Radiofrequency Ablation of Primary or Metastatic Liver Tumors

Description

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 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 a local recurrence, it occurs at the edge of the treated tissue and, in some cases, is retreated. Radiofrequency ablation may be performed percutaneously, laparoscopically, or as an open procedure.

OBJECTIVE

The objective of this evidence review is to determine whether radiofrequency ablation improves the net health outcome in individuals with primary hepatocellular carcinoma or hepatic metastases.
Radiofrequency ablation of primary, inoperable (eg, due to location of lesion[s] and/or comorbid conditions), hepatocellular carcinoma may be considered **medically necessary** under the following conditions:

- as a primary treatment of hepatocellular carcinoma meeting the Milan criteria (a single tumor of ≤5 cm or up to 3 nodules <3 cm).
- as a bridge to transplant, where the intent is to prevent further tumor growth and to maintain a patient's candidacy for liver transplant.

Radiofrequency ablation as a primary treatment of inoperable hepatic metastases may be considered **medically necessary** under the following conditions:

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

Radiofrequency ablation of primary, inoperable, hepatocellular carcinoma is considered **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.

Radiofrequency ablation of primary, operable hepatocellular carcinoma is **investigational**.

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 except colorectal cancer or neuroendocrine tumors.

**POLICY GUIDELINES**

None

**BENEFIT APPLICATION**

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**FDA REGULATORY STATUS**

Radiofrequency ablation 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.
**Inoperable Hepatocellular Carcinoma**

For individuals who have inoperable 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 morbidity events. When resection is not an option, nonsurgical options include RFA, PEI, transarterial chemoembolization (TACE), cyroablation, 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.

**Inoperable Hepatocellular Carcinoma Awaiting Liver Transplant**

For individuals who have inoperable HCC awaiting liver transplant who receive RFA, the evidence includes small case series. 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 TACE. 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 an 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. Relevant outcomes are OS, disease-specific survival, symptoms, change in disease status, morbidity events, quality of life, 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 8 years compared with chemotherapy alone. In addition, prospective studies have demonstrated that OS following RFA is at least equivalent to and likely better than 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 have suggested RFA of hepatic CRC 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 quality of life than chemotherapy and that RFA patients recover the quality of life 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 an 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. Relevant outcomes are OS, disease-specific survival, symptoms, change in disease status, morbidity events, quality of life, and treatment-related morbidity. Some meta-analyses 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 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 disease-free survival (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.
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 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 an 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. 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. However, the evidence is limited by study designs with a high-risk of bias and small sample sizes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Association for the Study of Liver Diseases

The American Association for the Study of Liver Diseases (2018) published a guideline on the treatment of hepatocellular carcinoma. For adults with Child-Pugh class cirrhosis and resectable T1 or T2 hepatocellular carcinoma (HCC), the guideline suggests using resection over radiofrequency ablation (RFA; moderate quality/certainty of evidence; conditional strength of recommendation). Technical remarks in the guideline note that "Stage T1 and T2 HCC include a wide range of tumor sizes from <1 cm to 5 cm, and the effectiveness of available therapies depend in large part on the size, number, and location of the tumors. Whereas smaller, single tumors (<2.5 cm) that are favorably located may be equally well treated by either resection or ablation, tumors larger than 2.5-3 cm, multifocal, or near major vascular or biliary structures may have limited ablative options." Additionally, the guideline highlighted that "[r]andomized trials performed to date comparing RFA to resection have been performed primarily in East Asian patients, in whom there is a higher etiologic prevalence of HBV [hepatitis B virus] (including noncirrhotic HBV - associated HCC) and a lower prevalence of other liver diseases such as NAFLD [non-alcoholic fatty liver disease] or HCV [hepatitis C virus] compared with Western patients. The impact of these demographic differences on oncologic outcomes of different therapies is unknown."

National Comprehensive Cancer Network

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

The NCCN (v.2.2021) guidelines on hepatobiliary cancers 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 combination of an arterially directed therapy and ablation as long as the tumor is accessible for ablation" (category 2A)." The NCCN (v.2.2021) guidelines on colon cancer metastatic to the liver state that "[r]adiosurgical and 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 RFA has the most supporting evidence.

The NCCN (v.1.2021) guidelines for neuroendocrine tumors state that "percutaneous thermal ablation, often using microwave energy (radiofrequency and cryoablation) 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 (category 2B). Ablative therapy in this setting is non-curative. For unresectable liver metastases, hepatic regional therapy (arterial embolization, chemoembolization, or radioembolization [category 2B]) is recommended.68

Society of Interventional Radiology

The Society of Interventional Radiology (2009) published a position statement on percutaneous RFA for the treatment of liver tumors.70 The Society indicated 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 does not support any recommendations for or against the use of RFA in other diseases.

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.

REFERENCES


Radiofrequency Ablation of Primary or Metastatic Liver Tumors

7.01.91 Radiofrequency Ablation of Primary or Metastatic Liver Tumors

### POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>December 2011</td>
<td>New policy</td>
<td>Policy updated with literature search; duplicate reference 29 was removed and references renumbered. References 4 and 29 added; references 5, 6 and 40-42 updated. Policy statements remain unchanged.</td>
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<tr>
<td>December 2012</td>
<td>Replace policy</td>
<td>Policy updated with literature search; References 4-5, 7-8 and 29-30 added; references 9 and 48 updated. Policy statements remain unchanged.</td>
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<tr>
<td>September 2013</td>
<td>Replace policy</td>
<td>Policy updated with literature search. References 2-6, 35, and 46 added; policy statements unchanged.</td>
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<tr>
<td>September 2014</td>
<td>Replace policy</td>
<td>Policy updated with literature review. References 2-6, 35, and 46 added; policy statements unchanged.</td>
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<tr>
<td>September 2015</td>
<td>Replace policy</td>
<td>Policy updated with literature review. References 2-6, 35, and 46 added; policy statements unchanged.</td>
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<tr>
<td>September 2017</td>
<td>Replace policy</td>
<td>Policy updated with literature review through June 2, 2017; references 2, 5, 11-12, 14, 18, 22, and 40-41, 44 added; references 58-60 updated. 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.</td>
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<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through May 7, 2018; references 14, 16, 18-21, 56, and 63-66 added. Policy statements unchanged.</td>
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<tr>
<td>September 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through May 13, 2019; references on NCCN updated. Policy statements unchanged.</td>
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<tr>
<td>September 2020</td>
<td>Replace policy</td>
<td>Policy updated with literature review through June 2, 2020; references added. Policy statements unchanged.</td>
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<tr>
<td>September 2021</td>
<td>Replace policy</td>
<td>Policy updated with literature review through June 2, 2021; references added. Policy statements unchanged.</td>
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