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Ultrasound-guided Laparoscopic Cryoablation of Hepatic Tumors: Preliminary Report

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Abstract. The purpose of this ongoing prospective study is to evaluate the feasibility, safety, and efficacy of a total laparoscopic approach for ultrasound-guided cryoablation of primary and secondary hepatic tumors. Of 56 patients who underwent ultrasound-guided cryoablation, a total laparoscopic approach was employed in 18 (5 men, 13 women; mean age 48.6 years, range 35–77 years). Fifteen patients were included for secondary hepatic tumors and three for primary hepatic tumors. Selection criteria were the presence of three or fewer nodules, less than 40% liver volume replaced by tumor, and absence of extrahepatic disease. Altogether 28 lesions were confirmed by intraoperative laparoscopic ultrasonography and were treated; 25 by ultrasound-guided laparoscopic cryoablation and 3 by laparoscopic wedge resection. After cryoablation, surface parenchymal splits with bleeding from the frozen tissue were observed in six patients and required conversion to open surgery in two patients whose lesions were located in segment 8. No major complication and no mortality were observed. One or more minor complications occurred in nine patients; they included pleural effusion (*n* = 8, 44.4%), subdiaphragmatic fluid collection (*n* = 3, 16.6%), worsening hepatic insufficiency in a cirrhotic patient (*n* = 1, 5.5%), and wound infection in a patient converted to open surgery (*n* = 1, 5.5%). The mean hospital stay was 6.4 days (range 3–14 days). At a mean follow-up of 10.8 months (range 5–16 months) all patients are alive and 14 are disease-free, as demonstrated by normalization of tumor markers and negative magnetic resonance imaging. In carefully selected patients total laparoscopic ultrasound-guided cryoablation is feasible and safe. A longer period of follow-up is required to evaluate the efficacy of the procedure and its impact on survival.

Liver resection offers the best chance of cure in the treatment of both primary and secondary hepatic tumors [1, 2]. Five-year disease-free survival rates of 20% to 25% and of 25% to 39% have been reported following curative resection of hepatic colorectal metastases and hepatocellular carcinoma, respectively [2, 3]. Curative hepatic resection, however, can be achieved in only 10% to 20% of patients [4] owing to the presence of multiple, bilateral lesions and underlying liver cirrhosis. For patients with unresectable lesions and liver metastases from colorectal tumors undergoing regional chemotherapy and those with hepatocellular carcinoma undergoing chemoembolization, median survivals of 12.7 and 13.0 months, respectively, have been reported [2, 5].

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Cryoablation, the in situ destruction of tumor with subsequent reabsorption of the frozen tissue [6], has traditionally been used to treat superficially located tumors [7]. Cryoablation is a focal treatment that spares more normal tissue than resection. When applied to liver tumors it allows one to treat multiple lesions located in both lobes at the same session [6]. The introduction of intraoperative ultrasound eliminated the major limitations of cryosurgery for lesions deep in the liver, that is, the difficulty of detecting and accurately treating the lesions in depth [7]. Hepatic cryoablation was originally introduced for the treatment of unresectable hepatic tumors to improve the poor survival results in patients who failed to respond to systemic chemotherapy and had progressive disease with multiple liver tumors [6–8]. In this category of patients with a formerly dismal prognosis, disease-free survival of 28% at 24 months after cryoablation was reported by Ravikumar et al. [9] and actual survival of 62% at 24 months was reported by Weaver et al. [10]. Zhou et al. reported 48.8% five-year survival in patients with primary liver cancer whose nodules were up to 5 cm in diameter [11].

Cryoablation has been proposed as an alternative to hepatic resection for the treatment of small lesions deep in the liver when an adequate margin is difficult to achieve [12]. More recently, laparoscopic cryoablation has been employed in the clinical setting [13] and experimentally [14], proving to be feasible and safe. Cuschieri et al. reported their experience with a specifically developed multineedle probe system employing cryoneedles 2 mm in diameter, with a total laparoscopic approach used for accessible lesions (segments 2–6) and a laparoscopy-assisted approach for posteriorly located tumors (segments 7 and 8) [13].

The purpose of our study was to evaluate the feasibility, safety, and efficacy of a total laparoscopic approach for cryoablation of hepatic tumors, including tumors located in segments 7 and 8 with different equipment than was previously reported. We employed cryoprobes with a larger diameter (3, 5, and 8 mm).

Materials and Methods

From February 1996 to August 1997 a total of 56 patients (27 men, 29 women; mean age 51.4 years, range 32–77 years) underwent hepatic cryoablation of primary or secondary hepatic tumors at our institution. Among them, 35 patients were referred for lesions that were considered to be unresectable because of the presence of multiple, bilateral nodules or the presence of cirrhosis. During the same time period, 12 more patients referred for hepatic cryoablation were excluded from any kind of surgical treatment after diagnostic laparoscopy and intraoperative laparoscopic ultrasonography (IOUS) due to the presence of conditions not previously identified by radiologic imaging [magnetic resonance imaging (MRI) or computed tomography (CT scan)], such as peritoneal carcinosis or infiltrated extrahepatic lymph nodes.

Of 56 patients who underwent hepatic cryoablation, the procedure was started laparoscopically in 20 cases but 2 patients were immediately converted to open surgery, leaving a total of 18 patients treated laparoscopically (5 men, 13 women; mean age 48.6 years, range 35–77 years). The reasons for immediate conversion of the two patients were the presence of extensive adhesions from previous surgery in one case and in the other case the presence of a lesion that was found, at laparoscopic IOUS, to be larger than previously described by preoperative radiologic imaging (8 cm in largest diameter). The 18 patients in whom total laparoscopic cryoablation was performed are the object of this paper. The remaining 38 patients were treated by open cryoablation.

Of the 18 patients treated laparoscopically, 15 were admitted for secondary hepatic tumors and 3 for primary hepatic tumors. In the group of patients with secondary hepatic tumors the primary tumor was a colorectal adenocarcinoma in 10 cases (metachronous 9, synchronous 1: stage I/Dukes A 4 cases; stage II/Dukes B 1 case; stage III/Dukes C 5 cases) [15], a breast adenocarcinoma in 4 cases (all metachronous: stage I 1 case; stage IIIA 3 cases) [15], and a uterine leiomyosarcoma in 1 case (metachronous). The mean disease-free interval in the 14 patients with metachronous lesions was 17.1 months (range 6–48 months) for colorectal metastases, 81.6 months (range 5–120 months) for breast metastases, and 3 months for uterine metastases. The single patient with synchronous hepatic metastases from a colorectal primary tumor underwent laparoscopic right hemicolectomy and laparoscopic hepatic cryoablation during the same operative session. Patients' characteristics, number of nodules, size of the largest lesion, and lesions' distribution by segment in the group of patients with secondary hepatic tumors are shown in Table 1. In the three patients with a primary hepatic tumor this was a unifocal hepatocellular carcinoma with cirrhosis in two cases (T2N0M0, stage II) [15] (one Child A patient with a 3 × 2 cm nodule located in segment 7; one Child B patient with 4 × 3 cm nodule located in segment 6–7) and a rapidly enlarging, 3 × 3 cm symptomatic adenoma located in segment 6 in a female patient.

The selection criteria for laparoscopic cryoablation of a primary or secondary hepatic tumor were the presence of three or fewer nodules, documented by rising levels of tumor markers and by ultrasonography or radiologic imaging of the lesion(s) (with or without histologic confirmation), liver volume replacement by tumor of $< 40\%$, and the absence of extrahepatic disease. All patients were included in this study with a curative intent. The lesions being located in posterior segments (7 and 8) was not a contraindication to laparoscopic cryoablation.

Before being included in the study all patients underwent a thorough clinical evaluation and a preoperative staging procedure, which included blood examination for tumor markers, hepatic ultrasonography, chest radiography, CT scans of the abdomen and chest, hepatic MRI with paramagnetic contrast agent (gadolinium), and a bone scan.

Table 1. Number, size, and location of nodules in patients with secondary hepatic tumors.

Sex	Age	No. of lesions	Size of largest lesion (cm)	Segment involved
M	71	1	3.0	5
F	49	2	2.5	5, 5–6
F	66	3	2.0	2–3, 3
F	70	1	4.0	8
F	63	3	4 × 3	2, 3
F	36	1	3.5 × 3.0	5
F	49	4	2.0	4, 5, 6
F	68	2	4.0	6
M	74	1	2.0	7
F	65	1	5.0	4
M	76	1	4.0	6
F	39	1	3 × 5	8
F	67	1	2.0	4
F	77	1	4.5	8
F	52	2	4.0	8

The patients' preparation began on the day preceding the operation by intravenous administration of 2000 ml saline solution to increase the glomerular filtration rate, a condition that was prolonged intra- and postoperatively, together with diuretics to facilitate elimination of the products of cryodestruction. Accurate intraoperative patient monitoring was carried out, including measurement of intraarterial pressure, end-tidal CO_2, central venous pressure, and esophageal temperature. Pneumoperitoneum was established with standard techniques. The first 10- or 12-mm trocar was positioned in the right upper quadrant along the midclavicular line, and the peritoneal cavity was explored with a 45° forward oblique viewing telescope to exclude the presence of peritoneal carcinosis and any other sign of extrahepatic abdominal involvement. Another 10- to 12-mm trocar was positioned in the right hypochondrium along the anterior axillary line to introduce a blunt instrument for palpating the liver and to remove any adhesions from previous operations.

After opening the falciform ligament with electrocautery to facilitate exploration of the left lateral segments, a 6.5-MHz laparoscopic ultrasound probe with articulating distal extremity (B&K Medicale, Naerum, Denmark) was introduced from the lateral trocar and employed to scan the entire surface of the liver in a systematic manner. All lesions preoperatively identified by radiologic imaging were sought and measured, defining their ultrasonographic pattern and their relation with surrounding vascular and biliary structures. The liver parenchyma was also carefully scanned to identify any new lesion that had not been identified preoperatively. A radiologist's expertise in ultrasonographic imaging was sought whenever in doubt about the ultrasonographic pattern of a lesion. Once ultrasound scanning of the liver was completed, a treatment plan was devised, and the position of the subsequent trocars in the right or left hypochondrium (one for each cryoprobe to be employed) was chosen according to the number of lesions to be treated and their location. The total number of trocars employed had to take into account the fact that two trocars, one for the telescope and one for the ultrasound probe, had to be available at all times during the operation to monitor the freezing process.

Tumor nodules located in segments 3, 4b, 5, and 8 were reached with cryoprobes directly from the anterior surface of the liver with no hepatic preparation. Tumors located in segments 2, 6, 7, and the apex of segments 4a and 8 required liver preparation to avoid freezing perihepatic tissues, such as the diaphragm. Liver preparation in these patients included division of the peritoneal reflection, the triangular ligament, and the coronary ligament on the side to be treated, followed by blunt dissection of the bare area of the liver to separate it from the retroperitoneal tissues. Lesions located deep into or in the superior portion of segment 7 required the greatest dissection from the retroperitoneal surface. With the operating table tilted to the left, the dissection began from the right aspect of the infrahepatic vena cava after division of the peritoneal reflection, followed the cleavage plane anterior to Gerota's fascia and to the right adrenal gland (in a manner similar to that employed at the beginning of transabdominal right adrenalectomy with patient supine), and was then prolonged cranially and medially until the posterior aspect of the right hepatic vein was seen entering the hepatic parenchyma. The superior right coronary ligament was likewise divided in a lateral-to-medial direction to obtain complete medial mobilization of the right lobe of the liver. An air-inflated balloon retractor (Extra-Hand, Origin Corporation, Menlo Park, CA, USA) introduced from an extra 12-mm trocar helped achieve medial liver retraction and was later employed during iceball formation to prevent contact and freezing of the diaphragm.

The point of entrance of the cryoprobes on the liver surface was then selected and marked by electrocautery, providing also a point of lesser resistance to facilitate introduction of the probe. When histologic confirmation was required, a biopsy specimen of the lesion was obtained with a Tru-Cut instrument. Under laparoscopic vision with ultrasound control, a 3-, 5-, or 8-mm cryoprobe (according to which type of probe was considered most appropriate with respect to the size of the lesion) was introduced by direct puncture in the liver and directed toward the middle of the nodule to be treated (CMS Accuprobe System; Cryomedical Sciences, Rockville, MD, USA). During cryoprobe introduction the ideal working conditions for accurate control of its advancement were the following: (1) that the ultrasound probe be oriented on the liver surface to display the largest diameter of the entire lesion; and (2) that the shaft of the ultrasound probe lies as much as possible parallel to the shaft of the cryoprobe. These conditions allow us to follow precisely the position of the cryoprobe with respect to the lesion. In fact, the cryoprobe is readily identified by its hyperechoic pattern with posterior acoustic shadow. To further visualize the correct position of the cryoprobe, the ultrasound probe was moved to another trocar site to obtain a transverse image of the cryoprobe with respect to the lesion, thereby reconstructing a three-dimensional vision of the probe inside the lesion.

Under ultrasound guidance the tip of the cryoprobe was advanced until it reached the margin of the lesion opposite the point of entrance of the probe. The maximum diameters of the iceballs that develop around the tip of the cryoprobes are approximately 5 cm for the 3-mm probe, 6 cm for the 5-mm probe, and 7 cm for the 8-mm probe. Considering that a tumoricidal temperature is obtained in a smaller iceball volume, due to the temperature gradient increasing by 10°C/mm of tissue with increasing distance from the probe, more than one cryoprobe was employed to treat larger or irregularly shaped lesions. In this case the probes were positioned in an asymmetric location with respect to the center of the lesion, so the expanding iceballs would eventually coalesce into a larger one that included the entire lesion and an adequate margin of normal liver tissue (1.0–1.5 cm).

When the correct position of the first cryoprobe was verified, liquid nitrogen was circulated through the probe. This rapidly brought the temperature of the surrounding tissue to −100°C when the cryoprobe became "stuck" in the lesion, thereby preventing its accidental dislodgement. At this point the other cryoprobes were positioned inside the lesion, if more than one probe was required, or inside the other lesions. Ideally, all the necessary probes had to be in the correct position and "stuck" to the tissue so the freezing process could be activated simultaneously. It required that the lesions be located in a position that can be reached by puncture with the cryoprobes from the same aspect of the liver (anterior or posterior). When the lesions were located in such a position that a different hepatic exposure was required for their respective treatment (to avoid damaging major vessels or biliary ducts), the freezing process could not be simultaneous but had to be performed sequentially, after the proper exposure was obtained. A useful maneuver for preventing diaphragmatic freezing during treatment of lesions in the uppermost portions of segments 2, 4a, 7, and 8 was to apply slight traction on the handles of the cryoprobes once the latter were "stuck" into the liver parenchyma, which resulted in "lifting" the prepared liver (its ligaments having been divided) by only a few millimeters but sufficient to increase the air interface between the liver and the diaphragm.

Whether simultaneous or sequential, the freezing process began when all the cryoprobes that could be activated at the same time were "stuck" in the correct position. At this point liquid nitrogen was again circulated through the probes until the temperature of the tissue in close proximity with the probe decreased from −100°C to −196°C. The development of the iceball was visualized on the ultrasound screen by the appearance of a hyperechoic rim with posterior acoustic shadowing. Special attention was paid to prevent accidental contact of bowel or duodenum with the probe shaft during the freezing. The freezing process continued for 20 minutes. During this time the hyperechoic rim progressively expanded on the ultrasound screen until the margins of the nodule were exceeded by 1.5 cm on each side. This was desumed by measuring the size of the iceball and comparing this size with that of the tumor. To obtain objective evidence that the entire lesion had been submitted to a tumoricidal temperature, a thermocouple was introduced through a separate 18-gauge percutaneous cannula, and its tip was positioned under ultrasound control into macroscopically normal liver tissue close to the margins of the lesion. When the temperature of the thermocouple decreases to −40°C, all the tissue between this point and the cryoprobe has been devitalized. One thermocouple was generally adequate for round or oval lesions with regular margins. In the case of multilobar lesions, more than one thermocouple was required. When doubt existed that a margin of the lesion had not been adequately treated and it was recognized by persistence on the ultrasound screen of an area of tumor that had not been included by the hyperechoic rim, or if a narrow margin was suspected, an additional cryoprobe entering through a separate trocar was positioned in the liver parenchyma to deliver additional cryodestruction at that point.

After 20 minutes the first freezing process was completed, and the circulation of liquid nitrogen was interrupted ("off" condition). This initiated the process of thawing—a slow, passive process of rewarming during which the temperature rises toward normal body temperature. When a single freeze was not considered adequate for complete devitalization of tumor tissue, a second freeze was performed. In this case the thawing process after the first freeze lasted only 10 minutes. The second freezing process was usually prolonged for up to 15 minutes and was also followed by a second thawing process. Active warming of the cryoprobes was initiated during the final thawing process, when the iceball temperature had risen to −100°C, to facilitate removal of the cryoprobes, leaving a hole in the tissue that was still frozen and therefore solid. This solid cryoprobe track was rapidly stuffed with regenerated cellulose mesh (Tabotamp; Johnson & Johnson, Gargrave Skipton, UK) which was sealed with cyanoacrylate glue. Alternatively, an original method to achieve hemostasis we developed has been employed in the last nine patients and has proved effective. After irrigating the cellulose mesh with saline, high-frequency electrocautery (Erbe, Tübingen, Germany) was applied to the mesh at the outer borders of the cryoprobe track. Transmission of the high-frequency current along the stuffed mesh was facilitated by saline until the mesh eventually became a solid plug adherent to the internal wall of the cryoprobe track, thereby achieving hemostasis.

Complete ablation of the tumor nodule, together with an adequate (1.0–1.5 cm) margin of normal tissue, was demonstrated after thawing was completed. In fact, the IOUS image of frozen normal liver parenchyma surrounding the nodule appeared hypoechoic compared to unfrozen normal liver tissue and, in contrast, with frozen and then thawed tumor, which maintained a different ultrasonographic pattern. Three-dimensional evidence of complete tumor ablation was obtained by visualizing the thawed tissue with the articulating ultrasound probe sequentially moved from one trocar to another. This practice allowed us to measure in every direction the amount of normal liver tissue surrounding the tumor nodule that had been included in the iceball, therefore allowing us to reconstruct a three-dimensional configuration of the frozen parenchyma.

When the iceball reached the surface of the liver capsule, surface parenchymal splits were occasionally observed during thawing, causing superficial bleeding. Hemostasis must be achieved readily in this case because bleeding from parenchymal splits may become copious if not adequately controlled and may require conversion to open surgery. Again, hemostasis was achieved by stuffing the crack with regenerated cellulose mesh and applying high-frequency electrocautery to the mesh.

After hemostasis is obtained, the frozen area was covered with formaldehyde-activated resorcinol glue or fibrin tissue glue to seal off the entire area and prevent delayed bleeding. When the iceball reached the wall of the gallbladder, laparoscopic cholecystectomy was performed to avoid the occurrence of postoperative cholecystitis. At the end of the procedure the trocars were removed, and two drains were positioned in the subdiaphragmatic and subhepatic spaces, exiting through the trocar incisions.

During the postoperative period, prior to discharge, the patients underwent tumor marker assays and MRI imaging to serve as a baseline for future comparison. After discharge, the patients underwent a close follow-up that included monthly assays of tumor markers for the first 4 months and then every 3 months, and MRI imaging of the liver every 2 months for the first 6 months and then every 4 months to monitor the evolution of the frozen tumors and identify any new lesion in other segments or recurrences at the treatment sites.

Results

Intraoperative ultrasonography confirmed the site and number of lesions diagnosed by preoperative liver imaging in 13 of 18 (72.2%) patients. In 3 of 10 patients who had been preoperatively diagnosed as having 10 nodules, only six lesions were confirmed by IOUS (four false-positive lesions). In two patients seven lesions (four and three nodules, respectively) were identified by IOUS compared to four lesions (three and one nodule, respectively) that were diagnosed preoperatively (three false-negative lesions). However, the size of these three lesions not identified by preoperative imaging was < 10 mm.

A total of 28 lesions were confirmed by laparoscopic IOUS and were treated: 25 by cryoablation and 3 by wedge resection or wide excisional biopsy (1.5 lesions per patient on average). Resection rather than cryoablation was employed to treat these three lesions because they were small (15, 5, and 2 mm in diameter, respectively), superficial lesions; and it was thought that excision with an adequate margin would have been safe and more rapidly accomplished. Cryoablation in the entire series was obtained with a total of 38 cryoprobes (thirty-six 5-mm probes, one 3 mm-probe, and one 8-mm probe). No significant fall in the core body temperature was observed. Laparoscopic cholecystectomy was performed in four cases. The mean total operative time was 131.2 minutes (range 90–240 minutes), and the mean total cryoablation time was 27.3 minutes (range 18–60 minutes).

Surface parenchymal splits were observed in 6 of 18 (33.3%) patients, who had been treated with 2.3 cryoprobes each, on average (range 2–3 probes), and a single freeze in all six cases except one who underwent a double freeze. No surface parenchymal splits were observed in the remaining 12 patients (66.6%), 8 of whom underwent cryoablation with two or more probes (mean of 2.0 cryoprobes per patient, range 1–5 cryoprobes), with a single freeze in seven cases and a double freeze in five cases. Of 18 patients who underwent laparoscopic cryoablation, conversion to open surgery was required in 2 patients after cryoprobe removal to obtain better control of bleeding from surface parenchymal splits. In both patients who underwent conversion the tumors were located in segment 8, high over the dome of the right lobe. After conversion, bleeding from these surface splits was easily controlled. These were the only two patients in the series who required intraoperative blood transfusions (4 and 5 units of red blood cells, respectively).

No major complications were observed. One or more minor complications that resolved nonoperatively occurred in nine patients and included pleural effusion in eight cases (44.4%), a subdiaphragmatic fluid collection in three cases (16.6%), transient worsening of preexisting hepatic insufficiency in a cirrhotic patient (5.5%), and wound infection in one of the two patients converted to open surgery (5.5%). Postoperative blood transfusions were required in three patients, who received 2 units of packed red blood cells each. Mortality was nil. The mean hospital stay was 6.4 days (range 3–14 days).

At an average follow-up of 10.8 months (range 5–16 months) all 18 patients are alive; 14 of the 18 are disease-free (77.8%) as demonstrated by the normalization of previously elevated tumor markers and by repeated MRI liver imaging. In four patients (22.2%) new lesions have been demonstrated at follow-up in liver segments different from those previously treated. Two patients with hepatic colorectal metastases and one patient with hepatic metastases from uterine leiomyosarcoma are presently undergoing chemotherapy and will be reevaluated in the future for possible repeat cryoablation. One patient with hepatocellular carcinoma has presently been classified as Child C and is therefore not considered a suitable candidate for repeat cryoablation.

Discussion

Cryosurgery is a focal treatment and has the advantage of sparing more normal liver than anatomic hepatic resection [6]. Therefore its principal use is to treat patients who are not considered candidates for major hepatic resection [6–8]. The introduction of IOUS has been critical for successful cryoablation because it not only provides more precise staging of the disease compared to preoperative radiologic imaging, it allows us to monitor precisely the freezing and thawing process so we can freeze the entire tumor plus an adequate margin of normal tissue. Another indication for cryotherapy is as an adjunct to hepatic resection when some residual tumor cannot be resected [4]. Moreover, cryoablation has been recognized as being equally as effective as resection for treatment of small nodules lying deep in the liver when an adequate margin is difficult to achieve with resection, and it does so with less morbidity and mortality than major hepatic resection [12].

Laparoscopic cryoablation has been proposed by Cuschieri for the treatment of primary and secondary hepatic tumors [13], with a total laparoscopic approach used for accessible lesions (segments 2–6) and a laparoscopically assisted approach used for posteriorly located tumors (segments 7 and 8). Specifically developed narrow cryoneedles 2 mm in diameter were employed by Cuschieri.

The present study has been initiated to evaluate the feasibility, safety, and efficacy of a total laparoscopic approach for lesions located in segments 7 and 8 employing larger cryoprobes (3–8 mm in diameter), with the 5-mm probe being the most frequently used. The present report is preliminary, and the limited sample size together with the shortness of follow-up (median 10.8 months) do not allow us at present to draw conclusions regarding the efficacy of the procedure and its impact on survival. Therefore only technical aspects regarding feasibility and the safety of the procedure are addressed in this report.

We chose to treat only three or fewer lesions, even though in one case a fourth 2×2 mm incidentally discovered lesion was excised. The reason for this is that we prefer to perform the freezing process simultaneously, whenever possible, to reduce the operating time. Laparoscopic surgery has fixed points of entrance for the instruments in the peritoneal cavity, and two ports are constantly occupied by the telescope and the ultrasound probe. Although not impossible, it would be difficult to freeze more than three lesions at the same time owing to space limitations. If additional freezing is required to treat an incompletely frozen area, we prefer to perform sequential freezing, as occurred in one patient of this series who underwent a first freezing with three 5-mm probes and a second freezing with two 5-mm probes after repositioning them in a different area of the same lesion.

As reported by other authors [13], most patients in this series had secondary hepatic tumors of colorectal origin, a biologically more favorable group of patients, although patients with primary hepatic tumors and those with secondary tumors from a different origin may be included as well, provided there is adequate hepatic functional reserve (Child A–B), there is $< 40\%$ of the total volume replaced by tumor, and there is no sign of extrahepatic disease.

Accurate preoperative staging including abdominal CT scan and MRI with a paramagnetic contrast agent (gadolinium) is essential to define the extent and location of intrahepatic disease, the involvement of major vessels and bile ducts, and the presence of extrahepatic disease. MR imaging has been reported to be superior to CT for lesion detection and characterization [16]. Moreover, diagnostic laparoscopy with laparoscopic IOUS should always be performed at the beginning of the operation and in patients who will obviously be treated by open cryoablation because it allows us to identify conditions that preclude treatment, such as peritoneal carcinosis and infiltrated extrahepatic lymph nodes, thereby avoiding an unnecessary laparotomy in these patients.

Laparoscopic IOUS is essential for more precise staging of the disease, as demonstrated by the presence of false-positive and false-negative lesions, even in this small series, although the limited sample size does not allow us to draw conclusions regarding the diagnostic accuracy of the preoperative examinations performed in these patients. Furthermore laparoscopic IOUS is mandatory to guide cryoprobe positioning, to monitor the entire freezing and thawing process, and to obtain evidence of complete tumor ablation, as described in Materials and Methods, above. For optimal cryodestruction of the entire lesion with an adequate 1.5-cm margin, precise positioning of the cryoprobes is the most critical aspect of the operation. On the basis of the position of the nodule with respect to surrounding major vessels and biliary ducts, as defined by ultrasonography, the most suitable point of entrance of the cryoprobes is selected and the trocars are positioned accordingly. Although IOUS provides adequate monitoring of complete tumor ablation, thermocouples were still employed in our experience to measure the temperature of normal liver tissue near the nodule and the time required for freezing. In fact, a rapidly decreasing temperature is equivalent to more effective cryodestruction, whereas a slower freezing process may be associated with inadequate tissue destruction.

As learned from open cryoablation, when a large volume of tissue is ablated, it is important to maintain a high urine output throughout the procedure and for 48 hours postoperatively to facilitate elimination of the products of cryodestruction and to prevent tubular necrosis.

Whether double freezing is better than single freezing is still an unresolved issue. The double freezing technique produces more cryodestruction than the single freezing technique, but it is also associated with a greater incidence of side effects, such as thrombocytopenia. As reported by other authors [17], thrombocytopenia correlates with hepatocellular injury; we observed it only after open cryoablation, when a large volume of tissue is frozen. In our experience laparoscopic cryoablation with single freezing was adequate to treat the entire lesion in most patients (12/18, 66.6%). In our experience double freezing was performed only when there was some doubt about the efficacy of the single freezing, as demonstrated by a safety margin of < 1.5 cm on ultrasonography after thawing or a slow rate of temperature decrease measured by the thermocouple at the periphery of the lesion.

As reported by others [13], surface parenchymal splits occurred only in cases where more than one cryoprobe was simultaneously employed to treat the same lesion; they are caused by different thermal gradients. However, this aspect requires further study, as no surface parenchymal splits were observed in the remaining eight patients of this series who underwent cryoablation with two or more simultaneously working probes.

Accurate hemostasis after cryoprobe removal is an important aspect of the procedure and is obtained with several hemostatic agents. In addition, our original technique of high-frequency electrocautery applied to regenerated cellulose mesh irrigated with saline proved to be effective when dealing with bleeding from cryoprobe tracks and from surface parenchymal splits. Nevertheless, conversion to open surgery to control bleeding was necessary in two patients with lesions located in segment 8, high over the dome of the liver, because laparoscopy was unable to provide adequate exposure of the entire length of the surface parenchymal splits.

The postoperative course for this series of patients was free of major complications, and there was no mortality. The most frequent minor complication was the occurrence of right-sided, self-limited pleural effusion, which resolved nonoperatively in every case. We now tend to consider it to be a side effect of freezing below the right hemidiaphragm, rather than a complication.

Laparoscopic cryoablation has been confirmed by this study to be feasible and safe, as reported by others [13], even with the use of large probes. A total laparoscopic approach to cryoablate lesions located in segments 7 and 8 is feasible, although extensive laparoscopic dissection of the bare area of the liver is required to obtain adequate exposure for the treatment of nodules in segment 7. Hemostasis of the cryoprobe track is generally not a problem. However, as reported by others [13], activation of cryoprobes close to each other creates different temperature gradients during iceball expansion, with subsequent parenchymal fractures. If more than one probe is simultaneously activated to treat lesions in segment 8, high over the liver dome, one must be aware of the risk of developing these superficial parenchymal splits, the entire length of which may be impossible to control laparoscopically because they may develop posteriorly. In such cases, conversion to open surgery may be required to control bleeding. A longer follow-up is required to evaluate the efficacy of laparoscopic cryoablation in terms of local tumor control.

Résumé

Le but de cette étude prospective a été d'évaluer la faisabilité, la sûreté et l'efficacité de la cryoablation échoguidée des tumeurs hépatiques primitives et secondaires par une approche laparoscopique totale. Parmi 56 patients qui ont eu une cryoablation échoguidée, l'approche laparoscopique totale a été réalisée chez 18 (5 hommes, 13 femmes, âge moyen 48.6 ans, extrêmes 35–77 ans). Quinze patients ont été opérés d'une tumeur secondaire et trois d'une tumeur primitive. Les critères de sélection ont été la présence de trois nodules ou moins, un volume tumoral de 40% du foie au plus et l'absence de maladie extra-hépatique. 28 lésions ont été confirmées par l'échographie peropératoire avant d'être traitées: 25 par cryoablation écho-guidée et trois par résection en coin par laparoscopie. Après cryoablation, une hémorragie sur la tranche de la cryosection a été observée dans six cas; on a du convertir dans deux cas de lésions localisées dans le segment 8. Aucune complication majeure ou mortalité n'a été enregistrée. Une ou plusieurs complications ont été observées chez 9 patients y compris un épanchement pleural (8 cas, 44.4%), une collection sous-diaphragmatique (3 cas, 16.6%), une aggravation de l'insuffisance hépatique chez un patient cirrhotique (1 cas, 5.5%) et une infection pariétale chez un patient converti en chirurgie ouverte (1 cas, 5.5%). La durée moyenne du séjour hospitalier a été de 6.4 jours (extrêmes: 3–14 jours). Avec un suivi moyen de 10.8 mois (extrêmes allant de 5 à 16 mois) tous les patients sont en vie et 14 sont sans maladie, comme en témoignent des taux de marqueurs normaux et des images de résonance magnétique normales. Chez les patients soigneusement sélectionnés, la cryoablation totalement effectuée par laparoscopie échoguidée est faisable et sûre. Un suivi plus long est nécessaire pour évaluer l'efficacité et son impact sur la survie.

Resumen

El propósito del presente estudio prospectivo y continuo es la evaluación de la factibilidad, seguridad y eficacia del método totalmente laparoscópico para la crioablación dirigida por ultrasonido de tumores hepáticos primarios y secundarios. En un grupo de 56 pacientes sometidos a crioablación dirigida por ultrasonido, se empleó el método laparoscópico total en 18 (5 hombres, 13 mujeres, con edad media de 48.6 años, rango 35–77 años). Quince tenían tumores hepáticos secundarios y tres tumores primarios. Los criterios de selección incluyeron la presencia de 3 o menos nódulos, un volumen tumoral inferior al 40% del volumen hepático y ausencia de enfermedad extrahepática. Veintiocho lesiones confirmadas mediante ultrasonografía laparoscópica intraoperatoria, pudieron ser tratadas, 25 por crioablación dirigida por ultrasonido y 3 por resección en cuña laparoscópica. Luego de la crioablación, se observaron áreas de sangrado en tejidos congelados del parénquima en 6 casos, lo cual requirió conversión a cirugía abierta en 2 casos, cuyas lesiones estaban ubicadas en el segmento 8. No se registraron complicaciones mayores ni mortalidad. Se presentaron una o más complicaciones, de carácter menor, en 9 pacientes, que incluyeron derrame pleural (8 casos, 44.4%), colección líquida subdiafragmática (3 casos, 16.6%), mayor deterioro de la función hepática en un paciente cirrótico (1 caso, 5.5%) e infección en un paciente que había requerido conversión a cirugía abierta (1 caso, 5.5%). La estancia hospitalaria media fue de 6.4 días (rango 3–14 días). En un seguimiento medio de 10.8 meses (rango 5–16 meses), la totalidad de los pacientes están vivos y 14 de ellos libres de enfermedad, a juzgar por el retorno a valores normales de los marcadores tumorales e imágenes de resonancia magnética normales. La crioablación laparoscópica total guiada por ultrasonido es un procedimiento factible y seguro en pacientes cuidadosamente seleccionados. Pero se requiere un mayor tiempo de seguimiento para la evaluación de su eficacia y de su impacto en la sobrevida.

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Invited Commentary

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In general, the results of laparoscopic cryosurgery for liver tumors reported by Lezoche and his group in this issue accords with the experience from my institution, although the Ancona group has treated patients with surgically resectable disease. Some would argue that in situ ablation, by whatever means, is appropriate only for patients with nonresectable hepatic disease, as surgical resection in these patients can be attended by long-term survival and must be considered the current orthodox management. It is not the remit of this commentary to discuss this issue except to stress that there are two sides to the argument. Surgical progress would come to a halt if we, as surgeons, failed to recognize the potential of technologic progress that inevitably leads to change in surgical practice. Surgeons must consider and explore new modalities of therapy, admittedly with caution and the necessary scientific methods that yield data from which valid assessments can be made. Otherwise others, particularly interventional radiologists, will take over management of these patients.

The advantages of in situ laparoscopic/ultrasound-guided cryosurgery (and for that matter other forms of in situ ablation) in the context of metastatic liver disease (usually from colorectal cancer) include precise targeting of the lesion, monitoring of the ablative process, and early detection of bleeding; most importantly, this therapy can be repeated. The latter point is obviously of seminal clinical relevance to patients with metastatic liver disease involving both lobes, as a protocol of staged in situ ablation can be implemented. Moreover, new lesions encountered during follow-up can be ablated. It is this aspect of laparoscopic cryosurgery that we have found to be particularly useful. In our series, with follow-up extending to 3.5 years, 6 of 29 patients have had three to six sessions over periods of 8 to 15 months.

Cryosurgery differs from other forms of in situ ablation (e.g., by thermal ablation using radiofrequency current or interstitial laser hyperthermia), in that after thawing of the iceball the lesion is revascularized for periods up to 12 hours. This has both benefits and disadvantages. The potential benefits include reperfusion injury (extending the area of kill) and the release of fixed tumor antigens, which can induce an immune response. Although confirmed in some animal studies [1, 2], the importance of the tumor-specific immune response in terms of tumor regression in humans remains based on anecdotal evidence [3]. Moreover, one experimental study has produced indirect evidence that cryosurgery may lead to increased dissemination [4], although this work has not been confirmed, and our own recently completed experimental studies do not support it [5]. The disadvantages of temporary revascularization of the cryolesion include bleeding from surface parenchymal splits of frozen normal hepatic parenchyma and an element of disseminated intravascular coagulation with thrombocytopenia during the postoperative period. The extent of this consumptive coagulopathy limits the total amount of liver volume that can be frozen at any one session, and we have encountered a hemorrhagic death in a patient who was treated with a combined hepatic freeze (four lesions) amounting to 12.0 cm^3. For this reason we now limit the total freeze to a maximum of 10.0 cm^3 during any one session. Even so, we have encountered thrombocytopenia (maximal on the second and third days) in 25% of cases. Although the Ancona study does not contain data on this consumptive coagulopathy after cryosurgery, I note that 3 of 18 patients required postoperative blood transfusion. We have solved the problem of liver parenchymal splits (which necessitated conversion in 2 of 18 patients in Lezoche et al.'s series) by applying biologic tissue glue to the parenchymal splits before thawing the lesion.

Although adequate monitoring of the iceball is possible by IOUS using contact linear array probes, it is not totally satisfactory for two reasons: (1) as the liver parenchyma cools, it becomes less compliant, and thus it is difficult to maintain good coupling between the probe and the liver; and (2) the acoustic shadow of the iceball precludes visualization of the depth of the frozen zone. There is no doubt that improvements in imaging technology for monitoring in situ ablation such as three-dimensional ultrasonography and open MRI systems coupled with surface viewing via the laparoscope (image-guided tomographic in situ ablation) will solve this problem in the near future.

I agree with the authors that measurement of liver temperatures at the edge of the ice is good practice and a fall to −40°C ensures tumor cell kill up to the point. However, it provides only one-site reading, and the surgeon has no information on the temperature at other points on the ellipsoid boundary of the iceball.

I share the authors' view that in situ laparoscopic image-guided ablation holds great promise for treatment of secondary hepatic tumors and, combined with a program of effective systemic chemotherapy, may change the current dismal prognosis for most of these patients. We as surgeons must adopt this treatment modality rather than defend, at all costs, the purely surgical option. Professor Lezoche and his group are to be complimented for a detailed, objectively analyzed, prospective study. We need more such reports from other centers involved in hepatobiliary disease to accumulate the necessary database on prima facie efficacy and safety before we contemplate randomized trials comparing in situ ablation with resection. If we limit in situ ablation exclusively to inoperable disease, we will never reach that stage.

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