Cryosurgical Ablation of Primary or Metastatic Liver Tumors

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Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers cryosurgical ablation (CSA) of either primary or metastatic tumors in the liver to be **investigational.***

Background/Overview

LIVER METATASES

Hepatic tumors can be due to primary liver cancer or metastases to the liver from nonhepatic primary tumors. Primary liver cancer can arise from hepatocellular tissue (hepatocellular carcinoma) or intrahepatic biliary ducts (cholangiocarcinoma). Multiple tumors metastasize to the liver, but there is particular interest in the treatment of hepatic metastases from colorectal cancer (CRC) given the propensity of CRC to metastasize to the liver and its high prevalence. Liver metastases from neuroendocrine tumors present a unique clinical situation. Neuroendocrine cells produce and secrete a variety of regulatory hormones (or neuropeptides), which include neurotransmitters and growth factors. Overproduction of the specific neuropeptides by cancerous cells causes various symptoms, depending on the hormone produced.

Treatment
Treatment of liver metastases is undertaken to reduce endocrine-related symptoms, in addition to prolonging survival and reducing symptoms related to the hepatic mass.

Surgical resection with tumor-free margins and liver transplantation are the primary treatments available that have curative potential. Many hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size, the number of lesions, or underlying liver reserve. Local therapy for hepatic metastasis is indicated only when there is no extrahepatic disease, which rarely occurs for patients with primary cancers other than CRC or certain neuroendocrine malignancies. For liver metastases from CRC, postsurgical adjuvant chemotherapy has been reported to decrease recurrence rates and prolong time to recurrence. Combined systemic and hepatic arterial chemotherapy may increase disease-free intervals for patients with hepatic metastases from CRC but apparently is not beneficial for those with unresectable hepatocellular carcinoma.

Various locoregional therapies for unresectable liver tumors have been evaluated: cryosurgical ablation (cryosurgery); radiofrequency ablation; laser ablation; transhepatic arterial embolization, chemoembolization, or radioembolization with yttrium-90 microspheres; microwave coagulation; and percutaneous ethanol injection. Cryosurgical ablation occurs in tissue that has been frozen by at least 3

mechanisms: (1) formation of ice crystals within cells, thereby disrupting membranes and interrupting cellular metabolism among other processes; (2) coagulation of blood, thereby interrupting blood flow to the tissue, in turn causing ischemia and cell death; and (3) induction of apoptosis (cell death).

Recent studies including a small randomized controlled trial and case series have reported experience with cryosurgical and other ablative methods used in combination with subtotal resection and/or procedures such as transarterial chemoembolization.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Several cryosurgical devices have been cleared by the U.S. FDA. For example, the Endocare™‡ Cryocare System (Endocare, Irvine, CA) was cleared for marketing through the 510(k) process in December 1996 for "use in general surgery, dermatology, neurology, thoracic surgery, ENT [ears, nose, throat], gynecology, oncology, proctology and urology for the ablation of tissue, including liver metastases, skin lesions, warts, and removal of prostate tissue." Product code: GEH.

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

Rationale/Source

Three patient groups have been treated with hepatic cryosurgery: those with primary HCC, those with neuroendocrine tumors metastatic to the liver, and those with liver metastases from CRC. The findings of the literature reviews are summarized next.

HEPATOCELLULAR CARCINOMA

Randomized Controlled Trials

Wang et al (2015) reported on a randomized controlled trial (RCT) comparing cryoablation with radiofrequency ablation (RFA) in 360 patients with HCC. One hundred eighty treatment-naive patients with Child-Pugh class A or B cirrhosis and 1 or 2 HCC lesions 4 cm or less and without metastasis were randomized to each treatment group. Of the 360 patients enrolled, 310 patients were ineligible for surgical resection due to significant portal hypertension. The median follow-up for the cryoablation group was 25 months (range, 8-64 months) and 25 months (range, 5-65 months) for the RFA group (p=0.767). At 1, 2, and 3 years, local tumor progression rates were 3%, 7%, and 7% for cryoablation and 9%, 11%, and 11% for RFA, respectively (p=0.043). Overall survival (OS) rates at 1, 3, and 5 years for cryoablation were 97%, 67%, and 40%, and 97%, 66%, and 38% for RFA, respectively (p=0.747). Tumor-free survival rates at 1, 3, and 5 years were 89%, 54%, and 35% in the cryoablation group and 84%, 50%, and 34% in the RFA group, respectively (p=0.628). Major complications were experienced in 7 (3.9%) patients following cryoablation and in 6 (3.3%) patients following RFA (p=0.776).

Overall, trial strengths included the randomized design, a well-characterized patient population with few dropouts, intention-to-treat analysis, and evaluation of clinical outcomes. However, there did not appear to be an accounting of the disposition of all patients approached for enrollment. Additionally, there was a suboptimal randomization scheme, lack of allocation concealment, and some evidence for noncomparability of groups at baseline. The lack of any local tumor progression after approximately 14 months (extrapolated from the graph) in either group seems unusual.

Nonrandomized Comparative Studies

Ei et al (2015) reported outcomes for consecutive patients with primary HCC treated with cryotherapy (n=55) or RFA or microwave coagulation therapy (MCT) (n=64) using prospectively collected data. The choice of locally ablative therapy was made by a multidisciplinary team based on the following criteria: cryoablation for tumors near major hepatic veins, hepatic hilum, secondary branches of the portal pedicles, or other organs; RFA or MCT for tumors of 1 cm or less; and patient preference. Groups were similar at baseline, with the exception that patients treated with cryotherapy had larger median tumor size (2.5 cm vs 1.9 cm, p<0.001). Rates of short-term complications did not differ significantly between groups. Over a median follow-up of 25 months, local recurrence-free survival was nonsignificantly higher in the cryoablation group (80% vs 68%, p=0.20). In a multivariable model to predict local recurrence, receiving cryoablation was significantly associated reduced risk of recurrence (adjusted hazard ratio, 0.3; 95% confidence interval, 0.1 to 0.9; p=0.02). For tumors greater than 2 cm in diameter, 2-year local recurrence was lower for patients treated with cryoablation (21% vs 56%, p=0.006).

In a smaller, retrospective comparative study including 42 patients with HCC and cirrhosis, Dunne et al (2014) reported short-term safety outcomes after cryoablation or RFA. Twenty-five patients underwent 33 cryoablation procedures, and 22 patients underwent 30 RFA procedures; 5 patients underwent both cryoablation and RFA procedures. No significant differences were observed in the overall complication rates, complication rates by severity, or specific complication types by cryoablation and RFA groups.

Noncomparative Studies

Noncomparative studies and systematic reviews of these studies have reported outcomes after the use of cryotherapy for HCC. Although these studies may provide useful information about complications and longer term recurrences after cryoablation, they do not provide evidence of the comparative effectiveness of cryotherapy.

A 2009 Cochrane review of cryotherapy for HCC included findings of 2 prospective cohort studies and 2 retrospective studies but no RCTs or quasi-RCTs. This review antedates Wang (2015). Only 1 study could be considered for the assessment of benefit. In that 2002 study, results were stratified by both the type of hepatic malignancy (primary or secondary) and the intervention group (percutaneous cryotherapy or percutaneous RFA). Sixty-four patients were treated based on the random availability of probes: 31 patients received cryotherapy and 33 received RFA. Of all patients treated, 26 (84%) of 31 who had cryotherapy and 24 (73%) of 33 who had RFA developed a local recurrence, all within 1 year. The distribution of primary cancers was not specified. Among the HCC patients, rates of initial tumor ablation were similar after

cryosurgery (65%) or RFA (76%), but local recurrences were more frequent after cryosurgery (38%) than after RFA (17%). Survival at 1 year did not differ by ablative technique (cryosurgery, 66%; RFA, 61%). The trial did not include controls managed with an established alternative. Cochrane reviewers concluded that there was no evidence to recommend or refute cryotherapy in the treatment of patients with HCC and that RCTs might be useful.

Since the 2009 Cochrane review, several studies have reported on series of patients with HCC treated using cryoablation. In 2012, Yang et al reported on a series of 300 patients treated between 2003 and 2006 with percutaneous argon-helium cryoablation for HCC. Complete tumor ablation occurred in 185 tumors in 135 patients with mean tumor diameter of 5.6 cm, while 223 tumors in 165 patients with a mean tumor diameter of 7.2 cm were incompletely ablated ($p<0.001$). Serious complications occurred in 19 (6.3%) patients, including liver hemorrhage in 5 patients, cryoshock syndrome in 6 patients, gastric bleeding in 4 patients, liver abscess in 1 patient, and intestinal fistula in 1 patient. Liver failure resulted in the death of 2 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, 6-63 months), local tumor recurrence was 31%. Larger tumors and tumor location were significantly related to tumor recurrence ($p=0.029$ and 0.037, respectively). OS was 80% at 1 year, 45% at 2 years, and 32% at 3 years.

Rong et al (2015) reported on longer term outcomes (median, 30.9 months) after cryoablation in a series of 866 patients with HCC treated at a single center in China. A total of 832 (96.1%) patients were considered to have a complete response after up to 3 cryoablation sessions. During the follow-up period, 502 (60.2%) patients with an initial complete response had a recurrence (n=99 [11.9%] local, n=396 [44.5%] distant intrahepatic, n=7 [0.85] extrahepatic). Two hundred sixteen subjects died (mortality rate, 25.9%), corresponding to a 5-year OS of 59.5%.

In a study not included in the 2009 Cochrane review, Zhou et al (2009) categorized 124 patients with primary nonresectable HCC into early, middle, and advanced stage groups using Barcelona Clinic Liver Cancer staging classification. After argon-helium cryoablation, serum level of α-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 had 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 virus–related HCC and tumors smaller than 5 cm in diameter who underwent curative cryoablation. One-, 2-, and 3-year OS rates were 92%, 82%, and 64%, respectively, and 1-, 2-, and 3-year recurrence-free survival rates were 72%, 56%, and 43%, respectively. The multivariate analysis showed that Child-Pugh class and expression of vascular endothelial growth factor in HCC tissues could be used as independent prognostic factors for OS. The expression of vascular endothelial growth factor in HCC tissues and hepatitis B virus basal core promoter variants were independent prognostic factors for recurrence-free survival.

Section Summary: Hepatocellular Carcinoma
The available RCT comparing cryoablation and RFA demonstrated lower rates of local tumor progression with cryoablation, but no differences in survival outcomes between groups. Although this trial provided suggestive evidence that cryoablation is comparable with RFA, trial limitations would suggest findings need to be replicated. Additional comparative evidence is needed to permit conclusions about the effectiveness of cryoablation compared with other locoregional therapies.

NEUROENDOCRINE CANCER LIVER METASTASES
Neuroendocrine tumors are relatively slow-growing malignancies (mean survival time, 5-10 years) that commonly metastasize to the liver. As with other cancers, the most successful treatment of hepatic metastasis is resection with tumor-free margins, but treatment benefits for a slow-growing tumor must be weighed against the morbidity and mortality of major surgery. The intent of cryosurgery in these cases is to minimize or eliminate symptoms caused by liver metastases while avoiding the complications of open surgery. Unlike other liver metastases, neuroendocrine tumors metastatic to the liver may cause systemic symptoms, including palpitations, flushing, and diarrhea, secondary to the release of neuropeptides.

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) with other interventions (chemotherapy, hormonotherapy, or immunotherapy) and studies comparing liver resection with thermal ablation (RFA or cryoablation) were sought. Cochrane reviewers reported finding that neither RCTs suitable for review nor any quasi-randomized, cohort, or case-control studies "could inform meaningfully." No analysis was performed, and reviewers referred to only RFA in their discussion, noting that radiofrequency is not suitable for large tumors (ie, >5-6 cm), and that neuroendocrine liver metastases are frequently larger than that. They concluded that randomized trials comparing surgical resection with RFA in selected patients would be appropriate.

Saxena et al (2012) retrospectively reviewed data on 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 1 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 1, 3, 5- and 10 years, respectively.

Chung et al (2001) reported on outcomes of cryosurgery for hepatic metastases from neuroendocrine cancer. This study used cytoreduction (resection, cryosurgery, RFA, or a combination of the three) and adjuvant therapy (octreotide, chemotherapy, radiotherapy, interferon-α) 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. Because 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.

Section Summary: Neuroendocrine Cancer Liver Metastases
The available evidence on unresectable liver metastases from neuroendocrine tumors amenable to locoregional therapy is very limited. The evidence does not permit conclusions on whether this technology effects health outcomes.

LIVER METASTASES FROM CRC
Although multiple tumor types metastasize to the liver, CRC is particularly likely to metastasize to the liver and has been the focus of the bulk of the literature on cryoablation for non-neuroendocrine tumor liver metastases.

A 2008 Cochrane review compared outcomes of resection of CRC liver metastases with no intervention or other treatment modalities, including RFA and cryosurgery. Only RCTs reporting on patients who had curative surgery for adenocarcinoma of the colon or rectum, who had been diagnosed with liver metastases, and who were eligible for liver resection were considered. Only 1 randomized trial by Korpan et al (1997) was identified, a trial from the Ukraine that compared surgical resection with cryosurgery in 123 subjects, 82 of whom had liver metastases from primary CRCs and the remainder who had metastases from other primary tumors. Survival outcomes were not provided by type of cryogenic procedure or primary tumor site. Reviewers concluded that local ablative therapies were probably useful but that the therapy would need further evaluation in an RCT. A 2013 Cochrane review examined cryoablation for liver metastases from various sites, primarily colorectal. Only the Korpan RCT, included in the 2008 Cochrane review, met inclusion criteria. The Korpan trial was considered to have a high risk of bias, and reviewers found the available evidence was insufficient to determine whether there were any benefits with cryoablation over conventional surgery or no intervention.

A 2010 Cochrane review considered liver resection (alone or in combination with RFA or cryoablation) versus nonsurgical treatments (neoadjuvant chemotherapy, chemotherapy, or RFA) in patients with colorectal liver metastases and hepatic node involvement. There were no RCTs, quasi-randomized trails, or cohort studies identified to address this clinical scenario.

Pathak et al (2011) reported on a systematic review of ablative therapies for CRC liver metastases. They selected 26 nonrandomized studies on cryoablation. Reviewers reported local recurrence rates in the studies ranging from 12% to 39%. Survival rates ranged from 46% to 92% at 1 year, 8% to 60% at 3 years, and 0% to 44% at 5 years. Mean survival rates at 1, 3, and 5 years were 84%, 37%, and 17%, respectively. Major complications ranged from 7% to 66%. Cryoshock was indicated to be of major concern.

A few studies have compared cryotherapy with other treatments for liver metastases. Ruers et al (2007) reported on a consecutive series of 201 CRC patients, without extrahepatic disease, treated between 1995 and 2004 and who underwent laparotomy for surgical treatment of liver metastases. These patients were prospectively followed for survival and quality of life. During laparotomy, 3 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 2 and 5 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 percentages were 83% and 51%, respectively (median, 61 months; n=117; p<0.001). Median disease-free survival (DFS) after local ablation was 9 months. The authors concluded that although OS of local ablation versus chemotherapy was not statistically significant, median DFS of 9 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. Additionally, this study used both cryotherapy and RFA for local ablation, and results are reported for the combined group further limiting interpretation of specific results in cryoablation.

Niu et al (2007) analyzed data collected prospectively for 415 patients who underwent hepatic resection for metastatic CRC 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 6 or more lesions (35% vs 3%, respectively). Additionally, 73% of this combined treatment group received hepatic arterial chemotherapy compared with 32% in the resection-only group. Median follow-up was 25 months (range, 1-124 months). The 30-day perioperative mortality was 3.1%. For the resection group, the median survival was 34 months, with 1-, 3-, and 5-year survival values rates of 88%, 47%, and 32%, respectively. The median survival for the resection/cryotherapy group was 29 months, with 1-, 3-, and 5-year survival rates of 84%, 43%, and 24%, respectively (p=0.206). The overall recurrence rate was 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 CRC, lesion size of 4 cm or less, a postoperative carcinoembryonic antigen of 5 ng/mL or less, and absence of liver recurrence. While the recurrence rates between groups did not differ, it is unclear how representative the patients who had resection/cryotherapy were of the total sample of 415 patients. The comparability of the 2 groups is uncertain, especially given the differential use of hepatic arterial chemotherapy. In this study, a direct comparison was not made with chemotherapy. Finally, the 16-year duration of the study raises concerns about intercurrent changes that could have had affected the results.

In a relatively small study, Joosten et al (2005) reported on 58 patients with unresectable colorectal liver metastases where CSA or RFA was performed on patients ineligible for resection. Median follow-up was 26 and 25 months for CSA and RFA, respectively. One- and 2-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, results raise questions about the relative efficacy of both techniques.

A number of series have reported outcomes for cryoablation for liver metastases from CRC. Some of the larger and more recent series are summarized here. Ng et al (2012) 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 (3%) patients and included liver abscess sepsis in 4 patients, cardiac events unrelated to treatment in 3 patients, and 1 case each of dilated cardiomyopathy, cerebrovascular event, and multiorgan failure. Median follow-up was 28 months (range, 0.1-220 months). OS rates were 87%, 41.8%, 24.2%, and 13.3% at 1, 3, 5, and 10 years, respectively.

Seifert et al (2005) reported on a series of patients with colorectal liver metastases treated from 1996 to 2002. In this series, 168 patients underwent resection, and 55 had CSA (in 25 of these patients, it was combined with resection.) Twenty-nine percent (16/55) 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 5-year survival rates following resection and cryotherapy were comparable, with 29 months and 29 months and 23% and 26%, respectively. However, the median DFS times and 5-year DFS rates following resection were superior at 10 months and 19%, respectively, for resection compared with 6 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. Study limitations included the small sample size, limited follow-up, and noncomparability of the groups.

Kornprat et al (2007) reported on thermoablation combined with resection in the treatment of hepatic metastasis from CRC. In this series, from January 1998 to December 2003, 665 patients with colorectal metastases underwent hepatic resection. Of these, 39 (5.9%) had additional intraoperative thermoablative procedures (19 RFA, 20 CSA). The overall morbidity rate was 41% (16/39). No RFA-related complications occurred; however, 3 patients developed an abscess at cryoablation sites. The median DFS was 12.3 months (range, 8.4-16.2 months). 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.

Xu et al (2008) reported on a series of 326 patients with nonresectable hepatic colorectal metastases treated with 526 percutaneous cryosurgery procedures. At 3 months posttreatment, carcinoembryonic antigen levels decreased to the normal range in 197 (77.5%) of patients who had elevated markers before cryosurgery. Among 280 patients who had computed tomography follow-up, cryo-treated lesions showed complete response in 41 (14.6%) patients, partial response in 115 (41.1%), stable disease in 68 (24.3%), and disease progression in 56 (20%). During a median follow-up of 32 months (range, 7-61 months), the recurrence rate was 47.2%. The recurrence rate at the cryo-treated site was 6.4% for all cases. During median follow-up of 36 months, the median survival of all patients was 29 months (range, 3-62 months). OS rates were 78%, 62%, 41%, 34%, and 23% at 1, 2, 3, 4, and 5 years, respectively, after treatment. For patients with tumor sizes smaller than 3 cm, tumors in right lobe of the liver, carcinoembryonic antigen levels less than 100 ng/dL, and post-cryosurgery transcatheter arterial chemoembolization had higher survival rates.

Section Summary: Liver Metastases From CRC
The available RCT comparing surgical resection with cryoablation was judged to be at high risk of bias. Some nonrandomized comparative studies have reported improved survival outcomes for patients managed with cryotherapy compared with those managed with resection alone; however, these studies were subject to bias in the selection of patients for treatments. Additional controlled studies are needed to allow conclusions about the effectiveness of cryoablation compared with other locoregional therapies.

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 0% to 83%, and were generally due to the same causes as treatment-related deaths. The likelihood of complications arising from cryosurgery might 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 OF EVIDENCE

For individuals who have unresectable primary hepatocellular carcinoma amenable to locoregional therapy who receive CSA, the evidence includes 1 RCT, several nonrandomized comparative studies, and multiple noncomparative studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The available RCT comparing cryoablation with radiofrequency ablation demonstrated lower rates of local tumor progression with cryoablation, but no differences in survival outcomes between groups. Although this trial provided suggestive evidence that cryoablation is comparable with radiofrequency ablation, trial limitations would suggest findings need to be replicated. Additional comparative evidence is needed to permit conclusions about the effectiveness of cryoablation compared with other locoregional therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have unresectable liver metastases from neuroendocrine tumors amenable to locoregional therapy who receive CSA, the evidence includes a Cochrane review and case series. Relevant outcomes are overall survival, disease-specific survival, symptoms, and treatment-related mortality and morbidity. The available evidence base is very limited. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have unresectable liver metastases from colorectal cancer amenable to locoregional therapy who have CSA, the evidence includes 1 RCT, a number of nonrandomized comparative and noncomparative studies, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The available RCT comparing surgical resection with cryoablation was judged at high risk of bias. Some nonrandomized comparative studies have reported improved survival outcomes for patients managed with cryotherapy compared with those managed with resection alone; however, these studies were subject to bias in the selection of

patients for treatments. Additional controlled studies are needed to permit conclusions about the effectiveness of cryoablation compared with other locoregional therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date: 06/20/2007
Current Effective Date: 06/20/2018

06/13/2007	Medical Director review
06/20/2007	Medical Policy Committee approval
06/04/2009	Medical Director review
06/17/2009	Medical Policy Committee approval
06/03/2010	Medical Policy Committee approval.
06/16/2010	Medical Policy Implementation Committee approval. No change to coverage.
06/02/2011	Medical Policy Committee approval.
06/15/2011	Medical Policy Implementation Committee approval. No change to coverage.
06/14/2012	Medical Policy Committee review
06/20/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2013	Medical Policy Committee review
06/25/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2015	Medical Policy Committee review
06/20/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017	Medical Policy Committee review
06/21/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/07/2018	Medical Policy Committee review

Cryosurgical Ablation of Primary or Metastatic Liver Tumors

Policy # 00220
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Current Effective Date: 06/20/2018

06/20/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 06/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	47371, 47381, 47383, 76940
HCPCS	No codes
ICD-10 Diagnosis	C22.0 C22.2-C22.4 C22.7-C22.8 C78.7

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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