Systematic Review

Effectiveness and Safety of Radiofrequency Ablation versus Liver Resection in the Treatment of Early-stage Hepatocellular Carcinoma: A Systematic Review and Meta-analysis

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Objective: To systematically evaluate the efficacy and safety of radiofrequency ablation and liver resection in the therapeutic management of early-stage hepatocellular carcinoma.
Method: We conducted a comprehensive search of domestic and foreign databases including PubMed, Web of Science, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang to retrieve literature on radiofrequency ablation and liver resection for the treatment of early hepatocellular carcinoma. The retrieved literature underwent thorough screening, and relevant data were extracted. Following the evaluation of the literature's quality, Meta-analysis was performed using RevMan 5.4 software.
Results: In this study, a total of 11 documents were selected, comprising 1334 patients with hepatocellular carcinoma. Meta-analysis results indicated that there was no statistically significant difference in the 1-year overall survival rate [Relative risk (RR) = 1.01, 95% confidence intervals (CI) (0.98; 1.04)] and the 3-year overall survival rate [RR = 0.95, 95% CI (0.90; 1.01)] between the radiofrequency ablation and liver resection groups ($p > 0.05$). Similarly, there was no statistically significant difference in the 1-year disease-free survival rate [RR = 0.94, 95% CI (0.87; 1.01)] between the two groups. However, the 3-year disease-free survival rate [RR = 0.84, 95% CI (0.74; 0.96)] of patients in the radiofrequency ablation group was significantly lower than that in the hepatectomy group ($p < 0.05$). Notably, the incidence of complications [RR = 0.42, 95% CI (0.33; 0.55)] was significantly lower in the radiofrequency ablation group compared to the hepatectomy group. Conversely, the local recurrence rate [RR = 1.45, 95% CI (1.22; 1.73)] was significantly higher in the radiofrequency ablation group compared to the hepatectomy group ($p < 0.05$).
Conclusion: During the treatment of hepatocellular carcinoma, hepatectomy demonstrates superior clinical efficacy compared to radiofrequency ablation, particularly in its ability to control tumor recurrence. However, radiofrequency ablation presents with fewer complications and a higher level of safety. These findings can serve as a valuable foundation for clinicians when selecting the most suitable treatment approaches for liver cancer.

Keywords: hepatocellular carcinoma; radiofrequency ablation; liver resection; clinical efficacy; meta-analysis

Introduction

As a common malignancy of the digestive system, hepatocellular carcinoma ranks as the fourth leading cause of cancer-related deaths worldwide [1]. In recent years, advancements in medical technology have introduced new avenues for the early screening of high-risk groups for hepatocellular carcinoma, as well as innovative approaches to early clinical intervention, ultimately enhancing patient prognosis [2]. Liver transplantation stands as the optimal treatment modality for hepatocellular carcinoma, boasting a remarkable 5-year survival rate ranging from 75% to 92%. However, its clinical application is hampered by limitations and expenses associated with donors [3,4]. Liver resection emerges as the primary therapeutic option for patients with hepatocellular carcinoma, offering the advantage of direct visualization for tumor lesion removal while sparing critical blood vessels. Notably, some patients can achieve complete remission through this approach [5]. Nevertheless, patients with hepatocellular carcinoma often exhibit poor liver reserve capacity, with subtle early clinical manifestations and low diagnosis rates, leading to only a minority being eligible for liver resection [6]. In Western countries, merely 5% of non-cirrhotic liver cancer patients undergo liver resection, while in Asian countries, this figure rises to approximately 40%. Despite this, the 5-year recurrence rate post-surgical intervention exceeds 70% [3].

In recent years, radiofrequency ablation has gained increasing recognition as a viable treatment option for early hepatocellular carcinoma, particularly for patients who are not candidates for liver transplantation or hepatectomy. Even for those eligible for liver transplantation or hepatectomy, radiofrequency ablation remains a safe and effective alternative, offering distinct advantages in terms of safety, cost-effectiveness, minimally invasive nature, and repeatability [7]. Both radiofrequency ablation and hepatectomy can be considered as first-line treatment options when the diameter

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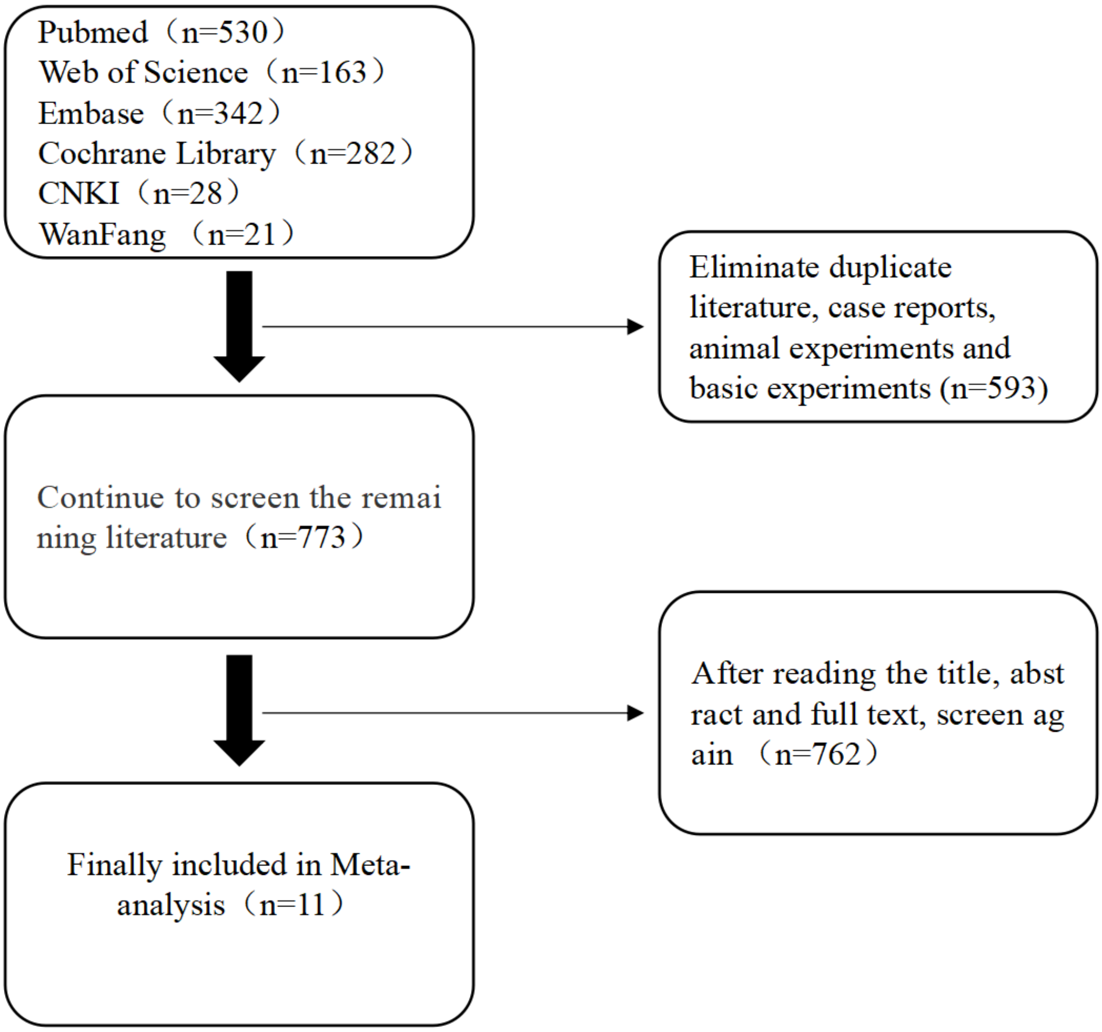

Fig. 1. Literature search flow chart. CNKI, China National Knowledge Infrastructure.

of liver cancer is less than 3 cm. However, when the tumor diameter exceeds 3 cm, hepatectomy demonstrates superior effectiveness compared to radiofrequency ablation [8].

The study has indicated that radiofrequency ablation is notably more effective and safer than liver resection in treating single liver cancer, particularly central liver cancer [9]. Despite numerous comparative studies in recent years investigating the efficacy of radiofrequency ablation versus liver resection for early-stage hepatocellular carcinoma, clinical controversy persists. Additionally, several Meta-analyses have been conducted to compare the therapeutic outcomes of radiofrequency ablation and hepatectomy in hepatocellular carcinoma treatment. However, due to variations in the quality of the included literature and the overall low level of evidence, reaching a consistent conclusion has proven challenging.

In this context, our study systematically examined recent research publications concerning various methods for treating early-stage hepatocellular carcinoma. The aim is to provide clinical guidance and serve as a reference for the treatment of hepatocellular carcinoma.

Materials and Methods

Search Strategy

Conduct a literature search on the treatment of early hepatocellular carcinoma using radiofrequency ablation and liver resection in both domestic and foreign databases. Utilize databases such as PubMed, Web of Science, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang, covering the period from their establishment to December 2023. Employ search terms such as "radiofrequency ablation", "ablation", "liver resection", "traditional surgery", "minimally invasive resection", "hepatocellular carcinoma", and "small liver cancer". Combine subject terms with free words for the search. For example, in PubMed, use the following search formula: "(radiofrequency ablation or ablation) and (hepatectomy or traditional surgery or minimally invasive resection) and (hepatocellular carcinoma or small liver cancer)". The search should primarily encompass Chinese and English languages.

Table 1. Basic characteristics of included literature.

Incorporated literature	Years	Nation	Type of study	n	Treatment
Ng [10]	2017	China	randomized controlled trial	109	radiofrequency ablation
				109	liver resection
Lee [11]	2018	South Korea	randomized controlled trial	34	radiofrequency ablation
				29	liver resection
Fang [12]	2014	China	randomized controlled trial	60	radiofrequency ablation
				60	liver resection
Guo [13]	2013	China	randomized controlled trial	94	radiofrequency ablation
				102	liver resection
Song [14]	2017	China	array research	94	radiofrequency ablation
				81	liver resection
Xu [15]	2017	China	array research	35	radiofrequency ablation
				30	liver resection
Casaccia [16]	2017	Italy	array research	22	radiofrequency ablation
				24	liver resection
Casaccia [17]	2015	Italy	array research	24	radiofrequency ablation
				26	liver resection
Song [18]	2016	China	array research	78	radiofrequency ablation
				78	liver resection
Vitali [19]	2016	Switzerland	array research	60	radiofrequency ablation
				45	liver resection
Zhang [20]	2019	China	array research	80	radiofrequency ablation
				60	liver resection

Literature Inclusion Criteria

(1) All cases involved hepatocellular carcinomas that met either the Milan criteria (i.e., a single tumor diameter of $\leq$5 cm or $\leq$3 tumors, with a maximum diameter of $\leq$3 cm) or the UCSF criteria (i.e., a single tumor diameter of $\leq$6.5 cm or $\leq$3 tumors, with a maximum diameter of $\leq$4.5 cm and a sum of tumor diameters of $\leq$8 cm), with cytohistological confirmation from liver biopsy specimens; (2) All cases were newly diagnosed and had not undergone any prior anti-tumor treatments such as surgery or chemotherapy; (3) There was no invasion of the main portal vein or hepatic vein, and no evidence of extrahepatic metastasis; (4) Study design: all were randomized controlled trials or cohort studies, with no restrictions on blinding; (5) Treatment modalities: radiofrequency ablation and liver resection; (6) Outcome measures: overall survival rates at 1 year and 3 years post-surgery, 1-year and 3-year disease-free survival rates, and rates of local recurrence.

Literature Exclusion Criteria

(1) The study subjects comprise patients diagnosed with hepatocellular carcinoma, excluding those who are newly diagnosed; (2) Patients with liver function grade C; (3) Documents lacking complete text and valid data are excluded from acquisition; (4) Documents issued repeatedly or of poor quality are excluded; (5) Literature with insufficient outcome indicators is excluded; (6) Animal experiments, basic research, case reports, etc., are excluded.

Literature Screening and Data Extraction

After obtaining bibliographic information using Clarivate Analytics (Version20.0.1, Clarivate, Philadelphia, PA, USA), two reviewers were chosen to independently assess articles based on the aforementioned inclusion and exclusion criteria. Duplicate publications were initially excluded, followed by a systematic review of document headings and abstracts. Full texts were examined if necessary for final selection. In cases of disagreement between the two reviewers, consensus was reached through negotiation or by involving a third party for adjudication. Subsequently, the entire text of selected articles was thoroughly reviewed, and any literature still failing to meet the standards was eliminated. Extracted data encompassed publication year, country, study design, primary author, sample size, treatment modalities, outcome measures, among other relevant factors.

Literature Quality Evaluation

Two researchers were tasked with assessing the quality of included literature according to the Cochrane Review Manual standards. For randomized controlled trials, six criteria were considered: generation of random sequences, concealment of allocation, utilization of blinding, completeness of outcome reporting, presence of selective bias reporting, and identification of other sources of bias. Each document was evaluated as “high risk”, “low risk”, or “unknown” for each criterion, and then graded accordingly. A document meet-

Table 2. Quality evaluation of included randomized controlled trials.

Included documents	Randomly assigned	Allocation hidden	Blind method	Full data report	Optional results reporting	Other sources of bias	Rating
Ng 2017 [10]	low risk	low risk	unknown	low risk	low risk	low risk	Class A
Lee 2018 [11]	low risk	high risk	unknown	low risk	low risk	low risk	Class B
Fang 2014 [12]	low risk	high risk	unknown	low risk	low risk	low risk	Class B
Guo 2013 [13]	low risk	high risk	unknown	low risk	low risk	low risk	Class B

Table 3. Quality evaluation of included cohort studies.

Included documents	Selectivity	Exposed	Comparability	NOS score
Song 2017 [14]	3	2	3	8
Xu 2017 [15]	4	2	2	8
Casaccia 2017 [16]	4	1	3	8
Casaccia 2015 [17]	3	2	3	8
Song 2016 [18]	4	2	3	9
Vitali 2016 [19]	4	2	2	8
Zhang 2019 [20]	3	2	3	8

NOS, Newcastle-Ottawa Scale.

ing all criteria was assigned Grade A, those meeting some criteria were assigned Grade B, while those failing to meet any criteria were classified as Grade C and subsequently excluded.

For cohort studies, the Newcastle-Ottawa Scale (NOS) was employed, focusing on four items: case selection, control selection, comparability between case and control groups, and completeness of exposure and follow-up. A score of 1–3 indicated low quality, 4–6 indicated medium quality, and 7–9 indicated high quality. In cases of disagreement between researchers regarding document ratings, resolution occurred through negotiation or intervention by a third party for adjudication.

Statistical Analysis

The RevMan software (version 5.4, Cochrane Collaboration, Oxford, UK) was utilized for analysis. Relative risk (RR) were employed as the effect indicators for enumeration data, and 95% confidence intervals (CI) were calculated and presented via forest plots. Heterogeneity among studies was assessed using the I^2 statistic. If $p > 0.1$ and $I^2 < 50\%$, it indicated minimal heterogeneity among the included studies, thus prompting the selection of the fixed-effect model for analysis. Conversely, if $p < 0.1$ and $I^2 > 50\%$, significant heterogeneity was inferred, and the random-effects model was chosen for analysis. Publication bias was evaluated using funnel plots.

Results

Literature Search Process

In total, 1366 documents were retrieved for this study. Following the exclusion of duplicate documents, case reports, animal experiments, and basic experiments, 773 documents remained. Upon thorough examination of titles, abstracts, and full texts, 762 irrelevant documents were subsequently removed, resulting in the identification of 11 relevant documents [10,11,12,13,14,15,16,17,18,19,20]. The literature search flow chart is depicted in Fig. 1.

Basic Characteristics and Quality Evaluation of Included Literature

The study comprised 11 included documents, consisting of 3 Chinese documents [14,15,20] and 8 English documents [10,11,12,13,16,17,18,19]. These documents were published between 2013 and 2019 and comprised 4 randomized controlled trials [10,11,12,13] and 7 cohort studies [14,15,16,17,18,19,20]. Collectively, they encompassed 1334 patients diagnosed with hepatocellular carcinoma, with 690 undergoing radiofrequency ablation and 644 undergoing liver resection. The randomized controlled trials were rated as Grades A and B, while the cohort studies achieved Newcastle-Ottawa Scale scores exceeding 7 points, indicating high-quality literature. The basic characteristics and quality assessment of the included literature are presented in Tables 1 (Ref. [10,11,12,13,14,15,16,17,18,19,20]), 2 (Ref. [10,11,12,13]), and 3 (Ref. [14,15,16,17,18,19,20]).

Meta-analysis

Generally Survival Rate One Year after Surgery

Eight documents [10,12,13,14,15,16,18,19] investigated the one-year total survival rate of patients following radiofrequency ablation and liver resection. These studies included 536 cases in the radiofrequency ablation group and 526 cases in the hepatectomy group. Heterogeneity testing revealed $I^2 = 0\%$ and $p = 0.69$, indicating no heterogeneity among the literature. Consequently, the fixed-effects model was employed to analyze the one-year overall survival rate of the groups. Forest plot results suggested no significant difference in the one-year overall survival rate statistically between the radiofrequency ablation group and the liver resection group [RR = 1.01, 95% CI (0.98; 1.04), $p > 0.05$]. Please refer to Fig. 2 for visualization.

Overall Survival Rate 3 Years after Surgery

Nine documents [10,11,12,13,14,15,16,18,19] investigated the 3-year overall survival rate of patients following radiofrequency ablation and liver resection. These studies included 586 cases in the radiofrequency ablation group and 558 cases in the hepatectomy group. Heterogeneity testing yielded $I^2 = 13\%$ and $p = 0.33$, indicating some variability among the literature. However, given the lack of sig-

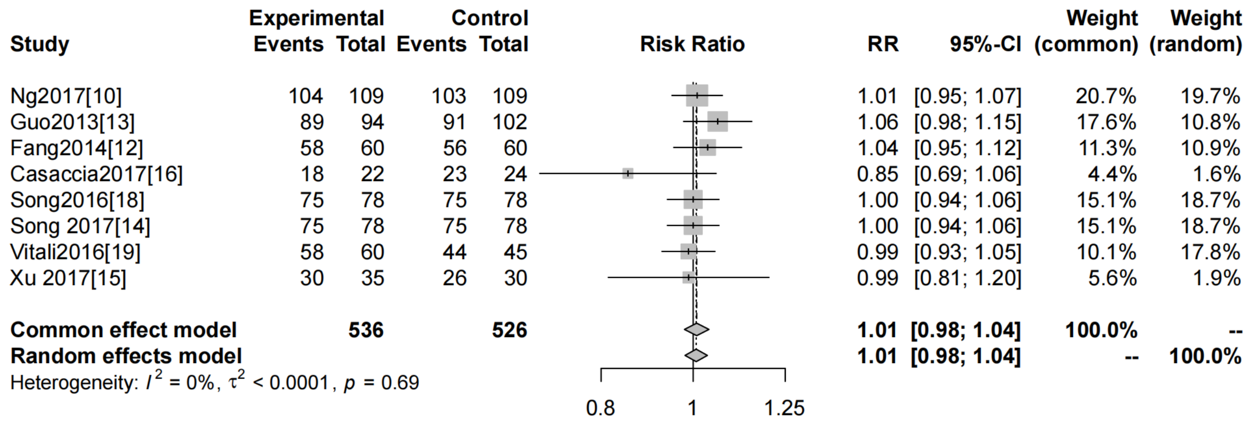

Fig. 2. Forest plot comparing the 1-year overall survival rates of the two groups of patients after surgery. RR, Relative risk; CI, confidence intervals.

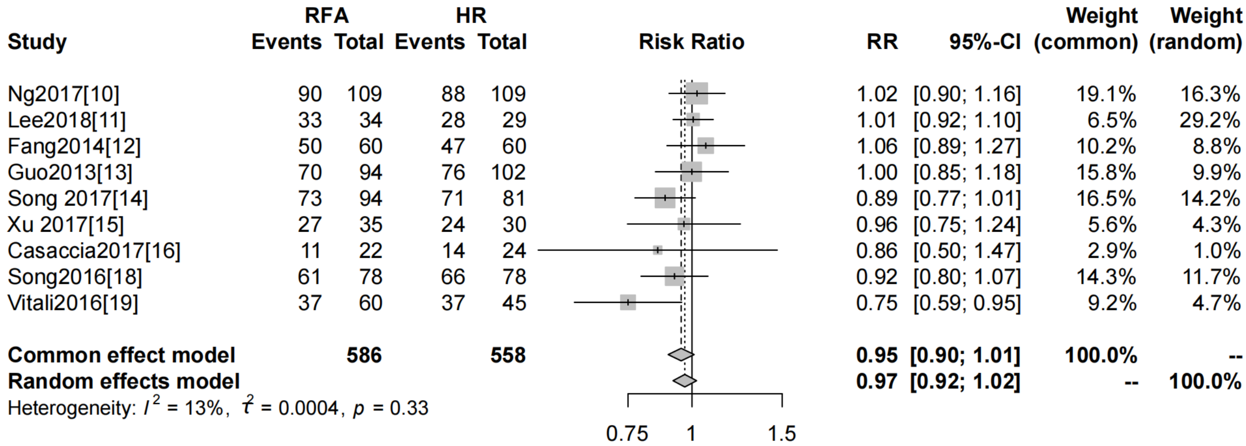

Fig. 3. Forest plot comparing the 3-year overall survival rate of the two groups of patients after surgery. RFA, Radiofrequency ablation; HR, hepatic resection.

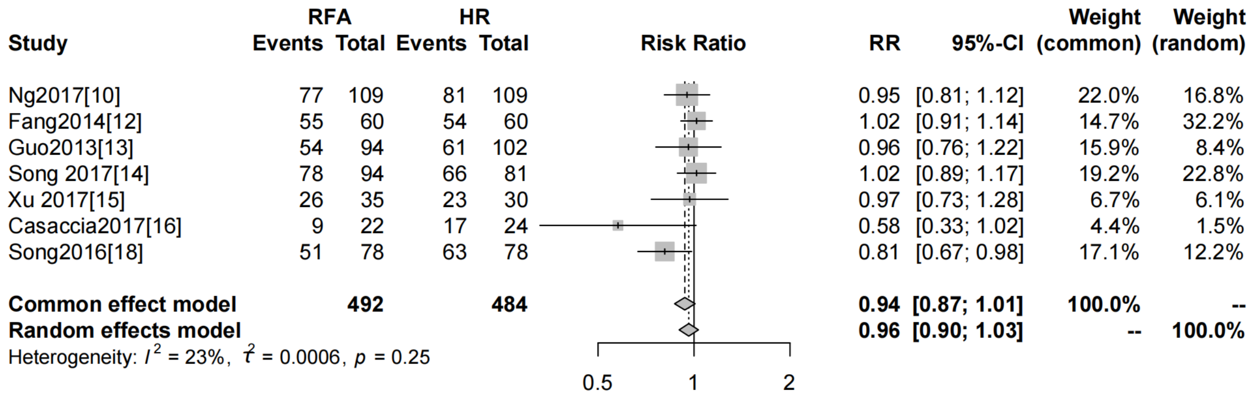

Fig. 4. Forest plot comparing the 1-year disease-free survival rates of the two groups of patients after surgery.

nificant heterogeneity, the fixed-effects model was selected to analyze the 3-year overall survival rate between the two groups. Forest plot results indicated no substantial difference in the 3-year overall survival rate statistically between the radiofrequency ablation group and the liver resection group [RR = 0.95, 95% CI (0.90; 1.01), $p > 0.05$]. Refer to Fig. 3 for visualization.

Disease-free Survival Rate One Year after Surgery

Seven documents [10,12,13,14,15,16,18] examined the 1-year disease-free survival rate of patients following radiofrequency ablation and liver resection. These studies included 492 cases in the radiofrequency ablation group and 484 cases in the hepatectomy group. Heterogeneity test-

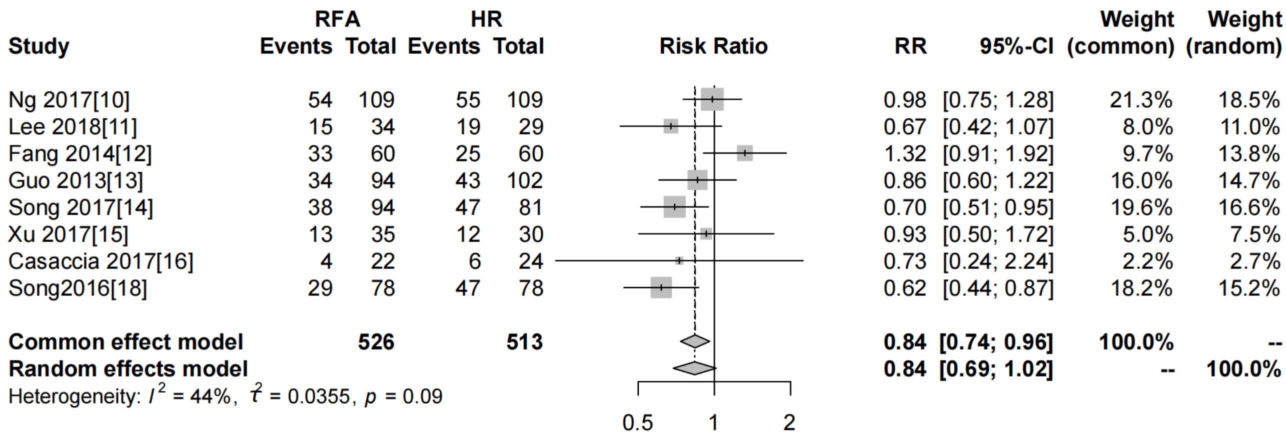

Fig. 5. Forest plot comparing the 3-year disease-free survival rates of the two groups of patients after surgery.

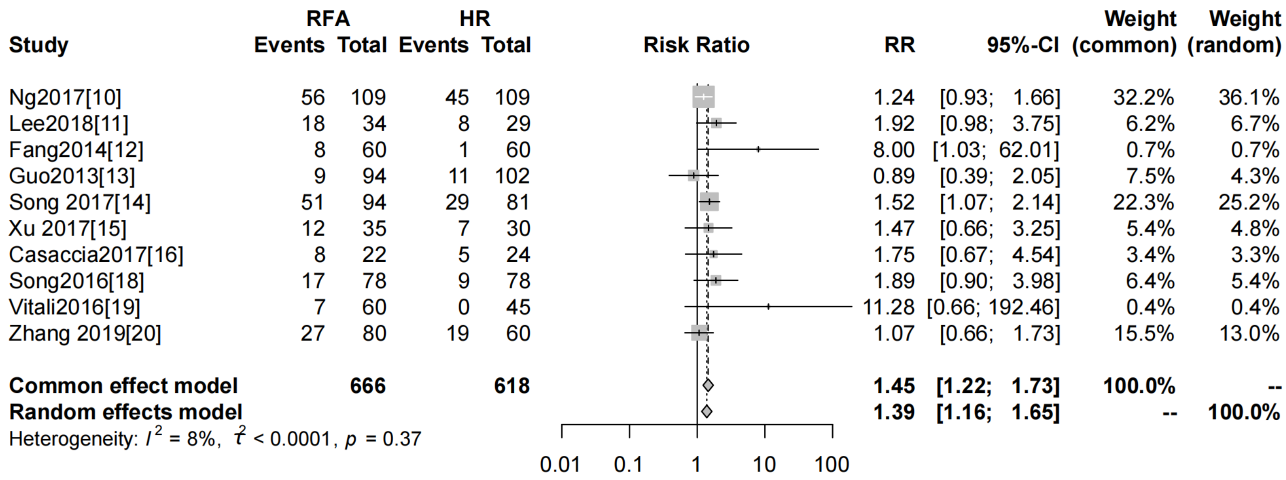

Fig. 6. Forest plot comparison of the postoperative local recurrence rates between the two groups of patients.

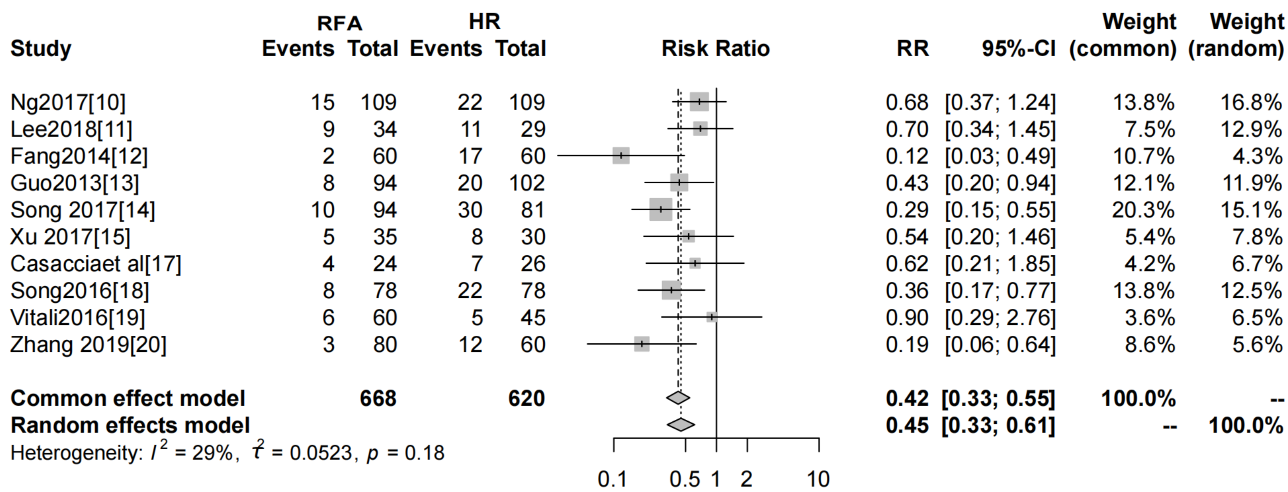

Fig. 7. Forest plot comparing the incidence of postoperative complications between the two groups of patients.

ing indicated I^2 = 23% and p = 0.25, suggesting no significant heterogeneity between the two groups in the literature. Consequently, the fixed-effects model was chosen to analyze the 1-year disease-free survival rate of the two groups. Forest plot outcomes demonstrated no significant difference in the 1-year disease-free survival rate statistically between the radiofrequency ablation group and the liver resection group [RR = 0.94, 95% CI (0.87; 1.01), p > 0.05]. Refer to Fig. 4 for visualization.

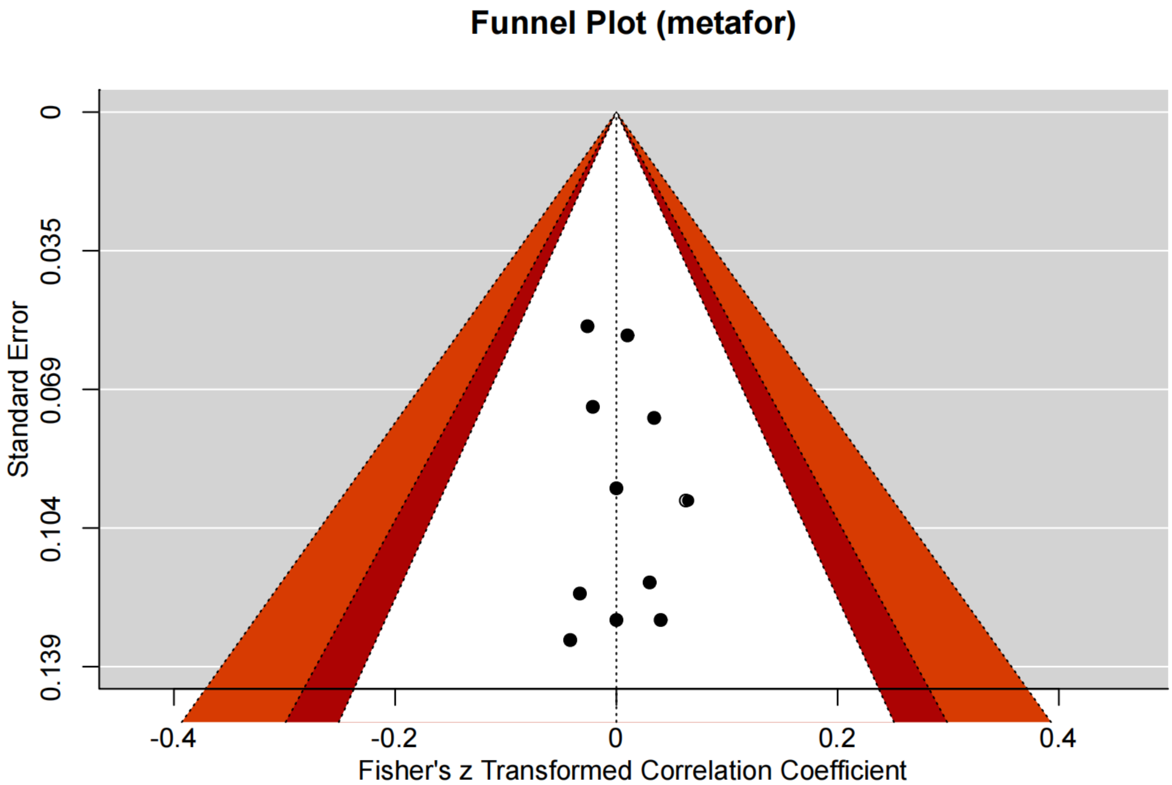

Fig. 8. Funnel plot incorporating risk of literature bias assessment.

Disease-free Survival Rate 3 Years after Surgery

Eight studies [10,11,12,13,14,15,16,18] examined the 3-year disease-free survival rate of patients following radiofrequency ablation and liver resection, involving 526 cases in the radiofrequency ablation group and 513 cases in the hepatectomy group. Heterogeneity testing revealed $I^2 = 44\%$ and $p = 0.09$, indicating some heterogeneity among the literature. However, given the borderline significance of heterogeneity, the fixed-effects model was selected to analyze the 3-year disease-free survival rate between the two groups. Forest plot results demonstrated that the 3-year disease-free survival rate of patients in the radiofrequency ablation group was significantly lower than that in the hepatectomy group [RR = 0.84, 95% CI (0.74; 0.96), $p < 0.05$]. To assess result stability and identify sources of heterogeneity, individual studies were systematically removed to observe their impact on the total combined effect size. Results showed no significant deviation from the total combined effect size, indicating robust and credible findings. Refer to Fig. 5 for details.

Postoperative Local Recurrence Rate

Ten studies [10,11,12,13,14,15,16,18,19,20] investigated the local recurrence rate of patients following radiofrequency ablation and liver resection, encompassing 646 cases in the radiofrequency ablation group and 618 cases in the hepatectomy group. Heterogeneity testing indicated $I^2 = 8\%$ and $p = 0.37$, suggesting no significant variation among the studies. Consequently, the fixed-effects model was selected to analyze the local recurrence rate between the two groups. Forest plot results indicated that the local recurrence rate in the radiofrequency ablation group was significantly higher than in the hepatectomy group [RR = 1.45, 95% CI (1.22; 1.73), $p < 0.05$]. Refer to Fig. 6 for visualization.

Postoperative Complication Rate

Ten studies [10,11,12,13,14,15,17,18,19,20] investigated the occurrence rate of complications in patients following radiofrequency ablation and liver resection, involving 668 cases in the radiofrequency ablation group and 620 cases in the hepatectomy group. Heterogeneity testing indicated $I^2 = 29\%$ and $p = 0.18$, suggesting some inconsistencies among the studies. Despite the presence of heterogeneity, the fixed-effects model was chosen to analyze the incidence of complications between the two groups. Forest plot results revealed that the incidence of postoperative complications in the radiofrequency ablation group was significantly lower than that in the hepatectomy group [RR = 0.42, 95% CI (0.33; 0.55), $p < 0.05$]. Refer to Fig. 7 for visualization.

Risk of Bias Assessment

The results of the funnel plot indicate an acceptable symmetry in the distribution of points corresponding to each study, centered on the vertical line. Furthermore, Egger's test yielded a p-value greater than 0.05, suggesting no obvious publication bias. These findings indicate that the research results are relatively reliable, and the conclusions drawn are relatively true. Please refer to Fig. 8 for visualization.

Discussion

Hepatocellular carcinoma poses a significant threat to individuals' lives, health, and safety, underscoring the importance of early diagnosis and timely intervention to improve patient outcomes [21,22]. Radiofrequency ablation and liver resection are crucial clinical therapies for hepatocellular carcinoma. However, there remains considerable controversy regarding which of these methods offers better prospects for prolonging patient life [23,24]. This study encompasses a total of 11 documents with a high level of evidence and low selection bias, representing medium to high-quality literature. Meta-analysis results indicate no significant differences in the 1- and 3-year overall survival rates and 1-year disease-free survival rates between the radiofrequency ablation and hepatectomy groups from a statistical perspective ($p > 0.05$).

Under normal circumstances, liver cancer patients rarely succumb to the disease within one year after diagnosis, with disease recurrence often exerting a gradual and progressive impact on patient survival rates. However, compared to the hepatectomy group, patients in the radiofrequency ablation group exhibited significantly lower 3-year disease-free survival rates and complication rates, along with a notably elevated local recurrence rate ($p < 0.05$). These findings are largely consistent with those of Li *et al.*'s study [23]. However, a significant difference was observed in the 3-year survival rates between the two patient groups in this study. It is worth noting that radiofrequency ablation, as a local treatment method, may overlook small lesions and lacks targeted precision.

This results in a significantly heightened risk of recurrence for hepatocellular carcinoma patients. Moreover, the liver's intricate vascular network poses challenges during treatment, as attacking surrounding large blood vessels can lead to a drop in treatment temperature, severely compromising clinical efficacy and increasing the risk of tumor residue and recurrence [25,26]. Additionally, there exists a risk of needle tract metastasis following radiofrequency ablation treatment [27]. Liver resection, on the other hand, can eradicate multiple lesions and tumor thrombi within the same anatomical area, playing a crucial role in controlling tumor recurrence [28,29]. However, in terms of reducing the risk of complications, radiofrequency ablation proves more effective than liver resection. This is attributed to radiofrequency ablation's minimally invasive nature, significantly reducing patients' hospitalization time and improving postoperative outcomes and quality of life [30]. Consequently, in clinical practice, a detailed analysis of specific patient conditions and treatment preferences is essential. Healthcare professionals should select appropriate treatment methods tailored to individual patients, taking into account their medical expertise and experience, ultimately benefiting the patients.

However, this study still has certain limitations: (1) The literature selected in this study primarily consists of English and Chinese sources, potentially excluding non-Chinese and non-English literature. This may limit the comprehensiveness of the study. (2) The overall sample size of the study is relatively small, which may impact the robustness of the analysis and interpretation of research findings. (3) This study exclusively included published literature, potentially overlooking unpublished studies, leading to bias in the findings.

Conclusion

In summary, in the treatment of hepatocellular carcinoma, hepatectomy demonstrates superior clinical efficacy compared to radiofrequency ablation, particularly in terms of controlling tumor recurrence. However, radiofrequency ablation offers the advantage of lower complication risks and higher safety. These findings serve as valuable guidance for clinicians when selecting the most appropriate treatment approach for liver cancer patients.

Availability of Data and Materials

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author Contributions

ZX: Conception, Design, Materials, Data Collection, Analysis, Literature Review, Writing. YH: Supervision, Materials, Analysis, Literature Review, Writing. LH: Materials, Data Collection, Analysis, Writing, Critical Review. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.3155.

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