The Treatment of Primary and Metastatic Hepatic Neoplasms Using Percutaneous Cryotherapy

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ABSTRACT

Cryotherapy has been used clinically in the treatment of metastatic liver malignancies since the 1980s. Rapid freezing to sub-zero temperatures promotes ice formation in the extracellular space and the exit of intracellular water. Cellular death is the result of dehydration, protein denaturation, and microcirculatory failure. Cryotherapy probes use nitrogen or argon gas as a coolant and the development of the ice ball can be monitored using ultrasound, computed tomography, or magnetic resonance imaging. Traditionally, cryotherapy has been performed during laparoscopy or laparotomy, using intraoperative ultrasound for image guidance. A decrease in cryoprobe size (from ~24 Fr to ~15 gauge) in conjunction with experience gained in open cryosurgical treatment has allowed the development of minimally invasive percutaneous approaches. In this review, we describe the use of cryotherapy for treatment of primary or secondary liver neoplasms using a percutaneous approach.

KEYWORDS: Liver malignancy, ablation, cryotherapy

Objectives: Upon completion of this article, the reader should be able to (1) understand the recent advances in cryotherapy, including the expanding clinical indications, (2) review the techniques currently used for cryotherapy of the liver, and (3) present the results reported in the current literature regarding results and complications of percutaneous cryotherapy.

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Primary and metastatic liver carcinomas have an exceedingly poor prognosis without treatment. For hepatocellular carcinoma (HCC), surgical resection offers the only possible cure. Unfortunately, secondary to multiple reasons such as poor liver reserve, number of metastases, tumor proximity to major vascular or biliary structures, or extrahepatic metastases, only 10% of patients with newly diagnosed HCCs are candidates for resection.[1]

Similarly, only 10 to 15% of patients presenting with colorectal liver metastases are candidates for surgical resection.[2] Hepatic metastases are the primary cause of death in patients with colorectal cancer.[3] Liver metastases are seen in up to 50% of patients with colorectal

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cancer and without treatment these patients survive a median of 7 months.[4,5]

Alternative treatment modalities including cryoablation, radiofrequency ablation (RFA), laser ablation, high-intensity ultrasound, microwave ablation, percutaneous ethanol or acetic acid injection, and chemoembolization have been developed.[6] Although certain percutaneous techniques may have advantages over others (e.g., chemoembolization for diffuse metastatic disease), there are no randomized clinical trials that show a clear survival benefit of any of these alternative modalities.

Cryotherapy has been used clinically in the treatment of metastatic liver malignancies since the 1980s.[7] Rapid freezing to subzero temperatures promotes ice formation in the extracellular space and the exit of intracellular water.[7] Irreversible tissue damage occurs at temperatures below -20 to -30°C. Cellular death is the result of dehydration, protein denaturation, and microcirculatory failure.[8] Cryotherapy probes use nitrogen or argon gas as a coolant and the development of the ice ball can be monitored using ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). A margin of freezing of at least 5 to 10 mm of normal liver parenchyma is considered adequate to ensure complete tumor ablation.[9]

Traditionally, cryotherapy has been performed during laparoscopy or laparotomy, using intraoperative ultrasound for image guidance. A decrease in cryoprobe size (from $\sim$24 Fr to $\sim$15 gauge) in conjunction with experience gained in open cryosurgical treatment has allowed the development of minimally invasive percutaneous approaches.[10] In this article, we describe the use of cryotherapy for treatment of primary or secondary liver neoplasms using a percutaneous approach.

TREATMENT OPTIONS

Surgery

Surgical resection of primary or metastatic liver neoplasms is the gold standard and generally considered the only curative approach.[11] In HCC patients without cirrhosis, partial hepatectomy is associated with a 5-year survival between 30 and 68%.[12–14] In patients with HCC and cirrhosis, intraoperative mortality is higher and 5-year survival is lower (25 to 30%).[15] The diameter of the primary tumor appears to be inversely correlated to survival; Wu et al evaluated 2051 HCCs and noted a trend toward increased 5-year survival rates following surgery of 79.8% in the >5 cm diameter group and 85.3% in the <3 cm diameter group.[15] HCC recurrence varies between 20 and 70% and occurs primarily in the first 2 years postresection.[15]

Liver transplantation has become an option in patients with HCC if the liver tumor burden is large or there are small lesions in the setting of cirrhosis. The 3- and 5-year survival rates range from 16 to 82% and 19.6 to 36%, respectively.[16–19]

Although both resection and transplantation have approximately the same results in terms of 5-year survival, recurrence is much lower in the transplant group if the HCC is >5 cm in size with fewer than three nodules (82.6% after resection versus 11.1% after transplantation, $P < 0.01$).[20]

Liver metastases are seen in 30 to 50% of patients with colorectal cancer.[21] Resection is possible in $\sim$10% of these patients, although the 5-year survival rate is less than 30%.[21]

When a completely resectable neoplasm is present, either an open or laparoscopic surgical approach can be taken. Complications with resection include bleeding, bile leakage, transient hemobilia, atelectasis, and inflammatory changes in the right lung. Perioperative mortality rates range from 5 to 24%.[22] Laparoscopic approaches present technical difficulties and complications that include bleeding, gas embolism, and the potential of malignant seeding.[23] A more in-depth discussion regarding surgical options can be found in the dedicated article written by Drs. Palesty, Al-kasspooles, and Gibbs in this issue (Semin Intervent Radiol 2006; 23:13–20).

Medical Options

There have been few randomized clinical trails assessing systemic chemotherapy for HCC. These studies have enrolled patients with impaired liver function, ascites, and/or jaundice; response rates have been less than 20% with median survival of 2 to 6 months.[24–26] Fluorouracil has shown response rates up to 10% with median survival of 2 to 6 months[24,27]; doxorubicin has shown response rates up to 32%, but randomized trials have failed to demonstrate a survival benefit.[28,29]

Chemotherapy for neuroendocrine metastases demonstrates a similar poor efficacy. Streptozotocin with 5-fluorouracil and/or other anthracyclines have not demonstrated objective responses or clear survival benefits.[30–32]

Current chemotherapy regimens for colorectal liver metastases use 5-fluorouracil alone or in combination with folinic acid. This combination has a response rate of $<25\%$ with a 12-month median survival.[33] The addition of irinotecan and oxaliplatin can increase the response rate to 50% and increase median survival to 20 months.[33] A new regimen involves using monoclonal antibodies against the epithelial growth factor receptor (cetuximab) or the vascular endothelial growth factor (bevacizumab) alone or in combination with other chemotherapeutic agents. Cetuximab shows efficacy in 10 to 23% of patients with irinotecan-refractory colorectal cancer as monotherapy or in combination

with irinotecan.[34] When compared with irinotecan/bolus-5-fluorouracil/folinic acid alone, bevacizumab in combination with irinotecan/bolus-5-fluorouracil/folinic acid significantly increased median free survival by 4.4 months and overall survival by 4.7 months.[35]

A more in-depth discussion regarding medical options can be found in the dedicated article written by Dr. Kevin Brown in this issue (Semin Intervent Radiol 2006;23:99–108).

ABLATION TECHNIQUES

Radiofrequency Ablation

RFA uses alternating current (>1 MHz) applied to an electrode that is placed in a lesion under ultrasound guidance. RFA can be performed with single or multiple electrodes during laparotomy or laparoscopy or may be placed percutaneously using local anesthetic.[36–38] The development of the ablation zone is monitored using real-time ultrasound and is seen as an elliptical lesion surrounding the probe tip. The demarcation between normal liver parenchyma and necrotic tissue is ill defined and confounds the evaluation of ablated tumor versus recurrent/residual disease.[39] CT may also be used to monitor lesion size and may visual necrosis more accurately.[37]

With most commercially available systems, the maximum diameter of tissue necrosis is ~3 to 5 cm. With a margin of 1 cm of normal tissue, the largest treatable lesion without multiple overlapping applications is ~1 to 2 cm. For this reason, many lesions are treated with repositioning of the probe in an overlapping fashion.

Although widely used clinically, definitive studies comparing RFA to other ablation techniques are lacking. Many of the studies describing the use of RFA use a patient population that includes both primary tumors and metastases.[37,40–42] Many studies report a technical success of 41 to 100%; however, clinical success rates are confounded by tumor recurrence at the site of ablation, new metastases, and/or the development of extrahepatic disease.[41,43–49] The likelihood of local recurrence may be related to the RFA approach; percutaneous, laparoscopic, and open surgical approaches report local recurrence rates of 4.2 to 76%, 12 to 20%, and 2.2 to 3.1%, respectively.[50]

In general, RFA is well tolerated and complications are related to the approach used. Complication rates for percutaneous, laparoscopic, simple open, and combined approaches are 7.2%, 9.5%, 9.9%, and 31.8%, respectively[51]; corresponding mortality rates are 0.5%, 0%, 0%, and 4.5%.[51] The most common complications include pain, intraperitoneal hemorrhage, liver abscess, biliary and hepatic vascular tract damage, tumor seeding along the RFA probe tract, and transient pyrexia.[52]

A more in-depth discussion regarding RFA options can be found in the dedicated article written by Drs. Venkatesan, Gervais, and Mueller in this issue (Semin Intervent Radiol 2006;23:73–84).

Percutaneous Ethanol Injection

Percutaneous ethanol injection (PEI) has been used extensively, but with the advent of newer treatment techniques is being used less often or in conjunction with other therapies. Ethanol injection results in cytoplasmic dehydration followed by coagulation necrosis, fibrosis, and small vessel thrombosis. The geometric parameters regarding the amount of tissue ablated are variable and difficult to predict. Variables include vascularization of the lesion, tissue density, and presence of septa and/or tumor capsule.

A review by Lencioni and Crocetti demonstrated similar survival rates between RFA and PEI for HCC ablation, although recurrence-free survival favored the RFA group.[53] A separate study compared RFA and PEI in the treatment of small HCCs, demonstrating that RFA had a 10% higher complete ablation rate coupled with a faster treatment time.[54] In a third study, large HCCs (>6 cm) treated with PEI after percutaneous cryoablation demonstrated a decreased tumor recurrence at the cryosite.[55] Finally, Koda et al showed a survival advantage for patients with small HCCs when using PEI and transarterial chemoembolization when compared with PEI alone.[56]

PEI appears to be most efficacious and reproducible when soft tumor tissue is surrounded by a denser liver parenchyma, decreasing the likelihood of alcohol tracking along the needle. For this reason, results are best when treating HCC in cirrhotic livers.

Cryoablation

Cryotherapy was first suggested by Cooper in 1963 and is the oldest of the local thermal ablation techniques.[57] Its use as a therapy for liver tumors originated in the 1980s in patients with metastatic disease.[58] Originally described as an open surgical technique due to the size of the cryoprobes (24 Fr), it has become increasingly used via the laparoscopic and percutaneous routes.

The advantages of cryoablation over other regional ablation techniques include: (1) clear visualization on ultrasound of the frozen interface as an echogenic rim with posterior acoustic shadowing, as a focal hypodensity on CT scan, or as a signal void on all MRI sequences; (2) tumors close to large vascular structures can be treated as the warm blood flowing in the portal vein and inferior vena cava renders these vessels resistant to freezing[59]; (3) in patients with a background of cirrhosis predisposing them to multiple HCCs, cryoablation is more effective in treating multiple new tumors[60]; and

(4) there is the potential to treat large lesions during one freeze-refreeze cycle (discussed below).

Cryoablation can be performed using ultrasound, CT, or MRI. Postprocedural imaging typically includes a CT scan. If ultrasound is used during the ablation, the growing ice ball is visualized as an echogenic rim with posterior acoustic shadowing. On CT, the ablation zone is visualized as an area of hypodensity around the cryoprobe. MRI offers the ability to do three-dimensional analyses and evaluate tumor volumes, percent of the tumor that has been ablated, and the volume of healthy tissue in the ablation zone.[61] This technology may help identify individuals with inadequate ablation margins and reduce the amount of tumor recurrence at the ablation bed.

Following therapy, patients can be evaluated by CT scan or MRI. On CT scan the ablated region is visualized as an area of low density that appears similar to an infarction or abcess.[62] Gadolinium-enhanced MRI may help evaluate tissue necrosis or zones of viable residual tumor.[63]

Selected patients generally have fewer than four lesions in multiple liver lobes, limited hepatic reserve that would not tolerate resection, and demonstrate lesions near the portal vein that preclude a clear surgical margin. Contraindications include extrahepatic disease or, in the case of laparoscopic or open techniques, inability to undergo general anesthesia.

A size of less than 5 cm in diameter for each treatable lesion is also often used as a criterion, although at the time this article was written, operators are treating lesions up to 8 cm in diameter. Zhou et al analyzed data from 113 cryoablation patients whose lesions were greater than or less than 5 cm. The 5- and 10-year survival rates were 22 and 8% for lesions greater than 5 cm and 49 and 17% for those less than 5 cm.[64] Several authors feel that the maximum size criteria can be overcome with multiple probes and/or multiple ablations.

Complications from cryoablation include bleeding, pleural effusions, abscess formation, splitting of the liver capsule, biliary strictures, and cryoshock. The complication rate is similar for percutaneous (15%) and laparoscopic approaches (18%).[65]

The need for blood transfusions during laparoscopic cryoablation has a negative impact on survival. Seifert and Junginger showed that the requirement for any transfusion decreased survival and that in patients transfused with more than 4 units the risk of death increased by 32% with each unit transfused.[66] The etiology of this marked increase in mortality is unclear, but it has been speculated that transfusions may be immunosuppressive.[67]

Although uncommon ($\sim$1%), cryoshock bears special mention as a potentially life-threatening complication.[68] It typically consists of thrombocytopenia, acute renal failure (likely secondary to myoglobinuria), adult respiratory distress syndrome, and disseminated intravascular coagulopathy. It is seen in conjunction with increases in inflammatory markers such as interleukin (IL)-1, IL-2, IL-6, tumor necrosis factor, urate, lactate dehydrogenase, and C-reactive protein.[65,69] Routine postablative care should include maintenance of postoperative urinary output at $>$ 100 mL/h to prevent renal damage from myoglobinuria, chest radiograph to evaluate for effusions, and measurements of serum leukocytes, transaminases, platelets, creatinine, electrolytes and C-reactive protein. The patient's leukocytes, platelets, C-reactive protein, transaminases, and electrolytes should normalize within 2 weeks. Additionally, a CT scan of the liver should be completed within the first week postablation as a baseline for later follow-up and to evaluate the liver for periprocedural complications.

CRYOTHERAPY TECHNIQUE

The techniques described in this article represent the protocol used at our institution for cryoablation of liver tumors. We use the PERCRYO system (Endocare, Irvine, CA) at our institution; although the following description is specific for use with this system, most of the steps are presumably applicable to other commercially available units.

Preprocedural planning is vital in this patient population. We obtain a triple-phase CT scan on all possible candidates. Information to be gleaned from the preprocedural scan includes: number and size of all lesions, amount of surrounding normal liver between the tumor and adjacent vessels and liver capsule, and patency of the portal vein. In addition, if the tumor is subcapsular, the location of important adjacent structures (e.g., bowel) is noted. Measurements of the lesions to be ablated are obtained and compared with isotherms of the available probes to ensure that the appropriate probes are available for the procedure.

We perform all cryotherapy procedures under CT guidance. The CT scanner on which we perform our procedures (SOMATOM, Siemens, New York, NY) is equipped with CT fluoroscopy, which we find significantly decreases the time required for procedures. Ultrasound can be used to guide the ablation procedure and may be more appropriate during cryoablation procedures than RFA. Although the latter procedure produces significant gas during the ablation procedure (thereby limiting visualization with ultrasound), cryoablation does not have this limitation.

The stepwise fashion for cryoablation is described here. The patient is placed on the scanner in the position determined by the preprocedural CT scan, after which a CT scan is performed without intravenous contrast. If an appropriate access route is visualized, the patient is placed on hemodynamic monitoring equipment and

sedation and analgesia are initiated. The skin is marked, prepped, and draped in sterile fashion. The skin and trajectory tract are anesthetized to the level of the liver capsule.

If an intercostal route is chosen, we routinely perform an intercostal nerve block. After identifying the intercostal space into which the probe(s) will be placed, the ribs surrounding the intercostal space are followed back to the posterior axillary line. A 25-gauge needle is advanced to the rib and marched inferiorly, until the needle slides underneath the costal margin. Aspiration of the needle is performed to ensure no blood return; if blood is not returned, 5 mL of buffered lidocaine (1 mL 8.4% sodium bicarbonate and 9 mL of 1% lidocaine) is injected. Injections are performed at the two ribs surrounding the interspace to be accessed with the probes, as well as one interspace above and below. A maximum of 40 mL of lidocaine is used during the procedure.

Once local analgesia and systemic sedation has been achieved, the probes are placed under CT guidance into the tumor. Unlike RFA, many probes may be placed and used concurrently (up to eight probes can be used at once with one generator with our system). Although using multiple probes at once increases the cost of the procedure, it can significantly decrease the duration of the treatment and, in the authors' opinion, can allow for a more predictable tumor freeze.

Once appropriate probe placement has been achieved, the probes are attached to the generator and the freeze cycle is initiated at 100% freeze. The authors use two freeze cycles of 10 minutes each. After each freeze cycle, a thaw period is initiated either passively (taking $\sim$5 to 10 minutes) or by active helium instillation (taking $\sim$2 minutes). The probes are not typically repositioned after the first freeze-thaw cycle, although an interval CT scan may demonstrate the need for such repositioning. Typically, a freeze zone that extends 5 to 10 mm beyond the tumor margin is recommended.

After the second freeze cycle, the intratumoral temperature is monitored (the temperature is displayed in the probe handle) until the temperature reaches $\sim$10 to 15°C. When the probes can be easily rotated, they can be safely removed. Freezing or embolizing the tract is not routinely recommended. Some clinicians use hypertonic saline and vasoconstrictive cocktails to increase the efficacy of ablation zone, but the details of these practices are not currently in the literature and there is no data to support their efficacy.

CRYOTHERAPY RESULTS

Many of the studies evaluating the efficacy of cryoablation therapy do not separate patient population by type of neoplasm. It is, therefore, difficult to ascertain whether cryoablation is more or less effective on specific tumor types. It is also problematic to compare survival statistics from cryoablation patients to patients who receive resections as curative therapy, as the patients referred for cryoablation are usually not candidates for curative surgery.

Primary HCC has been treated with cryoablation for several years.[70,71] The largest cryoablation series to report survival data found an overall 5-year survival in 191 treated patients to be 37.9%[72] A subset analysis of patients with smaller (<5 cm) tumors demonstrated improved 5-year survival (53.1%).[72] Many studies have demonstrated 5-year survival in the 30 to 60% range.[71,73–75] These results are comparable to those obtained for patients undergoing primary resection, although no prospective, randomized studies exist.

Although less of a problem for HCC than metastases, local recurrence can also be seen with primary HCC. Adam et al had 0% local recurrence in nine patients treated for HCC, and Cha et al had a local recurrence rate of 13.6% (12/88 patients) in a patient population with mixed tumor types.[71,75] In the latter study, 75% of the recurrences were adjacent to major vessels, indicating that the heat sink effect may help to protect tumor cells closely apposed to the vessel.[75] Bilchick and colleagues found that for lesions larger than 3 cm, recurrence may be more common in RFA-treated patients (38%) than in those treated with cryoablation (17%; $P = 0.06$).[76]

Hepatic metastases from colorectal cancer may be amenable to cryotherapy. One investigator demonstrated median survival following cryotherapy in a group of patients ($n = 119$) with colorectal liver metastases of 26 months, which is higher than reported values for intra-arterial chemotherapy of 14 to 16 months.[77] This study had 58 patients with more than four metastatic lesions, and subgroup analysis still demonstrated a median survival of 25 months.[77] In addition, tumor markers (carcinogenic embryonic antigen [CEA] levels) returned to normal in 60% of patients; a failure to observe a decrease in marker levels may have been due to inadequate ablation or extrahepatic disease.[77]

Seifert and Junginger attempted to identify variables that would increase median survival in patients who undergo cryotherapy.[66] Their data suggest that one lesion (less than 4 cm) treated with cryotherapy alone (versus cryotherapy with resection) gives the best outcome for of 3-year survival.[66]

Mala and colleagues treated 19 patients with colorectal metastases using MRI for image guidance.[78] They had a technical success rate of 72% and tumor recurrence at the ablation site in 44% of patients whose tumors were felt to be adequately treated.[78] Nearly half (48%) of the patients were tumor-free at the ablation site at 2-year follow-up, and 12/13 (97%) patients whose tumors were judged to be adequately ablated were alive at 2 years.[78]

There is some evidence that using a dual probe system is superior to a single probe system; this is likely secondary to an increased volume of ablated tissue.[65] Huang et al treated colorectal liver metastases with single or double probes and demonstrated that dual probe systems delayed liver metastatic growth and were accompanied by a decrease in CEA levels 14 days posttreatment.[65] The best results seem to be from patients with small individual lesions treated with adequate margins who had a decrease in CEA levels postprocedure.[65]

Cryotherapy of hepatic neuroendocrine metastatic disease has been used for symptom control for several years. The technical success rate has been high. Cozzi et al treated six such patients with hepatic cryotherapy, and all patients were alive and asymptomatic at a median follow-up of 24 months (range, 6 months to 6 years).[79] In those patients with elevated pretreatment tumor markers, an 89% decrease was noted in tumor markers following ablation.[79] Seifert et al had similar results in 13 patients with neuroendocrine metastases; 12 of their study patients were alive and largely asymptomatic at a follow-up of 13.5 months.[80] Again, the patients with elevated pretreatment tumor markers showed a significant decrease in serum markers following treatment.[80] In a separate investigation, five patients treated with cryotherapy for metastatic carcinoid had 6-month, 1-year, 2-year, and 2.5-year survival rates of 80%, 60%, 40%, and 20%, respectively.[81] Eighty percent of these patients had symptomatic relief in excess of 3 months.[81]

There are multiple methods available for the treatment of unresectable liver neoplasms. Cryoablation offers good technical success rates and apparent survival benefit. Cryotherapy may be particularly advantageous in patients with lesions close to vascular structures, lesions in HCC patients, and patients with multiple lesions and/or relatively large lesions. The development of percutaneous approaches and multiple imaging modalities promises to increase the specificity of the ablations and reduce periprocedural morbidity.

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