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Repeated hepatic resection for colorectal liver metastases: is this concept safe and feasible?

Maximilian von Heesen · Jochen Schuld · Sebastian Holländer · Antonios E. Spiliotis · Anna Merscher · Philipp R. Scherber · Dorian Igna · Gereon Gäbelein · Matthias Glanemann

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Summary
Background The beneficial outcomes of hepatectomy in patients with colorectal metastases have encouraged the attempts of repeated hepatectomy in patients with recurrent disease. Although studies have provided encouraging results regarding perioperative outcomes and survival rates following repeated hepatectomy, it remains unclear whether the reported outcomes reflect the therapeutic results of redo hepatectomy or rather reflect the effect of selection bias. The aim of this study was to investigate differences among patients who underwent single and repeated hepatectomy and to hereby identify prognostic factors that contribute to the premises of repeated resection.
Methods Patients who underwent hepatectomy due to colorectal metastases were listed in a retrospective database. Study participants were divided into a single partial hepatectomy group, a multiple partial hepatectomies group, and into subgroups of two or more than two hepatectomies.
Results A total of 338 patients with 439 partial liver resections were included in the analysis. The overall survival rate after 1, 3, and 5 years was 89%, 56%, and 36%, respectively. The survival benefit in patients who underwent multiple partial liver resections versus those with a single partial resection was 10%, 16%, and 4% after 1, 3, and 5 years, respectively. Repeated hepatectomy was not associated with increased rates of surgical and non-surgical complications.
Conclusion Beneficial outcomes have been found in terms of median overall survival and perioperative morbidity in patients with recurrence of colorectal hepatic metastases after partial and tissue-sparing repeated liver resections.

Keywords Colorectal neoplasms · Liver neoplasms · Hepatic metastases · Hepatectomy · Repeated hepatectomy

Main novel aspects

- Repeated hepatectomy with complete resection of recurrent colorectal hepatic metastases should be considered the treatment of choice.
- Tissue-saving redo hepatectomies with preservation of crucial anatomic structures are recommended.
- Repeated hepatectomy is associated with beneficial outcomes in median overall survival and perioperative morbidity in patients with recurrence of colorectal hepatic metastases.

The authors M. von Heesen and J. Schuld contributed equally to the manuscript.

M. von Heesen, MD
Department of General- and Visceral Surgery, HELIOS Hospital, 65199 Wiesbaden, Germany

J. Schuld, MD
Department of General and Visceral Surgery, Knappschaftsklinikum, 65843 Sulzbach, Germany

S. Holländer, MD · P. R. Scherber, MD · D. Igna, MD · G. Gäbelein, MD · Prof. M. Glanemann, MD
Department of General Surgery, Vascular-, Visceral- and Pediatric Surgery, Saarland University Medical Center, 66421 Homburg, Germany

A. E. Spiliotis, MD M.Sc. (✉)
Department of Surgery, Campus Charité Mitte and Campus Virchow-Klinikum, Charité—Universitätsmedizin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, 13353 Berlin, Germany
antonios.spiliotis@outlook.com

A. Merscher, MD
Department of General and Visceral Surgery, Hospital Bietigheim, 74321 Bietigheim-Bissingen, Germany

Introduction

Colorectal cancer represents the third most common cause of malignancy and the third leading cause of cancer-related mortality worldwide. It is estimated that up to 25% of patients have colorectal liver metastases at the time of diagnosis, whereas 30–50% of patients develop metastases during the course of their cancer disease [1, 2]. Compared to other therapeutic approaches such as locoregional ablation treatments, surgical resection is associated with the highest 5-year survival rate and is considered the gold standard in treatment of liver cancer [3, 4].

Hepatic or extrahepatic recurrence is reported in up to 80% of patients after hepatectomy [5, 6]. The beneficial outcomes of hepatectomy in patients with colorectal metastases have encouraged attempts of repeated hepatectomy in patients with recurrent liver disease. Repeated hepatectomy has been associated with acceptable rates of postoperative morbidity and mortality; however, recent studies have reported conflicting results regarding the impact of repeated hepatectomy on long-term survival [5, 7–9]. Although some studies have demonstrated a survival benefit following redo hepatectomy compared to single resection [5, 8, 10, 11], others have yielded comparable or less favorable long-term results [7, 12, 13].

It remains unclear whether the documented beneficial outcomes truly reflect the therapeutic impact of repeated resection or rather simply reflect the effect of selection bias. Furthermore, although attempts have been made to provide selection criteria for repeated hepatectomy, factors that predict the recurrence rate after hepatectomy are not clearly defined [5, 11].

The aim of this study is to investigate differences among patients who underwent single and repeated hepatic resections and to hereby identify prognostic factors that contribute to the premises of repeated hepatectomy. We investigated differences in the course of the first partial hepatectomy which potentially prejudice the possibility of repeated resection. The key question is whether redo hepatectomy for recurrent disease after successful index surgery improves overall survival.

Materials and methods

Within a period of 14 years, a total of 338 patients with colorectal liver metastases underwent 439 partial liver resections in curative intent due to one or more metastases and were included in the analysis. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

All cases were previously presented and discussed in an interdisciplinary tumor board. The primary tumor was resected either prior to the liver resection or synchronously. According to current guidelines and the initial tumor stage, radiation therapy and/or chemotherapy was performed.

Anatomical partial liver resections according to Couinaud liver segmentation, atypical partial liver resection, or a combination of both procedures was conducted. If necessary, the Pringle-maneuver technique was used to prevent blood loss. “Major partial hepatectomy” was defined as resection of three or more liver segments. All patients underwent an intraoperative ultrasound examination to verify the location and size of metastases and to detect potential previously unknown metastases. Perihepatic lymphadenectomy was only performed in case of lymph node enlargement, while cholecystectomy was conducted as standard. Parenchyma dissection was performed using an ultrasound dissection device (CUSA; Tyco Healthcare, Mansfield, MA, USA).

All patients were transferred to the intensive care unit postoperatively and were monitored for at least 1 day. Patients received red cell concentrates only in case of hemoglobin concentration less than 6 g/dl or less than 8 g/dl in patients with existing cardiovascular-related diseases.

All patients were registered in an Access database (Microsoft Access, Microsoft Office Professional Plus 2010; Microsoft Cooperation, Redmond, Washington, United States). Demographical and medical history data including stage and location of the primary tumor, initial tumor therapy, extent of partial liver resection, and course of inpatient treatment were listed. From January 2017 to December 2021, a retrospective analysis and completion of follow-up data were conducted. Institutional approval was obtained for the conduction of this retrospective study.

Study participants were divided into two groups. Patients with only one partial hepatectomy were assigned to the group “single partial hepatectomy” (sPhx); those with two or more partial liver resections were assigned to the group “multiple partial hepatectomies” (mPhx). The mPhx group was subdivided into the following subgroups: patients who underwent two (2Phx) or more than two (>2Phx) partial liver resections. The different groups were compared with regard to the above-mentioned data.

The collected data were analyzed using Microsoft Excel (Microsoft Excel, Microsoft Office Professional Plus 2010, Microsoft Cooperation) and SPSS 23.0® (IBM Corp., Armonk, NY, United States). Categorical values are given as absolute values and percentages. Continuous values are given as the mean value with standard deviation or median and 95% confidence range.

The comparison of categorical values was performed using chi-square test and Fisher’s exact test. Continuous values were compared using Mann–Whitney U test. Survival time was defined as the time after the first partial liver resection until the date of death. Overall survival was assessed using the method of

Table 1 Patient and primary tumor characteristics

	sPhx ($n=259$)	mPhx ($n=79$)	p-value	2Phx ($n=56$)	>2Phx ($n=23$)	p-value
Gender (male)	164 (63.3%)	51 (64.6%)	0.894	34 (60.7%)	17 (73.9%)	0.310
Age at first Phx (years)	64.5 ± 0.6	61.2 ± 1.2	0.018*	62.4 ± 1.4	58.4 ± 2.1	0.030*
BMI (kg/m^2)	27.4 ± 0.6	26.1 ± 0.5	0.554	26.4 ± 0.5	25.1 ± 0.9	0.408
ASA score	2.4 ± 0.0	2.2 ± 0.1	0.011*	2.2 ± 0.1	2.3 ± 0.1	0.182
Hepatitis (HBV/HCV)	12 (4.6%)	4 (5.1%)	0.758	2 (3.6%)	2 (8.7%)	0.576
Primary cancer rectum	102 (39.4%)	41 (51.9%)	0.052	28 (50.0%)	13 (56.5%)	0.629
Age at primary cancer (years)	62.5 ± 0.6	59.8 ± 1.1	0.025*	60.8 ± 1.3	57.4 ± 2.1	0.151
UICC stage IV	112 (43.2%)	47 (59.5%)	0.022*	33 (58.9%)	14 (60.9%)	0.769
T4 stage	47 (18.2%)	8 (10.1%)	0.083	8 (14.3%)	0 (0.0%)	0.097
Adjuvant chemotherapy for primary cancer	151 (59.3%)	54 (68.4%)	0.214	35 (62.5%)	(82.6%)	0.194
Adjuvant radiation for primary cancer	25 (9.7%)	12 (15.2%)	0.303	7 (12.5%)	5 (21.7%)	0.731

Values are indicated as absolute values and percentages or as mean value ± standard error of mean
Phx partial hepatectomy, *sPhx* single partial hepatectomy, *mPhx* multiple partial hepatectomy, *2Phx* two partial hepatectomies, *>2Phx* more than two partial hepatectomies, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *UICC* Union for International Cancer Control
*Statistically significant *p*-value

Kaplan–Meier. Survival rates were compared between groups using the log-rank test. The influence of each variable on overall survival was investigated using a Cox regression model. Statistical significance was interpreted considering a p-value <0.05.

Results

A total of 338 patients underwent 439 partial liver resections due to colorectal metastases. Single partial hepatectomy was performed in 259 patients (group sPhx), while 79 patients underwent multiple partial liver resections (group mPhx). Of the latter patients, 56 underwent two partial liver resections (group 2Phx), whereas 23 patients underwent more than two partial liver resections (group >2Phx). In the >2Phx group, three, four, and five hepatectomies were performed in 16, 7, and 1 patient, respectively.

Demographic data and data concerning the primary tumor are shown in Table 1. The mean age at the time of index hepatectomy in the mPhx group was 61.2 ± 1.2 years compared to 64.5 ± 0.6 years in the sPhx group ($p=0.018$). In addition, the age of the patients with >2Phx was significantly lower compared to the 2Phx group (>2Phx vs. 2Phx: 58.4 ± 2.1 vs. 62.4 ± 1.4 years, $p=0.03$).

With regard to gender distribution, body mass index, rate of rectal cancer, presence of hepatitis B or C, T4 stage of the primary tumor, and adjuvant chemotherapy or radiation therapy, there were no significant differences between the groups. Patients' ASA (American Society of Anesthesiologists) score was

Table 2 Characteristics of liver metastases and hepatic resections at the time of index hepatectomy

	sPhx ($n=259$)	mPhx ($n=79$)	p-value	2Phx ($n=56$)	>2Phx ($n=23$)	p-value
Interval between surgery for primary cancer and first Phx (months)	21.0 ± 2.0	17.0 ± 2.8	0.250	18.9 ± 3.6	12.4 ± 4.3	0.228
Synchronous liver metastases	108 (41.7%)	43 (54.5%)	0.053	29 (51.8%)	14 (60.9%)	0.620
Multiple liver metastases	169 (65.3%)	55 (69.6%)	0.500	39 (69.6%)	16 (69.6%)	1.000
Bilobular liver metastases	75 (34.8%)	26 (32.9%)	0.575	17 (30.4%)	9 (39.1%)	0.599
Anatomical Phx ≥ 3 segments	44 (17.0%)	10 (12.7%)	0.483	8 (14.3%)	2 (8.7%)	0.715
Bisegmentectomy	27 (10.4%)	6 (7.6%)	0.524	4 (7.1%)	2 (8.7%)	1.000
Segmentectomy	51 (19.7%)	7 (8.9%)	0.026*	7 (12.5%)	0 (0.0%)	0.100
Single-site non-anatomical Phx	67 (25.9%)	21 (26.6%)	0.883	13 (23.2%)	8 (34.8%)	0.402
Multiple non-anatomical Phx	66 (25.5%)	32 (40.5%)	0.016*	22 (39.3%)	10 (43.8%)	0.803
Combination of anatomical and non-anatomical Phx	25 (9.7%)	5 (6.3%)	0.498	3 (5.4%)	2 (8.7%)	0.625
Operating time (minutes)	178.1 ± 4.7	178.6 ± 7.8	0.718	176.3 ± 9.3	184.2 ± 14.9	0.863
Blood loss (ml)	577.7 ± 50.0	435.7 ± 52.1	0.884	431.5 ± 52.7	586.4 ± 125.5	0.252
Maximum diameter of resected liver tissue (cm)	9.3 ± 0.4	8 ± 0.7	0.380	8.4 ± 0.9	6.9 ± 1.1	0.351
Weight of resected liver tissue (g)	418.99 ± 43.2	384.8 ± 83.7	0.454	412.8 ± 97.9	233.55 ± 61.3	0.841

Values are indicated as absolute values and percentages or as mean value ± standard error of the mean
Phx partial hepatectomy, *sPhx* single partial hepatectomy, *mPhx* multiple partial hepatectomy, *2Phx* two partial hepatectomies, *>2Phx* more than two partial hepatectomies
*Statistically significant *p*-value

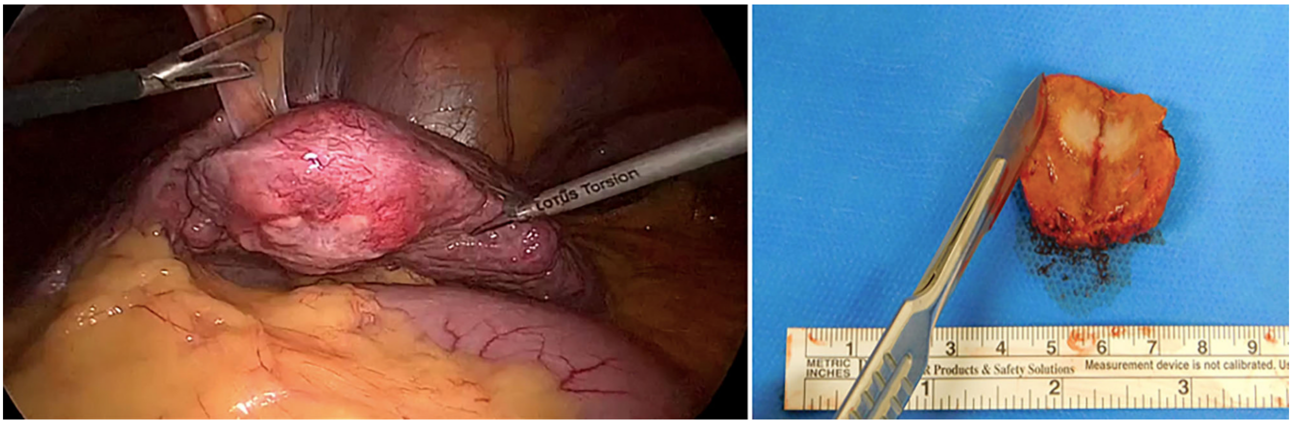

Fig. 1 Laparoscopic resection of colorectal hepatic metastases

higher in the sPhx group compared to mPhx (sPhx vs. mPhx: 2.4 ± 0.0 vs. 2.2 ± 0.1, $p = 0.011$). Tumor stage UICC IV at diagnosis was more frequent in the mPhx group (sPhx vs. mPhx: 43.2% vs. 59.5%, $p = 0.022$). There was no significant difference comparing these variables between the groups 2Phx and > 2Phx.

Characteristics of liver metastases at the time of index hepatectomy, type of first liver resection, and the macroscopic illustration of the tumors are demonstrated in Table 2 and Fig. 1. Although the interval between resection of the primary tumor and the first partial liver resection differed nonsignificantly, it is remarkable that patients out of the sPhx group underwent surgery on average 4 months later than patients out of the mPhx group. The time between surgery for primary cancer and the first Phx was on average 6.5 months earlier in the group with > 2Phx compared to the 2Phx group.

Synchronous liver metastases were diagnosed in 54.5% and 41.7% of patients in the mPhx and sPhx group, respectively ($p = 0.053$). Comparison of the two subgroups showed no significant difference in the incidence of synchronous liver metastases (> 2Phx vs. 2Phx: 60.9% vs. 51.8%, $p = 0.620$). The number of metastases and the presence of bilobular liver metastases differed nonsignificantly between the groups. Patients of the sPhx group underwent a segmentectomy significantly more frequently (sPhx vs. mPhx: 19.7% vs. 8.9%; $p = 0.026$), whereas atypical multiple partial liver resection was significantly more common in the mPhx group (sPhx vs. mPhx: 25.5% vs. 40.5%, $p = 0.016$).

Operating time was similar between the groups. The average amount of blood loss, the maximum diameter of tumor lesion, and the average weight of the resected liver tissue were not significantly different between the four groups.

Perioperative and long-term outcomes were comparable between the groups (Table 3). Specifically, patients in the sPhx and mPhx group spent 2 days on average in the intensive care unit and were hospitalized for 12 days. Moreover, comparison of the postoperative complications showed no significant differences between the groups (sPhx vs. mPhx: 26.3% vs. 24.1%, $p = 0.770$; 2Phx vs. > 2Phx: 17.9% vs. 39.1%, $p = 0.079$). Surgical or interventional revision was necessary in 22 cases (8.5%) in the sPhx group and in 5 cases (6.3%) in the mPhx group. Patients out of the 2Phx group required surgical revision in 5 cases (8.9%), whereas there was no necessity for revision in

Table 3 Perioperative and long-term outcomes

	sPhx ($n = 259$)	mPhx ($n = 79$)	*p*-value	2Phx ($n = 56$)	> 2Phx ($n = 23$)	*p*-value
ICU stay (days)	2.4 ± 0.3	2.0 ± 0.3	0.593	2.2 ± 0.4	1.5 ± 0.2	0.519
Hospital stay (days)	12.4 ± 0.6	11.5 ± 1.1	0.614	12.0 ± 1.5	10.2 ± 0.7	0.737
Complications (no. of patients)	63 (26.3%)	19 (24.1%)	0.770	10 (17.9%)	9 (39.1%)	0.079
Surgical complications	31 (12.0%)	6 (7.6%)	0.312	4 (7.1%)	2 (8.7%)	1.000
Other complications	43 (16.6%)	14 (17.7%)	0.864	8 (14.3%)	6 (26.1%)	0.330
Need for surgical or interventional revision	22 (8.5%)	5 (6.3%)	0.641	5 (8.9%)	0 (0.0%)	0.314
30-day mortality	6 (2.3%)	0 (0.0%)	0.342	0 (0.0%)	0 (0.0%)	–
Median survival (months)	25.1 (25.5–38.6)	44.7 (44.6–58.7)	0.072	40.3 (38.9–55.4)	66.6 (49.3–76.1)	0.148
Median recurrence-free survival (months)	10.0 (9.1–13.6)	13.5 (10.6–16.4)	0.147	12.0 (11.4–19.4)	9.0 (7.2–11.0)	0.046*

Values are indicated as absolute frequency and percentages or as mean value ± standard error of mean
Phx partial hepatectomy, *sPhx* single partial hepatectomy, *mPhx* multiple partial hepatectomy, *2Phx* 2 partial hepatectomies, *> 2Phx* more than 2 partial hepatectomies, *ICU* intensive care unit
*Statistically significant *p*-value

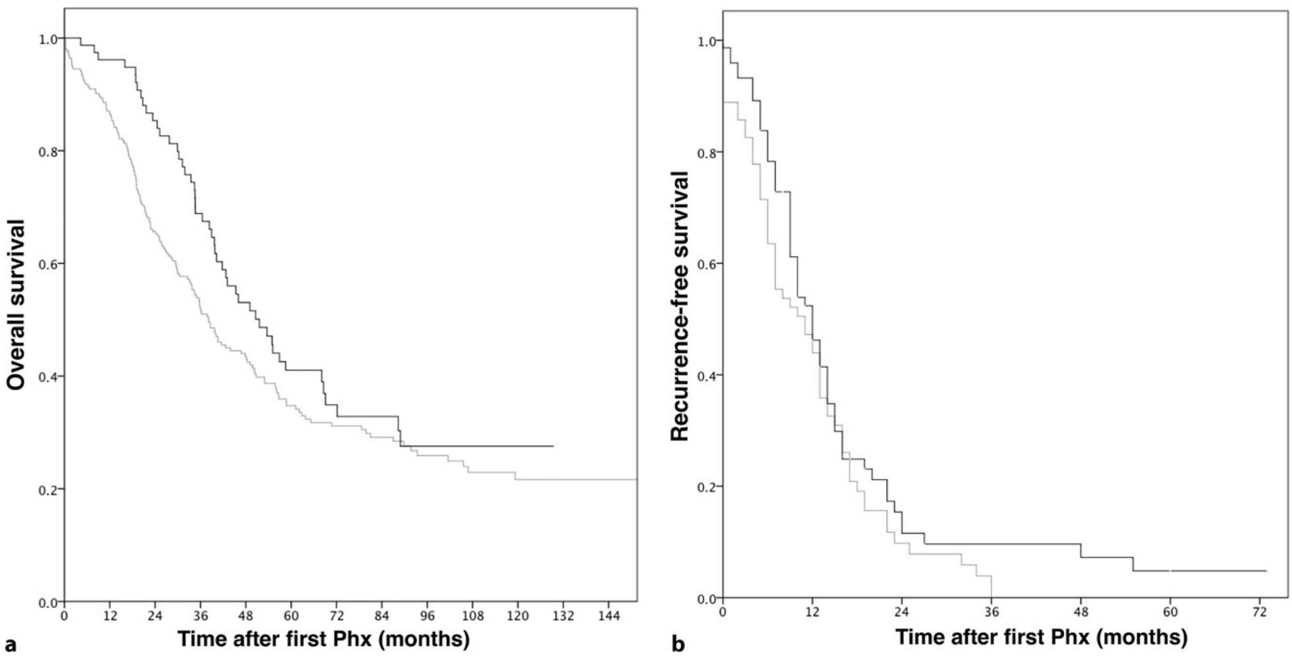

Fig. 2 Kaplan–Meier curves. Median overall survival after the first Phx (**a**) and recurrence-free survival (**b**) for the sPhx (*grey*) and mPhx (*black*) groups. *Phx* partial hepatectomy, *sPhx* single partial hepatectomy, *mPhx* multiple partial hepatectomy

the >2Phx group. Six patients (2.3%) in the sPhx group and none of the other groups died within 30 days after surgery.

Fig. 2 shows the Kaplan–Meier curves for overall survival and recurrence-free survival for the sPhx and mPhx groups. Median survival and median recurrence-free survival was 25.1 (25.5–38.6) and 10.0 (9.1–13.6) months in the sPhx group, respectively. Patients in the mPhx group survived longer; however, the level of significance was not reached (mPhx vs. sPhx: 44.7 vs. 25.1 months, $p = 0.072$). The median recurrence-free survival in the mPhx group was 13.5 (9.6–16.4) months and statistically comparable to the sPhx group. Patients out of the >2Phx group showed the longest overall survival (66.6 [49.3–76.1] months) and the shortest recurrence-free survival (9.0 [7.2–11.0] months). Overall and recurrence-free survival were 40.3 (38.9–55.4) and 12.0 (11.4–19.4) months in the 2Phx group, respectively (Table 3).

Table 4 Cox regression analysis of survival after index hepatectomy for the sPhx and mPhx groups

	sPhx (*n* = 259)				mPhx (*n* = 79)			
	Univariate analysis	Multivariate analysis			Univariate analysis	Multivariate analysis		
Factors	*p-value*	HR	95% CI	*p*-value	*p-value*	HR	95% CI	*p*-value
Gender	0.217	–	–	–	0.077	1.423	0.704–2.876	0.326
Age at first Phx > 70 years	0.100	1.324	0.941–1.862	0.107	0.031*	1.335	0.631–2.825	0.450
Primary rectal cancer	0.048*	1.406	1.029–1.920	0.032*	0.218	–	–	–
T4	0.649	–	–	–	0.507	–	–	–
Positive lymph nodes	0.227	–	–	–	0.558	–	–	–
CTx at primary tumor	0.247	–	–	–	0.109	1.485	0.874–2.525	0.144
Metachronous liver metastases	0.040*	0.737	0.540–1.008	0.056	0.299	–	–	–
Single liver metastases	0.950	–	–	–	0.095	0.767	0.325–1.807	0.544
Bilobular liver metastases	0.812	–	–	–	0.182	1.274	0.626–2.591	0.505
Type of resection	0.529	–	–	–	0.927	–	–	–
Non-anatomical multiple Phx	0.205	–	–	–	0.133	1.075	0.561–2.059	0.827
Segmentectomy only	0.906	–	–	–	0.542	–	–	–
Overall complications	0.244	–	–	–	0.005*	0.508	0.149–1.735	0.280
Surgical complications	0.027*	1.637	1.074–2.496	0.022*	0.702	–	–	–
Non-surgical complications	0.882	–	–	–	0.016*	0.670	0.149–3.007	0.601

Factors predicting survival were identified in univariate analysis and tested in a multivariate Cox regression model
CI confidence interval, *HR* hazard ratio, *sPhx* single partial hepatectomy, *mPhx* multiple partial hepatectomy, *Phx* partial hepatectomy, *CTx* chemoradiotherapy
*Statistically significant *p*-value

Factors influencing survival are shown in Table 4. Patients out of the sPhx group survived significantly longer in case of primary rectal cancer as indicated by uni- and multivariate analysis. In addition, surgical complications had a statistically significant impact on survival. Metachronous appearance of liver metastases seems to "positively" influence survival, since it was statistically associated with increased survival in univariate analysis ($p = 0.04$) but not in multivariate analysis ($p = 0.056$).

With respect to the patients with mPhx, factors such as age >70 years at the time of index hepatectomy and overall or non-surgical complications had an impact on survival in the univariate analysis. Using multivariate analysis, no factor was observed to predict survival in a statistically significant manner.

Discussion

Despite improvements in the treatment of colorectal liver metastases in recent decades, recurrence can be observed in up to 80% of cases after hepatectomy [5, 6, 14]. In 40% of patients, recurrence is isolated in the liver [15]. In case of potentially resectable disease, it is broadly accepted that repeated hepatectomy can be offered as a treatment option [16, 17]. Using multiple redo resections of liver-limited tumor recurrences, survival rates may match those of recurrence-free patients [18]. In recent studies, prolonged overall survival rates were reported in the repeated hepatectomy group compared to the sPhx group [5, 8, 10, 11, 17, 19]. This is explained by the fact that within the mostly retrospective studies, some of the patients with recurrences underwent a repeated resection that improved their prognosis, whereas patients with unresectable recurrences were assigned to the sPhx group. In some studies, long-term survival of patients undergoing repeated hepatectomy was compared with the entire cohort of patients who underwent index hepatectomy, including those patients with repeated resection for hepatic recurrence [5]. In other studies, the redo hepatectomy group was compared with patients who only underwent the index hepatectomy and did not undergo repeated resections [8, 10, 11, 19]. Furthermore, the favorable outcomes in terms of survival rates after salvage resection of recurrent disease could be attributed to the extreme selection bias. We conducted this retrospective study to evaluate survival rates following repeated hepatectomy for recurrent hepatic metastases and to identify prognostic factors that are associated with a repeated resection pattern of treatment.

In our analysis, median overall survival and recurrence-free survival were comparable in the sPhx and mPhx groups. Studies that evaluated survival rates after repeated hepatectomy for colorectal liver metastases are shown in Table 5; [10, 20–22]. A retrospective study with 488 patients reported 5-year overall survival rates of 48.4% and 26.2% in repeated and index resection groups, respectively. In accordance with those results, Kulik et al. reported in a retrospective study with a total of 1026 patients that repeated hepatectomy is associated with better median survival compared to single resection [8]. However, it was mentioned that no difference was found in median survival after the index operation and the last hepatectomy.

Yamazaki et al. included patients with similar tumor stage, number of lesions, and tumor size. They concluded that median overall survival was similar between the groups with one, two, and three hepatic resections [9]. On the contrary, Matsuoka et al. reported a significantly longer median survival time after single resection compared to multiple hepatectomies, with 83.2 and 35.3–42.9 months, respectively [7].

A meta-analysis reported similar rates of overall survival between patients who underwent only single resection and those who underwent redo hepatectomy [23]. However, it was mentioned that when the analysis included only high-quality studies or studies with more than 500 patients, a significant benefit in overall survival was detected in favor of repeated hepatectomy.

The question regarding prognostic factors that are associated with resectable recurrences is highly interesting. The following factors are suggested to be prognostically favorable after redo liver resection in the majority of studies: R0 resection, a long recurrence-free interval between the first and second liver resection, unilobular metastases, singular metastases, maximum diameter <5 cm, no extrahepatic metastases, and a non-advanced UICC stage of primary tumor [8, 9, 15, 18, 23, 24]. The R0 resection rate is influenced by the surgeon's experience and skills, while the other prognostic factors, such as long recurrence-free survival, unilobular recurrence, singular and small metastases, and the absence of extrahepatic recurrences, are at least in part tumor specific and indicative of a low tendency to metastasize and/or slower growth rate, which are associated with a better outcome.

The aim of this study was to identify specific prognostic factors that allow repeated partial liver resections. Patient-specific data in Table 1 show that neither gender nor body weight exerts an influence on the probability of repeated hepatectomy. On the other hand, there are significant differences concerning the age, ASA score, and UICC stage at first resection. Younger and healthier patients as well as patients with advanced UICC stage IV more frequently undergo redo hepatectomy. Furthermore, there is a trend towards multiple liver resections in patients with primary rectal cancer. In contrast, patients with primary T4 stage cancer at diagnosis undergo redo resections less often.

In general, the treatment strategy should be determined in an interdisciplinary tumor board. The decision for a more radical procedure with repeated re-

Table 5 Studies reporting results after repeat liver resections

Study	No. of Phx	No. of patients	Median survival (months)	3-year survival (%)	5-year survival (%)
Adam et al. (2003) [20]	sPhx	615	37	61	41
	2Phx	199	32	54	35
	3Phx	60	31	42	27
Shaw et al. (2006) [10]	sPhx	718	38	52	30
	mPhx	66	56	68	44
De Jong et al. (2009) [21]	sPhx	246	51	70	47
	2Phx	246	42	–	33
	3Phx	46	41	–	24
	4Phx	9	19	–	–
Andreou et al. (2011) [24]	mPhx	43	–	82	73
	2Phx	38	–	–	–
	3Phx	5	–	–	–
Yamazaki et al. (2013) [9]	sPhx	137	–	57.5	41.6
	2Phx	37	–	52.1	35.7
	3Phx	22	–	49	34.1
Kulik et al. (2013) [8]	sPhx	932	61.1	–	–
	mPhx	94	47.9	–	–
Battula et al. (2013) [15]	sPhx	916	–	58	43
	mPhx	53	45	61	52
Wicherts et al. (2013) [11]	sPhx	645	47	58	45
	2Phx	225	44	58	41
	3Phx	52	52	56	45
	4Phx	11	–	–	–
Lee et al. (2015) [22]	sPhx	406	–	59	43
	mPhx	55	–	63	53
Neal et al. (2017) [5]	sPhx	417	30.3	48	30.1
	mPhx	71	58.9	81.7	48.4
Matsuoka et al. (2019) [7]	sPhx	177	83.2	–	52.3
	mPhx	59	35.3–42.9	–	–
Present study	sPhx	256	38	50	30
	mPhx	78	52	80	40

Phx partial hepatectomy, *sPhx* single partial hepatectomy, *2-, 3-, 4Phx* two, three, four partial hepatectomies, *mPhx* multiple partial hepatectomies

section in case of isolated hepatic recurrences seems to be made more easily in young and healthy patients. Elderly patients and patients with comorbidities seem to be treated more often less invasively, with chemotherapy, local radiation therapy, or ablation. In this study, the mean age of patients who underwent single or multiple partial liver resections was 64.5 and 61.2 years, respectively. Life expectancy varies between 75.8 and 81.2 years for German men and between 81.8 and 85.7 years for German women [25], whereas a 75-year-old man has a mortality risk of approximately 40% (Federal Statistical Office, Germany). In an Australian study with 29 patients older than 75 years, Gandy et al. showed a 5-year survival rate of 58% after resection of colorectal liver metastases [26]. In 1997, Fong et al. concluded that colorectal liver metastases are resectable in elderly patients over 65 years [27]. In contrast, recent studies classify elderly patients from the age of 70 years onward [28, 29].

Repeated liver resection should be taken into consideration in case of high ASA score or the presence of comorbidities. There is a lack of evidence concerning the influence of comorbidities such as severe cardiovascular and pulmonary diseases, diabetes, or renal insufficiency on postoperative outcomes following repeated liver resection. Available data suggest that redo hepatectomy in obese patients and diabetics is associated with increased perioperative mortality and morbidity. Nevertheless, good long-time outcomes can also be achieved in this group of patients [30].

Patients who underwent multiple liver resections showed a shorter interval between primary cancer treatment and the first Phx. More synchronous liver metastases occurred in these patients. There was no difference between the mPhx and the sPhx group concerning the occurrence of multiple and bilobular liver metastases. This demonstrates that early metastasis leads tendentially more often to repeated liver resections in contrast to bilobular and multiple metastases. However, the presence of bilobular or multiple hepatic lesions at first Phx is not an exclusion criterion for repeated liver resections. Patients with >2Phx experienced the highest median survival with 66.6 months, although they had the shortest recurrence-free survival.

In our study, the rate of adjuvant chemotherapy or radiation of the primary tumor was similar between the groups. Lee et al. reported similar rates of adjuvant chemotherapy in patients treated with sPhx and those with mPhx [22]. In a retrospective study with 488 participants, neoadjuvant treatment was administrated in 43% of the patients in the index hepatectomy group and in 51% of the patients with a second hepatectomy [5]. Similarly, 41% and 48% of the patients received adjuvant treatment in each group. Neither treatment was associated with any difference in the survival rates of the patients compared to those who did not receive chemotherapy. According to the guidelines of the Japanese Society of Hepato-Biliary-Pancreatic Surgery, adjuvant chemotherapy is weakly recommended in patients with resectable colorectal metastases [31]. The ESMO guidelines recommend neoadjuvant and adjuvant chemotherapy in patients with an unfavorable prognosis, marginal resectable tumors, or synchronous onset of the metastases. In patients with favorable oncological and surgical criteria, there is no strong evidence to support the use of chemotherapy [32].

According to our study, repeated hepatectomy with complete resection of metastases should be considered as a treatment option in patients with recurrent disease. Tissue-saving redo hepatectomies should be preferred whenever possible, achieving voluminous anatomical resections and R0 surgical margins with maximum preservation of crucial anatomic structures. Repeated hepatectomy is associated with beneficial outcomes in terms of median overall survival and perioperative morbidity in patients with recurrence of colorectal hepatic metastases.

Author Contribution M. von Heesen and J. Schuld conceived of the presented idea and developed the study protocol. S. Holländer, A.E. Spiliotis, and A. Merscher conducted the retrospective analysis and verified the analytical methods. P.R. Scherber, D. Igna, G. Gäbelein, and M. Glanemann supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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Conflict of interest M. von Heesen, J. Schuld, S. Holländer, A.E. Spiliotis, A. Merscher, P.R. Scherber, D. Igna, G. Gäbelein, and M. Glanemann declare that they have no competing interests.

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