Hepatic Cryosurgery: Early Experience in Hawaii

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Liver cancer, both primary and metastatic, is often deemed hopeless and patients with advanced disease cannot be offered a treatment that is completely effective. Surgical resection is the treatment of choice, but less than 20% of patients are candidates for this treatment.

Hepatic cryosurgery is a relatively new procedure in which the tumor is localized intraoperatively with ultrasound guidance and exposed to liquid nitrogen at -196°C. Nine cases have been performed in Hawaii, and we present the first four cases here. Of these cases, there were no mortalities and only one patient required blood transfusion. All patients currently are alive with up to 11-month follow-up. Longer-term studies will be necessary to assess the effectiveness of this modality.

Primary hepatic neoplasms account for more than one million deaths a year worldwide. There is considerable geographic variation—as low as one death per 100,000 in the U.S. and as high as 100/100,000 deaths in parts of Asia and southern Africa. Risk factors for hepatoma include the presence of viral hepatitis B and C, exposure to certain toxins (aflatoxins or thorotrast), primary biliary cirrhosis, hemochromatosis, and alcoholic liver disease. Any chronic liver disease can predispose a patient to liver cancer and 70% of all hepatocellular cancers occur in those with cirrhosis.[1] Typically, symptoms occur late and most patients present with advanced disease.

Metastatic liver cancer frequently originates in the gastrointestinal (GI) tract, but can come from any primary tumor in the body. Colorectal cancer is the most common GI malignancy that metastasizes to the liver. More than 138,000 patients in the U.S. will develop colorectal cancer, and 55,000 will die of it yearly. Nearly 70% of patients who die of colorectal cancer will have metastatic lesions to the liver.[2]

The only potentially curative therapy for both primary and secondary liver cancer is surgical resection and liver transplantation in certain circumstances. The magnitude of this problem lies in the fact that less than 20% of all patients will be candidates for surgery and other therapies, such as chemotherapy, chemo-embolization, intrahepatic artery chemotherapy, and percutaneous ethanol injection, used only for palliative or adjunctive therapies. Hepatic cryosurgery is a new surgical treatment used to eradicate disease and possibly improve long-term survival. It can be used for unresectable lesions because of the presence of multiple lesions, bilobar disease, poor liver reserve, or proximity to major vessels. Morbidity and mortality are low and early studies are promising. In essence, it increases the number of patients who are surgical candidates and provides them with a potential cure. Early studies are promising; however, the long-term benefit of this treatment needs to be studied.

Methods and Materials

The four cases of hepatic cryosurgery performed at St Francis Medical Center all underwent general anesthesia with placement of central venous and arterial catheters for monitoring. Body temperature was carefully monitored and a Bair Hugger® was used for warming. All lesions were biopsied prior to treatment. All procedures were performed using a Cryotech LCS 2000 cryosurgical system with intraoperative ultrasound guidance. Various probes were used to freeze the tumor with liquid nitrogen to -180°C to -190°C: 5 mm, 10 mm, and flat. Each lesion was frozen until a halo of normal tissue measuring about 1 cm could be seen around the tumor on the ultrasound, about 7 to 10 minutes, after which the lesion was thawed completely. Each lesion underwent two freeze-thaw cycles. Areas were carefully inspected for liver cracking and hemorrhage; bleeding was controlled with Gelfoam and suture ligation. All patients remained in the intensive care unit for the first 24 hours and were maintained with mannitol and low-dose dopamine to prevent rhabdomyolysis and acute renal insufficiency. Bleeding parameters were monitored closely and liver enzymes were obtained daily. An ultrasound of the abdomen was done before the patient was discharged. CT scans were used for follow-up at one month, three months, and every three months thereafter and tumor markers were followed.

Case One

A 71-year-old man with Duke's B rectal carcinoma underwent abdominoperineal resection in 1991. No evidence of liver metastases was noted and his medical history was notable for non-insulin diabetes. He remained completely asymptomatic; a follow-up CT scan in September 1994 demonstrated a 2.5 cm lesion in the left medial segment of the liver, and a 1.0 cm lesion in the right lobe. Carcinoembryonic antigen or CEA: 2.0 ng/ml; alpha fetoprotein was normal. Percutaneous biopsies of these lesions were consistent with adenocarcinoma. Chest x-ray and bone scan were negative for metastatic disease. Exploration of the abdomen was notable for micronodular cirrhosis and two liver lesions: a 3.3 cm lesion in the left medial segment just adjacent to the falciform ligament and a 1.8 cm lesion in the right lobe of the liver. Frozen section liver biopsies were not diagnostic for carcinoma and the abdomen was closed. Permanent stains were consistent with hepatocellular carcinoma. The patient returned to the operating room 72 hours later and underwent hepatic cryosurgery on both lesions. He had no intraoperative problems, received no blood transfusions, and was discharged six days following the operation. His highest SGOT was 771. He had mild thrombocytopenia, 75,000/cc, which resolved by the time of discharge. At 11 months post-cryosurgery, he is doing well and the liver lesions have decreased on serial CT scans.

Case Two

A 52-year-old woman with invasive ductal breast carcinoma underwent left modified radical mastectomy and adjuvant chemotherapy in 1986. She did well until 1992 when she developed superior vena cava syndrome as a result of neck node metastases. She also had bony metastases and both areas were radiated. In 1994, she underwent autologous bone marrow transplantation with good response. She had several metastatic skin nodules that were excised. In September 1994, she underwent a routine CT scan of the liver and a 3 cm mass was noted in the left medial segment. The CT scan of the chest/head and bones were all negative. Because the liver mass appeared to be an isolated lesion, and she was in good health otherwise—working and gaining weight—she was considered for hepatic cryosurgery. On December 1, 1994, she underwent exploratory laparotomy and had an isolated lesion in the left medial segment that measured 3.9 cm in the greatest dimension. The biopsy was consistent with a breast primary and she underwent cryosurgery of the lesion. Although no problems were encountered during surgery, 3 U of packed red blood cells was administered postoperatively for a subcapsular hematoma. She also had thrombocytopenia to 60,000/mm^3. She was discharged six days following the procedure but was readmitted a week later with a large right pleural effusion and mild dyspnea that were managed with a tube thoracostomy and pleurodesis. Transient hyperbilirubinemia was detected, probably related to reabsorption of the subcapsular hematoma. Eleven months after surgery she is alive and the liver lesion is smaller; however, she recently developed brain metastases.

Case Three

A 51-year-old woman underwent low anterior resection for moderately well-differentiated adenocarcinoma of the rectum in November 1993. At the time of surgery, she had four metastatic lesions involving both right and left lobes of the liver and ranging from 1.0 cm to 4.0 cm. Postoperatively she received multiple courses of chemotherapy that included 5-FU and leucovorin. Serial CT scans were variable with the lesions sometimes appearing unchanged, and at other times much smaller. Cryosurgery was considered, but CT scans in November 1994 showed an increase in the largest lesion to about 6.0 cm. She underwent exploratory laparotomy and an intrahepatic arterial catheter was inserted. There was no evidence for extrahepatic metastases. She received intrahepatic arterial floxuridine and leucovorin and a decrease in lesion size was seen by CT scan. On February 28, 1995, she underwent exploratory laparotomy which revealed five liver lesions. A 6 cm mass in the left lateral segment was completely excised with segunentectomy. A 1.5 cm lesion at the edge of the right lobe anteriorly was wedge resected. The other three lesions (5.5 cm, 1 cm, and 1 cm) were all in the right lobe and each underwent cryoablation. She had no perioperative problems, received no transfusions, and was discharged seven days later. She is currently alive and the lesions have decreased in size on subsequent CT scans, but she recently has developed several small lesions elsewhere in the liver.

Case Four

A 65-year-old woman was found to have gall bladder carcinoma on elective laparoscopic cholecystectomy for symptomatic cholelithiasis. Her past history is otherwise unremarkable. A CT scan demonstrated a 1.5 cm lesion on the left medial segment of the liver. She underwent five courses of systemic chemotherapy with 5-FU, Adriamycin, and mitomycin-C. After chemotherapy, CT scan with arteriogram/portagram showed no change in the previous lesion and a small mass in the area of the cystic duct. On April 6, 1995, exploratory CT scan with arteriogram/portagram showed no change in the previous lesion and laparotomy showed four sites of metastatic disease. A 1.9 cm mass in the left medial segment was resected. Two small lesions, each less than 1 cm (left lateral segment and right lobe), were treated with cryosurgery. A 2 cm mass near the cystic duct stump was also positive for carcinoma and this was surgically debulked.

Cryosurgery could not be performed on this lesion due to the proximity of the bile ducts. She had no perioperative problems, received no blood transfusions, and was discharged five days following the procedure. Her highest SGOT was 725 IU/L. She also underwent adjuvant radiation therapy to the lesion near the bile duct, as well as brachytherapy through a common duct T-tube placed at the time of surgery. Her lesions have decreased on subsequent CT scans and she is doing well six months after surgery.

Discussion

Cryosurgery is an operative procedure whereby a tumor is localized with intraoperative ultrasound guidance and exposed to liquid nitrogen at -196°C. Use of ultrasound is especially important as it allows detection of lesions less than 2 cm which might otherwise be missed.[3] Cryosurgery has been used to treat both primary and metastatic liver cancers which are not resectable by conventional means due to multiple lesions, bi-lobar disease, poor liver reserve, or proximity to major vessels.

The biology of cryoablation is such that damage occurs primarily due to ice crystal formation. Ice forms in the extracellular fluid and with slow cooling, intracellular fluid migrates across an osmotic gradient to the extracellular space. This leads to cell shrinkage and death. The ice mass is then allowed to thaw and this increases the damage to the cells.[4] Repeating the freeze-thaw cycle has been shown to be more effective than a single cycle.[4-7] Other effects of freezing include denaturing of lipid-protein complexes which disrupts cell membranes and causes leakage of organelles. Freezing also damages the walls of the small vessels, leading to deposition of platelets and thrombus formation. After several days, the frozen lesion becomes necrotic and separates from the normal liver. It is essentially a sterile infarct that eventually becomes encapsulated by fibrous tissue.[4,8]

The advantages of cryosurgery are related to its low morbidity and mortality. Multiple studies have been done with no mortalities.[4-5,9-10] A review of the literature revealed three known deaths—two from hepatic failure and one from cardiac arrest.[7] Complications include liver cracking and hemorrhage which are easily controlled with sutures and packing. Blood loss is considerably less than with a standard liver resection. One unit of blood is the average requirement.[5] Cryosurgery can also injure the bile ducts, as freezing of the ducts can lead to edema and eventually stenosis.[4,11] Mild myoglobinuria occurs in most patients, and alkalization of the urine, low-dose dopamine, adequate hydration, and mannitol have been recommended.[7] Intraoperatively, patients may have mild hypothermia, but this is easily controlled with the use of warming devices such as the Bair Hugger®.[12]

To date, results of cryosurgery to the liver have been comparable to liver resection. Onik et al reported 57 patients with unresectable hepatic metastases and demonstrated a 27% disease-free survival with 21-month follow-up.[7] Zhou et al, in a study of 107 patients with hepatomas, yielded a 22% survival at five years. In smaller tumors (<5 cm) survival was 93.3% at one year and 48.8% at five years.[11] Ravikumar performed cryoablation for either metastatic or primary liver cancer in 24 patients, and 24% had a complete response at 14 months.[13]

Preliminary data also suggest that cryosurgery may be helpful in non-colorectal metastases. Rammings et al treated 16 patients with

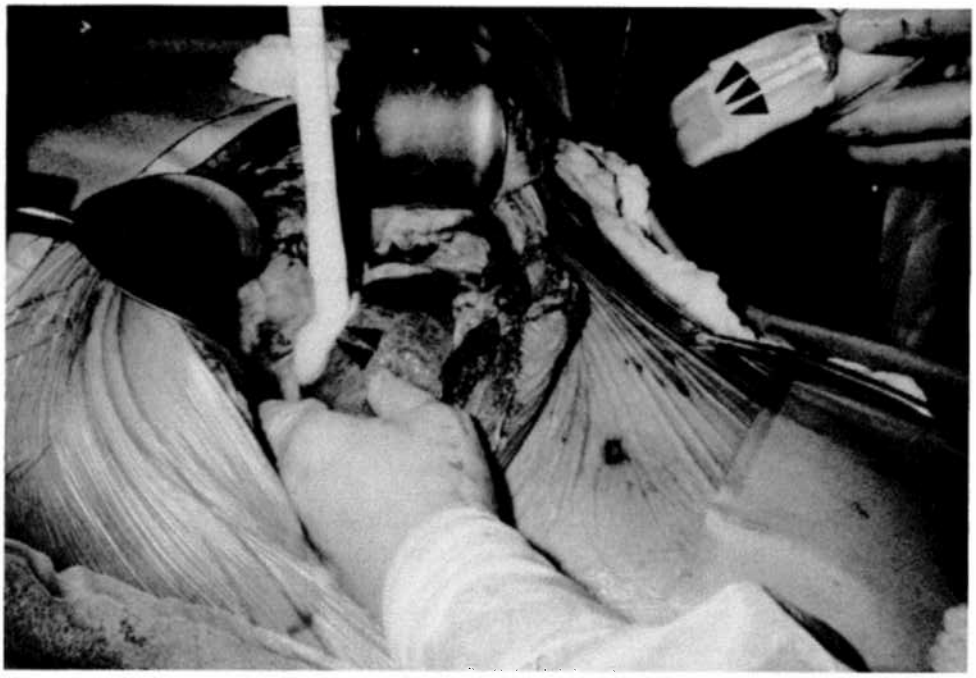

Fig 1.—Hepatic cryosurgery of a tumor in the right lobe. A larger (10 mm) probe (single arrow) is used to create an iceball (double arrow) including the tumor and a 1 cm rim of normal tissue. Ultrasound guidance is used to both locate the tumor and observe completeness of the freezing process (triple arrow).

metastases from ovary, breast, thyroid, and neuroendocrine tumors. They demonstrated a decrease in the appropriate tumor markers and an improvement in neuroendocrine symptoms. Mean overall survival was 9.1 months (range 1 to 21 months).[14] Cryoablation can be used to assist in hepatic resection in order to allow clearance of tumor margins.[15] At the moment, the results are not much worse than liver resection and the morbidity is considerably less. Long-term follow-up and controlled studies will be necessary to understand the true benefit of this modality.

Cryotherapy alone can be helpful in liver tumors, but when used in combination with other modalities may prove to be more beneficial. Tang et al, in evaluating unresectable primary liver cancers in 137 patients between 1966 and 1977, noted that the five-year survival was zero. In the period between 1978 and 1989, 345 unresectable liver tumors had a 16.9% five-year survival with the use of cytoreduction (hepatic artery ligation, hepatic artery infusion, cryotherapy, and/or radiation) and sequential resection.[16]

In our early experience, the four patients have undergone cryosurgery for varying tumors including hepatocellular carcinoma, and metastatic lesions from the rectum, breast, and gall bladder. There were no mortalities and only one patient had complications of a subcapsular hematoma of the liver requiring transfusion. Transfusions were not needed in the other patients. Three of the four patients have undergone multi-modality therapy with combinations of liver resection, cryosurgery, chemotherapy, intraarterial chemotherapy, and radiation. All patients are alive and functioning well; however, two patients have had progression of disease including development of metastatic lesions in the brain and elsewhere in the liver. (Since the four cases presented here, we have performed an additional five cases for hepatoma, metastatic breast cancer, and metastatic colon cancer. All patients are alive and without evidence of recurrence at two to five months.) Our results are consistent with those reported in the literature in that cryosurgery is excellent for controlling liver lesions, but lesions can occur elsewhere in the liver.[9] Longer follow-up will be necessary to assess the true benefit of cryosurgery.

Conclusion

Hepatic cryotherapy with ultrasound guidance allows us to treat a greater number of lesions and lesions not surgically resectable with clear margins. Morbidity and mortality are minimal. Although the prognosis with cryosurgery is not significantly better than with liver resection, we must consider that we are treating a group of patients that has a five-year survival of zero. Perhaps the addition of cryotherapy will allow us to improve on the dismal outlook of metastatic and primary liver cancer, using a technique that has minimal morbidity and mortality.

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