

Subject: Radiofrequency Ablation of Primary or Metastatic Liver Tumors	Original Effective Date: 12/9/2020
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.

RECOMMENDATION

This policy focuses on radiofrequency ablation (RFA) of **primary or metastatic liver** tumors and does not address other ablative therapies.

Enrollment in a clinical trial is encouraged for patients with hepatocellular carcinoma. For a list of trials recruiting patients with advanced disease, refer to clinicaltrials.gov.

All supporting documentation, including medical records and clinical documentation relevant to the medical condition being treated must be submitted for review.

A. Radiofrequency Ablation (RFA) of **UNRESECTABLE (Inoperable) Primary or Metastatic Hepatocellular Carcinoma (HCC)**

RFA may be considered medically necessary for members who are **not currently awaiting liver transplantation** when ANY of following are met **[ANY]**

- ☐ Tumor(s) is unresectable (e.g., due to comorbidities or an estimate of inadequate liver volume following resection). Prescriber **must** submit rationale for the determination that the **member** is not a surgical candidate or the tumor is unresectable.

AND ONE of the following: [ONE]

- ☐ Unresectable primary hepatocellular carcinoma when ALL of the following criteria are met:

- ☐ As a primary treatment meeting the Milan criteria:
 - ☐ A single tumor(s) 5 cm or less (≤ 5 cm) in diameter; and
 - ☐ No more than 3 hepatic nodules less than 3 cm (< 3 cm)

OR

- ☐ Hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid) when ALL of the following criteria are met:

- ☐ The disease is symptomatic. Documentation of tumor-related symptoms required; and
- ☐ Systemic therapy has failed to control symptoms, or the member is not a candidate for systemic therapy

OR

- ☒ Hepatic metastases from colorectal tumors, including but not limited to adenocarcinoma, when ALL of the following criteria are met **[ALL]**

- ☐ Metastases are of colorectal origin; and
- ☐ Meets the Milan criteria:
 - ☐ A single tumor(s) 5 cm or less (≤ 5 cm) in diameter; and
 - ☐ No more than 3 hepatic nodules less than 3 cm (< 3 cm)
- ☐ No extrahepatic metastatic disease is present

B. Inoperable Hepatocellular Carcinoma Awaiting Liver Transplant

RFA may be considered medically necessary for members who are currently awaiting liver transplantation when ALL of the following criteria are met **[ALL]**

- ☐ RFA is intended to *prevent tumor progression or decrease tumor size to achieve or maintain a member's candidacy for liver transplant*
AND
- ☐ Preserved liver function defined as Child-Pugh Class A or B
AND
- ☐ 3 or fewer encapsulated nodules and each nodule is less than or equal to 5 centimeters in diameter
AND
- ☐ No evidence of the following conditions:
 - ☐ Extra-hepatic metastases, OR
 - ☐ Severe renal function impairment; OR
 - ☐ Portal vein occlusion

EXCLUSIONS

Radiofrequency ablation (RFA) for hepatic metastasis is considered **experimental/investigational** as a treatment for all other indications not addressed in the coverage recommendations section because the safety and/or effectiveness of this procedure has not been established: [ANY]

- ☐ RFA is considered **experimental/investigational** as a treatment for all other benign or malignant liver tumors that do not meet the medical necessity criteria above, including but not limited to the following: [ANY]
 - ☐ More than 3 hepatocellular carcinoma tumors or when not all sites of tumor foci can be adequately treated; OR
 - ☐ More than 5 metastatic colorectal tumors in the liver; OR
 - ☐ Metastatic or primary liver tumors larger than 5 cm in diameter; OR
 - ☐ Metastases to the liver from organ tumors other than colorectal, asymptomatic neuroendocrine tumors, or neuroendocrine tumors with symptoms controlled by systemic therapy
- ☐ RFA ablation of primary hepatocellular carcinoma (HCC) is considered **experimental/investigational** when used to downstage (downsize) HCC in members being considered for liver transplant.
 - Downstaging can facilitate liver transplantation for patients outside of Milan criteria with more advanced HCC so that patients may qualify for the priority listing by the Milan criteria (Tsoulfas G, 2020); however, the optimal protocol and downstaging outcomes are poorly defined. It is noted that there is no universal or consensus of the optimal method for downstaging, selection criteria, and factors predicting effective downstaging from locoregional therapies prior to liver transplantation. To determine success and post-transplant survival in this cohort of patients, large prospective studies utilizing standardized reporting criteria are needed to compare downstaging modalities and protocols. (Parikh ND; 2016)

❑ Primary, Operable Hepatocellular Carcinoma

For individuals who have primary, operable HCC who receive RFA, the evidence includes RCTs, meta-analyses of these RCTs, and a database analysis. Systematic reviews and meta-analyses have also reported superior survival and lower recurrence rates with hepatic resection compared with RFA, though resection was accompanied by higher rates of complications. [Feng et al. (2014); Wang et al. (2014); Qi et al. (2014); Duan et al (2013); Jia et al. (2017); Xu et al. (2018)] These findings support the use of RFA only for unresectable HCC. **The evidence is insufficient to determine the effects of the technology RFA on health outcomes.**

❑ 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 which is not sufficient to determine whether RFA improves outcomes [Gastric Cancer Li et al (2017); Nasopharyngeal Cancer Li et al (2017); Ovarian Cancer Liu et al (2017); Pancreatic Cancer Hua et al (2017)]. The evidence is insufficient to determine the effects of the technology RFA on health outcomes.

Sarcoma

- Jones et al. (2010) evaluated RFA in a series of patients with sarcoma. 13 gastrointestinal stromal tumor (GIST) patients and 12 with other histologic subtypes received RFA for metastatic disease in the liver: 12 responded to the first RFA procedure and 1 patient achieved stable disease. 2 GIST patients received RFA on 2 occasions for separate lesions within the liver, and both responded to the second RFA procedure. Of the other subtypes, 7 patients underwent RFA to liver lesions, 5 of whom responded to RFA, 1 patient progressed, and another was not assessable at the time of analysis. It was reported that RFA was well-tolerated in this series of sarcoma patients. While RFA may have a role in patients with GIST who have progression in a single metastasis but stable disease elsewhere, the authors recommended that larger studies should be conducted to define the role of this RFA in this patient population.
- Pawlik et al. (2006) reported on a case series of 66 patients who underwent hepatic resection (n=35), resection and RFA (n=18), or RFA alone (n=13). 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 overall survival rates were 91.5%, 65.4%, and 27.1%, respectively.

Breast Cancer

- Veltri et al. (2014) analyzed 45 women treated with RFA for 87 breast cancer liver metastases (mean size, 23 mm). Complete ablation was reported on initial follow-up in 90% of tumors, but tumors recurred in 19.7% within 8 months. RFA did not impact overall survival rates, which at 1 year was 90% and at 3 years was 44%.
- Meloni et al. (2009), in a retrospective review, assessed local control and intermediate- and long-term survival in 52 patients. Local tumor progression occurred in 25% of patients, and new intrahepatic metastases developed in 53%. Median OS, from the time of first liver metastasis diagnosis, was 42 months, and 5-year survival was 32%. Patients with tumors 2.5 cm in diameter or larger had a worse prognosis than those with smaller tumors. The authors concluded that the survival rates comparable to those reported in the literature for surgery or laser ablation.
- Jakobs et al. (2009) in a case series (2009) of 43 breast cancer patients with 111 liver metastases, tumor ablation was achieved in 107 (96%) metastases. During follow-up, local tumor progression was

observed in 15 metastases. Estimated median OS was 58.6 months. Survival was significantly lower among patients with extrahepatic disease, except skeletal metastases.

- Lawes et al. (2006) reported a series of 19 patients (8 patients had disease confined to the liver, with 11 also having stable extrahepatic disease). At the time of reporting, 7 patients, with disease confined to the liver at presentation, were alive, as were 6 patients with extrahepatic disease (median follow-up after RFA, 15 months; range, 0-77 months). Survival at 30 months was 41.6%. It was noted that RFA failed to control hepatic disease in 3 patients.

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Hepatic tumors can arise either as primary liver cancer (such as hepatocellular carcinoma) or by metastasis to the liver from other primary cancer sites. Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor in the world, and the third leading cause of cancer death worldwide (Ghouri YA, et al. 2017). HCC is a primary malignancy of the liver that occurs predominantly in patients with underlying chronic liver disease and cirrhosis. Treatment options are based on staging, resectability, presence of comorbidities, performance status, and the metastatic burden. AASLD guidelines divide therapeutic options into curative and noncurative interventions (AASLD 2018). Curative therapies, which offer the chance of long-term response and improved survival, include the following: surgical resection, liver transplantation and ablative techniques (e.g., thermal ablation). Noncurative therapies, which attempt to prolong survival by slowing tumor progression, include transarterial chemoembolization (TACE), transarterial radioembolization (TARE), stereotactic body radiation therapy (SBRT), and systemic chemotherapy (AASLD 2018). Although surgical resection and liver transplantation provide potentially curative treatment, these procedures have limited applicability and unresectable at diagnosis due to either to anatomic location, size, number of lesions, underlying liver reserve or comorbid conditions. Local ablation is generally accepted as the best option for patients with small HCCs who are not candidates for surgical resection or liver transplantation and also used to control early stage HCC in patients awaiting transplantation. Local ablation includes including radiofrequency ablation, percutaneous ethanol injection, laser and microwave thermal ablation, and irreversible electroporation (Curley, SA 2020).

In radiofrequency ablation (RFA), a needle electrode is used to deliver high-frequency alternating electrical current, which results in cellular necrosis. The technique involves image-guided application of the probe primarily using ultrasound guidance. The cells killed by RFA are not removed but are gradually replaced by fibrosis and scar tissue. RFA is performed by surgical oncologists in an inpatient clinical setting.

Regulatory Status

Regulatory Status RFA devices are cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process. Food and Drug Administration product code GEI.

Radiofrequency Ablation (RFA) as a Treatment of Primary, Operable Hepatocellular Carcinoma

RFA provides a treatment option that is an alternative to, or an improvement on existing therapies, such as surgical resection, in patients with primary hepatocellular carcinoma (HCC).

Systematic Review and Meta-Analysis

Li et al. (2020) conducted a meta-analysis (1 RCT and 15 retrospective observational studies) of the efficacy of RFA compared with surgical resection for HCC with particular emphasis on overall survival and disease-free survival rates. The studies included patients with HCC meeting the Milan criteria with liver function Child-Pugh scores of grade A or B. Surgical resection was demonstrated to show superior 1-, 3- and 5-year overall survival and disease-free survival rates than RFA for patients with small HCC that were eligible for surgical treatment.

However, RFA can be an alternative therapeutic option for patients with small single HCC tumors that are not suitable for surgical resection. The results indicate that surgical resection is superior to RFA for promoting the survival of selected patients with resectable HCC. However, it was noted that future randomized controlled trials are required to investigate the specific relevance of these modalities in the treatment of HCC

Weis et al. (2013) evaluated studies on RFA for HCC versus other interventions in a Cochrane systematic review. Moderate-quality evidence demonstrated that hepatic resection had superior survival outcomes compared with RFA; however, resection might have greater rates of complications and longer hospital stays. It was noted that other systematic reviews and meta-analyses have also found superior survival with hepatic resection but higher rates of complications than RFA [Feng et al. (2015); Wang et al. (2014); Qi et al. (2014); Duan et al. (2013)]. **This finding reinforces the use of RFA only for unresectable HCC.** The Cochrane review also reported on the moderate quality evidence demonstrating superior survival with RFA over percutaneous ethanol injection (PEI). Evidence on RFA versus acetic acid injection, microwave ablation, or laser ablation was insufficient to draw conclusions.

RFA For Hepatic Metastases Of Neuroendocrine Origin

The available evidence indicates that durable tumor and symptom control of neuroendocrine liver metastases can be achieved by RFA in individuals whose symptoms are not controlled by systemic therapy. The evidence on RFA for patients with liver metastases of neuroendocrine origin consists of case series (Berber and Siperstein, 2008) and a systematic review of case series (Mohan H, et al. 2015). Reports of RFA treatment for neuroendocrine liver metastases includes small numbers of patients or subsets of patients in reports of multiple ablative methods (Elias et al. 2009), or very small subsets of larger case series of patients with various diagnoses (Mazzaglia et al. 2007).

Mohan H, et al. (2015) conducted a systematic review of RFA as a treatment for unresectable metastases from neuroendocrine tumors was published in 2015. The review included 7 unique studies (total N=301 patients), all retrospective case series from a single institution. The most common tumor type was carcinoid (59%), followed by nonfunctional pancreatic tumors (21%) and functional pancreatic tumors (13%). A high degree of variability in the length of follow-up and surveillance, and a wide range of local recurrence rates, from less than 5% to 50%, The reported 5-year survival rates ranged from 57% to 80%. There were 2 periprocedural deaths (rate, 0.7%), and

the overall rate of complications was 10%, including hemorrhage, abscess, viscus perforation, bile leak, biliopleural fistula, transient liver insufficiency, pneumothorax, grounding pad burn, urinary retention, pneumonia, pleural effusion. Improvement in symptoms was reported in 92% (117/127) of symptomatic patients, with a median duration of relief ranging from 14 to 27 months.

Practice Guidelines and Position Statements

American Association for the Study of Liver Diseases (AASLD)

The practice guideline from the AASLD in the 2011 update considered RFA a safe and effective therapy for unresectable HCC or as a bridge to liver transplantation.

National Comprehensive Cancer Network (NCCN)

The NCCN (v.3.2020) 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.3.2020) 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."

DEFINITIONS

Child-Pugh score: Used to assess prognosis of chronic liver disease and cirrhosis. It consists of five clinical features with values worth 1, 2, or 3 points. The number of points accumulated (5-15) indicate estimated chance of 1-year survival. Class A (5-6 points total) indicates an estimated 100% chance of 1-year survival.

Milan criteria: Defined as a single HCC less than 5 cm in the maximum diameter, having up to three nodules with each no larger than 3 cm, with no angio invasion and no extrahepatic involvement. AASLD 2018; ESMO 2018; NCCN 2020: Hepatobiliary cancers

Neuroendocrine tumors (NETs): A heterogeneous group of neoplasms that are thought to arise from neuroendocrine cells and their precursors located throughout the body; classically characterized by the ability to secrete peptides resulting in distinctive hormonal syndromes. Ablation can be used as a primary treatment modality for neuroendocrine liver metastases or as an adjunct to surgical resection. Neuroendocrine tumors include the following: Carcinoid Tumors; Islet Cell Tumors (also known as Pancreatic Endocrine Tumors); Neuroendocrine Unknown Primary; Adrenal Gland Tumors; Pheochromocytoma/paraganglioma; Poorly Differentiated (High Grade or Anaplastic)/Small Cell; Multiple Endocrine Neoplasia, Type 1 (also known as

MEN-1 syndrome or Wermer's syndrome); Multiple Endocrine Neoplasia, Type 2 a or b (also known as pheochromocytoma and amyloid producing medullary thyroid carcinoma, PTC syndrome, or Sipple syndrome)

CODING INFORMATION THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
47370	Laparoscopy, surgical, ablation of 1 or more liver tumor(s); radiofrequency
47380	Ablation, open, of 1 or more liver tumor(s); radiofrequency
47382	Ablation, 1 or more liver tumor(s), percutaneous, radiofrequency
76940	Ultrasound guidance for, and monitoring of, parenchymal tissue ablation

HCPCS	Description

ICD-10	Description: [For dates of service on or after 10/01/2015]

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Hepatic Metastases Of Neuroendocrine Origin

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American Association for the Study of Liver Diseases (AASLD)

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National Comprehensive Cancer Network (NCCN)

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- Tsoulfas G, et al. Liver transplantation for hepatocellular carcinoma. Topic 2490 Version 55.0. Topic last updated: Sep 22, 2020.

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