Liver Tumor Treatment

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INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☐ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

PHP Medicaid follows Oregon Administrative Rules (OARs) 410-141- 3820 to 3830 and Statement of Intent 1 and Guideline Notes 12, 78, & 185 of the OHP Prioritized List of Health Services for coverage of Chemoembolization and Radioembolization of Liver Tumors.
PHP Medicaid follows Oregon Administrative Rules (OAR) 410-120-1200 and 410-141-3820 through 3830 for coverage of Ablation of Primary and Metastatic Liver Tumors

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Ablation (Radiofrequency, Cryoablation, Percutaneous Ethanol Injection, Microwave)

I. Ablative therapies (radiofrequency ablation, cryoablation, percutaneous ethanol injection, and microwave ablation) for treatment of liver tumors may be considered **medically necessary** when **all** of the following (A.-D.) criteria are met:

   A. Karnofsky performance scale (KPS) of 60% or greater **or** the Eastern Cooperative Oncology Group (ECOG) performance scale of 2 or lower; **and**
   B. The patient has adequate liver reserve function; **and**
   C. The patient is a Child's Pugh Score A/B; **and**
   D. **At least one** of the following (1. or 2.) criteria are met:
      1. The patient is **not** currently awaiting liver transplantation **and** meets **at least one** of the following (a.-d.) criteria:
         a. The patient has been diagnosed with hepatocellular carcinoma confirmed by biopsy and/or imaging and meets **all** of the following (i.-iv.) criteria:
            i. There is clinical documentation that surgical resection is not feasible; **and**
            ii. The tumor(s) is in an accessible location for percutaneous, laparoscopic, or open approaches for ablation; **and**
            iii. There is a single tumor ≤ 5 cm **or** two to three tumors each ≤ 3 cm; **and**

iv. All tumor foci are amenable to ablative therapy and the goal of therapy is long term control with complete ablation; **or**

b. The patient has been diagnosed with hepatic metastases from colorectal tumors confirmed by biopsy and/or imaging and meets **all** of the following (i.-iv.) criteria:
   i. Surgical resection is not feasible or ablation is to be performed in conjunction with surgical resection; **and**
   ii. The tumor(s) are in an accessible location for percutaneous, laparoscopic, or open approaches for ablation; **and**
   iii. The metastatic tumor(s) is ≤ 5 cm; **and**
   iv. The metastatic lesions are confined to the liver**.**

c. The patient has been diagnosed with hepatic metastases from neuroendocrine tumors confirmed by biopsy and/or imaging and meets **all** of the following (i.-iii.) criteria:
   i. There is clinical documentation that surgical resection is not feasible; **and**
   ii. The metastatic tumor(s) is ≤ 5 cm; **and**
   iii. Tumor related symptoms (e.g., carcinoid syndrome) are refractory to medical treatment (e.g., somatostatin analogs); **or**

d. The patient has been diagnosed with hepatic metastases from breast cancer confirmed by biopsy and/or imaging and meets **all** of the following (i.-iii.) criteria:
   i. There is clinical documentation that surgical resection is not feasible; **and**
   ii. The metastatic tumor(s) is ≤ 5 cm; **and**
   iii. there is no evidence for extrahepatic disease (excluding stable bone metastasis) **or**

2. The patient is approved and listed for a liver transplant, and ablative therapy is intended to prevent further tumor growth while waiting for a transplant to become available.

II. Ablative therapies (radiofrequency ablation, cryoablation, percutaneous ethanol injection, and microwave ablation) are considered **not medically necessary** for the treatment of liver tumors when criterion I. above is not met.

Repeat Therapies

III. Repeat therapies using ablation may be considered **medically necessary** when the original treatment criteria above are met.

Not Medically Necessary Therapies

IV. Ablation for the treatment of hepatic metastases from melanoma (cutaneous or uveal/conjunctival) is considered **not medically necessary**.

V. High-intensity focused ultrasound (HIFU) or magnetic resonance guided focused ultrasound (MRgFUS), alone or in combination with another therapy, for the treatment of liver tumors is considered **not medically necessary**.

VI. Histotripsy is considered **not medically necessary** for the treatment of primary and metastatic liver malignancies.

VII. Electromagnetic fields (e.g. TheraBionic P1) is considered **not medically necessary** for the treatment of primary and metastatic liver malignancies.

VIII. Simulation angiogram with use of a pressure-generating catheter for subsequent therapeutic radioembolization of tumors is considered **not medically necessary**.

IX. 3D contour simulation of target liver lesion(s) and margin(s) ablation is considered **not medically necessary**.

Link to Evidence Summary

POLICY CROSS REFERENCES

None

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

Performance Scales

Table 1: Karnofsky Performance Scale (KPS)

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA (12)		
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
	40	Disabled; requires special care and assistance.

Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Table 2: Eastern Cooperative oncology Group (ECOG) Performance Status

GRADE	ECOG PERFORMANCE STATUS(11)
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Child-Pugh Score

According to Weerakkody et al., "(t)he Child-Pugh score is a scoring system to measure the severity of chronic liver disease inclusive of cirrhosis. The intention is to provide a system with which clinicians can objectively communicate about liver function."[1] The score is composed of several categories including, total bilirubin, serum albumin, and presence of ascites and hepatic encephalopathy. The higher Child-Pugh score indicates worsening liver function. Each category has different point levels, and the point scores are added up and classified as the following:

- Class A (5-6 points)
- Class B (7-9 points)
- Class C (10-15 points)

BACKGROUND

Liver (Hepatic) Tumors

Primary Liver Cancer (Hepatocellular Carcinoma [HCC])

According to a Hayes Medical Technology Review, "(a)lthough primary liver cancer, hepatocellular carcinoma (HCC), is relatively uncommon in the United States, incidence of this cancer is increasing."[2] HCC is often associated with liver cirrhosis, hepatitis B and C infection, and alcohol use. The only possible curative treatments of HCC are surgical resection or liver transplantation; however, the majority of patients with primary liver cancer are not suitable candidates for surgical resection.

Metastatic Liver Cancer

Hayes indicates, "(t)he liver ranks second only to the lymph nodes as a common site of metastasis of cancers from other organs."[2] Commonly, hepatic metastases arise from colorectal or neuroendocrine tumors. The standard treatment for hepatic metastases is surgical resection; however, only 10% to 25% of patients are candidates for surgical resection.

Neuroendocrine Tumors

According to the National Comprehensive Cancer Network, "(n)euroendocrine tumors are rare, slow-growing, hormone-secreting tumors that may occur in numerous locations in the body."[3] Examples of neuroendocrine tumors include:

- Carcinoid tumors
- Islet cell tumors (i.e., pancreatic endocrine tumors)
- Pheochromocytoma/paraganglioma
- Neuroendocrine unknown primary
- Adrenal gland tumors
- Poorly differentiated (high grade or anaplastic)/small cell
- Multiple endocrine neoplasia, Type 1 (i.e., MEN-1 syndrome, Wermer's syndrome)
- Multiple endocrine neoplasia, Type 2 a or b (i.e., pheochromocytoma and amyloid producing medullary thyroid carcinoma, PTC syndrome, Sipple syndrome)

Colorectal Tumors

According to the National Comprehensive Cancer Network, "(a)pproximately 50% to 60% of patients diagnosed with colorectal cancer develop colorectal metastases, and 80% to 90% of these patients have unresectable metastatic liver disease."[4,5] Types of cancer in the colon and rectum include[6]:

- Adenocarcinomas
- Carcinoid tumors
- Gastrointestinal stromal tumors (GISTs)
- Lymphomas
- Sarcomas

Breast Cancer Liver Metastasis (BCLM)

Hepatic metastases occur in over one-half of patients with metastatic breast cancer.[7] They are most commonly a late development and as associated with disseminated disease and a poorer prognosis than bone or soft tissue metastases. Only 5-12% of patients have isolated liver involvement, frequently those with hormone-positive disease.

<u>Intrahepatic Cholangiocarcinoma (ICC)</u>

ICC is the "second most common primary liver malignant tumor, after hepatocellular carcinoma (HCC), and represents 10% to 20% of all primary liver malignant tumors, or about 3,100 new cases every year in the US."[8] ICC is a silent disease that begins in the smaller bile duct and branches inside the liver.[9] The signs and symptoms often go unnoticed; therefore, a majority of patients are not candidates for surgical

resection because the time of diagnosis is beyond the limits of surgery. When symptoms do become present, they are typically vague and can be attributed to other diseases.

Ablative Therapies

Radiofrequency Ablation (RFA)

According to Hayes, "(r)adiofrequency ablation (RFA) is a technique in which electrodes inserted directly into target tissues emit an electrical current that causes local thermal destruction by coagulative necrosis."[2] RFA is intended for patients with unresectable primary or metastatic liver tumors in order to control the disease, relieve symptoms, and prolong survival. A device with single or multiple electrodes introduces radiofrequency electrical (RF) energy through a percutaneous, intraoperative, or laparoscopic approach. The goal of RFA is to destroy the entire area of tumor and an area of normal liver tissue in order to control the spread of the disease.

Percutaneous Ethanol Injection (PEI)

PEI is a type of ablative procedure where 100% alcohol is injected into the liver tumor(s) in order to kill cancer cells. According to a review of PEI by Fong, the "alcohol causes tumor destruction by drawing water out of tumor cells (dehydrating them) and thereby altering (denaturing) the structure of cellular proteins."[10] Five or six sessions of PEI may be required to completely destroy the tumors.

Cryoablation

Cryotherapy is an ablative procedure which involves the destruction of cancer cells using extremely cold temperatures via the formation of intracellular crystals.[11] A probe is placed at the center of the tumor and liquid nitrogen at a temperature of -196°C is released in order to initiate cell death. Commonly, two cycles of cryotherapy are necessary.

Microwave Ablation (MWA)

MWA destroys liver tumors using heat generated by microwave energy.[12] A thin antenna which emits microwaves is inserted into the tumor. The microwaves produce an intense heat that ablates tumor tissue in about 10 minutes. MWA has several advantages including speed, simultaneous tumor ablation, and the ability to ablate larger tumors.

Histotripsy

Histotripsy, a nonthermal focal ablative therapy, has been proposed as an alternative treatment of liver lesions.[13] Histotripsy utilizes short, high-pressure bursts of high-intensity focused ultrasound to induce tissue destruction via acoustic cavitation. The purported benefits of non-thermal focal ablative therapy include avoidance of any heat sink affects, which is theorized to allow histotripsy to be used in highly vascular areas. The HistoSonicx® System (HistoSonics, Ann Arbor, MI) is an automated, external sonic beam therapy platform which intended for ablative tissue in the liver.

Bridge Therapy

Under the Model for End-Stage Liver Disease (MELD), "liver transplant candidates with HCC must meet the Milan criteria (single tumor 5 centimeters [cm] in diameter or 2 or 3 tumors, each < 3 cm in diameter) to qualify for waiting list consideration. Prioritization is based on risk of progression beyond the Milan criteria."[14] According to the National Comprehensive Cancer Network guideline for hepatobiliary cancers, bridge therapy is used in patients who have met the transplant criteria in order to decrease tumor progression and the dropout rate from the liver transplant list.[15]

Not Medically Necessary Therapies

High-Intensity Focused Ultrasound (HIFU) and Magnetic Resonance (MR) Guided Focused Ultrasound (MRgFUS)

HIFU and MRgFUS use imaging systems (e.g., magnetic resonance imaging) to identify tumor location, confirm the target treatment area, and deliver high-energy ultrasound waves into the tissue; thus causing tumor necrosis. HIFU is a "method for tumor ablation that uses thermal energy produced by an ultrasonic beam to induce tissue necrosis."[16] The goal of MRgFUS is to "deliver focused high-energy ultrasound wave into tissue to cause thermal coagulation of the targeted tissue."[17] Both HIFU and MRgFUS are minimally invasive, and can selectively destroy tumor tissue without harming adjacent or overlying structures. An ultrasound transducer delivers a focused ultrasound beam to the target area, which is absorbed and converted to heat. A rapid increase in heat causes tumor necrosis.

Simulation Angiogram with Use of Pressure-Generating Catheter

Simulation angiogram with the use of a pressure-generating catheter is a diagnostic procedure aimed at mapping the blood vessels of the liver to facilitate subsequent therapeutic interventions, such as radioembolization of tumors. This process involves injecting a contrast medium into the hepatic arteries and utilizing imaging technology to visualize the vasculature, allowing for precise identification of areas with restricted blood flow or tumor presence. By understanding the vascular structure of the liver, healthcare professionals can plan and execute targeted therapies more effectively, ensuring that therapeutic agents are delivered directly to the affected areas while minimizing impact on healthy tissue.

3D Contour Simulation of Target Liver Lesion(s) and Margin(s) Ablation

The 3D contour simulation of target liver lesions and margins for ablation involves creating a detailed three-dimensional model of liver tumors and their surrounding tissue. This technology allows for precise mapping of the tumor's shape, size, and location, which is essential for planning effective ablation therapies aimed at destroying cancerous cells. By utilizing 3D simulation, clinicians can gain an enhanced visualization of the lesion and its margins, thereby improving the accuracy of treatment. This approach ensures that ablation is performed with high precision, targeting the malignant tissue while sparing as much healthy liver tissue as possible.

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

High Intensity Focused Ultrasound and Magnetic Resonance Guided Focused Ultrasound (HIFU and MRgFUS)

HIFU and MRgFUS devices have received FDA approval under the premarket approval (PMA) process. This list may not be all inclusive. Please see the FDA device database for more information.

Device & Manufacturer	Indications for Use
Sonablate® 450 by SonaCare Medical[18]	The Sonablate® is indicated for transrectal high intensity focused ultrasound (HIFU) ablation of prostatic tissue.
ExAblate Family of Magnetic Resonance Guided Focused Ultrasound Systems by InSightec, Inc.[19]	The ExAblate MRgFUS has been approved for the following indications: • The Exablate 4000 System is indicated for use in the unilateral Thalamotomy treatment of idiopathic Essential Tremor patients with medication-refractory tremor. Patients must be at least age 22. The designated area in the brain responsible for the movement disorder symptoms (ventralis intermedius) must be identified and accessible for targeted thermal ablation by the ExAblate device. • The ExAblate® 2000 System is intended for ablation of uterine fibroid tissue in pre- or peri-menopausal women with symptomatic uterine fibroids who desire a uterine sparing procedure. Patients must have a uterine size of less than 24 weeks and have completed child bearing. • The ExAblate is indicated for pain palliation of Metastatic Bone Cancer in patients 18 years of age or older who are suffering from bone pain due to metastatic disease and who are failures of standard radiation therapy, or not candidates for, or refused radiation therapy. The bone tumor to be treated must be visible on non-contrast MR and device accessible. • The ExAblate Neuro is intended for use in the unilateral Thalamotomy treatment of idiopathic Essential Tremor patients with medication-refractory tremor. Patients must be at least age 22. The designated area in the brain responsible for the movement disorder symptoms (ventralis intermedius) must be identified and accessible for targeted thermal ablation by the ExAblate device.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of ablative therapies as a treatment for primary and metastatic liver tumors. Below is a summary of the available evidence identified through October 2024.

Due to the large and extensive body of evidence surrounding cancer treatment, the evidence supporting the policy criteria was limited to systematic reviews and current National Comprehensive Cancer Network (NCCN) guidelines for hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and hepatic metastases from colorectal or neuroendocrine tumors.

Interventional Therapies for Hepatocellular Carcinoma (HCC)

- In 2022, Chow and colleagues completed a systematic review and network meta-analysis of overall survival data on patients that underwent different local treatments of liver cancer.[20] A total of 24 RCTs and propensity score matched (PSM) observational studies were included, reporting on 5549 patients that underwent one of the following treatment modalities: radiofrequency ablation, radiation therapy, transarterial chemoembolization, or yttrium 90. While overall survival was slightly greater for Y90 than TACE, all other one-year overall survival comparisons were similar. There were no differences across any modalities in the two- and three-year overall survival. The authors urged other factors such as toxicity rate may play a role in treatment modality selection, and additional studies are needed to evaluate this as well as complete response rates for definitive conclusions.

- In 2016, Lan et al. conducted a systematic review and meta-analysis to compare the efficacy of interventional therapies for early-stage HCC.[21] The interventional therapies included in this study were hepatic resection (HR), transarterial chemoembolization (TACE), radiofrequency ablation (RFA), and percutaneous ethanol injection (PEI). Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. Study authors were also contacted, if necessary, for additional information or data. The primary outcome was overall survival (OS) rate, defined as the difference value between the date of postintervention and the date of death. The treatments and treatment combinations were rank-ordered by results on OS.

  The authors identified 21 randomized controlled trials (RCTs) as eligible for inclusion; thus producing a sample size of 2,691 patients. The combination of TACE and RFA was associated with a better 1-year survival rate than HR, PEI, and RFA alone. The combination of TACE and RFA also had a higher 3-year survival rate than PEI or RFA alone. For 3-year survival rate, a statistically significant difference was identified between the combination of RFA and PEI versus PEI alone. The results of the rank test and meta-analysis identified the combination of TACE and RFA as the most effective strategy for early-stage HCC.

  Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers, large sample size, contacting study authors for additional information, assessment of heterogeneity, and sensitivity analyses. Limitations were present in the lower methodological quality of some selected studies and the heterogeneity present between studies. The authors concluded, “by using a Bayesian network meta-analysis involving 21 RCTs comparing 6 different interventional therapies, our research demonstrated that the combination therapy of TACE and RFA was the best therapeutic option for early-stage HCC in terms of improving outcomes of 1-year, 3-year, and 5-year survival rate.”[21]

Ablative Therapies

<u>Hepatocellular Carcinoma (HCC)</u>

- In 2020, Lee and colleagues conducted a systematic review and meta-analysis comparing radiofrequency ablation (RFA) and stereotactic body radiotherapy (SBRT) for liver malignancies.[22] Data collection was performed by two independent researchers, and 11 studies involving 2238 participants were included in the analysis. Among the 11 studies, 4 were abstracts from international conferences. Most studies were retrospective in design. Eight of the studies focused on patients with HCC, while 3 focused on liver metastases. When analyzing results of studies on HCC, there was no significant difference (p=0.431) in pooled 2-year local control rates between the RFA arm (79.5% [95% CI: 68.1-87.6]) and the SBRT arm (84.5% [95% CI: 74.9-90.9]). There was significant heterogeneity among the HCC studies in the pooled analysis. The pooled analysis of overall survival had an OR of 1.43 (95% CI: 1.05-1.95; p= 0.023), favoring the RFA arms. This meta-analysis suffers from a number of limitations, including nonrandomized, observational trials, mostly retrospective studies, and high heterogeneity and risk of bias in the pooled results.

- In 2019, Tan and colleagues conducted a systematic review and meta-analysis comparing microwave ablation (MWA) and radiofrequency ablation (RFA) for HCC. The reviewers included 4 randomized controlled trials (RCTs) and 10 cohort studies in the analysis.[23] There were no significant differences in complete ablation rate between the percutaneous RFA and MWA groups (OR 0.85%; 95% CI: 0.41-1.79, p= 0.67 in RCTs). There was also no significant difference between laparoscopic RFA and MWA groups (OR 0.78; 95% CI 0.26–2.36; p = 0.66). When looking at primary endpoints, there was no significant difference in local recurrence rates when using percutaneous ablation (p=0.77), but there was significantly lower local recurrence rate in patients treated with laparoscopic MWA versus laparoscopic RFA (p=0.01). There were no significant difference between groups in disease-free survival and overall survival at 5 years and in major complication rates. The study was limited by a small number of RCTs, and heterogeneity between study participants, methods, and outcomes. More randomized trials are needed to better compare the effects of RFA and MWA in patients with HCC.

- In 2019, Si and colleagues conducted a systematic review and meta-analysis comparing the safety and efficacy of radiofrequency ablation (RFA) versus minimally invasive liver surgery (MIS) for the treatment of small hepatocellular carcinoma (SHCC).[24] Independent investigators systematically searched the literature through July 2018, identified eligible studies, assessed study quality, extracted data and pooled results. Primary outcomes of interest were overall survival (OS), disease-free survival (DFS), local recurrence and complication rates. In total, 6 retrospective studies were analyzed evaluating 597 patients (RFA = 313, MIS = 284). Given the limitations of retrospective studies, evidence was assessed as being of low-quality. Overall survival rates were significantly higher in patients treated with MIS at 3-year follow-up relative to RFA patients (OR 0.55; 95% CI 0.36 to 0.84). Disease-free survival rates were also superior among MIS patients compared to RFA patients (OR 0.63; 95% CI 0.41 to 0.98) as were rates of local intrahepatic recurrences, (OR 2.24; 95% CI 1.47 to 3.42). Investigators concluded that MIS was superior to RFA but that RFA may be an alternative treatment for patients presenting a single SHCC nodule (≤ 3cm) due to the procedure's minimally invasive nature and comparable long-term efficacy. Limitations included the low-quality of studies included for review (all non-randomized, retrospective studies), inability to calculate hazard rates due to limited data, and significant heterogeneity of patient groups across studies. Authors called for high-quality studies to validate findings and establish RFA's comparative safety and efficacy.

- In 2019, Glassberg and colleagues conducted a systematic review and meta-analysis evaluating the safety and efficacy of microwave ablation (MWA) compared with hepatic resection for the treatment of hepatocellular carcinoma and liver metastases.[25] Independent investigators systematically searched the literature through March 2018, identified eligible studies, assessed study quality, extracted data and pooled results. The primary outcome of interest was local tumor recurrence (LTR). In total, 16 studies were included for review (1 RCT, 15 observational studies), assessing 2,522 patients. Follow-up duration ranged from 15 to 60 months. Random effects meta-analysis indicated that MWA patients experienced significantly higher LTR relative to patients receiving hepatic resection (RR =2.49, p = 0.016), and lower rates of overall survival and disease-free survival at 3- and 5-year follow-up. Limitations included the limited quantity and quality of studies included for review (e.g. only 1 RCT), the lack of studies reporting on both pre- and post-operative liver function tests, and the lack of subgroup analyses on primary tumor type due to limited data. Investigators concluded that MWA can be a safe and effective alternative to hepatic resectioning in patients/tumors that are not amenable to resection. Additional studies called for to validate findings and establish patient selection criteria for MWA.

- In 2013, Weis and colleagues conducted a Cochrane systematic review to evaluate radiofrequency ablation (RFA) versus no intervention or other intervention for HCC.[26] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The primary outcome was overall survival (OS) rate, defined as the difference value between the date of postintervention and the date of death.
  After systematic review, the authors identified 11 randomized controlled trials with 1,819 participants that included 4 comparisons: RFA versus hepatic resection (HR), RFA versus percutaneous ethanol injection (PEI), RFA versus microwave ablation (MWA), and RFA versus laser ablation. The risk of bias was considered low in five trials and high in six trials. "Regarding the comparison RFA versus hepatic resection, there was moderate-quality evidence from two low risk of bias trials that hepatic resection seems more effective than RFA regarding overall survival (HR 0.56; 95% CI 0.40 to 0.78) and two-year survival (HR 0.38; 95% CI 0.17 to 0.84). However, if we included a third trial with high risk of bias, the difference became insignificant (overall survival: HR 0.71; 95% CI 0.44 to 1.15)."[26] Although HR is more effective than RFA, surgical resection patients are at much higher odds for complications compared to RFA patients (odds ratio 8.24; 95% CI 2.12-31.95). The results also indicated RFA was superior to PEI for overall survival rate.

  Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers, large sample size, and assessment of heterogeneity. Limitations were present in the lower methodological quality of some selected studies and possible publication bias due to the small number of studies selected. The authors concluded (1) moderate-quality evidence indicates HR is superior to RFA for OS; however, RFA might be associated with fewer complication and shorter hospital stays (2) moderate-quality evidence indicates RFA is superior to PEI in regards to OS (3) the paucity of data did not allow recommendations for ablation techniques other than RFA and (4) more RCTs assessing the efficacy of RFA are required.

- In 2013, Huang et al. conducted a systematic review and meta-analysis to evaluate radiofrequency ablation (RFA) versus cryosurgery ablation (CSA) for hepatocellular carcinoma (HCC).[27] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. Primary outcomes were mortality, complications, and local recurrence.

The authors identified 4 studies as eligible for inclusion. This included 3 prospective studies and 1 retrospective study, giving a total sample size of 433 HCC patients (n=180 RFA; n=253 CSA). The results indicated cryoablation patients were at higher odds for complications compared to RFA patients (OR=2.80; 95% CI 1.54-5.09). In regards to local recurrence of tumor, RFA was also superior to CSA (OR=1.96; 95% CI 1.12-3.42). No significant differences were identified between RFA and CSA for mortality.

Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers, large sample size. Significant limitations of this study include the potential for publication bias due to the small number of included studies and the poor quality of some selected studies. The authors concluded "although multiple confounders exist in the clinical trials especially the bias in patient selection, RFA was significantly superior to CSA in the treatment of HCC."[27]

Hepatic Metastases from Colorectal Tumors

- In 2020, Lee and colleagues conducted a systematic review and meta-analysis comparing radiofrequency ablation (RFA) and stereotactic body radiotherapy (SBRT) for liver malignancies.[22] Data collection was performed by two independent researchers, and 11 studies involving 2238 participants were included in the analysis. Among the 11 studies, 4 were abstracts from international conferences. Most studies were retrospective in design. Eight of the studies focused on patients with HCC, while 3 focused on liver metastases. When analyzing results of studies on liver metastases, the pooled two-year local control rate was higher in the SBRT arm (83.6%) compared to the RFA arm (60.0%; p= 0.001). Among the two liver metastases studies that held comparative survival data, there were no significant differences between arms, with one study finding nonsignificant benefit of SBRT (p= 0.06) and the other study finding no difference worse secondary outcomes in the SBRT arm. This meta-analysis suffers from a number of limitations, including small sample size (3 studies), nonrandomized, observational trials, mostly retrospective studies, and high heterogeneity and risk of bias in the pooled results. The authors concluded that more randomized trials are needed to help identify suitable indications for each modality.

- In 2012, Weng et al. conducted a systematic review and meta-analysis comparing radiofrequency ablation (RFA) and liver resection (LR) for colorectal cancer liver metastases (CLM).[28] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The primary outcomes of interest were overall survival (OS) disease-free survival (DFS) at 3 and 5 years plus morbidity and mortality.

  After systematic review, 13 studies were identified as eligible for inclusion (1 prospective study and 12 retrospective studies) giving a total sample size of 1,886 patients (n=1,266 LR; n=620 RFA). In regards to 3-year and 5-year DFS, the LR group had significantly higher rates compared to RFA. "The postoperative morbidity was significantly higher in the LR group than in the RFA group. (9 trials reported the data, RR: 2.495, 95% CI: 1.881–3.308). However, no difference was observed in terms of postoperative mortality (8 trials involved, RR: 1.391, 95% CI: 0.306–6.326). The mean length of hospital stay was 11.02±0.11 days for LR group and 4.05±0.10 days for RFA (standardized mean difference: 3.284, 95% CI: 3.052–3.516, P<0.001)."[28]

Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers, large sample size, assessment of heterogeneity, and assessment of publication bias. A significant limitation of this study was the poor methodological quality of included studies; however, the authors noted a shortage of prospective randomized trials. The authors concluded, "(a)lthough multiple confounders exist in the clinical trials especially the bias in patient selection, LR was significantly superior to RFA in the treatment of CLM, even when conditions limited to tumor<3 cm, solitary tumor and open surgery or laparoscopic (lap) approach."[28]

Hepatic Metastases from Neuroendocrine Tumors

In 2015, Mohan and colleagues conducted a systematic review to evaluate radiofrequency (RF) ablation for neuroendocrine (NET) liver metastases.[29] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The primary outcomes of interest were symptom improvement, survival rate, and complications.

The authors identified 7 studies as eligible for inclusion; thus producing a sample size of 301 patients. A combination of surgical resection and RF ablation was performed in 48% of patients. Complications were reported in 10% of patients, and included hemorrhage, abscess, transient liver insufficiency, and pneumothorax. Symptom improvement was reported in 92% of patients, and the duration of symptom relief ranged from 14 to 27 months. Symptom recurrence was common and ranged from 63% to 87% of patients.

Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers, and assessment of heterogeneity. Significant limitations are present in the small number of selected studies (possible publication bias), the small sample size (the authors attributed this to the rarity of this disease), and the poor methodological quality of included studies (all were retrospective nonrandomized studies). The authors concluded, "RF ablation can provide symptomatic relief in NET liver metastases alone or in combination with surgery."[29]

Hepatic Metastases from Breast Cancer

- In 2021, Rivera and colleagues conducted a systematic review on liver directed therapies for treatment of breast cancer liver metastasis (BCLM).[30] Fifty-one studies were included in the review. The authors recognize that therapies including hepatic resection, radiofrequency ablation (RFA), transarterial chemo- and radioembolization (TACE/TARE), and hepatic arterial infusion (HAI) have been scarcely researched for BCLM. They found hepatic resection afforded the longest median overall survival and 5-year survival (45 months, 41%) across 23 studies. RFA was presented in six studies with pooled median overall survival and 5-year survival of 38 months and 11-33%. Disease burden and tumor size was lower amongst these two patient populations. TACE was reviewed in eight studies with a pooled median overall survival and 1-year survival of 19.6 months and 32-88.8%. TARE was presented in ten studies with pooled median overall survival and 1-year survival of 11.5 months and 34.5-86%. The TACE & PARE patients were selected from those with chemo-resistant, unresectable disease. Hepatic arterial infusion was in five of the reviewed articles and had a pooled median overall survival of 11.3 months. The authors recommended additional studies to delineate appropriate usage of liver

directed therapies in BCLM, but small studies suggest that hepatic resection and RFA (in well selected patients) can result in prolonged survival.

Intrahepatic Cholangiocarcinoma

- In 2019, Yousaf and colleagues published a systematic review and meta-analysis on the efficacy of ablative therapy for unresectable intrahepatic cholangiocarcinoma.[31] Ten studies were included for analysis, totalling 206 patients. There were no randomized trials and most studies were retrospective with no comparator groups. RFA was the more commonly practiced technique, with only 16.3% of patients receiving MWA. Follow up ranged from 8.7 to 29.9 months and median overall survival ranged from 8.7 to 52.4 months. High degrees of heterogeneity were found in 1-year, 3-year, and 5-year survival among trials. The authors conclude that ablation appears promising, but further investigation is warranted. Due to the fact that there were no randomized trials and the review did not compare MWA to RFA or other standard treatments, no conclusions can be made from the results. Randomized trials are needed to determine the most effective ablative treatments for intrahepatic cholangiocarcinoma.

- In 2015, Boehm and colleagues conducted a systematic review and meta-analysis to evaluate the effectiveness of hepatic artery based therapies for unresectable intrahepatic cholangiocarcinoma (ICC).[32] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The authors aimed to evaluate the comparative effectiveness of hepatic arterial infusion (HAI), transcatheter arterial chemoembolization (TACE), drug-eluting bead TACE (DEB-TACE), and Yttrium (90) radioembolization (Y-90). The primary outcome of interest was median overall survival (OS). Secondary outcomes included tumor response to therapy and toxicity.

  After systematic review, the authors identified 20 articles as eligible for inclusion; thus producing a sample size of 657 patients. The results indicated HAI had the highest median overall survival (22.8) followed by Y90 (13.9), TACE (12.4), and DEB-TACE (12.3). In regards to tumor response, HAI had the highest tumor response (56.9%) followed by Y90 (27.4%) and TACE (17.3%). Toxicity was highest for HA (0.35), TACE (0.26) and DEB-TACE (0.32).

  Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers, large sample size, assessment of heterogeneity prior, and assessment of publication bias. Limitations are present in the poor methodological quality of included studies and the heterogeneity between some study outcomes. The authors concluded, “for patients with unresectable ICC treated with HAT, HAI offered the best outcomes in terms of tumor response and survival but may be limited by toxicity.”[32]

Bridge to Transplant

- In 2019 (updated in 2022), Hayes conducted a health technology assessment on radioactive Y-90 for the treatment of primary unresectable liver cancer for downstaging or as a bridge to transplantation or surgery.[14] Eight studies were included in the analysis, 2 of which were randomized trials while the rest were retrospective in design. Hayes found that there was low-

quality evidence to suggest that Y-90 transarterial radioembolization has similar or better safety and efficacy outcomes compared to other treatments used to downstage or bridge primary HCC patients to transplantation or resection. There a paucity of evidence comparing treatments and many of the studies had major methodological limitations. Hayes concluded, "However, when considered as a whole, the evidence suggests that the potential benefits of treatment with 90Y TARE may outweigh the potential harms among patients who are awaiting liver transplant or who could benefit from reduced disease burden to become eligible for curative treatment. More robust evidence is needed to draw firm conclusions on the efficacy and safety of 90Y TARE and to establish definitive patient selection criteria to ensure optimal efficacy and safety."[14]

- The current published evidence, outside of the Hayes review, evaluating liver tumor treatment modalities as a bridge to liver transplant is limited to small case series and nonrandomized studies.[34-40] These studies do not permit evidence-based conclusions due to significant methodological limitations, including, but not limited to, lack of randomization, small sample size, lack of statistical analysis, and lack of a comparator group. However, the current NCCN guidelines for hepatobiliary cancers states that although the evidence limits the conclusions that can be drawn, "the use of bridge therapy in this setting is increasing, and it is administered at some NCCN Member Institutions."[15]
  The current Organ Procurement and Transplantation Network (OPTN) policy for the allocation of livers recognizes locoregional therapies to (1) downsize T3 tumors to T2 status to meet the United Network for Organ Sharing criteria for additional allocation points or (2) to prevent the progress of T2 tumors while on the transplant waiting list to maintain UNOS allocation points.[41] The OPTN policy defines Class 5T (treated) nodules as, "any OPTN Class 5 or biopsy-proven HCC lesion that was automatically approved upon initial application or extension and has subsequently undergone loco-regional treatment. OPTN Class 5T nodules qualify for continued priority points based on the pre-treatment classification of the nodules and are defined as:

    - Past loco-regional treatment for HCC (OPTN Class 5 lesion or biopsy proven prior to ablation).
    - Evidence of persistent/recurrent HCC such as, but not limited to, nodular or crescentic extra-zonal or intra-zonal enhancing tissue on late arterial imaging (relative to hepatic parenchyma) may be present."[41]

- In 2017, the OPTN Liver & Intestinal Organ Transplantation Committee released a board approved policy update proposal that states[42] "(i)t has been widely shown that successful downstaging of HCC in selected patients is associated with excellent post-transplantation outcome. However, language describing the eligibility criteria for candidates suitable for HCC downstaging through local-regional treatment is absent from current OPTN/UNOS policy, yet nearly all regions currently approve patients who present outside of T2 criteria and have undergone downstaging to within T2. This proposal seeks to make a more consistent national policy regarding HCC patients, increase equity in access to transplants and improve waitlisted patient and transplanted recipient outcomes through modifications to the current standardized HCC exception process."

Other Therapies

<u>Hepatic Metastases from Melanoma</u>

There is insufficient evidence to support the use of ablation for the treatment of hepatic metastases from melanoma (cutaneous or uveal/conjunctival). Additional randomized controlled trials are needed to support the efficacy, safety, and medical necessity of these treatment modalities for melanoma metastases of the liver.

- In 2015 (updated in 2018), Hayes assigned a "D2" rating (insufficient evidence) for the use of 90Y in patients with unresectable hepatic metastases from noncolorectal cancer.[43] Additional relevant studies of 90Y not addressed in the Hayes' review for patients with BCLM and extrahepatic disease suffer from small sample sizes, a lack of control groups, limited follow-up times, and/or a lack of statistically significant improvements in patient-relevant health outcomes such as survival.[44,45] One recent systematic review evaluated TACE for the treatment of breast cancer with liver metastasis.[46] While investigators concluded that TACE may improve patients' overall survival, validity was limited by the low quantity and quality of studies included for review.

<u>High-Intensity Focused Ultrasound (HIFU) and Magnetic Resonance (MR) Guided Focused Ultrasound (MRgFUS)</u>

The evidence evaluating HIFU or MRgFUS for treatment of liver tumors is limited to nonrandomized studies and small case series.[47-52] The poor methodological quality of these studies does not permit meaningful conclusions regarding the safety, efficacy, or medical necessity of this treatment modality. Furthermore, HIFU and MRgFUS is not FDA approved for the treatment of liver tumors; therefore, this would be considered an off-label use of the ultrasound device.

<u>Histotripsy</u>

- In 2024, Mendiratta-Lala and colleagues published results from the #HOPE4LIVER trial, a parallel pivotal multi-center single-arm trials conducted in the US and EU/UK to assess the safety and technical success of histotripsy for treating primary and metastatic liver tumors.[53] This study involved a larger cohort of 44 patients with 49 tumors, including HCC and metastases from the colon, rectum, breast, pancreas, and other primary origins. The co-primary endpoints were successfully met, with a primary technical success rate of 95.5% within 36 hours of the procedure and a major complication rate (CTCAE ≥3) of 6.8%, demonstrating a favorable safety profile. Limitations of this study include its single-arm design, which lacks a control group for comparison, and the need for longer follow-up to confirm sustained efficacy and safety outcomes.

- In 2022, Vidal-Jove and colleagues published results from the THERESA trial, a prospective, non-randomized, multi-center feasibility study aiming to evaluate the use of histotripsy in hepatic tumors.[54] Conducted on a small cohort of 8 patients with a total of 11 treated tumors, the population included cases of hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, breast metastasis, and colorectal metastases. The study demonstrated a 100% technical success rate, with results observed for up to 8 weeks post-procedure and no device or procedure-related adverse events reported. However, limitations include the small sample size and the non-randomized design, which may impact the generalizability of the findings.

No evidence was identified that assessed the clinical utility of 3D contour simulation of target liver lesion(s) and margin(s) ablation or simulation angiogram with use of pressure-generating catheter.

CLINICAL PRACTICE GUIDELINES

National Comprehensive Cancer Network (NCCN)

Hepatocellular Carcinoma

The Version 3.2024 NCCN evidence-based clinical practice guideline for hepatobiliary cancers state, "locoregional therapy (ablation and arterially directed therapies) 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."[15]

The guideline gives the following recommendations regarding ablation (radiofrequency, cryoablation, percutaneous alcohol injection, and microwave)

- All tumors should be amenable to ablation such that the tumor and, in the case of thermal ablation, a margin of normal tissue is treated. A margin is not expected following percutaneous ethanol injection.
- Tumors should be in a location accessible for percutaneous/laparoscopic/open approaches for ablation.
- Caution should be exercised when ablating lesions near major vessels, major bile ducts, diaphragm, and other intra-abdominal organs.
- Ablation alone may be curative in treating tumors ≤3 cm. In well-selected patients with small properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review. Lesions 3 to 5 cm may be treated to prolong survival using arterially directed therapies, or with combination of an arterially directed therapy and ablation as long as tumor location is accessible for ablation.
- Unresectable/inoperable lesions >5 cm should be considered for treatment using arterially directed or systemic therapy.
- Sorafenib should not be used as adjuvant therapy post-ablation.
- All tumors irrespective of location may be amenable to arterially directed therapies provided that the arterial blood supply to the tumor may be isolated without excessive non-target treatment.
- All arterially directed therapies are relatively contraindicated in patients with bilirubin >3 mg/dL unless segmental injections can be performed. RE with yttrium-90 microspheres has an increased risk of radiation-induced liver disease in patients with bilirubin over 2 mg/dL.
- Arterially directed therapies in highly selected patients have been shown to be safe in the presence of limited tumor invasion of the portal vein.
- The angiographic endpoint of embolization may be chosen by the treating physician.
- Sorafenib may be appropriate following arterially directed therapies in patients with adequate liver function once bilirubin returns to baseline if there is evidence of residual/recurrent tumor not amenable to additional local therapies. The safety and efficacy of the use of sorafenib concomitantly with arterially directed therapies has not been associated with significant benefit

in two randomized trials' other randomized phase III trials are ongoing to further investigate combination approaches.

Hepatic Metastases from Colorectal Tumors

The version 3.2024 NCCN guidelines for Colon Cancer and the Version 4.2024 NCCN guidelines for Rectal Cancer recommend ablative techniques alone or in conjunction with resection for colorectal liver metastases as long as all sites of disease are amenable to ablation or resection.[5,55]

Hepatic Metastases from Neuroendocrine Tumors

The Version 4.2024 NCCN evidence-based clinical practice guideline for neuroendocrine tumors state, "cytoreductive 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).[3]

Bridge Therapy

The Version 3.2024 NCCN evidence-based clinical practice guideline for hepatobiliary carcinoma recommended HCC patients who were candidates for liver transplantation be considered for bridge therapy as indicated. The guideline also states, "a number of studies have investigated the role of locoregional therapies as a bridge to liver transplantation in patients on a waiting list…[However], the small size of these studies and the heterogeneous nature of the study populations, as well as the absence of RCTs evaluating the utility of bridge therapy for reducing the liver transplantation waiting list drop-out rate, limited the conclusions that can be drawn. Nevertheless, the use of bridge therapy in this setting is increasing, and it is administered at some NCCN Member Institutions."[15]

American College of Radiology (ACR)

The 2022 evidence-based ACR Appropriateness Criteria® for the radiologic management of hepatic malignancy gave the following recommendations:[56]

- Management of hepatic malignancies can be complex because it encompasses of variety of primary and metastatic malignancies and an assortment of local and systemic treatment options.
- Resection and transplantation remain the best option for cure in properly selected patients for primary malignancy as well as secondary malignancy in some limited scenarios; however, the role of RFA and potentially SBRT as primary treatment options are worthy of future research.
- The choice between percutaneous ablative techniques and arterial methods will vary from institution to institution depending on operator expertise. However thermal ablative techniques are more commonly performed over nonthermal ablative techniques because of superior control and efficacy.
- Combining ablative and arterial treatments may yield better outcomes than arterial treatments alone.
- Due to the development and refinement of a wide range of therapies, particularly for secondary hepatic malignancies, protocols focusing on the proper combination and sequence of treatments may benefit from reexamination.[56]

EVIDENCE SUMMARY

Surgical resection of primary or metastatic liver lesions offers the best chance for increased survival or cure. However, only about 20% of liver cancer patients are surgical candidates. Although the evidence does not indicate ablative therapies are superior to surgical resection, they are frequently the only option to extend survival in liver cancer patients.

Although the evidence regarding liver transplant bridge therapy is limited, both the National Comprehensive Cancer Network and Organ Procurement and Transplantation Network consider ablative and arterially directed therapies as an option for bridging liver cancer patients to transplant.

National Comprehensive Cancer Network (NCCN) clinical practice guideline recommends locoregional therapy in hepatocellular carcinoma patients who are not candidates for surgical treatment, or as part of a bridge to liver transplant. For the treatment of unresectable intrahepatic cholangiocarcinoma, the NCCN recommends arterially directed therapies. The NCCN recommends ablative techniques for unresectable colorectal liver metastases, or arterially directed therapies in chemotherapy resistant patients. For liver metastases from neuroendocrine tumors, NCCN recommends ablative therapies if near-complete treatment of tumor burden can be achieved and arterially directed therapy for unresectable liver metastases.

Although the evidence regarding the treatment of breast cancer liver metastasis (BCLM) is limited, there are studies indicating the safety of the procedure. However, small studies have shown that RFA in select patients could result in prolonged survival. Therefore, RFA in patients without extrahepatic disease, aside from stable bone metastasis, may be medically necessary.

There is insufficient evidence to support the use of ablation or histotripsy for the treatment of hepatic metastases from melanoma (cutaneous or uvela/conjunctival). Large, randomized controlled trials with long-term follow-up are needed to establish the efficacy, safety, and medical necessity of these procedures.

There is insufficient evidence to conclude high-intensity focused ultrasound (HIFU) or magnetic resonance guided focused ultrasound (MRgFUS) is efficacious for the treatment of liver tumors. No evidence was identified that assessed the clinical utility of 3D contour simulation of target liver lesion(s) and margin(s) ablation or simulation angiogram with use of pressure-generating catheter. Additional high-quality studies are required in order to establish the effectiveness and safety of these treatment modalities. Furthermore, HIFU and MRgFUS do not have FDA-approval for the treatment of liver tumors; therefore, this would be considered an off-label use of the device. Therefore, high-intensity focused ultrasound (HIFU) or magnetic resonance guided focused ultrasound (MRgFUS) for the treatment of liver tumors is considered not medically necessary.

HEALTH EQUITY CONSIDERATIONS

The Centers for Disease Control and Prevention (CDC) defines health equity as the state in which everyone has a fair and just opportunity to attain their highest level of health. Achieving health equity requires addressing health disparities and social determinants of health. A health disparity is the occurrence of diseases at greater levels among certain population groups more than among others.

Health disparities are linked to social determinants of health which are non-medical factors that influence health outcomes such as the conditions in which people are born, grow, work, live, age, and the wider set of forces and systems shaping the conditions of daily life. Social determinants of health include unequal access to health care, lack of education, poverty, stigma, and racism.

The U.S. Department of Health and Human Services Office of Minority Health calls out unique areas where health disparities are noted based on race and ethnicity. Providence Health Plan (PHP) regularly reviews these areas of opportunity to see if any changes can be made to our medical or pharmacy policies to support our members obtaining their highest level of health. Upon review, PHP creates a Coverage Recommendation (CORE) form detailing which groups are impacted by the disparity, the research surrounding the disparity, and recommendations from professional organizations. PHP Health Equity COREs are updated regularly and can be found online here.

BILLING GUIDELINES AND CODING

CODES*		
CPT	0686T	Histotripsy (i.e., non-thermal ablation via acoustic energy delivery) of malignant hepatocellular tissue, including image guidance
	0944T	3D contour simulation of target liver lesion(s) and margin(s) for image-guided percutaneous microwave ablation
	47370	Laparoscopy, surgical, ablation of 1 or more liver tumor(s); radiofrequency
	47371	Laparoscopy, surgical, ablation of 1 or more liver tumor(s); cryosurgical
	47380	Ablation, open, of 1 or more liver tumor(s); radiofrequency
	47381	Ablation, open, of 1 or more liver tumor(s); cryosurgical
	47382	Ablation, 1 or more liver tumor(s), percutaneous, radiofrequency
	47383	Ablation, 1 or more liver tumor(s), percutaneous, cryoablation
	47399	Unlisted procedure, liver
	47379	Unlisted laparoscopic procedures on the liver
	77799	Unlisted procedure, clinical brachytherapy
HCPCS	C2616	Brachytherapy source, non-stranded, yttrium-90, per source
	C2698	Brachytherapy source, stranded, not otherwise specified, per source
	C2699	Brachytherapy source, non-stranded, not otherwise specified, per source
	C8004	Simulation angiogram with use of a pressure-generating catheter (e.g., one-way valve, intermittently occluding), inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the angiogram, for subsequent therapeutic radioembolization of tumors
	C9734	Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (mr) guidance
	E0767	Intrabuccal, systemic delivery of amplitude-modulated, radiofrequency electromagnetic field device, for cancer treatment, includes all accessories
	Q3001	Radioelements for brachytherapy, any type, each

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
2/2024	Annual review. Noncoverage position updated from investigational to NMN.
3/2024	Interim update. Remove criterion III.A.1.b for TACE treatment in hepatocellular carcinoma.
4/2024	Q2 2024 code set update.
10/2024	Q3 2024 code set update. New “not medically necessary” indication added.
12/2024	Annual update. Removed criterion.
1/2025	Q1 2025 code set update.
4/2025	Interim update and Q2 2025 code set update. Changes to criteria and coding.
5/6/2025	Interim update. Remove embolization, which will be addressed by Carelon.