

Embolization for Liver Tumors

MEDICAL POLICY NUMBER: 440

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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 (self-funded groups only)

☐ 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.

**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

This policy and the criteria therein only apply to self-funded employer groups. For all other commercial groups, please refer to the [Carelton Cardiovascular Guidelines](#).

Transarterial Chemoembolization (TACE)

- I. Transarterial chemoembolization (TACE) may be considered **medically necessary** when at **least one** of the following criteria are met:
 - A. The patient is **not** currently awaiting liver transplantation **and** meets **at least one** of the following criteria:
 1. The patient has been diagnosed with hepatocellular carcinoma 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 tumor(s) is confined to the liver; **and**
 - c. 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.
- II. Transarterial chemoembolization (TACE) is considered **not medically necessary** for the treatment of liver tumors when criterion II. above is not met.

Radioembolization

- III. Radioembolization (i.e., yttrium [Y-90], selective internal radiation therapy [SIRT]) may be considered **medically necessary** when **at least one** of the following criteria is met:
 - A. The patient is **not** currently awaiting liver transplantation and meets **at least one** of the following 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. Tumor-related symptoms (e.g., carcinoid syndrome) are refractory to medical treatment (e.g., somatostatin analogs); **and**
 - c. Any of the following are met (i.-iv.):
 - i. Symptomatic on a somatostatin analog (SSA) or following another form of systemic therapy; **or**
 - ii. Progressive on a somatostatin analog (SSA) or following another form of systemic therapy; **or**
 - iii. Presenting with bulky liver disease where embolization may be used as cytoreduction therapy without waiting for progression; **or**
 - 4. The patient has been diagnosed with unresectable intrahepatic cholangiocarcinoma confirmed by biopsy and/or imaging; **or**
 - 5. The patient has been diagnosed with hepatic metastases from well-differentiated neuroendocrine tumors with liver-dominant, unresectable metastases confirmed by biopsy and/or imaging.
 - 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.
- IV. 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 III. above is not met.

Combination Therapy: Radiofrequency Ablation + Transarterial Chemoembolization

- V. Combination therapy using both radiofrequency ablation (RFA) and transcatheter arterial chemoembolization (TACE) may be considered **medically necessary** 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.
- VI. Combination therapy using both radiofrequency ablation (RFA) and transcatheter arterial chemoembolization (TACE) is considered **not medically necessary** for the treatment of liver tumors when criterion V. above is not met.

Repeat Therapies

- VII. Repeat therapies using transarterial chemoembolization or radioembolization may be considered **medically necessary** when the original treatment criteria above are met.

Not Medically Necessary Therapies

- VIII. Transarterial chemoembolization or radioembolization for the treatment of hepatic metastases from melanoma (cutaneous or uveal/conjunctival) is considered **not medically necessary**.
- IX. Transarterial chemoembolization or radioembolization for the treatment of hepatic metastases from breast cancer, regardless of the presence of extrahepatic disease, is considered **not medically necessary**.

Link to [Evidence Summary](#)

POLICY CROSS REFERENCES

- Ablation for Liver Tumors (Company) MP151

The full Company portfolio of current Medical Policies is available online and can be [accessed here](#).

POLICY GUIDELINES

DOCUMENTATION REQUIREMENTS

In order to determine the medical necessity of the request, the following documentation must be provided at the time of the request. Medical records to include documentation of all of the following:

- All medical records and chart notes pertinent to the request. This includes:
 - History
 - Physical examination
 - Treatment plan

BACKGROUND

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.”¹ 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.”¹ 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.”² Examples of neuroendocrine tumors include:

- Carcinoid tumors
- Islet cell tumors (i.e., pancreatic endocrine tumors)
- Pheochromocytoma/paranglioma
- 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.”^{3,4} Types of cancer in the colon and rectum include⁵:

- 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.⁶ 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.

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.

Transarterial Chemoembolization (TACE)

The TACE procedure “involves injection of chemotherapy agents and occluding substances into the hepatic arteries that supply blood to tumors.”⁹ 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.”¹⁰ 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.”¹¹ 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.¹²

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.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of transarterial chemoembolization and radioembolization as a treatment for primary and metastatic liver tumors. Below is a summary of the available evidence identified through November 2025.

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.¹³ 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.¹⁴ 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.”¹⁴

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.¹⁵⁻¹⁸ 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.¹⁹ 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.²⁰ 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).”²⁰ 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.”²⁰

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.²¹⁻²⁶ 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.²⁷ 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).²⁸ 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.”²⁸

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.²⁹ 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 randomized clinical trials are needed to assess patient-centered 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.³⁰ 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, updated 2022, 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]).³¹ 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.”³¹ 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.³¹

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.³² 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.”³²

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.³²

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.³³ 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, Devic and colleagues conducted a systematic review and meta-analysis to evaluate the efficacy of hepatic 90Y resin radioembolization for metastatic neuroendocrine tumors (mNET).³⁴ 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)." ³⁴

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." ³⁴

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. ³⁵ A systematic literature search was conducted for publications between January 207 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."

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. ³⁶ 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.”³⁶

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).⁹ 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.”⁹ 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.”⁹

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.¹¹ 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.”¹¹
- 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.³⁷⁻⁴³ 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.”¹²
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.⁴⁴ 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.”⁴⁴
- In 2017, the OPTN Liver & Intestinal Organ Transplantation Committee released a board approved policy update proposal that states⁴⁵ “(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.”

Hepatic Metastases from Melanoma

There is insufficient evidence to support the use of 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.

- 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.³² 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.^{46,47} One recent systematic review evaluated TACE for the treatment of breast cancer with liver metastasis.⁴⁸ While investigators concluded that TACE may improve patients’ overall survival, validity was limited by the low quantity and quality of studies included for review.

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.”¹²

The guideline gives the following recommendations regarding arterially directed therapies (e.g., transarterial chemoembolization, radioembolization):

- Unresectable/inoperable lesions >5 cm should be considered for treatment using arterially directed or systemic therapy.
- 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.

Hepatocellular Carcinoma

The 2024 version 3.2024 NCCN evidence-based clinical practice guideline for hepatocellular carcinoma recommend arterially directed therapies (e.g., chemoembolization, radioembolization) for the treatment of unresectable and metastatic hepatocellular carcinoma.¹²

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). For unresectable liver metastases, hepatic regional therapy (arterial embolization, chemoembolization, or radioembolization [category 2B]) is recommended."² Authors stated that embolization is recommended for well-differentiated NETs with liver-dominant, unresectable metastases that are:

- Symptomatic on an SSA or following another form of systemic therapy;
- progressive on an SSA or following another form of systemic therapy;
- Presenting with bulky liver disease; embolization may be used as cytoreduction therapy without waiting for progression.

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."¹²

American College of Radiology (ACR)

The 2022 evidence-based ACR Appropriateness Criteria® for the radiologic management of hepatic malignancy gave the following recommendations:⁴⁹

- Management of hepatic malignancies can be complex because it encompasses a 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.⁴⁹

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 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.

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 at this time to support other liver treatments in patients with breast cancer as additional studies are needed to establish efficacy, safety, and medical necessity. This includes, but is not limited to, ablation techniques other than RFA, transarterial chemoembolization, or radioembolization. These procedures are considered not medically necessary.

HEALTH EQUITY CONSIDERATIONS

The Centers for Disease Control and Prevention (CDC) define 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

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

CODES*		
CPT	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
HCPCS	C9797	Vascular embolization or occlusion procedure with use of a pressure-generating catheter (e.g., one-way valve or occlusion balloon, intermittently or temporarily occluding), inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction

***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
5/6/2025	New policy
1/2026	Annual review. No changes to criteria.
10/2026	Q4 2026 code set update.