Cryosurgery for malignant tumours of the liver

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Objective: To evaluate the safety and efficacy of ultrasound-guided cryosurgery to treat malignant tumours of the liver.

Design: A prospective nonrandomized trial. The follow-up was complete and ranged from 8 to 35 months.

Setting: A university-affiliated hospital.

Patients: Ten patients with secondary malignant tumours of the liver; 1 with primary hepatoma.

Interventions: Computed portography for preoperative staging; laparotomy and ultrasonographic examination of the liver; cryosurgical ablation of liver tumours with or without a concomitant resection. Thirteen procedures were performed on 11 patients.

Main Outcome Measures: Preoperative morbidity, disease-free and overall survival.

Results: Of 24 lesions frozen, the procedure on 4 lesions was considered a technical failure because of persistent disease. There were no perioperative deaths. One patient had a liver abscess that resolved with percutaneous drainage. One patient had a biliary fistula that resolved spontaneously, and one had a transient rise in the serum creatinine level. Of 11 patients treated, 7 had a recurrence in the liver (persistent disease in 2 and new liver metastases in 5); 2 of these patients died. One patient died of distant disease with no local recurrence. At the time of writing, one patient was alive with extrahepatic disease and no local recurrence and two were free of disease.

Conclusions: Cryosurgery of the liver is a relatively safe procedure that allows treatment of otherwise unresectable malignant disease. Proof of long-term benefit requires further experience and follow-up.

Objectif : Évaluer la sûreté et l'efficacité d'une cryochirurgie guidée par ultrasons pour traiter des tumeurs malignes du foie.

Conception : Étude prospective non randomisée. Le suivi a été complet et a varié de 8 à 35 mois.

Contexte : Hôpital affilié à une université.

Patients : Dix patients atteints de tumeurs malignes secondaires du foie, dont un était atteint d'un hépatome primaire.

Interventions : Portographie assistée par ordinateur pour détermination du stade avant l'intervention; laparotomie et examen échographique du foie; ablation cryochirurgicale de tumeurs au foie avec ou sans résection simultanée. On a procédé à treize interventions sur 11 patients.

Principales mesures des résultats : Morbidité préopératoire, absence de maladies et survie globale.

Résultats : Sur 24 lésions congelées, l'intervention pratiquée sur 4 lésions a été considérée comme un échec technique parce que la maladie a persisté. Il n'y a pas eu de décès périopératoire. Un patient avait un abcès au foie qu'un drainage percutané a réglé. Un patient avait une fistule biliaire qui s'est résorbée spontanément et l'on a constaté une élévation provisoire du taux de créatinine sérique chez un autre sujet. Sur les 11 patients traités, la maladie est réapparue dans le foie dans 7 cas (maladie persistante dans 2 cas et nouvelles métastases dans le foie dans les cinq autres); 2 de ces patients sont morts. Un patient est mort d'une maladie distante sans rechute locale. Au moment d'aller sous presse, un patient vivant souffrait de maladie extrahépatique en récurrence locale et deux étaient libres de maladie.

Conclusions : La cryochirurgie du foie est une intervention relativement sûre qui permet de traiter des affections malignes autrement irrésécables. Pour en démontrer l'avantage à long terme, d'autres expériences et suivis s'imposent.

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Conventional methods of treatment for malignant disease of the liver include resection and chemotherapy. Chemotherapy has little impact on survival and offers no prospect for cure. Although resection has not been proven to improve survival in a prospective trial, retrospective analyses of its use in primary hepatocellular carcinoma and some metastatic tumours have shown long-term survival rates of up to 30%.[1] Unfortunately, resection is not always feasible, and in this case, 5-year survival approaches 0%.[1] Liver cryosurgery is a novel treatment by which tumours are destroyed in situ by freezing under ultrasonographic guidance.

This report describes our preliminary experience with cryosurgery of the liver.

Patients and methods

Eleven patients (6 men, 5 women) underwent 13 procedures. Patients ranged in age from 60 to 75 years (mean 64 years). A total of 24 liver lesions were treated with cryosurgery.

Malignant disease of the liver was documented in all patients by computed tomography (CT), biopsy or a history of intra-abdominal malignant disease. The size and location of the lesions were documented preoperatively by CT-portography. Eligibility criteria for treatment are outlined in Table I. Since the goal of cryosurgery was cure, only those patients with no extrahepatic disease were candidates. If the attending surgeon believed that the tumour was resectable, liver resection rather than cryosurgery was done. However, if the malignant lesion could not be totally eradicated by liver resection, cryosurgery or a combination of resection and cryosurgery was used. This judgement was necessarily arbitrary since "unresectable" may mean different things to different surgeons. However, in this series, the decision was made by a surgical team experienced in liver resections, and criteria for unresectability included multiple bilobar disease, proximity to unresectable vessels, such as the portal vein or both right and left hepatic veins, a large resection in the presence of cirrhosis or technical difficulty due to previous surgery. Patients were considered ineligible if more than five lesions were present or if any nonresectable lesions were greater than 6 cm in diameter. Tumours larger than 6 cm in diameter are difficult to freeze reliably with current technology.

These criteria were violated in one case: the patient had a functional gastrinoma with disease in both the liver and the porta hepatis. In this instance it was impossible to resect the metastasis in the porta hepatis, but cryosurgery was used in an attempt to debulk the hormone-producing tumour for palliation.

Two patients underwent combined resection and cryosurgery, in one because a lesion in the right lobe was too large to freeze reliably but was easily resectable. Four other lesions in the left lobe were not resectable and were therefore frozen. In the second combination procedure, two lesions in segments four and seven were easily resected, but a lesion near the vena cava in segment eight was frozen. This patient also demonstrated that although cryosurgery is feasible for tumours in awkward locations, the heat-sink effect of a high-volume flow through the vena cava can make adequate freezing difficult to achieve.

Because of technical difficulty, a long operation and severe blood loss, one patient had a staged procedure such that two out of three tumours were frozen during the first procedure and the third tumour was managed during a second procedure 6 weeks later.

Of the 13 procedures in this series, 5 were reoperations. One patient with a functional insulinoma had undergone pancreatectomy and multiple previous liver resections, one had undergone both a pancreaticoduodenectomy and a previous liver resection for a metastatic leiomyosarcoma of the duodenum, and one had had a cholodochojejunostomy and radiation to the epigastrium for an acinic cell tumour of the head of the pancreas. Two patients had a repeat cryosurgical procedure, one as a second stage and one for recurrent disease.

With respect to histopathology, six patients had colorectal metastases; two had neuroendocrine metastatic tumours; one had a sarcoma metastatic from the duodenum; one had an acinic cell carcinoma of the pancreas and one had a hepatoma.

Cryosurgery was performed in the following manner: after appropriate work-up, antibiotics were given preoperatively. At exploratory laparo-

Table I

Eligibility Criteria for Cryosurgery of the Liver

Malignant disease of liver (primary or secondary)
Tumour unresectable by conventional techniques
Five or fewer lesions
Each lesion 6 cm or less in diameter
Patient able to tolerate laparotomy
Complete eradication of unresectable tumour feasible
No evidence of extrahepatic disease

tomy, if there was no evidence of extrahepatic disease, the liver was mobilized completely and ultrasonography was used to assess the number and location of tumours in the liver. After a complete assessment, it was determined (a) if the disease was surgically treatable and (b) whether it was best treated by either resection or cryosurgery, or both. Cryosurgery was begun by first inserting one or more needles through the liver into or near the tumour under ultrasonographic guidance. A guide wire was then passed through the needles, and the needles were removed leaving the guide wires in place. Plastic dilators were then placed over the wires to dilate the tract to either 5 or 10 mm. A plastic sheath was passed over the dilator and left in place, thus allowing the introduction of the cryoprobe through the sheath. Ultrasonographic monitoring was used continuously to ensure proper placement. Five- or 10-mm probes were used, depending on the size of the lesion to be frozen. The cryosurgical machine used was the LCS 2000 (Trident Medical International, Minneapolis, Minn.) (two probes) for the first few cases, followed by the more advanced LCS 3000, which allowed up to five probes to be used simultaneously. Once the freezing had begun, the ice ball was monitored by ultrasonography to ensure that the lesion was entirely frozen along with a margin of normal liver tissue. After two freeze-thaw cycles, the probes were removed, the probe tracts were packed with a thrombostatic agent and the abdomen was closed. Drains were used when a resection was performed or a large area of the surface of the liver had been frozen.

Body temperature in all patients was monitored during the procedure by the anesthesiologist. Follow-up CT of the liver was done 7 days postoperatively to assess the extent of necrosis, and the patients were followed up every 3 to 4 months thereafter.

Results

The mean operating time was 5.1 hours (range from 3.2 to 6.5 hours). Up to four lesions were frozen in a single patient (mean 1.9 lesions). The mean blood loss was 734 mL per procedure (range from 200 to 1500 mL). Blood was transfused (mean 1.4 units [up to 5 units]) during or after 6 of the 13 procedures. Much of the blood loss occurred during resection or after a sizeable freeze of the liver capsule. As the capsule thaws, it can crack, leaving stellate fractures that can cause troublesome bleeding. If these fractures are accessible, the bleeding is relatively easy to control with sutures or thrombostatic agents. Control can be more difficult if the fracture is located on the posterior surface, especially if mobilization is difficult, as in a repeat procedure. With smaller lesions deep within the parenchyma, bleeding was not usually a problem, even in a cirrhotic patient with pancytopenia. This patient, who had hepatocellular carcinoma, required no red cell transfusion and had an estimated operative blood loss of 300 mL.

Operative complications (Table II) reflect the extent and magnitude of the surgery. There were no perioperative deaths. One patient had a liver abscess in the area of necrosis; the abscess was drained percutaneously and resolved. Another patient had an infected biliary fistula from her wound that resolved spontaneously. Both of these patients had previously undergone biliary–enteric bypass procedures: the former a Whipple resection for leiomyosarcoma of the duodenum and the latter a hepaticojejunostomy for acinic cell carcinoma of the pancreas. Two other patients had bilious drainage that resolved spontaneously.

The second patient in the series had an elevated serum creatinine level of 239 μmol/L on day 3 postoperatively. It gradually returned to normal over the subsequent 2 weeks. This elevation likely resulted from inadequate intraoperative fluid administration and renal tubular obstruction from the products of tumour lysis, particularly myoglobin.[2,3] Therefore, we changed our perioperative fluid management so that all patients received intraoperative mannitol and enough saline to ensure a urine output greater than 100 mL/h. They also received sodium bicarbonate (5 mmol/h) intravenously for at least 8 hours postoperatively. After we instituted this protocol, there were no further episodes of renal compromise.

All patients had a fall in platelet count (mean 123×10^9/L), but only one had a severe thrombocytopenia requiring a platelet transfusion. This patient with hepatoma and cirrhosis had pancytopenia and a preoperative

Table II

Complications Associated With 13 Cryosurgery Procedures

Complication	No. of procedures
Fever	13
Abscess	2
Biliary fistula	2
Elevated serum creatinine level	1
Thrombocytopenia (< 80×10^9/L)	1
Postoperative hemorrhage	1

platelet count of 101×10^9/L. His platelet count reached a nadir of 40×10^9/L and he was given 6 units of platelets. His postoperative course was otherwise uncomplicated.

Overall hospital stay was a mean of 12.4 days (median 10 days). Two patients were monitored in the intensive care unit for 1 and 2 days each.

Of 24 lesions frozen in 11 patients, 4 were thought to be persistent after cryosurgery, representing an inadequate procedure. Three of the inadequately frozen tumours were in one patient with metastatic insulinoma who had had two previous liver resections. Visualization of the metastases by intraoperative ultrasonography was difficult, probably resulting in underfreezing. The second technical failure occurred in a patient who was referred for cryosurgery after the primary pancreatic tumour (acinic cell carcinoma) was treated with a hepaticojejunostomy and radiation. Difficult mobilization of the liver and the large size of the metastatic tumour (6 cm) resulted in an inadequate freeze and local recurrence after 7 months.

The mean follow-up was 18.3 months (range from 8 to 35 months) (Table III). Three patients died of their disease, two of recurrent liver cancer and one of a brain metastasis with no evidence of liver recurrence. At the time of writing, six patients were alive with disease, five with persistent or recurrent liver metastases and one (gastrinoma) with persistent extrahepatic disease and no recurrence in the liver. Two patients remained free of disease at 16 months (hepatoma) and 10 months (colonic carcinoma) after cryosurgery.

Discussion

Different forms of cryosurgery have been used for many years to treat various types of tumour tissue.[4] Usually liquid nitrogen was applied directly to different tissues. The development of machines that can circulate liquid nitrogen through a metal probe in a controlled fashion has brought about a new era of cryosurgery, particularly in liver and prostate cancer. The development of ultrasonographic monitoring by Ravikumar and colleagues[5] allowed precise probe placement and monitoring of the "cryolesion" or ice ball to ensure that it encompasses and engulfs the tumour, thus destroying it completely.

Preliminary data from Ravikumar and colleagues[6] showed that long-term survival after successful cryoablation of metastatic and primary liver cancer is comparable to that after liver resection. A handful of other series have been reported, but the follow-up is short.[2,3,7,8] As investigators become more aggressive, however, the number of complications has increased.[2]

Following these encouraging data, the team at Foothills Hospital in Calgary began a protocol of cryosurgery for malignant hepatic disease in a selected group of patients. Analysis of our experience has been helpful in improving the selection of patients and in refining the operative technique.

The hope that cryosurgery would have fewer complications than resective surgery has so far not materialized. Liver cryosurgery is as difficult and dangerous an undertaking as liver resection. The complications in this series reflect this as well as the learning curve for the procedure and the difficult nature of the disease — for example, eradication of two small lesions located deep within either lobe is a safe and relatively easy procedure and can be done with little blood loss. On the other hand, reoperation in a patient with multiple 5-cm diameter lesions involving the surface of the liver can be extremely difficult, leading to inaccurate probe placement, surface cracking and severe blood loss. Cryosurgery under these circumstances should probably not be attempted.

A small amount of bile from a suction drain after extensive liver surgery is not uncommon and is usually self-limited. However, the development of

Table III

Patient Outcome After Cryosurgery

		Outcome (mo after cryosurgery)			
Patient no.	Type of tumour	LR	AWD	DOD	FOD
1*	Colorectal	24	35	—	—
2	Colorectal	7	—	10	—
3	Sarcoma	22	31	—	—
4	Colorectal	—	—	8	—
5	Insulinoma	Persistent	25	—	—
6	Pancreatic	7	19	—	—
7	Gastrinoma	—	19	—	—
8	Colorectal	5	17	—	—
9	Colorectal	5	—	12	—
10	Hepatoma	—	—	—	16
11	Colorectal	—	—	—	10

LR = local recurrence, AWD = alive with disease, DOD = died of disease, FOD = free of disease
*This patient had a second procedure at 24 mo but the tumour recurred 5 mo later.

a liver abscess is more problematic and can lead to prolonged hospitalization. Interestingly, the two patients with an existing biliary–enteric bypass both had an infection, possibly due to the increased bacterial contamination of the biliary tree. Fortunately, this situation is uncommon and is unlikely to arise in the future.

Others have reported that renal impairment is a problem because of tumour-lysis products, particularly myoglobin.[2,3] One patient in this series had a rise in serum creatinine concentration, which, although temporary, prompted a change in the protocol such that all patients received enough fluid and mannitol intraoperatively to ensure that urine output was greater than 100 mL/h. A number of subsequent patients were checked for myoglobin in the urine after surgery, but none was found. This problem, therefore, seems to be preventable.

Although patients requiring reoperation are theoretically appealing candidates for cryosurgery, ultrasonographic imaging of the tumour is compromised. Severe scarring of the liver makes accurate delineation of the tumour extremely difficult, resulting in less accurate placement of the probes and monitoring of the freezing. Difficulty in mobilizing a scarred liver also impairs strategic placement of cryoprobes.

Although treatment of lesions in awkward locations is possible, the proximity of tumours to large vessels such as the inferior vena cava makes adequate freezing difficult or impossible because of the heat-sink effect from the large volume of blood flow. Although several lesions close to branches of the portal vein were frozen, this has not been done to either the portal vein itself or the initial branches. The safety of clamping the hilum of the liver to allow more efficient freezing has not been established but is the subject of investigation.

The two patients with metastatic neuroendocrine tumours are interesting in that although neither procedure was curative, both patients obtained worthwhile palliation of their hormone-related symptoms. The patient with insulinoma had already failed surgical resection (pancreatectomy and two liver resections) as well as diazoxide, octreotide and cytotoxic chemotherapy. She continued to have frequent severe episodes of hypoglycemia from her metastatic tumour. Unfortunately, because of liver scarring only three out of four metastatic lesions could be identified and treated. However, she remained symptom-free for 9 months after surgery while off all medication. Recurrent tumour growth eventually resulted in further episodes of hypoglycemia, but she was again asymptomatic after treatment with liver chemoembolization.

The patient with metastatic gastrinoma had extrahepatic disease that was unresectable but nevertheless had two liver metastases that were successfully ablated with cryosurgery. In the postoperative period, he had complete relief of refractory diarrhea and was able to withdraw from octreotide chemotherapy. Functional endocrine tumours metastatic to the liver constitute an unusual situation in which a procedure that is not successful in completely eradicating all detectable tumour may still have palliative benefit.

Liver cryosurgery is still in its infancy and long-term follow-up is lacking. Clearly, if a liver tumour is resectable it should be removed. However, cryosurgery can be regarded as an extension of the surgeon's ability to treat such tumours, not by removing them but by destroying them in situ. Although it may spare liver tissue and allow treatment of bilobar disease, cryosurgery should not be regarded as anything less than a major cancer operation with serious potential morbidity. Because the final decision about the type of surgery best suited to the individual patient is made at the time of laparotomy, it is usually best to have both resection and cryosurgery as available options. Therefore, only those surgeons familiar with liver resection techniques should contemplate using hepatic cryosurgery.

Because of the rarity of patients who are currently suitable candidates, it is unlikely that liver cryosurgery will ever be tested in a prospective randomized trial. We currently recommend its use only in patients who do not have any other options for potentially curative treatment or when functional neuroendocrine tumours can be treated for palliation. The different types of tumour in this small series as well as the relatively short follow-up do not allow conclusions to be drawn with regard to survival. In theory, we hope the results of cryosurgery might parallel those of resection if patients are selected properly.

Conclusions

It is clear from our initial experience that liver cryosurgery is a relatively safe and worthwhile procedure in selected cases of hepatic malignant disease. The technique is still developing, however, and much work remains to be done to improve technical aspects of the procedure as well as to understand the nature and effect of the "cryolesion." Each case must be evaluated individually, and the decision made in advance if cryosurgery should be made available at the time of surgery. The decision to proceed must be based on the number, size and location of the lesions.

Acute postoperative renal failure is a risk but can be completely prevented with the simple precautions of ade-

quate intraoperative fluid administration, mannitol and alkalinization of the urine in the postoperative period. Postoperative thrombocytopenia has been identified as a problem and has not been investigated by other groups. So far this has not directly caused major morbidity but will continue to be a concern.

Our experience, along with growing documentation in the surgical literature, suggests that liver cryosurgery may have an important role to play in treating malignant hepatic disease, but this role remains to be defined.

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[Dr. R. Lapointe comments on this paper in the Quill on Scalpel section (pages 353 and 354).]