Radiofrequency Ablation of Primary or Metastatic Liver Tumors

Policy # 00182
Original Effective Date: 09/22/2005
Current Effective Date: 01/18/2017

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 Are 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 the use of radiofrequency ablation (RFA) of primary hepatocellular carcinoma (HCC) as a primary treatment of hepatocellular carcinoma (HCC) for patients when there are no more than three nodules and all tumor foci can be adequately treated to be eligible for coverage (see Clinical Guidelines).

Based on review of available data, the Company may consider the use of radiofrequency ablation (RFA) of primary hepatocellular carcinoma (HCC) as a bridge to transplant, where the intent is to prevent further tumor growth and to maintain a patient’s candidacy for liver transplant to be eligible for coverage.

Based on review of available data, the Company may consider the use of radiofrequency ablation (RFA) as a primary treatment of hepatic metastases 5 cm or less in diameter from (CRC) in the absence of extrahepatic metastatic disease when all tumor foci can be adequately treated to be eligible for coverage (see Clinical Guidelines).

Based on review of available data, the Company may consider the use of radiofrequency ablation (RFA) as treatment of hepatic metastases from neuroendocrine tumors in patients with symptomatic disease when systemic therapy has failed to control symptoms to be eligible for coverage (see Clinical Guidelines).

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of radiofrequency ablation (RFA) of primary hepatocellular carcinoma (HCC) when there are more than three nodules or when not all sites of tumor foci can be adequately treated to be investigational.*

Based on review of available data, the Company considers the use of radiofrequency ablation (RFA) of primary hepatocellular carcinoma (HCC) when used to downstage (downsize) hepatocellular carcinoma (HCC) in patients being considered for liver transplant to be investigational.*
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Based on review of available data, the Company considers the use of radiofrequency ablation (RFA) for hepatic metastasis to be **investigational** for the following indications:
- For hepatic metastases from colorectal cancer (CRC) or neuroendocrine tumors that do not meet the criteria above; and
- For hepatic metastases from other types of cancer with the exception of colorectal cancer (CRC) or neuroendocrine tumors.

**Clinical Guidelines**

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

For the eligible for coverage indications noted above for radiofrequency ablation (RFA) in those with primary hepatocellular carcinoma (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 hepatocellular carcinoma (HCC) should also not be candidates for liver transplantation unless radiofrequency ablation (RFA) is used as a bridge to transplant.

Candidacy for radiofrequency ablation (RFA) treatment of hepatocellular carcinoma (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 hepatocellular carcinoma (HCC) have included patients with three or fewer hepatic lesions measuring 5 cm or less (and often 3 cm or less) using current technology.

Candidacy for radiofrequency ablation (RFA) treatment of metastatic colorectal cancer (CRC) 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 (CRC) have included patients with 4-5 or fewer hepatic lesions measuring 5 cm or less using current technology.

**Background/Overview**

Hepatic tumors can arise either 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.

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.
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Radiofrequency ablation 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).

Rationale/Source
Radiofrequency Ablation as a Primary Treatment of Unresectable Hepatocellular Cancer

Systematic Reviews
A 2003 TEC Assessment addressed radiofrequency ablation (RFA) in the treatment of unresectable primary or metastatic liver tumors. Since that time, many systematic reviews and meta-analyses have been published on RFA for hepatocellular cancer (HCC). Some are discussed below.

In 2016, Lan et al published a network meta-analysis comparing different interventional treatments for early stage HCC. A total of 21 RCTs were included that compared transhepatic arterial chemoembolization (TACE), RFA, percutaneous ethanol injection (PEI), and hepatic resection, or combinations of treatments. These studies were all rated at a low-to-moderate risk of bias, with lack of blinding being the most substantial limitation. The primary outcome measures were overall survival (OS) at 1, 3, and 5 years posttreatment. The treatments and combinations of treatments were rank-ordered by results on OS. At each time point, the combination of RFA plus TACE was the number 1 ranked treatment. The combination of RFA plus TACE ranked second highest at 1 and 3 years, and was third highest at 5 years, with hepatic resection ranked second at 5 years. RFA alone was ranked as the fourth highest treatment at 1 year and the fifth highest treatment at 3 and 5 years.

In a 2013 Cochrane review, Weis et al reviewed 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. The Cochrane review also reported finding moderate quality evidence demonstrating superior survival with RFA over PEI. Evidence on RFA versus acetic acid injection, microwave ablation, or laser ablation was insufficient to draw conclusions.

Randomized and nonrandomized trials in the 1990s reported that PEI could safely achieve complete necrosis in small HCCs, with 5-year survival rates of 32% to 38%. A systematic review of randomized trials for HCC treated with percutaneous ablation therapies was conducted by Cho et al. The authors identified 4 RCTs (total N=652 patients) that compared RFA with PEI. The reviewers concluded that RFA demonstrated significantly improved 3-year survival in patients with HCC compared with ethanol injections. Most patients in these studies had 1 tumor, and more than 75% of the tumors were 3 cm or smaller in size. The 3-year survival with RFA ranged from 63% to 81%.

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. OS was significantly longer for RFA than
for PEI at 3 years (hazard ratio [HR], 0.66; 95% confidence interval [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.

In 2012, Xu et al reported on a meta-analysis of 13 studies that compared RFA with surgical resection for early HCC. Only 2 studies were RCTs. Surgical resection was done in 1233 patients and RFA was used in 1302 patients. Surgical resection patients had significantly longer OS rates at 1, 3 and 5 years than RFA patients (odds ratio [OR], 0.60; 95% CI, 0.42 to 0.86; \( OR=0.49; 95\%\ CI, 0.36\) to 0.65; \( OR=0.60; 95\%\ CI, 0.43\) to 0.84), respectively. When only HCC tumors of 3 cm or less were analyzed, resection still had significantly better OS than RFA at 1, 3, and 5 years. Recurrence rates were also significantly lower in the surgical resection group at 1, 3, and 5 years than in the RFA group (\( OR=1.48; 95\%\ CI, 1.05\) to 2.08; \( OR=1.76; 95\%\ CI, 1.49\) to 2.08; \( OR=1.68; 95\%\ CI, 1.21\) to 2.34; all respectively). Local recurrence rates did not differ significantly between procedures. Complication rates were higher with resection than with RFA (\( OR=6.25; 95\%\ CI, 3.12\) to 12.52; \( p=0.000 \)), but, in a subanalysis of HCC 3 cm or less, complication rates were significantly lower with resection than RFA.

Tiong and Maddern 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. 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 included in the 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. The 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. 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 2012, Feng et al reported on an RCT that compared 84 RFA patients to 84 surgical resection patients with up to 2 HCC nodules less than 4 cm in size. Patients were followed for 3 years, and OS and recurrence-free survival (RFS) did not differ statistically between groups (\( p=0.342 \) and \( p=0.122 \), respectively).
Section Summary: Radiofrequency Ablation as a Primary Treatment of Unresectable Hepatocellular Cancer

Randomized and nonrandomized trials have compared RFA to alternative treatments for HCC. RCTs of RFA versus hepatic resection have reported that resection is associated with greater OS, but also with more complications. RCT evidence has also 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. Overall, the evidence supports the use of hepatic resection as first-line therapy for HCC and the use of RFA in patients who are inoperable.

RFA for Patients with Unresectable 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 often 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
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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.”

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.

Most of the literature has focused either on TACE or other locoregional therapies. Given these limitations, the following case series have been reported. Fisher et al reported on 33 patients who received multimodality ablation therapy, consisting primarily of RFA or TACE. Five (12%) patients were removed from the waiting list after waits of 5 to 14 months. In this protocol, patients with tumors larger than 5 cm were not considered transplant candidates until the tumor was completely ablated using TACE, RFA, or another technique. Yamashiki et al reported on 288 patients given various ablative therapies; the dropout rate due to tumor progression at 1 and 3 years was 6.2% and 23%, respectively. Tumors greater than 3 cm affected the dropout rate due to tumor progression. Mazzaferrera et al 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. The median tumor size was 3 cm, and 80% of patients met the Milan criteria. Similarly, Lu et al 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.

In 2008, Belghiti et al reviewed the literature reporting efficacy of local management approaches including resection, TACE, RFA, and no treatment. The authors concluded that RFA can induce complete necrosis in most small tumors (<2.5 cm), and that no data had demonstrated that the treatment reduces the rate of dropout before transplantation or improves survival after transplant. None of the studies included data from U.S. centers for patients listed after adoption of the Milan criteria. Porrett et al retrospectively compared 31 patients treated with RFA with 33 untreated controls. 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 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: (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.

Pomfret et al 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 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. The workgroup on the role of downstaging in transplant candidates with
HCC noted inconsistent outcomes reported in the literature and proposed a definition of downstaging that
would include TACE and various ablative techniques but not resection. The group noted that only 2 regions
have adopted a downstaging protocol.

Yao et al 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.
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 in Those with T3 Tumors
An additional indication for locoregional therapies has focused on their use in patients with T3 tumors,
specifically 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 liver transplant, although most
experience recurrent tumor. For example, in the seminal 1996 study, 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. However, other institutions have reported similar outcomes with expanded criteria. For
example, Yao et al at UCSF reported similar RFS 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 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. Yao et al published a detailed analysis of 121
patients with HCC who underwent transplantation. Seventy-eight (64%) patients had T2 lesions, while an
additional 27 (22.3%) patients met the expanded UCSF criteria, termed T3A lesions. The rest had T1, T3B,
or T4 lesions. Individual patients received a variety of preoperative locoregional therapies, including TACE
or ablative therapies, such as PEI, RFA, or combined therapies. A total of 38.7% of patients did not receive
preoperative locoregional therapy. The 1- and 5-year RFS rates were similar in those with T2 and T3A
lesions, while the corresponding RFS rates were significantly lower for those with T3B and T4 lesions.

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
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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.

Section Summary: RFA for Patients with Unresectable 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 3-6 months for a transplant. Therefore, outcomes are improved for this group. For other uses of RFA in the transplant, such as to downstage tumors for eligibility for transplant, and/or to prevent disease recurrence, the evidence is insufficient to make conclusions.

RFA as Primary Treatment of Unresectable Liver Metastases of Colorectal and Neuroendocrine Origin Colon Cancer
More than half of patients with 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 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. Early clinical experience with RFA comprised case series to establish feasibility, safety, tolerability, and local therapeutic efficacy in short-term follow-up. A 2006 literature review encompassing 6 case series (total N=446 patients) showed that RFA of unresectable CRC metastases was associated with 1-, 2-, and 3-year survival rates that ranged from 87% to 99%, 69% to 77%, and 37% to 58%, respectively. While these results suggested RFA may have clinical benefit in this setting, a primary caveat is the definition of the term "unresectable" in the
different series and that different surgeons may have different opinions on this issue. Further, differences in lesion size, number, distribution, prior treatments, RFA technology, and physician experience may affect results, making it difficult to compare results of different studies.

**Systematic Reviews**

A 2012 systematic review by Cirocchi et al analyzed 17 nonrandomized studies and an meeting abstract of an RCT on RFA for CRC liver metastases. The RCT reported PFS was significantly higher in 60 patients receiving RFA plus chemotherapy than in 59 patients receiving only chemotherapy. The RCT did not report OS. This Cochrane review found different types of vulnerability in all reviewed studies. Of main concern was the imbalance in patient characteristics across studies reviewed, as well as heterogeneity in the interventions, comparisons, and outcomes. Therefore the reviewers concluded the evidence was insufficient to recommend RFA for CRC liver metastasis. In a 2014 Health Technology Assessment, Loveman et al also 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 review by Guenette and Dupuy in 2010 summarized the literature on the use of RFA for colorectal hepatic metastases. 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. 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.

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. 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 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). In the key relevant comparison, RFA versus chemotherapy in chemotherapy-naive patients with unresectable 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 consecutive series of well-defined, previously untreated patients (N=201) without extrahepatic disease underwent laparotomy to determine therapeutic approach. 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,
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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). 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).

Neuroendocrine Tumors

Systematic Reviews

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. A systematic review of RFA as treatment for unresectable metastases from neuroendocrine tumors was published in 2015. 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 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) 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 report on a series gathered over 10 years for 63 patients with neuroendocrine metastases who were treated with 80 sessions of LRFA. 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 report 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 reported on 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 Colorectal and Neuroendocrine Origin
There are no RCTs of RFA versus alternative treatments for patients with unresectable liver metastases. Two 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. 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). 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%.
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In a retrospective review, Meloni et al 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 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 prognoses 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. 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. 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 evaluated RFA in a series of patients with sarcoma. 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. 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.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.
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Table 1. Summary of Key Trials

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NCT: national clinical trial.

Summary of Evidence

For individuals who have primary, unresectable, 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, morbid events, hospitalizations, and treatment-related morbidity. 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have unresectable 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have unresectable hepatic metastases of colorectal or neuroendocrine origin who receive RFA, the evidence includes 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. Two 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 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.
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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. 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have unresectable 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.

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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.
01/01/2006 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
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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
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.
Next Scheduled Review Date: 01/20/2018

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