Clinical Policy Title: Radioembolization and chemoembolization for liver cancer and other indications

Clinical Policy Number: 05.02.08

Effective Date: February 1, 2016
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Related policies:

None.

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina's 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 Select Health of South Carolina 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. Select Health of South Carolina's 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. Select Health of South Carolina's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina's clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of radioembolization to be clinically proven and, therefore, medically necessary to treat cancer in the liver in the following instances (Katsanos, 2017; Rathman, 2015; Memon, 2013; Bester, 2012; Lau, 2012; Coldwell, 2012; Sangro, 2011; Kosmider, 2011; Salem, 2010; Ibrahim, 2008):

- Inoperable or unresectable primary hepatic cancer (i.e., hepatocellular carcinoma [HCC]).
- Colorectal cancer with exclusively liver metastases.
- Neuroendocrine tumors, such as octreotide-resistant carcinoid tumors or refractory pancreatic neuroendocrine tumors (PNETs), which have spread to the liver.
- Ocular melanoma that has spread to the liver when rendered in the context of an investigational review board (IRB)-approved clinical trial protocol.
- Cholangiocarcinoma (i.e., cholangiocellular carcinoma [CCC]) that has spread to the liver when rendered in the context of an IRB-approved clinical trial protocol.
- Liver tumors too large for surgery to shrink them to allow surgical removal.
- Cancers in the liver that cannot be removed surgically and are not responsive to systemic
chemotherapy.
• Preoperative treatment of liver cancer prior to orthotopic liver transplant (OLT).

Select Health of South Carolina considers the use of chemoembolization to be clinically proven and, therefore, medically necessary to treat cancer in the liver in the following instances (Katsanos, 2017; Spreafico, 2015; Cohen, 2014; Gulec, 2013; Lencioni, 2013; Akahori, 2013; Cannon, 2012; Yang, 2012; Cao, 2012; Kosmider, 2011; Tokh, 2010):
  • Inoperable or unresectable primary hepatic cancer (i.e., HCC).
  • Neuroendocrine tumors, such as octreotide-resistant carcinoid tumors or refractory PNETs, which have spread to the liver.
  • Gastrointestinal stromal tumors (GISTs) refractory to tyrosine kinase inhibitor therapy that have spread to the liver.
  • Ocular melanoma that has spread to the liver when rendered in the context of an IRB-approved clinical trial protocol.
  • Cholangiocarcinoma (i.e., CCC) that has spread to the liver when rendered in the context of an IRB-approved clinical trial protocol.
  • Preoperative treatment of liver cancer prior to OLT.
  • Postoperative treatment of recurrent liver cancer after OLT.

Limitations:

Select Health of South Carolina considers the use of radioembolization and chemoembolization to be investigational and, therefore, not medically necessary in the following instances:
  • Ocular melanoma metastatic to liver and primary cholangiocarcinoma, except when part of an IRB-approved clinical trial protocol.
  • Breast cancer, lung cancer, or other cancers, except as indicated above or when part of an IRB-approved clinical trial protocol.
  • Tumors ≤ 3 cm are optimally treated with ablation. Lesions between 3 and 5 cm may be treated using combination embolization and ablation as long as tumor location is favorable. Unresectable/inoperable lesions > 5 cm should be treated using arterial embolic approaches.
  • In patients with early stage HCC who are not candidates for liver resection or transplant, radiofrequency ablation (RFA) is considered the best therapeutic choice.
  • RFA is the recommended procedure for ≥ three unresectable colorectal liver metastases confined to the liver.
  • Neuroendocrine tumors have been shown to respond favorably to somatostatin analogs; however, refractory disease may become apparent in time and require additional therapy (e.g., RFA).

Note: The criteria of tumor > 5 cm or no more than three lesions in the liver are the indications for surgery for HCC and do not pertain to the treatments of radioembolization and chemoembolization.
addressed by this policy.

**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 American Cancer Society estimates there were 35,660 new cases (25,510 in men and 10,150 in women) of primary liver cancer and intrahepatic bile duct cancer diagnosed in the United States in 2015. An average man's lifetime risk of getting liver or intrahepatic bile duct cancer is about one in 81, while an average woman's risk is about one in 196. Most cases occur in people with certain risk factors (male; Asian or Pacific Island descent; use of anabolic steroids; cigarette smoking; prior hepatitis B or hepatitis C infection; cirrhosis; obesity; diabetes mellitus; various inherited conditions, such as hereditary hemochromatosis; and toxins such as aflatoxins, arsenic, and vinyl chloride). The average age at diagnosis of liver cancer is 63 years.

Angiography of the hepatic circulation can be used to show the arteries that supply blood to a liver cancer, which can help doctors plan treatment for liver cancer, and can also be used to guide some types of non-surgical treatment, such as embolization (a procedure that injects substances to try to block or reduce the blood flow to cancer cells in the liver). Angiography may be done with a computerized tomography (CT) scanner (CT angiography) or a magnetic resonance imaging (MRI) scanner (magnetic resonance [MR] angiography), instead of X-ray angiography, because they can give information about the blood vessels in the liver without the need for a catheter in the artery.

Formal staging systems, such as the 2010 American Joint Committee on Cancer (AJCC) TNM system, are helpful to get an idea about a patient's prognosis and to help determine the most appropriate treatment. This staging system is based on the results of the physical exam, imaging, and other tests to assess the patient for three key pieces of information: 1) T describes the number and size of the primary tumors, measured in centimeters, and whether the cancer has grown into nearby blood vessels or organs; 2) N describes the extent of the spread to nearby (regional) lymph nodes; and 3) M indicates whether the cancer has metastasized to other parts of the body. But for treatment purposes, doctors often classify liver cancers more simply, based on whether or not they can be entirely cut out (resected).

Potentially resectable or transplantable cancers are cancers that can be completely removed by surgery or treated with liver transplant with a patient is healthy enough to tolerate the surgery. This would include patients who do not have cirrhosis or other serious medical problems. If all of the cancer in the
liver is successfully removed, the overall five-year survival rate is over 50 percent. For people with early-stage liver cancers who have a liver transplant, the five-year survival rate is in the range of 60 percent – 70 percent. Unfortunately, only a small number of patients with liver cancer present in this group.

Inoperable with only local disease implies that the cancer is small enough and in the right place to be removed, but the patient is not healthy enough for surgery (e.g., liver cancer in the presence of severe cirrhosis) and surgery to remove the cancer might not leave enough liver to sustain life. Unresectable cancers are those cancers that have not spread to the lymph nodes or distant organs, but cannot be completely removed by surgery. This includes cancers that have grown throughout the liver such that they cannot be safely removed due to proximity to the great vessels or bile ducts. There is potential for use of embolization in the treatment of large unresectable cancers to reduce their size sufficiently to make resection feasible.

Advanced (metastatic) cancers are those that have spread to lymph nodes or other organs. Most advanced liver cancers cannot be successfully treated with surgery. Embolization is an option for some patients with tumors that cannot be removed by surgery. It can be used for tumors that are too large (usually larger than five centimeters across) to be treated with ablation (a treatment that kills tumor cells without removing them).

Finally, there is the case of a primary tumor elsewhere that has metastasized to the liver (e.g., colorectal cancer). When these metastases threaten liver function and life, it is possible to treat them with selective arterial embolization and adjuvant intrahepatic radiotherapy or chemotherapy.

Embolization does reduce some of the blood supply to the normal liver tissue, so it may not be a good option for those patients whose liver has been damaged by disease (i.e., hepatitis or cirrhosis). This type of treatment typically does not require a hospital stay.

**Searches**

Select Health of South Carolina searched PubMed and the databases of:
- UK National Health Services Center for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on December 18, 2017. Search terms were: "radioembolization (MeSH)," "chemoembolization (MeSH)," and "liver cancer."

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

Arterial embolization is also known as transarterial embolization (TAE). In this procedure, a catheter is introduced into the femoral artery and threaded up into the hepatic artery in the liver. Once the catheter is in place, small occlusive materials (e.g., Gel-foam® coil) are injected into the artery to plug it up.

Radioembolization technique combines embolization with radiation therapy and is sometimes known as transarterial radioembolization (TARE). In the United States, this is done by introducing small beads called “microspheres” (i.e., TheraSphere® and SIR-Spheres®) that are embedded with a radioactive isotope (yttrium-90 or Y-90) into the hepatic artery. The radio-infused beads lodge in the blood vessels near the tumor, where they give off small amounts of radiation to the tumor site for several days. The radiation travels a very short distance, so its effects are limited mainly to the tumor.

Radioembolization is used predominantly to treat cancer in the liver. The disease may take one of two forms: 1) primary hepatic cancer (i.e., HCC); and 2) cancer that has metastasized to the liver from a primary tumor elsewhere (e.g., colorectal cancer). Metastatic colorectal cancer to the liver and primary HCC are the cancers most often considered for radioembolization treatment.

Lau (2012) reported the results of an expert panel convened to assess radioembolization as therapy for HCC. The panel noted a number of variables in the outcome of treatment, such as the findings of imaging of the tumor and its vasculature, tumor and uninvolved liver characteristics, previous therapies, and localization of the microsphere infusion. There was consensus that radioembolization can improve the clinical outcomes for selected patients with inoperable liver cancer.

In a systematic review of results from eight European medical centers, Sangro (2011) found that radioembolization was effective in increasing survival of advanced HCC, demonstrating a median overall survival of 12.8 months. The authors noted that survival varied significantly by functional status, hepatic function, tumor burden (number of nodules), and the presence or absence of extrahepatic disease. Common adverse events were fatigue, nausea, vomiting, and abdominal pain.

In a large randomized controlled trial (RCT) of 291 patients, Salem (2010) administered 526 radioembolization treatments (range one to five) to patients with HCC with response rates of 42 percent – 57 percent and overall time to progression of 7.9 months. Within this group were a limited number (n = 56) of patients with portal vein thrombosis whose survival was only 5.6 months.
Radioembolization has also been used for other forms of cancer affecting the liver, such as 1) cholangiocarcinoma; 2) breast cancer with solely liver metastasis; 3) neuroendocrine tumors, such as carcinoid tumors, that have spread to the liver; and 4) gastrointestinal sarcoma, a stromal tumor of the gut also known as GIST.

A pilot study analyzing the use of Y-90 in 24 patients with biopsy-proven intrahepatic cholangiocarcinoma (ICC) showed a favorable response to treatment and survival outcomes (Ibrahim, 2008). Imaging follow-up of the study cohort demonstrated partial response in 27 percent, stable disease in 68 percent, and progression in 5 percent. Most patients (77 percent) showed > 50 percent tumor necrosis. Median overall survival was 14.9 months. Portal vein thrombosis was noted as a particularly ominous predictive factor, with patients achieving only 5.7 months of survival.

An ongoing, open clinical trial (Pitton, 2013) comparing selective internal radiotherapy (SIRT) versus transarterial chemoembolization with drug-eluting beads (DEBs) for the treatment of cholangiocarcinoma has not yet posted results. A second clinical trial (Leyvraz, 2013), also open to enrollment, is comparing systemic sorafenib (an anti-angiogenic agent) versus radioembolizatoin with Sir-Spheres® in the treatment of ocular melanoma.

Radioembolization for breast cancer metastases to liver (Coldwell, 2012) was evaluated in a narrative review, citing evidence to support the use of radioembolization in liver metastases from neuroendocrine and breast cancers. The authors also noted a number of other tumors (e.g., melanoma, lung) with similar radiobiologic profiles who may respond to this treatment. They noted sufficient liver functional reserve and good patient performance status in the absence of significant comorbidity was essential for success. Radioembolization was encouraged in patients showing progression of liver metastases during treatment hiatus, in tumors that respond poorly to chemotherapy or in treatment-refractory disease.

A systematic review (Yang, 2012) of 37 RCTs inclusive of 1,575 patients examined the use of radioembolization versus chemoembolization for unresectable neuroendocrine tumor liver metastases (NETLM). The review examined the efficacy and safety of the use of hepatic arterial chemoembolization, simple embolization, and radioembolization, and found comparable outcomes for all therapies with regard to response to treatment, survival, and toxicity. The authors noted that carcinoid had a particularly high response rate of 67 percent versus 35 percent overall, and concluded these therapies are safe and effective in the treatment of NETLM.

A small series looked at the impact of radioembolization for GIST metastases to the peritoneum and the liver in 11 patients failing tyrosine kinase inhibitor (TKI) therapy (Rathman, 2015). Following radioembolization, three patients showed complete response, five showed partial response, and one showed stable disease. No patient showed progressive disease after radioembolization. Median survival was 29.8 months (range, 10 – 72 months). The authors concluded that radioembolization is a safe and effective therapy for patients with GIST liver metastases, and offered their results as a challenge to the prevailing notion that GISTs are resistant to radiation therapy.
Radioembolization is often used in coordination with more well-established cancer treatments, such as surgery and chemotherapy: 1) radioembolization may be used on liver tumors too large for surgery to shrink them to allow surgical removal, and 2) chemotherapy and radioembolization may be provided in combination to maximize the destruction of cancer cells.

In an RCT inclusive of 24 patients with advanced unresectable liver cancer or colorectal cancer metastases to liver, Cohen (2014) documented the pharmacokinetics of capecitabine in combination with radioembolization. Radioembolization with Y-90 resin microspheres was administered using a sequential lobar approach with two cycles of capecitabine. The authors noted a partial response in four patients (16.7 percent), stable disease in 17 (70.8 percent), and progression in three (12.5 percent). Median time to progression and overall survival of the metastatic colorectal cancer cohort was 6.4 and 8.1 months, respectively.

Gulec (2013) compared radioembolization with selective arterial chemotherapy versus systemic chemotherapy for hepatic colorectal cancer metastases. Treatment was administered with Y-90 microspheres and with contemporary standard chemotherapy for colorectal metastases to the liver. Response to treatment was evaluated by serial fludeoxyglucose positron emission tomography and computed tomography performed at four weeks, two to four months, and six to eight months. A decrease in tumor size was seen in 19 of the 20 patients; however, the reduction of tumor size in the radioembolization with selective arterial chemotherapy group was markedly greater. The authors concluded that the chemo-radio combination produced superior objective responses compared with systemic chemo-only treatment in a front-line treatment setting of patients with colorectal cancer liver metastases.

A narrative review (Memon, 2013) reported on radioembolization employed for treating patients with unresectable HCC. The authors opined that this technique has proven useful for the majority of patients with HCC as most of them present in advanced stage, beyond potentially curative options (resection/liver transplantation). They also noted that radioembolization can be used in downstaging large tumors to bring them within transplantable criteria, in patients with portal venous thrombosis due to tumor invasion, and as palliative therapy.

Kosmider (2011) reported a series of 19 patients with unresectable liver metastases from colorectal cancer treated with radioembolization and chemotherapy. Most (74 percent) had metastatic disease confined to the liver. Concurrent treatment with 5-fluorourail/leucovorin (n = 7) or 5-fluorourail/leucovorin/oxaliplatin (FOLFOX; n = 12) was started three to four days before a single radioembolization treatment. Overall response was 84 percent. Median progression-free survival time was 10.4 months and median overall survival time was 29.4 months.

Radioembolization can also be a treatment option for cancers in the liver that can't be removed surgically and are not responsive to chemotherapy. Bester (2012) retrospectively evaluated the safety and survival of 339 patients with chemotherapy-refractory liver metastases treated with Y-90. The median overall survival after radioembolization was 12.0 months, versus 6.3 months for a standard-care
cohort (n = 51). At three months of follow-up, the incidence of serious adverse events was low. The authors concluded that radioembolization is an effective and safe treatment for patients with chemotherapy-refractory hepatic metastases and improves overall survival in a select population of patients.

Radioembolization is generally only considered as treatment for cancers whose spread is limited to the liver. Radioembolization is contraindicated in patients with severe liver disease where diminished hepatic circulation may precipitate hepatic failure, and in patients with abnormal blood flow between the liver and lungs (i.e., acquired arteriovenous malformation or shunting).

Chemoembolization, also known as transarterial chemoembolization (TACE), combines embolization with chemotherapy. Specifically, the technique permits dearterialization of the tumor and selective delivery of chemotherapeutic agents into the tumor's feeding vessels during angiography. Most often, this is done by using tiny beads that give off a chemotherapy drug for the embolization. TACE can also be done by giving chemotherapy through the catheter directly into the artery, and then plugging up the artery. Tumor ischemia raises the drug concentration compared to infusion alone and extends the retention of the chemotherapeutic drug.

Spreafico (2015) evaluated the short-term safety and effectiveness of the new generation of 70-150 µm DEBs (M1 DEB) in patients with hepatocellular carcinoma undergoing TACE as a primary therapy or as a bridge to liver transplantation. A total of 45 consecutive patients underwent TACE with M1 DEB loaded with doxorubicin (DEBDOX/M1). The mean number of TACE procedures per patient was 1.4. The objective response rate was 77.7 percent with a median time to best response of three months. In 13 patients, DEBDOX/M1 TACE served as a bridge/down-staging to hepatectomy or liver transplantation. The authors concluded that DEBDOX/M1 TACE is an effective modality of treatment with promising results in objective response rate and tumor down-staging.

In a narrative review, Lencioni (2013) stated that TACE is the current standard of care for patients with HCC and relatively preserved liver function, absence of cancer-related symptoms, and no evidence of vascular invasion or extrahepatic spread. TACE may also be offered to patients with early-stage HCC when surgical options or percutaneous ablation are precluded. The authors noted that in conventional TACE, the administration of the anticancer-in-oil emulsion is followed by mechanical embolization with either a spherical or a nonspherical embolic agent, but there is no consensus on the optimal chemotherapeutic agents to use. Worldwide, the most popular anticancer drug for TACE of HCC is doxorubicin. On the frequency of therapy, the authors noted that no randomized trials have been designed to evaluate the optimal frequency of therapy; and that the safety and effectiveness of more than four TACE procedures are unknown.

Cannon (2012) assessed the safety and effectiveness of chemoembolization with DEBDOX in the treatment of multi-nodular (greater than or equal to 10 lesions) HCC. At 12 months, a group of 42 patients with multi-nodular disease showed a response rate of 56 percent and median overall survival of 7.6 months. The authors concluded that DEBDOX treatment is safe and effective when compared to
historical controls and the current best systemic therapy for multi-nodular HCC.

In a narrative review of treatments for HCC, Biolato (2010) wrote “... as locoregional therapy, TACE allows complete local tumor control of 25 percent – 35 percent and permits an increase of survival in patients with HCC.” The authors also noted that percutaneous ethanol injection or radio frequency ablation as neoadjuvant therapy prior to hepectomy or transplantation was beneficial. The authors cited DEBs loaded with doxorubicin and sorafenib as a further refinement of interest and recommended their continued investigation. The authors concluded that TACE is the standard of care for treatment of unresectable HCC.

Tokh (2010) assessed the safety, efficacy, and survival among 63 patients with unresectable HCC treated with beads loaded with doxorubicin (DOX). Median tumor size was 4.8 cm (range of 2 – 12 centimeters). Overall, 81 percent showed tumor regression and alpha-feto protein (AFP) decreased in 79 percent of patients with elevated levels, with a median fall of 78.5 percent. Actuarial survival was 18.2 months, leading the authors to conclude that treatment of HCC using DEBDOX is at least equivalent, with milder toxicity, to conventional TACE.

An RCT of 28 patients with unresectable recurrent HCC following OLT randomized patients to lobaplatin-based chemoembolization or supportive care to assess response and survival (Zhou, 2010). Eight of the 14 patients in the chemoembolization group (57 percent) showed partial tumor response (> 30 percent reduction in tumor size), with significantly longer overall survival compared to those who did not. No severe complications developed during follow-up in patients receiving chemoembolization.

Chemoembolization has been successfully used as a palliative treatment of symptoms associated with functioning neuroendocrine tumors (i.e., carcinoid tumors) involving the liver. It has also been used in metastases to liver from GIST, and from PNETs that produce gastrin, insulin, or other pancreatic hormones.

Gupta (2003) retrospectively studied the outcomes of 81 patients with systemic chemotherapy-resistant carcinoid metastases to liver when treated with hepatic artery embolization or chemoembolization by evaluating the clinical and radiologic response rates, duration of response, and progression-free and overall survival rates of these patients. Fifty patients were treated with bland hepatic artery embolization, and 31 underwent chemoembolization. Of the 69 patients in whom radiologic response could be evaluated, partial response was observed in 46 patients (67 percent), minimal response in six (8.7 percent), stable disease in 11 (16 percent), and progressive disease in six (8.7 percent). The median duration of response in the 42 patients with partial response was 17 months (range, four – 51 months). Sixty-three percent of patients had a reduction in their tumor-related symptoms. The median progression-free survival duration was 19 months (95 percent confidence interval, 17 – 21 months); the probability of progression-free survival was 75 percent, 35 percent, and 11 percent at one, two, and three years, respectively. The median overall survival time was 31 months (95 percent confidence interval, 23 – 38 months); the survival probability was 93 percent at one year, 62 percent at two years, and 24 percent at five years.
Cao (2012) evaluated the efficacy and safety of TACE for GIST with liver metastases after the failure of TKI therapy. Sixty patients who were resistant and/or intolerant to prior imatinib and/or sunitinib were eligible for the study. The patients were divided into two groups: those in the TACE group (n = 22) received TACE treatment containing 5 – 20 mL iodized oil and 40 – 80 mg doxorubicin hydrochloride and TKI reintroduction or best supportive care, and those in control group (n = 38) only received TKI reintroduction or best supportive care. In the TACE group, 12 patients (54.5 percent) achieved liver partial response, five patients (22.7 percent) had stable disease, and five patients (22.7 percent) had progressive disease. Disease control rate of liver metastases was 77.3 percent in the TACE group and 39.5 percent in the control group. The median overall survival in TACE group was also longer than in control group (68.5 weeks, 95 percent confidence interval [CI]: 57.4 – 79.6 versus 25.7 weeks, 95 percent CI: 23.2 – 28.2) (P = 0.0001). TACE treatment significantly reduced the risk of death (hazard ratio: 0.109). Patients without extrahepatic metastases treated with TACE had significantly better prognosis. The authors concluded that TACE is effective and well tolerated in GIST patients with liver metastases after TKI failure, and it may be an optional treatment for this disease.

Akahori (2013) reported the use of TACE to treat hepatic metastases of PNETs. The authors administered cisplatin to unresectable PNET metastases with a total of 24 treatments in a small series of five patients. There was one complete response, three partial responses and one patient whose disease remained stable over the course of treatment and follow-up. Median survival of 36 months was achieved without severe toxicity or adverse effect.

A clinical trial of chemoembolization with DEBs versus radioembolization for intrahepatic CCC is currently recruiting participants at Johannes Gutenberg University Mainz (Pitton, 2013). No results have been posted.

A systematic review and meta-analysis (Glantzounis, 2016), inclusive of 40 articles and 2,144 patients, studied portal vein embolization (PVE) in patients with inadequate functional liver reserve (FLR) and found evidence that the practice before major hepatectomy allows resection of advanced primary hepato-biliary tumors with good long-term survival.

Policy updates:

A systematic review and meta-analysis (Glantzounis 2016) inclusive of 40 articles and 2144 patients studied PVE in patients with inadequate functional liver reserve (FLR) and found evidence that the practice before major hepatectomy allows resection of advanced primary hepato-biliary tumors with good long term survival.

During the past twelve months there has been further information published regarding radio- and chemoembolization for cancer.

A systematic review and network meta-analysis (Katsanos 2017) of different embolization options for
unresectable hepatocellular carcinoma evaluated bland transarterial embolization, conventional transarterial chemoembolization, drug-eluting beads-transarterial chemoembolization, and transarterial radioembolization, either alone or combined with adjuvant chemotherapy, local liver ablation, or external radiotherapy for unresectable hepatocellular carcinoma (n = 5,763 patients). The primary endpoint was patient survival expressed as hazard ratios and 95 percent credible intervals. Safety and objective response were calculated as odds ratios and accompanying 95 percent credible intervals. All embolization strategies achieved a significant survival gain over control treatment (hazard ratio range, 0.42 – 0.76; very low-to-moderate quality of evidence). However, transarterial chemoembolization, drug-eluting beads-transarterial chemoembolization, transarterial radioembolization, and adjuvant systemic agents did not confer any survival benefit over bland transarterial embolization alone (moderate evidence, except low in the case of transarterial radioembolization). There was moderate evidence that transarterial chemoembolization combined with external radiation or liver ablation achieved the best patient survival. Estimated median survival was 13.9 months in control, 18.1 months in transarterial chemoembolization, 20.6 months with drug-eluting beads-transarterial chemoembolization, 20.8 months with bland transarterial embolization, 30.1 months in transarterial chemoembolization plus external radiotherapy, and 33.3 months in transarterial chemoembolization plus liver ablation. Transarterial radioembolization was the safest treatment; however, all examined therapies were associated with a significantly higher risk of toxicity over control (odds ratio range, 6.35 to 68.5). Transarterial chemoembolization, drug-eluting beads-transarterial chemoembolization, transarterial radioembolization, and adjuvant systemic agents did not improve objective response over bland embolization alone (odds ratio range, 0.85 to 1.65). There was clinical diversity among included randomized controlled trials, but statistical heterogeneity was low.

**Summary of clinical evidence:**

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<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tr>
<td>Katsanos (2017)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td></td>
<td>• Systematic review and network meta-analysis of different embolization options for unresectable hepatocellular carcinoma evaluated bland TAE, conventional TACE, DEB-TACE, or TARE, either alone or combined with adjuvant chemotherapy, local liver ablation, or external radiotherapy for unresectable hepatocellular carcinoma (n = 5,763 patients).</td>
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<td>• However, TACE, DEB-TACE, TARE, and adjuvant systemic agents did not confer any survival benefit over bland TAE alone (moderate evidence, except low in case of TARE).</td>
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| Glantzounis (2016)            | TACE plus external radiotherapy, and 33.3 months in TACE plus liver ablation.  
|                               | - TARE was the safest treatment; however, all examined therapies were associated with a significantly higher risk of toxicity over control (OR range, 6.35 to 68.5). TACE, DEB-TACE, TARE, and adjuvant systemic agents did not improve objective response over bland embolization alone (OR range, 0.85 to 1.65).  
|                               | - There was clinical diversity among included RCTs, but statistical heterogeneity was low.                                                                                                                                               |
| Key points:                   | Systematic meta-analysis inclusive of 40 articles and 2,144 patients reviewed indications for PVE in patients with inadequate FLR and analyzed other parameters such as resection rate, morbidity, mortality, survival after PVE and hepatectomy for primary hepatobiliary tumors.  
|                               | Participants’ median age was 61 years.  
|                               | The median excision rate was 90% for HCCs and 86% for hilar cholangiocarcinomas.  
|                               | The main indications for PVE in patients with HCC and presence of liver fibrosis or cirrhosis was FLR < 40% when liver function was good; FLR < 50% when liver function was impaired.  
|                               | The combination of TACE and PVE increased hypertrophy rate and was associated with better overall survival and disease free survival.  
|                               | The authors concluded that PVE before major hepatectomy allows resection in a patient group with advanced primary hepatobiliary tumors and inadequate FLR, with good long-term survival. |
| Spreafico (2015)              | Evaluated the short-term safety and effectiveness of the new generation of 70 – 150 µm M1 DEB.  
|                               | Objective response rate was 77.7% with a median time to best response of three months.  
|                               | In 13 patients, DEBDOX/M1 TACE served as a bridge/down-staging to hepatectomy or liver transplantation.                                                                                                                               |
|                               | No patient showed progressive disease after radioembolization.  
|                               | Median survival was 29.8 months (range, 10 – 72 months).                                                                                                                                                                              |
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</table>
| yttrium-90 resin microspheres (SIR-Spheres) in patients with advanced cancer | patients (70.8%) and progression in three patients (12.5%).  
• Median time to progression and overall survival of the metastatic colorectal cancer cohort was 6.4 and 8.1 months, respectively. |
| Gulec (2013)                  | Key points:                                                                                                                                  
• Compared radioembolization with chemotherapy versus systemic chemotherapy for hepatic colorectal cancer metastases.  
• Reduction of tumor size in the radioembolization with selective arterial chemotherapy group was markedly greater. |
| Memon (2013)                 | Key points:                                                                                                                                  
• Narrative review on radioembolization employed for treating patients with unresectable HCC.  
• The authors opined that this technique has proven useful for the majority of patients with HCC.  
• Noted that radioembolization can be used in downstaging large tumors to bring them within transplantable criteria. |
| Lencioni (2013)              | Key points:                                                                                                                                  
• Narrative review stated TACE is the current standard of care for patients with HCC and relatively preserved liver function, absence of cancer-related symptoms, and no evidence of vascular invasion or extrahepatic spread.  
• There is no consensus on the optimal chemotherapeutic agent(s) to use, but worldwide the most popular is DOX.  
• No randomized trials have been designed to evaluate the optimal frequency of therapy. |
| Akahori (2013)               | Key points:                                                                                                                                  
• Reported the use of TACE to treat hepatic metastases of PNETs.  
• Administered cisplatin to unresectable PNET metastases with a total of 24 treatments in a small series of five patients.  
• There was one complete response, three partial responses, and one patient with stable disease.  
• Median survival of 36 months was achieved. |
| Pitton (2013)                | Key points:                                                                                                                                  
• Open study comparing SIRT versus TACE with DEBs for the treatment of intrahepatic CCC.  
• No study results posted. |
| Leyvraz (2013)               | Key points:                                                                                                                                  
• Open study evaluating chemotherapeutic agent sorafenib and radioembolization with Sir-Spheres® for the treatment of metastatic ocular melanoma. |
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannon (2012)</td>
<td>Management of diffuse hepatocellular carcinoma (≧ 10 lesions) with DOX-loaded DC beads is a safe and effective treatment option. No study results posted.</td>
</tr>
</tbody>
</table>
| Bester (2012) | Radioembolization versus standard care of hepatic metastases: comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. Key points:  
- Evaluated the safety and survival of chemotherapy-refractory liver metastases treated with Y-90.  
- The median overall survival after radioembolization was 12.0 months, versus 6.3 months for a standard-care cohort (n = 51). |
| Lau (2012) | Patient selection and activity planning guide for SIRT with yttrium-90 resin microspheres. Key points:  
- Expert panel convened to assess radioembolization as therapy for HCC.  
- Consensus that radioembolization can improve the clinical outcomes for selected patients with inoperable liver cancer. |
| Yang (2012) | Radioembolization and chemoembolization for unresectable neuroendocrine liver metastases — a systematic review. Key points:  
- Systematic review of 37 RCTs inclusive of 1,575 patients examined radioembolization versus chemoembolization for unresectable NETLM.  
- Carcinoid had a particularly high response rate of 67% versus 35% overall. |
| Cao (2012) | Transcatheter arterial chemoembolization for gastrointestinal stromal tumors with liver metastases. Key points:  
- Evaluated TACE for GIST with liver metastases after the failure of TKIs in 60 patients, who were resistant and/or intolerant to prior imatinib and/or sunitinib.  
- Twelve (54.5%) patients achieved liver partial response, five patients (22.7%) had stable disease, and five patients (22.7%) had progressive disease.  
- Median overall survival of 12.8 months. |
| Coldwell (2012) | Radioembolization in the treatment of unresectable liver tumors: experience across a range of primary cancers. Key points:  
- Presented evidence to support the use of radioembolizatoin in liver metastases from neuroendocrine and breast cancers.  
- The narrative review noted a number of other tumors (e.g., melanoma, lung) with similar radiobiologic profiles who may respond to this treatment.  
- Radioembolization was advocated in patients showing progression of liver metastases during treatment hiatus, in tumors that respond poorly to chemotherapy, or in treatment-refractory disease. |
<p>| Sangro (2011) | Key points: |</p>
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
</table>
• Survival varied significantly by functional status, hepatic function, tumor burden (number of nodules), and presence or absence of extrahepatic disease. |
| Kosmider (2011) | **Key points:**  
• Series of 19 patients with unresectable liver metastases from colorectal cancer were treated with radioembolization and chemotherapy.  
• Overall response was 84%.  
• Median progression-free survival time was 10.4 months and median overall survival time was 29.4 months. |
| Biolato (2010) | **Key points:**  
• Wrote “...as locoregional therapy, TACE allows complete local tumor control of 25% – 35% and permits an increase of survival in patients with HCC.”  
• The authors concluded that TACE is the standard of care for treatment of unresectable HCC. |
| Tokh (2010) | **Key points:**  
• Series of 63 patients with unresectable HCC treated with beads loaded with DOX.  
• 81% showed tumor regression, and AFP decreased in 79% of patients.  
• Actuarial survival was 18.2 months. |
| Zhou (2010) | **Key points:**  
• RCT of 28 patients with unresectable recurrent HCC following OLT randomized to lobaplatin-based chemoembolization or supportive care.  
• 57% showed partial tumor response (> 30 percent reduction in tumor size) with significantly longer overall survival. |
| Salem (2010) | **Key points:**  
• RCT of 291 patients administered HCC radioembolization treatment.  
• Response rates of 42% – 57% and overall time to progression of 7.9 months. |
| Ibrahim (2008) | **Key points:**  
• Pilot study of yttrium-90 in 24 patients with ICC.  
• Partial response in 27%, stable disease in 68%, and progression in 5%.  
• Median overall survival was 14.9 months. |
References

Professional society guidelines/other:


Peer-reviewed references:


Hassan MM, Spitz MR, Thomas MB, et al. Effect of different types of smoking and synergism with
hepatitis C virus on risk of hepatocellular carcinoma in American men and women: Case-control study. 


CMS National Coverage Determination (NCDs):

No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):

No LCDs 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 in accordance with those manuals.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>37243</td>
<td>Vascular embolization for tumors</td>
<td></td>
</tr>
<tr>
<td>75894</td>
<td>Transcatheter therapy, embolization, any method, radiologic supervision and interpretation</td>
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<table>
<thead>
<tr>
<th>ICD-10 Code</th>
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<tr>
<td>C22.0</td>
<td>Liver cell carcinoma</td>
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<tr>
<td>C22.1</td>
<td>Intrahepatic bile duct carcinoma</td>
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<td>C22.8</td>
<td>Malignant neoplasm, liver, unspecified as to type</td>
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<td>C25.4</td>
<td>Malignant neoplasm of the endocrine pancreas</td>
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<td>C69.90</td>
<td>Malignant neoplasm of unspecified site, unspecified eye</td>
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<tr>
<td>C69.91</td>
<td>Malignant neoplasm of unspecified site, right eye</td>
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<td>C69.92</td>
<td>Malignant neoplasm of unspecified site, left eye</td>
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<td>C78.7</td>
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<td>Z09</td>
<td>Encounter for f/u exam after completed treatment for conditions other than malignant neoplasm</td>
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<table>
<thead>
<tr>
<th>HCPCS Level II Code</th>
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