Narrative Review
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Unlocking the Potential of Radiofrequency Ablation in Treating Hepatocellular Carcinoma Among Elderly Patients: A Literature Review

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Abstract

Objective. This study aimed to thoroughly assess and evaluate recent studies comparing radiofrequency ablation (RFA) and surgical resection in older patients with hepatocellular carcinoma (HCC). **Methods.** We searched the databases PubMed, Scopus, and Cochrane for articles published up to 31 October 2024. This review included studies comparing RFA and surgical resection in individuals with HCC aged 65 years or older. The exclusion criteria were non-human research, case reports, editorials, and studies involving patients with liver metastases or cholangiocarcinoma. **Results.** We found four retrospective cohort studies. The derived data showed no difference in one-year survival rates. However, the RFA group exhibited a better disease-free survival rate and a lower mortality rate than the surgical resection group. **Conclusion.** RFA outperformed surgical resection in terms of overall and disease-free survival rates while showing no appreciable variation in the occurrence of complications. However, this study underscores the need for more extensive research utilizing larger sample sizes, particularly in low- and middle-income countries.

Key Words: RFA ▪ Surgical Resection ▪ HCC ▪ Elderly Patients ▪ Literature Review.

Introduction

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver and one of the most common and aggressive forms of cancer worldwide (1, 2). The prevalence of HCC varies geographically, with higher rates in regions such as East Asia and sub-Saharan Africa, largely due to the endemic nature of hepatitis B virus infections in these areas (2, 3). However, in developed regions such as Europe, the United States, or Japan, the hepatitis C virus (HCV) has been identified as a leading etiological factor for HCC (3). The relationship between HCC and HCV infection is well established. Studies conducted between 1992 and 2000 indicated that over 70% of patients with HCC tested positive for HCV, highlighting a strong connection between the virus and the onset of liver cancer. The process through which HCV causes HCC involves chronic inflammation and liver damage that can eventually lead to cirrhosis and, subsequently, the onset of cancer (4, 5).

The demographic profile of HCC patients is changing, with a notable increase in the number of older patients, especially in Japan. This trend can be attributed to several factors, including advancements in healthcare that have increased life expectancy, an aging population, and the increasing age of individuals infected with HCV. As these individuals age, their risk of developing HCC increases due to the prolonged latency period between HCV infection and the onset of liver cancer. The aging HCV-infected population poses a significant public health challenge, as it increases the number of older HCC patients and complicates treatment. Compared with younger patients,

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older patients frequently encounter additional health concerns and may have a reduced capacity to endure aggressive treatments. This trend has resulted in an increased demand for research into HCC treatments that are more suitable for elderly patients. Such research focuses on advancing less invasive therapies, personalized treatment strategies that consider the patient's overall health and specific cancer traits, and exploring new therapeutic agents with reduced side effects (6).

Physicians primarily treat HCC with transcatheter arterial embolization, percutaneous ablation therapy, and surgical resection. While surgery has long been viewed as the preferred method, its application is frequently limited by factors such as underlying liver cirrhosis or the existence of multiple tumors (7). Liver transplantation can be highly effective in certain cases. However, the limited supply of donor organs constrains the availability of liver transplantation (8). Radiofrequency ablation (RFA) has gained significant global popularity among non-surgical options. RFA is especially effective for early-stage HCC, providing a minimally invasive and highly curative treatment that is now recognized as a standard option alongside liver resection. However, recent guidelines have not fully recommended the use of RFA in place of surgical resection, which may be due to the lack of studies supporting its efficacy and safety (9, 10).

Elderly patients often present with multiple health concerns and are generally considered at higher risk for major surgical procedures (11). Recent studies have demonstrated that RFA can be performed in older HCC patients with satisfactory efficacy (12-15). However, the findings of various studies still differ. Peng et al. indicated that RFA demonstrated superior efficacy compared with hepatic resection in patients with HCC ≥3 cm (15) Guangzhou, China. Written informed consent was obtained from each patient before treatment. As an initial treatment, 89 patients were treated by RFA and 91 patients by HR. The survival curves were constructed by the Kaplan-Meier method and compared by log-rank test.\nRESULTS: The 1-, 3-, and 5-year overall survivals were 93.2%, 71.1%, and 55.2% for the RFA group and 88.8%, 62.8%, and 51.9% for the HR group, respectively (P = .305. Furthermore, a recent study by Kim et al. revealed that RFA exhibits a non-inferior therapeutic effect compared to resection (12). Yoo et al. published a systematic review of this topic encompassing a literature search up to March 2022, which also discusses that RFA has shown similar results to surgical treatment for earlier stages of HCC and is of peak interest as it may be a better management option for elderly patients who are more prone to surgical complications (14). However, recent studies have provided new evidence, so an updated meta-analysis is warranted.

Consequently, this study aimed to review and synthesize the latest research comparing RFA and surgical resection in older patients with HCC.

Methods

Information Sources and Search Strategy

We conducted a literature search using the databases PubMed, Scopus, and Cochrane. This study focused on identifying research that compares the efficacy and safety of RFA and surgical resection in elderly patients with HCC . The main outcomes assessed were efficacy, measured by overall survival or disease-free survival rates, and safety, evaluated based on postprocedural complications. We used the following key terms : "Elderly", "Hepatocellular Carcinoma", "Radiofrequency Ablation", and "Surgical Resection". We used the term 'elderly' as a key term since it aligns with commonly used terminology in gerontological research (≥65 years old). Figure 1 shows the study's PRISMA flowchart.

Study Eligibility Criteria

The two authors established the eligibility criteria. We defined the following inclusion criteria: (1) clinical trials as the research design; (2) RFA or surgical resection as the intervention; (3) elderly patients (≥65 years old) with HCC as the study population; (4) surgical resection as the comparison; and (5) outcomes, including safety

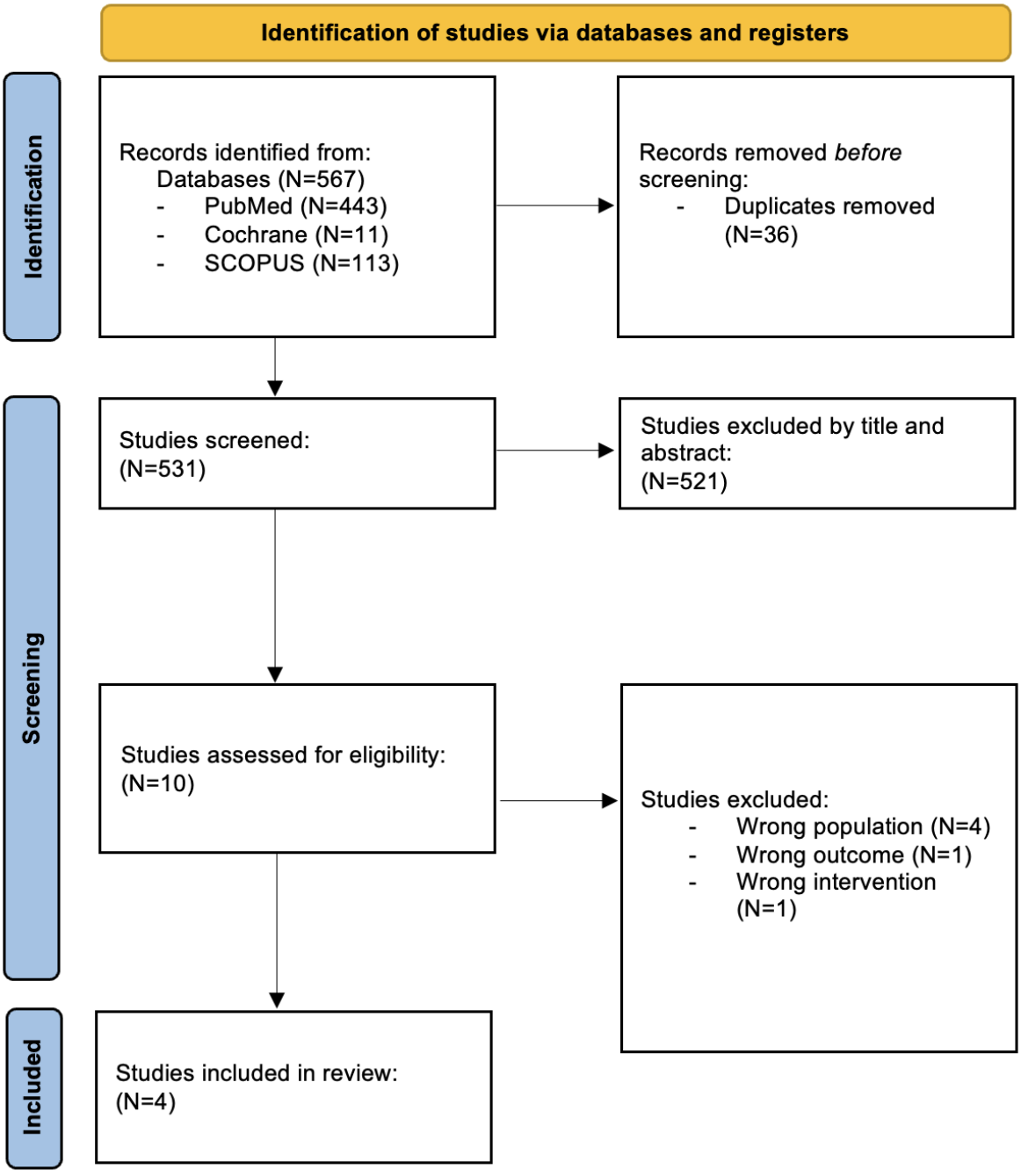

Figure 1. Flow diagram of the literature search strategy.

from complications and efficacy on the overall survival rate or the disease-free survival rate. We established the following exclusion criteria: non-human research (1), case reports (2), editorials (3), patients with liver metastases (4), and cholangiocarcinoma. . Table 1 summarizes the research eligibility criteria.

Table 1. Study Eligibility Criteria

Category	Inclusion Criteria	Exclusion Criteria
Participants	Elderly patients (≥ 65 years old) with HCC	Studies with patients <65 years old, patients with liver metastases, and cholangiocarcinoma
Intervention	RFA or surgical resection	-
Comparison	Surgical resection	-
Outcome	Safety from complications and efficacy on the overall survival rate or the disease-free survival rate	-
Study design	Clinical trials	Non-human research, case reports, and editorials

Data Extraction

The authors thoroughly documented the main conclusions and pertinent data from all the studies included in this review. The following information was acquired: (1) author and publication year; (2) study attributes, including design and setting; (3) study population, including sample size and average age; (4) intervention; and (5) study results, which include the evaluated parameters and significance (P-values). The two authors of this study created the data extraction criteria .

Results

Study Characteristics

This research included four retrospective cohort studies : two conducted in Italy, one in South Korea, and one in China. The studies were conducted between 2013 and 2024. Older individuals with HCC diagnosed with Child-Pugh class A or B, without evidence of hepatic metastases, participated in the included trials. The patients were categorized into two groups: the first group received RFA treatment, whereas the second group underwent surgical resection. In both groups, the assessed outcomes were effectiveness and the safety profile. Survival rates at one, three, and five years were used to assess effectiveness. Following each surgery, issues related to the safety profile were reported. We present a summary of the included studies in Table 2.

Overall Survival Rate

The data derived from the studies show no discernible difference in one-year survival rates between the two intervention groups. Despite variations in study design and patient populations, the collective findings suggest that both interventions do not confer a meaningful benefit in extending survival at the one-year mark. For example, Kim et al. (12) report a one-year overall survival rate of 95.6% for RFA and 98.6% for resection—a difference of only 3%. Similarly, Filippo et al. (16) report rates of 86% for RFA and 89% for resection. However, the three-year survival rate shown by Peng et al. (15) shows a significant association between RFA and enhanced survival outcomes, with RFA at 71.1% and resection at 62.8%. Peng et al.'s findings show that patients who underwent RFA had notably higher survival three years post-treatment than the surgery group. There were only two studies that assessed the 5-year overall survival rate. Both studies indicate that individuals who underwent surgical procedures may have significantly reduced survival probabilities over a five-year period.

Disease-free Survival Rate

Two studies were conducted to ascertain disease-free survival rates. The findings of the studies reveal a robust and statistically substantial impact of RFA compared to the surgical approach, which significantly enhanced the 1-year and 3-year disease-free survival rates. This minimally invasive technique improves overall survival and demonstrates a

Table 2. A Summary of the Included Studies

Author, year	Study location	Study design	Study population			Efficacy				Complications
			Characteristics	Sample size (N)	Mean age, years (SD)	Parameter	RFA (%)	Resection (%)	P	
Peng et al., 2013 (15)	Guangzhou, China	Retrospective cohort	Older people aged over 65 One HCC lesion with a diameter of 5.0 cm, or three HCC lesions with a diameter of less than 3.0 cm each No radiologic indication of an invasion into the main branches of the portal or hepatic vein No metastases outside the liver Lesions that are apparent on ultrasonography and that have a reasonable and secure passage from the lesion to the skin Class A or B Child-Pugh illness	RFA: 89 LR: 91	RFA: 70.4 (4.9) LR: 68.7 (3.3)	1-year survival rate 3-year survival rate 5-year survival rate	93.20 71.10 55.20	88.80 62.80 51.90	0.305	90-day mortality rate: RFA: 0% LR: 1.1% Pain (P=0.025) Grade 1 (RFA: 19, LR: 10) Grade 2 (RFA: 13, LR: 29) Grade 3 (RFA: 1, LR: 9) Fever (>38.5) (P=0.014) Grade 1 (RFA: 24, LR: 25) Grade 2 (RFA: 2, LR: 17) Ascites (P<0.001) Grade 1 (RFA: 0, LR: 5) Grade 2 (RFA: 0, LR: 8)
Conticchio et al., 2020 (13)	Multicenter: France, Spain, Switzerland, Italy	Retrospective cohort	Older people aged over 70 A single HCC with a diameter of less than 3 cm and no signs of extrahepatic illness or significant portal/hepatic vein branch invasion Completed LLR/RFA A or B Child-Pugh class	RFA: 98 LLR: 86	RFA: 75 (5.48) LLR: 75.7 (4.91)	1-year disease-free survival (DFS) 3-year disease-free survival (DFS) 1-year overall survival (OS) 3-year overall survival (OS)	66.40 38 90.10 67	89.90 67 96.30 90	0.001 0.001	90-day mortality rate (P=1.0) RFA: 3% LLR: 2% Liver failure (P=0.03) RFA: 1% LLR: 8% Ascites (P=0.15) RFA: 2% LLR: 6% Postoperative complications RFA: 15% LLR: 31%

Continuation of Table 2.

Author, year	Study location	Study design	Study population			Efficacy				Complications
			Characteristics	Sample size (N)	Mean age, years (SD)	Parameter	RFA (%)	Resection (%)	P	
Filippo et al., 2023 (16)	Multicenter: France, Spain, Switzerland, Italy	Retrospective cohort	Older people aged 80 and above HCC in BCLC stage 0/A, with a maximum diameter of 5 cm A maximum of three tumor nodules Lack of metastases outside the liver There is no radiological proof that the tumor has invaded the main portal or hepatic vein branches A or B Child-Pugh class	RFA: 37 LR: 65	RFA: 82.2 (2.5) LR: 82.4 (2.4)	1-year disease-free survival (DFS)	59.40	87	0.007	90-day mortality rate (P=0.707) RFA: 2% LR: 6% Liver failure (P=0.048) RFA: 0% LR: 12% Ascites (P=0.013) RFA: 0% LR: 15% Postoperative complications (P<0.001) RFA: 11% LR: 49%
						2-year disease-free survival (DFS)	50.70	76		
						3-year disease-free survival (DFS)	42.40	60.50		
						1-year overall survival (OS)	86	89	0.144	
						2-year Overall Survival (OS)	68	87		
						3-year overall survival (OS)	60.50	77		
Kim et al., 2024 (12)	South Korea	Retrospective cohort	Older people aged 65 and above Tumor size smaller than 3 cm HCC in BCLC stage 0/A	RFA: 225 LR: 141	RFA: 70 (4.44) LR: 68 (4.44)	1-year overall survival (OS)	95.6	98.6	<0.001	N/A
						3-year overall survival (OS)	82.7	91.5		
						5-year overall survival (OS)	67.9	83.8		

HCC=Hepatocellular carcinoma; RFA=Radiofrequency ablation ; LR=Liver resection; LLR=Laparoscopic liver surgery; BCLC=Barcelona Clinic Liver Cancer.; DFS=Disease-free survival; OS=Overall survival.

notable advantage in achieving disease-free intervals compared to surgical interventions.

Safety Profiles

According to Peng et al. (15), the surgical resection group exhibited a mortality rate of 1.1%, as one patient died during the same hospital stay. In contrast, no in-hospital mortality was reported for the RFA group. Additionally, according to Conticchio

et al. (13), the RFA group' s 90-day mortality rate was slightly higher than that of the surgical resection group (3% vs. 2%, respectively). However, Filippo et al. (16) discovered that the RFA group exhibited a lower mortality rate (2% vs. 6%) than the surgical resection group.

Discussion

RFA is a minimally invasive treatment option for various liver tumors, including HCC. By generating heat through radiofrequency waves, it induces coagulative necrosis, effectively destroying cancer cells. RFA involves inserting a small needle electrode into the tumor utilizing ultrasonic or CT scan guidance. Once installed, radiofrequency radiation is applied, causing ions to rapidly vibrate and generate heat, which destroys tumor cells within minutes. When a patient is not eligible for a liver transplant or has small, early-stage HCC that cannot be treated with surgery, RFA is highly effective. Additionally, it can be applied to individuals with multiple tumors or in conjunction with other therapies. RFA offers several benefits over conventional surgery, including reduced postoperative discomfort, shorter hospital stays, and faster recovery times (17).

Furthermore, Peng et al. (15) also found that 26 patients in the RFA group and 42 patients in the surgical resection group developed post-treatment fever, defined as an axillary temperature exceeding 38.5 °C after treatment (P=0.014). Thirty-three patients in the RFA group and forty-eight patients in the resection group required analgesics (P=0.025). Ascites, cardiac issues, liver failure, transient ischemic attacks, pulmonary infections, hepatobiliary disorders, pleural effusions, postoperative hemorrhage, and acute renal injury were among the other significant side effects that the hepatic resection (HR) group encountered. One patient in the RFA group was diagnosed with hepatobiliary disease and pleural effusion. The RFA group experienced significantly shorter hospital stays (8.01 days ± 2.70 days versus 13.50 days ± 4.05 days, P<0.001) than the HR group.

This study indicates that RFA is more effective than surgical resection in survival and disease-free survival rates for older patients with HCC. These findings are consistent with those of previous studies on non-elderly populations. According to Huang et al., resection and RFA demonstrate comparable efficacy regarding long-term survival rates and tumor recurrence in HCC patients (18). Numerous studies have demonstrated the effectiveness and safety of surgical interventions for HCC in older adults, with most indicating similar survival rates and safety profiles to those of younger patients (19-21). However, research specifically examining these aspects of RFA in older populations is limited. In a cohort of 1 000 patients treated with RFA, Tateishi et al. found no statistically significant difference in the 3-year survival rate between patients older than 68 years (76%) and those younger than 68 years (79.2%) (22).

In addition to the effectiveness of RFA , it can also be used in multi-modality with laparoscopy and thoracoscopy, which has been associated with a shorter hospital stay and a less invasive procedure. However, further studies may be needed to consider it the standard treatment for HCC (23). Although RFA has demonstrated beneficial effects, it is currently recommended primarily for patients who are ineligible for surgery due to comorbidities or a high risk of surgical complications. There are suggestions to combin e RFA with transcatheter arterial chemoembolization to prevent local and distant tumor rec urrence in patients with HCC with a diameter of >3 cm. Hence, RFA alone is not recommended for patients with HCC with a diameter of >3 cm, as it is related to poor prognosis of distant tumor recurrence, even though patients with good liver function (Child-Pugh class A) might be eligible for RFA treatment (24).

Strengths and Limitations

This review has both advantages and disadvantages. Direct comparisons were possible because of significant similarities in the outcomes of the included studies. However, the authors acknowledge that this study has several limitations. The included studies exhibit a considerable degree of heterogeneity. Therefore, future research should focus on conducting randomized controlled trials with larger sample sizes to generate more robust clinical recommendations.

Conclusion

In conclusion, RFA treatment offers similar overall and disease-free survival rates compared to surgical resection. Furthermore, there is no identifiable difference in the incidence of complications between the two therapies. This study recommends further research with larger sample sizes to achieve more definitive conclusions, particularly in low- to middle-income countries or regions with predominantly older populations.

What Is Already Known on This Topic:
Hepatocellular carcinoma (HCC) can be treated by transplantation, surgical resection, transcatheter arterial embolization, or percutaneous ablation therapy. Although surgery has traditionally been considered the preferred approach, its use is frequently limited by considerations such as underlying conditions. Radiofrequency ablation (RFA) has gained significant global popularity among non-surgical options.

What This Study Adds:
RFA treatment achieves comparable rates of overall and disease-free survival.

Authors' Contributions: Conception and design: DAA and DD; Acquisition, analysis and interpretation of data: DAA and DD; Drafting the article: DAA and DD; Revising it critically for important intellectual content: DAA; Approved final version of the manuscript: DAA and DD.

Conflict of Interest: The authors declare that they have no conflict of interest.

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