



BlueCross BlueShield
of Alabama

Name of Blue Advantage Policy:

Locoregional Therapies for Hepatocellular Carcinoma and Metastatic Liver Carcinoma and Metastatic Carcinoid Tumors of the Liver

Policy #: 070

Latest Review Date: September 2024

Category: GI/GU

BACKGROUND:

Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:

- 1. Safe and effective;*
- 2. Not experimental or investigational*;*
- 3. Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
 - Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
 - Furnished in a setting appropriate to the patient's medical needs and condition;*
 - Ordered and furnished by qualified personnel;*
 - One that meets, but does not exceed, the patient's medical need; and*
 - At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000, which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill **Original Medicare for covered services that are related to **clinical trials** that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **radiofrequency ablation (RFA)** as a **covered benefit** for individuals with one of the following indications:

- hepatocellular carcinoma (HCC)
- metastatic liver carcinoma

Blue Advantage will treat **percutaneous ethanol injection (PEI)** as a **covered benefit** for individuals with one of the following indications:

- hepatocellular carcinoma (HCC)
- metastatic liver carcinoma

Please refer to Policy #178 “MRI-Guided Focused Ultrasound (MRgFUS)” for coverage information on ultrasound ablation of the bone.

Please refer to Policy #119 “Radiofrequency Ablation of Solid Tumors Excluding Liver Tumors” for coverage information on radiofrequency ablation of solid tumors excluding liver.

Please refer to NCD (230.9) for Cryosurgery of Prostate.

Please refer to Policy #429 “Cryosurgical Ablation of Miscellaneous Solid Tumors Other than Liver, Prostate, or Dermatologic Tumors” for coverage information on cryosurgical ablation of these tumors.

Please refer to Policy #512 “Microwave Tumor Ablation” for coverage information on microwave tumor ablation.

Please refer to Policy MP# 737 “Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver” for coverage information on Transcatheter Arterial Chemoembolization.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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. A study from 2016 determined that the incidence of liver cancer was higher among White individuals, Black individuals, and Hispanic individuals born after 1938. The incidence of hepatocellular carcinoma was twice as high for US-born Hispanic men compared to Hispanic men born outside of the US. This may be due to the increased risk of smoking, hepatitis B or C infection, and diabetes among US-born Hispanic individuals.

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

Treatment options for hepatocellular carcinoma (HCC) range from potentially curative treatments, such as resection or liver transplantation, to nonsurgical options, which include ablative therapies (radiofrequency ablation [RFA], cryoablation, microwave ablation, percutaneous ethanol or acetic acid injection), transarterial embolization, radiation therapy, and systemic therapy. Choice of therapy depends on the severity of the underlying liver disease, size, and distribution of tumors, vascular supply, and patient overall health. Treatment of liver metastases is undertaken to prolong survival and 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. Comorbid conditions may also make patients unqualified for surgical resection.

Radiofrequency Ablation (RFA)

Radiofrequency ablation 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. 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. Radiofrequency ablation 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).

Percutaneous Ethanol Injection (PEI)

PEI induces tumor necrosis by cellular dehydration, protein denaturation, and thrombosis of small vessels. HCC is softer than the surrounding cirrhotic liver and is often encapsulated, allowing selective diffusion of ethanol within the tumor mass. The hypervascularization of HCC also favors ethanol injection therapy by enhancing the distribution of ethanol within the network of the tumor vessels. A fine needle is inserted into the tumor under ultrasonographic guidance, and absolute ethanol is then injected slowly into the tumor until the whole area of tumor appears hypoechogenic on the ultrasound. PEI may be performed under CT guidance for tumors not visualized by ultrasounds. The injection is repeated once or twice a week for up to six to eight sessions, depending on the tumor size. PEI can be done as an outpatient procedure under local anesthesia.

Histotripsy

Histotripsy, a nonthermal focal ablative therapy, has been proposed as an alternative treatment of liver lesions. Histotripsy utilizes short, high-pressure bursts of high-intensity focused ultrasound to induce tissue destruction via acoustic cavitation, rendering the target into acellular debris. The material in the histotripsy ablation zone is absorbed by the body within 1–2 months, leaving a minimal remnant scar. Histotripsy has also been shown to stimulate an immune response and induce abscopal effects in animal models, which may have positive implications for future cancer treatment. Histotripsy has been investigated for a wide range of applications in preclinical studies, including the treatment of cancer, neurological diseases, and cardiovascular diseases. The benefits of non-thermal focal ablative therapy include avoidance of any heat sink effects which is theorized to allow histotripsy to be used in highly vascular areas.

KEY POINTS:

The most recent literature update was performed through May 20, 2024.

Summary of Evidence

For individuals who have primary, operable hepatocellular carcinoma (HCC) who receive radiofrequency ablation (RFA), the evidence includes meta-analyses of randomized controlled trials (RCTs) and/or retrospective observational studies, an RCT and additional observational studies. Relevant outcomes are overall survival (OS), disease-specific survival, change in disease status, and morbid events. The majority of data found that patients undergoing surgical resection experienced longer survival outcomes and lower recurrence rates than patients receiving RFA, though complication rates were higher with surgical resection. Some meta-analyses and an RCT of specifically selected populations (eg, small tumor sizes or Child-Pugh Class A liver function or HCC within the Milan criteria) found that OS and disease-free survival (DFS) rates were not significantly different between RFA and surgical resection. Results from observational studies have suggested that RFA alone or RFA plus percutaneous ethanol injection (PEI) could be as effective as a resection for small HCC tumors as OS and DFS rates were not significantly different between RFA and surgical resection. An exact tumor cutoff size 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 other ablative or arterial directed therapies, is as effective as surgical resection in treating HCC tumors 3 cm or smaller. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have inoperable, hepatocellular carcinoma (HCC) who receive RFA, the evidence includes RCTs and several systematic reviews and meta-analyses. Relevant outcomes are OS, disease-specific survival, change in disease status, and morbid events. When resection is not an option, nonsurgical options include RFA, PEI, transarterial chemoembolization (TACE), cryoablation, microwave ablation, and systemic therapy. Meta-analyses comparing RFA to other local ablative therapies have found that RFA and microwave ablation are similarly effective, that RFA is more effective than PEI, and that RFA may be better than cryoablation. The evidence comparing RFA with TACE is limited, and no conclusions can be drawn. RFA has also been shown to improve survival in patients with unresectable HCC as an adjunct to chemotherapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with hepatic metastases of colorectal origin who receive RFA, the evidence includes an RCT, systematic reviews and meta-analyses, prospective cohort series, and retrospective case series. Relevant outcomes are overall survival, disease-specific survival, symptoms, changes in disease status, morbid events, quality of life, and treatment-related morbidity. There are no RCTs comparing RFA with alternative treatments for patients with unresectable colorectal liver metastases. However, an RCT assessing RFA combined with chemotherapy found improved survival at 8 years compared with chemotherapy alone. In addition, prospective studies have demonstrated that overall survival 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 colorectal cancer (CRC) who do not have extrahepatic disease. Results from a number of uncontrolled case series also suggest 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 one comparative study suggests RFA has less deleterious effect on quality of life than chemotherapy and that RFA patients recover quality of life significantly faster than chemotherapy recipients. It should be noted, however, that patients treated with RFA in different series may have better prognosis than those who undergo chemotherapy, suggesting patient selection bias may at least partially explain the apparent better outcomes observed following RFA. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have inoperable hepatic metastases of neuroendocrine origin who receive RFA, the evidence includes case series and a systematic review of case series. Relevant outcomes are OS, disease-specific survival, symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. Most reports of RFA treatment for neuroendocrine liver metastases have assessed small numbers of patients or subsets of patients in reports of more than 1 ablative method or very small subsets of larger case series of patients with various diagnoses. The available evidence indicates that durable tumor and symptom control of neuroendocrine liver metastases can be achieved using RFA in individuals whose symptoms are

not controlled by systemic therapy or who are ineligible for resection. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For individuals who have hepatic metastases not of colorectal or neuroendocrine origin who receive RFA, the evidence includes a systematic review, small nonrandomized comparative studies and small case series. Relevant outcomes are OS, disease-specific survival, symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. Similar to primary HCC, resection appears to have the most favorable outcomes. For patients who are ineligible for resection, RFA may provide a survival benefit. Complete ablation of tumors was seen in $\geq 90\%$ of tumors in most studies; however, there was tumor recurrence. Although there are only small case series available, OS was documented as being at least 90% at 1 year in 2 studies. The available evidence indicates that symptom control may be achieved using RFA, therefore the evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Percutaneous Ethanol Injection

For patients who have inoperable hepatocellular carcinoma, PEI can be considered. The evidence includes several RCTs, non-randomized trials and a comparative analysis. It has been noted that to achieve complete necrosis of liver tumors using PEI, multiple treatment sessions are usually needed.

Histotripsy

There are U.S. clinical trials underway to evaluate the safety and technical efficacy of histotripsy in patients with primary and secondary liver tumors. A phase I trial provided the initial safety and efficacy data regarding the use of hepatic histotripsy in individuals with hepatocellular carcinoma and hepatic metastasis. A total of 8 individuals with multifocal liver tumors were followed for 8 weeks post-procedure. There were no significant procedure related events. The study focused on technical safety and did not address cancer follow-up. The HistoSonics System for Treatment of Primary and Metastatic Liver Tumors Using Histotripsy trial is a single arm, non-randomized prospective trial where following histotripsy treatment of liver tumor(s), subjects will undergo imaging < 36 hours post-index procedure to determine technical success then will be followed for 30 days. Participants will be evaluated at 6 months and followed annually for up to 5 years post-procedure. There are no published studies evaluating the treatment effects of histotripsy. The current evidence regarding the histotripsy procedure does not support that this form of locally ablative therapy is a clinically appropriate treatment of hepatic malignancies.

Practice Guidelines and Position Statements

RFA:

American Association for the Study of Liver Diseases

The American Association for the Study of Liver Diseases (AASLD) published a guideline in 2018 on the treatment of hepatocellular carcinoma (HCC), which was subsequently updated in 2023. Relevant guidance statements related to radiofrequency ablation (RFA) are listed below:

- "Thermal ablation (radiofrequency or microwave ablation) should be considered the treatment of choice for patients with early-stage HCC ≤ 3 cm who are ineligible for or decline surgery (Level 1, Strong Recommendation).
 - AASLD does not advise 1 thermal ablative modality over another."

Society of American Gastrointestinal and Endoscopic Surgeons

The Society of American Gastrointestinal and Endoscopic Surgeons with the Americas Hepato-Pancreato-Biliary Association developed guidelines (2023) for the use of microwave and radiofrequency liver ablation for the surgical treatment of hepatocellular carcinoma or colorectal liver metastases less than 5 cm. A systematic review was conducted to address key questions and GRADE methodology was used to provide evidence-based recommendations. All guideline recommendations were assigned "conditional" recommendations based on the weak evidence found. The key questions and subsequent recommendations related to RFA addressed by the guideline are summarized in Table 1.

Table 1. SAGES/AHPBA recommendations for use of ablative therapy

Key questions addressed by the guideline	Recommendations
Should MWA (laparoscopic or open) vs. RFA (laparoscopic or open) be used for HCC or CRLM less than 5 cm ineligible for other therapies?	The panel suggests MWA and RFA are both safe and feasible. There was insufficient evidence to recommend one modality over another in terms of oncologic outcomes (conditional recommendation, very low certainty of evidence).

AHPBA: Americas Hepato-Pancreato-Biliary Association; MWA: microwave ablation; RFA: radiofrequency ablation; SAGES: Society of American Gastrointestinal and Endoscopic Surgeons.

Society of Interventional Radiology

The Society of Interventional Radiology published a position statement on percutaneous radiofrequency ablation for the treatment of liver tumors in 2009. It is the position of the Society that "percutaneous RFA 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

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

The NCCN guidelines recommend:

- The NCCN (v.1.2024) guidelines on HCC note that "locoregional therapy should be considered in patients who are not candidates for surgical curative treatments, or as part of a strategy to bridge patients for other curative therapies." The guideline further states 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, or with the combination of an arterially directed therapy and ablation as long as the tumor is accessible for ablation".

- The NCCN (v.2.2024) guidelines on colon cancer metastatic to the liver state that "[a]blative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection". Of all ablative techniques, the guidelines note that RFA has the most supporting evidence.
- The NCCN (v.1.2023) guidelines for neuroendocrine and adrenal tumors state that "percutaneous thermal ablation, often using microwave energy (radiofrequency and cryoablation are also acceptable), can be considered for oligometastatic liver disease, generally up to 4 lesions each smaller than 3 cm. Feasibility considerations include safe percutaneous imaging-guided approach to the target lesions, and proximity to vessels, bile ducts, or adjacent non-target structures that may require hydro- or aero-dissection for displacement [category 2B]." Additionally, "cytoreductive surgery or ablative therapies such as RFA or cryoablation may be considered if near-complete treatment of tumor burden can be achieved. Ablative therapy in this setting is non-curative. For unresectable liver metastases, hepatic regional therapy (arterial embolization, chemoembolization, or radioembolization [category 2B]) is recommended."

Percutaneous Ethanol Injection:

National Comprehensive Cancer Network

The 2018 NCCN guidelines (v2.2018) state that "locoregional therapy should be considered in patients who are not candidates for surgical curative treatments, or as a part of a strategy to bridge patients for other curative therapies." PEI is included in the locoregional therapies.

- Tumors should be amenable to ablation, but a margin is not expected following PEI
- Tumors should be accessible for ablation

U.S. Preventive Services Task Force Recommendations

RFA of tumors is not a preventive service.

KEY WORDS:

Locoregional liver therapy, Locoregional liver treatment, Radiofrequency Ablation (RFA), Percutaneous Ethanol Injection (PEI), liver cryotherapy, cryotherapy, histotripsy, HistoSonics

APPROVED BY GOVERNING BODIES:

Chemoembolization for hepatic tumors is a medical procedure, and as such is not subject to FDA regulations. However, the embolizing agents and drugs are subject to FDA approval.

Radiofrequency ablation devices have been cleared through the U.S. Food and Drug Administration (FDA) 510(k) process.

Several cryosurgical devices have clearance by the U.S. Food and Drug Administration (FDA). For example, the ENDOcare™ CRYOcare Cryosurgical System (Endocare, Inc., Irvine, CA) was

cleared for marketing through the 510(k) process in December 1996 for “use in general surgery, dermatology, neurology, thoracic surgery, ENT, gynecology, oncology, proctology and urology for the ablation of tissue, including liver metastases, skin lesions, warts, and removal of prostate tissue.”

TheraSphere® has been granted Humanitarian Device Exception status by the FDA on December 10, 1999

SIR-Spheres was given a 510(k) PMA, March 5, 2002

In October 2023, the U.S. Food and Drug Administration (FDA) authorized marketing of the HistoSonics® Inc. Edison® Histotripsy System. It is the first histotripsy platform available in the United States for the non-invasive destruction of liver tumors, including unresectable liver tumors. The FDA cautioned that non-thermal focused ultrasound should only be considered in patients with a sufficient amount of functional liver reserve to withstand the destruction of the planned volume of liver tissue.

BENEFIT APPLICATION:

Coverage is subject to member’s specific benefits. Group-specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT:

47370	Laparoscopy, surgical, ablation of one or more liver tumor(s); radiofrequency
47380	Ablation, open, of one or more liver tumor(s); radiofrequency
47382	Ablation, open, of one or more liver tumor(s); percutaneous, radiofrequency
47399	Unlisted procedure, liver
76940	Ultrasound guidance for, and monitoring of, parenchymal tissue ablation
77013	Computerized tomography guidance for, and monitoring of, parenchymal tissue ablation
77022	Magnetic resonance guidance for, and monitoring of, parenchymal tissue ablation
0686T	Histotripsy (ie, non-thermal ablation via acoustic energy delivery) of malignant hepatocellular tissue, including image guidance

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POLICY HISTORY:

Adopted for Blue Advantage, March 2005
 Available for comment May 1-June 14, 2005
 Medical Policy Group, September 2008
 Medical Policy Group, October 2009
 Available for comment October 20-December 3, 2009
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 Medical Policy Group, August 2015
 Medical Policy Group, September 2015
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 Medical Policy Group, December 2015
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 Medical Policy Group, September 2017

Medical Policy Group, July 2018: Updates to Description, Key Points, Coding and References. No change to policy statement. Removed ICD 9 diagnosis codes from Current Coding. Removed radioembolization HCPCS code and CPT codes from Current Coding (77300, 77370, 77470, 77750, 77778, 77790, 79445, 79900, S2095). Removed CPT code 37204 (deleted 2014) from Previous Coding. Changed policy statement for microwave ablation (per 5) since it is referred to in the Blue Advantage policy #512. Also deleted Policy statements prior to November 2015.

Medical Policy Group, October 2019

Medical Policy Group, August 2020: Removed CPT codes 37243 and 75894. Policy statement updated to remove TACE. See medical policy #737 for TACE.

Medical Policy Group, September 2020

Medical Policy Group, July 2021

Medical Policy Group, July 2022

Medical Policy Group, July 2023

UM Committee, December 2023: Policy approved by UM Committee for use for Blue Advantage business.

Medical Policy Group, July 2024

Medical Policy Group, October 2024: Update to Current Coding removing 77261-77263 & adding 76940. No change to policy statement.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.