Radiofrequency Ablation of Primary or Metastatic Liver Tumors

Policy # 00182
Original Effective Date: 09/22/2005
Current Effective Date: 05/11/2020

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.

Note: Cryosurgical Ablation of Primary or Metastatic Liver Tumors is addressed separately in medical policy 00220.

Note: Transcatheter Arterial Chemoembolization (TACE) to Treat Primary or Metastatic Liver Malignancies is addressed separately in medical policy 00227.

Note: Radiofrequency Ablation of Primary or Metastatic Liver Tumors is addressed separately in medical policy 00182.

When Services May Be Eligible for Coverage

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

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

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

Patient Selection Criteria

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

- As a primary treatment of hepatocellular carcinoma meeting the Milan criteria (a single tumor of ≤5 cm or up to 3 nodules <3 cm); or

- As a bridge to transplant, where the intent is to prevent further tumor growth and to maintain a patient's candidacy for liver transplant.

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

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

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

When Services Are Considered Investigational

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

Based on review of available data, the Company considers radiofrequency ablation of primary, inoperable, hepatocellular carcinoma to be **investigational*** under the following conditions:

- When there are more than 3 nodules or when not all sites of tumor foci can be adequately treated.
- When used to downstage (downsize) hepatocellular carcinoma in patients being considered for liver transplant.

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

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

- Hepatic metastases from colorectal cancer or neuroendocrine tumors that do not meet the criteria above; and

- For hepatic metastases from other types of cancer except colorectal cancer or neuroendocrine tumors.

Background/Overview

Hepatic and Neuroendocrine Tumors

Hepatic tumors can arise as primary liver cancer (hepatocellular cancer) or by metastasis to the liver from other tissues. Local therapy for hepatic metastasis may be indicated when there is no extrahepatic disease, which rarely occurs for patients with primary cancers other than colorectal carcinoma or certain neuroendocrine malignancies.

Neuroendocrine tumors are tumors of cells that possess secretory granules and originate from the neuroectoderm. Neuroendocrine cells have roles both in the endocrine system and in the nervous system. They produce and secrete a variety of regulatory hormones, or neuropeptides, which include neurotransmitters and growth factors. Overproduction of the specific neuropeptides produced by the cancerous cells causes various symptoms, depending on the hormone produced. They are rare, with an incidence of 2 to 4 per 100000 per year.

Treatment

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

At present, surgical resection with adequate margins or liver transplantation constitutes the only treatments available with demonstrated curative potential for hepatic tumors. However, most hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size, number of lesions, or underlying liver reserve. Patients may also have comorbid conditions and do not qualify for surgical resection.

Alternative therapies available include liver transplantation, systemic therapies, or ablation procedures (radiofrequency ablation [RFA], cryoablation, microwave ablation, percutaneous ethanol or acetic acid injection). Choice of therapy depends on the severity of the underlying liver disease, size, and distribution of tumors, vascular supply, and patient overall health.

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Radiofrequency Ablation
RFA is a procedure in which a needle electrode is inserted into a tumor either percutaneously, through a laparoscope, or through an open incision. The electrode is heated by a high-frequency, alternating current, which destroys tissue in a 3 to 5 cm sphere of the electrode. RFA has been investigated as a treatment for unresectable hepatic tumors, both as a primary intervention and as a bridge to a liver transplant. In the latter setting, RFA is being tested to determine whether it can reduce the incidence of tumor progression in patients awaiting transplantation and thus maintain patients' candidacy for liver ablation, transhepatic arterial chemoembolization, microwave coagulation, percutaneous ethanol injection, and radioembolization (yttrium-90 microspheres).

FDA or Other Governmental Regulatory Approval

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

Rationale/Source

Radiofrequency ablation (RFA) is a procedure in which a probe is inserted into the center of a tumor and heated locally by a high-frequency, alternating current that flows from electrodes. The local heat treats the tissue adjacent to the probe, resulting in a 3 to 5cm sphere of dead tissue. The cells killed by RFA are not removed but are gradually replaced by fibrosis and scar tissue. If there is a local recurrence, it occurs at the edge of the treated tissue and, in some cases, is retreated. RFA may be performed percutaneously, laparoscopically, or as an open procedure.

Primary, Operable Hepatocellular Carcinoma
For individuals who have primary, operable HCC who receive RFA, the evidence includes randomized controlled trials (RCTs), meta-analyses of these RCTs, database analyses, and observational studies. The relevant outcomes are overall survival (OS), disease-specific survival, change in disease status, and morbid events. Results from these studies have suggested that RFA alone or RFA plus transhepatic arterial chemoembolization may be as effective as a resection for small resectable HCC tumors, although the exact size cutoff has not been established. Some studies found that OS was similar in patients receiving RFA or resection when tumor size was 3 cm or less; however, OS was significantly longer in patients undergoing resection if the tumor size was between 3.1 cm and 5 cm. Further study in a multicenter RCT would permit greater certainty whether RFA,

with or without transhepatic arterial chemoembolization, is as effective as surgical resection in treating HCC tumors 3 cm or smaller. The evidence is insufficient to determine the effects of the technology RFA on health outcomes.

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

Inoperable HCC Awaiting Liver Transplant
For individuals who have inoperable HCC awaiting liver transplant who receive RFA, the evidence includes small case series. The relevant outcomes are OS, disease-specific survival, and change in disease status. A number of approaches are used in this patient population, including RFA and other locoregional therapies, particularly transarterial chemoembolization. Locoregional therapy has reduced the dropout rate of patients with HCC awaiting a liver transplant. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Inoperable Hepatic Metastases of Colorectal Origin
For individuals who have inoperable hepatic metastases of colorectal origin who receive RFA, the evidence includes an RCT, systematic reviews and meta-analyses, prospective cohort series, and retrospective case series. The relevant outcomes are OS, disease-specific survival, symptoms, change in disease status, morbid events, quality of life (QOL), and treatment-related morbidity. There are no RCTs comparing RFA with alternative treatments for patients who have unresectable colorectal liver metastases. However, an RCT assessing RFA plus chemotherapy found

improved survival at eight years compared with chemotherapy alone. In addition, prospective studies have demonstrated that OS following RFA is at least equivalent to and likely better than for currently accepted systemic chemotherapy in well-matched patients with unresectable hepatic metastatic colorectal cancer who do not have extrahepatic disease. Results from a number of uncontrolled case series also have suggested RFA of hepatic colorectal cancer metastases produces long-term survival that is at a minimum equivalent to but likely superior to historical outcomes achieved with systemic chemotherapy. Evidence from a comparative study has indicated RFA has fewer deleterious effects on QOL than chemotherapy and that RFA patients recover the QOL significantly faster than chemotherapy recipients. It should be noted that patients treated with RFA in different series might have had better prognoses than those who had chemotherapy, suggesting patient selection bias might at least partially explain the better outcomes observed following RFA. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Inoperable Hepatic Metastases of Neuroendocrine Origin
For individuals who have inoperable hepatic metastases of neuroendocrine origin who receive RFA, the evidence includes case series and a systematic review of case series. The relevant outcomes are OS, disease-specific survival, symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. Most reports of RFA treatment for neuroendocrine liver metastases have assessed small numbers of patients or subsets of patients in reports of multiple ablative methods or very small subsets of larger case series of patients with various diagnoses. The available evidence has indicated that durable tumor and symptom control of neuroendocrine liver metastases can be achieved using RFA in individuals whose symptoms are not controlled by systemic therapy or who are ineligible for resection. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

small sample sizes. The evidence is insufficient to determine the effects of the technology RFA on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

Society of Interventional Radiology

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

National Comprehensive Cancer Network

Several NCCN guidelines are relevant to this review.

The NCCN (v.2.2019) guidelines on hepatobiliary cancers state that "ablation alone may be curative in treating tumors ≤ 3 cm. In well-selected patients with small, properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review. Lesions 3 to 5 cm may be treated to prolong survival using arterially directed therapies, alone or with combination of an arterially directed therapy and ablation as long as the tumor is accessible for ablation" (category 2A).

The NCCN (v.2.2019) guidelines on colon cancer metastatic to the liver state that "Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection" (category 2A). Of all ablative techniques, the guidelines note that radiofrequency ablation has the most supporting evidence.

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

U.S. Preventive Services Task Force Recommendations
Not applicable.

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

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
MCT02243384	A Randomized Controlled Trial of Laparoscopic Hepatectomy and Radiofrequency Ablation in the Treatment of Early Hepatocellular Carcinoma	110	Sep 2019
NCT02535117	Laparoscopic Surgery Versus Radiofrequency Ablation for Recurrent Hepatocellular Carcinoma after Initial Partial Hepatectomy: a Multicenter Experience	216	Jul 2020

NCT03127072	A Prospective, Randomized, One-center Study Assessing Overall Survival Using RFA Plus Chemotherapy ± Target Therapy and Chemotherapy ± Target Therapy Alone in Patients With Unresectable Colorectal Cancer Liver Metastases	200	Dec 2021
Unpublished			
NCT02169765	Hepatic Resection Versus Radiofrequency Ablation for Early-stage Hepatocellular Carcinoma: a Randomized Controlled Trial	120	Dec 2017 (unknown)
NCT02192671	Hepatic Resection Versus Radiofrequency Ablation for Patients With Hepatocellular Carcinoma and Portal Hypertension	120	Dec 2018 (unknown)

NCT: national clinical trial.

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Policy History

Original Effective Date: 09/22/2005
Current Effective Date: 05/11/2020

09/07/2005	Medical Director review
09/20/2005	Medical Policy Committee review
09/22/2005	Quality Care Advisory Council approval
07/07/2006	Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
01/10/2006	Medical Director review
01/17/2006	Medical Policy Committee approval. Coverage eligibility updated to include investigational status of RFA as a bridge to liver transplant.

01/09/2008	Medical Director review
01/23/2008	Medical Policy Committee approval. Added "in the absence of extrahepatic metastatic disease" to the patient selection criteria.
01/07/2009	Medical Director review
01/14/2009	Medical Policy Committee approval. No change to coverage eligibility.
01/07/2010	Medical Policy Committee approval
01/20/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/06/2011	Medical Policy Committee review
01/19/2011	Medical Policy Implementation Committee approval. Extensively revised coverage statements and added policy guidelines.
01/06/2011	Medical Policy Committee review
01/19/2011	Medical Policy Implementation Committee approval. Rationale revised. No change to coverage.
03/01/2012	Medical Policy Committee review
03/21/2012	Medical Policy Implementation Committee approval
01/03/2013	Medical Policy Committee review
01/09/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/09/2014	Medical Policy Committee review
01/15/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/08/2015	Medical Policy Committee review
01/21/2015	Medical Policy Implementation Committee approval. Added phrase "unless RFA is used as a bridge to transplant" to the medically necessary indication for RFA in those with primary HCC and metastatic colorectal or neuroendocrine tumors for HCC should also not be candidates for liver transplantation.
01/07/2016	Medical Policy Committee review
01/22/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017	Medical Policy Committee review
01/18/2017	Medical Policy Implementation Committee approval. No change to coverage.
11/02/2017	Medical Policy Committee review

11/15/2017 Medical Policy Implementation Committee approval. Policy statements reformatted and edited for clarity and specificity, including the distinction between operable and non-operable tumors and the Milan criteria. The intent of the statements is unchanged. A statement has been added that RFA for operable HCC is considered investigational.
11/08/2018 Medical Policy Committee review
11/21/2018 Medical Policy Implementation Committee approval. No change to coverage.
11/07/2019 Medical Policy Committee review
11/13/2019 Medical Policy Implementation Committee approval. No change to coverage. Three new policies referenced as notes for cross reference including: Cryosurgical Ablation of Primary or Metastatic Liver Tumors medical policy 00220, Transcatheter Arterial Chemoembolization (TACE) to Treat Primary or Metastatic Liver Malignancies medical policy 00227 and Radiofrequency Ablation of Primary or Metastatic Liver Tumors medical policy 00182.
04/02/2020 Medical Policy Committee review
04/08/2020 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 04/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	47370, 47380, 47382, 76940, 77013, 77022
HCPCS	No codes
ICD-10 Diagnosis	C22.0-C22.9, C78.7, C7B.02

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

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

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

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

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

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.