

## Medical Policy



### Title: Cryosurgical Ablation of Primary or Metastatic Liver Tumors

<i>Related Policies:</i>	<ul style="list-style-type: none"> <li>▪ <i>Microwave Tumor Ablation</i></li> <li>▪ <i>Radiofrequency Ablation of Primary or Metastatic Liver Tumors</i></li> <li>▪ <i>Radiofrequency Ablation (RFA) of Miscellaneous Solid Tumors Excluding Liver Tumors</i></li> <li>▪ <i>Radioembolization for Primary and Metastatic Tumors of the Liver</i></li> <li>▪ <i>Cryoablation of Tumors Located in the Kidney, Lung, Breast, Pancreas, or Bone</i></li> <li>▪ <i>Transcatheter Arterial Chemoembolization (TACE) to Treat Primary or Metastatic Liver Malignancies</i></li> </ul>
--------------------------	---

#### **Professional**

Original Effective Date: April 8, 2003  
 Revision Date(s): May 10, 2012;  
 March 26, 2013; January 1, 2015;  
 June 12, 2015; July 11, 2017;  
 September 12, 2018; February 24, 2021;  
 November 5, 2021  
 Current Effective Date: June 12, 2015

#### **Institutional**

Original Effective Date: April 8, 2003  
 Revision Date(s): May 10, 2012;  
 March 26, 2013; January 1, 2015;  
 June 12, 2015; July 11, 2017;  
 September 12, 2018; February 24, 2021;  
 November 5, 2021  
 Current Effective Date: June 12, 2015

**State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact [Blue Cross and Blue Shield of Kansas Customer Service](#).**

**The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.**

**The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.**

**If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.**

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>• With unresectable primary hepatocellular carcinoma amenable to locoregional therapy</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Cryosurgical ablation</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Radiofrequency ablation</li> <li>• Microwave tumor ablation</li> <li>• Locoregional ablation other than radiofrequency ablation</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Disease-specific survival</li> <li>• Treatment-related mortality</li> <li>• Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With unresectable liver metastases from neuroendocrine tumors amenable to locoregional therapy</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Cryosurgical ablation</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Radiofrequency ablation</li> <li>• Microwave tumor ablation</li> <li>• Locoregional ablation other than radiofrequency ablation</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Disease-specific survival</li> <li>• Symptoms</li> <li>• Treatment-related mortality</li> <li>• Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With unresectable liver metastases from colorectal cancer amenable to locoregional therapy</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Cryosurgical ablation</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Radiofrequency ablation</li> <li>• Microwave tumor ablation</li> <li>• Locoregional ablation other than radiofrequency ablation</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Disease-specific survival</li> <li>• Treatment-related mortality</li> <li>• Treatment-related morbidity</li> </ul>

## DESCRIPTION

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

## OBJECTIVE

The objective of this evidence review is to determine whether cryoablation improves the net health outcome in individuals with unresectable primary and metastatic liver tumors.

## BACKGROUND

### Liver Metastases

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 apoptosis; and (3) induction of apoptosis.

Some have reported on experience with cryosurgical and other ablative methods used in combination with subtotal resection and/or procedures such as trans arterial chemoembolization.

### **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,<sup>1</sup> but much of the treatment-related morbidity and mortality reflect the generally poor health status of patients with advanced hepatic disease.

### **REGULATORY STATUS**

Several cryosurgical devices have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. " i Use includes general surgery, urology, gynecology, oncology, neurology, dermatology, ENT[ears, nose, throat], proctology, pulmonary surgery, and thoracic surgery. The system is designed to freeze/ablate tissue by the application of extreme cold temperatures.

FDA product code: GEH.

### **POLICY**

Cryosurgical ablation of either primary or metastatic tumors in the liver is **experimental / investigational**.

## **RATIONALE**

The evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through July 28, 2021.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

### **Hepatocellular Carcinoma**

#### **Clinical Context and Therapy Purpose**

The purpose of cryosurgical ablation (CSA) in patients who have unresectable primary hepatocellular carcinoma (HCC) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of CSA improve health outcomes for individuals with unresectable primary HCC?

The following PICO was used to select literature to inform this review.

#### ***Populations***

The relevant population of interest is individuals with unresectable primary HCC amenable to locoregional therapy.

#### ***Interventions***

The therapy being considered is CSA.

#### ***Comparators***

The following therapies are currently being used: radiofrequency ablation (RFA), microwave tumor ablation, and locoregional ablation other than RFA.

## Outcomes

The general outcomes of interest are disease-free and overall survival (OS). Other outcomes include recurrence rates, symptom reductions, and treatment-related adverse events. Estimates for disease-related mortality can range from 3 to 6 months, and sometimes longer.

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

### Randomized Controlled Trials

Wang et al (2015) reported an RCT comparing cryoablation with RFA in 360 patients with HCC.<sup>2</sup> 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 ( $p=.767$ ). 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 ( $p=.043$ ). OS rates at 1, 3, and 5 years for cryoablation were 97%, 67%, and 40%, and 97%, 66%, and 38% for RFA, respectively ( $p=.747$ ). 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 ( $p=.628$ ). Major complications were experienced in 7 (3.9%) patients following cryoablation and in 6 (3.3%) patients following RFA ( $p=.776$ ).

Overall, trial strengths included its 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

Chen et al (2021) performed a retrospective analysis of data from the Surveillance, Epidemiology, and End Results database on patients with single HCC who underwent cryoablation ( $n=104$ ) compared with patients who underwent RFA ( $n=3510$ ).<sup>3</sup> After propensity score matching, median OS and cancer-specific survival were not significantly different between cryotherapy and RFA (32 vs 33 months,  $p=.724$ ; and 34 vs 36 months,  $p=.651$ ; respectively). Results were consistent in subgroup analyses based on tumor size and American Joint Committee on Cancer stage.

Cha et al (2020) performed a retrospective analysis of patients with perivascular HCC who underwent cryoablation (n=61) with patients who underwent RFA (n=50) at a hospital in Korea.<sup>4</sup> After propensity score matching, the primary outcome, cumulative incidence of local tumor progression, was not significantly different between cryoablation and RFA at 3 years (8.7% and 26.1%; p=.379). Treatment modality was not predictive of local tumor progression in univariable or multivariable analyses. Secondary outcomes of vascular thrombosis and hepatic infarction were nonsignificant more frequent with RFA (16.0% vs 9.8%, p=.493; and 12.0% vs 3.3%, p=.137, respectively).

Ko et al (2020) reported on procedure-related complications identified in a retrospective analysis of patients with HCC undergoing RFA (n=31) or cryoablation (n=25).<sup>5</sup> Compared with cryoablation, RFA was associated with a significantly higher incidence of biliary complications (67.7% vs 28%; p=.007) and significantly higher severity of complications (p=.002). In multivariable analysis, RFA was associated with greater odds of biliary complications (odds ratio, 4.66; 95% confidence interval [CI], 1.38 to 15.73).

Wei et al (2020) retrospectively compared the efficacy and safety of transcatheter arterial chemoembolization (TACE) combined with either microwave ablation (n=48) or with cryoablation in patients with HCC (n=60).<sup>6</sup> After propensity score matching, microwave ablation and cryoablation did not significantly differ in median OS (20.9 vs 13.5 months, respectively; p=.096) or time to progression (8.8 vs 8.6 months, respectively; p=.675). Ablation-related complications were less frequent with microwave ablation (66.7% vs 88.3%; p=.006).

Ei et al (2015) reported on outcomes for consecutive patients with primary HCC treated with cryotherapy (n=55) or RFA or microwave coagulation therapy (n=64) using prospectively collected data.<sup>7</sup> 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 microwave coagulation therapy for tumors of 1 cm or less; and patient preference. Groups were similar at baseline, with the exception that patients treated with cryotherapy had a larger median tumor size (2.5 cm vs 1.9 cm, p<.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 nonsignificant higher in the cryoablation group (80% vs 68%, p=.20). In a multivariable model to predict local recurrence, receiving cryoablation was significantly associated with reduced risk of recurrence (adjusted hazard ratio, 0.3; 95% CI, 0.1 to 0.9; p=.02). For tumors greater than 2 cm in diameter, the 2-year local recurrence rate was lower for patients treated with cryoablation (21% vs 56%, p=.006).

In a smaller, retrospective comparative study including 42 patients with HCC and cirrhosis, Dunne et al (2014) reported on short-term safety outcomes after cryoablation or RFA.<sup>8</sup> 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.

In a Cochrane review, Awad et al (2009) evaluated cryotherapy for HCC, identifying 2 prospective cohort studies and 2 retrospective studies but no RCTs or quasi-RCTs.<sup>9</sup> This review antedates Wang et al (2015). Only 1 study could be considered for the assessment of benefit. In that study, Adam et al (2002) stratified results by both the type of hepatic malignancy (primary or secondary) and the intervention group (percutaneous cryotherapy or percutaneous RFA).<sup>10</sup> 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% vs 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.

Since the 2009 Cochrane review, several studies have reported on series of patients with HCC treated using cryoablation. Yang et al (2012) reported on 300 patients treated between 2003 and 2006 with percutaneous argon-helium cryoablation for HCC.<sup>11</sup> 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 ( $p < .001$ ). 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 trans arterial catheter embolization or a multikinase inhibitor (sorafenib). During the median follow-up of 36.7 months (range, 6-63 months), the local tumor recurrence rate was 31%. Larger tumors and tumor location were significantly related to tumor recurrence ( $p = .029$  and  $0.037$ , respectively). The OS rates were 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.<sup>12</sup> A total of 832 (96.1%) patients were considered to have a complete response after up to 3 cryoablation sessions. During follow-up, 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 rate 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 the early, middle, and advanced stage groups using Barcelona Clinic Liver Cancer staging classification.<sup>13</sup> After argon-helium cryoablation, the 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 had survived and 110 had died. To determine risk factors that predict metastasis and recurrence, Wang et al (2009) also studied a series of 156 patients with hepatitis B virus-related HCC and tumors smaller than 5 cm in diameter who underwent curative cryoablation.<sup>14</sup> 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 with 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 to RFA, trial limitations would suggest findings need to be replicated. Nonrandomized comparative studies have failed to find consistent benefit with cryoablation in outcomes related to tumor recurrence and survival. Additional randomized 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.<sup>15</sup> The intent of cryosurgery in these cases is to minimize or eliminate symptoms caused by liver metastases while avoiding the complications of open surgery.

### **Clinical Context and Therapy Purpose**

The purpose of CSA in patients who have unresectable liver metastases from neuroendocrine tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of CSA improve health outcomes for individuals with unresectable liver metastases from neuroendocrine tumors?

The following PICO was used to select literature to inform this review.

#### ***Populations***

The relevant population of interest is individuals with unresectable liver metastases from neuroendocrine tumors amenable to locoregional therapy.

#### ***Interventions***

The therapy being considered is CSA.

#### ***Comparators***

The following therapies are currently being used: RFA, microwave tumor ablation, and locoregional ablation other than RFA.



### **Outcomes**

The general outcomes of interest are disease-free and OS. Other outcomes include recurrence rates, symptom reductions, and treatment-related adverse events. 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. Given the nature of neuroendocrine tumors, treatment outcomes can be measured over a 5- to 10-year period.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

### **Systematic Reviews**

A Cochrane review by Gurusamy et al (2009) compared the benefits and harms of liver resection with those of other treatments in patients who had resectable liver metastases from gastro-entero-pancreatic neuroendocrine tumors.<sup>16</sup> Trials comparing liver resection (alone or in combination with RFA or cryoablation) with other interventions (chemotherapy, hormone therapy, or immunotherapy) and studies comparing liver resection with thermal ablation (RFA or cryoablation) were sought. Cochrane reviewers reported finding that none of the 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 (i.e., >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.

### **Cohort Studies**

Saxena et al (2012) retrospectively reviewed data on 40 patients treated with cryoablation and surgical resection for hepatic metastases from neuroendocrine cancer.<sup>17</sup> The median period of follow-up was 61 months (range, 1-162 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.<sup>18</sup> This study used cytoreduction (resection, cryosurgery, RFA, or a combination of the 3) and adjuvant therapy (octreotide, chemotherapy, radiotherapy, interferon- $\alpha$ ) 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 for unresectable liver metastases from neuroendocrine tumors amenable to locoregional therapy is very limited. Current evidence does not permit conclusions on whether this technology affects health outcomes.

**Liver Metastases From Colorectal Cancer**

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.

**Clinical Context and Therapy Purpose**

The purpose of CSA in patients who have unresectable liver metastases from CRC is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of CSA improve health outcomes for individuals with unresectable liver metastases from CRC?

The following PICO was used to select literature to inform this review.

***Populations***

The relevant population of interest is individuals with unresectable liver metastases from CRC amenable to locoregional therapy.

***Interventions***

The therapy being considered is CSA.

***Comparators***

The following therapies are currently being used: RFA, microwave tumor ablation, and locoregional ablation other than RFA.

***Outcomes***

The general outcomes of interest are disease-free and OS. Other outcomes include recurrence rates, symptom reductions, and treatment-related adverse events. Estimates for disease-related mortality can range up to 2 years, with subsets of populations surviving 5 to 10 years.

**Systematic Reviews**

A Cochrane review by Al-Asfoor et al (2008) compared outcomes of resection of CRC liver metastases with no intervention or other treatment modalities, including RFA and cryosurgery.<sup>19</sup> 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 (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.<sup>20</sup> Survival outcomes were not provided by the type of cryogenic procedure or primary tumor site. Cochrane reviewers concluded that local ablative therapies were probably useful but that the therapy would need further evaluation in an RCT. A Cochrane review by Bale

et al (2013) examined cryoablation for liver metastases from various sites, primarily colorectal.<sup>21</sup> Only the Korpan (1997) RCT,<sup>20</sup> included in the 2008 Cochrane review, met inclusion criteria. The Korpan (1997) 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 Cochrane review by Gurusamy et al (2010) compared liver resection (alone or in combination with RFA or cryoablation) with nonsurgical treatments (neoadjuvant chemotherapy, chemotherapy, or RFA) in patients with colorectal liver metastases and hepatic node involvement.<sup>22</sup> No RCTs, quasi-randomized trials, or cohort studies were identified to address this clinical scenario.

Pathak et al (2011) reported on a systematic review of ablative therapies for CRC liver metastases.<sup>23</sup> 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.

### Case Series

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 the extrahepatic disease, treated between 1995 and 2004 and who underwent laparotomy for surgical treatment of liver metastases.<sup>24</sup> 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 rates at 2 and 5 years were 56% and 27%, respectively (median, 31 months; n=45); for the chemotherapy group, 51% and 15%, respectively (median, 26 months; n=39; p=.252). After resection, these rates were 83% and 51%, respectively (median, 61 months; n=117; p<.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 groups. Additionally, this study used both cryotherapy and RFA for local ablation, and results were 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.<sup>25</sup> A decision about respectability 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 rate 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 plus cryotherapy group was 29 months, with 1-, 3-, and 5-year survival rates of 84%, 43%, and 24%, respectively ( $p=.206$ ). The overall recurrence rate was 66% for resection only but 78% for resection plus cryotherapy. Five factors were independently associated with improved survival: the 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 plus 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.<sup>26</sup> 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 ( $p=.052$ ). 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 on outcomes for cryoablation for liver metastases from CRC. Summarized here are some of the larger and more recent series. Ng et al (2012) conducted a retrospective review of 293 patients treated between 1990 and 2009 for colorectal liver metastases with cryoablation with or without surgical resection.<sup>27</sup> 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.<sup>28</sup> 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 the 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.<sup>29</sup> In this series, from 1998 to 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 the number of ablated tumors was 14% for RFA and 12% for CSA. Tumor size correlated directly with recurrence ( $p=.02$ ) 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.<sup>30</sup> 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 a 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 the 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 Colorectal Cancer**

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 permit conclusions on the effectiveness of cryoablation compared with other locoregional therapies.

### **Summary of Evidence**

For individuals who have unresectable primary HCC amenable to locoregional therapy who receive CSA, the evidence includes a RCT, several nonrandomized comparative studies, and multiple noncomparative studies. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. The available RCT comparing cryoablation with 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. Nonrandomized comparative studies have failed to find consistent benefit with cryoablation in outcomes related to tumor recurrence and survival. Additional randomized comparative evidence is needed to permit conclusions about the effectiveness of cryoablation compared with other locoregional therapies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 OS, disease-specific survival, symptoms, and treatment-related mortality and morbidity. The available evidence base is very limited. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable liver metastases from colorectal cancer amenable to locoregional therapy who have CSA, the evidence includes an RCT, several nonrandomized comparative and noncomparative studies, and systematic reviews of these studies. Relevant outcomes are OS, 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 that the technology results in an improvement in the net health outcome.

### **SUPPLEMENTAL INFORMATION**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

#### **Clinical Input 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 the use of cryoablation for liver tumors and, in general, cited the studies reviewed in the Rationale section. Some reviewers considered cryoablation as 1 of several ablative techniques that could be used in these patients.

#### **Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

The National Comprehensive Cancer Network (NCCN) indicates that ablative techniques may be used in the treatment of certain hepatic tumors. The NCCN guidelines on hepatobiliary cancer (v.3.2021 ) include cryoablation in a list of ablative techniques, along with radiofrequency ablation (RFA), percutaneous alcohol ablation, and microwave ablation; however, the literature cited in the guidelines reports on only RFA and ethanol ablation.<sup>31</sup> For hepatocellular carcinoma, the NCCN makes the following category 2A recommendation:

"All patients with HCC [hepatocellular carcinoma] should be evaluated for potential curative therapies (resection, transplantation, and for small lesions, ablative strategies). Locoregional therapy should be considered in patients who are not candidates for surgical curative treatments, or as a part of a strategy to bridge patients for other curative therapies.

Ablation (radiofrequency, cryoablation, percutaneous alcohol injection, microwave):

- All tumors should be amenable to ablation such that the tumor and, in the case of thermal ablation, a margin of normal tissue is treated. A margin is not expected following percutaneous ethanol injection.
- Tumors should be in a location accessible for percutaneous/laparoscopic/open approaches for ablation.
- Caution should be exercised when ablating lesions near major vessels, major bile ducts, diaphragm, and other intra-abdominal organs.
- Ablation alone may be curative in treating tumors  $\leq 3$  cm. In well-selected patients with small properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review. Lesions 3 to 5 cm may be treated to prolong survival using arterially directed therapies, or with combination of an arterially directed therapy and ablation as long as tumor location is accessible for ablation.
- Unresectable/inoperable lesions  $>5$  cm should be considered for treatment using arterially directed or systemic therapy.
- Sorafenib should not be used as adjuvant therapy post-ablation."

For intrahepatic cholangiocarcinoma (isolated intrahepatic mass), the guidelines recommend locoregional therapy using arterially directed therapies or external-beam radiotherapy.

The NCCN guidelines on neuroendocrine and adrenal tumors (v.2.2021 ) address the use of hepatic-directed therapies for patients with unresectable hepatic-predominant progressive metastatic neuroendocrine tumors.<sup>32</sup> These guidelines support consideration of ablative therapies such as RFA or cryoablation if near-complete tumor burden can be achieved (category 2B recommendation).

For ablative therapy, the NCCN makes the following category 2B recommendation:

"Percutaneous thermal ablation, often using microwave energy (radiofrequency and cryoablation are also acceptable), can be considered for oligometastatic liver disease, generally up to four lesions each smaller than 3 cm. Feasibility considerations include safe percutaneous imaging-guided approach to the target lesions, and proximity to vessels, bile ducts, or adjacent non-target structures that may require hydro- or aero-dissection for displacement."

The NCCN guidelines on the treatment of colon cancer with liver metastases (v.2.2021 ) consider patients with liver oligometastases as candidates for tumor ablation therapy. Ablative techniques include RFA, microwave ablation, cryoablation, percutaneous ethanol injection, and electro-coagulation. Use of surgery, ablation, or the combination "with the goal of less-than-complete resection/ablation of all known sites of disease, is not recommended other than in the scope of a clinical trial" (category 2A recommendations).<sup>33</sup>

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

Not applicable.

### **Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov in July 2021 did not identify any ongoing or unpublished trials that would likely influence this review.

**CODING**

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**CPT/HCPCS**

47371 Laparoscopy, surgical, ablation of 1 or more liver tumor(s); cryosurgical  
 47381 Ablation, open, of 1 or more liver tumor(s); cryosurgical  
 47383 Ablation, 1 or more liver tumor(s), percutaneous, cryoablation  
 76940 Ultrasound guidance for, and monitoring of, parenchymal tissue ablation

**ICD-10 Diagnoses**

Experimental / Investigational for all diagnoses related to this medical policy.

<b>REVISIONS</b>	
05-10-2012	Policy added to the bcbsks.com web site.
03-26-2013	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> <li>▪ Updated Coding nomenclature.</li> <li>▪ Added ICD-10 codes.</li> </ul>
	Updated Reference section.
01-01-2015	In Coding section: <ul style="list-style-type: none"> <li>▪ Added CPT Code: 47383 (Effective January 1, 2015)</li> </ul>
06-12-2015	Policy published to the website on 05-13-2015.
	Description section updated
	Rationale section updated
	In Policy section: <ul style="list-style-type: none"> <li>▪ Policy position changed to:                "Cryosurgical ablation of either primary or metastatic tumors in the liver is experimental / investigational." from:                "A. Cryosurgical ablation of primary hepatocellular carcinoma (HCC) may be considered medically necessary as a primary treatment of HCC for patients when all tumor foci can be adequately treated.                B. Cryosurgical ablation of primary hepatocellular carcinoma (HCC) is considered medically necessary as a bridge to transplant, where the intent is to prevent further tumor growth and to maintain a patient's candidacy for liver transplant.                C. Cryosurgical ablation of primary hepatocellular carcinoma (HCC) is considered investigational when not all sites of tumor foci can be adequately treated.                D. Cryosurgical ablation may be considered medically necessary as a primary treatment of hepatic metastases from colorectal cancer in the absence of extrahepatic metastatic disease when all tumor foci can be adequately treated.</li> </ul>



<b>REVISIONS</b>	
	<p>E. Cryosurgical ablation may be considered medically necessary as treatment of hepatic metastases from neuroendocrine tumors in patients with symptomatic disease.</p> <p>F. Cryosurgical ablation for hepatic metastasis is considered experimental / investigational:</p> <ol style="list-style-type: none"> <li>for hepatic metastases from colorectal cancer or neuroendocrine tumors that do not meet the criteria above; and</li> <li>for hepatic metastases from other types of cancer with the exception of colorectal cancer or neuroendocrine tumors."</li> </ol> <p>In Coding section:</p> <ul style="list-style-type: none"> <li>Updated ICD nomenclature: C22.0, C22.2, C22.3, C22.4, C22.7, C22.8, C22.9, C78.7, C7B.02</li> </ul> <p>References updated</p>
07-11-2017	<p>Description section updated</p> <p>Rationale section updated</p> <p>In Coding section:</p> <ul style="list-style-type: none"> <li>Added the customary Diagnosis E/I statement of "Experimental / Investigational for all diagnoses related to this medical policy." and removed reference to the ICD codes. This revision has no impact on the policy as the policy statement has been E/I since June 2015.</li> </ul> <p>References updated.</p>
09-12-2018	<p>Description section updated</p> <p>Rationale section updated</p> <p>References updated.</p>
02-24-2021	<p>Description section updated</p> <p>Rationale section updated</p> <p>References updated.</p>
11-5-2021	<p>Updated Description section</p> <p>Updated Rationale section</p> <p>Updated Reference section</p>

## **REFERENCES**

- Sohn RL, Carlin AM, Steffes C, et al. The extent of cryosurgery increases the complication rate after hepatic cryoablation. *Am Surg.* Apr 2003; 69(4): 317-22; discussion 322-3. PMID 12716090
- Wang C, Wang H, Yang W, et al. Multicenter randomized controlled trial of percutaneous cryoablation versus radiofrequency ablation in hepatocellular carcinoma. *Hepatology.* May 2015; 61(5): 1579-90. PMID 25284802
- Chen L, Ren Y, Sun T, et al. The efficacy of radiofrequency ablation versus cryoablation in the treatment of single hepatocellular carcinoma: A population-based study. *Cancer Med.* Jun 2021; 10(11): 3715-3725. PMID 33960697
- Cha SY, Kang TW, Min JH, et al. RF Ablation Versus Cryoablation for Small Perivascular Hepatocellular Carcinoma: Propensity Score Analyses of Mid-Term Outcomes. *Cardiovasc Intervent Radiol.* Mar 2020; 43(3): 434-444. PMID 31844951
- Ko SE, Lee MW, Rhim H, et al. Comparison of procedure-related complications between percutaneous cryoablation and radiofrequency ablation for treating periductal hepatocellular carcinoma. *Int J Hyperthermia.* Nov 17 2020; 37(1): 1354-1361. PMID 33297809

6. Wei J, Cui W, Fan W, et al. Unresectable Hepatocellular Carcinoma: Transcatheter Arterial Chemoembolization Combined With Microwave Ablation vs. Combined With Cryoablation. *Front Oncol.* 2020; 10: 1285. PMID 32850395
7. Ei S, Hibi T, Tanabe M, et al. Cryoablation provides superior local control of primary hepatocellular carcinomas of 2 cm compared with radiofrequency ablation and microwave coagulation therapy: an underestimated tool in the toolbox. *Ann Surg Oncol.* Apr 2015; 22(4): 1294-300. PMID 25287439
8. Dunne RM, Shyn PB, Sung JC, et al. Percutaneous treatment of hepatocellular carcinoma in patients with cirrhosis: a comparison of the safety of cryoablation and radiofrequency ablation. *Eur J Radiol.* Apr 2014; 83(4): 632-8. PMID 24529593
9. Awad T, Thorlund K, Gluud C. Cryotherapy for hepatocellular carcinoma. *Cochrane Database Syst Rev.* Oct 07 2009; (4): CD007611. PMID 19821432
10. Adam R, Hagopian EJ, Linhares M, et al. A comparison of percutaneous cryosurgery and percutaneous radiofrequency for unresectable hepatic malignancies. *Arch Surg.* Dec 2002; 137(12): 1332-9; discussion 1340. PMID 12470093
11. Yang Y, Wang C, Lu Y, et al. Outcomes of ultrasound-guided percutaneous argon-helium cryoablation of hepatocellular carcinoma. *J Hepatobiliary Pancreat Sci.* Nov 2012; 19(6): 674-84. PMID 22187145
12. Rong G, Bai W, Dong Z, et al. Long-term outcomes of percutaneous cryoablation for patients with hepatocellular carcinoma within Milan criteria. *PLoS One.* 2015; 10(4): e0123065. PMID 25849963
13. Zhou L, Yang YP, Feng YY, et al. Efficacy of argon-helium cryosurgical ablation on primary hepatocellular carcinoma: a pilot clinical study. *Ai Zheng.* Jan 2009; 28(1): 45-8. PMID 19448416
14. Wang C, Lu Y, Chen Y, et al. Prognostic factors and recurrence of hepatitis B-related hepatocellular carcinoma after argon-helium cryoablation: a prospective study. *Clin Exp Metastasis.* 2009; 26(7): 839-48. PMID 19784786
15. Jaeck D, Oussoultzoglou E, Bachellier P, et al. Hepatic metastases of gastroenteropancreatic neuroendocrine tumors: safe hepatic surgery. *World J Surg.* Jun 2001; 25(6): 689-92. PMID 11376398
16. Gurusamy KS, Ramamoorthy R, Sharma D, et al. Liver resection versus other treatments for neuroendocrine tumors in patients with resectable liver metastases. *Cochrane Database Syst Rev.* Apr 15 2009; (2): CD007060. PMID 19370671
17. Saxena A, Chua TC, Chu F, et al. Optimizing the surgical effort in patients with advanced neuroendocrine neoplasm hepatic metastases: a critical analysis of 40 patients treated by hepatic resection and cryoablation. *Am J Clin Oncol.* Oct 2012; 35(5): 439-45. PMID 21654315
18. Chung MH, Pisegna J, Spirt M, et al. Hepatic cytoreduction followed by a novel long-acting somatostatin analog: a paradigm for intractable neuroendocrine tumors metastatic to the liver. *Surgery.* Dec 2001; 130(6): 954-62. PMID 11742323
19. Al-Asfoor A, Fedorowicz Z, Lodge M. Resection versus no intervention or other surgical interventions for colorectal cancer liver metastases. *Cochrane Database Syst Rev.* Apr 16 2008; (2): CD006039. PMID 18425932
20. Korpan NN. Hepatic cryosurgery for liver metastases. Long-term follow-up. *Ann Surg.* Feb 1997; 225(2): 193-201. PMID 9065296
21. Bala MM, Riemsma RP, Wolff R, et al. Cryotherapy for liver metastases. *Cochrane Database Syst Rev.* Jun 05 2013; (6): CD009058. PMID 23740609

22. Gurusamy KS, Ramamoorthy R, Imber C, et al. Surgical resection versus non-surgical treatment for hepatic node positive patients with colorectal liver metastases. *Cochrane Database Syst Rev*. Jan 20 2010; (1): CD006797. PMID 20091607
23. Pathak S, Jones R, Tang JM, et al. Ablative therapies for colorectal liver metastases: a systematic review. *Colorectal Dis*. Sep 2011; 13(9): e252-65. PMID 21689362
24. Ruers TJ, Joosten JJ, Wiering B, et al. Comparison between local ablative therapy and chemotherapy for non-resectable colorectal liver metastases: a prospective study. *Ann Surg Oncol*. Mar 2007; 14(3): 1161-9. PMID 17195903
25. Niu R, Yan TD, Zhu JC, et al. Recurrence and survival outcomes after hepatic resection with or without cryotherapy for liver metastases from colorectal carcinoma. *Ann Surg Oncol*. Jul 2007; 14(7): 2078-87. PMID 17473951
26. Joosten J, Jager G, Oyen W, et al. Cryosurgery and radiofrequency ablation for unresectable colorectal liver metastases. *Eur J Surg Oncol*. Dec 2005; 31(10): 1152-9. PMID 16126363
27. Ng KM, Chua TC, Saxena A, et al. Two decades of experience with hepatic cryotherapy for advanced colorectal metastases. *Ann Surg Oncol*. Apr 2012; 19(4): 1276-83. PMID 21913018
28. Seifert JK, Springer A, Baier P, et al. Liver resection or cryotherapy for colorectal liver metastases: a prospective case control study. *Int J Colorectal Dis*. Nov 2005; 20(6): 507-20. PMID 15973545
29. Kornprat P, Jarnagin WR, DeMatteo RP, et al. Role of intraoperative thermoablation combined with resection in the treatment of hepatic metastasis from colorectal cancer. *Arch Surg*. Nov 2007; 142(11): 1087-92. PMID 18025338
30. Xu KC, Niu LZ, He WB, et al. Percutaneous cryosurgery for the treatment of hepatic colorectal metastases. *World J Gastroenterol*. Mar 07 2008; 14(9): 1430-6. PMID 18322961
31. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers. Version 3.2021. [https://www.nccn.org/professionals/physician\\_gls/PDF/hepatobiliary.pdf](https://www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf). Accessed July 28, 2021.
32. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors. Version 2.2021. [https://www.nccn.org/professionals/physician\\_gls/PDF/neuroendocrine.pdf](https://www.nccn.org/professionals/physician_gls/PDF/neuroendocrine.pdf). Accessed July 28, 2021.
33. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 2.2021. [https://www.nccn.org/professionals/physician\\_gls/PDF/colon.pdf](https://www.nccn.org/professionals/physician_gls/PDF/colon.pdf). Accessed July 28, 2021.