Cryotherapy for Liver Tumors

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The curative management of primary and metastatic liver tumors has traditionally relied on surgical resection. Unfortunately, fewer than 10% of newly diagnosed patients have tumors that are considered to be surgically resectable.

Introduction

Primary and metastatic liver tumors are a common cause of cancer-related mortality worldwide. In 1997, the estimated annual incidence of primary liver tumors in the United States was 13,600, with an estimated mortality of 12,400.[1] Although the relative incidence of primary liver tumors in the United States is low (2.5% of all new cancers), hepatocellular carcinoma constitutes one of the most common cancers in other parts of the world, including certain areas of Asia and Africa. Overall, however, the incidence of malignant hepatic tumors is dominated by metastatic disease.

The estimated annual incidence of colorectal cancer in the United States during 1997 was 131,200.[1] As many as 75% of patients with colorectal cancer will develop synchronous or metachronous liver metastases, and about 25% of these, or approximately 25,000 to 30,000 patients, will have disease limited to the liver. Moreover, of the estimated 70,000 patients who succumbed to colorectal cancer in 1997, approximately 25% had metastases confined to the liver.

The natural course of untreated primary liver cancer is characterized by rapid progression, with median survival times of 2 to 4 months and few long-term survivors (Table 1).[2-4] Most patients have disease limited to the liver at diagnosis, and approximately 90% will have isolated hepatic disease at the time of death.[5]

Historically, complete surgical resection has been the only form of curative therapy available for patients with hepatic carcinoma, resulting in 5-year survival rates of 10% to 40% (Table 2). Unfortunately, underlying hepatic disease, including cirrhosis, hepatitis B, hemochromatosis, and alpha-1-anti-trypsin deficiency, is common and can markedly complicate surgical resection or render resection impossible. In fact, 70% to 90% of primary liver cancers are surgically unresectable. Although hepatic transplantation has been associated with 5-year survival rates of 20% to 40%, it is contraindicated in many patients and unavailable to most. Other treatment options, including palliative resection and regional or systemic chemotherapy, have had little impact on overall survival. Clearly, the prognosis for patients with unresectable primary liver tumors has been dismal.

The natural history of patients with hepatic metastases depends on several factors, including tumor histology, the extent of metastases, and the presence or absence of extraparenchymatic disease (Table 1). A collective review of 673 untreated patients with colorectal liver metastases cited a median survival duration of 6 to 13 months.[6] When only 142 untreated patients with isolated liver metastases (defined as unilobar, localized disease consisting of fewer than four lesions) were considered, the median survival time was 18 months with a 5-year survival rate of 1%.

Systemic chemotherapy generally achieves response rates of 20% to 30% in patients with liver metastases but offers no significant survival advantage compared to the natural course of untreated disease.[7] In addition, regional chemotherapy, delivered via hepatic artery infusion, results in a prolonged disease-free interval but has not improved overall survival compared with systemic fluorouracil alone.[8-11]

Again, complete surgical resection offers the only potentially curative therapy for patients with colorectal liver metastases. The Hepatic Registry Group data of 859 patients treated with surgical resection indicate a 5-year overall survival of 33%.[7] Several other series report 5-year survival rates of 25% to 40% in patients with surgically resected colorectal metastases (Table 2). Other less frequent, yet potentially still curable, tumors that metastasize to liver include neuroendocrine, renal, adrenal, uterine, ovarian, and cervical cancers; sarcoma; melanoma; and, perhaps, breast cancer. Surgical resection of these noncolorectal liver metastases has resulted in 5-year survival rates of 10% to 40% (Table 2).[12-15] Unfortunately, 70% to 90% of patients...
diagnosed with isolated hepatic metastases have surgically unresectable lesions. It has become clear that primary and metastatic liver tumors represent a significant therapeutic challenge and increasingly important health-care problem. Driven by the low resectability rate, limited treatment options, and correspondingly dismal prognosis, recent emphasis has focused on regional ablative therapies, including cryosurgery, alcohol or laser ablation, interstitial radiation, hyperthermia, chemoembolization, and radiofrequency ablation. Of these various modalities, accumulating data suggest that cryotherapy is a safe, efficacious treatment alternative for many patients with surgically unresectable tumors. In fact, cryoablation of selected unresectable primary and metastatic liver tumors may result in long-term survival rates similar to those reported in series of surgically resected hepatic tumors.

**History of Cryosurgery**

Initial attempts at performing cryotherapy date back to the early 1800s. Simple techniques using iced saline solutions were employed to try to alleviate pain in patients with advanced breast or cervical cancer. Since then, significant advances in cryogenics have allowed for the application of this technique to local tissues as a means of controlling various cancers, including tumors of the skin, breast, prostate, oropharynx, larynx, and lung.[16-19] However, it was not until 1963 that Irving Cooper, a neurosurgeon using cryosurgery to treat Parkinson’s disease and other neuromuscular disorders, suggested the possible use of this technique for the management of primary and metastatic liver tumors.[20] Although Cooper was instrumental in developing the cryosurgical apparatus and delivery system for liquid nitrogen, limitations in the accurate imaging of tumors prohibited the safe application of this technique to deeper tissues, including the liver. This obstacle was eventually overcome with the advent of intraoperative ultrasound (IOUS). Today, liver tumors can be accurately imaged and real-time monitoring of the freezing process can be effectively achieved utilizing IOUS. Accordingly, hepatic cryosurgery has now emerged as a viable therapeutic strategy for unresectable liver tumors.

**Principles of Cryotherapy**

The fundamental effect of cryosurgery is based on in situ tissue destruction using subzero temperatures. Cell death results from complex physiologic mechanisms that rely on direct and indirect mechanical effects. These effects include ice crystal formation and cellular anoxia during the frozen state, followed by microvascular thrombosis. Experimental evidence also suggests an adaptive immunologic tumor response in the post-frozen state. The overall results are cell membrane destruction, enzyme denaturation, osmotic dehydration, anoxia, and cellular necrosis.[21] Although the mechanism of cryo-ablation is tissue-nonspecific, different tissues have inherently variable sensitivities to the cryogenic effect. Similarly, within the liver itself, different cells have varying degrees of sensitivity to subzero temperatures. Hepatocytes, bile duct epithelial cells, and connective tissue cells demonstrate resiliency to temperatures as low as -10 °C but are completely destroyed at -40 °C. In contrast, larger blood vessels seem to be resistant to temperatures of these extremes. This effect, which may be due, in large part, to the thermal sink effects of warm blood within the vessel itself, serves to protect the vessel intima and media. Experimental evidence suggests that complete perivascular and intralesional tissue necrosis results following hepatic cryoablation near large vessels.[22] Exploiting this phenomenon allows for the application of this technique to the hepatic tissue surrounding these vessels. By using IOUS guidance, malignant lesions can be completely encompassed and ablated while the remaining liver tissue is preserved. Thus, the fundamental principle of cryosurgery is the ablation of malignant tumor deposits while selectively sparing normal hepatic parenchyma that would otherwise require removal by formal surgical resection.

**Patient Selection**

General indications for hepatic cryosurgery include the following:

1. A documented primary or metastatic liver tumor,
2. The absence of extrahepatic metastasis,
3. Surgically unresectable disease, and/or

4. Tumor involving surgically resected margins.

Following the diagnosis of a primary or metastatic liver tumor, a careful preoperative evaluation and staging work-up are essential. Preoperative liver imaging is important to determine the extent of hepatic tumor involvement and to exclude the presence of extrahepatic disease. Tumor markers are often measured preoperatively and may be important in the postoperative follow-up period as well. These include alpha-fetoprotein (AFP) for hepatocellular carcinoma, carcinoembryonic antigen (CEA) for colorectal liver metastases, and/or 5-hydroxyindoleacetic acid (5-HIAA) for metastatic carcinoid tumors.

**Imaging Tests**

Many preoperative imaging tests are currently available and vary in their ability to detect primary and metastatic disease.

- **CT and MRI**—The extent of hepatic tumor involvement may be assessed using computed tomographic (CT) imaging with either contrast-enhanced, spiral CT or dynamic CT arterial portography (CTAP). The potential advantage of CTAP is its ability to define the hepatic vascular anatomy and its relationship to the tumor. Compared to conventional CT, CTAP has a higher sensitivity (90% to 95% vs 60% to 80%) but lower specificity (30% to 50% vs 60% to 70%), and is even less accurate in the presence of hepatic vascular flow abnormalities, such as cirrhosis.[23,24] Unfortunately, CTAP requires invasive angiography and is more costly than conventional CT. In addition, the high false-positive rate associated with CTAP limits its usefulness.

- Alternatively, magnetic resonance imaging (MRI) of the hepatobiliary system is a promising tool with rapidly progressing technology that may improve the preoperative detection of liver tumors. Although MRI was less sensitive than conventional CT in a prospective, randomized trial (78% vs 94%),[25] newer MRI techniques may improve its sensitivity. In particular, fast MRI with breath-hold technique and the use of new contrast agents, such as gadolinium chelates and/or iron oxides, hold promise for the future.

Ongoing studies should help delineate the most appropriate candidates for this evolving technology. Currently, contrast-enhanced spiral CT is the imaging modality most commonly used in the preoperative assessment of patients with liver tumors. This technique accurately predicts the extent of disease in approximately 70% of patients (Figure 1).

**Nuclear medicine scans** are increasingly being used to preoperatively evaluate the extent of metastatic disease. The most commonly performed technique is external immunoscintigraphy using tumor antigen-specific radiolabeled monoclonal antibodies or tumor-specific receptor ligands. The most extensive experience has been gained in colorectal cancer using indium-111 CYT-103 (Oncoscint; Cytogen Corp., Princeton, New Jersey), a murine monoclonal antibody against the TAG72 antigen. Unfortunately, a frequent human antimurine antibody (HAMA) response limited repeat imaging, and coupling to indium-111 resulted in hepatic Kupffer cell accumulation and subsequent poor hepatic visualization.

Newer-generation murine antibodies, antibody fragments, and hybrid murine/human antibody constructs, as well as coupling to different radioisotopes, appear to be more promising. In a recent phase III trial involving 210 patients with a history of colorectal carcinoma and rising CEA, Moffat et al demonstrated improved detection rates of recurrent colorectal metastases with a technetium-99m-labeled anti-CEA-specific murine Fab¢ antibody fragment (IMMU4 or CEA-Scan; Immunomedics Inc., Morris Plains, New Jersey) than with conventional diagnostic modalities alone (98% vs 70%).[26] In addition, there was a significantly lower HAMA immune response (1%), and the use of technetium-99m instead of indium-111 allowed for improved visualization of the liver. Comparable results were seen in a recent follow-up study,[27] and other investigators have reported similar findings.[28]

Currently, Oncoscint and CEA-Scan are the only nuclear medicine scans approved by the FDA for use in imaging colorectal cancer.

Other tumor-associated antigens being targeted for this approach include AFP for the imaging of hepatocellular carcinoma and somatostatin analogs for neuroendocrine tumors. In a recent phase II clinical trial comparing a technetium-99m-labeled anti-AFP antibody (AFP-Scan; Immunomedics, Inc.) with CT imaging in 20 patients with hepatocellular carcinoma, Dressel et al demonstrated improved sensitivity (95% vs 63%), specificity (67% vs 17%), and overall accuracy (88% vs 52%) of the AFP-Scan.[29] In addition, no HAMA reactions were noted.
Thus, nuclear medicine imaging may enhance preoperative tumor detection of primary and metastatic tumors. Ongoing clinical trials should help define the patient population most likely to benefit from this technique.

**Cryosurgical Technique**

Following routine preoperative evaluation, cryosurgery is performed through an open laparotomy. Standard intraabdominal surgical exploration is completed to exclude extrahepatic metastases, and a thorough examination of the liver, including IOUS, is performed. Laparoscopy may be considered in the unusual circumstance in which cryosurgery might be employed on 1 or 2 anterior lesions. For most lesions, complete liver mobilization and protection of adjuvant tissues mandates an open exploration.

**Imaging With IOUS**

Intraoperative ultrasound has overcome many of the limitations associated with hepatic cryosurgery and has proven to be the most sensitive and specific imaging modality for the detection of liver neoplasms. Important benefits of IOUS include the identification of multicentric and deep tumors, provision of anatomic detail of the tumor in relation to major vascular or biliary structures, guidance of the placement of cryosurgery probes, and monitoring of the freeze-thaw process.

Experience to date suggests that IOUS can detect approximately 25% more lesions than preoperative imaging studies alone, including CT, CTAP, MRI, angiography, or ultrasound. Moreover, IOUS can identify lesions as small as 0.4 cm, and approximately 40% of the lesions identified by IOUS cannot be seen or palpated by the surgeon. Overall, the use of IOUS alters the planned operative procedure in 20% to 40% of cryosurgical patients.

Presently, a wide variety of useful IOUS equipment is commercially available, including hand-held linear array and sector transducers in a variety of configurations. For liver imaging, 5.0- or 7.5-mHz, L- or T-shaped, real-time, B-mode or linear array transducers are commonly used.

Initially, a 7.5-mHz, hand-held, T-shaped linear array transducer is used to image the liver and its vascular and biliary anatomy. The relationships of the portal, biliary, and hepatic vessels to the tumor are discerned. The abdominal contents are then protected from the operative field, and, using IOUS guidance, a small finder needle (usually a 22-gauge spinal needle) is placed into the lesion.

**Placement of the Cryoprobe**

The "cryoprobe" is then inserted, taking care to avoid major vascular and/or biliary structures (Figure 2). For certain deep lesions, a peel-away sheath may be inserted over a guidewire to allow for more precise positioning.

Cryoprobe selection is based on the size and location of the lesion; the extent of tumor and hepatic parenchymal freezing depend on the diameter and shape of the cryoprobe. In general, 3-mm probes produce an ice ball ~ 3 cm in size, while 5-mm probes produce ~ 4-cm ice balls. Larger probes (8- or 10-mm) can generate ice balls ~ 5- to 7-cm in size. In general, a probe size is selected to completely encompass the lesion and ensure 1-cm frozen margins at the periphery of the tumor.

**Freezing and Thawing**

Following accurate placement of the cryoprobe, the cryogen (usually liquid or gaseous nitrogen) is circulated through the insulated cryoprobe shaft to the uninsulated cryoprobe tip (Figure 3). Circulating liquid nitrogen results in a probe tip temperature of -196 °C and adjacent tissue temperature of -100 °C to -160 °C.

As the freezing begins, the ice ball emigrates outward from the tip of the cryoprobe and is monitored by real-time IOUS. Characteristic IOUS changes include a rim of hyperechogenicity surrounding the ice ball with posterior acoustic shadowing (Figure 4).

Thermal gradients of up to 10 °C per millimeter of tissue may occur, resulting in dramatically reduced temperatures at the tumor margins. Because temperatures at the edge of the ice ball are 0 to -5 °C, freezing 1 cm beyond the tumor margin is recommended; this ensures a lethal temperature of -30 to -50 °C at the tumor margin. The thawing cycle is seen as a rim of hypoechogenicity (corresponding to thawed normal hepatic tissue) surrounding the malignant lesion and is indicative of adequate tumor ablation.

Principles to maximize the tumoricidal effect include[30-33]:

1. Rapid freezing to temperatures at or below -35 °C,
2. Maintaining the frozen state for several minutes,
3. Slow rethawing, and
4. Employing more than one freeze-thaw cycle.

Following completion of the procedure, the probes are removed, the tracts are packed with a hemostatic agent, and the abdomen is closed.

**Complications**

Complications of hepatic cryosurgery have been infrequent.[32,34] Transient intraoperative hypothermia is common, and the use of warming blankets and fluid warmers should be considered for every case. Temporary elevation of hepatic parenchymal enzymes, thrombocytopenia, and hypoglycemia may occur as well. Liver enzymes usually fall to the normal range by 48 hours after the procedure. Delayed bleeding has been reported in fewer than 1% of cases.[35] and platelet transfusions are seldom required. Pulmonary atelectasis and occasional right pleural effusion may be seen; however, pleural drainage is rarely needed.

Coagulopathy and myoglobinuria occur frequently, especially when freezing large tumors, (usually > 5 cm). Vigorous hydration, alkalinization of the urine, and osmotic diuresis is routinely performed to avoid acute tubular necrosis. Low-dose dopamine (2 to 5 µg/min) can be employed to improve renal perfusion.

Biliary leak or subsequent stenosis occurs in approximately 6% of patients and should be anticipated when cryotherapy is carried out near major bile ducts. Bile duct stenosis can be avoided by an intrabiliary warm saline infusion.

Lastly, hepatic cracking can occur, especially with freezing of large lesions or in the presence of a cirrhotic liver. This can be readily controlled with suture ligation, electrocautery, or packing. Fortunately, serious sequelae of hepatic cryosurgery are rare, and rapid postoperative recovery is the rule. In general, hospital stay is less than 6 days.

**Results**

Reports on the safety and efficacy of cryosurgery for the treatment of unresectable primary and metastatic liver tumors have been accumulating at a rapid pace (Table 3).

**Primary Hepatic Carcinoma**

The initial clinical experience with hepatic cryosurgery occurred in Shanghai, China, where Zhou et al used plate-like probes for freezing and monitored the freezing process visually and/or with intrahepatic thermocouples. In the initial 35 patients with hepatocellular carcinoma treated in this manner, 1-, 2-, and 3-year overall survival rates were 55.5%, 24.3%, and 10%, respectively.[36] Encouraged by these results, Zhou et al used the new IOUS/cryoprobe technique to treat 167 patients with primary liver tumors and reported overall 1-, 3-, and 5-year survival rates of 73.5%, 47.7%, and 31.7%, respectively.[36] To date, this is the largest reported experience of cryosurgery for primary liver tumors. As expected, tumor size was predictive of survival: The 5-year overall survival rate was 47.8% for tumors < 5 cm, as compared with 24.5% for tumors > 5 cm.

Of the 167 patients treated by Zhou et al, 76 underwent cryosurgery alone, while 89 were treated with cryosurgery plus additional therapy (hepatic artery ligation, perfusion, and/or resection). For the 76 patients treated with cryosurgery alone, the 1-, 3-, and 5-year overall survival rates were 75.5%, 41.6%, and 29.1%, respectively.

Other reported series, although smaller in size, support the Chinese experience.[6,37,38] Our own experience using cryosurgery to treat eight patients with hepatocellular carcinoma also supports these findings, demonstrating an actuarial 5-year overall survival rate of 70% at a median follow-up of 16 months.[39]

**Hepatic Metastases**

Significantly more data on the cryosurgical management of liver metastases are emerging. Encouraging reports from the United States, Australia, Britain, France, and other parts of the world have fueled the use of this technique for the treatment of metastatic liver tumors. Ravikumar et al pioneered this effort, performing phase I/II clinical trials that established the acceptable toxicity and feasibility of cryosurgery, as well as tumor response. In their initial clinical experience, they reported on 24 patients with colorectal hepatic metastases treated with cryosurgery and IOUS between 1985 and 1990.[40] At a median follow-up of 24 months, 29% of patients remained disease-free and 34% were alive with disease, while 37% had died. Intrahepatic
tumor recurrence was seen in 35%, although only 8% were felt to have developed a recurrence in previously treated sites. These results were supported by other investigators, including Onik et al, who reported a 22% disease-free survival rate at a median follow-up of 29 months. Local recurrence was noted in 22% of patients but was only seen in patients with tumors > 4 cm, supporting the hypothesis that tumor size is a significant predictor of recurrence. Mean tumor number per patient in this series was 6 (range, 1 to 12).

In a study of 140 patients with liver metastasis treated with cryosurgery with or without additional resection, Weaver et al achieved a 22-month median survival. Our own experience treating 27 patients with colorectal liver metastases with IOUS/cryosurgery demonstrated actuarial 5-year overall and disease-free survival rates of 30% and 19%, respectively. Although the intrahepatic recurrence rate was 62.5%, local recurrence within a previously cryoablated area occurred in only 2.3% of patients. Of the 62.5% whose disease recurred within the liver, 60% had an isolated regional hepatic recurrence.

The series discussed above include several cryoablated noncolorectal liver metastases. Thus, it appears from numerous studies that the long-term survival rate following cryosurgery for hepatic metastases ranges from 20% to 60%, with local recurrence rates of 3% to 20%. These values are comparable to results obtained with surgical resection. Regional intrahepatic failure rates continue to be a problem with cryosurgery but are similar to regional failure rates observed following surgical resection (ie, 30% to 60%).

**Postoperative Findings**

Within a few weeks after therapy, the cryoablated lesion appears as a large, hypodense area on CT imaging (Figure 5), and hemorrhage or air may be seen in the area. This cryosurgical scar gradually diminishes over the ensuing months and may be seen as a dense, rim-enhancing mass as the surrounding liver tissue regenerates (Figure 5). Ultimately, a small area of scar surrounded by normal liver tissue will be observed. Continued tissue growth in the area should be evaluated for persistent disease or local recurrence.

Tumor markers may rise in the initial postoperative period due to the release of tumor-associated antigen but should fall to normal within 30 to 60 days. Persistent tumor marker elevation may be a sign of inadequate treatment or the presence of additional metastatic disease.

**Future Directions**

One area of future investigation is the use of adjuvant systemic and regional therapies to decrease systemic and regional intrahepatic recurrence rates after cryotherapy. A cooperative effort is now underway to determine the benefit of regional chemotherapy, either hepatic arterial or portal venous, as an adjuvant to cryosurgery.

In addition, chemical agents to enhance the local cryogenic effect are being investigated, including "antifreeze" proteins. A third area of interest is the development of less invasive surgical techniques to decrease morbidity and shorten hospital stay. For example, less invasive laparoscopic cryoprobes and laparoscopic ultrasound transducers are currently being tested.

**Summary**

Studies have documented the safety and therapeutic efficacy of cryosurgical ablation in the management of unresectable primary and metastatic liver tumors. This technique provides a potentially curative treatment for patients with hepatic tumors that cannot be surgically removed, who would otherwise fare poorly. Long-term survival rates of 20% to 40% in selected patients treated with cryosurgery suggest that this option should be included in the treatment armamentarium for hepatic tumors. Integration of cryosurgery with other adjuvant regional therapies, enhancement of the local cryogenic effect, and development of less invasive surgical techniques are exciting prospects in cryosurgery that merit further investigation.

**References:**


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