Cryosurgery in the Treatment of Hepatic Tumors

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Background: Primary and metastatic tumors in the liver are difficult to treat. When surgical resection is not feasible, cryotherapy is one of the several alternative approaches.

Methods: The data on outcomes from hepatic resections are reviewed, and the rationale and techniques of performing cryosurgery for unresectable hepatic cancers are described. The literature is reviewed and combined with the experiences of the authors on cryosurgery for management of hepatic tumors.

Results: The indications and techniques for performing cryosurgery are now well established. The procedure is relatively safe, and long-term survival rates of over 20% may be achieved.

Conclusion: While cryotherapy is effective for localized tumors in the liver, additional adjuvant approaches are required to control disease in the untreated liver. Endoscopic techniques may minimize patient morbidity.

Introduction

Surgery of the liver has undergone significant advances in recent years. Improvements in anesthesia, postoperative care, and surgical techniques have resulted in safer operations on the liver. The operative mortality rate from major hepatic resection is now less than 5%. The development of operative ultrasound has increased the safety of resections for primary and metastatic liver tumors and has led to the accurate delineation of surgical margins. These are important factors in achieving local tumor control with improved patient outcomes. Ultrasound also enhances the detection of unsuspected bilobar liver disease and the evaluation of the proximity of tumors to critical vascular structures.[1]

Some patients, however, will not benefit from resection or cannot tolerate resection due to poor hepatic reserve. For example, Wanebo et al.[2] reviewed outcomes in 74 patients with resected colorectal metastases over a 14-year period. Those with Dukes B colon primaries, one to three hepatic metastases, and unilobar disease had five-year survival rates of 36%, 24%, and 26%, respectively, and benefit from hepatic resection in these patients was clear. Conversely, a high mortality rate ensued in 12 patients who underwent trisegmentectomies or had extended resections.

Several options for treatment of the patients with inoperable liver tumors are available, including cryotherapy (Table). Percutaneous injection of 95% alcohol into small hepatocellular carcinomas under ultrasound guidance has been investigated, particularly for cirrhotic patients.[3] Systemic chemotherapy has been largely unsuccessful, and external beam radiation, radioimmunotherapy, and injection of Lipiodol into the hepatic artery are all used, as are various forms of intra-arterial chemotherapy and embolization of branches of the hepatic arterial supply to the tumors.[4] Cyto reduction with sequential resection is another strategy. In a series from the Liver Cancer Institute in Shanghai on 663 patients with hepatocellular carcinoma found to be unresectable on initial exploration, 72 of those patients underwent resection.[5] They were subsequently treated with hepatic artery ligation and hepatic artery infusion of chemotherapy before the second operation several months later. Survival in the resected group at five years was 62%.[5] Orthotopic liver transplantation is useful for a select group of patients but is limited by the shortage of organs and the high rate of recurrence in the transplanted liver.[6]

Biophysics of Cryotherapy

Cryosurgery or cryoablation is a technique involving the use of extremely low temperatures to destroy tumors that are left in place to be reabsorbed. It is a focal therapy that allows treatment of specific lesions with preservation of normal tissue. Cryosurgery has been used in other organs such as the skin by direct contact with liquid nitrogen at low temperatures. The initial approach involved the application of liquid nitrogen to the surface of the liver, but liquid nitrogen delivery systems and vacuum-insulated, recirculating nitrogen probes have been developed that allow its use to treat tumors in virtually any segment of the liver. Real-time ultrasound now permits accurate placing of probes and monitoring of the extent of freezing, since the developing iceball or cryolesion and the margin of normal tissue frozen around the tumor can be seen. Thus, the same principles that guide surgical resection are used.[7,8]

Cryosurgery destroys cells directly by affecting physicochemical properties and indirectly by affecting the structure of vascular channels. The process begins when liquid nitrogen circulates at -196 °C through a vacuum probe and the probe is placed in direct contact with the tissue to be treated. In the liver, the probe is placed under sonographic guidance through the liver substance into the tumor. Ice crystals form both inside and outside of the cells when the tissues are exposed to temperatures below the melting point. As ice forms, electrolytes and organic compounds are excluded from the crystal. A hyperosmolar environment is created in the extracellular compartment that draws water from inside the cells. As a result, the tissue shrinks, the cell membranes are disrupted, and intracellular protein is denatured, thus destroying cell function. Freezing propagates from one cell to another through communication channels. As more tissue crystallizes when small ice crystals grow together with large crystals, a grinding action is created that mechanically disrupts the tissue. A cycle is complete when the thawing process occurs. Rapid freezing and slow thawing lead to further tissue damage. As the treated area warms, water passes into the cells and increases in volume, thus bursting the cell membranes. This process is repeated with a second or third cycle until any remaining viable tumor cells are destroyed.[8,9]

Animal experiments have confirmed the destruction of tumor cells.[9] Rats were implanted with tumor cells on one of the lobes of the liver and were randomized to three groups: no therapy, resection, or cryotherapy. The animals randomized to cryotherapy survived as long as those undergoing resection. Another set of experiments involved implantation of cryotherapy-treated tumor cells into rat thighs. Tumor growth was seen in all the control tumor grafts and in only 10% in those implanted with frozen and thawed cells.[9]
Cryotherapy also obliterates tumor vessels leading to hypoxia and necrosis. This occurs in small-caliber arteries and veins as they undergo thrombosis due to direct contact with subzero temperatures. Large vessels such as the hepatic veins and portal veins are protected from this effect because they are activated by the flow of warm blood as thermal reservoirs, thus protecting their intima and media. For maximum effectiveness, the temperature is lowered rapidly to at least -35 °C and warmed slowly. Two or three freeze-thaw cycles are needed to achieve adequate lysis of tumors.[9]

Cold injury affects different tissues in different ways. In the liver, -15 °C is generally lethal to tissues. In the skin, however, much lower temperatures are required. The rate at which the tissue freezes is another important factor. In studies using cellular suspensions of hepatocytes, intermediate rates of freezing were found to be most effective in destroying tumor cells. In the liver itself, slow cooling results in long structures of ice along blood vessels and the hepatic sinusoids, with surrounding tissue dehydrolysis. When the liver is frozen at intermediate and high rates of cooling, significant intracellular ice formation occurs with minimal hepatocyte dehydration. Freezing to -40 °C results in the complete destruction of hepatocytes, bile ducts, and connective tissues, while freezing to -10 °C will spare normal hepatic parenchyma.

Once cryosurgery is performed, the tumor undergoes necrosis and is left in place. A cellular repair process begins immediately and may last several months. Collagen scar formation takes place in the treated area, and most lesions treated successfully will show gradual shrinkage on follow-up with computed axial tomography with focal hepatic atrophy. Some lesions, particularly small ones, may undergo full resorption and disappear completely.[10]

Cryosurgery can be used for a variety of liver tumors, both primary and metastatic. The worldwide experience with cryotherapy reflects the patterns and prevalence of treated tumors. CEA levels fall and then return to pretreatment levels when recurrence developed.[17] The fall in CEA usually occurs between four to eight months after surgery if cryotherapy has been effective.

### Technical Aspects of Cryotherapy

The freezing process involves hollow metallic probes through which liquid nitrogen circulates. The probes are insulated except at the end of the shaft, which comes in contact with the tumor. Probes are available in different shapes and diameters (Fig 1). Disc-type probes can be used for superficial lesions, while deeper lesions require trocar-type probes. The size and shape of the ice ball is determined by the diameter of the probes (3 mm to 10 mm) and the length of the freezing zone (2 cm to 4 cm). Freezing begins from the probe outward, (ie, from the center of the tumor to the periphery). The process can be monitored effectively with intraoperative ultrasonography while the ice ball develops to the desired margin (approximately 1 cm) around the lesion.

Cryosurgery requires a laparotomy under general anesthesia, although new instrumentation allows the use of the laparoscope in selected cases. In general, the principles that apply to liver resection also apply to cryosurgery. Preoperative studies include an imaging module such as computed tomography scan, magnetic resonance imaging, or ultrasonography to note the number and size of the lesions and their proximity to critical structures.[7] The patient should be well hydrated, since myoglobinuria with acute tubular necrosis has been reported, particularly with a large volume of freezing.[12] Intraoperative management by the anesthesiology team should include adequate measures to maintain body temperature. Exposure of a large volume of liver to subfreezing temperatures may lead to significant hypothermia in a patient who is under general anesthesia with an open body cavity. Onik et al.[13] recommend using the Bair-Hugger warming system in addition to standard maneuvers. This recommendation is based on their finding significantly lower core body temperatures in 28 patients who had undergone surgery without this device.

The abdomen is entered through a standard incision that allows adequate visualization and exposure. The abdomen is thoroughly explored, and the liver is mobilized and palpated bimanually. The liver is then scanned using ultrasound to assess the number and size of lesions, as well as their location in relation to vascular structures. Several ultrasound transducers are available commercially, and hand-held linear-array transducers are available in a variety of configurations including "I" and "T" shapes. Generally, 5.0 MHz or 7.5 MHz transducers are used. With the aid of the ultrasound transducer, the shortest and least traumatic path to the tumor - which avoids major branches of the hepatic and portal veins and bile ducts - is chosen for cryoablation placement. The surrounding viscera and diaphragm are packed to protect them from accidental injury during the freezing process. The liver is mobilized before probe placement to allow adequate access to it in case of bleeding.[7]

The size of the lesion determines the size of the cryoprobe to be used. A 3-mm or 5-mm probe creates an iceball approximately 3 cm in size. A 5-mm probe creates an iceball approximately 4 cm in diameter, and 8-mm and 10-mm cryoprobes create iceballs approximately 5 cm to 6 cm in diameter. Two 10-mm probes can be placed to create an iceball that is 10 cm in diameter.[7,9] A Penrose drain is then passed around the porta hepatis to perform a Pringle maneuver, if needed. The probe is then positioned through the middle of the lesion and that the tip is at the far end of tumor margin, the freeze-thaw process can begin.

The goal of cryosurgery for liver tumors should be similar to modern standards of hepatic resection. Adequate margins of normal tissue should be obtained; 1 cm margins are recommended by most authors. As the ice forms from the center outward, the central area freezes rapidly, the intermediate area freezes at a moderate rate, and the periphery cools slowly. Thermal gradients can range to 10 °C for every millimeter of tissue, depending on the efficiency of the probe. These factors must be considered to ensure adequate tumoricidal temperatures (ie, -35 °C) in the periphery of the iceball.[9]

Ultrasonographic features of the advancing cryolesion are characteristic. In most cases, the freeze front appears as a hyperechoic rim with post-acoustic shadowing beyond this rim (Fig 2). After thawing, the normal frozen liver (which is treated as a margin) appears hypoecholic when compared to normal unfrozen liver. The treated tumor remains hyperechogenic after thawing. This creates a halo effect of hypoecholic normal liver tissue around a hyperechogenic cryolesion, which helps in evaluating the adequacy of margins.[14,15] Usually, the freezing process lasts approximately 8 minutes and a complete thaw lasts 15 to 20 minutes, depending on the size of the tumor and the diameter of the cryoprobe. To achieve optimal tumor destruction, two to three freeze-thaw cycles are recommended. When thawing the lesion completely before starting the next cycle would be time consuming, and since most recurrences develop at the tumor margin, it is our practice to thaw the peripheral 1-cm margin zone following the first freeze before beginning the second freeze cycle.[9,16] Following the second cycle, the probe is rewarmed and rotated gently on its axis before removing to avoid cracking of the liver and hemorrhaging. The probe is not pulled vigorously. Bleeding from the tract of the probe is controlled by packing with a hemostatic agent. The abdomen is then closed in a standard fashion without drains. In most cases, the postoperative course is benign, and the patient is discharged after five or six postoperative days.

Follow-up of tumors treated with cryosurgery consists of computed tomography scans and tumor markers. Successfully treated lesions initially appear larger than the original tumor and then gradually decrease in size or disappear. Necrosis of the tumor is demonstrated by gas bubbles in the tumor, which may be of no clinical significance. Hepatic abscess is rare. The lesions shrink over a three- to six-month period, and an area of fibrosis and architectural distortion persists in most patients.[10] The kinetics of tumor markers such as carcinoembryonic antigen (CEA) have been studied in cryotherapy-treated patients with colorectal cancer. In most patients treated with cryosurgery, CEA levels fall and then return to pretreatment levels when recurrence developed.[17] The fall in CEA usually occurs between four to eight weeks after surgery if cryotherapy has been effective.

### Experience With Cryosurgery

Cryosurgery has been used for a variety of liver tumors, both primary and metastatic. The worldwide experience with cryotherapy reflects the patterns and prevalence...
of hepatobiliary tumors in different parts of the world. Investigators from China have dealt almost exclusively with early and advanced hepatocellular carcinomas, while those in the United States, Great Britain, and Australia have dealt with metastases to the liver from colorectal primaries and some neuroendocrine tumors. Zhou et al.[18] reported on China's initial experience of 35 patients with hepatocellular carcinoma, half of whom had tumors less than 5 cm in diameter. The overall three-year survival was 10%, and the patients experienced no jaundice, ascites, or liver failure. They later reported on 60 patients treated with cryotherapy alone, cryotherapy with hepatic artery ligation, or cryotherapy with resection. In 21 patients with cancers less than 5 cm in size, the one-year and five-year survival rates were 76% and 37.5%, respectively.[19] Overall survival rates were 51% at one year and 11% at five years, while in the cryosurgery-alone group, the survival rates were 33% and 4.3% at one and five years, respectively. Their experience was then expanded to 107 patients with hepatocellular carcinoma, 86% of whom had cirrhosis. Five-year and 10-year survival rates were 22% and 8.2%, respectively, for the whole series, while in 32 patients with small tumors (less than 5 cm), the survival rate was 48% at five years and 17% at 10 years. This series was accomplished with no operative mortalities and no serious complications such as rupture of tumor, delayed bleeding, or bile fistula.[20]

In a pilot study[15] in the United States of 10 patients with colorectal metastases, the first five patients underwent resection after cryoablation with pathology of the resected specimen showing coagulative necrosis of the tumor. A subsequent study[21] reported on 20 patients with liver tumors who were treated with cryosurgery. Sixteen of these patients with colorectal metastasis showed a gradual fall in CEA levels, and two patients with liver lesions from neuroendocrine tumors became asymptomatic with normalization of their tumor markers (5-hydroxyindoleacetic acid and glucagon). The usefulness of ultrasound in cryosurgery was shown in a review of 110 consecutive patients who underwent exploration for hepatic tumors.[22] Ultrasound identified 21 patients unsuitable for resection who were then treated with cryotherapy. At 14 months' median follow-up in this study, 52% of recurrences were noted in the liver, while 24% had systemic recurrence. The authors concluded that cryosurgery was effective in controlling some of the unresectable tumors but that regional or systemic therapy was needed as an adjunct to cryoablation.

In order to evaluate the long-term response, Ravi Kumar et al.[14] evaluated their five-year experience with cryosurgery to treat unresectable hepatic tumors. In this study of 32 patients, 75% had colorectal liver metastases. There were no postoperative deaths and only two major complications. Overall survival was 62% and disease-free survival was 24%, using actuarial analysis. Of the 22 patients who developed recurrence, 12 (54%) failed in the liver and extrahepatic sites; seven (32%) had recurrence in the untreated remaining liver, and three (14%) developed disease in other sites. Of the whole group of 32 patients, however, only three (9%) developed recurrence in the cryosurgery-treated site. Onik et al.[12] reported similar findings on 18 patients with colorectal metastases with a 22% long-term remission rate at a median follow-up of 28.8 months. This group also analyzed their four-year experience with 53 patients with metastatic lesions from ovarian, carcinoid, and head and neck primaries, as well as hepatoma and leiomyosarcoma.[23] An average of four tumors per patient were frozen, with up to 16 lesions treated in one patient. Approximately half of these patients had at least a wedge resection of the liver in addition to cryoablation, and several patients had cryoablation applied to treat a close margin. Long-term survival data are lacking in this series. Data from Australia[17] showed long-term remissions in 18 of 170 patients, while in the New England Deaconess experience, 25% disease-free survivorship is reported.[9] A group in Hawaii reported on nine cases with no mortality at 11 months of follow-up.[24]

Based on the worldwide data from colorectal metastases to the liver and primary hepatic tumors, long-term control appears to be possible in approximately 20% of cases. While the experience with other metastatic tumors of the liver is small, experience with neuroendocrine tumors from the gastrointestinal tract should grow during the next few years, especially for amelioration of symptoms from endocrine activity.[9]

Whether cryotherapy will become an alternative to resection is questionable. Reports currently appear in the literature on the use of cryotherapy as an adjunct to resection. Welling and Lamping[25] described a technique in which the cryoprobe is used as a "handle" to assist in segmental resections of the liver. This technique was initially described in 10 patients, but little information was available on outcome data. In another recent study by Polk et al.[26] involving 13 patients with 16 tumors, the cryoprobe was inserted into the tumor under ultrasound guidance, and a margin of up to 1 cm was frozen. The iceball was maintained, and the probe was used for traction on the specimen while a segmental resection was performed in standard fashion. The authors found this technique useful for wedge resections in the dome of the liver as well as in patients who required a liver resection for a unilateral lesion and had a small contralateral lesion. One postoperative death was reported. The authors suggest that this may allow excision of small tumors with adequate margins and maximal preservation of liver function.

The safety of cryoablation in the management of liver tumors has been documented in several studies. Operative mortalities and major complications have been rare in more than 300 reported patients. Complications include pleural effusion (of little clinical significance), hemorrhage due to liver cracking, hepatorenal syndrome, and acute tubular necrosis ascribed to myoglobinuria. Bile leaks and fistulas also have been reported, as well as subphrenic and intrahepatic abscesses.[7,8,12] The length of hospital stay for patients who undergo cryosurgery is approximately six days compared to an average of 10 to 12 days for those who undergo major hepatic resection. Acute tubular necrosis and acute tubular necrosis ascribed to myoglobinuria have been reported. Bile leaks and fistulas also have been reported, as well as subphrenic and intrahepatic abscesses. Bile leaks and fistulas also have been reported, as well as subphrenic and intrahepatic abscesses.

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Impact of Cryosurgery Technology for the Future of Hepatobiliary Surgery

While cryoablation has expanded the possibilities of tumor control and disease progression, limitations remain for patients with inoperable hepatic malignancies. A laparotomy is still required in most cases for adequate performance of the procedure. A new area of exploration is the use of laparoscopic surgery to perform these procedures. Another limitation is the persistently high rate of failure in the untreated part of the liver, presumably due to micrometastatic disease. Combinations of cryoablation and regional infusion chemotherapy may improve control in the liver.

While laparoscopy has been used to perform many abdominal procedures, it is not currently applicable to major hepatic resection. However, the technology has been developed that allows the use of ultrasound of the liver through the laparoscope. Our experience has been with the B&K Ultrasound System (Marboro, Mass), which uses convex array laparoscopic transducers with various depths of penetration (5.0 MHz, 6.5 MHz, and 7.5 MHz) and a 90°-degree flexion and extension tip that ensure direct contact with the liver anteriorly, laterally, and over the dome. A 10/11 port is necessary, and adequate sagittal and transverse views of the liver can be obtained by changing the position of the transducer. Prospective studies of laparoscopic ultrasonography followed by open sonography have shown that laparoscopic transducers can accurately delineate hepatic anatomy, can localize occult tumors, and can delineate the relationship of tumors to major vessels and bile ducts.[27]

The cryoprobe developed for laparoscopy are a modification of those used for conventional open surgery. We have used a 4.8-mm diameter probe that fits through a 5-mm laparoscopic port and is 40-mm long. In open surgery, the appropriate diameter and length of the probe depend on the size of the lesion. However, in contrast to open surgery, the placement of the laparoscopic trocars must be individualized in accordance to the location of the lesion. Instead of using standard trocar sites, the trajectory of the cryoprobe may need to be defined before inserting the trocar. Once this is established using ultrasound, the tumor is localized with a long needle that can be passed percutaneously or through one of the ports. A J-type guide wire is passed, the needle is removed, and a dilator with a sheath is passed over the guide wire. The cryoprobe is then passed through the sheath. The sheath used for laparoscopic cryosurgery is stiffer than usual to avoid collapsing or bending. The sheath is pulled back to the edge of the liver surface, and cryoablation is completed under laparoscopic vision and ultrasound monitoring. The sheath is then pulled up to the frozen tumor, and the cryoprobe is removed. The tract of the probe can then be packed with a hemostatic material in the same way as the open technique to minimize bleeding. The pneumoperitoneum is well maintained with this technique.[8]

Experience with the laparoscope and cryosurgery is limited and has been confined to solitary tumors in accessible locations. In a report from Scotland[28] in which laparoscopic cryoablation was used to treat 18 patients, complications were similar to those seen with a standard approach, but data on longer-term outcome are not
Recurrence Following Cryotherapy

Recurrence in the untreated liver after cryotherapy poses a significant problem, and alternative or adjunctive therapies must be explored as part of a multimodality treatment. Systemic chemotherapy has been ineffective in malignant tumors of the liver. Compared to systemic therapy, regional chemotherapy (particularly fluorouridine [FUdR]) administered through pumps placed in the hepatic artery has shown improved response rates, but survival with advanced tumors has not improved.[29] At the present time, intrahepatic chemotherapy is being tested as an adjunct to resection, based on the assumption that recurrences in the liver are the result of micrometastatic deposits that are undetected at the time of treatment. An Australian group has applied the same principle to tumors treated with cryotherapy.[30,31] In their experience with unresectable colorectal metastases, 11 patients were treated with cryotherapy alone, and 38 patients were treated with cryotherapy and hepatic artery infusion of 5fluorouracil and folic acid in a four-day regimen repeated monthly. They concluded that patients with cryotherapy alone were three times as likely to die of disease as patients treated with cryotherapy and intra-arterial 5fluorouracil. Median survival for the cryotherapy-only group was 245 days compared to 570 days for the treated group. However, this was not a randomized trial, and pumps were placed in all 38 patients with the intention of administering intra-arterial chemotherapy. The 11 patients in the cryotherapy-only group were either those in whom the delivery system failed or those who could not receive intra-arterial chemotherapy for other reasons.[32]

A trial to evaluate cryotherapy and regional chemotherapy is ongoing at our institute. It is based on the rationale that in randomized trials of intrahepatic chemotherapy, patients with lower liver tumor burden and lower lactate dehydrogenase and CEA levels showed significant benefit in tumor response and time to progression when compared to systemic chemotherapy.[29] In our phase I/II trial using 5fluorouracil and FUdR, we have shown that cryotherapy with regional chemotherapy can be used safely without increasing hepatic toxicity. Preliminary results show an intermediate remission rate of 67% compared to the 20% to 25% remission rate that has been achieved with cryotherapy alone. We are completing two-year median follow-up data and are incorporating a quality-of-life assessment protocol before recommending the study as a multi-institutional phase II or phase III study in the near future.

Conclusions

Cryotherapy is a treatment modality that can offer reasonable hope to not only the patient with unresectable primary or metastatic tumor in the liver, but also the patient with poor hepatic reserve or comorbid conditions that preclude a major resection. Cryotherapy can be used for more than one liver lesion, for bilobar disease, and as an aid in segmental resections. It is useful for the treatment of hepatocellular carcinoma, colorectal cancer, and metastatic neuroendocrine tumors. The high rate of recurrence in multifocal liver tumors after cryotherapy suggests the need for effective adjuvant therapies; one option may be the addition of intrahepatic infusion of cytotoxic drugs. Minimally invasive techniques for ultrasound-guided cryoblolation will continue to evolve with the hope that technology development will be parlayed to the optimal patient outcome.

References


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