

Protocol

Cryosurgical Ablation of Primary or Metastatic Liver Tumors

(70175)

Medical Benefit		Effective Date: 07/01/10	Next Review Date: 01/21
Preauthorization	No	Review Dates: 02/07, 02/08, 01/09, 01/10, 01/11, 01/12, 01/13, 01/14, 01/15, 01/16, 01/17, 01/18, 01/19, 01/20	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With unresectable primary hepatocellular carcinoma amenable to locoregional therapy	Interventions of interest are: • Cryosurgical ablation	Comparators of interest are: • Radiofrequency ablation • Microwave tumor ablation • Locoregional ablation other than radiofrequency ablation	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity
Individuals: • With unresectable liver metastases from neuroendocrine tumors amenable to locoregional therapy	Interventions of interest are: • Cryosurgical ablation	Comparators of interest are: • Radiofrequency ablation • Microwave tumor ablation • Locoregional ablation other than radiofrequency ablation	Relevant outcomes include: • Overall survival • Disease-specific survival • Symptoms • Treatment-related mortality • Treatment-related morbidity
Individuals: • With unresectable liver metastases from colorectal cancer amenable to locoregional therapy	Interventions of interest are: • Cryosurgical ablation	Comparators of interest are: • Radiofrequency ablation • Microwave tumor ablation • Locoregional ablation other than radiofrequency ablation	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity

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.

SUMMARY OF EVIDENCE

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. Relevant outcomes are overall survival, disease-specific survival,

and treatment-related mortality and morbidity. The available RCT comparing cryoablation with radiofrequency ablation demonstrated lower rates of local tumor progression with cryoablation but no differences in survival outcomes between groups. Although this trial provided suggestive evidence that cryoablation is comparable with radiofrequency ablation, trial limitations would suggest findings need to be replicated. Additional comparative evidence is needed to permit conclusions about the effectiveness of cryoablation compared with other locoregional therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

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

POLICY

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

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 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.

Recent studies, including a small randomized controlled trial and case series, have reported on experience with cryosurgical and other ablative methods used in combination with subtotal resection and/or procedures such as transarterial chemoembolization.^{1,2}

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,³ 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 by the U.S. Food and Drug Administration. 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. Food and Drug Administration product code: GEH.

RELATED PROTOCOLS

Cryosurgical Ablation of Miscellaneous Solid Tumors Other Than Liver, Prostate, or Dermatologic Tumors

Microwave Tumor Ablation

Radioembolization for Primary and Metastatic Tumors of the Liver

Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors

Radiofrequency Ablation of Primary or Metastatic Liver Tumors

Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary

Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. 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.
2. 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.
3. 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.
4. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Cryosurgical Ablation of Unresectable Hepatic Tumors. TEC Assessments. 2000;Volume 15:Tab 14.
5. 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.
6. 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.
7. 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.
8. Awad T, Thorlund K, Gluud C. Cryotherapy for hepatocellular carcinoma. *Cochrane Database Syst Rev.* Oct 07 2009(4):CD007611. PMID 19821432.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.

15. 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.
16. 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.
17. 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.
18. 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.
19. Korpan NN. Hepatic cryosurgery for liver metastases. Long-term follow-up. *Ann Surg*. Feb 1997;225(2):193-201. PMID 9065296.
20. Bala MM, Riemsma RP, Wolff R, et al. Cryotherapy for liver metastases. *Cochrane Database Syst Rev*. Jun 05 2013;6(6):CD009058. PMID 23740609.
21. 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.
22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.
30. 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. Accessed June 8, 2018.
31. 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. Accessed June 8, 2018.
32. 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. Accessed June 8, 2018.