ANNALS OF SURGERY
Vol. 225, No. 2, 193–201

Hepatic Cryosurgery for Liver Metastases

Long-Term Follow-Up

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Objective
The aim of this prospective study was to evaluate the applicability of cryogenic and conventional surgery in treating liver metastases (LM) with respect to intraoperative tumor reduction and survival rate.

Summary Background Data
As have been shown in animal experiments as well as in clinical investigations, cryosurgery has been used for the treatment of many benign and malignant conditions. For the first time, this report summarizes a 10-year follow-up clinical experience with cryosurgery for treatment of LM from 1983 to 1992.

Methods
One hundred twenty-three patients with LM (87 males and 36 females, a ratio 2.4:1.0; age, 41.3 ± 12.1 years) were stratified and entered into a long-term prospective, randomized clinical trial for cryogenic surgery in group 1 (n = 63) and conventional surgical techniques in group 2 (control subjects, n = 60). Principally, a self-constructed cryogenic clamp was used for hepatic cryoresection with preliminary freezing of the margin resection by a cryosurgical system "Cryoelectronic-2" or "Cryoelectronic-4." Hepatic cryoextirpation (cryoablation) and hepatic cryodestruction were performed by means of probes of different roughly disk design from ϕ 5 mm to 55 mm by volume of frozen zone of 40 cm^3 to 180 cm^3 for approximately 7 to 32 minutes.

Results
In most cases in group 1 and group 2, LM were based on colorectal cancers (65% *vs.* 68%). The hepatic cryosurgical procedures in group 1 included cryoextirpation (29 patients, 46%), cryoresection (20 patients, 32%), and cryodestruction (14 patients, 22%) solely. Clinical and laboratory parameters showed that the curative effects were significantly higher in group 1 than in group 2. The 3-year survival rate was in group 1 and group 2 (60% *vs.* 51%, respectively). The 5-year survival rate was 44% in group 1 and 36% in group 2. Twelve patients (19%) *versus* 5 patients (8%) in group 1 and group 2, respectively, survived 10 years. The disease-free survival was in group 1 and group 2 (30% *vs.* 18%, respectively). During a follow-up period, recurrence in the liver was observed in 54 patients (85%) in group 1 and in 57 patients (95%) in control subjects. After a 10-year follow-up

period in group 1 and group 2, 9 patients (14%) *versus* 3 patients (5%) remained disease free, 3 patients (4%) *versus* 2 patients (3%) were surviving with disease, and 51 patients (81%) *versus* 55 patients (92%) died.

Conclusions

The data of this 10-year prospective, randomized clinical trial suggest that hepatic cryosurgery is effective in the treatment of resectable and nonresectable LM. The results show intraoperative tumor reduction (≥90% ≤97%) and extended higher survival in these patients. The study indicated a 5-year and 10-year survival rate of 44% and 19% after cryosurgery, respectively.

Cryosurgery can be used for the treatment of many benign and malignant tumors. For the first time, this study shows the results of a 10-year follow-up clinical experience with cryosurgery for the treatment of liver metastases (LM). The data of this prospective, randomized clinical trial suggest that hepatic cryosurgery is effective in the treatment of resectable and nonresectable liver cancer.

Treatment options for LM include aggressive surgical resection of all large tumors as well as administration of systemic and regional therapeutic procedures.[1-6] Several novel strategies are being explored for the treatment of LM.[7-9]

The use of low temperatures to destroy abnormal tissues is the basis of cryosurgery. The application of cryogenic techniques for resection of parenchymal organs[10] and *in situ* ablation of tumors using subzero temperatures for surface malignancies[11] have been described. The advances in this technology have encouraged interest in applying cryosurgery in the treatment of hepatic malignancies.[12-17]

Surgical resection of isolated LM is now widely accepted as the only curative treatment method available. Approximately 25% of patients with isolated LM have tumors that are resectable, and 20% to 35% will survive 5 years or more.[18-20] It is speculated that the cryoablation should be carried out for liver tumors that were deemed unresectable: central tumor localization straddling the line of demarcation between right and left lobes, multiple tumors in both lobes.[21] Currently, however, no data are available regarding the long-term benefits for attaining curative effects on liver metastatic tumors.

As have been shown, major hepatic resections of LM can be performed with acceptable morbidity and mortality rates, but they only should be contemplated when the quality and quantity of life can be justifiably extended.[22,23]

For the first time, this prospective, randomized study has been summarized as a 10-year follow-up clinical experience with cryosurgery for treatment of LM.

MATERIALS AND METHODS

One hundred twenty-three consecutive patients with LM received surgical treatment, and they were observed over a 10-year period, from 1983 to 1992, at the Department of General Surgery of the State Medical University of Kiev (Ukraine), a specialized, state-supported center for the surgical treatment of liver, bile ducts, and pancreas diseases.

All 123 patients were stratified according to age, gender, disease, primary lesions, metastatic liver tumors, and disease-free interval and gave their consent to participate into a prospective, randomized trial. Patients with hepatic metastases from a variety of primaries were randomized, and they were assigned to two surgical treatment groups. One treatment group (63 patients, group 1) included the use of all types of cryogenic surgery. The other treatment group (60 patients, group 2) used conventional surgical techniques only and excluded all cryotechnology.

The inclusive criteria were isolated primary manifestation of solitary metastases in the liver, as well as multiple nodules in one lobe or both lobes of the liver. There were 87 males and 36 females (male/female ratio, 2.4/1.0). The mean age of the subjects was 41.3 ± 12.1 years (range, 34–83 years) at the time of the initial evaluation. The age and gender distribution and various metastatic characteristics for these patients in both groups are listed in Table 1. There were no significant differences between the two groups regarding age, gender, symptoms, LM, and disease-free interval. Disease-free survival time was calculated from the primary tumor resection to the first metastatic liver manifestation.

Presented in part by the European School of Oncology (October 24–28, 1994, Lugano, Switzerland); XXIX World Congress of the International College of Surgeons (November 13–16, 1994, London, England); European Institute of Oncology (May 22–24, 1995, Milan, Italy); 36th World Congress of Surgery, International Surgical Week ISW 95 (August 27–September 2, 1995, Portugal); Pre and Post Course Symposium. Colorectal Disease in 1996: An International Exchange of Medical and Surgical Concepts (February 5–23, 1996, Cleveland Clinic Florida, Fort Lauderdale, Florida); XXX World Congress of the International College of Surgeons (November 25–29, 1996, Kyoto, Japan).

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Accepted for publication March 8, 1996.

Table 1. AGE, GENDER, AND METASTASES DISTRIBUTION FOR PATIENTS WITH LIVER METASTASESS*

	Group I (n = 63)	Group II (n = 60)
Age (yrs)		
Mean ± 1 SD	42.0 ± 11.2	40.6 ± 13
Range	34–83	35–81
Gender		
Male	44	43
Female	19	17
Symptoms		
Yes	14	12
No	49	48
Metastases		
Solitary	19	18
Multiple	44	42
Unilobar	24	23
Bilobar	20	19
No. of metastases		
1	19	18
2	23	23
≥3	21	19
Size of solitary lesions (cm)		
<3	41	40
>3	22	20

SD = standard deviation.
* No significant differences between randomized groups.

The patients with LM were examined before surgery, and the diagnoses were verified. The preoperative standardized examination of each patient included, according to a previous schema, general medical evaluation, laboratory data (*i.e.,* complete hemogram, biochemistry including parameters to evaluate hepatorenal function), chest x-ray, electrocardiogram, and liver ultrasonography. In 31 patients (49%) of group 1 and in 29 patients (48%) of group 2, abdominal computed tomography as well as magnetic resonance imaging in both groups (17% *vs.* 18%, respectively) were performed. Before surgery and after surgery, tumor marker levels (carcinoembryonic antigen [CEA], alpha-feta protein [AFP], carbohydrate antigen [CA 19-9]) were measured in 43 patients (68%) of group 1 and in 42 patients (70%) of group 2 to characterize the liver tumors individually.

At laparotomy, the extent of liver replacement by tumor was estimated by inspection and palpation, and a search was done for extrahepatic metastatic disease. Additionally, biopsy of LM, other suspected intra-abdominal disease, or lymph node metastases have been performed.

If, at hepatic resection, tumor was >1 cm far from the cut surface of the unfixed liver specimen, the surgical margin was considered to be negative. If the distance between tumor and cut surface was <1 cm, the margin was considered to be positive.[24] Involvement of Glisson's capsule was not considered to be positive. The patients were classified according to the TNM classification.[25] All patients had histologic confirmation of the metastases.

The postoperative follow-up regimen recommended was a physical examination, liver function tests with CEA, and liver ultrasonography at 3-month periods. The time between examinations was lengthened after 1 year to 6-month periods and 3 years after surgery at 6-month intervals. A chest x-ray and computed tomography were added at 6-month and 1-year intervals. In both groups, postoperative treatment and other concomitant therapy were comparable. In addition to the routine therapy, all patients in both groups received systemic chemotherapy (12 mg/kg 5-fluorouracil and 500 mL 0.9% NaCl or 5% glucose, one time at a week, 6 weeks running).

Statistical Analysis

Survival rates of treated patients with LM were calculated by the life-table method of Kaplan–Meier.[26] All data were statistically analyzed using the Mann–Whitney *U* test for independent samples or the two-test. The null hypothesis was rejected if $p \leq 0.05$.

RESULTS

One hundred twenty-three patients with LM were entered prospectively into this study from 1983 to 1992. All patients were randomized, 63 for cryogenic surgery (group 1) and 60 for conventional surgery (group 2, control subjects). Data analysis did not show any significant difference between both groups with regard to age, gender, primary lesions, metastases distribution, and disease-free interval.

Histologic Review of Patients

Histologic diagnosis of LM in patients undergoing cryosurgery for liver cancer (group 1) and in patients after conventional surgical resection of metastatic liver tumors (group 2, control subjects) is listed in Table 2. In most cases in both groups, LM were colorectal cancers metastatic to the liver (65% *vs.* 68%). Of the 41 patients in group 1, the stage of the primary colon cancer was Dukes' stage A in 6 patients (15%), Dukes' stage B in 14 patients (34%), and Dukes' stage C in 21 patients (51%). At the same time of the 41 patients in group 2, Dukes' stage A was in 7 patients (17%), Dukes' stage B was in 15 patients (37%), and Dukes' stage C was in 19 patients (46%).

The size of the metastatic lesion (mean, 3.1 cm), as well as its site, determined the extent of resection. Nineteen patients (30%) in group 1 and 18 patients (30%) in group 2 had solitary lesions resected. The rest in group

Table 2. DISTRIBUTION OF PRIMARY LESIONS IN PATIENTS WITH LIVER METASTASES UNDERGOING HEPATIC CRYOSURGERY (n = 63) AND CONVENTIONAL SURGICAL TECHNIQUES (n = 60)*

Type of Lesion	Group I No. (%)	Group II No. (%)	Total No. (%)
Colorectal cancer	41 (65.1)	41 (68.3)	82 (66.6)
Stomach cancer	5 (7.8)	4 (6.7)	9 (7.3)
Breast cancer	4 (6.3)	4 (6.7)	8 (6.5)
Melanoma	3 (4.8)	3 (5)	6 (4.9)
Ovarian adenocarcinoma	3 (4.8)	2 (3.3)	5 (4.1)
Uterus cancer	2 (3.2)	2 (3.3)	4 (3.3)
Kidney cancer	2 (3.2)	2 (3.3)	4 (3.3)
Intestinal cancer	1 (1.6)	1 (1.7)	2 (1.6)
Pancreatic cancer	1 (1.6)	1 (1.7)	2 (1.6)
Unknown primary	1 (1.6)	—	1 (0.8)
Total	63 (100)	60 (100)	123 (100)

* $p < 0.05$.

1 and group 2 (44 patients *vs.* 42 patients, respectively) had multiple lesions removed from one or both lobes of the liver. Multiple unilobar resectable metastases had been observed in group 1 (24 patients, 38%) and in group 2 (23 patients, 38%).

Cryogenic and Conventional Surgery

In each patient with LM, the liver was mobilized at laparotomy. The liver was examined bimanually, and the peritoneal cavity was explored to rule out extrahepatic disease. Then, an intraoperative ultrasonography (Echotomoskop ETCR-1, UdSSR; Bruel and Kjaer, Denmark, Sweden; SSD-256 Alloka, Japan) was performed to obtain real-time scans of the entire liver.

One important instrument of the principal technical devices in this investigation was a self-constructed cryogenic clamp (Patent N° 1454408, 1988, UdSSR): Its branches were refrigerated by liquid nitrogen. The source of liquid nitrogen was driven by a cryosurgical system, "Cryoelectronic-2" and "Cryoelectronic-4" (UdSSR), that circulated liquid nitrogen through the probe at −196 C. The cryogenic clamp was used for hepatic cryoresection with preliminary freezing of the margin resection. The cryogenic clamp was applied across the desired incision line of the liver and gradually frozen by liquid nitrogen refrigeration (Fig. 1). When the incision line in the liver has been frozen completely at a temperature of −196 C, the liquid nitrogen refrigeration was stopped, and the resection could be carried out effectively without any blood and bile loss. Thus, the small capillaries and venules as well as biliary ducts $\phi \leq 1.5$ mm within the cryogenically frozen zone have been destroyed. The large arteries and veins or biliary ducts $\phi < 1.5$ mm passing across the suture line will not have been destroyed.

Hepatic cryoextirpation (cryoablation) and hepatic cryodestruction were performed by means of probes of roughly disk design ϕ 5-mm, 10-mm, 15-mm, 20-mm, 35-mm, 45-mm, or 55-mm by volume of frozen zone of 40 cm^3 to 180 cm^3 approximately 7 to 32 minutes (Fig. 2). When cryoextirpation or cryodestruction was used, the thawing of each freeze-thaw cycle took automatically approximately 2.5 to 3.0 minutes. Two or three freeze-thaw cycles were performed for each lesion. The tip of the disk was passed into the center of each metastasis or using intraoperative ultrasound to localize inpalpable lesions. Freezing was continued until the diameter of the ice zone was 1.5 to 2.0 cm larger than that of the metastasis. The necrotic mass of the LM generally was similar to that of the frozen zone. Cryoextirpation was considered to be satisfactory if the ice zone completely encompassed the area of the lesion during all cycles (verified by intraoperative ultrasonography). The abdominal incisions were closed with drainage for early postoperative controlled bleeding and bile leakage.

The hepatic cryosurgical procedures (Fig. 3) in group 1 included cryoextirpation (29 patients, 46%), cryoresection (20 patients, 32%), and cryodestruction (14 patients, 22%) alone. Twelve patients (32%) who were treated by cryoresection underwent cryogenic anatomic lobectomy (25%), cryogenic right trisegmentectomy (3%), cryogenic extended left-sided lobectomy (2%), and extended right-sided lobectomy (2%). The median size of solitary lesions removed with a cryoresection was 3.1 cm (range, from 1.3–12 cm) and with a cryoextirpation was 2.1 cm (range, from 1.2–3.2 cm). Cryodestruction was carried out in patients with nonresectable LM (22%). The median size of metastatic lesions was 5.1 cm (range, from 4.6–17.0 cm). The initial hepatic surgeries (Fig. 4) in group 2 included wedge resection of one or more metastases (40%), anatomic lobectomy (28%), right bisegmentectomy (5%), right trisegmentectomy (3%), extended left-sided lobectomy, and extended right-sided lobectomy (2% *vs.* 2%). In 12 patients (20%), only an exploratory laparotomy was performed.

Of the 63 patients in group 1, hepatic cryoresection was carried out in 16 patients (25.4%) by our developed cryogenic clamp. In four patients (6.3%) hepatic cryoresection was performed with the help of a modified cryoscalpel.[27] A good cholestasis and hemostasis was achieved during freezing.

All patients tolerated hepatic cryosurgery well without any operative mortality. Clinical and laboratory parameters showed that the curative effects were higher in group 1 than in group 2. The patients in

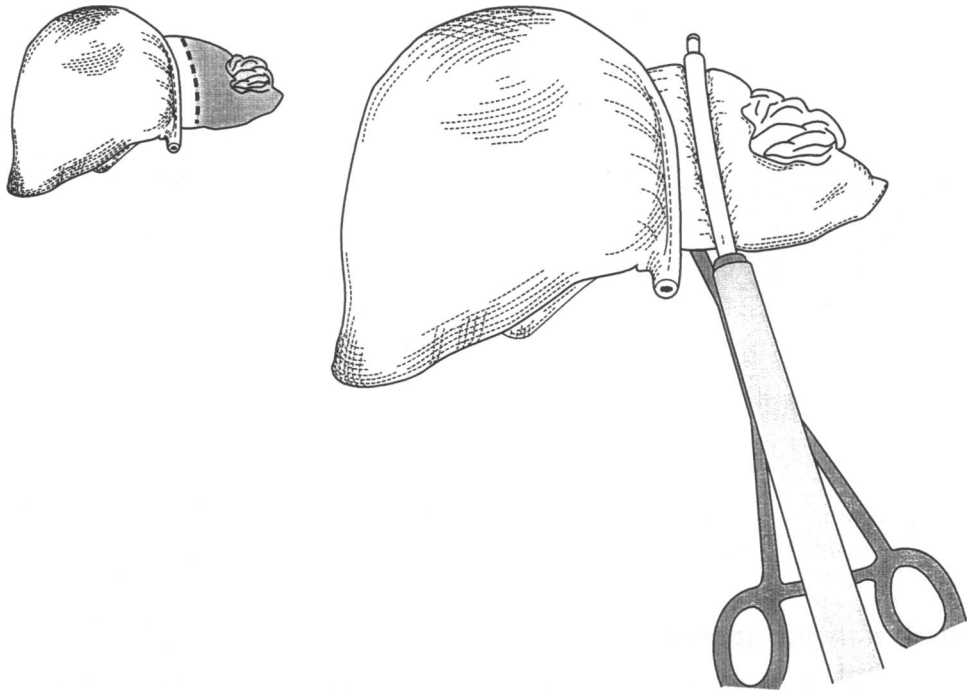

Figure 1. Hepatic cryoresection by means of cryogenic clamp in patients with liver metastases.

group 1 and group 2 have suffered from fever for 3 to 4 days (38.4 ± 0.7 C *vs.* 38.7 ± 0.6 C). Abdominal pain reduction after surgery in group 1 was significantly accelerated in comparison with that of group 2. At postoperative day 5, insignificant pain was observed in 83% of cases and pronounced pain in 17% of cases (group 1). At the same time, 62% of patients have reported on insignificant pain, 9% of patients

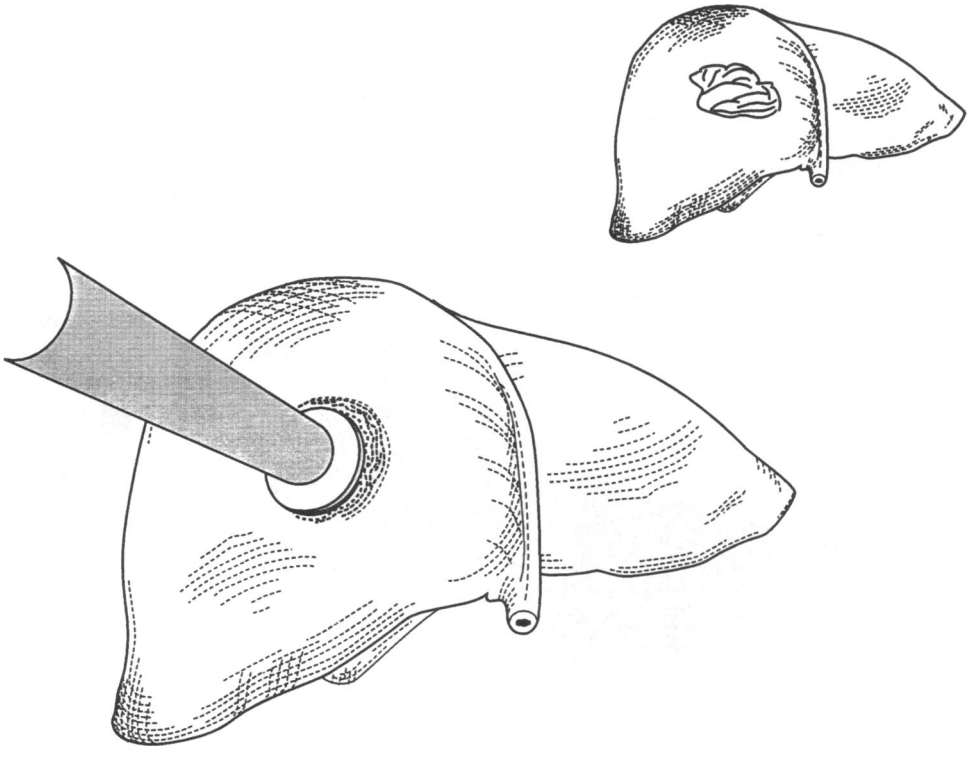

Figure 2. Hepatic cryoextirpation or cryodestruction in patients with liver metastases.

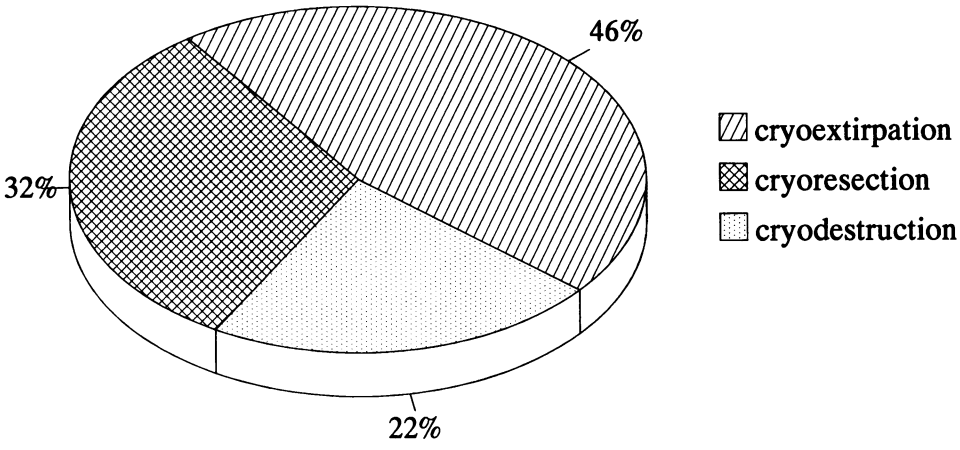

Figure 3. Hepatic cryosurgical procedures in patients with liver metastases (group 1, n = 63).

reported on pronounced pain, and 29% of patients reported on intense pain.

Clinical Investigations

Alkaline phosphatase and transaminases were increased in both groups, but these parameters of liver function were significantly higher in group 2 than those in group 1 and returned to normal in group 2 later than those in group 1 ($p < 0.05$). At week 2, alkaline phosphatase and transaminase in group 1 were normalized (mean ± standard deviation): alkaline phosphatase from 647 ± 102 U/L to 124 ± 26 U/L; transaminases: aspartate aminotransferase (glutamine–oxaloacetic transaminase) from 118 ± 16 U/L to 17 ± 4 U/L; ALAT (glutamic-pyruvic transaminase) from 133 ± 19 U/L to 22 ± 5 U/L). At the same time, alkaline phosphatase and transaminase in control subjects still were abnormally high: alkaline phosphatase from 593 ± 87 U/L to 198 ± 21 U/L; transaminases: ASAT (glutamine–oxaloacetic transaminase) from 114 ± 9 U/L to 25 ± 6 U/L; ALAT (glutamic-pyruvic transaminase) from 141 ± 14 U/L to 28 ± 4 U/L. In control subjects, those levels returned to normal at the third postoperative week.

The CEA level after hepatic resection (17 patients *vs.* 19 patients) was lower in group 1, and its decrease to normal was accelerated compared with that of control subjects ($p < 0.05$).

In 47 patients (75%) with LM in group 1 and 39 patients (65%) in group 2, an uneventful postoperative course was observed, and they underwent routine postoperative treatment. Patients in the intensive care unit were treated with fresh blood and plasma, or human albumin in 16 (25%) cases in group 1 and in 21 (35%) cases in group 2. In 6 patients in group 1 and 12 patients in group 2, the postoperative course has not been totally uneventful. In group 1, three patients (5%) had postoperative pneumonia and two patients (3%) had postoperative septic wound. There has been no case of bleeding, bile leakage, or abdominal infection after operation. In group 2, four patients (7%) had subphrenic abscess, three patients (5%) had pleural effusion, 2 patients (3%) had postoperative

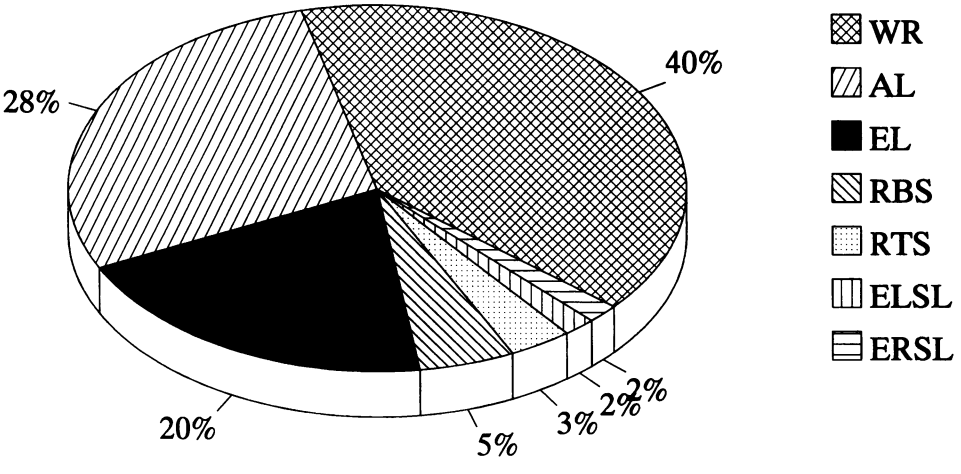

Figure 4. Conventional surgical techniques in patients with liver metastases (group 2, n = 60). WR: wedge resection; AL: anatomic lobectomy; EL: exploratory laparotomy; RBS: right bisegmentectomy; RTS: right trisegmentectomy; ELSL: extended left-sided lobectomy; and ERSL: extended right-sided lobectomy.

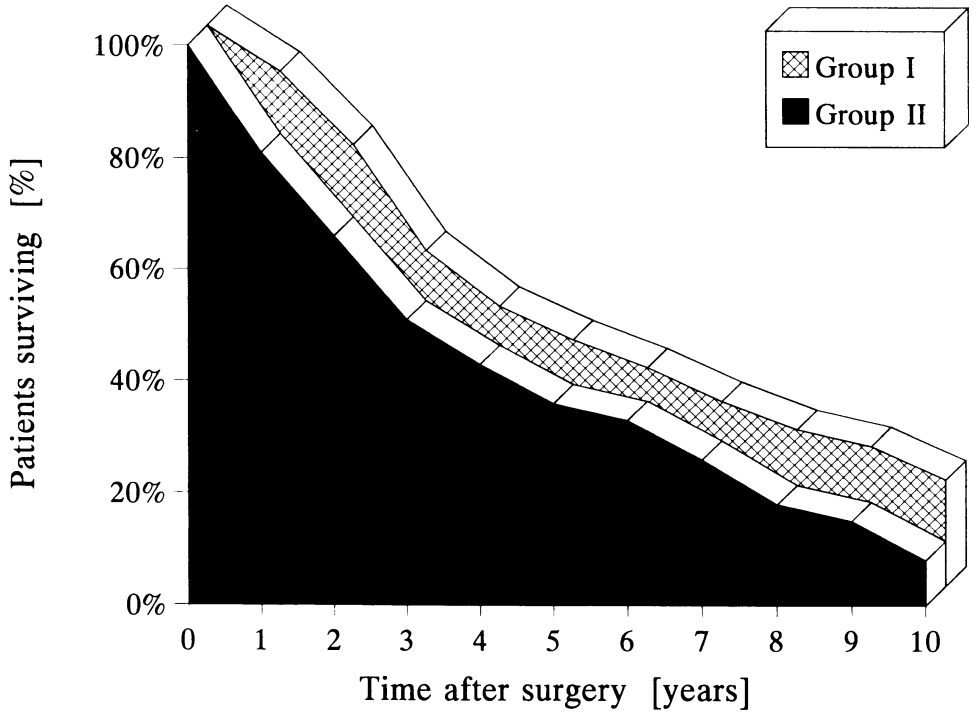

Figure 5. Survival curves after cryogenic and conventional hepatic surgery.

bleeding, two patients (3%) had postoperative pneumonia, and one patient (2%) had postoperative septic wound. There was no operative mortality in either groups. After operation, patient postoperative hospital stay was significantly shorter in group 1 (7.5 ± 0.5) than in group 2 (8.6 ± 0.4).

All patients of both groups received systemic chemotherapy (12 mg/kg 5-fluorouracil and 500 mL 0.9% NaCl or 5% glucose, one time at a week, 6 weeks running) in addition to the postoperative therapy.

Survival Analysis

The tumor was reduced significantly (≥90% ≤97%) in all patients with nonresectable LM treating by cryodestruction in group 1. The follow-up period in patients with LM in group 1 ranged from 6 months to 10 years and in control subjects from 5 months to 10 years (Fig. 5). The 3-year survival rate was higher in group 1 (60%) than in group 2 (51%). The 5-year survival rate was 44% in group 1 and 36% in group 2. Twelve patients (19%) in group 1 and 5 patients (8%) in group 2 survived 10 years. The disease-free survival rate also was higher in group 1 (30%) than in group 2 (18%). During a follow-up period 1, recurrence in the liver was observed in 54 patients (85%) in group 1 and in 57 patients (95%) in control subjects. After a 10-year follow-up period in group 1 and group 2, 9 patients (14%) *versus* 3 patients (5%) remained disease free, 3 patients (4%) *vs.* 2 patients (3%) were surviving with disease, and 51 patients (81%) *vs.* 55 patients (92%) died.

DISCUSSION

The increasing number of reports concerning LM and their encouraging survival rates reflects the importance of clinical investigations in this particular field.[28–32] The presence of LM without other evidence of cancer spread is a clinical setting in which aggressive local and regional treatment should be considered. Surgical removal of all macroscopic tumors from the liver is the most obvious treatment option. Other techniques for nonresectable disease also are being evaluated.[33] No effective option exists for patients with unresectable LM. Systemic and regional chemotherapy have not been effective.[7]

The behavior and the morphology of living tissues subjected to low temperatures have been the subject of many studies.[10,34–37] Cryosurgery is one of the new treatment strategies being explored for the management of nonresectable liver tumors. Several publications have reported on trials using cryosurgical methods in the treatment of hepatic metastases.[7,18,38,39] Cryosurgery has certain advantages that make it particularly appealing in the treatment of metastatic liver tumors[10,14,38–40]:

1. Cryosurgery's anesthetic action by sensory nerve destruction (*e.g.*, in palliation of advanced carcinoma) is appealing.

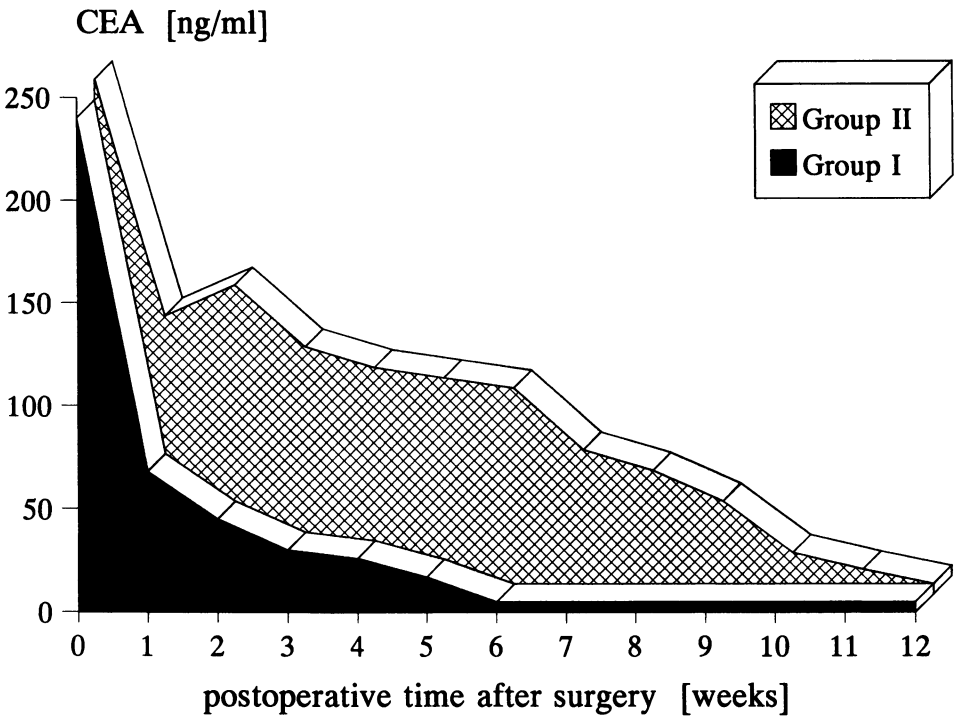

Figure 6. Postoperative reduction of carcinoembryonic antigen titer in patients with liver metastases after cryogenic and conventional hepatic surgery.

2. The avascular nature of the lesion produced is advantageous, thus avoiding problems of hemorrhage.
3. The cryogenic approach can result in irreversible necrosis of cancer cells, the rapid formation of a clean granulating base underlying the necrotic tissue produced by the freezing.
4. Freezing with liquid nitrogen might produce an autoimmune reaction against surviving or recurrent neoplastic cells.
5. Cryosurgery does not require the resection of large volumes of healthy surrounding tissue.
6. Cryosurgery prevents malignant cell dissemination by the stasis induced in the frozen field.
7. Cryosurgery allows retreatment of lesions that have recurred.

The results indicate our 10-year clinical experience in treating LM by cryosurgery with liquid nitrogen and conventional surgical techniques. Our results suggest that cryogenic hepatic techniques could be used safely to treat LM. The range of indications for hepatic cryosurgery in patients with LM is at least in this study comparable with that after conventional hepatic techniques. In contrast, cryodestruction was carried out in 14 patients (22%) with bilateral and multiple LM in group 1 that were deemed nonresectable (see Fig. 3). After the cryosurgery, a considerable reduction of the intraoperative tumor ($\geq$90%, $\leq$97%) was reached. At the same time, in 12 patients (20%), only an exploratory laparotomy was performed in group 2 because the cause of unresectability in those patients was multiple bilobar metastases. However, survival rate was significantly higher in those patients in group 1 and group 2 (mean, $\pm$8 months *vs.* mean, $\pm$3 months).

Figure 6 shows that both groups were preoperatively equivalent concerning CEA parameter. Nevertheless, after hepatic resection, the CEA level was higher in group 2, and it was decreased to normal date than in group 1 ($p < 0.05$).

We suggest that preoperative and postoperative adjuvant chemotherapy in patients with resectable and nonresectable LM in addition to cryosurgical treatment will favor an excellent response rate and survival time. The patients of both groups received systemic chemotherapy with 5-fluorouracil to postpone second recurrence of disease after hepatic surgery. Currently, there is no evidence that chemotherapy after cryosurgery of LM will improve survival. Recurrence after hepatic resection may be limited initially to the liver in 40% of patients whose disease recurs.[20,41] In the present study, during a 10-year follow-up period, recurrence in the liver was observed in 85% of cases in group 1 and in 95% of cases in group 2 (control subjects). After a follow-up period, 14% of patients in group 1 and 5% of patients in group 2 remained disease free, and 4% of patients *versus* 3% of patients were surviving with disease. Hence, the combination of hepatic cryosurgery with several (neo)-adjuvant conservative treatments, such as chemotherapy or radiation, and its

role in the curative and palliative treatment of LM and its possible improvement in survival time clearly requires investigations in future studies.

Acknowledgments

The author thanks Professor V. S. Zemskov for his review of the manuscript and J. V. Zharkov for their technical assistance by cryogenic systems "Cryoelectronic-2" and "Cryoelectronic-4," Kiev, Ukraine.

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