



Louisiana

Radiofrequency Ablation of Primary or Metastatic Liver Tumors

Policy # 00182

Original Effective Date: 09/22/2005

Current Effective Date: 11/21/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors is addressed in medical policy 00175.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider radiofrequency ablation of primary, inoperable (eg, due to location of lesion[s] and/or comorbid conditions), hepatocellular carcinoma to be **eligible for coverage** under the following conditions:

Patient Selection Criteria

Coverage eligibility will be considered when any of the following criteria are met:

- As a primary treatment of hepatocellular carcinoma meeting the Milan criteria (a single tumor of ≤ 5 cm or up to 3 nodules < 3 cm); or
- As a bridge to transplant, where the intent is to prevent further tumor growth and to maintain a patient's candidacy for liver transplant.

Based on review of available data, the Company may consider radiofrequency ablation as a primary treatment of inoperable hepatic metastases to be **eligible for coverage** under the following conditions:

Patient Selection Criteria

Coverage eligibility will be considered when any of the following criteria are met:

- Metastases are of colorectal origin and meet the Milan criteria (a single tumor of ≤ 5 cm or up to 3 nodules < 3 cm); or
- Metastases are of neuroendocrine in origin and systemic therapy has failed to control symptoms.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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Based on review of available data, the Company considers radiofrequency ablation of primary, inoperable, hepatocellular carcinoma to be **investigational*** 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) hepatocellular carcinoma in patients being considered for liver transplant.

Based on review of available data, the Company considers radiofrequency ablation of primary, operable hepatocellular carcinoma to be **investigational.***

Based on review of available data, the Company considers radiofrequency ablation for hepatic metastasis to be **investigational*** for:

- Hepatic metastases from colorectal cancer or neuroendocrine tumors that do not meet the criteria above; and
- For hepatic metastases from other types of cancer except colorectal cancer or neuroendocrine tumors.

Background/Overview

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 100,000 per year.

Treatment

At present, surgical resection with adequate margins or liver transplantation constitutes the only treatments available with demonstrated curative potential. 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.

Treatment of liver metastases is undertaken to prolong survival and to reduce endocrine-related symptoms and hepatic mass-related symptoms.

Alternative therapies available include liver transplantation, systemic therapies, or ablation procedures (radiofrequency ablation [RFA], cryoablation, microwave ablation, percutaneous ethanol or acetic acid

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injection). Choice of therapy depends on the severity of underlying liver disease, size and distribution of tumors, vascular supply, and patient overall health.

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 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).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

RFA devices have been cleared for marketing by the U.S. FDA through the 510(k) process. FDA product code GEI.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to 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 a technology, 2 domains are examined: the relevance and the 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.

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RADIOFREQUENCY ABLATION OF PRIMARY OR METASTATIC LIVER TUMORS

The evidence is evaluated separately for operable and inoperable tumors. If data are available, separate analyses by tumor size are evaluated.

Clinical Context and Test Purpose

The purpose of radiofrequency ablation (RFA) in patients who have either primary or metastatic liver tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of RFA improve the net health outcome in patients with primary or metastatic liver tumors?

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

Patients

The relevant populations of interest are patients with either primary or metastatic liver tumors.

Interventions

The test being considered is RFA. 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.

Comparators

The following therapy is currently being used to make decisions about operable tumors: surgical resection. The following therapies are currently being used for inoperable tumors: systemic therapy, other locally ablative procedures (eg, percutaneous ethanol injection [PEI], percutaneous acetic acid injection, transhepatic arterial chemoembolization, cryoablation, microwave ablation), and standard of care.

Outcomes

Outcomes of interest include overall survival (OS), tumor progression, recurrence, and treatment response.

Timing

Recurrence may occur weeks or months following initial treatment. OS can be measured in months or years of follow-up.

Setting

RFA is typically delivered in a tertiary care setting.

RFA to Treat of Primary, Operable Hepatocellular Carcinoma

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

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Systematic Reviews

Lan et al (2016) published a network meta-analysis comparing different interventional treatments for early-stage HCC. Patients in these studies met the Milan criteria, with a single tumor of 5 cm or less or up to 3 nodules of 3 cm or less. Over two-thirds of the studies limited tumor size to 3 cm or less. Twenty-one RCTs with 2691 patients were included and compared 6 treatments: TACE, RFA, PEI, hepatic resection, TACE plus RFA, and RFA plus PEI. The studies were rated at a low-to-moderate risk of bias, lack of blinding being the most substantial limitation. The primary outcome measures were OS at 1, 3, and 5 years posttreatment, and the treatments were rank-ordered using both direct and indirect comparisons. The combination of RFA plus TACE led to the highest OS rates at 1, 3, and 5 years. RFA alone ranked fifth out of the 6 treatments and had a superior rank only to PEI. In a matched comparison of RFA and surgical resection, RFA led to OS rates that were statistically lower than those of resection at 3 years but did not differ significantly from resection at 1 or 5 years. Interpretation of this network meta-analysis is limited by the heterogeneous patient populations. For example, a study by Peng et al (2010) included patients with recurrent tumors, while one by Morimoto et al (2010) included patients who had inoperable tumors. Additionally, the studies by Cheng et al (2008) and DeAngelis et al (2009), with the most direct comparison with TACE plus RFA, were withdrawn.

In a Cochrane review, Weis et al (2013) compared studies of RFA for HCC with other interventions. Moderate-quality evidence demonstrated hepatic resection had survival outcomes superior to those for RFA; however, resection might have greater complication rates and longer hospital stays.

Other systematic reviews and meta-analyses have also reported superior survival and lower recurrence rates with hepatic resection compared with RFA, though resection was accompanied by higher rates of complications. These findings support the use of RFA only for unresectable HCC.

Randomized Controlled Trials

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). OS and recurrence-free survival at 1, 3, 5, and 10 years did not differ statistically between the 2 groups (see Table 1).

Liu et al (2016) published an RCT that compared surgical resection with TACE plus RFA for HCC. A total of 200 patients within the Milan criteria were included in the trial and followed for 5 years. Tumor sizes ranged from 0.6 to 5.0 cm, with a median of 3.0 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 (see Table 1). 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 3.0 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. Hepatitis B DNA was a significant risk factor for OS. Complications were

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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 surgical resection for small tumors.

Table 1. Survival Following Surgical Resection vs RFA Alone or TACE Plus RFA for Resectable HCC

Outcomes	1 Year, %	2 3 Years, %	3 5 Years, %	10 Years, %
Ng et al (2017)				
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)				
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; RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization.

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. 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 2).

Table 2. 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	0.02
Surgical resection, n=70	89.4	65.1	61.9	
3.1 to 5.0 cm				
RFA-PEI, n=64	86.4	65.1	55.4	0.13
Surgical resection, n=60	88.9	64.5	49.6	
Recurrence-free survival				
2.1 to 3.0 cm				
RFA plus PEI	79.6	54.7	45.1	0.02
Surgical resection	57.6	43.9	31.7	
3.1 to 5.0 cm				
RFA plus PEI	53.5	29.4	24.0	

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Surgical resection	42.2	26.6	21.9	0.71
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Adapted from Chen et al (2018).
HCC: hepatocellular carcinoma; PEI: percutaneous ethanol injection; RFA: radiofrequency ablation.

Kutlu et al (2017) compared outcomes for RFA, resection, or transplantation in patients from the Surveillance, Epidemiology, and End Results database. A total of 1894 patients treated between 2004 and 2013 with HCC tumors measuring up to 50 mm met study criteria. Outcomes from the 3 treatment arms were compared for lesions 20 mm or smaller, 21 to 30 mm, 31 to 35 mm, or 31 to 50 mm in order to identify the upper limit of lesion size appropriate for RFA. Transplantation resulted in significant improvements in OS compared with RFA for all tumor sizes ($p < 0.001$; see Table 3). In tumors up to 30 mm, there were no significant differences in OS between RFA and resection. However, OS was significantly lower with RFA compared with resection for tumors measuring 31 to 35 mm (adjusted HR=1.90; 95% confidence interval [CI], 1.07 to 3.38; $p=0.028$) or 31 to 50 mm (HR=1.69; 95% CI, 1.24 to 2.31; $p=0.001$). The study found that even a small increase in lesion size over 30 mm decreased OS compared with resection or transplantation.

Table 3. Mean Percent Overall Survival in Months by Treatment and Lesion Size

Lesion Size	RFA (95% CI), %	Resection (95% CI), %	Transplantation (95% CI), %
≤20 mm	60.47 (50.12 to 70.82)	69.81 (62.81 to 76.80)	80.78 (75.72 to 85.85)
21 to 30 mm	60.92 (54.11 to 67.73)	69.71 (63.55 to 75.86)	77.28 (71.04 to 83.54)
31 to 35 mm	47.31 (40.02 to 54.60)	62.34 (56.10 to 68.58)	76.66 (68.65 to 84.67)
31 to 50 mm	48.87 (43.49 to 54.25)	65.44 (60.77 to 70.50)	76.74 (70.91 to 82.57)

Adapted from Kutlu et al (2017).

CI: confidence interval; RFA: radiofrequency ablation.

Additional observational studies published since the systematic reviews have reported inconsistent results, with some finding no difference in survival outcomes between RFA and resection, and some finding resection to be superior to RFA.

Section Summary: RFA to Treat Primary, Operable Hepatocellular Carcinoma

The evidence on RFA as a primary treatment of primary, operable HCC includes RCTs, meta-analyses of these RCTs, database analyses, 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. Results from observational studies have suggested that RFA alone or RFA plus TACE could be as effective as resection for small HCC tumors. 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. In a network meta-analysis, TACE plus RFA was found to be more effective than surgery, TACE, or RFA alone. This network meta-analysis did not evaluate efficacy based on lesion size. Additionally, the results of this analysis were based on indirect comparisons with heterogeneous populations and should be confirmed in a prospective randomized trial. Further study in a multicenter RCT



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would permit greater certainty whether RFA, with or without TACE, is as effective as surgical resection in treating HCC tumors 30 mm or smaller.

RFA as a Primary Treatment of Inoperable HCC

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

Systematic Reviews

A TEC Assessment (2003) addressed RFA for the treatment of unresectable primary or metastatic liver tumors. 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. Reviewers included 14 RCTs (total 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 (total N=766 patients), comparing RFA with PEI for treatment of HCC nodules up to 3 cm. 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. 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, disease-free survival (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). 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. 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

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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

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. The HCC nodules ranged in size from 2.1 to 6.5 cm. The primary outcome was OS at 3 years. The OS rates at 1, 2, and 3 years were 60%, 35%, and 26% in the combined therapy group and 37% and 0% at 1 and 2 years in the chemotherapy-alone arm (HR=2.87; 95% CI, 1.61 to 5.39), respectively.

Section Summary: RFA as a Primary Treatment of Inoperable HCC

Randomized and nonrandomized trials have compared RFA with alternative treatments for HCC in individuals 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.

RFA for Inoperable HCC as a Bridge to Liver Transplant

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, relevant parts of which were most recently updated in 2018. In considering how to allocate the scarce donor organs, UNOS sought to balance the risk of death on the waiting list against the risk of recurrence after transplant. Under UNOS criteria, patients with T1 lesions (1 nodule ≤ 1.9 cm) are considered at low risk of death on the waiting list, while those with T3 lesions (1 nodule > 5.0 cm, or 2 or 3 nodules with at least 1 > 3.0 cm) are at high risk of posttransplant recurrence. Patients with T2 tumors (1 nodule ≥ 2.0 cm and ≤ 5.0 cm, or 2 or 3 nodules ≥ 1 cm and ≤ 3.0 cm) have an increased risk of dying while on the waiting list compared with those with T1 lesions and 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, in reference to a key 1996 study that examined recurrence rates of HCC by the size of the initial tumor. Note that liver transplantation for those with T3 HCC is 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 additional allocation points.

The UNOS allocation system incentivizes the use of locoregional therapies in 2 different settings: (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.

The UNOS policy addresses the role of locoregional therapy in the pretransplant setting as follows:

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“Any OPTN [Organ Procurement and Transplantation Network] Class 5 or biopsy-proven HCC lesion that was automatically approved upon initial application or extension and has subsequently undergone loco-regional treatment. OPTN Class 5T nodules qualify for continued priority points predicated on the pre-treatment classification of the nodule(s) and are defined as:

Past loco-regional treatment for HCC (OPTN Class 5 lesion or biopsy proven prior to ablation).

Evidence of persistent/recurrent HCC such as nodular or crescentic extra-zonal or intra-zonal enhancing tissue on late arterial imaging (relative to hepatic parenchyma) may be present.”

OPTN guidelines also indicate “candidates whose tumors have been ablated after previously meeting the criteria for additional MELD/PELD [Pediatric End-Stage Liver Disease] points (OPTN Class 5T) will continue to receive additional MELD/PELD points (equivalent to a 10-percentage point increase in candidate mortality) every 3 months without RRB [regional review board] review, even if the estimated size of residual viable tumor falls below stage T2 criteria.”

Candidates with HCC not meeting transplant criteria, “including those with downsized tumors whose original or presenting tumor was greater than a stage T2, must be referred to the applicable RRB for prospective review in order to receive additional priority.”

Pomfret et al (2010) summarized findings and recommendations from a national conference on outcomes of liver transplantation for patients with HCC. 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 also discussed pretransplant locoregional therapy to allow patients to maintain transplant candidacy and to downstage tumors to meet MELD criteria.

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RFA 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. 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 tumor was 9 (7.4%). Intention-to-treat analysis of all patients estimated 8-year OS at 60.0% and disease-specific survival at 89.5%.

Mazzaferro et al (2004) presented 50 patients with HCC who underwent RFA while awaiting transplantation; no patient had to be removed from the waiting list due to tumor progression over a mean wait time of 9.5 months. 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. 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. Study end points 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.

RFA to Downgrade HCC

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. Eligibility criteria for downstaging included the following: (1) 1 lesion between 5 and 8 cm; (2) 2 to 3 lesions with at least 1 lesion between 3

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and 5 cm, with total tumor diameter up to 8 cm; or (3) 4 to 5 lesions with none greater than 3 cm, with total tumor diameter up to 8 cm. 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 3 months after downstaging was required before liver transplant. Tumor downstaging was successful in 43 patients (70.5%). Thirty-five (57.4%) patients received a liver transplant, including 2 with live-donor liver transplantation. Treatment failure was observed in 18 (29.5%) patients, primarily due to tumor progression. In the explant of 35 patients who underwent a transplant, 13 had complete tumor necrosis, 17 met T2 criteria, and 5 exceeded T2 criteria. The Kaplan-Meier intention-to-treat survival rates at 1 and 4 years after downstaging were 87.5% and 69.3%, respectively. The 1- and 4-year posttransplantation survival rates were 96.2% and 92.1%, respectively. No patient had HCC recurrence after a median posttransplantation follow-up of 25 months. The only factor predicting treatment failure was pretreatment α -fetoprotein level greater than 1000 ng/mL. From this small series, the authors concluded that successful downstaging could be achieved with excellent posttransplant outcomes.

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

RFA 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. 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) 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. 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. This T3 subset was defined as a single lesion 6.5 cm or less or 3 or fewer lesions with none greater than 3 cm and with a sum of tumor diameters of 8 cm or less. These expanded criteria are known as the UCSF criteria.

The question is whether locoregional therapies (including both RFA and chemoembolization) decrease the recurrence rate in patients meeting the UCSF criteria. The authors also compared the RFS rates of those who did and did not receive locoregional therapy. For those with T2 lesions, recurrence rates were similar

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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 (described above), of 89 patients with HCC who received RFA before the liver transplant, 5 (5.6%) had HCC recurrence.

Section Summary: RFA for Inoperable HCC as a Bridge to Liver Transplant

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

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

RFA FOR INOPERABLE HEPATIC METASTASES OF COLORECTAL ORIGIN

More than half of patients with colorectal cancer (CRC) will develop liver metastases, generally with a poor prognosis. 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. 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 actuarial survival rates that historically range from 28% to 38%, but may reach 58% in appropriately selected, resectable patients without widely disseminated disease. 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

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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

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.

Weng et al (2012) reported on a meta-analysis comparing RFA with liver resection for the treatment of CRC liver metastases. 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 3 subgroups: tumors less than 3 cm, solitary tumor, and open or laparoscopic approach. However, hospital stays were significantly shorter (9.2 days vs 3.9 days, $p<0.01$) 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. 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 end points were not reported uniformly, with varying definitions of survival time, recurrence time, and complication rates. Cryotherapy (26 studies) had local recurrence rates ranging from 12% to 39%, with mean 1-, 3-, and 5-year survival rates of 84%, 37%, and 17%, respectively. Major complication rates ranged from 7% to 66%. Microwave ablation (13 studies) had local recurrence rates ranging from 5% to 13%, with mean 1-, 3-, and 5-year survival rates of 73%, 30%, and 16%, respectively, and major complication rates ranging from 3% to 16%. 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. 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]) included in the review consisted of 423 patients, with average tumor size of 2.7 cm, 4

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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 5-year survival rates following RFA were similar to those following resection, but that long-term data associated with RFA and colorectal hepatic metastases were sparse, 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. This RCT, originally designed as a phase 3 study, was completed as a phase 2 study due to slow accrual (N=119). To be included in the trial, patients had to have nonresectable liver metastases with fewer than 10 nodes and without extrahepatic disease. In the experimental arm, RFA, with or without additional resection, was given in combination with systemic therapy. The primary end point 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 4). 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 4. 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).

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. 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 53.0% for hepatic resection (p=0.98).

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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). In the key relevant comparison, RFA vs chemotherapy in chemotherapy-naïve 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=NS).

A consecutive series by Ruers et al (2007) of well-defined, previously untreated patients (N=201) without extrahepatic disease underwent laparotomy to determine therapeutic approach. 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 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). 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: RFA 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 8 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

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has fewer deleterious effects on quality of life than chemotherapy and that RFA patients recover 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.

RFA for Inoperable Hepatic Metastases of Neuroendocrine Origin

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). Seven unique studies (total 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 2 periprocedural deaths (rate, 0.7%), and the overall complication rate was 10%, including hemorrhage, abscess, viscus perforation, bile leak, biliopleural fistula, transient liver insufficiency, pneumothorax, grounding pad burn, urinary retention, pneumonia, 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%. Five-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. 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. 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, 0.5-10.0 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 vs 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. Tumor types were 36 carcinoids, 18 pancreatic islet cell, and 9 medullary thyroid cancer. Indications for study enrollment were liver metastases from neuroendocrine

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tumors, enlarging liver lesions, worsening of symptoms, and/or failure to respond to other treatment modalities and the predominance of liver disease. Patients with 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 at 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: RFA 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.

RFA for Hepatic Metastases Not of Colorectal or Neuroendocrine Origin

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). 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. Inclusion criteria were fewer than 5 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 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. 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.

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A series of 19 patients was reported by Lawes et al (2006). Eight patients had disease confined to the liver, with 11 also having stable extrahepatic disease. At the time of reporting, 7 patients, with disease confined to the liver at presentation, were alive, as were 6 patients with extrahepatic disease (median follow-up after RFA, 15 months; range, 0-77 months). Survival at 30 months was 41.6%. RFA failed to control hepatic disease in 3 patients.

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. 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. Results showed improved OS and PFS when RFA was combined with chemotherapy (hazard ratio, 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. 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. 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 cm and 5 cm predicted poorer survival.

Sarcoma

Jones et al (2010) evaluated RFA in a series of patients with sarcoma. Thirteen gastrointestinal stromal tumor patients and 12 with other histologic subtypes received RFA for metastatic disease of the liver: 12 responded to the first RFA procedure and 1 patient achieved stable disease. Two gastrointestinal stromal tumor patients received RFA on 2 occasions for separate lesions within the liver, and both responded to the second RFA procedure. Of the other subtypes, 7 patients underwent RFA to liver lesions, 5 of whom responded to RFA, 1 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 progression of a single metastasis but stable disease elsewhere.

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Louisiana

Radiofrequency Ablation of Primary or Metastatic Liver Tumors

Policy # 00182

Original Effective Date: 09/22/2005

Current Effective Date: 11/21/2018

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). 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 higher risk of recurrence and lower DFS compared with resection alone.

Section Summary: RFA 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 HCC who receive RFA, the evidence includes RCTs, meta-analyses of these RCTs, database analyses, and observational studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and morbid events. Results from these studies have suggested that RFA alone or RFA plus transhepatic arterial chemoembolization may be as effective as resection for small resectable HCC tumors, although the exact size cutoff has not been established. Some studies found that overall survival was similar in patients receiving RFA or resection when tumor size was 3 cm or less; however, overall survival 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 transhepatic arterial chemoembolization, 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 HCC

For individuals who have inoperable HCC who receive RFA, the evidence includes randomized trials and several systematic reviews and meta-analyses. Relevant outcomes are overall survival, 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.

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Inoperable HCC Awaiting Liver Transplant

For individuals who have inoperable HCC awaiting liver transplant who receive RFA, the evidence includes small case series. Relevant outcomes are overall survival, 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 overall survival, 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 8 years compared with chemotherapy alone. In addition, prospective studies have demonstrated that overall survival 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 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 overall survival, 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.

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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 overall survival, 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.

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Policy History

Original Effective Date: 09/22/2005

Current Effective Date: 11/21/2018

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| 09/07/2005 | Medical Director review |
| 09/20/2005 | Medical Policy Committee review |
| 09/22/2005 | Quality Care Advisory Council approval |
| 07/07/2006 | Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged. |
| 01/10/2006 | Medical Director review |
| 01/17/2006 | Medical Policy Committee approval. Coverage eligibility updated to include investigational status of RFA as a bridge to liver transplant. |
| 01/09/2008 | Medical Director review |
| 01/23/2008 | Medical Policy Committee approval. Added "in the absence of extrahepatic metastatic disease" to the patient selection criteria. |
| 01/07/2009 | Medical Director review |
| 01/14/2009 | Medical Policy Committee approval. No change to coverage eligibility. |
| 01/07/2010 | Medical Policy Committee approval |
| 01/20/2010 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 01/06/2011 | Medical Policy Committee review |
| 01/19/2011 | Medical Policy Implementation Committee approval. Extensively revised coverage statements and added policy guidelines. |
| 01/06/2011 | Medical Policy Committee review |
| 01/19/2011 | Medical Policy Implementation Committee approval. Rationale revised. No change to coverage. |
| 03/01/2012 | Medical Policy Committee review |
| 03/21/2012 | Medical Policy Implementation Committee approval |
| 01/03/2013 | Medical Policy Committee review |
| 01/09/2013 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 01/09/2014 | Medical Policy Committee review |
| 01/15/2014 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 01/08/2015 | Medical Policy Committee review |

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- 01/21/2015 Medical Policy Implementation Committee approval. Added phrase “unless RFA is used as a bridge to transplant” to the medically necessary indication for RFA in those with primary HCC and metastatic colorectal or neuroendocrine tumors for HCC should also not be candidates for liver transplantation.
 - 01/07/2016 Medical Policy Committee review
 - 01/22/2016 Medical Policy Implementation Committee approval. No change to coverage.
 - 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
 - 01/05/2017 Medical Policy Committee review
 - 01/18/2017 Medical Policy Implementation Committee approval. No change to coverage.
 - 11/02/2017 Medical Policy Committee review
 - 11/15/2017 Medical Policy Implementation Committee approval. Policy statements reformatted and edited for clarity and specificity, including the distinction between operable and non-operable tumors and the Milan criteria. The intent of the statements is unchanged. A statement has been added that RFA for operable HCC is considered investigational.
 - 11/08/2018 Medical Policy Committee review
 - 11/21/2018 Medical Policy Implementation Committee approval. No change to coverage.
- Next Scheduled Review Date: 11/2019

Coding

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Code Type	Code
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HCPCS	No codes
ICD-10 Diagnosis	C22.0-C22.9, C78.7, C7B.02

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Louisiana

Radiofrequency Ablation of Primary or Metastatic Liver Tumors

Policy # 00182

Original Effective Date: 09/22/2005

Current Effective Date: 11/21/2018

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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