Medical Policy

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Title: Radiofrequency Ablation of Primary or Metastatic Liver Tumors

Related Policies:	▪ *Cryosurgical Ablation of Primary or Metastatic Liver Tumors* ▪ *Microwave Tumor Ablation* ▪ *Radiofrequency Ablation (RFA) of Miscellaneous Solid Tumors Excluding Liver Tumors* ▪ *Radioembolization for Primary and Metastatic Tumors of the Liver* ▪ *Transcatheter Arterial Chemoembolization (TACE) to Treat Primary or Metastatic Liver Malignancies*

Professional / Institutional
Original Effective Date: July 1, 2003 / August 1, 2006
Latest Review Date: September 8, 2026
Current Effective Date: January 19, 2021

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Populations	Interventions	Comparators	Outcomes
Individuals: • With primary, operable	Interventions of interest are: • Radiofrequency ablation	Comparators of interest are: • Surgical resection	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status

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Populations	Interventions	Comparators	Outcomes
hepatocellular carcinoma			• Morbid events
Individuals: • With inoperable hepatocellular carcinoma	Interventions of interest are: • Radiofrequency ablation	Comparators of interest are: • Systemic therapy • Other locally ablative techniques	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Morbid events
Individuals: • With inoperable hepatocellular carcinoma awaiting liver transplant	Interventions of interest are: • Radiofrequency ablation	Comparators of interest are: • Other locoregional therapies	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status
Individuals: • With inoperable hepatic metastases of colorectal origin	Interventions of interest are: • Radiofrequency ablation	Comparators of interest are: • Chemotherapy • Other locally ablative techniques • Best supportive care	Relevant outcomes include: • Overall survival • Disease-specific survival • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related morbidity
Individuals: • With inoperable hepatic metastases of neuroendocrine origin	Interventions of interest are: • Radiofrequency ablation	Comparators of interest are: • Chemotherapy • Other locally ablative techniques • Best supportive care	Relevant outcomes include: • Overall survival • Disease-specific survival • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related morbidity
Individuals: • With hepatic metastases not of colorectal or neuroendocrine origin	Interventions of interest are: • Radiofrequency ablation	Comparators of interest are: • Chemotherapy • Other locally ablative techniques • Other therapy • Best supportive care	Relevant outcomes include: • Overall survival • Disease-specific survival • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related morbidity

DESCRIPTION

Radiofrequency ablation (RFA) is a procedure in which a probe is inserted into the center of a tumor and heated locally by a high-frequency, alternating current that flows from electrodes. The local heat treats the tissue adjacent to the probe, resulting in a 3 to 5 cm sphere of dead tissue. The cells killed by RFA are not removed but are gradually replaced by fibrosis and scar tissue. If there is a local recurrence, it occurs at the edge of the treated tissue and, in some cases, is retreated. Radiofrequency ablation may be performed percutaneously, laparoscopically, or as an open procedure.

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OBJECTIVE

The objective of this evidence review is to determine whether radiofrequency ablation improves the net health outcome in individuals with primary hepatocellular carcinoma or hepatic metastases.

BACKGROUND

Hepatic and Neuroendocrine Tumors

Hepatic tumors can arise as primary liver cancer (hepatocellular cancer) or by metastasis to the liver from other tissues. Local therapy for hepatic metastasis may be indicated when there is no extrahepatic disease, which rarely occurs for patients with primary cancers other than colorectal carcinoma or certain neuroendocrine malignancies. A study from 2016 determined that the incidence of liver cancer was higher among White individuals, Black individuals, and Hispanic individuals born after 1938.[1,] The incidence of hepatocellular carcinoma was twice as high for US-born Hispanic men compared to Hispanic men born outside of the US. This may be due to the increased risk of smoking, hepatitis B or C infection, and diabetes among US-born Hispanic individuals.

Neuroendocrine tumors are tumors of cells that possess secretory granules and originate from the neuroectoderm. Neuroendocrine cells have roles both in the endocrine system and in the nervous system. They produce and secrete a variety of regulatory hormones, or neuropeptides, which include neurotransmitters and growth factors. Overproduction of the specific neuropeptides produced by the cancerous cells causes various symptoms, depending on the hormone produced. They are rare, with an incidence of 2 to 4 per 100,000 per year.

Treatment

Treatment options for hepatocellular carcinoma (HCC) range from potentially curative treatments, such as resection or liver transplantation, to nonsurgical options, which include ablative therapies (radiofrequency ablation [RFA], cryoablation, microwave ablation, percutaneous ethanol, or acetic acid injection), transarterial chemoembolization, radiation therapy, and systemic therapy. Choice of therapy depends on the severity of the underlying liver disease, size, and distribution of tumors, vascular supply, and patient overall health. Treatment of liver metastases is undertaken to prolong survival and reduce endocrine-related symptoms and hepatic mass-related symptoms.

At present, surgical resection with adequate margins or liver transplantation constitutes the only treatments available with demonstrated curative potential for hepatic tumors. However, most hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size, number of lesions, or underlying liver reserve. Comorbid conditions may also make patients unqualified for surgical resection.

Radiofrequency Ablation

Radiofrequency ablation is a procedure in which a needle electrode is inserted into a tumor either percutaneously, through a laparoscope, or through an open incision. The electrode is heated by a high-frequency, alternating current, which destroys tissue in a 3 to 5 cm sphere of the electrode. The cells killed by RFA are not removed but are gradually replaced by fibrosis and

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scar tissue. If there is a local recurrence, it occurs at the edge of the treated tissue and, in some cases, is retreated. Radiofrequency ablation has been investigated as a treatment for unresectable hepatic tumors, both as a primary intervention and as a bridge to a liver transplant. In the latter setting, RFA is being tested to determine whether it can reduce the incidence of tumor progression in patients awaiting transplantation and thus maintain patients' candidacy for liver ablation, transhepatic arterial chemoembolization, microwave coagulation, percutaneous ethanol injection, and radioembolization (yttrium-90 microspheres).

REGULATORY STATUS

Radiofrequency ablation devices have been cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process. Food and Drug Administration product code: GEI.

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POLICY

A. Radiofrequency ablation of primary, inoperable (e.g., due to location of lesion[s] and/or comorbid conditions), hepatocellular carcinoma (HCC) may be considered **medically necessary** for any of the following conditions:
   1. as a primary treatment of HCC for individuals meeting the Milan criteria (a single tumor of ≤5 cm or up to 3 nodules <3 cm)
   2. as a bridge to transplant, where the intent is to prevent further tumor growth and to maintain an individual's candidacy for liver transplant

B. Radiofrequency ablation as a primary treatment of inoperable hepatic metastases may be considered **medically necessary** for any of the following conditions:
   1. metastases are of colorectal origin and meet the Milan criteria (a single tumor of ≤5 cm or up to 3 nodules <3 cm)
   2. metastases are of neuroendocrine in origin and systemic therapy has failed to control symptoms

C. Radiofrequency ablation of primary, inoperable, hepatocellular carcinoma (HCC) is considered **experimental / investigational** for any of the following conditions:
   1. when there are more than 3 nodules or when not all sites of tumor foci can be adequately treated
   2. when used to downstage (downsize) HCC in individuals being considered for liver transplant

D. Radiofrequency ablation of primary, operable hepatocellular carcinoma is **experimental/ investigational**.

E. Radiofrequency ablation for hepatic metastasis is considered **experimental / investigational** for the following conditions:
   1. hepatic metastases from colorectal cancer or neuroendocrine tumors that do not meet the criteria above; **AND**
   2. hepatic metastases from other types of cancer except colorectal cancer or neuroendocrine tumors

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RATIONALE

This evidence review was created using with searches of the PubMed database. The most recent literature update was performed through May 13, 2026.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and

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whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Radiofrequency Ablation to Treat Primary, Operable Hepatocellular Carcinoma
The evidence is evaluated separately for operable and inoperable tumors. If data are available, separate analyses by tumor size are evaluated.

Clinical Context and Therapy Purpose
The purpose of radiofrequency (RFA) is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as surgical resection, in individuals with primary, operable hepatocellular carcinoma (HCC).

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with primary, operable HCC.

Interventions
The therapy being considered is RFA.

Comparators
Comparators of interest include surgical resection. Surgical resection is a potentially curative therapy for individuals with HCC with adequate/preserved liver functional reserve (Child-Pugh Class A or Class B in certain circumstances). Some staging systems can be used to direct treatment or predict survival after therapeutic intervention. Two notable systems include the Barcelona Clinic Liver Cancer (BCLC) staging system and Milan criteria. The BCLC system is currently the standard classification system for the clinical management of individuals with HCC. Hepatic resection is proposed for early-stage HCC (BCLC-0/A). Milan criteria can aid in determining eligibility for transplantation. Milan criteria include: single tumor <5 cm, no more than 3 foci with each not exceeding 3 cm, absence of angioinvasion, and absence of extrahepatic involvement. Individuals with resectable HCC are also potentially eligible for a liver transplant. However, the availability of liver donors limits its use.

Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival, change in disease status, and morbid events (Table 1).

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Table 1. Outcomes of Interest for Individuals with Primary, Operable Hepatocellular Carcinoma

Outcomes	Details
Overall survival	Survival rate or proportion dead [30 days to 10 years]
Disease-specific survival	Disease/recurrence-free survival [1 year to 10 years]
Morbid events	Complications, adverse events [peri- or post-procedure]

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

The evidence on RFA as a treatment of resectable HCC includes RCTs, meta-analyses, and observational studies that combined RFA with transhepatic arterial chemoembolization (TACE) or other locally ablative procedures.

Systematic Reviews

Several systematic reviews are available comparing health outcomes between RFA, with or without other locally ablative procedures, and surgical resection. The most recent evaluations in patients with early HCC who are suitable candidates for either RFA or surgical resection are summarized below and in Tables 2, 3, and 4. The vast majority of trials included in available systematic reviews were conducted in China, Japan, and Korea.

Dai et al (2026) published a meta-analysis comparing the safety and efficacy of surgical resection versus RFA in patients with small HCC (≤3 cm).[2,] The literature search focused on recently published data, from January 2020 through June 2024, and identified 25 studies comprising 10,322 patients (surgical resection n=5,062; RFA n=5,260), including 1 RCT, 9 propensity score-matched studies, and 15 retrospective studies. The primary outcomes were overall survival and recurrence-free survival. Compared with RFA, surgical resection was associated with improved survival outcomes, including higher 3-year overall survival (HR, 0.73; 95% CI, 0.66 to 0.80; p<.001) and 5-year overall survival (HR, 0.70; 95% CI, 0.62 to 0.79; p<.001), while 1-year overall survival did not differ significantly. Surgical resection also demonstrated superior recurrence-free survival at 1 year (HR, 0.55; 95% CI, 0.47 to 0.65; p<.001), 3 years (HR, 0.66; 95% CI, 0.59 to 0.73; p<.001), and 5 years (HR, 0.76; 95% CI, 0.68 to 0.85; p=.001). Local recurrence was significantly lower with surgical resection (odds ratio [OR], 0.24; 95% CI, 0.15 to 0.40; p<.001), whereas RFA was associated with shorter operative time, shorter hospital stay, and fewer complications. Subgroup analyses indicated that overall survival and recurrence-free survival were similar between treatments in patients with tumors ≤2 cm or multiple lesions.

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Yang et al (2025) compared the efficacy of liver resection to RFA in patients with single HCC tumors measuring ≤3 cm.[3,] The analysis included 39 trials (2 RCTs, 37 nonrandomized), which included 6356 patients with tumors ≤3 cm and 5829 patients with tumors ≤2 cm. There was no difference in OS when only the RCTs were analyzed. When only the nonrandomized studies were included, there was an improvement in OS (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.68 to 0.93; p=.005) with resection compared to RFA. Similarly, DFS was better with resection compared to RFA (HR, 0.63; 95% CI, 0.49 to 0.81). When tumor size was considered, resection led to improved OS (HR, 0.73; 95% CI, 0.54 to 0.97) and DFS (HR, 0.74; 95% CI, 0.57 to 0.90) in patients with tumors ≤2 cm, compared to RFA.

Zhang et al (2022) compared the efficacy of liver resection, RFA alone, and RFA plus TACE in patients with very early or early stage HCC.[4,] Randomized trials (n=10) and propensity score-matched cohort analyses (n=15) were included. In a network meta-analysis, 1-year OS was similar between resection and RFA alone, but 3-year and 5-year OS favored resection (HR, 0.74; 95% CI, 0.56 to 0.96 and HR, 0.73; 95% CI, 0.55 to 0.94, respectively). Recurrence-free survival at 1, 3, and 5 years was also significantly higher with resection compared to RFA alone. There were no significant differences in survival outcomes at any time point between resection and RFA plus TACE.

Jia et al (2021) performed a meta-analysis to compare clinical efficacy between RFA and surgical resection in patients with HCC meeting Milan criteria.[5,] The analysis included RCTs, accounting for 8 trials (N=1177). There were no significant differences found between RFA and surgical resection in OS and disease-free survival (DFS) rates. In a subgroup analysis stratifying by tumor size, there was still no significant difference between the 2 therapies for both tumors ≤4 cm and >4 cm. Limitations of the analysis include the inclusion of clinical trials with small sample sizes and a lack of double-blinding.

Shin et al (2021) compared the efficacy of surgical resection with local ablative therapies for HCC meeting Milan criteria.[6,] The analysis included 7 RCTs and 18 non-randomized trials (N=5629) that compared surgical resection with either RFA, microwave ablation, or RFA plus TACE. Four of the RCTs were judged to be at high risk of bias overall, due to either a lack of reported randomization method or missing data. All non-randomized trials were classified as having a high risk for bias due to the missing data. There was no significant difference between surgical resection and RFA alone when the RCTs were analyzed; the 3- and 5-year OS favored surgical resection in the analysis of the non-randomized trials. A multiple treatment meta-analysis using a frequentist framework random effect model found that 5-year recurrence-free survival was highest with surgical resection (HR, 0.64; 95% CI, 0.56 to 0.74 vs. RFA), followed by RFA plus TACE (HR, 0.70; 95% CI, 0.53 to 0.92 vs. RFA); no difference was found between microwave ablation and RFA (HR, 0.93; 95% CI, 0.63 to 1.37). However, the latter comparisons were limited by the number of trials evaluating RFA plus TACE (5 studies) and microwave ablation (2 studies).

Li et al (2020) also evaluated the comparative efficacy of RFA and surgical resection in patients with HCC meeting Milan criteria with liver function Child-Pugh scores of grade A or B.[7,] One RCT and 15 retrospective observational studies were included in their analysis. Surgical resection was associated with significantly improved OS and DFS rates. In a subgroup analysis stratified by tumor size, 5-year OS rates were significantly improved in patients receiving surgical resection in patients with tumors ≤3 cm and >3 cm. The authors noted that the observational studies, which

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comprised most of the data, had significant heterogeneity and were prone to potential selection biases.

The network meta-analysis by Zhu et al (2018) compared the safety and effectiveness of several treatments for small HCC, including RFA, percutaneous ethanol injection (PEI), percutaneous acetic acid injection, and surgical resection.[8,] The authors identified 12 RCTs and 2 quasi-RCTs with a mean follow-up period of 22 months for most trials. The directed meta-analysis assessed mortality, local recurrence, and adverse events. It showed that PEI had a higher risk of proportion dead than RFA, and RFA had a higher risk of proportion dead than surgical resection; a single study found that percutaneous acetic acid injection had a higher risk of proportion dead than RFA (Table 2). For local recurrence, PEI had a higher recurrence rate than RFA, RFA had a higher recurrence rate than surgical resection, and percutaneous acetic acid injection had a higher recurrence rate than RFA. Adverse events were fewer with RFA than with surgical resection (OR, 0.11; 95% CI, 0.03 to 0.34), but there were no significant effects in reducing adverse events between PEI versus RFA and percutaneous acetic acid injection versus RFA. The authors used GRADE (Grading of Recommendations Assessment, Development, and Evaluation) to rate the quality of evidence for primary outcomes and found it to be very low for most comparisons. Further interpretation of results is limited due to the heterogeneity of the data, as well as the small sample sizes in the included studies.

Jia et al (2017) evaluated the comparative efficacy of RFA and surgical resection in patients with HCC and Child-Pugh Class A liver function.[9,] Two RCTs and 13 retrospective observational studies were selected for inclusion. In the overall population, patients receiving surgical resection had increased odds for 3-year and 5-year survival compared to RFA. In studies that were limited to patients with solitary tumors or those with tumors ≤3 cm, the OS and DFS rates were not significantly different between RFA and surgical resection. Limitations of the meta-analysis are similar to those of others, including the use of observational data, which increased heterogeneity and potentially compares groups that may not have equivalent baseline characteristics.

Feng et al (2015) compared RFA to surgical resection in patients with small HCC.[10,] Three RCTs and 20 retrospective observational studies were included in the analysis. Rates of OS and recurrence-free survival with surgical resection were significantly higher than RFA. However, complication rates were higher in the surgical resection group compared to RFA (OR, 0.37; 95% CI, 0.24 to 0.58).

Table 2. Comparison of Meta-Analyses of Radiofrequency Ablation for Primary, Operable Hepatocellular Carcinoma[a]

Study	Study type	Country	Feng et al (2015)[10],	Jia et al (2017)[9],	Zhu et al (2018)[8],	Li et al (2020)[7],	Jia et al (2021)[5],	Shin et al (2021)[6],	Zhang et al (2022)[4],	Yang et al (2025)[3],	Dai et al (2026)[2],
Alessandro et al (2024)	NRT	Italy									●
Maher et al (2024)	NRT	Australia									●
Wei et al (2024)	NRT	China									●

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Kang et al (2023)	NRT	Korea								●	●
Kim et al (2023)	NRT	Korea									●
Min et al (2023)	NRT	Korea									●
Rasic et al (2023)	NRT	USA									●
Conticchio et al (2022)	NRT	Italy								●	●
Ivanics et al (2022)	NRT	Canada								●	●
Ko et al (2022)	NRT	Korea								●	
Lee et al (2022)	NRT	Korea								●	●
Liu et al (2022)	NRT	Taiwan									●
Seong et al (2022)	NRT	Korea									●
Takayama et al (2022)	RCT	China									●
Zhang et al (2022)	NRT	China								●	●
Delvecchio et al (2021)	NRT	Italy								●	●
Lee et al (2021)	NRT	Korea							●	●	●
Li et al (2021)	NRT	China							●	●	●
Ogiso et al (2021)	NRT	Japan									●
Suh et al (2021)	NRT	South Korean									●
Takayama et al (2021)	RCT	Japan								●	
Wu et al (2021)	NRT	China								●	●

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Study	Study type	Country	Feng et al (2015)[10] ,	Jia et al (2017)[9] ,	Zhu et al (2018)[8] ,	Li et al (2020)[7] ,	Jia et al (2021)[5] ,	Shin et al (2021)[6] ,	Zhang et al (2022)[4] ,	Yang et al (2025)[3] ,	Dai et al (2026)[2] ,
Zhang et al (2021)	RCT	China							●		
Cha et al (2020)	NRT	Korea								●	
Dong et al (2020)	NRT	Korea									●
Hsiao et al (2020)	NRT	Taiwan									●
Lin et al (2020)	NRT	China								●	●
Magistri et al (2020)	NRT	Italy									●
Pan et al (2020)	NRT	China						●	●		
Zheng et al (2020)	NRT	China								●	●
Chong et al (2019)	NRT	China						●	●		
Chu et al (2019)	NRT	Korea						●		●	
Kim et al (2019)	NRT	Korea						●	●	●	
Lee et al (2019)	NRT	Korea							●		
Wang et al (2019)	NRT	China								●	
Yi et al (2019)	NRT	China							●		
Lee et al (2018)	RCT	Korea					●	●	●	●	
Takayasu et al (2018)	NRT	Japan								●	
Bholee et al (2017)	NRT	China							●		
Lee et al (2017)	NRT	Korea							●		
Ng et al (2017)	RCT	Japan					●	●	●		

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Kang et al (2016)	NRT	Korea						●	●		
Kato et al (2018)	NRT	Japan						●			
Kim et al (2016)	NRT	Korea						●		●	
Liu et al (2016)	NRT	Taiwan						●	●		
Liu et al (2016)	RCT	China							●	●	
Santambrogio et al (2016)	NRT	italy								●	
Song et al (2016)	NRT	China								●	
Vitali et al (2016)	NRT	France								●	
Jiang et al (2015)	NRT	China						●	●		
Kang et al (2015)	NRT	Korea								●	
Lee et al (2015)	NRT	Taiwan		●							
Song et al (2015)	NRT	China						●	●		
Fang et al (2014)	RCT	China			●		●	●	●		
Kim et al (2014)	NRT	Korea		●						●	
Yang et al (2014)	NRT	Korea								●	
Desiderio et al (2013)	NRT	Italy	●	●							
Guo et al (2013)	NRT	China	●								
Hasegawa et al (2013)	NRT	Japan	●								

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Imai et al (2013)	NRT	Japan	●							●	
Pompili et al (2013)	NRT	Italy	●	●				●	●	●	
Takuma et al (2013)	NRT	Japan							●		
Tohme et al (2013)	NRT	United States	●	●							
Wong et al (2013)	NRT	Taiwan	●	●						●	
Feng et al (2012)	RCT	China	●		●		●	●	●		
Peng et al (2012)	NRT	China	●	●						●	
Wang et al (2012)	NRT	Taiwan	●							●	
Giorgio et al (2011)	RCT	Italy			●						
Huang et al (2011)	NRT	China				●					
Hung et al (2011)	NRT	Taiwan	●			●		●		●	
Ikeda et al (2011)	NRT	Japan	●								
Kong et al (2011)	NRT	China	●								
Nishikawa et al (2011)	NRT	Japan	●			●				●	
Tashiro et al (2011)	NRT	Japan				●					
Yun et al (2011)	NRT	Korea	●							●	
Huang et al (2010)	RCT	China	●	●	●		●	●	●	●	
Morimoto et al (2010)	RCT	Japan							●		
Nanashima et al (2010)	NRT	Japan		●							

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Takayama et al (2010)	NRT	Japan								●	
Santambrogio et al (2009)	NRT	Italy		●		●					
Shibata et al (2009)	RCT	Japan							●		
Ueno et al (2009)	NRT	Japan	●								
Abu-Hilal et al (2008)	NRT	United Kingdom	●			●					
Brunello et al (2008)	RCT	Italy			●						
Guglielmi et al (2008)	NRT	Italy	●			●					
Hiraoka et al (2008)	NRT	Japan	●			●				●	
Ueno et al (2008)	NRT	Japan				●					
Lupo et al (2007)	NRT	Italy	●			●					
Chen et al (2006)	RCT	China	●	●	●	●	●	●	●	●	
Lu et al (2006)	RCT	China					●				
Wakai et al (2006)	NRT	Japan				●					
Chen et al (2005)	RCT	China					●				
Cho et al (2005)	NRT	Korea		●		●					
Hong et al (2005)	NRT	Korea		●		●					
Lin et al (2005)	RCT	Taiwan			●						
Montorsi et al (2005)	NRT	Italy				●					

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Study	Study type	Country	Feng et al (2015)[10] ,	Jia et al (2017)[9] ,	Zhu et al (2018)[8] ,	Li et al (2020)[7] ,	Jia et al (2021)[5] ,	Shin et al (2021)[6] ,	Zhang et al (2022)[4] ,	Yang et al (2025)[3] ,	Dai et al (2026)[2] ,
Ogihara et al (2005)	NRT	United States				●					
Shiina et al (2005)	NRT	Japan			●						
Sung et al (2005)	NRT	Korea	●								
Lin et al (2004)	RCT	Taiwan			●						
Vivarelli et al (2004)	NRT	Italy		●		●					
Guglielmi et al (2003)	NRT	Italy		●							
Lencioni et al (2003)	RCT	Italy			●						
Livraghi et al (1999)	RCT	Italy			●						

NRT: non-randomized trial; RCT: randomized controlled trial; RFA: radiofrequency ablation.
[a]For meta-analyses that evaluated more than 1 ablative therapy, only trials that evaluated RFA are listed in the table.

Table 3. Characteristics of Meta-Analyses of Radiofrequency Ablation for Primary, Operable Hepatocellular Carcinoma

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Dai et al (2026)[2,]	2020-2024	25	Pts with HCC lesions ≤3 cm	N=10,322	RCTs and NRTs	NR
Yang et al (2025)[3,]	2006-2023	39	Pts with solitary HCC lesions ≤3 cm	N=6356 (73 to 2550)	RCTs and NRTs	NR
Zhang et al (2022)[4,]	2006-2021	25	Pts with HCC.	N=4249 (19 to 354)	RCTs and NRTs	Mean follow-up, range 24.2 to 93 months
Jia et al (2021)[5,]	2005-2019	8	Pts with primary HCC meeting Milan criteria[a]; liver function Child-Pugh class A or B; suitable candidates for surgical resection and/or RFA.	N=1177 (63 to 230)	RCTs	Mean follow-up range, 27.9 to 92.4 months

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Study	Dates	Trials	Participants	N (Range)	Design	Duration
Shin et al (2021)[6,]	2006-2020	25	Pts with primary HCC meeting Milan criteria.[a]	N=5629 (52 to 1208)	RCTs and NRTs	NR
Li et al (2020)[7,]	2000-2018	25	Pts with primary HCC meeting Milan criteria[a] ; liver function Child-Pugh class A or B; suitable candidates for surgical resection and/or RFA.	N=13,147 (NR)	RCT and observational comparative studies	1 to 5 years
Zhu et al (2018)[8,]	1998-2013	14	Pts diagnosed with small HCC meeting Milan criteria.	N=2096 (29 to 143)	RCTs and quasi-RCTs	Mean, 22 months
Jia et al (2017)[9,]	2003-2015	15	Pts with early-stage HCC; liver function Child-Pugh class A; suitable candidates for surgical resection and/or RFA.	N=3627 (67 to 1061)	RCTs and observational comparative studies	1 to 5 years
Feng et al (2015)[10,]	2005-2013	23	Pts with small HCC not previously treated with RFA or surgical resection; suitable candidates for surgical resection and/or RFA.	N=15,482 (63 to 10,909)	RCTs and NRTs	1 to 5 years

HCC: hepatocellular carcinoma; NR: not reported; NRT: non-randomized trial; Pts: patients; RCT: randomized controlled trial; RFA: radiofrequency ablation.
[a] The Milan criteria are defined as a single HCC less than 5 cm in the maximum diameter having up to three nodules, each no larger than 3 cm, with no angio invasion and no extrahepatic involvement.

Table 4. Results of Meta-Analyses of Radiofrequency Ablation for Primary, Operable Hepatocellular Carcinoma

Study	Overall Survival OR or HR (95% CI)			Disease-free Survival OR or HR (95% CI)		
	1 yr	2/3 yr	5 yr	1 yr	2/3 yr	4/5 yr
Dai et al (2026)[2,]	NR	NR	NR	NR	NR	NR
SR vs RFA	0.86 (0.63 to 1.18)	0.73 (0.66 to 0.80)	0.70 (0.62 to 0.79)	0.55 (0.47 to 0.65)	0.66 (0.59 to 0.73)	0.66 (0.59 to 0.73)
p-value	.256	.001	.001	.001	.001	.001
Yang et al (2025)[3,]						
N	NR			NR		
SR vs. RFA (HR)	Survival duration not			Survival duration not specified		

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Study	Overall Survival OR or HR (95% CI)			Disease-free Survival OR or HR (95% CI)		
	specified RCTs: 0.73 (0.26 to 2.05) NRTs: 0.80 (0.68 to 0.93)			RCTs: not analyzed NRTs: 0.63 (0.49 to 0.81)		
I^2 (p)	RCTs: 0% (.55) NRTs: 58% (.005)			RCTs: NA NRTs: 81% (<.00001)		
Feng et al (2015)[10,]						
N	4199	15,414 (3-yr)	14,686	3544	3389 (3-yr)	2984 (5-yr)
RFA vs. SR (OR)	0.71 (0.52 to 0.96)	0.62 (0.49 to 0.78)	0.55 (0.47 to 0.66)	0.58 (0.45 to 0.76)	0.52 (0.40 to 0.68)	0.50 (0.34 to 0.76)
I^2 (p)	30% (.10)	NR (<.001)	NR (.02)	53% (.004)	NR (<.001)	NR (.00)
Jia et al (2017)[9,]						
N	NR (14 studies)	NR (15 studies; 3-yr)	NR (9 studies)	NR (9 studies)	NR (9 studies; 3-yr)	NR (6 studies; 5-yr)
RFA vs. SR (OR)	1.095 (0.636 to 1.885)	1.753 (1.197 to 2.567)	1.552 (1.026 to 2.348)	1.209 (0.935 to 1.563)	1.517 (1.076 to 2.140)	1.810 (1.071 to 3.058)
I^2 (p)	49% (.02)	74.2% (.000)	72.6% (.000)	20.4% (.261)	68.3% (.001)	68.5% (.007)
Zhu et al (2018)[a8,]						
PEI vs. RFA (OR)	-	1.66 (1.13 to 2.44)	-	-	2.74 (1.42 to 5.29)	-
PAI vs. RFA (OR)	-	1.63 (0.67 to 3.96)	-	-	2.79 (1.19 to 6.54)	-

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Study	Overall Survival OR or HR (95% CI)			Disease-free Survival OR or HR (95% CI)		
RFA vs. SR (OR)	-	1.21 (0.62 to 2.35)	-	-	2.02 (1.01 to 4.02)	-
Li et al (2020)[7,]						
N	3921	4053 (3-yr)	3397	3394	3326 (3-yr)	3076 (5-yr)
RFA vs. SR (OR)	0.757 (0.578 to 0.989)	0.530 (0.401 to 0.700)	0.566 (0.423 to 0.758)	0.569 (0.456 to 0.711)	0.418 (0.267 to 0.653)	0.374 (0.231 to 0.606)
I^2 (p)	0% (.55)	61% (.0005)	71% (<.0001)	42% (.06)	70% (.0001)	57% (.01)
Jia et al (2021)[5,]						
N	1177	947 (3-yr)	281	1114	1072 (3-yr)	-
RFA vs. SR (OR)	0.91 (0.45 to 1.83)	0.82 (0.56 to 1.19)	1.03 (0.61 to 1.73)	0.87 (0.63 to 1.21)	0.79 (0.58 to 1.07)	-
I^2 (p)	37% (.13)	23% (.25)	0% (.80)	0% (.76)	31% (.19)	-
Shin et al (2021)[b6,]				Recurrence-free survival	Recurrence-free survival (3-yr)	Recurrence-free survival (5-yr)
N (RCTs)	916	916 (3-yr)	691	978	978	690
SR vs. RFA (HR)	0.76 (0.31 to 1.83)	0.72 (0.45 to 1.14)	0.85 (0.55 to 1.29)	0.86 (0.64 to 1.15)	0.83 (0.65 to 1.06)	0.75 (0.62 to 0.92)
I^2 (p)	53% (.08)	61% (.04)	56% (.08)	2% (.40)	46% (.10)	10% (.35)
N (NRT)	1750	3412 (3-yr)	2928	3012	3012	2658
SR vs. RFA (HR)	1.91 (0.76 to 4.80)	0.75 (0.59 to 0.95)	0.72 (0.58 to 0.89)	0.54 (0.42 to 0.70)	0.61 (0.53 to 0.70)	0.61 (0.52 to 0.72)
I^2 (p)	44% (.08)	18% (.27)	33% (.15)	50% (.03)	31% (.16)	52% (.03)
Zhang et al (2022)[4,]						

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Study	Overall Survival OR or HR (95% CI)			Disease-free Survival OR or HR (95% CI)		
N	2734	2995	1785	2738	2999	1785
SR vs. RFA (OR)	0.93 (0.59 to 1.47)	0.75 (0.58 to 0.97)	0.71 (0.55 to 0.92)	0.66 (0.51 to 0.84)	0.69 (0.58 to 0.82)	0.61 (0.48 to 0.78)
I^2 (p)	28% (.76)	53% (.03)	53% (.009)	40% (.006)	60% (<.0001)	70% (<.0001)

CI: confidence interval; HR: hazard ratio; NA: not applicable; NR: not reported; NRT: non-randomized trial; OR: odds ratio; PAI: percutaneous acetic acid injection; PEI: percutaneous ethanol injection; RCT: randomized controlled trial; RFA: radiofrequency ablation; SR: surgical resection.
[a]Zhu et al (2018) reported proportion dead vs overall survival and local recurrence vs disease-free survival.
[b]Shin et al (2021) conducted separate meta-analyses for RCTs and NRTs.

Zhang et al (2022) conducted a meta-analysis of 16 studies (1 RCT, 15 nonrandomized) that compared surgical resection and RFA in patients with HCC and cirrhosis.[11,] Most measures of survival were better with resection than RFA, including 3-year OS (OR, 0.48; 95% CI, 0.35 to 0.67), 5-year OS (OR, 0.49; 95% CI, 0.38 to 0.63), 1-year DFS (OR, 0.42; 95% CI, 0.32 to 0.54), 3-year DFS (OR, 0.36; 95% CI, 0.24 to 0.53), and local recurrence. RFA had better postoperative complication rates and operative times. Most analyses had significant heterogeneity. The authors concluded that high quality multicenter prospective studies are needed to identify patient subgroups that would benefit most from each treatment. This analysis is not included in Tables 2, 3, and 4 since the studied population (ie, with cirrhosis) does not match the populations in the other analyses.

Randomized Controlled Trials

Kawaguchi et al (2025) published the results of a phase 3 randomized, controlled trial (SURF-RCT) with a parallel prospective observational cohort (SURF-Cohort) evaluating surgery versus RFA in patients with HCC meeting the inclusion criteria of ≤3 nodules with maximum diameter ≤3 cm and eligibility for both interventions.[12,] In the SURF-RCT conducted from 2009 to 2015, 302 patients were randomized (surgery n=150; RFA n=152) and followed for a median of approximately 6.4 to 6.6 years; co-primary outcomes were recurrence-free survival and overall survival. Surgery did not improve survival compared with RFA (HR, 0.96; 95% confidence interval [CI], 0.64 to 1.43; p=.84), with 5-year overall survival rates of 74.6% (95% CI, 66.5 to 81.0) versus 70.4% (95% CI, 62.2 to 77.3), respectively. Recurrence-free survival was also similar (HR, 0.90; 95% CI, 0.67 to 1.22; p=.50), with 5-year recurrence-free survival of 42.9% (95% CI, 34.3 to 51.2) for surgery and 42.7% (95% CI, 34.4 to 50.7) for RFA. Local recurrence was lower with surgery (8.0% vs 15.8%; p=.03), while serious adverse events occurred in 3.3% of surgical patients and 0% with RFA. In the SURF-Cohort (n=753; surgery n=382, RFA n=371; median follow-up 6.7 to 6.8 years), unadjusted analyses showed no difference in overall survival (HR, 0.92; 95% CI, 0.70 to 1.20; p=.54; 5-year overall survival 79.8% vs 78.0%) but improved recurrence-free survival with surgery (HR, 0.80; 95% CI, 0.66 to 0.97; p=.02; 5-year recurrence-free survival 47.2% vs 37.5%). However, in this study, the proportion of patients with the largest HCC diameter of ≤2.0 cm was significantly lower in the surgery cohort group than in the RFA-cohort group: 50% versus 72% (p<.01) at baseline. After adjustment, neither overall survival (HR, 0.96; 95% CI, 0.73 to 1.26; p=.77) nor recurrence-free survival (HR 0.84; 95% CI 0.69 to 1.02; p=0.08) differed significantly between groups.

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Song et al (2024) published results from a single-center, unblinded RCT in China comparing resection to RFA for treatment of HCC.[13,] Patients with HCC were eligible if they had a single nodule no larger than 5 cm, or up to 3 nodules of 3 cm or smaller. Patients were randomized to receive either liver resection or RFA (N=150). The primary outcome of OS did not differ between groups. Similarly, the secondary outcome of recurrence-free survival did not differ between groups. The 1-, 3-, and 5- year OS rates with laparoscopic resection were 94.7%, 80%, and 74.7%, respectively, and with RFA were 93.3%, 78.7%, and 67.9%, respectively. Tables 5 and 6 describe trial characteristics and results, respectively. The incidence of postoperative complications was higher in the resection group compared to the RFA group (22 [29.3%] vs. 8 [10.7%] adverse events; p=.004). Results are limited by the small sample size and single-center design.

Table 5. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Kawaguchi et al (2025)[12,]	Japan	118	2009-1025	Patients with the largest HCC diameter of up to 3 cm and up to 3 HCC nodules	RFA (n=152)	SR (n=150)
Song et al (2024)[13,]	China	1	2014-2015	Adults aged less than 70 years with small HCC (1 nodule no larger than 5 cm, or up to 3 nodules of 3 cm or smaller); liver function Child-Pugh class A or B; suitable candidates for surgical resection and/or RFA.	RFA (n=73)	SR (n=77)

HCC: hepatocellular carcinoma; RCT: randomized controlled trial; RFA: radiofrequency ablation; SR: surgical resection.

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Table 6. Summary of Key RCT Results

Study	OS	1 year OS, n (%)	3 years OS, n (%)	5 year OS, n (%)	RFS	1 year RFS, n (%)	3 year RFS, n (%)	5 year RFS, n (%)
Kawaguchi et al (2025)[12,]								
RFA	n=152			70.4%				42.7%
SR	n=150			74.6%				42.9%
HR (95% CI)	0.96 (0.64 to 1.43)				HR, 0.90 (95% CI, 0.67 to 1.22)			
p-value	.84				.84			
Song et al (2024)[13,]								N
RFA	n=73	70 (93.3%)	59 (78.7%)	49 (67.9%)	n=73	52 (69.3%)	40 (53.3%)	29 (41.0%)
SR	n=77	71 (94.7%)	60 (80.0%)	53 (74.7%)	n=77	59 (78.7%)	46 (61.3%)	36 (51.6%)
HR (95% CI)	1.26 (0.69 to 2.30)				1.34 (0.86 to 2.08)			
p-value	.451				.189			

CI: confidence interval; HR: hazard ratio; OS: overall survival; RCT: randomized controlled trial; RFA: radiofrequency ablation; RFS: recurrence-free survival; SR: surgical resection.

The purpose of the study limitations tables (see Tables 7 and 8) is to display notable limitations identified in each study.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Kawaguchi et al (2025)[Kawaguchi Y, Hasegawa K, Kashiwabara K, et al. Sur.... (23): 2628-2638. PMID 40554738	4. all study sites were in Japan				
Song et al (2024)[13,]	4. single-center in				

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Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
	China; main cause of HCC was HBV infection, which may differ from causes of HCC in non-Asian regions				

HBV: hepatitis B virus; HCC: hepatocellular carcinoma.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Kawaguchi et al (2025)[Kawaguchi Y, Hasegawa K, Kashiwabara K, et al. Sur.... (23): 2628-2638. PMID 40554738		4. blinding was not described				
Song et al (2024)[13,]		1. not blinded, would be unable to blind due to surgical procedure				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

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[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Observational Studies

Chen et al (2018) retrospectively analyzed data from 2 hospitals and compared a combination of RFA plus PEI (n=141) with surgical resection (n=130) in patients with HCC.[14,] The study included patients with tumors 2.1 to 5 cm in size. The race and ethnicity of the included patients were not described. Overall, patients receiving RFA plus PEI experienced significantly better OS and relapse-free survival than patients undergoing resection. However, subgroup analysis by tumor size showed that significant improvements in OS and relapse-free survival were only experienced by patients with tumors 2.1 to 3 cm (see Table 9).

Table 9. Survival Following Surgical Resection or Radiofrequency Ablation Plus Percutaneous Ethanol Injection for Resectable Hepatocellular Carcinoma

Outcomes	1 Year, %	3 Years, %	5 Years, %	p-value
Overall survival				
2.1 to 3.0 cm				
RFA plus PEI, n=77	98.0	82.3	74.2	
Surgical resection, n=70	89.4	65.1	61.9	.02
3.1 to 5.0 cm				
RFA plus PEI, n=64	86.4	65.1	55.4	
Surgical resection, n=60	88.9	64.5	49.6	.13
Recurrence-free survival				
2.1 to 3.0 cm				
RFA plus PEI	79.6	54.7	45.1	
Surgical resection	57.6	43.9	31.7	.02
3.1 to 5.0 cm				
RFA plus PEI	53.5	29.4	24.0	
Surgical resection	42.2	26.6	21.9	.71

Adapted from Chen et al (2018).[14,]
PEI: percutaneous ethanol injection; RFA: radiofrequency ablation.

Zhao et al (2019) compared outcomes for RFA, resection, or transplantation in patients from the Surveillance, Epidemiology, and End Results database.[15,] A total of 7664 patients treated between 2004 and 2015 with a single HCC tumor measuring up to 50 mm met study criteria. Outcomes for the 3 treatment arms were evaluated for both the unadjusted population and a propensity score-adjusted population to account for differences in baseline characteristics between patients.

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Median follow-up for the whole cohort was 55 months for OS. In the overall cohort, liver transplantation was associated with an improved OS (5-year OS, 66%) compared to RFA and resection in both unadjusted and adjusted populations (5-year OS [adjusted], 66% vs. 53% vs. 52%, respectively), but no significant difference was found between RFA and resection. Stratification by tumor size generally showed more survival benefits with resection compared to RFA. Further analysis by prognostic factors found that RFA may be the preferred treatment strategy for patients with low tumor risk (eg, tumor size <20 mm, tumor grade 0, fibrosis score/F0) and good general health condition (Table 10).

Table 10. Overall Survival Probability for Overall Cohort and Stratified by Lesion Size

	Overall Survival, HR (95% CI)		
Group Analyzed[a]	**SR vs. RFA**	**LT vs. RFA**	**LT vs. SR**
Total Cohort	1.0 (0.9 to 1.1)	0.6 (0.6 to 0.7)	0.7 (0.6 to 0.7)
Tumor Size			
<20 mm	0.7 (0.6 to 0.8)	0.3 (0.2 to 0.4)	0.8 (0.6 to 1.2)
21 to 30 mm	1.1 (0.1 to 9.5)	0.5 (0.1 to 3.7)	0.9 (0.6 to 1.2)
31 to 35 mm	0.2 (0.0 to 2.1)	0.1 (0.0 to 1.2)	0.9 (0.6 to 1.2)
31 to 50 mm	0.8 (0.7 to 0.9)	0.1 (0.0 to 0.2)	0.5 (0.3 to 0.6)

[a]Results for inverse of probability treatment-weighted adjusted population shown.
CI: confidence interval; HR: hazard ratio; LT: liver transplantation; RFA: radiofrequency ablation; SR: surgical resection.
Adapted from Zhao et al (2019)[15,]

Additional observational studies published since the systematic reviews have reported inconsistent results, with some finding no difference in survival outcomes between RFA and resection[16,17,] and some finding resection to be superior to RFA, particularly in cases with tumor sizes measuring between 3 and 5 cm, though some studies favored resection in smaller tumors as well.[18,19,20,21,22,23,]

Section Summary: Radiofrequency Ablation to Treat Primary, Operable Hepatocellular Carcinoma

The evidence on RFA as a primary treatment for primary, operable HCC includes meta-analyses of RCTs and/or retrospective observational studies, RCTs, and additional observational studies. Numerous meta-analyses have shown that patients undergoing surgical resection experienced longer survival outcomes and lower recurrence rates than patients receiving RFA, though complication rates were higher with surgical resection. Some meta-analyses of specifically selected populations (eg, small tumor sizes or Child-Pugh Class A liver function or HCC within the Milan criteria) found that OS and DFS rates were not significantly different between RFA and surgical resection. A 2024 RCT found similar results in a similarly specifically selected population, but was limited by its sample size and single-center design. A 2025 RCT also did not demonstrate that surgery was superior to RFA for small HCC. Generally, results from meta-analyses were limited by heterogeneous populations and a lack of randomization, leading to potential selection bias. Results from observational studies have suggested that RFA alone or RFA plus PEI could be as effective as a resection for small HCC tumors. However, other studies have found resection to be superior to RFA for survival outcomes regardless of tumor size. An exact tumor cutoff size has

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not been established; however, some studies have shown that survival outcomes following RFA and resection for tumors 3 cm or smaller may be similar, while survival outcomes for tumors 3.1 to 5 cm may favor resection.

RADIOFREQUENCY ABLATION AS A PRIMARY TREATMENT OF INOPERABLE HEPATOCELLULAR CARCINOMA

Clinical Context and Therapy Purpose

The purpose of RFA is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as systemic therapy and other locally ablative techniques, in individuals with inoperable HCC.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with inoperable HCC. Examples of individuals not eligible for hepatic resection include those with inadequate liver function, presence of major vascular invasion, and presence of extrahepatic metastases.

Interventions

The therapy being considered is RFA.

Comparators

Comparators of interest include systemic therapy and other locally ablative techniques. For individuals with liver-confined disease, locoregional therapies are the preferred treatment option (eg, PEI, cryoablation, TACE, external beam radiation therapy). Systemic therapy is considered for those with advanced disease, especially if an individual has progressed after receiving locoregional therapies or if they have extrahepatic metastases. Potential first-line systemic options include sorafenib, lenvatinib, and FOLFOX (folinic acid, fluorouracil, and oxaliplatin).

Outcomes

The general outcomes of interest are OS, disease-specific survival, change in disease status, and morbid events (Table 11).

Table 11. Outcomes of Interest for Individuals with Inoperable Hepatocellular Carcinoma

Outcomes	Details
Overall survival	Survival or mortality rate [Timing: 6 months to 3 years]
Change in disease status	Local/tumor recurrence [Timing: 1 year to 3 years] Tumor progression [Timing: 1 year to 3 years]
Morbid events	Complications [Timing: peri- or post-procedure]

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

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- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
The evidence on the use of RFA as a primary treatment option for inoperable HCC includes RCTs comparing RFA with other nonsurgical interventions, RFA as an adjunct to chemotherapy, and systematic reviews of the RCTs.

Systematic Reviews
A TEC Assessment (2003) addressed RFA for the treatment of unresectable primary or metastatic liver tumors.[24,] Since that report, many systematic reviews and meta-analyses have assessed RFA for HCC. Several are discussed below.

Cheng et al (2023) performed a systematic review and meta-analysis of 26 studies with locally ablative therapies in patients with inoperable HCC (RFA, microwave ablation, stereotactic ablative radiotherapy, and particle radiotherapy).[25,] For the primary outcome of local control, microwave ablation and particle radiotherapy showed improved outcomes compared to RFA (both p<.001). Regional progression was also significantly better with microwave ablation (p=.002) and particle radiotherapy (p=.036) compared to RFA. Distant progression was better with stereotactic ablative radiotherapy and particle radiotherapy compared to RFA (p<.001 and p=.002, respectively). The highest overall survival at 2, 3, and 4 years was with RFA, which was statistically similar to microwave ablation but superior to the other 2 therapies.

Yu et al (2021) performed a meta-analysis of RCTs comparing RFA with microwave ablation for the treatment of localized, very early- or early-stage HCC.[26,] Five RCTs comparing RFA (n=413) and microwave ablation (n=431) were identified. The OS between microwave ablation and RFA was not significantly different at 1 year (OR, 0.705; 95% CI, 0.382 to 1.301) or 3 years (OR, 0.972; 95% CI, 0.615 to 1.538). Similarly, there was no difference observed in recurrence-free survival between microwave ablation and RFA at 1 year (OR, 1.167; 95% CI, 0.568 to 2.396) and 3 years (OR, 0.981; 95% CI, 0.616 to 1.562). Among the procedure-related complications evaluated, there were no statistically significant differences between the 2 groups.

Han et al (2020) also evaluated RFA compared with microwave ablation for early-stage HCC in a meta-analysis, but included both RCT and observational trial data.[27,] There were 5 RCTs, 1 prospective cohort, and 20 retrospective cohorts included in the analysis, providing data for 2393 patients treated with RFA and 2003 treated with microwave ablation. The median 1-year, 3-year, and 5-year OS rates were 93.3%, 71.3%, and 57.4%, respectively, in the microwave ablation group compared with 89.5%, 68.1%, and 55.5%, respectively, in the RFA group. Pooled HR for OS did not show any difference between microwave ablation versus RFA (HR, 0.891; 95% CI, 0.740 to 1.072). There was also no difference observed between groups for DFS (HR, 1.014; 95% CI, 0.811 to 1.209).

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Majumdar et al (2017) published a Cochrane review and network meta-analysis on the management of early and very early-stage HCC.[28,] Reviewers included 14 RCTs (N=2533 patients with unresectable HCC) of nonsurgical treatments compared with each other, sham, or no intervention in patients. The quality of the evidence was rated as low or very low for all outcomes. Follow-ups ranged from 6 to 37 months. Compared with RFA, mortality was higher for percutaneous acetic acid injection (HR, 1.8; 95% CI, 1.1 to 2.8; 1 trial; n=125) and PEI (HR, 1.49; 95% CI, 1.2 to 1.9; 5 trials; n=882). No trials reported health-related quality of life.

Shen et al (2013) conducted a systematic review of 4 RCTs and quasi-RCTs (N=766 patients), comparing RFA with PEI for the treatment of HCC nodules up to 3 cm.[29,] Overall survival was significantly longer for RFA than for PEI at 3 years (HR, 0.66; 95% CI, 0.48 to 0.90; p=.009), and local recurrence risk was lower with RFA (HR, 0.38; 95% CI, 0.15 to 0.96; p=.040). However, there was no difference in distant intrahepatic recurrence, and RFA resulted in more complications.

Tiong and Maddern (2011) conducted a systematic review of the literature from 2000 to 2010 and a meta-analysis of survival and disease recurrence after RFA for HCC.[30,] Studies reporting on patients with HCC who were treated with RFA, either in comparison to or in combination with other interventions (eg, surgery, PEI), were eligible for inclusion. Outcomes were OS, DFS, and disease recurrence rates. Only RCTs, quasi-RCTs, and nonrandomized comparative studies with more than 12 months of follow-up were included. Forty-three articles, including 12 RCTs, were selected for review. Most articles reported on the use of RFA for unresectable HCC, often in combination with other treatments (eg, PEI, TACE, surgery). A meta-analysis of 5 RCTs showed that RFA was better than PEI, with higher OS and DFS rates. Data comparing RFA with microwave ablation were inconclusive. Reviewers concluded that RFA could achieve good clinical outcomes for unresectable HCC.

In a meta-analysis comparing RFA with cryoablation for HCC, Huang et al (2013) evaluated 3 prospective studies and 1 retrospective study.[31,] Included in the studies were 180 RFA and 253 cryoablation patients. RFA was significantly superior to cryoablation in complication rates (OR, 2.80; 95% CI, 1.54 to 5.09), local recurrence rates (OR, 4.02; 95% CI, 1.93 to 8.39), and local tumor recurrence rates (OR, 1.96; 95% CI, 1.12 to 3.42). However, mortality rates did not differ significantly (OR, 2.21; 95% CI, 0.45 to 10.8) between groups.

Randomized Controlled Trials

Sugimoto et al (2024) conducted an RCT that compared RFA to microwave ablation in patients (N=236) with HCC tumors up to 4 cm who were not surgical candidates.[32,] Local progression after 2 years of follow-up was lower with microwave ablation compared to RFA (16.4% vs. 30.4%; p=.007). There was no difference between groups in OS or recurrence-free survival.

Giorgio et al (2016) conducted an RCT comparing RFA plus chemotherapy with chemotherapy alone in 99 patients who had unresectable HCC invading the portal vein.[33,] The HCC nodules ranged in size from 2.1 to 6.5 cm. The primary outcome was OS at 3 years. The OS rates at 1, 2, and 3 years were 60%, 35%, and 26% in the combined therapy group and 37% and 0% at 1 and 2 years in the chemotherapy-alone arm (HR, 2.87; 95% CI, 1.61 to 5.39), respectively.

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Section Summary: Radiofrequency Ablation as a Primary Treatment of Inoperable Hepatocellular Carcinoma
Randomized and nonrandomized trials have compared RFA with alternative treatments for HCC in individuals ineligible for surgery. Meta-analyses comparing RFA to other local ablative therapies have found that RFA and microwave ablation are similarly effective, that RFA is more effective than PEI, and that RFA may be better than cryoablation. The evidence comparing RFA with TACE is limited, and no conclusions can be drawn. Radiofrequency ablation has also been shown to improve survival in patients with unresectable HCC as an adjunct to chemotherapy. Overall, the evidence supports the use of RFA in patients who are inoperable.

RADIOFREQUENCY ABLATION FOR INOPERABLE HEPATOCELLULAR CARCINOMA AS A BRIDGE TO LIVER TRANSPLANT

Clinical Context and Therapy Purpose
The purpose of RFA is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as other locoregional therapies, in individuals with inoperable HCC awaiting a liver transplant.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with inoperable HCC awaiting a liver transplant.

Interventions
The therapy being considered is RFA.

Comparators
Comparators of interest include other locoregional therapies. Potential locoregional therapies include ablative strategies (eg, PEI, cryoablation), arterially directed therapies (eg, TACE), and radiation therapy (eg, external beam radiation therapy).

Outcomes
The general outcomes of interest are OS, disease-specific survival, and change in disease status (Table 12). The goal of receiving bridge therapy is to reduce tumor progression and the dropout rate while waiting for liver transplantation.

Table 12. Outcomes of Interest for Individuals with Inoperable Hepatocellular Carcinoma Awaiting Liver Transplant

Outcomes	Details
Overall survival	Survival rate [Timing: ≤10 years]
Disease-specific survival	Posttransplant relapse-free survival [Timing: ≤5 years]
Change in disease status	Tumor progression/de-listed rated [Timing: 3 months to 4 years] Tumor downgrading rate Posttransplant tumor recurrence Waitlist dropout rate

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Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
In 2002, the United Network for Organ Sharing (UNOS) introduced a new liver allocation system-Model for End-stage Liver Disease (MELD)-for adults awaiting a liver transplant; MELD was most recently reaffirmed in 2024.[34,] In considering how to allocate donor organs, UNOS sought to balance the risk of death on the waiting list against the risk of tumor recurrence after transplant. Under UNOS criteria, patients with T1 lesions (1 nodule ≤1.9 cm) are considered at low-risk of death while on the waiting list, and those with T3 lesions (1 nodule >5 cm, or 2 or 3 nodules with at least 1 nodule >3 cm) are at high-risk of posttransplant recurrence. Patients with T2 tumors (1 nodule 2 to 5 cm, or 2 or 3 nodules 1 to 3 cm) are more likely to die while on the waiting list than those with T1 lesions and carry an acceptable risk of post-transplant tumor recurrence. Therefore, UNOS criteria prioritize T2 HCC and makes a standardized MELD exception if the patient has an alpha-fetoprotein level >1000 ng/mL at any time or ≤1000 ng/mL and meets Milan criteria. The definition of T2 lesions is also referred to as the Milan criteria.[35,] Liver transplants for patients with T3 HCC are not prohibited but these patients do not receive priority on the waiting list. All patients with HCC awaiting transplantation are reassessed at 3-month intervals. Those whose tumors have progressed and are no longer T2 tumors lose allocation points.

The UNOS allocation system incentivizes the use of locoregional therapies for 2 purposes: (1) to prevent the progression of T2 tumors while on the waiting list and (2) to downsize T3 tumors to T2 status to meet the UNOS criteria for additional allocation points.

Pomfret et al (2010) summarized findings and recommendations from a national conference on outcomes of liver transplantation for patients with HCC.[36,] The workgroup on locoregional therapy found compelling evidence that pretransplant locoregional therapy decreases waitlist dropout, especially for patients who wait more than 3 to 6 months for a transplant. The group noted that "there is a paucity of data comparing RFA with transarterial therapies for the treatment of HCC prior to liver transplant and most single-center trials have a mixture of [locoregional therapies] included in the study population" and that, while early studies have suggested a high rate of tumor seeding with percutaneous RFA, it is rare in larger series from experienced centers. The workgroup considering evidence to support the expansion of MELD criteria for patients with HCC reported wide regional variation in the risk of death for patients without HCC. The "MELD score of the non-HCC patients was quite low in some regions. Posttransplant survival in HCC patients ranged from 25% in regions with few non-HCC patients with high MELD scores to greater than 70% in regions in which there was a greater need for liver transplant (higher MELD scores) in the

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non-HCC population." The workgroup observed that there is extreme variability in the time to transplantation of patients with HCC in the United States, suggesting that management of patients on the waitlist and outcomes may vary. Additionally, "[c]oncern has been raised that short times to liver transplant may lead to an increase in posttransplant recurrence because the tumor biology [aggressiveness] has not had enough time to be expressed. The lack of national data on recurrence rates limits one's ability to study this national experiment of nature based on the divergent waiting times for transplantation for HCC." There was a consensus for the development of a calculated continuous HCC priority score for ranking HCC candidates on the list that would incorporate the calculated MELD score, α-fetoprotein, tumor size, and rate of tumor growth. Only candidates with at least stage T2 tumors would receive additional HCC priority points. Pomfret et al (2010) also discussed pretransplant locoregional therapy to allow patients to maintain transplant candidacy and to downstage tumors to meet MELD criteria.

OBSERVATIONAL STUDIES

Radiofrequency Ablation to Prevent Tumor Progression

Several studies have reported dropout rates of waitlisted patients treated with locoregional therapy. However, lacking controlled data, it is difficult to assess the contributions of locoregional therapy to time on the waiting list. Additionally, in 2002, as previously discussed, UNOS revised its liver allocation policy, such that wait times for patients with HCC meeting the Milan criteria have now declined. Given these limitations, the following case series and cohort studies have been reported.

Lee et al (2017) reported on a 10-year intention-to-treat analysis of RFA to prevent progression and reduce the chance of posttransplant HCC.[37,] Patients were selected for analysis if they had cirrhosis with treatment-naive HCC, were on the transplant waiting list, and had RFA as a stand-alone treatment. Only tumors that could safely be treated with a 5 mm margin received RFA. Of 1016 patients who had HCC and were on the transplant waiting list, 121 were treated with RFA and were included in this analysis. Patients returned for follow-up imaging every 3 to 6 months. The outcomes of interest were the dropout rate from the waitlist, posttransplant recurrence, and OS at 10 years. The mean time on the waiting list was 10.2 months (range, 0.3 to 38 months). At the end of follow-up, 89 (73.6%) patients had undergone a liver transplant, 16 (13.2%) were delisted, 14 (11.6%) died, and 2 (1.7%) remained on the waitlist. The number of patients delisted due to the tumor was 9 (7.4%). Intention-to-treat analysis of all patients estimated 8-year OS at 60.0% and disease-specific survival at 89.5%.

Mazzaferro et al (2004) presented 50 patients with HCC who underwent RFA while awaiting transplantation; no patient had to be removed from the waiting list due to tumor progression over a mean wait time of 9.5 months.[38,] The median tumor size was 3 cm, and 80% of patients met the Milan criteria. Similarly, Lu et al (2005) reported on 52 patients who underwent RFA as a bridge to transplantation, 42 of whom met the Milan criteria.[39,] After a mean of 12 months, 5.8% had dropped off the waiting list due to tumor progression.

Porrett et al (2006) retrospectively compared 31 patients treated using RFA with 33 untreated controls.[40,] Study endpoints included OS and DFS, tumor recurrence, explant tumor viability, and the ability of magnetic resonance imaging to detect viable tumors after therapy. Both cohorts had similar demographic, radiographic, and pathologic characteristics, although untreated patients waited longer for transplantation (119 days [untreated] vs. 54 days [RFA] after MELD

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assignment; p=.05). Only 20% of treated tumors demonstrated complete ablation (necrosis) as defined by histologic examination of the entire lesion. Only 55% of lesions with histologic viable tumors were detected by magnetic resonance imaging after pretransplant therapy. After 36 months of follow-up, there was no difference between the treated and the untreated groups in OS (84% vs. 91%), DFS (74% vs. 85%), cancer recurrence (23% vs. 12%), or mortality from cancer recurrence (57% vs. 25%) rates, all respectively p>.1. The authors concluded that viable tumor frequently persists after pretransplant locoregional therapy, and neoadjuvant treatment does not appear to improve posttransplant outcomes in the current MELD era.

Radiofrequency Ablation to Downgrade Hepatocellular Carcinoma

Yao et al (2008) analyzed longer-term outcomes data on HCC downstaging in a cohort of 61 patients with tumor stage exceeding T2 criteria enrolled between 2002 and 2007.[41,] Eligibility criteria for downstaging included the following: (1) 1 lesion between 5 and 8 cm; (2) 2 to 3 lesions with at least 1 lesion between 3 and 5 cm, with total tumor diameter up to 8 cm; or (3) 4 to 5 lesions with none greater than 3 cm, with total tumor diameter up to 8 cm. The main methods used were TACE and laparoscopic RFA either alone or in combination as follows: 11 patients received laparoscopic RFA alone, 14 received TACE and laparoscopic RFA, and 9 received TACE and percutaneous RFA. A minimum observation period of 3 months after downstaging was required before liver transplant. Tumor downstaging was successful in 43 patients (70.5%). Thirty-five (57.4%) patients received a liver transplant, including 2 with live-donor liver transplantation. Treatment failure was observed in 18 (29.5%) patients, primarily due to tumor progression. In the explant of 35 patients who underwent a transplant, 13 had complete tumor necrosis, 17 met T2 criteria, and 5 exceeded T2 criteria. The Kaplan-Meier intention-to-treat survival rates at 1 and 4 years after downstaging were 87.5% and 69.3%, respectively. The 1- and 4-year posttransplantation survival rates were 96.2% and 92.1%, respectively. No patient had HCC recurrence after a median posttransplantation follow-up of 25 months. The only factor predicting treatment failure was pretreatment α-fetoprotein level greater than 1000 ng/mL. From this small series, the authors concluded that successful downstaging could be achieved with excellent posttransplant outcomes.

Yao et al (2005) also reported on a case series of 30 patients with HCC who underwent locoregional therapy specifically to downstage tumors to meet the University of California San Francisco (UCSF) criteria (see below for brief discussion of the UCSF criteria).[42,] Eligibility for locoregional therapy seeking to downstage patients included either (1) 1 nodule between 5 and 8 cm in diameter; (2) 2 or 3 nodules with at least 1 between 3 and 5 cm in diameter, with a sum of diameters no greater than 8 cm; or (3) 4 or 5 nodules all 3 cm or less, with a sum of diameters less than 8 cm. Among the 30 patients, 21 (70%) met the criteria for locoregional therapy and 16 of them were successfully downstaged and underwent transplantation. No tumors recurred at a median follow-up of 16 months. The authors concluded that downstaging could be successfully achieved in most patients but that data on tumor recurrence required longer follow-up.

Radiofrequency Ablation to Reduce Risk of Recurrence

An additional indication for locoregional therapies has focused on their use to reduce the incidence of recurrence posttransplant. If the incidence of recurrence can be reduced, then advocates have argued that the UNOS allocation criteria should not discriminate against patients with larger tumors.[43,44,45,46,47,] Some patients with T3 lesions are cured with a liver transplant, although most experience tumor recurrence. For example, in the seminal study, Mazzaferro et al (1996)[35,] reported that 4-year recurrence-free survival was 92% in those who met the Milan

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criteria compared with 59% in those who did not; additional studies have confirmed this difference in the recurrence-free survival rate.[42,] However, other institutions have reported similar outcomes with expanded criteria. For example, Yao et al (2002) reported similar recurrence-free survival rates after transplant in patients with T2 tumors and a subset of those with T3 tumors.[45,] This T3 subset was defined as a single lesion 6.5 cm or less or 3 or fewer lesions with none greater than 3 cm and with a sum of tumor diameters of 8 cm or less. These expanded criteria are known as the UCSF criteria.

The question is whether locoregional therapies (including both RFA and chemoembolization) decrease the recurrence rate in patients meeting the UCSF criteria. The authors also compared the recurrence-free survival rates of those who did and did not receive locoregional therapy. For those with T2 lesions, recurrence rates were similar whether or not the patient received locoregional therapy. However, for T3 lesions (including both T3A and T3B), the 5-year recurrence-free survival rate was 85.9% for those who received locoregional therapy compared with 51.4% for those who did not. When data for T2 and T3 lesions were pooled, the 5-year recurrence-free survival rate was 93.8% for those who received locoregional therapy and 80.6% for those who did not. The authors concluded that preoperative locoregional therapy might confer a survival benefit in those with T2 or T3 lesions.

The authors noted several study limitations, including the retrospective nature of the data and the marginal statistical significance of the improved survival, given the small numbers of patients in each subgroup. For example, only 19 patients were in the T3A (ie, UCSF expanded criteria) subgroup. Additionally, no protocol specified which type of locoregional therapy to offer different patients. These therapies are only offered to patients with adequate liver reserve; such patients may have an improved outcome regardless of the preoperative management.

In the 2017 study by Lee et al (2017; described above), of 89 patients with HCC who received RFA before the liver transplant, 5 (5.6%) had HCC recurrence.[37,]

Section Summary: Radiofrequency Ablation for Inoperable Hepatocellular Carcinoma as a Bridge to Liver Transplant

Evidence on the use of RFA for HCC in patients awaiting transplant consists of case series and uncontrolled trials. There is sufficient evidence to conclude that locoregional therapy with RFA or alternatives decreases the dropout rate from the transplant list. This is especially true if patients wait more than 3 to 6 months for a transplant. Therefore, outcomes are improved for this group.

For other uses of RFA in patients awaiting transplant, such as to downgrade tumors for eligibility for transplant, and/or to prevent disease recurrence, the evidence is insufficient to make conclusions.

RADIOFREQUENCY ABLATION FOR INOPERABLE HEPATIC METASTASES OF COLORECTAL ORIGIN

Clinical Context and Therapy Purpose

The purpose of RFA is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as chemotherapy, other locally ablative techniques, and the best supportive care, in individuals with inoperable hepatic metastases of colorectal origin.

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The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with inoperable hepatic metastases of colorectal origin.

Interventions
The therapy being considered is RFA.

Comparators
Comparators of interest include chemotherapy, other locally ablative techniques (eg, microwave ablation, cryoablation, or elecro-coagulation), and the best supportive care.

Outcomes
The general outcomes of interest are OS, disease-specific survival, symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity (Table 13).

Table 13. Outcomes of Interest for Individuals with Inoperable Hepatic Metastases of Colorectal Origin

Outcomes	Details
Overall survival	Survival or mortality rate [Timing: 30 days to 9.7 years]
Disease-specific survival	Disease-free survival [Timing: 30 days to 5 years]
Change in disease status	Progression-free survival [Timing: ≤5 years] Recurrence rate [Timing: ≤5 years]

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
More than half of patients with colorectal cancer (CRC) will develop liver metastases, generally with a poor prognosis.[48,] A median survival of 21 months has been observed in patients with a single CRC liver metastasis; those with several unilobar lesions have a median survival of 15 months, and those with disseminated metastases have a median survival of less than 1 year. A number of first-line systemic chemotherapy regimens have been used to treat metastatic CRC, with a 2-year survival rate of 25% for those treated with 5-fluorouracil or 5-fluorouracil plus leucovorin.[48,] With the introduction of newer agents (eg, irinotecan, oxaliplatin) and targeted drugs (eg, cetuximab, bevacizumab), 2-year survival rates have increased to between 30% and

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39%, with marked improvement in OS. Because the liver is often the only site of metastases from CRC, locoregional therapies have been investigated. Surgical resection is considered the criterion standard for treatment of CRC liver metastases, with 5-year OS rates that historically range from 28% to 38%, but may reach 58% in appropriately selected, resectable patients without the widely disseminated disease.[49,50,] However, only 10% to 25% of patients with CRC metastases are eligible for surgical resection because of the extent and location of the lesions within the liver or because of the presence of comorbid conditions or disseminated disease. Unresectable cases or cases in which surgery is contraindicated typically are treated with systemic chemotherapy, with poor results and considerable adverse events. Alternatively, RFA has been proposed to treat metastatic CRC in the liver.

Systematic Reviews

A meta-analysis by Meijerink et al (2018) compares RFA and microwave ablation to systemic chemotherapy and to partial hepatectomy (PH) for the treatment of colorectal liver metastases.[51,] Forty-eight articles were identified, most of which were observational studies and case series, although 2 RCTs and 8 systematic reviews were included. The authors found 18 observational studies of very low quality that looked at RFA alone compared to PH alone or PH plus RFA. For OS, their analysis concluded that PH alone was superior to RFA alone (HR, 1.78; 95% CI, 1.35 to 2.33). The meta-analysis for 30-day mortality comparing RFA alone to PH alone showed no difference between the 2 interventions (risk ratio [RR], 0.64; 95% CI, 0.21 to 1.95). Disease-free survival was higher for PH alone over RFA alone (HR, 1.49; 95% CI, 1.23 to 1.81), as well as local progression-free survival (HR, 5.36; 95% CI, 1.64 to 17.52). However, complication rates were lower for RFA alone than for PH alone (RR, 0.47; 95% CI, 0.28 to 0.78). One limitation of this review is that the included observational studies were all confounded by indication because RFA was only performed on unresectable lesions. Observational studies are also at increased risk for publication bias.

In a Health Technology Assessment, Loveman et al (2014) found insufficient evidence to draw conclusions on the clinical effectiveness of ablative therapies, including RFA, for liver metastases.[52,]

Weng et al (2012) reported on a meta-analysis comparing RFA with liver resection for the treatment of CRC liver metastases.[53,] One prospective study and 12 retrospective studies were included in the analysis. Overall survival at 3 and 5 years was significantly longer after liver resection than after RFA (RR, 1.38; 95% CI, 1.25 to 1.52 vs. RR, 1.47; 95% CI, 1.28 to 1.69, respectively). Disease-free survival was also significantly longer after liver resection than after RFA at 3 and 5 years (RR, 1.73; 95% CI, 1.48 to 2.03; RR, 2.23; 95% CI, 1.82 to 2.72, respectively). While postoperative morbidity with liver resection was significantly higher than with RFA (RR, 2.49; 95% CI, 1.88 to 3.31), mortality did not differ significantly between treatments. Liver resection also produced significantly better outcomes than RFA when data were analyzed in 3 subgroups: tumors less than 3 cm, solitary tumor, and open or laparoscopic approach. However, hospital stays were significantly shorter (9.2 days vs. 3.9 days; $p<.01$) and rates of complications lower (18.3% vs. 3.9%; $p<.01$) with RFA than with liver resection. Interpretation of the meta-analysis was limited by the retrospective design of most studies.

A systematic review by Pathak et al (2011) assessed the long-term outcome and complication rates of various ablative therapies used in the management of colorectal liver metastases.[34,] The literature search was from 1994 to 2010, and inclusion criteria were a minimum of 1-year follow-

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up and a sample size greater than 10 patients. In all, 75 met inclusion criteria. Most studies were single-arm, single-center, and retrospective or prospective. There was wide variability in patient groups, adjuvant therapies, and management approaches within individual studies. Several studies combined results for colorectal and non-colorectal metastases, often reporting combined outcomes. The endpoints were not reported uniformly, with varying definitions of survival time, recurrence time, and complication rates. Cryotherapy (26 studies) had local recurrence rates ranging from 12% to 39%, with mean 1-, 3-, and 5-year survival rates of 84%, 37%, and 17%, respectively. Major complication rates ranged from 7% to 66%. Microwave ablation (13 studies) had local recurrence rates ranging from 5% to 13%, with mean 1-, 3-, and 5-year survival rates of 73%, 30%, and 16%, respectively, and major complication rates ranging from 3% to 16%. Radiofrequency ablation (36 studies) had local recurrence rates ranging from 10% to 31%, with mean 1-, 3-, and 5-year survival rates of 85%, 36%, and 24%, respectively, and major complication rates ranging from 0% to 33%. Reviewers concluded that ablative therapies offer significantly improved survival compared with palliative chemotherapy alone, with 5-year survival rates ranging from 17% to 24%, and that complication rates of commonly used techniques are low.

A review by Guenette and Dupuy (2010) summarized the literature on the use of RFA for colorectal hepatic metastases.[54,] Seventeen studies with more than 50 patients treated with RFA for colorectal hepatic metastases reported survival. Average tumor size, reported in 15 studies, ranged from 2.1 to 4.2 cm. Five-year OS rates, reported in 12 studies, ranged from 2% to 55.3% (mean, 24.5%). The largest study series (Lencioni et al [2004][50,]) included in the review consisted of 423 patients, with an average tumor size of 2.7 cm, 4 or fewer metastases, each 5 cm or less at the greatest dimension, and no extrahepatic disease. Overall survival rates in that study at 1, 3, and 5 years were 86%, 47%, and 24%, respectively. Guenette and Dupuy concluded that 5-year survival rates following RFA were similar to those following resection, but that long-term data associated with RFA and colorectal hepatic metastases were sparse, as randomized trials had failed recruitment, and patients with the resectable disease should undergo resection if possible. However, given the efficacy of RFA compared with chemotherapy alone, they noted that RFA should be considered a primary treatment option for patients with unresectable disease.

Randomized Controlled Trials

Ruers et al (2012, 2017) published the results of a multicenter RCT that compared RFA plus systemic treatment with systemic treatment alone for unresectable colorectal liver metastases.[55,56,] This RCT, originally designed as a phase 3 study, was completed as a phase 2 study due to slow accrual (N=119). To be included in the trial, patients had to have nonresectable liver metastases with fewer than 10 nodes and without extrahepatic disease. In the experimental arm, RFA, with or without additional resection, was given in combination with systemic therapy. The primary endpoint was a 30-month survival greater than 38% in the experimental arm based on intention-to-treat analysis. At 3 years, OS did not differ significantly between groups (see Table 14). However, there was a significant improvement in progression-free survival (HR, 0.74; 95% CI, 0.42 to 0.95; p=.03) at 3 years, with 10.6% in the systemic therapy arm and 27.6% in the combined treatment arm. At a median follow-up of 9.7 years, 39 (65%) of 60 patients in the combined treatment arm had died compared with 53 (89.8%) of 59 in the systemic treatment arm (HR, 0.58; 95% CI, 0.38 to 0.88; p=.01).

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Table 14. Percent Overall Survival at 3, 5, and 8 Years

Treatment	3 Years (95% CI), %	5 Years (95% CI), %	8 Years (95% CI), %
Combined treatment	56.9 (43.3 to 68.5)	43.1 (30.3 to 55.3)	35.9 (23.8 to 48.2)
Systemic alone	55.2 (41.6 to 66.9)	30.3 (19.0 to 42.4)	8.9 (3.3 to 18.1)

Ruers et al (2017).[56,]
CI: confidence interval.

van der Lei et al (2025) published the COLLISION trial, an international, randomized, controlled, phase 3 noninferiority study comparing thermal ablation with surgical resection for small (≤3 cm) colorectal liver metastases.[57,] Adults with ≤10 liver metastases and no extrahepatic disease were randomized 1:1 to thermal ablation or surgical resection, with the primary outcome of OS assessed in the intention-to-treat population. Among 300 randomized patients (148 per group after exclusions), with a median follow-up of 28.9 months, thermal ablation demonstrated noninferior overall survival versus resection (HR, 1.05; 95% CI, 0.69 to 1.58; p=.83). Local tumor control was also noninferior (HR, 0.13; 95% CI, 0.02 to 1.06; p=0.057), with no significant differences in local tumor progression-free survival, while per-tumor local control favored ablation (HR, 0.09; 95% CI, 0.01 to 0.74; p=.024). Thermal ablation was associated with fewer adverse events (19% vs 46%), fewer serious adverse events (7% vs 20%), and shorter median hospital stay (1 vs 4 days), with no treatment-related deaths in the ablation arm versus three (2%) in the resection arm. The trial was stopped early after meeting predefined criteria for noninferiority and superior safety.

Nonrandomized Comparative Studies

Nonrandomized studies have compared RFA with resection or systemic chemotherapy in patients with localized CRC metastases and no evidence of additional metastatic disease.

Kong et al (2025) conducted a retrospective evaluation of 157 patients with inoperable CRC metastases who received chemotherapy with or without RFA.[58,] Median follow-up was 38 months in the RFA + chemotherapy group, and 23.9 months in the chemotherapy only group. Both OS (34.9 vs. 21.2 months; p<.0001) and progression-free survival (17.16 vs. 8.35 months; p=.00064) were improved in the group that received RFA compared to the group that received chemotherapy only (after propensity score matching). Results without propensity score matching were consistent (OS, p<.0001; progression-free survival, p<.0001).

Sarioglu et al (2024) conducted a single-center, retrospective study of RFA versus microwave ablation for patients (N=242) with CRC liver metastases.[59,] Local recurrence among patients with at least 1 year of follow-up was 29% in the RFA group and 13% in the microwave ablation group (p<.001). Survival analysis among a matched cohort found that local recurrence-free survival was higher with microwave ablation than with RFA (HR, 1.87; 95% CI, 1.30 to 2.68; p=.0005).

Hof et al (2016) analyzed data from 431 patients in an institutional database.[60,] All patients underwent locoregional treatment for hepatic metastases from CRC. Initial treatment was either hepatic resection (n=261), open RFA (n=26), percutaneous RFA (n=75), or a combination of resection plus RFA (n=69). Mean follow-up was 38.6 months. The overall recurrence rate was 83.5% (152/182) in patients treated with RFA compared with 66.6% (201/302) in patients

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treated with hepatic resection (p<.001). The 5-year OS estimate by Kaplan-Meier analysis was 51.9% for RFA and 53% for hepatic resection (p=.98).

Abdalla et al (2004) examined recurrence and survival rates for clinically similar patients treated with hepatic resection only (n=190), resection plus RFA (n=101), RFA only (n=57), open laparotomy with biopsy or systemic chemotherapy alone (n=70).[61,] In the key relevant comparison, RFA versus chemotherapy in chemotherapy-naive patients with nonresectable CRC metastases (median, 1 lesion per patient; range, 1 to 8; median tumor size, 2.5 cm), OS at 4 years was 22% in the RFA group and 10% in the chemotherapy group (p=.005). Median survival was estimated at 25 months in the RFA group and 17 months in the chemotherapy group (p-value not reported). Recurrence at a median follow-up of 21 months was 44% in the RFA group and 11% in the resection-only group (p<.001), although the proportion of patients with distant recurrence as a component of failure was similar (41% resection vs. 40% RFA, p-value not significant).

A consecutive series by Ruers et al (2007) of well-defined, previously untreated patients (N=201) without extrahepatic disease underwent laparotomy to determine the therapeutic approach.[62,] Three groups were identified: patients amenable to hepatic resection (n=117); patients amenable to resection plus local ablation (RFA, n=27; cryoablation, n=18); and patients deemed unresectable and ineligible for local ablation (n=39) who received systemic chemotherapy. Median OS was 61 months (95% CI, 41 to 81 months) in resected patients (median, 1 tumor per patient; range, 1 to 9; median diameter, 3.8 cm), 31 months (95% CI, 20 to 42 months) in locally ablated patients (median, 4 tumors per patient; range, 1 to 19; median diameter, 3 cm), and 26 months (95% CI, 17 to 35 months) in the chemotherapy patients (median, 4 tumors per patient; range, 1 to 17; median diameter, 4 cm; p=.052, ablated vs. chemotherapy). Results from 2 validated quality of life instruments (EuroQol-5D, European Organization for Research and Treatment of Cancer core questionnaire [EORTC QLQ C-30]) showed that patients treated with local ablation returned to baseline values within 3 months, whereas those treated with chemotherapy remained significantly lower (ie, worse quality of life) than the baseline over 12 months posttreatment (p<.05).

Van Tilborg et al (2011) reported on long-term results for 100 patients with unresectable colorectal liver metastases who underwent a total of 126 RFA sessions (237 lesions).[63,] Lesion size ranged from 0.2 to 8.3 cm (mean, 2.4 cm). Mean follow-up was 29 months (range, 6 to 93 months). Major complications (including abscess, hemorrhage, grounding pad burns, and diaphragm perforation) occurred in 8 patients. Factors that determined procedural success included lesion size and the number and location of the lesions. Local tumor site recurrence was 5.6% for tumors less than 3 cm, 19.5% for tumors 3 to 5 cm, and 41.2% for those greater than 5 cm. Centrally located lesions recurred more often than peripheral (21.4% vs. 6.5%, respectively; p=.009). Mean survival from the time of RFA was 56 months (95% CI, 45 to 67 months).

Section Summary: Radiofrequency Ablation for Inoperable Hepatic Metastases of Colorectal Origin

There are no RCTs comparing RFA with alternative treatments for patients with unresectable colorectal liver metastases. However, an RCT of RFA combined with chemotherapy found improved survival at 8 years compared with chemotherapy alone. Additionally, prospective studies have demonstrated that OS following RFA is at least equivalent and likely better than that

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obtained with currently accepted systemic chemotherapy in well-matched patients with unresectable hepatic metastatic CRC who do not have extrahepatic disease. Results from a number of case series have also suggested RFA of hepatic CRC metastases produces long-term survival that is at least equivalent and likely superior to systemic chemotherapy, compared with historical outcomes. Evidence from a comparative study has suggested RFA has fewer deleterious effects on quality of life than chemotherapy and that RFA patients recover their quality of life significantly faster than chemotherapy patients. Patient selection bias may partially explain the better outcomes in the case series because patients chosen to receive RFA might have had better prognoses than patients given chemotherapy.

RADIOFREQUENCY ABLATION FOR INOPERABLE HEPATIC METASTASES OF NEUROENDOCRINE ORIGIN

Clinical Context and Therapy Purpose

The purpose of RFA is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as chemotherapy, other locally ablative techniques, and the best supportive care, in individuals with inoperable hepatic metastases of neuroendocrine origin.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with inoperable hepatic metastases of neuroendocrine origin.

Interventions

The therapy being considered is RFA.

Comparators

Comparators of interest include chemotherapy, other locally ablative techniques (eg, cryoablation), and the best supportive care.

Outcomes

The general outcomes of interest are OS, disease-specific survival, symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity (Table 15).

Table 15. Outcomes of Interest for Individuals with Inoperable Hepatic Metastases of Neuroendocrine Origin

Outcomes	Details
Overall survival	Survival rate [Timing: ≤11 years]
Symptoms	Symptom relief [Timing: ≤27 months]
Change in disease status	Local recurrence rate [Timing: ≤11 years]

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

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- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Below is a discussion of a systematic review and several case series which were not included in the systematic review or published after the systematic review.

Systematic Reviews
A systematic review of RFA as a treatment for unresectable metastases from neuroendocrine tumors was published by Mohan et al (2015).[64,] Seven unique studies (N=301), all retrospective case series from a single institution, were included. The most common tumor type was carcinoid (59%), followed by nonfunctional pancreatic tumors (21%) and functional pancreatic tumors (13%). There were 2 periprocedural deaths (rate, 0.7%), and the overall complication rate was 10%, including hemorrhage, abscess, viscus perforation, bile leak, biliopleural fistula, transient liver insufficiency, pneumothorax, grounding pad burn, urinary retention, pneumonia, and pleural effusion. Improvement in symptoms was reported in 92% (117/127) of symptomatic patients, with a median duration of relief ranging from 14 to 27 months. There was a high degree of variability in the length of follow-up and surveillance, and a wide range of local recurrence rates, from less than 5% to 50%; 5-year survival rates ranged from 57% to 80%.

Case Series
Fairweather et al (2017) compared OS in patients with neuroendocrine liver metastases (N=649) from a large prospective database.[65,] Primary treatment modalities included: systemic therapy (n=316), chemoembolization (n=130), observation (n=117), surgical resection (n=58), and RFA (n=28). The most favorable 10-year OS estimates were achieved with surgical resection (70%), followed by RFA (55%), systemic therapy (31%), chemoembolization (28%), and observation (20%).

Berber and Siperstein (2008) analyzed a large series of liver tumors treated with RFA.[66,] Of 1032 tumors assessed, 295 were neuroendocrine tumor metastases. The mean number of lesions treated was 5.6 (range, 1 to 16 lesions) and mean lesion size was 2.3 cm (range, 0.5 to 10 cm). Local recurrence rates were lower in patients with neuroendocrine tumors than in patients with other tumor types: neuroendocrine tumors (19/295 [6%]); colorectal metastases (161/480 [24%]); non-colorectal, non-neuroendocrine metastases (28/126 [22%]); and HCC (23/131 [18%]). In patients with neuroendocrine tumors, 58% of the recurrences were evident at 1 year and 100% at 2 years versus 83% at 1 year and 97% at 2 years for colorectal metastases. Seven of the 8 neuroendocrine tumors were eligible for repeat RFA. Symptom control and survival were not reported.

Mazzaglia et al (2007) reported on a series collected over 10 years for 63 patients with neuroendocrine metastases treated with 80 sessions of RFA.[67,] Tumor types were 36 carcinoids, 18 pancreatic islet cell, and 9 medullary thyroid cancer. Indications for study enrollment were liver metastases from neuroendocrine tumors, enlarging liver lesions, worsening of symptoms,

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and/or failure to respond to other treatment modalities and the predominance of liver disease. Patients with the additional minor extrahepatic disease were not excluded. Radiofrequency ablation was performed 1.6 years (range, 0.1 to 7.8 years) after diagnosis of liver metastases. Fourteen patients had repeat sessions for disease progression. The mean number of lesions treated in the first RFA session was 6 (mean tumor size, 2.3 cm). One week after surgery, 92% of patients had at least partial symptom relief, and 70% had complete relief. Symptom control lasted 11 months. Median survival times were 11 years postdiagnosis of the primary tumor, 5.5 years postdiagnosis of the neuroendocrine hepatic metastases, and 3.9 years after the first RFA treatment.

Section Summary: Radiofrequency Ablation for Inoperable Hepatic Metastases of Neuroendocrine Origin

The evidence on RFA for patients with inoperable liver metastases of neuroendocrine origin consists of case series and a systematic review of case series. Most reports of RFA treatment for neuroendocrine liver metastases include small numbers of patients or subsets of patients in reports of multiple ablative methods or very small subsets of larger case series of patients with various diagnoses. The available evidence has indicated that durable tumor and symptom control of neuroendocrine liver metastases can be achieved by RFA in individuals whose symptoms are not controlled by systemic therapy or who are ineligible for surgical resection.

RADIOFREQUENCY ABLATION FOR HEPATIC METASTASES NOT OF COLORECTAL OR NEUROENDOCRINE ORIGIN

Clinical Context and Therapy Purpose

The purpose of RFA is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as chemotherapy, other locally ablative techniques, other therapy, and the best supportive care, in individuals with hepatic metastases not of colorectal or neuroendocrine origin.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with hepatic metastases not of colorectal or neuroendocrine origin.

Interventions

The therapy being considered is RFA.

Comparators

Comparators of interest include chemotherapy, other locally ablative techniques, other therapy, and the best supportive care. Specific comparators would be dependent on the underlying origin and treatment options.

Outcomes

The general outcomes of interest are OS, disease-specific survival, symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity (Table 16).

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Table 16. Outcomes of Interest for Individuals with Hepatic Metastases Not of Colorectal or Neuroendocrine Origin

Outcomes	Details
Overall survival	Survival rate [Timing: 1 year to 5 years]
Change in disease status	Tumor recurrence rate [Timing: ≤5 years] Tumor progression rate [Timing: ≤5 years]

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

SYSTEMATIC REVIEW

Breast Cancer

Rangarajan et al (2023) conducted a systematic review of patient-level data from 54 studies of treatments for breast cancer liver metastases.[68,] Chemotherapy (n=3062), surgery (n=2063), and RFA (n=305) resulted in 1-year survival of 53%, 90%, and 83%, respectively. Survival at 3 and 5 years had similar trends (24%, 65.9%, and 49%, respectively and 14%, 53%, and 35%, respectively).

OBSERVATIONAL STUDIES

Breast Cancer

A number of case series have reported on the use of RFA to treat breast cancer related to liver metastases.

Schullian et al (2021) reported on local control and long-term outcomes in 42 female patients treated with stereotactic RFA for breast cancer liver metastases.[69,] Race and ethnicity of patients included were not described. The procedures were performed at a single center covering 110 breast cancer liver metastases (median tumor size, 3 cm) in 48 ablation sessions. Additionally, 18 (42.9%) patients had extrahepatic metastasis. The technical success rate was 100%, and 107 of the 110 liver metastases were successfully ablated on the first RFA. Four grade 1 (arterial bleeding from subcapsular liver vessels) and 1 grade 2 (major pleural effusion) periprocedural complications occurred. Local recurrence developed in 7.3% of the tumors after a median imaging follow-up of 10.9 months. The 1-year, 3-year, and 5-year OS rates from the date of the first RFA were 84.1%, 49.3%, and 20.8%, respectively, with a median OS of 32.3 months (95% CI, 20.6 to 50.3). The 1-year, 3-year, and 5-year DFS rates from the date of the first RFA were

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45.3%, 22.3%, and 15.9%, respectively, with a median OS of 10.5 months (95% CI, 6.8 to 25.0).

Veltri et al (2014) analyzed 45 women treated with RFA for 87 breast cancer liver metastases (mean size, 23 mm).[70,] Race and ethnicity of patients included were not described. Complete ablation was seen on initial follow-up in 90% of tumors, but the tumor recurrence rate was 19.7% within 8 months. Radiofrequency ablation did not impact OS rates at 1 year (90%) or at 3 years (44%).

In a retrospective review, Meloni et al (2009) assessed local control and intermediate- and long-term survival in 52 patients.[71,] Inclusion criteria were fewer than 5 tumors, maximum tumor diameter of 5 cm, and disease confined to the liver or stable with medical therapy. The race and ethnicity of patients included were not described. Complete tumor necrosis was achieved in 97% of tumors. Median time to follow-up from diagnosis of liver metastasis and from RFA was 37.2 months and 19.1 months, respectively. Local tumor progression occurred in 25% of patients, and new intrahepatic metastases developed in 53%. Median OS, from the time of first liver metastasis diagnosis, was 42 months, and the 5-year survival rate was 32%. Patients with tumors 2.5 cm or larger in diameter had a worse prognosis than those with smaller tumors. Survival rates were comparable to those reported in the literature for surgery or laser ablation.

In another series of 43 breast cancer patients with 111 liver metastases, Jakobs et al (2009) reported that tumor ablation was successful in 107 (96%) metastases.[72,] Race and ethnicity of patients included were not described. During follow-up, local tumor progression was observed in 15 metastases. Estimated median OS was 58.6 months. Survival was significantly lower among patients with extrahepatic disease, except for skeletal metastases.

Gastric Cancer
Li et al (2017) conducted a retrospective cohort study to compare surgical resection (n=46) with RFA and/or TACE (n=73) in the treatment of patients with gastric cancer with liver metastases.[73,] Overall survival rates at 1, 3, and 5 years were significantly better in patients undergoing surgical resection compared with patients receiving RFA and/or TACE (1-year: 80.5% vs. 85.4%; 3-year: 41.5% vs. 21.9%; 5-year: 24.4% vs. 12.2%, respectively). There was no difference in OS between patients receiving RFA only and patients receiving TACE only.

Nasopharyngeal Cancer
Li et al (2017) conducted a propensity score matching analysis on 37 pairs of patients receiving chemotherapy plus RFA or chemotherapy alone for nasopharyngeal cancer with oligometastases in the liver.[74,] Results showed improved OS and progression-free survival when RFA was combined with chemotherapy (HR, 0.53; 95% CI, 0.30 to 0.93) compared with chemotherapy alone (HR, 0.60; 95% CI, 0.36 to 0.97).

Ovarian Cancer
Liu et al (2017) presented a case series of 11 patients (22 metastases) receiving ultrasound-guided RFA for the treatment of liver metastasis from ovarian cancer.[75,] Race and ethnicity for patients included were not described. They reported 100% complete ablation of the lesions and 1-, 3-, and 5-year OS rates of 100%, 61%, and 61%, respectively.

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Pancreatic Cancer

Hua et al (2017) conducted a retrospective analysis of 102 patients with pancreatic cancer and synchronous liver oligometastases who had undergone RFA.[76,] Race and ethnicity for patients included were not described. The 1-year survival rate was 47%, with a median OS of 11.4 months. A multivariate regression analysis found that metastatic tumors between 3 and 5 cm predicted poorer survival.

Sarcoma

Jones et al (2010) evaluated RFA in a series of patients with sarcoma.[77,] Thirteen gastrointestinal stromal tumor patients and 12 with other histologic subtypes received RFA for metastatic disease of the liver: 12 responded to the first RFA procedure and 1 patient achieved stable disease. Two gastrointestinal stromal tumor patients received RFA on 2 occasions for separate lesions within the liver, and both responded to the second RFA procedure. Of the other subtypes, 7 patients underwent RFA to liver lesions, of whom 5 responded to RFA, 1 progressed, and another was not assessable at the time of analysis. Radiofrequency ablation was well-tolerated in this series. Radiofrequency ablation might have a role in patients with a gastrointestinal stromal tumor who have a progression of a single metastasis but stable disease elsewhere.

A case series of 66 patients who underwent hepatic resection (n=35), resection and RFA (n=18), or RFA alone (n=13) was reported by Pawlik et al (2006).[78,] After a median follow-up of 35.8 months, 44 patients had a recurrence (intrahepatic only, n=16; extrahepatic only, n=11; both, n=17). The 1-, 3-, and 5-year overall OS rates were 91.5%, 65.4%, and 27.1%, respectively. Analyses suggested that RFA with or without resection was associated with a higher risk of recurrence and lower DFS compared with resection alone.

Section Summary: Radiofrequency Ablation for Hepatic Metastases Not of Colorectal or Neuroendocrine Origin

For hepatic metastases in cancers other than CRC or neuroendocrine tumors, the evidence consists of small nonrandomized comparative studies and small case series. Similar to primary HCC, resection appears to be the most favorable treatment when possible. For patients who are ineligible for resection, RFA may provide a survival benefit; however, the currently available evidence is not sufficient to determine whether RFA improves outcomes.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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American Association for the Study of Liver Diseases
The American Association for the Study of Liver Diseases (AASLD) published a guideline in 2018 on the treatment of hepatocellular carcinoma (HCC),[79,] which was subsequently updated in 2023.[80,] Relevant guidance statements related to radiofrequency ablation (RFA) are listed below:

- "Thermal ablation (radiofrequency or microwave ablation) should be considered the treatment of choice for patients with early-stage HCC ≤3 cm who are ineligible for or decline surgery (Level 1, Strong Recommendation).
    - AASLD does not advise 1 thermal ablative modality over another."

An additional update of this guideline in 2025 did not further address the use of RFA in this setting.[81,]

National Comprehensive Cancer Network
Several National Comprehensive Cancer Network (NCCN) guidelines are relevant to this review.

The NCCN (v1.2026) guidelines on HCC note that "locoregional therapy should be considered in patients who are not candidates for surgical curative treatments, or as part of a strategy to bridge patients for other curative therapies." The guideline further states that "The efficacy of thermal ablation is directly related to tumor size. In well-selected patients with properly located tumors ≤3 cm, ablation should be considered as definitive curative-intent treatment when performed at experienced centers. Local control diminishes for tumors 3 to 5 cm and may require combination approaches or alternative treatments. Ablation is not recommended for tumors >5 cm.. [82,]

The NCCN (v2.2026) guidelines on colon cancer metastatic to the liver state that " Resection is preferred over locally ablative procedures for liver metastases. For small (≤3 cm) thermal ablation is equivalent to resection.".[83,] Of all ablative techniques, the guidelines note that RFA has strong supporting evidence, although newer data suggest that microwave ablation has advantages compared to RFA.

The NCCN (v1.2026) guidelines for neuroendocrine and adrenal tumors state that "percutaneous thermal ablation, often using microwave energy (radiofrequency and cryoablation are also acceptable), can be considered for oligometastatic liver disease, generally up to 4 lesions each smaller than 3 cm. Feasibility considerations include safe percutaneous imaging-guided approach to the target lesions, and proximity to vessels, bile ducts, or adjacent non-target structures that may require hydro- or aero-dissection for displacement." [84,]

Society of American Gastrointestinal and Endoscopic Surgeons
The Society of American Gastrointestinal and Endoscopic Surgeons with the Americas Hepato-Pancreato-Biliary Association developed guidelines (2023) for the use of microwave and radiofrequency liver ablation for the surgical treatment of hepatocellular carcinoma or colorectal liver metastases less than 5 cm.[85,] A systematic review was conducted to address key questions and GRADE methodology was used to provide evidence-based recommendations. All guideline recommendations were assigned "conditional" recommendations based on the weak evidence found. The key questions and subsequent recommendations related to RFA addressed by the guideline are summarized in Table 17.

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Table 17. SAGES/AHPBA recommendations for use of ablative therapy

Key questions addressed by the guideline	Recommendations
Should MWA (laparoscopic or open) vs. RFA (laparoscopic or open) be used for HCC or CRLM less than 5 cm ineligible for other therapies?	The panel suggests MWA and RFA are both safe and feasible. There was insufficient evidence to recommend one modality over another in terms of oncologic outcomes (conditional recommendation, very low certainty of evidence).

AHPBA: Americas Hepato-Pancreato-Biliary Association; MWA: microwave ablation; RFA: radiofrequency ablation; SAGES: Society of American Gastrointestinal and Endoscopic Surgeons.

Society of Interventional Radiology

The Society of Interventional Radiology (2009) published a position statement on percutaneous RFA for the treatment of liver tumors.[86,] The Society indicated that "percutaneous RFA of hepatic tumors is a safe and effective treatment for selected patients with HCC and colorectal carcinoma metastases" and that the current literature does not support any recommendations for or against the use of RFA in other diseases.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 18.

Table 18. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06609434	The Role and Safety of Radiofrequency Ablation in the Multidisciplinary Treatment of Intrahepatic Recurrence After Colorectal Cancer Liver Metastasis Surgery	111	Dec 2026 (not yet recruiting)
NCT06682377	Evaluation of Clinical Efficacy of Radiofrequency Ablation Using Combined RF Energy Delivery Mode and Octopus Electrodes for Hepatocellular Carcinoma: a Prospective Multicenter Study	159	Dec 2025 (active, not recruiting)
NCT06766643	A Prospective, Randomized, Controlled Phase II Clinical Trial of Stereotactic Radiosurgery Versus Radiofrequency Ablation in Primary Liver Cancer in a Special Site of Surgical Evaluation for Non-operable	130	Dec 2026 (recruiting)
NCT05433701	A Phase III Randomized Controlled Non-inferiority Trial to Compare Stereotactic Body Radiotherapy Versus Radiofrequency Ablation for Unresectable, Small (≤ 3 cm) Hepatocellular Carcinoma	178	Dec 2026 (active, not recruiting)
NCT04798898	Improving Survival of COlorectal LIver Metastases by RFA-mediated Immunostimulation	200	Dec 2026 (recruiting)
Unpublished			
NCT03988998	radioFrequency Ablation With or Without RadioTherapy for Small HEpatocellulaR Carcinoma: a Randomized Control Trial	100	Jan 2023 (unknown status)

NCT: national clinical trial.
[a]Denotes sponsorship or cosponsorship by manufacturer

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CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
47370	Laparoscopy, surgical, ablation of one or more liver tumor(s); radiofrequency
47380	Ablation, open, of one or more liver tumor(s); radiofrequency
47382	Ablation, 1 or more liver tumor(s), percutaneous, radiofrequency
76940	Ultrasound guidance for, and monitoring of, parenchymal tissue ablation

REVISIONS	
05-10-2012	Policy added to the bcbsks.com web site.
08-21-2013	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 Diagnosis *(Effective October 1, 2014)*
	Updated Reference section.
10-01-2016	Policy published 09-01-2016. Policy effective 10-01-2016.
	Description section updated
	In Policy section: ▪ In Item A added "there are no more than 3 nodules and" and "(see Policy Guidelines)" to read "Radiofrequency ablation of primary hepatocellular carcinoma (HCC) may be considered medically necessary as a primary treatment of HCC for patients when there are no more than 3 nodules and all tumor foci can be adequately treated (see Policy Guidelines)." ▪ In Item C added "there are no more than 3 nodules or when" to read "Radiofrequency ablation of primary hepatocellular carcinoma (HCC) is considered experimental / investigational when there are more than 3 nodules or when not all sites of tumor foci can be adequately treated." ▪ Added Item E and F "E. Radiofrequency ablation of primary hepatocellular carcinoma (HCC) is considered experimental / investigational when used to downstage (downsize) HCC in patients being considered for liver transplant. F. Radiofrequency ablation may be considered medically necessary as a primary treatment of hepatic metastases 5 cm or less in diameter from colorectal cancer in the absence of extrahepatic metastatic disease when all tumor foci can be adequately treated (see Policy Guidelines section)." ▪ In Item G added "when systemic therapy has failed to control symptoms (see Policy Guidelines section)" to read "Radiofrequency ablation may be considered medically necessary as treatment of hepatic metastases from neuroendocrine tumors in patients

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REVISIONS	
	with symptomatic disease when systemic therapy has failed to control symptoms (see Policy Guidelines section)." ▪ Added Policy Guidelines
	Rationale section updated
	In Coding section: ▪Added CPT Code: 47382 ▪Added ICD-10 Code: C7B.02
	References updated
01-19-2021	Updated Description section
	In Policy section Item A and B combined to new Item A Added • inoperable (e.g., due to location of lesion[s] and/or comorbid conditions), hepatocellular carcinoma (HCC) • Milan criteria (a single tumor of ≤5 cm or up to 3 nodules <3 cm). Item D, F, G combined to make the new Item B Item E combined with new Item C Item H now the new Item E
	In Coding section • Deleted all ICD9 155.0, 155.2, 197.7, 209.71 • Added ICD10 C22.0, C22.9, C7B.02, C78.7
	Updated Rationale section
	Updated References section
08-23-2022	Updated Description Section
	Update Rationale Section
	Updated Coding Section ▪ Removed ICD-10 codes: C22.2, C22.3, C22.4, C22.7, C22.8
	Updated References Section
09-12-2023	Updated Description Section
	Update Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Codes
	Updated References Section
08-27-2024	Updated Description Section
	Update Rationale Section
	Updated References Section
08-26-2025	Updated Description Section
	Update Rationale Section
	Updated References Section
09-08-2026	Updated Description Section
	Update Rationale Section
	Updated References Section

REFERENCES

1. Singh SK, Singh R. Liver cancer incidence and mortality: Disparities based on age, ethnicity, health and nutrition, molecular factors, and geography. Cancer Health Disparities. Mar 2020; 4: e1-e10. PMID 34164612

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

2. Dai LA, Sun M, Li T, et al. Comparison of surgical resection and radiofrequency ablation for the treatment of small hepatocellular carcinoma (≤ 3 cm): an updated meta-analysis. Syst Rev. Jan 19 2026; 15(1): 59. PMID 41549287
3. Yang M, Li G, Chen K, et al. Liver resection versus radiofrequency ablation for solitary small hepatocellular carcinoma measuring ≤3 cm: a systematic review and meta-analysis. Int J Surg. May 01 2025; 111(5): 3456-3466. PMID 39998503
4. Zhang Y, Qin Y, Dong P, et al. Liver resection, radiofrequency ablation, and radiofrequency ablation combined with transcatheter arterial chemoembolization for very-early- and early-stage hepatocellular carcinoma: A systematic review and Bayesian network meta-analysis for comparison of efficacy. Front Oncol. 2022; 12: 991944. PMID 36387091
5. Jia Z, Zhang H, Li N. Evaluation of clinical outcomes of radiofrequency ablation and surgical resection for hepatocellular carcinoma conforming to the Milan criteria: A systematic review and meta-analysis of recent randomized controlled trials. J Gastroenterol Hepatol. Jul 2021; 36(7): 1769-1777. PMID 33569810
6. Shin SW, Ahn KS, Kim SW, et al. Liver Resection Versus Local Ablation Therapies for Hepatocellular Carcinoma Within the Milan Criteria: A Systematic Review and Meta-analysis. Ann Surg. Apr 01 2021; 273(4): 656-666. PMID 33074898
7. Li JK, Liu XH, Cui H, et al. Radiofrequency ablation vs. surgical resection for resectable hepatocellular carcinoma: A systematic review and meta-analysis. Mol Clin Oncol. Jan 2020; 12(1): 15-22. PMID 31814972
8. Zhu GQ, Sun M, Liao WT, et al. Comparative efficacy and safety between ablative therapies or surgery for small hepatocellular carcinoma: a network meta-analysis. Expert Rev Gastroenterol Hepatol. Sep 2018; 12(9): 935-945. PMID 30025486
9. Jia JB, Zhang D, Ludwig JM, et al. Radiofrequency ablation versus resection for hepatocellular carcinoma in patients with Child-Pugh A liver cirrhosis: a meta-analysis. Clin Radiol. Dec 2017; 72(12): 1066-1075. PMID 28851491
10. Feng Q, Chi Y, Liu Y, et al. Efficacy and safety of percutaneous radiofrequency ablation versus surgical resection for small hepatocellular carcinoma: a meta-analysis of 23 studies. J Cancer Res Clin Oncol. Jan 2015; 141(1): 1-9. PMID 24889505
11. Zhang T, Hu H, Jia Y, et al. Efficacy and safety of radiofrequency ablation and surgery for hepatocellular carcinoma in patients with cirrhosis: A meta-analysis. Medicine (Baltimore). Dec 30 2022; 101(52): e32470. PMID 36595979
12. Kawaguchi Y, Hasegawa K, Kashiwabara K, et al. Surgery Versus Ablation for Hepatocellular Carcinoma: A Randomized Controlled Trial (SURF-RCT Trial) and a Nonrandomized Prospective Observational Trial (SURF-Cohort Trial). J Clin Oncol. Aug 10 2025; 43(23): 2628-2638. PMID 40554738
13. Song J, Cao L, Ma K, et al. Laparoscopic liver resection versus radiofrequency ablation for small hepatocellular carcinoma: randomized clinical trial. Br J Surg. Apr 03 2024; 111(4). PMID 38650579
14. Chen S, Peng Z, Lin M, et al. Combined percutaneous radiofrequency ablation and ethanol injection versus hepatic resection for 2.1-5.0 cm solitary hepatocellular carcinoma: a retrospective comparative multicentre study. Eur Radiol. Sep 2018; 28(9): 3651-3660. PMID 29600474
15. Zhao WJ, Zhu GQ, Wu YM, et al. Comparative Effectiveness of Radiofrequency Ablation, Surgical Resection and Transplantation for Early Hepatocellular Carcinoma by Cancer Risk Groups: Results of Propensity Score-Weighted Analysis. Onco Targets Ther. 2019; 12: 10389-10400. PMID 31819521

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Contains Public Information

16. Lee HJ, Kim JW, Hur YH, et al. Combined Therapy of Transcatheter Arterial Chemoembolization and Radiofrequency Ablation versus Surgical Resection for Single 2-3 cm Hepatocellular Carcinoma: A Propensity-Score Matching Analysis. J Vasc Interv Radiol. Sep 2017; 28(9): 1240-1247.e3. PMID 28688816
17. Cucchetti A, Mazzaferro V, Pinna AD, et al. Average treatment effect of hepatic resection versus locoregional therapies for hepatocellular carcinoma. Br J Surg. Nov 2017; 104(12): 1704-1712. PMID 28745399
18. Conticchio M, Inchingolo R, Delvecchio A, et al. Radiofrequency ablation vs surgical resection in elderly patients with hepatocellular carcinoma in Milan criteria. World J Gastroenterol. May 14 2021; 27(18): 2205-2218. PMID 34025074
19. Lee SH, Jin YJ, Lee JW. Survival benefit of radiofrequency ablation for solitary (3-5cm) hepatocellular carcinoma: An analysis for nationwide cancer registry. Medicine (Baltimore). Nov 2017; 96(44): e8486. PMID 29095307
20. Min JH, Kang TW, Cha DI, et al. Radiofrequency ablation versus surgical resection for multiple HCCs meeting the Milan criteria: propensity score analyses of 10-year therapeutic outcomes. Clin Radiol. Jul 2018; 73(7): 676.e15-676.e24. PMID 29709236
21. Lin Y, Pan XB. Differences in Survival Between First-Line Radiofrequency Ablation versus Surgery for Early-Stage Hepatocellular Carcinoma: A Population Study Using the Surveillance, Epidemiology, and End Results Database. Med Sci Monit. May 28 2020; 26: e921782. PMID 32461542
22. Zheng L, Zhang CH, Lin JY, et al. Comparative Effectiveness of Radiofrequency Ablation vs. Surgical Resection for Patients With Solitary Hepatocellular Carcinoma Smaller Than 5 cm. Front Oncol. 2020; 10: 399. PMID 32296638
23. Kim SJ, Jeong WK, Han HJ, et al. Comparison of initial treatments for resectable hepatocellular carcinoma within Milan criteria: an observational study based on a nationwide survey. Ann Surg Treat Res. May 2025; 108(5): 279-294. PMID 40352802
24. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Radiofrequency ablation of unresectable hepatic tumors. TEC Assessments. 2003;Volume 18:Tab 13.
25. Cheng PL, Wu PH, Kao WY, et al. Comparison of local ablative therapies, including radiofrequency ablation, microwave ablation, stereotactic ablative radiotherapy, and particle radiotherapy, for inoperable hepatocellular carcinoma: a systematic review and meta-analysis. Exp Hematol Oncol. Apr 12 2023; 12(1): 37. PMID 37046292
26. Yu Q, Liu C, Navuluri R, et al. Percutaneous microwave ablation versus radiofrequency ablation of hepatocellular carcinoma: a meta-analysis of randomized controlled trials. Abdom Radiol (NY). Sep 2021; 46(9): 4467-4475. PMID 33870454
27. Han J, Fan YC, Wang K. Radiofrequency ablation versus microwave ablation for early stage hepatocellular carcinoma: A PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore). Oct 23 2020; 99(43): e22703. PMID 33120763
28. Majumdar A, Roccarina D, Thorburn D, et al. Management of people with early- or very early-stage hepatocellular carcinoma: an attempted network meta-analysis. Cochrane Database Syst Rev. Mar 28 2017; 3(3): CD011650. PMID 28351116
29. Shen A, Zhang H, Tang C, et al. Systematic review of radiofrequency ablation versus percutaneous ethanol injection for small hepatocellular carcinoma up to 3 cm. J Gastroenterol Hepatol. May 2013; 28(5): 793-800. PMID 23432154
30. Tiong L, Maddern GJ. Systematic review and meta-analysis of survival and disease recurrence after radiofrequency ablation for hepatocellular carcinoma. Br J Surg. Sep 2011; 98(9): 1210-24. PMID 21766289

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Contains Public Information

31. Huang YZ, Zhou SC, Zhou H, et al. Radiofrequency ablation versus cryosurgery ablation for hepatocellular carcinoma: a meta-analysis. Hepatogastroenterology. 2013; 60(125): 1131-5. PMID 23321123
32. Sugimoto K, Imajo K, Kuroda H, et al. Microwave ablation vs. single-needle radiofrequency ablation for the treatment of HCC up to 4 cm: A randomized-controlled trial. JHEP Rep. Jan 2025; 7(1): 101269. PMID 39802807
33. Giorgio A, Merola MG, Montesarchio L, et al. Sorafenib Combined with Radio-frequency Ablation Compared with Sorafenib Alone in Treatment of Hepatocellular Carcinoma Invading Portal Vein: A Western Randomized Controlled Trial. Anticancer Res. Nov 2016; 36(11): 6179-6183. PMID 27793949
34. Organ Procurement and Transplant Network. Policy 9: Allocation of Livers and Liver-Intestines. Updated May 7, 2026; https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf. Accessed May 13, 2026.
35. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. Mar 14 1996; 334(11): 693-9. PMID 8594428
36. Pomfret EA, Washburn K, Wald C, et al. Report of a national conference on liver allocation in patients with hepatocellular carcinoma in the United States. Liver Transpl. Mar 2010; 16(3): 262-78. PMID 20209641
37. Lee MW, Raman SS, Asvadi NH, et al. Radiofrequency ablation of hepatocellular carcinoma as bridge therapy to liver transplantation: A 10-year intention-to-treat analysis. Hepatology. Jun 2017; 65(6): 1979-1990. PMID 28170115
38. Mazzaferro V, Battiston C, Perrone S, et al. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. Ann Surg. Nov 2004; 240(5): 900-9. PMID 15492574
39. Lu DS, Yu NC, Raman SS, et al. Percutaneous radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. Hepatology. May 2005; 41(5): 1130-7. PMID 15841454
40. Porrett PM, Peterman H, Rosen M, et al. Lack of benefit of pre-transplant locoregional hepatic therapy for hepatocellular cancer in the current MELD era. Liver Transpl. Apr 2006; 12(4): 665-73. PMID 16482577
41. Yao FY, Kerlan RK, Hirose R, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. Hepatology. Sep 2008; 48(3): 819-27. PMID 18688876
42. Yao FY, Hirose R, LaBerge JM, et al. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. Liver Transpl. Dec 2005; 11(12): 1505-14. PMID 16315294
43. Sauer P, Kraus TW, Schemmer P, et al. Liver transplantation for hepatocellular carcinoma: is there evidence for expanding the selection criteria?. Transplantation. Sep 27 2005; 80(1 Suppl): S105-8. PMID 16286885
44. Fernández JA, Robles R, Marin C, et al. Can we expand the indications for liver transplantation among hepatocellular carcinoma patients with increased tumor size?. Transplant Proc. Aug 2003; 35(5): 1818-20. PMID 12962807
45. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. Liver Transpl. Sep 2002; 8(9): 765-74. PMID 12200775

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Contains Public Information

46. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology. Jun 2001; 33(6): 1394-403. PMID 11391528
47. Merli M, Nicolini G, Gentili F, et al. Predictive factors of outcome after liver transplantation in patients with cirrhosis and hepatocellular carcinoma. Transplant Proc. 2005; 37(6): 2535-40. PMID 16182736
48. Kemeny N. Management of liver metastases from colorectal cancer. Oncology (Williston Park). Sep 2006; 20(10): 1161-76, 1179; discussion 1179-80, 1185-6. PMID 17024869
49. McKay A, Dixon E, Taylor M. Current role of radiofrequency ablation for the treatment of colorectal liver metastases. Br J Surg. Oct 2006; 93(10): 1192-201. PMID 16983740
50. Lencioni R, Crocetti L, Cioni D, et al. Percutaneous radiofrequency ablation of hepatic colorectal metastases: technique, indications, results, and new promises. Invest Radiol. Nov 2004; 39(11): 689-97. PMID 15486530
51. Meijerink MR, Puijk RS, van Tilborg AAJM, et al. Radiofrequency and Microwave Ablation Compared to Systemic Chemotherapy and to Partial Hepatectomy in the Treatment of Colorectal Liver Metastases: A Systematic Review and Meta-Analysis. Cardiovasc Intervent Radiol. Aug 2018; 41(8): 1189-1204. PMID 29666906
52. Loveman E, Jones J, Clegg AJ, et al. The clinical effectiveness and cost-effectiveness of ablative therapies in the management of liver metastases: systematic review and economic evaluation. Health Technol Assess. Jan 2014; 18(7): vii-viii, 1-283. PMID 24484609
53. Weng M, Zhang Y, Zhou D, et al. Radiofrequency ablation versus resection for colorectal cancer liver metastases: a meta-analysis. PLoS One. 2012; 7(9): e45493. PMID 23029051
54. Guenette JP, Dupuy DE. Radiofrequency ablation of colorectal hepatic metastases. J Surg Oncol. Dec 15 2010; 102(8): 978-87. PMID 21166002
55. Ruers T, Punt C, Van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Ann Oncol. Oct 2012; 23(10): 2619-2626. PMID 22431703
56. Ruers T, Van Coevorden F, Punt CJ, et al. Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. J Natl Cancer Inst. Sep 01 2017; 109(9). PMID 28376151
57. van der Lei S, Puijk RS, Dijkstra M, et al. Thermal ablation versus surgical resection of small-size colorectal liver metastases (COLLISION): an international, randomised, controlled, phase 3 non-inferiority trial. Lancet Oncol. Feb 2025; 26(2): 187-199. PMID 39848272
58. Kong Y, Huang X, Peng G, et al. Efficacy of first-line radiofrequency ablation combined with systemic chemotherapy plus targeted therapy for initially unresectable colorectal liver metastases. Int J Hyperthermia. Dec 2025; 42(1): 2432988. PMID 39894452
59. Sarioglu AG, Wehrle CJ, Akgun E, et al. Radiofrequency ablation versus microwave ablation for colorectal liver metastases: long-term results of a retrospective cohort surgical experience. Hepatobiliary Surg Nutr. Oct 01 2024; 13(5): 759-770. PMID 39507739
60. Hof J, Wertenbroek MW, Peeters PM, et al. Outcomes after resection and/or radiofrequency ablation for recurrence after treatment of colorectal liver metastases. Br J Surg. Jul 2016; 103(8): 1055-62. PMID 27193207

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Contains Public Information

61. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. Jun 2004; 239(6): 818-25; discussion 825-7. PMID 15166961
62. Ruers TJ, Joosten JJ, Wiering B, et al. Comparison between local ablative therapy and chemotherapy for non-resectable colorectal liver metastases: a prospective study. Ann Surg Oncol. Mar 2007; 14(3): 1161-9. PMID 17195903
63. Van Tilborg AA, Meijerink MR, Sietses C, et al. Long-term results of radiofrequency ablation for unresectable colorectal liver metastases: a potentially curative intervention. Br J Radiol. Jun 2011; 84(1002): 556-65. PMID 21159807
64. Mohan H, Nicholson P, Winter DC, et al. Radiofrequency ablation for neuroendocrine liver metastases: a systematic review. J Vasc Interv Radiol. Jul 2015; 26(7): 935-942.e1. PMID 25840836
65. Fairweather M, Swanson R, Wang J, et al. Management of Neuroendocrine Tumor Liver Metastases: Long-Term Outcomes and Prognostic Factors from a Large Prospective Database. Ann Surg Oncol. Aug 2017; 24(8): 2319-2325. PMID 28303430
66. Berber E, Siperstein A. Local recurrence after laparoscopic radiofrequency ablation of liver tumors: an analysis of 1032 tumors. Ann Surg Oncol. Oct 2008; 15(10): 2757-64. PMID 18618182
67. Mazzaglia PJ, Berber E, Milas M, et al. Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10-year experience evaluating predictors of survival. Surgery. Jul 2007; 142(1): 10-9. PMID 17629995
68. Rangarajan K, Lazzereschi L, Votano D, et al. Breast cancer liver metastases: systematic review and time to event meta-analysis with comparison between available treatments. Ann R Coll Surg Engl. Apr 2023; 105(4): 293-305. PMID 35175853
69. Schullian P, Johnston E, Laimer G, et al. Stereotactic Radiofrequency Ablation of Breast Cancer Liver Metastases: Short- and Long-Term Results with Predicting Factors for Survival. Cardiovasc Intervent Radiol. Aug 2021; 44(8): 1184-1193. PMID 33825059
70. Veltri A, Gazzera C, Barrera M, et al. Radiofrequency thermal ablation (RFA) of hepatic metastases (METS) from breast cancer (BC): an adjunctive tool in the multimodal treatment of advanced disease. Radiol Med. May 2014; 119(5): 327-33. PMID 24297589
71. Meloni MF, Andreano A, Laeseke PF, et al. Breast cancer liver metastases: US-guided percutaneous radiofrequency ablation--intermediate and long-term survival rates. Radiology. Dec 2009; 253(3): 861-9. PMID 19709994
72. Jakobs TF, Hoffmann RT, Schrader A, et al. CT-guided radiofrequency ablation in patients with hepatic metastases from breast cancer. Cardiovasc Intervent Radiol. Jan 2009; 32(1): 38-46. PMID 18575933
73. Li J, Zhang K, Gao Y, et al. Evaluation of hepatectomy and palliative local treatments for gastric cancer patients with liver metastases: a propensity score matching analysis. Oncotarget. Sep 22 2017; 8(37): 61861-61875. PMID 28977910
74. Li W, Bai Y, Wu M, et al. Combined CT-guided radiofrequency ablation with systemic chemotherapy improves the survival for nasopharyngeal carcinoma with oligometastasis in liver: Propensity score matching analysis. Oncotarget. Aug 08 2017; 8(32): 52132-52141. PMID 28881719
75. Liu B, Huang G, Jiang C, et al. Ultrasound-Guided Percutaneous Radiofrequency Ablation of Liver Metastasis From Ovarian Cancer: A Single-Center Initial Experience. Int J Gynecol Cancer. Jul 2017; 27(6): 1261-1267. PMID 28640176

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Contains Public Information

76. Hua YQ, Wang P, Zhu XY, et al. Radiofrequency ablation for hepatic oligometastatic pancreatic cancer: An analysis of safety and efficacy. Pancreatology. 2017; 17(6): 967-973. PMID 29129384
77. Jones RL, McCall J, Adam A, et al. Radiofrequency ablation is a feasible therapeutic option in the multi modality management of sarcoma. Eur J Surg Oncol. May 2010; 36(5): 477-82. PMID 20060679
78. Pawlik TM, Vauthey JN, Abdalla EK, et al. Results of a single-center experience with resection and ablation for sarcoma metastatic to the liver. Arch Surg. Jun 2006; 141(6): 537-43; discussion 543-4. PMID 16785353
79. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. Jan 2018; 67(1): 358-380. PMID 28130846
80. Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. Dec 01 2023; 78(6): 1922-1965. PMID 37199193
81. Taddei TH, Brown DB, Yarchoan M, et al. Critical Update: AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. Jul 01 2025; 82(1): 272-274. PMID 39992051
82. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hepatocellular Carcinoma. v1.2026. Updated March 10, 2026. https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf. Accessed May 13, 2026.
83. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 2.2026. Updated April 7, 2026. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed May 12, 2026.
84. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors. Version 1.2026. Updated April 21, 2026. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed May 14, 2026.
85. Ceppa EP, Collings AT, Abdalla M, et al. SAGES/AHPBA guidelines for the use of microwave and radiofrequency liver ablation for the surgical treatment of hepatocellular carcinoma or colorectal liver metastases less than 5 cm. Surg Endosc. Dec 2023; 37(12): 8991-9000. PMID 37957297
86. Gervais DA, Goldberg SN, Brown DB, et al. Society of Interventional Radiology position statement on percutaneous radiofrequency ablation for the treatment of liver tumors. J Vasc Interv Radiol. Jul 2009; 20(7 Suppl): S342-7. PMID 19560023

OTHER REFERENCES

1. Blue Cross and Blue Shield of Kansas Radiology Liaison Committee: January 2021.

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