Radiofrequency Ablation of Primary or Metastatic Liver Tumors

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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 may be considered medically necessary as a primary treatment of hepatic metastases 5 cm or less in diameter from colorectal cancer in the absence of extrahepatic metastatic disease when all tumor foci can be adequately treated (see Considerations Section).

Radiofrequency ablation may be considered medically necessary as treatment of hepatic metastases from neuroendocrine tumors in patients with symptomatic disease when systemic therapy has failed to control symptoms. (see Considerations Section).

Radiofrequency ablation of primary hepatocellular carcinoma (HCC) may be considered medically necessary as a primary treatment of HCC for patients who are not candidates for curative therapy (resection or transplant) when there are no more than 3 nodules and all tumor foci can be adequately treated (see Considerations Section).

Radiofrequency ablation of primary hepatocellular carcinoma (HCC) is considered medically necessary as a bridge to transplant, where the intent is to prevent further tumor growth and to maintain a patient's candidacy for liver transplant.

When Policy Topic is not covered
Radiofrequency ablation of primary hepatocellular carcinoma (HCC) is considered investigational when there are more than three nodules or when not all sites of tumor foci can be adequately treated.

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 with the exception of colorectal cancer or neuroendocrine tumors.

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.

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.

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**

In radiofrequency ablation (RFA), a probe is inserted into the center of a tumor and the non-insulated electrodes, which are shaped like prongs, are projected into the tumor, heat is generated locally by a high frequency, alternating current that flows from the electrodes. The local heat treats the tissue adjacent to the probe resulting in a 3 cm. 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. Radiofrequency ablation may be performed percutaneously, laparoscopically, or as an open procedure.

Hepatic tumors can arise either as primary liver cancer (hepatocellular cancer (HCC)) 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, the majority of 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 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 a variety of symptoms depending on the hormone produced. They are rare, with an incidence of 2-4 per 100,000 per year. Treatment of liver metastases is undertaken to prolong survival and reduce endocrine-related symptoms as well as symptoms related to the hepatic mass.

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, it is hoped that RFA will reduce the incidence of tumor progression while awaiting transplantation, and thus maintain a patient’s candidacy for liver transplant during the wait time for a donor organ. This issue has become less problematic with additional priority now assigned for patients with stage T2 hepatocellular cancer.

Various locoregional therapies for unresectable liver tumors have been investigated: radiofrequency ablation, cryosurgical ablation (cryosurgery), laser ablation, trans-hepatic artery embolization/chemoembolization (TACE), microwave coagulation, percutaneous ethanol injection, and radioembolization (Yttrium-90 microspheres).

**Rationale**

This policy was created in 2000 and updated with periodic literature reviews, the most recent review covering the period between May 2013 and June 20, 2014.
Radiofrequency Ablation as a Primary Treatment of Unresectable Hepatocellular Liver Cancer

Systematic Reviews: A 2003 TEC Assessment (1) 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). In a Cochrane review, Weis et al reviewed studies on RFA for HCC versus other HCC interventions. (2) 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. (3-6) This reinforces the use of RFA for only unresectable HCC. The Cochrane review also reported finding moderate quality evidence demonstrating superior survival with RFA over percutaneous ethanol injection (PEI). (2) Evidence on RFA versus acetic acid injection, microwave ablation, or laser ablation was insufficient to draw conclusions. (2)

One of the first methods devised to ablate liver tumors involved PEI. Several nonrandomized trials in the 1990s confirmed that PEI could safely achieve complete necrosis in small HCCs, with 5-year survival rates of 32% to 38%. (7) However, the technique had several drawbacks, including the need for multiple treatment sessions and a high local progression rate of 17% to 38%. Several randomized controlled trials (RCTs) have compared PEI and RFA in the treatment of small HCC. A systematic review of randomized trials for HCC treated with percutaneous ablation therapies was conducted by Cho et al. (8) The authors identified 4 RCTs involving 652 patients that compared RFA with PEI. The review 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 2013, Shen et al reported on a meta-analysis of 4 RCTs and quasi-RCTs, totaling 766 patients, to compare RFA with PEI for treatment of HCC nodules up to 3 cm. (9) Overall survival (OS) was significantly longer for RFA than PEI at 3 years (hazard ratios [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 to compare RFA with surgical resection for early HCC. (10) Only 2 of the studies were RCTs. Surgical resection occurred 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 (odds ratio [OR]=0.60, 95% confidence interval [CI], 0.42 to 0.86, OR=0.49, 95% CI, 0.36 to 0.65, and OR=0.60, 95% CI, 0.43 to 0.84, respectively). When only HCC tumors of 3 cm or less were analyzed, resection was still significantly better in 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 RFA (OR=1.48, 95% CI, 1.05 to 2.08, OR=1.76, 95% CI, 1.49 to 2.08, and OR=1.68, 95% CI, 1.21 to 2.34, respectively). Local recurrence rates did not differ significantly between procedures. Complication rates were higher with resection than 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. (11) Studies reporting on patients with HCC who were treated with RFA, either in comparison or in combination with other interventions, such as surgery or 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’ follow-up were included. Forty-three articles, including 12 RCTs, were included in the review. Most of the articles reported the use of RFA for unresectable HCC, often in combination with other treatments such as PEI, transarterial chemoembolization (TACE), and/or surgery. A 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 authors 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. (12) Included in the studies were 180 RFA and 253 cryoablation patients. RFA was found to be 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 was not significantly different (OR=2.21, 95% CI, 0.45 to 10.8) between groups.

RCTs: In 2012, Feng et al reported on an RCT of 84 RFA patients compared with 84 surgical resection patients with up to 2 HCC nodules less than 4 cm in size. (13) Patients were followed for 3 years and OS and recurrence-free survival (RFS) were not statistically different between groups, (p=0.342 and p=0.122, respectively).

RFA in the Transplant Setting for Unresectable HCC

In 2002, the United Network for Organ Sharing (UNOS) introduced a new liver allocation system—model for endstage liver disease (MELD)—for adult patients awaiting liver transplant. (14) The MELD score is a continuous disease severity scale incorporating bilirubin, prothrombin time (ie, International Ratio for Prothrombin Activity [INR]), and creatinine into an equation, producing a number that ranges from 1 to 40. Aside from those in fulminant liver failure, donor livers are prioritized to those with the highest MELD number. This scale accurately predicts the risk of dying from liver disease except for those with HCC, who often have low MELD scores because bilirubin, INR, and creatinine levels are near normal.

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. Patients with T1 lesions (1 nodule 1.9 cm or smaller) were 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 post-transplant recurrence. Patients with T2 tumors (1 nodule >2.0 cm and <5.0 cm, or 2 or 3 nodules >1 cm and <3.0 cm) have an increased risk of dying while on the waiting list compared with those having T1 lesions and an acceptable risk of post-transplant 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 are 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. (15) Note that liver transplantation for those with T3 HCC is not prohibited, but these patients do not receive any 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 will lose the additional allocation points.

Therefore, the UNOS allocation system provides incentives to use locoregional therapies in 2 different settings:

- To downsize T3 tumors to T2 status to meet the UNOS criteria for additional allocation points; or
- To prevent progress of T2 tumors while on the waiting list.

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:

Organ Procurement and Transplant Network (OPTN) Class 5T (Treated) nodules are defined as 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:

1. 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 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 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/presenting tumor was greater than a stage T2, must be referred to the applicable RRB [Regional Review Board] for prospective review in order to receive additional priority.” (14)

### Locoregional Therapy as a Technique to Prevent Tumor Progression While on the Waiting List

Several prior studies have reported drop-out rates of wait-listed patients treated with locoregional therapy. However, lacking controlled data, it is difficult to assess 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 a variety of 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 patients (12%) were removed from the waiting list after waits of 5 to 14 months. (16) 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. (17)

Mazzaferro 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. (18) 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. (19) After a mean of 12 months, 5.8% had dropped off the waiting list due to tumor progression.

In a 2008 paper, Belghiti et al reviewed the literature reporting efficacy of local management approaches including resection, TACE, RFA, and no treatment. (20) They concluded that RFA can induce complete necrosis in most small tumors (<2.5 cm), and that there are no data demonstrating 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. (21) Study end points included patient 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] 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 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 post-transplant outcomes in the current MELD era.
Current UNOS policy on allocation of livers indicates that candidates whose tumors have been ablated after meeting the criteria for additional MELD/PELD (PELD – calculator for persons younger than age 12 years) points (OPTN Class 5T) will continue to receive additional points (equivalent to a 10% increase in mortality) every 3 months without review, even if the estimated size of residual viable tumor falls below stage T2 criteria. The policy also notes that candidates may be removed from the listing if they are determined to be unsuitable for transplantation based on progression of HCC.

Locoregional Therapies to Downgrade HCC Before Transplant

RFA to Downstage HCC Before Transplant

Yao et al analyzed longer-term outcome data on HCC downstaging in a cohort of 61 patients with tumor stage exceeding T2 criteria enrolled between June 2002 and January 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 patients (57.4%) received liver transplant, including 2 with live-donor liver transplantation. Treatment failure was observed in 18 patients (29.5%), 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 at 1 and 4 years after downstaging were 87.5% and 69.3%, respectively. The 1-year and 4-year post-transplantation survival rates were 96.2% and 92.1%, respectively. No patient had HCC recurrence after a median post-transplantation follow-up of 25 months. The only factor predicting treatment failure was pretreatment alpha-fetoprotein greater than 1000 ng/mL. From this small series, the authors conclude that successful downstaging can be achieved with excellent post-transplant outcomes.

A national conference involving transplant physicians was held to better characterize the long-term outcomes of liver transplantation for patients with HCC and to discuss the policy of assigning increased priority for candidates with stage T2 HCC on the transplant waiting list in the U.S. Goals of the conference were to standardize pathology reporting, develop specific imaging criteria, expand the Milan criteria (the criteria used to measure tumor size to determine if a patient qualifies for transplant), discuss locoregional therapy, define criteria for downstaging transplantation, and review current liver allocation system for HCC patients. Pomfret et al summarized the conference findings and recommendations.

The workgroup on locoregional therapy found compelling evidence that pretransplant locoregional therapy decreases waitlist dropout, especially for patients who wait longer than 3 to 6 months for transplant. They note “there is a paucity of data comparing radiofrequency ablation (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 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. Post-transplant 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 country 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 post-transplant 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 agreement that the allocation policy should result in similar risks of removal from the waiting
list and similar transplant rates for HCC and non-HCC candidates. In addition, the allocation policy should select HCC candidates so that there are similar post-transplant outcomes for HCC and non-HCC recipients. 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, alpha-fetoprotein, tumor size, and rate of tumor growth. Only candidates with at least stage T2 tumors would receive additional HCC priority points. The article discusses pretransplant local 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. (24) 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 these 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 regarding tumor recurrence require longer follow-up.

**Locoregional Therapies to Reduce Risk of Recurrence in Those with T3 tumors**

An additional indication for locoregional therapies focuses on their use in patients with T3 tumors, specifically to reduce the incidence of recurrence post-transplant. 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. (25-29) Some patients with T3 lesions apparently are cured with liver transplant, although most experience recurrent tumor. For example, in the seminal 1996 study, (15) the 4-year RFS was 92% in those who met the “Milan criteria” compared with 59% in those who did not; additional studies confirm this difference in the RFS rate. (24) 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 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. (27)

The question is whether locoregional therapies (including both RFA and chemoembolization) may 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. (30) Seventy-eight patients (64%) had T2 lesions, while an additional 27 patients (22.3%) 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 rate was 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 RFS of those who did and did not receive locoregional therapy. For those with T2 lesions, the 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% in those who did not. When the data for T2 and T3 lesions were grouped together, the 5-year RFS was 93.8% for those who received locoregional therapy compared with 80.6% in 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 note 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 (i.e., 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.

**RFA as a Primary Treatment of Unresectable Liver Metastases from Colorectal Cancer**

More than half of patients with colorectal cancer (CRC) will develop liver metastases, generally with a poor prognosis. (31) 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. (31) With the introduction of newer agents, including irinotecan and oxaliplatin, and targeted drugs such as cetuximab and bevacizumab, 2-year survival rates have increased to 30% to 39%, with marked improvement in OS duration. As 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. (32, 33) 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 as an approach 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 (n=446) 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. (32) While these results suggest 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 1 abstract on a RCT from a 2010 American Society of Clinical Oncology (ASCO) meeting on RFA for CRC liver metastases. (34) The RCT reported progression-free survival was significantly higher in 60 patients receiving RFA plus chemotherapy compared with 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 of patient characteristics in the studies reviewed, as well as heterogeneity in the interventions, comparisons, and outcomes. Therefore the authors 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. (35)

In 2013, Weng et al reported on a systematic review and meta-analysis to compare RFA with liver resection for the treatment of CRC liver metastases. (36) 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 RFA (risk ratio [RR]=1.377, 95% CI, 1.246 to 1.522 and 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 and RR=2.227, 95% CI, 1.823 to 2.720). While postoperative morbidity with liver resection was significantly higher than with RFA (RR=2.495, 95% CI, 1.881 to 3.308), mortality was not significantly different between liver resection and RFA. Liver resection also
still 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 + 0.6 vs 3.9 + 0.4, p<0.01) and rates of complications lower (18.3% vs 3.9%, p<0.01) with RFA over 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. (37) The literature search was from 1994 to 2010, and study inclusion criteria included a minimum 1-year follow-up and more than 10 patients. In all, 226 potentially relevant studies were identified, 75 of which met the inclusion criteria. Most of the 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 noncolorectal 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. (38) Approximately 17 studies in the literature 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 cm to 4.2 cm. Five-year OS, reported in 12 studies, ranged from 2% to 55.3% with a mean of 24.5%. The largest study series included in the review was by Lencioni et al and 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. (33) OS in the Lencioni et al study at 1, 3, and 5 years was 86%, 47%, and 24%, respectively. The authors of the Guenette/Dupuy review concluded that 5-year survival rates following RFA appear to rival those following resection but that long-term data associated with RFA and colorectal hepatic metastases are 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, RFA should be considered as a primary treatment option in patients with unresectable disease.

Cohort Studies: Prospective studies in which RFA was compared with resection or systemic chemotherapy in well-defined consecutive cohorts of patients with localized CRC metastases and no evidence of additional metastatic disease have been conducted. In the first study, 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). (39) In the key relevant comparison, RFA versus chemotherapy in chemotherapy-naive patients with non-resectable 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 compared with 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 anywhere in the liver at 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, 40% RFA, p not significant).

In a second trial, a consecutive series of well-defined, previously untreated patients (n=201) without extrahepatic disease underwent laparotomy to determine therapeutic approach. (40) 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 not significant, ablated vs chemotherapy). Results from 2 validated quality-of-life instruments (EuroQol-5D and 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 post-treatment (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). (41) Lesion size ranged from 0.2 to 8.3 cm (mean 2.4 cm). The 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 ones, 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).

**RFA as a Treatment of Unresectable Liver Metastases from Neuroendocrine Tumors**

Most reports of RF treatment of neuroendocrine liver metastases include small numbers of patients or subsets of patients in reports of more than one ablative method or very small subsets of larger case series of patients with various diagnoses.

Berber and Siperstein analyzed a large series of liver tumors treated with RFA. (42) 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 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%), noncolorectal, nonneuroendocrine 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 in this study.

Mazzaglia et al report on a series gathered over 10 years of 63 patients with neuroendocrine metastases who were treated with 80 sessions of LRFA. (43) Tumor types were 36 carcinoid, 18 pancreatic islet cell, and 9 medullary thyroid cancer. Indications for enrollment in the study 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; however, patients with additional minor extrahepatic disease were not excluded from the study. 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 +/- 2.3 months. Median survival times were 11 years postdiagnosis of primary tumor, 5.5 years postdiagnosis of neuroendocrine hepatic metastases, and 3.9 years post first RFA treatment.

Elias et al report on 16 patients who underwent a one-step procedure comprising a combination of hepatectomy and RFA for treatment of gastroenteropancreatic endocrine tumors. (44) A mean of 15 +/- 9 liver tumors per patient were surgically removed, and a mean of 12 +/- 8 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 report
on 6 patients treated for pheochromocytoma metastases. (45) Complete ablation was achieved in 6 of 7 metastases. Mean follow-up was 12.3 months (range 2.5-28 months).

**RFA as a Primary Treatment of Unresectable Liver Metastases from Tumors other than Colorectal Cancer and Neuroendocrine Tumors**

**Breast Cancer**
A number of case series report RFA of breast cancer liver metastases. In 2014, Veltri et al analyzed 45 women treated with RFA for 87 breast cancer liver metastases of a mean size of 23 mm. (46) 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 assessed local control and intermediate- and long-term survival in 52 patients. (47) Inclusion criteria were fewer than 5 tumors, maximum tumor diameter of 5 cm or smaller, 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%. Overall median survival time, from the time the first liver metastasis was diagnosed, 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 conclude that these survival rates are comparable with those reported in the literature for surgery or laser ablation. In another series of 43 breast cancer patients with 111 liver metastases, technical success was achieved in 107 metastases (96%). (48) During follow-up, local tumor progression was observed in 15 metastases. The estimated overall median survival 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. (49) 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 extra-hepatic 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.

Other reports include few subjects. Authors report that RFA of breast cancer liver metastases is technically feasible and may provide a survival benefit in woman without extra-hepatic or stable extra-hepatic disease (excluding bone metastases).

**Sarcoma**
Jones et al evaluated RFA in a series of patients with sarcoma. (50) Thirteen gastrointestinal stromal tumor (GIST) patients and 12 with other histological subtypes received RFA for metastatic disease in the liver: 12 of these responded to the first RFA procedure and 1 achieved stable disease. Two GIST patients received RFA on 2 occasions to 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 these responded to RFA, 1 progressed and 1 was not assessable for response 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 advise that further larger studies are required 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. (51) 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 recommend that patients with metastatic disease who can be rendered surgically free of disease be considered for potential hepatic resection.

**Ongoing and Unpublished Clinical Trials**
A search of online site ClinicalTrials.gov on June 20, 2014 identified 7 ongoing phase 3 and 4 trials on RFA of the liver for HCC and CRC liver metastases.

Summary

In radiofrequency ablation (RFA), a probe that generates heat is inserted into the center of a tumor 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.

For treating patients with unresectable hepatocellular cancer (HCC), numerous studies including randomized trials demonstrate that in patients with small foci of HCC (no more than 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. Thus, the policy statement notes that this indication for RFA in patients with HCC who are not candidates for resection or transplant may be considered medically necessary.

A substantial body of literature has been published on the use of RFA to treat colorectal cancer (CRC) metastases in the liver. Two prospective studies comprise good evidence that overall survival (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. Additional evidence from 1 comparative study suggests RFA has a lesser deleterious effect on quality of life than chemotherapy and that RFA patients recover quality of life significantly faster than chemotherapy recipients. Quicker recovery of quality of life may be viewed as a net health benefit when viewed in the context of expected survival durations of patients with metastatic cancer. In addition, results from a number of uncontrolled case series also suggest RFA of hepatic CRC metastases produces long-term survival that is at minimal equivalent and likely superior to historical outcomes achieved with systemic chemotherapy. Although indirect comparisons of series results are difficult, the body of data shows consistent change in direction and magnitude of effect that suggests an RFA benefit. It should be recognized, however, that patients treated with RFA in different series may have better prognosis than those who undergo chemotherapy, suggesting patient selection bias may at least partially explain the apparent better outcomes observed following RFA. Given the caveats just outlined, the available body of clinical evidence is sufficient to conclude that RFA of unresectable CRC metastases to the liver, absent extrahepatic metastatic disease, may be considered medically necessary according to the Policy Guidelines noted earlier.

Evidence shows that durable tumor and symptom control of neuroendocrine liver metastases can be achieved by RFA. This evidence is based on case series; neuroendocrine tumors are uncommon. Thus, a statement indicating that RFA of hepatic metastases of neuroendocrine tumors may be considered medically necessary in patients whose symptoms are not controlled by systemic therapy has been added.

Transplant clinicians find the evidence compelling that use of locoregional therapy reduces the dropout rate of patients with HCC awaiting a liver transplant. After listing for transplant, UNOS does not reassign status based on tumor shrinkage from locoregional therapy. A number of approaches are accepted for use in this situation, including TACE and RFA. Small case series conclude that patients managed on the transplant list with locoregional therapy have outcomes comparable with patients who do not receive pretransplant treatment. However, earlier liver transplant for HCC patients may reduce the need for RFA in this situation. Thus, given the strong clinical support, UNOS position, and clinical studies, the policy statement has been changed to indicate that RFA may be considered medically necessary as a bridge to liver transplant.
Currently, there is less evidence available for patients treated with RFA to specifically downsize (downstage) tumors (tumors of stage >T2) to meet priority transplant criteria, and its use for this application is considered investigational.

The published evidence for demonstrating improved health outcomes with RFA of other hepatic metastatic tumors (eg, breast cancer and sarcoma) is lacking. Comparative trials are needed for these malignancies that may have associated systemic disease. Use of RFA in these tumors is considered investigational under this policy; the data are insufficient to change this policy statement.

**Practice Guidelines and Position Statements**

The Society of Interventional Radiology published a position statement on percutaneous radiofrequency ablation for the treatment of liver tumors in 2009. (52) It is the position of the Society that “percutaneous RF ablation of hepatic tumors is a safe and effective treatment for selected patients with HCC 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 2014 guidelines recommend:
- For HCC, the guidelines address RFA in a list of ablative techniques and recommend that all tumors should be accessible and amenable to ablation, and that in well selected patients with small, properly located tumors, ablation should be considered a definitive treatment, and that lesions 3-5 cm may be treated with a combination of embolization and ablation if the location is favorable. [category 2A] (53)
- For colorectal cancer metastatic to the liver, the guidelines state that ablative techniques may be considered alone or in conjunction with resection if amenable to ablation or resection. [category 2A] (54)
- For neuroendocrine tumors metastatic to the liver, the guidelines state that hepatic regional therapies such as RFA may be considered for unresectable liver metastases if near complete treatment of tumor is possible. [category 2A] (55)

The National Institute for Health and Care Excellence published guidance on RFA for colorectal liver metastases in 2009 stating that current evidence on safety and effectiveness is sufficient to support use of the procedure in patients unfit or otherwise unsuitable for hepatic resection, or in those who have previously had hepatic resection, (56) and published guidance in 2003 stating that current evidence of the safety and efficacy of RFA for hepatocellular carcinoma appears adequate to support use of the procedure. (57)

RFA of tumors is not a preventive service.

**Medicare National Coverage**

No national coverage determination (NCD) was identified. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**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

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.

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.