Clinical Policy Title: Radioembolization and chemoembolization of hepatic malignancies

Clinical Policy Number: CCP.1203

Effective Date: February 1, 2016
Initial Review Date: November 18, 2015
Most Recent Review Date: February 5, 2019
Next Review Date: February 20, 2020

Related policies:
CCP.1361 Radiofrequency ablation of tumors
CCP.1212 Liver transplantation

ABOUT THIS POLICY: AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas’ clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas considers the use of radioembolization with yttrium-90 and chemoembolization to be clinically proven and, therefore, medically necessary for treatment of primary and secondary hepatic malignancies, when the following criteria are met:

- Early-stage hepatocellular carcinoma¹ (InterQual®, 2018a):
  - Ineligible for resection or liver transplantation with no or minimal extrahepatic disease and tumor size > 3 cm and ≤ 5 cm.
  - As bridge therapy to orthotopic liver transplantation.

- Intermediate stage hepatocellular carcinoma² (InterQual, 2018a):

- Unresectable liver metastases of neuroendocrine origin with continued symptoms or

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¹ Barcelona Clinic Liver Cancer Stage A defined as ≤ three nodules < 3 cm, Child-Pugh A-B, and performance status 0.
² Barcelona Clinic Liver Cancer Stage B defined as a single large tumor > 5 cm or multinodular disease, preserved liver function, and no extrahepatic spread or macrovascular invasion.
findings after medical treatment (e.g., somatostatin analogs) (InterQual, 2018a).

- Unresectable colorectal liver metastases not amenable or responsive to thermal ablation, and with preserved liver function and performance status, and no extrahepatic spread (Gaba, 2017; Zacharias, 2015).
- Downstaging liver tumors to meet Milan criteria and no extrahepatic spread (Duran, 2015; National Comprehensive Cancer Network, 2018a).
- Gastrointestinal stromal tumors with progressing metastatic disease (e.g., refractory to tyrosine kinase inhibitor therapy) confined to the liver (chemoembolization only) (National Comprehensive Cancer Network, 2018b).
- Preoperative portal vein embolization with limited tumor invasion of the portal vein and an estimated future liver remnant/total liver volume ratio below recommended values in members who would be otherwise eligible for liver resection (Abdel-Rahman, 2016; National Comprehensive Cancer Network, 2018a).

Limitations:

Other tumors that may manifest with liver-dominant metastases include breast carcinoma and gynecologic malignancies. Treatment of liver metastases from these tumors with radioembolization or chemoembolization may be considered on a case-by-case basis in the presence of limited progressive disease not responsive to systemic therapy (Gaba, 2017).

Relative contraindications to radioembolization and chemoembolization include (Duran, 2015):

- Diffuse tumor burden involving more than 50 percent of the liver.
- Segmental or branch portal venous thrombosis.
- Extrahepatic metastases (Child-Pugh Class C).
- Ascites.
- Serum bilirubin greater than 3 mg/dL, unless segmental treatment can be performed (National Comprehensive Cancer Network, 2018a).
- High serum levels of lactate dehydrogenase (> 425 units/L).
- High serum levels of aspartate aminotransferase and alanine aminotransferase (greater than five times the upper limit of normal).
- Biliary obstruction.
- Severe thrombocytopenia (< 50,000 platelets/µL).
- Recent variceal bleeding.
- Intractable arteriovenous fistula.
- Right-to-left cardiopulmonary shunting.
- Prior hepatic radiotherapy.

Absolute contraindications to radioembolization and chemoembolization include (Duran, 2015):

- Eastern Cooperative Oncology Group performance status greater than 2.
- Severely reduced portal flow by branch or main portal vein thrombosis (e.g., hepatofugal blood flow).
- Active systemic infection.
- Uncorrectable bleeding disorder.
- Uncorrectable contrast media sensitivity.
- Leukopenia (white blood cell count < 1,000/µL).
- Renal insufficiency (serum creatinine < 2 mg/dL, glomerular filtration rate < 30 mL/min).
- Hepatic encephalopathy.
- Excessive hepatopulmonary shunting.
- Technetium-99m—macroaggregate albumin scan showing gastrointestinal deposition technically not correctable.

Alternative covered services:

- Surgical resection of liver cancer.
- Liver transplantation.
- Somatostatin-analog treatment of endocrine-active hepatic metastases.
- Chemotherapy of liver cancer.
- Radiotherapy of liver cancer.

Background

The therapeutic objectives of image-guided transcatheter tumor therapy using embolic agents with or without other agents are (Gaba, 2017): cytoreduction through targeted delivery of high-dose antineoplastic therapy to the tumor; ischemic devascularization of the tumor; and preservation of normal surrounding tissue. Developed for the treatment of hepatic malignancy, these therapies involve embolic agents alone (embolization), with chemotherapy (chemoembolization), or with radiation therapy (radioembolization). They are performed typically by an interventional radiologist or oncologist, usually as an outpatient procedure.

Two forms of chemoembolization (also called transarterial chemoembolization) are conventional and drug-eluting (Gaba, 2017). Conventional chemoembolization infuses single or multiple chemotherapeutic agents with or without ethiodized oil, and with or without concurrent or tandem embolization. Drug-eluting chemoembolization infuses embolic agents coated with an antineoplastic drug directly to the tumor and sequesters the chemotherapeutic agent for controlled release. As a medical procedure, chemoembolization is not subject to U.S. Food and Drug Administration regulation, but the embolizing and chemotherapeutic agents are.

Radioembolization (also called selective internal radiation therapy or SIRT) infuses resin-based or glass microspheres containing the radioactive isotope yttrium-90 to irradiate the tumor. The U.S. Food and Drug Administration (2018a, 2018b) has approved two devices:
- SIR-Spheres® (Sirtex Medical, Woburn, Massachusetts) are resin-based microbeads approved for treatment of unresectable hepatic malignancies from primary colorectal cancer (premarket approval P990065).
- TheraSphere® (MDS Nordion, Kanata, Ontario, Canada) are glass microspheres approved for: 1) radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma who can have placement of appropriately positioned hepatic arterial catheters, and 2) patients with hepatocellular carcinoma with partial or branch portal vein thrombosis/occlusion, when clinical evaluation warrants the treatment (Humanitarian Device Exemption H980006).

Searches

AmeriHealth Caritas searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality.
- The Centers for Medicare & Medicaid Services.

We conducted searches on November 9, 2018. Search terms were: “Liver Neoplasms” (MeSH) and free text terms “radioembolization,” “radioembolisation,” “chemoembolization,” and “transarterial chemoembolization.”

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

Findings from systematic reviews and meta-analyses (Abdel-Rahman, 2016; Devcic, 2014; Yang, 2012; Zacharias, 2015), one comprehensive review (Duran, 2015), and two guidelines (Lau, 2012; National Comprehensive Cancer Network, 2014) support the safety and effectiveness of radioembolization and chemoembolization administered alone or in combination with local ablative or adjuvant systemic options for treatment of primary and secondary hepatic malignancies. Both embolization procedures offer an acceptable treatment efficacy, a modest improvement in survival, and lower or comparable toxicity to other local treatment options. The superiority of any transarterial embolization procedure, chemotherapeutic agent, or treatment protocol cannot be determined, due to insufficient comparative effectiveness data from randomized controlled trials or other well-designed comparative studies.
Major prognostic factors such as liver function, portal vein invasion, performance status, tumor burden, and treatment response will affect outcomes. The ideal candidate for radioembolization and chemoembolization will have asymptomatic, unresectable intermediate-stage disease (Barcelona-Clinic Liver Cancer stage B), preserved liver function (Child-Pugh A), no extrahepatic metastases, and good general health (Eastern Cooperative Oncology Group ≤ 2). In the setting of portal vein invasion, radioembolization offers a safe, palliative option due to the minimally embolic effect of yttrium-90 microspheres.

The strongest evidence from randomized controlled trials supports chemoembolization as primary therapy for unresectable, intermediate-stage hepatocellular carcinoma (Duran, 2015). Other clinical indications supported by lower-quality evidence include: treatment of secondary malignancies (neuroendocrine or colorectal) without extrahepatic metastases (Devcic, 2014; Yang, 2012; Zacharias, 2015); radioembolization for unresectable hepatocellular carcinoma with or without portal vein invasion (Abdel-Rahman, 2016; Lau, 2012); use of drug-eluting beads (Duran, 2015); downstaging hepatocellular carcinoma to Milan criteria for surgical treatment (Duran, 2015); as bridge therapy to surgical tumor resection or liver transplantation when waiting times are estimated to exceed six months (Duran, 2015); and treatment of early-stage hepatocellular carcinoma (Barcelona-Clinic Liver Cancer stage A) who fail local ablation (Duran, 2015).

There is inconclusive evidence supporting the medical necessity of adjuvant chemoembolization or transarterial embolization without chemotherapy. Chemoembolization is discouraged in patients with decompensated liver disease, advanced liver dysfunction, macroscopic invasion, or extrahepatic spread (Duran, 2015).

Relative contraindications to radioembolization and chemoembolization include (Duran, 2015):
- Diffuse tumor burden involving more than 50 percent of the liver.
- Segmental or branch portal vein thrombosis.
- Extrahepatic metastases.
- Ascites.
- Serum bilirubin greater than 3 mg/dL.
- High serum levels of lactate dehydrogenase (> 425 units/L).
- High serum levels of aspartate aminotransferase and alanine aminotransferase (greater than five times the upper limit of normal).
- Biliary obstruction.
- Severe thrombocytopenia (< 50,000 platelets/µL).
- Recent variceal bleeding.
- Intractable arteriovenous fistula.
- Right-to-left cardiopulmonary shunting.
- Prior hepatic radiotherapy.
Absolute contraindications to radioembolization and chemoembolization include (Duran, 2015):

- Eastern Cooperative Oncology Group performance status greater than 2.
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- Active systemic infection.
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- Hepatic encephalopathy.
- Excessive hepatopulmonary shunting.
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Policy updates:

Limited evidence from a systematic review of four retrospective studies (n = 166 total patients) with hepatocellular carcinoma suggests that compared to portal vein embolization alone, a combination of portal vein embolization with transarterial chemoembolization may offer better survival outcomes and treatment response in patients with large tumors or with vascular thrombosis (Glantzounis, 2017). These results require confirmation in more rigorous studies.

A systematic review and network meta-analysis of 55 randomized controlled trials (n = 5,763 patients with unresectable hepatocellular carcinoma) evaluated several arterial embolization options either alone or combined with adjuvant chemotherapy, local liver ablation, or external radiotherapy (Katsanos, 2017). All embolization strategies achieved a significant survival gain over control treatment (hazard ratio range 0.42 to 0.76; very low-to-moderate quality of evidence). Conventional chemoembolization with or without drug-eluting beads, radioembolization, and adjuvant systemic agents did not confer superior treatment response or survival benefit over transarterial embolization alone (moderate quality of evidence, except low quality of evidence in the case of radioembolization). Radioembolization was the safest treatment; however, all embolization therapies were associated with a significantly higher risk of toxicity over control (odds ratio range 6.35 to 68.5). There was clinical diversity among included studies, but statistical heterogeneity was low.

In 2019, we added five systematic reviews and meta-analyses (Finn, 2018; Jia, 2018; Kulik, 2018; Roccara, 2017; Stevens, 2017), two updated guidelines (National Comprehensive Cancer Network, 2018a, 2018b), one quality improvement guideline (Gaba, 2017), and InterQual criteria (2018) to the policy. The new evidence from the systematic reviews and meta-analyses is consistent with previous findings. The criteria for medical necessity were modified to align with current InterQual criteria (2018) and guideline recommendations (Gaba, 2017; National Comprehensive Cancer Network, 2018a, 2018b). The policy ID was changed from CP# 05.02.09 to CCP.1203.
References

Professional society guidelines/other:


Peer-reviewed references:


**Centers for Medicare & Medicaid Services National Coverage Determinations:**
National Coverage Determination for therapeutic embolization (20.28).

Local Coverage Determinations:

No Local Coverage Determinations identified as of the writing of this policy.

Commonly submitted codes

Below are the most commonly submitted codes for the services and items subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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