Cryosurgical Ablation of Hepatic Neoplasms

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Cryosurgical ablation involves the in situ freezing and resultant devitalization of neoplastic lesions. It offers a number of potential advantages over surgical resection that make it particularly appealing for the treatment of hepatic neoplasms. Recent improvements in imaging modalities used to monitor cryosurgery, particularly ultrasonography, have made it a reasonable procedure in select patients.

Colorectal carcinoma accounts for the second highest cancer-related mortality in the United States with nearly 70,000 annual deaths from this disease.[1] Approximately 150,000 new cases are diagnosed each year. The liver represents the sole site of metastatic spread in approximately 20% of cases, reflective of the preferential spread of colorectal cancer to the liver via the portal venous system.[2] Unfortunately, fewer than 25% of these patients (i.e., 4000 to 5000 patients) are candidates for surgical resection secondary to bilobar involvement, proximity to major vessels, poor liver reserve, or co-morbid disease states. Currently, systemic chemotherapy offers no significant impact on survival in patients with colorectal liver metastases with response rates in the range of 20% to 30%.[3]

Although less common in the United States than in Asia and Africa, hepatocellular carcinoma is the most prevalent malignant neoplasm worldwide. It accounts for 80% of primary liver tumors. These cancers frequently arise in association with cirrhosis. This association, coupled with the poor overall condition of most patients with hepatocellular carcinoma and the usual advanced stage of the tumor at presentation, often precludes surgical resection for patients in this group. Furthermore, results of regional and systemic therapy for unresectable hepatocellular tumors have been uniformly disappointing with no evidence of improved survival. A variety of alternative methods have been evaluated to treat the large number of patients with either primary or metastatic liver tumors not amenable to surgical resection.

Cryosurgical ablation has recently been proposed as a potential therapy for select patients with hepatic neoplasms. Cryosurgery involves the in situ freezing or devitalization of neoplastic lesions. A liquid coolant (nitrogen) is circulated through insulated probes which are strategically placed in contact with the tumor (Fig. 1). Early applications of this process were primarily for superficial lesions, but the emergence of advanced complimentary modalities such as high-resolution intraoperative ultrasound has made possible the cryosurgery of less accessible visceral lesions. Even tumors deep within hepatic parenchyma can be destroyed with minimal loss of surrounding normal tissue.[4] This feature has allowed for

focal treatment of hepatic lesions that might not otherwise be amenable to therapy.

In general, cryosurgery has been used primarily with a curative intent not only for metastatic colorectal carcinomas to the liver but also for primary liver cancers. In addition, it has been used as palliative treatment for metastatic neuroendocrine tumors to the liver. Although prospective comparison trials are still needed, cryosurgery appears to be an effective treatment modality in select patients. Intraoperative placement of cryoprobes and monitoring of tumor freezing by ultrasound has produced complete remission in 22% to 29% of patients with unresectable, metastatic colorectal carcinoma to the liver.[5,6] In addition, Zhou has demonstrated excellent long-term disease control in patients with hepatocellular carcinoma.[7]

CRYODESTRUCTION

The coldest temperature reached in tissue has been shown to be the most important determinant in causing cellular necrosis.[8] Early investigations have suggested that all living tissue subjected to a temperature of –20°C or below for one minute or longer would undergo necrosis.[9] More recent studies, however, recommend a treatment goal of at least –40°C or below in all areas of tumor so as to minimize local recurrence and to compensate for errors in clinical judgment (i.e., assessment of the actual margin, etc.).[8] To achieve these lethal temperatures within the tumor, liquid nitrogen is supercooled and then circulated at –196°C through cryoprobes which are well insulated throughout their length, except at the distal tip (Figs. 2a-c). It is the tip, placed within the tumor, where the freezing process occurs.

The damaging effects on cellular integrity result from both the severe hypothermic environment as well as from the processes of freezing and thawing. *Hypothermia* deprives cells of the thermal energy necessary to drive cellular processes, resulting in both metabolic uncoupling and the compromised integrity of organized membranous structures. *Tissue freezing* results in both the extracellular and intracellular ice propagation of pure water, excluding electrolytes and proteins. This exposes cells to an extremely hypertonic milieu that draws additional water out from within intracellular spaces, leading to further cell shrinkage and membrane damage. Additionally, the shearing forces from the ice crystals themselves are mechanically disruptive to both organelles and cellular membranes.[10] Rapid freezing maximizes the cellular injury. *Thawing* is also a damaging process since any remaining viable cells are then subjected to additional destructive forces. In early warming, smaller ice crystals recrystallize into larger ones–producing continued destructive shearing activity.[11] As warming progresses and melting occurs, intact cells become exposed to a now hypotonic environment. These cells may burst from the resulting osmotic forces and volume expansion. In contrast to the rate of freezing, a slow thaw is associated with optimal cellular damage. Thrombosis and obliteration of tissue microvasculature also occur throughout the entire cryodestructive process and further contribute to both tissue anoxia and hypoxic cell death.[12]

Studies have suggested that two freeze-thaw cycles may be necessary to achieve maximal tissue kill.[6] Although there is some debate as to the necessity for more than one freezing treatment, in clinical practice, the freeze-thaw cycle is generally repeated to assure maximum tissue destruction. With cryosurgical ablation of a liver neoplasm, the initial tumor freeze is followed by a slow passive thaw, and the second freeze is followed by a relatively active thaw (with warm nitrogen gas circulated through the cryoprobe).

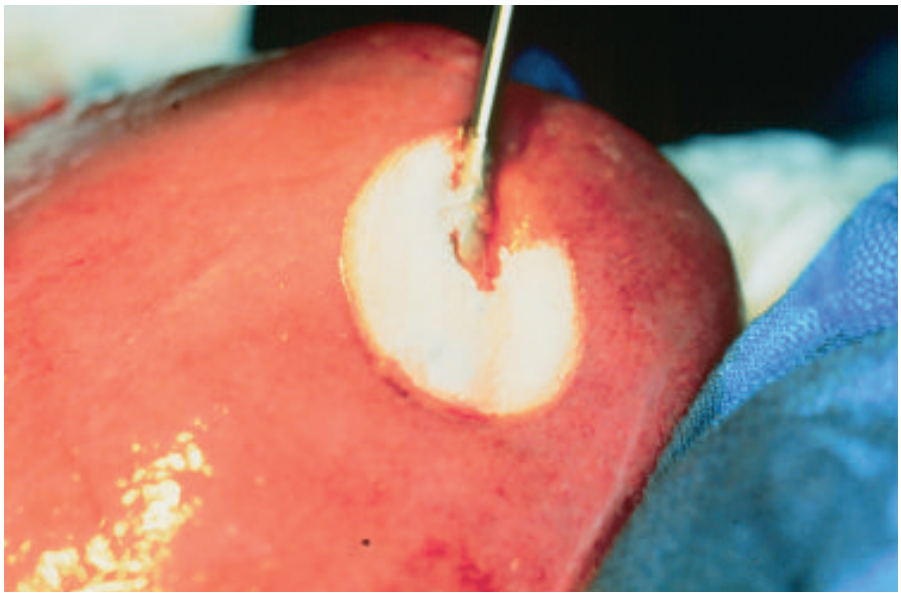

Figure 1. Freeze zone around a cryoprobe located within a superficial colorectal metastasis to the liver.

MONITORING

Dramatic advances in imaging technology, particularly the development of computer-enhanced, real-time intraoperative ultrasonography and high-frequency transducers, have allowed for the safe and precise monitoring of cryotherapy for deep-seated visceral lesions. The freezing interface may be visualized as an advancing hyperechoic hemispheric rim with complete posterior acoustic shadowing (Fig. 3).[5,13,14] As the iceball expands, the hyperechoic rim increases in size as does the posterior acoustic shadowing.

The temperature at the periphery of the cryolesion visualized on ultrasound corresponds to 0°C. There is an approximately 10 to 20°C/mm decrement in temperature from the outer rim of the iceball toward the center. Since –40°C is felt to be required to assure tissue necrosis, there is a small rim of frozen tissue inward from the iceball's edge which potentially may contain viable cells. Therefore, as with traditional surgical resection, a margin of normal liver parenchyma surrounding a neoplasm is encompassed to assure adequate treatment. Generally, a 0.5- to 1-cm freeze zone beyond the lesion is included to create a tumor-free margin of devitalized tissue.

While external ultrasound may be as accurate as computed tomography for detection of metastatic tumors in the liver of at least 2 cm in size, intraoperative ultrasound has been shown to be

the most accurate method for detecting the presence of occult liver metastases. Several studies have shown that intraoperative ultrasound will detect an additional 10% to 30% of lesions not identified by preoperative imaging modalities.[15-17] Furthermore, it is important for determining the relationship of these lesions to critical vascular or biliary structures. As such, prior to performing any cryosurgical ablation, the entire liver is carefully scanned by ultrasound. Special attention is directed toward lesions already identified by preoperative imaging studies. Both palpable and nonpalpable masses are evaluated for their size, shape, and relationship to other structures within the liver.

The liver may be scanned using a variety of available ultrasound transducers. It has been our preference to use both 5.0 MHz and 7.5 MHz intraoperative transducers in association with the B&K Medical Systems 3535 Ultrasound Scanning System (Fig. 4). The 5.0 MHz transducer has a flatter contour with finger grooves that facilitate evaluation of the dome of the liver beneath the diaphragm. In addition, its lower frequency allows for an increased depth of penetration which may be necessary to image more deep-seated lesions. Alternatively, the 7.5 MHz transducer allows for better resolution, particularly of more superficial metastases. It is the transducer we use most frequently to guide needles for biopsy or localization prior to cryoprobe insertion. If not previously done, when a tumor is identified by intraoperative ultrasound, a biopsy may be obtained utilizing an automated core-biopsy needle with ultrasound guidance and the biopsy sent for pathologic confirmation prior to initiation of the cryosurgical procedure.

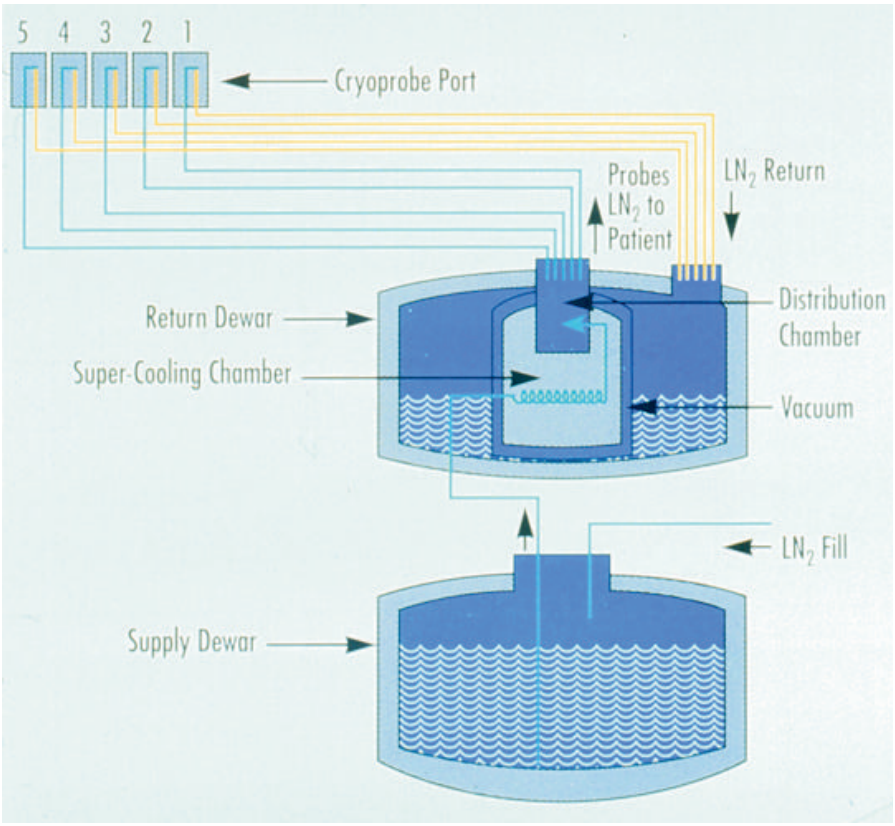

Figure 2a. Graphic demonstration of the circulation pathway of supercooled liquid nitrogen from the cryosystem then to and from the cryoprobes.

TECHNIQUE

The patient is prepared and draped in a standard fashion appropriate for any major hepatic resection. Abdominal, thoracic, and vascular instruments should be available in addition to the ultrasound and cryoprobe systems. To help maintain normothermic conditions, warming blankets are placed beneath the patient and over the lower extremities. Anesthesia is requested to heat inspired gases as well as intravenous fluids, and the operating room itself is maintained at a slightly elevated temperature.

Operative liver exposure is achieved using either an extended right subcostal incision or an upper midline incision. The liver and abdomen are inspected for lesions. If no disease suggesting incurability is identified, such as extrahepatic disease or unexpected disease

Figure 2b. Graphic demonstration of the circulation of the liquid nitrogen through the inner and outer cannula at the cryoprobe tip.

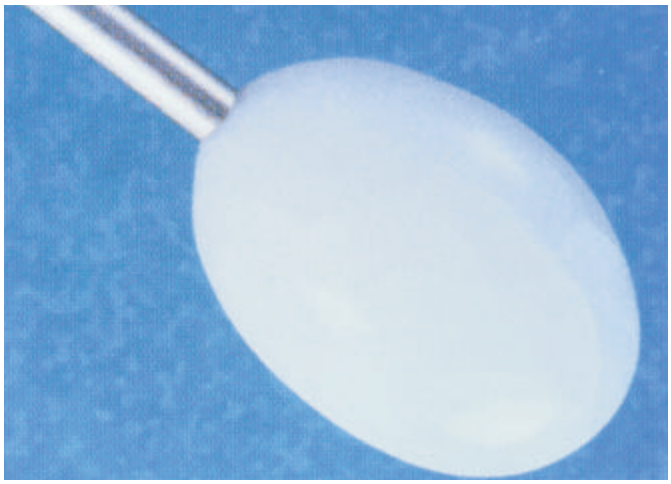

Figure 2c. Gross demonstration of an iceball formed at the distal tip of a 3-mm cryoprobe.

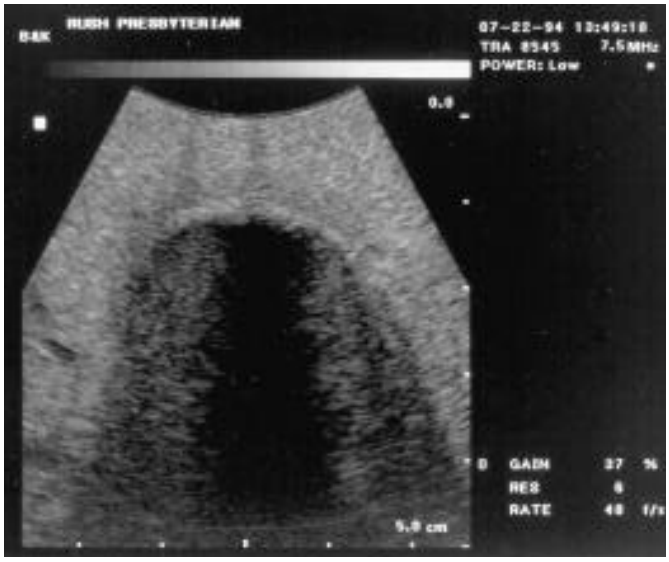

Figure 3. Intraoperative ultrasound image of the freezing interface advancing over a liver neoplasm and visualized as a hyperechoic rim with posterior acoustic shadowing.

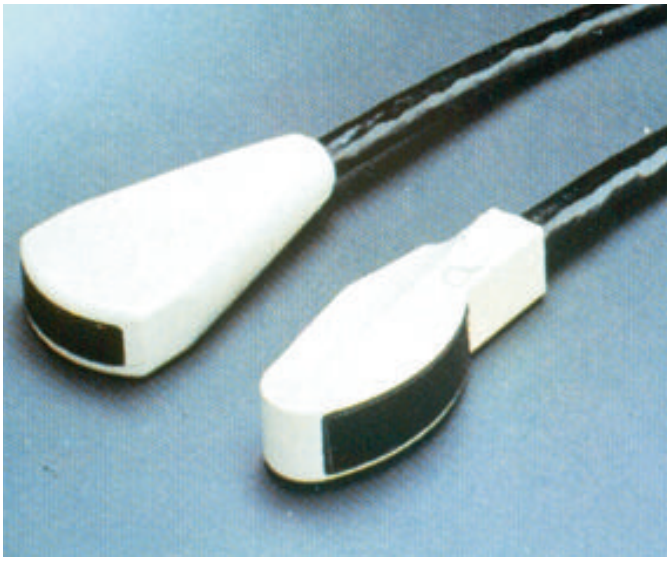

Figure 4. Intraoperative transducers of the 7.5 MHz type shown on the left and the 5.0 MHz type on the right.

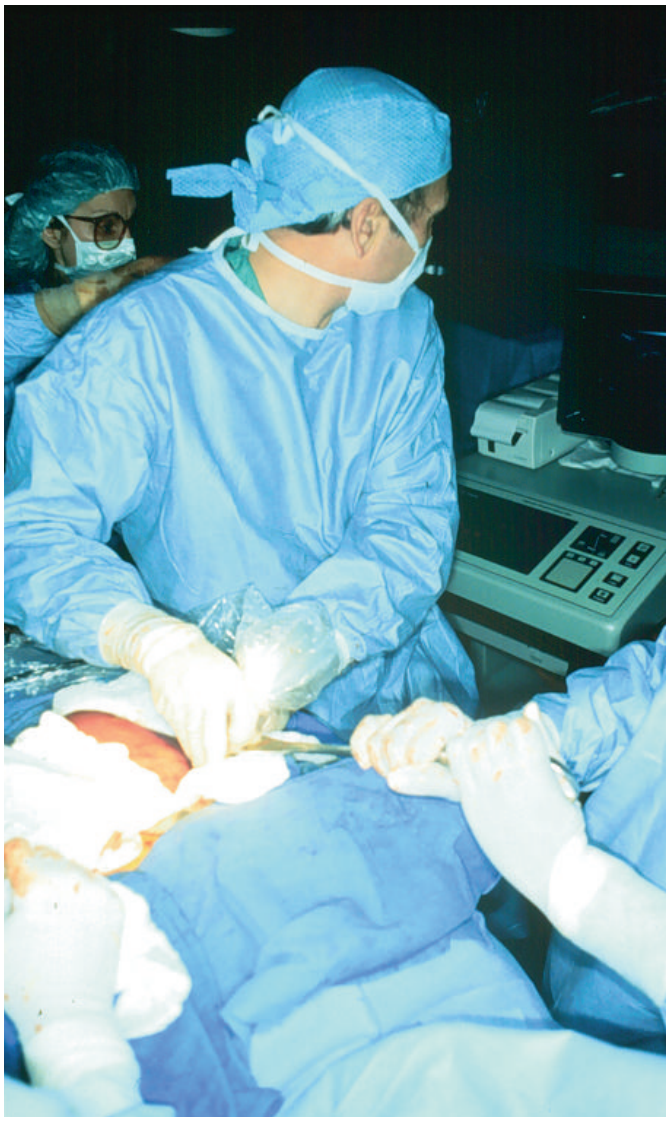

Figure 5. Demonstration of the technique of intraoperative ultrasound scanning of the liver prior to performance of cryosurgery.

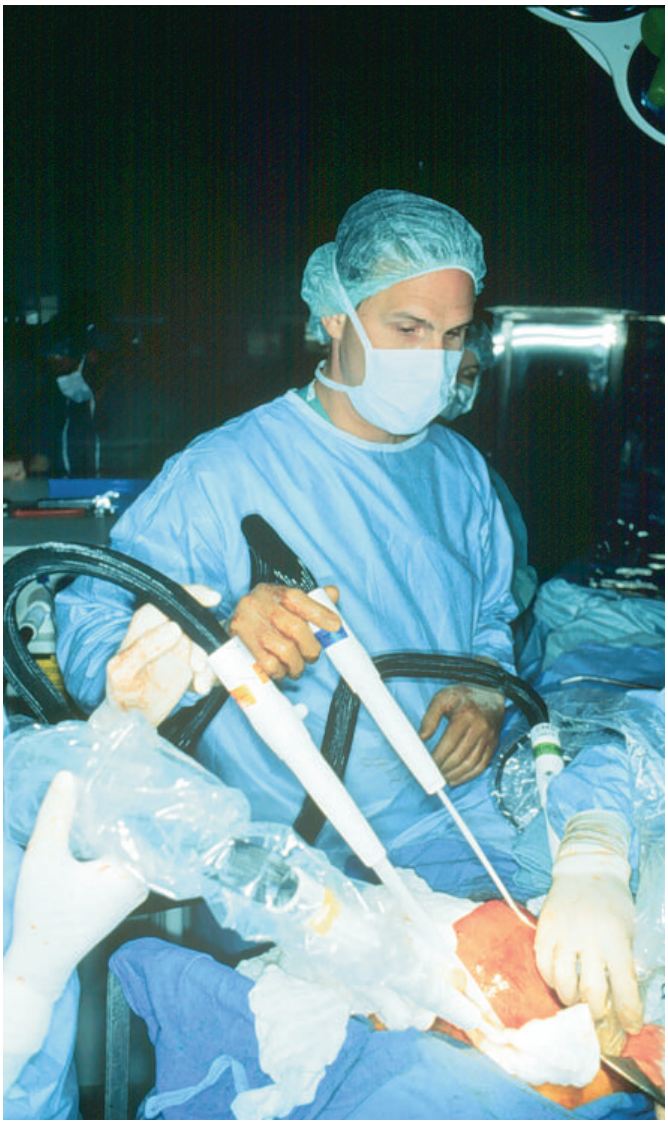

Figure 6. Demonstration of the use of multiple cryoprobes to treat two large hepatic neoplasms simultaneously.

within the liver itself, the procedure is allowed to continue. Palliative procedures for metastatic neuroendocrine cancers represent an exception for excluding patients based on unresectability, and these patients are prepared for cryoablation as well. The liver is fully mobilized by lysing all adhesions and ligaments attaching it to the abdominal wall, diaphragm, and adjacent viscera. The liver is carefully palpated for intrahepatic tumors. It is then thoroughly scanned with both the 7.5 and 5.0 MHz ultrasound transducers for both palpable and nonpalpable disease as previously described (Fig. 5). Lesions to be frozen are marked on the liver surface with electrocautery to designate safe pathways for the insertion of needles and cryoprobes so as to avoid injury to major vessels and bile ducts.

In some circumstances, we perform a laparotomy with the intention of surgically resecting a hepatic neoplasm only to find that the patient's condition is more amenable to cryosurgical ablation. The reverse of the above, although less common, does occur as well. In approximately 50% of cases, neither procedure is performed secondary to unexpected extrahepatic disease or extensive intrahepatic disease. Occasionally, despite a planned cryosurgical intervention for an appropriate tumor(s), one or more smaller, generally superficial tumors may be identified which are easily amenable to minor wedge resection. When possible, we excise these lesions and carefully obtain hemostasis prior to treatment of any remaining lesions best thought treated by cryoablation (i.e., those larger, deep-seated, and/or in proximity to major vascular structures). In general, we limit treatment (regardless of type) to no more than six hepatic tumors and will not cryotreat individual tumors larger than 8 cm in greatest dimension.

There are two primary sizes of probes available for cryosurgery of hepatic neoplasms. A 3-mm diameter probe which creates a spherical freeze zone up to 4 cm in diameter, and an 8-mm diameter probe which creates a freeze zone up to 6 cm in diameter (and does so more rapidly than the smaller probe). The appropriate number and sizes of probes are determined according to the number and size of hepatic neoplasms. Multiple lesions may be treated simultaneously using the Cryomedical Sciences AccuProbe

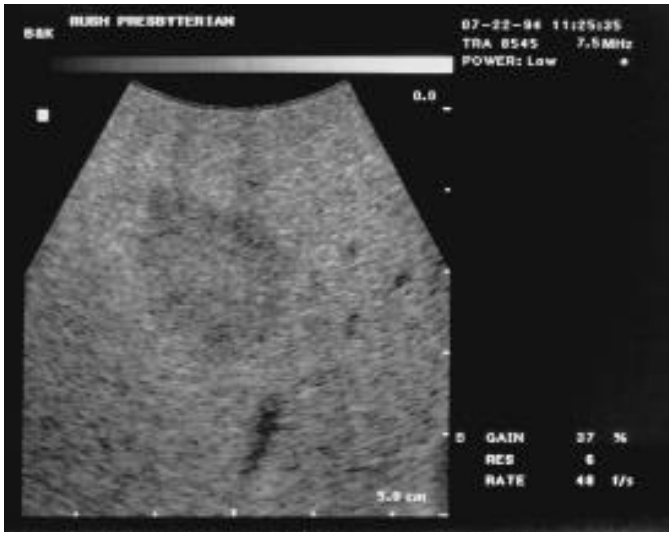

Figure 7a. Ultrasound image of an irregularly shaped 2.5 x 2 cm hypoechoic liver metastasis.

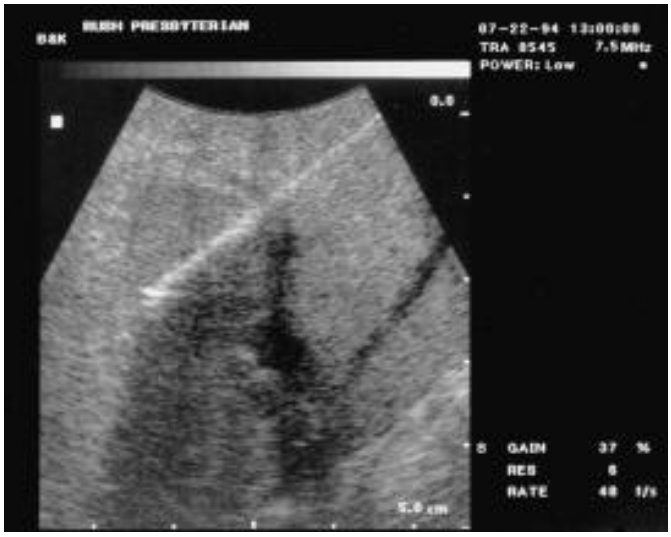

Figure 7b. Ultrasound-guided placement of an 18-gauge needle through the center of the metastasis to its opposite periphery.

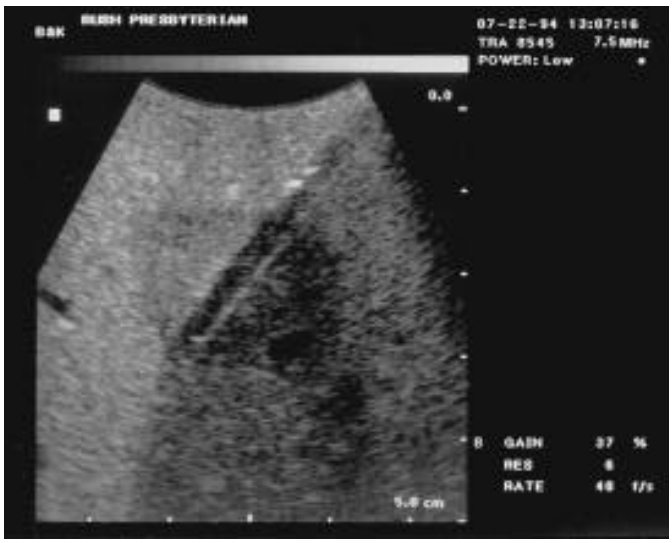

Figure 7c. Ultrasound image of proper placement of the sheath through the metastasis to the opposite periphery after removal of the guidewire and dilator.

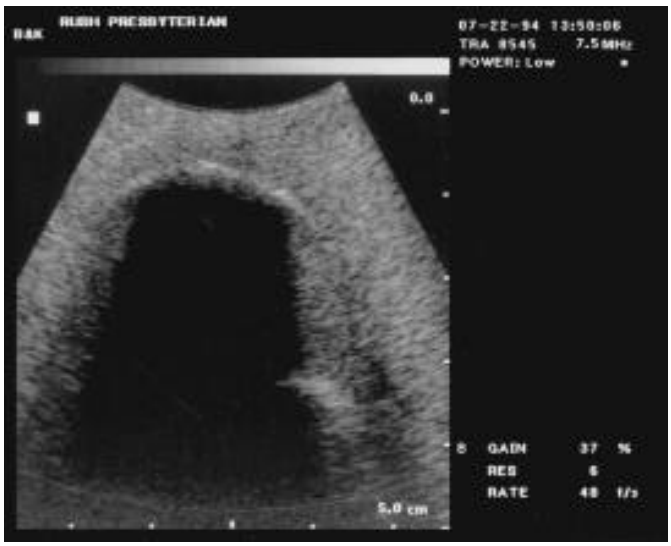

Figure 7d. Ultrasound image of the freezing front from the iceball beginning to encompass the hepatic metastasis.

System which has the capability of accommodating up to five probes. Treatment of larger tumors may require the use of multiple cryoprobes within the same tumor because of the limits in the size of the freeze zone obtained with any single probe (Fig. 6). In practical terms, the number of probes inserted into the liver at any one time is limited to three and rarely four so as not to compromise adequate ultrasound monitoring of the freezing process.

After all lesions have either been excised or marked for cryosurgery, the liver is insulated from surrounding structures with laparotomy pads or rubber tissue protectors to prevent inadvertent extrahepatic thermal injury. Cryoprobes may then be placed directly through liver parenchyma into the lesions or be inserted utilizing a modified Seldinger technique described by Onik.[18] We prefer the latter technique out of concern for the potential malpositioning of large probes which may necessitate replacement. Under ultrasound guidance, an 18-gauge echogenic-tipped needle is advanced into the liver parenchyma via a previously designated safe pathway (marked by electrocautery) into and through the tumor to its opposite periphery (Figs. 7a-d). A guidewire is then placed through the needle until the *j*-portion is visualized exiting the needle tip at the margin of the tumor. Grasping the wire, the needle is carefully withdrawn and a dilator and sheath advanced over the guidewire through the tumor. An 11-Fr dilator and sheath are used for the 3-mm cryoprobes and a 24-Fr dilator and sheath for the 8-mm cryoprobes. Once in proper position, the guidewire and dilator are removed, leaving the sheath in place. Instillation of a small amount of saline into the lumen of the sheath improves the relative echogenicity of the sheath, enhancing its visualization on ultrasound and confirming its proper position. The cryoprobe is slowly advanced through the sheath while monitoring its location with ultrasound guidance. Once the cryoprobe reaches the proper position, the sheath is pulled back to expose the distal tip. To secure the location of the probe its temperature is cooled to –100°C to "stick it" to surrounding tissue. Additional probes are then inserted in an identical fashion as necessary.

The freeze-thaw cycles are then accomplished by reducing the probe temperatures to "maximum freeze," i.e., –196°C. The initial freeze is followed by a brief passive thaw and the second freeze is followed by an active thaw. Each freezing period is maintained for approximately 15 minutes while the passive thaw is approximately 10 minutes in length. Recent evidence suggests that it is probably necessary to maintain each freeze for only as long as it takes to obtain a satisfactory margin. The cryolesion is monitored by ultrasound to assure that the freezing front encompasses both the hepatic tumor as well as a 0.5-cm to 1.0-cm margin of normal parenchyma. After the second freeze the cryoprobes may be dislodged and removed with a slight rotatory motion once the temperature has decreased to approximately –20°C. After removal of the cryoprobes, the tracts may be packed with a variety of hemostatic agents as required. We generally use small thrombin-soaked pellets of Gelfoam (Upjohn Co., Kalamazoo, MI); this alone controls the intraoperative bleeding quite effectively in most cases. After adequate hemostasis is achieved, the abdomen is closed in the usual fashion. Most patients are able to be discharged on the fifth to sixth postoperative day.

Hepatic cryosurgery has been shown to be associated with minimal morbidity and rare mortality. Patients routinely experience transient elevations of their liver function tests, white blood cell counts, and temperature postoperatively. Other common sequelae include mild to moderate pleural effusions. Patients may have a transient prolongation of their coagulation studies. Myoglobinuria has been reported to occur in direct relation to the quantity of tissue frozen. Prior to awareness of this side effect and the institution of appropriate precautionary measures, rare cases of acute tubular necrosis were reported. Lastly, isolated cases of biliary fistula, hepatic abscess, hepatic failure, and cardiac arrest have been reported.

CONCLUSION

Cryoablation of unresectable hepatic neoplasms has left the realm of a purely investigational procedure and would now appear to represent a viable option in the management of these patients. It is reasonable to consider evaluating whether it will provide an effective alternative to surgical resection despite the latter's being technically feasible. For now, cryosurgical ablation of the liver should be limited to unresectable, metastatic carcinomas of the colon and rectum, unresectable hepatocellular carcinomas, and to the palliative treatment of metastatic neuroendocrine tumors. STI

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