

## ***Ablation of Primary and Metastatic Liver Tumors***

**Effective:** March 1, 2024

**Next Review:** November 2024

**Last Review:** January 2024

### **IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### **DESCRIPTION**

Ablation is a method of locoregional therapy used to treat cancerous lesions, including hepatocellular carcinoma and hepatic metastases from other primary cancers.

### **MEDICAL POLICY CRITERIA**

**Note:** This policy addresses locoregional therapies, specifically, percutaneous ethanol injection, cryoablation, radiofrequency and microwave ablation for primary and metastatic liver tumors. Please see Cross References for other ablative techniques and indications.

- I. Percutaneous ethanol injection, cryoablation, radiofrequency and microwave local ablative techniques may be considered **medically necessary** for treatment of liver tumors when either of the following (A. or B.) are met:
  - A. In patients *not* currently awaiting liver transplantation, and one or more of the following criteria are met:
    1. Unresectable primary liver tumors [hepatocellular carcinoma] when **all** of the following criteria (a.-c.) are met:
      - a. The tumor(s) is 5 cm or less in diameter; and

- b. There are no more than 3 hepatic lesions; and
      - c. There is documentation that the tumor(s) is unresectable (e.g., due to comorbidities or an estimate of inadequate liver volume following resection).
    - 2. Hepatic metastases from colorectal tumors, including but not limited to adenocarcinoma when **all** of the following criteria (a.-d.) are met
      - a. The metastatic tumor(s) is 5 cm or less in diameter; and
      - b. There are no more than 5 hepatic lesions; and
      - c. There is documentation that the tumor(s) is unresectable (e.g., due to comorbidities, or an estimate of inadequate liver volume following resection); and
      - d. No extrahepatic metastatic disease is present.
    - 3. Hepatic metastases from neuroendocrine tumors when **all** of the following criteria (a.-c.) are met:
      - a. The disease is symptomatic; and
      - b. Systemic therapy has failed to control symptoms; and
      - c. There is documentation that the tumor(s) is unresectable (e.g., due to comorbidities or an estimate of inadequate liver volume following resection)
  - B. As a bridge to liver transplantation when the intent is to prevent tumor progression or decrease tumor size to achieve or maintain a patient's candidacy for liver transplant.
- II. Percutaneous ethanol injection, cryoablation, radiofrequency and microwave ablation are considered **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:
- A. More than 3 hepatocellular carcinoma tumors; more than 5 metastatic colorectal tumors in the liver; or metastatic or primary liver tumors larger than 5 cm in diameter
  - B. Metastases to the liver from organ tumors other than colorectal, asymptomatic neuroendocrine tumors, or neuroendocrine tumors with symptoms controlled by systemic therapy

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

## POLICY GUIDELINES

### NEUROENDOCRINE TUMORS

Neuroendocrine tumors are rare, slow-growing, hormone-secreting tumors that may occur in numerous locations in the body.<sup>[1]</sup> 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)

Neuroendocrine tumors may also be referred to by their location (e.g., pulmonary neuroendocrine tumors; gastroenteropancreatic neuroendocrine tumors).

Some appendiceal carcinoids, also called adenocarcinoids, goblet cell carcinoids, or crypt cell carcinoids, have mixed histology, including elements of adenocarcinoma. While these biphasic tumors have both neuroendocrine and adenocarcinoma components, the National Comprehensive Cancer Network (NCCN) recommends they be managed according to colon cancer guidelines.

## LIST OF INFORMATION NEEDED FOR REVIEW

### REQUIRED DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

1. Specific description of the tumor(s) targeted for treatment including the following:
  - Tumor type (primary vs. metastatic; primary tumor type)
  - The location of tumor(s)
  - The number and size(s) of lesion(s) being treated
2. Rationale for the determination that the patient is not a surgical candidate or the tumor is unresectable
3. Whether the goal of treatment is curative or palliative
4. Comorbidities and any contraindicated treatments (e.g., surgery; radiation therapy)
5. Prior treatments, if any, and tumor response
6. Documentation of whether this treatment is to preserve organ function
7. Include documentation of the presence or absence of extra-hepatic disease

## CROSS REFERENCES

1. [Radioembolization, Transarterial Embolization \(TAE\), and Transarterial Chemoembolization \(TACE\)](#), Medicine, Policy No. 140
2. [Radiofrequency Ablation \(RFA\) of Tumors Other than Liver](#), Surgery, Policy No. 92
3. [Cryosurgical Ablation of Miscellaneous Solid Tumors](#), Surgery, Policy No. 132
4. [Magnetic Resonance \(MR\) Guided Focused Ultrasound \(MRgFUS\) and High Intensity Focused Ultrasound \(HIFU\) Ablation, Surgery](#), Policy No. 139
5. [Microwave Tumor Ablation](#), Surgery, Policy No. 189
6. [Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy for Tumors Outside of Intracranial, Skull Base, or Orbital Sites](#), Surgery, Policy No. 214

### ABLATIVE TECHNIQUES

#### THERMAL ABLATION

##### Radiofrequency Ablation

Radiofrequency ablation (RFA) is one of a number of locoregional thermal ablation therapies to treat various benign or malignant tumors. RFA kills cells (cancerous and normal) by applying a heat-generating rapidly alternating radiofrequency current through probes inserted into the tumor. 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 of this scar tissue and, in some cases, may be retreated. RFA can be performed as an open surgical procedure, laparoscopically, or percutaneously with ultrasound or computed tomography (CT) guidance. The goals of RFA may include 1) controlling local tumor growth and preventing recurrence; 2) palliating symptoms; and 3) extending survival duration for patients with certain cancerous tumors.

Reports have been published on use of RFA to treat renal cell carcinomas, breast cancer, pulmonary (including primary and metastatic lung tumors), bone, and other tumors including those that are non-cancerous (benign). Well-established local or systemic treatment alternatives are available for each of these tumor types.

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, 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).

##### Microwave Ablation

Microwave ablation (MWA) is a technique in which the use of microwave energy induces an ultra-high speed, 915 MHz or 2.450 MHz (2.45 GHz), alternating electric field which causes water molecule rotation and the creation of heat. This results in thermal coagulation and localized tissue necrosis. In MWA, a single microwave antenna or multiple antennas connected to a generator are inserted directly into the tumor or tissue to be ablated; energy from the antennas generates friction and heat. The local heat coagulates the tissue adjacent to the probe, resulting in a small, approximately 2 to 3 cm elliptical area (5 x 3 cm) of tissue ablation. In tumors greater than 2 cm in diameter, 2 to 3 antennas may be used simultaneously to increase the targeted area of MWA and shorten operative time. Multiple antennas may also be used simultaneously to ablate multiple tumors. Tissue ablation occurs quickly, within one minute after a pulse of energy, and multiple pulses may be delivered within a treatment session depending on the size of the tumor. The cells killed by MWA are typically not removed but are gradually replaced by fibrosis and scar tissue. If there is local recurrence, it occurs at the edges. Treatment may be repeated as needed. MWA may be used to: 1) control local tumor growth and prevent recurrence; 2) palliate symptoms; and 3) extend survival duration.

Complications from MWA are usually considered mild and may include pain and fever. Other potential complications associated with MWA include those caused by heat damage to

normal tissue adjacent to the tumor (e.g., intestinal damage during MWA of the kidney or liver), structural damage along the probe track (e.g., pneumothorax as a consequence of procedures on the lung), liver enzyme elevation, liver abscess, ascites, pleural effusion, diaphragm injury or secondary tumors if cells seed during probe removal. MWA should be avoided in pregnant patients since potential risks to the patient and/or fetus have not been established and in patients with implanted electronic devices such as implantable pacemakers that may be adversely affected by microwave power output.

MWA is an ablative technique similar to radiofrequency or cryosurgical ablation; however, MWA may have some advantages. In MWA, the heating process is active, which produces higher temperatures than the passive heating of radiofrequency ablation and should allow for more complete thermal ablation in a shorter period of time. The higher temperatures reached with MWA (over 100° C) can overcome the “heat sink” effect in which tissue cooling occurs from nearby blood flow in large vessels potentially resulting in incomplete tumor ablation. MWA does not rely on the conduction of electricity for heating, and therefore, does not have electrical current flow through patients and does not require grounding pads be used during the procedure to prevent skin burns. Unlike radiofrequency ablation, MWA does not produce electric noise, which allows ultrasound guidance to occur during the procedure without interference. Finally, MWA can be completed in less time than radiofrequency ablation since multiple antennas can be used simultaneously.

### Regulatory Status

There are several devices cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for MWA. Covidien’s (a subsidiary of Tyco Healthcare) Evident Microwave Ablation System has 510(k) clearance for soft tissue ablation, including partial or complete ablation of non-resectable liver tumors. The following devices have 510(k) clearance for MWA of (unspecified) soft tissue:

- BSD Medical Corporation’s MicroThermX® Microwave Ablation System (MTX-180);
- MicroSurgeon Microwave Soft Tissue Ablation Device;
- Angiodynamics’ Solero Microwave Tissue Ablation System;
- Surgnova Healthcare Technologies’ Microwave Ablation System;
- Microsulis Medical’s Acculis Accu2i; and
- Johnson & Johnson’s NEUWAVE Microwave Ablation System

FDA determined that these devices were substantially equivalent to existing radiofrequency and MWA devices. FDA product code: NEY.

### **CRYOSURGICAL ABLATION**

Cryosurgical ablation (also called cryosurgery, cryotherapy, or cryoablation) kills cells (cancerous and normal) by freezing target tissues, most often by inserting a probe into the tumor through which coolant is circulated. Cryosurgery may be performed as an open surgical technique or as a closed procedure under laparoscopic or ultrasound guidance.

The goals of cryosurgery may include the following:

- Destruction or shrinkage of tumor tissue
- Controlling local tumor growth and preventing recurrence
- Palliating symptoms

- Extending survival duration for patients with certain tumors.

Potential complications associated with cryosurgery in any organ include the following:

- Hypothermic damage to normal tissue adjacent to the tumor (e.g., nerve damage)
- Structural damage along the probe track
- Secondary tumors if cancerous cells are seeded during probe removal.

## Regulatory Status

There are several cryoablation devices cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for use in open, minimally invasive or endoscopic surgical procedures in the areas of general surgery, urology, gynecology, oncology, neurology, dermatology, proctology, thoracic surgery and ear, nose and throat. Examples include:

- Cryocare® Surgical System by Endocare;
- CryoGen Cryosurgical System by Cryosurgical, Inc.;
- CryoHit® by Galil Medical;
- IceRod® CX, IcePearl® 2.1 CX and IceFORCE® 2.1 CX Cryoablation Needles by Galil Medical;
- SeedNet™ System by Galil Medical;
- Visica® System by Sanarus Medical;
- Visual-ICE® Cryoablation System by Galil;
- ERBECRYO 2® Cryosurgical Unit, ERBE USA Incorporated

## PERCUTANEOUS ETHANOL INJECTION

Using a needle, percutaneous ethanol injection (PEI) delivers an injection of 95 percent ethanol directly into a tumor. Multiple treatment sessions may be performed in order to achieve tumor destruction. Prior to RFA, PEI was the most widely accepted, minimally invasive method to treat hepatocellular carcinoma. Like other local ablative techniques, PEI is most successful in small HCC tumors when resection is not an option.

## LIVER (HEPATIC) TUMORS

Hepatic tumors can arise either as primary liver cancer (such as hepatocellular carcinoma, HCC) or by metastasis to the liver from other primary cancer sites. 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. Partial liver resection, hepatectomy, is considered the gold standard. However, the majority of hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size, number of lesions, or underlying liver reserve.

Locoregional therapies are proposed as a treatment for unresectable hepatic tumors, both as primary treatment, palliative treatment, and as a bridge to liver transplant. In the case of liver transplants, it is hoped that locoregional ablative techniques 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.

## MULTIPLE ABLATIVE TECHNIQUES

## Systematic Reviews

Lu (2022) performed a systematic review of ten studies, including 854 patients with histologically proven HCC who received a combination of RFA and PEI or RFA alone.<sup>[2]</sup> The results demonstrated that patients who received RFA-PEI had slight improvements in 1-year overall survival (OS) [risk ratio (RR): 1.11; 95% CI: 1.03, 1.19] 2-year OS (RR: 1.25; 95% CI: 1.12, 1.40), 3-year OS (RR: 1.42; 95% CI: 1.11, 1.83), 1-year local recurrence-free (LRF) proportion (RR: 1.2; 95% CI: 1.01, 1.42), and complete tumor necrosis (CTN) (RR: 1.32; 95% CI: 1.14, 1.53). Common complications, such as fever, were found to be significant (RR: 1.78, 95% CI: 1.13, 2.80). Despite RFA-PEI appearing to be superior for HCC patients with a compensated liver in terms of OS, current evidence contained moderate to significant heterogeneity, and it was difficult to draw a definite conclusion regarding the therapeutic management in terms of LRF and CTN.

Yu (2021) performed a meta-analysis of RCTs comparing RFA with microwave ablation for the treatment of localized, very early- or early-stage HCC.<sup>[3]</sup> Five RCTs comparing RFA (n=413) and microwave ablation (n=431) were identified. The OS between microwave ablation and RFA was not significantly different at one year (OR=0.705; 95% CI 0.382 to 1.301) or three years (OR=0.972; 95% CI 0.615 to 1.538). Similarly, there was no difference observed in recurrence-free survival between microwave ablation and RFA at one year (OR=1.167; 95% CI: 0.568 to 2.396) and three years (OR=0.981; 95% CI 0.616 to 1.562). Among the procedure-related complications evaluated, there were no statistically significant differences between the two groups.

A similar analysis was published by Gupta in 2021 that compared outcomes for very early and early HCC following RFA, MWA, or cryoablation.<sup>[4]</sup> A total of 19 studies (six RCTs and 13 observational studies) met inclusion criteria. No statistically significant differences between groups were identified for OS or local recurrence (LR).

Shin (2021) compared the efficacy of surgical resection with local ablative therapies for HCC meeting Milan criteria.<sup>[5]</sup> The analysis included seven RCTs and 18 non-randomized trials (n=5,629) that compared surgical resection with either RFA, microwave ablation, or RFA plus TACE. Four of the RCTs were judged to be at high risk of bias overall, due to either lack of reported randomization method or missing data. All non-randomized trials were classified as having a high risk for bias due to the missing data. There was no significant difference between surgical resection and RFA alone when the RCTs were analyzed; the three- and five-year OS favored surgical resection in the analysis of the non-randomized trials. A multiple treatment meta-analysis using a frequentist framework random effect model found that 5-year recurrence free survival was highest with surgical resection (hazard ratio [HR]=0.64, 95% CI 0.56 to 0.74 vs RFA), followed by RFA plus TACE (HR=0.70, 95% CI 0.53 to 0.92 vs RFA); no difference was found between microwave ablation and RFA (HR=0.93, 95% CI 0.63 to 1.37). However, the latter comparisons were limited by the number of trials evaluating RFA plus TACE (five studies) and microwave ablation (two studies).

Cui (2020) conducted a systematic review and meta-analysis of MWA compared to various treatment modalities for the treatment of hepatocellular carcinoma.<sup>[6]</sup> The analysis included four RCTs, with three comparing MWA to RFA and one comparing MWA to TACE. The

remaining 11 studies were nonrandomized trials comparing MWA to RFA (eight studies), resection (two studies), or ethanol ablation (one study). Meta-analyses were not performed for MWA versus TACE or ethanol ablation, because these comparisons were only examined in one study each. Meta-analyses of studies comparing MWA to RFA found no difference in three-year OS, five-year OS, local tumor progression at one year, progression-free survival at three years, or major complications. A meta-analysis of two nonrandomized studies comparing MWA to resection found no difference in three-year OS between treatments; however, this comparison is limited by the small number of studies included and the lack of RCTs included. The reviewers concluded that MWA showed similar safety and efficacy compared with RFA, but higher quality clinical studies are needed to validate the superiority of MWA.

Gui (2020) reported a systematic review and meta-analysis of trans-arterial chemoembolization plus RFA compared to surgical resection for hepatocellular carcinoma.<sup>[7]</sup> One RCT and eight retrospective studies met inclusion criteria. According to the unadjusted pooled analysis, there was no significant difference in one-, three-, and five-year OS and one-year disease-free survival between TACE+RFA and surgical resection. There were statistically significant differences favoring surgical resection in three-year disease-free survival (odds ratio [OR] 0.78, 95% confidence interval [CI] 0.62 to 0.98,  $p=0.03$ ) and five-year disease-free survival (OR 0.74, 95% CI 0.58 to 0.95,  $p=0.02$ ) compared to TACE+RFA. In the propensity matched analysis, the difference in three- and five-year disease-free survival was not significant.

Han (2020) reported a systematic review comparing MWA and RFA for early stage hepatocellular carcinoma.<sup>[8]</sup> Five RCTs, one prospective cohort studies and 20 retrospective cohort studies were included, for a total of 4,396 patients. Four of the RCTs were rated as high quality and one as low quality. Of the remaining studies, 16 were rated as high quality and five as low quality. According to the meta-analysis, there were no statistically significant differences between MWA and RFA for disease progression (OR=0.877, 95% CI 0.710 to 1.084,  $I^2=0\%$ ,  $p=0.225$ ), or survival, either overall or disease-free (hazard ratio [HR]=0.891 and 1.014,  $p=0.222$  and 0.852, respectively). Only six studies reported the OS rates, with five reporting one-year, five reporting three-year, and three reporting five-year OS. The one-, three-, and five-year OS estimates were 88.00% (95% CI 72.30% to 100%), 47.00% (95% CI 23.50 to 70.50%), and 17.00% (95% CI 0 to 34.60%) for LITT; 95.10% (95% CI 91.20 to 99.00%), 76.83% (95% CI 67.00 to 86.60%), and 27.00% (95% CI 11.00 to 51.00%) for RFA; not reported, 66.67% (95% CI 29.40 to 103.90%), and 33.33% (95% CI 0 to 70.60%) for MWA; and 91.49% (95% CI 83.70 to 99.30%), 79.3% (95% CI 59.70 to 98.90%), and not reported for PC.

Xiang (2020) published a systematic review and pooled analysis of multiple types of magnetic resonance-guided ablation techniques for the treatment of liver tumors.<sup>[9]</sup> Thirty studies (14 on RFA, one on MWA and RFA, eight on LITT, two on percutaneous cryoablation, and one on percutaneous ethanol injection) met inclusion criteria. No quality assessment was reported. The rates of complete ablation were 95.60%, 98.86%, 77.78%, 47.92%, and 85.71% in patients who underwent RFA, MWA, LITT, PC, and PEI, respectively.

Glassberg (2019) performed a systematic review and meta-analysis comparing MWA and RFA for the treatment of liver cancer.<sup>[10]</sup> A total of 28 RCTs and observational studies met inclusion criteria. The overall quality of the studies was rated as acceptable and most studies had low or unclear risk of bias across most domains. The meta-analysis indicated that local tumor progression was significantly reduced in patients treated with MWA as compared to RFA,

whether the analysis included all studies (30% reduction, risk ratio [RR]=0.70, p=0.02) or RCTs only (45% reduction, RR=0.55, p=0.007). No other efficacy or safety outcomes were found to be significantly different between groups.

Di Martino (2019) compared local ablative therapies for resectable colorectal liver metastases in a systematic review and meta-analysis.<sup>[11]</sup> Therapies evaluated included RFA, MWA, cryoablation and electroporation. A total of 20 studies with 860 patients met inclusion criteria. Surgical resection was superior to local ablative therapies with respect to disease-free survival, tumor progression, and overall survival. Compared to surgical resection, RFA reduced one-year disease-free survival (RR 0.83, 95% CI 0.71 to 0.98), three-year disease-free survival (RR 0.5, 95% CI 0.33 to 0.76), five-year DFS (RR 0.53, 95% CI 0.28 to 0.98) and five-year OS (RR 0.76, 95% CI 0.58 to 0.98).

A meta-analysis by Meijerink (2018) compared RFA and MWA to systemic chemotherapy and to partial hepatectomy (PH) for the treatment of colorectal liver metastases.<sup>[12]</sup> Forty-eight articles were identified, most of which were observational studies and case series, although two RCTs and eight systematic reviews were included. The authors found 18 observational studies of very low quality that looked at RFA alone compared to PH alone or PH plus RFA. For OS, their analysis concluded that PH alone was superior to RFA alone (HR=1.78; 95% CI 1.35 to 2.33). The meta-analysis for 30-day mortality comparing RFA alone to PH alone showed no difference between the two interventions (RR=0.64; 95% CI 0.21 to 1.95). DFS was higher for PH alone over RFA alone (HR=1.49; 95% CI 1.23 to 1.81), as well as for local progression-free survival (HR=5.36; 95% CI 1.64 to 17.52). However, complication rates were lower for RFA alone than for PH alone (risk ratio=0.47; 95% CI 0.28 to 0.78). One limitation of this review is that the included observational studies were all confounded by indication because RFA was only performed on unresectable lesions. Observational studies are also at increased risk for publication bias.

Majumdar (2017) published a Cochrane review and network meta-analysis of the management of early and very early-stage HCC.<sup>[13]</sup> Reviewers included 14 RCTs (total n=2533 patients) of nonsurgical treatments compared with each other, sham, or no intervention in patients with unresectable HCC. The quality of the evidence was rated as low or very low for all outcomes. Follow-up ranged from 6 to 37 months. Compared with RFA, mortality was higher for percutaneous acetic acid injection (HR=1.8; 95% CI 1.1 to 2.8; one trial; n=125) and PEI (HR=1.49; 95% CI 1.2 to 1.9; five trials; n=882). No trials reported health-related quality of life.

In 2016, Lan published a network meta-analysis comparing different interventional treatments for early stage HCC.<sup>[14]</sup> A total of 21 RCTs were included that compared transhepatic arterial chemoembolization (TACE), RFA, percutaneous ethanol injection (PEI), and hepatic resection, or combinations of treatments. These studies were all rated at a low-to-moderate risk of bias, with lack of blinding being the most substantial limitation. The primary outcome measures were overall survival (OS) at one, three, and five years posttreatment. The treatments and combinations of treatments were rank-ordered by results on OS. At each time point, the combination of RFA plus TACE was the number one ranked treatment. The combination of RFA plus TACE ranked second highest at one and three years, and was third highest at five years, with hepatic resection ranked second at five years. RFA alone was ranked as the fourth highest treatment at one year and the fifth highest treatment at three and five years.

In 2016, Facciorusso reported results from a systematic review and meta-analysis of one RCT and six retrospective studies (n=774) comparing RFA and MWA for the treatment of

unresectable hepatocellular carcinoma (HCC).<sup>[15]</sup> The authors found a non-significant trend of higher complete response rates in the patients treated with MWA (OR=1.12, 95% CI 0.67 to 1.88,  $p = 0.67$ ). Overall local recurrence was similar between the two treatment groups (OR 1.01, 95% CI 0.53 to 1.87,  $p=0.98$ ) but MWA outperformed RFA in cases of larger nodules (OR 0.46, 95% CI 0.24 to 0.89,  $p=0.02$ ). Three-year survival was higher after RFA without statistically significant difference (OR 0.95, 95% CI 0.58 to 1.57,  $p=0.85$ ). Major complications were more frequent, although not significantly, in MWA patients (OR 1.63, 95% CI 0.88 to 3.03,  $p=0.12$ ).

In a 2013 Cochrane review, Weis reviewed studies on RFA for HCC versus other interventions.<sup>[16]</sup> 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.<sup>[17-20]</sup> This finding reinforces the use of RFA only for unresectable HCC. The Cochrane review also reported finding moderate quality evidence demonstrating superior survival with RFA over PEI.<sup>[16]</sup> Evidence on RFA versus acetic acid injection, microwave ablation, or laser ablation was insufficient to draw conclusions.<sup>[16]</sup>

## RADIOFREQUENCY ABLATION

### RFA AS A PRIMARY TREATMENT OF HEPATOCELLULAR CANCER

#### Systematic Reviews

Jia (2021) performed a meta-analysis to compare clinical efficacy between RFA and surgical resection in patients with HCC meeting Milan criteria.<sup>[21]</sup> The analysis only included RCTs, accounting for eight trials ( $n=1,177$ ). There were no significant differences found between RFA and surgical resection in OS and disease-free survival (DFS) rates. In a subgroup analysis stratifying by tumor size, there was still no significant differences between the two therapies for both tumors  $\leq 4$  cm and  $>4$  cm. Limitations of the analysis include inclusion of clinical trials with small sample sizes and a lack of double blinding as it is not feasible.

Pan (2020) reported a systematic review comparing stereotactic body radiotherapy and RFA for hepatocellular carcinoma.<sup>[22]</sup> No RCTs and 10 retrospective studies ( $n=2,732$  patients) met inclusion criteria. Over half of the studies were giving a medium score for quality because of inconsistent comparability. According to the meta-analysis, SBRT had significantly higher one- and three-year local control (OR 0.42, 95% CI 0.24 to 0.74,  $p=0.003$ ; and OR 0.54, 95% CI 0.37 to 0.80,  $p=0.002$ , respectively) and significantly shorter one- and two-year OS (OR 1.52, 95% CI 1.21 to 1.90,  $p=0.0003$ ; and OR 1.66, 95% CI 1.38 to 2.01,  $p<0.00001$ , respectively). When used as a bridge to treatment, no significant differences were identified between groups in transplant rate or post-transplant pathological necrosis rate (OR 0.57, 95% CI 0.32 to 1.03,  $p=0.060$ ; and OR 0.49, 95% CI 0.13 to 1.82,  $p=0.290$ , respectively).

Jin (2020) performed a systematic review of RCTs comparing laparoscopic hepatectomy and RFA for HCC.<sup>[23]</sup> Seven RCTs met inclusion criteria. The studies were at unclear risk of bias for allocation concealment and blinding (participants, personnel, and outcome assessment) and low risk of reporting and attrition bias. Pooling of the five studies that reported duration of surgery showed that the RFA group had significantly shorter duration than the hepatectomy group (MD=-99.04; 95% CI -131.26 to -66.82;  $p<0.001$ ;  $I^2=95\%$ ). Four studies reported the incidence of cancer recurrence, and pooled data from these RCTs indicated a higher rate of

recurrence in the RFA group (OR=2.68; 95% CI 1.72 to 4.18;  $p<0.001$ ;  $I^2=23\%$ ). The pooled data from the four RCTs that reported on estimated bleeding volume during surgery and duration of hospital stay showed that the RFA group had significantly lower volume (MD=-241.97; 95% CI -386.93 to -97.02;  $p<0.001$ ;  $I^2=97\%$ ) and shorter duration (MD=-3.4; 95% CI -5.22 to -1.57;  $p<0.001$ ;  $I^2=94\%$ ) than the hepatectomy group. Pooling of the three studies that reported the incidence of blood transfusion during surgery indicated significantly lower incidence in the RFA group (OR=0.08; 95% CI 0.02 to 0.37;  $p=0.001$ ;  $I^2=0\%$ ).

Li (2019) performed a systematic review and meta-analysis to compare the effectiveness of laparoscopic hepatectomy and RFA.<sup>[24]</sup> A total of 10 studies met inclusion criteria. This included 1,570 HCC patients treated with laparoscopic hepatectomy or RFA. The pooled five-year OS rate was significantly higher in the hepatectomy group (OR=0.53, 95% CI=0.40, 0.69,  $p<0.001$ ) analyzed as a whole and in a subgroup analysis of small HCCs (OR=0.47, 95% CI=0.33, 0.66,  $p<0.001$ ). The hepatectomy group also had better one- and three-year disease-free survival rate and a lower recurrence rate, but additionally a higher complication rate (OR=0.64, 95% CI 0.46 to 0.89,  $p=0.008$ ).

Si (2019) reported results of a systematic review and meta-analysis of minimally invasive liver surgery compared to RFA for the treatment of small HCC nodules.<sup>[25]</sup> A total of six studies met inclusion criteria, including 313 RFA-treated and 284 surgically treated patients. Three-year OS rates were significantly higher in the surgically treated patients (OR 0.55; 95% CI 0.36 to 0.84), as were three-year disease-free survival rates (OR 0.63; 95% CI 0.41 to 0.98). RFA-treated patients experienced significantly higher rates of local intrahepatic recurrence (OR 2.24; 95% CI 1.47 to 3.42), lower incidence of postoperative complications (OR 0.34; 95% CI 0.22 to 0.53), and shorter operation (OR - 145.31, 95% CI - 200.24 to - 90.38) and hospitalization (OR - 4.02, 95% CI - 4.94 to - 3.10) durations.

Another systematic review comparing surgery to RFA, this one of early HCC, was reported by Tan (2019).<sup>[26]</sup> A total of 11 studies met inclusion criteria. These included 1,691 patients undergoing hepatic resection or RFA. The hepatic resection group had statistically significantly higher three- and five-year OS, as well as three-year disease-free survival. This group also had a lower local recurrence rate that did not reach statistical significance. Patients undergoing laparoscopic radiofrequency ablation had higher three- and five-year OS than other minimally invasive ablation techniques.

In 2012, Xu reported on a meta-analysis of 13 studies that compared RFA with surgical resection for early HCC.<sup>[27]</sup> Only two studies were RCTs. Surgical resection was done in 1233 patients and RFA was used in 1302 patients. Surgical resection patients had significantly longer OS rates at one, three, and five years than RFA patients (OR 0.60; 95% CI 0.42 to 0.86, OR=0.49; 95% CI 0.36 to 0.65; OR=0.60; 95% CI 0.43 to 0.84), respectively. When only HCC tumors of 3 cm or less were analyzed, resection still had significantly better OS than RFA at one, three, and five years. Recurrence rates were also significantly lower in the surgical resection group at one, three, and five years than in the RFA group (OR=1.48; 95% CI 1.05 to 2.08; OR=1.76; 95% CI 1.49 to 2.08; OR=1.68; 95% CI 1.21 to 2.34; all respectively). Local recurrence rates did not differ significantly between procedures. Complication rates were higher with resection than with 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.

## Randomized Controlled Trials

No randomized trials published after the above systematic reviews were identified.

## **Nonrandomized Studies**

A large body of case series, meta-analyses, and retrospective evidence has been published on RFA as a treatment of unresectable primary liver tumors.<sup>[28-34]</sup> These articles reported disease-free survival rates consistent with those reported in the randomized controlled trials.

## **RFA AS A PRIMARY TREATMENT OF INTRAHEPATIC CHOLANGIOCARCINOMAS**

Cholangiocarcinomas are tumors that originate in the bile duct epithelium; 90% are adenocarcinomas. Intrahepatic cholangiocarcinomas (ICC) are located within the hepatic parenchyma. They may also be referred to as peripheral cholangiocarcinomas. Extrahepatic cholangiocarcinomas (ECC) are more common than intrahepatic cholangiocarcinoma and are located within the extrahepatic bile duct. Complete resection with negative margin is potential curative, though recurrence is common and most cases are unresectable due to advanced disease when diagnosed. For unresectable or metastatic cholangiocarcinomas at any location, the primary treatment may include chemotherapy, treatment within a clinical trial, or best supportive care. RFA and other locoregional therapies may be an option. Biliary drainage with biliary stenting may be warranted for unresectable or metastatic extrahepatic disease. Liver transplantation is potentially curative in carefully selected patients with lymph node negative, nondisseminated locally advanced hilar cholangiocarcinomas and otherwise normal biliary and hepatic function or underlying liver disease precluding surgery.

A number of small ( $n < 20$ ) retrospective analyses and case series have been published for ablation of ICC.<sup>[35-43]</sup> These studies consistently reported high technical effectiveness with early tumor necrosis, and a low rate of major adverse effects.

## **RFA AS A PRIMARY TREATMENT OF LIVER METASTASES OF COLORECTAL AND NEUROENDOCRINE ORIGIN**

### **Colon Cancer**

More than half of patients with colorectal cancer (CRC) will develop liver metastases, generally with a poor prognosis.<sup>[44]</sup> 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 one year. A number of first-line systemic chemotherapy regimens have been used to treat metastatic CRC, with a two-year survival rate of 25% for those treated with 5-fluorouracil (5-FU) or 5-FU plus leucovorin.<sup>[44]</sup> With the introduction of newer agents (e.g., irinotecan, oxaliplatin) and targeted drugs (e.g., cetuximab, bevacizumab), two-year survival rates have increased to between 30% and 39%, with marked improvement in OS. Because 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 five-year actuarial survival rates that historically range from 28% to 38%, but may reach 58% in appropriately selected, resectable patients without widely disseminated disease.<sup>[45, 46]</sup> 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 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 six case series (total n=446 patients) showed that RFA of unresectable CRC metastases was associated with one-, two-, and three-year survival rates that ranged from 87% to 99%, 69% to 77%, and 37% to 58%, respectively.<sup>[45]</sup> While these results suggested 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

Hao (2020) reported a systematic review and meta-analysis of RFA versus liver resection for solitary colorectal liver metastases.<sup>[47]</sup> A total of 10 studies met inclusion criteria. Study quality was not assessed. Significant interstudy heterogeneity was identified. Statistically significant differences were identified in the meta-analysis for one-year PFS (RR 0.77 95% CI 0.630 to 0.940, p=0.009), three-year OS (RR 0.860, 95% CI 0.760 to 0.980, p=0.021, and five-year OS (RR 0.66, 95% CI 0.52 to 0.85, p=0.001), with superior outcomes in the resection group. There was significantly lower incidence of postoperative complication in the RFA group (RR 0.340, 95% CI 0.230 to 0.510, p=0.000). The subgroup analysis identified the following variables as contributing to the heterogeneity: publication year, geographic location, tumor size, adjuvant chemotherapy, and synchronous metastases.

A 2017 systematic review with meta-analyses by van Amerongen compared the RFA to surgery as a curative treatment for patients with colorectal liver metastases.<sup>[48]</sup> Authors found that all studies included had risk of patient selection bias.

A 2012 systematic review by Cirocchi analyzed 17 nonrandomized studies and a meeting abstract of an RCT on RFA for CRC liver metastases.<sup>[49]</sup> The RCT reported PFS was significantly higher in 60 patients receiving RFA plus chemotherapy than in 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 in patient characteristics across studies reviewed, as well as heterogeneity in the interventions, comparisons, and outcomes. Therefore, the reviewers concluded the evidence was insufficient to recommend RFA for CRC liver metastasis. In a 2014 Health Technology Assessment, Loveman also found insufficient evidence to draw conclusions on the clinical effectiveness of ablative therapies, including RFA, for liver metastases.<sup>[50]</sup>

In 2012, Weng reported a meta-analysis comparing RFA with liver resection for the treatment of CRC liver metastases.<sup>[51]</sup> One prospective study and 12 retrospective studies were included in the analysis. OS at three and five years was significantly longer in liver resection than in RFA (relative risk [RR], 1.377; 95% CI 1.246 to 1.522; RR=1.474; 95% CI 1.284 to 1.692, respectively). DFS was also significantly longer in liver resection than RFA at three and five years (RR=1.735; 95% CI 1.483 to 2.029; RR=2.227; 95% CI 1.823 to 2.720, respectively). While postoperative morbidity with liver resection was significantly higher than with RFA (RR=2.495; 95% CI 1.881 to 3.308), mortality did not differ significantly between treatments. Liver resection also performed significantly better than RFA when data were analyzed in three subgroups: tumors less than 3 cm, solitary tumor, and open or laparoscopic approach.

However, hospital stays were significantly shorter (9.2 days vs 3.9 days,  $p < 0.01$ ) and rates of complications lower (18.3% vs 3.9%,  $p < 0.01$ ) with RFA than liver resection. Interpretation of the meta-analysis is limited by the retrospective nature of most studies.

### Randomized Controlled Trials

In 2012 and 2017, Ruers published the results of a multicenter RCT that compared RFA plus systemic treatment with systemic treatment alone for unresectable colorectal liver metastases.<sup>[52, 53]</sup> This RCT, originally designed as a phase 3 study, was completed as a phase 2 study due to slow accrual ( $n=119$  patients). To be included in the trial, patients had to have nonresectable liver metastases with fewer than 10 nodes and without extrahepatic disease. In the experimental arm, RFA, with or without additional resection, was given in combination with systemic therapy. The primary end point was a 30-month survival higher than 38% in the experimental arm with intention-to-treat analysis. At three years, OS did not differ significantly between groups. However, there was a significant improvement in progression-free survival (HR=0.74; 95% CI 0.42 to 0.95;  $p=0.025$ ), which corresponded to a difference in progression-free survival at three years from 10.6% in the systemic therapy arm to 27.6% in the combined treatment arm. At a median follow-up of 9.7 years, 39 (65%) of 60 patients in the combined treatment arm had died compared with 53 (89.8%) of 59 in the systemic treatment arm (HR=0.58; 95% CI 0.38 to 0.88;  $p=0.01$ ).

### Nonrandomized Studies

Nonrandomized studies in which RFA was compared to resection or systemic chemotherapy in patients with localized CRC metastases and no evidence of additional metastatic disease have been conducted. Tago reported a retrospective analysis in 2021 of CRC patients with liver metastases who underwent RFA ( $n=26$ ), resection ( $n=92$ ), or chemotherapy ( $n=29$ ).<sup>[54]</sup> Median OS was 44.9, 49.5, and 11.6 months in the RFA, resection, and chemotherapy groups, respectively, with statistically significant differences between RFA and resection ( $p=0.027$ ), and RFA and chemotherapy ( $p=0.003$ ). Five-year OS was not significantly different between RFA and resection ( $p=0.508$ ).

In 2016, Hof compared outcomes from RFA or hepatic resection in patients with hepatic metastases from CRC.<sup>[55]</sup> There were 431 patients included from an institutional database. All patients underwent locoregional treatment for hepatic metastases from CRC. Initial treatment was either hepatic resection ( $n=261$ ), open RFA ( $n=26$ ), percutaneous RFA ( $n=75$ ), or a combination of resection plus RFA ( $n=69$ ). Mean follow-up was 38.6 months. The overall recurrence rate was 83.5% (152/182) in patients treated with RFA compared to 66.6% (201/302) in patients treated with hepatic resection ( $p < 0.001$ ). The five-year OS estimate by Kaplan-Meier analysis was 51.9% for RFA and 53.0% for hepatic resection ( $p=0.98$ ).

Abdalla 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 ( $n=70$ ).<sup>[56]</sup> In the key relevant comparison, RFA versus chemotherapy in chemotherapy-naïve patients with nonresectable CRC metastases (median, one lesion per patient; range, 1 to 8; median tumor size, 2.5 cm), OS at four years was 22% in the RFA group and 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 at a 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 vs 40% RFA,  $p=NS$ ).

In a second trial, a consecutive series of well-defined, previously untreated patients ( $n=201$ ) without extrahepatic disease underwent laparotomy to determine therapeutic approach.<sup>[57]</sup> 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, one tumor per patient; range, 1 to 9; median diameter, 3.8 cm), 31 months (95% CI 20 to 42 months) in locally ablated patients (median, four 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, four tumors per patient; range, 1 to 17; median diameter, 4 cm per lesion;  $p=NS$ , ablated vs chemotherapy). Results from two validated quality-of-life instruments (EuroQol-5D, EORTC QLQ C-30) showed that patients treated by local ablation returned to baseline values within three months, whereas those treated with chemotherapy remained significantly lower (ie, worse quality of life) than baseline over 12 months posttreatment ( $p<0.05$ ).

In 2011, Van Tilborg reported long-term results in 100 patients with unresectable colorectal liver metastases who underwent a total of 126 RFA sessions (237 lesions).<sup>[58]</sup> Lesion size ranged from 0.2 to 8.3 cm (mean 2.4 cm). Mean follow-up time was 29 months (range, 6-93 months). Major complications (including abscess, hemorrhage, grounding pad burns, and diaphragm perforation) occurred in eight 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, 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).

## **Neuroendocrine Cancer**

Unlike the above liver tumors, the treatment benefit for RFA of neuroendocrine metastases in the liver is related to symptom control rather than survival or local recurrence. Therefore, patient selection and outcome measures in related studies focused on the level of symptoms rather than lesion size, number, and location. The primary treatment of symptomatic neuroendocrine tumor (NET) metastases is chemotherapy.

### Systematic Reviews

Most reports of RFA treatment for 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. A systematic review of RFA as treatment for unresectable metastases from neuroendocrine tumors was published in 2015.<sup>[59]</sup> Seven unique studies (total  $n=301$  patients) included in the review, all were 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%). There were two 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 symptom relief ranging from 14 to 27 months. There was a high degree of variability in the length of follow-up and surveillance used for follow-up, and a wide range of local recurrence rates, from less than 5% to 50%. The reported five-year survival rates ranged from 57% to 80%.

### Randomized Controlled Trials

No randomized controlled trials of RFA as a treatment for neuroendocrine metastases in the liver were identified.

### Nonrandomized Studies

Fairweather (2017) compared OS in patients with neuroendocrine liver metastases (N=649) from a large prospective database.<sup>[60]</sup> Primary treatment modalities included: systemic therapy (n=316), chemoembolization (n=130), observation (n=117), surgical resection (n=58), and RFA (n=28). The most favorable 10-year OS estimates were achieved with surgical resection (70%), followed by RFA (55%), systemic therapy (31%), chemoembolization (28%), and observation (20%).

Berber (2008) analyzed a large series of liver tumors treated with RFA.<sup>[61]</sup> Of 1,032 tumors in the study, 295 were neuroendocrine tumor metastases. The mean number of lesions treated was 5.6 (range, 1 to 16) and mean lesion size was 2.3 cm (range, 0.5 to 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%]), non-colorectal, non-neuroendocrine metastases (28/126 [22%]), and HCC (23/131 [18%]). In patients with neuroendocrine tumors, 58% of the recurrences were evident at one year and 100% at two years versus 83% at one year and 97% at two years for colorectal metastases. Eight neuroendocrine tumors were eligible for repeat RFA; seven were retreated, and one was not. Symptom control and survival were not reported.

Mazzaglia reported on a series gathered over 10 years for 63 patients with neuroendocrine metastases who were treated with 80 sessions of LRFA.<sup>[62]</sup> Tumor types were 36 carcinoid, 18 pancreatic islet cell, and nine medullary thyroid cancer. Indications for study enrollment 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; patients with additional minor extrahepatic disease were not excluded. RFA was performed 1.6 years (range, 0.1 to 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 six 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 months. Median survival times were 11 years postdiagnosis of the primary tumor, 5.5 years postdiagnosis of the neuroendocrine hepatic metastases, and 3.9 years after the first RFA treatment.

Elias reported on 16 patients who underwent a one-step procedure comprising a combination of hepatectomy and RFA for treatment of gastroenteropancreatic endocrine tumors.<sup>[63]</sup> A mean of 15 liver tumors per patient were surgically removed, and a mean of 12 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 seven liver tumors per patient. Venkatesan reported on six patients treated for pheochromocytoma metastases.<sup>[64]</sup>

Complete ablation was achieved in six of seven metastases. Mean follow-up was 12.3 months (range, 2.5 to 28 months).

## **RFA AS A PRIMARY TREATMENT OF UNRESECTABLE LIVER METASTASES OF OTHER ORIGIN**

### **Breast Cancer**

A number of case series have reported on use of RFA to treat breast cancer liver metastases. In 2014, Veltri analyzed 45 women treated with RFA for 87 breast cancer liver metastases (mean size, 23 mm).<sup>[65]</sup> Complete ablation was seen on initial follow-up in 90% of tumors, but tumor recurrence occurred in 19.7% within eight months. RFA did not impact OS, which at one year was 90% and at three years was 44%.

In a retrospective review, Meloni assessed local control and intermediate- and long-term survival in 52 patients.<sup>[66]</sup> Inclusion criteria were fewer than five tumors, maximum tumor diameter of 5 cm, 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%. Median OS, from the time of first liver metastasis diagnosis, was 42 months, and five-year survival was 32%. Patients with tumors 2.5 cm in diameter or larger had worse prognoses than those with smaller tumors. The authors concluded that these survival rates were comparable to those reported in the literature for surgery or laser ablation. In another series of 43 breast cancer patients with 111 liver metastases, technical success (tumor ablation) was achieved in 107 (96%) metastases.<sup>[67]</sup> 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, with the exception of skeletal metastases.

A series of 19 patients was reported by Lawes.<sup>[68]</sup> Eight patients had disease confined to the liver, with 11 also having stable extrahepatic disease. At the time of the report, seven patients, with disease confined to the liver at presentation, were alive, as were six with extrahepatic disease; median follow-up after RFA was 15 months (range, 0 to 77 months). Survival at 30 months was 41.6%. RFA failed to control hepatic disease in three patients.

### **Sarcoma**

Jones evaluated RFA in a series of patients with sarcoma.<sup>[69]</sup> Thirteen 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 one achieved stable disease. Two GIST patients received RFA on two occasions for separate lesions within the liver, and both responded to the second RFA procedure. Of the other subtypes, seven underwent RFA to liver lesions, five of whom responded to RFA, one progressed, and one was not assessable 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 advised conducting further larger studies 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.<sup>[70]</sup> 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 one-, three-, and five-year OS rates were 91.5%, 65.4%, and 27.1%, respectively. The authors recommended that patients with metastatic disease who can be rendered surgically free of disease be considered for potential hepatic resection.

## **RFA AS A TREATMENT OF UNRESECTABLE HCC TUMORS IN THE TRANSPLANT SETTING**

The goal of RFA prior to transplantation is to maintain a patient's eligibility for liver transplant by either downsizing a large tumor or by preventing progression of a smaller tumor. The literature related to locoregional therapy for HCC in the transplant setting can be divided into three objectives:

- Prevention of tumor progression while on the waiting list
- Downgrading HCC prior to transplantation
- To reduce risk of post-transplantation tumor recurrence in patients with T3 tumors

Assessment of the effects of pre-transplantation RFA on these objectives would, ideally, include clinical trials that compare the recurrence-free survival of patients who received pretransplant locoregional therapies with those who did not and to study recurrence-free survival in patients who received locoregional therapies to downsize larger tumor(s) or to prevent progression of smaller tumor(s) in order to meet transplant waiting list criteria.

The current published evidence is limited to case series and retrospective reviews which are considered unreliable due to methodologic limitations such as lack of randomization and lack of a control group for comparison.<sup>[71-80]</sup> In addition to these limitations, current studies targeted only a subset of candidates for liver transplant to treat HCC. Because only patients with adequate liver reserves were offered treatment, it cannot be determined whether any reported increase in recurrence-free survival was related to the pretransplant locoregional therapy or liver reserve status. It is unknown whether patients with adequate liver reserves have improved outcomes regardless of pretransplant management.

### **United Network for Organ Sharing policy**

The United Network for Organ Sharing (UNOS) recognizes pretransplant locoregional therapies including RFA as a component of patient management during the waiting period for a donor liver.<sup>[81]</sup> In allocating donor organs, UNOS sought to balance risk of death on the waiting list against risk of recurrence after transplant. For HCC, part of this balance included tumor size and number of nodules as follows:

T1: 1 nodule 1.9 cm or smaller

T2: 1 nodule between 2.0–5.0 cm, or 2 or 3 nodules each smaller than 3.0 cm

T3: 1 nodule larger than 5.0 cm, or 2 or 3 nodules with at least 1 larger than 3.0 cm

Patients with T1 lesions were considered at low risk of death on the waiting list, while those with T3 lesions were considered at high risk of post-transplant recurrence. Patients with T2 tumors were considered to have an increased risk of dying while on the waiting list compared with T1 lesions, and an acceptable risk of post-transplant tumor recurrence. Therefore, the UNOS criteria prioritized T2 HCC. In addition, patients could be removed from the waiting list if they were determined to be unsuitable for transplantation based on progression of HCC. Thus these criteria provide incentives to use locoregional therapies to maintain T2 classification.

The UNOS allocation system provides incentives to use locoregional therapies in two 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 to maintain the UNOS allocation points.

These two 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 locoregional treatment. OPTN Class 5T nodules qualify for continued priority points predicated on the pre-treatment classification of the nodule(s) and are defined as:

- 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 or 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.”<sup>[81]</sup>

## **ADVERSE EVENTS**

Complication rates for RFA of liver tumors are reported in approximately 7% of patients, as compared with that of open liver resection which may be as high as 22%.<sup>[82]</sup>

Specific complications reported in the literature to date include the following:<sup>[58, 61, 82-85]</sup>

1. Hemorrhage
2. Liver Abscess
3. Liver infarction
4. Liver failure
5. Cutaneous burn
6. Diaphragm perforation
7. Bowel perforation
8. Seeding of the needle tract with cancer cells
9. Hydrothorax or hemothorax requiring drainage
10. Bile duct injury
11. Death

## MICROWAVE ABLATION

### MWA AS A TREATMENT OF HEPATOCELLULAR CARCINOMA

#### Systematic Reviews

Dou (2022) conducted a systematic review and meta-analysis that compared the safety and efficacy of MWA compared to RFA in patients with HCC.<sup>[86]</sup> The analysis included 28 cohort studies and 5 RCTs. Overall, there was no significant difference in disease-free survival, OS, or major complications between the two groups. In the cohort studies, MWA had a lower local tumor progression rate than RFA (OR, 0.78; 95% CI, 0.64 to 0.96;  $p=0.02$ ). The authors concluded that there were various differences in the included studies (e.g., equipment used, operator experience) and that more high-quality RCTs are needed to draw a definitive conclusion on MWA and RFA in this patient population.

Glassberg (2019) conducted a systematic review of MWA compared to resection in patients with HCC or metastatic liver cancer. One RCT (Xu 2015)<sup>[87]</sup> was included; the other studies ( $n=15$ ) were observational (2 prospective, 13 retrospective).<sup>[88]</sup> Patients who received MWA had significantly higher risk of LTR compared to those who received resection (RR=3.04;  $p<0.001$ ). At one year, overall survival did not differ between MWA and resection, but three- and five-year overall survival was significantly higher in patients who had received resection. Overall complications and major complications were lower with MWA compared to resection. Additionally, operative time, intraoperative blood loss, and hospital length of stay were significantly lower with MWA. Some studies included patients that were nonresectable in the MWA treatment arm, but due to limited reporting and patient preference affecting which treatment was performed, the reviewers were not able to calculate the number of patients who were nonresectable or to conduct subgroup analyses by resectable vs unresectable tumors. Microwave ablation was typically selected for patients with smaller and/or deeper tumors, more comorbidities, and a preference for a less invasive procedure. The reviewers concluded that MWA can be an effective and safe alternative to HR in patients or tumors that are not amenable to resection, but more studies are needed to determine the target population that would benefit most from MWA.

In 2017, Zhang reported results from a systematic review and meta-analysis comparing hepatic resection with microwave ablation as a treatment of hepatocellular carcinoma.<sup>[89]</sup> Nine studies with follow-up time of three years or greater were included overall, totalling 1,480 participants. For overall survival (seven reports), studies were not found to have statistical bias, and overall heterogeneity amongst studies was not significant ( $I^2=0.0\%$ ,  $p=0.749$ ), however, heterogeneity amongst studies included for meta-analysis of disease-free survival (five reports) was significant ( $I^2=71.1\%$ ,  $p=0.008$ ). No difference was found comparing MWA to resection for OS and DFS (HR =0.98, 95% CI 0.76 to 1.26,  $p=0.878$ , and HR =1.16, 95% CI 0.79 to 1.71,  $p=0.442$ , respectively). Meta-analysis demonstrated that MWA was associated with shorter operation time (standardized mean difference [SMD] -1.37, 95% CI -1.92 to -0.81,  $p=0.000$ ), less amount of blood loss in operation (SWD -1.19, 95% CI -1.76 to -0.61,  $p=0.000$ ), and less complications (OR 0.22, 95% CI 0.12 to 0.40,  $p=0.000$ ) than resection. The authors concluded that MWA may be superior given there were no differences identified in OS and DFS, but demonstrated fewer complications and improved intraoperative outcomes.

In 2011, Bertot conducted a systematic review evaluating mortality and complication rates of ablation techniques for primary and secondary liver tumors.<sup>[90]</sup> This review included two studies using MWA totaling 1,185 patients.<sup>[91, 92]</sup> The pooled mortality rate for MWA was 0.23% (95%

CI 0.0 to 0.58%). Major complication rates were 4.6% for MWA (calculated by using a random effects model since there was significant heterogeneity). The authors concluded that percutaneous ablation techniques, including MWA, are safe and have acceptable complication rates for the treatment of liver tumors.

In 2009, Ong conducted a systematic review of studies on MWA for primary and secondary liver tumors.<sup>[93]</sup> Based on the results from 25 clinical studies, the authors concluded that MWA was an effective and safe technique for liver tumor ablation with low complication rates and survival rates comparable to hepatic resection. However, rates of local recurrence after MWA were noted to be higher than hepatic resection. In most studies of MWA, hepatocellular carcinoma recurrence rates were approximately 10% but were also noted to be as high as 50%, which the authors indicated could be addressed with further ablation. Survival rates in the studies on MWA for hepatocellular carcinoma were as high as 92% at three years and 72% at five years, which was noted to be comparable to radiofrequency ablation (RFA) and percutaneous ethanol injections. Pain and fever were the most frequently reported complications, but complications increased when there were more tumors, larger tumors, and more microwave antennas used. The authors concluded that MWA may be a promising option for the treatment of HCC tumors but should be reserved for patients not amenable to hepatic resection. The authors also noted further randomized clinical trials are warranted to compare MWA to other ablation procedures.

### **Randomized Controlled Trials**

Zaitoun (2021) compared the safety and efficacy of combination therapy with TACE and MWA (n=89) compared to TACE (n=84) or MWA (n=92) only in patients with solitary HCC lesions measuring between 3 to 5 cm.<sup>[94]</sup> TACE was performed first, followed by MWA after 15 days. Mean tumor size was 3.6 cm, 3.9 cm, and 3.7 cm in the TACE, MWA, and combination groups, respectively (p=0.053). Complete response at one month was achieved by 86.5% of patients who received combination therapy compared with 54.8% of patients treated with TACE and 56.5% of patients treated with MWA. Patients treated with combination therapy had a significantly lower recurrence rate at 12 months (p=0.0001) and a significantly higher OS rate at three years (69.6%; p=0.02). Post-procedural minor adverse events (e.g., nausea, vomiting, abdominal pain, and low-grade fever) were reported in 24.7%, 47.6%, and 38% of patients in the combined, TACE, and MWA groups, respectively. Severe hepatic dysfunction was observed in one patient in the combined group and three patients in the TACE group. Tumor seeding was reported in two patients in the MWA group. A decrease in alpha-fetoprotein (AFP) concentration was observed in 75%, 63%, and 48% of patients who underwent combined therapy, MWA, or TACE, respectively.

Chong (2020) conducted an RCT comparing MWA to RFA in 93 patients with HCC (up to 3 lesions of 5 cm or smaller).<sup>[95]</sup> Mean tumor size was 3.1 cm in the MWA group and 2.8 cm in the RFA group. The primary outcome of this study was the rate of complete ablation at one month, which did not differ significantly for MWA (95.7%) versus RFA (97.8%; p>0.99). Rates of OS up to five years and rates of disease-free survival up to three years were similar between groups. However, the sample size calculations were based on rates of complete ablation at one month, so the study may not have been adequately powered to detect differences in OS or disease-free survival.

Fang (2019) randomized hepatic carcinoma patients to receive conventional surgical excision (n=47) or ultrasound-guided microwave ablation (n=47).<sup>[96]</sup> Statistically significant differences

( $p < 0.05$ ) between groups were reported for duration of operation (shorter for MWA), quantities of intraoperative bleeding and blood transfusions (lower for surgical excision), effective rate of treatment (higher for MWA), occurrence rate of complications (lower for MWA). In addition significantly higher albumin and total bilirubin and lower alanine aminotransferase and aspartate transaminase were reported for the MWA group ( $p < 0.05$ ).

Older RCTs are included in the SRs above.

## Nonrandomized Studies

In addition to the studies noted above, a number of nonrandomized studies have been published on the use of MWA in patients with hepatocellular carcinoma. Several examples are cited, below. The results of these studies should be interpreted with caution due to the following limitations:

- Results from small sample sizes ( $n < 100$ ), limit the ability to rule out the role of chance as an explanation of study findings.<sup>[97-104]</sup>
- Results from studies with short-term follow-up (<one year) are not adequate to determine the durability of the treatment effect.<sup>[97, 105, 106]</sup>
- A lack of comparison group, without which it is not possible to account for the many types of bias that can affect study outcomes.<sup>[91, 92, 103-112]</sup>

Given the limitations noted above, nonrandomized studies do not provide reliable data to demonstrate the efficacy of MWA treatment in patients with HCC.

## MWA AS A TREATMENT OF HEPATIC METASTASIS

### Systematic Reviews

Mimmo (2022) conducted a systematic review of MWA for colorectal liver metastases.<sup>[113]</sup> Twelve studies ( $N=741$ ) were included, and 395 patients were treated with MWA versus conventional surgical procedure ( $n=346$ ). The mean follow-up duration was 20.5 months. Pooled data analysis showed mean recurrence free rates for MWA at one, three, and five years were 65.1%, 44.6%, and 34.3%, respectively. Mean OS rates for MWA at one, three, and five years were 86.7%, 59.6%, and 44.8%, respectively. Mean local recurrence rates for MWA at 3, 6, and 12 months were 96.3%, 89.6%, and 83.7%, respectively.

A 2014 Health Technology Assessment<sup>[50]</sup> and a 2013 Cochrane review<sup>[114]</sup> also identified only one RCT on ablation for liver metastasis, Shibata.<sup>[115]</sup> The reviewers found insufficient evidence to determine any benefits of MWA for liver metastasis over surgical resection.

In 2013, Vogl reviewed evidence regarding RFA, laser-induced thermotherapy (LITT) and MWA treatment of breast cancer liver metastasis.<sup>[116]</sup> Local tumor response, progression and survival rates were evaluated. Authors reported positive response rates of 63 % to 97 % in RF-ablated lesions, 98.2 % in LITT-treated lesions and 34.5-62.5 % in MWA lesions. Median survival was 10.9-60 months with RFA, 51-54 months with LITT and 41.8 months with MWA. Five-year survival rates were 27-30 %, 35 % and 29 %, respectively. Local tumour progression ranged from 13.5 % to 58 % using RFA, 2.9 % with LITT and 9.6 % with MWA. The authors called for additional, large RCTs to further explore the benefits of ablation therapies.

In the Ong review described above<sup>[93]</sup>, local recurrence rates for liver metastases after treatment with MWA averaged approximately 15% but varied between 0 and 50% in the seven studies reviewed that addressed liver metastases. As noted above, Ong concluded MWA may be a promising treatment option for the treatment of liver tumors but should be reserved for patients not amenable to hepatic resection.

In 2011, Pathak also conducted a systematic review of ablation techniques for colorectal liver metastases, which included 13 studies on MWA, totaling 406 patients with a minimum of 1-year follow-up.<sup>[117]</sup> Mean survival rates were 73%, 30% and 16% and ranged from 40–91.4%, 0–57% and 14–32% at one-, three-, and five-years' follow-up, all respectively. Minor and major complication rates were considered acceptable and ranged from 6.7–90.5% and 0–19%, respectively. Local recurrence rates ranged from 2-14%. The authors acknowledged limitations in the available studies but concluded survival rates for MWA are more favorable than for palliative chemotherapy alone.

### **Randomized Controlled Trials**

Only one RCT comparing the use of MWA for hepatic metastases to the gold standard of surgical resection was identified. In 2000, Shibata reported on a trial of 30 patients with hepatic metastases from colorectal cancer randomly assigned without stratification to treatment with either MWA after laparotomy (n=14) or hepatectomy (n=16).<sup>[115]</sup> The study began with 40 patients, but 10 patients were excluded because the researchers discovered intraoperatively that these patients did not meet study criteria due to having extensive metastasis or equal to or greater than 10 tumors. The treatment groups of MWA vs. hepatectomy were not significantly different in age (mean age 61 in both groups) number of tumors (mean 4.1 vs. 3.0, respectively) or tumor size (mean 27 mm vs. 34 mm, respectively). The authors reported no significant differences in survival rates following MWA or hepatectomy (27 months vs. 25 months, respectively) and mean disease-free survival (11.3 vs. 13.3 months, respectively). However, intraoperative blood loss was significantly lower and no blood transfusions were required in the MWA group whereas six patients in the hepatectomy group required blood transfusions. Complications in the microwave group consisted of one hepatic abscess and one bile duct fistula. In the hepatectomy group, complications were one intestinal obstruction, one bile duct fistula and one wound infection.

### **Nonrandomized Studies**

Several nonrandomized trials regarding MWA treatment in patients with liver metastases were identified; however, these studies were limited by a lack of comparison group,<sup>[118-120]</sup> short-term follow-up<sup>[118, 119]</sup> and small sample size.<sup>[118, 120]</sup>

## **CRYOSURGICAL ABLATION**

### **CRYOSURGICAL ABLATION AS A TREATMENT OF HEPATOCELLULAR CARCINOMA**

The evidence regarding cryoablation as a treatment for hepatocellular carcinoma (HCC) remains controversial. However, use of cryotherapy for HCC became a standard of care and published research increased through the late 1990's and early 2000's. Awad published a systematic Cochrane Review in 2009, noting that the literature consisted of two prospective cohort studies and two retrospective cohort studies.<sup>[121]</sup> Overall, the Review concluded that the evidence is not sufficient to evaluate potential harms and benefits; large well-designed

randomized clinical trials (RCTs) are feasible and necessary to define the role of cryotherapy in the treatment of HCC.

A 2023 meta-analysis by Kim compared the benefits and harms of locoregional treatments for HCC in patients who had early HCCs of <4 cm with no extrahepatic spread of portal invasion [122]. While this study included 19 trials, the only cryoablation study included was the one included below by Wang (2015). Overall, cryoablation had similar overall survival, progression-free survival, and local progression-free survival scores as radiofrequency ablation. Further research is needed with additional participants to examine the effect of cryoablation on patient health outcomes compared to standard care.

Since the 2009 Cochrane Systematic Review, Wang (2015) reported results from one RCT comparing the safety and efficacy of cryotherapy vs RFA.<sup>[1]</sup> One hundred eighty participants were randomized to each group, with no significant differences found at baseline between the arms, with the exception of number of tumors – 10.56% of the cryo group participants had two tumors at enrollment, compared to 5% in the RFA group. Participants were followed for five years, and there were no differences in local recurrence, new recurrence, overall survival, or tumor-free survival. At the end of follow-up, 52 patients (28.9%) in the CRYO group and 55 patients (30.6%) in the RFA group died. The causes of death included HCC progression in 44 (24.4%), hepatic failure in five (2.8%), and variceal bleeding in three (1.7%) in the CRYO group, and HCC progression in 47 (26.1%), hepatic failure in four (2.2%), variceal bleeding in two (1.1%), and refractory ascites-induced renal failure in two (1.1%) in the RFA group. Overall, the authors concluded that patients with Child-Pugh class A-B cirrhosis and HCC lesions less than or equal to 4cm and no more than two lesions in total, percutaneous cryoablation and RFA are equally safe and effective ablation treatments. For HCC 3.1 to 4.0 cm, cryoablation was associated with a lower rate of local tumor progression than RFA.

## **CRYOSURGICAL ABLATION AS A TREATMENT OF LIVER METASTASES**

A 2019 Cochrane SR was published by Bala evaluation the use of cryotherapy for the treatment of liver metastases.<sup>[123]</sup> The selection criteria included RCTs assessing effects of cryotherapy and its comparators for liver metastases. One RCT was identified. It compared cryotherapy with conventional surgery for patients with liver metastases from the following primary sites: colon and rectum (66.6%), stomach (7.3%), breast (6.5%), skin (4.9%), ovaries (4.1%), uterus (3.3%), kidney (3.3%), intestines (1.6%), pancreas (1.6%), and unknown (0.8%). The SR authors were not able to calculate the risk of bias of the randomization process, allocation concealment, presence of blinding, incomplete outcome data, or selective outcome reporting bias due to insufficient reporting by the RCT authors. Follow-up was five months to 10 years. The trial reported mortality at 10 years (81% vs. 92% for cryotherapy vs. conventional therapy) and the SR authors calculated the relative risk (RR=0.88, 95% CI 0.77 to 1.02). The evidence regarding mortality was rated as low-certainty. The SR authors also calculated chance of recurrence in the liver, which was 86% in the cryotherapy group and 95% in the conventional surgery group (RR 0.90, 95% CI 0.80 to 1.01; low-certainty evidence). The SR authors concluded that the evidence is limited and they cannot determine whether cryotherapy is beneficial or harmful compared to conventional surgery.

## **PERCUTANEOUS ETHANOL INJECTION**

Like RFA, percutaneous ethanol injection (PEI) is most often considered a treatment option for patients with small HCC lesions who are not resection candidates. RFA and PEI are the most commonly performed ablation therapies.

Weis (2015) published a Cochrane Systematic Review that evaluated the harms and benefits of percutaneous ethanol injection (PEI) and percutaneous acetic acid injection (PAI) in adults with early HCC defined by Milam criteria, i.e., one cancer nodule up to 5 cm in diameter or up to three cancer nodules up to 3 cm in diameter compared with no intervention, sham intervention, each other, other percutaneous interventions, or surgery.<sup>[124]</sup> One randomized trial compared PEI versus surgery; we included 76 participants in the analyses. There was no significant difference in the overall survival (HR 1.57; 95% CI 0.53 to 4.61) and recurrence-free survival (HR 1.35; 95% CI 0.69 to 2.63). No serious adverse events were reported in the PEI group while three postoperative deaths occurred in the surgery group. Given the data on PEI were available for only one RCT, the authors concluded there is insufficient evidence to determine whether PEI versus surgery was more effective for early HCC.

In a number of RCT's, the safety and efficacy of RFA and PEI have been investigated in the treatment of Child-Pugh class A patients with early stage HCC tumors.<sup>[125-131]</sup> Complication rates were relatively low for both methods.

## PRACTICE GUIDELINE SUMMARY

### NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

The NCCN guidelines for hepatocellular carcinoma cancers (v.2.2023) recommend ablation be considered in patients who are not candidates for transplant, surgical curative treatments, or as part of a strategy to bridge patients for other curative therapies (category 2A).<sup>[132]</sup> In addition, they state that "ablation alone may be curative in treating tumors  $\leq 3$  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. Unresectable/inoperable lesions greater than 5 cm should be considered for treatment using arterially directed therapy, systemic therapy, or RT. (category 2A).

The NCCN guidelines for rectal (v.6.2023) and colon (v.2.2022) 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."<sup>[133, 134]</sup> (category 2A).

The NCCN guidelines for neuroendocrine and adrenal tumors (v.1.2023) recommend ablation be considered as a primary therapy in locally advanced/metastatic disease. The recommendations 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]."<sup>[135]</sup>

### AMERICAN COLLEGE OF RADIOLOGY (ACR)

The 2014 ACR Appropriateness Criteria<sup>®</sup> for metastatic rectal cancer states that RFA "yields excellent local control of small (<3 cm) CRC liver metastases."<sup>[136]</sup>

The 2011 ACR Appropriateness Criteria<sup>®</sup> considered RFA by percutaneous, open, or laparoscopic methods effective for treatment of small ( $\leq 5$  cm) HCC tumors.<sup>[137]</sup> While ablative

therapy is most effective for these small HCCs, moderate success has also been described with tumors  $\leq 7$  cm. With larger tumor number and/or size, "the operator may want to focus on arterial-based therapies and adjuvant or neoadjuvant therapy." The 2016 guidelines were consistent with the previous recommendations.<sup>[138]</sup>

## 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.<sup>[139]</sup> 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 "randomized 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."

## SUMMARY

For primary tumors of the liver, and hepatic metastases from colorectal tumors or neuroendocrine tumors, there is limited research regarding locoregional ablative therapies; however, treatment options are limited in this population. Clinical practice guidelines based on research recommend ablative therapies in carefully selected patients. Therefore, percutaneous ethanol injection, cryoablation, radiofrequency and microwave ablation may be considered medically necessary when policy criteria are met.

Due to a lack of research and clinical practice guidelines, percutaneous ethanol injection, cryoablation, radiofrequency and microwave ablation are considered investigational when the policy criteria are not met.

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<b>Codes</b>	<b>Number</b>	<b>Description</b>
CPT	47370	Laparoscopy, surgical, ablation of one or more liver tumor(s); radiofrequency
	47371	Laparoscopy, surgical, ablation of 1 or more liver tumor(s); cryosurgical
	47380	Ablation, open, of one or more liver tumor(s); radiofrequency
	47381	Ablation, open, of 1 or more liver tumor(s); cryosurgical
	47382	Ablation, 1 or more liver tumor(s), percutaneous, radiofrequency
	47383	Ablation, 1 or more liver tumor(s), percutaneous, cryoablation
	47399	Unlisted procedure, liver
HCPCS	None	

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