

Surgery in hepatic and extrahepatic colorectal metastases

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SUMMARY: Surgery in hepatic and extrahepatic colorectal metastases.

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Extrahepatic disease (EHD) has been considered a contraindication to hepatectomy. Over the last few years, some series reported interesting 5-year survival rates after resection with hepatic colorectal metastases and EHD free margins.

Between August 1989 and October 2005, 116 patients underwent liver resection for colorectal metastases at Surgical Department of the University of Udine, Italy. Among these, we reviewed the data of 5 patients affected by EHD. In 3 patients there were also an anastomotic recurrence of the primary tumor, in 3 patients diaphragm was infiltrated by contiguous liver metastases.

We performed in all the patients minor liver resections. We have associated the radiofrequency ablation of a lesion not surgically resectable with liver resection in one case. The surgical procedure was always considered as curative. We observed no case of operative mortality. The mean survival of the entire cohort is 23.2 months (range 4-42 months).

Our study, even if based upon a limited number of patients, supports the thesis that extrahepatic disease in patients affected by colorectal cancer with hepatic metastases should not be considered as an absolute contraindication to liver resection especially for the cases in which local radical cure exceresis is achievable.

RIASSUNTO: Il ruolo della chirurgia nelle metastasi epatiche ed extraepatiche da neoplasie coloretali.

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La presenza di localizzazioni neoplastiche extraepatiche viene generalmente considerata come una controindicazione alle resezioni epatiche per metastasi coloretali. Negli ultimi anni alcuni studi hanno tuttavia riportato interessanti sopravvivenze a 5 anni dopo resezione di metastasi epatiche da neoplasia del colon-retto e di metastasi extraepatiche con margini liberi da malattia sul preparato chirurgico.

Tra il 1989 ed il 2005, 116 pazienti sono stati sottoposti a resezione epatica per metastasi da cancro del colon-retto presso la Clinica di Chirurgia Generale dell'Università di Udine. Di essi, abbiamo preso in considerazione 5 pazienti affetti anche da patologia neoplastica metastatica extraepatica: in 3 vi era anche una recidiva anastomotica del tumore primitivo, in 3 il diaframma era infiltrato da metastasi epatiche contigue.

Abbiamo eseguito in tutti i pazienti delle resezioni epatiche minori. In un caso abbiamo associato anche la radioablazione di una metastasi non resecabile. L'intervento chirurgico in tutti i casi è stato curativo. Non abbiamo registrato mortalità operatoria. La sopravvivenza media dell'intero gruppo è stata di 23.2 mesi (range 4-42 mesi).

Il nostro studio, sebbene svolto su un numero limitato di pazienti, supporta l'ipotesi che metastasi di altri organi e strutture in presenza di metastasi epatiche da cancro coloretale non dovrebbero essere considerate una controindicazione assoluta alla resezione epatica soprattutto nei casi in cui sia conseguibile un intervento radicale.

KEY WORDS: Colorectal cancer - Liver metastases - Liver resection.
Cancro coloretale - Metastasi epatiche - Resezione epatica.

Introduction

Extrahepatic disease (EHD) has been considered a contraindication to hepatic resections in colorectal

metastasis because subgroup analyses of large series published before 1990 showed an unfavorable prognosis (1, 2). However, some series reported interesting 5-year survival rates after resection of colorectal liver metastases and EHD free margins (Tab. 1); therefore, currently, this pathological situation has not been considered by many Authors as an absolute contraindication to resection (3-8).

The rational of this approach is based on different

convictions. Traditionally, it was considered that only a local treatment, such as surgery, could cure a cancer with local extension. Micrometastases and circulating cancer cells in blood, bone marrow, and lymph nodes are always present in advanced stage cancer (9), and it was shown that most cells derived from the primary tumor are not stopped by the liver and enter the systemic circulation (10). Thus, radical surgery is, from a point of view, only cytoreductive, even if all visible disease is resected; so the cure can be achieved by patients' natural immunological defences and chemotherapy. Surgical tumor reduction may provide an immunological benefit, as tumor cells produce immunosuppressive cytokines, precipitate immune complexes, and peptidoglycans that interfere with normal defences (11, 12); reducing the total tumor volume also substantially diminishes the risk for development of drug resistance, which increases directly with the number of cancer cells and the treatment duration (13). Furthermore, according to the log-kill hypothesis, each dose of chemotherapeutic agent kills a constant fraction of cells, rather than a specific number of cells, therefore, reducing the initial tumor volume, increases the likelihood that chemotherapy will reduce the number of cells toward the targeted end point (zero) (13).

Patients and methods

Between 1989 and 2005, 116 patients underwent liver resection for colorectal metastases at Surgical Department of the University of Udine, Italy. Among these we reviewed the data of 5 patients affected by EHD (1 female and 4 males, mean age 61 years with range 52-79). In 3 patients there was also an anastomotic recurrence of the primary tumor, in 3 patients diaphragm was infiltrated by contiguous liver metastases. In all cases, the preoperative diagnosis was based on triphasic spiral CT scan done during follow up. The evaluation of liver function was based on "synthesis values" (serum albumin, PT, PTT and INR), as well as "detoxification values" (direct and total bilirubinemia). We usually perform a preoperative prophylaxis with low weight molecular heparin, one shot antibiotic agent (third generation cephalosporin), and H2-receptor antagonists.

In 3 patients we performed a median line laparotomy and in the other 2 cases a right subcostal incision extended to the left side. In all cases an intraoperative ultrasound scan was performed. In all cases the resection was performed according to a trans-parenchymal vessel approach, and clamping of the hilum according to Pringle was performed in 4 cases (mean clamping time 27 minutes). The hemostasis was performed with sutures for larger vessels and electrocoagulation and/or argon-beam coagulator for smaller ones. After liver resection we always use abdominal drainage.

Couinaud's segment nomenclature was used for the definition of the intervention. We performed in all the patients minor liver resections when considering the major ones those comprising 3 or more hepatic segments. We associated the radiofrequency ablation (Radionics Cool Tip RS System) of a lesion not surgically resectable with liver resection in one case.

Results

The hepatic lesions involved only one lobe in all patients. The number of lesions ranged between 1 and 2. The diameter of the metastases varied greatly from 5 mm up to 9 cm. It was performed a lymphadenectomy of the hepatoduodenal ligament macroscopically involved lymph nodes in 2 patients. In one case there was frozen section confirmation of malignancy, thereafter we performed a larger lymphadenectomy up to celiac axis nodes. The surgical intervention was always considered as curative because the resection margin was macroscopically free for 1 cm, and was not infiltrated upon the histological evaluation.

We observed no case of operative mortality during hospitalization or within 1 month after the resection. These complications were reported: in 2 patients pleural effusion with pneumonia (requiring thoracentesis and antibiotic therapy); in 3 perihepatic fluid collection (requiring sonography or computed tomography-guided percutaneous drainage). At the time of the control, 1 patient is still alive. The mean survival of the entire cohort was 23.2 months (range 4-42 months) (Tab. 2).

Discussion

Over the last few years, some series reported interesting 5-year survival rates after resection of hepatic colorectal metastases and EHD free margins (Tab. 1).

Most of the authors consider not a contraindication to hepatic resection the infiltration of diaphragm by liver metastases (14, 15). Diaphragm resection associated with liver resection are reported in different studies (5, 6, 16). Extended hepatic resection with 'en bloc' removal of adjacent abdominal or thoracic involved organs have been reported by various institutions (17). However, if three or more hepatic segments were resected, the major organ resection resulted in not only significantly increased blood loss, transfusion requirements, length of stay, intensive care unit admission, and morbidity, but also in doubled mortality (16). In our series the patient with an advanced disease (the anastomotic ileocolic recurrence infiltrated gallbladder and the fourth hepatic segment) had the worst survival (4 months).

Anastomotic recurrence of the primary tumor should not dissuade the surgeon from resecting any hepatic metastases, as long as complete resection of both sites is possible (7, 8, 18).

In the presence of extrahepatic disease synchronous of hepatic one (abdominal, pelvic or peritoneal),

TABLE 1 - HEPATIC METASTASES WITH EXTRAHEPATIC DISEASE (EHD) IN THE LITERATURE.

Study	Year	Number patients	Patients with EHD	Lung	Hepatoduodenal ligament lymph node metastases	Peritoneal carcinomatosis	Locoregional recurrence	Other	5-year overall survival (%)
Huges et al. [1]	1986	859	37	NS	24	NS	NS	NS	0
Norlinger et al. [2]	1992	1895	213	43	104	NS	51	NS	Without lung: 10† Lung: 31†
Scheele et al. [3]	1995	469	47	NS	NS	NS	NS	NS	26
Jamison et al. [4]	1997	280	31	5	NS	NS	12	14	Lung: 40 Locoregional recurrence: 13 Other: 7
Fong et al. [5]	1999	1001	43	21	10	7	NS	5	18
Minagawa et al. [6]	2000	235	17	NS	6	NS	NS	NS	21
Elias et al. [7]	2003	376	111	22	12	37	23	12	20
Elias et al. [8]	2005	308	84	14	11	37	19	31	32

Legend: NS = not specified; † = 3 year survival;

many surgeons (5-8) perform resection when radicality can be achieved. The statistical analysis of the survival obtained, in order to find new resectability criteria, shows that patients with more than five liver metastases simultaneously with extrahepatic disease do not benefit from resection (7); moreover a recent study of Elias and colleagues (8) found that the total number of the metastases, whatever their location, has a stronger prognostic power than the site of the metastases: 5-year survival rates were 38% in the group with one to three metastases, 29% in patients with four to six metastases, and 18% in patients with more than six metastases.

Pulmonary resection is a well established therapy for colorectal lung metastases and, like liver metastases, is the only treatment associated with long-term survival. In some studies, patients undergoing resection of colorectal hepatic and pulmonary metastases have better survival than patients undergoing hepatic and other extrahepatic localizations (2, 4). Currently, resectable hepatic lesions with pulmonary metastases are not a contraindication to resection: beginning with the organ with the most difficult lesion to resect first, but occasional simultaneous resections should be con-

sidered in selected patients where limited hepatic and pulmonary resections are required (19). Five year survival rates ranging between 11% and 52% have been published, but in limited series (19-23).

The situation when the extrahepatic metastases are represented by the extrahepatic lymph nodes is an argument of dispute. Perihepatic (portal, hepatic and celiac axis) lymph node involvement has not been considered as lymphatic metastases of colorectal primary but recognized as 'remetastases' of liver secondaries (19). Traditionally their involvement is a contraindication to resection because of an unfavorable prognosis (24). A recent study has modified this idea (25). This study divides the main hepatic lymphatic drainage in two areas: lymph nodes of the hepatoduodenal ligament and retropancreatic portion (area 1) and nodes around the common hepatic artery and celiac axis (area 2). Area 1 has not been considered an absolute contraindication to hepatic resection, and a larger lymphadenectomy should be performed if these lymph nodes are histologically involved. In our series in 1 patient hepatic hilar lymph node was infiltrated by neoplasm: in this patient we have performed a larger lymphadenectomy of hepatoduodenal ligament

TABLE 2 - HEPATIC METASTASES WITH EXTRAHEPATIC DISEASE IN OUR SERIES.

Patient	Age	Sex	Intraoperative diagnosis	Surgery	Pringle clamping (minutes)	Number hepatic lesions	Diameter hepatic lesions	Hilar lymph-adenectomy (infiltration)	Morbidity	Survival	Follow up
1	60	M	Transverse colon cancer with hepatic metastases and diaphragmatic metastasis	Transverse colon resection, VII HS resection, VIII HS wedge resection and diaphragm resection	No	2	-	No	-	29	D
2	58	M	Right flexure colon cancer with hepatic metastasis infiltrating diaphragm	Right hemicolectomy, VI and VII HS resection and diaphragm resection	Yes (30')	1	9 cm	Yes (no)	Hepatic collection	4	D
3	79	M	Ileocolic anastomotic recurrence with hepatic metastasis	Ileocolic resection and IV HS wedge resection	Yes (20')	1	5 mm	No	Pneumonia + hepatic collection	17	D
4	56	F	Colocolic anastomotic recurrence with hepatic metastasis	Descending colon resection with VI and VII HS resection	Yes (33')	1	-	Yes (yes)	Pneumonia	42	D
5	52	M	Ileocolic anastomotic recurrence with hepatic metastases	Ileocolic resection, wedge resection between V and VI HS, radiofrequency ablation of a metastatic lesion between VII and VIII HS and single peritoneum metastasis resection	Yes (25')	2	4 and 3 cm	No	Hepatic collection	24	A

Legend: M = male; F = female; HS = hepatic segment; D = died; A = alive.

and along the hepatic arteria up to the celiac axis; thereafter we obtained a good survival at the follow up (42 months). When are involved area 2 lymph nodes, there is no gain in survival rates than the case of involvement of area 1 alone (3-year survival rate: 0% versus 38%, $p < .001$) (25). The Authors suggest sampling and intraoperative histological control of hepatic pedicle lymph nodes during surgery for colorectal liver metastases in patients who are at high risk of lymph node involvement as those who present with more than three metastases, metastases of segment IV or V, a resectable solitary peritoneal deposit, or a

poorly differentiated carcinoma of liver metastases.

Conclusion

Our study, even if based upon a limited number of patients, supports the thesis that extrahepatic disease in patients affected by colorectal cancer with hepatic metastases should not be considered as an absolute contraindication to resection especially for the cases in which local radical exeresis is achievable. Therefore further studies are necessary to develop this matter correctly.

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