I. POLICY

Cryosurgical ablation of either primary or metastatic tumors in the liver is investigational. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Cross-references:
- **MP-1.088** Cryosurgical Ablation of Miscellaneous Solid Tumors other than Liver, Prostate or Dermatologic Tumors
- **MP-1.055** Radiofrequency Ablation of Primary or Metastatic Liver Tumors
- **MP-1.084** Radiofrequency Ablation of Miscellaneous Solid Tumors, Excluding Liver Tumors
- **MP-4.006** Transcatheter Arterial Chemoembolization

II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO*

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* Refer to FEP Medical Policy Manual MP-7.01.75, Cryosurgical Ablation of Primary or Metastatic Liver Tumors. The FEP Medical Policy Manual can be found at: [www.fepblue.org](http://www.fepblue.org).
Hepatic tumors can due to primary liver cancer or metastases to the liver from nonhepatic primary tumors. Primary liver cancer can arise from hepatocellular tissue (hepatocellular carcinoma [HCC]) or intrahepatic biliary ducts (cholangiocarcinoma). Multiple tumors metastasize to the liver, but there is particular interest in the treatment of hepatic metastases from colorectal carcinoma (CRC) given the propensity of CRC to metastasize to the liver and the high prevalence of CRC. 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 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 or 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, 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 HCC.

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

This review includes literature searches of the MEDLINE database, most recently through November 17, 2015. The findings of the literature reviews are summarized next.

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

**Hepatocellular Carcinoma**

**Randomized Controlled Trials**

In 2014, Wang et al reported on a randomized controlled trial (RCT) comparing cryoablation with radiofrequency ablation (RFA) in 360 patients with HCC. One-hundred eighty treatment-naïve patients with Child-Pugh class A or B cirrhosis and 1 or 2 HCC lesions 4 cm or less and without metastasis were randomly assigned to each treatment group. Of the 360 patients enrolled, 310 patients were ineligible for surgical resection due to having 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 RFA group, respectively (p=0.628). Major complications were experienced in 7 patients (3.9%) following cryoablation and in 6 patients (3.3%) following RFA (p=0.776).

Overall, strengths of this study include a randomized design, a well-characterized patient population with few dropouts, intention-to-treat analysis, and evaluation of clinical outcomes. However, there does not appear to be an accounting of the disposition of all patients approached for enrollment. In addition, 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 graph) in either group seems unusual.

**Nonrandomized Comparative Studies**

In 2015, Ei et al reported outcomes for consecutive patients with primary HCC treated with cryoablation (n=55) or RFA/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/MCT for tumors of 1 cm or less; and patient preference. Groups were similar at baseline, with the exception that patients treated with cryoablation 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 (RFS) 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 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 between the 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 about the comparative effectiveness of cryotherapy.

A 2009 Cochrane review of cryotherapy for HCC included finding 2 prospective cohort studies and 2 retrospective studies but no RCTs or quasi-RCTs. Only 1 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 RFA). Sixty-four patients were treated based on 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 or RFA (65% and 76%, respectively), 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 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 RCTs may be useful.

Since the 2009 Cochrane review, several studies have reported on series of patients with HCC treated using cryoablation. In 2011, 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 (0.8) cm, while 223 tumors in 165 patients with a mean tumor diameter of 7.2 (2.8) cm were incompletely ablated (p<0.001). Serious complications occurred in 19 patients (6.3%) and included 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.

In 2015, Rong et al 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 patients (96.1%) were considered to have a complete response after up to 3 cryoablation sessions. During the follow-up period, 502 patients with an initial complete response (60.2%) 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, 25.9%), corresponding to a 5-year OS of 59.5%.

In a 2009 study not included in the 2009 Cochrane review, Zhou et al 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 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 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 (HBV)-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 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 OS. The expression of VEGF in HCC tissues and HBV basal core promoter mutations were independent prognostic factors for RFS.

### 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) 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 nor 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 (ie, >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 et al 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 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-year survival, respectively.

In 2001, Chung et al 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-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.

Liver Metastases From Other Cancers Including 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 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 1 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 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. The authors of the Cochrane review concluded that local ablative therapies are probably useful but that they need to be further evaluated in an 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 et al reported on a systematic review of ablative therapies for colorectal cancer liver metastases.18 Included in the review were 26 nonrandomized studies on cryoablation. The authors reported local recurrence rates in the studies reviewed ranged 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 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.19 These patients were prospectively followed up for survival and quality of life. At 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 figures were 83% and 51%, respectively (median, 61 months; n=117; p<0.001). The median DFS after local ablation was 9 months. The authors concluded that although OS of local ablation versus chemotherapy did not reach statistical significance, the 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. In addition, this study used both cryotherapy and RFA for local ablation, and results are reported for the combined group.

Niu et al reported on an analysis of data collected prospectively for patients who underwent hepatic resection for metastatic CRC with or without cryoablation from 1990 to 2006.20 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). In addition, 73% of this combined treatment group received HAC 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 of 88%, 47%, and 32%, respectively. The median survival for the resection/cryotherapy group was 29 months, with 1-, 3-, and 5-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 CRC, largest lesion size being 4 cm or less, a postoperative carcinoembryonic antigen (CEA) of 5 ng/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 2 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 intercurrent changes that could have had an impact on the results.

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 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, it does 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. In 2012, Ng et al 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 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 was 87%, 41.8%, 24.2%, and 13.3% at 1, 3, 5, and 10 years, respectively.

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 (16/55) 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 disease-free survival (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. Limitations of this study include the small sample size, limited follow-up, and noncomparability of the groups.

Kornprat et al reported on thermoablation combined with resection in the treatment of hepatic metastasis from CRC. 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, 3 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 article, 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 3 months posttreatment, 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 follow-up, cryo-treated 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 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 was 78%, 62%, 41%, 34%, and 23% at 1, 2, 3, 4, and 5 years, respectively, after treatment. Patients with tumor size smaller than 3 cm, tumor in right lobe of liver, CEA levels less than 100 ng/dL and after 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 0% 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.

**Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov in November 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

**Summary of Evidence**

The evidence for the use of cryosurgical ablation in individuals with unresectable primary hepatocellular carcinoma amenable to locoregional therapy includes 1 randomized controlled trial (RCT), several nonrandomized comparative studies, and multiple noncomparative studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The single available RCT comparing cryoablation and radiofrequency ablation (RFA) demonstrated lower rates of local tumor progression with cryoablation, but no differences in survival outcomes between groups. Although this study provides suggestive evidence that cryoablation is comparable to RFA, the study has several limitations that suggest findings need to be replicated. Additional comparative evidence is needed to allow 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.
The evidence for the use of cryosurgical ablation in individuals with unresectable liver metastases from neuroendocrine tumors includes a Cochrane review and case series. Relevant outcomes are overall survival, disease-specific survival, symptoms, and treatment-related morbidity and mortality. The available evidence base is very limited. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for the use of cryosurgical ablation in individuals with unresectable liver metastases from colorectal cancer amenable to locoregional therapy includes 1 RCT, a number of nonrandomized comparative studies and noncomparative studies, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The single available RCT comparing surgical resection with cryoablation was judged to be at high risk of bias. Some nonrandomized comparative studies report 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 2 physician specialty societies and 3 academic medical centers while this policy was under review in 2008. All reviewers supported use of cyclosporine for liver tumors and, in general, cited the studies previously reviewed in the policy rationale. Some reviewers viewed this as one of several ablative techniques that could be used in these patients.

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, along with RFA, percutaneous alcohol ablation, and microwave ablation; however, the literature cited in the guideline reports on only RFA and ethanol ablation. For hepatocellular carcinoma, the guidelines recommend ablation for the following (category 2A recommendations):

- Tumors that are potentially resectable or transplantable, in patients who are operable by performance status or comorbidity, with Child-Pugh class A or B, no portal hypertension, suitable tumor location, adequate liver reserve, and suitable liver remnant.
- Tumors that are unresectable in patients who are not transplant candidates (locoregional therapy preferred).
• Tumors that are inoperable by performance status or comorbidity, with local disease or local disease with minimal extrahepatic disease only (locoregional therapy preferred).

For intrahepatic cholangiocarcinoma, the guidelines recommend locoregional therapy (including ablative therapy) the following (category 2B recommendations):

• Unresectable tumors.
• Metastatic disease.
• Post-resection with residual local disease.

NCCN guidelines on neuroendocrine tumors address the use of hepatic-directed therapies for patients with unresectable hepatic-predominant progressive metastatic neuroendocrine. These guidelines state, “Cytoreductive surgery or ablative therapies such as radiofrequency ablation (RFA) or cryoablation may be considered if near-complete tumor burden can be achieved” (category 2B recommendation).

NCCN guidelines on the treatment of colon cancer address the treatment of liver metastases, stating “ablative techniques may be considered alone or in conjunction with resection.” RFA, cryoablation, microwave ablation, percutaneous ethanol injection, and electrocoagulation are listed as examples of ablative therapies.

U.S. Preventive Services Task Force Recommendations
Not applicable.

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

V. DEFINITIONS

Denaturation refers to a change in conditions (temperature, addition of a substance) that causes irreversible change in a protein's structure, usually resulting in precipitation of the protein.

Extrahepatic refers to outside or unrelated to the liver.

Hepatic pertains to the liver.

Hyperthermia refers to the use of microwave or radiofrequency energy to increase body temperature.

Metastasis is the movement of body cells (esp. cancer cells) from one part of the body to another.

Neuroendocrine malignancies refer to a diverse group of tumors, such as carcinoid, islet cell tumors, neuroblastoma, and small-cell carcinomas of the lung.
PERCUTANEOUS refers to that which is passed or affected through the skin.

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore not covered:

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IX. REFERENCES


### Medical Policy

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<th>Cryosurgical Ablation of Primary or Metastatic Liver Tumors</th>
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### X. Policy History

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