

# Laparoscopic Cryoablation of Hepatic Metastases

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**Objective:** To evaluate the feasibility of laparoscopic cryoablation for the management of hepatic metastases.

**Design:** Retrospective review.

**Setting:** Tertiary referral center.

**Patients:** Nine patients were evaluated by laparoscopy for planned laparoscopic cryoablation of hepatic metastases at The Cleveland Clinic Foundation, Cleveland, Ohio, from April 1996 to May 1997.

**Results:** Laparoscopic exploration revealed diffuse extrahepatic disease not identified by preoperative studies in 2 patients. The remaining 7 patients underwent 9 cryotherapy sessions. During 4 of the cryotherapy sessions, ultrasonography demonstrated unrecognized additional treatable hepatic lesions. An average of 3 lesions (range, 2-5) were treated. Operative time averaged 3.5 hours with a mean intraoperative blood loss of 235 mL. One patient had significant intraoperative hemorrhage

requiring conversion to open hepatic resection for bleeding control. Eight of the 9 patients tolerated normal diets and ambulated independently on the first postoperative day. Following cryotherapy, 4 of the patients developed fever without an infectious source. One patient developed a postoperative bile leak requiring percutaneous biliary stenting. Postoperative hospital stay averaged 4.5 days (median, 4 days; range, 2-14 days). At a mean follow-up of 9 months, 4 of the 7 patients treated are alive without evidence of disease, 2 are alive with disease, and 1 patient with a pancreatic primary tumor has died of disease.

**Conclusions:** Laparoscopy with laparoscopic ultrasonography is a useful tool in evaluating patients with hepatic metastases. Laparoscopic cryoablation is feasible and may result in lower postoperative morbidity in patients receiving aggressive treatment for inoperable hepatic metastases.

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**T**HE LIVER is a common site for metastatic cancer. After the regional lymph nodes, the liver is the next most common site of metastasis from organs drained by the portal venous system. The United States reports approximately 150 000 new cases of colorectal cancer per year. Up to 25% of the cases have liver metastases at the time of presentation and 50% develop liver metastases within 5 years. Therefore, 75 000 patients per year are at risk of developing liver metastases from colorectal cancer. Twenty percent of patients with liver metastases (15 000 cases per year) have disease limited to this organ. Unfortunately, only 25% of these patients are candidates for surgical resection. The remaining 11 000 patients with liver-only metastatic colorectal cancer per year are the group of patients for whom interstitial therapies such as cryosurgical ablation may potentially be curative or provide improved survival.<sup>1-3</sup>

Cryotherapy has been used to treat a wide variety of disorders, including can-

cer. The concept of tissue destruction by freezing has been in existence for more than 100 years. In situ destruction was initially used to treat dermatologic cancers. In the 1960s, development of a liquid nitrogen delivery system led to the expansion of uses for cryosurgery. Cryoablation is presently used to treat tumors in the brain, oropharynx, lung, breast, uterus, prostate, and liver.<sup>4</sup>

Open cryosurgical hepatic procedures have been well described in the North American, Australian, and Asian literature, and their role is established in highly selected patients.<sup>4-9</sup> Most patients undergoing hepatic cryotherapy have liver metastases from colorectal carcinoma or primary hepatocellular carcinoma. Cryoablation involves insertion of a cryoprobe through liver parenchyma into a hepatic neoplasm. Destruction of the lesion occurs as it is frozen to  $-190^{\circ}\text{C}$  and subsequently thawed. Detection and destruction of the lesions are monitored with intraoperative ultrasonography. Recently, the development of laparoscopic ultrasonographic and cryosurgical probes has en-

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## MATERIALS AND METHODS

### EQUIPMENT

Equipment needed to perform laparoscopic cryoablation of liver tumors includes standard laparoscopic equipment, a liquid nitrogen delivery system, cryotherapy probes, and a laparoscopic ultrasonographic probe. The liquid nitrogen delivery system (CMS AccuProbe 450 System, CryoMedical Sciences Inc, Rockville, Md) uses a closed-circuit, double-dewar system. A computer monitors, displays, and controls the functions of the delivery unit. The computer also graphically demonstrates flow activity through cryoprobe channels, probe placement, and probe temperatures plotted against time. This information is continually updated throughout the freeze-thaw cycles of the cryotherapy session. Cryotherapy probes (CryoMedical Sciences Inc) for laparoscopic use are available in a variety of lengths and sizes. Each probe produces a spherical ice ball whose size depends on the diameter of the probe. The 4.8-mm  $\times$  40-cm cryoprobe provides the adequate length and ice ball size required for most laparoscopic uses.

Laparoscopic ultrasonography is essential to perform any cryosurgical procedure. It is used to identify and characterize the size, shape, and location of hepatic lesions. Ultrasonography is also essential for proper placement of the cryotherapy probe and monitoring the development and progression of the ice ball. An example of a probe is the Laparoscopic Ultrasound Transducer type 8555 ultrasound unit (B&K Medical Systems Inc, Marlborough, Mass). It has a 60° convex array capable of transducing at 5 to 7.5 MHz and fits through a 10- to 11-mm laparoscopic port. Doppler color flow is useful for distinguishing biliary structures from blood vessels and better characterizes hepatic lesions.

### OPERATIVE TECHNIQUE

Patients undergoing cryotherapy of hepatic lesions were prepared similarly to patients undergoing hepatic resections. Measures to prevent systemic hypothermia, such as warming blankets and warmed intravenous fluids, are recommended.<sup>10</sup> Patient positioning was dependent on the location of the hepatic tumors to be treated. The supine position was most often adequate. Patients with lesions in the posterior sector of the right lobe of the liver (segments VI and VII) were placed in an oblique position with the right side elevated up to 45° and the right arm elevated and across the chest. This

position provided added exposure to the flank and facilitated placement of cryotherapy probes posteriorly.

All patients in this study had had previous abdominal surgery. Because adherence of abdominal viscera to the anterior abdominal wall was a concern, the open method of initial port placement using a blunt-tipped trochar was preferred. A minimum of 3 ports was required. However, to perform an adequate lysis of adhesions, additional ports were often needed to clear the anterior abdominal wall. The liver was freed from adherent structures on its inferior surface as well as from adhesions to the diaphragm. The falciform and round ligaments may or may not be divided depending on the exposure required.

The abdominal cavity was explored for the presence of extrahepatic disease not identified by preoperative radiographic imaging. Suspicious tissue was excised and sent for immediate pathologic examination. Extrahepatic disease precluded local treatment for the hepatic lesions. The liver was then evaluated by laparoscopic ultrasonography. All liver segments, major portal tracts, hepatic veins, and inferior vena cava were visualized. All hepatic lesions were characterized with reference to size, shape, and location relative to hepatic and vascular structures.

The capsule of the liver overlying the tumor was scored using electrocautery. The cryotherapy probe was inserted through the capsule under ultrasonographic guidance into the tumor. The tip of the cryotherapy probe was positioned at the distal or deep edge of the tumor. When proper placement of the probe was confirmed, the freezing process was begun (**Figure 1**). Tissue temperature was continuously monitored through the cryotherapy probe. Progressive development of the ice ball was monitored by ultrasonography (**Figure 2**). Freezing was completed when the tissue temperature reached  $-190^{\circ}\text{C}$  and the ice ball had obtained 1-cm margins beyond the tumor edge or reached adjacent hepatic or vascular structures (**Figure 3**). Thawing follows the completed freeze phase. This is a passive process that is affected by ice ball size, location, and regional blood flow. When the temperature reached  $-20^{\circ}\text{C}$ , the cryotherapy probe was removed. The exit site of the cryosurgical probe was inspected for bleeding and bile leakage. Hemostatic agents, electrocautery, or suturing of the hepatic capsule was sometimes required.

One or more closed suction drains were placed at the cryotherapy probe entry sites. These drains were used to monitor the patient for ongoing bleeding and bile leakage. If there was no evidence of these complications, the drains were removed by 48 hours postoperatively.

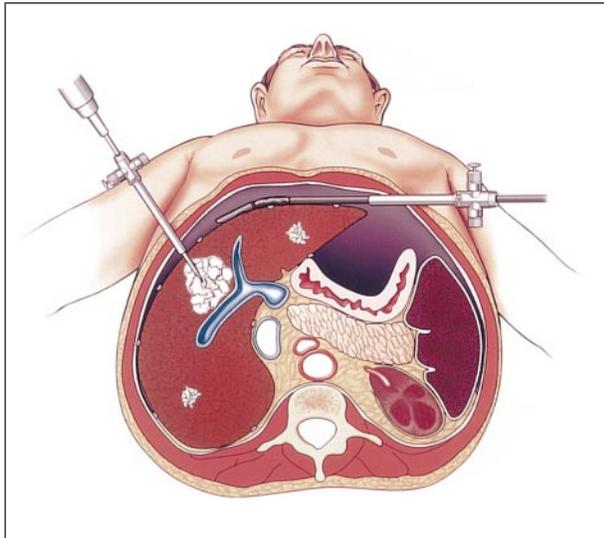
abled this procedure to be performed completely laparoscopically.<sup>9</sup> Laparoscopic cryoablation of hepatic tumors is a developing technology within the realm of minimally invasive surgery. Continued studies are needed to prove the efficacy of cryoablation and to better select a patient group that may benefit from this modality of treatment.

### RESULTS

Nine patients were evaluated by laparoscopy and laparoscopic ultrasonography for planned laparoscopic cryoablation for hepatic metastases. Pathologic abnormalities in these patients included metastatic disease from colorectal cancer in 6 patients; the remaining patients had hepatic

metastases from pancreatic, carcinoid, and pelvic sarcoma primary lesions. The indication for laparoscopic cryoablation in these patients was unresectable disease in 7 patients, significant comorbid cardiovascular disease precluding hepatic resection in 1 patient, and a request for cryoablation despite advice to have surgical resection in 1 patient.

Laparoscopy and laparoscopic ultrasonography proved to be useful in this patient group. Previously unrecognized extrahepatic disease was identified in 2 patients at the time of laparoscopy. These patients did not undergo any further surgical treatment for their disease. The remaining 7 patients underwent 9 laparoscopic cryoablation sessions. Of note, 3 of these patients had had previous open hepatic resections for metastatic disease. Lapa-



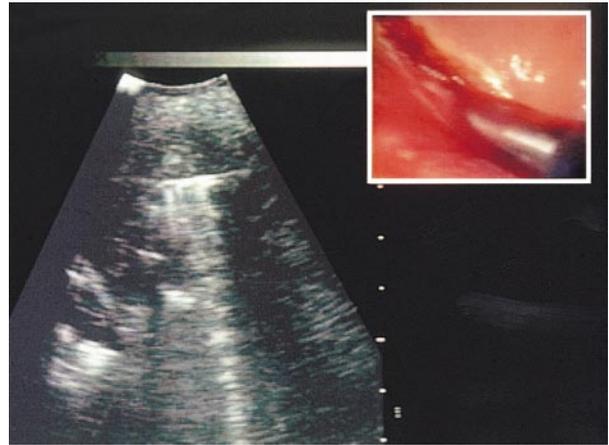
**Figure 1.** Cross-sectional view demonstrating the technique of laparoscopic hepatic cryosurgery. The ultrasonographic probe is used to identify lesions, follow placement of the cryoprobe, and monitor destruction of the tumor.

roscopic ultrasonography identified an average of 1.3 (range, 1-3) additional treatable hepatic lesions during 4 of the 9 cryoablation sessions. The mean number of lesions treated per session was 3 (range, 1-5), with an average lesion size of 3.4 cm (range, 1-10 cm). Operative time averaged 3.5 hours. A significant portion of these procedures was spent lysing adhesions and mobilizing the liver.

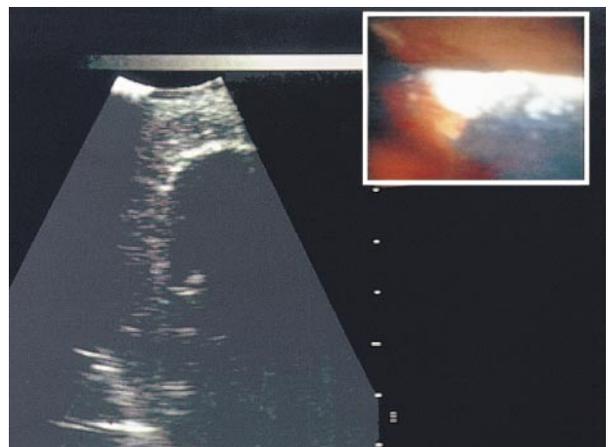
Most procedures proceeded uneventfully with a mean estimated blood loss of 235 mL (range, <50-1000 mL). Significant difficulties were encountered during a laparoscopic cryotherapy session of a 10-cm metastatic sarcoma of the left lateral segments of the liver. The patient had a second 10-cm lesion in the right lobe. Bleeding occurred as the cryotherapy probe was removed. An emergent open left lateral segmentectomy was performed to control the hemorrhage. The patient subsequently recovered uneventfully and the right lobe lesion was treated at a later date by chemoembolization. None of the other patients had significant bleeding, coagulopathy, or systemic hypothermia during laparoscopic cryoablation.

The postoperative recovery following laparoscopic cryotherapy is remarkable. Eight of the 9 patients were tolerating a regular diet and ambulating independently on the first postoperative day. Fever without an identifiable infectious cause was noted in 4 patients. One patient developed a postoperative bile leak. This patient had cryoablation of a large lesion at the portal vein bifurcation. Preoperative imaging studies revealed segmental dilation of the biliary tree superficial to the lesion. The cryotherapy probe was inserted through this portion of the liver, resulting in the leak. He was successfully treated with a radiographically placed internal-external biliary stent. Mean time to hospital discharge for the group was 4.5 days (range, 2-14 days).

Follow-up consisted of serial evaluations of tumor markers (if evaluated preoperatively) and abdominal computed tomographic or magnetic resonance imaging scans every 3 to 6 months.<sup>11</sup> Long-term follow-up is limited; however, at a mean follow-up of 9 months, 4 patients are alive without evidence of disease, 2 are alive with disease, and 1 pa-



**Figure 2.** Intraoperative image demonstrating the picture-in-picture mode. The smaller image demonstrates the laparoscopic view of the cryosurgical probe passing into the liver substance. The laparoscopic ultrasonographic image shows the echogenic cryotherapy probe parallel within the center of the tumor.



**Figure 3.** The laparoscopic view reveals frost formation on the cryotherapy probe. Ultrasonography monitors the development of the ice ball within the tumor.

tient with a pancreatic primary tumor is dead of disease at 12 months following cryotherapy. The 2 patients excluded because of extrahepatic tumors are dead of disease.

#### COMMENT

Cryotherapy for ablation of hepatic tumors has been in use since the 1980s.<sup>12</sup> Destruction of tissue by freezing occurs by several mechanisms that are dependent on the rate of freezing. These include protein denaturation, osmosis-driven shifts of intracellular and extracellular water, membrane destabilization, cellular rupture, and tissue ischemia.<sup>13,14</sup> Approximately 10% of cells remain viable following 1 freeze-thaw cycle. When 2 or more cycles are used, 100% of the cells are destroyed. These values have yet to be confirmed for human hepatic neoplasms in vivo. Because tumor cells are more resistant to dehydration and retain intracellular water, a rapid freeze-slow thaw cycle may be more efficacious for killing tumor cells.<sup>15,16</sup>

Approximately 400 patients have undergone cryosurgical ablation of hepatic lesions to date. In North America most of these patients have had metastatic dis-

ease from colorectal cancer.<sup>5,6</sup> The Asian experience with hepatic cryosurgery is more extensive for the treatment of hepatocellular carcinoma.<sup>17</sup> Although a moderate amount of outcome data is being collected retrospectively, to our knowledge there is only 1 published controlled trial evaluating cryotherapy for liver tumors.<sup>18</sup>

The operative technique for open cryosurgical ablation has been well described.<sup>19,20</sup> Unlike the laparoscopic approach, the open approach requires exposure of the liver through an extended right or bilateral subcostal incision. The liver is fully mobilized and is evaluated by inspection, palpation, and real-time intraoperative ultrasonography.<sup>21</sup> The lesions to be treated are identified and ablated. Cryoprobes have also been used to freeze hepatic lesions to facilitate their removal.<sup>22</sup> Postoperative hospitalization averages 1 week. Procedure-related complications are infrequent and include death (secondary to hepatic failure), fever, thrombocytopenia, bile leak, hepatic abscess, and subphrenic abscess.<sup>4,23,24</sup>

Several centers worldwide are performing cryotherapy of hepatic tumors. The role of cryoablation of hepatic metastases continues to be evaluated in clinical practice. Total numbers of patients from each center and time of follow-up is limited in current published data. Furthermore, several reports do not break down survival outcomes according to pathologic features of the lesions, obscuring survival results. Results from available data in patients with metastatic colorectal carcinoma suggest an improvement in survival.<sup>6,25,26</sup> Historically, patients with multicentric unilobar and bilobar involvement of hepatic metastases have a median survival of 5 to 15 months, with no long-term survivors if untreated.<sup>3</sup> Cryoablation in patients with this degree of disease offers an 18- to 36-month median survival time and the possibility of 50% and 24% survival rates at 2 and 5 years, respectively. The higher survival rates were seen in patients with no demonstrable residual disease following cryosurgical ablation.<sup>27</sup> At 2 years, survival rates range from 50% to 80%, with disease-free survival at 28% to 50%. For patients with residual disease following cryosurgical ablation, median survival averages 24 months with no 4-year survivors. Long-term follow-up is reported in only a small number of patients with 5-year survival estimated at 24%, with a range of 0% to 40%.<sup>4,5,18,25,27</sup> Results of cryoablation of primary hepatocellular carcinoma also seem to be favorable when compared with the historical results of other treatment modalities.<sup>17</sup> As experience and patient numbers expand, long-term survival will be able to be assessed more accurately.

In recent years there has been an explosion of technology in laparoscopic surgery. Laparoscopic approaches to a variety of hepatobiliary disorders are becoming commonplace. Hepatic procedures that have traditionally been performed only by open surgery are now beginning to be performed laparoscopically. These include hepatic resection, marsupialization of hepatic cysts, pyogenic abscesses, and cryosurgical ablation of hepatic tumors.<sup>9,19,28-30</sup> The laparoscopic approach to cryosurgery seems to be feasible, and may achieve similar operative results to open cryosurgery with the possibility of lower morbidity.

Presently, laparoscopic cryoablation for hepatic tumors can be offered to patients in selected clinical con-

ditions. Indications for cryoablation include patients with unresectable secondary or primary lesions of the liver, comorbid medical conditions precluding hepatic resection, or limited hepatic reserve. Patients with recurrent metastatic or primary tumors to the liver may also be good candidates for cryoablative treatment.<sup>31</sup> As demonstrated in this study, previous abdominal surgery or partial hepatectomy is not a contraindication to the laparoscopic approach.

Types of tumors that are acceptably treated by hepatic cryoablation include hepatocellular, colorectal, carcinoid, neuroendocrine, sarcoma, Wilm, renal cell, and adrenocortical tumors.<sup>6,17,32,33</sup> There may be a role in treating unresectable intrahepatic cholangiocarcinoma, locally invasive gallbladder cancer, or a deeply located hepatic adenoma. Patients with metastases from melanoma, breast, esophagus, lung, stomach, pancreas, and gynecologic organs have historically not demonstrated improved survival following hepatic resection.<sup>4,34</sup> The value of hepatic cryosurgical ablation for metastases from these lesions remains undetermined. Further studies with larger patient groups and longer follow-up times are needed to better define survival outcomes and the role of cryosurgical ablation.

Future direction of clinical application and continued research in this field is needed. Several issues remain unanswered. The true cytodestructive effect and efficacy for human hepatic tumors in vivo is not known. In a few reported patients who had subsequent resections or autopsy examinations of lesions treated with cryoablation, no viable tumor cells were identified.<sup>5</sup> However, in 9% of the patients with recurrent disease, the tumor recurs locally at the cryotherapy site.<sup>5,25</sup> This suggests that tumor cells can survive treatment. Intraoperative and/or postoperative biopsy may better define tumor survival and guide further interventions. Other modalities of ablation are currently being investigated. These include microwave coagulation necrotic therapy and radiofrequency ablation, both of which may be applied laparoscopically.<sup>35-38</sup> Finally, the role of systemic and/or regional chemotherapy in conjunction with cryoablation or other ablative techniques should be addressed.<sup>39-42</sup> Hepatic artery infusion catheters can be placed laparoscopically to deliver chemotherapeutic agents.<sup>43</sup> Resolving these issues and continued technical advancement are the current challenges in laparoscopic cryoablation of hepatic tumors.

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## IN OTHER AMA JOURNALS

### ARCHIVES OF INTERNAL MEDICINE

#### A Prospective Study of Association of Monounsaturated Fat and Other Types of Fat With Risk of Breast Cancer

Alicja Wolk, PhD; Reinhold Bergström, PhD; David Hunter, MD; Walter Willett, MD; Håkan Ljung, MSc; Lars Holmberg, MD; Leif Bergkvist, MD; Åke Bruce, MD; Hans-Olov Adami, MD

**Background:** Animal studies suggest that monounsaturated and polyunsaturated fat may have opposite effects on the risk of breast cancer.

**Methods:** We performed a population-based prospective cohort study, including 61 471 women aged 40 to 76 years from 2 counties in central Sweden who did not have any previous diagnosis of cancer; 674 cases of invasive breast cancer occurred during an average follow-up of 4.2 years. All subjects answered a validated 67-item food frequency questionnaire at baseline. Cox proportional hazards models were used to obtain adjusted rate ratio (RR) estimates with 95% confidence intervals (CIs).

**Results:** After mutual adjustment of different types of fat, an inverse association with monounsaturated fat and a positive association with polyunsaturated fat were found. The RR for each 10-g increment in daily intake of monounsaturated fat was 0.45 (95% CI, 0.22-0.95), whereas the RR for a 5-g increment of polyunsaturated fat was 1.69 (95% CI, 1.02-2.78); the increments correspond to approximately 2 SDs of intake in the population. Comparing the highest quartile of intake with the lowest, we found an RR of 0.8 (95% CI, 0.5-1.2) for monounsaturated fat and 1.2 (95% CI, 0.9-1.6) for polyunsaturated fat. Saturated fat was not associated with the risk of breast cancer.

**Conclusions:** Our results indicate that various types of fat may have specific opposite effects on the risk of breast cancer that closely resemble the corresponding effects in experimental animals. Research investigations and health policy considerations should take into account the emerging evidence that monounsaturated fat might be protective for risk of breast cancer. (1998;158:41-45)

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