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Subject: Radiofrequency and Microwave Ablation of Liver Tumors

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DESCRIPTION:

Hepatic tumors can arise as primary liver cancer (hepatocellular cancer) or by metastasis to the liver from other tissues. Local therapy for hepatic metastasis may be indicated when there is no extrahepatic disease, which rarely occurs for those with primary cancers, other than colorectal carcinoma or certain neuroendocrine malignancies.

Treatment options for hepatocellular carcinoma (HCC) range from potentially curative treatments, such as resection or liver transplantation, to nonsurgical options, which include ablative therapies .

Radiofrequency ablation (RFA) is a procedure in which a probe is inserted into the center of a tumor and heated locally by a high-frequency, alternating current that flows from electrodes. The local heat treats the tissue adjacent to the probe, resulting in a 3 to 5 cm sphere of dead tissue. The cells killed by RFA are not removed but are gradually replaced by fibrosis and scar tissue. If there is a local recurrence, it occurs at the edge of the treated tissue and, in some cases, is retreated. Radiofrequency ablation may be performed percutaneously, laparoscopically, or as an open procedure.

Microwave ablation (MWA) uses microwave energy to induce an ultra-high-speed, alternating electric field which causes water molecule rotation and creates heat. This results in thermal coagulation and localized tissue necrosis. The cells killed by MWA are typically not removed but are gradually replaced by fibrosis and scar tissue. If there is a local recurrence, it occurs at the margins. Treatment may be repeated as needed. Microwave ablation may be used for the following purposes: (1) to control local tumor growth and prevent recurrence; (2) to palliate symptoms; and (3) to prolong survival.

Summary and Analysis of Evidence: Song et al (2024) published results from a single-center, unblinded RCT in China comparing resection to radiofrequency ablation (RFA) for treatment of hepatocellular carcinoma (HCC). Patients with HCC were eligible if they had a single nodule no larger than 5 cm, or up

to 3 nodules of 3 cm or smaller. Patients were randomized to receive either liver resection or RFA (N=150). The primary outcome of overall survival (OS) did not differ between groups. Similarly, the secondary outcome of recurrence-free survival did not differ between groups. The 1-, 3-, and 5- year OS rates with laparoscopic resection were 94.7%, 80%, and 74.7%, respectively, and with RFA were 93.3%, 78.7%, and 67.9%, respectively. The incidence of postoperative complications was higher in the resection group compared to the RFA group (29.3% vs. 10.7%). Results are limited by the small sample size and single-center design. Zhang et al (2022) compared the efficacy of liver resection, RFA alone, and RFA plus transarterial chemoembolization (TACE) in patients with very early or early stage HCC. Randomized trials (n=10) and propensity score-matched cohort analyses (n=15) were included. In a network meta-analysis, 1-year OS was similar between resection and RFA alone, but 3-year and 5-year OS favored resection. Recurrence-free survival at 1, 3, and 5 years was also significantly higher with resection compared to RFA alone. There were no significant differences in survival outcomes at any time point between resection and RFA plus TACE. Jia et al (2021) performed a meta-analysis to compare clinical efficacy between RFA and surgical resection in patients with HCC meeting Milan criteria. The analysis included RCTs, accounting for 8 trials (N=1177). 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 difference between the 2 therapies for both tumors ≤4 cm and >4 cm. Limitations of the analysis include the inclusion of clinical trials with small sample sizes and a lack of double-blinding. Shin et al (2021) compared the efficacy of surgical resection with local ablative therapies for HCC meeting Milan criteria. The analysis included 7 RCTs and 18 non-randomized trials (N=5629) 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 3- and 5-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, followed by RFA plus TACE; no difference was found between microwave ablation and RFA. However, the latter comparisons were limited by the number of trials evaluating RFA plus TACE (5 studies) and microwave ablation (2 studies). Cheng et al (2023) performed a systematic review and meta-analysis of 26 studies with locally ablative therapies in patients with inoperable HCC (RFA, microwave ablation, stereotactic ablative radiotherapy, and particle radiotherapy). For the primary outcome of local control, microwave ablation and particle radiotherapy showed improved outcomes compared to RFA. Regional progression was also significantly better with microwave ablation and particle radiotherapy compared to RFA. Distant progression was better with stereotactic ablative radiotherapy and particle radiotherapy compared to RFA. The highest overall survival at 2, 3, and 4 years was with RFA, which was statistically similar to microwave ablation but superior to the other 2 therapies. Yu et al (2021) performed a meta-analysis of RCTs comparing RFA with microwave ablation for the treatment of localized, very early- or early-stage HCC. 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 1 year or 3 years. Similarly, there was no difference observed in recurrence-free survival between microwave ablation and RFA at 1 year and 3 years. Among the procedure-related complications evaluated, there were no statistically significant differences between the 2 groups. Han et al (2020) also evaluated RFA compared with microwave ablation for early-stage HCC in a meta-analysis, but included both RCT and observational trial

data. There were 5 RCTs, 1 prospective cohort, and 20 retrospective cohorts included in the analysis, providing data for 2393 patients treated with RFA and 2003 treated with microwave ablation. The median 1-year, 3-year, and 5-year OS rates were 93.3%, 71.3%, and 57.4%, respectively, in the microwave ablation group compared with 89.5%, 68.1%, and 55.5%, respectively, in the RFA group. Pooled HR for OS did not show any difference between microwave ablation versus RFA. There was also no difference observed between groups for DFS. Pomfret et al (2010) summarized findings and recommendations from a national conference on outcomes of liver transplantation for patients with HCC. The workgroup on locoregional therapy found compelling evidence that pretransplant locoregional therapy decreases waitlist dropout, especially for patients who wait more than 3 to 6 months for a transplant. The group noted that "there is a paucity of data comparing RFA with transarterial therapies for the treatment of HCC prior to liver transplant and most single-center trials have a mixture of [locoregional therapies] included in the study population" and that, while early studies have suggested a high rate of tumor seeding with percutaneous RFA, it is rare in larger series from experienced centers. The workgroup considering evidence to support the expansion of MELD criteria for patients with HCC reported wide regional variation in the risk of death for patients without HCC. The "MELD score of the non-HCC patients was quite low in some regions. Posttransplant survival in HCC patients ranged from 25% in regions with few non-HCC patients with high MELD scores to greater than 70% in regions in which there was a greater need for liver transplant (higher MELD scores) in the non-HCC population." The workgroup observed that there is extreme variability in the time to transplantation of patients with HCC in the United States, suggesting that management of patients on the waitlist and outcomes may vary. Additionally, "[c]oncern has been raised that short times to liver transplant may lead to an increase in posttransplant recurrence because the tumor biology [aggressiveness] has not had enough time to be expressed. The lack of national data on recurrence rates limits one's ability to study this national experiment of nature based on the divergent waiting times for transplantation for HCC." There was a 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, α-fetoprotein, tumor size, and rate of tumor growth. Only candidates with at least stage T2 tumors would receive additional HCC priority points. The authors also discussed pretransplant locoregional therapy to allow patients to maintain transplant candidacy and to downstage tumors to meet MELD criteria. Lee et al (2017) reported on a 10-year intention-to-treat analysis of RFA to prevent progression and reduce the chance of posttransplant HCC. Patients were selected for analysis if they had cirrhosis with treatment-naive HCC, were on the transplant waiting list, and had RFA as a stand-alone treatment. Only tumors that could safely be treated with a 5 mm margin received RFA. Of 1016 patients who had HCC and were on the transplant waiting list, 121 were treated with RFA and were included in this analysis. Patients returned for follow-up imaging every 3 to 6 months. The mean time on the waiting list was 10.2 months (range, 0.3 to 38 months). At the end of follow-up, 89 (73.6%) patients had undergone a liver transplant, 16 (13.2%) were delisted, 14 (11.6%) died, and 2 (1.7%) remained on the waitlist. The number of patients delisted due to the tumor was 9 (7.4%). Intention-to-treat analysis of all patients estimated 8-year OS at 60.0% and disease-specific survival at 89.5%. A meta-analysis by Meijerink et al (2018) compares RFA and microwave ablation to systemic chemotherapy and to partial hepatectomy (PH) for the treatment of colorectal liver metastases. Forty-eight articles were identified, most of which were observational studies and case series, although 2 RCTs and 8 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. The meta-analysis for 30-day

mortality comparing RFA alone to PH alone showed no difference between the 2 interventions. Disease-free survival was higher for PH alone over RFA alone, as well as local progression-free survival. However, complication rates were lower for RFA alone than for PH alone. 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. Fairweather et al (2017) compared OS in patients with neuroendocrine liver metastases (N=649) from a large prospective database. 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%). Schullian et al (2021) reported on local control and long-term outcomes in 42 female patients treated with stereotactic RFA for breast cancer liver metastases. Race and ethnicity of patients included were not described. The procedures were performed at a single center covering 110 breast cancer liver metastases (median tumor size, 3 cm) in 48 ablation sessions. Additionally, 18 (42.9%) patients had extrahepatic metastasis. The technical success rate was 100%, and 107 of the 110 liver metastases were successfully ablated on the first RFA. Four grade 1 (arterial bleeding from subcapsular liver vessels) and 1 grade 2 (major pleural effusion) periprocedural complications occurred. Local recurrence developed in 7.3% of the tumors after a median imaging follow-up of 10.9 months. The 1-year, 3-year, and 5-year OS rates from the date of the first RFA were 84.1%, 49.3%, and 20.8%, respectively, with a median OS of 32.3 months. The 1-year, 3-year, and 5-year DFS rates from the date of the first RFA were 45.3%, 22.3%, and 15.9%, respectively, with a median OS of 10.5 months. The NCCN (V3.2024) guidelines on HCC note that "locoregional therapy should be considered in patients who are not candidates for surgical curative treatments, or as part of a strategy to bridge patients for other curative therapies." The guideline further states that "ablation alone may be curative in treating tumors ≤3 cm. In well-selected patients with small, properly located tumors, ablation should be considered a definitive treatment in the context of a multidisciplinary review. Lesions 3 to 5 cm may be treated to prolong survival using arterially directed therapies, or with the combination of an arterially directed therapy and ablation as long as the tumor is accessible for ablation". The NCCN (V5.2024) guidelines on colon cancer metastatic to the liver state that “(t)hermal ablation can be considered alone, or in conjunction with surgery, in appropriately selected patients with small metastases that can be treated with margins. All original sites of disease need to be amenable to thermal ablation or resection. Image guided thermal ablation may be considered in selected surgical candidates or medically non-surgical candidates with small tumors that can be completely ablated with margins.” The guideline also states “Image guided thermal ablation can be considered in selected patients with recurrence after hepatectomy or ablation as long as all visible disease can be ablated with margins.” The NCCN (V2.2024) guidelines for neuroendocrine and adrenal tumors state that "(p)ercutaneous thermal ablation, often using microwave energy (radiofrequency and cryoablation are also acceptable), can be considered for oligometastatic liver disease, generally up to four 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.” Additionally, " (c)ytoreductive surgery or ablative therapies such as radiofrequency ablation (RFA) or cryoablation may be considered if near-complete treatment of tumor burden can be achieved (category 2B). Ablative therapy in this setting is non-curative. Data on the use of these interventions are emerging.’

Dou et al (2022) conducted a systematic review and meta-analysis that compared the safety and efficacy of microwave ablation (MWA) compared to RFA in patients with HCC. 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 2 groups. In the cohort studies, MWA had a lower local tumor progression rate than RFA. The reviewers concluded that there were various differences in the included studies (eg, equipment used, operator experience) and that more high-quality RCTs are needed to draw a definitive conclusion on the pros versus cons of MWA and RFA in this patient population. Cui et al (2020) conducted a systematic review and meta-analysis of MWA compared to various treatment modalities. The analysis included 4 RCTs, with 3 comparing MWA to RFA, and 1 comparing MWA to TACE. Meta-analyses of studies comparing MWA to RFA found no difference in 3-year OS, 5-year OS, local tumor progression at 1 year, progression-free survival at 3 years, or major complications. A meta-analysis of 2 nonrandomized studies comparing MWA to resection found no difference in 3-year OS between treatments; however, this comparison is limited by the small number of studies and 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. Glassberg et al (2019) conducted a systematic review of MWA compared to resection in patients with HCC or metastatic liver cancer. One RCT was included; the other studies (n=15) were observational. Patients who received MWA had a significantly higher risk of local tumor progression compared to those who received resection. At 1 year, OS did not differ between MWA and resection but 3- and 5-year OS was significantly higher in patients who had received resection. Overall and major complications were lower with MWA compared to resection. 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 non-resectable or to conduct subgroup analyses by resectable versus 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 hepatic resection 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. Chinnaratha et al (2016) published a systematic review of RCTs and observational studies that compared the effectiveness and safety of RFA with MWA in patients who had primary hepatocellular carcinoma (HCC). PubMed, EMBASE, and Cochrane Central databases were searched between 1980 and 2014 for human studies comparing the 2 technologies. The primary outcome was the risk of local tumor progression; secondary outcomes were complete ablation, OS, and major adverse events. Ten studies (1 RCT, 1 prospective cohort, 8 retrospective) were included. One study was conducted in Australia and the others in China or Japan. The overall local tumor progression rate was 14% (176/1298). There was no difference in local tumor progression rates between RFA and MWA. The complete ablation rate, 1- and 3-year OS, and major adverse events were similar between the 2 modalities. Subgroup analysis showed local tumor progression rates were lower with MWA for treatment of larger tumors. No significant publication bias was detected nor was interstudy heterogeneity observed for any measured outcomes. The reviewers concluded that both MWA and RFA are effective and safe. Chong et al (2020) conducted a RCT comparing MWA to RFA in 93 patients with HCC (up to 3 lesions of 5 cm or smaller). 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 1 month, which did not differ significantly for MWA (95.7%) versus RFA

(97.8%; p>.99). Rates of OS up to 5 years and rates of disease-free survival up to 3 years were similar between groups. However, the sample size calculations were based on rates of complete ablation at 1 month, so the study may not have been adequately powered to detect differences in OS or disease-free survival. Mimmo et al (2022) conducted a systematic review of MWA for colorectal liver metastases. 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 1, 3, and 5 years were 65.1%, 44.6%, and 34.3%, respectively. Mean OS rates for MWA at 1, 3, and 5 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.

POSITION STATEMENT:

Radiofrequency ablation of primary, inoperable (eg, due to location of lesion[s] and/or comorbid conditions) hepatocellular carcinoma **meets the definition of medical necessity** under the following conditions:

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

Radiofrequency ablation as a primary treatment of inoperable hepatic metastases **meets the definition of medical necessity** under the following conditions:

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

Microwave ablation of primary or metastatic inoperable (eg, due to location of lesions[s] and/or comorbid conditions) hepatic tumors **meets the definition of medical necessity** under the following condition:

- There is a single tumor of ≤ 5cm, **OR** up to 3 nodules ≤ 3cm each

Radiofrequency ablation of primary, inoperable hepatocellular carcinoma is considered **experimental or investigational** in the following situations:

- When there are more than 3 nodules or when not all sites of tumor foci can be adequately treated, **OR**
- When used to downstage (downsize) hepatocellular carcinoma in individuals being considered for liver transplant

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

Radiofrequency ablation for hepatic metastasis is considered **experimental or investigational** for:

- Hepatic metastases from other types of cancer except colorectal cancer or neuroendocrine tumors

For the above experimental or investigational indications, data in published medical literature are inadequate to permit scientific conclusions on long-term and net health outcomes.

BILLING/CODING INFORMATION:

CPT Coding:

47370	Laparoscopy, surgical, ablation or 1 or more liver tumor(s); radiofrequency
47380	Ablation, open, or 1 or more liver tumor(s); radiofrequency
47382	Ablation, 1 or more liver tumor(s), percutaneous, radiofrequency
76940	Ultrasound guidance for, and monitoring of parenchymal tissue ablation
77013	Computerized tomography guidance for, and monitoring of parenchymal tissue ablation
77022	Magnetic resonance guidance for, and monitoring of parenchymal tissue ablation

ICD-10 Diagnosis Codes That Support Medical Necessity:

C22.0	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.2	Hepatoblastoma
C22.7	Other specified carcinomas of liver
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
D01.5	Carcinoma in situ of liver, gallbladder and bile ducts
D37.6	Neoplasm of uncertain behavior of liver, gallbladder and bile ducts

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline reviewed date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if

based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Extra-hepatic metastases: cancer that has spread from its original location to other sites within the body, other than the liver.

Hepatic metastases: cancer that has spread from its original location in the body to the liver.

Primary hepatocellular cancer: a cancer that originates within liver cells, as opposed to having spread from other organs; malignant hepatoma.

Unresectable: a property of a tumor where it is unable to be removed surgically.

RELATED GUIDELINES:

Cryoablation of Liver Tumors, 02-40000-22

OTHER:

None applicable.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 10/24/24.

GUIDELINE UPDATE INFORMATION:

02/15/04	Reviewed Radiofrequency/Cryoablation of Liver Tumors MCG #02-40000-22 and separated into two different policies Radiofrequency Ablation of Liver Tumors and Cryosurgical Ablation of Liver Tumors; coverage statement changed for radiofrequency ablation of liver tumors.
06/15/04	Revision consisting of removal of ICD-9 diagnosis code for benign liver tumors.
05/15/05	Scheduled review; no change in coverage statement.
03/15/06	Scheduled review; expand coverage to include metastatic liver tumors.
03/15/07	Scheduled review; no change in coverage statement; update coding section and references.
06/15/07	Reformatted guideline.
03/15/08	Scheduled review; no change in position statement. Update references.
04/15/09	Scheduled review; no change in position statement. Update references.
01/01/10	Annual HCPCS coding update: revise descriptors for CPT codes 47370, 47380, & 47382.
04/15/10	Annual review; no change in position statement. References updated.
10/15/10	Revision; related ICD-10 codes added.
05/11/14	Revision: Program Exceptions section updated.
11/01/15	Revision: ICD-9 Codes deleted.
10/15/17	Scheduled review. Revised description section and position statement section. Updated references.
03/15/20	Scheduled review. Revised description and reformatted position statement. Updated references.

02/15/22	Scheduled review. Revised description, maintained position statement and updated references.
12/15/22	Revision. Revised description; added medical necessity criteria for microwave ablation and updated references.
05/25/23	Update to Program Exceptions section.
01/01/24	Position statements maintained.
11/15/24	Scheduled review. Revised description, maintained position statement and updated references.