# Cryosurgical Ablation of Primary or Metastatic Liver Tumors

**Policy #** 00220
Original Effective Date: 06/20/2007
Current Effective Date: 07/12/2021

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

*Note: Microwave Tumor Ablation is addressed separately in medical policy 00569.*

*Note: Radiofrequency Ablation of Primary or Metastatic Liver Tumors is addressed separately in medical policy 00182.*

*Note: Cryosurgery Ablation of Miscellaneous Tumors other Than Liver or Prostate Tumors or Breast Fibroadenomas is addressed separately in medical policy 00023.*

*Note: Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors is addressed separately in medical policy 00175.*

*Note: Transcatheter Arterial Chemoembolization (TACE) to Treat Primary or Metastatic Liver Malignancies is addressed separately in medical policy 00227.*

*Note: Radioembolization for Primary and Metastatic Tumors of the Liver is addressed separately in medical policy 00110.*

## Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

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

## Background/Overview

**Liver MetaStases**

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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 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, but much of the treatment-related morbidity and mortality reflect the generally poor health status of patients with advanced hepatic disease.

# FDA or Other Governmental Regulatory Approval

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

# Rationale/Source

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.

For individuals who have unresectable primary hepatocellular carcinoma amenable to locoregional therapy who receive CSA, the evidence includes a randomized controlled trial (RCT), several nonrandomized comparative studies, and multiple noncomparative studies. The relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The available RCT comparing cryoablation with radiofrequency ablation demonstrated lower rates of local tumor progression with cryoablation but no differences in survival outcomes between groups. Although this trial provided suggestive evidence that cryoablation is comparable with radiofrequency ablation, trial limitations would suggest findings need to be

replicated. Additional comparative evidence is needed to permit conclusions about the effectiveness of cryoablation compared with other locoregional therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

For individuals who have unresectable liver metastases from colorectal cancer amenable to locoregional therapy who have CSA, the evidence includes an RCT, several nonrandomized comparative and noncomparative studies, and systematic reviews of these studies. The relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The available RCT comparing surgical resection with cryoablation was judged at high-risk of bias. Some nonrandomized comparative studies have reported improved survival outcomes for patients managed with cryotherapy compared with those managed with resection alone; however, these studies were subject to bias in the selection of patients for treatments. Additional controlled studies are needed to permit conclusions about the effectiveness of cryoablation compared with other locoregional therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

# Supplemental Information

### 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 one of several ablative techniques that could be used in these patients.

**Practice Guidelines and Position Statements**
The National Comprehensive Cancer Network (NCCN) indicates that ablative techniques may be used in the treatment of certain hepatic tumors. The NCCN guidelines on hepatobiliary cancer (v.4.2020) 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. 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 ≤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."

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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.2.2020) address the use of hepatic-directed therapies for patients with unresectable hepatic-predominant progressive metastatic neuroendocrine. These guidelines support consideration of ablative therapies such as RFA or cryoablation if near-complete tumor burden can be achieved (category 2B recommendation).

The NCCN guidelines on the treatment of colon cancer with liver metastases (v.4.2020) 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).

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

**Medicare National Coverage**
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**
A search of ClinicalTrials.gov in July 2020 did not identify any ongoing or unpublished trials that would likely influence this review.

# References


1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, “Cryosurgical Ablation of Primary or Metastatic Liver Tumors”, 7.01.75, 10:2020.
2. Li Z, Fu Y, Li Q, et al. Cryoablation plus chemotherapy in colorectal cancer patients with liver metastases. Tumour Biol. Nov 2014;35(11):10841-10848. PMID 25081377.
3. Huang C, Zhuang W, Feng H, et al. Analysis of therapeutic effectiveness and prognostic factor on argon-helium cryoablation combined with transcatheter arterial chemoembolization for the

treatment of advanced hepatocellular carcinoma. J Cancer Res Ther. Dec 2016;12(Supplement):C148-c152. PMID 28230008.
4. 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):317-322; discussion 322-313. PMID 12716090.
5. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Cryosurgical Ablation of Unresectable Hepatic Tumors. TEC Assessments. 2000;Volume 15:Tab 14.
6. 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):1579-1590. PMID 25284802.
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):1294-1300. 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):632-638. 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):1332-1339; 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. Dec 21 2012;19(6):674-684. 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. Apr 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):45-48. 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. Sep 26 2009;26(7):839-848. 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):689-692. PMID 11376398.
16. Gurusamy KS, Ramamoorthy R, Sharma D, et al. Liver resection versus other treatments for neuroendocrine tumours 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):439-445. 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):954-962. 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(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):e252-265. 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):1161-1169. 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):2078-2087. 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):1152-1159. 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):1276-1283. 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):507-520. 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):1087-1092. 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):1430-1436. PMID 18322961.
31. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers. Version 2.2018. https://www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf.
32. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors. Version 2.2018. https://www.nccn.org/professionals/physician_gls/PDF/neuroendocrine.pdf. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 2.2018. https://www.nccn.org/professionals/physician_gls/PDF/colon.pdf.

# Policy History

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|---|---|
| 06/13/2007 | Medical Director review |
| 06/20/2007 | Medical Policy Committee approval |
| 06/04/2009 | Medical Director review |
| 06/17/2009 | Medical Policy Committee approval |
| 06/03/2010 | Medical Policy Committee approval. |
| 06/16/2010 | Medical Policy Implementation Committee approval. No change to coverage. |
| 06/02/2011 | Medical Policy Committee approval. |
| 06/15/2011 | Medical Policy Implementation Committee approval. No change to coverage. |
| 06/14/2012 | Medical Policy Committee review |
| 06/20/2012 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 06/06/2013 | Medical Policy Committee review |

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| 06/25/2013 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 06/05/2014 | Medical Policy Committee review |
| 06/18/2014 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 06/04/2015 | Medical Policy Committee review |
| 06/20/2015 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 08/03/2015 | Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed. |
| 06/02/2016 | Medical Policy Committee review |
| 06/20/2016 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |
| 06/01/2017 | Medical Policy Committee review |
| 06/21/2017 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 06/07/2018 | Medical Policy Committee review |
| 06/20/2018 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 06/06/2019 | Medical Policy Committee review |
| 06/19/2019 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 06/04/2020 | Medical Policy Committee review |
| 06/10/2020 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 06/03/2021 | Medical Policy Committee review |
| 06/09/2021 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |

Next Scheduled Review Date: 06/2022

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# Coding

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

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

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into

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

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