



Liver Cryoablation Bibliography

Hepatic Cryoablation Review Papers

(Articles that Highlight Cryoablation as procedure but do not report out patient outcome data)

Hinshaw JL, Lee FT Jr., Cryoablation for liver cancer. *Tech Vasc Interv Radiol*. 2007 Mar;10(1):47-57.

- Management of primary liver cancer (hepatocellular carcinoma [HCC]) and metastatic cancer are common and have become progressively complex as available treatment options have improved and propagated.
 - One option - image-guided tumor ablation.
 - Radiofrequency ablation has been the most widely studied and utilized ablation modality.
 - However, cryoablation has several relative advantages (most significantly, the ability to produce larger and more precise zones of ablation) over RF ablation and the other heat-based ablation modalities.
 - This manuscript is designed to be an up to date, practical and thorough review of the indications for, techniques of, and patient management issues associated with hepatic cryoablation.
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Siperstein AE, Berber E Cryoablation, percutaneous alcohol injection, and radiofrequency ablation for treatment of neuroendocrine liver metastases. *World J Surg*. 2001 Jun;25(6):693-6.

- Neuroendocrine liver metastases are associated with slow clinical progression, prolonged patient survival, and symptoms of hormone oversecretion and most of the patients are not candidates for resection which is gold standard
 - 5-year survival of patients with neuroendocrine liver metastases is 11% to 40%.
 - Cryotherapy, percutaneous alcohol injection, and radiofrequency thermal ablation are among the alternative regional treatment options available for these patients.
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Cha C, Lee FT, Rikkers LF, *et al*: Rationale for the combination of cryoablation with surgical resection of hepatic tumors. *Journal of Gastrointestinal Surgery* 5: 206-213, 2001.

- Only 5% to 10% of metastatic and primary liver tumors are amenable to surgical resection.
- Hepatic cryoablation has increased the number of patients who are suitable for curative treatment.
- Study aim - evaluate survival and intrahepatic recurrence in patients treated with cryoablation and resection.
- Thirty-eight surgically unresectable patients underwent cryoablative procedures - Twenty patients underwent cryoablation alone, and 18 patients were treated with a combination of resection and cryoablation, with a minimum of 18 months' follow-up.
- Major complications included bleeding in three patients and acute renal failure, transient liver insufficiency, and postoperative pneumonia in one patient each. Two patients (5%) died during the early postoperative interval;
- Median follow-up was 28 months (range 18 to 51 months).

- Overall survival 82%, 65%, and 54% at 12, 24, and 48 months, respectively.
 - Forty-eight-month survival was not significantly different between those patients undergoing cryoablation alone (64%) and those treated with a combination of resection and cryoablation (42%).
 - Disease-free survival at 45 months was 36% for patients undergoing cryoablation plus resection compared to 25% for those undergoing cryoablation alone. Local recurrences were detected at five cryosurgical sites, for a rate of 12% overall (5 of 42), 11% (2 of 18) for patients in the cryoablation plus resection group, and 12% (3 of 24) for those in the cryoablation alone group. For patients with colorectal metastases, survival was 70% at 30 months compared to 33% for hepatocellular cancer and 66% for other types of tumors.
 - Cryoablation of hepatic tumors is a safe and effective treatment for some patients not amenable to resection. The combination of cryoablation and resection results in survival comparable to that achieved with cryoablation alone.
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Dodd GD, Soulen MC, Kane RA, *et al*: Minimally invasive treatment of malignant hepatic tumors: At the threshold of a major breakthrough. *RadioGraphics* 20: 9-27, 2000.

- Review of potentially curative options for non surgical hepatic cancer patients – these include 6 treatment options
 - States Cryoablation is the oldest of the local thermal ablation techniques
 - Liver cancer patients have very poor prognosis and cryoablation may provide cure for some – patient selection: unresectable primary hepatic cancer or secondary liver involvement from colorectal and is generally limited to those with four or fewer lesions.
 - Follow-up post cryo is with CT 6 months and 12 months. Lesions appear on CT images as an avascular low-attenuation lesion that slowly decrease in size overtime.
 - Follow-up is 90% for 1 year, 40% for 3 years and 20% for 5 years. Mean overall survival for at he entire group of 107 patiетns is 38 months.
 - Major complications of bleeding were in less than 20%; no tumor seeding reported. Local failure occurred in 13%.
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McCarthy TM, Kuhn JA: Cryotherapy for liver tumors. *Oncology*: 979-993, 1998.

- Review of the potential of cryoablation
 - Only 10% of newly diagnosed patients with primary or metastatic tumors are surgical candidates. 5 year survival for Hepatic resection for primary and mets liver tumors range from 11% to 39%.
 - Cryoablation is treatment option
 - Hepatocytes, bile duct epithelial cells and connective tissue cells demonstrate resiliency to temperatures as low as -10 C but are completely destroyed at -40C. Larger blood vessels seem to be resistant to temperatures of this extreme.
 - Experimental evidence suggests that complete per-vascular and intrapersonal tissue necrosis results following hepatic cryoablation near large vessels.
 - Patient Selection –
 - primary or mets liver tumor
 - absence of extrahepatic mets
 - surgically unrespectable disease and or
 - tumor involving surgically resected margins.
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Gage AA, Baust JG. Cryosurgery for tumors. *J Am Coll Surg*. 2007 Aug;205(2):342-56. Epub 2007 Jun 18.

Kohli V and Clavien PA. Cryoablation of liver tumors. British Journal of Surgery 85: 1171-1172, 1998.

Sarantou T, Bilchik A, and Ramming KP. Complications of hepatic cryosurgery. Seminars in Surgical Oncology 14: 156-162, 1998. □

- Cryosurgery a consideration for patients whose hepatic lesions are not amenable to surgical resection
 - Cryosurgery has the advantage of being a focal technique that spares much more noncancerous liver tissue than surgical resection due to the size of the iceball created during the procedure can be carefully controlled
 - Major complications of hepatic cryosurgery are the same as those of hepatic resection: hemorrhage, pleural effusion, bile leak fistula, perihepatic abscess, and hepatic failure.
 - Risk of coagulopathy when large tumors are frozen using multiple freeze-thaw cycles.
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Bilchik AJ, Sarantou T, Foshag LJ, Giuliano AE, Ramming KP. Cryosurgical palliation of metastatic neuroendocrine tumors resistant to conventional therapy. Surgery. 1997 Dec;122(6):1040-7; discussion 1047-8.

- Hepatic cryosurgery is a well-recognized modality for hepatic colon metastases
 - Potential use for refractory neuroendocrine tumors causing progressive symptoms.
 - 19 patients (with islet cell, 7; carcinoid, 8; vasoactive intestinal peptide, 1; gastrinoma, 3) underwent cryosurgery with ultrasonography.
 - Lesions ranged from 1 to 16 (median, 8), and their diameters ranged from 2 to 15 cm with an average of 4 cm.
 - RESULTS: The reduction in tumor markers reached 90% (5-hydroxyindoleacetic acid), 80% (vasoactive intestinal peptide), 90% (gastrin), 90% (pancreatic polypeptide), and 80% (serotonin).
 - At a median follow-up of 17 months, the metastases had progressed in 11 patients (two underwent a second cryosurgical procedure that eliminated symptoms) and five had died.
 - CONCLUSIONS: Cryosurgery dramatically relieved symptoms with significant reduction in tumor markers. The reduced tumor burden may explain the subsequent response to systemic therapy. Cryosurgery is a useful adjuvant in symptomatic patients with refractory hepatic neuroendocrine metastases.
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Sotomayor R, and Ravikumar TS: Cryosurgery in the treatment of hepatic tumors. Cancer control: JMCC 5: 414-420, 1996.

- Cryoablation of hepatic tumors in non surgical candidates
- This is an early study but concludes that long term survival of over 20 % may be attainable

Surgical Hepatic Cryoablation Clinical Results

Paganini AM, Rotundo A, Barchetti L, Lezoche E., Cryosurgical ablation of hepatic colorectal metastases. Surg Oncol. 2007 Dec;16 Suppl 1:S137-40

- Only 15 to 25% of patients with hepatic colorectal mets are eligible for hepatic resection.
- Cryosurgical ablation (CSA) option

- Sixty-four patients (35 males, 29 females, mean age 58.8 years, range 30-79 years) with hepatic colorectal metastases underwent CSA, under laparoscopic control (15 cases) or with open surgery (49 cases)
- Intraoperative bleeding occurred in 32 out of 49 patients in the open group and only in 2 patients in the laparoscopic group.
- Minor morbidity that resolved with conservative treatment was 54.8% in the open group and 53.3% in the laparoscopic group.
- Major morbidity occurred in 11 cases (26.2%) in the open group and in 1 case (6.7%) in the laparoscopic group.
- Mortality occurred in two patients, both in the open group, from renal insufficiency in one case and from liver failure in the other case.
- Mean hospital stay was 16.7 days in the open group (range 8-72 days) and 10.6 days in the laparoscopic group (range 3-18 days).
- Mean follow-up of 87.1 months (range 52.2-125.2 months), selected patients undergoing laparoscopic CSA had an overall survival rate of 66.7% (10 patients), with 30% of patients (3) who are disease-free.
- Median survival was 94.2 months. Recurrence was observed in seven patients. None of the intrahepatic recurrences was at the cryoablation site.
- In selected patients, laparoscopic CSA is associated with survival rates which are similar to those after hepatic resection. In patients with a larger tumor burden, CSA offers a curative treatment to patients with otherwise a dismal prognosis and it improves survival as compared to patients receiving chemotherapy alone. However, the procedure is associated with substantial morbidity, particularly bleeding, and therefore careful patient selection is recommended.

Kerkar S, Carlin AM, Sohn RL, Steffes C, Tyburski J, Littrup P, Weaver D Long-term follow up and prognostic factors for cryotherapy of malignant liver tumors Surgery 136:770-9, 2004

- 300 tumors treated in 98 patients who were deemed non-surgical candidates
- Median survival: 33 months
- Three year survival: 48%, five year survival: 28%
- Conclusion: "cryoablation is an important option for a wide range of unresectable malignant hepatic tumors and provides the potential for long term survival"

Seifert JK, Junginger T. Cryotherapy for liver tumors: current status, perspectives, clinical results, and review of literature Technol Cancer Res Treat. 3:151-63, 2004

- Review of the cryoablation literature and report of personal experience
- 77 patients with non-resectable liver tumors were treated
- 40 patients had cryo only – 37 had cryo and resection
- Morbidity – 22% and mortality 1.3%
- Median survival was 28 months
- 16 of 76 patients had complications (bleeding, esophageal bleeding, fistula, wound infection, pleural effusion, pneumonia.
- Local recurrent at the cryosite in 13 of 65 patients – 20%
- Survival less than resection, partly due to patient selection and local site re-occurrence
- Three year survival: 39%, five year survival: 26%
- Median survival of patients with liver mets with no therapy is less than one year.
- 5 year survival with liver resections is 20 to 50%. But only feasible for a small portion of patients.
- In the last two decades cryotherapy of liver tumors has evolved from an experimental technique to a clinical widely applied method.
- Discusses cryo shock – defined as multi-organ failure, severe coagulopathy and DIC

Cha C, Lee FT, Rikkers LF, *et al*: Rationale for the combination of cryoablation with surgical resection of hepatic tumors. *Journal of Gastrointestinal Surgery* 5: 206-213, 2001.

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Wong WS, Patel SC, Cruz FS, *et al*: Cryosurgery as a treatment for advanced stage hepatocellular carcinoma: results, complications, and alcohol ablation. *Cancer* 82: 1268-1278, 1998.

- 12 patient trial of cryoablation for non-resectable liver tumors
 - 9 of 12 patients had no evidence of residual cancer following cryoablation
 - 1 year survival: 50 %, 2 year survival: 30 %
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Onik GM, Atkinson D, Zemel R, Weaver ML. Cryosurgery of liver cancer. *Semin Surg Oncol.* 9:309-17, 1993 (Abstract)

- 57 patients with unresectable tumors were treated
 - 42% receive cryo and resection
 - At a mean follow-up of 21 months 27 % had no evidence of disease
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Onik G, Rubinsky B, Zemel R, *et al*: Ultrasound-guided hepatic cryosurgery in the treatment of metastatic colon carcinoma: preliminary results. *Cancer* 67: 901-907, 1991.

- 18 patients with non-resectable tumors were treated, mean follow-up 28.8 months
 - 4 patients were in complete remission (based on CT scans and carcinoembryonic antigen levels)
 - Median survival of the remaining 14: 21.4 months
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Ravikumar TS, Steele G Jr, Kane R, *et al*: Experimental and clinical observations on hepatic cryosurgery for colorectal metastases. *Cancer Res* 51: 6323-6327, 1991.

- 24 patient study, median follow-up 24 months
 - 29 % are disease free & 33.5% are alive with recurrent tumors
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Lee FT, Littrup PJ, and Chosy SG. Minimally invasive alternatives to traditional operative hepatic cryoablation: works in progress. Surgical Technology International VII, 1998.
