Cigna Medical Coverage Policy

Hyperlink to Related Coverage Policies
Radioembolization with Yttrium-90 (90Y) Microspheres

Coverage Policy

Cigna covers transarterial chemoembolization as medically necessary for EITHER of the following indications:

- unresectable primary hepatocellular carcinoma (HCC)
- palliative treatment of liver-dominant metastatic disease when previous therapy has failed to control symptoms

Cigna does not cover transarterial chemoembolization for any other indication because it is considered experimental, investigational or unproven.

General Background

Primary and Secondary Liver Cancer
Hepatocellular carcinoma (HCC) is primary liver cancer; it originates in the liver. HCC is the most common solid tumor worldwide, accounting for more than 600,000 deaths each year. However, most of the time when cancer is found in the liver it did not originate from the liver, but spread to the liver from somewhere else. This is secondary liver cancer or metastatic liver cancer. In the United States and Europe, secondary (metastatic) liver tumors are more common than primary liver cancer. Cancer that has metastasized to the liver can cause pain. Neuroendocrine tumors usually originate in hormone-producing cells that line the small intestine or other cells of the digestive tract. When these tumors (e.g., carcinoid, islet cell/pancreatic cell) have metastasized to the liver, the liver is unable to process the substances being released by the tumors before they begin circulating throughout the body. Depending on which substances or hormones are being released, a person can have the
various symptoms of carcinoid syndrome, insulinoma syndrome, Zollinger Ellison syndrome, or VIPoma syndrome. The carcinoid tumor is the most common type. Carcinoid syndrome is characterized by debilitating flushing, wheezing and diarrhea.

Treatments
Unlike most other organs, the liver gets blood from two sources: the hepatic artery supplies the liver with blood rich in oxygen from the heart, and the portal vein brings nutrient-rich blood from the intestines. This fact provides additional treatment options not available for other cancer locations. Important factors to consider when choosing a treatment option include the stage (extent) of the cancer and the health of the rest of the liver. Treatment options for primary or secondary liver cancer may include:

- surgery (partial hepatectomy or liver transplant)
- chemotherapy
- locoregional therapies
- radiation therapy

In some cases, doctors may recommend combining more than one of these treatments. Frequently at the time of diagnosis, hepatic tumors are found to be unresectable and treatments are provided to decrease tumor bulk and control symptoms (American Cancer Society, 2014).

Locoregional therapy is a treatment that affects only a localized area of the body rather than being systemic or throughout the body. In the context of liver cancer or metastasis to the liver, locoregional therapy should be considered in those patients not candidates for surgical curative treatments and are broadly categorized into ablation and arterial-directed therapies. Ablation (radiofrequency, cryoablation, percutaneous alcohol injection, microwave) used alone may be curative, generally in treating tumors ≤ 3 centimeters (cm). The most widely used ablation techniques are percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA). Lesions 3-5 cm may be treated to prolong survival using arterial-directed therapies, or with combination of an arterial direct therapy and ablation

Treatments / Arterial Directed Therapies
All tumors irrespective of location may be amenable to arterial directed therapies provided that the arterial blood supply to the tumor may be isolated without non-target embolization. Arterial directed therapies include transarterial bland embolization (TAE), transarterial chemoembolization (TACE) and TACE with drug-eluting beads (DEB-TACE), and radioembolization with yttrium 90 microspheres. Arterial directed therapies are relatively contraindicated in: cases of main portal vein thrombosis; and patient with bilirubin > 3 mg/dL unless segmental injections can be performed. Arterial directed therapies are relatively contraindicated for Child-Pugh Class C. Generally, unresectable/inoperable lesions > 5cm should be considered for treatment using arterial directed therapies or systemic therapy (National Comprehensive Cancer Network®, 2014).

Food and Drug Administration (FDA)
Approvals for chemotherapeutic and embolic agents used in chemoembolization are not specific for use in chemoembolization. Chemotherapeutic agents may be approved for numerous oncologic indications. Several embolic beads are FDA-approved (e.g., LC Bead™ and Bead Block™ [Biocompatibles UK Ltd., Farnham, Surrey, UK]; EmboSphere, EmboGold, and QuadraSphere [BioSphere Medical, Inc., Rockland, MA, USA]; Contour SE Microspheres [Boston Scientific Corporation, Natick, MA, USA]). Drug-eluting chemoembolic beads (e.g., DC Bead™, PRECISION Bead, PARAGON Bead [Biocompatibles UK Ltd, Farnham, Surrey, UK]) are not FDA-approved but their ingredients may be FDA-approved on a stand-alone basis.

Hepatocellular Carcinoma (HCC)
Compared to Supportive Care: Lo et al. (2002) conducted a randomized controlled trial including 80 patients newly diagnosed unresectable HCC. These patients were randomly assigned to treatment with chemoembolization using a variable dose of an emulsion of cisplatin in lipiodol and gelatin-sponge particles injected through the hepatic artery (chemoembolization group, 40 patients) or symptomatic treatment (control group, 40 patients). Chemoembolization resulted in a marked tumor response, and the actuarial survival was significantly better in the chemoembolization group (1 year, 57%; 2 years, 31%; 3 years, 26%) than in the control group (1 year, 32%; 2 years, 11%; 3 years, 3%; P = .002). In the same year, Llovet et al. (2002) also conducted a randomized controlled trial including 107 patients: 34 were assigned arterial embolization; 38 were assigned chemoembolization; and 35 assigned control treatment. The trial was stopped when the ninth sequential inspection showed that chemoembolization had survival benefits compared with conservative
treatment. A total of 25 of 35 assigned conservative treatments died. Survival probabilities at 1 year and 2 years were 75% and 50% for embolization; 82% and 63% for chemoembolization, and 63% and 27% for control (chemoembolization vs. control p=0.009). These trials have shown a survival benefit for TACE compared with supportive care in patients with unresectable HCC.

**Drug-eluting Beads (DEB):** In the multicenter, randomized controlled trial PRECISION V, Lammer et al. (2010) included patients with HCC unsuitable for resection or percutaneous ablation. Additional inclusion factors were: no previous chemotherapy, radiotherapy or transarterial embolization (with or without chemotherapy); a confirmed diagnosis of HCC according to EASL, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and preserved liver function (Child-Pugh Class A or B). A total of 201 patients participated; 93 receiving drug-eluting bead (DEB) TACE, and the other receiving conventional (c) TACE. DEB TACE was associated with improved tolerability, with a significant reduction in serious liver toxicity (P < 0.001) and a significantly lower rate of doxorubicin-related side effects (P = 0.0001). The DEB TACE group showed higher rates of complete response, objective response, and disease control compared with the cTACE group (27% vs. 22%, 52% vs. 44%, and 63% vs. 52%, respectively). Malagari et al. (2010) conducted a randomized controlled trial on the hypothesis that since drug-eluting bead (DEB)-TACE is standardized and reproducible, a comparison with bland TACE can readily reveal the potential value of the chemotherapeutic. Two groups were randomized in this prospective study: group A (n = 41) was treated with doxorubicin DEB-TACE, and group B (n = 43) with bland embolization (total n= 84). At six months a complete response was seen in 11 patients (26.8%) in the DEB TACE group and in six patients (14%) in the bland embolization group; a partial response was achieved in 19 patients (46.3%) and 18 (41.9%) patients in the DEB TACE and bland embolization groups, respectively. Recurrences at 9 and 12 months were higher for bland embolization (78.3% vs. 45.7%) at 12 months. Time to progression (TTP) was longer for the DEB TACE group (42.4 +/- 9.5 and 36.2 +/- 9.0 weeks), at a statistically significant level (p = 0.008). This study did not report overall survival. Dhanasekaran et al. (2010) performed a prospective, randomized study including 71 patients: 45 (63.4%) received therapy with DEB (group A); and 26 (36.6%) underwent conventional chemoembolization (group B). Median survival from diagnosis of HCC in groups A and B were 610 and 284 days (p = 0.03), respectively. In Child-Pugh classes A and B, survival in groups A and B were 641 and 323 days (p = 0.002). TACE with DEBs is at least as effective as conventional TACE.

**Bridge to Transplant:** Chemoembolization may be utilized in order for a liver transplantation candidate to receive higher priority on the waiting list. Studies in the peer-reviewed scientific literature support the use of chemoembolization for down-staging patients with advanced HCC to allow eligibility for liver transplant, although studies remain mixed regarding what if any long-term survival advantage is gained (Bouchard-Fortier, et al., 2011; Lewandowski, et al., 2009; Chapman, et al 2008; Alba, et al., 2008; Heckman, et al., 2008; Decaens, et al., 2005; Graziaidei, et al., 2003).

**TACE vs. other Treatments:** Liao et al. (2013) conducted a meta-analysis to evaluate the effectiveness of combination therapy of TACE with radiofrequency ablation (RFA), percutaneous ethanol injection (PEI) RFA, radiotherapy (RT), three-dimensional conformal radiation therapy (3DCRT) or high-intensity focused ultrasound (HIFU) in patients with HCC. Liao et al. included (1) studies if they were randomized controlled trials, or observational studies comparing TACE combined other supplement therapy with TACE alone; (2) there were no evidence for extra-hepatic metastasis before the first TACE process; (3) overall survival was assessed as an outcome measure of the effect of the treatment. Studies were excluded if they received surgery or if they were published only in abstract form. Data for three-year survival rate were reported in 8 RCTs and 12 observational studies. Meta-analysis of RCTs indicated that combined therapies, especially the additional PEI (p<0.001) and RT (p=0.001) significantly improved the three-year survival compared with TACE alone. A random-effect model yielded a similar result from the observational studies, furthermore, it also showed TACE +HIFU (p=0.011) and 3D-CRT treatment (p<0.001) were associated with higher three-year survival. However, researches of TACE+RFA/TACE were inadequate to obtain a comment.

In a randomized controlled trial, Peng et al. (2013) evaluated RFA with or without TACE in the treatment of HCC. A total of 189 patients with HCC less than 7 cm were randomized to receive TACE combined with RFA (TACE-RFA; n = 94) or RFA alone (n = 95). There were no treatment-related deaths. The 1-, 3-, and 4-year overall survivals for the TACE-RFA group and the RFA group were 92.6%, 66.6%, and 61.8% and 85.3%, 59%, and 45.0%, respectively. The corresponding recurrence-free survivals were 79.4%, 60.6%, and 54.8% and 66.7%, 44.2%, and 38.9%, respectively. Patients in the TACE-RFA group had better overall survival and recurrence-free survival than patients in the RFA group (p = .002; p = .009, respectively).
TACE-RFA was superior to RFA alone in improving survival.

A randomized controlled trial (TRACE) comparing chemoembolization and radioembolization for the treatment of HCC will provide comparative results in the future (Seinstra, et al., 2012).

**Professional Societies/Organizations:** The National Comprehensive Cancer Network® (The NCCN Practice Guideline™ for Hepatobiliary Cancers (v.1.2014) notes the following under the algorithm for Ineligible for Transplant and Unresectable HCC: If a patient is not a transplant candidate, options include Systemic therapy (Child-Pugh Class A), Clinical trial, Locoregional therapies (i.e., Ablation, Arterial-directed therapies, external beam RT) and Supportive Care. The algorithm for Intrahepatic Cholangiocarcinoma lists treatment options, including locoregional therapy for unresectable and metastatic disease (2B recommendation).

Principles of Locoregional Therapy: All patients with HCC should be evaluated for potential curative therapies (resection, transplantation, and for small lesions ablative strategies). Locoregional therapy should be considered in those patients not candidates for surgical curative treatments, or as a part of a strategy to bridge patients for other curative therapies. These are broadly categorized into ablation and arterial-directed therapies.

Principles of Locoregional Therapy/ Ablation (Radiofrequency, Cryoablation, Percutaneous alcohol injection, Microwave): Ablation alone may be curative in treating tumors ≤ 3 cm. Lesions 3-5 cm may be treated to prolong survival using arterial-directed therapies, or with combination of an arterial direct therapy and ablation. Unresectable/inoperable lesions > 5cm should be considered for treatment using arterial directed therapies or systemic therapy.

Principles of Locoregional Therapy/ Arterial directed therapies: All tumors irrespective of location may be amenable to arterial directed therapies provided that the arterial blood supply to the tumor may be isolated without non-target embolization. Arterial directed therapies include transarterial bland embolization (TAE), transarterial chemoembolization (TACE) and TACE with drug-eluting beads (DEB-TACE), and radioembolization with yttrium 90 microspheres. Arterial directed therapies are relatively contraindicated in: cases of main portal vein thrombosis; and patient with bilirubin > 3 mg/dL unless segmental injections can be performed. Arterial directed therapies are relatively contraindicated for Child-Pugh Class C. Sorafenib is appropriate following arterial 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 TACE is being investigated in ongoing clinical trials.

In the NCCN background, Bridge to Liver Transplant: Studies have investigated the role of locoregional therapies as a bridge to liver transplantation in patients on a waiting list. The small size of the studies and the heterogeneous nature of the study populations as well as the absence of randomized clinical trials evaluating the utility of bridge therapy for reducing the liver transplantation waiting list drop-out rate, limit the conclusion that can be drawn. Nevertheless, the use of bridge therapy in this setting is increasing and it is administered at some NCCN member institutions (NCCN®, 2014).

**Palliative Treatment of Liver-dominant Metastatic Disease**

Evidence in the published, peer-reviewed scientific literature defining TACEs’ palliative clinical utility such as tumor and symptom control is lacking. However, the treatment of liver-dominant metastases from primary sites (e.g., neuroendocrine tumors, ocular/uvaeal melanoma, colorectal cancer, ovarian cancer, breast cancer) with TACE is performed for palliative and not curative purposes. The NCCN Practice Guideline™ for Occult Primary (v.2.2014) notes under the algorithm for unresectable liver cancer from an unknown primary, treat as disseminated disease and/or consider locoregional therapeutic options. In the background under locoregional therapeutic options, NCCN states in patients with unresectable localized liver lesions (either adenocarcinoma or neuroendocrine), locoregional therapeutic options may be considered (e.g., hepatic artery infusion, chemoembolization, hepatic cryosurgery, radiofrequency ablation of hepatic lesions, or percutaneous ethanol injections) (NCCN®, 2014).

**Neuroendocrine Tumors (NET) Metastases to the Liver:** To date, hepatic resection remains the only potentially curative option for patients with neuroendocrine liver metastasis, with 5-year survival after hepatectomy ranging from 60% to 80% in recent series. Metastasis will develop in almost 40% of patients with NETs during the course of their disease, most commonly to the liver. In contrast to other malignancies, in a proportion of patients with neuroendocrine liver metastasis disabling clinical symptoms can develop secondary
to the production of specific biogenic amines and polypeptide hormones. Therefore, treatment of patients with neuroendocrine liver metastasis is focused on optimizing quality of life through reduction of such hormone-related symptoms, and improving survival in patients with disease amenable to liver-directed therapy, including hepatic resection, thermal ablation, and arterial directed therapies (Mayo, et al., 2013).

Although the existing literature consists mainly of small retrospective reports, studies support the use of chemoembolization as a palliative treatment (Hur, et al., 2013; Dong, et al., 2010; Ho, et al., 2007; Gupta, et al., 2005). Dong et al. (2010) retrospectively analyzed 123 patients with unresectable NETs with hepatic metastases. An average of seven cycles of chemoembolization was administered. There were no technical delivery failures and no >grade 2 treatment toxicities. Mean survival for the entire cohort was 5.47 years. Overall 3-, 5- and 10-year survivals were 59, 36, and 20%. The authors noted baseline low serum albumin levels, high prothrombin time and old age are variables identifying patients at risk of poorer survival. The authors stated overall patient survival in this cohort was comparable to previous observations. These studies have no comparator to evaluate.

**Neuroendocrine Tumors (NET) Metastases to the Liver / Professional Societies/Organizations:** The NCCN Practice Guideline™ for Neuroendocrine Tumors (v.2.2014) states in the Carcinoid Tumors algorithm and the NET of the Pancreas algorithm, for unresectable and clinically significant progressive disease, consider hepatic regional therapy (including chemoembolization) 2B recommendation. Under Surgical Principles for Management of NETs, NCCN states liver-directed therapies (e.g., liver resection, thermal ablation, chemoembolization) for hepatic metastasis from NETs following panreatoduodenectomy are associated with increased risk for perihepatic sepsis and liver abscess.

In the background, NCCN states under Hepatic-directed Therapies for metastatic carcinoid tumors: For patients with unresectable hepatic-predominant progressive disease, hepatic directed therapies may be considered, mainly with the palliative goals of extending life and reliving hormonal symptoms.

In the background, NCCN states under Hepatic-directed therapies for NET of the Pancreas: For unresectable symptomatic patients, those who initially present with clinically significant tumor burden, several different options can be considered. Systemic options (e.g., everolimus, sunitinib) (2A Recommendation), treatment with cytotoxic chemotherapy (2A), or treatment with octreotide (2B Recommendation). For patients with progressive, hepatic-predominant disease, hepatic directed therapies may be considered, mainly with the palliative goals of extending life and reliving hormonal symptoms (2B Recommendation) (NCCN®, 2014).

**American Society for the Study of Liver Disease (AASLD):** The AASLD Practice Guideline “Management of Hepatocellular Carcinoma: An Update” states that TACE is recommended as first line non-curative therapy for non-surgical patients with large/ multifocal HCC who do not have vascular invasion or extrahepatic spread. The AASLD notes that the development of polyvinyl chloride spheres that release chemotherapy after being injected (DEBs) have allowed a reduction of the side effects of the passage of chemotherapy into systemic circulation (Bruix ,et al., 2011).

**Ocular / Uveal Melanoma Metastases to the Liver:** The incidence of uveal melanoma is 4.3 cases per million populations. Despite successful treatment of the primary uveal melanoma, up to 50% of patients will subsequently develop a systemic metastasis, with the liver involved in up to 90% of these individuals. Approximately 90% of metastatic uveal melanoma patients die with liver metastasis. In general, after the development of liver metastases, the survival estimates range from 2 to 9 months. Systemic chemotherapy has failed to show clinical efficacy against metastatic uveal melanoma. Recognition of the poor prognosis associated with liver metastasis has led to the evaluation of various locoregional treatment modalities primarily designed to control tumor progression in the liver (Sato, et al., 2010). Published small retrospective studies show poor progression-free survival and overall survival (Gupta, et al., 2010; Kamat, et al., 2008; Sharma, et al., 2008; Agarwala, et al., 2004). These studies are retrospective in design. No conclusions can be drawn from these studies. Survival outcomes are reported.

**NCCN Practice Guideline™ for Melanoma and also Head and Neck do not address uveal melanoma.**

**Colorectal Metastases to the Liver:** In a retrospective report, Gruber-Rouh et al. (2014) describes 564 patient results with unresectable liver metastases from CRC who were treated with TACE. The primary tumor was located in the rectum in 43.4% (n = 245) patients and in the colon in 56.6% of patients (n = 319). With a mean of
six TACE sessions per patient, the 1-year survival rate after chemoembolization was 62%, the 2-year survival rate was 28% and the 3-year survival rate was 7%. Median survival from the start of chemoembolization treatment was 14.3 months. Albert et al. (2011) retrospectively evaluated 121 patients with metastatic colorectal carcinoma. Indication for treatment was most commonly failure of systemic chemotherapy to control unresectable liver-dominant disease. Median survival was 33 months from diagnosis of the primary colon cancer, 27 months from development of liver metastases, and 9 months from chemoembolization. From time of diagnosis of liver metastases, survival at 1, 2, and 5 years was 85%, 55%, and 6%, respectively. These studies are retrospective in design and have no comparator.

Martin et al. (2010) conducted a prospective, observational trial including 55 patients with liver dominant metastatic colon cancer. After failing other therapies, these patients underwent TACE. Median follow-up for this patient cohort was 18 months. In an evaluation of 99 separate treatments, adverse events occurred in 28% (n=28 treatments), with a majority of adverse events being nausea, vomiting, and liver dysfunction. There were no deaths at 30 days post-procedure. The 12-month response rates were 40%, with 15% (n=8) showing complete response and 25% (n = 14) showing partial response. Overall survival in these patients was 19 months, with progression-free survival of 11 months. Drug-eluting beads were used in this study.

Vogl et al. (2009) prospectively evaluated 463 patients with unresectable liver metastases of colorectal cancer that had previously not responded to systemic chemotherapy. The indication for chemoembolization of liver metastases in patients with colorectal cancer was primarily palliative. Results demonstrated a median survival time from the start of chemoembolization of 14 months. Hong et al. (2009) conducted a retrospective records review of patients who underwent either (n=21) or radioembolization (n=15) for palliation. Similar results were seen with a median survival of 7.7 months for the chemoembolization group and 6.9 months for the radioembolization group. Tellez et al. (1998) retrospectively reported on 30 patients with previously treated metastatic colorectal cancer to the liver who underwent chemoembolization. Median survival for all 30 patients was 8.6 months following initiation of chemo-embolization. Sanz-Altamira et al. (1997) reported a median survival from date of first chemoembolization of ten months in a retrospective review of 40 patients. No conclusions can be drawn from these studies. Survival outcomes are reported.

Colorectal Metastases to the Liver / Professional Societies/Organizations: The NCCN Practice Guideline™ for Colon Cancer (3.2014) and Rectal Cancer (3.2014) states in the background that the NCCN panel lists arterial directed embolic therapy as a Category 3 recommendation.

Other Cancer Metastases to the Liver: The majority of studies are retrospective in design and has no comparator Also; no conclusions can be drawn from these studies. Survival outcomes are reported.

Use Outside of the US
No relevant information.

Summary
Evidence in the published, peer-reviewed scientific literature demonstrates that transarterial chemoembolization (TACE), whether conventionally delivered or delivered with drug-eluting beads, provides a significant survival benefit for the treatment of unresectable primary hepatocellular carcinoma (HCC) when compared with supportive care only or when added as an additional therapy. Although there is little peer-reviewed, scientific literature regarding the effects of chemoembolization used in the preoperative setting, it has become a standard treatment for those patients awaiting a liver transplant. TACE can be effective as a palliative treatment (e.g., pain or other symptom control, tumor growth control) of liver-dominant metastatic disease when previous therapy has failed.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Covered when medically necessary when used to report transarterial chemoembolization:
<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>37204</td>
<td>Transcatheter occlusion or embolization (e.g., for tumor destruction, to achieve hemostasis, to occlude a vascular malformation), percutaneous, any method, non-central nervous system, non-head or neck (Code deleted 12/31/2013)</td>
</tr>
<tr>
<td>37243</td>
<td>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 (Code effective 1/1/2014)</td>
</tr>
<tr>
<td>96420</td>
<td>Chemotherapy administration, intra-arterial; push technique</td>
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**References**


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