Cryotherapy for liver metastases

Abstract Cryotherapy is undergoing a renaissance in the treatment of nonresectable liver tumors. In a prospective case control study we assessed the morbidity, mortality, and efficacy of hepatic cryotherapy for liver metastases. Between January 1996 and September 1999 a total of 54 cryosurgical procedures were performed on 49 patients (median age 66 years, 21 women) with liver metastases. Patient, tumor, and operative details were recorded prospectively. Liver metastases originated from colorectal cancer (n=37), gastric cancer (n=3), renal cell carcinoma (n=2), and other primaries (n=7). Median follow-up was 13 months (1–32). The median number of liver metastases was 3 (range 1–10) with a median diameter of 3.9 cm (range 1.5–11). Twenty-one patients (43%) had cryoablation only, and 28 (57%) had liver resection in combination with cryoablation. One patient (2%) died within 30 postoperative days. Another 13 patients (27%) developed reversible complications. In 19 of 25 patients (76%) with preoperatively elevated serum CEA and colorectal metastases it returned to the normal range postoperatively. Twenty-eight patients (57%) developed tumor recurrence, eight of which with involvement of the cryosite. Overall median survival patients was 23 months, and survival in patients with colorectal metastases was 29 months. Hepatic cryotherapy is associated with tolerable morbidity and mortality. Efficacy is demonstrated by tumor marker results. Survival data are promising; however, long-term results must be provided to allow comparison with other treatment modalities.

Keywords Cryosurgery · Cryotherapy · Liver metastases · Colorectal cancer · Liver resection

Introduction

Liver resection is the treatment of choice for most primary and secondary liver tumors. For colorectal liver metastases, liver resection is associated with 5-year survival rates of 25–50% [4]. However, in only 10–25% of these patients is liver resection feasible [30]. The use of cold temperatures for the destruction of cancerous tissue has long been known [7]. Increasing knowledge in the field of cryobiology and the use of intraoperative ultrasound for localization of lesions and monitoring of the freezing process has led to increased use of cryotherapy in the treatment of nonresectable liver tumors [1, 17, 20, 22, 24, 25, 34, 35, 36, 48]. In a prospective case control study we assessed the morbidity, mortality, and efficacy of hepatic cryotherapy for liver metastases.

Patients and methods

Between January 1996 and September 1999 a total of 54 cryosurgical procedures were performed on 49 patients (21 women) with liver metastases. Patient, tumor, and operative details were recorded prospectively. Patients' median age was 66 years (range 37–78).
Liver metastases originated from colorectal cancer in 37 patients. In some patients with liver metastases from noncolorectal primaries where other treatment modalities were not feasible cryotherapy was used as well: gastric cancer \( (n=3) \), renal cell carcinoma \( (n=2) \), and other primaries \( (n=7) \). In 14 patients the metastases were synchronous and in 33 metachronous. Eleven patients had recurrent liver metastases following prior liver resection.

Preoperative staging included abdominal ultrasound and abdominal computed tomography (CT), chest radiography, serum analysis of tumor markers, liver function tests, and further investigations to exclude local recurrence of the primary tumor in patients with metachronous metastases. Recently we have tended increasingly to use magnetic resonance imaging of the liver, particularly to improve the assessment of tissue changes following cryotherapy.

Cryotherapy was used when complete resection of all liver metastases was not feasible, and when no extrahepatic disease was diagnosed. We performed cryosurgery alone or in combination with liver resection when we assumed all liver metastases may be destroyed completely. Metastases were judged nonresectable, if: (a) they were multiple in both liver lobes, (b) they were in an anatomic position that did not allow liver resection without sacrificing an unreasonable amount of liver parenchyma, or (c) if resection would have involved excessive risk to the patient. Postoperatively all patients were monitored in the intensive care unit, usually for 24 h. CT or magnetic resonance imaging of the liver was performed prior to discharge.

For cryotherapy we used a CMS AccuProbe 450-System with single-use cryoprobes having an isolated shaft and a diameter of 3 or 8 mm at the tip. Only the last 4 cm of the probe-tip are cooled, allowing the treatment of central lesions deep within the liver parenchyma without freezing the liver surface. Following laparotomy, exclusion of abdominal extrahepatic disease and intraoperative ultrasound of the liver the cryoprobe is inserted into the tumor. The probe insertion and the freezing process are controlled by intraoperative ultrasound. All tumors are frozen with a surrounding margin of at least 1 cm of normal tissue, and the freezing process is continued at least 15 min. After a passive thaw of the iceball a second freeze cycle is used to optimize tumor destruction [26]. Patients were followed up until September 1999 or death. Median follow-up time was 13 months (1–32). Patients had regular 3-monthly follow-up investigations for local recurrence or hepatic recurrence at other locations and extrahepatic recurrence. Statistical analysis used SPSS for Windows, version 7.0.

Results

Twenty-seven patients (55%) had received systemic chemotherapy before presenting for surgical treatment of their liver disease. The median number of liver metastases per patient was three (range one to ten) with a median diameter of the largest metastasis in an individual patient of 3.9 cm (range: 1.5–11). Twenty-eight (57%) patients had bilobar disease. Twenty-one patients (43%) had cryoablation only and 28 patients (57%) had liver resection in combination with cryoablation. The following liver resections were performed: extended hemihepatectomy \( (n=6) \), hemihepatectomy \( (n=5) \), and peripheral or segmental resections \( (n=17) \). Median duration of the operation was 300 min (range: 155–564). The median periods of postoperative hospital and intensive care unit stay were 14 days (range 7–59) and 1 day (range 0–16), respectively. The median perioperative blood replacement was 14 days (range 7–59) and 1 day (range 0–16), respectively. The median perioperative blood replacement was 2 U packed red cells (range 0–33), and 25 patients (51%) received no blood transfusion intraoperatively. One patient (2%) who underwent extended right hemihepatectomy and cryotherapy of two lesions in segments 2 and 3 had major intraoperative hemorrhage and died within 30 postoperative days from multiorgan failure and sepsis.

Of the 48 patients who were discharged from hospital 13 (27%) developed complications: hemorrhage \( (n=3) \), intra-abdominal abscess \( (n=3) \), wound infection \( (n=1) \), transient liver failure \( (n=2) \), pleural effusion necessitating drainage \( (n=4) \), pneumonia \( (n=1) \), and pulmonary embolus \( (n=1) \). Of the 37 patients with colorectal primary 25 had preoperatively elevated serum CEA levels (>4 ng/ml). All patients had a significant drop in serum CEA postoperatively; in 19 of 25 (76%) it returned to the normal range. Twenty-eight patients (57%) developed tumor recurrence: 14 in the liver only (4 with involvement of the cryosite), 13 in the liver and at extrahepatic sites (4 with involvement of the cryosite), and one extrahepatic only. The exact sites of recurrence are summarized in Fig. 1.