Medical Policy

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Title: Radiofrequency Ablation of Primary or Metastatic Liver Tumors

Professional
Original Effective Date: July 1, 2003
Revision Date(s): May 10, 2012; August 21, 2013; October 1, 2016; January 19, 2021
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Institutional
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Populations	Interventions	Comparators	Outcomes
Individuals: • With primary, operable hepatocellular carcinoma	Interventions of interest are: • Radiofrequency ablation	Comparators of interest are: • Surgical resection	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • 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:	Interventions of interest are:	Comparators of interest are:	Relevant outcomes include: • Overall survival

Populations	Interventions	Comparators	Outcomes
• With inoperable hepatic metastases of colorectal origin	• Radiofrequency ablation	• Chemotherapy • Other locally ablative techniques • Best supportive care	• 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 local recurrence, it occurs at the edge of the tissue and, in some cases, is retreated. RFA may be performed percutaneously, laparoscopically, or as an open procedure.

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.

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 100000 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 embolization, 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 to 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. Patients may also have comorbid conditions and do not qualify for surgical resection.

Radiofrequency Ablation

RFA 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. RFA 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).

Note that RFA of extrahepatic tumors is addressed in evidence review 7.01.95.

Regulatory Status

RFA 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.

POLICY

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

B. Radiofrequency ablation as a primary treatment of inoperable hepatic metastases may be considered **medically necessary** under the following conditions:
   - metastases are of colorectal origin and meet the Milan criteria (a single tumor of ≤5 cm or up to 3 nodules <3 cm).
   - 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 / investigationa**l under the following conditions
   - when there are more than 3 nodules or when not all sites of tumor foci can be adequately treated
   - when used to downstage (downsize) HCC in patients 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:
   - hepatic metastases from colorectal cancer or neuroendocrine tumors that do not meet the criteria above; **AND**
   - hepatic metastases from other types of cancer except colorectal cancer or neuroendocrine tumors.

RATIONALE

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through May 13, 2019.

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 (QOL), 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 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, two domains are examined: the relevance, and quality and credibility. To be relevant,

studies must represent one 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. RCTs 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 RFA is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as surgical resection, in patients with primary, operable HCC.

The question addressed in this evidence review is: Does RFA improve the net health outcome in individuals with primary HCC or hepatic metastases?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with primary, operable HCC.

Interventions
The therapy being considered is RFA.

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. RFA may be performed percutaneously, laparoscopically, or as an open procedure.

RFA is performed by surgical oncologists in an inpatient clinical setting.

Comparators
Comparators of interest include surgical resection.

Surgical resection is performed by a surgical oncologist in an inpatient clinical setting.

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

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

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

HCC: hepatocellular carcinoma

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
d. Studies with duplicative or overlapping populations were excluded.

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.

Review of Evidence

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.

Yu et al (2020) performed a meta-analysis focused on comparative OS and disease-free survival (DFS) between percutaneous RFA and partial hepatectomy in patients with primary HCC meeting Milan criteria.[1] The analysis included only RCTs, accounting for 5 trials (N=761). The authors evaluated the quality of the included studies and judged 4 of 5 to be high quality based on the Jadad score. Overall survival and DFS were similar between groups, but RFA was associated with a higher long-term recurrence rate (2-year overall recurrence: relative risk [RR]=1.56, 95% confidence interval [CI]: 1.12 to 2.16; 5-year overall recurrence: RR=1.48, 95% CI: 1.19 to 1.84). Treatment-related complications with RFA were significantly lower compared to partial hepatectomy (RR=0.23; 95% CI: 0.09 to 0.56), but the analysis had a high degree of heterogeneity (I^2=79%).

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

The network meta-analysis by Zhu et al (2018) compares safety and effectiveness of several treatments for small HCC, RFA, percutaneous ethanol injection (PEI), percutaneous acetic acid injection (PAI), and surgical resection.[3] 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 the proportion dead (PD), local recurrence, and adverse events. It showed that PEI had a higher PD than RFA, and RFA had a higher PD than surgical resection; a single study found that PAI had a higher PD than RFA (Table 2). For local recurrence, PEI had a higher recurrence than RFA, RFA had a higher recurrence than surgical resection, and PAI had a higher recurrence than RFA. Adverse events were fewer with RFA than with surgical resection (odds ratio [OR]=0.11; 95% CI: 0.03 to 0.34), but there were no significant effects in reducing adverse events between PEI vs RFA and PAI vs 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.[4] 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 others including 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.[5] Three RCTs and 20 retrospective observational studies were included in the analysis. OS and recurrence-free survival rate of 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 RFA for Primary, Operable HCC

Study	Feng (2015)[5]	Jia (2017)[4]	Zhu (2018)[3]	Yu (2020)[1]	Li (2020)[2]
Lee (2018)				X	
Lee (2015)		X			
Fang (2014)			X	X	
Kim (2014)		X			
Desiderio (2013)	X	X			
Guo (2013)	X				
Hasegawa (2013)	X				
Imai (2013)	X				
Pompili (2013)	X	X			
Tohme (2013)	X	X			
Wong (2013)	X	X			
Feng (2012)	X		X	X	
Peng (2012)	X	X			
Wang (2012)	X				
Giorgio (2011)			X		
Huang (2011)					X
Hung (2011)	X				X

Study	Feng (2015)[5]	Jia (2017)[4]	Zhu (2018)[3]	Yu (2020)[1]	Li (2020)[2]
Ikeda (2011)	X				
Kong (2011)	X				
Nishikawa (2011)	X				X
Tashiro (2011)					X
Yun (2011)	X				
Huang (2010)	X	X	X	X	
Nanashima (2010)		X			
Santambrogio (2009)		X			X
Ueno (2009)	X				
Abu-Hilal (2008)	X				X
Brunello (2008)			X		
Guglielmi (2008)	X				X
Hiraoka (2008)	X				X
Ueno (2008)					X
Lupo (2007)	X				X
Chen (2006)	X	X	X	X	X
Wakai (2006)					X
Cho (2005)		X			X
Hong (2005)		X			X
Huang (2005)			X		
Lin (2005)			X		
Montorsi (2005)					X
Ogihara (2005)					X
Shiina (2005)			X		
Sung (2005)	X				
Lin (2004)			X		
Vivarelli (2004)		X			X
Guglielmi (2003)		X			
Huo (2003)			X		
Lencioni (2003)			X		
Livraghi (1999)			X		
Ohnishi (1998)			X		

HCC: hepatocellular carcinoma; RFA: radiofrequency ablation.

Table 3. Characteristics of Meta-Analyses of RFA for Primary, Operable HCC

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Yu (2020)[1]	2006-2019	5	Pts with primary HCC meeting Milan criteria[a]; suitable candidates for surgical resection and/or RFA.	N=761 (68-230)	RCTs	3 yr to 5 yr
Li (2020)[2]	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	RCT and observational comparative studies	1 yr to 5 yr
Zhu (2018)[3]	1998-2013	14	Pts diagnosed with small HCC meeting Milan criteria.	N=2096 (29-143)	RCTs and quasi-RCTs	Mean 22 mo

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Jia (2017)[4]	2003-2015	15	Pts with early-stage HCC; liver function Child-Pugh class A; suitable candidates for surgical resection and/or RFA.	N=3627 (67-1061)	RCTs and observational comparative studies	1 yr to 5 yr
Feng (2015)[5]	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 (63-10,909)	RCTs and NRCTs	1 yr to 5 yr

HCC: hepatocellular carcinoma; NRCT: nonrandomized controlled trial; Pts: patients; RCT: randomized controlled trial; RFA: radiofrequency ablation; yr: year(s).
[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.
[b] UCSF (University of California at San Francisco) criteria are a single tumor up to 6.5 cm in diameter or up to 3 nodules each no larger than 4.5 cm in diameter and 8 cm total tumor diameter.
[c] The Child-Pugh score is used to assess prognosis of chronic liver disease and cirrhosis. It consists of five clinical features with values worth 1, 2, or 3 points. The number of points accumulated (5-15) indicate estimated chance of 1-year survival. Class A (5-6 points total) indicates an estimated 100% chance of 1-year survival.

Table 4. Results of Meta-Analyses of RFA for Primary, Operable HCC

Study	Overall Survival OR or RR (95% CI)			Disease-free Survival OR or RR (95% CI)		
	1 yr	2/3 yr	5 yr	1 yr	2/3 yr	4/5 yr
Feng (2015)[5]						
N	4199	15,414 (3-yr)	14,686	3544	3389 (3-yr)	2984 (5-yr)
RFA vs SR-OR	0.71 (0.52, 0.96)	0.62 (0.49, 0.78)	0.55 (0.47, 0.66)	0.58 (0.45, 0.76)	0.52 (0.40, 0.68)	0.50 (0.34, 0.76)
I^2 (p)	30% (0.10)	NR (<0.001)	NR (0.02)	53% (0.004)	NR (<0.001)	NR (0.00)
Jia (2017)[4]						
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, 1.885)	1.753 (1.197, 2.567)	1.552 (1.026, 2.348)	1.209 (0.935, 1.563)	1.517 (1.076, 2.140)	1.810 (1.071, 3.058)
I^2 (p)	49% (0.02)	74.2% (0.000)	72.6% (0.000)	20.4% (0.261)	68.3% (0.001)	68.5% (0.007)
Zhu (2018)[a3]						
PEI vs RFA-OR	-	1.66 (1.13, 2.44)	-	-	2.74 (1.42, 5.29)	-
PAI vs RFA-OR	-	1.63 (0.67, 3.96)	-	-	2.79 (1.19, 6.54)	-

Study	Overall Survival OR or RR (95% CI)			Disease-free Survival OR or RR (95% CI)		
RFA vs LR-OR	-	1.21 (0.62, 2.35)	-	-	2.02 (1.01, 4.02)	-
Yu (2020)[1]						
N	761	761 (3-yr)	293	363	363 (3-yr)	243 (4-yr)
RFA vs SR-RR	0.99 (0.96, 1.03)	0.92 (0.80, 1.07)	0.86 (0.60, 1.25)	0.97 (0.84, 1.12)	0.93 (0.67, 1.29)	0.85 (0.66, 1.11)
I^2 (p)	0% (0.55)	76% (0.002)	84% (0.01)	69% (0.04)	64% (0.06)	27% (0.24)
Li (2020)[2]						
N	3921	4053 (3-yr)	3397	3394	3326 (3-yr)	3076 (5-yr)
RFA vs SR-OR	0.757 (0.578, 0.989)	0.530 (0.401, 0.700)	0.566 (0.423, 0.758)	0.569, (0.456, 0.711)	0.418 (0.267, 0.653)	0.374 (0.231, 0.606)
I^2 (p)	0% (0.55)	61% (0.0005)	71% (<0.0001)	42% (0.06)	70% (0.0001)	57% (0.01)

CI: confidence interval; HCC: hepatocellular carcinoma; NR: not reported; OR: odds ratio; PAI: percutaneous acetic acid injection; PEI: percutaneous ethanol injection; RFA: radiofrequency ablation; SR: surgical resection; RR: relative risk.

[a]Zhu et al (2018) reported proportion dead vs overall survival and local recurrence vs disease-free survival.

Randomized Controlled Trials

Randomized controlled trials not included in previously discussed systematic reviews are summarized below. Ng et al (2017) conducted an RCT in which patients with early-stage HCC were randomized to RFA (n=109) or surgical resection (n=109).[6] OS and recurrence-free survival at one, three, five, and ten years did not differ statistically between the two groups. Further, postoperative complication rate was numerically higher, but not statistically different, with resection (16.5%) compared to RFA (9.2%).

Liu et al (2016) published an RCT that compared surgical resection with TACE plus RFA for HCC.[7] Tumor sizes ranged from 0.6 to 5 cm, with a median of 3 cm in the surgical resection group and 2.8 cm in the TACE plus RFA group. OS (p=0.007) and recurrence-free survival (p=0.026) were significantly longer in the surgical resection group. Local tumor progression occurred in 1 patient in the surgical resection group and in 18 in the TACE plus RFA group (p<0.001). There were no significant differences in recurrence or OS between the groups for HCC lesions 3 cm or smaller, but there were significant benefits for surgery in recurrence (p=0.032) and OS (p=0.012) in patients with lesions larger than 3 cm. Tumor size was an independent prognostic factor for recurrence-free survival (hazard ratio [HR]=1.76; p=0.006) along with hepatitis B DNA and platelet count. Complications were higher in the surgical resection group (23.0%) than in the TACE plus RFA group (11.0%; p=0.24). It could not be determined from this trial whether RFA alone is as effective as a surgical resection for small tumors.

Table 5. Key Randomized Controlled Trial Characteristics For Resectable HCC

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Ng et al (2017)[6]	China	1	2002-2007	Pts with early-stage HCC with a maximum tumor diameter of 5 cm; ≤3 tumor nodules; no extrahepatic involvement; Child–Pugh grade A or B liver function; suitable candidates for surgical resection and/or RFA.	RFA	Hepatic resection
Liu et al (2016)[7]	China	1	2006-2009	Pts with early-stage HCC meeting Milan criteria[a]; Child–Pugh grade A or B liver function; suitable candidates for surgical resection and/or RFA.	TACE + RFA	Partial hepatectomy

HCC: hepatocellular carcinoma; Pts: patients; RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization.
[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 6. Survival Following Surgical Resection vs RFA Alone or TACE Plus RFA for Resectable HCC

Outcomes	**1 Year, %**	**3 Years, %**	**5 Years, %**	**10 Years, %**
Ng et al (2017)[6]				
Overall survival				
Surgical resection	95.4	82.3	66.4	41.8
RFA	94.5	80.6	66.5	47.6
Recurrence-free survival				
Surgical resection	70.6	46.6	33.6	18.6
RFA	74.1	50.9	41.5	31.9
Liu et al (2016)[7]				
Overall survival				
Surgical resection	97.0	83.7	61.9	NR
TACE plus RFA	96.0	67.2	45.7	NR
Recurrence-free survival				
Surgical resection	94.0	68.2	48.4	NR
TACE plus RFA	83.0	44.9	35.5	NR

HCC: hepatocellular carcinoma; NR: not reported; RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization.

Table 7. Study Relevance Limitations

Study	**Population[a]**	**Intervention[b]**	**Comparator[c]**	**Outcomes[d]**	**Follow-up[e]**
Ng et al (2017)[6]	4. HCC diagnosis confirmed via CT, which is not the currently preferred				

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
	diagnostic method				
Liu et al (2016)[7]	4. Majority of population had HBV-related HCC, which may not be representative of other groups	4. Evaluated combination of RFA with TACE, not RFA alone			

CT: computed tomography; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization.
The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Ng et al (2017)[6]		1. Trial was not blinded, though likely not feasible due to nature of intervention			1. Sample size calculation not reported	
Liu et al (2016)[7]		1. Trial was not blinded, though likely not feasible due to nature of intervention	1. Study was retrospectively registered			

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.
b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
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).
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
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.

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.[8] The study included patients with tumors 2.1 to 5 cm in size. Overall, patients receiving RFA plus PEI experienced significantly better OS and relapse-free survival (RFS) than patients undergoing resection. However, subgroup analysis by tumor size showed that significant improvements in OS and RFS were only experienced by patients with tumors 2.1 to 3 cm (see Table 9).

Table 9. Survival Following Surgical Resection or RFA Plus PEI for Resectable HCC

Outcomes	1 Year, %	3 Years, %	5 Years, %	p
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	0.02
3.1 to 5.0 cm				
RFA-PEI, n=64	86.4	65.1	55.4	
Surgical resection, n=60	88.9	64.5	49.6	0.13
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	0.02
3.1 to 5.0 cm				
RFA plus PEI	53.5	29.4	24.0	
Surgical resection	42.2	26.6	21.9	0.71

Adapted from Chen et al (2018).[8]
HCC: hepatocellular carcinoma; 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.[9] 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. Median follow-up for the whole cohort was 55 months for OS. In the overall cohort, liver transplantation was associated with an improved overall survival (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. 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, 1.1)	0.6 (0.6, 0.7)	0.7 (0.6, 0.7)
Tumor Size			
<20 mm	0.7 (0.6, 0.8)	0.3 (0.2, 0.4)	0.8 (0.6, 1.2)

Group Analyzed[a]	Overall Survival, HR (95% CI) SR vs RFA	LT vs RFA	LT vs SR
21-30 mm	1.1 (0.1, 9.5)	0.5 (0.1, 3.7)	0.9 (0.6, 1.2)
31-35 mm	0.2 (0.0, 2.1)	0.1 (0.0, 1.2)	0.9 (0.6, 1.2)
31-50 mm	0.8 (0.7, 0.9)	0.1 (0.0, 0.2)	0.5 (0.3, 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.

Additional observational studies published since the systematic reviews have reported inconsistent results, with some finding no difference in survival outcomes between RFA and resection[10,11,] 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.[12,13,14,15,16,]

Section Summary: Radiofrequency Ablation to Treat Primary, Operable Hepatocellular Carcinoma
The evidence on RFA as a primary treatment of primary, operable HCC includes RCTs, meta-analyses of RCTs and retrospective observational studies, 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-analysis of specifically selected populations (eg, small tumor sizes or Child-Pugh Class A liver function) found that OS and DFS rates were not significantly different between RFA and surgical resection. Generally results from meta-analyses were limited by heterogeneous populations and a lack of randomization leading to potential selection bias. Recent RCTs not incorporated into available meta-analysis have found surgical resection to be similar to and superior to RFA or RFA plus TACE, respectively, based on OS and DFS. 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 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 patients with inoperable HCC.

The question addressed in this evidence review is: Does RFA improve the net health outcome in individuals with primary HCC or hepatic metastases?

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

Patients
The relevant population of interest is individuals with inoperable HCC. Examples of patients 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 patients 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 a patient 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). Systemic therapy and other locally ablative techniques are performed by oncologists and primary care providers in an outpatient clinical setting.

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

Table 11. Outcomes of Interest for Individuals with Inoperable HCC

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

HCC: hepatocellular carcinoma.

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.

Review of Evidence
Systematic Reviews
A TEC Assessment (2003) addressed RFA for the treatment of unresectable primary or metastatic liver tumors.[17,] Since that report, many systematic reviews and meta-analyses have assessed RFA for HCC. Several are discussed below.

Majumdar et al (2017) published a Cochrane review and network meta-analysis on the management of early and very early-stage HCC.[18,] 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-up 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 treatment of HCC nodules up to 3 cm.[19,] OS was significantly longer

for RFA than for PEI at 3 years (HR=0.66; 95% CI, 0.48 to 0.90; p=0.009), and local recurrence risk was lower with RFA (HR=0.38; 95% CI, 0.15 to 0.96, p=0.040). 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.[20.] 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.[21.] 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

An RCT by Vietti Violi et al (2018) compares the effectiveness of RFA and microwave ablation (MWA) on treating inoperable HCC with up to 3 lesions of 4 cm or smaller.[22.] In this trial, MWA was the experimental treatment and RFA was the control. A total of 152 patients were randomly assigned, with 76 to undergo MWA and 76 to undergo RFA. At 2 years, 6% (6/98) of lesions treated with MWA had local tumor progression vs 12% (12/104) of lesions treated with RFA (risk ratio =1.62; 95% CI: 0.66 to 3.94; P=0.27). Few complications and no treatment-related deaths were reported for either group. Based on the investigators' interpretation of the data, MWA is not more effective than RFA for treating HCC tumors of 4 cm or less; however, the proportion of local tumor progression at two years post-procedure was low for both ablation methods. A Kaplan-Meier analysis revealed that OS at 2 years was not significantly different between the groups either, as OS for the MWA group was 86% (95% CI: 73 to 92) and 84% (95% CI: 70 to 90) for the RFA group. Because some patients did not receive the allocated treatment or were lost to follow-up, the analyses were per-protocol rather than intention-to-treat. In addition, the investigators had planned to assess the effects of the treatments on larger lesions, but only a few patients had lesions of nearly 4 cm, making a detailed analysis impossible. A five-year follow-up is planned for this study.

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.[23.] The HCC nodules ranged in size from 2.1 to 6.5 cm. The primary outcome was OS at three 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.

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 individual's ineligible for surgery. RCT evidence has established that RFA is more effective than PEI in this population, and some evidence has suggested that RFA may be better than cryoablation. The evidence comparing RFA with TACE is limited, and no conclusions can be drawn. RFA 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 patients with inoperable HCC awaiting a liver transplant.

The question addressed in this evidence review is: Does RFA improve the net health outcome in individuals with primary HCC or hepatic metastases?

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

Patients

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). Other locoregional therapies are performed by oncologists and primary care providers in an outpatient clinical setting.

Outcomes

The general outcomes of interest are OS, disease-specific survival, and change in disease status. 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 HCC Awaiting Liver Transplant

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

HCC: hepatocellular carcinoma.

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 updated in 2018.[24,] 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 (one nodule ≤1.9 cm) are considered at low-risk of death while on the waiting list, and those with T3 lesions (one nodule >5 cm, or two or three nodules with at least one nodule >3 cm) are at high-risk of posttransplant recurrence. Patients with T2 tumors (one nodule 2 to 5 cm, or two or three 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 posttransplant tumor recurrence. Therefore, UNOS criteria prioritize T2 HCC by allocating additional points equivalent to a MELD score predicting a 15% probability of death within 3 months. The definition of T2 lesions is also referred to as the Milan criteria.[25,] 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 two purposes : (1) to prevent the progress 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.[26,] 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 non-HCC population." The workgroup observed that there is extreme variability of 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.

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.[27,] 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 dropout rate from the waitlist, posttransplant recurrence, and OS at 10 years. The mean time on the waiting list was 10.2 months (range, 0.3-38 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 nine (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.[28,] 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.[29,] 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.[30,] Study endpoints included OS and DFS, tumor recurrence, explant tumor viability, and the ability of magnetic resonance imaging to detect viable tumor 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 assignment; p=0.05). 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 tumor 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>0.1). 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.[31,] Eligibility criteria for downstaging included the following: (1) one lesion between 5 and 8 cm; (2) two to three lesions with at least one lesion between 3 and 5 cm, with total tumor diameter up to 8 cm; or (3) four to five lesions with none greater than 3 cm, with total tumor diameter up to 8 cm.

TACE and laparoscopic RFA either alone or in combination were the main methods used the following: 11 patients received laparoscopic RFA alone, 14 received TACE and laparoscopic RFA, and 9 received TACE and percutaneous RFA. A minimum observation period of three 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).[32,] Eligibility for locoregional therapy seeking to downstage patients included either (1) one nodule between 5 and 8 cm in diameter; (2) two or three nodules with at least one between 3 and 5 cm in diameter, with a sum of diameters no greater than 8 cm; or (3) four or five 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.[33,34,35,36,37,] 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)[25,] reported the 4-year RFS was 92% in those who met the Milan criteria compared with 59% in those who did not; additional studies have confirmed this difference in the RFS rate.[32,] However, other institutions have reported similar outcomes with expanded criteria. For example, Yao et al (2002) reported similar RFS rates after transplant in patients with T2 tumors and a subset of those with T3 tumors.[35,] This T3 subset was defined as a single lesion 6.5 cm or less or three 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 RFS 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 RFS 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 RFS 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.[27,]

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 three to six 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 patients with inoperable hepatic metastases of colorectal origin.

The question addressed in this evidence review is: Does RFA improve the net health outcome in individuals with primary HCC or hepatic metastases?

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

Patients
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.
Chemotherapy, other locally ablative techniques and the best supportive care are performed by oncologists and primary care providers in an outpatient clinical setting.

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

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

Review of Evidence
More than half of patients with colorectal cancer (CRC) will develop liver metastases, generally with a poor prognosis.[38,] 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.[38,] 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 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 overall survival rates that historically range from 28% to 38%, but may reach 58% in appropriately selected, resectable patients without the widely disseminated disease.[39,40,] 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 MWA to systemic chemotherapy and to partial hepatectomy (PH) for the treatment of colorectal liver metastases.[41,] 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 =0.64; 95% CI: 0.21 to 1.95). DFS was higher for PH alone over RFA alone (HR=1.49; 95% CI: 1.23 to 1.81), as well as for 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 (risk ratio=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.[42,]

Weng et al (2012) reported on a meta-analysis comparing RFA with liver resection for the treatment of CRC liver metastases.[43,] One prospective study and 12 retrospective studies were included in the analysis. OS at 3 and 5 years was significantly longer after liver resection than after RFA (relative risk [RR], 1.38 [95% CI, 1.25 to 1.52] vs RR=1.47 [95% CI, 1.28 to 1.69], respectively). DFS 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 three 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, $p<0.01$) and rates of complications lower (18.3% vs 3.9%, $p<0.01$) with RFA than 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.[44,] The literature search was from 1994 to 2010, and inclusion criteria were a minimum of 1-year follow-up and more than 10 patients. In all, 75 met inclusion criteria. Most studies were single-arm, single-center, retrospective, and 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%. MWA (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%. RFA (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, with 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.[45,] 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][40,]) included in the review consisted of 423 patients, with average tumor size of 2.7 cm, 4 or fewer metastases, each 5 cm or less at greatest dimension, and no extrahepatic disease. OS rates in that study at 1, 3, and 5 years were 86%, 47%, and 24%, respectively. Guenette and Dupuy concluded that five-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, 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 as 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.[46,47] 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 ten 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=0.03) at 3 years, 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=0.01).

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).[47]
CI: confidence interval.

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.

Hof et al (2016) analyzed data from 431 patients in an institutional database.[48] 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 treated with hepatic resection (p<0.001). The 5-year OS estimate by Kaplan-Meier analysis was 51.9% for RFA and 53% for hepatic resection (p=0.98).

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).[49] In the key relevant comparison, RFA vs chemotherapy in chemotherapy-naive patients with nonresectable CRC metastases (median, 1 lesion per patient; range, 1-8; median tumor size, 2.5 cm), OS at 4 years was 22% in the RFA group and 10% in the chemotherapy group (p=0.005). Median survival was estimated at 25 months in the RFA group and 17 months in the chemotherapy group (p 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<0.001), 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.[50,] 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, 1-9; median diameter, 3.8 cm), 31 months (95% CI, 20 to 42 months) in locally ablated patients (median, 4 tumors per patient; range, 1-19; median diameter, 3 cm), and 26 months (95% CI, 17 to 35 months) in the chemotherapy patients (median, 4 tumors per patient; range, 1-17; median diameter, 4 cm; p=0.052, ablated vs chemotherapy). Results from 2 validated quality of life instruments (EuroQol-5D, 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<0.05).

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).[51,] Lesion size ranged from 0.2 to 8.3 cm (mean, 2.4 cm). Mean follow-up was 29 months (range, 6-93 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=0.009). Mean survival from the time of RFA was 56 months (95% CI, 45 to 67 months).

Section Summary: Radiofrequency Ablation for of 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 eight years compared with chemotherapy alone. Additionally, prospective studies have demonstrated that OS following RFA is at least equivalent and likely better than that 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 the 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 patients with inoperable hepatic metastases of neuroendocrine origin.

The question addressed in this evidence review is: Does RFA improve the net health outcome in individuals with primary HCC or hepatic metastases?

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

Patients
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. 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]

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).[52] Seven unique studies (N=301 patients), 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 two 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, 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.[53] 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.[54,] Of 1032 tumors assessed, 295 were neuroendocrine tumor metastases. The mean number of lesions treated was 5.6 (range, 1-16 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.[55,] 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, 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. RFA was performed 1.6 years (range, 0.1-7.8 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, and the best supportive care, in patients with hepatic metastases not of colorectal or neuroendocrine origin.

The question addressed in this evidence review is: Does RFA improve the net health outcome in individuals with primary HCC or hepatic metastases?

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

Patients
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, 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. Outcomes of Interest for Individuals with Hepatic Metastases Not of Colorectal or Neuroendocrine Origin

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

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

Veltri et al (2014) analyzed 45 women treated with RFA for 87 breast cancer liver metastases (mean size, 23 mm).[56,] Complete ablation was seen on initial follow-up in 90% of tumors but the tumor recurrence rate was 19.7% within 8 months. RFA 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.[57,] Inclusion criteria were fewer than five tumors, maximum tumor diameter of 5 cm, and disease confined to the liver or stable with medical therapy. 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.[58,] 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 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.[59,] OS rates at 1, 3, and 5 years was 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.[60,] 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.[61,] They reported 100% complete ablation of the lesions and 1-, 3-, and 5-year OS rates of 100%, 61%, and 61%, respectively.

Pancreatic Cancer
Hua et al (2017) conducted a retrospective analysis of 102 patients with pancreatic cancer and synchronous liver oligometastases who had undergone RFA.[62,] 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.[63,] 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 two occasions for separate lesions within the liver, and both responded to the second RFA procedure. Of the other subtypes, seven patients underwent RFA to liver lesions, five of whom responded to RFA, one patient progressed, and another was not assessable at the time of analysis. RFA was well-tolerated in this series. RFA 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).[64,] 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.

Summary of Evidence

Primary, Operable Hepatocellular Carcinoma

For individuals who have primary, operable hepatocellular carcinoma (HCC) who receive RFA, the evidence includes randomized controlled trials (RCTs), meta-analyses RCTs and retrospective observational studies, and additional observational studies. Relevant outcomes are overall survival (OS), disease-specific survival, change in disease status, and morbid events. The majority of data found 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. Results from observational studies have suggested that RFA alone or RFA plus PEI could be as effective as a resection for small HCC tumors as OS and DFS rates were not significantly different between RFA and surgical resection. Although the exact size cutoff has not been established, current National Comprehensive Cancer Network guidelines suggest use of ablation as a treatment option when tumors are 3 cm or smaller. Some studies found that OS was similar in patients receiving RFA or resection when tumor size was 3 cm or less; however, OS was significantly longer in patients undergoing resection if the tumor size was between 3.1 cm and 5 cm. Further study in a multicenter RCT would permit greater certainty whether RFA, with or without other ablative or arterial directed therapies , is as effective as surgical resection in treating HCC tumors 3 cm or smaller. The evidence is insufficient to determine the effects of the technology RFA on health outcomes.

Inoperable Hepatocellular Carcinoma

For individuals who have inoperable HCC who receive RFA, the evidence includes randomized trials and several systematic reviews and meta-analyses. Relevant outcomes are OS, disease-specific survival, change in disease status, and morbid events. When resection is not an option, nonsurgical options include RFA, percutaneous ethanol injection, transarterial chemoembolization, cryoablation, microwave ablation, and systemic therapy. Meta-analyses comparing these nonsurgical options have shown improved survival outcomes with RFA alone or combined with other treatments (eg, with percutaneous ethanol injection or systemic therapy) compared with other nonsurgical treatments alone. Response rates have demonstrated that, in patients with small foci of HCC (≤3 lesions), RFA appears to be better than percutaneous ethanol injection in achieving complete ablation and preventing local recurrence. Three-year survival rates of 80% have been reported. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Inoperable Hepatocellular Carcinoma Awaiting Liver Transplant

For individuals who have inoperable HCC awaiting liver transplant who receive RFA, the evidence includes small case series. Relevant outcomes are OS, disease-specific survival, and change in disease status. A number of approaches are used in this patient population, including RFA and other locoregional therapies, particularly transarterial chemoembolization. Locoregional therapy

has reduced the dropout rate of patients with HCC awaiting a liver transplant. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Inoperable Hepatic Metastases of Colorectal Origin
For individuals who have inoperable hepatic metastases of colorectal origin who receive RFA, the evidence includes an RCT, systematic reviews and meta-analyses, prospective cohort series, and retrospective case series. Relevant outcomes are OS, disease-specific survival, symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. There are no RCTs comparing RFA with alternative treatments for patients who have unresectable colorectal liver metastases. However, an RCT assessing RFA plus chemotherapy found improved survival at eight years compared with chemotherapy alone. In addition, prospective studies have demonstrated that OS following RFA is at least equivalent to and likely better than for currently accepted systemic chemotherapy in well-matched patients with unresectable hepatic metastatic colorectal cancer who do not have extrahepatic disease. Results from a number of uncontrolled case series also have suggested RFA of hepatic colorectal cancer metastases produces long-term survival that is at a minimum equivalent to but likely superior to historical outcomes achieved with systemic chemotherapy. Evidence from a comparative study has indicated RFA has fewer deleterious effects on quality of life than chemotherapy and that RFA patients recover the quality of life significantly faster than chemotherapy recipients. It should be noted that patients treated with RFA in different series might have had better prognoses than those who had chemotherapy, suggesting patient selection bias might at least partially explain the better outcomes observed following RFA. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Inoperable Hepatic Metastases of Neuroendocrine Origin
For individuals who have inoperable hepatic metastases of neuroendocrine origin who receive RFA, the evidence includes case series and a systematic review of case series. Relevant outcomes are OS, disease-specific survival, symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. Most reports of RFA treatment for neuroendocrine liver metastases have assessed 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 using RFA in individuals whose symptoms are not controlled by systemic therapy or who are ineligible for resection. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Hepatic Metastases Not of Colorectal or Neuroendocrine Origin
For individuals who have hepatic metastases, not of colorectal or neuroendocrine origin who receive RFA, the evidence includes small nonrandomized comparative studies and small case series. Relevant outcomes are OS, disease-specific survival, symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. Similar to primary HCC, resection appears to have the most favorable outcomes. For patients who are ineligible for resection, RFA may provide a survival benefit. However, the evidence is limited by study designs with a high-risk of bias and small sample sizes. The evidence is insufficient to determine the effects of the technology RFA on health outcomes.

SUPPLEMENTAL INFORMATION
Practice Guidelines and Position Statements

Society of Interventional Radiology
The Society of Interventional Radiology (2009) published a position statement on percutaneous radiofrequency ablation for the treatment of liver tumors.[65] The Society indicated that "percutaneous RF ablation of hepatic tumors is a safe and effective treatment for selected patients with HCC [hepatocellular carcinoma] and colorectal carcinoma metastases" and that the current literature does not support any recommendations for or against the use of radiofrequency ablation in other diseases.

National Comprehensive Cancer Network
Several National Comprehensive Cancer Network (NCCN) guidelines are relevant to this review. The NCCN (v.3.2020) guidelines on hepatobiliary cancers state that "ablation alone may be curative in treating tumors ≤ 3 cm. In well-selected patients with small, properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review. Lesions 3 to 5 cm may be treated to prolong survival using arterially directed therapies, alone or with combination of an arterially directed therapy and ablation as long as the tumor is accessible for ablation" (category 2A).[66]

The NCCN (v.3.2020) guidelines on colon cancer metastatic to the liver state that "Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection" (category 2A).[67] Of all ablative techniques, the guidelines note that radiofrequency ablation has the most supporting evidence.

The NCCN (v.1.2019) guidelines for neuroendocrine tumors state that "…ablative therapies such as radiofrequency ablation (RFA) or cryoablation may be considered if near-complete treatment of tumor burden can be achieved (category 2B). For unresectable liver metastases,...(arterial embolization, chemoembolization, or radioembolization [category 2B]) is recommended."[68]

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 17.

Table 17. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02243384	A Randomized Controlled Trial of Laparoscopic Hepatectomy and Radiofrequency Ablation in the Treatment of Early Hepatocellular Carcinoma	110	Sep 2019 (estimated)
NCT02535117	Laparoscopic Surgery Versus Radiofrequency Ablation for Recurrent Hepatocellular Carcinoma after Initial Partial Hepatectomy: a Multicenter Experience	216	Jul 2020
NCT03127072	A Prospective, Randomized, One-center Study Assessing Overall Survival Using RFA Plus Chemotherapy ± Target	200	Dec 2021

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Therapy and Chemotherapy ± Target Therapy Alone in Patients With Unresectable Colorectal Cancer Liver Metastases		
NCT02169765	Hepatic Resection Versus Radiofrequency Ablation for Early-stage Hepatocellular Carcinoma	120	Dec 2022
Unpublished			
NCT02192671	Hepatic Resection Versus Radiofrequency Ablation for Patients With Hepatocellular Carcinoma and Portal Hypertension	120	Dec 2018 (unknown)

NCT: national clinical trial

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. 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.

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

ICD-10 Diagnoses (Effective October 1, 2015)

C22.0	Liver cell carcinoma
C22.2	Hepatoblastoma
C22.3	Angiosarcoma of liver
C22.4	Other sarcomas of liver
C22.7	Other specified carcinomas of liver
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C7B.02	Secondary carcinoid tumors of liver
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct

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 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 (eg, 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

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