Hepatic Colorectal Metastases Involving Infra-Hepatic Inferior Vena Cava in High Risk Patients for Extended Resection: An Alternative Method for Achieving Radical Resection in Patient with Borderline Liver Remnant

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Abstract Resection is the only chance of cure for isolated liver metastases from colorectal cancer. In the case of extended parenchymal resections, one crucial point is the ischemic damage to the remnant liver. We report an alternative technique for extremely extended liver resections without total hilar clamping for borderline liver remnants. Two patients presented with invasion of the infrahepatic vena cava, both with an estimated live remnant $\leq 20\%$. The crucial point of the technique is the absence of a portal triad clamping in under beating heart-extracorporeal circulation. In both patients resection margins were free of disease. No signs of liver insufficiency were noted. Survival was more than 2 years in both cases. We believe that aggressive treatment of liver colorectal metastases should be given to all suitable patients. This operation may be added to the techniques that can be offered to these patients.

Keywords Liver metastases · Colorectal cancer · Caval invasion · Extracorporeal circulation · Small liver remnant

Background

Patients with isolated liver metastases from colorectal cancer have a poor prognosis, often a few months. Even the most successful regimens of multimodal treatment for this condition achieve marginal results [1], with a median survival no longer 2 years [2]. Surgical resection is thus the only chance of cure. Over the past decades, there has been a change in the concept of liver surgery, and more attention is now paid on what and how much will remain rather than what and how to resect [1, 2]. In this setting a number of new techniques have been developed to increase the resectability of liver metastases from colorectal cancer—portal vein embolization to increase the remnant liver volume [3], multistaged resections to treat bilobar disease, total vascular exclusion of the liver to treat major hepatic veins and caval involvement with or without veno-venous bypass [4], in situ cold perfusion of the liver, and ex situ resections [5]. Major problems in this subset of patients are the volume of the liver remnant and the cellular damage provoked by the ischemia following hilar clamping. There is a general agreement about the volume of the liver remnant that should be at least 20 % of the total liver volume for normal livers and must be increased at 30–60 % in the case of previous toxicity from regional and or systemic chemotherapy [6–9]. Both preconditioning and cold perfusion techniques are focused on the reduction of liver cell damage [10, 11]. In some instances the fear of an ischemic damage on a

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borderline liver remnant may yield tumors as unresectable. Aiming at giving a chance of cure even to this small group of patients, we applied the technique described here.

Patients and Methods

Among 442 patients treated for hepatic metastases of colorectal origin over a 5 years' period, we selected 13 patients showing an involvement of the hepatic veins and/or inferior vena cava (IVC) and requiring extended resections for treatment. Isolated invasion of hepatic veins (11 patients) was treated by extended parenchymal resection with hepatic total vascular exclusion (HTVE) in 3 cases and without HTVE in 6 cases. The remaining 2 cases are discussed in this article (see Table 1).

All patients were evaluated preoperatively by our team of hepatic surgeons and dedicated anesthesiologists. HTVE was considered when gross caval/hepatic vein invasion was diagnosed. Veno-venous bypass was considered according to the liver functions tests, the estimated volume of the liver remnant, and the estimated duration of the resection. However, the final decision was taken intraoperatively.

Tolerance to HTVE was defined as the maintenance of more than 50 % of the cardiac index and more than 30 % of

the mean arterial pressure after 5 min of test clamping. A fail in reaching these results suggested a course of volemic expansion followed by a second test clamping. Intolerance to the second test after expansion of the circulating volume was defined as intolerance to HTVE. In these cases veno-venous bypass was then established.

Both patients in this study were studied preoperatively by abdominal ultrasound (US), thin-cut triphasic CT-scan of the thorax and abdomen, and angio-computerized tomography of the upper abdomen to exclude extrahepatic disease. Complete liver and renal function tests were carried out, and the nutritional status was assessed by clinical evaluation and prealbumin measurement. Both patients showed negative hepatic viral serologies and absence of the other underlying liver disease. Carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19.9 were assessed for evaluating treatment response. Both patients had a preoperative volumetric CT scan to foresee the volume of postresection liver parenchyma.

Patient 1 had a 14 cm right-sided synchronous metastasis from right colon cancer arising from segment 8 and invading segment 4 and the median hepatic vein and a second minor lesion of 2 cm on segment 6 and of 1 cm on segment 5. He underwent former operation of right colectomy plus right portal vein ligation and the positioning into the

Table 1 Patient's characteristics

	Case 1	Case 2
Sex	Male	Female
Age	43 years	67 years
Height	1.65 m	1.59 m
Weight	58 kg	47 kg
BMI	21.3	18.5
Comorbidity	None	Chronic atrial fibrillation, mild dilated cardiomyopathy
Primary tumor site	Right colon	Right colon
Type of metastases	Synchronous	Metachronous, 1 year
Number of metastases	3	2
Size of metastases	14 cm plus satellite lesions of 2 cm on segment 6 and 1 cm on segment 5	6 cm on segment 8, 3 cm on segment 5
Treatments before liver resection	Right colectomy, hepatic artery incannulation, intra-arterial chemotherapy, systemic chemotherapy, right portal vein ligation	Right colectomy, no chemotherapy due to anaphylaxis to 5-FU and subsequent refusal to other chemotherapies
Preoperative bilirubin	0.9 mg/dl	1.1 mg/dl
Preoperative INR	1	1
Preoperative prealbumin	28 mg/dl	23 mg/dl
Preoperative AST	86 U/l	70 U/l
Preoperative ALT	34 U/l	59 U/l
Preoperative BUN	37 mmol/l	29 mmol/l
Preoperative CEA	3 ng/ml	56 ng/ml
Preoperative CA 19.9	237 U/ml	28 U/ml

common hepatic artery of an intra-arterial catheter for regional chemotherapy. After operation he received chemotherapeutic regimen of systemic FOLFOX plus intra-arterial Oxaliplatin. At postchemotherapy evaluation, the main liver lesion showed a slight decrease in maximum diameter but the median hepatic vein invasion was still present. There was no extrahepatic progression of disease. Postportal ligation hypertrophy showed an estimated volume increase of less than 20 % of the left liver.

Patient 2 suffered from a metachronous metastasis from a previously (1 year before) operated right colon cancer. The lesion was 6 cm in maximum diameter and was localized on segment 8 but presented a gross invasion of the median hepatic vein down to the confluence with the left hepatic vein and the anterior wall of the IVC. A minor, 2 cm, lesion was present in segment 5. The patient did not receive any chemotherapy due to anaphylactic shock following 5-FU infusion and subsequent refusal to any other treatment.

Estimated liver remnant was considered a borderline in both patients, in both about 20–30 % of the total liver volume.

Specific informed consent was obtained before the procedure.

Complete records from preoperative, operation, and postoperative period were collected. Complications had been recorded according to the usual definitions.

Description of the Technique

Both patients received general anesthesia with continuous hemodynamic monitoring via an arterial line and a Swan-Ganz catheter. Access to the upper abdomen was obtained by a bilateral subcostal laparotomy. At the beginning a complete abdominal exploration and biopsies of any suspicious lesion were undertaken (two grossly enlarged hilar nodes in patient 1 and another in patient 2; both resulted negative on frozen sections and definitive pathologic report). Liver mobilization and dissection of the hilum were then performed. Intraoperative hepatic US was undertaken to exclude occult metastases, evaluate the extent of disease and its relations with intraparenchymal vessels, and identify the leading lines for liver resection. No lesions other than the known ones had been found at intraoperative US. The right adrenal vein was ligated during mobilization of the liver, and complete caval exposure was obtained from the right renal vein to the diaphragm. The infrarenal IVC and the renal veins were clear in both cases. On the confirmation of resectability, the right femoral access was established and the common femoral vein was isolated, prepared, and cannulated by a 30 F dedicated cannula and the patient was heparinized. A median sternotomy was done and, on opening the pericardium, a pericardial patch was taken from the anterior aspect of the heart. The patch was

prepared in an ovoid shape of approximately 8 cm×5 cm and preserved in isotonic normothermic saline solution. A 29 F cannula was placed in the right atrium and secured with a purse-string suture. Under selective ligation of the proper hepatic pedicle, the resection began and vessels for the segments to be resected were isolated and ligated intraparenchymally. On completion of the parenchymal transection, when the invaded vessels were exposed, beating-heart cardiopulmonary bypass was established by the mean of a heart-lung machine equipped with an electrostatic defoamer filter; the filter allowed for the separation of an air–blood mixture with reinfusion of blood alone. This allowed us to perform the resection and the caval reconstruction without ever closing the vascular outflow of the liver. Blood by IVC was aspirated by a suction cannula and then sent to the filter in the pump that divided air from blood and reinfused blood into the aorta. In patient 1, resection consisted of an extended right hepatectomy with resection of the anterior wall of IVC and reimplantation of the left suprahepatic vein on the patch. In patient 2, the left extended hepatectomy as well as resection of segments 5 and 8 was performed. The anterior wall of IVC was resected to the confluence of the right hepatic vein and replaced with the pericardial patch. After completion of the caval reconstruction, the patient was weaned from cardiopulmonary bypass; the heparin was neutralized and satisfactory hemostasis was confirmed. Bile leaks were excluded by dye injection in the main bile duct. Drains were placed and the incisions were closed in the usual fashion (see Table 2). Operating times were 535 and 572 min, respectively, with the extracorporeal circulation time of 163 and 132 min. There had been no warm or cold ischemia to the liver remnant.

Postoperative Course

Initial postoperative care took place in the intensive care unit. Patient 1 was discharged from ICU on postoperative day 2. Patient 2 experienced acute renal failure due to previously undisclosed bilateral renal artery stenosis and required 24 h on CVVH; renal function improved quickly and the stenosis was treated 2 months later by endovascular

Table 2 Intervention topics

	Case 1	Case 2
Operating time	8 h 55 min	9 h 32 min
Duration of extracorporeal circulation	2 h 43 min	2 h 12 min
Segments resected	1-4-5-6-7-8	1-2-3-4-5-8
Estimated liver residual volume	400 cm ³	300 cm ³
Blood loss	3,800 ml	2,550 ml
Transfused blood units	12	8
Fresh frozen plasma units	4	4

stenting. She was discharged from ICU on postoperative day 3. Transaminase peaks on postoperative day 3 did not exceed 350 and 380 U/L, respectively, and returned to normal range on postoperative day 6 in both cases. Both patients started oral feeding on postoperative day 4. No signs of liver insufficiency were noted. One patient was discharged on postoperative day 16 and the other on day 28. At pathologic examination, resection margins were free of disease in both cases. Patient 1 underwent adjuvant FOLFOX plus infliximab chemotherapy. Fifteen months after the liver resection, the patient developed multiorgan recurrence including the liver and died of disease progression at 32 months. Patient 2 developed a low-output biliary fistula that healed spontaneously on postoperative day 18 (Figs. 1 and 2). She did not receive adjuvant chemotherapy according to her wish. She died from a post-trauma deep vein thrombosis complicated by massive pulmonary embolism at 35 months; autopsy showed no recurrence of the disease. Data from postoperative period are summarized in Table 3.

Discussion

It is widely accepted that resection is the only chance of cure for patients with colorectal liver metastases. Crucial points for the resectability of liver metastases are the possibility of achieving a radical en bloc resection and the viability of the liver remnant. A viable liver remnant is considered as 20 % of the initial liver volume for normal livers but increases to 30–60 % for the liver suffering from cellular damage due to hepatitis to chemotherapy [12, 13]. Even in the presence of hepatic vein confluence or caval invasion, resection is not contraindicated unless it is technically infeasible [5, 9, 14–16]. Techniques to achieve radical resection are various and related to the surgeon's experience and technical facilities available. Total vascular exclusion of the liver is the procedure of widest use for “en bloc” resections of the liver

Fig. 1 CT scan showing metastatic invasion of left and middle hepatic vein and possible caval invasion (later confirmed by preoperative US)

Fig. 2 The same case as Fig. 1 on postoperative day 6 (control CT scan)

and vena cava. It allows for control of bleeding and avoids air aspiration; nonetheless, it carries a high morbidity rate and implies a wide range of not always predictable hemodynamic changes [17–19]. Furthermore, HTVE is related to a well-recognized ischemia/reperfusion injury at a cellular level. To avoid ischemia/reperfusion damage, some experts advocate the routine use of ischemic preconditioning or intermittent clamping of the liver inflow; the results are various as described by the authors, but postoperative hepatic failure cannot be excluded preoperatively [12, 13, 20–23]. Furthermore, the risk of postoperative hepatic failure is related to the volume of remnant, to the duration of the ischemic period, and to the previous administration of chemotherapy [20–23]. Hemodynamic instability while performing HTVE is a contraindication to continue the resection [14, 15, 23]. In such cases, the surgeon still has the chance of performing resection using a bypass pump [17, 19]. Veno-venous bypass is the most commonly used system; it preserves venous backflow to the right atrium, allowing better hemodynamic control. However, it does not prevent hepatic ischemia that may lead to postoperative liver failure, and thus its use may be questionable in the setting of a very small residual liver and especially in the setting of an existing chemotherapy-induced liver damage. Some authors advocate the use of cardiopulmonary bypass under hypothermia and cardiac arrest because they think this allows better bleeding control, provides hypothermic protection to the remnant liver, and offers good surgical exposure of the intrapericardial vena cava [24–26]. Both of our patients had invasion of the infrahepatic vena cava; one of them (patient 1) had a heavy neoadjuvant chemotherapy with Oxaliplatin that is known as a hepatotoxic agent at a sinusoidal level [12]. Thus, we had to deal with the idea of performing extended liver resection that was planned at preoperative CT volumetric scan to leave in place no more than 25–30 % of liver parenchyma in both cases. Moreover, a prolonged warm ischemia was predictable in both cases. Considering

Table 3 Main postoperative features

	Case 1	Case 2
Length of postoperative ICU	2 days	3 days
Complication	None	Acute renal failure, low-output biliary leakage
Peak AST serum concentration	350 U/l	312 U/l
Peak ALT serum concentration	380 U/l	297 U/l
INR on postoperative day 3	1.6	1.8
Postoperative CEA	6 ng/ml	3 ng/ml
Postoperative CA 19.9	21 U/ml	18 U/ml
Hospital stay	16 days	25 days
Follow-up	32 months	35 months
Current status	Dead of disease, 32 months	Dead to unrelated causes, 35 months

the high risk of postoperative liver failure, we had to decide whether to renounce to operation or to apply an extremely invasive technique. After obtaining an appropriate informed consent, we performed hepatic resection using a heart-beating normothermic aspiring continuous bypass. This approach allows for excellent control of the vena cava, control on air aspiration, and preserves venous return to the right atrium. Bleeding control was obtained by selective hilar clamping of the portal triad, so the remnant liver never suffered ischemic insult. The technique allowed us to perform a long and complex operation without excluding the remnant parenchyma from the portal/arterial blood flow, nor from the hepatic vein outflow. We consider this as a crucial point in the management of such extreme cases. Moreover, the maintaining of the cardiac activity allowed us not to use hypothermia. To our knowledge, these had been the first two cases done under heart-beating cardiopulmonary bypass. Both patients had histologically proven R0 resection. CEA and CA 19.9 returned to the normal range postoperatively, and there were no signs of ischemic liver damage. The technique provoked a slight increase in the bleeding due to either the perfused liver backflow or the heparin-induced bleeding from the transected liver bed. Although a cell saver was used while the resection was completed with clear margins, there was an increased requirement for blood transfusion compared to a routine liver resection. No major complications were seen due to the cardiopulmonary bypass. The postoperative monitoring of AST and ALT showed a low peak on postoperative day 3 in both cases confirming a limited cellular damage on the remnant liver, and the liver function tests (albumin, INR, serum bilirubin) showed a persistent acceptable hepatic function without drug supplementation. Both patients were discharged in good general conditions. Patient 1 experienced a recurrence at 4 months; he received Infliximab and died of recurrence (lung and bone) at 32 months following surgery. Patient 2 died from a post-trauma deep vein thrombosis

complicated by massive pulmonary embolism at 35 months. Autopsy showed no recurrence of the disease. The use of pericardium in caval reconstruction had previously been described [27]. The choice of using pericardium instead of a venous patch or prosthetic material was based on the ease of obtaining the patch once the sternotomy was done and the need for shortening a very long operating time. Synthetic prosthetic replacement is a widely used method for reconstructing major veins defects. It is considered safe and carries a low complication rate [28, 29]. Neither of our patients developed complications related to the use of the pericardial patch. We are convinced that aggressive treatment of liver colorectal metastases should be given to all suitable patients. Even in most complex and difficult cases, the use of extremely invasive methods may produce good results. Our described method may be a useful tool that adds to the range of interventions that be offered to these highly selected patients. The limited size of the population does not allow us to predict long-time survival with statistical significance, but we can conclude that, in highly selected cases, this complex operation may be done with a limited morbidity and no mortality, and offers a reasonable survival advantage.

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