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ORIGINAL ARTICLE

Outcome after repeat resection of liver metastases from colorectal cancer

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Abstract
Introduction Although advances in multimodal treatment have led to prolongation of survival in patients after resection of colorectal liver metastasis (CRC-LM), most patients develop recurrence, which is often confined to the liver. Repeat hepatic resection (RHR) may prolong survival or even provide cure in selected patients. We evaluated the perioperative and long-term outcomes after RHR for CRC-LM in a single institution series.
Patients and methods Since 1999, 92 repeat hepatic resections (63 % wedge/segmental, 37 % hemihepatectomy or greater) for recurrent CRC-LM were performed in 80 patients. Median interval from initial liver resection to first RHR was 1.25 years. Any kind of chemotherapy (CTx) had been given in 88 % before RHR. Neoadjuvant CTx was given in 38 %.
Results Hepatic margin-negative resection was achieved in 79 %. Mortality was 3.8 %. Overall complication rates were 53 %, including infection (17 %), operative re-intervention (12 %), and hepatic failure (5.4 %). Overall 5-year survival after first RHR was 50.3 %. Univariately, primary tumor stage, the extent of liver resection, postoperative complications, and the overall resection margin correlated with survival. By multivariate analysis, primary T stage, size of metastasis, and overall R0 resection influenced survival. Survival was not independently influenced by hepatic resection margins or (neoadjuvant) CTx.
Conclusions Repeat hepatic resection for recurrent CRC-LM can be performed with low mortality and acceptable morbidity. Survival after repeat hepatic resection in this selected group of patients is encouraging and comparable to results after first liver resections.

Keywords Colorectal liver metastasis · Repeat hepatectomy · Survival · Neoadjuvant chemotherapy

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Introduction

In the past 30 years, treatment of metastatic disease from colorectal cancer (CRC) has substantially changed. Even before the advent of new chemotherapeutic agents, "therapeutic nihilism," especially in colorectal liver metastasis (CRC-LM), has been abandoned [1, 2]. Advances in hepatic surgery and also modern chemotherapeutic regimens have clearly prolonged survival in patients with metastatic CRC. Hepatic resection today is undoubtedly standard of care for all resectable CRC-LM, providing the only possible chance for cure [3–6]. However, this paradigm shift has probably not fully translated into the treatment of recurrent CRC-LM.

With an increasing number of patients being "curatively" resected (margin-negative resection with no further distant metastatic spread) for CRC-LM, "recurrence" as such becomes more and more evident. This has been described already in the 1980s [1]. It has to be estimated according to de Jong et al. that within less than 3 years more than half of the patients with CRC-LM develop recurrence [7]. While this is confined to extrahepatic sites in one third of patients, roughly 20–30 % develop both intra- and extrahepatic recurrence. Another 30–40 % develop intrahepatic recurrence only. In those patients with isolated intrahepatic recurrence, the liver will also remain the only place of recurrence in approximately 90 % [7, 8].

As a consequence, treatment strategies for recurrent intrahepatic disease should aim at overall margin-free resections if technically feasible. For CRC-LM recurrence, this has been done in various centers around the world, leading to an increased rate of repeat hepatic resection with excellent results regarding 5-year survival, morbidity, and mortality over the past decade [9–19]. Although repeat hepatic resection is not an entirely new concept [20, 21], treatment strategies and patient selection for recurrence of CRC-LM are far from being clearly defined. Today, much as in initial liver resection, neoadjuvant chemotherapy, surgery, as well as combined additional locally ablative therapy and surgery, all play a role in the treatment of recurrent CRC-LM. Criteria for resectability of recurrent CRC-LM are the same as for initial liver resection: curative intent (including locally ablative therapies and resection of extrahepatic disease in, e.g., the lung), preservation of hepatic in- and outflow and adequate residual liver volume.

In this series, we investigated the surgical aspects, possible risk factors for adverse outcome including (neoadjuvant) chemotherapy together with long-term results in 92 cases of repeat hepatectomies done in 80 patients.

Patients and methods

A total of 481 hepatic resections for CRC-LM were performed at the Department of Surgery at the University Hospital in Freiburg between 1999 and 2011. Ninety-two of those (19 %) were performed as repeat hepatic resections for recurrent CRC-LM in 80 patients. For operative and perioperative details, all 92 cases were evaluated. For survival analysis, 77 of the 80 patients were analyzed from the date of their first repeat hepatectomy (three patients with postoperative in-hospital mortality were not included in survival analysis).

Indication for repeat hepatic resection

All liver resections were carried out under potentially curative intent. Curative intent was defined at the discretion of the attending surgeon following the same basic principles as in initial hepatic resection for CRC-LM: The absence of other irresectable extrahepatic metastatic sites, sufficient hepatic in- and outflow, as well as sufficient future liver remnant apart from general operability were required. Preoperatively, all patients had recent imaging for tumor staging (computed tomography or magnetic resonance imaging). Selected patients also had undergone PET imaging during the course of their disease. If deemed necessary (resection planned greater than hemihepatectomy), volumetry of the liver was added. Concomitant or intermediate locally ablative therapies were no exclusion criterion, as they have become routine use in surgical practice. Previous non-surgical locally ablative therapies before repeat hepatectomy were also no exclusion criterion.

Repeat hepatic resection

Teams of experienced hepatobiliary surgeons performed all repeat hepatic resections. It was generally carried out in a two-surgeon fashion using Cavitron ultrasonic aspiration (CUSA Excel™, Integra, New Jersey, USA) and irrigated bipolar forceps for the transection. All resections apart from atypical or segmental resections were classified as major resections (hemihepatectomy, extended hemihepatectomy, or central resection).

Preoperative chemotherapy

The term "chemotherapy" was defined by the use of any antitumoral agents including biological agents such as bevacizumab, cetuximab, or panitumumab. "Neoadjuvant" chemotherapy was defined in our analysis as any chemotherapy (including biological agents) given within the last 6 months before repeat hepatic resection as described before [22].

Data collection and statistics

Demographic data, tumor characteristics, and all other patient-related perioperative results of this study were gained by retrospective analysis of our prospective hepatic surgery database. Subgroup comparison of frequencies was done using Chi-square test.

Actuarial survival was estimated using the Kaplan–Meier method. During subgroup analyses, differences between groups were assessed by a log rank test. Multivariate survival analysis was performed using the Cox proportional hazard model (inclusion p value 0.15). Two different/alternative models were used with regard to local and overall resection status in order to avoid multicollinearity of data (see also legend of Table 3; all positive hepatic resection margins are included in the overall resection margin, but not vice versa). A p value of $p<0.05$ was considered statistically significant. All parameters were processed through an SPSS® database (IBM® SPSS® for Windows version 19.0, IBM, Armonk, New York, USA).

Results

Demographic and tumor data

Eighty patients (70 % male) underwent 92 hepatic repeat resections. Primary tumor stage in these 80 patients was T3

or higher in 79 %, 63 % were node positive. Nine patients had a total of three hepatic resections (two repeat resections), three patients had four (three repeat resections) (Table 1). Median time interval between initial and first repeat hepatic resection was 1.25 years. Between first and second repeat resection, time interval was also 1.25 years. The third repeat resection (n=3) was carried out after a median interval of 0.9 years. Median follow-up for survival was 61 months.

Table 1 Demographic, tumor-, and treatment-related data of 92 repeat hepatic resections for recurrent colorectal liver metastases

Demography		Number	Percent
Gender (n=80)	Male	56	70.0
	Female	24	30.0
Primary tumor (site) (n=80)	Colon	48	60.0
	Rectum	32	40.0
Primary tumor (stage) (n=80)	T1	2	2.5
	T2	14	17.5
	T3	52	65.0
	T4	11	13.8
	Unknown	1	1.3
Primary tumor (nodal status) (n=80)	Negative	29	36.3
	Positive	50	62.5
	Unknown	1	1.3
Number of repeat resections	First	80	87.0
	Second	9	9.8
	Third	3	3.3
Interval between liver resections	≤1.5 years	57	62.0
	>1.5 years	35	38.0
Type of liver resection	Atypical/wedge	36	39.1
	Segmental	22	23.9
	Hemihepatectomy	16	17.4
	Extended hemihepatectomy	16	17.4
	Central resection	2	2.2
Number of CRC-LM (category)	1	41	44.6
	>1	48	52.2
	Unknown	3	3.3
Tumor size (largest)	≤30 mm	54	58.7
	>30 mm	36	39.1
	Unknown/ uncertain	2	2.2
Hepatic margin	Negative	73	79.3
	Positive	17	18.5
	Unknown/ uncertain	2	2.2
Overall margin	Negative	65	70.7
	Positive	25	27.2
	Unknown/ uncertain	2	2.2

Operative details

Median number of metastases was 2 (range 1–11). More than one recurrent liver metastasis was present in 52.2 % at the time of repeat hepatic resection. Median diameter of the largest lesion was 29 mm (range 4–120 mm).

Thirty-seven percent of patients underwent major liver resection. Sixty-three had minor resections (wedge/segmental). Free hepatic margins were achieved in 73 of 92 cases (79.3 %). The 17 margin positive resections included four local R2 resections. Overall margin-free (R0) resection rate (including absence of extrahepatic disease) was achieved in 65 of 92 cases (70.7 %) (Table 1).

Chemotherapeutic regimens before repeat resection

Eleven patients (12 %) never received any chemotherapy (neither for hepatic metastases nor for the primary tumor). In 88 % (81/92) of cases, patients had been given chemotherapy before repeat hepatic resection. Regimens were all 5-FU based. In 47 cases (58 %), regimens contained oxaliplatin, and 23 (28 %) contained irinotecan. Of those cases, six had a combination of oxaliplatin and irinotecan (7 %). Biological agents at anytime were additionally used in 28 of 81 cases (35 %). Neoadjuvant chemotherapy (i.e., within 6 months prior to liver resection) was given in 36 % of cases (33/92). In only 13 cases (14 %) that neoadjuvant chemotherapy included biological agents.

Perioperative morbidity and mortality

In 12 %, operative revisions were necessary for complications after hepatic re-resection (Clavien–Dindo grade IIIb or greater) [23]. Any kind of complication (Clavien–Dindo grade I or greater) was seen in 53.3 %; 17.4 % were surgical infections (ranging from subcutaneous collections (14.1 %) to deep abscesses or both (7.6 %)). Liver insufficiency (as defined by peak postoperative bilirubin at or above 6.0 mg/dl) was seen in 5.4 %. Biliary complications ranging from small biliomas (detection via ultrasound or CT, no intervention) to biliary fistulas (i.e., with the need for intervention) were present in 14.1 %. There were three postoperative bleeding episodes requiring re-operations (3.3 %).

In-hospital mortality was 3.3 % (three patients). One 63-year-old male developed fatal multi-organ failure 5 months postoperatively due to an enteric fistula after first repeat hepatic resection (R0 resection). Another 66-year-old male, having undergone extrahepatic resection and hepatic radiofrequency ablation before repeat hepatectomy, died of septic complications due to liver failure after 4.5 months (R1 resection). The third patient was an 85-year-old male with central biliary obstruction and jaundice 4 years after primary CRC. After percutaneous transhepatic drainage of

the biliary system, an extended hepatectomy (R0 resection) was performed. The patient died of septic complications with subsequent septic liver failure from a subphrenic abscess in combination with cholangitis.

Long-term outcome after first repeat hepatic resection

One-, 3-, and 5-year survival rates in 77 patients from the time of first hepatic repeat resection were 97.2, 62.0, and 50.3 %, respectively (Table 2). Median survival was 5.0 years. Of the patients, 58.4 % were deceased at the end of the follow-up period (Fig. 1).

Univariate analysis of survival showed a better outcome for primary T1 and T2 tumors (vs. T3/T4; p=0.04; Table 2). Patients with overall free margins showed a better survival than patients with residual extra- or intrahepatic disease (p=0.05) (Fig. 2). Patients suffering from any kind of postoperative complication univariately had a worse outcome (p=0.05). Outcome was also poorer after major liver resection (vs. minor liver resections; p=0.05; Table 2). There were significantly larger tumors in the subgroup of major resections (median 37 vs. 23 mm, p=0.02 data not shown), which are independent predictors of survival, see below.

Gender, site of primary tumor, primary tumor nodal status, size of largest metastasis, time between resections, number of metastases, liver resection margins, and chemotherapy (at anytime or <6 months prior to resection) were not influencing long-term outcome in univariate survival analysis.

On multivariate analysis, two different models were employed. In the hepatic resection margin model, the primary T stage (OR 4.07, range 1.18–14.01; p=0.03) and the size of the largest metastasis >30 mm (OR 2.18, range 1–4.78; p=0.05) were independent prognostic factors for better survival (Table 3). The local hepatic margin was not an independent prognostic factor. In the Cox regression model including the overall resection margin, only the achievement of curative intra- and extrahepatic resections (overall margin) but no other factor was associated with better survival (OR 2.42, range 1.12–5.24; p=0.025) (Table 3).

Table 2 Actuarial survival in 77 patients after first repeat hepatic resection for recurrent colorectal liver metastases

Survival after first repeat hepatic resection		Number	1 year %	3 year %	5 year %	p value
Overall		77	97.2	62.0	50.3	
Gender	Male	53	96.1	54.3	46.0	0.37
	Female	24	100.0	80.2	57.3	
Primary tumor (site)	Colon	46	95.2	64.5	53.2	0.94
	Rectum	31	100.0	58.3	52.5	
Primary tumor (stage)	T1 / T2	16	93.3	76.4	76.4	**0.04**
	T3 / T4	60	100.0	59.8	44.4	
Primary tumor (nodal status)	Negative	27	100.0	61.7	41.1	0.95
	Positive	49	95.7	63.7	53.0	
Size largest metastasis I	≤30 mm	45	100.0	71.7	66.9	0.10
	>30 mm	30	93.1	52.7	27.1	
Interval between liver resections	≤1.5 yrs	49	97.7	70.9	51.5	0.66
	>1.5 yrs	28	96.3	46.9	46.9	
Liver resection	Minor	48	97.7	67.8	63.3	**0.05**
	Major	29	96.4	53.6	34.0	
Number of CRC-LM	1	35	100.0	76.9	59.2	0.18
	>1	39	94.5	52.9	46.3	
Intraoperative transfusion	Yes	23	95.5	49.5	41.2	0.27
	No	50	100.0	69.2	58.9	
Any complication	Yes	40	94.5	51.9	31.1	**0.05**
	No	37	100.0	72.6	62.9	
Chemotherapy (anytime)	Yes	67	96.8	59.8	50.4	0.89
	No	10	100.0	80.0	40.0	
Biological agents (anytime)	Yes	20	94.4	50.7	50.7	0.36
	No	57	98.1	64.6	52.3	
Hepatic margin	Negative	61	96.5	64.8	48.2	0.27
	Positive	16	100.0	53.8	53.8	
Overall margin	Negative	56	98.1	69.9	52.0	**0.05**
	Positive	21	94.7	44.2	44.2	

Bold indicate statistically "significant" values

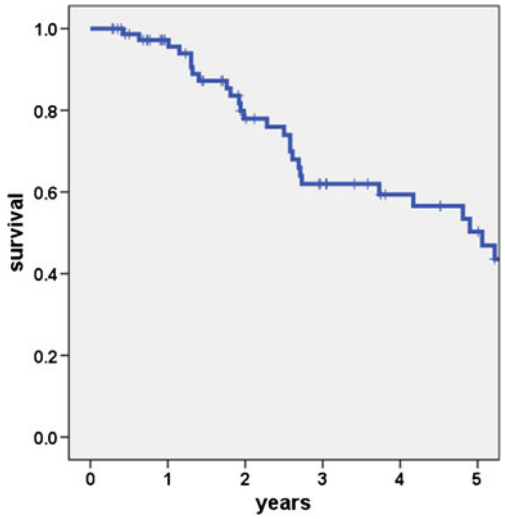

Fig. 1 Overall actuarial 5-year survival in 77 patients after first repeat hepatic resection for recurrent colorectal liver metastases

Discussion

Margin-negative resection remains the only possible chance for cure in colorectal cancer. The same holds true for metastatic colorectal cancer in the liver and also the lung [24–29]. However, recurrence of metastatic disease is common, clearly exceeding 50 % or even up to 75 % in recent studies [7, 8]. Reports on hepatic repeat resections have been published since the mid-1980s [1, 20, 30]. This approach has gained more and more acceptance in present times [9–18]. Data supporting this approach almost unanimously come from retrospective single-center experiences such as the one described here. There is no doubt that the

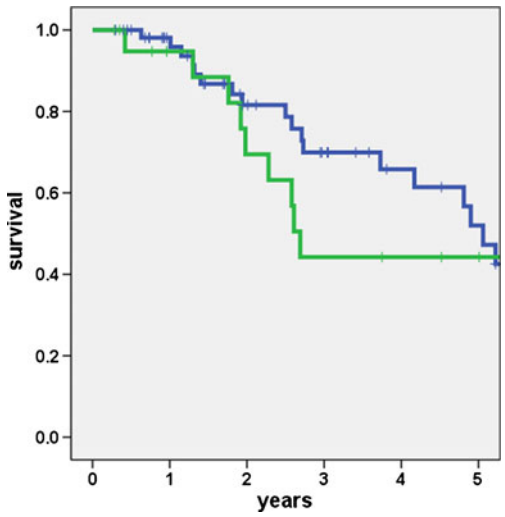

Fig. 2 Overall resection margin: actuarial 5-year survival in 77 patients after first repeat hepatic resection for recurrent colorectal liver metastases (resection margin negative (*blue line*), positive (*green line*); $p=0.05$)

Table 3 Multivariate survival analysis (Cox) in 77 patients after first repeat hepatic resection. To prevent multicollinearity of data, the clinically overlapping parameters "hepatic margin" and "overall margin" were analyzed in alternate models (model 1 with hepatic resection margin and model 2 with overall resection margin)

	OR	*p*	95 % CI
Model 1 with hepatic resection margin			
Primary CRC T stage	4.07	0.026	1.18–14.01
Size largest metastasis >30 mm	2.18	0.05	1–4.78
Hepatic margin	–	(0.39)	–
Model 2 with overall resection margin			
Overall margin	2.42	0.025	1.12–5.24
Primary CRC T stage	(3.31)	(0.064)	(0.93–11.76)
Size largest metastasis >30 mm	(2.01)	(0.11)	(0.84–2.01)

favorable results regarding 5-year survival, equaling survival after primary hepatic resections, come from careful selection of patients. Therefore, identifying risk factors in this selected group is of paramount importance when trying to introduce this concept into standard clinical care. General surgical principles have always been applied for repeat hepatic resections. They include feasibility of (overall) margin-negative resections, sufficient liver remnant, and preservation of hepatic in- and outflow [31]. With the advent of modern chemotherapeutic regimens including biological agents, so-called targeted therapy, overall survival of patients with metastatic colorectal disease has clearly improved [32, 33]. Concern has been raised as to whether theses chemotherapies are beneficial for surgical approaches such as repeat resections in terms of tumor downsizing or detrimental in terms of limiting the amount of liver parenchyma that can be resected due to adverse effects of chemotherapy on liver function. It could be shown that liver resections can be carried out safely (i.e., same mortality and morbidity) after chemo- and targeted therapy compared to chemotherapy-naïve patients, but it has to be kept in mind that strict requirements regarding future liver remnants have to be met [34–36].

The results gained from retrospectively analyzing "prognostic factors" in hepatic repeat resections unfortunately are very conflicting. Almost all single-center studies have been able to provide some individual risk factors for survival after repeat hepatic resection in univariate analysis. For the most part, prognostic factors described in these studies are general risk factors in metastatic colorectal disease. They include high CEA levels, advanced T or N stages, large tumor size, and, e.g., extrahepatic disease [11, 14, 15, 17]. In multivariate analysis, Adam et al. could show that margin-negative resection after second hepatectomy and an interval of more than 1 year between those procedures were significantly influencing survival [37]. Petrowsky et al. identified the

number of lesions and tumor size above 5 cm to be multivariately influencing survival [9]. Tumor size was also a prognostic factor in multivariate analysis in further studies [10, 11, 14, 17] as well as ours. In the only study with more than 200 patients from two different centers, only extrahepatic disease and the receipt of chemotherapy was significant on multivariate analysis [18].

Apparently, prognostic factors are not continuously described but vary between different reports and centers. The reasons for this cannot easily be explained. Compared to large analyses after first liver resection [3, 38], sample size in most studies regarding repeat hepatic resection is below 100 (such as ours). On the other hand, there is good evidence for prolonged overall survival in patients undergoing hepatic repeat resections, even if disease-free survival after liver resection seems to be very limited.

It is of note that in most studies no results with regard to local resection margins are shown. While negative local resection margins are the primary goal in curative intent liver surgery and highly correlated with outcome [4], the role of local resection margins in recurrent metastatic disease is less clearly defined. For instance, the local resection margins did not show any influence on recurrence-free survival in the study by de Jong et al. [7]. In a recent study by Adair et al., 5-year overall survival was shown to be 29 %, albeit a quite high rate of local margin positive resections at repeat hepatectomy of 51 % [19]. As suggested by Ayez et al., these effects could be attributed to the increasing use of neoadjuvant chemotherapy [39]. While local R1 resection or local recurrence still allow for acceptable long-term survival in our studies and others [17, 19], failure to achieve overall R0 resections for various reasons was associated with poor prognosis in this study as well as others [40].

Another important challenge in today's multidisciplinary treatment of metastatic colorectal disease is to identify patients who benefit from neoadjuvant chemotherapies in recurrent disease. The lines between "palliative" or "additive" chemotherapy and neoadjuvant chemotherapy are vanishing. This is mainly due to the short intervals in which primary surgeries are followed by adjuvant therapies and are again followed by surgeries for (recurrent) metastatic disease. While time to recurrence in this study was 1.25 years, many chemotherapeutic regimens thus fall into the time interval of <6 months prior to surgery. However even with 40 % of patients being on chemotherapy <6 months prior to repeat resection neither benefits nor disadvantages of such a treatment could be shown by this study as well as others [17, 19]. On the other hand, one study has shown a survival benefit after chemotherapy [18]. If modern "targeted therapy," which was given in only 12 % of patients in this study, will eventually change this fact, it cannot be answered from our data at present times.

Conclusion

This study shows that repeat hepatic resection is beneficial for selected patients suffering from recurrent liver metastases in colorectal carcinoma. Survival rates comparable to those after primary resection for colorectal liver metastasis can be expected in this patient group. Advanced primary T stages, major liver resections, and postoperative complications as well as local resection margins, but not chemotherapy, univariately influenced survival in this study. Multivariately, the possibility to achieve overall margin-negative resection (i.e., absence of extrahepatic disease) is the strongest predictor of survival. Multimodal therapeutic strategies in the future should therefore strongly consider repeat hepatic resection in recurrent hepatic disease.

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