Name of Policy:
Locoregional Therapies for Hepatocellular Carcinoma and Metastatic Liver Carcinoma and Metastatic Carcinoid Tumors of the Liver

Policy #: 070       Latest Review Date: July 2014
Category: Surgical       Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**

**Transcatheter Arterial Chemoembolization (TACE)**

TACE was developed as an alternative to conventional systemic or intra-arterial chemotherapy for unresectable hepatocellular carcinoma (HCC) and for liver transplant. TACE combines the infusion of chemotherapeutic drugs with particle embolization. Tumor ischemia secondary to the embolization raises the drug concentration compared to infusion alone, extending the retention of the chemotherapeutic agent and decreasing systemic toxicity. During the procedure, iodized poppy-seed oil (Lipiodol) and chemotherapeutic agents (doxorubicin, cisplatin, or mitomycin C) are administered through the feeding artery of the tumor. This is followed by arterial embolization with gelatin sponge particles. The rationale for TACE is that infusions of this material will occlude arterial blood, causing an infarct and subsequent necrosis of tumors in the infarcted region. The liver is especially amenable to such an approach given the distinct lobular anatomy of the liver, the existence of two independent blood supplies, and the ability of healthy hepatic tissue to compensate for tissue mass lost during chemoembolization. Another rationale is that TACE provides for effective local dose intensity while avoiding systemic toxicities associated with intravenous chemotherapy.

TACE requires hospitalization. Prior to the procedure, the patency of the portal vein must be demonstrated to ensure an adequate post-treatment hepatic blood supply. Under local anesthesia and mild sedation, a superselective catheter is inserted via the femoral artery and threaded into the hepatic artery. Angiography is then performed to delineate the hepatic vasculature, followed by injection of the embolic chemotherapy mixture. Embolic material varies, but may include a viscous collagen agent, polyvinyl alcohol particles, or ethiodized oil. Typically, only one lobe of the liver is treated during a single session, with subsequent embolization procedures scheduled from five days to six weeks later. Since the embolized vessel recanalize, chemoembolization can be repeated as many times as necessary.

**Radio-frequency Ablation (RFA)**

Another alternative to surgical resection of liver tumors is RFA. RFA uses the energy of 450-to-500-KHz radiowave for hyperthermic ablation of liver tumors. During the procedure, a needle electrode with an uninsulated tip and an insulated needle shaft is inserted into the tumor. A flux of high-frequency alternating current passes through the needle tip into the surrounding tissue, generating rapid vibration of the ions in the tissue and frictional heat. The heat created around the electrode is subsequently conducted into the surrounding tissue in a predictable manner, causing coagulative necrosis. The current’s intensity and length, the gauge of the electrode tip, and the duration of energy applied determine the size of the ablated area usually a 3cm to 5cm area. The cells killed by RFA are not removed but are gradually replaced by fibrosis and scar tissue. If there is local recurrence, it occurs at the edge, and in some cases may be retreated. RFA can be performed percutaneously, laparoscopically, or through laparotomy.

**Percutaneous Ethanol Injection (PEI)**

PEI induces tumor necrosis by cellular dehydration, protein denaturation, and thrombosis of small vessels. HCC is softer than the surrounding cirrhotic liver and is often encapsulated, allowing selective diffusion of ethanol within the tumor mass. The hypervascularization of HCC also favors ethanol injection therapy by enhancing the distribution of ethanol within the network of the tumor vessels. A fine needle is inserted into the tumor under ultrasonographic guidance,
and absolute ethanol is then injected slowly into the tumor until the whole area of tumor appears hypoechoogenic on the ultrasound. PEI may be performed under CT guidance for tumors not visualized by ultrasounds. The injection is repeated once or twice a week for up to six to eight sessions, depending on the tumor size. PEI can be done as an outpatient procedure under local anesthesia.

**Cryosurgical Ablation (CSA)**

Cryotherapy is usually performed during surgery by inserting a cryoprobe cooled with liquid nitrogen or liquid argon into the tumor mass using ultrasound guidance. Rapid freezing to subzero temperature leads to ice formation in the extracellular space and leakage of water from the cells, which causes cellular damage by dehydration and destruction of the normal cellular structures. Cryotherapy is usually performed through laparotomy.

**Microspheres, Radioembolization**

Radioembolization (RE), referred to as selective internal radiation therapy or SIRT in older literature, is the intra-arterial delivery of small beads (microspheres) impregnated with yttrium-90 (Y-90) via the hepatic artery.

Microsphere (TheraSphere®, SIR-Sphere) is a therapeutic device consisting of insoluble glass microspheres in which the radionuclide yttrium-90 (Y-90) is an integral constituent. Because Y-90 emits a beta particle during radioactive decay that has an average tissue penetration of 2.5 mm and a maximum tissue penetration less than 1 cm. Therefore, it is suitable to deliver highly localized radiation doses to tumors while minimizing the damage to surrounding healthy liver tissue. Microspheres are delivered into the liver tumor through a catheter placed into the hepatic artery. The hepatic artery provides the main blood supply to the tumor in the liver, as opposed to normal liver parenchyma, which is dependent on the portal vein. Microspheres are unable to transverse the tumor vasculature so is embolized with the tumor and exerts a local beta radiation radiotherapeutic effect with relatively limited concurrent injury to surrounding normal tissue.

Microspheres are used to treat liver tumors where the blood supply is delivered by the hepatic artery. The size of the microspheres causes them to be embolized in the in the tumor vasculature and retained within the tumor. The microspheres are not biodegradable and do not redistribute to other organs of the body. The administration set facilitates the transfer of the radioactive microspheres from their container into the tumor via a catheter inserted in the hepatic artery. Treatment with microspheres is an outpatient procedure.

**Microwave ablation**

Microwave ablation is a technique similar to radiofrequency ablation. This technique involves destroying the liver tumor with the application of a probe directly into the tumor, typically under ultrasound guidance. However, unlike radiofrequency ablation, which utilizes alternating radiofrequency energy, microwave ablation utilizes microwave energy to destroy the tumor. Heat is generated by the vibration of water molecules and, since there is no electrical flow through the patient, there is no need for grounding pads. The system will allow ablations to be performed faster, meaning less time under anesthesia for patients. The Evident™ microwave ablation system by Covidien is the first such system available globally. Covidien, formerly known as Valleylab, received 510(k) clearance for their device Microwave Ablation Generator on November 25, 2008.
Policy:

Transcatheter Arterial Chemoembolization (TACE) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for patients with one of the following indications:
- hepatocellular carcinoma (HCC)
- metastatic liver carcinoma

Radio-frequency Ablation (RFA) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for patients with one of the following indications:
- hepatocellular carcinoma (HCC)
- metastatic liver carcinoma

Percutaneous Ethanol Injection (PEI) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for patients with one of the following indications:
- hepatocellular carcinoma (HCC)
- metastatic liver carcinoma

Microwave Ablation (MW ablation) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for patients with one of the following indications: (Effective 07/09/2009)
- hepatocellular carcinoma (HCC)
- metastatic liver carcinoma

Radioembolization or intra-hepatic microspheres (TheraSpheres®, SIRSpheres®) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for patients with one of the following indications:
- unresectable hepatocellular carcinoma (HCC)
- unresectable liver metastases from colorectal carcinoma
- unresectable liver metastases from neuroendocrine tumors (carcinoid and noncarcinoid)

Cryosurgical ablation (CSA) does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage when used for the treatment of liver tumors and is considered investigational.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.
Key Points:
Hepatocellular carcinoma (HCC) is one of the most common malignancies, ranking fifth in frequency in the world. While areas with higher incidences of Hepatitis C, such as Asia and Africa, have the highest incidences of HCC, its incidence is on the rise in the United States. Males are more commonly affected than females.

Surgical resection is the treatment of choice for HCC. However, only 10%-15% of patients are candidates for surgical resection due to tumor size, tumor location near major intrahepatic vessels, or poor hepatic functional reserve. Systemic chemotherapy has poor results with a response rate of less than 20% and no significant survival benefit has been shown compared with symptomatic management. Liver transplantation is an option for solitary tumors less than five centimeters or in patients with up to three tumors each smaller than three centimeters. However its use is limited because of the severe shortage of organs. Locoregional therapies are offered if patients with inoperable or operable liver tumors. Most patients have unresectable disease at the time of diagnosis.

Radiofrequency ablation
Carcinoid tumors are extremely rare. When tumor burden overtakes hepatic metabolic function, patients develop malignant carcinoid syndrome characterized by flushing, diarrhea, cardiac valve damage, bronchoconstriction, and asthma symptoms. RFA appears to be particularly well suited for the debulking of neuroendocrine metastases, as these patients can achieve significant symptomatic relief. Repeated treatments may be necessary.

Neuroendocrine tumors are tumors of cells that possess secretory granules and originate from the neuro ectoderm. 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 2 to 4 per 100,000 per year. Treatment of liver metastases is undertaken to prolong survival and reduce endocrine-related symptoms as well as symptoms related to the hepatic mass.

Primary Treatment of Unresectable Hepatocellular Liver Cancer
A 2003 TEC Assessment addressed radiofrequency ablation (RFA) in the treatment of unresectable primary or metastatic liver tumors. Since that time, many systematic reviews and meta-analyses have been published on RFA for hepatocellular cancer (HCC). In a Cochrane review, Weis et al reviewed studies on RFA for HCC versus other HCC interventions. Moderate quality evidence demonstrated hepatic resection had superior survival outcomes compared with RFA; however, resection might have greater rates of complications and longer hospital stays. Other systematic reviews and meta-analyses have also found superior survival with hepatic resection but higher rates of complications than RFA. This reinforces the use of RFA for only unresectable HCC. The Cochrane review also reported finding moderate quality evidence demonstrating superior survival with RFA over percutaneous ethanol injection (PEI). Evidence on RFA versus acetic acid injection, microwave ablation, or laser ablation was insufficient to draw conclusions.
One of the first methods devised to ablate liver tumors involved percutaneous ethanol injection (PEI). Several nonrandomized trials in the 1990s confirmed that PEI could safely achieve complete necrosis in small hepatocellular cancers (HCCs), with five-year survival rates of 32-38%. However, the technique had several drawbacks, including the need for multiple treatment sessions and a high local progression rate of 17-38%. Several randomized controlled trials (RCTs) have compared PEI and RFA in the treatment of small HCC. A systematic review of randomized trials for HCC treated with percutaneous ablation therapies was conducted by Cho and colleagues. The authors identified four RCTs involving 652 patients that compared RFA with PEI. The review concluded that RFA demonstrated significantly improved three-year survival in patients with HCC compared to ethanol injections. The majority of patients in these studies had one tumor, and more than 75% of the tumors were 3cm or smaller in size. The three-year survival with RFA ranged from 63 to 81%.

In a 2013, Shen and colleagues reported on a meta-analysis of four RCTs and quasi-RCTs, totaling 766 patients, to compare RFA to PEI for treatment of HCC nodules up to 3 cm. Overall survival was significantly longer for RFA than PEI at three years (hazard ratios [HR]: 0.66, 95% confidence interval [CI]: 0.48-0.90, p=0.009), and local recurrence risk was lower with RFA (HR: 0.38, 95% CI: 0.15-0.96, p=0.040). However, there was no difference in distant intrahepatic recurrence and RFA resulted in more complications.

In 2012, Xu et al reported on a meta-analysis of 13 studies to compare RFA to surgical resection for early HCC. Only two of the studies were RCTs. Surgical resection occurred in 1,233 patients and RFA was used in 1,302 patients. Surgical resection patients had significantly longer overall survival rates at one, three and five years than RFA (odds ratio [OR]: 0.60, 95% confidence interval [CI]: 0.42 to 0.86, OR: 0.49, 95% CI: 0.36 to 0.65, and OR: 0.60, 95% CI: 0.43 to 0.84, respectively). When only HCC tumors <3 cm were analyzed, resection was still significantly better in overall survival than RFA at one, three and five years. Recurrence rates were also significantly lower in the surgical resection group at one, three and five years than RFA (OR: 1.48, 95% CI: 1.05 to 2.08, OR: 1.76, 95% CI: 1.49 to 2.08, and OR: 1.68, 95% CI: 1.21 to 2.34, respectively). Local recurrence rates did not differ significantly between procedures. Complication rates were higher with resection than RFA (OR: 6.25, 95% CI: 3.12 to 12.52; p=0.000), but in a subanalysis of HCC <3 cm, complication rates were significantly lower with resection than RFA.

Tiong and Maddern conducted a systematic review of the literature from 2000 to 2010 and a meta-analysis of survival and disease recurrence after RFA for HCC. Studies reporting on patients with HCC who were treated with RFA, either in comparison or in combination with other interventions, such as surgery or percutaneous ethanol injection (PEI), were eligible for inclusion. Outcome data collected were overall survival, disease-free survival and disease recurrence rates. Only RCTs, quasi-RCTs, and non-randomized comparative studies with more than 12 months’ follow-up were included. Forty-three articles, including 12 RCTs, were included in the review. The majority of the articles reported the use of RFA for unresectable HCC, often in combination with other treatments such as PEI, transarterial chemoembolization, and/or surgery. A meta-analysis of five RCTs showed that RFA was better than PEI, with higher overall and disease-free survival rates. Data on RFA compared to microwave ablation were
inconclusive. The authors concluded that RFA can achieve good clinical outcomes for unresectable HCC.

In a 2013 meta-analysis comparing RFA to cryoablation for HCC, Huang and colleagues evaluated three prospective studies and one retrospective study. Included in the studies were 180 RFA and 253 cryoablation patients. RFA was found to be significantly superior to cryoablation in rates of complications (OR: 2.80, 95% CI: 1.54-5.09), local recurrence of patient (OR: 4.02, 95% CI: 1.93-8.39), and local recurrence of tumor (OR: 1.96, 95% CI: 1.12-3.42). However, mortality was not significantly different (OR 2.21, 95% CI: 0.45-10.8) between groups.

Randomized controlled trials
In 2012, Feng et al reported on a randomized controlled trial of 84 RFA patients compared to 84 surgical resection patients with up to two HCC nodules less than 4cm in size. Patients were followed for three years and overall survival and recurrence-free survival were not statistically different between groups, (p=0.342 and p=0.122, respectively).

Primary Treatment of Unresectable Liver Metastases from Colorectal Cancer
More than half of patients with colorectal cancer (CRC) will develop liver metastases, generally with a poor prognosis. A median survival of 21 months has been observed in patients with a single CRC liver metastasis; those with several unilobar lesions have median survival of 15 months; and, those with disseminated metastases have median survival of less than one year. A number of first-line systemic chemotherapy regimens have been used to treat metastatic CRC, with a two-year survival rate of 25% for those treated with 5-fluorouracil (5-FU) or 5-FU plus leucovorin. With the introduction of newer agents, including irinotecan and oxaliplatin, and targeted drugs such as cetuximab and bevacizumab, two-year survival rates have increased to 30–39%, with marked improvement in overall survival duration. As the liver is often the only site of metastases from CRC, however, locoregional therapies have been investigated. Surgical resection is considered the gold standard for treatment of CRC liver metastases, with five-year actuarial survival rates that historically range from 28% to 38% but may reach 58% in appropriately selected, resectable patients without widely disseminated disease. However, only 10–25% of patients with CRC metastases are eligible for surgical resection because of the extent and location of the lesions within the liver or because of the presence of comorbid conditions or disseminated disease. Unresectable cases or those for whom surgery is contraindicated typically are treated with systemic chemotherapy, with poor results and considerable adverse side effects.

Alternatively, RFA has been proposed as an approach to treat metastatic CRC in the liver. Early clinical experience with RFA comprised case series to establish feasibility, safety, tolerability, and local therapeutic efficacy in short-term follow-up. A 2006 literature review encompassing six case series (n=446) showed that RFA of unresectable CRC metastases was associated with one, two, and three-year survival rates that ranged from 87–99%, 69–77%, and 37–58%, respectively. While these results suggest RFA may have clinical benefit in this setting, a primary caveat is the definition of the term “unresectable” in the different series, and that different surgeons may have different opinions on this issue. Further, differences in lesion size, number, distribution, prior treatments, RFA technology, and physician experience may affect results, making it difficult to compare results of different studies.
Systematic Reviews
A 2012 systematic review by Cirocchi et al analyzed 17 nonrandomized studies and one abstract on a RCT from a 2010 American Society of Clinical Oncology (ASCO) meeting on RFA for CRC liver metastases. The RCT reported progression-free survival was significantly higher in 60 patients receiving RFA plus chemotherapy when compared to 59 patients receiving only chemotherapy. The RCT did not report overall survival. This Cochrane review found different types of vulnerability in all reviewed studies. Of main concern was the imbalance of patient characteristics in the studies reviewed, as well as heterogeneity in the interventions, comparisons and outcomes. Therefore the authors concluded the evidence was insufficient to recommend RFA for CRC liver metastasis. In a 2014 Health Technology Assessment, Loveman et al also found insufficient evidence to draw conclusions on the clinical effectiveness of ablative therapies, including RFA, for liver metastases.

In 2013, Weng and colleagues reported on a systematic review and meta-analysis to compare RFA to liver resection for the treatment of CRC liver metastases. One prospective study and 12 retrospective studies were included in the analysis. Overall survival at three and five years was significantly longer in liver resection than RFA (risk ratio [RR]: 1.377, 95% CI: 1.246-1.522 and RR: 1.474, 95% CI: 1.284-1.692, respectively). Disease-free survival was also significantly longer in liver resection than RFA at three and five years (RR: 1.735, 95% CI: 1.483-2.029 and RR: 2.227, 95% CI: 1.823-2.720). While postoperative morbidity with liver resection was significantly higher than with RFA (RR: 2.495, 95% CI: 1.881-3.308), mortality was not significantly different between liver resection and RFA. Liver resection also still performed significantly better than RFA when data were analyzed in three subgroups: tumors <3 cm, solitary tumor and open or laparoscopic approach. However, hospital stays were significantly shorter (9.2 + 0.6 vs. 3.9 + 0.4, p<0.01) and rates of complications lower (18.3% vs. 3.9%, p<0.01) with RFA over liver resection. Interpretation of the meta-analysis is limited by the retrospective nature of the majority of studies.

A 2011 systematic review by Pathak and colleagues assessed the long-term outcome and complication rates of various ablative therapies used in the management of colorectal liver metastases. The literature search was from 1994 to 2010, and study inclusion criteria included minimum one-year follow-up and greater than 10 patients. In all, 226 potentially relevant studies were identified, 75 of which met the inclusion criteria. The majority of the studies were single-arm, single-center, retrospective and prospective. There was wide variability in patient groups, adjuvant therapies, and management approaches within individual studies. Several studies combined results for colorectal and non-colorectal metastases, often reporting combined outcomes. Endpoints were not always reported uniformly, with varying definitions of survival time, recurrence time, and complication rates. Cryotherapy (26 studies) had local recurrence rates of 12-39%, with mean one-, three- and five-year survival rates of 84%, 37% and 17%, respectively. The major complication rate ranged from 7% to 66%. Microwave ablation (13 studies) had a local recurrence rate of 5-13%, with a mean one-, three- and five-year survival of 73%, 30% and 16%, respectively, and a major complication rate ranging from 3% to 16%. Radiofrequency ablation (36 studies) had a local recurrence rate of 10-31%, with a mean one-, three- and five-year survival of 85%, 36% and 24%, respectively, with major complication rate ranging from 0% to 33%. The authors concluded that ablative therapies offer significantly
improved survival compared with palliative chemotherapy alone with five-year survival rates of 17-24%, and that complication rates of commonly used techniques are low.

A review by Guenette and Dupuy in 2010 summarized the literature on the use of RFA for colorectal hepatic metastases. Approximately 17 studies in the literature with greater than 50 patients treated with RFA for colorectal hepatic metastases reported survival. Average tumor size, reported in 15 studies ranged from 2.1 cm-4.2 cm. Five-year overall survival (OS) reported in 12 studies, ranged from 2% to 55.3% with a mean of 24.5%. The largest study series included in the review was by Lencioni et al. and consisted of 423 patients with average tumor size of 2.7cm, four or fewer metastases, each 5cm or less in greatest dimension, and no extrahepatic disease. Overall survival in the Lencioni et al study at one, three and five years was 86%, 47% and 24%, respectively. The authors of the Guenette/Dupuy review concluded that five-year survival rates following RFA appear to rival those following resection but that long-term data associated with RFA and colorectal hepatic metastases are sparse, randomized trials have failed recruitment, and patients with resectable disease should undergo resection if possible. However, given the efficacy of RFA as compared to chemotherapy alone, RFA should be considered as a primary treatment option in patients with unresectable disease.

Cohort Studies
Prospective studies in which RFA was compared with resection or systemic chemotherapy in well-defined consecutive cohorts of patients with localized CRC metastases and no evidence of additional metastatic disease have been conducted. In the first study, Abdalla and coworkers examined recurrence and survival rates for clinically similar patients treated with hepatic resection only (n=190), resection plus RFA (n=101), RFA only (n=57, open laparotomy by hepatobiliary surgeon), and systemic chemotherapy alone (n=70). In the key relevant comparison, RFA versus chemotherapy in chemotherapy-naive patients with non-resectable CRC metastases (median one lesion per patient, range 1 to 8, median tumor size 2.5 cm), overall survival at four years was 22% in the RFA group compared with 10% in the chemotherapy group (p=0.005). Median survival was estimated at 25 months in the RFA group and 17 months in the chemotherapy group (p not reported). Recurrence anywhere in the liver at median follow-up of 21 months was 44% in the RFA group and 11% in the resection-only group (p<0.001), although the proportion of patients with distant recurrence as a component of failure was similar (41% resection, 40% RFA, p not significant).

In a second trial, a consecutive series of well-defined, previously untreated patients (n=201) without extrahepatic disease underwent laparotomy to determine therapeutic approach. Three groups were identified: those amenable to hepatic resection (n=117); those for whom resection plus local ablation were indicated (RFA, n=27; cryoablation, n=18); and those deemed unresectable and unsuitable for local ablation (n=39) who received systemic chemotherapy. Median overall survival was 61 months (95% confidence interval [CI]: 41 to 81 months) in resected patients (median one tumor per patient, range 1 to 9, median diameter 3.8 cm), 31 months (95% CI: 20 to 42 months) in locally ablated patients (median four tumors per patient, range 1 to 19, median diameter 3cm per lesion), and 26 months (95% CI: 17–35 months) in the chemotherapy patients (median four tumors per patient, range 1 to 17, median diameter 4 cm per lesion, p not significant, ablated vs. chemotherapy). Results from two validated quality-of-life instruments (EuroQoL-5D and EORTC QLQ C-30) showed that patients treated by local ablation
returned to baseline values within three months, whereas those treated with chemotherapy remained significantly lower (i.e., worse quality of life) than baseline over 12 months post-treatment (p<0.05).

In 2011, van Tilborg and colleagues reported long-term results in 100 patients with unresectable colorectal liver metastases who underwent a total of 126 RFA sessions (237 lesions). Lesion size ranged from 0.2-8.3 cm (mean 2.4 cm). The mean follow-up time was 29 months (range 6 to 93 months). Major complications (including abscess, hemorrhage, grounding pad burns, and diaphragm perforation) occurred in eight patients. Factors that determined the success of the procedure included lesion size and the number and location of the lesions. Local tumor site recurrence was 5.6% for tumors less than 3cm, 19.5% for tumors 3 to 5 cm, and 41.2% for those greater than 5cm. Centrally located lesions recurred more often than peripheral ones, at 21.4% versus 6.5%, respectively, p=0.009. Mean survival time from the time of RFA was 56 months (95% CI: 45-67 months).

**Treatment of Unresectable Liver Metastases from Neuroendocrine Tumors**

Most reports of radiofrequency treatment of neuroendocrine liver metastases include small numbers of patients or subsets of patients in reports of more than one ablative method or very small subsets of larger case series of patients with various diagnoses.

Berber and Siperstein analyzed a large series of liver tumors treated with RFA. Of 1,032 tumors in the study, 295 were neuroendocrine tumor metastases. The mean number of lesions treated was 5.6 (range: 1-16) and mean size was 2.3 cm (range: 0.5–10.0 cm). Local recurrence rates were lower in patients with neuroendocrine tumors than in patients with other tumor types; neuroendocrine tumors (19/295, 6%), colorectal metastases (161/480, 24%), noncolorectal, nonneuroendocrine metastases (28/126, 22%), and HCC (23/131, 18%). In patients with neuroendocrine tumors, 58% of the recurrences were evident at one year and 100% at two years versus 83% at one year and 97% at two years for colorectal metastases. Eight neuroendocrine tumors were eligible for repeat RFA; seven were retreated, and one was not. Symptom control and survival were not reported in this study.

Mazzaglia et al report on a series gathered over ten years of 63 patients with neuroendocrine metastases who were treated with 80 sessions of LRFA. Tumor types were 36 carcinoid, 18 pancreatic islet cell, and nine medullary thyroid cancer. Indications for enrollment in the study were liver metastases from neuroendocrine tumors, enlarging liver lesions, worsening of symptoms, and/or failure to respond to other treatment modalities, and predominance of disease in the liver; however, patients with additional minor extrahepatic disease were not excluded from the study. RFA was performed 1.6 years (range, 0.1 to 7.8 years) after diagnosis of liver metastases. Fourteen patients had repeat sessions for disease progression. The mean number of lesions treated at the first RFA session was six and the mean tumor size was 2.3 cm. One week after surgery, 92% of patients had at least partial symptom relief and 70% had complete relief. Symptom control lasted 11 +/- 2.3 months. Median survival times were 11 years postdiagnosis of primary tumor, 5.5 years postdiagnosis of neuroendocrine hepatic metastases, and 3.9 years postfirst RFA treatment.
Elias et al report on 16 patients who underwent a one-step procedure comprising a combination of hepatectomy and RFA for treatment of gastroenteropancreatic endocrine tumors. A mean of 15 +/- 9 liver tumors per patient were surgically removed, and a mean of 12 +/-8 were ablated using RFA. Three-year survival and disease-free survival rates were similar to those observed in the authors’ preliminary series of 47 patients who had hepatectomy with a median of seven liver tumors per patient. Venkatesan and colleagues report on six patients treated for pheochromocytoma metastases. Complete ablation was achieved in six of seven metastases. Mean follow-up was 12.3 months (range: 2.5 to 28 months).

Primary Treatment of Unresectable Liver Metastases from Tumors other than Colorectal Cancer and Neuroendocrine Tumors

Breast Cancer
A number of case series report RFA of breast cancer liver metastases. In 2014, Veltri et al analyzed 45 women treated with RFA for 87 breast cancer liver metastases of a mean size of 23 mm. Complete ablation was seen on initial follow-up in 90% of tumors, but tumor recurrence occurred in 19.7% within eight months. RFA did not impact OS, which at 1 year was 90% and at three years was 44%.

In a retrospective review, Meloni et al assessed local control and intermediate- and long-term survival in 52 patients. 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 conclude that these survival rates are comparable with those reported in the literature for surgery or laser ablation. In another series of 43 breast cancer patients with 111 liver metastases, technical success was achieved in 107 metastases (96%). 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.

A series of 19 patients was reported by Lawes et al. 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: 0-77 months). Survival at 30 months was 41.6%. RFA failed to control hepatic disease in three patients.

Other reports include 16 or fewer subjects. All of the authors report that RFA of breast cancer liver metastases is technically feasible and may provide a survival benefit in women without extra-hepatic or stable extrahepatic disease (excluding bone 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. 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. RFA was well-tolerated in this series of sarcoma patients. RFA may have a role in patients with GIST who have progression in a single metastasis but stable disease elsewhere. The authors advise that further larger studies are required to better define the role of this technique in this patient population.

A case series of 66 patients who underwent hepatic resection (n=35), resection and RFA (n=18), or RFA alone (n=13) was reported by Pawlik et al. 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 recommend that patients with metastatic disease who can be rendered surgically free of disease be considered for potential hepatic resection.

Summary

In radiofrequency ablation (RFA), a probe that generates heat is inserted into the center of a tumor resulting in a 3- to 5-cm sphere of dead tissue. The cells killed by RFA are not removed but are gradually replaced by fibrosis and scar tissue. If there is local recurrence, it occurs at the edge, and in some cases may be retreated. RFA may be performed percutaneously, laparoscopically, or as an open procedure.

For treating patients with unresectable HCC, numerous studies including randomized trials demonstrate that in patients with small foci of HCC (no more than three lesions), RFA appears to be better than ethanol injection in achieving complete ablation and preventing local recurrence. Three-year survival rates of 80% have been reported. Thus, the policy statement notes that this indication for RFA in patients with HCC who are not candidates for resection or transplant may be considered medically necessary.

A substantial body of literature has been published on the use of RFA to treat colorectal cancer metastases in the liver. Two prospective studies comprise good evidence that overall survival following RFA is at least equivalent and likely better than that obtained with currently accepted systemic chemotherapy in well-matched patients with unresectable hepatic metastatic colorectal cancer who do not have extrahepatic disease. Additional evidence from one comparative study suggests RFA has a lesser deleterious effect on quality of life than chemotherapy and that RFA patients recover quality of life significantly faster than chemotherapy recipients. Quicker recovery of quality of life may be viewed as a net health benefit when viewed in the context of expected survival durations of patients with metastatic cancer. In addition, results from a number of uncontrolled case series also suggest RFA of hepatic colorectal cancer metastases produces long-term survival that is at minimal equivalent and likely superior to historical outcomes achieved with systemic chemotherapy. Although indirect comparisons of series results are difficult, the body of data shows consistent change in direction and magnitude of effect that suggests an RFA benefit. It should be recognized, however, that patients treated with RFA in different series may have better prognosis than those who undergo chemotherapy, suggesting patient selection bias may at least partially explain the apparent better outcomes observed.
following RFA. Given the caveats outlined above, the available body of clinical evidence is sufficient to conclude that RFA of unresectable colorectal cancer metastases to the liver, absent extrahepatic metastatic disease, may be considered medically necessary.

Evidence shows that durable tumor and symptom control of neuroendocrine liver metastases can be achieved by radiofrequency ablation. This evidence is based on case series; neuroendocrine tumors are uncommon. Thus, a statement indicating that radiofrequency ablation of hepatic metastases of neuroendocrine tumors may be considered medically necessary in patients whose symptoms are not controlled by systemic therapy has been added.

The published evidence for demonstrating improved health outcomes with RFA of other hepatic metastatic tumors (e.g., breast cancer and sarcoma) is lacking. Comparative trials are needed for these malignancies that may have associated systemic disease.

**Practice Guidelines and Position Statements**

The Society of Interventional Radiology published a position statement on percutaneous radiofrequency ablation 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 that the current literature is insufficient to support any recommendations supporting or refuting the use of RFA in other diseases.

The National Comprehensive Cancer Network (NCCN) 2014 guidelines recommend:

- For HCC, the guidelines address RFA in a list of ablative techniques and recommend that all tumors should be accessible and amenable to ablation, and that in well selected patients with small, properly located tumors, ablation should be considered a definitive treatment, and that lesions 3-5 cm may be treated with a combination of embolization and ablation if the location is favorable. [category 2A]
- For colorectal cancer metastatic to the liver, the guidelines state that ablative techniques may be considered alone or in conjunction with resection if amenable to ablation or resection. [category 2A]
- For neuroendocrine tumors metastatic to the liver, the guidelines state that hepatic regional therapies such as RFA may be considered for unresectable liver metastases if near complete treatment of tumor is possible. [category 2A]

The National Institute for Health and Clinical Excellence (NICE) published guidance on radiofrequency ablation for colorectal liver metastases in 2009 stating that current evidence on safety and effectiveness is sufficient to support use of the procedure in patients unfit or otherwise unsuitable for hepatic resection, or in those who have previously had hepatic resection, and published guidance in 2003 stating that current evidence of the safety and efficacy of radiofrequency ablation for hepatocellular carcinoma appears adequate to support use of the procedure.

**U.S. Preventive Services Task Force Recommendations**

RFA of tumors is not a preventive service.
Microspheres/Radioembolization (RE)
Three clinical studies have been conducted with TheraSphere®. All three studies with observational with mortality, response to treatment, and safety as major endpoints. To be eligible for a study, patients had to have:

- Histologically confirmed unresectable hepatocellular carcinoma confined to the liver and at least one measurable lesion
- Eastern Cooperative Oncology Group (ECOG) performance status 0-3
- Estimated life expectancy greater than 12 weeks
- Absolute granulocyte count 2.0 x 10^8/L or greater
- Platelet count 100 x 10^9/L or greater
- Prothrombin time (PT) and activated partial thromboplastin time (aPTT) within normal limits
- Bilirubin less than 1.5 x upper normal limit
- Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (AP) less than 5 x upper normal limit
- Normal pulmonary function defined as no more than 30% greater or less than the expected normal.

Patients were excluded if the following criteria were met:
- Previous chemotherapy or radiation
- Any contraindication to hepatic artery catheterization such as vascular abnormalities, bleeding diathesis, allergy to contrast dye, or portal vein thrombosis
- Any medical or psychosocial condition, which would not permit the patient to be managed according to the protocol.

Based on the results of preclinical and clinical trials, the FDA concluded that these trials “provide evidence of the safety of TheraSphere® in the treatment of patients with surgically unresectable hepatocellular carcinoma. In addition, the probable benefit from the use of TheraSphere® in this patient population outweighs the risks when compared to the safety and probable benefits of currently available alternative therapies.”

SIR-Spheres are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy of floxuridine. The FDA-approved product labeling for SIR-Spheres states that treatment with SIR-Spheres may be indicated when the metastatic colorectal cancer in the liver is considered unresectable. Resectability may be evaluated via imaging with a triple phase contrast angio-portal CT scan or MRI.

Unresectable Primary Hepatocellular Carcinoma (HCC)
Salem et al (2010) reported the results of a single-center, prospective, longitudinal cohort study of 291 patients with HCC treated between January 2004 and December 2008. The patient population was heterogeneous and included patients with portal vein thromboses (43%), advanced disease and extrahepatic metastases (16%), which are usually exclusionary criteria for studies using locoregional therapy. Data were collected prospectively and included toxicity, imaging, and survival outcomes. Patients were staged by Child Pugh scores. Eighty seven percent of patients had received no prior therapy. A total of 526 treatments were administered...
Scans were performed 4 to 6 weeks after each treatment and then at two to three month intervals once all disease was treated. Median follow-up time was 30.9 months. Imaging follow-up was available in 273 patients, with an average of 4.3 scans per patient. By World Health Organization (WHO) criteria, response rates were 42%; by European Association for the Study of the Liver (EASL) criteria, 57%, with 23% complete response (CR) and 34% partial response (PR). Response rates were better in patients with Child Pugh A disease (WHO, 49%; EASL 66%) than those with Child Pugh B disease (WHO, 36%; EASL 51%), and WHO response rates varied by baseline largest tumor size: smaller than 5 cm, 44%; 5-10 cm, 42%; and larger than 10 cm, 33%. Survival for patients with Child Pugh disease A and B was 17.2 months and 7.7 months, respectively (p=0.002). The authors concluded that patients with Child Pugh A disease, with or without portal vein thrombosis, benefitted most from the treatment but that the role of yttrium-90 in certain patients with HCC requires further exploration, including controlled studies comparing yttrium-90 with alternative locoregional therapies (radiofrequency ablation [RFA] and transarterial chemoembolization [TACE]) and yttrium-90 in various combinations with systemic targeted therapies in advanced disease.

Carr et al (2010) reported on a consecutive series of patients with HCC who were seen at a single medical center and who were not candidates for surgical resection. Patients either received conventional cisplatin-TACE between the years 1992 and 2000 (n=691), yttrium-90 microspheres between 2000 and 2005 (n=99), or no treatment (n=142). Median overall survival (OS) for the yttrium-90 group versus the TACE group was 11.5 months [95% confidence interval [CI]: 8 to 16 months] versus 8.5 months [95% CI: 8-10 months], respectively (p<0.05). Untreated patients had a median survival of two months. Although the authors felt there was a slight selection bias toward milder disease in the yttrium-90 group, they concluded that yttrium-90 and TACE appear to be equivalent regional therapies for patients with unresectable, nonmetastatic HCC.

Vente and colleagues (2009) conducted a meta-analysis on tumor response and survival in patients who received yttrium-90 glass or resin microsphere radioembolization (RE) for the treatment of primary liver cancer (HCC) or metastases from colorectal cancer. (See below under unresectable metastatic [colorectal carcinoma] CRC section for the data from the meta-analysis as pertains to that disease.) Included studies were from 1986 onward. Articles written in a language other than English or German were excluded, as were articles that did not present tumor response measured by computed tomography (CT) scans or that did not present data on median survival times. To allow comparability of results with regard to tumor response, the category of “any response” was introduced, and included CR, PR, and stable disease. Overall tumor response could only be assessed as any response because response categories were not uniformly defined in the analyzed studies.

In 14 articles, clinical data were presented on tumor response and survival for 425 patients with HCC who had received yttrium-90 RE. Treatment with resin microspheres was associated with a significantly higher proportion of any response than glass microsphere treatment (0.89 vs. 0.78, respectively; p=0.02). Median survival was reported in seven studies in which survival time was defined as survival from microsphere treatment or from diagnosis or recurrence of HCC. Median survival from microsphere treatment varied between 7.1 and 21.0 months, and median survival from diagnosis or recurrence was 9.4–24.0 months.
The authors of the meta-analysis concluded that yttrium-90 RE is associated with high response rates, both in salvage and first-line settings, but that the true impact on survival will only become known after publication of several ongoing and/or to-be-initiated Phase III studies, as well as the results of trials in which yttrium-90 RE and modern chemotherapy agents are combined with novel biologic agents.

Lewandowski and colleagues (2009) compared RE with chemoembolization in the efficacy of downstaging 86 patients with HCC from stage T3 to T2 (potentially making patients liver transplant candidates). Patients were treated with either RE using yttrium-90 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 vs. RE, respectively.) Partial response rates were 61% versus 37% for RE vs. TACE, respectively, with downstaging from T3 to T2 in 58% of patients treated with RE versus 31% with TACE (p<0.05).

A comparison of tumor response and survival among subgroups of patients with and without portal vein thrombosis (PVT) was reported by Kulik and colleagues in 2008. Thirty-four percent of this Phase II open-label cohort of 108 unresectable HCC patients treated with TheraSphere® had had either branch or main PVT. At six months, WHO criteria PR was observed in 42.2% of the overall cohort and in 34% and 66% of those with and without PVT, respectively. Kaplan Meier survival was statistically longer in the PVT-free group (467 days) than the branch (304 days) and main PVT (133.5 days) groups. At baseline, the PVT groups had higher tumor burden, Okuda stage, pretreatment bilirubin concentrations, and proportion of patients with portal hypertension than the non-PVT groups. Adverse events for the PVT groups were presented among those with and without baseline cirrhosis. Cirrhotic patients with main PVT were more likely than those without PVT to have worsening of baseline ascites (55% and 15%, respectively) with yttrium-90 microsphere treatment; no difference was seen among those without cirrhosis, although the numbers were small.

A large single series was reported by Salem and colleagues in 2002 that described treating approximately 300 patients with liver carcinoma with selective internal radiation therapy (SIRT) under a humanitarian device exemption (HDE) at eight unnamed institutions. The report provided no additional details on baseline characteristics of the patients and did not specify inclusion or exclusion criteria for treatment. Investigators only reported outcomes for a cohort of 54 HCC patients with Okuda Stage I and II (median survival: 23 and 11 months, respectively; overall survival (OS) at one year: 68% and 37%, respectively).

**Intrahepatic Cholangiocarcinoma (ICC)**

Cholangiocarcinomas originate in the epithelium of the bile duct. Several case series on use of RE in ICC are summarized here.

In 2013 Mouli et al reported on 46 patients treated with RE for ICC. Survival varied depending on level of disease, multifocal, infiltrative and bilobar and ranged from 5.7 to 15.6 months. Five patients achieved resectable status and underwent curative resection.
A study by Hoffman et al of RE with yttrium-90 resin microspheres included 24 patients with nonresectable chemorefractory intrahepatic ICC and no extrahepatic disease. The mean age of the sample was 65.2 years and the sample was 45.5% female. Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 51.5%, 1 in 21.2% and 2 in 27.3%. Previous therapy included chemotherapy in 78.8%, surgery in 36.4%, TACE in 9.1%, RFA in 5.1% and external beam radiotherapy (EBRT) in 3.0%. Tumor response was assessed by RECIST criteria. A CR was seen in 0%, PR in 36.4%, stable disease (SD) in 51.5% and progressive disease in 15.2%. Follow-up ranged between 3.1 and 44 months (median: 10 months). Median overall survival was 22 months and median time to progression was 9.8 months. Favorable subgroups with respect to survival included those with ECOG performance status of 0, tumor burden as percentage of liver volume of 25% or less, response by CA-19-9 criterion and RECIST PR. The same subgroups except those with a CA-19-9 response had favorable time to progression results. Data were collected retrospectively and no toxicity results were reported.

A 2011 study by Haug et al addressed 26 consecutive patients with unresectable ICC who underwent RE with yttrium-90 glass microspheres. All patients had a Karnofsky performance status of 60% or more. Mean age was 64.3 years, 31% had extrahepatic disease and 42% were female. Previous treatments included chemotherapy in 65%, surgery in 28%, local therapy in 20% and none in 24%. Tumor response results according to RECIST criteria were: CR in 0%, PR in 22%, SD in 65% and progressive disease (PD) in 13%. Median overall survival was 51 weeks and multivariate analysis found that a partial response from quantitative interpretation of positron emission tomography was a significant independent predictor of survival. Authors found no cases of Grade 3 toxicity in transaminases or bilirubin.

In 2010, Saxena et al published results for 25 patients with unresectable intrahepatic cholangiocarcinoma (ICC) who received RE with yttrium-90 resin microspheres. Extrahepatic disease was present in 48%, mean age was 57 years and 48% of patients were female. Prior treatment included surgery in 40%, chemotherapy in 72%, RFA in 6.1% and EBRT in 3.0%. By RECIST tumor response criteria, CR was seen in 0%, PR in 24%, SD in 48% and PD in 20%. Follow-up was collected between 0.4 and 55 months (median: 8.1 months). In the entire group, median overall survival was 9.3 months. Among subgroups, longer survival duration was seen in patients with peripheral tumors and those with ECOG performance status of 0. The proportion of patients with both Grade 3 albumin toxicity and Grade 3 bilirubin toxicity was 8%. Grade 3 alkaline phosphatase toxicity was observed in 4%. One patient (4%) experienced duodenal ulcer due to malperfusion of yttrium-90 microspheres.

A study by Ibrahim and colleagues from 2008 reported results on RE with yttrium-90 glass microspheres among 24 patients with unresectable ICC. The group was 33% female and had a median age of 68 years. Extrahepatic disease was present in 33%. ECOG performance status was 0 in 42%, one in 50% and two in 8%. Prior chemotherapy had been used in 29%. Using the WHO tumor response criteria, CR was observed in 0%, CR in 27%, SD in 68% and PD in 5%. Follow-up was collected over a median of 17.7 months and median overall survival was 14.9 months. Subgroups that had favorable survival results included those with ECOG performance status of 0, no previous chemotherapy and peripheral tumor. Grade 3 albumin toxicity was found in 17%, Grade 3 bilirubin toxicity in 4% and one patient (4%) developed a duodenal ulcer.
Unresectable Metastatic Colorectal Carcinoma

In a 2013 systematic review, Saxena et al evaluated 20 studies on RE for chemoresistant, unresectable CRC liver metastasis totaling 979 patients. After RE, the average reported CRs and PRs from 16 studies was 0% (range, 0%-6%) and 31% (range, 0%-73%), respectively. Nine months was the median time to intrahepatic progression (range, 6–16 months). Eleven studies reported OS rates and 12 months was the median survival time (range, 8.3-3.6).

In another 2013 systematic review, Rosenbaum et al evaluated 13 relevant articles on RE as monotherapy and 13 studies on RE combined with chemotherapy for chemoresistant, unresectable CRC liver metastasis. CR, PR, and SD rates ranged from 29% to 90% with only RE and from 59% to 100% for RE with chemotherapy At 12 months, survival ranged from 37% to 59% with only RE and from 43% to 74% for RE combined with chemotherapy.

A study was published by Gray and colleagues in 2001 and randomly assigned 74 patients with bilobar unresectable liver metastases to monthly hepatic arterial infusion (HAI) with 5-fluorodeoxyuridine (5-FUDR) alone or with the same chemotherapy plus a single infusion of yttrium-90 microspheres. The investigators closed the study after entering 74 patients (n=70 eligible for randomization). The original goal was 95 patients. Reasons cited for the early closure included: 1) increasing patient and physician reluctance to participate; 2) decision by the FDA to accept intermediate endpoints to support applications for premarket application approval; and 3) lack of funding to complete the study. The smaller study population was adequate to detect increases in response rate (from 20% to 55%) and median time to disease progression (by 32% from 4.5 months), with 80% power and 95% confidence, but lacked sufficient statistical power to detect changes in survival. To monitor responses to therapy, investigators serially measured serum levels of carcinoembryonic antigen (CEA) and estimated tumor cross-sectional area and volume from repeated computerized tomographic scans read by physicians blinded to treatment assignment. They reported increased overall responses (complete plus partial) measured by area (44% vs. 18%, p=0.01; HAI plus SIRT vs. HAI, respectively) and volume (50% vs. 24%, respectively; p=0.03), or by serum CEA levels (72% vs. 47%, respectively; p=0.004). They also reported increased time to disease progression detected by increased area (9.7 vs. 15.9 months, respectively; p=0.001) or volume (7.6 vs. 12.0 months, respectively; p=0.04). However, there were no significant differences between treatment arms in actuarial survival rates (p=0.18 by log rank test) or in 11 quality-of-life measures. Treatment-related complications (Grades 3–4) included 23 events in each arm (primarily changes in liver function tests). Nevertheless, investigators concluded that a “single injection of SIR-Spheres® plus HAI is substantially more effective” than the same HAI regimen delivered alone.

Despite the investigators’ assertions, these results are inadequate to support their conclusions for the following reasons: 1) Accrual was halted early, leaving the study underpowered. 2) Although the study involved oversight by an institutional review board, the report suggests early closure was at the sole discretion of the principal investigator without independent review or prospectively designed data monitoring procedures and stopping rules. 3) While in this study, response rate and time to progression after SIRT plus HAI appeared superior to the same outcomes after HAI alone, results for the SIRT plus HAI group are within the range reported by other randomized trials of HAI in comparable patients. 4) Results of this study may reflect use of a shorter-than-standard duration of HAI therapy and are confounded by administration of
nonprotocol chemotherapy before and after SIRT. 5) The reported increases in response rates and time to progression improved neither duration of survival nor quality of life.

Another randomized trial was a Phase II study published in 2004 by the same research group as the Phase III trial. The study involved 21 patients with advanced colorectal liver metastases; a total of 11 patients received SIR-Spheres plus systemic chemotherapy (fluorouracil and leucovorin), and 10 received the same systemic chemotherapy alone. While the time to progressive disease was greater in those receiving combination therapy (18.6 versus 3.6 months, respectively; p<0.0005), the small size of the study limits any conclusions.

A Phase III study, involved 46 patients and compared intravenous 5-fluorouracil (5-FU) to hepatic intra-arterial injection of yttrium-90 microspheres (SIR-Spheres) with intravenous 5-FU in colorectal cancer metastatic only to the liver and refractory to standard chemotherapy. The time to liver progression, the primary outcome, was significantly improved in the group receiving SIR-Spheres, 2.1 versus 5.5 months, respectively (p=0.003). However, there was no difference in the more important outcome of median survival; this was 7.3 and 10.0 months, respectively (p=0.80).

A technology assessment (2010) from the California Technology Assessment Forum (CTAF) assessed 25 studies on the use of RE and inoperable metastatic colorectal cancer to the liver, including the two previously described randomized studies, one small retrospective study comparing SIRT to chemoembolization (n=36), and 21 case series. The assessment concluded that the three comparative studies all used different control interventions and that the nonrandomized study did not show any convincing improvements over chemoembolization. The author stated that the assessment showed it is feasible to deliver radiation therapy to liver metastases and achieve at least PR in a substantial portion of patients with relatively few serious adverse events and that the results of the two randomized studies were encouraging but not definitive, as the trials were very small, the response rates in the control groups were lower than expected, and the control groups were not given what is currently considered standard first-line chemotherapy for metastatic colorectal cancer. The assessment concluded that the use of SIRT for unresectable colorectal cancer did not meet any of the CTAF technology assessment criteria, with the exception of criterion number one (i.e., the technology has final approval from the appropriate government regulatory bodies).

A 2009 Cochrane review assessed the above-outlined randomized controlled trials (RCTs). The authors concluded that there was a lack of evidence that SIRT improves survival or quality of life in patients with metastatic colorectal cancer, whether it is given alone or with chemotherapy, and that there is a need for well-designed, adequately powered Phase III trials assessing the effect of SIRT when used with modern combination chemotherapy regimens.

In the aforementioned 2009 meta-analysis by Vente et al, in a total of 19 eligible studies, 792 patients with metastatic colorectal cancer had undergone yttrium-90 RE. Included in the meta-analysis were the two randomized trials previously addressed in this section of the policy. Two covariates were included in the meta-regression model: 1) whether an older generation of cytostatic agents (5-FU/LV or floxuridine) or a newer generation (5-FU/LV [leucovorin] plus oxaliplatin [FOLFOX] or 5-FU/LV plus irinotecan [FOLFIRI]) was used, and 2) whether
yttrium-90 RE was given as salvage therapy or as first-line treatment with adjuvant chemotherapy. The specific cytostatic agent(s) that were used did not affect response (p=0.96). Tumor response to yttrium-90 RE was high, with any response rates of approximately 80% in a salvage setting, and more than 90% when used as first-line treatment as neoadjuvant to chemotherapy, regardless of the chemotherapy regimen used. Median survival after yttrium-90 RE, irrespective of differences in determinants (microspheres type, chemotherapy protocol, and salvage or first-line) varied from 6.7 to 17.0 months.

A single arm, open-label study was reported by Mulcahy and colleagues (2009) and involved 72 patients with unresectable hepatic colorectal metastases treated with yttrium-90 microspheres (TheraSphere®). To determine response, 128 lesions were used. A PR rate using WHO criteria was noted in 29 of 72 patients (40.3%), and at the lesional level, the response rate was 40.6% (PR rate 37.5%; CR rate 3.1%). Stable disease was observed in 44.5% of patients, and disease progression was found in 14.8% of patients. Median follow-up was 26.2 months. Median OS was 40.3 months (95% CI: 29.0–51.6 months) for all patients from the time of cancer diagnosis, 34.6 months (95% CI: 24.4–41.8 months) from the time liver metastases were diagnosed, and 14.5 months (95% CI: 9.6–21.9) from the time of yttrium-90 therapy. A substratification analysis was performed, and favorable prognostic factors that indicated a benefit from yttrium-90 therapy included an Eastern Cooperative Oncology Group (ECOG) performance status of 0, a liver tumor burden of 25% or less, and the absence of extrahepatic disease. For the patients with an ECOG performance status of 0 at the time of yttrium-90 treatment, the overall median survival from the onset of liver metastases was 42.8 months, or a five-year survival rate of 25.9%, which are comparable outcomes to survival data for patients treated with primary resection, chemotherapy followed by resection, or RFA.

Jakobs and colleagues retrospectively reviewed case files of patients with colorectal cancer liver metastases in whom chemotherapy had failed and who therefore received a single-session, whole-liver treatment with yttrium-90 radioembolization (n=41). Response was partial in seven patients, 25 patients had stable disease, and four had progressive disease. Median OS was 10.5 months. Median survivals for patients with PR, stable disease, and progressive disease were 29.3 months, 10.9 months, and 4.3 months, respectively. No severe toxicities were observed.

Kennedy and colleagues reported results for use of resin microspheres in 208 patients with liver metastases from colorectal cancer who had failed or were not candidates for standard chemotherapy. There were no CRs but 35% PRs by computed tomography (CT; as determined by a 50% decrease in one tumor measure at 12 weeks). Median survival was 10.5 months for responders but 4.5 months for nonresponders. The authors noted that the majority of patients died with persistent liver disease and had uncontrolled systemic metastases. No quality of life or functional status measures were reported. In addition, the authors noted that their report was a retrospective review with associated problems of a mixture of patients and a lack of a controlled treatment protocol.

A retrospective, matched-pair comparison of radioembolization and best-supportive care (n=29) versus best-supportive care alone (n>500) for chemo-refractory, liver-dominant colorectal metastases showed prolongation of survival in the group of patients who received radioembolization.
Unresectable Metastatic Neuroendocrine Tumors

The data on the use of radioembolization for unresectable liver metastases from neuroendocrine tumors include one open-label Phase 2 study, retrospective reviews and case series.

In 2010, Cao and colleagues reported the outcomes of 58 patients with unresectable neuroendocrine liver metastases from two different hospitals treated with yttrium-90 microspheres (SIR-Spheres) from 2003 to 2008. Data were examined retrospectively from a database. Response was assessed with radiographic evidence before and after radioembolization and measured by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Patients typically had a CT scan within three months of treatment and every three to six months until disease progression or death. Systemic chemotherapy was routinely given at one institution but not the other. Mean patient age at the time of RE was 61 (range: 29-84 years), and 67% of patients were men. Primary tumor site was variable and included small bowel, pancreas, colon, thyroid, lung, and unknown. Thirty-one patients underwent surgical resection of their primary tumor, which was classified as low-grade in 15, intermediate-grade in seven, and high-grade in seven. Forty-three percent of patients had extrahepatic metastatic disease at study entry. Prior therapies before RE included liver resection in 19 patients, transarterial embolization (TAE) or TACE in six, ablation or percutaneous ethanol injection in 10, previous chemotherapy in 20, concurrent chemotheraphy in 34, and post-RE chemotherapy in five patients. Median follow-up was 21 months (range 1 to 61 months). Fifty-one patients were evaluable, and 6 achieved a CR, 14 a PR, 14 had stable disease, and 17 had disease progression. Overall survival rates at one, two, and three years were 86, 58, and 47%, respectively. Median survival was 36 months (range: 1 to 61 months). Prognostic factors for survival included extent of tumor involvement of the liver, radiographic response to treatment, presence of extrahepatic disease at the time of RE, histological grade of tumor, and whether patients were responders (vs. nonresponders) to RE. Factors that were not significant prognostic features included age, sex, ECOG status, and previous therapy.

King and colleagues reported outcomes in patients treated in a single-institution prospective study. Thirty-four patients with unresectable neuroendocrine liver metastases were given radioactive microspheres [SIR-Spheres] and concomitant seven-day systemic infusion of 5-FU, between 2003 and 2005. Mean patient age was 61 years (range: 32-79 years), and 65% were men. Mean follow-up was 35.2 +/- 3.2 months. The mean interval from diagnosis of hepatic metastases and treatment with SIR therapy was 36.6 +/- 6.7 months. Primary tumor sites were variable and included bronchus (n=1), thyroid (n=2), gastrointestinal (n=15), pancreas (n=8), and unknown (n=8). Subjective changes from baseline hormone symptoms were reported every 3 months. Twenty-four patients (71%) had, at baseline assessment, symptoms of carcinoid syndrome, including diarrhea, flushing, or rash. At three months, 18 of 33 patients (55%) reported improvement of symptoms, as did 16 of 32 (50%) at six months. Radiologic tumor response was observed in 50% of patients and included six CR (18%), and 11 PR (32%). Mean OS was 29.4 +/- 3.4 months.

Kennedy and colleagues conducted a retrospective review of 148 patients from 10 institutions with unresectable hepatic metastases from neuroendocrine tumors who received resin microspheres. All patients had completed treatment of the primary tumor and metastatic disease
and were not excluded based on prior therapy. Total number of resin microsphere treatments was 185; with retreatment in 22.3% of patients (19.6% received two treatments, and 2.7%, three treatments). All patients were followed with imaging studies at regular intervals to assess tumor response (using either WHO or RECIST criteria) until death, or they were censured if a different type of therapy was given after the microspheres. The male to female ratio was 49% to 51%, respectively, and median age was 58 years (range: 26-95 years). Median follow-up was 42 months. By imaging, response rates were stable disease 22.7%, PR 60.5%, CR 2.7%, and progressive disease 4.9%. Hepatic and extrahepatic metastases contributed to death in the majority of patients, with 7% lost to follow-up. Median survival was 70 months. The authors conclude that RE can deliver high doses of radiation preferentially to hepatic metastases from neuroendocrine tumors with encouraging response rates by imaging and symptomatic improvement (although there were no data presented in the study regarding symptoms).

Rhee and colleagues reported the results of a multicenter, open label Phase II study to assess the safety and efficacy of RE, using glass or resin microspheres, in 42 patients with metastatic neuroendocrine liver disease who had failed prior treatment(s), including medical (e.g., octreotide), surgical resection, bland or chemoembolization, and RFA or cryoablation. Mean patient age was 58 +/- 12 years for glass and 61 +/- 11 years for resin microspheres. RECIST criteria were used to assess tumor response, which showed 92% of glass patients and 94% of resin patients were partial responders or had stable disease at six months after treatment. Median survival was 22 and 28 months for glass and resin, respectively.

Additional case series in patients with treatment-refractory, unresectable neuroendocrine hepatic metastases have shown good tumor response and improvement in clinical symptoms with radioembolization.

Miscellaneous Tumors

Breast

Data on the use of RE in metastatic breast cancer is limited to the use of RE alone (i.e., not in combination with chemotherapy), and studies have been conducted either during a hiatus between lines of chemotherapy or in patients refractory to standard of care chemotherapy. In 2013, Smits et al reviewed six studies on RE for metastatic breast cancer with a total of 198 study participants. CR, PR, and SD control rates at two to four months after treatment varied from 78% to 96%. In four studies, the median survival ranged from 10.8 to 20.9 months. Ten patients had gastric ulceration, and three patients had mortality related to treatment.

A 2013 study by Cianni and colleagues included 52 women with chemotherapy-refractory breast cancer and inoperable liver metastases. RE treatment entailed yttrium-90 resin microspheres. The median age was reported as 57.5 years. ECOG performance status was 0 in 55.7%, one in 26.9% and two in 17.3%. Extrahepatic disease was present in 46.1%. Chemotherapy had been administered previously in all patients, surgery in 17.3%, TACE in 3.8% and RFA in 3.8%. Tumor response results by RECIST criteria were: CR in 0%, PR in 56%, SD in 35% and PD in 10%. Median overall survival was 11.5 months. Patients were retrospectively divided into two risk groups based on ECOG performance status, degree of liver tumor burden and whether extrahepatic disease was present. Median survival in the low-risk group was 14.3 months,
significantly better than in the high-risk group (8.2 months). Grade 3 gastritis was seen in two patients (4%).

Haug et al published a case series of 58 women with chemotherapy-refractory breast cancer and unresectable hepatic metastases. They received RE with yttrium-90 resin microspheres. The mean age was 58 years and all patients had a Karnofsky performance status of 60% or higher. Extrahepatic disease was present in 66%. Prior treatments were not mentioned. By RECIST criteria, a CR was seen in 0%, PR in 25.6%, SD in 62.8% and PD in 11.6%. Mean follow-up covered 27.5 weeks. The median overall survival for the sample was 47 weeks. Two indices derived from quantitative interpretation of positron emission tomography were significant predictors of survival. Bilirubin toxicity was at Grade 3 in 3% and Grade 4 in 2%. Transaminase toxicity was Grade 3 in 5% and Grade 4 in 2%.

Jakobs and colleagues reported on the safety and survival of 30 patients (29 women and one man) who underwent RE with resin microspheres in a single-session, whole-liver treatment for breast cancer metastases. All patients had failed prior polychemotherapy regimens (including at least anthracyclines and taxanes, hormonal therapy, and trastuzumab, when applicable). Twenty-three patients had follow-up data. At median follow-up of 4.2 months, PR, stable disease, and progressive disease was observed in 61%, 35%, and 4% of patients, respectively. Clinically significant toxicities were observed in eight of 30 patients and included increasing liver enzymes and bilirubin levels, nausea and vomiting, gastric ulcers and ascites; one death was due to treatment-related hepatic toxicity. Median follow-up was 14.2 months, with a median OS of 11.7 months. Median survival of responders versus nonresponders was 23.6 and 5.7 months, respectively. Median survival of patients with and without extrahepatic disease was 9.6 versus 16 months, respectively.

Bangash and colleagues reported on the safety and efficacy of the use of RE with glass microspheres in 27 female patients with progressing liver metastases from breast cancer while on polychemotherapy. Seventeen patients received 20 left lobe of liver treatments, and 20 received 22 right lobe of liver treatments. At the 90-day follow-up CT, CR and PR was observed in nine patients (39%), stable disease in 12 (52%), and PD in two (9%). Median survival for ECOG 0 versus 1 to 3 was 6.8 versus 2.6 months, respectively, and for patients with tumor burden less than 25% versus greater than 25% was 9.4 and 2.0 months, respectively.

Hepatic metastases from breast cancer in 44 patients at three hospitals were retrospectively reviewed by Coldwell and colleagues. Patients had failed first-, second-, or third-line treatment for their primary tumor and were not candidates for RFA, TACE, resection, intensity-modulated radiotherapy (IMRT), or stereotactic radiotherapy. At 12 weeks, a PR (using WHO criteria, at least 50% reduction in the cross-product of the tumor dimensions) to SIR-Spheres was observed by CT in 47% of patients with recorded follow-up (82% of the total). Symptoms were reported to improve, although no specifics were provided. There were no radiation-related liver failures observed, and, at a median follow-up of 14 months, the cohort had not yet reached its expected median survival of 14 months.
Melanoma
Four studies have reported on use of RE in patients with hepatic metastases from melanoma. Three studies included only patients with ocular melanoma, and the fourth included patients with either ocular or cutaneous melanoma. Sample sizes ranged between 11 and 32 patients. Three studies excluded those with poor performance status. Median age was in the 50s for three studies and 61 in the fourth. One article did not describe any previous treatment and one described it incompletely. Three studies reported tumor response data, by RECIST criteria. Among 32 patients in the study by Gonsalves et al (2011), one patient had a CR (3%), one had a PR, 18 patients had SD (56%) and 12 patients had PD (38%). In the study of 13 patients published by Klingenstein et al (2013), none had a CR, eight had a PR (62%), two had SD (15%) and three had PD (23%). Nine of 11 patients in the article by Kennedy et al (2009) provided response data: one had CR, 6 had PR, one had SD and one had PD. Median survival in Gonsalves, Klingenstein, and Kennedy were 10.0 months, 19 months and not yet reached, respectively. Gonsalves reported 4 patients (12.5%) with Grade 3-4 liver toxicity. Klingenstein observed one patient with marked hepatomegaly. Kennedy described one Grade 3 gastric ulcer. The fourth study (Pidurut et al, 2012, n=12) did not include any toxicity data.

Pancreatic
Michl et al reported on RE for pancreatic cancer in 2014. Response was seen in 47% with median local progression-free survival (PFS) in the liver of 3.4 months (range, 0.9-45.0). Median OS was 9.0 months (range, 0.9-53.0), and one-year survival was 24%.

Data on the use of RE in other tumors metastatic to the liver are limited and are composed of patient numbers too small to draw meaningful conclusions.

National Comprehensive Cancer Network (NCCN) Guidelines
Primary hepatocellular carcinoma
Guidelines recommend that patients with unresectable/inoperable disease who are eligible to undergo embolization therapy and have tumor lesions larger than 5 cm should be treated using arterial embolic approaches (chemoembolization, bland embolization, or radioembolization) or systemic therapy, whereas patients with lesions 3 to 5 cm can be considered for combination therapy with ablation and arterial embolization, and tumors of or less than 3 cm should be treated with ablation (all category 2A) but that randomized, controlled studies on the use of radioembolization therapy in the treatment of patients with HCC are needed and participation in prospective clinical trials is preferred for all stages of disease.

Primary Cholangiocarcinoma
Recommendations for unresectable intrahepatic cholangiocarcinoma include chemotherapy, clinical trial and supportive care. The guidelines note there have been no RCTs on locoregional therapies such as radioembolization for cholangiocarcinoma.

Metastatic colorectal cancer
“Use of arterial-directed therapies such as radioembolization in highly select patients… remains a Category 3 recommendation based on the relatively limited amount of evidence and different institutional practices.”
**Metastatic neuroendocrine tumors**
For unresectable liver metastases (carcinoid or neuroendocrine tumors of the pancreas, e.g., islet cell), recommendations include hepatic regional therapy with radioembolization (category 2B).

**Metastatic breast cancer**
Current recommendations do not address the use of radioembolization in the treatment of metastatic breast cancer.

**Metastatic melanoma**
Current recommendations do not address the use of radioembolization in the treatment of metastatic melanoma.

**Radioembolization Brachytherapy Oncology Consortium**
Members met as an independent group of experts in interventional radiology, radiation oncology, nuclear medicine, medical oncology, and surgical oncology. Using level 2A evidence (panel consensus with low-level evidence), 14 recommendations were made. Conclusions included that there was sufficient evidence to support the safety and efficacy of yttrium-90 microsphere therapy and that its use requires multidisciplinary management, adequate patient selection, and meticulous angiographic technique. They also stated that the initiation of clinical trials was necessary to further define the role of yttrium-90 microsphere therapy in relation to other currently available therapies.

**Summary**
Radioembolization (RE), referred to as selective internal radiation therapy, or “SIRT” in older literature, is the intra-arterial delivery of small beads (microspheres) impregnated with yttrium-90 via the hepatic artery. The microspheres, which become permanently embedded, are delivered to tumor preferentially to normal liver, as the hepatic circulation is uniquely organized, whereby tumors greater than 0.5 cm rely on the hepatic artery for blood supply while normal liver is primarily perfused via the portal vein.

- **Hepatocellular carcinoma (HCC):** Studies have demonstrated that radioembolization is comparable to TACE (which is considered to be therapy of choice) for patients with unresectable HCC in terms of tumor response and OS. Disadvantages of TACE include the necessity of multiple treatment sessions and hospitalization, its contraindication in patients with portal vein thrombosis, and its poorer tolerance by patients.

- **Intrahepatic cholangiocarcinoma (ICC):** To date, studies on use of radioembolization in patients with intrahepatic cholangiocarcinoma consist of small case series. No studies have been published comparing radioembolization to other treatments such as chemotherapy or chemoradiation. Available studies varied with respect to patient characteristics, particularly presence of extrahepatic disease, previous therapy and performance status.

- **Metastatic colorectal cancer:** A major cause of morbidity and mortality in patients with colorectal disease metastatic to the liver is liver failure, as this disease tends to progress to diffuse, liver-dominant involvement. Therefore, the use of radioembolization to decrease tumor bulk and/or halt the time to tumor progression and liver failure, may lead to prolonged progression free and overall survival in patients with no other treatment options (i.e., those with chemotherapy refractory liver-dominant disease). Other uses include palliation of symptoms from tumor bulk. Two Phase III trials are currently
underway that compare first-line chemotherapy with and without radioembolization in patients with metastatic colorectal cancer.

- Metastatic neuroendocrine tumors: Studies have included heterogeneous patient populations, and interpretation of survival data using radioembolization is difficult. Few studies report relief of symptoms from carcinoid syndrome in a proportion of patients. Surgical debulking of liver metastases has shown palliation of hormonal symptoms; debulking by radioembolization may lead to symptom relief in some patients.
- Miscellaneous: A few studies on the use of radioembolization in metastatic breast cancer and melanoma to the liver have shown promising initial results; however, the data are limited and the studies have been small and composed of heterogeneous patients. The use of radioembolization in other tumors metastatic to the liver is too limited to draw meaningful conclusions; this use is considered investigational.

**Cryosurgical ablation (CSA)**

Four patient groups have been treated with hepatic cryosurgery: those with primary HCC, liver metastases from colorectal cancer, neuroendocrine tumors metastatic to the liver, and liver metastases from other non-colorectal cancers.

**Hepatocellular carcinoma (HCC)**

Authors of a 2009 Cochrane review of cryotherapy for HCC reported finding two prospective cohort studies and two retrospective studies in their literature search but no randomized controlled trials (RCTs) or quasi-randomized, controlled trials. Only one study could be considered for the assessment of benefit. In that study, results were stratified according to both the type of hepatic malignancy (primary or secondary) and the intervention group (percutaneous cryotherapy or percutaneous radiofrequency ablation [RFA]). Sixty-four patients were treated based on random availability of probes; 31 patients received cryotherapy and 33 received RF. Of all patients treated, 26 (84%) of 31 who had cryotherapy and 24 (73%) of 33 who had RF developed a local recurrence, all within one year. The distribution of primary cancers was not specified. Among the HCC patients, rates of initial tumor ablation were similar after cryosurgery or RFA (65% and 76%, respectively), but local recurrences were more frequent after cryosurgery (38%) than after RFA (17%). Survival at one year did not differ by ablative technique (cryosurgery, 66%; RFA, 61%). The study did not include controls managed with an established alternative. Authors of the Cochrane review concluded that there is no evidence to recommend or refute cryotherapy in the treatment of patients with HCC and that randomized, clinical trials may be useful.

In 2011, Yang and colleagues reported on a series of 300 patients treated between 2003 and 2006 with percutaneous argon-helium cryoablation for hepatocellular carcinoma. Complete tumor ablation occurred in 185 tumors in 135 patients with mean tumor diameter of 5.6 + 0.8 cm, while 223 tumors in 165 patients with a mean tumor diameter of 7.2 + 2.8 cm were incompletely ablated (p=0.0001). Serious complications occurred in 19 patients (6.3%) and included liver hemorrhage in five patients, cryoshock syndrome in six patients, gastric bleeding in four patients, liver abscess in one patient and intestinal fistula in one patient. Liver failure resulted in the death of two patients. Patients with incomplete ablation received additional treatment with transarterial catheter embolization or a multikinase inhibitor (sorafenib). During the median follow-up of 36.7 months (range 6 to 63 months), local tumor recurrence was 31%. Larger tumors and tumor
location were significantly related to tumor recurrence \((p=0.029\ and 0.037,\ \text{respectively})\). Overall survival was 80% at one year, 45% at two years, and 32% at three years.

Clavien et al treated 15 patients with cirrhosis and a single liver lesion (biopsy-proved HCC or suspicious mass on imaging) using open cryosurgery after transhepatic arterial chemoembolization. In all patients, cryosurgery was offered because the tumor was “unresectable or surgical resection was not thought to be feasible because of tumor location or size, or patient comorbidity.” Actuarial survival rate of these patients after cryosurgery was 79% at five years. The study did not include a control group.

In a 2009 study, Zhou and colleagues divided 124 patients with primary nonresectable HCC into early, middle, and advanced stage groups by Barcelona Clinic Liver Cancer staging classification. After argon-helium cryoablation, serum level of alpha-fetoprotein was reduced in 76 (82.6%), and 205 (92.3%) of 222 tumor lesions were diminished or unchanged. Median survival time was 31.35 months in the early stage, 17.4 months in the middle stage, and 6.8 months in the late stage groups. As of April 2008, 14 patients survived and 110 had died. To determine risk factors that predict metastasis and recurrence Wang et al studied a series of 156 patients with hepatitis B (HBV)-related HCC and tumors smaller than 5 cm in diameter who underwent curative cryoablation. One-, two-, and three-year overall survival rates were 92%, 82%, and 64%, respectively, and one-, two-, and three-year recurrence-free survival (RFS) rates were 72%, 56%, and 43%, respectively. The multivariate analysis showed that Child-Pugh class and expression of vascular endothelial growth factor (VEGF) in HCC tissues could be used as independent prognostic factors for overall survival. The expression of VEGF in HCC tissues and HBV basal core promoter mutations were independent prognostic factors for RFS.

In a nonrandomized comparative study, Xu and colleagues evaluated outcomes of cryosurgery alone and transcatheter arterial chemoembolization (TACE) followed by cryosurgery in 420 patients with nonresectable HCC. Patients in the sequential TACE-cryosurgery group tended to have larger tumors and a greater number of tumors than patients in the cryoablation alone group. Tumors larger than 10 cm were seen only in the sequential group. During mean follow-up of 42 months (range: 24–70), the local recurrence rate at the ablated area was 17% for all patients, 11% in the sequential group, and 23% in the cryosurgery alone group \((p=0.001)\). One- and 2-year survival rates were similar in both treatment groups \((p=0.69)\); however, five-year survival rates were 39% in the sequential group and 23% in the cryosurgery alone group \((p=0.001)\). Eighteen patients with large HCC (i.e., larger than 5 cm) survived for more than five years after sequential TACE-cryosurgery, while no patient with large HCC and cryosurgery alone survived more than five years. The incidence of hepatic bleeding was higher in the cryosurgery alone group. The authors conclude that precryosurgical TACE may increase the efficacy of cryoablation and reduce adverse effects.

**Neuroendocrine cancer liver metastases**

Neuroendocrine tumors are relatively slow-growing malignancies (mean survival times of 5 to 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.
A 2009 Cochrane review evaluated the benefits and harms of liver resection versus other treatments in patients with resectable liver metastases from gastro-entero-pancreatic neuroendocrine tumors. Trials comparing liver resection (alone or in combination with RFA or cryoablation) versus other interventions (chemotherapy, hormonotherapy, or immunotherapy) and studies comparing liver resection and thermal ablation (RFA or cryoablation) were sought. Authors of the Cochrane review reported finding neither an RCT suitable for review or any quasi-randomized, cohort, or case-control studies “that could inform meaningfully.” No analysis was performed, and the authors refer to only RFA in their discussion, noting that RF is not suitable for large tumors (i.e., larger than 5-6 cm) and that neuroendocrine liver metastases are frequently larger than that. The authors conclude that further randomized trials comparing surgical resection and RFA in selected patients may be appropriate.

In 2012, Saxena and colleagues reported on a retrospective review of 40 patients treated with cryoablation and surgical resection for hepatic metastases from neuroendocrine cancer. The median period of follow-up was 61 months with a range of one to 162 months. One death occurred within 30 days of treatment. No other complications were reported. Median survival was 95 months, and the rate of survival was 92%, 73%, 61% and 40% at one-, three-, five-, and ten-year survival, respectively.

In 2001, Chung and colleagues reported on outcomes of cryosurgery for hepatic metastases from neuroendocrine cancer. This study used cytoreduction (resection, cryosurgery, RFA, or a combination) and adjuvant therapy (octreotide, chemotherapy, radiation, interferon alfa) in 31 patients with neuroendocrine metastases to the liver and “progressive symptoms refractory to conventional therapy.” Following treatment, symptoms were eliminated in 87% of patients; median symptom-free interval was 60 months with octreotide and 16 months with alternatives. Since outcomes were not reported separately for different cytoreductive techniques, it was not possible to compare the benefits of cryosurgery with those of other cytoreductive approaches or octreotide alone.

Liver metastases from other cancers including colorectal cancer
A 2008 Cochrane review was undertaken to compare outcomes of resection of colorectal cancer liver metastases to no intervention or other modalities of intervention, including RFA and cryosurgery. Only RCTs reporting on patients who had curative surgery for adenocarcinoma of the colon or rectum and who had been diagnosed with liver metastases and who were eligible for liver resection were considered. Only one randomized trial by Korpan et al was identified, a 1997 study from the Ukraine comparing surgical resection and cryosurgery in 123 subjects, 82 of whom had liver metastases from primary colorectal cancers and the remainder who had metastases from other primary tumors. Survival outcomes were not provided by type of cryogenic procedure or primary tumor site. The authors of the Cochrane review conclude that local ablative therapies are probably useful but that they need to be further evaluated in a RCT. A subsequent 2013 Cochrane review examined cryoablation for liver metastases from various sites, primarily colorectal. Only the RCT by Korpan et al, included in the 2008 Cochrane review, met inclusion criteria for the 2013 review. The Korpan study was considered to have a high risk of bias, and the reviewers found the available evidence was insufficient to determine whether there
were any benefits with cryoablation over conventional surgery or no intervention. The reviewers recommended cryoablation only be used in RCTs.

In 2011, Pathak and colleagues reported on a systematic review of ablative therapies for colorectal liver metastases. Included in the review were 26 nonrandomized studies on cryoablation. The authors reported local recurrence rates in the studies reviewed ranged from 12-39%. Survival rates ranged from 46-92% at one year, 8-60% at three years, and 0-44% at five years. Mean survival rates at one, three, and five years were 84%, 37% and 17%, respectively. Major complications ranged from 7% to 66%. Cryoshock was indicated to be of major concern.

In a 2002 review of the literature, Sotsky and Ravikumar summarized the results of 27 studies reporting outcomes of cryosurgery in more than 1,000 patients. In studies with only patients with colorectal cancer, outcomes diverged markedly (median survival ranged from 18 to greater than 33 months), liver recurrences were frequent (20–50%), and significant procedure-related complications were common. While the review’s authors asserted that cryosurgery is an established procedure, the data reported in the studies cited in the review appear inconclusive, since baseline characteristics of study populations were heterogeneous, and published outcomes were variable and inconsistently reported.

In 2012, Ng and colleagues reported on a retrospective review of 293 patients treated between 1990 and 2009 for colorectal liver metastases with cryoablation with or without surgical resection. Perioperative death occurred in 10 patients (3%) and included liver abscess sepsis in four patients, cardiac events unrelated to treatment in three patients, and one case each of dilated cardiomyopathy, cerebrovascular event, and multiorgan failure. Median follow-up was 28 months (range 0.1 to 220 months). Overall survival was 87%, 41.8%, 24.2%, and 13.3% at one, three, five, and ten years, respectively.

A Phase I comparison of single versus dual cryoprobe configurations in 15 patients given multiple treatments (25 single-probe and 14 dual-probe) did not report long-term outcomes or health benefits. Three studies administered cryosurgery as a planned or incidental adjunct to surgery in patients with hepatic tumors. Two of these were retrospective studies, and all three pooled results across patients with heterogeneous disease characteristics (e.g., tumors of varied numbers and location). A prospective study did not adequately describe criteria used to select patients for cryosurgery. Another report was a “retrospective review of prospectively collected data” on 172 patients treated with cryosurgery with (n=157) or without (n=25) post-procedure 5-fluorouracil or 5-fluorodeoxyuridine as hepatic arterial chemotherapy (HAC), and with (n=80) or without (n=92) resection. The authors concluded that the results of cryosurgery in their study (25% survival at five years) are encouraging but may partly reflect the effects of HAC, completeness (or, rather, incompleteness) of cryosurgery in some patient groups, and patient selection.

Niu and colleagues reported on an analysis of data collected prospectively for patients who underwent hepatic resection for metastatic colorectal cancer with or without cryoablation from 1990 to 2006. A decision about resectability was determined at the time of surgery. Patients who had resections and cryoablation were more likely to have bilobar disease (85% vs. 27%, respectively) and to have six or more lesions (35% vs. 3%, respectively). In addition, 73% of this
combined treatment group received HAC compared to 32% in the resection-only group. Median follow-up was 25 months (range: 1 to 124 months). The 30-day perioperative mortality was 3.1%. For the resection group, the median survival was 34 months, with one, three and five-year survival values of 88%, 47%, and 32%, respectively. The median survival for the resection/cryotherapy group was 29 months, with one, three and five-year survival values of 84%, 43%, and 24%, respectively (p=0.206). The overall recurrence rates were 66% for resection only, but 78% for resection/cryotherapy. Five factors were independently associated with an improved survival: absence of extrahepatic disease at diagnosis, well- or moderately differentiated colorectal cancer, largest lesion size being 4 cm or less, a postoperative carcinoembryonic antigen (CEA) of 5ng/mL or less, and absence of liver recurrence. While the recurrence rates between groups were not different in this study, it is not clear how representative the patients who had resection/cryotherapy are of the total potential patients. The comparability of the two groups is uncertain, especially given the differential use of HAC. In this study, a direct comparison was not made to chemotherapy. Finally, the 16-year duration of the study raises concerns about inter-current changes that could have had an impact on the results.

Seifert et al reported on a series of patients with colorectal liver metastases that were treated from 1996–2002. In this series, 168 patients underwent resection and 55 had cryosurgical ablation (CSA) (in 25 of these patients, it was combined with resection.) Twenty-nine percent (16 of 55) 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 cryotherapy were comparable, with 29 months and 29 months and 23% and 26%, respectively. However, the median disease-free survival (DFS) times and five-year DFS rates following resection were superior at 10 months and 19%, respectively, for resection compared with six months and 12%, respectively for cryotherapy. Overall recurrence was 61% in the resection group and 76% in the cryotherapy group, and liver recurrence was 45% and 71%, respectively. Limitations of this study include the small sample size, limited follow-up, and noncomparability of the groups.

Ruers and colleagues reported on a consecutive series of 201 colorectal cancer patients, without extrahepatic disease, treated between 1995 and 2004 and who 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 and received local ablative therapy (with or without resection), and patients in whom resection or local ablation was not feasible for technical reasons and who received systemic chemotherapy. The study reported that patients in the chemotherapy and local ablation groups were comparable for all prognostic variables tested. For the local ablation group, OS 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). After resection, these figures were 83% and 51%, respectively (median: 61 months; n=117; p<0.001). The median DFS after local ablation was nine months. The authors concluded that although overall survival (OS) of local ablation versus chemotherapy did not reach statistical significance, the median DFS of nine months suggested a beneficial effect of local tumor ablation. However, given the heterogeneity of the groups in this
study, it is very difficult to compare outcomes among the groups. In addition, this study used both cryotherapy and RF for local ablation, and results are reported for the combined group.

In a relatively small study, Joosten et al reported on 58 patients with unresectable colorectal liver metastases where CSA or RFAs were performed in patients not eligible for resection. Median follow-up was 26 and 25 months for CSA and RFA, respectively. One- and two-year survival rates were 76% and 61% for CSA and 93% and 75% for RFA, respectively. In a lesion-based analysis, the local recurrence rate was 9% after CSA and 6% after RFA. Complication rates were 30% and 11% after CSA and RFA, respectively (p=0.052). While the small size of this study makes drawing conclusions difficult, it does raise questions about the relative efficacy of both techniques.

Kornprat and colleagues reported on thermoablation combined with resection in the treatment of hepatic metastasis from colorectal cancer. In this series, from January 1, 1998, to December 31, 2003, 665 patients with colorectal metastases underwent hepatic resection. Of these, 39 (5.9%) had additional intraoperative thermoablative procedures (19 RFA, 20 CSA). The total morbidity rate was 41% (16 of 39). No RFA-related complications occurred; however, three patients developed an abscess at cryoablation sites. The median DFS was 12.3 months (range: 8.4–16.2 months). Overall, the local in situ recurrence rate according to number of ablated tumors was 14% for RFA and 12% for CSA. Tumor size correlated directly with recurrence (p=0.02) in RFA-treated lesions. In the comment section of this paper, the authors indicate that an ongoing controversy is whether resection of extensive disease combined with chemotherapy is better than either treatment alone.

Xu et al reported on a series of 326 patients with nonresectable hepatic colorectal metastases treated with 526 percutaneous cryosurgery procedures. At three months post-treatment, CEA levels decreased to normal range in 197 (77.5%) of patients who had elevated markers before cryosurgery. Among 280 patients who had computed tomography (CT) follow-up, cryotreated lesions showed complete response in 41 patients (14.6%), partial response in 115 (41.1%), stable disease in 68 (24.3%), and progressive disease in 56 (20%). During median follow-up of 32 months (range: 7–61 months), the recurrence rate was 47.2%. The recurrence rate at the cryotreated site was 6.4% for all cases. During median follow-up of 36 months, the median survival of all patients was 29 months (3 to 62 months). OS was 78%, 62%, 41%, 34%, and 23% at one, two, three, four, and five years, respectively, after treatment. Patients with tumor size smaller than 3cm, tumor in right lobe of liver, CEA levels less than 100 ng/dL and post-cryosurgery TACE had higher survival rates.

Procedure-related complications
Cryosurgery is not a benign procedure. Treatment-related deaths occur in approximately 2% of study populations and are most often caused by cryoshock, liver failure, hemorrhage, pneumonia/sepsis, and acute myocardial infarction. Clinically significant nonfatal complication rates in the reviewed studies ranged from zero to 83% and were generally due to the same causes as treatment-related deaths. The likelihood of complications arising from cryosurgery may be predicted, in part, by the extent of the procedure, but much of the treatment-related morbidity and mortality reflect the generally poor health status of patients with advanced hepatic disease.
**Summary**

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 (US) guidance.

Most patients in published series were candidates for cryosurgery because of unresectable disease, due either to large number of metastases, inaccessible location (e.g., near large vessels), or insufficient hepatic reserve to support resection. However, some of the studies included patients with resectable tumors, as well as patients with unresectable tumors. Furthermore some studies pooled results for mixed series of patients with liver metastases from various non-colorectal cancers (e.g., breast, sarcoma, ovarian, testicular, pancreatic, esophageal, head and neck) despite the differing characteristics and prognoses of these malignancies. Few controlled studies were found and those had methodological weaknesses including lack of randomization and noncomparable groups. Therefore, published outcomes of cryosurgery are inconclusive. The recent literature provides little new information on cryosurgical techniques, and interest appears to be concentrated on radiofrequency ablation. Thus, cryoablation for primary or metastatic liver tumors is investigational.

**Practice Guidelines and Position Statements**

The National Comprehensive Cancer Network (NCCN) indicates that ablative techniques may be used in the treatment of certain hepatic tumors. The guideline on hepatobiliary cancer includes cryoablation in a list of ablative techniques; however, the literature cited in the guideline reports on only radiofrequency ablation and ethanol ablation. The NCCN neuroendocrine guidelines indicate cryotherapy is an option for unresectable liver metastases. The guideline on treatment of metastatic hepatic lesions for colon cancer indicates that ablative techniques may be considered alone or in conjunction with resection. However, cryoablation is not listed anywhere in the guideline. The potential role of chemotherapy in converting unresectable to resectable hepatic lesions is also discussed.

**Transcatheter Arterial Chemoembolization (TACE)**

**TACE for unresectable hepatocellular carcinoma (HCC)**

A 2011 systematic review included nine trials with 645 patients treated with TACE or transarterial embolization for unresectable HCC. Six of these trials compared TACE versus control. The review concluded that all of the trials suffered from bias, larger trials should be conducted and that, despite the fact that TACE has been advocated as standard loco-regional treatment, there was no firm evidence to support or refute the use of TACE in patients with unresectable HCC. Also in 2011, Xie and colleagues reported on a meta-analysis of 13 studies on treatment for unresectable HCC using chemoembolization (1,233 patients) or microsphere embolization (597 patients, using a glass or resin hepatic artery infusion). Microsphere embolization treatment was found to result in statistically significant longer overall survival (HR: 0.73; 95% CI: 0.60–0.88; p=0.0009) and time to progression (HR: 0.61; 95% CI: 0.41–0.89; p=0.01) than chemoembolization. However, this meta-analysis included uncontrolled observational studies, which limits interpretation.
Two randomized studies comparing TACE to conservative treatment enrolled consecutive patients who met study criteria for unresectable HCC from among larger series of patents seeking treatment at the respective institutions. Patients in the Lo et al study tended to have more advanced disease based on Okuda stage, Eastern Cooperative Oncology Group (ECOG) performance status, and presence of tumor-related symptoms. The studies used a similar embolization regimen (lipiodol and gelatin sponge) but different cytotoxic agents (doxorubicin or cisplatin). Both studies reported significantly increased response and overall survival rates following treatment with TACE. In the Lo study, the chemoembolization group received a total of 192 courses of chemoembolization with a median of 4.5 (range: 1 to 15) courses per patient. Chemoembolization resulted in a marked tumor response, and the actuarial survival was significantly better in the TACE group (one year, 57%; two years, 31%; three years, 26%) than in the control group (one year, 32%; two years, 11%; three years, 3%; p=0.002). After adjustments for baseline variables that were prognostic on univariate analysis made with a multivariate Cox model, the survival benefit of chemoembolization remained significant (relative risk of death, 0.49; 95% confidence interval [CI]: 0.29–0.81; p=0.006). In the Llovet et al study, patients received arterial embolization with gelatin sponge, TACE, or conservative therapy. The trial was stopped when it was shown that chemoembolization had survival benefits compared with conservative treatment (hazard ratio [HR] of death: 0.47 [95% CI: 0.25–0.91], p=0.025). Survival probabilities at one year and two years were 75% and 50% for embolization; 82% and 63% for chemoembolization, and 63% and 27% for the control group (chemoembolization vs. control p=0.009), all respectively. Neither the Lo nor the Llovet study reported an increase in serious or life-threatening treatment-related adverse events after TACE.

A randomized controlled trial compared TACE versus systemic chemotherapy for patients with unresectable HCC. Mabed and colleagues randomized 100 patients to be treated with either TACE or intravenous doxorubicin. Fifty patients were treated with TACE using lipiodol, doxorubicin, and cisplatin, and 50 patients were treated with systemic doxorubicin alone. A significantly higher response rate was seen in patients treated with TACE, with a partial response achieved in 32% versus 10% of patients in the chemotherapy arm (p=0.007). A significantly more favorable tumor response to TACE was observed in patients with a single lesion (p=0.02), Child class A (p=0.007), Okuda stage 1 (p=0.005) and alpha-fetoprotein less than 400 ng/mL (p<0.001). The probability of tumor progression was significantly lower with TACE, where the median progression-free survival was 32 weeks (range: 16–70 weeks) versus 26 weeks (range: 14–54 weeks) for patients treated with systemic chemotherapy (p=0.03). The median overall survival did not differ significantly in cases treated with TACE (38 weeks) versus those treated with chemotherapy (32 weeks) (p=0.08), except for patients with serum albumin greater than 3.3 g/dL (60 vs. 36 weeks; p=0.003). Mortality in the chemoembolization arm was due to tumor progression in 53% of patients, liver failure in 32%, and gastrointestinal tract bleeding in 15%. Mortality in the chemotherapy arm was due to tumor progression in 64% of patients, liver failure in 25%, and gastrointestinal bleeding in 11%. Treatment-related mortality was 4% in the TACE arm versus 0% in the chemotherapy arm. The authors concluded that the overall survival benefits of TACE and systemic doxorubicin were similar for patients with unresectable HCC amenable to either treatment and that it is necessary to optimize the risk/benefit ratio of TACE and select the proper patient population that may benefit from this procedure.
Takayasu and colleagues reported results from an eight-year prospective cohort study of TACE from Japan. In this study, 8,510 patients with unresectable HCC underwent TACE using emulsion of lipiodol and anticancer agents followed by gelatin sponge particles as an initial treatment. Exclusion criteria were extrahepatic metastases and/or any previous treatment prior to the present TACE. The mean follow-up period was 1.77 years. For overall survival rates by TACE, median and one, two, and five-year survivals were 34 months, 82%, 47%, and 26%, respectively. The multivariate analyses showed significant difference in degree of liver damage (p=0.0001), alpha-fetoprotein value (p=0.0001), maximum tumor size (p=0.0001), number of lesions (p=0.0001), and portal vein invasion (p=0.0001). The TACE-related mortality rate after the initial therapy was 0.5%.

A large cohort study from Biselli and colleagues reported on 56 cirrhotic patients with unresectable HCC undergoing at least one course of TACE who were matched 1:1 for sex, age (in five-year periods), parameters of Child-Pugh score, Okuda stage, and tumor type with a control group who had received only supportive care. The two groups were comparable for cause of cirrhosis, alpha-fetoprotein serum levels, and “Cancer of the Liver Italian Program” (CLIP) score. The 56 patients in the TACE group received a total of 123 treatment courses. Survival rates at 12, 24, and 30 months in patients receiving TACE were 74.3%, 52.1%, and 38.8%, respectively, with a median survival time of 25 months, whereas in supportive-care patients, the rates were 39.4%, 25.4%, and 19%, respectively, with a median survival time of seven months (p=0.0004). At univariate analysis, TACE, tumor type, presence of ascites, alpha-fetoprotein serum level, CLIP score, and Okuda stage were associated significantly with survival. Only TACE and CLIP score proved to be independent predictors of survival at multivariate analysis.

In a prospective study from a single center in Canada, Molinari and colleagues reported on the effectiveness of TACE for HCC in a North American population. Child-Pugh A cirrhosis or better patients with unresectable HCC and without radiologic evidence of metastatic disease or segmental portal vein thrombosis were assessed between November 2001 and May 2004. Of 54 patients who satisfied the inclusion criteria, 47 underwent 80 TACE sessions. Chemoembolization was carried out using doxorubicin and lipiodol followed by an injection of embolic particles, when necessary. Repeat treatments were carried out at two to three-month intervals for recurrent disease. The survival probabilities at one, two, and three years were 76.6%, 55.5%, and 50%, respectively. At six months after the first intervention, 31% of patients had a partial response and 60% had stable disease. Major adverse events occurred after 20% of sessions, including two treatment-related deaths (4% of patients). The authors concluded that these survival probabilities at one and two years after TACE were comparable with results in randomized studies from Europe and Asia.

TACE for resectable hepatocellular carcinoma (HCC) - (TACE as neoadjuvant or adjuvant therapy)

Preoperative TACE

In 2013, Zhou et al. reported on a meta-analysis of 21 studies evaluating preoperative TACE. Included in the studies were 4 were randomized controlled trials and 17 nonrandomized studies with a total of 3,210 patients. Preoperative TACE was given to 1,431 patients with the remaining 1,779 serving as controls. In 18 studies, 5-year disease-free survival for preoperative TACE ranged from 7.0–57% and 8.0–48.8% in the controls. In 16 studies, the 5-year overall survival
for preoperative TACE was 15.4–62.7% and 19.0–62.5% in the controls. In the pooled analyses, there were no significant improvements with preoperative TACE versus controls in 5-year disease-free (32.1% vs. 30.0%, p=0.17) and overall survival (40.2% vs. 45.2%, p=0.37). Intra- and extra-hepatic recurrence were also not significantly different in the pooled analyses (51.2% vs. 53.6% and 12.9% vs. 10.3%, p=0.19, respectively).

In 2009, Chua and colleagues conducted a systematic review of neoadjuvant transarterial chemoembolization for resectable hepatocellular carcinoma. They evaluated 18 studies, including three randomized trials and 15 observational studies, some of which are outlined in detail in the following section. The review comprised 3,927 patients, 1,293 of whom underwent neoadjuvant TACE. The conclusions were that TACE could be used safely and resulted in high rates of pathologic responses but did not appear to improve disease-free survival in the TACE group. No conclusions could be drawn with respect to overall survival differences between the TACE and non-TACE groups due to the heterogeneity of the results across studies.

From July 2001 to December 2003, Zhou and colleagues randomized 108 patients with resectable HCC (≥5 cm suitable for a partial hepatectomy) to preoperative TACE treatment (n=52) or no preoperative treatment (control group) (n=56). Five patients (9.6%) in the preoperative TACE group did not receive surgical therapy because of extrahepatic metastasis or liver failure. The preoperative TACE group had a lower resection rate (n=47, 90.4% vs. n=56, 100%; p=0.017), and longer operative time (mean: 176.5 minutes vs. 149.3 minutes; p=0.042). No significant difference was found between the 2 groups in mortality. At a median follow-up of 57 months, 41 (78.8%) of 52 patients in the preoperative TACE group and 51 (91.1%) of 56 patients in the control group had recurrent disease (p=0.087). The one, three, and five-year disease-free survival rates were 48.9%, 25.5%, and 12.8%, respectively, for the preoperative TACE group and 39.2%, 21.4%, and 8.9%, respectively, for the control group (p=0.372). The one, three, and five-year overall survival rates were 73.1%, 40.4%, and 30.7%, respectively, for the preoperative TACE group and 69.6%, 32.1%, and 21.1%, respectively, for the control group (p=0.679). Preoperative TACE did not improve surgical outcome, and it resulted in drop-out from definitive surgery because of progression of disease and liver failure.

Kaibori et al reported on a trial of 124 patients randomized to receive preoperative tumor-targeted TACE (42 patients), whole liver TACE (39 patients), or no TACE (43 patients) prior to surgical resection for HCC. No significant differences were found between the pooled preoperative TACE groups and the control group in disease-free survival (p=0.6603) or overall survival (p=0.4115). Nor were there significant differences between the three groups in disease-free survival (p=0.8303) or overall survival (p=0.7126). Disease-free survival at one and three years for the tumor-targeted TACE group was 67% and 29%, 63% and 27% for the whole liver TACE group and 53% and 32% for the control group. Overall survival at one and three years for the tumor-targeted TACE group was 91% and 80%, 84% and 70% for the whole liver TACE group and 83% and 60% in the control group.

Zhang et al retrospectively analyzed the therapeutic results of 1,457 HCC patients treated with hepatectomy, 120 of whom had received TACE before surgical resection. They showed that the five-year disease-free survival rates of the patients who received more than two sessions of TACE, those who received one session of TACE, and no TACE patients were 51.0%, 35.5%,
and 21.4%, respectively, and that the mean disease-free survival times of the three groups were 66.4, 22.5 and 12.5 months, respectively. They concluded that effective preoperative TACE may be one of the best methods that can be clinically performed at present for resectable HCC, including small HCC, for improving disease-free survival after hepatectomy. On the other hand, Choi et al studied 273 patients who underwent curative resection for HCC; 120 of whom underwent preoperative TACE. The one, three, and five-year disease-free survival rates were 76.0%, 57.7%, and 51.3%, respectively, in the TACE group and 70.9%, 53.8%, and 46.8%, respectively, in the non-TACE group. Although a difference was noted between the TACE and non-TACE groups, it was not significant.

Postoperative TACE

Li and colleagues described the results of their randomized study exploring the efficacy of postoperative TACE and portal vein chemotherapy (PVC) for patients with HCC complicated by portal vein tumor thrombosis (PVTT) and to evaluate prognostic factors. The study cohort consisted of 112 patients with HCC and PVTT randomly divided into three groups: Group A (37 patients), surgery only; Group B (35 patients), operation plus TACE; Group C (40 patients), operation plus TACE and PVC. Portal vein thrombus extirpation was performed at the time of surgery. Adverse effects and complications were mostly related to the operation, catheters, and local chemotherapy and included liver decompensation (15.0%), catheter obstruction (11.6%), and nausea and loss of appetite (22.1%). The disease-free survival curve was significantly different among the three groups, as estimated by the Kaplan-Meier method (both p<0.05). Group C showed a higher disease-free survival rate than Group A (p<0.05), but no statistical differences were found between group A and group B, or group B and group C (both p>0.05). The one, three, and five-year disease-free survival rates in Group A (resection only, n=37) were 50.7, 17.8, and 0%, respectively; in Group B (resection + TACE, n=35), rates were 62.3, 23.7, and 4.0%, respectively, and in Group C (resection + TACE + PVC, n=40) increased to 74.4, 46.1, and 11.5%, respectively. Tumor size, tumor number, PVTT location, and treatment modalities were independent prognostic factors (p<0.05). The authors concluded that postoperative TACE combined with PVC may benefit the survival of patients with HCC complicated by PVTT in the short-term (less than 60 months), but long-term efficacy is not yet certain and needs to be confirmed by further studies.

TACE for cholangiocarcinoma

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy after HCC (10% vs. 90%, respectively). Surgical resection represents the only form of curative therapy; however, the majority of ICC patients are not surgical candidates due to their advanced disease at the time of diagnosis which is caused by the lack of symptoms until late in the disease. The overall prognosis of ICC is far worse than for extrahepatic cholangiocarcinoma because of its late presentation. Most patients with ICC qualify for palliative therapy, including systemic chemotherapy and radiation therapy. However, such palliative options afford little to no survival improvement over supportive therapy alone, as ICC responds poorly to such existing therapies. The prognosis for patients with unresectable ICC is approximately five to eight-month survival.

Park and colleagues conducted a retrospective review of the medical and imaging records of 155 patients with unresectable ICC who were treated between 1996 and 2009 with TACE. Patients who had undergone previous local or systemic therapy were excluded. A total of 72 patients
underwent TACE, and 83 received supportive care, based on physician and patient preference. Supportive care included pain and ascites control and biliary drainage. Survival was the primary endpoint. Baseline patient and tumor characteristics were well-balanced between the two groups. Most patients had Stage 3 or 4 disease. Tumor multiplicity was single and multiple or diffuse in 43% and 57% of the TACE patients, respectively, and 53% and 47% in the supportive group, respectively. Maximum tumor size in the TACE group was 8.1 cm +/- 3.4 cm and 7.8 cm +/-3.1 cm in the supportive group. The median number of sessions per patient in the TACE group was 2.5 (range 1-17 sessions). After TACE, the incidence of significant (≥Grade 3) hematologic and nonhematologic toxicities was 13% and 24%, respectively, and no patients died within 30 days following TACE. The Kaplan-Meier survival analysis showed a median survival in the TACE group of 12.2 months, versus a median of 3.3 months in the supportive therapy group (p<0.0001). Survival rates also differed significantly between the two groups according to the presence or absence of extrahepatic metastases. In patients with liver-only disease, the median survival period was 13.3 months (95% CI: 9.2-17.4 months) for the TACE group and four months (95% CI: 3-5 months; p<0.001) for the supportive treatment group. In patients with extrahepatic metastases, the median survival period was 11.3 months (95% CI: 8.9-13.7 months) for the TACE group and 3.2 months for the supportive treatment group (95% CI: 2.6-3.8 months; p<0.001).

Knüppel and colleagues reported a retrospective review of 195 patients with intrahepatic (57%) or extrahepatic (43%) cholangiocarcinoma. Patients received either chemotherapy or a combination of photodynamic therapy or TACE with chemotherapy. Some of the patients underwent surgical resection. Patients who only received palliative care (no surgery) survived 9.8 months longer with combination chemotherapy and TACE (n=14) versus chemotherapy alone (n=81) (median survival for chemotherapy plus TACE 22.0 months versus for chemotherapy alone 12.2 months; p=0.039). Survival was not reported for extrahepatic versus intrahepatic cholangiocarcinoma.

Shen et al retrospectively compared 53 patients who received TACE after surgical resection of intrahepatic cholangiocarcinoma to 73 patients who had surgical resection without TACE. Disease-free survival rates at one, three, and five-years (24.5%, 17.0%, and 17.0%, respectively) in the patients receiving TACE were not significantly different from the group that did not receive post-surgical TACE [33.3%, 19.4%, and 15.3%, respectively (p=0.659)]. Overall survival rates were significantly better in the TACE group at one, three, and five-years (69.8%, 37.7%, and 28.3%, respectively) than the non-TACE group [54.2%, 25.0%, and 20.8%, respectively (p=0.045)]. However, the retrospective nature of this study limits interpretation of its findings.

Herber and colleagues conducted a retrospective study in 15 patients with inoperable ICC treated with TACE between 2000 and 2006. None of the patients had extrahepatic tumor spread. The decision for TACE was made by an interdisciplinary tumor board in each individual case. Fifty-eight TACE sessions were performed in the 15 patients (3.9 +/- 3.8; range 1-15). Eight patients had unifocal tumor and seven had multifocal disease. The mean tumor size was 10.8 +/- 4.6 cm (range 2.0-18.0 cm). No deaths and no acute liver failure occurred under TACE therapy. Major complications were observed in two patients, having anaphylactic shock owing to contrast
medium administration in one and gastric ulceration due to lipiodol displacement in the second patient. Mean survival was 21.1 months (95% CI: 9.4-32.5 months).

Burger and colleagues prospectively collected data on 17 patients with unresectable cholangiocarcinoma treated with TACE at their institution between 1995 and 2004. Among the 17 patients, 11 presented without any previous treatment, whereas six had received previous therapy including chemotherapy with or without radiation with evidence of progression. Fifteen patients had intrahepatic tumors and two had perihilar tumors. The procedure was well-tolerated by 82% of the patients, who experienced mild or no side effects that resolved with conservative therapy alone. Two patients had minor complications (12%), which were managed successfully, and one had a major complication that resulted in a fatal outcome with a rapidly declining course from the time of diagnosis to death shortly after TACE. Median survival for the 17 patients was 23 months (95% CI: 15.4-30.6 months). Two patients with previously unresectable disease underwent successful resection after TACE.

TACE for hepatic metastases from neuroendocrine tumors

Neuroendocrine tumors are a heterogeneous group of tumors that are typically slow-growing tumors with an indolent course, with the capacity to synthesize and secrete hormones. Liver metastases may result in significant hormonal symptoms and are associated with a poor prognosis. Systemic chemotherapy for these tumors has shown modest response rates of limited duration, and although somatostatin analogs are usually effective in controlling symptoms, the disease eventually becomes refractory. Therefore, liver-directed therapies aim to reduce tumor burden to reduce hormone levels and palliate symptoms in patients with unresectable neuroendocrine metastases to the liver.

A 2010 review by Nazario and Gupta summarizes the experience to date with TACE (and transarterial embolization [TAE]), which is composed of many nonrandomized, retrospective reports that have demonstrated reduced tumor burden, reduced hormone levels, and palliation of symptoms with these interventions. The article summarizes the experience with TACE and TAE and metastatic neuroendocrine tumors as showing radiologic response ranging from 25–95%, and symptomatic response in 53–100% of patients. Five-year overall survival rates have varied from 14–75%, likely a reflection of the heterogeneity of the patient populations and regimens of treatment used. Some of the studies in the review are detailed below.

Ruutiainen and colleagues reported on a study of 67 patients that compared bland embolization to TACE in neuroendocrine tumors metastatic to the liver. In this study, 67 patients underwent 219 embolization procedures: 23 patients received primarily bland embolization with polyvinyl alcohol with or without iodized oil and 44 primarily received chemoembolization with cisplatin, doxorubicin, mitomycin-C, iodized oil, and polyvinyl alcohol. Patients with disease relapse were treated again when feasible. Ten of 67 patients (15%) were lost to follow-up. Toxicities of Grade 3 or worse in severity occurred after 25% of chemoembolization procedures and 22% of bland embolization procedures. Rates of freedom from progression at one, two, and three years were 49%, 49%, and 35%, respectively, after chemoembolization and 0%, 0%, and 0%, respectively, after bland embolization, respectively (log-rank test, p=0.16). Patients treated with chemoembolization and bland embolization experienced symptomatic relief for means of 15 and 7.5 months, respectively (p=0.14). Survival rates at one, three, and five years after therapy were
86%, 67%, and 50%, respectively, after chemoembolization and 68%, 46%, and 33%, respectively, after bland embolization (p=0.18). The authors concluded that chemoembolization demonstrated trends toward improvement in TTP (time to progression), symptom control, and survival and indicated that a multicenter prospective randomized trial is warranted. These results are similar to those reported previously by Gupta et al, who noted that in a retrospective series of 81 patients, hepatic artery embolization or chemoembolization resulted in symptomatic and radiographic response in most patients with carcinoid metastases to the liver.

Osborne and colleagues reported on a nonrandomized study of 59 patients with neuroendocrine tumors who received either cytoreduction or embolization for symptomatic hepatic metastases. The duration of symptom relief (35 vs. 22 months) and survival (43 vs. 24 months) both favored the cytoreduction approach. The authors commented that cytoreduction should be pursued when possible even if complete resection may not be achievable.

**TACE for hepatic metastases from uveal (ocular) melanoma**

Uveal (ocular) melanoma is the most common primary 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. 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.

A 2010 review by Sato addresses the locoregional management of hepatic metastases from primary uveal melanoma and summarizes the published studies to date, many of which are detailed in the following section.

Huppert et al reported the results of a pilot trial of 14 patients with hepatic metastases from uveal melanoma who underwent TACE. Patients received a mean of 2.4 treatments (34 total treatments among the 14 patients). Responses were partial for eight patients (57%). Four patients (29%) had stable disease and two (14%) had tumor progression. Median time to progression was 8.5 months (range: 5 to 35 months), and median survival after the first TACE treatment was 14.5 months in responders and 10 months in nonresponders (p=NS). In this study, the survival rate was 86% at six months, 50% at 12 months, 28% at 18 months, and 14% at 24 months after the first TACE treatment. Survival advantage was most pronounced for patients with tumor occupying less than 25% of the liver volume (n=7) with a median of 17 months versus 11 months in the seven patients with more than 25% involvement of the liver (p=0.02). The authors state that, for comparison, with no treatment, survival after detection of liver metastases is two to seven months with a median one-year survival rate less than 30%. Response rates for systemic chemotherapy are less than 10%, and 20–50% with immunochemotherapy, but with only a median survival of five to nine months and serious toxicity.

Sharma and colleagues reported on the use of TACE in the treatment of melanoma metastatic to the liver reported in a series of 20 patients (17 with ocular melanoma) treated between 2004 and 2007. The 20 patients underwent 46 TACE sessions (mean: 2.4 sessions; range: 1-5). The mean and median overall survival times were 334 and 271 days, respectively. There were no deaths within 30 days of treatment. The authors noted that this treatment resulted in longer survival than
has been noted among historical controls. This work builds on results reported by Bedikien and colleagues in 1995 that showed that TACE had a 36% response rate (cisplatin chemoembolization) compared to a 1% response rate to systemic chemotherapy.

Patel and colleagues reported on BCNU treatment for uveal melanoma and demonstrated that those who responded had improved survival. In this study, 18 of the 24 patients experienced regression or stabilization of hepatic metastases for at least six weeks. The overall response rates (complete and partial responses) for the intention-to-treat population and for patients who were evaluable for response were 16.7% and 20.4%, respectively. The median overall survival of the entire intention-to-treat group of patients was 5.2 months, for patients with complete or partial response in hepatic metastases it was 21.9 months, for patients with stable disease, 8.7 months, and for patients with progressive disease, 3.3 months. Thus, for patients with metastatic uveal melanoma who have disease confined to the liver, the metastatic liver disease may respond to TACE treatment and patients who respond to TACE have improved survival.

TACE for hepatic metastases from colorectal cancer
For patients with liver metastases from colorectal cancer who do not qualify for surgical resection, traditionally, systemic chemotherapy is first-line treatment. However, in more than 60% of cases, the treatment fails and disease progresses. For the large proportion of patients in whom second- and third-line medical treatment has failed, other palliative therapies to control disease progression and symptoms have been studied, including TACE.

The literature has reported a median survival in patients with liver-dominant colorectal metastases treated with chemoembolization from seven to 23 months. However, studies are difficult to compare, as some patients who were treated were still eligible for systemic chemotherapy, and survival was sometimes calculated and reported as a mean time from the date of diagnosis of liver metastases rather than from the first treatment with TACE.

Vogl and colleagues evaluated tumor control and survival in 463 patients with unresectable liver metastases of colorectal origin that did not respond to systemic chemotherapy and were treated with TACE. Of the 463 patients, 67% had five or more metastases, 8% had one metastasis, 10% had two, and 14% had three or four. Patients were treated at four-week intervals, with a total of 2,441 chemoembolization procedures performed (mean, 5.3 sessions per patient), using one of three local chemotherapy protocols. Local tumor control was partial response in 68 patients (14.7%), stable disease in 223 patients (48.2%), and progressive disease in 172 patients (37.1%). Median survival from the start of TACE treatments was 14 months (compared to the results from a previous study by the same author, in which untreated patients had a survival rate of seven to eight months). One-year survival rate after TACE was 62% and 28%, respectively, at two years. No difference in survival was observed between the three different local chemotherapy protocols.

Hong and colleagues compared salvage therapy for liver-dominant colorectal metastatic adenocarcinoma using TACE or 90-yttrium radioembolization. Mean dominant lesion sizes were 9.3 cm and 8.2 cm in the chemoembolization and radioembolization groups, respectively. Multilobar disease was present in 67% and 87% of the respective groups, and extrahepatic metastases were present in 43% and 33%, respectively. Of 36 patients, 21 underwent TACE,
with a median survival of 7.7 months (survival measured from the date of the first TACE treatment to the date of death or to April 2007, if still living). Survival results were comparable to other studies addressing colorectal cancer and TACE, which ranged from seven to ten months. Median survival was 6.9 months for the radioembolization group (p=0.27). The one, two, and five-year survival rates for the two groups were 43%, 10%, and 0%, respectively, for the chemoembolization group and 34%, 18%, and 0%, respectively, for the radioembolization group.

Richardson and colleagues reported on a systematic review of 1 RCT and 5 observational studies on TACE with irinotecan-eluting beads for unresectable colorectal liver metastasis. Survival times ranged from a median of 15.2 months to 25 months. The most common adverse event was post-embolization syndrome (abdominal pain, nausea, and vomiting) followed by hypertension. In the RCT included in the Richardson systematic review, Fiorentini et al. reported on 74 patients randomly allocated to TACE with irinotecan-eluting beads (n=36) or systemic irinotecan, fluorouracil and leucovorin (n=38). With irinotecan-eluting beads, overall survival was significantly longer with a median overall survival of 22 months (95% CI: 21-23 months) versus 15 months (95% CI: 12-18) for the systemic chemotherapy group (p=0.031). Progression-free survival was significantly longer at 7 months (95% CI: 3-11) in the irinotecan-eluting beads group compared to 4 months (95% CI: 3-5) months in the systemic chemotherapy group (p=0.006). However, larger studies are needed to confirm these findings.

TACE for hepatic metastases from breast cancer
Vogl and colleagues reported the efficacy of repeated treatments with TACE in 208 patients with unresectable hepatic metastases from breast cancer. A total of 1,068 chemoembolizations were performed (mean 5.1 sessions per patient, range: 3-25). Mean patient age was 56.4 years (range: 29-81). Patients received either one of two chemotherapeutic agents alone (mitomycin-C or gemcitabine) or in combination. Tumor response was evaluated by magnetic resonance imaging (MRI) according to RECIST criteria. For all chemotherapy protocols, local tumor control was partial response 13% (27/208), stable disease 50.5% (105/208), and progressive disease 36.5% (76/208). The one, two, and three-year survival rates after TACE were 69, 40, and 33%. Median and mean survival times from the beginning of the TACE sessions were 18.5 and 30.7 months. Treatment with mitomycin-C only showed median and mean survival times of 13.3 and 24 months, and with gemcitabine only 11 and 22.3 months. With a combination of mitomycin-C and gemcitabine, median and mean survival was 24.8 and 35.5 months – all results are respectively.

2013 National Comprehensive Cancer Network (NCCN) Guidelines
Hepatocellular carcinoma (v.2.2013): chemoembolization is listed as an option for patients with unresectable hepatocellular carcinoma with tumors not amenable to ablation therapy only and in the absence of large volume extrahepatic disease [category 2A] with the additional recommendation that tumor lesions larger than 5cm should be treated using arterial embolic approaches, whereas those tumors 3 to 5cm can be considered for combination therapy with ablation and arterial embolization. Additionally, TACE is relatively contraindicated in patients with portal vein thrombosis and bilirubin levels greater than 3 mg/dL and absolutely contraindicated with Child-Pugh class C liver function.

Intrahepatic cholangiocarcinoma (v.2.2013): does not address the use of TACE in intrahepatic cholangiocarcinoma.
Neuroendocrine tumors, carcinoid, and islet cell tumors (v.2.2013): chemoembolization is recommended for patients with unresectable liver metastases [category 2B].

Colon cancer (v.3.2013): the use of arterially-directed embolic therapy for metastatic colon cancer to the liver has a Category 3 recommendation (based upon any level of evidence, there is major NCCN disagreement about whether the intervention is appropriate).

No NCCN guidelines were identified for ocular malignancies.

Breast cancer (v3.2013): TACE is not addressed as a treatment option for breast cancer metastatic to the liver.

Summary
Transcatheter arterial chemoembolization (TACE) of the liver is a proposed alternative to conventional systemic or intra-arterial chemotherapy, and to various nonsurgical ablative techniques, to treat resectable and nonresectable tumors. TACE combines the infusion of chemotherapeutic drugs with particle embolization. Tumor ischemia secondary to the embolization raises the drug concentration compared to infusion alone, extending the retention of the chemotherapeutic agent and decreasing systemic toxicity.

- Unresectable HCC: Studies (including randomized trials) of TACE for patients with unresectable HCC confined to the liver who meet specific selection criteria (i.e., good hepatic function/reserve and no portal vein thrombosis) have shown improved survival compared to only supportive care. A systematic review highlighted some of the possible biases associated with these studies.
- Resectable HCC: There are little data on the use of TACE in the neoadjuvant or adjuvant setting, and a significant long-term survival benefit has not been demonstrated. A meta-analysis found no significant improvements in survival or recurrence with the use of preoperative TACE for resectable HCC.
- TACE in the liver transplant setting for HCC: TACE has become an accepted method to prevent tumor growth while patients are on the liver transplant wait list.
- Cholangiocarcinoma: Most of the data for the use of TACE to treat unresectable cholangiocarcinoma is for unresectable intrahepatic cholangiocarcinoma. Although the data suggest a survival advantage with TACE versus supportive care or systemic chemotherapy alone, the data consist mostly of retrospective reviews without matched patient controls, and clinical vetting did not uniformly support the use of TACE for this indication.
- Metastatic neuroendocrine tumors: Studies have included heterogeneous patient populations, and interpretation of survival data using TACE is difficult. Several studies have shown reduced tumor burden, reduced hormone levels, and palliation of symptoms with TACE.
- Metastatic uveal melanoma: Several studies have shown a survival advantage using locoregional treatment modalities, including TACE, in patients who have liver-dominant metastases from ocular melanoma.
- Metastatic colorectal cancer and other metastases: Studies have consisted of small numbers of patients, and the results have been variable across studies due to variation in
patient selection criteria and regimens used between different studies. At this time, the
data do not support the use of TACE in these settings.

Microwave ablation
Hepatocellular Carcinoma
Hepatic tumors can arise either as primary liver cancer (hepatocellular carcinoma, HCC) or by
metastasis to the liver from other primary cancer sites. Local therapy for hepatic metastasis may
be indicated 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 adequate margins or liver transplantation constitutes the only treatments
available with demonstrated curative potential. Partial liver resection, hepeatectomy, is considered
the gold standard. However, the majority of hepatic tumors are unresectable at diagnosis, due
either to their anatomic location, size, number of lesions, or underlying liver reserve. Various
locoregional therapies for unresectable liver tumors have been investigated including: microwave
coaulation, radiofrequency ablation, cryosurgical ablation (cryosurgery), laser ablation, trans-
hepatic artery embolization/chemoembolization (TACE), percutaneous ethanol injection, and
radioembolization (Yttrium-90 microspheres). MWA has been investigated as a treatment for
unresectable hepatic tumors, both as primary treatment, palliative treatment, and as a bridge to
liver transplant. In the latter setting, it is hoped that MWA will reduce the incidence of tumor
progression while awaiting transplantation and thus maintain a patient’s candidacy for liver
transplant during the wait time for a donor organ.

In 2009, Ong and colleagues conducted a systematic review of studies on MWA for primary and
secondary liver tumors. Based on the results from 25 clinical studies reporting outcomes on
MWA, the authors concluded MWA is an effective and safe technique for liver tumor ablation
with low complication rates and survival rates comparable to hepatic resection. However, rates
of local recurrence after MWA were noted to be higher than hepatic resection. In most studies,
hepatocellular carcinoma recurrence rates were approximately 10% but were also noted to be as
high as 50%, which the authors indicated can be addressed with further ablation. Survival rates
in the studies on MWA for hepatocellular carcinoma were as high as 92% at three years and 72%
at five years, which was noted to be comparable to radiofrequency ablation and percutaneous
ethanol injections. Pain and fever were the most frequently reported complications, but
complications increased when there were more tumors, larger tumors, and more microwave
antennas used. Ong and colleagues concluded MWA is a promising treatment option for the
treatment of liver tumors but should be reserved for patients not amenable to hepatic resection.
The authors also noted further randomized clinical trials are warranted to compare MWA to
other ablation procedures. Bertot and colleagues conducted a systematic review in 2011 of
ablation techniques for primary and secondary liver tumors. This review included two studies
using MWA totaling 1,185 patients. The pooled mortality rate for MWA was 0.23% (95%
confidence interval [CI]: 0.0–0.58%). Major complication rates were 4.6% for MWA (calculated
by using a random effects model since there was significant heterogeneity). The authors
concluded percutaneous ablation techniques, including MWA, are safe and have acceptable
complication rates for the treatment of liver tumors.

In 2002, Shibata and colleagues reported on 72 consecutive patients with 94 small hepatocellular
carcinoma nodules randomized by sealed envelopes to receive either percutaneous MWA or
radiofrequency ablation performed by a single surgeon. No significant differences were identified between the two treatment group characteristics, e.g., sex, age, nodule size, Child-Pugh cirrhosis class and number of nodules. In the radiofrequency ablation group, complete therapeutic effect was seen in 46 (96%) of 48 nodules (mean size 2.3 cm, range 1.0-3.7) versus 41 (89%) of 46 nodules (mean size 2.2 cm, range 0.9-3.4) treated with percutaneous MWA (p=0.26). Treatment outcomes were not significantly different between the percutaneous MWA and radiofrequency ablation groups in the rates of untreated disease during a follow-up range of 6-27 months (eight of 46 nodules vs. four of 48 nodules, respectively), and major complication rates (four vs. one, respectively). Major complications included one case of segmental hepatic infarction in the radiofrequency ablation group. In the MWA group, major complications included one case of each of the following: liver abscess, cholangitis with intrahepatic bile duct dilatation, subcutaneous abscess with skin burn and subcapsular hematoma. Life-threatening complications were not experienced. The number of treatment sessions required per nodule in the radiofrequency ablation group was significantly lower than in the percutaneous MWA group (1.1 vs. 2.4; p<0.001). However, treatment time per session was significantly shorter in the MWA group (33 minutes ± 11) than the radiofrequency ablation group (53 minutes ± 16).

Taniai and colleagues, in 2006, reported on 30 patients with multiple hepatocellular carcinoma tumors who underwent reduction hepatectomy with postoperative transcatheter arterial embolization. Prior to surgery, patients were randomly assigned to receive no intraoperative adjuvant therapy (n=15) or intraoperative adjuvant therapy with either MWA (n=10) or radiofrequency ablation (n=5) of satellite lesions. No significant differences in characteristics were identified between the two treatment groups of no intraoperative adjuvant therapy vs. intraoperative adjuvant therapy, e.g., sex, age, nodule size (maximum tumor size 42.7 mm ± 23.5 vs. 37.8 mm ± 16, respectively), Child-Pugh cirrhosis class and number of nodules. Cumulative survival rates at three and five years were not significantly different in the group that did not receive intraoperative adjuvant therapy (35.0% and 0%, respectively) versus the intraoperative adjuvant therapy group (35.7% and 7.7%, respectively). A-fetoprotein, number of tumors, maximum tumor size and clinical stage, but not intraoperative adjuvant therapy, were identified as independent prognostic survival factors.

In April 2011, Simo and colleagues retrospectively compared laparoscopic MWA (13 patients with 15 tumors) to radiofrequency ablation (22 patients with 27 tumors) performed by a single surgeon for the treatment of HCC. No significant differences were identified between the two treatment group characteristics except for sex (54% vs. 86% male, respectively). Average tumor size was 2.31 cm in the MWA group versus 2.53 cm in the radiofrequency ablation group. The authors reported average tumor ablation volumes were not significantly different at 28.99 cm for MWA and 23.43 cm for radiofrequency ablation. In the MWA group, at a mean follow-up of seven months, disease-free survival was 54%, with two patients having received liver transplants, 31% having disease progression and 15% deceased. The RFA group was followed for a longer period of time at a mean of 19 months. This group experienced 50% survival without evidence of disease, with four patients having received liver transplants, 9% having disease progression, 36% deceased, and 5% lost to follow-up. Operative times were shorter in the MWA group (112 ± 40 vs. 149 ± 35 minutes). In 2013, Ding et al. also reported on a retrospective comparison of 113 patients treated with MWA for 131 HCC tumors and 85 patients treated with radiofrequency ablation (RFA) for 98 HCC tumors. Rates of complete ablation, local recurrence,
disease-free and cumulative survival (at 1, 2, 3, and 4 years), and major complications were not significantly different between groups. In 2013, Ding et al. also reported on a retrospective comparison of 113 patients treated with MWA for 131 HCC tumors and 85 patients treated with radiofrequency ablation (RFA) for 98 HCC tumors. Rates of complete ablation, local recurrence, disease-free and cumulative survival (at 1, 2, 3, and 4 years), and major complications were not significantly different between groups. In another 2013 study by Ding et al., complications were retrospectively compared between 556 patients treated with MWA for 1,090 tumors (491 HCC, 18 cholangiocarcinoma, and 47 liver metastases) and 323 patients treated with RFA for 562 liver tumors (279 HCC, 6 cholangiocarcinoma, and 38 liver metastases). Rates of death (2 of 556 MWA and 1 of 323 RFA patients), major complications and minor complications did not differ significantly between MWA and RFA groups.

In 2011, Zhou and colleagues prospectively evaluated percutaneous MWA for hepatocellular carcinoma in 215 patients with tumors equal to or less than 60 mm (median size 29 mm) in a single center, Phase II study. The authors reported technical effectiveness in all patients. Overall survival rates at one, two, three, four and five years were 94%, 82.9%, 66%, 54.1% and 44.4%, respectively, and median survival time was 40 months (range 4 to 106 months). Complications related to the procedure included three cases of pleural effusion and one case of bile duct injury. In another prospective study by Zhou et al in 2009, percutaneous MWA was performed on 124 patients with 144 hepatocellular carcinoma lesions and 28 patients with 35 lesions of hepatic metastases. Included in this total of 152 patients were 59 patients with 61 lesions (mean size 27 mm) located less than 5 mm from the gastrointestinal tract and 93 patients with 126 lesions (mean size 24 mm) located more than 5 mm from the gastrointestinal tract. For lesions less than 5 mm from the gastrointestinal tract, the temperatures of the margins were monitored closely during ablation and to prevent thermal injury, ethanol injections were placed into marginal tumor tissue in 33 lesions that were protruding or in contact with the gastrointestinal tract. No procedural complications were noted; however, tumor seeding occurred in three patients. Complete ablation was achieved in 47 of 53 lesions (88.7%) in the group with tumors near the gastrointestinal tract and in 116 of the other 126 lesions (92.1%) as confirmed by imaging during the follow-up period ranging from three to 32 months. Local tumor progression occurred in 16 tumors during one to nine months’ follow-up. Separate treatment outcomes for hepatocellular tumors and hepatic metastasis were not provided.

Lu and colleagues, in 2005, reported on a retrospective comparison of 102 patients with hepatocellular carcinoma treated with either percutaneous MWA (49 patients with 98 nodules, mean size 2.5 cm) or radiofrequency ablation (53 patients with 72 nodules, mean size 2.6 cm). Patient follow-up was 25.1 months in the MWA group and 24.8 months in the radiofrequency ablation group. Complete ablation was not significantly different in the treatment groups and was achieved in 93 of 98 tumors (94.9%) in the MWA group and in 67 of 72 tumors (93.1%) in the radiofrequency ablation group. However, complete ablation rates increased in tumors less than or up to 3 cm in size to 98.6% (73 of 74) in the MWA group and 98% (50 of 51) in the radiofrequency ablation group. In tumors greater than 3 cm, complete ablation rates decreased to 83.3% (20 of 24) in the MWA group and 81% (17 of 21) in the radiofrequency ablation group. There were also no significant differences found in the MWA group versus the radiofrequency ablation group in rates of local tumor recurrence (11.8% vs. 20.9%, respectively), major
complications (8.2% vs. 5.7%, respectively) or disease-free survival at one, two and three years (45.9%, 26.9% and 26.9% vs. 37.2%, 20.7%, and 15.5%, respectively).

In 2012, Takami and colleagues reported on 719 patients treated with intraoperative MWA for hepatocellular carcinoma (HCC) (mean tumor size 26.9mm) at a single institution. The overall survival rates were 97.7% at one year, 62.1% at five years, and 34.1% at ten years. Overall survival rates for 390 patients with three or fewer tumors measuring 3cm or less were 97.9% at one year, 70.0% at five years, and 43.0% at ten years. When MWA results were compared to 34 patients treated at the same institution with hepatic resection, overall survival, disease-free survival, and local recurrence rates were not significantly different.

In 2009, Liang et al reported on a retrospective review of complications experienced with percutaneous MWA for the treatment of 1,928 malignant liver tumors in 1,136 patients at a single institution. Each patient received an average of 1.8 treatment sessions for a total of 3,697 treatment sessions. Thirty patients (2.6%) experienced major complications, which included five cases of liver abscess and empyema, two bile duct injuries, two colon perforations, five tumor seedings, 12 pleural effusions requiring thoracentesis, one hemorrhage requiring arterial embolization, and three skin burns requiring resection for a total of 30 (2.6%) patient complications. Two deaths occurred within 30 days after MWA in patients with Child class B uncompensated cirrhosis. One patient (age 78) had multi-organ failure and died 14 days after treatment and another patient (age 83) had respiratory and cardiac failure and died 14 days after treatment. Minor complications included fever (83.4%), pain (80.1%), asymptomatic pleural effusion (10.4%), thickening of the gallbladder wall (2.8%), and arteriportal shunt (0.3%), small stricture of the bile duct (0.4%), and skin burn requiring no treatment (1.6%). A significantly higher rate of major complications and more ablation sessions were experienced when a noncooled-shaft antenna was used during the period of 1994 to 2005 (n=583) than with newer technology; cooled-shaft antennas were used beginning in 2005 (n=583). In a report on needle-track seeding from this same institution, Yu and colleagues followed 1,462 patients treated with percutaneous MWA for 2,530 liver tumors over a 14-year period. Twelve seeding nodules with a mean size of 2.3 + 0.7 cm (range 1.3 to 3.9 cm) were found in 11 patients within six to 37 months (median 10 months) after receiving MWA.

Hepatic Metastasis from Primary Cancers from Other Sites
The literature searches identified many small studies on MWA for hepatic metastases and three systematic reviews. In the Ong review described above, local recurrence rates for liver metastases after treatment with MWA averaged approximately 15% but varied between 0 and 50% in the seven studies reviewed that addressed liver metastases. As noted above, Ong and colleagues concluded MWA is a promising treatment option for the treatment of liver tumors but should be reserved for patients not amenable to hepatic resection. Bertot and colleagues conducted a systematic review described above. In 2011, Pathak and colleagues also conducted a systematic review of ablation techniques for colorectal liver metastases, which included 13 studies on MWA totaling 406 patients with a minimum of one-year follow-up. Mean survival rates were 73%, 30% and 16% and ranged from 40–91.4%, 0–57% and 14–32% at one, two and five-year follow-up, all respectively. Minor and major complication rates were considered acceptable and ranged from 6.7–90.5% and 0–19%, respectively. Local recurrence rates ranged
from 2-14%. The authors acknowledged limitations in the available studies but concluded survival rates for MWA are more favorable than for palliative chemotherapy alone.

Only one RCT comparing the use of MWA for hepatic metastases to the gold standard of surgical resection was identified. In 2000, Shibata et al reported on a trial of 30 patients with hepatic metastases from colorectal cancer randomly assigned without stratification to treatment with either MWA after laparotomy (n=14) or hepatectomy (n=16). The study began with 40 patients, but 10 patients were excluded because the researchers discovered intraoperatively that these patients did not meet study criteria due to having extensive metastasis or equal to or greater than 10 tumors. The treatment groups of MWA vs. hepatectomy were not significantly different in age (mean age 61 in both groups) number of tumors (mean 4.1 vs. 3.0, respectively) or tumor size (mean 27 mm vs. 34 mm, respectively). The authors reported no significant differences in survival rates following MWA or hepatectomy (27 months vs. 25 months, respectively) and mean disease-free survival (11.3 vs. 13.3 months, respectively). However, intraoperative blood loss was significantly lower and no blood transfusions were required in the MWA group whereas six patients in the hepatectomy group required blood transfusions. Complications in the microwave group consisted of one hepatic abscess and one bile duct fistula. In the hepatectomy group, complications were one intestinal obstruction, one bile duct fistula and one wound infection.

In 2011, Lorentzen and colleagues reported on a retrospective review of percutaneous or open MWA in 39 patients with 125 liver metastases from the primary sites of colorectal cancer (n=31), breast cancer (n=6), carcinoid tumor (n=1), and gastrointestinal stromal tumor (n=1). Complete ablation was achieved in 100% of tumors (median size of 1.5 cm) with one treatment session in 34 patients, two sessions for four patients, and three sessions for one patient. One case of liver abscess, which resolved after percutaneous drainage, was the only major complication reported. Four minor complications included one incidence of ascites and three complaints of puncture site pain. Upon median follow-up of 11 months, local tumor progression was seen in 12 of 125 tumors (9.6%) in 10 of the 39 patients (26%).

In a prospective, single institution Phase II study in 2010, Martin et al reported on 100 patients treated with 270 open or laparoscopic MWAs for hepatocellular carcinoma (n=17) and liver metastases from the primary sites of colorectal (n=50), carcinoid (n=11) and other cancers (n=22 and included cholangiocarcinoma, metastatic breast, renal cell carcinoma, bladder, carcinoid, melanoma, and sarcoma). Median tumor size was 3.0 cm. Thirty-eight patients were treated with MWA alone, 53 patients had MWA with concomitant hepatic resection while another nine patients had MWA concomitant with other organ resection. Only two patients had incomplete ablations after the procedure. No bleeding complications were experienced, but two cases of hepatic abscess and two cases of hepatic insufficiency occurred. At median follow-up of 36 months, five patients were found to have incomplete ablations and only two patients (2%) had local tumor recurrence, while 37 patients (37%) developed recurrence at other nonablated sites.

In 2013, Liu et al. reported on 35 patients treated with MWA for 62 tumors and 54 patients treated with RFA for 70 tumors from liver metastases. Ablation was complete in 88.6% (117 of 132) of tumors and was not significantly different between tumor types: 86.2% for metastatic colorectal cancer (56/65) and 91% for other metastatic disease 61/67). Nor was there a
significant difference between MWA and RFA in the complete ablation rate. Tumors 3.0 cm or less were completely ablated significantly more often than tumors greater than 3.0 cm (93.5 vs. 66.7%, p=0.001).

Practice Guidelines and Position Statements
The National Comprehensive Cancer Network (NCCN) guidelines on hepatobiliary cancers lists MWA (along with radiofrequency ablation, cryoablation and percutaneous alcohol injection) as a treatment option for hepatocellular carcinoma tumors in patients who are not candidates for potential curative treatments (e.g., resection and transplantation) and do not have large-volume extrahepatic disease. Ablation should only be considered when tumors are accessible by percutaneous, laparoscopic or open approaches. The guidelines indicate hepatocellular carcinoma tumors equal to or less than three centimeters may be curatively treated with ablation alone. Hepatocellular carcinoma tumors between three to five centimeters may also be treated with ablation to prolong survival when used in combination with arterial embolization. Additionally, the tumor location must be accessible to permit ablation of the tumor and tumor margins without ablating major vessels, bile ducts, the diaphragm or other abdominal organs. However, there are only two reviews cited in the guideline on ablative techniques to support these recommendations that are not specific to MWA [category 2A].

Percutaneous Ethanol Injection (PEI)
One of the first methods devised to ablate liver tumors involved percutaneous ethanol injection (PEI). Several nonrandomized trials in the 1990s confirmed that PEI could safely achieve complete necrosis in small HCCs, with five-year survival rates of 32%-38%. However, the technique had several drawbacks, including the need for multiple treatment sessions and a high local progression rate of 17%-38%. Several randomized controlled trials (RCTs) have compared PEI and RFA in the treatment of small HCC. A systematic review of randomized trials for HCC treated with percutaneous ablation therapies was conducted by Cho et al. The authors identified four RCTs involving 652 patients that compared RFA with percutaneous ethanol injection. The review concluded that RFA demonstrated significantly improved three-year survival in patients with HCC compared to ethanol injections. The majority of patients in these studies had one tumor, and over 75% of the tumors were 3cm or smaller in size. The three-year survival with RFA ranged from 63 to 81%.

A review by McWilliams reports that complete ablation rates for small to medium HCC exceed 80% in a single treatment session, and exceed 90% with two sessions. Five-year survival rates in the largest studies are 40-58%, and local progression after complete ablation is uncommon (1 to 12%).

Key Words:
Locoregional liver therapy, Locoregional liver treatment, Transcatheter Arterial Chemoembolization (TACE), Radio-frequency Ablation (RFA), Percutaneous Ethanol Injection (PEI), liver cryotherapy, cryotherapy. Therasphere, SIR-Spheres®, cryosurgery, cryosurgical ablation of liver, CSA, microwave ablation, microwave, radioembolization, RE
Approved by Governing Bodies:
TheraSphere® has been granted Humanitarian Device Exception status by the FDA on December 10, 1999
SIR-Spheres was given a 510(k) PMA, March 5, 2002
Covidien, formerly known as Valleylab, a Division of Tyco Healthcare LP, received 510 (k) clearance November 25, 2008 for their Valleylab Microwave Ablation Generator

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:
CPT coding:

37243 Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction (Effective 01/01/2014)
47370 Laparoscopy, surgical, ablation of one or more liver tumor(s); radiofrequency
47371 Laparoscopy, surgical, ablation of one or more liver tumor(s); cryosurgical
47380 Ablation, open, of one or more liver tumor(s); radiofrequency
47381 Ablation, open, of one or more liver tumor(s); cryosurgical
47382 Ablation, open, of one or more liver tumor(s); percutaneous, radiofrequency
47399 Unlisted procedure, liver
75894 Transcatheter therapy, embolization, any method, radiological supervision and interpretation
76940 Ultrasound guidance for, and monitoring of, parenchymal tissue ablation
77013 Computerized tomography guidance for, and monitoring of, parenchymal tissue ablation
77022 Magnetic resonance guidance for, and monitoring of, parenchymal tissue ablation
77261 Therapeutic radiology treatment planning; simple
77262 Therapeutic radiology treatment planning; intermediate
77263 Therapeutic radiology treatment planning; complex
77300 Basic radiation dosimetry calculation, central axis depth dose calculation, TDF, NSD, gap calculation, off axis factor, tissue inhomogeneity factors, calculation of non-ionizing radiation surface
and depth dose, as required during course of treatment, only when prescribed by the treating physician.

77370 Special medical radiation physics consultation
77470 Special treatment procedure (e.g., total body irradiation, hemibody radiation, per oral, or endocavitary irradiation)
77750 Infusion or instillation of radioelement solution (includes three months follow-up care)
77776 Interstitial radiation source application; simple
77777 Interstitial radiation source application; intermediate
77778 Interstitial radiation source application; complex
77790 Supervision, handling, loading of radiation source
79445 Radiopharmaceutical therapy, by intra-arterial particulate administration
79900 Provision of therapeutic radiopharmaceutical(s)

HCPCS code:
S2095 Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using Ytrium-90 microspheres

ICD-9-CM:
155.0 Malignant neoplasm of liver, primary
155.1 Malignant neoplasm of intrahepatic bile ducts
155.2 Malignant neoplasm of liver, not specified as primary or secondary
156.1 Malignant neoplasm of extra-hepatic bile ducts
197.7 Secondary malignant neoplasm of liver
209.72 Secondary neuroendocrine tumor of liver

ICD-10-CM (effective 10/01/2014):
C22.0 Liver cell carcinoma
C22.1 Intrahepatic bile duct carcinoma
C22.2 Hepatoblastoma
C22.3 Angiosarcoma of liver
C22.4 Other sarcomas of liver
C22.8 Malignant neoplasm of liver, primary, unspecified as to type
C22.9 Malignant neoplasm of liver, not specified as primary or secondary
C24.0 Malignant neoplasm of extrahepatic bile duct
C78.7 Secondary malignant neoplasm of liver and intrahepatic bile duct
C7B.02 Secondary carcinoid tumors of liver

Previous Coding:
37204 Transcatheter occlusion or embolization (e.g., for tumor destruction, to achieve hemostasis, to occlude a vascular malformation), percutaneous, any method, non-central nervous system, non-head or neck (Deleted effective 01/01/2014)
76362  Computerized axial tomographic guidance for, and monitoring of, tissue ablation *(deleted 01/01/2007)*

76394  Magnetic resonance guidance for, and monitoring of, tissue ablation *(deleted 01/01/2007)*

76490  Ultrasound guidance for, and monitoring of, tissue ablation *(deleted 04/01/2004)*

References:


83. Mabed M, Esmaeel M, El-Khodary T et al. A randomized controlled trial of transcatheter arterial chemoembolization with lipiodol, doxorubicin and cisplatin versus intravenous


Policy History:
TEC, December 2001
TEC, May 2001
Medical Review Committee, May 2001
Medical Policy Group, August 2002
Medical Policy Group, November 2002
Medical Policy Administration Committee, November 2002
Medical Policy Group, January 2003
Medical Policy Administration Committee, February 2003
Available for comments November 27, 2002-January 10, 2003
Available for comments February 7-March 25, 2003
Medical Policy Group, September 2004 (1)
Medical Policy Group, September 2006 (1)
Medical Policy Group, September 2008 (1)
Medical Policy Group, October 2009 (1)
Medical Policy Administration Committee, October 2009
Available for comment October 20-December 3, 2009
Medical Policy Group July 2010 (1): Added info in description and Key Points regarding radioembolization and radiofrequency
Medical Policy Administration Committee, August 2010
Available for comment August 5-September 18, 2010
Medical Policy Group, October 2010 (1): Description and Key points updated for TACE
Medical Policy Group, July 2011 (1): Update to Key Points and References related to cryotherapy, microspheres, PEI and RFA
Medical Policy Group, April 2012 (1): Update to Policy, Key Points, Coding and References related to MPP update, microspheres and TACE; entire policy reformatted and streamlined; policy statement coverage criteria added related to liver mets for microspheres
Medical Policy Administrative Committee, May 2012
Medical Policy Group, July 2012 (1): Update to Key Points and References related to MPP update for RFA; no change to policy statement
Medical Policy Panel, March 2013
Medical Policy Group, June 2013 (1): Update to Key Points and References related to RE, TACE, cryoablation and microwave ablation; no change to policy statements
Medical Policy Panel, July 2013
Medical Policy Group, September 2013 (1): Update to Key Points and References related RFA; no change to policy statement
Medical Policy Panel, October 2013
Medical Policy Group, October 2013 (1): Update to Key Points and References related to MWA and TACE; no change to policy statements
Medical Policy Group, December 2013 (3): 2014 Coding Update – added new code 37243 to current coding effective 01/01/2014; moved code 37204 to previous coding (deleted effective 01/01/2014)
Medical Policy Panel, December 2013
Medical Policy Group, January 2013 (1): Update to Key Points and References related to cryosurgical ablation; no change to policy statement
Medical Policy Panel, March 2014
Medical Policy Group, March 2014 (1): Update to Key Points and References related to microspheres/radioembolization; no change to policy statement
Medical Policy Group, March 2014 (5): Added ICD-9 CM and ICD-10 CM diagnosis under Coding section; no change to policy statement
Medical Policy Group, June 2014 (3): Updated the Policy section with the addition of a statement referring readers to CareCore (included link) for Radioembolization or Intra-hepatic microshperes (TheraSpheres®, SIRSpheres®) effective August 1, 2014
Medical Policy Administration Committee, June 2014
Available for comment June 16 through July 31, 2014
Medical Policy Group, July 2014: Removed CareCore link and ‘Draft’. Transfer to CareCore is on hold until further notice.
Medical Policy Panel, July 2014
Medical Policy Group, July 2014 (1): Updated Key Points and References related to radio-frequency ablation; no change to policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.