Description
Cryosurgical ablation involves the freezing of target tissues, most often by inserting into the tumor a probe through which coolant is circulated. Cryosurgical ablation can be performed as an open surgical technique or percutaneously or laparoscopically, typically with ultrasound guidance.

Related Policies
- Liver Transplant
- Microwave Tumor Ablation
- Radioembolization for Primary and Metastatic Tumors of the Liver
- Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors
- Radiofrequency Ablation of Primary of Metastatic Liver Tumors
- Transcatheter Arterial Chemoembolization (TACE) to Treat Primary or Metastatic Liver Malignancies

Policy
Cryosurgical ablation may be considered medically necessary for the treatment of patients with hepatic lesions with any of the following conditions:

- Primary hepatocellular carcinoma (HCC) when the all of the following criteria are met:
  - Patient is not a candidate for curative hepatic surgical resections due to limited hepatic reserve and/or comorbid conditions and/or the location (e.g., adjacent to a major vein) or number of lesions
  - Patient is not a candidate for liver transplantation* (see exception below)
  - Presence of three or fewer hepatic lesions
  - Each lesion measures 5 centimeters (cm) or less in diameter using current technology
  - Absence of extrahepatic metastatic disease
  - All tumor foci can be adequately treated (complete ablation determined by preoperative imaging)
• Primary HCC, as a bridge to transplantation*, when **all** of the following criteria are met:
  - Patient is not a candidate for curative hepatic surgical resections due to limited hepatic reserve and/or comorbid conditions and/or the location (e.g., adjacent to a major vein) or number of lesions
  - Intent is to prevent further tumor growth and to maintain a patient’s candidacy for liver transplant
  - Presence of three or fewer hepatic lesions
  - Each lesion measures 5 centimeters (cm) or less in diameter using current technology
  - No evidence of extrahepatic spread and/or macrovascular involvement (i.e., portal or hepatic veins)
  
  Note: Criteria for ablative therapies as a bridge to transplantation are generally consistent with the United Network for Organ Sharing (UNOS) policy on Organ Distribution: Liver Transplant Candidates with Hepatocellular Carcinoma (HCC); Section 3.6.4.4 (11/9/2010).

• Hepatic metastases from colorectal cancer when **all** of the following criteria are met:
  - Patient is not a candidate for curative hepatic surgical resections due to limited hepatic reserve and/or comorbid conditions and/or the location (e.g., adjacent to a major vein) or number of lesions
  - Presence of four to five or fewer hepatic lesions
  - Each lesion measures 5 centimeters (cm) or less in diameter using current technology
  - Absence of extrahepatic metastatic disease
  - All tumor foci can be adequately treated (complete ablation determined by preoperative imaging)

• Hepatic metastases from neuroendocrine tumors when **all** of the following criteria are met:
  - Patient has symptomatic disease (e.g., wheezing, flushing of the skin, abdominal cramps, diarrhea, heart disease)
  - Systemic therapy has failed to control symptoms (e.g., Octreotide therapy)
  - Patient is not a candidate for curative hepatic surgical resections due to limited hepatic reserve and/or comorbid conditions and/or the location (e.g., adjacent to a major vein) or number of lesions
  - Absence of extrahepatic metastatic disease
  - Each lesion measures 5 centimeters (cm) or less in diameter using current technology

Cryosurgical ablation for primary HCC or hepatic metastases is considered **investigational** for treatment of **any** of the following:

• Primary HCC when there are either of the following:
  - More than three hepatic lesions nodules
When not all sites of tumor foci can be adequately treated

- Primary HCC when used to downstage (downsize) HCC in patients being considered for liver transplant
- Hepatic metastasis from colorectal cancer or neuroendocrine tumors not meeting the medically necessary criteria above
- Hepatic metastases from other types of cancer with the exception of colorectal or neuroendocrine cancer tumors

**Policy Guidelines**

Downstaging (downsizing) therapy is used to reduce the tumor burden in selected patients with more advanced HCC (without distant metastasis) that are beyond the accepted transplant criteria.

**Neuroendocrine Tumors**

Neuroendocrine tumors (NETs) may be referred to by their anatomic location (e.g., pulmonary neuroendocrine tumor, gastrointestinal neuroendocrine tumor). Neuroendocrine tumors include the following:

- Carcinoid tumors
- Islet cell tumors (or pancreatic endocrine tumors)
- Neuroendocrine unknown primary
- Adrenal gland tumors
- Pheochromocytoma/paraganglioma
- Poorly differentiated (high grade or anaplastic)/small cell
- Multiple endocrine neoplasia, Type 1 (also known as MEN-1 syndrome or Wermer's syndrome)
- Multiple endocrine neoplasia, Type 2 a or b (also known as pheochromocytoma and amyloid producing medullary thyroid carcinoma, PTC syndrome, or Sipple syndrome)

Symptomatic disease from neuroendocrine tumors may include hot, red flushing of the face, severe and debilitating diarrhea, asthma attacks, palpitations, low blood pressure, fatigue, dizziness, and weakness. Extreme symptoms may include heart disease, bronchial constriction, and bowel obstruction.

Systemic therapies for neuroendocrine tumors vary depending on the location and characteristics. Therapies may include, but are not limited to: octreotide, interferon, cytotoxic chemotherapy, angiogenesis inhibitors, and epidermal growth factor inhibitors.

**Coding**

The following CPT codes describe cryosurgical ablation specific to liver tumors:

- **47371**: Laparoscopy, surgical, ablation of 1 or more liver tumor(s); cryosurgical
- **47381**: Ablation, open, 1 or more liver tumor(s); cryosurgical
- **47383**: Ablation, 1 or more liver tumor(s), percutaneous, cryoablation (new code 01/01/15)
CPT code 76940 would be used to describe the ultrasound guidance for, and monitoring of, parenchymal tissue ablation.

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Rationale**

**Background**

Hepatic tumors can arise either as primary liver cancer or by metastasis to the liver from other tissues. Local therapy for hepatic metastasis is indicated only when there is no extrahepatic disease, which rarely occurs for patients with primary cancers other than colorectal carcinoma or certain neuroendocrine malignancies. At present, surgical resection with tumor-free margins or liver transplantation represent the only treatments with curative potential. For liver metastases from colorectal cancer, postsurgical adjuvant chemotherapy has been reported to decrease recurrence rates and prolong time to recurrence. However, most hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size, number of lesions, or underlying liver reserve.

Combined systemic and hepatic arterial chemotherapy may increase disease-free intervals for patients with hepatic metastases from colorectal cancer but apparently is not beneficial for those with unresectable hepatocellular carcinoma.

Various locoregional therapies for unresectable liver tumors are being studied: cryosurgical ablation (cryosurgery), radiofrequency ablation, laser ablation, transhepatic artery embolization/chemoembolization, microwave coagulation, and percutaneous ethanol injection. Ablation occurs in tissue that has been frozen by at least 3 mechanisms: (1) formation of ice crystals within cells, thereby disrupting membranes and interrupting cellular metabolism among other processes; (2) coagulation of blood, thereby interrupting blood flow to the tissue, in turn causing ischemia and cell death; and (3) induction of apoptosis (cell death).

Recent studies report experience with cryosurgical and other ablative methods used in combination with subtotal resection and/or procedures such as transarterial chemoembolization.

**Primary Hepatocellular Carcinoma**

Primary hepatocellular carcinoma (HCC) commonly occurs in the context of chronic liver disease and cirrhosis and is often diagnosed in its later stages. In 2006, Brown et al reported that although patients with localized HCC are best managed with complete surgical resection, less than 20% are viable candidates because of the extent or location of the lesions, comorbid conditions, or disseminated disease. The National Comprehensive
Cancer Network (NCCN) Guidelines for HCC stated, “All HCC patients should be evaluated for potential curative therapies (resection, transplantation).” Locoregional therapies are recommended when there is no extrahepatic disease and progression is limited, but cure is less likely. The NCCN does not discriminate among the ablative therapies in the treatment of HCC. They propose ablation for hepatic lesions less than or equal to 3 centimeters (cm) in size. The NCCN additionally stated unresectable or inoperable lesions greater than 5 cm should be considered for treatment using arterial embolic approaches or systemic therapy.

The NCCN principles of locoregional therapy are as follows:

For ablation (radiofrequency (RFA), cryoablation (cryosurgical ablation, CSA), percutaneous ethanol or alcohol injection (PEI or PAI), and microwave ablation (MWA)):

- All tumors should be amenable to ablation such that the tumor and margin of normal tissue is treated.
- Tumors should be in a location accessible for percutaneous/laparoscopic/open approaches for ablation.
- Tumors less than 3 cm are optimally treated with ablation. Lesions between 3 and 5 cm may be treated using a combination of embolization and ablation as long as the tumor location is favorable. Unresectable or inoperable lesions greater than 5 cm should be considered for treatment using arterial embolic approaches or systemic therapy.
- Caution should be exercised when ablating lesions near major vessels, major bile ducts, diaphragm, and other intra-abdominal organs.

The National Cancer Institute’s (NCI) Physician Data Query (PDQ) regarding adult primary liver cancer treatment listed PEI, CSA, RFA, and chemoembolization as standard treatment alternatives for patients with unresectable primary HCC tumors under 5 cm in diameter. Identified contraindications to embolization (with or without chemotherapy) include portal hypertension, portal vein thrombosis, and clinical jaundice. New medical approaches are being researched in clinical trials including, but not limited to, targeted therapy after chemoembolization or combined with chemotherapy, and combination therapy with surgery, chemotherapy, and radiation therapy.

Neuroendocrine Cancer Liver Metastases

Neuroendocrine tumors are relatively slow-growing malignancies (mean survival times, 5-10 years) that commonly metastasize to the liver. As with other cancers, the most successful treatment of hepatic metastasis is resection with tumor-free margins, but treatment benefits for a slow-growing tumor must be weighed against the morbidity and mortality of major surgery. The intent of cryosurgery in these cases is to minimize or eliminate symptoms caused by liver metastases while avoiding the complications of open surgery.

Hepatic tumors may also occur as metastasis from other sites. More than half of patients with colorectal cancer (CRC) will develop liver metastases, either at the time of initial presentation or as a result of disease recurrence, and generally with a poor prognosis. For one-third, the liver is the only site of metastases. Like primary HCC, surgical resection is considered the gold standard for treatment of metastatic CRC in the absence of extrahepatic metastases. However, only 10% to 25% of patients with CRC metastases are eligible for surgical resection due to the extent and location of the lesions within the liver or because of the presence of comorbid conditions or disseminate disease. Unresectable cases or those for whom surgery is contraindicated typically are treated
Medical Policy

with systemic chemotherapy, with poor results and considerable adverse effects.7

The NCCN Clinical Practice Guidelines for Colon Cancer and Rectal Cancers indicated ablative techniques may be considered either "alone or in conjunction with resection." for the treatment of CRC metastasis and the best outcomes are achieved with small single lesions.8 Additionally, all original sites of the disease need to be amenable to ablation. Similarly, the NCI recommended local ablative techniques such as RFA and CSA for CRC patients who are not viable surgical candidates.3

Neuroendocrine tumors are tumors of cells that possess secretory granules and originate from the neuroectoderm. The various types of neuroendocrine tumors include carcinoid, islet cell, medullary thyroid carcinomas, pheochromocytomas, and neuroendocrine carcinomas of the skin. Neuroendocrine cells have roles both in the endocrine system and the nervous system. They produce and secrete a variety of regulatory hormones, or neuropeptides, which include neurotransmitters and growth factors. Overproduction of the specific neuropeptides produced by the cancerous cells causes a variety of symptoms depending on the hormone produced. They are rare, with an incidence of two to four per 100,000 persons per year and presentation with metastatic disease accounts for 12% to 22%.9 The liver is also a common site of metastases from neuroendocrine cancers. Treatment of liver metastases is undertaken to prolong survival and reduce endocrine-related symptoms, as well as symptoms related to the hepatic mass.

The NCCN Guidelines and NCI PDQ for neuroendocrine tumors advised the management of unresectable liver metastases may include, hepatic regional therapy (arterial embolization, chemoembolization, radioembolization), or ablative therapies such as RFA, cryotherapy, or MWA.10,11 For pancreatic islet cell tumors, the NCI PDQ database stated patients with hepatic-dominant disease and intractable symptoms due to tumor bulk or aberrant hormone release "may benefit from procedures that reduce hepatic arterial blood flow to metastases (hepatic arterial occlusion with embolization or with chemoembolization)."11 For select patients, locoregional treatment in combination with chemotherapy may be appropriate.

The NCI PDQ for ocular melanoma, also called uveal melanoma, is the second most common form of melanoma; striking about 2,000 adults in the United States (U.S.) each year.12 It is the most common primary eye ocular malignancy in adults and shows a strong predilection for liver metastases. Even with successful treatment of the primary tumor, up to 50% of patients will subsequently develop systemic metastases, with liver involvement in up to 90% of these patients, which is universally fatal. Metastatic uveal melanoma is resistant to systemic chemotherapy, leading to the evaluation of locoregional treatment modalities to control tumor progression in the liver, including TACE. It can affect patients at any age but is most common in patients over 50.

There were no NCCN Clinical Practice Guidelines identified for ocular melanoma. The NCI PDQ database made no specific recommendations regarding locoregional therapies in the treatment of hepatic metastases from intraocular melanoma.12

Liver Metastases from other Cancers Including Colorectal Cancer

Ablative therapy as a primary treatment of metastatic tumors in the liver other than CRC and neuroendocrine tumors has also been investigated. However, evidence is absent or limited to small case series and retrospective reviews.

Breast Cancer

A number of case series reported on RFA of breast cancer liver metastases. A series of 19 patients was described by Lawes et al.13 Eight patients had disease confined to the liver, with 11 also having stable extrahepatic disease. At the time of the report, seven patients
with disease confined to the liver at presentation, were alive, as were six with extra-hepatic disease; median follow-up after RFA was 15 months (range: 0 to 77 months). Survival at 30 months was 41.6%. Radiofrequency ablation failed to control hepatic disease in three patients.

A case series of 66 patients with breast cancer liver metastases who underwent hepatic resection (n = 35), resection and RFA (n = 18), or RFA alone (n = 13) was reported by Pawlik et al.14 After a median follow-up of 35.8 months, 44 patients had recurrence (intrahepatic only, n = 16; extrahepatic only, n = 11; both, n = 17). The one-, three-, and five-year overall survival rates were 91.5%, 65.4%, and 27.1%, respectively. The authors recommended patients with metastatic disease who can be rendered surgically free of disease be considered for potential hepatic resection.

In a retrospective review, Meloni et al assessed local control as well as intermediate- and long-term survival in 52 patients.15 Inclusion criteria were fewer than five tumors, maximum tumor diameter of 5 cm or smaller, and disease confined to the liver or stable with medical therapy. Complete tumor necrosis was achieved in 97% of tumors. Median time to follow-up from diagnosis of liver metastasis and from RFA was 37.2 and 19.1 months, respectively. Local tumor progression occurred in 25% of patients and new intrahepatic metastases developed in 53% Overall median survival time, from the time the first liver metastasis was diagnosed, was 42 months, and five-year survival was 32%. Patients with tumors 2.5 cm in diameter or larger had a worse prognosis than those with smaller tumors. The authors concluded these survival rates were comparable to those reported in the literature for surgery or laser ablation. In another series of 43 breast cancer patients with 111 liver metastases, Jakobs et al reported that technical success was achieved in 107 metastases (96%).16 During follow-up, local tumor progression was observed in 15 metastases. The estimated overall median survival was 58.6 months. Survival was significantly lower among patients with extrahepatic disease, with the exception of skeletal metastases.

While many of the authors reported RFA of breast cancer liver metastases was technically feasible and may provide a survival benefit in woman without extrahepatic or stable extrahepatic disease (excluding bone metastases); there are not clinical practice guidelines or position statements from U.S. professional associations recommending RFA for breast cancer liver metastases.

Sarcoma

Jones et al evaluated RFA in a series of patients with sarcoma. Thirteen gastrointestinal stromal tumor (GIST) patients and 12 with other histological subtypes received RFA for metastatic disease in the liver; 12 of these responded to the first RFA procedure and one achieved stable disease.17 Two GIST patients received RFA on two occasions to separate lesions within the liver and both responded to the second RFA procedure. Of the other subtypes; seven underwent RFA to liver lesions, five of these responded to RFA, one progressed, and one was not assessable for response at the time of analysis. Radiofrequency ablation was well-tolerated in this series of sarcoma patients and may have a role in patients with GIST who have progression in a single metastasis but stable disease elsewhere. The authors advised larger studies were required to better define the role of this technique in this patient population.

Other Tumors

Other retrospective studies and case series performing ablative therapy for hepatic metastases from other primary tumor sites have been published by Martin et al and Lorentzen et al; however, the studies only report the feasibility of the procedures and propose improved progression-free survival.18,19 Additionally, studies were small, and
selection criteria were not identified or uniformly adopted. Several authors advised larger prospective trials were needed to confirm results.

Gervais et al reported that the Society of Interventional Radiology published a position statement on percutaneous RFA for the treatment of liver tumors in 2009. It is the position of the society that “percutaneous RF ablation of hepatic tumors is a safe and effective treatment for selected patients with HCC and colorectal carcinoma metastases” and the current literature was insufficient to support any recommendations supporting or refuting the use of RFA in other diseases.

The published evidence for demonstrating improved health outcomes with ablative therapies of other hepatic metastatic tumors is lacking. Comparative trials are needed for these malignancies that may have associated systemic disease. While locoregional ablative therapy is included in the NCCN Guidelines for CRC and neuroendocrine tumors, ablative therapy is not recommended for all other metastatic tumors to the liver.

**Locoregional Ablative Therapies**

There is research available for each of the ablative therapies. However, many of the studies combine multiple ablative procedures or utilize ablative techniques as an adjunct to surgical resection or chemotherapy. Studies also include patients with a broad range of tumor size and etiology. As a result, it is sometimes difficult to draw specific conclusions regarding the efficacy of an ablative technique. Careful selection of candidates for each treatment option and expert application of these treatments are required to achieve best outcomes.

**Cryosurgical Ablation**

Cryosurgical ablation, also known as cryoablation, involves the destruction of targeted abnormal tissue through freezing. The procedure is typically performed by inserting a cryoprobe into the tumor through which coolant is circulated. The freezing process is monitored to limit damage to surrounding healthy liver tissue. Cryosurgical ablation is usually performed as an open surgical technique, but may also be percutaneous or laparoscopic with imaging guidance. Cryosurgical ablation may be a stand-alone intervention or performed in conjunction with surgical resection or in combination with other ablative techniques. Potential advantages of CSA include local control of tumor progression and preservation of parenchymal tissue. In 1999, Seifert & Moris reported that potential complications include hypothermic damage to surrounding normal tissue, structural damage along the probe track and secondary tumors from seeding during probe removal.

Seifert et al reported on a series of patients with colorectal liver metastases treated from 1996 to 2002. In this series, 168 patients underwent resection and 55 had CSA (in 25 of these patients it was combined with resection). Twenty-nine percent of the ablation group had prior liver resection compared with only 5% in the resection group. Twenty percent of both groups had extrahepatic disease at the time of surgery. With a median follow-up of 23 months, median and five-year survival rates following resection and CSA were comparable at 29 months; 23% and 26%, respectively. While median disease-free survival times and five-year disease-free survival rates following resection were superior for resection (10 months and 19%) compared to CSA (six months and 12%), 29% of the patients in the CSA group had undergone prior resection, suggesting more advanced disease.

Joosten et al evaluated the efficacy of CSA and RFA in a mixed group of resected and unresected patients. There was no significant difference in survival between patients treated with CSA or RFA alone versus those treated by local ablation combined with...
resection (p = 0.55). Overall complication rates were higher for the CSA group (30%) than for the RFA group (11%). It was concluded that CSA and RFA can be used either alone or as an adjunct to resection in patients with unresectable colorectal liver metastases. The authors noted additional comparative study in randomized trials were indicated.

Ruers et al reported on a consecutive series of 201 CRC patients, without extrahepatic disease, treated between 1995 and 2004 that underwent laparotomy for surgical treatment of liver metastases. These patients were prospectively followed up for survival and quality of life. At laparotomy, three groups were identified: patients in whom radical resection of metastases proved feasible, patients in whom resection was not feasible who received local ablative therapy (CSA or RFA), and patients in whom resection or local ablation was not feasible for technical reasons who received systemic chemotherapy. The study reported patients in the chemotherapy and local ablation groups were comparable for all prognostic variables tested. For the RFA and CSA group, overall survival at two and five years was 56% and 27%, respectively (median 31 months, n = 45), for the chemotherapy group 51% and 15%, respectively (median 26 months, n = 39) (p = 0.252). The median disease-free survival after local ablation was nine months. The authors concluded although overall survival of local ablation versus chemotherapy did not reach statistical significance, the median disease-free survival of nine months suggested a beneficial effect of local tumor ablation.

Cryosurgical ablation is included as one of the ablative techniques in the treatment of hepatic tumors by the NCCN guidelines; although, the literature cited in the guideline reported predominantly on RFA and PEI. The majority of literature regarding CSA consists of uncontrolled case series that did not report survival data, or papers describing technical aspects of this technique. Based on the literature, RFA appears to be the most common ablation technique used in the United States; however, the choice of ablative technique is most often based on individual clinician and the institution's experience and preference.

The evidence indicates locally ablative techniques, including CSA, are a viable treatment option when resection is not feasible, or in some cases, as an adjunct to resection. In addition, ablative procedures such as CSA may offer a survival benefit over chemotherapy.

Unresectable Hepatocellular Carcinoma Tumors in the Transplant Setting

As noted earlier, liver transplantation is the only curative alternative for unresectable HCC. Locoregional therapies (e.g., ablation, TACE) have been explored in various settings including as a technique to prevent tumor progression in patients on the liver transplant waiting list, downstaging tumors such that the patient will be considered a better candidate for liver transplantation, and decreasing the incidence of post-transplant recurrence in patients with larger (T3) tumors. All of these indications are in part related to the United Network for Organ Sharing (UNOS) liver allocation policy, which prioritizes patients for receiving donor livers. The UNOS policy recognized pretransplant locoregional therapies including “chemoembolization of lesion, radiofrequency, cryo, or chemical ablation of the lesion,” as a component of patient management during the waiting period.

In 2002, UNOS introduced a new liver allocation system, model for endstage liver disease (referred to as MELD) for adult patients awaiting liver transplant. The MELD score is a continuous disease severity scale incorporating bilirubin, prothrombin time (i.e., international normalized ratio [INR]), and creatinine into an equation, producing a number that ranges from 6 (less ill) to 40 (gravely ill). Aside from those in fulminant liver failure, donor livers are prioritized to those with the highest MELD number. This scale
accurately predicts the risk of dying from liver disease except for those with HCC, who often have low MELD scores since bilirubin, INR, and creatinine levels are near normal. Therefore, patients with HCC are assigned additional allocation points according to the size and number (T stage) of tumor nodules as follows:

T1: One nodule, 1.9 cm or smaller

T2: One nodule between 2.0 to 5.0 cm, or two or three nodules each smaller than 3.0 cm

T3: One nodule larger than 5.0 cm, or two or three nodules with at least one larger than 3.0 cm

In considering how to allocate the scarce donor organs, UNOS sought to balance risk of death on the waiting list against risk of recurrence after transplant. Patients with T1 lesions were considered at low risk of death on the waiting list, while those with T3 lesions are at high risk of post-transplant recurrence, and are generally not considered transplant candidates. Patients with T2 tumors have an increased risk of dying while on the waiting list compared to those with T1 lesions and an acceptable risk of post-transplant tumor recurrence. Therefore, UNOS criteria prioritize T2 HCC by allocating additional points equivalent to a MELD score predicting a 15% probability of death within three months. This definition of T2 lesions is often referred to as the “Milan criteria,” in reference to a key study reported by Mazzaferro et al that examined the recurrence rate of HCC according to the size of the initial tumor.\textsuperscript{27} Note that liver transplantation for those with T3 HCC is not prohibited, but these patients do not receive any priority on the waiting list. All patients with HCC awaiting transplantation are reassessed at three-month intervals. Those whose tumors have progressed and are no longer T2 tumors will lose the additional allocation points.

Therefore, the UNOS allocation system provides strong incentives to use locoregional therapies to downsize tumors to T2 status and to prevent progression while on the waiting list. Promfet et al report of a national conference on liver allocation in patients with HCC in the U.S. addressed the need to better characterize the long-term outcomes of liver transplantation for patients with HCC and to assess whether it is justified to continue the policy of assigning increased priority for candidates with early stage HCC on the transplant waiting list in the U.S.\textsuperscript{28} At the completion of the meeting, there was a general consensus for the development of a calculated continuous HCC priority score for ranking HCC candidates on the list that would incorporate the calculated MELD score, alpha-fetoprotein, tumor size, and rate of tumor growth and that only candidates with at least stage T2 tumors would receive additional HCC priority points.

Locoregional Therapies as a Bridge to Transplant

Several studies have reported dropout rates of wait-listed patients treated with locoregional therapy. However, lacking controlled data, it is difficult to assess contributions of locoregional therapy to time on the waiting list. In addition, in 2002, as discussed above, UNOS revised its liver allocation policy, such that wait times for patients with HCC meeting the “Milan criteria” have now declined.\textsuperscript{26}

The majority of the literature has focused either on TACE or a variety of locoregional therapies. Given these limitations the following case series have been reported:

Graziadei et al reported on 48 patients with HCC awaiting transplantation; all underwent TACE every six to eight weeks until a complete response or a donor organ became available.\textsuperscript{29} No patients were removed from the list due to tumor progression and mean waiting time was 178 (+/- 105) days. Maddala et al studied the dropout rates of 54 patients receiving TACE while awaiting transplantation.\textsuperscript{30} During a median waiting time of 211 days (range: 28 to 1,099 days), the dropout rate was 15%. Obed et al reported on 20
patients with non-progression of lesions after TACE who had liver transplantation; median survival in this group was 92.3 months.\textsuperscript{31}

Fisher et al reported on 33 patients who received multimodality ablation therapy, consisting primarily of RFA or TACE.\textsuperscript{32} Five patients (12\%) were removed from the waiting list after waits of five to 14 months. In this protocol, patients with tumors larger than 5 cm were not considered transplant candidates until the tumor was completely ablated using TACE, RFA, or another technique. Yamashiki et al reported on 288 patients given various ablative therapies; the dropout rate due to tumor progression at one and three years was 6.25 and 23\% respectively.\textsuperscript{33} Tumors larger than 3 cm affected the dropout rate due to tumor progression. Mazzaferro et al reported on 50 patients with HCC who underwent RFA while awaiting transplantation; no patient had to be removed from the waiting list due to tumor progression over a mean wait time of 9.5 months.\textsuperscript{34} The median tumor size was 3 cm, and 80\% of patients met the Milan criteria. Similarly, Lu et al reported on 52 patients who underwent RFA as a bridge to transplantation, 42 of whom met the Milan criteria.\textsuperscript{35} After a mean of 12 months, 5.8\% had dropped off the waiting list due to tumor progression.

In a 2008 paper, Belghiti et al reviewed the literature reporting efficacy of local management approaches including resection, TACE, RFA, and no treatment.\textsuperscript{36} They concluded RFA can induce complete necrosis in the majority of small tumors (<2.5 cm) and there was no data demonstrating that the treatment reduced the rate of drop out before transplantation or improved survival after transplant. None of the studies included data from U.S. centers for patients listed after adoption of the Milan criteria. Porrett et al retrospectively compared 31 patients treated with RFA with 33 untreated controls.\textsuperscript{37} Only 20\% of treated tumors demonstrated complete ablation (necrosis) as defined by histologic examination of the entire lesion. Only 55\% of lesions with histologic viable tumor were detected by MRI after pretransplant therapy. After 36 months of follow-up, there was no difference between the treated and untreated groups in overall survival (84 versus 91\%), disease-free survival (74\% versus 85\%), cancer recurrence (23\% versus 12\%), or mortality from cancer recurrence (57\% versus 25\% - all respectively) (p > 0.1). The authors concluded viable tumor frequently persisted after pretransplant locoregional therapy and neoadjuvant treatment did not appear to improve post-transplant outcomes in the current MELD era.

The UNOS policy on allocation of livers indicated candidates whose tumors have been ablated after meeting the criteria for additional MELD/PELD (PELD - calculator for persons under age 12 years) points will continue to receive additional points (equivalent to a 10\% increase in mortality) every three months without review, even if the estimated size of residual viable tumor falls below stage T2 criteria.\textsuperscript{38} The policy also noted candidates may be removed from the listing if they are determined to be unsuitable for transplantation based on progression of HCC.

Locoregional Therapy to Downstage HCC Prior to Transplant

Yao et al analyzed longer-term outcome data on HCC downstaging in a cohort of 61 patients with tumor stage exceeding T2 criteria enrolled between June 2002 and January 2007.\textsuperscript{39} Eligibility criteria for downstaging included: 1) one lesion larger than 5 cm and up to 8 cm; 2) two to three lesions with at least one lesion larger than 3 cm and not exceeding 5 cm, with total tumor diameter up to 8 cm; or 3) four to five lesions with none larger than 3 cm, with total tumor diameter up to 8 cm. Transcatheter arterial chemoablation and laparoscopic RFA (LRFA) either alone or in combination were the main methods used: 11 patients received LRFA alone, 14 received TACE and LRFA, and nine received TACE and percutaneous RFA. A minimum observation period of three months after downstaging was required before liver transplant.
Tumor downstaging was successful in 43 patients (70.5%). Thirty-five patients (57.4%) received liver transplant, including two with live-donor liver transplantation. Treatment failure was observed in 18 patients (29.5%), primarily due to tumor progression. In the explant of 35 patients who underwent transplant, 13 had complete tumor necrosis, 17 met T2 criteria, and five exceeded T2 criteria. The Kaplan-Meier intention-to-treat survival analysis at one and four years after downstaging was 87.5% and 69.3%, respectively. The one-year and four-year post-transplantation survival rates were 96.2% and 92.1%, respectively. No patient had HCC recurrence after a median post-transplantation follow-up of 25 months. The only factor predicting treatment failure was pretreatment alpha-fetoprotein greater than 1,000 ng/mL. From this small series, the authors concluded successful downstaging can be achieved with excellent post-transplant outcomes.

Lewandowski et al compared radioembolization with chemoembolization (TACE) in the efficacy of downstaging 86 patients with HCC from stage T3 to T2.40 Patients were treated with either 90-yttrium microspheres (n = 43) or TACE (n = 43). Median tumor size was similar between the two treatment groups (5.7 and 5.6 cm, for TACE versus radioembolization, respectively). Partial response rates were 61% versus 37% for radioembolization versus TACE, respectively, with downstaging from T3 to T2 in 58% of patients treated with radioembolization versus 31% with TACE (p < 0.05).

As part of a national conference involving transplant physicians, workgroups were formed to discuss the policy of assigning increased priority for candidates with stage T2 HCC on the transplant list in the U.S. The workgroup assigned to the role of downstaging in transplant candidates with HCC noted inconsistent outcomes reported in the literature and proposed a definition of downstaging that would include TACE and various ablative techniques but not resection. Promfet et al noted that only two regions have adopted a downstaging protocol.28

The results and efficacy of downstaging with TACE to achieve a reduction in tumor burden to a T2 lesion remain controversial. There are retrospective data showing the ability to downstage patients with TACE, however, there is no randomized evidence that tumor downstaging prior to liver transplant confers a survival advantage.

Locoregional Therapies to Reduce Risk of Recurrence of T3 Tumors

Published literature by Pomfret et al reflects an ongoing discussion as to whether the UNOS allocation criteria should expand to include patients with larger tumors.28 An additional indication for locoregional therapies focused on their use in patients with T3 tumors, specifically to reduce the incidence of recurrence post-transplant. If the incidence of recurrence can be reduced, then Yao et al, Yao et al, Fernandez et al, Merli et al, and Sauer et al reported that advocates have argued the UNOS allocation criteria should not discriminate against patients with larger tumors.41,42,43,44,45 Some patients with T3 lesions apparently are cured with liver transplant, although most experience recurrent tumor. For example, in the seminal 1996 study by Mazzaferro et al, the four-year recurrence-free survival was 92% in those who met the Milan criteria (T2 lesion) compared to 59% in those who did not; Sauer et al reported additional studies confirmed this difference in recurrence-free survival rate.27,45 However, other institutions have reported similar outcomes with expanded criteria. For example, Yao and colleagues at University of California at San Francisco (UCSF) reported similar recurrence-free survival after transplant in patients with T2 and a subset of those with T3 tumors. This T3 subset was defined as a single lesion <6.5 cm or <three lesions with none greater than 3 cm and with a sum of tumor diameters <8 cm. These expanded criteria are known as the UCSF criteria reported by Yao et al.42

The question is whether locoregional therapies (including both RFA and TACE) may
decrease the recurrence rate in patients meeting the UCSF criteria. Yao and colleagues published a detailed analysis of 121 patients with HCC who underwent transplantation.\(^4^6\) Seventy-eight patients (64%) had T2 lesions, while an additional 27 patients (22.3%) met the expanded UCSF criteria, termed T3A lesions. The rest had T1, T3B, or T4 lesions. Individual patients received a variety of preoperative locoregional therapies, including TACE or ablative therapies, such as PEI, RFA, or combined therapies. A total of 38.7% of patients did not receive preoperative locoregional therapy. The one- and five-year recurrence-free survival was similar in those with T2 and T3A lesions, while the corresponding recurrence-free rates were significantly lower for those with T3B and T4 lesions.

The authors also compared recurrence-free survival of those who did and did not receive locoregional therapy. For those with T2 lesions, the recurrence rates were similar whether or not the patient received locoregional therapy. However, for T3 lesions (including both T3A and T3B), the five-year recurrence-free survival was 85.9% for those who received locoregional therapy compared to 51.4% in those who did not. When the data for T2 and T3 lesions were grouped together, the five-year recurrence-free survival was 93.8% for those who received locoregional therapy compared to 80.6% in those who did not. The authors concluded preoperative locoregional therapy may confer a survival benefit in those with T2 or T3 lesions. The authors noted several limitations to the study, including the retrospective nature of the data and the marginal statistical significance of the improved survival given the small numbers of patients in each subgroup. For example, only 19 patients were in the T3A (i.e., UCSF expanded criteria) subgroup. In addition, no protocol specified which type of locoregional therapy to offer different patients. These therapies are only offered to those patients with adequate liver reserve; such patients may have an improved outcome regardless of the preoperative management.

Summary

In conclusion, although comparisons among the various locoregional therapies are difficult due to factors such as interstudy patient and treatment heterogeneity, differences in patient management protocols and multimodality treatment protocols, the body of data illustrates the likely overall benefit of certain locoregional therapies for specific patient populations.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force has not addressed cryoablation of liver tumors.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References

http://optn.transplant.hrsa.gov/policiesAndBylaws/policies.asp.


**Documentation Required for Clinical Review**

Please provide the following documentation:

- History and physical, and/or consultation reports and progress notes including:
  - Clinical indications/justification of procedure
  - Previous treatment(s), duration, and response(s)
  - Treatment plan
  - Tumor type and description (i.e., resectable or unresectable, primary or metastatic, tumor burden [e.g., liver dominant])
- Pertinent radiological imaging results (i.e., abdominal CT and/or MRI and/or PET)
- Pathology report including tumor node metastasis (TNM) classification
- Current serum chemistry, liver function tests, and tumor marker results

**Post Service**

- Procedure report(s)
**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services are considered investigational and therefore not covered for any indication.

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<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tr>
<td>CPT®</td>
<td>20983</td>
<td>Ablation therapy for reduction or eradication of 1 or more bone tumors (e.g., metastasis) including adjacent soft tissue when involved by tumor extension, percutaneous, including imaging guidance when performed; cryoablation</td>
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<td>Laparoscopy, surgical, ablation of 1 or more liver tumor(s); cryosurgical</td>
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<td>47381</td>
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<td>Ablation, 1 or more liver tumor(s), percutaneous, cryoablation (new code 01/01/15)</td>
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<td></td>
<td>76940</td>
<td>Ultrasound guidance for, and monitoring of, parenchymal tissue ablation</td>
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<td>HCPCS</td>
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**Policy History**
This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>2/27/2015</td>
<td>BCBSA medical policy adoption</td>
<td>Medical Policy Committee</td>
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</table>

**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements**

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.