Cryosurgery in the Treatment of Liver Metastasis From Colorectal Cancer

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The practice of using ultrasound in the operating room has allowed resections for primary and metastatic liver cancer to be performed with increased safety and has permitted the accurate delineation of surgical margins—important concepts in achieving localized tumor control with improved patient outcome. Further, ultrasound enables the identification of unsuspected bilobar liver disease and demonstrates the proximity of tumors to critical vascular structures. Although the operative mortality of major hepatic resection is now in the range of less than 5%, there are clearly patients who will not benefit from resection or simply will not tolerate resection because of poor hepatic reserve. A recent article by $u et al. reviewed 74 patients with colorectal metastases over a 14-year period; patients with Dukes’ B primary colon cancer, one to three lesions, and unilobar disease had 5-year survival rates of 36%, 24%, and 26%, respectively. These patients were demonstrated to benefit from hepatic resection. However, these same investigators reported a very high mortality rate in 12 patients who underwent trisegmentectomy or extended resection. The treatment of unresectable liver metastases has traditionally relied on systemic chemotherapy. Since systemic therapy did not change the survival or patterns of failure, several regional therapy options (chemotherapy and ablative approaches) have been explored.

There are various options for treating inoperable liver tumors, with cryotherapy being one of them. Percutaneous injection of 95% alcohol, although useful for treating small hepatocellular carcinomas, particularly in cirrhotic patients, has not found success in colorectal liver metastasis. Various forms of intraarterial chemotherapy and embolization of branches of the hepatic arterial supply to the tumors are useful in unresectable liver tumors. Cytoreduction and sequential resection is another strategy that has been reported. A series from the Liver Cancer Institute in Shanghai reported on 72 patients with hepatocellular carcinoma who were resected out of a group of 663 patients deemed unresectable on initial exploration. These patients 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 5 years was 62%. Data on such an approach for colorectal liver metastasis are lacking.

CRYOSURGERY—BIOLOGIC CONSIDERATIONS

Cryosurgery or cryoablation is a technique that involves the use of extremely low temperatures to destroy tumors, which are then left in place to be reabsorbed. It is a focal therapy that allows treatment of lesions with preservation of normal tissue. Cryosurgery has been used in other organs such as the skin and entails direct contact with liquid nitrogen at low temperatures. This was the initial form of therapy used in the liver and involved application of liquid nitrogen on the surface of the liver. Modern liquid nitrogen delivery systems and vacuum-insulated recirculating nitrogen probes have now been developed that allow this technique to be used to treat tumors in virtually any segment of the liver. Real-time ultrasound permits accurate placement of probes and monitoring of the extent of freezing; the ice ball or "cryolesion" can actually be seen as it develops, along with the margin of normal tissue frozen around the
tumor, thus utilizing the same principle of surgical resection \(^5,6\) (Fig. 1).

Cryosurgery works by destroying cells directly as a result of physicochemical effects and indirectly by affecting the structure of vascular channels. The process begins when liquid nitrogen circulates at \(-196^\circ C\) through a probe that is placed in direct contact with the tissue to be treated; in this case the probe is placed under ultrasonographic guidance through the liver substance into the tumor. As ice forms, electrolytes and organic compounds are excluded from the crystal. A hyperosmolar environment is created in the extracellular compartment, which 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 and more tissue crystallizes when small ice crystals grow together with large crystals, a grinding action is created that mechanically disrupts the tissue. Rapid freezing and slow thawing enhances tissue damage. As the treated area warms, water passes into the cells, leading to an increase in volume and bursting of the cell membranes. This process is repeated more than once so that any remaining viable tumor cells are destroyed on the second or third cycle. \(^6,7\) Animal experiments confirmed the destruction of tumor cells in in vivo and in vitro studies. \(^7\) The effectiveness of cryosurgery to control experimental colorectal liver metastasis was investigated in a rat model. Rat livers were implanted with tumor cells on one of the lobes of the liver; the animals were randomly assigned to one of three groups: no therapy, resection, or cryotherapy. The animals randomized to the cryotherapy group did just as well as those undergoing resection.

Cryotherapy also causes obliteration of tumor vessels leading to hypoxia and necrosis. This occurs in small-caliber arteries and veins as they undergo thrombosis as a result of direct contact with subzero temperatures. Fortunately, large vessels such as the hepatic veins and portal veins are protected from this effect because the flow of warm blood makes them act as thermal sinks, thus protecting their intima and media. To achieve the maximum effect, the temperature should be lowered rapidly to at least \(-35^\circ C\) and

![Figure 1](image-url)