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ORIGINAL PAPERS

Recurrence of liver metastases from colorectal cancer and repeat liver resection

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ABSTRACT

Objective: The purpose of this study was to assess the resectability and effectiveness of repeat hepatectomy for relapsing liver metastases of colorectal origin in terms of morbidity, mortality, overall survival, and disease-free survival.

Methods: A retrospective study was performed on a prospective cohort of patients with colorectal liver metastases who underwent repeat surgery at Hospital Universitario San Cecilio, Granada (Spain), from March 2003 to June 2013. Primary outcome variables included survival and morbidity within 30 days post-surgery.

Results: A total of 147 patients with colorectal liver metastases underwent surgical excision during the study period; 61 patients had liver recurrence, and 34 of these received repeat surgery. The overall survival rate at 5 and 10 years for resected patients (n = 27/34) was 48% and 48%. Mean hospital stay was 8.9 ± 3.5 days, morbidity was 9%, and mortality was 0%.

Conclusion: Repeat liver resection for colorectal liver metastases is a safe, effective surgical procedure whose results are similar to those obtained after initial liver resection.

Key words: Colorectal cancer. Liver metastasis. Recurrence. Repeat hepatectomy. Survival. Efficacy. Surgery.

INTRODUCTION

Colorectal cancer is the malignancy with the highest incidence in Spain, reaching 15% in 2012. Among women it is only second to breast cancer both in incidence (29% *vs.* 14.9%) and mortality (15.5% *vs.* 15.2%). Among men it is third in incidence after prostate and lung cancer (21.7% *vs.* 16.9% *vs.* 15%) and second in mortality after lung cancer (27.4% *vs.* 13.7%) (1). In the aforementioned year, colon and rectum neoplasms accounted for 45,380 hospital discharges (27,523 men; 17,857 women), with a total of 577,878 stays (354,901 men; 222,977 women) (2). Worldwide, colorectal cancer represented 1.1% of all deaths (twentieth position in overall mortality) in 2004, and is expected to increase to 1.4% by 2030, becoming the fourteenth most common cause of mortality (3).

The liver is the primary organ where metastases develop from colorectal cancer, involving up to 50-60% of patients during the course of disease; in fact, their diagnosis is concomitant in 15-25% of cases, with metastases developing within 3-4 years for the rest of patients (4-9). In these subjects liver resection is the most effective therapy, and increases survival to 5 years in 50% of patients, and even to 10 years in 17-25% of patients (10-12), thus decreasing mortality by 1-2% (13,14). However, not all patients are amenable to such resection, and appropriate selection is most important for a successful procedure. In the last few years, inclusion criteria have increased (15,16), and now the one criterion for resection is whole tumor resectability with safety margins and adequately functional liver remnant (17).

While liver resection has curative intent, 60% of patients operated on for CRCLM will develop recurrent disease within 2 years (18,19). In all, 20-30% of patients recurring after an initial liver resection will have metastatic disease susceptible to repeat hepatectomy with identical inclusion criteria (20).

OBJECTIVE

The objective of this study was to assess the resectability and effectiveness of repeat hepatectomy for recurrent colorectal liver metastases in terms of morbidity, mortality, overall survival, and disease-free survival.

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PATIENTS AND METHODS

Patients

A retrospective data assessment was undertaken for a prospective cohort of patients undergoing repeat surgery for colorectal liver metastases between March 2003 and June 2013 at Unidad de Cirugía Hepatobiliar, Hospital Universitario San Cecilio, Granada (Spain).

A total of 61/147 patients with recurrent liver metastases were identified, and 34/61 of these underwent reoperation because of their meeting inclusion criteria; patients were excluded where prior therapy included RFA or exploratory laparotomy; these 34 patients had local recurrence (at the surgical margin) in 41% of cases and new lesions in the remaining 59%; furthermore, there was extrahepatic disease in 24%, which involved the lungs in 12% and was intraabdominal in the rest (Fig. 1).

Demographics, surgery date, primary tumor stage, perioperative and postoperative outcomes, and chemotherapy were all prospectively entered into a database (Table I).

Most appropriate therapy indication was assessed by a digestive tumor committee. Regarding inclusion criteria both anatomic and functional aspects were considered; anatomic inclusion criteria involved location, size and number of metastases for resectability. Multiple metastases, large metastases, insufficient healthy parenchyma, and presence of unresectable extrahepatic recurrence were exclusion criteria. Functional criteria included potential for R0 resection (hepatic and extrahepatic liver disease), two contiguous segments with adequate bile and venous blood flow, and expected liver remnant (volumetric CT) above 25% (normal liver), 30% (after CTx) or 40% (liver dysfunction, cirrhosis).

The study was approved by the Granada Province Ethics Committee.

Preoperative workup

All patients were tested for tumor markers (CEA, CA-19.9), underwent complete colonoscopy, and had their primary tumor histology report reviewed to confirm the appropriateness of their colic resection.

The diagnosis of recurrence was reached using helical computerized tomography (CT) with a liver protocol (150 ml of intravenous contrast in rapid injection with image reconstruction using a liver slice thickness of 2.5 to 5 mm) or magnetic resonance imaging (MRI). Recurrence was identified as local when in the prior resection's surgical margin, the rest being described as new lesions. PET-CT was used to rule out extrahepatic disease and assess the metastatic nature of lesions; when recurrence was suspected but not confirmed by imaging techniques, PET-CT and CT scans were ordered one month afterwards; should doubts remain recurrence was

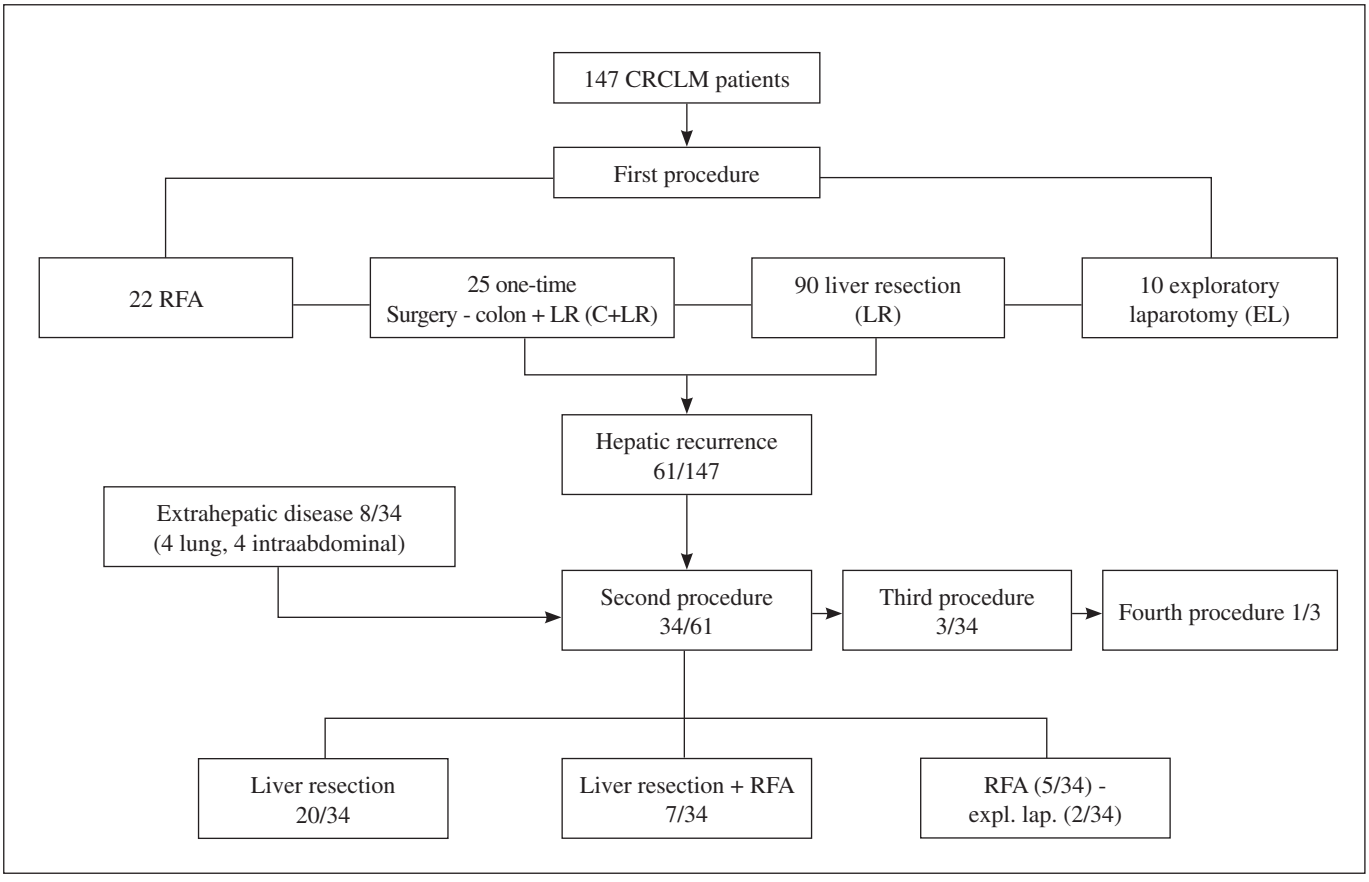


Fig. 1. Flow chart of patients and procedures: 147 patients; relapsed 61/147, reoperated on 34/61.

confirmed using liver biopsy. Once confirmed the digestive tumor committee elects a surgical procedure after assessing surgical risk. The decision to administer preoperative chemotherapy was based on recurrence size, presence of extrahepatic disease, prior response, and chemotherapy toxicity.

In all, 29% of patients had received neoadjuvant chemotherapy for 3 months with FOLFOX (*FOL*inic acid + *F*luorouracil + *OX*aliplatin) associated with anti-EGFR therapy (cetuximab or panitumumab) or anti-VEGF therapy (bevacizumab) followed by surgery; we recommend a rest period of 4 weeks (4-6 weeks if bevacizumab was used) between the last cycle and surgical procedure (21).

Table I. Demographic and clinical characteristics

	Patients (n = 34)	
	n	%
Sex		
Male	24	71
Female	10	29
Age		
Mean	62,99 ± 10,9 (28-85)	
≥ 70 yrs	9	
Metastases		
Synchronous	20	59
Metachronous	14	41
No. of nodules		
≤ 3	28	82
≥ 3	6	18
Size (mm)		
≤ 30	25	74
≥ 30	9	26
Site of primary tumor		
Colon	21	71
Rectum	13	38
Primary tumor stage		
Stage IV	20	59
Stage IIIB	9	26
Stage IIA	5	15
Grade		
Grade I	8	24
Grade II	24	71
Grade III	2	6
KRAS		
Mutated	17	50
Non-mutated	17	50
Chemotherapy		
Neoadjuvant	10	29
Adjuvant	16	47
Extrahepatic disease		
Lung	4	12
Other	4	12

Patients with lung metastases in addition to liver metastases (4/34) underwent liver resection first and lung resection second (22).

Surgery

Surgery was indicated with curative intent (complete tumor mass excision); during laparotomy the peritoneal cavity was inspected to rule out extrahepatic recurrence; bimanual papation and intraoperative ultrasonography were performed for all patients to better define the location of liver metastases and their relation to portal pedicles and suprahepatic veins. All procedures were carried out by the same surgeon (FNF) and classified using the Brisbane terminology of liver anatomy (23).

Resectability index

Patients undergoing exploratory laparotomy (EL) and RFA with no associated liver resection were excluded.

Follow-up

Following hospital discharge patients were discussed at a joint clinical session with the oncology dept., and then followed up on an outpatient basis according to the colorectal cancer procedure of the Andalusian health service (24). Any relapsing lesion considered resectable was surgically treated.

Study variables

Primary outcome variables included overall survival and disease-free survival after the repeat procedure; in order to identify in our study predictive factors for survival the Fong and Basingstoke scores (25,26) were taken into account and included in the univariate analysis; regarding morbidity at 30 days in the postoperative period, the Clavien-Dindo classification was used (27). Date of death was obtained from medical records or national registries.

Statistical analysis

Results were expressed as frequencies and percentages for qualitative variables, and as means and standard deviations for quantitative variables. Overall and disease-free survival data, estimated from date of liver resection to date of patient death (overall survival) or date of disease recurrence (neoplasm-free survival). Survival curves were estimated using the Kaplan-Meier method. Differences in survival were estimated with the log-rank test. Chi-squared tests were used for frequency comparisons.

RESULTS

This study analyzes the outcome of patients after repeat surgery (n = 34) for a total of 61/147 patients with CRCLM

following initial liver resection and meeting resectability criteria.

Figure 1 represents the flow chart of patients and procedures.

Patient characteristics

Of all 34 patients undergoing reintervention 24 were males (71%), with a mean age of 63 ± 10.95 years (64.30 ± 9.98 for men, 60.70 ± 12.21 for women). The primary tumor was localized in the rectum for 38.2% and in the colon for 62%, of which 52.4% occurred in the sigma. As regards the primary CRC, 59% of patients were in stage IV according to the TNM classification. Regarding histopathological differentiation extent, 24% were grade 1, 71% were grade 2, and 6% were grade 3; KRAS was mutated in 50% of cases (n = 17). Table I lists the demographic, clinical, and pathological characteristics of patients.

Chemotherapy

Following the initial hepatic surgery adjuvant CTx was provided for 62.5%; during follow-up, in the presence of liver recurrence, neoadjuvant CTx was used for 29%, with a partial tumor-size response (> 30%) in 50% and stable response (< 30%) in 10% according to RECIST criteria (27). Following the second procedure 47% underwent adjuvant CTx.

Chemotherapy agents for all 34 patients included: 5FU in 93.33%; oxaliplatin in 80%; irinotecan in 30%; bevacizumab in 30%; anti-EGFR in 6.67%, in Folfox or Folfiri regimens associated with anti-EGFR (cetuximab or panitumumab) or anti-VEGF (bevacizumab) therapy.

CRC presentation with hepatic metastatic disease was synchronous in 59% and metachronous in 41% of cases. The median disease-free period from initial procedure for CRCLM to recurrence was 19.2 months (IQ range, 3 to 57 months). At the time of liver recurrence patients had a median of 2 lesions (IQ range, 1-3 lesions) and a median tumor size of 3 cm (IQ range, 0.5 to 8.7 cm); 12% of patients had lung metastases that were resected after liver resection. Metastatic disease to other intra-abdominal organs was 12%: 2 peritoneal, 1 renal and 1 diaphragmatic; all were resected. A patient had a recurrence at the colonic anastomosis, which was resected within the same surgical procedure.

Resectability

All patients (n = 34) were reoperated upon with curative intent; however, in 7 patients resection could not be achieved because of multiple, bilateral, small metastases in two cases, and of widespread presence of up to 4 lesions smaller than 3 cm in size in 5, who received RFA. Resectability index was 79.4%.

Surgical procedures used

Besides exploratory laparotomy (EL) for 6% and radiofrequency (RFA) for 15% of patients, liver resection was performed for 59.4% and resection plus RFA for 21% of cases.

Intraoperative characteristics

Resections were R0 as per the Brisbane classification in 74% of cases, with predominant segmentectomies (one or two segments) and one major hepatectomy (more than 3 segments), and R1 in 26% because of associated RFA. We used the intermittent Pringle maneuver in 59% of cases.

Of the total number of patients operated on, 50% were transfused - 65% received two units, 35% received more than two units.

Postoperative results

Perioperative mortality was 0% at 30 days. Hospital stay was 8.9 days on average (IQ range, 2-15) with a standard deviation of 9.2. In all, 93.8% had no complications; two patients (6.4%) had intestinal fistula as a result of adhesiolysis, and there was a case of minor bile leak, all of which resolved with medical treatment. These complications were classified as type II (2%) and type IIIa (1%) according to the Clavien-Dindo classification. In the immediate postoperative period pain was managed with patient-controlled analgesia (PCA) plus a central antiemetic agent (ondansetron); oral feeding was initiated at 24 h. Median follow-up is 6 years (IQ range, 1-10 yrs).

Hepatic and extrahepatic recurrence

Hepatic recurrence rate after repeat surgery was 44%, and extrahepatic recurrence rate was 15%; of all recurrences, 7% were seen in the lungs, and the remaining cases were bone recurrences. All were managed with chemotherapy, and 4 of 12 patients with hepatic recurrence were rescued by repeat liver resection (Fig. 1).

Predictive factors for survival

The results of the univariate analysis of factors predictive for survival are shown in table II. Synchronous metastases, more than 3 nodules, margin < 10 mm, more

than 3 EC transfusions, extrahepatic disease, and increased CEA are predictive of poor prognosis in the long run (60 and 120 months), although without statistical significance.

Overall and disease-free survival

Overall survival at 5 and 10 years was 48%, and tumor progression-free survival at 5 and 10 years was 48% – hence patients alive at 5 years remained alive at 10 years (Fig. 2).

DISCUSSION

The liver is the natural site of tumor relapse after hepatectomy for CRC metastasis. Repeat hepatectomy has been associated with a 5-year survival equivalent to that seen after the initial procedure, with a similarly low surgical risk (28,29).

For the last 15 years CRCLM management has progressed, including recurrent disease, primarily in three settings: Oncology (newer, more effective antineoplastic agents), interventionist radiology (portal embolization and radiofrequency), and surgery (improved instruments, novel techniques) (30-32).

Regarding factors determinant of success after repeat hepatectomy, larger resection at first surgery may be associated with lower success at repeat surgery because of an insufficiently functional liver remnant or inadequate resection margin. It is recommended that initial surgery only

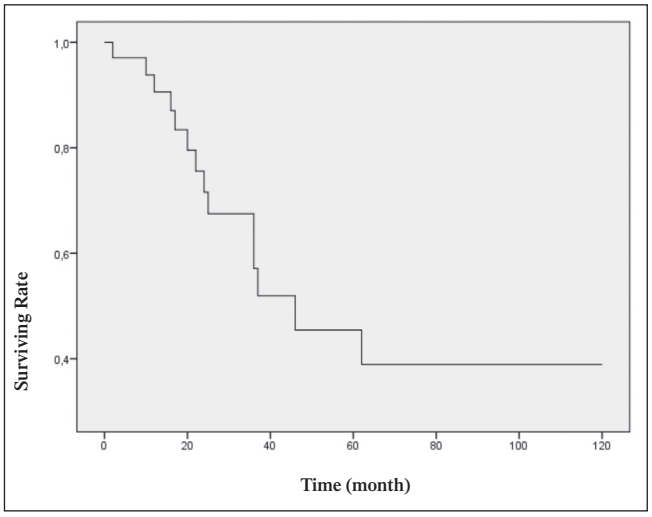


Fig. 2. Overall survival at 5 and 10 years in the series: 48%. Tumor progression-free survival rate: 48%.

Table II. Mortality predictive factors. Univariate analysis

Parameters (months)	*Cases (n = 34)*		*Actuarial survival rate*					*Log-rank test*
	n	*%*	*12*	*24*	*36*	*60*	*120*	
Male	24	71	87	72	58	46	31	p < 0,898
Females	10	29	100	75	63	50	50	
≤ 3 nodules	28	82	96	74	62	44	44	p < 0,672
> 3 nodules	6	18	67	67	50	33	33	
Synchronous	20	59	100	71	51	51	0	p < 0,757
Metachronous	14	41	88	73	62	46	46	
Size < 5	25	74	96	76	63	42	42	p < 0,661
Size > 5	9	26	87	71	47	0	0	
Extrahepatic disease	10	29	80	70	59	46	31	p < 0,741
No extrahepatic disease	24	71	96	74	58	48	48	
No transfusions	17	50	88	80	63	54	42	p < 0,859
Transfusions ≤ 3 RCCs	11	32	91	61	45	45	45	
Transfusions > 3 RCCs	6	18	100	78	78	0	0	
Resection margin < 10 mm	16	47	87	74	52	34	25	p < 0,235
Resection margin ≥ 10 mm	18	53	94	72	72	72	72	
CEA < 5	14	41	100	76	66	51	51	p < 0,453
CEA > 5	20	59	84	71	54	45	33	
RFA	5	15	100	100	78	78	39	
Liver resection	20	59	95	67	54	54	54	p < 0,698
Liver resection + RFA	7	20	100	86	71	43	43	
Overall*	32	100	91	73	59	47	40	

*Two patients with EL were excluded.

involve major resection when a negative margin cannot be obtained (33,34).

As regards surgery, the factor with the highest predictive value is adequate resection margin –the only one surgeons may act upon. Difficulties in indication assessment include presence of extrahepatic tumors, ability to obtain a tumor-free margin, and actual metastasis numbers, which are only revealed during laparotomy (35). Prognostic factors serve as guidelines for patient advice and information on the potential benefits of surgery, but their reliability is inadequate to contraindicate resection on absolute grounds (25,36).

Prior studies suggested the feasibility of this approach (28), but repeat hepatectomy demands technical changes that combine the difficulties of surgery on a usually frail liver potentially damaged by chemotherapy and regeneration, and of initial surgery-related intraabdominal adhesions between the liver and neighboring structures such as the diaphragm (37-41).

Regarding efficacy, with a median follow-up of 71 (12-120) months, our series shows an overall survival rate at 5 and 10 years of 48%, and a progression-free survival rate at 5 and 10 years of 48%, that is, 14 of 34 reoperated upon patients are still living after 10 years; these results are similar to those reported by series with a similar number of patients during a similar period of time (42).

Hepatic recurrence was 44% with a mean free interval of 20 months; in another study with similar characteristics (43) 36.9% had hepatic recurrence –70% occurred at 12 months and the percentage reached 95% at 2 years. Recurrent lesions were identified in the liver (12), lungs (2) and bones (2). Two patients had simultaneously recurrences in the liver and lungs.

As regards morbidity, 9% of patients had complications, which were managed medically in 100% of cases. Other studies have shown higher morbidity rates with a median 21% (0-42) (42). Mean hospital stay in our study was 8.9 days, slightly lower than in reported studies (7 to 11 days) (36).

Mortality at 30 days was 0%, despite the fact that 63.3% of patients were ASA (American Society of Anesthesiologists) III, and 27% were older than 70 years. Mortality rates in reported series oscillate between 0% and 3% (42).

For liver resection, most authors usually recommend anatomic resection as opposed to limited resection or tumorectomy. From a practical viewpoint segmentectomy seems a reasonable technique of choice whenever feasible, as it meets oncological radicality criteria, preserves the parenchyma, and has lower mobidity and mortality rates when compared to major hepatectomy (37,38). Extended resection does not warrant improved results and considerably increases the risk for morbidity and mortality; leaving an adequate resection margin is of utmost importance (38,39).

In total, 96% of our resections were anatomical, with segmentectomy being most common. Our resectability index was 79.4%, and 7 patients had RFA associated for a contralateral lesion.

In the univariate analysis, outcome predictors such as size (> 5 cm), number of transfusions (> 3), number of metastases (> 3), extrahepatic disease, and surgical margins (< 10 mm) were associated with poorer overall survival (Table II).

No statistically significant variables are found in this series, possibly because of sample size; however, in our series of 147 patients, number of metastases > 3, size, and presence of extrahepatic involvement were all significant (36).

Despite our good survival results at 5 years (48%), a high rate of recurrence was seen after repeat hepatectomy at 44%. The relative discrepancy between high overall survival rate and significant risk of subsequent recurrence may be accounted for by the fact that 37.5% of recurring patients after hepatectomy received surgery plus RFA or had a resection margin inferior to 10 mm. Among prognostic factors related to repeat hepatectomy only negative surgical margins (> 10 mm) were associated with a lower risk of additional recurrence and 5-year overall survival at 72%. To date, in the absence of other relevant variables, the ability to provide negative margins is likely the key factor to be considered when selecting patients for repeat resection; oncological outcomes for patients with positive margins at repeat resection are poorer than 25% (Table II).

Furthermore, the liver is also the most common site of recurrence after repeat surgery, as was after primary surgery. The present finding highlights the challenge of completely eradicating disease with combined surgery and systemic chemotherapy. In our series we used chemotherapy schemes including monoclonal antibodies; however, there is no evidence that these agents may reduce recurrence rates versus chemotherapy alone for stage-III CRC (44). These patients with high overall survival and tumor progression-free survival rates most likely benefited from combining an aggressive surgical approach with relatively favorable tumor biology. Approximately, one third of 5-year survivors eventually die from their cancer, whereas those surviving for 10 years are seemingly cured (45).

The main weakness of this study is limited sample size, which prevented statistical significance from being reached. Since our analysis encompasses 10 years and newer imaging techniques, chemotherapy agents, and surgical approaches such as hepatic bipartition are now available, it is possible that some of our patients would have benefited from such improvements. However, the fact that all patients were assessed by the same multidisciplinar team and operated upon by only one surgeon should reduce the bias of treatment variability.

To conclude, these data reinforce the usefulness of repeat hepatectomy for recurrent CRCLM as a safe therapy associated with excellent long-term survival and results similar to those of primary liver resection.

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