Radiofrequency Ablation of Primary or Metastatic Liver Tumors

Policy Number: 7.01.91  Last Review: 9/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for radiofrequency ablation of liver tumors when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Radiofrequency ablation of primary, inoperable (eg, due to location of lesion[s] and/or comorbid conditions), hepatocellular carcinoma may be considered medically necessary under the following conditions:

- as a primary treatment of hepatocellular carcinoma 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.

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.

When Policy Topic is not covered
Radiofrequency ablation of primary, inoperable, hepatocellular carcinoma is considered 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.

Radiofrequency ablation of primary, operable hepatocellular carcinoma is investigational.
Radiofrequency ablation for hepatic metastasis is considered **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.

**Considerations**
Explicit criteria have not been established for radiofrequency ablation of hepatocellular carcinoma (HCC) or cancer metastatic to the liver.

For the medically necessary indications noted above for RFA in those with primary HCC and metastatic colorectal or neuroendocrine tumors, patients should not be candidates for curative resections (e.g., due to location of lesion(s) and/or comorbid conditions) and for HCC should also not be candidates for liver transplantation unless RFA is used as a bridge to transplant.

Candidacy for RFA treatment of HCC is based on several factors that include number of tumor foci (nodules), size of tumor foci, and accessibility. In general, the randomized trials for HCC have included patients with 3 or fewer hepatic lesions measuring 5 cm or less (and often 3 cm or less) using current technology.

Candidacy for RFA treatment of metastatic colorectal cancer or is based on several factors that include number of tumor foci, size of tumor foci, and accessibility. In general, published studies with metastatic colorectal cancer have included patients with 4-5 or fewer hepatic lesions measuring 5 cm or less using current technology.

### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| 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: With inoperable hepatic metastases of | Interventions of interest are:  
- Radiofrequency ablation | Comparators of interest are:  
- Chemotherapy  
- Other locally | Relevant outcomes include:  
- Overall survival  
- Disease-specific survival  
- Symptoms |
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 and, in some cases, may be retreated. RFA may be performed percutaneously, laparoscopically, or as an open procedure.

### 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 of these RCTs, and a database analysis. Relevant outcomes are overall survival (OS), 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. The studies reviewed have suggested that RFA is inferior to hepatic resection for tumors of 50 mm or less in size but may lead to OS rates similar to resection of tumors less than 3 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 30 mm 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. Surgical resection of HCC, compared with RFA, has shown superior survival, supporting the use of RFA for unresectable HCC and for those who are not candidates for surgical resection. Response rates have demonstrated that, in patients with small foci of HCC (≤3 lesions), RFA appears to be better than 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 with unresectable colorectal liver metastases. However, an RCT assessing RFA combined with chemotherapy found improved survival at 8 years compared with chemotherapy alone. In addition, prospective studies have demonstrated that OS following RFA is at least equivalent to and likely better than that 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 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 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 more than 1 ablative method or very small subsets of larger case series of patients with various diagnoses. The available evidence indicates 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. 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 case series. Relevant outcomes are OS, disease-specific survival, symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology RFA on health outcomes.

**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. 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.

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

**RADIOFREQUENCY ABLATION**
Radiofrequency ablation (RFA) has been investigated as a treatment for unresectable hepatic tumors, both as primary treatment 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).

Note that RFA of extrahepatic tumors is addressed in a separate policy.

**Rationale**

This evidence review was originally created in December 2000 and has been updated regularly with searches of the MEDLINE database. The most recent literature review was performed through June 2, 2017.

Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

**RADIOFREQUENCY ABLATION AS A TREATMENT OF OPERABLE HEPATOCELLULAR CARCINOMA**

The evidence on radiofrequency ablation (RFA) as a treatment of resectable hepatocellular carcinoma (HCC) includes randomized controlled trials (RCTs), meta-analyses, an analysis from a multicenter database, and an RCT that combined RFA with transhepatic arterial chemoembolization (TACE).

**Systematic Reviews**

In 2016, Lan et al published a network meta-analysis comparing different interventional treatments for early-stage HCC.(1) Patients in these studies met the Milan criteria, with a single tumor of 5 cm or less or up to 3 nodules less than 3 cm. Over two-thirds of the studies limited tumor size to 3 cm or less. A total of 21 RCTs with 2691 patients were included that compared 6 different treatments. These were TACE with RFA, percutaneous ethanol injection (PEI), and 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 overall survival (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 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, 1 study included patients with recurrent tumors,(2) while another included patients who had inoperable tumors.(3) In addition, one of the studies with the most direct comparison with TACE plus RFA has been withdrawn.(4)
In a 2013 Cochrane review, Weis et al assessed studies on RFA for HCC versus other interventions. Moderate-quality evidence demonstrated hepatic resection had superior survival outcomes compared with RFA; however, resection might have greater rates of complications and longer hospital stays. Other systematic reviews and meta-analyses have also found superior survival with hepatic resection but higher rates of complications than RFA. This finding reinforces the use of RFA only for unresectable HCC.

**Randomized Controlled Trials**

In 2016, Liu et al published a RCT that compared surgical resection to 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 higher 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 (HBV-DNA) and platelet count. HBV-DNA was a significant risk factor for OS. Complications were higher in the surgical resection group (23.0%) than in the TACE plus RFA group (11.0%; p=0.24). It cannot be determined from this trial whether RFA alone is as effective as surgical resection for these small tumors.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>1 Year</th>
<th>2 Years</th>
<th>3 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical resection</td>
<td>97.0</td>
<td>83.7</td>
<td>61.9</td>
</tr>
<tr>
<td>TACE plus RFA</td>
<td>96.0</td>
<td>67.2</td>
<td>45.7</td>
</tr>
<tr>
<td>Recurrence-free survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical resection</td>
<td>94.0</td>
<td>68.2</td>
<td>48.4</td>
</tr>
<tr>
<td>TACE plus RFA</td>
<td>83.0</td>
<td>44.9</td>
<td>35.5</td>
</tr>
</tbody>
</table>

HCC: hepatocellular carcinoma; RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization.

**Observational Studies**

In 2017, Kutlu et al compared outcomes for RFA, resection, or transplantation in patients from the Surveillance, Epidemiology, and End Results (SEER) 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 treatments 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 2). 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 to 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 2. Mean Percent Overall Survival in Months by Treatment and Lesion Size

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

CI: confidence interval; RFA: radiofrequency ablation.

Section Summary: Radiofrequency Ablation as a Treatment of Early-Stage Hepatocellular Carcinoma

The evidence on RFA ablation as a primary treatment of early-stage resectable HCC includes RCTs, meta-analyses of these RCTs, and a database analysis. Results from these studies have suggested that RFA alone or RFA plus TACE may be as effective as resection for small HCC tumors, although the exact size cutoff has not been clearly established. The studies reviewed have suggested that RFA is inferior to hepatic resection for tumors of 5 cm or less, but may lead to OS rates similar to those for resection of tumors less than 3 cm. In a network 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. In addition, the results of this network meta-analysis were based on indirect comparisons with heterogeneous populations and should be confirmed in a prospective randomized trial. Further study in a multicenter RCT would permit greater certainty whether RFA, with or without TACE, is as effective as surgical resection in treating HCC tumors 30 mm or smaller. (See evidence review 8.01.11 for further information on TACE.)

RFA AS A PRIMARY TREATMENT OF INOPERABLE HCC

The evidence includes RCTs comparing RFA to other nonsurgical interventions, as an adjunct to chemotherapy, and systematic reviews of the RCTs.

Systematic Reviews

A 2003 TEC Assessment addressed RFA in the treatment of unresectable primary or metastatic liver tumors.(12) Since that report, many systematic reviews and meta-analyses have been published on RFA for HCC. We discuss some below.

Majumdar et al (2017) published a Cochrane systematic review and network meta-analysis of management of early and very early stage HCC.(13) Reviewers included 14 RCTs (total N=2533 patients) of nonsurgical treatments compared to each other, sham or no intervention in patients with unresectable HCC. 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.

In a 2013, Shen et al reported on a systematic review of 4 RCTs and quasi-RCTs (total N=766 patients), to compare RFA with PEI for treatment of HCC nodules up to 3 cm.(14) 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.(15) 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. Outcome data collected 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 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 on RFA compared with microwave ablation were inconclusive. Reviewers concluded that RFA can achieve good clinical outcomes for unresectable HCC.

In a 2013 meta-analysis comparing RFA with cryoablation for HCC, Huang et al evaluated 3 prospective studies and 1 retrospective study.(16) Included in the studies were 180 RFA and 253 cryoablation patients. RFA was significantly superior to cryoablation in rates of complications (OR=2.80; 95% CI, 1.54 to 5.09), local recurrence of patient (OR=4.02; 95% CI, 1.93 to 8.39), and local recurrence of tumor (OR=1.96, 95% CI, 1.12 to 3.42). However, mortality did not differ significantly (OR=2.21; 95% CI, 0.45 to 10.8) between groups.

Randomized Controlled Trials
In 2016, Giorgio et al reported on an RCT comparing RFA plus chemotherapy with chemotherapy alone in 99 patients with unresectable HCC invading the portal vein.(17) The HCC nodules ranged in size from 2.1 to 6.5 cm. The primary outcome was OS at 3 years. 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).

Section Summary: RFA as a Primary Treatment of Inoperable HCC
Randomized and nonrandomized trials have compared RFA to alternative treatments for HCC in individuals who do not qualify 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
on RFA versus 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 PATIENTS WITH INOPERABLE HCC AWAITING TRANSPLANT

In 2002, the United Network for Organ Sharing (UNOS) introduced a new liver allocation system—Model for End-stage Liver Disease (MELD)—for adult patients awaiting liver transplant. In considering how to allocate the scarce donor organs, UNOS sought to balance risk of death on the waiting list against 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 to 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 the recurrence rate of HCC according to 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 loses additional allocation points.

Therefore, the UNOS allocation system provides incentives to use locoregional therapies in 2 different settings: (1) to prevent progress of T2 tumors while on the waiting list; or (2) to downsize T3 tumors to T2 status to meet the UNOS criteria for additional allocation points.

These 2 indications are discussed further here. It should be noted that the UNOS policy addresses the role of locoregional therapy in the pretransplant setting as follows:

“Any OPTN 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.” (18)

Pomfret et al (2010) summarized findings and recommendations from a national conference on outcomes of liver transplantation for patients with HCC. (20) 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 transplant. They 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 had 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 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. In addition, “Concern 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 general 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. The article discussed pretransplant loco regional therapy to allow patients to maintain transplant candidacy, as well as to downstage to meet MELD criteria.

**RFA to Prevent Tumor Progression**

Several prior studies have reported dropout rates of wait-listed 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. In addition, 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.

In 2017, Lee et al reported a 10-year intention-to-treat analysis of RFA to prevent progression and reduce the chance of posttransplant HCC.(21) Patients were included in this analysis if they had cirrhosis with treatment-naive HCC, were on the transplant waiting list, and had RFA alone 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 with 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 liver transplant, 16 (13.2%) were delisted, 14 (11.6%) died, and 2 (1.7%) remained on the waitlist. The number of patients who were 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) reported on 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.(22) 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.(23) 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 with RFA with 33 untreated controls.(24) Study end points included patient survival and DFS, tumor recurrence, explant tumor viability, and the ability of magnetic resonance imaging (MRI) to detect viable tumor after therapy. Both cohorts had similar demographic, radiographic, and pathologic characteristics, although untreated patients waited longer for transplantation (119 [untreated] days vs 54 [RFA] days 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 MRI 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%), 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.(25) Eligibility criteria for downstaging included: (1) 1 lesion larger
than 5 cm and up to 8 cm; (2) 2 to 3 lesions with at least 1 lesion larger than 3 cm and not exceeding 5 cm, with total tumor diameter up to 8 cm; or (3) 4 to 5 lesions with none larger than 3 cm, with total tumor diameter up to 8 cm. TACE and laparoscopic RFA (LRFA) either alone or in combination were the main methods used: 11 patients received LRFA alone, 14 received TACE and LRFA, 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 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 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 greater than 1000 ng/mL. From this small series, the authors concluded that successful downstaging can be achieved with excellent posttransplant outcomes.

Yao et al (2005) 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.(26)

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 can 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.(27-31) Some patients with T3 lesions are cured with liver transplant, although most experience recurrent tumor. For example, in the seminal 1996 study,(19) the 4-year RFS was 92% in those who met the Milan criteria compared with 59% in those who did not; additional studies confirmed this difference in the RFS rate.(26) However, other institutions have reported similar outcomes with expanded criteria. For example, Yao et al (2002) reported similar RFS after transplant in patients with T2 tumors and a subset of those with T3 tumors.(29) 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
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 was 85.9% for those who received locoregional therapy compared with 51.4% for those who did not. When the data for T2 and T3 lesions were grouped, the 5-year RFS was 93.8% for those who received locoregional therapy compared with 80.6% for those who did not. The authors concluded that preoperative locoregional therapy may confer a survival benefit in those with T2 or T3 lesions.

The authors noted several limitations to the study, 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. In addition, no protocol specified which type of locoregional therapy to offer different patients. These therapies are only offered to those patients with adequate liver reserve; such patients may have an improved outcome regardless of the preoperative management.

In the study by Lee et al (described above), of 89 patients with HCC who received RFA prior to liver transplant, 5 (5.6%) had HCC recurrence. (21)

**Section Summary: RFA for Patients With Inoperable HCC Awaiting Transplant**

The 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 the 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 LIVER METASTASES OF COLORECTAL ORIGIN**

**Colon Cancer**

More than half of patients with colorectal cancer (CRC) will develop liver metastases, generally with a poor prognosis. (32) A median survival of 21 months has been observed in patients with a single CRC liver metastasis; those with several unilobar lesions have median survival of 15 months; and those with disseminated metastases have 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 (5-
FU) or 5-FU 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, however, 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 those for whom surgery is contraindicated typically are treated with systemic chemotherapy, with poor results and considerable adverse effects. Alternatively, RFA has been proposed to treat metastatic CRC in the liver.

**Systematic Reviews**

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

In 2012, Weng et al reported 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 in liver resection than in RFA (relative risk [RR], 1.377; 95% CI, 1.246 to 1.522; RR=1.474; 95% CI, 1.284 to 1.692, respectively). DFS was also significantly longer in liver resection than RFA at 3 and 5 years (RR=1.735; 95% CI, 1.483 to 2.029; RR=2.227; 95% CI, 1.823 to 2.720, respectively). While postoperative morbidity with liver resection was significantly higher than with RFA (RR=2.495; 95% CI, 1.881 to 3.308), mortality did not differ significantly between treatments. Liver resection also performed significantly better 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 is limited by the retrospective nature of most studies.

A 2011 systematic review by Pathak et al 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 study inclusion criteria were minimum 1-year follow-up and more than 10 patients. In all, 226 studies were identified, 75 of which 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. End points were not always reported uniformly, with varying definitions of survival time, recurrence time, and complication rates. Cryotherapy (26 studies) had local
recurrence rates of 12% to 39%, with mean 1-, 3-, and 5-year survival rates of 84%, 37%, and 17%, respectively. The major complication rate ranged from 7% to 66%. Microwave ablation (13 studies) had a local recurrence rate of 5% to 13%, with a mean 1-, 3-, and 5-year survival of 73%, 30%, and 16%, respectively, and a major complication rate ranging from 3% to 16%. RFA (36 studies) had a local recurrence rate of 10% to 31%, with a mean 1-, 3-, and 5-year survival of 85%, 36%, and 24%, respectively, with major complication rate ranging from 0% to 33%. The authors concluded that ablative therapies offer significantly improved survival compared with palliative chemotherapy alone, with 5-year survival rates of 17% to 24%, and that complication rates of commonly used techniques are low.

A 2010 review by Guenette and Dupuy summarized the literature on the use of RFA for colorectal hepatic metastases.(38) Approximately 17 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, reported in 12 studies, ranged from 2% to 55.3% (mean, 24.5%). The largest study series (Lencioni et al) 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 in greatest dimension, and no extrahepatic disease.(34) OS in the Lencioni study at 1, 3, and 5 years was 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 have failed recruitment, and patients with 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 in patients with unresectable disease.

Randomized Controlled Studies

In 2012 and 2017, Ruers et al published the results of a multicenter RCT that compared RFA plus systemic treatment to systemic treatment alone for unresectable colorectal liver metastases.(39,40) This RCT, originally designed as a phase 3 study, was completed as a phase 2 study due to slow accrual (N=119 patients). 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 higher than 38% in the experimental arm with ITT analysis. At 3 years, OS did not differ significantly between groups (see Table 3). However, there was a significant improvement in PFS, (HR=0.74; 95% CI,0.42 to 0.95; p=0.025), which corresponded to a difference in PFS at 3 years from 10.6% in the systemic therapy arm to 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 3. Percent Overall Survival at 3, 5, and 8 Years

<table>
<thead>
<tr>
<th>Treatment</th>
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<th>5 Years (95% CI)</th>
<th>8 Years (95% CI)</th>
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<tr>
<td>Combined treatment, %</td>
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<td>43.1 (30.3 to 55.3)</td>
<td>35.9 (23.8 to 48.2)</td>
</tr>
<tr>
<td>Systemic alone, %</td>
<td>55.2 (41.6 to 66.9)</td>
<td>30.3 (19.0 to 42.4)</td>
<td>8.9 (3.3 to 18.1)</td>
</tr>
</tbody>
</table>

CI: confidence interval.

Nonrandomized Comparative Studies

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

In 2016, Hof et al compared outcomes from RFA or hepatic resection in patients with hepatic metastases from CRC.(41) There were 431 patients included from 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 to 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).

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 by hepatobiliary surgeon), and systemic chemotherapy alone (n=70).(42) In the key relevant comparison, RFA versus 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=NS).

In a second trial, a 2007 consecutive series of well-defined, previously untreated patients (N=201) without extrahepatic disease underwent laparotomy to determine therapeutic approach.(43) Three groups were identified: those amenable to hepatic resection (n=117); those for whom resection plus local ablation were indicated (RFA, n=27; cryoablation, n=18); and those deemed unresectable and unsuitable 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 per lesion), 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 per lesion; p=NS, ablated vs chemotherapy). Results from 2 validated quality of life instruments (EuroQol-5D, EORTC QLQ C-30)
showed that patients treated by 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).

In 2011, Van Tilborg et al reported long-term results in 100 patients with unresectable colorectal liver metastases who underwent a total of 126 RFA sessions (237 lesions).(44) Lesion size ranged from 0.2 to 8.3 cm (mean, 2.4 cm). Mean follow-up time 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 the success of the procedure 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, at 21.4% versus 6.5%, respectively (p=0.009). Mean survival time from the time of RFA was 56 months (95% CI, 45 to 67 months).

**Section Summary: RFA as a Primary Treatment of Inoperable Liver Metastases of Colorectal**

There are no RCTs of RFA versus alternative treatments for patients with unresectable colorectal liver metastases. However, an RCT of RFA combined with chemotherapy found improved survival at 8 years compared to chemotherapy alone. In addition, 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 uncontrolled 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, based on historical outcomes. Evidence from 1 comparative study has suggested RFA has less deleterious effect on quality of life than chemotherapy and that RFA patients recover quality of life significantly faster than chemotherapy recipients. Patients treated with RFA in different series may have better prognosis than those who undergo chemotherapy, meaning that patient selection bias may at least partially explain the better outcomes observed following RFA.

**RFA FOR INOPERABLE LIVER METASTASES OF NEUROENDOCRINE ORIGIN**

A systematic review of RFA as treatment for unresectable metastases from neuroendocrine tumors was published in 2015.(45) Seven unique studies (total N=301 patients) included in the review, all were retrospective case series from a single institution. 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 rate of complications 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 symptom relief ranging from 14 to 27 months. There was a high degree of variability in the length of follow-up and surveillance used for follow-up, and a
wide range of local recurrence rates, from less than 5% to 50%, The reported 5-year survival rates ranged from 57% to 80%.

**Case Series**

Berber and Siperstein (2008) analyzed a large series of liver tumors treated with RFA. Of 1032 tumors in the study, 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 versus 83% at 1 year and 97% at 2 years for colorectal metastases. Eight neuroendocrine tumors were eligible for repeat RFA; 7 were retreated, and 1 was not. Symptom control and survival were not reported.

Mazzaglia et al (2007) reported on a series gathered over 10 years for 63 patients with neuroendocrine metastases who were treated with 80 sessions of RFA. Tumor types were 36 carcinoid, 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 predominance of disease in the liver; 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 and the mean tumor size was 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.

Elias et al (2009) reported on 16 patients who underwent a 1-step procedure comprising a combination of hepatectomy and RFA for treatment of gastroenteropancreatic endocrine tumors. A mean of 15 liver tumors per patient were surgically removed, and a mean of 12 were ablated using RFA. Three-year survival and DFS rates were similar to those observed in the authors’ preliminary series of 47 patients who had hepatectomy with a median of 7 liver tumors per patient.

Venkatesan et al (2009) assessed 6 patients treated for pheochromocytoma metastases. Complete ablation was achieved in 6 of 7 metastases. Mean follow-up was 12.3 months (range, 2.5-28 months).
Section Summary: RFA as a Primary Treatment of Unresectable Liver 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 more than 1 ablative method or very small subsets of larger case series of patients with various diagnoses. The available evidence indicates 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.

RFA AS A PRIMARY TREATMENT OF UNRESECTABLE LIVER METASTASES OF OTHER ORIGIN

Breast Cancer
A number of case series have reported on use of RFA to treat breast cancer liver metastases. In 2014, Veltri et al analyzed 45 women treated with RFA for 87 breast cancer liver metastases (mean size, 23 mm).(50) Complete ablation was seen on initial follow-up in 90% of tumors, but tumor recurrence occurred in 19.7% within 8 months. RFA did not impact OS, which at 1 year was 90% and at 3 years was 44%.

In a retrospective review, Meloni et al (2009) assessed local control and intermediate- and long-term survival in 52 patients.(51) 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 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 5-year survival was 32%. Patients with tumors 2.5 cm in diameter or larger had a worse prognosis than those with smaller tumors. The authors concluded that these 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, technical success (tumor ablation) was achieved in 107 (96%) metastases.(52) 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, with the exception of skeletal metastases.

A series of 19 patients was reported by Lawes et al (2006).(53) Eight patients had disease confined to the liver, with 11 also having stable extrahepatic disease. At the time of the report, 7 patients, with disease confined to the liver at presentation, were alive, as were 6 with extrahepatic disease; median follow-up after RFA was 15 months (range, 0-77 months). Survival at 30 months was 41.6%. RFA failed to control hepatic disease in 3 patients.
Sarcoma
Jones et al (2010) evaluated RFA in a series of patients with sarcoma.(54) Thirteen gastrointestinal stromal tumor (GIST) patients and 12 with other histologic subtypes received RFA for metastatic disease in the liver: 12 responded to the first RFA procedure and 1 achieved stable disease. Two GIST 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 underwent RFA to liver lesions, 5 of whom responded to RFA, 1 progressed, and 1 was not assessable at the time of analysis. RFA was well-tolerated in this series of sarcoma patients. RFA may have a role in patients with GIST who have progression in a single metastasis but stable disease elsewhere. The authors advised conducting further larger studies to better define the role of this technique in this patient population.

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).(55) After a median follow-up of 35.8 months, 44 patients had recurrence (intrahepatic only, n=16; extrahepatic only, n=11; both, n=17). The 1-, 3-, and 5-year OS rates were 91.5%, 65.4%, and 27.1%, respectively. The authors recommended that patients with metastatic disease who can be rendered surgically free of disease be considered for potential hepatic resection.

Section Summary: RFA as a Primary Treatment of Unresectable Liver Metastases of Other Origin
For cancers other than CRC or neuroendocrine tumors, small case series are not sufficient evidence to determine whether RFA improves outcomes.

SUMMARY OF EVIDENCE
For individuals who have operable hepatocellular carcinoma (HCC) who receive radiofrequency ablation, the evidence includes RCTs, meta-analyses of these RCTs, and a database analysis. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and morbid events. Results from these studies suggest that RFA alone or RFA plus TACE may be as effective as resection for small resectable HCC tumors, although the exact size cutoff has not been clearly established. The studies reviewed suggest that RFA is inferior to hepatic resection for tumors of 5 cm or less in size, but may lead to OS rates that are similar to resection for tumors that are less than 3 cm. Further study in a multicenter RCT would permit greater certainty regarding whether RFA, with or without TACE, is as effective as surgical resection in treating HCC tumors 30 mm or smaller. The evidence is insufficient to determine the effects of the technology RFA on health outcomes.

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. Surgical resection of HCC, compared with RFA, has shown superior survival, supporting the use of RFA for unresectable HCC and for those who are not candidates for surgical resection. Response rates have demonstrated
that, in patients with small foci of HCC (≤3 lesions), RFA appears to be better than 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.

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.

For individuals with 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 of RFA versus alternative treatments for patients with unresectable colorectal liver metastases. However, an RCT of RFA combined with chemotherapy found improved survival at 8 years compared to chemotherapy alone. In addition, prospective studies have demonstrated that overall survival following RFA is at least equivalent and likely better than that for currently accepted systemic chemotherapy in well-matched patients with unresectable hepatic metastatic colorectal cancer (CRC) who do not have extrahepatic disease, and results from a number of uncontrolled case series also have suggested RFA of hepatic CRC metastases produces long-term survival that is at minimum equivalent but likely superior to historical outcomes achieved with systemic chemotherapy. Evidence from 1 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, however, that patients treated with RFA in different series may have had better prognoses than those who underwent chemotherapy, suggesting patient selection bias may at least partially explain the apparent better outcomes observed following RFA. can be achieved by RFA in individuals whose symptoms are not controlled by systemic therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

The evidence on RFA for patients with inoperable liver metastases of neuroendocrine origin consists of 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 include small numbers of patients or subsets of patients in reports of more than 1 ablative method or very small subsets of larger case series of patients with various diagnoses. The available evidence indicates 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have hepatic metastases other than colorectal or neuroendocrine origin who receive RFA, the evidence includes 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. 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 published a position statement on percutaneous radiofrequency ablation (RFA) for the treatment of liver tumors in 2009.(56) 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 is insufficient to support any recommendations supporting or refuting the use of RFA in other diseases.

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

NCCN guidelines on hepatobiliary cancers (v.2. 2017) 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).(57)

The guidelines on colon cancer metastatic to the liver (v.2. 2017) 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).(58)

NCCN guidelines for neuroendocrine tumors (v.2. 2017) 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.(59)
U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

MEDICARE NATIONAL COVERAGE
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT02169765</td>
<td>Hepatic Resection Versus Radiofrequency Ablation for Early-stage Hepatocellular Carcinoma: a Randomized Controlled Trial</td>
<td>120</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT02192671</td>
<td>Hepatic Resection Versus Radiofrequency Ablation for Patients With Hepatocellular Carcinoma and Portal Hypertension</td>
<td>120</td>
<td>Dec 2018</td>
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<tr>
<td>NCT03127072</td>
<td>A Prospective, Randomized, One-center Study Assessing Overall Survival Using RFA Plus Chemotherapy ± Target Therapy and Chemotherapy ± Target Therapy Alone in Patients With Unresectable Colorectal Cancer Liver Metastases</td>
<td>200</td>
<td>Dec 2021</td>
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<td>Unpublished</td>
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<tr>
<td>NCT01233544</td>
<td>The International Liver Tumor Group RAS-trial Radiofrequency Ablation Versus Stereotactic Body Radiation Therapy for Colorectal Liver Metastases: A Randomized Trial</td>
<td>300</td>
<td>Dec 2016</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References:


Billing Coding/Physician Documentation Information

47370 Laparoscopy, surgical, ablation of one or more liver tumor(s); radiofrequency

47379 Unlisted laparoscopic procedure, liver

47380 Ablation, open, of one or more liver tumor(s); radiofrequency

47382 Ablation, one or more liver tumor(s), percutaneous, radiofrequency

47399 Unlisted procedure, liver

49203 Excision or destruction, open, intra-abdominal tumors, cysts or endometriomas, 1 or more peritoneal, mesenteric, or retroperitoneal
primary or secondary tumors; largest tumor 5 cm diameter or less

49204 Excision or destruction, open, intra-abdominal tumors, cysts or endometriomas, 1 or more peritoneal, mesenteric, or retroperitoneal primary or secondary tumors; largest tumor 5.1-10.0 cm diameter

49205 Excision or destruction, open, intra-abdominal tumors, cysts or endometriomas, 1 or more peritoneal, mesenteric, or retroperitoneal primary or secondary tumors; largest tumor greater than 10.0 cm diameter

76940 Ultrasound guidance for, and monitoring of, visceral tissue ablation

**ICD-10 Codes**

C22.0 Liver cell carcinoma
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

**Policy Implementation/Update Information**

2/1/96 New policy, considered investigational
2/1/00 Added Cryoablation of the Liver to this policy which is also considered investigational.
1/1/01 No policy statement changes.
5/1/01 Policy statement updated to include medical necessity indications for RFA and cryoablation:
  - There is no evidence of spread beyond the liver
  - 5 or fewer lesions are present
  - No single lesion is more than 5 cm in diameter
  - There will be intra-operative ultrasound monitoring and localization during the procedure
  - With the use of cryoablation and RFA all liver cancer would be destroyed.

Other indications remain investigational
5/1/02 No policy statement changes.
5/1/03 No policy statement changes.
5/1/04 Policy statement revised to remove Cryoablation of the Liver (covered under a separate policy). Policy statement for RFA remains unchanged.
5/1/05 No policy statement changes.
6/1/06 Policy statement revised to include the investigational status of RFA as a bridge to liver transplantation.
5/1/07 Policy statement format was revised.
5/1/08 Policy statement was revised to reflect that, under specific criteria (see Considerations section), RFA as a primary treatment of hepatic metastases from colorectal cancer in the absence of extrahepatic metastatic disease may be considered medically necessary.
5/1/09 No policy statement changes.
5/1/10 No policy statement changes.
10/1/10 Three changes made to medically necessary statements: For HCC
modified to indicate that this is for those who cannot undergo a curative procedure and who have no more than 3 nodules; added use in HCC as a bridge to transplant; added selective use in metastatic neuroendocrine tumors. No other changes to policy statements.

5/1/11 No policy statement changes.
5/1/12 Policy statement added indicating radiofrequency ablation of primary hepatocellular carcinoma (HCC) is considered investigational when used to downstage (downsize) hepatocellular carcinoma (HCC) in patients being considered for liver transplant.

9/1/12 No policy statement changes.
9/1/13 No policy statement changes.
9/1/14 No policy statement changes.
9/1/15 No policy statement changes.
10/1/15 No policy statement changes.
9/1/16 No policy statement changes.
9/1/17 No policy statement changes.
10/1/17 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.

9/1/18 No policy statement changes.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.