


MEDICAL POLICY	Liver Tumor Treatment (All Lines of Business Except Medicare)
Effective Date: 12/1/2021  12/1/2021	Medical Policy Number: 151 Technology Assessment Committee Approved Date: 10/10; 12/13; 12/14; 1/15; 1/16; 3/17 Medical Policy Committee Approved Date: 6/05; 7/06; 5/08; 3/09; 11/09; 12/10; 6/2011; 3/12; 6/13; 10/17; 12/18; 9/19; 5/2020; 10/2020; 11/2021
Medical Officer Date	

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

SCOPE:

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

APPLIES TO:

All lines of business except Medicare

BENEFIT APPLICATION

Medicaid 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.

POLICY 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 and covered** 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.-c.) 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.-v.) 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; **and**
 - v. All tumor foci are amenable to ablative therapy and the goal of therapy is long term control with complete ablation; **or**
 - 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**
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 and are not covered** for the treatment of liver tumors when criterion I. above is not met.

Transarterial Chemoembolization (TACE)

- III. Transarterial chemoembolization (TACE) may be considered **medically necessary and covered** when **at least one** of the following (A. or B.) criteria are met:
- A. The patient is **not** currently awaiting liver transplantation **and** meets **at least one** of the following (1.-3.) criteria:
 1. The patient has been diagnosed with hepatocellular carcinoma confirmed by biopsy and/or imaging and meets **all** of the following (a.-d.) criteria:
 - a. There is clinical documentation that surgical resection is not feasible; **and**
 - b. The tumor(s) is classified as intermediate stage (measured using the BCLC Staging and Treatment Strategy); **and**

- c. The tumor(s) is confined to the liver; **and**
 - d. There is no portal vein tumor invasion; **or**
 2. The patient has been diagnosed with hepatic metastases from neuroendocrine tumors confirmed by biopsy and/or imaging and meets **all** of the following (a.-c.) criteria:
 - a. There is clinical documentation that surgical resection is not feasible; **and**
 - b. The metastatic tumor(s) is ≤ 5 cm; **and**
 - c. Tumor related symptoms (e.g., carcinoid syndrome) are refractory to medical treatment (e.g., somatostatin analogs); **or**
 3. The patient has been diagnosed unresectable intrahepatic cholangiocarcinoma confirmed by biopsy and/or imaging; **or**
 - B. The patient is approved and listed for a liver transplant, and TACE is intended to prevent further tumor growth while waiting for a transplant to become available.
- IV. Transarterial chemoembolization (TACE) is considered **not medically necessary and is not covered** for the treatment of liver tumors when criterion III. above is not met.

Radioembolization

- V. Radioembolization (i.e., yttrium [Y-90], selective internal radiation therapy [SIRT]) may be considered **medically necessary and covered** when **at least one** of the following criteria (A. or B.) is met:
- A. The patient is **not** currently awaiting liver transplantation and meets **at least one** of the following (1.-4.) criteria:
 1. The patient has been diagnosed with hepatocellular carcinoma confirmed by biopsy and/or imaging **and** surgical resection is not feasible; **or**
 2. The patient has been diagnosed with hepatic metastases from colorectal tumors confirmed by biopsy and/or imaging and meets **all** of the following (a.-c.) criteria:
 - a. There is clinical documentation that surgical resection is not feasible; **and**
 - b. The patient has predominant hepatic metastases; **and**
 - c. The tumor(s) is chemotherapy-resistant/refractory; **or**
 3. The patient has been diagnosed with hepatic metastases from neuroendocrine tumors confirmed by biopsy and/or imaging and meets **all** of the following (a.-c.) criteria:
 - a. There is clinical documentation that surgical resection is not feasible; **and**
 - b. The patient has predominant hepatic metastases and is symptomatic; **and**
 - c. Tumor related symptoms (e.g., carcinoid syndrome) are refractory to medical treatment (e.g., somatostatin analogs); **or**
 4. The patient has been diagnosed with unresectable intrahepatic cholangiocarcinoma confirmed by biopsy and/or imaging; **or**
 - B. The patient is approved and listed for a liver transplant, and radioembolization is intended to prevent further tumor growth while waiting for a transplant to become available.

- VI. Radioembolization (i.e., yttrium [Y-90], selective internal radiation therapy [SIRT]) is considered **not medically necessary and is not covered** for the treatment of liver tumors when criterion V. above is not met.

Combination Therapy: Radiofrequency Ablation + Transarterial Chemoembolization

- VII. Combination therapy using both radiofrequency ablation (RFA) and transcatheter arterial chemoembolization (TACE) may be considered **medically necessary and covered** when **all** of the following criteria are met:
- A. The patient has been diagnosed with hepatocellular carcinoma confirmed by biopsy and/or imaging; **and**
 - B. There is clinical documentation that surgical resection is not feasible; **and**
 - C. The tumor(s) is 3 cm to 5 cm; **and**
 - D. The tumor(s) are in an accessible location for percutaneous, laparoscopic, or open approaches for ablation.
- VIII. Combination therapy using both radiofrequency ablation (RFA) and transcatheter arterial chemoembolization (TACE) is considered **not medically necessary and is not covered** for the treatment of liver tumors when criterion VII. above is not met.

Repeat Therapies

- IX. Repeat therapies using ablation, transarterial chemoembolization, or radioembolization may be considered **medically necessary and covered** when the original treatment criteria above are met.

Investigational Therapies

- X. Ablation, transarterial chemoembolization, or radioembolization for the treatment of hepatic metastases from melanoma (cutaneous or uveal/conjunctival) is considered **investigational and is not covered**.
- XI. Transarterial chemoembolization, or radioembolization for the treatment of hepatic metastases from breast cancer, regardless of the presence of extrahepatic disease, is considered **investigational and is not covered**.
- XII. 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 **investigational and is not covered**.

Link to [Policy Summary](#)

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POLICY GUIDELINES

Performance Scales

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.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	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

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

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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)

BILLING GUIDELINES

A code from the range 36245-36248 for catheter placement would be billed in conjunction with 37243. Code 75726 may also be billed if diagnostic angiography is performed prior to 37243 and the decision to perform embolization was based on this angiography.

Vascular embolization or occlusion (37243) only requires prior authorization when paired with any of the following diagnosis codes for liver malignancy:

- C22.0
- C22.1
- C22.2
- C22.3
- C22.4
- C22.7
- C22.8
- C22.9
- C78.7
- C7B.02
- D01.5

CPT/HCPCS CODES

All Lines of Business	
Prior Authorization Required	
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
C9734	Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (mr) guidance
Q3001	Radioelements for brachytherapy, any type, each
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

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47383	Ablation, 1 or more liver tumor(s), percutaneous, cryoablation
<p>Prior Authorization Required</p> <p><u>Note:</u> The following code requires prior authorization only when billed with a diagnosis code for liver malignancy.</p>	
37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
<p>Unlisted Codes</p> <p>All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then prior-authorization is required.</p>	
47399	Unlisted procedure, liver
47379	Unlisted laparoscopic procedures on the liver
77799	Unlisted procedure, clinical brachytherapy

DESCRIPTION

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 include⁶:

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

Intrahepatic Cholangiocarcinoma (ICC)

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."⁷ ICC is a silent disease that begins in the smaller bile duct and branches inside the liver.⁸ 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."⁹ 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.¹⁰ 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.¹¹ 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.

Transarterial Chemoembolization (TACE)

The TACE procedure “involves injection of chemotherapy agents and occluding substances into the hepatic arteries that supply blood to tumors.”¹² The goals of this technique are to (1) deliver chemotherapy directly to the tumor in order to avoid the side effects of traditional chemotherapy and (2) cut off the blood supply to the tumor. In order to cut off the blood supply, special embolization beads are sent to the tumor. These beads contain the chemotherapy agents, which are released slowly over time.

Radioembolization (i.e., Yttrium [Y-90], Selective Internal Radiation Therapy [SIRT])

Radioembolization (i.e., Yttrium [Y-90], Selective Internal Radiation Therapy [SIRT]) is a “minimally invasive procedure that combines embolization and radiation therapy to treat liver cancer.”¹³ Small beads filled with the radioactive isotope yttrium Y-90 are placed inside the blood vessels that feed the tumor. These beads then block the supply of blood to the cancer cells and deliver a high dose of radiation directly to the tumor.

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

Investigational TherapiesHigh-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.

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of ablative therapies, transarterial chemoembolization, and radioembolization as a treatment for primary and metastatic liver tumors. Below is a summary of the available evidence identified through October 2021.

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 2016, Lan et al. conducted a systematic review and meta-analysis to compare the efficacy of interventional therapies for early-stage HCC.¹⁸ 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.”¹⁸

Ablative Therapies

Hepatocellular Carcinoma (HCC)

- In 2020, Lee and colleagues conducted a systematic review and meta-analysis comparing radiofrequency ablation (RFA) and stereotactic body radiotherapy (SBRT) for liver malignancies.¹⁹ 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.²⁰ 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).²¹ 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 ($\leq 3\text{cm}$) 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.²² 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.²³ 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)."²³ 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).²⁴ 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.”²⁴

- In 2009, Cho and colleagues conducted a systematic review and meta-analysis of randomized trials to evaluate hepatocellular carcinoma treated with percutaneous ablation therapies.²⁵ Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The primary outcome of interest was survival benefit of any percutaneous ablation therapy compared with percutaneous ethanol injection (PEI). Secondary outcomes included initial tumor response, local tumor progression, and complications.

The authors identified 4 randomized controlled trials as eligible for inclusion, giving a total sample size of 652 patients. The 3-year survival rate of PEI patients ranged from 48% to 67% while the RFA treated survival rate ranged from 63% to 81%. “A meta-analysis of the four RCTs demonstrated a significant improvement in 3-year survival favoring RFA over PEI (odds ratio 0.477, 95% confidence interval 0.340-0.670; P < 0.001). Heterogeneity among the four trials was not significant (Q = 4.586; P= 0.205). Egger's test revealed that the publication bias was not significant (P = 0.647).”²⁵ No statistically significant differences were identified for the outcome of initial tumor response. Meta-analysis was not possible for local tumor progression or adverse events due to significant heterogeneity between studies.

Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers and the assessment of heterogeneity prior to conducting meta-analyses. A significant limitation of this study is the potential for publication bias due to the small number of included studies. The authors also noted that insufficient data in some selected studies limited their ability to perform quantitative analysis. Ultimately, the authors

concluded, “despite many potential limitations, RFA showed an improved 3-year overall survival status for patients with small HCCs compared with PEI.”²⁵

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.¹⁹ 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).²⁶ 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, $P<0.001$).”²⁶

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.”²⁶

Hepatic Metastases from Neuroendocrine Tumors

In 2015, Mohan and colleagues conducted a systematic review to evaluate radiofrequency (RF) ablation for neuroendocrine (NET) liver metastases.²⁷ 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.”²⁷

Transarterial Chemoembolization (TACE)

Hepatocellular Carcinoma (HCC)

- Several recent systematic reviews and meta-analyses evaluated the safety and efficacy of TACE for the treatment of hepatocellular carcinoma.²⁸⁻³¹ Each study reported comparable or improved overall survival rates for TACE patients relative to patients receiving alternative therapies, but called for additional high-quality studies to further validate findings.
- In 2019, Lu et al. conducted a Cochrane systematic review and meta-analysis to evaluate transcatheter arterial chemoembolization (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus transcatheter arterial chemoembolization alone for primary hepatocellular carcinoma in adults.³² Independent reviewers systematically searched the literature through May 2018, identified eligible studies, assessed quality, and extracted data. In total, 8 RCT's were included for review, evaluating 632 patients. Follow-up duration was 12 months (range: 2 months to 38 months). Results from studies assessed as “low-quality” indicated that TACE plus 3-DCRT may have reduced all-cause mortality at 3-years' follow-up (RR 0.80, 95% CI 0.73 to 0.88). TACE followed by 3-DCRT compared with TACE alone may have reduced the proportion of participants without tumor response (complete response plus partial response) (RR 0.49, 95% CI 0.39 to 0.61). One trial reported improved quality of life for the TACE plus 3-DCRT group compared to patients receiving TACE alone, but data were ill-defined. Limitations included a lack of sub-group analysis due to insufficient data and a lack of reported protocol in included studies. Authors concluded that TACE plus 3-DCRT may be associated with lower all-cause mortality and increased tumor response, but noted that findings should be interpreted cautiously given weaknesses in

included trials. Investigators called for additional RCTs to further assess the role of TACE plus 3-DCTR for unresectable hepatocellular carcinoma.

- In 2011, Oliveri et al. conducted a Cochrane systematic review and meta-analysis to evaluate transarterial (chemo)embolization (TAE or TACE) for unresectable hepatocellular carcinoma.³³ 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 outcomes of interest were survival and tumor response.

After systematic review, the authors identified 9 randomized controlled trials giving a total sample size of 645 participants. Of the nine studies, 6 evaluated TACE versus control and 3 evaluated TAE versus control. The authors deemed 7 trials to be of low risk for selection bias; however, all included trials had other risks of bias. “Meta-analysis of trials with low risk of selection bias showed that TACE or TAE versus control does not significantly increase survival (HR 0.88; 95% CI 0.71 to 1.10).”³³ The authors also performed trial sequential analysis which indicated an absence of evidence for a beneficial effect of TACE or TAE on survival. In regards to tumor response, meta-analysis was not possible due to substantial heterogeneity between studies for this outcome.

Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers and the assessment of heterogeneity prior to conducting meta-analyses. A significant limitation of this study is the potential for publication bias due to the small number of included studies. The authors also noted incomplete data reporting in three trials due to early study termination. Ultimately, the authors concluded, “(t)here is no firm evidence to support or refute TACE or TAE for patients with unresectable HCC. More adequately powered and bias-protected trials are needed.”³³

Hepatic Metastases from Neuroendocrine Tumors

No systematic reviews or randomized controlled trials were identified that evaluated transarterial chemoembolization (TACE) for hepatic metastases from neuroendocrine tumors. Therefore, the evidence summary will be limited to nonrandomized studies.

A total of six nonrandomized studies (3 prospective studies and 3 retrospective studies) were identified evaluating TACE for hepatic metastases from neuroendocrine tumors.³⁴⁻³⁹ Sample sizes ranged from 19 patients to 248 patients, and follow-up times for the prospective studies varied from 2 to 5 years. Overall, all studies concluded that TACE resulted in improvements for symptom control and time to progression for patients with hepatic metastases from neuroendocrine tumors.

Intrahepatic Cholangiocarcinoma

- In 2019, Yousaf and colleagues published a systematic review and meta-analysis on the efficacy of ablative therapy for unresectable intrahepatic cholangiocarcinoma.⁴⁰ 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).⁴¹ 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.”⁴¹

Radioembolization (i.e., Yttrium [Y-90], Selective Internal Radiation Therapy [SIRT])

Hepatocellular Carcinoma (HCC)

- In 2020, a Cochrane review was published on Yttrium-90 (Y-90) microsphere radioembolization for unresectable hepatocellular carcinoma.⁴² Six randomized trials met inclusion criteria with 1340 participants in total. Cochrane found that all trials were at high risk of bias and the certainty of evidence was low to very low.

One trial compared radioembolization plus sorafenib versus sorafenib alone in people with advanced HCC, only reporting on adverse events. Serious adverse events were reported in 39.6% of participants in the radioembolization plus sorafenib group and 38.5% in the sorafenib only group. Two trials compared radioembolization versus sorafenib for locally advanced, unresectable HCC. One-year, all-cause mortality was 62.7% in the radioembolization group versus 53.0% in the sorafenib group. There were no differences in quality of life and global health status was better in the radioembolization group. Fewer participants in the radioembolization group experienced serious adverse events compared to the sorafenib group. Three trials compared radioembolization versus

chemoembolization in people with intermediate-stage HCC. There were no differences in relative risk of serious events and quality of life. Median time to progression was not reached in the radioembolization group and was 6.8 months in the chemoembolization group, although the difference was not significant.

Overall, Cochrane reviewers found the current evidence for radioembolization compared to sorafenib or chemoembolization highly insufficient. Many of the trials did not report on patient-centered outcomes and had short follow up time. The authors stated, “Further high-quality placebo-controlled randomised clinical trials are needed to assess patient-centred outcomes.”

- In 2019, Yang and colleagues conducted a systematic review and meta-analysis evaluating the safety and efficacy of yttrium-90 transarterial radioembolization (TARE) versus conventional transarterial chemoembolization (cTACE) for the treatment of hepatocellular carcinoma.⁴³ Independent investigators systematically searched the literature through July 2017, identified eligible studies, assessed study quality, extracted data and pooled results. In total, 11 studies were included for review (9 observational studies and 2 RCTs) (n=1,652). Results indicated that TARE 90Y increased 2-year overall survival rates in the observational subgroup and resulted in better odds ratio rates compared to cTACE patients. Limitations included a lack of randomized trials included for review, significant heterogeneity in study protocol and patient populations. Investigators called for additional, large RCTs to confirm the validity of results and the overall safety and efficacy of cTACE and TARE (90Y).
- In 2019, Hayes conducted an evidence review to evaluate radioactive yttrium-90 microspheres (i.e., radioembolization) for the treatment of primary unresectable liver cancer (i.e., hepatocellular carcinoma [HCC]).⁴⁴ The evidence review identified 18 studies (15 retrospective comparative studies, 2 RCTs and 1 nonrandomized controlled studies) of adult patients undergoing transarterial radioembolization (TARE) with ⁹⁰Y. Sample sizes ranged from 48 to 790 patients, and follow-up times varied from 6 to 53 months. The outcome measures of interest were survival, tumor response, time-to-progression, hospitalization, and safety. The quality of evidence for 90Y-Tare was assessed as “low.” Hayes review found consistent evidence that TARE has comparable efficacy on survival outcomes, potentially superior efficacy on tumor response and better tolerance relative to TACE in intermediate HCC. Studies reported comparable findings between TAR with sorafenib and other groups regarding survival and tumor progression outcomes. In regards to safety, the proportion of patients experience any complication with TARE, TACE, DEB-TACE, or sorafenib ranged from 10% to 59%, 48.6% to 70%, 14% to 34% and 84.6% to 94% respectively. “The predominant complications associated with TARE were lymphopenia; fatigue; abdominal pain, discomfort, or cramping; fever; postembolization syndrome; and nausea and/or vomiting.”⁴⁴ Hayes assigned a “C” rating (potential but unproven benefit) for 90Y hepatic radioembolization compared with TACE in patients who are diagnosed with unresectable primary HCC. Hayes also assigned a “C” rating for 90y hepatic radioembolization compared with sorafenib. Hayes assigned “D2” ratings (insufficient evidence) for 90Y hepatic radioembolization compared with both drug-eluting bead TACE and resin microspheres.⁴⁴

Hepatic Metastases from Colorectal Tumors

In 2015 (archived in 2020), Hayes conducted an evidence review to evaluate radioactive yttrium-90 microspheres (i.e., radioembolization) for the treatment of secondary liver cancer.⁴⁵ The evidence review identified 17 studies (2 randomized controlled trials, 1 comparative prospective study, 8 noncomparative prospective studies, 1 comparative retrospective study, 5 noncomparative retrospective studies, and 2 subanalyses) of adult patients undergoing transarterial radioembolization (TARE) with ⁹⁰Y for liver-predominant metastases. Sample sizes ranged from 42 to 390, and follow-up times varied from 7 months to 5 years. The outcome measures of interest were survival, tumor response, time to progression, and safety.

Although limited, the Hayes review found evidence in favor of TARE over standard care and ⁹⁰Y with an intra-arterial chemotherapeutic agent over an intra-arterial chemotherapeutic agent alone. Median survival rates ranged from 7.5 months to 28 months in ⁹⁰Y-treated patients, while median survival in the comparator groups ranged from 6.3 months to 7.3 months. Tumor response rates varied from 0% to 17% complete response, 10% to 60.5% partial response, 4.8% to 76% stable disease, and 4.9% to 71.4% progressive disease. Median time to progression ranged from 2.8 to 15.4 months. In regards to safety, all studies reported toxicities or complications related to ⁹⁰Y. "Predominate complications included: abdominal pain, discomfort, or cramping; fatigue; nausea and/or vomiting; fever; alkaline phosphatase (ALP) related; bilirubin related; gastric ulceration; alanine aminotransferase (ALT)/aspartate aminotransferase (AST) related; ascites; gall bladder related; and radiation hepatitis."⁴⁵

Although Hayes rated the quality of evidence as very low, a C rating was given "for the use of yttrium-90 (90Y) radioembolization, using either glass (TheraSphere) or resin (SIR-Spheres) microspheres, for performing selective internal radiation therapy in patients with unresectable hepatic metastases from colorectal cancer." A "D2" rating (insufficient evidence) was assigned for 90Y hepatic radioembolization for patients diagnosed with unresectable hepatic metastases from noncolorectal cancer.⁴⁵

Hepatic Metastases from Neuroendocrine Tumors

- In 2018, Jia and colleagues conducted a systematic review evaluating the efficacy of 90Y radioembolization for the treatment of unresectable metastatic neuroendocrine liver tumors.⁴⁶ Independent reviewers systematically searched the literature through February 2016 identified eligible studies, assessed quality, and extracted data. Outcomes of interest were survival rate and tumor response. Median follow-up was 25 months. In total, 11 studies and 7 abstracts were included for review, assessing 870 patients. 11 of these 18 studies, nearly 20% of patients had undergone either transarterial bland embolization (TABE) or TACE prior to 90Y therapy. At three months' follow-up post-90Y treatment, the median disease control rate among all patients was 86%. The median survival was 28 months, with 1-, 2-, and 3-year survival rates of 72.5%, 57% and 45% respectively. Limitations included the limited quantity and quality of reviewed studies, heterogeneous patient selection and treatment regimes, and inadequate follow-up. Nonetheless, investigators concluded that 90Y radioembolization is an effective treatment of unresectable liver metastases of neuroendocrine tumors, regardless of patients' previous exposure to TABE/TACE therapy.

- In 2014, Devcic and colleagues conducted a systematic review and meta-analysis to evaluate the efficacy of hepatic 90Y resin radioembolization for metastatic neuroendocrine tumors (mNET).⁴⁷ Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The primary outcomes of interest were tumor response and survival.

After systematic review, the authors identified 12 studies (6 retrospective, 3 prospective, 1 prospectively collected but retrospectively reviewed, and 2 did not specify). This gave a total of 435 procedures in 414 patients with response data. A critical appraisal of the selected studies identified a median of 75% of the desired criteria included. Disease control rates (defined as complete response, partial response plus stable disease) ranged from 62% to 100%, with the average being 86% (95% CI 78%-92%). The radiographic response rates (defined as complete response plus partial response) ranged from 12% to 80%, with the average being 50% (95% CI 38%-62%). "The median OS ranged from 14 up to 70 months, with a median of 28.5 months (95% confidence interval, 18–49.5 months)."⁴⁷

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. Ultimately, the authors concluded "this meta-analysis confirms radioembolization to be an effective treatment option for patients with hepatic mNET. The pooled data demonstrated a high response rate and improved survival for patients responding to therapy."⁴⁷

Intrahepatic Cholangiocarcinoma

In 2015, Al-Adra et al. conducted a systematic review and meta-analysis to evaluate yttrium-90 radioembolization as a treatment of unresectable intrahepatic cholangiocarcinoma.⁴⁸ 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 outcomes of interest were overall survival (OS) and radiological response to radioembolization therapy with yttrium-90 microspheres. The secondary outcomes of interest were the ability of yttrium-90 treatment to convert unresectable cholangiocarcinoma to resectable, mortality, and morbidity.

Following systematic review, the authors identified 12 studies (7 prospective case series and 5 retrospective cohort studies) as eligible for inclusion; thus giving a total sample size of 298 patients. The overall weighted median survival was 15.5 months (range: 7-22.2 months). In regards to radiological response of the tumors, a weighted mean partial response was seen in 28% of patients and stable disease was seen in 54% of patients at 3 months. Of the 3 studies (n=73 patients) that evaluated the ability of yttrium-90 radioembolization to convert unresectable to resectable disease, 7 patients were able to undergo surgical resection post-radioembolization. A total of 3 studies reported mortality data, of which, there was 1 radioembolization-related death. The most common complications reported after radioembolization therapy was fatigue (33%), abdominal pain (28%), and nausea (25%).

Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers, assessment of heterogeneity prior, and assessment of publication bias. Although possibly attributable to the rarity of intrahepatic cholangiocarcinoma, the

study is limited by the small number of patients included in the review. Limitations were also identified in the small number of included studies (possible publication bias) and the poor methodological quality of selected studies. The authors concluded, “overall survival of patients with ICC after treatment with yttrium-90 microspheres is higher than historical survival rates and shows similar survival to those patients treated with systemic chemotherapy and/or trans-arterial chemoembolization therapy. Therefore, the use of yttrium-90 microspheres should be considered in the list of available treatment options for ICC. However, future randomized trials comparing systemic chemotherapy, TACE and local radiation will be required to identify the optimal treatment modality for unresectable ICC.”⁴⁸

Combination Therapy: Radiofrequency Ablation + Transarterial Chemoembolization

In 2012 (archived in 2018), Hayes conducted an evidence review to evaluate transarterial chemoembolization (TACE) plus radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC).¹² The review identified 13 studies (4 randomized controlled trials, 8 retrospective cohort studies, and 1 retrospective case-matched controlled trial) evaluating TACE plus RFA for HCC. A majority of the included studies enrolled patients with small- to intermediate-size tumors, and did not include any patients with hepatic metastases. The sample sizes of the nonrandomized studies ranged from 103 to 1,126 patients. The sample sizes of the randomized studies ranged from 37 to 139 patients.

Of the selected studies, “seven evaluated TACE combined with RFA versus RFA alone for HCC, and six of these studies found that use of the combined therapy provided statistically significant improvements in tumor control, patient survival, or both measures.”¹² A total of five studies evaluated TACE combined with RFA versus TACE alone, and four of these studies found that RFA+TACE resulted in statistically significant improvements in patient survival, tumor recurrence, or both. The results were inconclusive for TACE combined with RFA versus surgical resection. In regards to safety, the most common complications of TACE combined with RFA included pain (5% to 72% of patients), fever (30% to 39%), and vomiting (30%).

The Hayes evidence review rated the body of evidence for TACE combined with RFA for treating HCC as large in size and moderate in quality. Limitations were identified in the lack of randomization, incomplete reporting of outcomes, incomplete statistical analysis, no reporting of complications, and unequal duration of follow-up between treatment groups. Hayes assigned the following ratings:

- “B – For TACE combined with RFA as a treatment for HCC in patients with small- to intermediate-size tumors who are not candidates for surgery.
- D2 – For TACE combined with RFA as a treatment for HCC in patients who are suitable candidates for surgery. This Rating reflects the limited number, poor quality, and divergent results of studies comparing these modalities.
- D2 – For TACE combined with RFA as a treatment for hepatic metastases of colorectal cancer or other types of cancer. This Rating reflects the absence of controlled studies evaluating TACE combined with RFA for these indications.”¹²

Bridge to Transplant

- In 2019 (updated in 2021), 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.⁴⁹⁻⁵⁵ 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.⁵⁶ 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.”⁵⁶

- In 2017, the OPTN Liver & Intestinal Organ Transplantation Committee released a board approved policy update proposal that states, “(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.”⁵⁷

Investigational TherapiesHepatic Metastases from Melanoma

There is insufficient evidence to support the use of ablation, transarterial chemoembolization, or radioembolization 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.

Hepatic Metastases from Breast Cancer

- In 2020, Feretis and Solodkyy conducted a systematic review on the efficacy of yttrium-90 (Y-90) as a treatment for unresectable hepatic metastases of breast cancer.⁵⁸ A systematic literature search was conducted for publications between January 2007 and December 2018. Twelve studies with 452 participants total were included in the review. No randomized trials were identified. Only 4 trials clearly reported follow up period timelines, which ranged from 6 months to 15.7 months. From the available data, complete response rate occurred in 8.2% of participants, partial response occurred in 30.8%, and stable disease occurred in 26%, totalling to 77% of patients deemed to have achieved disease control. Overall survival, which was reported in 9 studies, ranged from 3.6 to 20.9 months with a mean survival of 11.3 months. Limitations of this study include the lack of randomized trials, the high heterogeneity between studies, the varied treatment protocols and lengths of follow up. The authors conclude that while there may be a potentially beneficial role of radio-embolization with Y-90 with inoperable liver metastases secondary to breast cancer, “future randomized trials are need comparing systemic chemotherapy, local radiation and transarterial chemoembolization in order to identify the most suitable treatment modality.... Standardization of the method that radioembolization is delivered by and the reporting systems used would be highly desirable.”
- 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.⁴⁵ 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.^{59,60} One recent systematic review evaluated TACE for the treatment of breast cancer with liver metastasis.⁶¹ While investigators concluded that TACE may improve patients’ overall survival, validity was limited by the low quantity and quality of studies included for review.

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

The evidence evaluating HIFU or MRgFUS for treatment of liver tumors is limited to nonrandomized studies and small case series.⁶²⁻⁶⁷ 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.

CLINICAL PRACTICE GUIDELINES

National Comprehensive Cancer Network (NCCN)

Hepatocellular Carcinoma

The Version 5.2021 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) and arterially directed therapies (e.g., transarterial chemoembolization, radioembolization):

- 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.

Intrahepatic Cholangiocarcinoma

The 2021 version 5.2021 NCCN evidence-based clinical practice guideline for hepatobiliary cancers recommend arterially directed therapies (e.g., transarterial chemoembolization, radioembolization) for the treatment of unresectable and metastatic intrahepatic cholangiocarcinoma.¹⁵

Hepatic Metastases from Colorectal Tumors

The version 3.2021 NCCN guidelines for Colon Cancer and the Version 2.2021 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.^{4,5} The guidelines also state, “arterially directed catheter therapy, and in particular yttrium 90 microspheres selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.”⁴

Hepatic Metastases from Neuroendocrine Tumors

The Version 3.2021 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). For unresectable liver metastases, hepatic regional therapy (arterial embolization, chemoembolization, or radioembolization [category 2B]) is recommended.”³

Bridge Therapy

The Version 5.2021 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 2007 (updated 2015) evidence-based ACR Appropriateness Criteria® for the radiologic management of hepatic malignancy gave the following recommendations:⁶⁸

- “Management of primary and secondary hepatic malignancy remains a complex issue due to the multitude of treatment options. For this reason, a multidisciplinary approach offers the best hope for optimal treatment with respect to any individual patient.
- 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.

- SIRT is likely as effective as TACE or TAE for both primary and secondary hepatic malignancy and is often better tolerated.
- The choice between percutaneous ablative techniques and arterial methods will vary from institution to institution depending on operator expertise.
- 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.⁶⁸

POLICY 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, transarterial chemoembolization (TACE), or radioembolization (RE) are superior to surgical resection, these therapies 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.

There is insufficient evidence to support the use of ablation, transarterial chemoembolization, or radioembolization for the treatment of hepatic metastases from melanoma (cutaneous or uvea/conjunctival) and breast cancer. Randomized controlled trials are needed to establish the efficacy, safety, and medical necessity of ablation, transarterial chemoembolization, or radioembolization for the treatment of hepatic metastases from melanoma (cutaneous or uvea/conjunctival) and breast cancer. Therefore, of ablation, transarterial chemoembolization, or radioembolization for the treatment of hepatic metastases from melanoma (cutaneous or uvea/conjunctival) and breast cancer is considered investigational.

There is insufficient evidence to concluded high-intensity focused ultrasound (HIFU) or magnetic resonance guided focused ultrasound (MRgFUS) is efficacious for the treatment of liver tumors. Additional high-quality studies are required in order to establish the effectiveness and safety of this treatment modality. 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 investigational.

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 Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days’ notice of policy changes that are restrictive in nature.

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.

REGULATORY STATUS

U.S. Food and Drug Administration (FDA)

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 ⁶⁹	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. ⁷⁰	<p>The ExAblate MRgFUS has been approved for the following indications:</p> <ul style="list-style-type: none"> • 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.

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	<p>The bone tumor to be treated must be visible on non-contrast MR and device accessible.</p> <ul style="list-style-type: none"> • 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.
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Mental Health Parity Statement

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.

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