9%] females	23 [82.1] males	RFA [percutaneous] and HR	2.05 cm [1-4.8 cm]		recurrence rate
			HR [25]	61 [34-76 years]	11 [44%] females	14 [56%] males		4 cm [0.7-9.7 cm]		
Tanis et al. [2014]	UK	136	RFA [55]	64 [39- 79 years]	22 [40%]females	33 [60%] males	RFA and HR	cm [1-3.9 cm]	4.7 years and 8.2 years	recurrence rate
			HR [81]	61 [29 - 77years]	3 [3.7%] females	78 [96.3%] males		2.8 cm [5-4 cm]		
Kim et al. [2015]	south korea	60	RFA [17]	63.2 years	5 [29.4%] females	12 [70.6%] males	RFA [percutaneous] and HR	2.3 cm	for OS 57 and 30 months , for DFS 22 and 11 months	OS , DFS
			HR [43]	55.9 years	15 [34.9%] females	28 [65.1%] males		3.1 cm		
Hof et al. [2016]	UK	362	RFA [101]	65.7 years	32 [3.7%] females	69 [68.5%] males	RFA [open or percutaneous] and HR	2.2 cm [1.5 -35 cm]	38.6 months [19.5-61.7 months]	OS, recurrence rate
			HR [261]	63.4 years	110 [42.1%] females	151 [57.9%] males		4 cm [2.5 - 5.7 cm]		

Authors	Country	Sample size	Groups	Age [Mean±SD]	Sex [Female, male]		Treatment	Tumor size	Follow up time	main outcome
Schiffman et al. [2010]	USA	140	RFA [45]	62.1 years	21 [46.7%] females	24 [53.3%] males	RFA and HR	3.9 cm	25.9 months	complications, recurrence rate
			HR [95]	60.6 years	47 [49.5%] females	48 [50.5%] males		5.6 cm		
HE et al. [2016]	China	53	RFA [21]	64.05±9.05 years	13 [61.9%] females	8 [38.1%] males	RFA [percutaneous] and HR	1.89±0.62 cm	every 3 months in first 2 years and every 6 months thereafter	OS, DFS
			HR [32]	62.03±9.79 years	14 [43.8%] females	18 [56.3%] males		2.25±0.68cm		
Berber et al. [2008]	USA	158	RFA [68]	67 ±1.4 years	25 [36.8%] females	43 [63.2%] males	RFA and HR	3.7±0.2 cm	23 months for RFA group and 33 months for HR group	OS, recurrence rate
			HR [90]	63.7 ± 1.3 years	33 [36.7%] females	57 [63.3%] males		3.8 ± 0.2		
van de Geest et al. [2022]	USA [Netherland]	72	RFA [36]	69 [53-86] years	13 [36.1%]females	23 [63.9%] males	RFA [percutaneous or open] and HR	2.5cm [0.8-6.5 cm]	24 months for RFA group and 33 months for HR group	OS, DFS, recurrence rate complication
			HR [36]	68 [50-86] years	11 [30.6%]females	25 [69.45] males		3.4cm [1-7.5cm]		
Mao et al. [2019]	China	104	RFA [61]	59 [37-79] years	25 [41%] females	36 [59%] males	percutaneous RFA and HR	2.7cm [0.9-4 cm]	28.9 months	OS, recurrence rate
			HR [43]	57 [32-76] years	22 [51.2%] females	21 [48.8%] males		3.2cm [1-4 cm]		
Reuter, [2008]	USA	192	RFA [66]	63.5 years	20 [30.3%] females	46 [69.7%] males	RFA and HR	3.2cm [largest]	20 months	OS, recurrence rate, complication
			HR [126]	61.9 years	57 [45.2%] females	69 [54.8%] males		5.3 cm [largest]		
Wang et al. [2018]	China	138	RFA [46]	58.5 [50.8- 67] years	17 [37%] females	29 [63%] males	RFA and HR	2.25cm [1.68-3.63cm]	44 months [6-96 months]	OS, recurrence rate
			HR [92]	58[51-68.5] years	34 [37%] females	58 [63%] males		3cm [1.85-3.58cm]		
Li et al. [2020]	China	20	RFA [9]	62.7 ± 7 years	3 [33.3%] females	6 [66.7%] males	percutaneous RFA and HR	2.2 cm ± 0.9 cm	7years [2-11 years]	OS, DFS, complication
			HR [11]		6 [54.5%] females	5 [45.5%] males		2.6 cm ± 1.1 cm		
Abdalla et al. [2004]	USA	247	RFA [57]	60 years [23-88 years]			intraoperative RFA and HR	2.5cm [1-8 cm]	21 months [4 - 11 months]	OS, recurrence rate
			HR [190]							
White et al. [2007]	USA	52	RFA [22]	62 years [48-77years]	14 [63.6%] females	8 [36.4%] males	percutaneous RFA and wedge resection	2cm [1-5 cm]	every 3-6 months for the first 2-3 years	complications and hospital stay
			HR [30]	62 years [42-81years]	10 [33.3%] females	20 [66.7%] males		2.5cm [1-5 cm]		
Yashodhan et al. [2011]	USA	99	RFA [35]	60 years [57-74 years]			RFA and HR	2.8 cm [2.6 -3cm]	31.36 ±21.18 months	OS and hospital stay
			HR [64]	60 years [57-74 years				3.4 cm [3.8-4.2cm]		

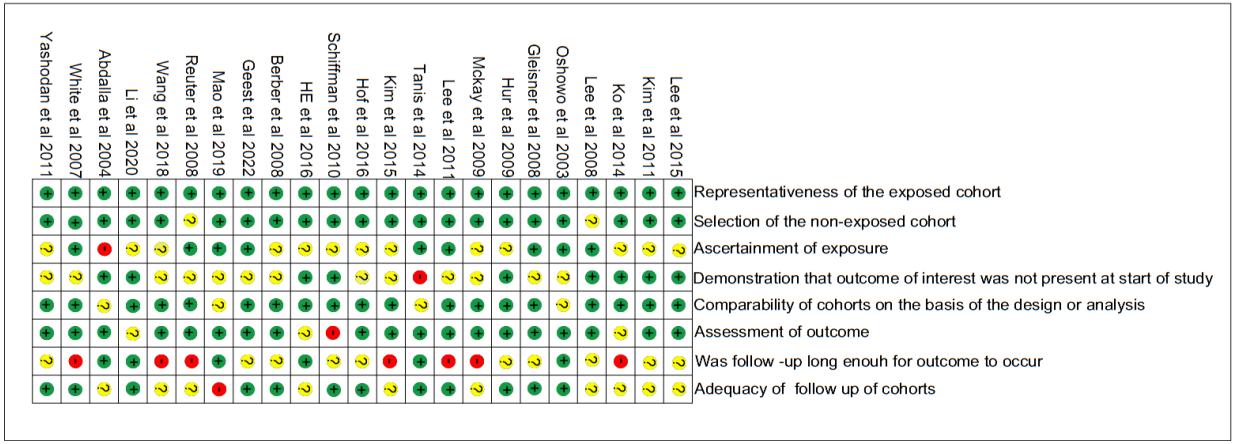

Figure [2]: The risk of bias assessment of the included studies.

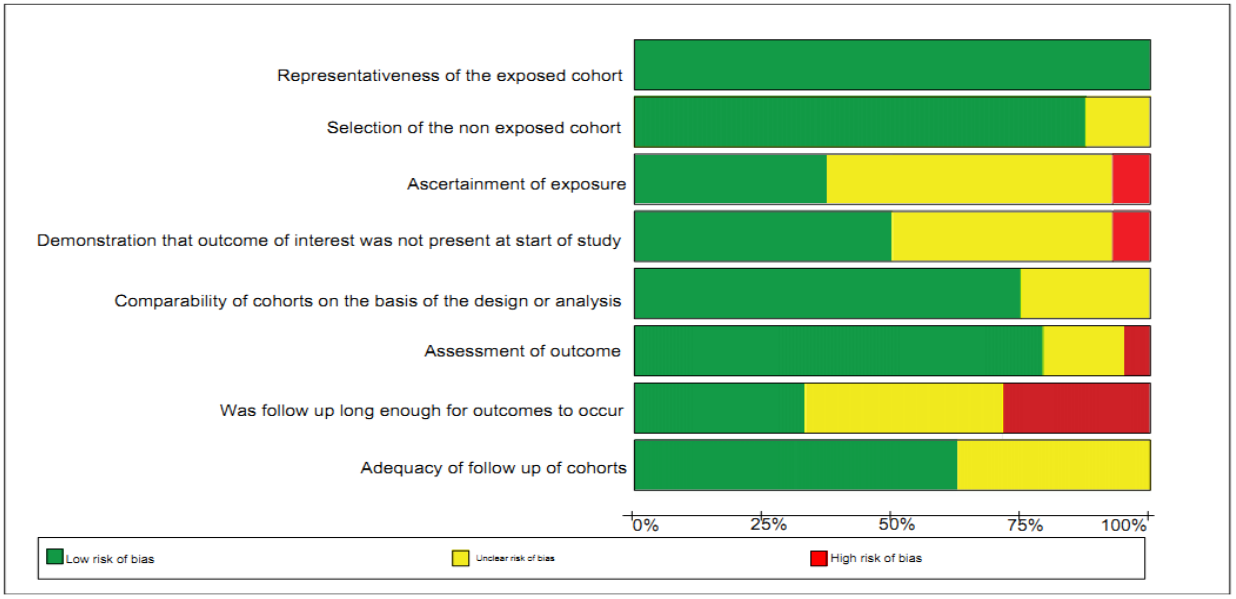

Figure [3]: Figure the risk of bias assessment of the included studies, representing the percentage of studies with low, high, and unclear risk of bias.

Table [3]: Quality assessment of the included observational studies using the Newcastle-Ottawa scale.

	Study name	Selection score	Comparability score	Outcome score	Total score	Study quality
1	Lee et al [2015]	**3**	**2**	**2**	**7**	**Good**
2	Kim et al [2011]	**3**	**1**	**3**	**7**	**Good**
3	Ko et al [2014]	**3**	**2**	**2**	**7**	**Good**
4	Lee et al [2008]	**2**	**2**	**3**	**7**	**Good**
5	Oshowo et al [2003]	**2**	**2**	**2**	**6**	**Fair**
6	Gleisner at al. [2008]	**3**	**2**	**2**	**7**	**Good**
7	Hur et al. [2009]	**3**	**2**	**2**	**7**	**Good**
8	Mckay et al. [2009]	**3**	**1**	**3**	**7**	**Good**
9	Lee et al. [2011]	**3**	**2**	**3**	**8**	**Good**
10	Tanis et al. [2014]	**3**	**1**	**3**	**7**	**Good**
11	Kim et al. [2015]	**3**	**1**	**2**	**6**	**Fair**
12	Hof et al. [2016]	**3**	**2**	**2**	**7**	**Good**
13	Schiffman et al. [2010]	**3**	**2**	**3**	**8**	**Good**
14	HE et al. [2016]	**3**	**2**	**2**	**7**	**Good**
15	Berber et al. [2008]	**3**	**1**	**3**	**7**	**Good**
16	Van de Geest et al. [2022]	**3**	**2**	**3**	**8**	**Good**
17	Mao et al. [2019]	**3**	**2**	**2**	**8**	**Good**
18	Reuter, [2008]	**2**	**1**	**3**	**6**	**Fair**
19	Wang e al. [2018]	**3**	**1**	**3**	**7**	**Good**
20	Li et al. [2020]	**3**	**2**	**2**	**7**	**Good**
21	Abdalla et al. [2004]	**3**	**2**	**3**	**8**	**Good**
22	White et al. [2007]	**3**	**1**	**3**	**7**	**Good**
23	Yashodhan et al. [2011]	**3**	**1**	**2**	**6**	**Fair**

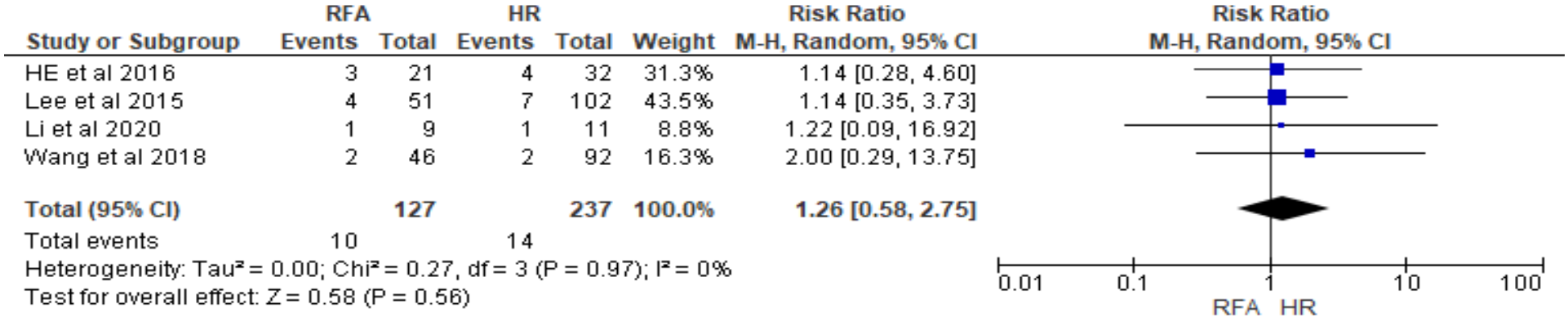

Figure [4]: Forest plot of overall survival rate 1-year for RFA and HR.

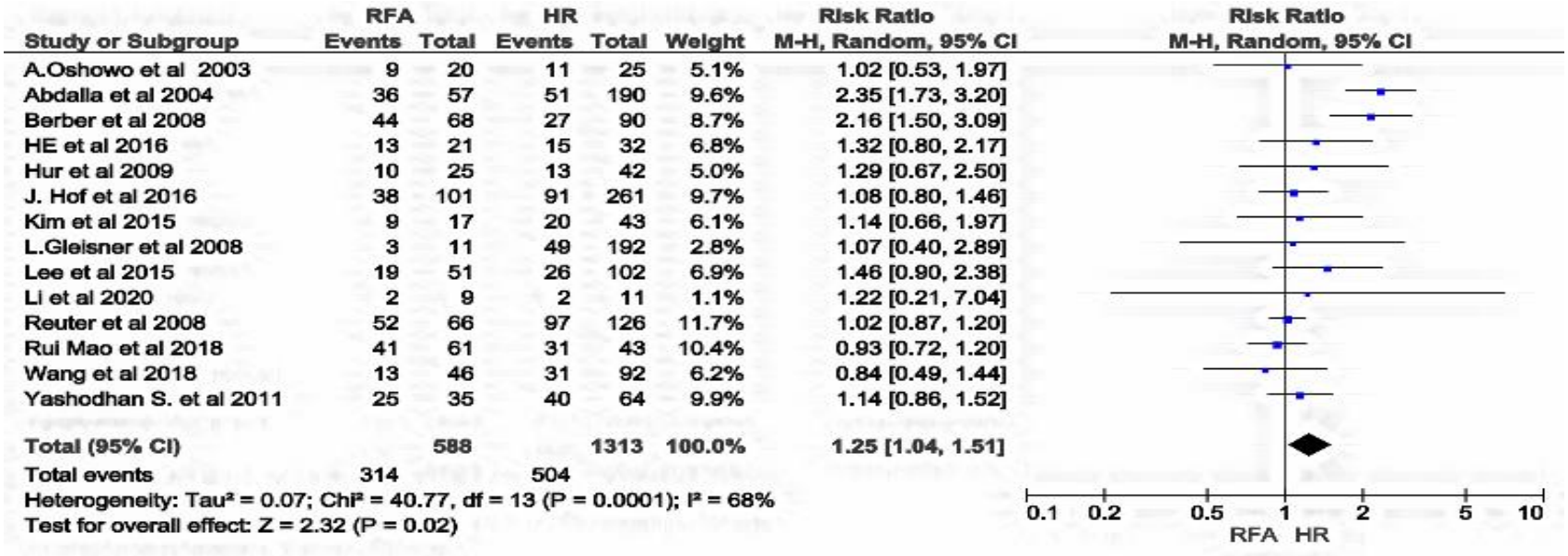

Figure [5]: Forest plot of overall survival rate three years for RFA and HR.

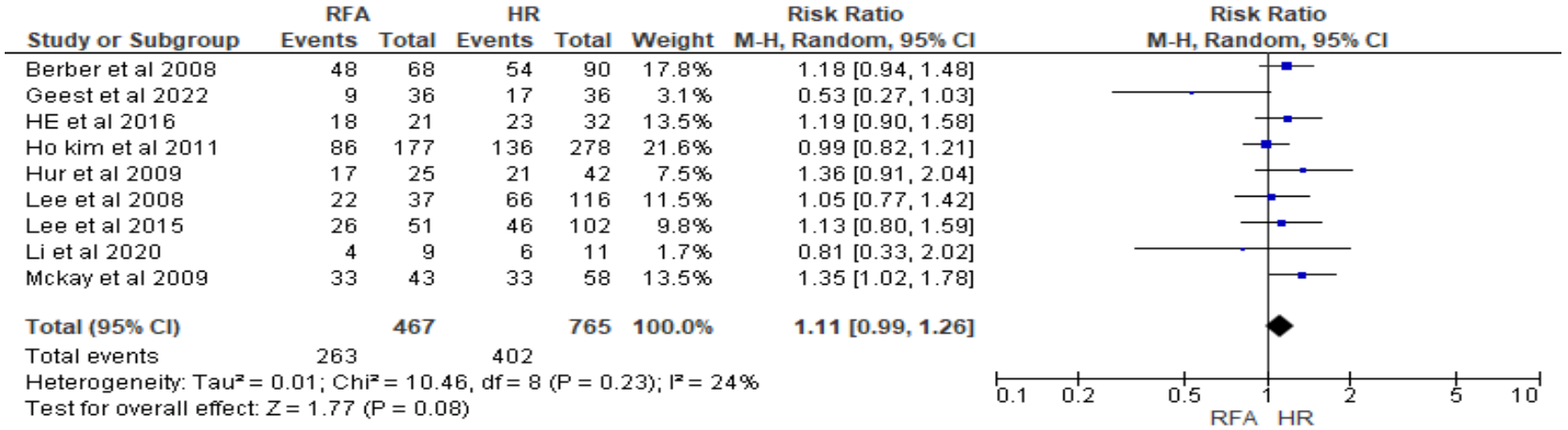

Figure [6]: Forest plot of overall survival rate five years for RFA and HR.

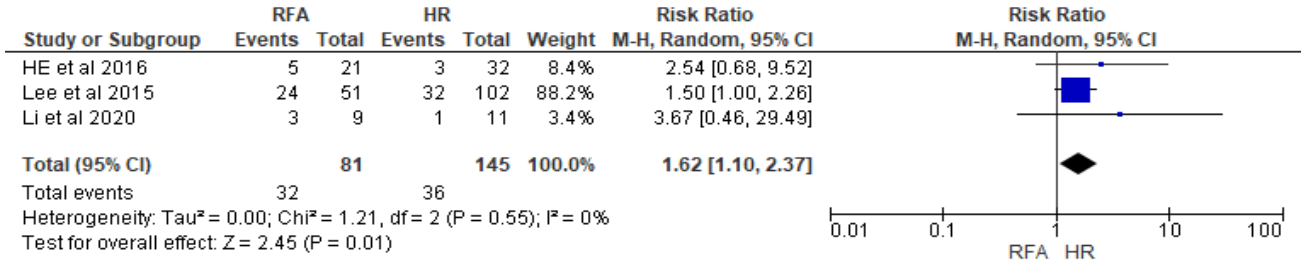

Figure [7]: Forest plot of DFS 1 Year for RFA and HR.

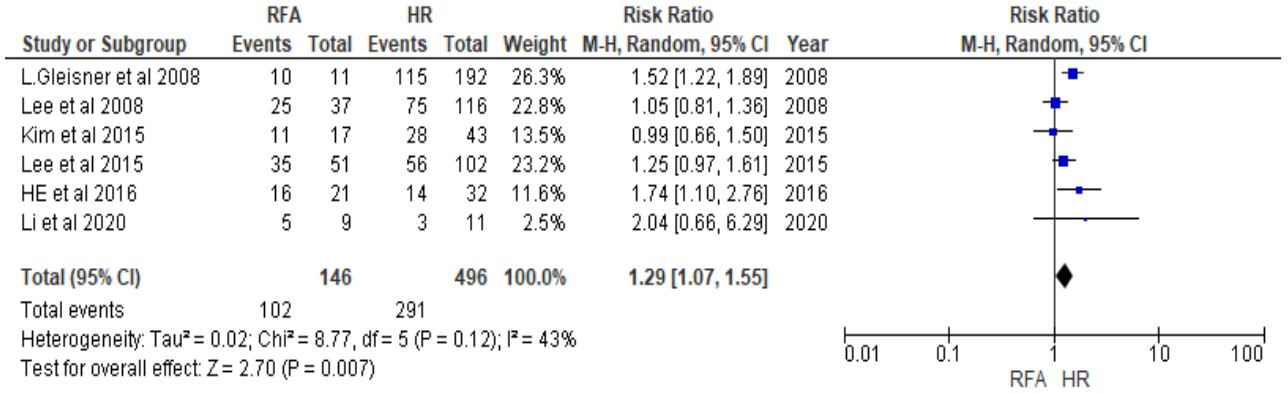

Figure [8]: Forest plot of DFS 3 Year for RFA and HR

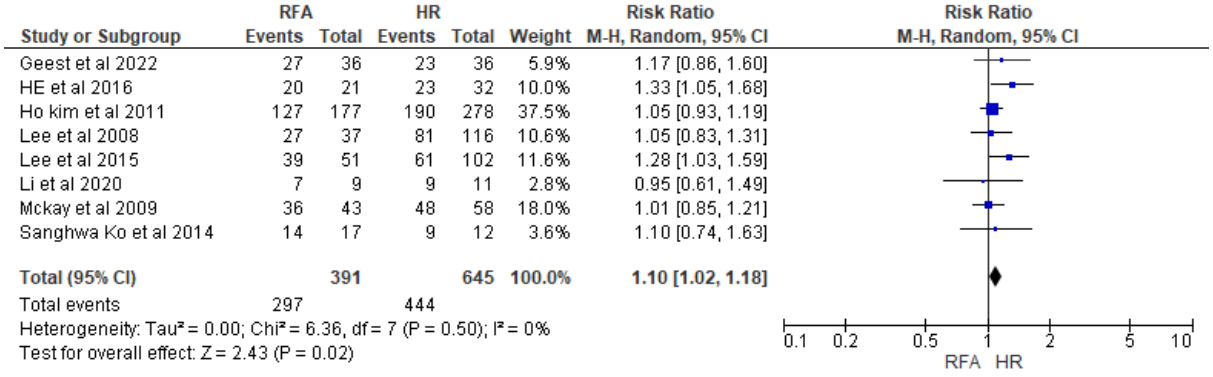

Figure [9]: Forest plot of DFS 5 Year for RFA and HR.

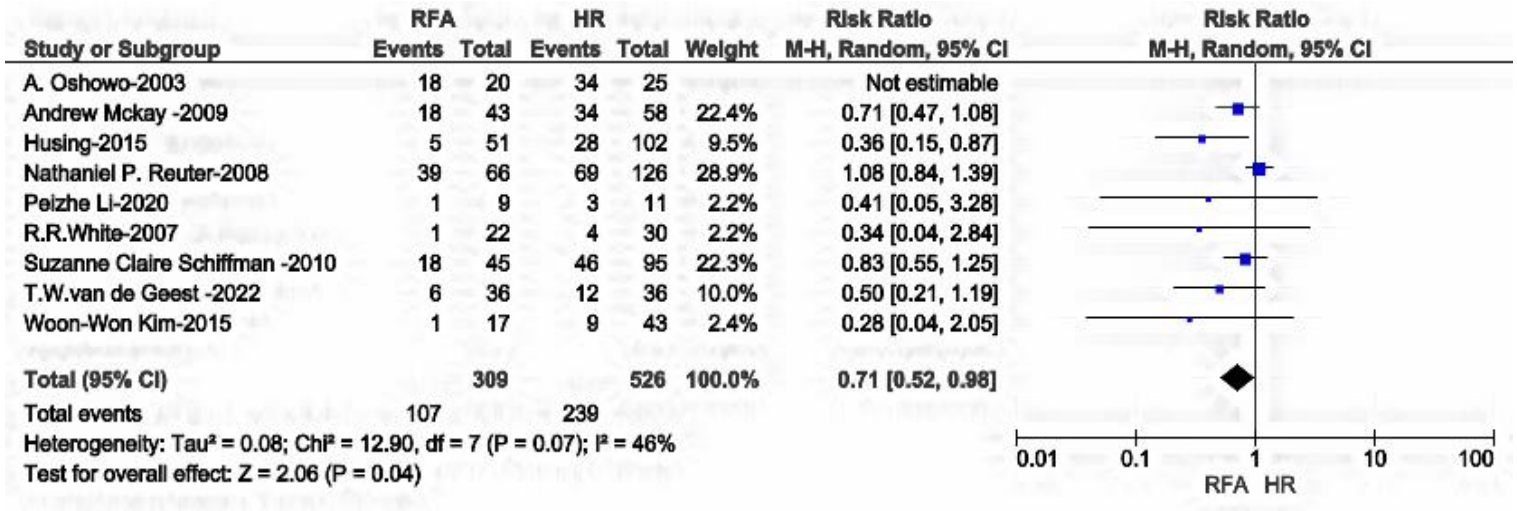

Figure [10]: Forest plot of complications for RFA and HR.

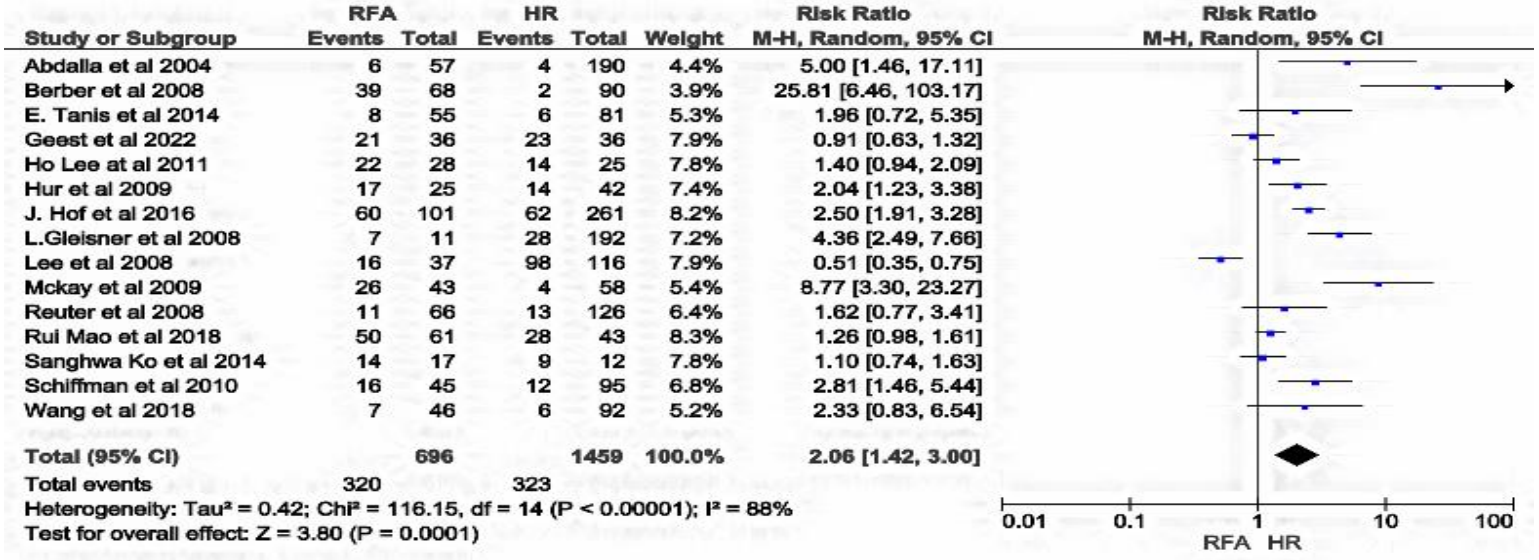

Figure [11]: Forest plot of total recurrence for RFA and HR

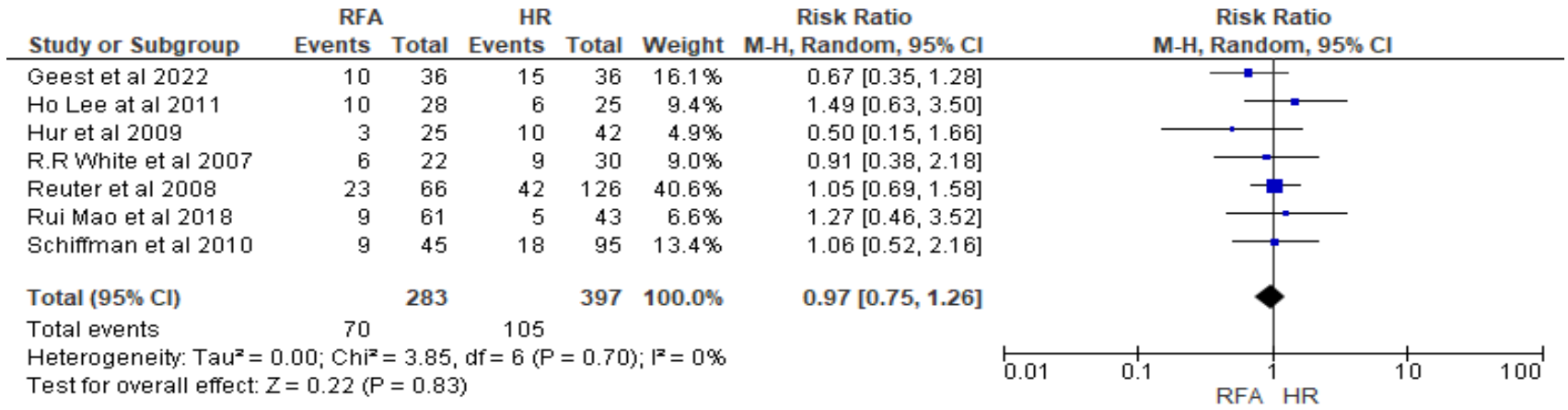

Figure [12]: Forest plot of extrahepatic recurrence for RFA and HR

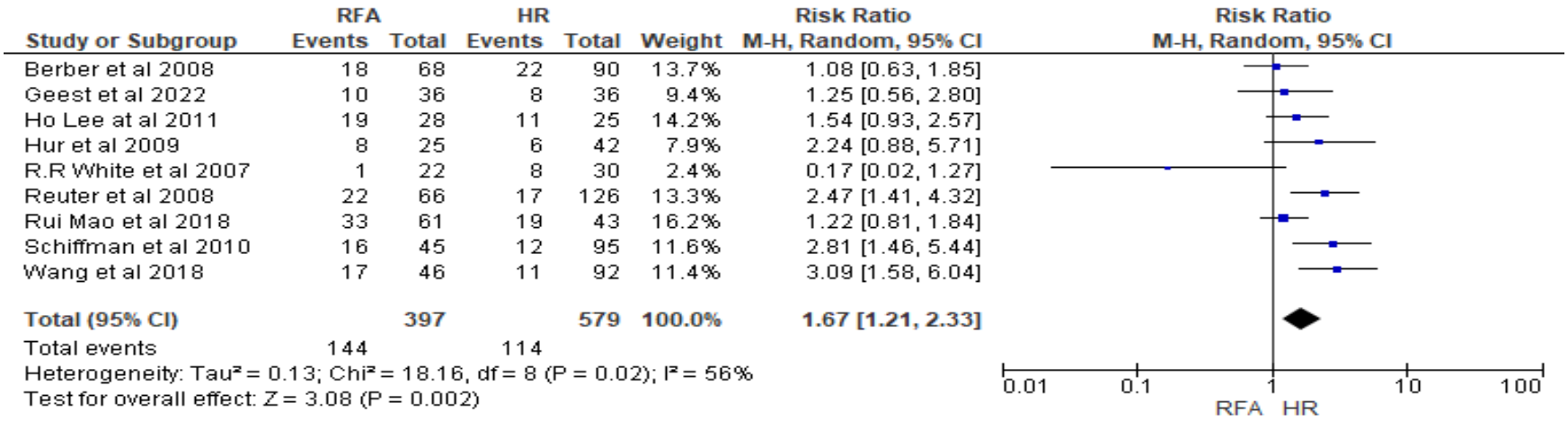

Figure [13]: Forest plot of intrahepatic Recurrence rate for RFA and HR.

Study or Subgroup	RFA Events	RFA Total	HR Events	HR Total	Weight	Risk Ratio M-H, Random, 95% CI
Berber et al 2008	11	68	2	90	11.9%	7.28 [1.67, 31.77]
Geest et al 2022	5	36	3	36	14.1%	1.67 [0.43, 6.46]
Hur et al 2009	7	25	4	42	20.1%	2.94 [0.96, 9.05]
R.R White et al 2007	8	22	0	30	3.4%	22.91 [1.39, 377.06]
Reuter et al 2008	11	66	3	126	16.6%	7.00 [2.02, 24.22]
Schiffman et al 2010	5	45	2	95	10.2%	5.28 [1.06, 26.17]
Wang et al 2018	7	46	6	92	23.7%	2.33 [0.83, 6.54]
Total (95% CI)		**308**		**511**	**100.0%**	**3.76 [2.25, 6.30]**
Total events	54		20			

Heterogeneity: Tau² = 0.02; Chi² = 6.19, df = 6 (P = 0.40); I² = 3%
Test for overall effect: Z = 5.03 (P < 0.00001)

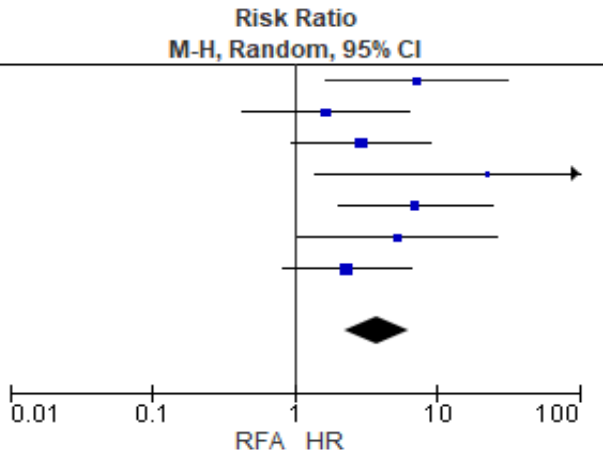

Figure [14]: Forest plot of local Recurrence rate for RFA and HR.

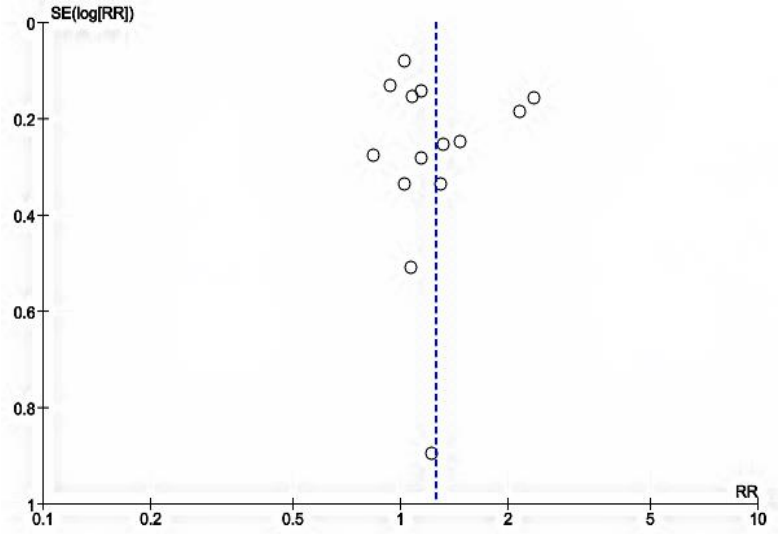

Figure [15]: Funnel plot of 3-year overall survival rate.

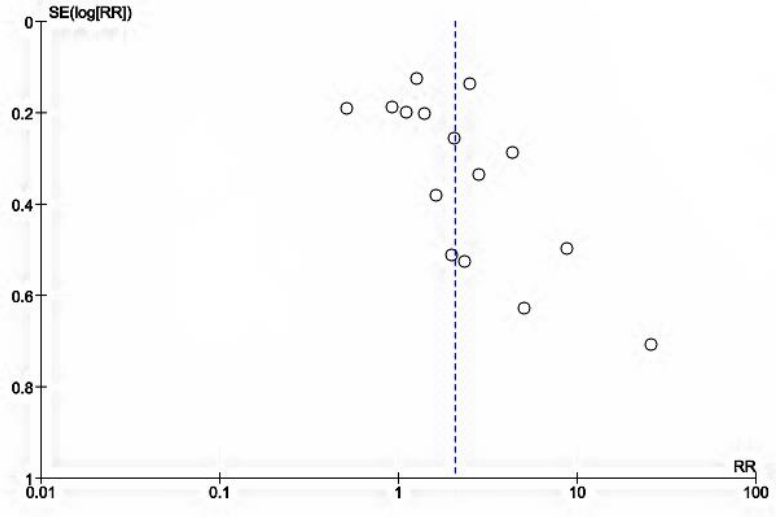

Figure [16]: Funnel plot of total recurrence.

DISCUSSION

After combining all search terms and applying all applicable limits, we were able to identify a total of 63 articles through PubMed search, 474 articles through Scopus search, 171 articles through WOS search, 1900 articles through Google Scholar search, and 13 articles through Cochrane search [Figure 1].

We manually eliminated all duplicates from the studies after screening them all. Next, we eliminated any irrelevant articles based on their titles and abstracts. Lastly, we examined all full-text articles to determine whether they met our inclusion and exclusion criteria and could be included in the final views. There were 23 trials, totaling 3092 patients, ultimately included in our review. Information is taken from every paper that was considered, along with results such as overall survival rate [1, 3, 5 OS years], disease-free survival rate [1, 3, 5 DFS], complication rate, and recurrence rate [total, intrahepatic, extrahepatic, and local]**.**

A non-significant relative risk [RR] was found between RFA and HR in our analysis of the overall survival rate, 1, 3 years OS [please refer to figures 4 and 6 in the results]. The pooled Relative Risk [RR] was 1.26 {95% CI: [0.58, 2.74]} and 1.11 {95% CI: [0.99, 1.26]}, respectively. Nonetheless, a noteworthy Relative Risk was seen after three years of OS between RFA and HR [refer to Figure 5 in the data]. The pooled relative risk was 1.25 {95%CI: [1.04, 1.51]}, suggesting that RFA had a lower three-year OS rate than HR.

Our meta-analysis also showed that metachronous metastasis, numerous tumors, primary node-positive status, and tumor size greater than 3 cm were independent risk factors for OS. The distribution seemed lopsided in the 3year OS funnel plot.

As previously stated, this discrepancy might result from including several populations with varying nations, racial backgrounds, and socioeconomic statuses in the various meta-analyses. We also looked at the DFS rate between RFA and HR at 1,3, 5 years. The significant results [please refer to figures 7, 8, 9] show that the DFS rate in RFA was lower than the rate in HR in the pooled results, with a pooled Relative Risk of 1.62 {95% CI: [1.10, 2.37]}, 1.29 {95% CI: [1.07, 1.55]}, and 1.10 {95% CI: [1.02, 1.18]}, respectively.

Our meta-analysis found that one study [22] with a population size of 455 demonstrates that, in a single tumor less than 3 cm, the 5-year overall survival [OS] in RFA patients was 51.1%, while in HR patients, it was 51.2%.

Additionally, in a single tumor less than 3 cm, the 5-year disease-free survival [DFS] was 33.6% in RFA patients and 31.6% in HR patients, indicating that there are nearly no differences between HR and RFA in tumors of this size. Another study [20] shows that in a single tumor less than 3 cm, the three-year overall survival [OS] in RFA patients is 77.9% and 55.4%, and in HR patients, 81% and 56.1%, respectively.

The overall survival rate and disease-free survival rate, which demonstrate a greater 3-year overall survival rate and 1,3,5 disease-free survival rate in HR than RFA, were among the postoperative outcomes that our findings revealed to be different between RFA and HR. However, when compared to the RFA group, there was a noticeably more significant rate of perioperative death and complications linked to HR. However, an earlier study found that HR was linked to higher DFS and similar OS rates [37-39].

Figure [10], which illustrates the overall effect of our investigation, indicates a significant risk ratio between RFA and HR with a greater complication rate in HR compared with RFA and a pooled RR of 0.71 ~95% CI [0.52, 0.98]. Age over 60, obstructive lung disease, and more than 8 hours of surgery were linked to perioperative difficulties. These variables are considered risk factors for complications. This was corroborated by **Lau *et al.* [40],** who found that RFA's minimally invasive nature should be why HR was linked to a higher incidence of significant problems than RFA. RFA can also be carried out percutaneously, significantly reducing the surgical impact compared to HR.

With a high incidence of total recurrence rate, intrahepatic recurrence rate, and local recurrence rate in RFA patients compared to HR patients, the overall effect of the current study demonstrated a significant risk ratio between RFA and HR. There was moderate heterogeneity among our studies [please refer to figures 11, 13, and 14 in the results], and the pooled RRs were 2.06 {95% CI: [1.42, 3.00]}, 1.67 {95% CI: [1.21, 2.33]}, and 3.76 {95% CI: [2.25,6.30]}, respectively, with some publication bias present. Figure [12] illustrates the non-significant RR relation between RFA and HR in extrahepatic recurrence, with a pooled RR of 0.97 {95% CI [0.75, 1.26]}. RFA and the primary placement in the rectum were linked to any recurrence, while synchronous related to intrahepatic recurrence. Tumor size < 3m was negatively associated with local recurrence of CRLMs.

The results suggest that tumor recurrence may be among the most significant factors influencing OS in patients with CRLM. Tumor recurrence is related to various parameters, of which the safety margin and comprehensiveness of the treatment are crucial [41].

Using 2-dimensional ultrasonography makes it challenging to properly generate a suitable safety margin in the 3-dimensional liver during the RFA process [42].

Additionally, there aren't many impartial analyses of the ablation impact and safety margin. Furthermore, RFA is linked to some recurrence risk variables but not resection. For instance, challenging sites, like a tumor on the surface of the liver, near the main hepatic arteries, or in the hilum, are a worsening sign of ablation [43].

For tiny liver metastases of less than 3 cm, RFA can provide practical local control, according to different research by **Abitabile *et al.* [44].** The total local recurrence rate was 8.8%, and the rate for CRLM with a diameter less than 3 cm was 1.6%.

RFA and surgical resection had comparable 5-year survival rates, including overall and local recurrence-free survival rates, according to **Hur *et al.* [20].** This finding lends additional credence to RFA as a treatment option for patients with solitary CRLM smaller than 3 cm who are not good candidates for hepatic resection. Along with the size and number of metastases, dedifferentiation and tumor-infiltrating inflammation of the metastatic lesion may be risk factors for aggressive behavior and tumor recurrence.

Six patients in the **Park *et al.*** study [45] experienced tumor recurrence after six months of liver resection, and three more patients showed recurrence within 12 months of CRLM, even though 13 patients had strong prognostic characteristics, as mentioned in the

results session. Despite the lack of statistical significance, these patients appeared to have poorer recurrence-free survival rates than the others. A short sample size may be related to this type II mistake [45].

Our study's overall result indicated a substantial risk ratio between RFA and HR concerning tumor size. The combined research was uniform and conducted in CRLM ≤3 cm; in this case, RFA produced OS and DFS rates comparable to HR.

Prior research has indicated a strong correlation between a reduced tumor size and a higher likelihood of successful ablation [46]. This could be because for CRLM ≤3 cm, RFA can achieve a higher safety margin than HR.

As anticipated, for patients with a CRLM diameter of less than 3 cm, the studies showed improved OS following RFA than following HR. When it was possible to obliterate every tumor while keeping a suitable amount of liver remaining, HR considered whether the patient had a single tumor or an oligo nodular tumor within a mono-segment of the liver [47].

Our meta-analysis revealed no heterogeneity for extrahepatic recurrence, moderate heterogeneity for intrahepatic and local recurrence, and mild heterogeneity for total recurrence. An uneven distribution was seen in the funnel plot of the overall 1-, 3-, and 5-year OS and DFS, suggesting some publication bias in the analysis. The uneven distribution of the funnel plots for the intrahepatic, total, extrahepatic, and local recurrences indicated that the analysis might have included some publication bias. The results of **Yang *et al.*'s** study [41], which revealed significant heterogeneity in the meta-analysis of serious complications, further supported this conclusion.

This was taken from the **Liang *et al.*** paper. Major complications were defined in Liang et al.'s study as complications with Clavien-Dindo classification grade II or higher; however, grade III or higher was applied in the other included studies. This heterogeneity resulted from Liang's study's overestimation of the incidence of significant complications [48].

The strengths of our study

The large number of citations found and analyzed, the methodical and reasonable reasons for citation exclusions, and the thorough and robust statistical analysis of the extracted data are among the strengths of our systematic review and meta-analysis. The random effect model was only used to control for methodological and statistical heterogeneity [I^2=88%]. Additionally, this analysis included an evaluation of a wide range of different time point postoperative outcomes, such as the 1,3,5-year survival rate, and the risk factors of CRLM survival were also investigated.

Conclusions:

Our findings revealed no significant differences in RFA and HR in tumors less than 3 cm in diameter; we found them to be similar regarding postoperative outcomes, including overall and disease-free survival rates. However, a significantly higher rate of complications was associated with HR compared to the RFA group. RFA showed a lower long-term survival rate and a greater recurrence rate in CRLM patients. Independent predictors of survival included tumor size, number of tumors, age, original node-positive status, and metachronous metastasis were noted. These findings, however, were restricted to baseline inequality between comparison groups. A fundamental limitation of this meta-analysis was that all studies were observational [no RCT studies], as no RCT studies were found discussing our review. Furthermore, although several outcomes were assessed in this study, only some studies reported on pre- and post-operative liver function tests. It would have been interesting to analyze the extent of benefit RFA could have over resection for preserving liver function and, thus, appropriateness in patients with liver comorbidities. In addition, we restricted the search strategy to include studies published in the English language only, exposing our meta-analysis to missing relevant studies.

Recommendation:

Future analyses, including a large sample size of patients, should establish selection criteria based on patient characteristics [age, comorbidities], primitive tumor [site, molecular biology, grading], and metastasis features [number, size, right- or left-liver] to determine which patients would truly benefit from a simultaneous approach. Another systematic review and meta-analysis should be done to assess the safety and the quality of life using RFA and HR. Randomized or propensity score matching studies should be performed to clear the efficacy of RFA and to determine the target population that benefits most from RFA in the future.

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Authors contributions: All authors had been contributed equally in this work.

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