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ORIGINAL ARTICLE

Parenchyma-preserving hepatic resection for colorectal liver metastases

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Abstract

Background Hepatic resection of colorectal liver metastases is the only curative treatment option. As clinical and experimental data indicate that the extent of liver resection correlates with growth of residual metastases, the present study analyzes the potential benefit of a parenchyma-preserving liver surgery approach.

Methods Data from a prospectively maintained database of patients undergoing liver resection for colorectal metastases were reviewed. Evaluation of outcome was performed using the Kaplan–Meier method. Correlations were calculated between clinical–pathological variables.

Results One hundred sixty-three patients underwent 198 liver resections for colorectal metastases: 26 major hepatectomies, 65 minor anatomical resections, 78 non-anatomical resections, as well as 29 combinations of minor anatomical and non-anatomical procedures. Overall 1-, 3-, and 5-year survival was 93%, 62%, and 40%, respectively. Patients with repeated liver resections had a 5-year survival of 27%. Interestingly, large dissection areas were associated with a significant reduction of the 5-year survival rate (33%). Five-year survival after major hepatectomy was not significantly reduced.

Conclusion For colorectal liver metastases, minor resections offer a prolonged survival compared to major hepatectomies. As patients with stage IV colorectal disease are candidates for repeat resections, preservation of hepatic parenchyma is of increasing importance in the setting of multi-modal and repeated therapy approaches.

Keywords Colorectal cancer · Metastasis · Liver resection · Hepatectomy

Introduction

Colorectal cancer is the third leading cause of cancer-related mortality in the USA [1]. Death of these patients usually results from uncontrolled metastatic disease. The liver is the most common site of metastasis for colorectal cancer with poor prognosis associated with a median survival of 6–12 months in untreated cases [2–4]. As shown in the last years, surgical resection is the only curative treatment option with an overall 5-year survival rate of approximately 40% [5–11]. Modern surgical strategies from major hepatobiliary centers have demonstrated that hepatectomy of as much as 70% of the liver can be performed with a mortality rate of less than 5% [12–15].

Although it is well recognized that the liver regenerates completely after major hepatectomy, the effect of hepatic regeneration on intra- and extrahepatic tumor growth is still controversially discussed. Experimental studies demonstrate enhanced growth of colorectal liver metastasis after both minor (30%) and major (60–70%) hepatectomy [16–20]. Furthermore, Rupertus et al. showed in a standardized model that growth of extrahepatic tumors correlates with the extent of liver resection due to enhancement of neovascularization and tumor cell migration [21]. These studies conclude that in experimental models, the magnitude of tumor stimulation of tumor growth is thought to be proportional to the volume of the resected liver tissue, whereas the cause for enhanced

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tumor growth in the regenerating liver is likely multifactorial [19, 20].

In contrast to older clinical trials recommending a standard right or left hemihepatectomy for the treatment of colorectal liver metastases [5–7], numerous different surgical approaches to hepatectomy have been developed, allowing a resection appropriate to the pathology being treated with the aim of leaving maximal residual functional liver parenchyma [22, 23]. In this context, several studies analyzed the impact of the resected liver volume on survival of patients with colorectal liver metastases leading to the conclusion that patient survival correlates negatively with the extent of liver resection [8–11, 22–24]. Therefore, parenchyma-preserving resection has been introduced as standard for patients with colorectal liver metastases at our center since March 2001. The aim of this study was to analyze the potential benefit of a low hemihepatectomy rate of less than 15% in the context of the new multi-modal therapy concepts for colorectal cancer stage IV.

Patients and methods

Data from all patients undergoing colorectal surgery and liver resection at our hepatobiliary center were prospectively entered in an ISH-Med (GSD, Berlin, Germany) database running on a SAP platform (SAP, St. Leon-Roth, Germany). For this study, patients undergoing liver resections for colorectal metastases during a 6-year period until December 2006 were reviewed. In all patients, resection of the primary colorectal cancer was categorized as formally curative defined by removal of all macroscopically detectable disease and microscopically clear resection margins. Colorectal operations were performed in combination with or without chemotherapy and radiotherapy using neoadjuvant and adjuvant protocols. Overall survival data for patients with colorectal cancer stage IV according to the international union against colorectal cancer (UICC) were obtained from the Saarland Cancer Registry [25].

All patients received intravenous antibiotic prophylaxis before surgery. The operative procedure selected to ensure adequate oncological resection margins and leave a maximal volume of hepatic parenchyma was based on the result of preoperative diagnostics, findings after laparotomy, and intra-operative ultrasound. The criteria for non-resectability were infiltration of all three liver veins, diffuse liver metastases, and non-resectable extrahepatic tumor manifestations. Partial hepatectomy (Phx) was performed as anatomical resection according to Couinaud, non-anatomical or wedge resection, and combination of anatomical and non-anatomical resections with or without “Pringle” maneuver, selective vascular clamping, or selective vascular occlusion. Major hepatectomy was defined as resection of three or more anatomical liver segments [15]. Tissue destruction within the parenchymal dissection line was usually created by ultrasonic dissection, and the resection margins of the remnant liver were coagulated by argon plasma beamer. Cholecystectomy was performed in all cases if the gallbladder was still in situ. If necessary, resection of extrahepatic manifestations was performed in all included cases. Lymph node dissection of the hepatoduodenal ligament/retropancreatic area (area 1) and along the common hepatic artery/celiac axis (area 2) was only performed if increased size and firmness of the lymph nodes as well as preoperative radiologic imaging were suspicious for malignant infiltration. Para-aortic lymph nodes (area 3) were not dissected.

Data were recorded prospectively in our database system including all demographic details, disease-related data, medical data, and data from the perioperative and postoperative course. Recurrence and follow-up information of the patients were determined from the medical records or were assessed retrospectively.

Statistical analysis

Data are expressed as absolute numbers or mean ± standard error of the mean (SEM) unless indicated otherwise. The length of follow-up was calculated from the date of liver resection at our institution. Comparisons of categorical and continuous variables were performed using the χ^2 test (Fisher's exact test) and the Wilcoxon rank–sum test as applicable. Differences between more than two groups were calculated by ANOVA, followed by the recommended post hoc test. To clarify and structure our data, patients with pretreatment of liver metastases before liver surgery in our center and loss of follow-up were excluded from univariate and survival analyses. Survival analyses were estimated according to the Kaplan–Meier method and compared with the log–rank test using the software package SPSS 14.0® (SPSS GmbH Software, Munich, Germany). Patients who died from unknown disease were also counted as an “event” in the Kaplan–Meier analysis as well as other patients who died from tumor recurrence. Correlations were calculated between clinical–pathological variables and the endpoints of overall survival after primary colorectal cancer operation, survival after first liver resection, recurrence-free survival, and liver recurrence-free survival. The p values of <0.05 were considered significant.

Results

Between March 2001 and December 2006, 163 patients underwent 198 liver resections for colorectal liver metastases. These 198 resections accounted for 40% of a total of 498 curative hepatic resections for benign and malign liver diseases over the same 6-year time period within our center. With respect to demographic data (Table 1), there were 102 male (62.6%) and 61 female (37.4%) patients with a mean ± SEM [range] age of 62.9±0.8 years [range, 27–84] at the time of liver surgery. Previous abdominal operations other than for primary colorectal cancer were performed in 23.3% of the patients. Regarding the primary tumor (Table 2), 46% of the patients suffered from rectal cancer and 54% from colon cancer. A pT4 stage determined according to the UICC was diagnosed in 19 patients (11.7%), and positive lymph nodes were detectable in 65.6% of the resected specimens. Synchronous liver metastases, defined as liver metastases occurring within 6 months after diagnosis of the colorectal primary tumor, were evident in 42.9% of the patients. Twenty-two patients had already previous treatment of liver metastases (Table 2). Bilobular liver metastases were treated in 30.1% of the patients. Multiple different chemotherapeutic protocols were applied in 104 patients as an adjuvant regime for the primary colorectal cancer (Table 2). Thirty-four patients received neoadjuvant chemotherapy for their liver metastases before resection, including patients with a neoadjuvant protocol for their primary tumor. Furthermore, a total of 95 patients had neoadjuvant or adjuvant chemotherapy related to the liver resection procedure (Table 2).

The surgical procedures performed are listed in Tables 3 and 4. Twenty-six major hepatectomies with three or more liver segments (13.1%), 65 minor anatomical resections, 78 non-anatomical resections, and 29 combinations of minor anatomical and non-anatomical procedures were performed. Twenty-six out of the 163 patients underwent repeat liver resection procedures (61 procedures overall). Additional surgical procedures were performed in 48 out of 198 liver resection procedures. Simultaneous resection of the primary

Table 1 Demographics and characteristics (n=163) of patients undergoing liver resection for colorectal metastases at the time of the first procedure

Parameters	Mean ± SEM or n
Gender (female/male)	61/102
ASA score	2.4±0.1
Body mass index (BMI, kg/cm²)	26.4±0.3
Age (years)	62.9±0.89
Age >70 years	35 (21.5%)
Hepatitis (B/C)	3/2 (1.8/1.2%)
Diabetes	19 (11.7%)
Chronic kidney disease	5 (3.1%)
Chronic heart disease	24 (14.7%)
Chronic pulmonary disease	9 (5.5%)
Hypertension	62 (38.0%)
Previous abdominal operation	38 (23.3%)

Table 2 Histological classification of the primary tumor as well as characteristics and pretreatment of colorectal liver metastases of 163 patients undergoing liver resection at the time of the first procedure

Parameters	Mean ± SEM or n
Primary rectum/colon cancer	75/88
pT stage of the primary	2.9±0.1
pT4 stage of the primary	19 (11.7%)
pN + stage of the primary	107 (65.6%)
Grading	2.2±0.0
Synchronous liver metastases (M1 liver)	70 (42.9%)
Previous treatment of liver metastases (n=22 patients)	28
• Liver resection (n=12 patients)	19
• Cryotherapy (n=6 patients)	6
• Radiofrequency ablation (n=4 patients)	4
• Previous resection of primary colorectal cancer synchronous with liver resection procedure	6
Adjuvant chemotherapy for the primary tumor	104 (63.8%)
Chemotherapy before liver resection	34 (20.9%)
Chemotherapy before and/or after liver resection	95 (58.3%)
Time (months) between surgery for colorectal cancer and first liver resection [range]	21.2±1.9 [0–136.3]
Bilobular liver metastases	49 (30.1%)
CEA before liver resection [range]	276.0±207.1 [1–13609]
CA-19-9 before liver resection [range]	752.4±623.1 [1–39928]

Table 3 Operative technique of liver resections for colorectal liver metastases in all cases (n=198) and at the time of the first procedure (n=134)

Parameters	n=198
Anatomical resection of ≥3 segments	26 (13.1%)
• Right hemihepatectomy	17
• Left hemihepatectomy	0
• Extended right resection	7
• Extended left resection	1
• Resection of segment II+III and VI+VII	1
Segmentectomy	35 (17.7%)
Bisegmentectomy	30 (15.2%)
Combination of anatomical and non-anatomical resections	29 (14.6%)
Non-anatomical resections only	78 (39.4%)
Number of non-anatomical resections [range]	1.2±0.1 [1–6]
Repeat liver resection procedures (patients)	26
Pringle's maneuver	24
Selective vascular ligation before dissection	62
Selective vascular clamping before dissection	45

Repeated procedures (n=61) were performed in 26 out of 163 patients ranging from two to four procedures per patient

Table 4 Additional surgical procedures during liver resections for colorectal liver metastases (n=48 of 198 operations)

Parameters	n=198
Resection of primary colorectal cancer (colectomy, n=1; rectum resection, n=11; right hemicolectomy, n=6; left hemicolectomy, n=1)	19 (9.5%)
Resection of intra-abdominal extrahepatic diseases other than of the primary tumor	7 (3.5%)
Hepatoduodenal lymph node dissection	19 (9.6%)
Cryosurgery of liver metastases	4 (2%)
Cryosurgery of the resection margin	6 (3%)
Radiofrequency of liver metastases	5 (2.5%)
Bile duct reconstruction	1 (0.5%)
Portal vein reconstruction	1 (0.5%)
Reconstruction of the inferior vena cava	4 (2%)
Partial diaphragm resection	6 (3%)
Abdominal wall resection	1 (0.5%)
Hepatic arterial infusion pump placement	1 (0.5%)

colorectal cancer together with the liver metastases was performed in 19 (9.6%) patients (Table 4).

The operative and perioperative data are shown in Tables 5 and 6. Operative time was 199.3±5.2 minutes [range, 40–491]. Mean blood loss was 694±65 ml. The maximum diameter of the resection area was 9.3±0.4 cm [range, 2–29]. The mortality rate of the 198 procedures was 2%. Two patients died after extended liver resection due to liver insufficiency and further two patients of multi-organ failure (Table 6). The overall rate of major and minor postoperative complication was low in all 198 liver resection procedures. Twenty-nine patients developed pleural effusion requiring interventional drainage.

Table 5 Operative parameters of 198 liver resections in 163 patients

Parameters	Mean±SEM or n
Central venous pressure before liver resection (mmHg)	4.8±0.2
Operative time (min)	199.3±5.2
Resection time (min)	41.8±2.6
Dissection devices	
•Ultrasonic dissection	91
•Waterjet dissection	31
•Monopolar electricity only	35
•Inline radiofrequency/stapler/others	41
Blood loss (ml)	694±65
Blood loss during liver resection procedure (ml)	558±88
Maximum diameter of the resection area (cm)	9.28±0.37 [2.0–29.0]
Red blood cell transfusion (units)	0.69±0.16 [0–20]
Fresh frozen plasma transfusion (units)	0.63±0.14 [0–12]
Thrombocyte transfusion (units)	0.01±0.01 [0–1]

Table 6 Length of hospital stay as well as morbidity and mortality of 163 patients undergoing 198 liver resections for colorectal metastases

Parameters	Mean±SEM or n
Hospital stay (days)	11.2±0.4
ICU stay (days)	2.6±0.4
Ventilation on ICU for >6 h postoperatively (patients)	22
Mortality	4 (2.0%)
Multi-organ failure	2 (1.0%)
Liver insufficiency	4 (2.0%)
Bleeding requiring reoperation	5 (2.5%)
Bile leakage requiring reoperation	3 (1.5%)
Anastomotic leakage requiring reoperation and protective stoma	2 (2.0%)
Liver abscess	3 (1.5%)
Pleural effusion requiring interventional drainage	29 (14.7%)
Other medical-related complications (heart, lung, kidney)	20 (10.1%)

Comparing the type of liver resection, univariate analysis showed that non-anatomical resections as well as combined resections were significantly (p<0.001) used more often in patients with bilobular metastases than anatomical resections, accompanied with a significant higher incidence of a positive resection margin (p=0.015). Comparing anatomical and combined resections with non-anatomic resections, non-anatomic resection was associated with significant shorter operation time (p=0.006), lower blood loss (p<0.001), and lower number of red blood cell transfusions (p<0.001). Anatomical resections had a significant higher incidence of pleural effusions requiring interventional drainage than non-anatomic and combined resection (p=0.027). Univariate analysis of patients with a major hepatectomy versus minor resections showed that CEA levels >100 ng/ml were significantly (p=0.025) higher in patients with extended resections. Major resections required significant more red blood cell transfusions (p=0.017) due to a higher blood loss (p=0.003) and were accompanied by a higher incidence of interventional pleural drainages (p=0.005) compared to minor resections. Patients undergoing repeated liver resections had significantly (p=0.005) more rectal than colon cancer and significantly more synchronous (p=0.021) as well as bilobular metastases (p=0.015) compared to patients with single liver resection procedure only. Comparing the time interval between diagnosis of the primary cancer and occurrence of the liver metastases (≤6 vs. >6 months or ≤12 vs. >12 months, respectively), no significant differences could be found using univariate analysis.

For survival analyses, all patients with pretreatment of liver metastases before liver surgery (n=22) and loss of follow-up (n=7) were excluded. Out of these 134 patients, the mean follow-up interval was 31.7±1.6 months. The overall 5-year survival rate for the entire cohort was 61% after operation of the primary colorectal cancer tumor and 40% after the first liver resection procedure, with an overall recurrence-free survival rate of 30% and a liver-related recurrence-free survival rate of 58% (Fig. 1). For subgroup analyses, already known predictors of poor long-term outcome were analyzed [6, 9, 13, 15]. Morphological predictors and factors related to the primary tumor are presented in Table 7. Patients with liver metastases from colon cancer had a significantly longer overall survival after resection of the primary tumor ($p=0.048$) and a longer overall recurrence-free survival ($p=0.030$) than patients with rectal cancer. Patients with a pT4 and a nodal positive stage of their primary tumor had a shorter survival rate after resection of the primary tumor as well as after liver resection, but these data were not statistically significant. The temporal relationship (Table 7) between diagnosis of the primary tumor and occurrence of the liver metastases (synchronous vs. metachronous and <12 vs. >12 months, respectively) was found as a significant predictor for the overall survival after operation of the primary tumor ($p<0.001$ and $p<0.001$, respectively) and the recurrence-free survival ($p=0.011$ and $p=0.005$, respectively) as well as the liver-related recurrence-free survival ($p<0.001$, $p<0.001$). The hepatic distribution of metastases (Table 7) showed that patients with unilobular metastases had a higher survival rate than patients with bilobular metastases, however, without statistical significance. Size (≤5 vs. >5 cm) and number of liver metastases (≤3 vs. >3) had no influence on the survival rates of the patients (Table 7).

Additionally, possible predictors of poor long-term outcome related to surgical techniques for the resection of liver tumors were analyzed (Table 8). Comparing the type of liver resection for the first procedure, patients undergoing non-anatomical resections had a longer survival after liver resection compared to anatomical or combined procedures, without showing statistical significance (Fig. 2, Table 8). If

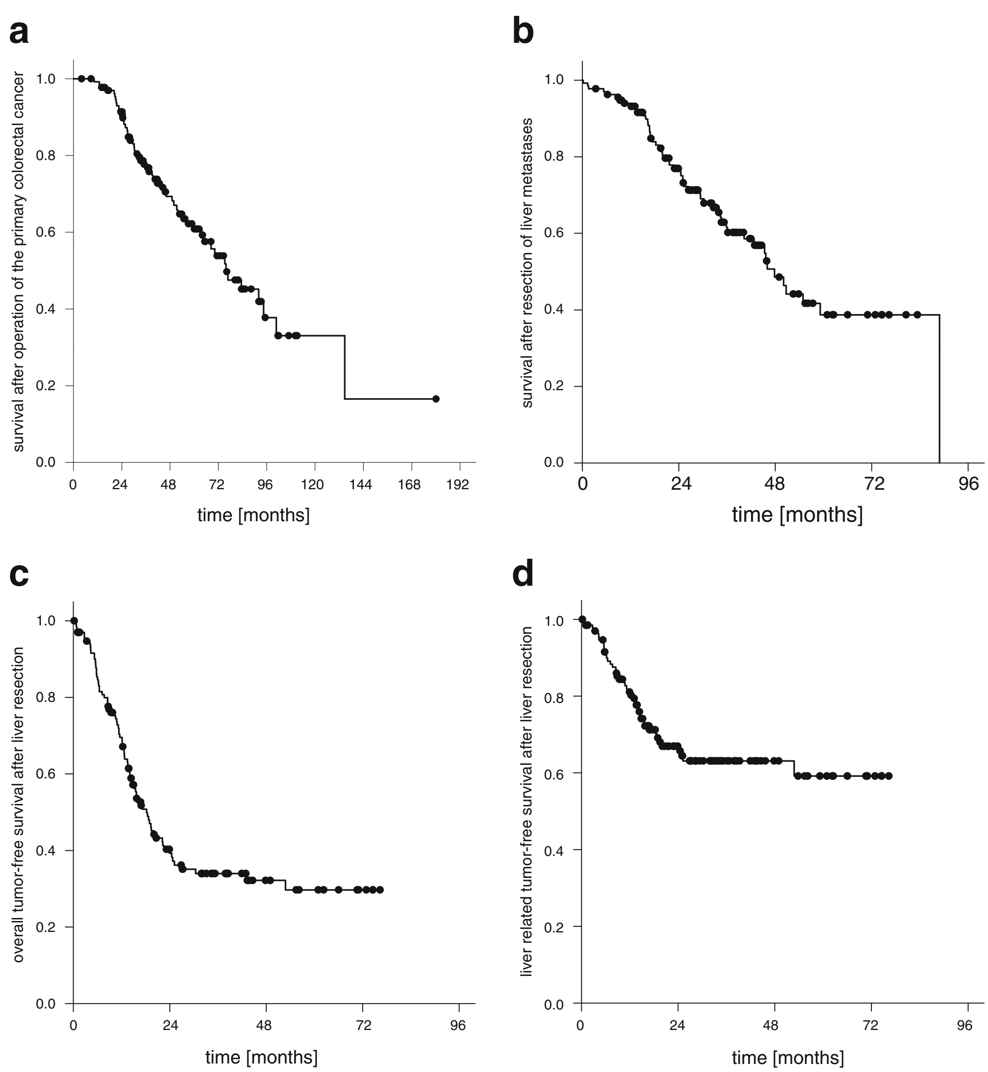

Fig. 1 Patients' ($n=134$) overall survival after operation of the primary colorectal tumor (**a**) and after the first resection procedure of liver metastases (**b**). Overall tumor-free survival (**c**); liver-related tumor-free survival after liver resection (**d**)

Table 7 Survival analyses of 134 patients with hepatic colorectal cancer metastases undergoing liver resection related to variables of the primary tumor and their liver metastases

Variable	Number	Survival after primary CRC operation			Survival after Phx			Recurrence-free survival			Liver recurrence-free survival		
		1 year	3 years	5 years	1 year	3 years	5 years	1 year	3 years	5 years	1 year	3 years	5 years
Overall	134	99	77	61	93	62	40	70	34	30	81	62	58
Primary tumor site													
Colon	72	99	84	70*	94	68	41	74	43	36*	82	71	65
Rectum	62	100	67	48	92	55	43	65	22	22	80	51	51
pT4 stage of the primary tumor													
Yes	15	93	62	43	86	50	36	86	60	60	100	90	90
No	116	100	78	62	95	63	40	67	31	25	78	59	53
pN^{+} stage of the primary tumor													
Positive	90	99	75	57	94	63	37	65	29	25	80	66	59
Negative	41	100	80	64	93	58	45	79	43	38	82	53	53
Temporal relationship													
Synchronous (<6 months)	57	98	61	42	93	55	31	59	25	17	69	48	36
Metachronous (>6 months)	77	100	87	71*	93	67	46	78	40	37*	90	74	74*
<12 months after primary tumor surgery	65	98	57	43	92	53	36	62	25	19	73	49	40
>12 months after primary tumor surgery	69	100	93	75*	94	70	44	77	42	39*	89	75	75*
Hepatic distribution													
Unilobular metastases	109	99	79	64	92	62	43	72	33	30	83	64	59
Bilobular metastases	25	100	62	36	96	60	27	60	38	27	71	57	57
Metastases >5 cm													
Yes	40	100	84	64	95	64	42	73	40	35	84	67	67
No	94	99	74	60	92	61	40	69	32	28	80	61	54
Number of metastases >3													
Yes	14	100	56	56	100	51	51	63	16	16	78	50	50
No	119	99	79	63	92	64	40	70	36	30	81	64	59

Data are expressed for the 1-, 3-, and 5-year period relative survival (percent) after operation of the primary colorectal cancer (CRC), after the first resection of liver metastases (Phx), for the overall tumor-free survival rate after first Phx and the liver-related tumor-free survival rate

*$p<0.05$

Table 8 Survival analyses of 134 patients with hepatic colorectal cancer metastases undergoing liver resection related to surgical techniques

Variable	Number	Survival after primary CRC operation			Survival after Phx			Recurrence-free survival			Liver recurrence-free survival		
		1 year	3 years	5 years	1 year	3 years	5 years	1 year	3 years	5 years	1 year	3 years	5 years
Type of liver resection													
Anatomical	47	100	82	60	93	58	37	82	37	37	93	63	63
Non-anatomical	61	98	82	66	92	71	48	67	31	27	75	60	54
Combination of anatomical and non-anatomical	26	100	58	51	96	46		57	38		76	65	
>1 non-anatomical resection	47	98	79	68	91	71	37	68	30	19	72	56	46
1 non-anatomical resection	40	100	69	55	95	55	50	59	35	35	79	69	69
Repeated resections (>1)	23	100	81	35	96	66	27	48	0	0	48	3	0
One liver resection procedure	111	99	76	66	93	61	45	75	42	37*	89	78	73*
≥3 segments	20	100	78	65	90	54	54	77	43	43	94	69	69
<3 segments	114	99	77	60	94	64	39	69	33	28	79	61	57
Diameter of the resection area ≥10cm													
Yes	55	100	69	46	93	43	33	72	35	28	88	68	68
No	63	98	81	70*	92	72	46*	71	38	38	80	64	64
Resection margin <1 mm													
Yes	38	100	72	62	95	61	20	66	25	19	76	54	54
No	96	99	79	60	93	62	47	72	37	34	83	65	60
Additional resection of extrahepatic disease													
Yes	7	100	86	70	100	85	51	71	71	71	86	86	86
No	127	99	76	60	93	60	40	70	32	27	81	61	56

Data are expressed for the 1-, 3-, and 5-year period relative survival (percent) after operation of the primary colorectal cancer (CRC), after first occurrence/resection of liver metastases (Phx), for the overall tumor-free survival rate after first Phx and the liver-related tumor-free survival rate

*$p<0.05$

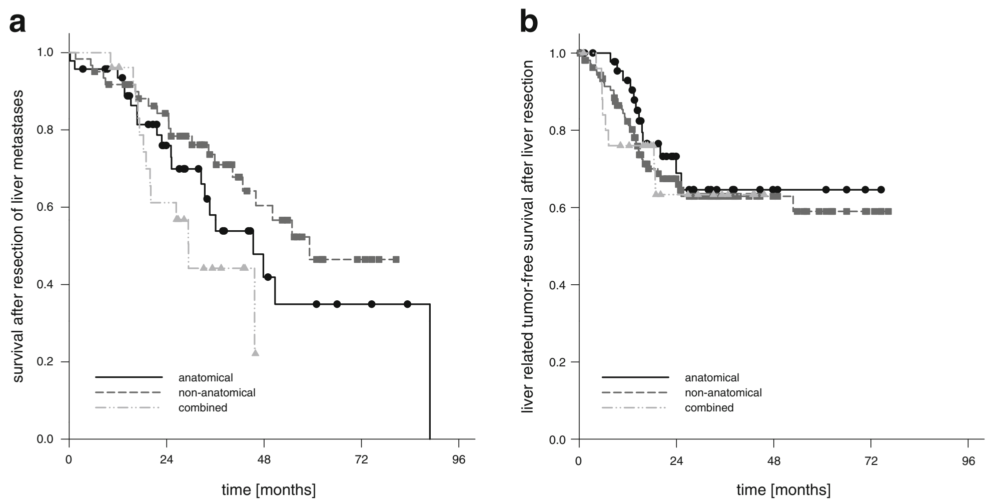

Fig. 2 Patients' (n=134) overall survival after the first resection procedure of liver metastases (**a**) and the liver-related tumor-free survival after liver resection (**b**), according to the type of liver resection (anatomical vs. non-anatomical vs. combined anatomical and non-anatomical procedures)

multiple non-anatomic resections due to the number of metastases were needed, these patients had a shorter survival after the liver resection procedure than those with only one non-anatomic resection (Table 8). In case of intrahepatic recurrence, 23 of 134 patients underwent at least a second hepatectomy, with a maximum of four repeated procedures during the time period reported (Table 8). Following repeated hepatectomy, these patients had a comparable 3-year survival rate after liver resection (66% versus 61%) with a notable high 5-year survival rate (27% versus 45%) compared to

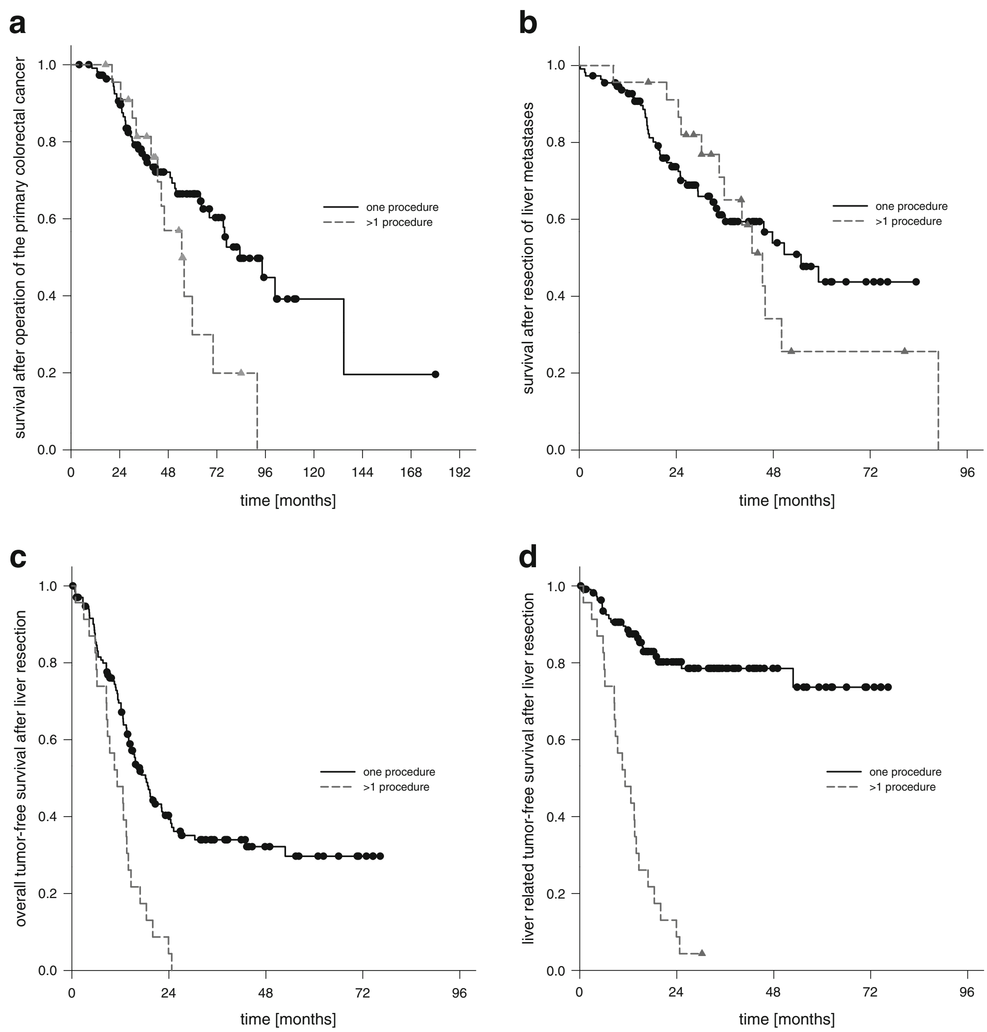

Fig. 3 Patients' (n=134) overall survival after operation of the primary colorectal tumor (**a**) and after the first resection procedure of liver metastases (**b**), according to the number of liver resection procedures (1 procedure vs. >1 procedure). Overall tumor-free survival ($p<0.001$) (**c**) and liver-related tumor-free survival after liver resection ($p<0.001$) (**d**)

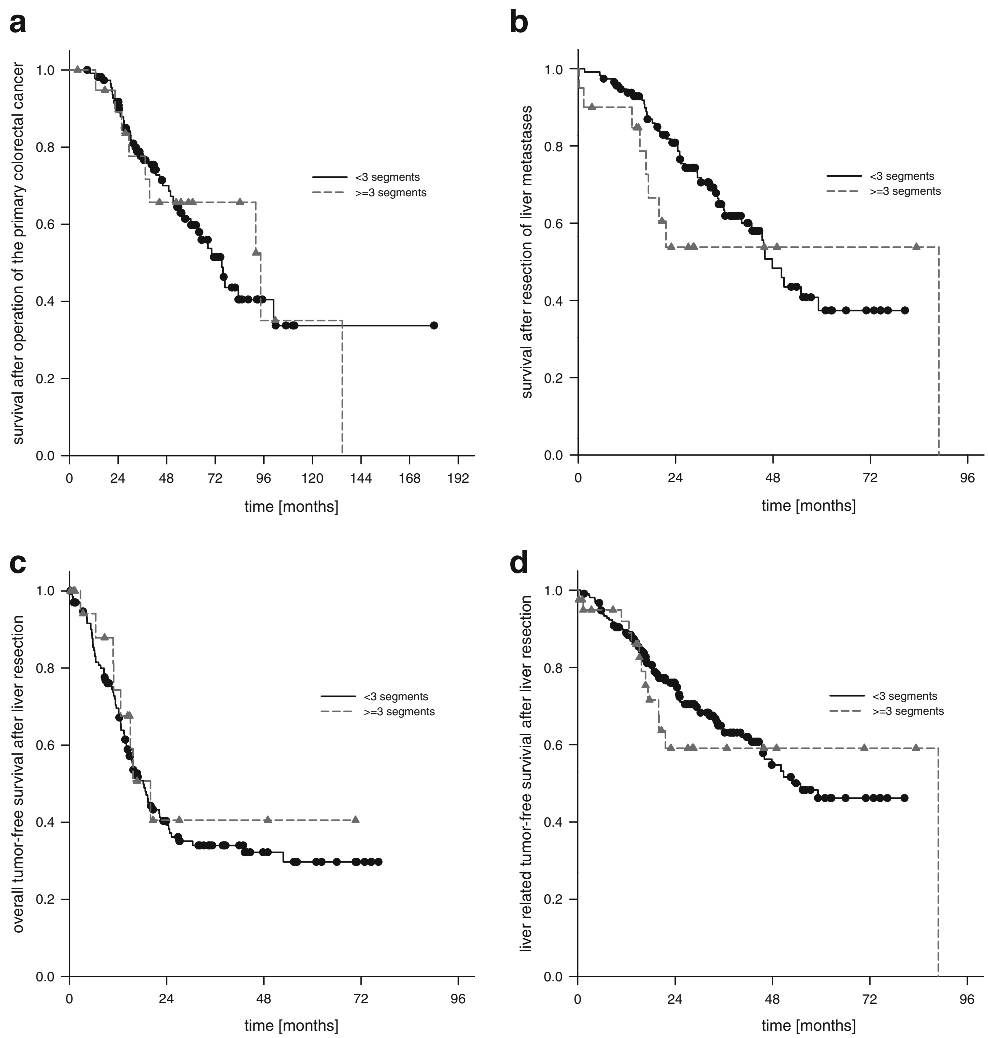

Fig. 4 Patients' (n=134) overall survival after operation of the primary colorectal tumor (**a**) and after the first resection procedure of liver metastases (**b**), according to the extent of hepatectomy (<3 segments vs. ≥3 segments). Overall tumor-free survival (**c**) and liver-related tumor-free survival after liver resection (**d**)

patients with only one liver resection procedure (Fig. 3). Patients undergoing major hepatectomy had a lower 3-year related survival rate (54% versus 64%) than those with minor resections (Fig. 4, Table 8). Interestingly, a diameter of the resection area of ≥10 cm (Fig. 5), as an indicator for major liver resection surgery, had a significant influence on the overall survival of the patients (p=0.043) and the survival after the liver resection procedure (p=0.015). Additionally, although 38 patients had a positive resection margin of <1 mm with a lower 5-year survival rate (20%) compared to

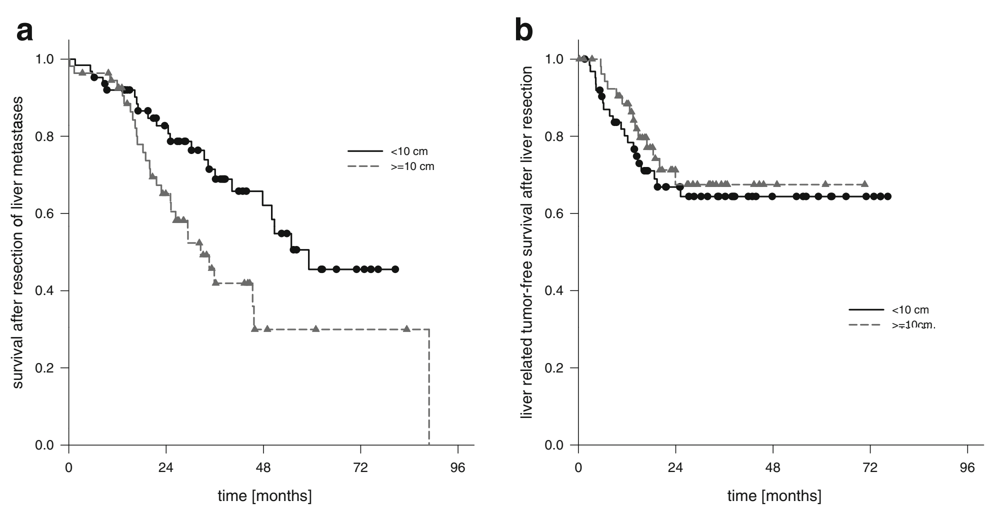

Fig. 5 Patients' (n=134) overall survival after the first resection procedure of liver metastases (**a**, p=0.015)) and the liver-related tumor-free survival after liver resection (**b**), according to the extent of the dissection area (<10 vs. ≥10cm)

patients with R0 resection, these data failed to be statistically significant (Table 8). Additional resection of known extrahepatic diseases during the liver resection procedure positively influenced the 5-year survival in these patients, however, again without statistical significance (Table 8).

Discussion

A variety of possible explanations for the improved outcome of patients with colorectal liver metastases within the last decades can be considered. Advantages in preoperative imaging, sophisticated surgical techniques, as well as neoadjuvant and adjuvant chemotherapeutic protocols may have contributed to the improvement in long-term outcome. Nevertheless, patients with stage IV disease of colorectal cancer still have a poor prognosis. During March 2001 and December 2006, 225 patients with colorectal cancer UICC stage IV were registered in the Saarland Cancer Registry [25]. Survival analysis of these 225 patients according to the data from the Saarland Cancer Registry showed a relative survival rate of 77% after 1 year, 38% after 3 years, and 14% after 5 years. If surgical resection for hepatic colorectal metastases with curative intent is possible, long-term survival and potential to cure could be demonstrated by our study presenting a 5-year survival rate of up to 40% which is in line with the new literature [5–11, 22]. Patients with bilateral colorectal metastases usually have either large or multiple tumors. Multiple tumors (≥4 tumors) and large tumor size (≥5 cm) are the most important independent adverse predictors of survival in patients undergoing hepatic resection for colorectal liver metastases [9, 26, 27]. Recurrence after resection of bilateral colorectal metastases is common with only 18% remaining recurrence free at 5 years [9].

The optimal therapeutic strategy for synchronous resectable colorectal liver metastases—defined as metastases occurring within 6 months after diagnosis of the primary tumor—has not been defined yet. Comparing patients with synchronous vs. metachronous colorectal liver metastases, Bockhorn et al. demonstrated similar 5-year survival rates after liver resection [28]. As shown by the present study, the temporal relationship between the occurrence of the primary tumor and liver metastasis seems to be an important prognostic factor for survival. Survival data after the first liver resection showed longer 5-year survival after resection of metachronous metastases, however without reaching statistical significance. The liver metastases and colorectal tumors may be removed in a simultaneous or staged fashion. As shown by Martin et al. simultaneous resection avoids a second laparotomy and reduces the overall complication rate without increasing operative mortality [29]. Therefore simultaneous resection is recommended at our institution. If the liver and colorectal resections are both extensive (i.e., extended hepatic resection and low anterior resection), a staged approach with neoadjuvant chemotherapy will be preferred according to the recommendations of Bentrem et al. [30].

The role of liver resection for colorectal metastases in the setting of associated hilar or para-aortic lymph node metastasis still remains controversial. As lymph node dissection was not routinely performed; the current study could not define a potential benefit of surgical resection. As shown by Pulitano C. et al., the presence of limited resectable lymph node metastases is not an absolute contraindication for the liver resection procedure, as subgroups of patients have a long-term survival benefit [31]. Especially, lymph nodes of areas 1 and 2 should always be removed if involved by metastases, whereas long-term survival of patients with metastases within area 3 is rare [31, 32].

Within the last decade, a shift toward parenchyma-sparing liver surgery can be observed in the reports of most hepatobiliary centers [8–11, 22–24]. Several studies report that perioperative mortality can be decreased using a segment-oriented approach to hepatic resection, obviating the need for resection of large amounts of uninvolved parenchyma [12–15]. As shown by Gold et al., this concept has become evident by the decreased use of major and extended hepatectomies and by the decreasing number of segments resected in a large series of patients [9]. To spare uninvolved surrounding parenchyma, similarly wedge resections and ablations were used more often. Interestingly, this change in management was not related to tumor size and tumor numbers. Wanebo et al. showed with a multivariate analysis that bilobular distribution of metastases and extent of liver resection (wedge and segmental versus hemihepatectomy and trisegmentectomy) directly correlate with patient survival [24]. Furthermore, Stewart et al. showed a median survival of 51 months after standard hepatectomies, of 23 months following extended resections, and of 59 months after segmental resection; however, there was no statistical difference between the three groups regarding the 5-year survival [22]. Interestingly, Jonas et al. demonstrated that survival after minor resections was significantly longer than after major resections (both groups were not defined in this analysis) [7], but the authors point out that in solitary liver metastases, the extent of the liver resection was not always determined by the extent of the tumor. Although only a randomized controlled trial could provide exact data regarding the impact of liver resection volume on patient survival taking into account the aspects of tumor size, distribution, and localization, the current analysis and the known literature recommend parenchyma-sparing liver surgery for patients with colorectal liver metastases.

In contrast to published data [7], in the present study, the extent of the liver resection procedure was strictly determined by the extent of the tumor. No standard hemihepatectomy was performed, so that the concept of parenchyma-preserving resection as a standard for patients with colorectal liver metastases resulted in an overall major hepatectomy rate of 13.1% (Table 9). Although no statistical significance of patient survival could be observed between patients undergoing major vs. minor liver resection, the data of the dissection area as an indicator for a large trauma of parenchyma indicate that major resections with high parenchymal loss (dissection diameter ≥10 cm) are associated with a shorter 5-year survival. Furthermore, the predicted and current survival rates compare favorably with results from other centers. In context with experimental findings, demonstrating that the extent of liver resection correlates with growth of residual liver or extrahepatic metastases [21], our clinical data indicate a correlation between loss of hepatic parenchyma and overall survival after liver resection.

The effect of surgical techniques for the resection of colorectal liver metastases comparing anatomical segment resections with non-anatomical wedge resections is still controversially discussed in the literature [33, 34]. Whereas some authors showed that anatomical resections are superior to wedge resections according to a better tumor clearance and improved survival [35], others demonstrated equivalent results for both techniques [11, 36–39]. Additionally, the present study shows that non-anatomical resections are not associated with impaired survival after liver resection. The non-anatomical liver resection is an oncological equivalent alternative and should remain an integral component of surgical treatment of colorectal liver metastases. Furthermore, Kokudo et al. demonstrate that major hepatectomy was unnecessary in >80% of the cases when the tumors were resectable by non-anatomical limited resections [36]. Taken together, the type of resection should be based on the anatomy of the lesion and the goal of preserving an adequate volume of functional liver parenchyma. Several studies recommend repeated liver resection as an option in multi-modal treatment of recurrent colorectal cancer [40–43]. In this context, evaluation for repeated hepatectomy should be performed at first. As demonstrated by the present study, repeated liver resection is safe and provides prolonged survival.

R0 resection is a positive prognostic factor for the outcome of patients with colorectal liver metastases. Colorectal liver metastases are well circumscribed, and micro- or satellite-metastases are not common. Therefore, a surgical resection margin of 2–5 mm has become a clinically acceptable minimum requirement reducing the risk of margin-related recurrence [7, 26, 44, 45]. Patients with positive margins were more likely to have surgical margin recurrence [45]. Otherwise, as liver resection provides the only chance of cure, complete removal of the tumor with a minimal margin is justified when technically unavoidable. This is not always achievable when multiple lesions are present or when they are located deep inside the liver and close to major vessels. Interestingly, this point is of major interest in patients with colorectal cancer metastases involving the caudate lobe. Due to its special anatomy, these cases of cancer-involved resection margins of over 50% were reported in the literature, leading to a 1-year overall survival of up to 90% with a 1-year recurrence-free survival of 60–70% [46]. Furthermore, as described by de Hass et al., optimal surgical techniques allowed an overall 10-year survival of 37% of patients with an R1 status compared to 43% of patients with an R0 resection [47]. In this context, the results of the present study with an R1 status of 28% are in line with the literature. In our center, all patients undergoing liver resection received treatment of the resection margin using the argon plasma coagulation device for further parenchymal cell destruction to achieve a deeper clear resection margin. Cryosurgery is only indicated to obtain deep parenchymal destruction next to major vessels. Together with the actual literature and the new multi-modal chemotherapy treatment options, a predicted positive surgical resection margin no longer should be an absolute contraindication for aggressive or advanced surgery of liver metastases. Although an R1 resection should clearly be avoided, the tumor biology is the more important predictor for intrahepatic recurrence and survival rather than millimeters of the resection margin [48, 49].

In conclusion, the availability of a highly effective systemic chemotherapy enables patients with stage IV disease to survive long enough to develop new metastases, making them

Table 9 Review of the literature of the last decade indicating the rate of major hepatectomy (≥3 segments) for resection of colorectal liver metastases

	Number	Years	Rate of major hepatectomy	1-year OS (%)	3-year OS (%)	5-year OS (%)
Fong et al. [5]	1,001	07/1985–10/1998	63%	89	57	37
Choti et al. [6]	226	01/1984–12/1999	56%	93	57	40
Jonas et al. [7]	660	01/1988–08/2004	66%	84	–	37
Tanaka et al. [8]	85	1987–2006	58%	89	52	41
Gold et al. [9]	440	01/1992–02/2003	84%	87	55	30
Sarpel et al. [11]	183	08/1987–08/2007	40%	89	67	55
de Haas et al. [47]	1,028	1990–2010	34.3%	–	65	50
Own data	134	03/2001–12/2006	14%	93	62	40

OS overall survival

candidates for repeated hepatectomy. Therefore, maximizing the amount of residual liver tissue is of considerable importance, and non-anatomical, parenchyma-preserving liver resections pursue this aim. Patients undergoing minor liver resections have the longest survival suggesting adequate oncological resection margins, whereas major hepatectomy has its role in selected patients with bilobular or large solitary colorectal metastases.

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