Microwave ablation (MWA) is a technique to destroy tumors and soft tissue by using microwave energy to create thermal coagulation and localized tissue necrosis. MWA is used to treat tumors considered to be inoperable or not amenable to resection or to treat patients ineligible for surgery due to age, presence of comorbidities, or poor general health. MWA may be performed as an open procedure, laparoscopically, percutaneously or thoracoscopically under image guidance (e.g., ultrasound, computed tomography [CT] or magnetic resonance imaging [MRI]) with sedation, or local or general anesthesia. This technique may also be referred to as microwave coagulation therapy.

Related Policies

- Cryosurgical Ablation of Primary or Metastatic Liver Tumors
- Liver Transplant
- Radioembolization for Primary and Metastatic Tumors of the Liver
- Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors
- Radiofrequency Ablation of Primary of Metastatic Liver Tumors
- Transcatheter Arterial Chemoembolization (TACE) to Treat Primary or Metastatic Liver Malignancies

Policy

Locoregional Ablation

Laser ablation for the treatment of patients with primary or metastatic hepatic lesions is considered investigational.

Microwave ablation may be considered medically necessary for the treatment of patients with hepatic lesions with any of the following conditions:

- Primary hepatocellular carcinoma (HCC) when the all of the following criteria are met:
  - Patient is not a candidate for curative hepatic surgical resections due to limited hepatic reserve and/or comorbid conditions and/or the location (e.g., adjacent to a major vein) or number of lesions
  - Patient is not a candidate for liver transplantation* (see exception below)
  - Presence of three or fewer hepatic lesions
  - Each lesion measures 5 centimeters (cm) or less in diameter using current technology
• Absence of extrahepatic metastatic disease
• All tumor foci can be adequately treated (complete ablation determined by preoperative imaging)

• Primary HCC, as a bridge to transplantation*, when all of the following criteria are met:
  o Patient is not a candidate for curative hepatic surgical resections due to limited hepatic reserve and/or comorbid conditions and/or the location (e.g., adjacent to a major vein) or number of lesions
  o Intent is to prevent further tumor growth and to maintain a patient’s candidacy for liver transplant
  o Presence of three or fewer hepatic lesions
  o Each lesion measures 5 centimeters (cm) or less in diameter using current technology
  o Absence of extrahepatic metastatic disease
  o All tumor foci can be adequately treated (complete ablation determined by preoperative imaging)

• Hepatic metastases from colorectal cancer when all of the following criteria are met:
  o Patient is not a candidate for curative hepatic surgical resections due to limited hepatic reserve and/or comorbid conditions and/or the location (e.g., adjacent to a major vein) or number of lesions
  o Presence of four to five or fewer hepatic lesions
  o Each lesion measures 5 centimeters (cm) or less in diameter using current technology
  o Absence of extrahepatic metastatic disease
  o All tumor foci can be adequately treated (complete ablation determined by preoperative imaging)

• Hepatic metastases from neuroendocrine tumors when all of the following criteria are met:
  o Patient has symptomatic disease (e.g., wheezing, flushing of the skin, abdominal cramps, diarrhea, heart disease)
  o Systemic therapy has failed to control symptoms (e.g., Octreotide therapy)
  o Patient is not a candidate for curative hepatic surgical resections due to limited hepatic reserve and/or comorbid conditions and/or the location (e.g., adjacent to a major vein) or number of lesions
  o Absence of extrahepatic metastatic disease
  o Each lesion measures 5 centimeters (cm) or less in diameter using current technology
Microwave ablation for primary HCC or hepatic metastases is considered **investigational** for treatment of **any** of the following:

- Primary HCC when there are either of the following:
  - More than three hepatic lesions nodules
  - When not all sites of tumor foci can be adequately treated
- Primary HCC when used to downstage (downsize) HCC in patients being considered for liver transplant
- Hepatic metastasis from colorectal cancer or neuroendocrine tumors not meeting the medically necessary criteria above
- Hepatic metastases from other types of cancer with the exception of colorectal or neuroendocrine cancer tumors

**Policy Guidelines**

Downstaging (downsizing) therapy is used to reduce the tumor burden in selected patients with more advanced HCC (without distant metastasis) that are beyond the accepted transplant criteria.

**Neuroendocrine Tumors**

Neuroendocrine tumors (NETs) may be referred to by their anatomical location (e.g., pulmonary neuroendocrine tumor, gastroenteropancreatic neuroendocrine tumor). Neuroendocrine tumors include the following:

- Carcinoid tumors
- Islet cell tumors (or 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)

Symptomatic disease from neuroendocrine tumors may include hot, red flushing of the face, severe and debilitating diarrhea, asthma attacks, palpitations, low blood pressure, fatigue, dizziness, and weakness. Extreme symptoms may include heart disease, bronchial constriction, and bowel obstruction.

Systemic therapies for neuroendocrine tumors vary depending on the location and characteristics. Therapies may include, but are not limited to: octreotide, interferon, cytotoxic chemotherapy, angiogenesis inhibitors, and epidermal growth factor inhibitors.
Coding

There are no CPT codes specific to microwave ablation. The following CPT code would likely be used:

32998: Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, radiofrequency, unilateral

47370: Laparoscopy, surgical, ablation of 1 or more liver tumor(s); radiofrequency

47380: Ablation, open, of 1 or more liver tumor(s); radiofrequency

47382: Ablation, 1 or more liver tumor(s), percutaneous, radiofrequency

47383: Ablation, 1 or more liver tumor(s), percutaneous, cryoablation (new code 01/01/15)

50592: Ablation, 1 or more renal tumor(s), percutaneous, unilateral, radiofrequency

Note: According to a 2012 American Medical Association publication (Clinical Examples in Radiology, Vol. 8, Issue 3; Summer 2012), “microwave is part of the radiofrequency spectrum, and simply uses a different part of the radiofrequency spectrum to develop heat energy to destroy abnormal tissue.” Therefore, they instruct that microwave ablation should be reported using the CPT codes for radiofrequency ablation – 32998 (pulmonary), 47382 (liver), and 50592 (renal).

If there is no specific CPT code for ablation, the unlisted CPT code for the anatomic area should be reported such as code 60699 for unlisted procedure, endocrine system (for adrenal or thyroid ablation).

CPT code 76940 would be used to describe the ultrasound guidance for, and monitoring of, parenchymal tissue ablation.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Rationale

Background

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 (5x3 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 1 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 because 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 has some potential hypothetical advantages over RFA or cryosurgical ablation. In MWA, the heating process is active, which produces higher temperatures than the passive heating of RFA and should allow for more complete thermal ablation in a shorter period of time. The higher temperatures reached with MWA (>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 that grounding pads be used during the procedure, because there is no risk of skin burns. Additionally, MWA does not produce electric noise, which allows ultrasound guidance to occur during the procedure without interference, unlike RFA. Finally, MWA can be completed in less time than RFA, because multiple antennas can be used simultaneously.

MWA was first used percutaneously in 1986 as an adjunct to liver biopsy. Since that time, MWA has been used for ablation of tumors and tissue for the treatment of many conditions including: HCC, colorectal cancer metastatic to the liver, renal cell carcinoma, renal hamartoma, adrenal malignant carcinoma, non-small-cell lung cancer, intrahepatic primary cholangiocarcinoma, secondary splenomegaly and hypersplenism, abdominal tumors and other tumors not amenable to resection. Well-established local or systemic treatment alternatives are available for each of these malignancies. The hypothesized advantages of MWA for these cancers include improved local control and those common to any minimally invasive procedure (e.g., preserving normal organ tissue, decreasing morbidity, decreasing length of hospitalization).

**Hepatic Tumors**

Hepatic tumors can arise either as primary liver cancer (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.
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 criterion standard. However, most hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size, number of lesions, or underlying liver reserve.

Various locoregional therapies for unresectable liver tumors have been investigated including: microwave coagulation, RFA, cryosurgical ablation (cryosurgery), laser ablation, transhepatic artery embolization/chemoembolization (TACE), percutaneous ethanol injection, and radioembolization (Yttrium-90 microspheres).

MWA has been investigated as a treatment for unresectable hepatic tumors, both as primary treatment, palliative treatment, and as a bridge to liver transplant. In the latter setting, it is hoped that MWA 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.

Renal Cell Carcinoma

Radical nephrectomy remains the principal treatment of renal cell carcinoma; however, partial nephrectomy or nephron-sparing surgery has been shown to be as effective as radical nephrectomy, with comparable long-term recurrence-free survival rates, in a select group of patients. Prognosis drops precipitously if the tumor extends outside the kidney capsule, because chemotherapy is relatively ineffective against metastatic renal cell carcinoma. Alternative therapies such as MWA are of interest in patients with small renal tumors when preservation of renal function is necessary (e.g., in patients with marginal renal function, a solitary kidney, bilateral tumors) and in patients with comorbidities that would render them unfit for surgery. Another consideration would be in patients at high risk of developing additional renal cancers (as in von Hippel-Lindau disease).

Regulatory Status

There are several devices cleared for marketing by 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 nonresectable 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);
- Valleylab’s (a subsidiary of Covidien) VivaWave® Microwave Ablation System;
- Vivant’s (acquired by Valleylab in 2005) Tri-Loop™ Microwave Ablation Probe;
- MicroSurgeon Microwave Soft Tissue Ablation Device;
- Microsulis Medical’s (now part of AngioDynamics) Acculis® Accu2i; and
- NeuWave Medical’s Certus 140™

These devices are considered substantially equivalent to previously FDA-approved radiofrequency and MWA devices. FDA product code: NEY.

This policy does not address MWA for the treatment of splenomegaly or ulcers or as a surgical coagulation tool.
Breast

A 2010 review of ablation techniques by Zhao et al for breast cancer found only 0% to 8% of breast tumors were completely ablated with microwave ablation (MWA). The authors noted the studies identified for the review were mostly feasibility and pilot studies conducted in research settings. In 2012, W. Zhou et al reported on 41 patients treated with MWA directly followed by mastectomy for single breast tumors with a mean volume of $5.26 \pm 3.8$ cm (range, 0.09-14.14 cm). Complete tumor ablation was found by microscopic evaluation in 37 of the 41 tumors ablated (90%; 95% confidence interval [CI]: 76.9% to 97.3%). Reversible thermal injuries to the skin and pectoralis major muscle occurred in 3 patients.

Hepatocellular Carcinoma

Primary Hepatocellular Carcinoma

Primary hepatocellular carcinoma (HCC) commonly occurs in the context of chronic liver disease and cirrhosis and is often diagnosed in its later stages. In 2006, Brown et al reported that although patients with localized HCC are best managed with complete surgical resection, less than 20% are viable candidates because of the extent or location of the lesions, comorbid conditions, or disseminated disease. The National Comprehensive Cancer Network (NCCN) Guidelines for HCC stated, “All HCC patients should be evaluated for potential curative therapies (resection, transplantation).” Locoregional therapies are recommended when there is no extrahepatic disease and progression is limited, but cure is less likely. The NCCN does not discriminate among the ablative therapies in the treatment of HCC. They propose ablation for hepatic lesions less than or equal to 3 centimeters (cm) in size. The NCCN additionally stated unresectable or inoperable lesions greater than 5 cm should be considered for treatment using arterial embolic approaches or systemic therapy.

The NCCN principles of locoregional therapy are as follows:

For ablation (radiofrequency (RFA), cryoablation (cryosurgical ablation, CSA), percutaneous ethanol or alcohol injection (PEI or PAI), and microwave ablation (MWA):

- All tumors should be amenable to ablation such that the tumor and margin of normal tissue is treated.
- Tumors should be in a location accessible for percutaneous/laparoscopic/open approaches for ablation.
- Tumors less than 3 cm are optimally treated with ablation. Lesions between 3 and 5 cm may be treated using a combination of embolization and ablation as long as the tumor location is favorable. Unresectable or inoperable lesions greater than 5 cm should be considered for treatment using arterial embolic approaches or systemic therapy.
- Caution should be exercised when ablating lesions near major vessels, major bile ducts, diaphragm, and other intra-abdominal organs.

The National Cancer Institute’s (NCI) Physician Data Query (PDQ) regarding adult primary liver cancer treatment listed PEI, CSA, RFA, and chemoembolization as standard treatment alternatives for patients with unresectable primary HCC tumors under 5 cm in diameter. Identified contraindications to embolization (with or without chemotherapy) include portal hypertension, portal vein thrombosis, and clinical jaundice. New medical approaches are being researched in clinical trials including, but not limited to, targeted therapy after chemoembolization or combined with chemotherapy, and combination therapy.
therapy with surgery, chemotherapy, and radiation therapy.

The literature search identified many publications on studies of MWA for hepatocellular carcinoma (HCC), primarily small case series and retrospective reviews conducted in China and Japan. Only 2 studies were indexed in the PubMed database as randomized controlled trials (RCTs). No RCTs comparing the use of MWA for HCC with the criterion standard of surgical resection were identified. The following summarizes systematic reviews\(^6,9\) and select studies reporting on 25 or more patients. All of the studies demonstrated that the technique of MWA provided good tumor ablation (87%-100% ablation of targeted tumors) with low procedural complication rates. Associated morbidity and mortality, as well as overall survival (OS) and disease-free survival rates with MWA are similar to radiofrequency ablation (RFA), which would be an appropriate comparator in patients with tumors not amenable to surgical resection. However, only 1 RCT comparing MWA directly with RFA was identified.\(^10\)

In 2009, Ong et al conducted a systematic review of studies on MWA for primary and secondary liver tumors.\(^8\) Based on the results from 25 clinical studies reporting outcomes on MWA, the authors concluded MWA is an effective and safe technique for liver tumor ablation with low complication rates and survival rates comparable with hepatic resection. However, rates of local recurrence after MWA were noted to be higher than hepatic resection. In most studies, HCC recurrence rates were approximately 10% but were also noted to be as high as 50% which the authors indicated can be addressed with further ablation. Survival rates in the studies on MWA for HCC were as high as 92% at 3 years and 72% at 5 years, which was noted to be comparable with 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. Ong et al concluded MWA is a promising treatment option for the treatment of liver tumors but should be reserved for patients not amenable to hepatic resection. The authors also noted further RCTs are warranted to compare MWA with other ablation procedures. Bertot et al conducted a systematic review in 2011 of ablation techniques for primary and secondary liver tumors.\(^9\) This review included 2 studies using MWA totaling 1185 patients.\(^13,14\) 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, because there was significant heterogeneity). The authors concluded percutaneous ablation techniques, including MWA, are safe and have acceptable complication rates for the treatment of liver tumors.

In 2002, Shibata et al reported on 72 consecutive patients with 94 small HCC nodules randomized by sealed envelopes to receive either percutaneous MWA or RFA performed by a single surgeon.\(^6\) No significant differences were identified between the 2 treatment group characteristics, eg, sex, age, nodule size, Child-Pugh cirrhosis class and number of nodules. In the RFA group, complete therapeutic effect was seen in 46 (96%) of 48 nodules (mean size, 2.3 cm; range, 1.0-3.7) versus 41 (89%) of 46 nodules (mean size, 2.2 cm; range, 0.9-3.4) treated with percutaneous MWA (p=0.26). Treatment outcomes were not significantly different between the percutaneous MWA and RFA groups in the rates of untreated disease during a follow-up range of 6 to 27 months (8/46 nodules vs 4/48 nodules, respectively), and major complication rates (4 vs 1, respectively). Major complications included 1 case of segmental hepatic infarction in the RFA group. In the MWA group, major complications included 1 case of each of the following: liver abscess, cholangitis with intrahepatic bile duct dilatation, subcutaneous abscess with skin burn and subcapsular hematoma. Life-threatening complications were not experienced. The number of treatment sessions required per nodule in the RFA group was significantly lower than in the percutaneous MWA group (1.1 vs 2.4; p<0.001). However, treatment
time per session was significantly shorter in the MWA group (33±11 minutes) than the RFA group (53±16 minutes).

Taniai et al, in 2006, reported on 30 patients with multiple HCC tumors who underwent reduction hepatectomy with postoperative transcatheter arterial embolization. Before surgery, patients were randomly assigned to receive no intraoperative adjuvant therapy (n=15) or intraoperative adjuvant therapy with either MWA (n=10) or RFA (n=5) of satellite lesions. No significant differences in characteristics were identified between the 2 treatment groups of no intraoperative adjuvant therapy versus intraoperative adjuvant therapy, e.g., sex, age, nodule size (maximum tumor size, 42.7±23.5 mm vs 37.8±16 mm, respectively), Child-Pugh cirrhosis class and number of nodules. Cumulative survival rates at 3 and 5 years were not significantly different in the group that did not receive intraoperative adjuvant therapy (39.0% and 0%, respectively) versus the intraoperative adjuvant therapy group (35.7% and 7.7%, respectively). A-fetoprotein, number of tumors, maximum tumor size, and clinical stage, but not intraoperative adjuvant therapy, was identified as independent prognostic survival factors.

In April 2011, Simo et al retrospectively compared laparoscopic MWA (13 patients with 15 tumors) with RFA (22 patients with 27 tumors) performed by a single surgeon for the treatment of HCC. No significant differences were identified between the 2 treatment group characteristics except for sex (54% vs 86% male, respectively). Average tumor size was 2.31 cm in the MWA group versus 2.53 cm in the RFA group. The authors reported average tumor ablation volumes were not significantly different at 28.99 cm for MWA and 23.43 cm for RFA. In the MWA group, at a mean follow-up of 7 months, disease-free survival was 54% with 2 patients having received liver transplants, 31% having disease progression and 15% deceased. The RFA group was followed for a longer period of time at a mean of 19 months. This group experienced 50% survival without evidence of disease, with 4 patients having received liver transplants, 9% having disease progression, 36% deceased, and 5% lost to follow-up. Operative times were shorter in the MWA group (112±40 vs 149±35 minutes). In 2013, Ding et al also reported on a retrospective comparison of 113 patients treated with MWA for 131 HCC tumors and 85 patients treated with RFA for 98 HCC tumors. Rates of complete ablation, local recurrence, disease-free and cumulative survival (at 1, 2, 3, and 4 years), and major complications were not significantly different between groups. In another 2013 study by Ding et al, complications were retrospectively compared between 556 patients treated with MWA for 1090 tumors (491 HCC, 18 cholangiocarcinoma, 47 liver metastases) and 323 patients treated with RFA for 562 liver tumors (279 HCC, 6 cholangiocarcinoma, 38 liver metastases). Rates of death (2/556 MWA, 1/323 RFA patients), major complications and minor complications did not differ significantly between MWA and RFA groups.

In 2011, Zhou et al prospectively evaluated percutaneous MWA for HCC in 215 patients with tumors of 60 mm or less (median size, 29 mm) in a single center, Phase 2 study. The authors reported technical effectiveness in all patients. OS rates at 1, 2, 3, 4, and 5 years were 94%, 82.9%, 66%, 54.1%, and 44.4%, respectively, and median survival time was 40 months (range, 4-106 months). Complications related to the procedure included 3 cases of pleural effusion and 1 case of bile duct injury. In another prospective study by Zhou et al in 2009, percutaneous MWA was performed on 124 patients with 144 HCC lesions and 28 patients with 35 lesions of hepatic metastases. Included in this total of 152 patients were 59 patients with 61 lesions (mean size, 27 mm) located less than 5 mm from the gastrointestinal tract and 93 patients with 126 lesions (mean size 24 mm) located more than 5 mm from the gastrointestinal tract. For lesions less than 5 mm from the gastrointestinal tract, the temperatures of the margins were monitored closely during ablation and to prevent thermal injury, ethanol injections were placed into marginal tumor tissue in 33 lesions that were protruding or in contact with the gastrointestinal tract.
No procedural complications were noted; however, tumor seeding occurred in 3 patients. Complete ablation was achieved in 47 of 53 lesions (88.7%) in the group with tumors near the gastrointestinal tract and in 116 of the other 126 lesions (92.1%), as confirmed by imaging during the follow-up period ranging from 3 to 32 months. Local tumor progression occurred in 16 tumors during 1- to 9-month follow-up. Separate treatment outcomes for hepatocellular tumors and hepatic metastasis were not provided.

Lu et al, in 2005, reported on a retrospective comparison of 102 patients with HCC treated with either percutaneous MWA (49 patients with 98 nodules; mean size, 2.5 cm) or RFA (53 patients with 72 nodules; mean size, 2.6 cm).10 Patient follow-up was 25.1 months in the MWA group and 24.8 months in the RFA group. Complete ablation was not significantly different in the treatment groups and was achieved in 93 of 98 tumors (94.9%) in the MWA group and in 67 of 72 tumors (93.1%) in the RFA group. However, complete ablation rates increased in tumors less than or up to 3 cm in size to 98.6% (73/74) in the MWA group and 98% (50/51) in the RFA group. In tumors greater than 3 cm, complete ablation rates decreased to 83.3% (20/24) in the MWA group and 81% (17/21) in the RFA group. There were no significant differences found in the MWA group versus the RFA group in rates of local tumor recurrence (11.8% vs 20.9%, respectively), major complications (8.2% vs 5.7%, respectively) or disease-free survival at 1, 2, and 3 years (45.9%, 26.9%, and 26.9% vs 37.2%, 20.7%, and 15.5%, respectively).

In 2012, Takami et al reported on 719 patients treated with intraoperative MWA for HCC (mean tumor size, 26.9 mm) at a single institution.17 The OS rates were 97.7% at 1 year, 62.1% at 5 years, and 34.1% at 10 years. OS rates for 390 patients with 3 or fewer tumors measuring 3 cm or less were 97.9% at 1 year, 70.0% at 5 years, and 43.0% at 10 years. When MWA results were compared with 34 patients treated at the same institution with hepatic resection, OS, disease-free survival, and local recurrence rates were not significantly different.

In 2009, Liang et al reported on a retrospective review of complications experienced with percutaneous MWA for the treatment of 1928 malignant liver tumors in 1136 patients at a single institution.11 Each patient received an average of 1.8 treatment sessions for a total of 3697 treatment sessions. Thirty patients (2.6%) experienced major complications, which included 5 cases of liver abscess and empyema, 2 bile duct injuries, 2 colon perforations, 5 tumor seedings, 12 pleural effusions requiring thoracentesis, 1 hemorrhage requiring arterial embolization, and 3 skin burns requiring resection for a total of 30 (2.6%) patient complications. Two deaths occurred within 30 days after MWA in patients with Child class B uncompensated cirrhosis. One patient (age 78) had multi-organ failure and died 14 days after treatment and another patient (age 83) had respiratory and cardiac failure and died 14 days after treatment. Minor complications included fever (83.4%), pain (80.1%), asymptomatic pleural effusion (10.4%), thickening of the gallbladder wall (2.8%), and arterioportal shunt (0.3%), small stricture of the bile duct (0.4%), and skin burn requiring no treatment (1.6%). A significantly higher rate of major complications and more ablation sessions were experienced when a noncooled-shaft antenna was used during the period of 1994 to 2005 (n=583) than with newer technology; cooled-shaft antennas were used beginning in 2005 (n=583). In a report on needle-track seeding from this same institution, Yu et al followed 1462 patients treated with percutaneous MWA for 2530 liver tumors over a 14-year period.18 Twelve seeding nodules with a mean size of 2.3±0.7 cm (range, 1.3-3.9 cm) were found in 11 patients within 6 to 37 months (median 10 months) after receiving MWA.
Hepatic Metastasis From Primary Cancers From Other Sites

The literature searches identified many small studies on MWA for hepatic metastases, 1 RCT, and several systematic reviews.19-21 A 2014 Health Technology Assessment and a 2013 Cochrane review also identified only 1 RCT on ablation for liver metastasis. Shibata et al22 (described next). The reviewers found insufficient evidence to determine any benefits of MWA for liver metastasis over surgical resection. In the Ong systematic review (previously described) local recurrence rates for liver metastases after treatment with MWA averaged approximately 15% but varied between 0% and 50% in the 7 studies reviewed that addressed liver metastases. As noted earlier, Ong et al concluded MWA is a promising treatment option for the treatment of liver tumors but should be reserved for patients not amenable to hepatic resection. Bertot et al conducted a systematic review, also described earlier.19 In 2011, Pathak et al 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. Mean survival rates were 73%, 30%, and 16% and ranged from 40% to 91.4%, 0% to 57%, and 14% to 32% at 1-, 3-, and 5-year follow-up, respectively. Minor and major complication rates were considered acceptable and ranged from 6.7% to 90.5% and 0% to 19%, respectively. Local recurrence rates ranged from 2% to 14%. The authors acknowledged limitations in the available studies but concluded that survival rates for MWA are more favorable than for palliative chemotherapy alone.

Only 1 RCT comparing the use of MWA for hepatic metastases to the criterion standard of surgical resection was identified. In 2000, Shibata et al 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).22 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 10 or more tumors. The treatment groups of MWA versus hepatectomy were not significantly different in age (mean age, 61 years 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 6 patients in the hepatectomy group required blood transfusions. Complications in the microwave group consisted of 1 hepatic abscess and 1 bile duct fistula. In the hepatectomy group, complications were 1 intestinal obstruction, 1 bile duct fistula, and wound infection.

In 2011, Lorentzen et al reported on a retrospective review of percutaneous or open MWA in 39 patients with 125 liver metastases from the primary sites of colorectal cancer (n=31), breast cancer (n=6), carcinoid tumor (n=1), and gastrointestinal stromal tumor (n=1).23 Complete ablation was achieved in 100% of tumors (median size, 1.5 cm) with 1 treatment session in 34 patients, 2 sessions for 4 patients, and 3 sessions for 1 patient. One case of liver abscess, which resolved after percutaneous drainage, was the only major complication reported. Four minor complications included 1 incidence of ascites and 3 complaints of puncture site pain. At median follow-up of 11 months, local tumor progression was seen in 12 of 125 tumors (9.6%) in 10 of the 39 patients (26%).

In a prospective, single institution Phase 2 study in 2010, Martin et al reported on 100 patients treated with 270 open or laparoscopic MWAs for HCC (n=17) and liver metastases from the primary sites of colorectal (n=50), carcinoid (n=11), and other cancers (n=22 and included cholangiocarcinoma, metastatic breast, renal cell...
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carcinoma, bladder, carcinoid, melanoma, and sarcoma). Median tumor size was 3.0 cm. Thirty-eight patients were treated with MWA alone, 53 patients had MWA with concomitant hepatic resection while another 9 patients had MWA concomitant with other organ resection. Only 2 patients had incomplete ablations after the procedure. No bleeding complications were experienced, but 2 cases of hepatic abscess and 2 cases of hepatic insufficiency occurred. At median follow-up of 36 months, 5 patients were found to have incomplete ablations and only 2 patients (2%) had local tumor recurrence, while 37 patients (37%) developed recurrence at other nonablated sites.

In 2013, Liu et al reported on 35 patients treated with MWA for 62 tumors and 54 patients treated with RFA for 70 tumors from liver metastases. Ablation was complete in 88.6% (117/132) of tumors and was not significantly different between tumor types: 86.2% for metastatic colorectal cancer (56/65) and 91% for other metastatic disease (61/67). Nor was there a significant difference between MWA and RFA in the complete ablation rate. Tumors 3.0 cm or less were completely ablated significantly more often than tumors greater than 3.0 cm (93.5 vs 66.7%, p=0.001).

Lung

Several studies have reported experience using MWA for lung tumors. In 2012, Lu et al reported on a retrospective review of 69 patients treated with MWA for inoperable lung cancer or metastatic pulmonary metastases. OS rates for patients with pulmonary metastases at 1 year, 2 years, and 3 years were 47.6%, 23.8%, and 14.3%, respectively. The recurrence-free survival rates for patients with non-small cell lung cancer at 1 year, 2 years, and 3 years were 72.9%, 50.0%, and 27.1%, respectively. OS rates were 66.7% at 1 year, 44.9% at 2 years, and 24.6% at 3 years. No deaths occurred within 30 days of the procedure; however, pneumothorax occurred in 24.6%. In 2012, Belfiore et al reported on a retrospective review of 56 patients treated with MWA for inoperable lung cancer or metastatic pulmonary metastases. Disease-specific survival rates were 69% at 1 year, 54% at 2 years, and 49% at 3 years. Pneumothorax was reported in 18 patients (32.1%). In 2011, Vogl et al reported on a prospective study of 80 patients treated with MWA for inoperable pulmonary metastases. Survival rates were 91.3% at 1 year and 75% at 2 years. No deaths occurred within 60 days of the procedure; however, pneumothorax occurred in 11 of 130 MWA sessions (8.5%), and pulmonary hemorrhage occurred in 8 of 130 sessions (6.2%).

Primary Renal Tumors

In a 2014 systematic review and meta-analysis, Katsanos et al compared thermal ablation (MWA and RFA) with surgical nephrectomy for small renal tumors (mean size 2.5 cm). Included in the analysis were 1 randomized study on MWA (described next) and 5 cohort studies on RFA with a total of 587 patients. In the ablation group, the complication rates and renal function decline were significantly lower than in the nephrectomy group (p=0.04 and p=0.03, respectively). The local recurrence rate was 3.6% in both groups (risk ratio=0.92, 95% CI: 0.4 to 2.14, p=0.79) and disease-free survival up to 5 years was not significantly different between groups (hazard ratio=1.04, 95% CI: 0.48 to 2.24, p=0.92).

Martin et al reported on a meta-analysis of MWA versus cryoablation for small renal tumors in 2013. Included in the analysis were 7 MWA studies (n=164) and 44 cryoablation studies (n=2989). The studies were prospective or retrospective, nonrandomized, noncomparative studies. The mean follow-up duration was shorter for MWA than cryoablation (17.86 months vs 30.22 months, p=0.07). While the mean tumor size was significantly larger in the MWA studies than the cryoablation studies (2.58 cm vs 3.13 cm, respectively, p=0.04), local tumor progression (4.07% vs 2.53%, respectively;
p=0.46), and progression to metastatic disease (0.8% vs 0%, respectively; p=0.12) were not significantly different.

In 2012, Guan et al reported on a prospective randomized study to compare the use of MWA with partial nephrectomy (the criterion standard of nephron-sparing surgical resection) for solitary renal tumors less than 4 cm. Forty-eight patients received MWA and 54 had partial nephrectomy. Patients in the MWA group had significantly fewer postoperative complications than the partial nephrectomy group (6 [23.5%] vs 18 [33.3%]; p=0.019). MWA patients also had significantly less postoperative renal function declines (p<0.009) and estimated perioperative blood loss (p<0.001) than partial nephrectomy patients. At last follow-up, estimated glomerular filtration rate declines in both groups were similar (p=1.000). Disease-specific deaths did not occur, and overall local recurrence-free survival by Kaplan-Meier estimates at 3 years were 91.3% for MWA and 96.0% for partial nephrectomy (p=0.541). Longer follow-up is needed.

Several small case studies on renal tumors have been reported. In 2012, Yu et al reported on a retrospective review of 46 patients treated with MWA for renal cell carcinoma. Complete ablation occurred in 98% of tumors (48 of 49), which had a mean tumor size of 3.0±1.5 cm. At a median follow-up of 20.1 months, all 46 patients were metastasis-free. OS rates were 100% at 1 and 2 years and 97.8% at 3 years.

In 2011, Muto et al reported complete tumor coagulation necrosis in 10 patients treated with laparoscopic MWA for clear cell renal carcinoma with a median tumor size of 2.75 cm. Depending on tumor size, the microwave antennas were used 1 to 3 times for a mean application time of 14.1 minutes. No complications were reported during or after the procedure. Bai et al in 2010, reported complete laparoscopic MWA in 17 of 18 clear cell renal carcinoma tumors with a mean tumor size of 2.8 cm. In this study, evidence of disease progression was not found in any of the patients followed up for a median of 20 months, including the patient with an incomplete ablation who was followed for 31 months. Complications reported were mild (18.2%), and renal function did not significantly deteriorate. However, in a 2011 study of 10 patients with solid-enhancing renal tumors (median size of 3.65 cm), treated with laparoscopic (n=7) or percutaneous (n=3) MWA, Castle et al reported tumor recurrence was seen in 3 of 8 tumors on mean follow-up time of 17.9 months. Because tumor size was larger in this study, mean ablation time was 21 minutes. Additionally, 20% of patients experienced intraoperative complications while 40% experienced postoperative complications including perinephric hematoma, splenic capsular tear, pleuritic chest pain, skin burn, fever, hematuria, genitofemoral neuralgia, and urinoma.

In another study, Guan et al reported on the safety of retroperitoneoscopic MWA for renal hamartoma in 2010. In this case series report, 15 of 16 patients had complete tumor ablation. Disease recurrence was not found in all 16 patients at a median follow-up of 16 months.

**Other Tumors or Conditions**

No RCTs on the use of MWA for other tumors or conditions were identified. Case studies and retrospective reviews on MWA for adrenal carcinoma, metastatic bone tumors, intrahepatic primary cholangiocarcinoma, benign thyroid tumors, and other nononcologic conditions (ie, bleeding peptic ulcers, esophageal varices, secondary hypersplenism) were identified.

A systematic review of ablation therapies, including MWA, for locally advanced pancreatic cancer was published in 2014. The reviewers found limited available evidence on MWA for pancreatic cancer. Therefore, without randomized studies, no conclusions could be drawn on thermal ablation methods for pancreatic cancer.
The Society of Interventional Radiology published a position statement in 2009 on percutaneous RFA for the treatment of liver tumors. It is the position of the society that “percutaneous RF ablation of hepatic tumors is a safe and effective treatment for selected patients with HCC and colorectal carcinoma metastases” and the current literature was insufficient to support any recommendations supporting or refuting the use of RFA in other diseases.

The published evidence for demonstrating improved health outcomes with ablative therapies of other hepatic metastatic tumors is lacking. Comparative trials are needed for these malignancies that may have associated systemic disease. While locoregional ablative therapy is included in the NCCN Guidelines for CRC and neuroendocrine tumors, ablative therapy is not recommended for all other metastatic tumors to the liver.

**Locoregional Ablative Therapies**

There is research available for each of the ablative therapies. However, many of the studies combine multiple ablative procedures or utilize ablative techniques as an adjunct to surgical resection or chemotherapy. Studies also include patients with a broad range of tumor size and etiology. As a result, it is sometimes difficult to draw specific conclusions regarding the efficacy of an ablative technique. Careful selection of candidates for each treatment option and expert application of these treatments are required to achieve best outcomes.

**Laser Ablation**

Laser ablation (LA), also known as laser coagulation therapy, laser interstitial tumor therapy (LITT), and laser interstitial photocoagulation, refers to thermal tissue destruction by conversion of absorbed light (usually infrared) into heat. The infrared energy penetrates tissue directly for a distance of 12 to 15 millimeters (mm) and temperatures above 60 degrees centigrade cause rapid coagulative necrosis and instant cell death. The most widely used device for LA techniques is the Nd: YAG (neodymium:yttrium-aluminium-garnet) laser (Flexilase; Living Technology, Glasgow, Scotland) with a wavelength of 1064 nanometers (nm). Additionally, more compact diode lasers with shorter wavelengths (800 nm to 980 nm) have been utilized. A range of imaging modalities have been used to guide percutaneous LA techniques including ultrasound-guided needle placement, and magnetic resonance (MR) with contrast. However, the use of this technique is limited by the amount of local experience and resource/machine availability.

Laser ablation has been primarily studied in the treatment of brain, spine, and prostate tumors, but has been cleared by the U.S. Food and Drug Administration (FDA) for any soft tissue tumor (FDA, 2010). Percutaneous LA has received increasing attention for the treatment of a variety of primary and secondary malignant tumors, including hepatic tumors. However, of all the ablation techniques for hepatic tumors, LA has the least amount of published literature. Laser ablation is mainly applied in Europe and the majority of data reported on laser ablative techniques came from Italy, Germany, and the United Kingdom (Gough-Palmer & Gedroyc, 2008). The majority of long-term survival data was reported on hepatic metastases and varied in the literature; virtually no data has been published for HCC LA.

Five-year survival rates of 26% and median survival rates of 27 to 39 months have been reported. Pacella and colleagues reported on a series of 148 patients (144 biopsy proven HCC) treated with 239 laser ablative sessions. The authors quoted long-term survival rates of 89% at one year, 52% at three years, and 27% at five years and an overall complete lesion ablation rate of 82%. Pulsetal reported on 87 consecutive patients with 180 liver metastases from CRC who underwent laser ablation with MR thermometry in 170
Median survival time was 54 months and survival rates were 95.7% at one year, 86.2% at two years, 72.4% at three years, 50.1% at four years, and 33.4% at five years. Although these results appeared encouraging, direct comparison with other ablative therapies (e.g., RFA) in prospective clinical trials are needed to show definitively which modality is superior.

Selection criteria in these studies varied on the technique used and the facilities available but were in general, similar to other locally ablative techniques such as RFA and MWA. Many of the studies were performed on multiple tumor types, making it difficult to evaluate the efficacy of laser ablation. The range of imaging modalities used at follow-up combined with a variety of definitions of treatment success, made comparison of the data difficult.

The NCCN guidelines for HCC do not include or discuss LA as a technique of locoregional ablation. While laser ablation appears safe, evaluation of its effectiveness is limited by lack of good comparative trials and hampered by constantly changing technologies. The clinical efficacy of laser ablation has not been established at this time. Further data from randomized studies evaluating the impact of LA on survival, quality of life, and cost-effectiveness for both primary and secondary liver tumors is required.

Unresectable Hepatocellular Carcinoma Tumors in the Transplant Setting

As noted earlier, liver transplantation is the only curative alternative for unresectable HCC. Locoregional therapies (e.g., ablation, TACE) have been explored in various settings including as a technique to prevent tumor progression in patients on the liver transplant waiting list, downstaging tumors such that the patient will be considered a better candidate for liver transplantation, and decreasing the incidence of post-transplant recurrence in patients with larger (T3) tumors. All of these indications are in part related to the United Network for Organ Sharing (UNOS) liver allocation policy, which prioritizes patients for receiving donor livers. The UNOS policy recognized pretransplant locoregional therapies including “chemoembolization of lesion, radiofrequency, cryo, or chemical ablation of the lesion,” as a component of patient management during the waiting period.

In 2002, UNOS introduced a new liver allocation system, model for endstage liver disease (referred to as MELD) for adult patients awaiting a liver transplant. The MELD score is a continuous disease severity scale incorporating bilirubin, prothrombin time (i.e., international normalized ratio [INR]), and creatinine into an equation, producing a number that ranges from 6 (less ill) to 40 (gravely ill). Aside from those in fulminant liver failure, donor livers are prioritized to those with the highest MELD number. This scale accurately predicts the risk of dying from liver disease except for those with HCC, who often have low MELD scores since bilirubin, INR, and creatinine levels are near normal. Therefore, patients with HCC are assigned additional allocation points according to the size and number (T stage) of tumor nodules as follows:

T1: One nodule, 1.9 cm or smaller
T2: One nodule between 2.0 to 5.0 cm, or two or three nodules each smaller than 3.0 cm
T3: One nodule larger than 5.0 cm, or two or three nodules with at least one larger than 3.0 cm

In considering how to allocate the scarce donor organs, UNOS sought to balance risk of death on the waiting list against risk of recurrence after transplant. Patients with T1 lesions were considered at low risk of death on the waiting list, while those with T3 lesions are at
high risk of post-transplant recurrence, and are generally not considered transplant candidates. Patients with T2 tumors have an increased risk of dying while on the waiting list compared to those with T1 lesions and an acceptable risk of post-transplant tumor recurrence. Therefore, UNOS criteria prioritize T2 HCC by allocating additional point's equivalent to a MELD score predicting a 15% probability of death within three months. This definition of T2 lesions is often referred to as the “Milan criteria,” in reference to a key study reported by Mazzaferro et al that examined the recurrence rate of HCC according to the size of the initial tumor.57 Note that liver transplantation for those with T3 HCC is not prohibited, but these patients do not receive any priority on the waiting list. All patients with HCC awaiting transplantation are reassessed at three-month intervals. Those whose tumors have progressed and are no longer T2 tumors will lose the additional allocation points.

Therefore, the UNOS allocation system provides strong incentives to use locoregional therapies to downsize tumors to T2 status and to prevent progression while on the waiting list. Promfet et al report of a national conference on liver allocation in patients with HCC in the U.S. addressed the need to better characterize the long-term outcomes of liver transplantation for patients with HCC and to assess whether it is justified to continue the policy of assigning increased priority for candidates with early stage HCC on the transplant waiting list in the U.S.58 At the completion of the meeting, there was a general consensus for the development of a calculated continuous HCC priority score for ranking HCC candidates on the list that would incorporate the calculated MELD score, alpha-fetoprotein, tumor size, and rate of tumor growth and that only candidates with at least stage T2 tumors would receive additional HCC priority points.

Locoregional Therapies as a Bridge to Transplant

Several studies have reported dropout rates of wait-listed patients treated with locoregional therapy. However, lacking controlled data, it is difficult to assess contributions of locoregional therapy to time on the waiting list. In addition, in 2002, as discussed above, UNOS revised its liver allocation policy, such that wait times for patients with HCC meeting the “Milan criteria” have now declined.56 The majority of the literature has focused either on TACE or a variety of locoregional therapies. Given these limitations the following case series have been reported:

Graziadei et al reported on 48 patients with HCC awaiting transplantation; all underwent TACE every six to eight weeks until a complete response or a donor organ became available.59 No patients were removed from the list due to tumor progression and mean waiting time was 178 (+/- 105) days. Maddala et al studied the dropout rates of 54 patients receiving TACE while awaiting transplantation.60 During a median waiting time of 211 days (range: 28 to 1,099 days), the dropout rate was 15%. Obed et al reported on 20 patients with non-progression of lesions after TACE who had liver transplantation; median survival in this group was 92.3 months.61

Fisher et al reported on 33 patients who received multimodality ablation therapy, consisting primarily of RFA or TACE.62 Five patients (12%) were removed from the waiting list after waits of five to 14 months. In this protocol, patients with tumors larger than 5 cm were not considered transplant candidates until the tumor was completely ablated using TACE, RFA, or another technique. Yamashiki et al reported on 288 patients given various ablative therapies; the dropout rate due to tumor progression at one and three years was 6.25 and 23%, respectively.63 Tumors larger than 3 cm affected the dropout rate due to tumor progression. Mazzaferro et al reported on 50 patients with HCC who underwent RFA while awaiting transplantation; no patient had to be removed from the waiting list due to tumor progression over a mean wait time of 9.5 months.64 The median tumor size was 3
cm, and 80% of patients met the Milan criteria. Similarly, Lu et al reported on 52 patients who underwent RFA as a bridge to transplantation, 42 of whom met the Milan criteria.\textsuperscript{65} After a mean of 12 months, 5.8% had dropped off the waiting list due to tumor progression.

In a 2008 paper, Belghiti et al reviewed the literature reporting efficacy of local management approaches including resection, TACE, RFA, and no treatment.\textsuperscript{66} They concluded RFA can induce complete necrosis in the majority of small tumors (<2.5 cm) and there was no data demonstrating that the treatment reduced the rate of drop out before transplantation or improved survival after transplant. None of the studies included data from U.S. centers for patients listed after adoption of the Milan criteria. Porrett et al retrospectively compared 31 patients treated with RFA with 33 untreated controls.\textsuperscript{67} Only 20% of treated tumors demonstrated complete ablation (necrosis) as defined by histologic examination of the entire lesion. Only 55% of lesions with histologic viable tumor were detected by MRI after pretransplant therapy. After 36 months of follow-up, there was no difference between the treated and untreated groups in overall survival (84 versus 91%), disease-free survival (74\% versus 85\%), cancer recurrence (23\% versus 12\%), or mortality from cancer recurrence (57\% versus 25\%- all respectively) (p > 0.1). The authors concluded viable tumor frequently persisted after pretransplant locoregional therapy and neoadjuvant treatment did not appear to improve post-transplant outcomes in the current MELD era.

The UNOS policy on allocation of livers indicated candidates whose tumors have been ablated after meeting the criteria for additional MELD/PELD (PELD-calculator for persons under age 12 years) points will continue to receive additional points (equivalent to a 10\% increase in mortality) every three months without review, even if the estimated size of residual viable tumor falls below stage T2 criteria.\textsuperscript{68} The policy also noted candidates may be removed from the listing if they are determined to be unsuitable for transplantation based on progression of HCC.

Locoregional Therapies to Downstage HCC Prior to Transplant

Yao et al analyzed longer-term outcome data on HCC downstaging in a cohort of 61 patients with tumor stage exceeding T2 criteria enrolled between June 2002 and January 2007.\textsuperscript{69} Eligibility criteria for downstaging included: 1) one lesion larger than 5 cm and up to 8 cm; 2) two to three lesions with at least one lesion larger than 3 cm and not exceeding 5 cm, with total tumor diameter up to 8 cm; or 3) four to five lesions with none larger than 3 cm, with total tumor diameter up to 8 cm. Transcatheter arterial chemoablation and laparoscopic RFA (LRFA) either alone or in combination were the main methods used: 11 patients received LRFA alone, 14 received TACE and LRFA, and nine received TACE and percutaneous RFA. A minimum observation period of three months after downstaging was required before liver transplant.

Tumor downstaging was successful in 43 patients (70.5\%). Thirty-five patients (57.4\%) received liver transplant, including two with live-donor liver transplantation. Treatment failure was observed in 18 patients (29.5\%), primarily due to tumor progression. In the explant of 35 patients who underwent transplant, 13 had complete tumor necrosis, 17 met T2 criteria, and five exceeded T2 criteria. The Kaplan-Meier intention-to-treat survival analysis at one and four years after downstaging was 87.5\% and 69.3\%, respectively. The one-year and four-year post-transplantation survival rates were 96.2\% and 92.1\%, respectively. No patient had HCC recurrence after a median post-transplantation follow-up of 25 months. The only factor predicting treatment failure was pretreatment alpha-fetoprotein greater than 1,000 ng/mL. From this small series, the authors concluded successful downstaging can be achieved with excellent post-transplant outcomes.
Lewandowski et al compared radioembolization with chemoembolization (TACE) in the
efficacy of downstaging 86 patients with HCC from stage T3 to T2.\textsuperscript{70} Patients were treated
with either 90-yttrium microspheres (n = 43) or TACE (n = 43). Median tumor size was similar
between the two treatment groups (5.7 and 5.6 cm, for TACE versus radioembolization,
respectively). Partial response rates were 61\% versus 37\% for radioembolization versus
TACE, respectively with downstaging from T3 to T2 in 58\% of patients treated with
radioembolization versus 31\% with TACE (p < 0.05).

As part of a national conference involving transplant physicians, workgroups were formed
to discuss the policy of assigning increased priority for candidates with stage T2 HCC on
the transplant list in the U.S. The workgroup assigned to the role of downstaging in
transplant candidates with HCC noted inconsistent outcomes reported in the literature
and proposed a definition of downstaging that would include TACE and various ablative
techniques but not resection. Promfet et al noted that only two regions have adopted a
downstaging protocol.\textsuperscript{58}

The results and efficacy of downstaging with TACE to achieve a reduction in tumor
burden to a T2 lesion remain controversial. There are retrospective data showing the
ability to downstage patients with TACE, however, there is no randomized evidence that
tumor downstaging prior to liver transplant confers a survival advantage

\textbf{Locoregional Therapies to Reduce Risk of Recurrence of T3 Tumors}

Published literature by Pomfret et al reflects an ongoing discussion as to whether the UNOS
allocation criteria should expand to include patients with larger tumors.\textsuperscript{58} An additional
indication for locoregional therapies focused on their use in patients with T3 tumors,
specifically to reduce the incidence of recurrence post-transplant. If the incidence of
recurrence can be reduced, then Yao et al, Yao et al, Fernandez et al, Merli et al, and
Sauer et al reported that advocates have argued the UNOS allocation criteria should not
discriminate against patients with larger tumors.\textsuperscript{71,72,73,74,75} Some patients with T3 lesions
apparently are cured with liver transplant, although most experience recurrent tumor. For
example, in the seminal 1996 study by Mazzaferro et al, the four-year recurrence-free
survival was 92\% in those who met the Milan criteria (T2 lesion) compared to 59\% in those
who did not; Sauer et al reported additional studies confirmed this difference in
recurrence-free survival rate.\textsuperscript{71,72} However, other institutions have reported similar
outcomes with expanded criteria. For example, Yao and colleagues at University of
California at San Francisco (UCSF) reported similar recurrence-free survival after transplant
in patients with T2 and a subset of those with T3 tumors. This T3 subset was defined as a
single lesion <6.5 cm or < three lesions with none greater than 3 cm and with a sum of
tumor diameters <8 cm. These expanded criteria are known as the UCSF criteria reported
by Yao et al.\textsuperscript{72}

The question is whether locoregional therapies (including both RFA and TACE) may
decrease the recurrence rate in patients meeting the UCSF criteria. Yao and colleagues
published a detailed analysis of 121 patients with HCC who underwent transplantation.\textsuperscript{76}
Seventy-eight patients (64\%) had T2 lesions, while an additional 27 patients (22.3\%) met
the expanded UCSF criteria, termed T3A lesions. The rest had T1, T3B, or T4 lesions.
Individual patients received a variety of preoperative locoregional therapies, including
TACE or ablative therapies, such as PEI, RFA, or combined therapies. A total of 38.7\% of
patients did not receive preoperative locoregional therapy. The one- and five-year
recurrence-free survival was similar in those with T2 and T3A lesions, while the
 corresponding recurrence-free rates were significantly lower for those with T3B and T4
lesions.

The authors also compared recurrence-free survival of those who did and did not receive
locoregional therapy. For those with T2 lesions, the recurrence rates were similar whether or not the patient received locoregional therapy. However, for T3 lesions (including both T3A and T3B), the five-year recurrence-free survival was 85.9% for those who received locoregional therapy compared to 51.4% in those who did not. When the data for T2 and T3 lesions were grouped together, the five-year recurrence-free survival was 93.8% for those who received locoregional therapy compared to 80.6% in those who did not. The authors concluded preoperative locoregional therapy may confer a survival benefit in those with T2 or T3 lesions. The authors noted several limitations to the study, including the retrospective nature of the data and the marginal statistical significance of the improved survival given the small numbers of patients in each subgroup. For example, only 19 patients were in the T3A (i.e., UCSF expanded criteria) subgroup. In addition, no protocol specified which type of locoregional therapy to offer different patients. These therapies are only offered to those patients with adequate liver reserve; such patients may have an improved outcome regardless of the preoperative management.

Ongoing and Unpublished Clinical Trials

A September 16, 2014, a search of online site ClinicalTrials.gov identified 1 randomized trial on MWA. In this Phase III, prospective RCT, MWA will be compared with RFA in the treatment of unresectable HCC no more than 6 cm in diameter (NCT01340105). Patients may only have up to 3 nodules that are amenable to ablation and do not have any major vascular or bile duct invasion. Patients with resectable tumors may be included in the study if local ablation is preferred. The trial began in April 2011 in Hong Kong, China and expects to recruit 92 patients. This study is expected to be completed in April 2016.

Summary of Evidence

Studies show MWA results in a wide range of complete tissue ablation (50%-100%) depending on tumor size with complete ablation common and nearing 100% with smaller tumors (eg, ≤3 cm). Recurrence of tumors at ablated sites is very low. However, recurrence of tumors at nonablative sites is common and may be due to the nature of the disease state (eg, in HCC). Intraoperative and postoperative minor and major complications are low, especially in cases where tumors are smaller and more accessible. While some earlier studies found MWA required more treatment sessions to achieve adequate ablation, more recent studies using newer MWA technology that deliver larger ablation zones with cooled-shaft antennas have demonstrated shorter ablation times and fewer complications.

In conclusion, although comparisons among the various locoregional therapies are difficult due to factors such as interstudy patient and treatment heterogeneity, differences in patient management protocols and multimodality treatment protocols, the body of data illustrates the likely overall benefit of certain locoregional therapies for specific patient populations.

Supplemental Information

Practice Guidelines and Position Statements

The National Comprehensive Cancer Network guidelines on hepatobiliary cancers lists MWA (along with RFA, cryoablation, and percutaneous alcohol injection) as a treatment option for HCC tumors in patients who are not candidates for potential curative treatments (eg, resection and transplantation) and do not have large-volume extrahepatic disease. Ablation should only be considered when tumors are accessible by percutaneous, laparoscopic, or open approaches. The guidelines indicate HCC tumors of 3 centimeters or less may be curatively treated with ablation alone. HCC tumors between 3 and 5 centimeters may also be treated with ablation to prolong
survival when used in combination with arterial embolization. Additionally, the tumor location must be accessible to permit ablation of the tumor and tumor margins without ablating major vessels, bile ducts, the diaphragm or other abdominal organs. However, there are only 2 reviews cited in the guideline on ablative techniques to support these recommendations, but these reviews are not specific to MWA [category 2A].

In the NCCN guidelines on neuroendocrine tumors, MWA is listed as 1 treatment option (along with RFA or cryoablation) for liver metastases as hepatic regional therapy in carcinoid tumors and pancreatic endocrine (islet cell) tumors when there is unresectable disease and/or distant metastases. These guidelines note, currently, there are limited prospective data and no RCTs on ablative therapies (including MWA), and data on these ablative techniques are emerging. Additionally, the 2 articles cited in the guideline on ablative techniques are not specific to MWA [category 2B].

The National Institute for Health and Clinical Excellence (NICE) published updated guidance on MWA for the Treatment of Metastases in the Liver in August 2011. This guidance indicates “Current evidence on microwave ablation for the treatment of liver metastases raises no major safety concerns. The evidence on efficacy is inadequate in quantity and quality. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.” NICE also published guidance on MWA for HCC in 2007. This guidance indicates “Current evidence on the safety and efficacy of microwave ablation of hepatocellular carcinoma appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance.” The guidance also states there are no major concerns regarding the efficacy of MWA but notes there is limited long-term survival data available.

The American College of Chest Physicians 2013 evidence-based guidelines on the treatment of non-small cell lung cancer (NSCLC) note that the role of ablative therapies in the treatment of high-risk patients with stage I NSCLC is evolving. RFA, the most studied of the ablative modalities, has been used effectively in medically inoperable patients with small (<3 cm) peripheral NSCLC that are clinical stage I.

U.S. Preventive Services Task Force Recommendations

Microwave tumor ablation is not a preventive service.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References

5. National Cancer Institute. Adult Primary Liver Cancer Treatment (PDQ ®). Health


**Documentation Required for Clinical Review**

Please provide the following documentation:

- History and physical, and/or consultation reports and progress notes including:
  - Clinical indications/justification of procedure
  - Clinical indications/justification of procedure
  - Eastern Cooperative Oncology Group functional status (if applicable)
  - Previous treatment(s), duration, and response(s)
  - Treatment plan
  - Tumor type and description (i.e., resectable or unresectable, primary or metastatic, tumor burden [e.g., liver dominant])

- Pertinent radiological imaging results (i.e., abdominal CT and/or MRI and/or PET)

- Pathology report including tumor node metastasis (TNM) classification

- Current serum chemistry, liver function tests, and tumor marker results
Post Service

- Procedure report(s)

## Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services are considered investigational and therefore not covered for any indication.

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<td></td>
<td>50.25</td>
<td>Laparoscopic ablation of liver lesion or tissue</td>
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<td>50.29</td>
<td>Other destruction of lesion of liver</td>
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<td>Open ablation of renal lesion or tissue</td>
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<tr>
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<td>55.33</td>
<td>Percutaneous ablation of renal lesion or tissue</td>
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<tr>
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<td>55.34</td>
<td>Laparoscopic ablation of renal lesion or tissue</td>
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<tr>
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<td>55.39</td>
<td>Other local destruction or excision of renal lesion or tissue</td>
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<tr>
<td>ICD-10 Procedure</td>
<td>For dates of service on or after 10/01/2015</td>
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<td>0F500ZZ</td>
<td>Destruction of Liver, Open Approach</td>
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<td>0F503ZZ</td>
<td>Destruction of Liver, Percutaneous Approach</td>
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<td>Destruction of Liver, Percutaneous Endoscopic Approach</td>
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<td>Destruction of Right Lobe Liver, Open Approach</td>
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<td>Destruction of Right Lobe Liver, Percutaneous</td>
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Medical Policy

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<th>ICD-10 Diagnosis</th>
<th>All Diagnoses</th>
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<table>
<thead>
<tr>
<th>ICD-9 Diagnosis</th>
<th>All Diagnoses</th>
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### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is

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**Effective Date** | **Action** | **Reason**
--- | --- | ---
2/27/2015 | BC BSA Medical Policy adoption | Medical Policy Committee
not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements**

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine medical necessity.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.