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Cryosurgery for Isolated Liver Tumors or Associated with Complex Liver Resection: A Series of 38 Patients

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Rezumat

Criochirurgia tumorilor hepatice izolate sau asociată rezecțiilor hepatice complexe: o serie de 38 pacienți

Introducere: Scopul acestui studiu prospectiv este de a analiza rezultatele criodistrucției tumorilor hepatice, ca tratament singular sau asociat rezecțiilor hepatice însoțite sau nu de alte rezecții viscerale.
Material și Metodă: Între 2001 și 2011, în instituția noastră, 70 de tumori hepatice au fost tratate prin criodistrucție la un număr 38 de pacienți. Au fost analizate complicațiile și supraviețuirea la distanță, în funcție de natura tumorilor hepatice și complexitatea tratamentului.
Rezultate: Mortalitatea post-operatorie, în prima lună, a fost de 2,6%. Urmărirea medie postoperatorie a fost de 25,8 luni (limite 0-41,85 luni). Complicațiile mai numeroase au fost asociate tratamentelor complexe. Ratele morbidității, mortalității, supraviețuirii globale și fără recidivă neoplazică nu au diferit semnificativ statistic, în funcție de tipurile de tumori (valoare p > 0,05). Durata medie globală, fără semne de boală a fost de 9,5 luni, cu recidiva bolii la nivelul zonei de crioablație la 21,5% din pacienți şi cu recidiva în alte regiuni hepatice de 28,9%.
Concluzii: Crioterapia singură sau asociată rezecțiilor hepatice cu sau fără alte rezecții viscerale este o procedură eficientă. Efectul antitumoral al tratamentului a fost demonstrat, dar complicațiile şi rata mare a recidivelor hepatice, în special la pacienții cu tumori mari, necesită utilizarea cu precauție.

Cuvinte cheie: criodistrucție hepatică, tumori hepatice, metastaze hepatice, ablație tumorală

Abstract

Background: The aim of this prospective study is to assess the outcomes of cryosurgery for liver tumors, as a single treatment or associated to liver resections in conjunction or not with other visceral resections.
Material and Methods: Between 2001 and 2011, in our institution, 70 hepatic tumors have been treated through cryosurgery in 38 patients. Complications and survival were assessed, according to different types of hepatic tumors and treatment complexity.
Results: Operative mortality within 1 month was 2.6% related to cryosurgery. The median follow up was 25.8 months (range from 0-41.85 months). The number of complications was associated to complex treatment. The morbidity, mortality, disease-free and overall survival rates were not statistically significantly different between the different types of tumors (p value > 0.05). The median disease free survival was 9.5 months, with cryosite recurrent disease in 21.5% patients, and 28.9% recurrences in other liver sites.
Conclusion: Cryotherapy, single or associated with liver resections combined or not with other visceral resections is an effective procedure. The antitumoral effects of treatment were demonstrated, but complications and high local recurrence rate, especially in patients with extensive disease, should caution against its use.

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Key words: hepatic cryosurgery, liver tumors, liver metastases, tumor ablation

Introduction

Nowadays, the curative treatment of liver tumors is multimodal and involves radical resection of the tumors and complete resection of liver metastases, chemotherapy, "in situ" ablation therapies and sometimes radiotherapy (1-3). Radical surgical excision offers prolonged survival and the only chance of cure for hepatic tumors but only 20% of patients with primary or secondary liver tumors are suitable for resection because of extrahepatic disease or of the anatomical distribution of their disease (4,5). These patients could be treated by "in situ" ablation of the tumors, thus preserving functioning liver. During the last decade numerous published reports state that cryoablation alone or in combination with hepatic resection increases the number of patients with liver tumors which can be treated surgically (5-9).

The purpose of this single institutional prospective study is to assess the outcomes following cryosurgical ablation of liver tumors with or without hepatic resection in conjunction or not with other visceral resection.

Materials and Methods

Patient selection

Hepatic cryosurgery was performed for all unresectable liver tumors. When liver tumors resectability criteria were achieved, cryosurgery was associated with liver resections. In voluminous unresectable metastases, preoperative chemotherapy was performed in all patients in an attempt to downsize the lesions. The patients' tumors, operative details and follow-up were recorded prospectively. We performed cryosurgery alone or in combination with liver resection, associated or not with other visceral resection, if we could assume that all the liver tumors may be destroyed completely and the primary tumors can be totally removed.

Inclusion criteria for cryosurgery included bilateral hepatic disease, multiple liver metastases, anatomic constraints (proximity of the major vessels) and high operative risk because of poor clinical status. Exclusion criteria included: extrahepatic disease detected before, during preoperative or intraoperative assessment judged as being unresectable; unresectable liver tumors that measured more than 6 cm in the largest dimension were considered unsuitable for cryotherapy; cirrhosis, Child grade B and C and coagulopathy. Subgroup analysis compared outcome measures between different tumor groups (colorectal metastases, primary liver tumors and metastases from other primary sites).

Preoperative assessment

Standard preoperative investigations included: clinical examination, abdominal ultrasound, chest X-ray, CT scans (chest, abdomen and pelvis), liver function tests, tumor markers and colonoscopy. The bone scan to exclude extrahepatic disease was done only for selected patients. If an operation was planned, abdominal angio-CT and portography was used for assessment of hepatic disease (number, volume, and localization) and resectability. A biopsy of the hepatic tumor was not usually done preoperatively to confirm diagnosis.

Operative techniques

A bilateral subcostal or Mercedes-type incision was used and the liver was fully mobilized. A thorough examination of the liver was performed both by palpation and by intraoperative ultrasound using 7.5 MHz intraoperative linear array T-probe transducer (Versa Pro Sonoline, Siemens Medical System Inc.). Frozen section of suspicious lesions, lymph nodes or peritoneal nodules was performed.

Cryoablation was performed, under intraoperative ultrasound guidance to confirm the location of all lesions and their relationship to major biliary and vascular structures. For cryotherapy we have employed liquid nitrogen machine, ERBO CRYO 6® (ERBE Elektromedizin GmbH, Tubingen, Germany), using up to six 3.2 mm probes. The number of probes used was determined based on the required ice-ball size that would be necessary to create a 1 cm margin, around the tumor. Multiple cryoprobes were placed simultaneously in lesions larger than 3 cm, when necessary to achieve a 1 cm margin and to ensure a total clearance (*Fig. 1*). Intraoperative ultrasound was performed to monitor ice-ball formation and its extension to assure that the cryolesion encompasses the hepatic tumor in all planes by a margin of 1 cm (*Fig. 2*). A double freeze–thaw cycle was used: a 15-20 minute freeze at - 196°C with the ice-ball edge extended 1 cm beyond the tumor, followed by a 10-minute thaw and then a 15-minute freeze. When the liver tumor was close to a major portal sheath or hepatic vein, the Pringle maneuver was performed during cryotherapy to avoid "heat sink" effect (10).

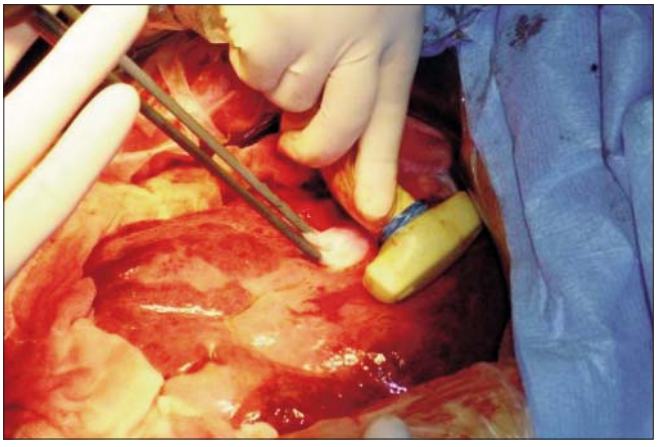


Figure 1. *Intraoperative aspect of cryosurgery. Two cryoprobes in place under ultrasound control*

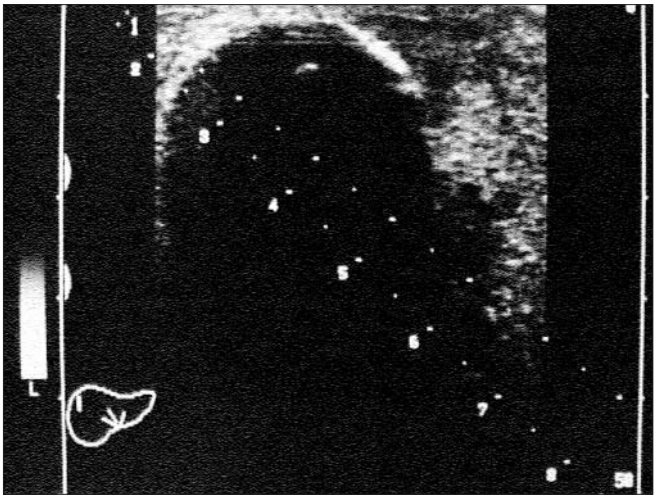


Figure 2. *Hypoechogenic aspect of the "ice-ball" and the hyperechogenic aspect of the edge of the cryolesion*

Upon removal of the probes, all tracts were packed with Surgicel®or Gelaspon®, resolving almost all bleeding. If the crack of the cryolesions with any subsequent bleeding occurred, the management was performed using one or two Prolene™ 4-0 suture. To help maintain normothermic conditions, warming blankets type Bair Hugger® are placed over the lower extremities of the patients and during the freezing process patients were given warm saline, low dose dopamine and bicarbonate to prevent hypothermia, to induce a high urine output and to alkalinize the urine, in the prevention of renal injury due to myoglobinuria.

In patients who had cryotherapy and liver resection, resection was used preferentially for large tumors because of the relationship of cryovolume and cryoshock phenomenon (multi-organ failure, severe coagulopathy, and disseminated intravascular coagulation) and the remaining smaller metastases in the contralateral liver were treated with cryotherapy (6).

The resection was performed first, followed by cryoablation of the remaining lesions. Liver resection was performed using ultrasonic dissector (Sharplan Lasers, Inc., Needham, MA, USA) or crushing technique, with Pringle maneuver only in selected patients to minimize blood loss or to maximize efficacy of cryotherapy (7). In patients who had cryotherapy associated with other visceral resections (colorectal resections, hysterectomy with bilateral salpingo-oophorectomy, etc), cryotherapy was performed after removal of the primary tumors.

Postoperative follow-up

All patients were managed in the intensive care unit for the first 24-48 h. Liver enzymes, coagulation factors and blood cell count were obtained on a daily basis until normalization and chest X-ray and serum and urine myoglobin levels for selected patients.

The first follow up CT scan was obtained on day seven, and served as reference to evaluate the progression of the disease. Systematic contrast-enhanced CT-scans and MRI were performed every 3 months for the first year of follow-up and every 6 months thereafter. Tumor markers (CEA, AFP levels) were obtained at 6-month intervals and any time when the suspicion of recurrent disease arose. Postoperative adjuvant IV chemotherapy was initiated within 1 month of cryotherapy to patients with synchronous metastatic disease at the indication of the oncological staff.

Statistical analyses

The difference in baseline characteristics of patients with colorectal metastatic disease (MCR group), primary hepatic tumors (HCC group) and non-colorectal metastatic liver disease (MET group) was compared. Overall survival estimates were based on Kaplan-Meier method and significant difference was assumed for $p < 0.05$. The statistical analyses were performed using Microsoft Excel 2013 version with WinSTAT and XLstat adds.

Results

Between February 2001 and December 2011, 70 out of 133 liver tumors (primary tumors, colorectal and other primary site metastases) from 38 patients were treated with hepatic cryotherapy alone or with additional hepatic resection associated or not with other visceral resections at "Carol Davila" University Military Hospital, Bucharest. Twenty patients were men, while 18 were women with combined mean age of 55.8 years (range, 42-80). Overall, 5 patients had primary hepatocellular carcinomas (HCC group) on cirrhotic liver, 27 patients had colorectal liver metastases (CRM group), synchronous in 20 patients (74%) and metachronous in 7 patients (26%). The rest of 6 patients (MET group) had malignant metastatic lesions from non-colorectal sites (breast adenocarcinoma, gastric adenocarcinoma, cervical adenocarcinoma, thyroid adenocarcinoma). *Table 1* summarizes patients, tumors and treatment characteristics.

In the HCC group, all patients had cirrhotic liver, Child A at the operative time and additional to cryotherapy the treatment consisted in alchoholization of small and disseminated superficial tumors.

In the CRM group, 3 patients (7.89%) had extrahepatic tumor localizations, 2 patients with pulmonary metastases and 1 patient with inguinal lymph node metastases from rectal adenocarcinoma and underwent preoperatively abdomino-perineal resection. In this group, only 9 patients (23.68%) received neoadjuvant FOLFOX chemotherapy.

The number of liver tumors treated per patient varied from 1 to 7 (mean 1.84) and the size of treated lesions ranged from 5 to 60 mm (mean 27.6 mm). In seven (18.42%) patients, 10 new liver tumors were discovered during peroperative ultrasonography. The tumors were localized in the proximity of the vessels in 22 patients (58%) and among them, in 14 patients (63%), around the hepatic veins. Overall, 67 cryosessions (one or more freezing-thawing cycles) were performed in 38 patients, with an average of 1.76 sessions per operation (range 1-7 freezing-thawing cycles per operation). In eighteen patients (47.3%) we have used simultaneous multiple (2-4) cryoprobe to

Table 1. *Patient, tumor and treatment characteristics*

Characteristics	No. of Patients
Age (yrs.)	
(Mean) / (Range)	(55.8) / (42-80)
Sex ratio	
Male 20 (52.63%)	
Female 18 (47.36%)	
Tumor	
Primary hepatocellular carcinoma (group I)	5 (13%)
Colorectal metastases (group II)	27 (71%)
Synchronous	20 (52.63%)
Metachronous	7 (18.42%)
Non-colorectal metastases (group III)	6 (13%)
Breast adenocarcinoma	2
Gastric adenocarcinoma	2
Cervical adenocarcinoma	1
Thyroid adenocarcinoma	1
Mean follow-up months (range)	25.8 (0-41.85)
Number of tumors	133
Number of tumors treated by cryosurgery	70
Treatment	
Number of tumors (mean) per patient (range)	(3.59); (1-15)
Number of tumors (mean) per patient (range) treated by cryosurgery	(1.84); (1-7)
Size of tumors treated by cryosurgery, (mean); (range)	(27.66 mm); (5-60 mm)
Number of cryosessions (mean) per tumor (range)	(1.76); (1-7)
(Mean) cryosession time and (range) per tumor	(18.35 min); (5-80)
Additional procedures	
Liver resections	18
Minor	10
Right lateral sectionectomy	2
Anatomical segmentectomy	4
Wedge resection	4
Major	8
Right hepatectomy	5
Left hepatectomy	3
Bowel resections	11
Right hemicolectomy	4
Transverse colon colectomy	1
Sigmoidectomy	2
Left hemicolectomy	2
Anterior resection	2
Total hysterectomy with bilateral salpingo-oophorectomy	2
Cholecystectomy	8
Portal vein ligation	2
Ethanol injections	6
Mortality related to cryosurgery	1 (2.6%)

ensure adequate therapy. The mean cryoablation time per tumor was 18.35 min (range from 10-85 min) and the mean operative time was 210 min (range from 100 to 360 min). Additional liver resections were performed in 18 patients (47.36%), in 8 patients major liver resection (three anatomical segments or more) and in 10 patients minor liver resections. Apart from liver resections we have performed bowel resections in 11 patients, total hysterectomy with bilateral salpingo-oophorectomy in 2 patients, cholecystectomy in 8 patients, portal vein ligation in 2 patients and ethanol injection in 6 patients. Peroperative complications occurred in 12 (31.5%) patients with a majority of hepatic fracture (crack) treated conservatively using haemostatic agents and sutures. In 2 patients the cryoprobe was deployed from the right position and the patients had one more freezing-thawing cycle and in 2 other patients pneumothorax has occurred.

Mortality and morbidity

There was one postoperative death (2.63%) of a 78 year-old patient with synchronous bipolar colorectal metastasis and poor clinical status (coronary disease, atrial fibrillation denutrition, COPD), on day 17, due to multiorgan failure and adult respiratory distress syndrome (ARDS). During cryoablation time, associated hemorrhage occurred, most probably after injury of middle hepatic vein, at which time patient required packing of the abdomen to control the hemorrhage. He was reopened twice, on day 6, for abdominal collection and right subphrenic haematoma and on day 10, for generalized peritonitis due to a parcellar necrosis of the last ileal loop, which cannot be related to cryoablation.

The overall morbidity rate was 68% in 38 patients, including per-operative complications seen in 10 (26.3%) patients. Postoperative hemorrhage arising from the liver was encountered in 4 patients, and was managed conservatively using red blood, fresh frozen plasma and platelet transfusions. Postoperative complications were recorded in 20 patients, some patients counting one or more complications.

Pleural effusion on the right side, secondary to the irritating process beneath the diaphragm was recorded in 10 patients and treated conservatively. Pulmonary atelectasis was present in 5 patients, gastro-oesophagitis in 3 patients, long term cholestasis in 1 patient and intense cytolysis (50 times normal range) in 3 patients. All these complications were treated conservatively. Infectious complications arose in 6 patients: wound infections in 5 patients, subphrenic abscess in 2 patients, subhepatic abscess in 2 patients and infected ascites in 1 patient. Two patients with abscess were reoperated and the rest were treated conservatively.

Transitory myoglobinuria was demonstrated to some degree in 4 patients and appeared to be related to the patients with high volume of tissue frozen and high duration of the operation. Perioperative and postoperative complications are summarized in *Table 2*. The mean hospital stay was 16.4 (6-32) days in the 38 patients.

Table 2. *Perioperative and postoperative complications; *Patients had one or more complications concomitantly*

Complications	No. of patients
Perioperative complications*	10 (26.3%)
Hepatic fracture (crack)	8
Cryoprobe displacement	2
Pneumothorax	2
Postoperative complications*	16 (42.1%)
Hemorrhage	4
Subphrenic abscess	2
Subhepatic abscess	2
Pleural effusion	10
Pulmonary atelectasis	5
Wound infections	5
Gastro-oesophagitis	3
Cholestasis (long term)	1
Intense cytolysis (up to 50 times normal range)	3
Transitory myoglobinuria	4

Table 3. *Survival characteristics after treatment based on tumor class*

Type of tumors	No. of pts.	Survival in years (%)			Mean survival (mo)	Median survival (mo)	Pts. alive	Pts. death	Pts. with no recurrence	Recurrent disease (no. of pts)		
		1	2	3						cryo site	liver	extra hepatic
CRM	27	81.4%	73.6%	20.6%	27.4	30	16	11	7	3	3	6
HCC	5	80%	60%	-	21.6	28	3	2	2	-	1	-
MET	6	66.7%	33.3%	26.7%	21.3	21	3	3	1	1	2	2

Survival

The mean follow up was 25.8 months (range 1-41.85) with equivalence between the 3 groups: CRM, MET and HCC respectively 27.43 months, 21.33 months and 21.6 months. The survivals in the 3 groups were statistically insignificant (p=0.65). In the CRM group, the 1 year survival rate was 81.48%, at 2 years it was 73.68% and at 3 years it was 20.68%. Sixteen out of 28 patients (59.2%) remained alive at the last time of contact, 7 patients (25.9%) with no sign of recurrent disease and 11 patients (40.7%) were deceased (*Table 3*). In the MET group survival at 1-, 2-, 3- years was 66.67%, 33.33% and 26.67%. Three out of 6 patients were deceased at 6 months, 17 months and 24 months and only 1 out of 3 remaining patients has no signs of recurrent disease. In the HCC group 2 out of 5 patients were dead at 9 months and 14 month and the surviving rate was 80% after 1 year and 60% after 2 years. The overall 1-, 2-, 3- year survival rates were 76.32%, 61.85%, and 18.89% (*Fig. 3*). There were no statistically significant differences in survival when comparing CRM patients with HCC patients (p=0.65), CRM patients with MET patients, (p=0.32) and HCC patients with MET, (p=0.89).

Recurrence rate

Thirty-six patients (94.7%) had complete tumor eradication (R0 operation) with at least a 1-cm margin of clearance and the remaining 2 patients (5.2%) had residual liver disease. This happened because the hepatic involvement was so extensive that adequate functional liver tissue could not be preserved if total ablation was achieved.

Mean recurrence-free disease survival intervals for the CRM, MET and HCC groups were 7.6 months, 9.8 months, 11.3 months, with a globally mean recurrence-free survival of 9.5 months and range 1-32 months.

Overall, 13 patients (34.21%) developed hepatic recurrent disease. Four patients (10.52%) had a recurrence at a cryosite, based on follow-up CT scans (3 patients in CRM group and 1 patient in HCC group) and 11 patients (28.94%) developed a tumor recurrence within the liver at locations other than the cryosite (8 patients in CRM group, 2 patients in MET and 1 patient in HCC group).

Extrahepatic recurrence occurred in 8 patients (21%). Distribution of recurrence in groups recorded pulmonary metastases in 4 patients (10.5%), two patients in CRM group and 2 patients in CHH group and brain metastases in 3 patients (7.9%), peritoneal recurrence in 2 patients (5.2%) and bony metastases in 1 patient (2.6%), all in the CRM group.

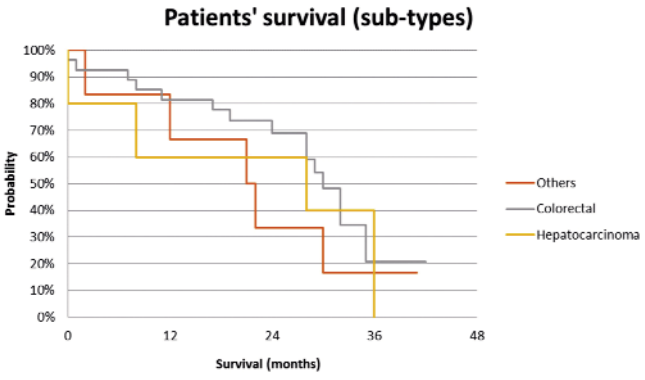


Figure 3. *Overall survival based on tumor class*

Discussion

Surgical resection remains the effective treatment for liver tumors, but 80-90% of patients with hepatic tumors are unsuitable for surgical resection at the time of diagnosis due to: anatomical factors, presence of extrahepatic disease, inadequate functional hepatic reserve and poor biological status (4,12,13,14).

The present study evaluates the midterm outcomes of cryosurgery as a treatment for hepatic tumors, associated or not with liver resections and additional visceral resections, with intentions to achieve complete oncological treatment.

Up-to-date, no data were published for resectable liver tumors treated by cryosurgery, in the same intraoperative session with liver resections and resections of primary tumor with the aim of saving liver tissue. Overall, 18 out of 38 patients (47.3%) had complex treatment, associating cryosurgery to liver resections with or without visceral resections (*Fig. 4, 5*).

In our study, 6 out of 18 patients had cryoablation with concomitant liver resections and colorectal resections in the same operatory session. Two patients underwent major liver resections (right liver resections) associated in 1 patient with right hemicolectomy and in the other with anterior resection of the rectum. In four out of 18 patients we performed minor liver resections (right lateral sectionectomy

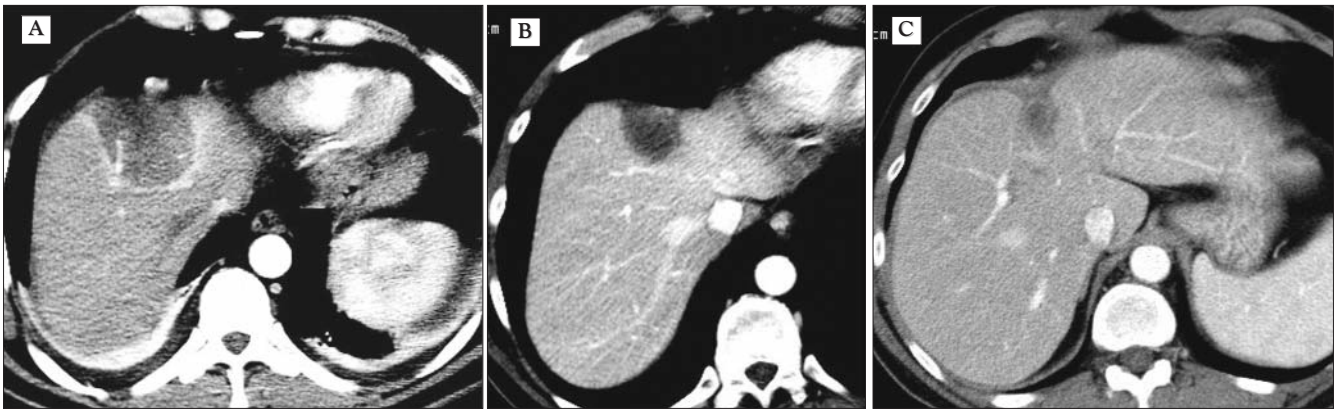


Figure 4. *Cryolesion aspect. A - day 7; B - 1 month; C - 3 months*



Figure 5. *Left hepatectomy associated to cryosurgery. Cryolesion aspect. A - day 7; B - 1 month; C - 3 months*

in 1 patient, segmentectomy for S6, in 1 patient and 7 wedge resections in 2 patients). In six patients we have performed cryoablation associated only with liver resections (major resections in 3 patients and minor resections in 3 patients) and in 5 patients we have associated only bowel resections. Two patients underwent cryoablation associated with total hysterectomy with bilateral salpingo-oophorectomy and bowel resections in the same time.

There are reports of over 2000 patients treated with cryotherapy for malignant liver tumors, and relatively few studies have reported 5-year survival rates (15,16,17). After surgical resection, the 5-year survival rate ranges from 20 to 35% of patients, but without resection it is less than 5% of patients. The median overall survival in resected patients with hepatic metastases from colorectal cancer is 24 months and around 3 months for unresected patients (18,19).

Our overall median survival was 25.8 months. These results compare favorably to other outcome studies for cryotherapy of liver tumors that have shown median survival of 18 to 38 months (20,21)

In our study, we find that CRM group has the longest mean survival, but at the same time, there is a difference between the numbers of recurrences in the CRM group and other types of liver tumors. The average size of the CRM was 34 mm versus 28 mm for the rest of liver tumors and this difference can be in favor of size related recurrence-free survival. As a favorable prognosis we found association of cryotherapy with resection, cryotherapy-treated lesion of less than 3 cm, total tumor eradication, normal range of tumor markers, absence of disease recurrence at the cryosite, remaining liver and extrahepatic sites.

To maximize tumor destruction most of them are treated with double freeze-thaw cycles. The cryolesion is very easily seen on ultrasound, as a hypoechogenic area with posterior shadow around the tip probe. Liquid nitrogen at - 196°C delivered at the tip of the cryoprobe, induces intracellular crystallization during a rapid freezing process followed by membrane disruption, microvascular thrombosis and cell death (22,23).

In the past, cryosurgery was performed in patients with unresectable liver tumors (13,24-26) or as a definitive treatment for resectable liver metastases, in attempt to save more normal liver parenchyma (27-30).

Encouraging results with 5 year survival rates of 44%-58% after cryosurgery for unresectable tumors were reported (13,25).

The high incidence of recurrences within the liver, outside the treated area or at the cryosite is a very disturbing fact. Gignoux et al. (17), in a review of hepatic cryosurgery, reports hepatic recurrence rates between 59 and 82% and extrahepatic recurrence rates between 25 and 66%. With regard to cryosite recurrence, our rate subscribes to the range reported by other investigators from 19 to 44% (16,21,28,31).

The proximity of major venous structures with high warm

inflow and posterior area of the cryolesion, where echogenicity of the ice-ball makes tumor margins determination uncertain (16,32) are main reasons for local recurrence after hepatic cryosurgery.

Conclusion

Cryosurgery remains an important option for the treatment of liver tumors and provides the potential for long term survival. Associated to liver resections and visceral resections in the same operative session, with the aim of sparing more liver parenchyma, cryosurgery is an efficient option to ensure good oncological treatment. Local recurrences should caution against the use of cryosurgery as a single therapy to treat resectable lesions.

The aggressive complex surgical strategy may represent an interesting approach and more controlled data are needed to properly assess this modality.

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