# Medical Policy

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# Title: Cryosurgical Ablation of Primary or Metastatic Liver Cancer

## Description/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 [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 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. In the U.S, the incidence rates of liver cancer are estimated to continually increase through 2030. [1] Some racial groups are more affected by liver cancer than others due to differences in the prevalence of risk factors and disparities in access to quality care; the mortality rate for African Americans with HCC is higher than other racial groups in the U.S.

**Treatment**

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 the 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 three 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 studies have reported experience with cryosurgical and other ablative methods used in combination with subtotal resection and/or procedures such as transarterial 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[2], but much of the treatment-related morbidity and mortality reflect the generally poor health status of patients with advanced hepatic disease.

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## Regulatory Status

Several cryosurgical devices have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. 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.

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## Medical Policy Statement

Cryosurgical ablation for individuals with unresectable primary or metastatic liver cancer is **established**. It is considered a useful therapeutic alternative in specific situations when criteria are met.

## Inclusionary and Exclusionary Guidelines

**Inclusions: Cryosurgical ablation is established when the ALL of following criteria are met:**

- Primary or metastatic hepatic cancer that is 3-5 cm or less in size and occupy less than 50% of the liver parenchyma; **AND**
- Individuals have cancer in the liver that are not surgically resectable due to the location or extent of the liver disease or due to co-morbid conditions such that the individual is unable to tolerate an open surgical resection; **AND**
- All cancer in the liver would be potentially destroyed by cryotherapy

**And also any ONE of the following is met:**

- Metabolically active liver cancer (ie, neuroendocrine cancer) to reduce metabolic activity; **OR**
- Individuals with hepatic metastases from a colorectal primary cancer in the absence of extrahepatic metastatic disease when all tumor foci can be adequately treated**; OR**
- Individuals with hepatocellular cancer with no evidence of extra-hepatic metastases; **OR**
- Intrahepatic cholangiocarcinoma, especially high-risk disease with a single hepatic tumor <3 cm

**Exclusions:**

All other primary and metastatic hepatic cancer not meeting the above criteria.

## CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

### *Established codes:*

47371 47381 47383

### *Other codes (investigational, not medically necessary, etc.):*

N/A

## Rationale

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, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 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 in individuals 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 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 cryosurgical ablation.

#### *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. 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.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

## REVIEW OF EVIDENCE

Li-Zhi Niu et al (2014) in the Journal of Clinical Translation Hepatology reviewed, the application of percutaneous cryoablation (PCA) as a treatment for liver cancer. PCA is a minimally invasive technique that involves freezing tumor tissues using cryoprobes, leading to cancer cell destruction. The method is particularly suited for patients who are not candidates for surgery due to underlying health conditions or advanced disease. They concluded that overall, percutaneous cryoablation represents a promising alternative for managing liver cancer, particularly in patients who cannot undergo surgery.[46]

Wong et al (1998) in the article “Cryosurgery as a Treatment for Advanced Stage Hepatocellular Carcinoma: Results, Complications, and Alcohol Ablation”, evaluates the effectiveness, safety, and outcomes of cryosurgery in treating advanced hepatocellular carcinoma (HCC), The study provides insights into patient survival, procedure-related complications, and the role of adjunctive therapies like alcohol ablation. The article highlights cryosurgery as a viable treatment option for advanced stage HCC, with potential for integration with other therapies like alcohol ablation.[47]

### Systematic Reviews

A network meta-analysis by Kim et al (2023) compared the benefits and harms of locoregional treatments for hepatocellular carcinoma (HCC) in patients who had early HCCs of ≤ 4 cm with no extrahepatic spread of portal invasion.[3] Databases (PubMed, Embase, Cochrane Library, CINAHL, and Web of Science) were searched from January 1, 2000 to February 17, 2023. A total of 19 trials comparing 11 different treatment strategies in 2,793 patients were pooled in this review; outcomes of interest included overall survival (OS), progression-free survival (PFS) and local PFS. The interventions assessed by the authors included: radiofrequency ablation (RFA; n=1,124), cryoablation (CSA; n=180), laser ablation (LA; n=70), microwave ablation (MWA; n=276), percutaneous acetic acid injection (PAI; n=159), (PBT; n=72), (PEI; n=585), trans-arterial chemoembolization (TACE; n=84), TACE+MWA (n=89), TACE+PEI (n=39), and TACE+RFA (n=115). Risk of bias assessment was performed using the revised Cochrane Risk of Bias (ROB) tool for randomized controlled trials. Only a single trial, discussed below by Wang et al (2015), was included for the CSA group. A summary of the pooled OS, PFS, and local PFS are presented in Table 1 along with the pairwise comparisons of cryoablation to alternative interventions for HCC. Cryoablation had similar OS, PFS, and local PFS to the reference group of RFA. Indirect pairwise comparisons of cryoablation to other treatments showed the superiority of CSA to PAI for OS and superiority over PAI and PEI for PFS; all other indirect comparisons to CSA were not significantly different.

A meta-analysis by Keshavarz et al (2022) compared the efficacy of TACE, TACE+RFA, TACE+MWA, and TACE+CSA in patients with HCC.[4] Databases (Scopus, Web of Science, PubMed, Embase, Chinese National Knowledge Infrastructure, Google Scholar, and Cochrane

Library) were searched from January 1, 2010 to August 29, 2021. A total of 42 studies (n=5,468) were included in this analysis with 21 studies identified for TACE+RFA (n=3,398), 14 studies for TACE+MWA (n=1,477), and 7 studies for TACE+CSA (n=593). OS at 1-year follow-up for TACE+CSA compared to TACE had odds ratios (OR) of 2.96 (95% CI 1.95, 4.48, p<.001) with low heterogeneity across 6 pooled studies ($I^2$=*0*.0%). At 3 years follow-up OS compared to TACE remained superior with an OR of OR 3.33 (95% CI, 1.15 to 9.64; p =.026); however, this included only a single study. Tumor response rates compared to TACE found a significantly higher number of complete responders (OR 4.18; 95% CI, 2.62 to 6.67) and a significantly lower rate of progressive disease (OR, 0.25; 95% CI, 0.13 to 0.46) with low levels of heterogeneity. The objective response rate and disease control rate also favored the combined TACE+CSA group over TACE with ORs of 3.61 (95% CI, 1.85 to 7.05; p<.001) and 4.05 (95% CI, 1.68 to 9.74; p=.002); these comparisons had moderate heterogeneity between studies.

**Table 1. Summary of Meta-Analyses Outcomes in Kim et al (2023)**

| Intervention | OS, HR (95% CI; p-value vs RFA) | PFS, HR (95% CI; p-value vs RFA) | Local PFS, HR (95% CI; p-value vs RFA) | OS Pair-wise Comparison to CSA, HR (95% CI) | PFS Pair-wise Comparison to CSA, HR (95% CI) |
|---|---|---|---|---|---|
| TACE+RFA | 0.52 (0.33 to 0.82; p=.951) | 0.61 (0.42 to 0.88; p=.964) | 0.63 (0.25 to 1.59; p=.786) | 0.62 (0.29 to 1.32) | 0.70 (0.43 to 1.11) |
| TACE+MWA | 0.69 (0.25 to 1.93; p=.797) | NA | NA | 0.82 (0.25 to 2.70) | NA |
| PBT | 1.07 (0.58 to 1.98; p=.561) | 0.99 (0.70 to 1.41; p=.575) | 0.73 (0.39 to 1.37; p=.736) | 0.78 (0.33 to 1.87) | 0.89 (0.56 to 1.40) |
| MWA | 1.25 (0.78 to 2.01; p=.441) | 1.06 (0.71 to 1.57; p=.508) | 1.39 (0.85 to 2.27; p=.334) | 0.67 (0.31 to 1.45) | 0.83 (0.51 to 1.36) |
| LAa | 1.34 (0.73 to 2.46; p=.384) | NA | 0.86 (0.43 to 1.74; p=.632) | 0.63 (0.27 to 1.48) | NA |
| TACE+PEI | 1.46 (0.62 to 3.41; p=.342) | 1.12 (0.42 to 2.97; p=.505) | NA | 0.58 (0.20 to 1.65) | 0.78 (0.28 to 2.17) |
| PEI | 1.51 (1.16 to 1.96; p=.281) | 1.88 (1.41 to 2.5; p=.148) | 2.71 (1.66 to 4.41; p=.064) | 0.56 (0.29 to 1.09) | 0.47 (0.31 to 0.70) |
| TACE | 1.53 (0.74 to 3.16; p=.279) | NA | NA | 0.55 (0.21 to 1.42) | NA |
| PAI | 1.99 (1.30 to 3.06; p=.091) | 3.85 (1.25 to 11.79; p=0.03) | 2.54 (1.4 to 4.59; p=.098) | 0.42 (0.2 to 0.89) | 0.23 (0.07 to 0.73) |
| CSA | 0.84 (0.46 to 1.55; p=.728) | 0.88 (0.65 to 1.18; p=.717) | 0.57 (0.19 to 1.67; p=.817) | Ref | Ref |
| RFA | Ref | Ref | Ref | 0.84 (0.46 to 1.55) | 0.88 (0.65 to 1.18) |

CSA: cryosurgical ablation; CI: confidence interval; HR: hazard ratio; LA: laser ablation; MWA: microwave ablation; NA, not applicable; OS: overall survival; PAI: percutaneous acetic acid injection; PBT: proton beam therapy; PEI: percutaneous ethanol injection; PFS: progression free survival; Ref: reference group for comparison; RFA: radiofrequency ablation; TACE: transarterial chemoembolization

### Randomized Controlled Trials

Wang et al (2015) reported on an RCT comparing cryoablation with RFA in 360 patients with HCC.[5] 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 to 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). Overall Survival 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

Wang et al (2022) retrospectively compared the efficacy and safety of transcatheter arterial chemoembolization (TACE) combined with either microwave ablation (n=41) or with cryoablation in patients with HCC (n=40).[6.] There was no statistically significant difference in primary outcomes between the 2 groups. The median OS for the microwave ablation group was 19.2 months compared to 18.6 months in the cryoablation group (p=.64); the median PFS was 9.3 months for the microwave ablation group and 12.3 months for the cryoablation group (p=.6). There was a significant difference regarding rates of surgery-related complications and adverse reactions. Gastrointestinal reactions and abdominal pain were observed in 26.8% and 31.7% of patients in the microwave ablation group, respectively, while 5.0% and 10.0% of patients in the cryoablation group experienced these reactions, respectively (p<.05).

Luo et al (2022) reported on a prospective multicenter study in elderly patients with HCC undergoing cryoablation (n=112) or RFA (n=111). [7] Patients in both groups had similar local tumor progression at 1, 3, and 5 years after treatment (p=.735). For lesions that were >3cm in diameter, the local tumor progression rates at 1 and 3 years were 13% and 22% in the cryoablation group and 22% and 42% in the RFA group, respectively (p=.039). Secondary endpoints of OS and tumor-free survival at 1, 3, and 5 years after treatment were similar for both groups.

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).[8] 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.[9] 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 non-significantly 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).[10] 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 (TACE) combined with either microwave ablation (n=48) or with cryoablation in patients with HCC (n=60).[11] 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.[12] 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 larger median tumor size (2.5 cm versus 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 non-significantly higher in the cryoablation group (80% versus 68%, p=.20). In a multivariable model to predict local recurrence, receiving cryoablation was significantly associated with reduced risk of recurrence (adjusted hazard ratio [HR], 0.3; 95% CI, 0.1 to 0.9; p=0.2). For tumors greater than 2 cm in diameter, the 2-year local recurrence rate was lower for patients treated with cryoablation (21% versus 56%, p=.006).

In a smaller, retrospective comparative study including 42 patients with HCC and cirrhosis, Dunne et al (2014) reported short-term safety outcomes after cryoablation or RFA.[13] 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 on 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.[14] This review antedates Wang (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).[15] 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% versus 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.[16] 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 two patients. Patients with incomplete ablation received additional treatment with transarterial catheter embolization or a multikinase inhibitor (sorafenib). During the median follow-up of 36.7 months (range, 6-63 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 overall survival 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.[17] A total of 832 (96.1%) patients were considered to have a complete response after up to 3 cryoablation sessions. During the follow-up period, 502 (60.2%) patients with an initial complete response had a recurrence (n=99 [11.9%] local, n=396 [44.5%] distant intrahepatic, n=7 [0.85] extrahepatic). Two hundred sixteen subjects died (mortality rate, 25.9%), corresponding to a 5-year overall survival 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 early, middle, and advanced stage groups using the Barcelona Clinic Liver Cancer staging classification.[18] After argon-helium cryoablation, serum level of α-fetoprotein was reduced in 76 (82.6%), and 205 (92.3%) of 222 tumor lesions were diminished or unchanged. Median survival time was 31.35 months in the early-stage, 17.4 months in the middle-stage, and 6.8 months in the late-stage groups. As of April 2008, 14 patients had survived and 110 had died. To determine risk factors that predict metastasis and recurrence, Wang et al studied a series of 156 patients with hepatitis B virus–related HCC and tumors smaller than 5 cm in diameter who underwent curative cryoablation.[19] One-, 2-, and 3-year overall survival 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**

A network meta-analysis reported that cryoablation had similar overall survival and progression-free survival compared to RFA; indirect comparisons showed superiority for both overall survival and progression-free survival over percutaneous acetic acid injection but no differences with other treatment groups. Another meta-analysis comparing cryoablation and TACE versus TACE alone found that the combined treatment was superior for overall survival and tumor progression outcomes. 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. The NCCN guidelines on hepatocellular carcinoma include cryoablation in a list of ablative techniques. A Pub Med article by Wong (1998) et al. found cryosurgery to be promising in the treatment of this extremely aggressive form of cancer, with the ability to prolong patient survival. Li-Zhi Niu et. al (2014). “Percutaneous cryoablation for liver cancer” concluded that experimental and clinical applications have shown that hepatic cryosurgery is safe and effective. Cryosurgery can be performed on its own or in combination with other methods, such as radiation therapy, chemotherapy, immunology, or surgery.

**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.[20] 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 cryosurgical ablation in individuals 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 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 cryosurgical ablation.

### *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 overall survival. 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
See information under the first indication.

### Review of Evidence

Joachim et al (1998) summarized that cryotherapy is a technique that involves freezing tumor tissues, has been explored as a treatment for neuroendocrine liver metastases. This method aims to reduce tumor size and alleviate symptoms associated with hormonal excess. While cryotherapy offers a minimally invasive alternative to traditional surgical resection its effectiveness and long-term outcomes require further investigation. The procedure's success depends on factors such as tumor size, location, and patient's overall health. Potential complications include damage to surrounding liver tissue and the risk of incomplete tumor destruction. Overall, cryotherapy presents a promising option for managing neuroendocrine liver metastases, particularly in patients who are not candidates for surgery.[48]

Khanmohammadi et al (2023) in the article "Survival outcomes and quality of life after percutaneous cryoablation for liver metastasis: A systematic review and meta-analysis" did a prospective and retrospective review which included patients with different types of primary cancer. (colorectal, neuroendocrine, bile duct, sarcoma lung, ovarian cancer) with metastases to the liver. It reviewed the effectiveness of percutaneous cryoablation as a minimally invasive treatment of liver metastases, with a focus on overall survival, local recurrence, quality of life (QoL), and complications. Cryoablation was found to improve QoL significantly, with favorable outcomes in terms of local recurrence rates. It is particularly beneficial for patients who are not candidates for surgical resection. Cryoablation is an effective treatment for liver metastases, offering improved QoL and manageable recurrence rates, making it a viable alternative for high-risk surgical candidates. Cryoablation is a promising but underutilized treatment option. [49]

### Systematic Reviews
A Cochrane review by Gurusamy et al (2009) compared the benefits and harms of liver resection versus other treatments in patients who had resectable liver metastases from gastro-entero-pancreatic neuroendocrine tumors.[21] Trials comparing liver resection (alone or in combination with RFA or cryoablation) with other interventions (chemotherapy,

hormonotherapy, or immunotherapy) and studies comparing liver resection with thermal ablation (RFA or cryoablation) were sought. Cochrane reviewers reported finding that none of the RCTs were suitable for review nor any quasi-randomized, cohort, or case-control studies "could inform meaningfully." No analysis was performed, and reviewers referred to only RFA in their discussion, noting that radiofrequency is not suitable for large tumors (ie, >5-6 cm), and that neuroendocrine liver metastases are frequently larger than that. They concluded that randomized trials comparing surgical resection with RFA in selected patients would be appropriate.

**Cohort Studies**

Saxena et al (2012) retrospectively reviewed data on 40 patients treated with cryoablation and surgical resection for hepatic metastases from neuroendocrine cancer.[22] The median period of follow-up was 61 months (range 1 to 162 months). One death occurred within 30 days of treatment. No other complications were reported. Median survival was 95 months, and the rate of survival was 92%, 73%, 61% and 40% at 1, 3, 5 and 10 years, respectively.

Chung et al (2001) reported on outcomes of cryosurgery for hepatic metastases from neuroendocrine cancer.[23] This study used cytoreduction (resection, cryosurgery, RFA, or a combination of the three) and adjuvant therapy (octreotide, chemotherapy, radiotherapy, interferon-α) in 31 patients with neuroendocrine metastases to the liver and "progressive symptoms refractory to conventional therapy." Following treatment, symptoms were eliminated in 87% of patients; median symptom-free interval was 60 months with octreotide and 16 months with alternatives. Because outcomes were not reported separately for different cytoreductive techniques, it was not possible to compare the benefits of cryosurgery with those of other cytoreductive approaches or octreotide alone.

**Section Summary: Neuroendocrine Cancer Liver Metastases**

The available evidence on unresectable liver metastases from neuroendocrine tumors amenable to locoregional therapy is very limited. However, The NCCN guidelines on neuroendocrine and adrenal tumors address principles of liver-directed therapy for neuroendocrine tumor metastases. These guidelines support consideration of ablative therapies, including RFA or cryoablation for generally up to four lesions each smaller than 3 cm. Joachim et al (1998) cryotherapy presents a promising option for managing neuroendocrine liver metastases, particularly in patients who are not candidates for surgery. Khanmohammadi et al (2023) summarized that cryoablation is an effective treatment for liver metastases including from neuroendocrine cancer, offering improved quality of life and manageable recurrence rates, making it a viable alternative for high-risk surgical candidates.

## 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 cryosurgical ablation in individuals 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 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 cryosurgical ablation.

### *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 overall survival. 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.

## 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.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

Korpan et al.(2021) explores the field of cryoimmunology, which combines cryobiology and immunology. The authors review advancements and challenges in using cryogenic techniques to enhance immune responses for medical applications. They discuss how cryoimmunology holds promise in treating disease like cancer, by using cryoablation to stimulate anti-tumor immunity.[40]

Korpan et al(1997) examined the effectiveness of hepatic cryosurgery in treating liver metastases. The study followed patients over the long term to assess outcomes and survival rates after undergoing cryosurgery. Results show that hepatic cryosurgery can be effective in controlling metastatic liver tumors, with some patients experiencing extended survival times. The author discusses the potential benefits of this technique, including minimal invasiveness and targeted tumor destruction, as well as limitations such as potential complications and the need for careful patient selection. The findings support hepatic cryosurgery as a viable option for treating liver metastases in selected cases.[41]

The preliminary report summarized by Lezoche et al (1998) discussed early findings on the use of laparoscopic cryoablation from treating liver tumors. In this study, ultrasound was used to guide the laparoscopic procedure, allowing for precise targeting and freezing of hepatic tumors while minimizing invasiveness. The preliminary results indicate that this approach may be effective in managing liver tumors, with potential benefits such as reduced recovery times and lower complication rates compared to open surgery. However, the authors note that further research and long-term follow-up are needed to confirm the procedure's efficacy and safety.[42]

Iannitti et al (1998) summarized reports on the use of laparoscopic cryoablation as a treatment for liver metastases. This study examined the feasibility, safety, and effectiveness of using a minimally invasive laparoscopic approach to freeze and destroy metastatic liver tumors. The results suggest that laparoscopic cryoablation is a promising option for managing liver metastases, with advantages such as smaller incisions, shorter recovery time, and fewer complications, compared to traditional open surgery. The authors conclude that while the technique appeals effective, additional studies are needed to assess long-term outcomes and optimize patient selection.[43]

Paganini et al (2007) reviewed the use of cryosurgery for treating liver metastases from colorectal cancer. The study assesses the effectiveness and potential benefits of cryoablation, which involves freezing metastatic tumors in the liver to destroy cancerous cells. Findings indicate that cryosurgical ablation can be a viable treatment option for selected patients offering a less invasive alternative to resection with the potential for prolonged survival. The authors discuss the advantages of cryoablation, including its precision and reduced recovery time, but also highlight the need for further research to evaluate long-term outcomes and optimal patient selection criteria.[44]

Seifert et al. (2004) summarized the factors that affect outcomes for patients undergoing cryotherapy to treat liver metastases from colorectal cancer. The study identifies key prognostic factors influencing patient survival and treatment effectiveness, such as tumor size, number of metastases, and patient health. The findings suggest that these factors should be carefully considered when selecting patients for cryotherapy to improve outcomes. The authors conclude that understanding these prognostic factors can help optimize patient selection and enhance the effectiveness of cryotherapy as a treatment for colorectal liver metastases.[45]

**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.[24] 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 (1997) was identified, a trial from the Ukraine comparing surgical resection and cryosurgery in 123 subjects, 82 of whom had liver metastases from primary colorectal cancers and the remainder who had metastases from other primary tumors.[25] Survival outcomes were not provided by 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.[26] Only the Koran (1997) RCT,[25] 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.[27] No RCTs, quasi-randomized trails, 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.[28] 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 Studies**

A few studies have compared cryotherapy with other treatments for liver metastases. Ruers et al (2007) reported on a consecutive series of 201 CRC patients, without extrahepatic disease, treated between 1995 and 2004 and who underwent laparotomy for surgical treatment of liver metastases.[29] 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, overall survival 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 after local ablation was nine months. The authors concluded that although overall survival of local ablation versus chemotherapy was not statistically significant, median disease-free survival of nine months suggested a beneficial effect of local tumor ablation. However, given the heterogeneity of the groups in this study, it is very difficult to compare outcomes among 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.[30] 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% versus 27%, respectively) and to have 6 or more lesions (35% versus 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 to 124 months). The 30-day perioperative mortality was 3.1%. For the resection group, the median survival was 34 months, with 1-, 3-, and 5-year survival values rates of 88%, 47%, and 32%, respectively. The median survival for the resection/cryotherapy group was 29 months, with 1-, 3-, and 5-year survival rates of 84%, 43%, and 24%, respectively (p=.206). The overall recurrence rate was 66% for resection only, but 78% for resection plus cryotherapy. Five factors were independently associated with an 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 affected the results.

In a relatively small study, Joosten et al (2005) reported on 58 patients with unresectable colorectal liver metastases where cryosurgical ablation or RFA was performed in patients ineligible for resection.[31] Median follow-up was 26 and 25 months for cryosurgical ablation and RFA, respectively. One- and 2-year survival rates were 76% and 61% for cryosurgical ablation and 93% and 75% for RFA, respectively. In a lesion-based analysis, the local recurrence rate was 9% after cryosurgical ablation and 6% after RFA. Complication rates were 30% and 11% after cryosurgical ablation 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 outcomes for cryoablation for liver metastases from CRC. Some of the larger and more recent series are summarized here. 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.[32] 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 to 220 months). Overall survival 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 that were treated from 1996 to 2002.[33] In this series, 168 patients underwent resection, and 55 had cryosurgical ablation (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 times and 5-year disease-free survival rates following resection were superior at 10 months and 19%, respectively, 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.[34] 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 cryosurgical ablation). The overall morbidity rate was 41% (16/39). No RFA-related complications occurred; however, 3 patients developed an abscess at cryoablation sites. The median disease-free survival was 12.3 months (range, 8.4 to 16.2 months). The local in situ recurrence rate according to a number of ablated tumors was 14% for RFA and 12% for cryosurgical ablation. Tumor size correlated directly with recurrence (p=0.02) in RFA-treated lesions.

Xu et al (2008) reported on a series of 326 patients with nonresectable hepatic colorectal metastases treated with 526 percutaneous cryosurgery procedures.[35] 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 to 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 to 62 months). Overall survival rates were 78%, 62%, 41%, 34%, and 23% at 1, 2, 3, 4, and 5 years, respectively, after treatment. 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. Based on studies by Korpan et al. published in 1997 and 2021,the findings support hepatic cryosurgery as a viable option for treating liver metastases from colorectal cancer.

## SUMMARY OF EVIDENCE
There is evidence in the peer-reviewed medical literature that cryosurgery can effectively destroy tumor tissue in patients with biopsy-proven primary and metastatic liver cancer. The data suggest that cryosurgery is relatively safe and feasible in selected patients without extrahepatic disease who have tumors deemed unresectable due to number, size, multifocality, site or proximity to major vascular structures. Cryosurgery can also serve as an adjunct to surgery or other techniques for achieving tumor eradication or reduction in patients.

## 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 Received through Physician Specialty Societies and Academic Medical Centers
In response to requests, input was received by Blue Cross Blue Shield Association from 2 physician specialty societies and 3 academic medical centers while their policy was under

review in 2008. All reviewers supported use of cryoablation for liver tumors and, in general, cited the studies reviewed in the Rationale section. Some reviewers viewed 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.

**National Comprehensive Cancer Network**

The National Comprehensive Cancer Network (NCCN) indicates that ablative techniques may be used in the treatment of certain hepatic tumors. The NCCN guidelines on hepatocellular carcinoma (v3.2024) include cryoablation in a list of ablative techniques, along with radiofrequency ablation (RFA), percutaneous alcohol ablation, and microwave ablation.[36] 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…"

Treatment Information:

"Ablation (microwave/radiofrequency, surgical, or percutaneous ethanol injection):

- 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 ≤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, systemic therapy, or RT [radiation therapy]."

The NCCN guidelines on biliary tract cancer (v.4.2024)[37] recommend that patients with intrahepatic cholangiocarcinoma should be evaluated for potentially curative therapies such as ablation, arterially directed therapies, and RT. Specific recommendations for ablation include (category 2A recommendation):

- "All tumors should be amenable to complete ablation so that the tumor and a margin of normal tissue up to 1 cm can be treated."

- "For small single tumors <3 cm, whether recurrent or primary, thermal ablation is a reasonable alternative to surgical resection, particularly in patients with high-risk disease."
- "Options for ablation include cryoablation, radiofrequency ablation, microwave ablation, and irreversible electroporation."

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 (v2.2024) address principles of liver-directed therapy for neuroendocrine tumor metastases.[38] These guidelines support consideration of ablative therapies, including RFA or cryoablation for generally up to four lesions each smaller than 3 cm (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 (v5.2024)[39] Thermal ablation creates tumor cell death through deposition of tumoricidal heat (radiofrequency or microwave) or cold (cryoablation) in the tumor and surrounding margins. Liver Tumor Ablation. Thermal ablation can be considered alone, or in conjunction with surgery, in appropriately selected patients with small metastases that can be treated with margins. All original sites of disease need to be amenable to thermal ablation or resection. Image guided thermal ablation may be considered in selected surgical candidates or medically non-surgical candidates with small tumors that can be completely ablated with margins. (category 2A recommendations)

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

Not applicable.

### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 2.

### Table 2. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| ***Ongoing*** | | | |
| NCT06530784 | Cryoablation Combined With PD-1 Antibody and Bevacizumab for Hepatocellular Carcinoma After Progression of PD-1/L1 Antibody Treatment: a Pilot Clinical Study | 36 | May 2026 (not recruiting yet) |

| | | | |
|---|---|---|---|
| NCT06265350 | Cryoablation Combined With Cardonilizumab and Bevacizumab in Hepatocellular Carcinoma With Pulmonary Metastases: A Single-center, Prospective, Randomized Controlled Phase II Study | 80 | Jan 2027 (recruiting) |
| NCT04724226 | Cryoablation Combined With Camrelizumab and Apatinib in Advanced Hepatocellular Carcinoma (C-couple) | 34 | Aug 2024 (unknown status) |
| NCT05897268 | Cryoablation Combined With Tislelizumab Plus Lenvatinib in 1L Treatment of Advanced HCC (CASTLE-10) (CASTLE-10) | 25 | Dec 2025 (recruiting) |
| NCT05057845 | Cryoablation Combined With Tislelizumab Plus Lenvatinib as Second-line or Later Therapy in Advanced Hepatocellular Carcinoma | 25 | Sep 2024 (unknown status) |
| NCT05303038 | Cryoablation Combined With Tirelizumab and Bevacizumab in Liver Metastatic TNBC Patients Failed by Multiline Therapy (Castle06(BC)) | 15 | April 2024 (unknown status) |
| NCT05057052 | Cryoablation Combined With Sintilimab Plus Regorafenib In Previously Treated Colorectal Cancer Liver Metastasis | 25 | Sep 2024 (unknown status) |
| NCT05622825 | Valuation of the Safety and Efficacy of Combination of Cryoablation and Dendric Cell/Cytokine-induced Killers Cells Treatment for Advanced Liver Cancers | 15 | Dec 2024 (not yet recruiting) |

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

## Government Regulations

### National:

There is no national coverage determination on this topic.

### Local:

There is no local coverage determination on this topic.

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

## Related Policies

- Radioembolization for Primary and Metastatic Tumors of the Liver
- Radiofrequency Ablation of Primary or Metastatic Liver Tumors
- Transcatheter Arterial Chemoembolization of Hepatic Tumors (TACE)

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*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 11/15/24, the date the research was completed.*

**Joint BCBSM/BCN Medical Policy History**

| Policy Effective Date | BCBSM Signature Date | BCN Signature Date | Comments |
|---|---|---|---|
| 7/21/03 | 7/21/03 | 7/7/03 | Joint policy established |
| 3/1/07 | 1/3/07 | 10/23/07 | Routine maintenance; policy retired |
| 11/1/12 | 8/21/12 | 8/21/12 | Policy unretired for updates |
| 1/1/15 | 10/24/14 | 11/3/14 | Routine maintenance |
| 7/1/16 | 4/19/16 | 4/19/16 | Routine maintenance<br>Added CPT code 47383 |
| 7/1/17 | 4/18/17 | 4/18/17 | Routine maintenance |
| 11/1/17 | 8/15/17 | 8/15/17 | Routine maintenance |
| 11/1/18 | 8/21/18 | 8/21/18 | Routine maintenance |
| 11/1/19 | 8/20/19 | | Routine maintenance<br>Medicaid information deleted |
| 11/1/20 | 8/18/20 | | Routine maintenance |
| 11/1/21 | 8/17/21 | | Routine maintenance |
| 3/1/22 | 12/14/21 | | Routine maintenance<br>Ref 3,4,5,6 added |
| 3/1/23 | 12/20/22 | | Routine maintenance (jf)<br>Ref 1,4, 5 added |
| 3/1/24 | 12/19/23 | | Routine maintenance (jf)<br>Vendor Managed: NA<br>Added ref: 3, 4 |
| 3/1/25 | 12/17/24 | | Routine maintenance (jf)<br>Vendor Managed: NA<br>Added ref: 40-49<br>MPS-Removal of “The safety and effectiveness of”<br>Edits to the inclusions, exclusions and updates to the rationale and summary of evidence .<br>Title Change: Previous Title Cryosurgical Ablation of Primary or Metastatic Liver Tumors<br>New Title: Cryosurgical Ablation of Primary or Metastatic Liver Cancer |

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Next Review Date: 4th Qtr, 2025

## I. Coverage Determination:

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|---|---|
| **Commercial HMO (includes Self-Funded groups unless otherwise specified)** | Covered; criteria applies |
| **BCNA (Medicare Advantage)** | See Government Regulations section. |
| **BCN65 (Medicare Complementary)** | Coinsurance covered if primary Medicare covers the service. |

## II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.