Surgery xxx (2020) 1–8

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Recurrence at surgical margin following hepatectomy for colorectal liver metastases is not associated with R1 resection and does not impact survival

Andreas Andreou, MD[a], Sebastian Knitter, MD[b], Moritz Schmelzle, MD[b], Daniel Kradolfer, MD[a], Martin H. Maurer, MD[c], Timo Alexander Auer, MD[d], Uli Fehrenbach, MD[d], Anja Lachenmayer, MD[a], Vanessa Banz, MD[a], Wenzel Schöning, MD[b], Daniel Candinas, MD[a], Johann Pratschke, MD[b], Guido Beldi, MD[a,*]

[a] *Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland*
[b] *Department of Surgery, Campus Charité Mitte and Campus Virchow Klinikum, Charité—Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Germany*
[c] *Department of Diagnostic, Interventional and Pediatric Radiology, Inselspital, Bern University Hospital, University of Bern, Switzerland*
[d] *Department of Radiology, Charité—Universitätsmedizin Berlin, Germany*

ARTICLE INFO

Article history:
Accepted 16 November 2020
Available online xxx

ABSTRACT

Background: Resection margin status has traditionally been associated with tumor recurrence and oncological outcome following liver resection for colorectal liver metastases. Previous studies, however, did not address the impact of resection margin on the site of tumor recurrence and did not differentiate between true local recurrence at the resection margin and recurrence elsewhere in the liver. This study aimed to determine whether positive resection margins determine local recurrence and whether recurrence at the surgical margin influences long-term survival.

Methods: Clinicopathological data and oncological outcomes of patients who underwent curative resection for colorectal liver metastases between 2012 and 2017 at 2 major hepatobiliary centers (Bern, Switzerland, and Berlin, Germany) were assessed. Cross-sectional imaging following hepatectomy was reviewed by radiologists in both centers to distinguish between recurrence at the resection margin, defined as hepatic local recurrence, and intrahepatic recurrence elsewhere. The association between surgical margin status and location of tumor recurrence was evaluated, and the impact on overall survival was determined.

Results: During the study period, 345 consecutive patients underwent hepatectomy for colorectal liver metastases. Histologic surgical margins were positive for tumor cells (R1) in 63 patients (18%). After a median follow-up time of 34 months, tumor recurrence was identified in 154 patients (45%). Hepatic local recurrence was not detected more frequently after R1 than after R0 resection ($P = .555$). Hepatic local recurrence was not associated with worse overall survival ($P = .436$), while R1 status significantly impaired overall survival ($P = .025$). Additionally, overall survival was equivalent between patients with hepatic local recurrence and patients with any intrahepatic and/or extrahepatic recurrence. In patients with intrahepatic recurrence only, oncological outcomes improved if local hepatic therapy was possible (resection or ablation) in comparison to patients treated only with chemotherapy or best supportive care (3-year overall survival: 85% vs 39%; $P < .0001$).

Conclusion: The incidence of hepatic local recurrence after hepatectomy for colorectal liver metastases is independent of R1 resection margin status. Additionally, hepatic local recurrence at the resection margin is not associated with worse overall survival compared with any other intra- or extrahepatic recurrence. Therefore, R1 status at hepatectomy seems to be a surrogate factor for advanced disease without

Andreas Andreou and Sebastian Knitter contributed equally as first authors.
Johann Pratschke and Guido Beldi contributed equally as senior authors.
This manuscript was presented at the 106th Annual Congress of the Swiss Surgical Association in Bern, Switzerland, May 2019 (awarded for the best first oral presentation) and was accepted for presentation at the 137th Annual Congress of the German Surgical Association, Berlin, Germany, April 2020.

* Reprint requests: Guido Beldi, MD, Department of Visceral Surgery und Medicine, Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse 18, 3010 Bern, Switzerland.
E-mail address: guido.beldi@insel.ch (G. Beldi).

https://doi.org/10.1016/j.surg.2020.11.024

influencing location of recurrence and thereby oncological outcome. This finding may support decision-making when extending the indication for surgery in borderline resectable colorectal liver metastases.

Introduction

Liver resection may improve the oncological outcome of patients with colorectal liver metastases (CRLM) and is associated with 5-year overall survival (OS) rates of up to 58% within the framework of multimodal treatment strategies including modern systemic therapy.[1,2] Resectability rates and oncological outcome have increasingly improved in recent years owing to advances in surgical techniques,[3,4] preoperative imaging,[5] interventional radiology,[6] perioperative management,[7] and systemic therapy.[8,9] In particular, parenchymal-sparing liver resection allowed for an increase in resectability.[10] Increasing implementation of parenchymal-sparing hepatectomy, however, potentially increases the risk for local recurrence.[11] Despite state-of-the-art treatment, a significant proportion of patients undergoing hepatectomy for CRLM, (between 45%[12] and 70%[13]), suffer from tumor recurrence. Nevertheless, in case of intrahepatic recurrence,[14] favorable outcomes are still achievable, especially if repeat hepatectomy is technically feasible.[15]

Previous authors have suggested that histologically positive resection margins (R1 resection: tumor free margin <1 mm) are associated with higher recurrence rates, lower disease-free survival, and worse OS.[16–18] R1 resection has also been associated with higher surgical margin recurrence during an older era lacking standardized perioperative chemotherapy with modern cytotoxic and biological agents.[19] Therefore, one of the criteria used to select patients for hepatectomy for CRLM has traditionally been the predicted ability to achieve pathologically negative surgical margins. However, survival is not only a function of technically feasible resectability but is also dependent on biological aggressiveness, which translates into the presence of somatic gene mutations.[20] Thus, it remains unclear if R1 resection margin only represents a surrogate factor of advanced disease while not determining the location of recurrence. Importantly, current studies examining tumor recurrence patterns following hepatectomy for CRLM did not differentiate between true local recurrence at the resection margin and recurrence elsewhere in the liver and thus could not adequately evaluate the effect of marginal tumor relapse on oncological outcome.[21]

Our study defined the association between surgical margin status (R0 versus R1) and location of tumor recurrence (hepatic surgical margin versus intrahepatic recurrence versus extrahepatic recurrence). We further assessed the impact of margin status and location of recurrence on OS in patients undergoing curative-intended hepatectomy for CRLM.

Materials and methods

Patient inclusion criteria

This study was initiated after obtaining approval from the Ethics Committee of the Canton of Bern (2018-01576) and the Ethics Committee of the Charité—Universitätsmedizin Berlin (EA2/006/16). Clinicopathological data from 345 consecutive patients who underwent resection for CRLM from 2012 to 2017 at the Department of Visceral Surgery und Medicine, Inselspital, Bern University Hospital or the Department of Surgery, Campus Charité Mitte and Campus Virchow Klinikum, Charité—Universitätsmedizin Berlin were evaluated.

Patients were included in the analysis if curative-intended resection, defined as the ability to remove all radiologically evident disease, was performed. Patients were excluded if they were <18 years old, or if microwave ablation was performed concomitant to surgery.

Preoperative assessment

Patients with CRLM were evaluated preoperatively in each center according to standardized protocols, including medical history, physical examination, serum laboratory tests, and an anesthesia evaluation. The extent of disease, type of resection, and the future liver remnant (FLR) volume were assessed using cross-sectional imaging (triphasic contrast-enhanced computed tomography or magnetic resonance imaging with liver-specific contrast agents).

Weekly multidisciplinary tumor boards in each center attended by hepatobiliary surgeons, hepatologists, oncologists, radiologists, and pathologists found a consensus on the best individual treatment strategy for each patient. Hepatectomy was recommended if CRLM could be resected with preservation of a sufficient FLR. In patients with an anticipated insufficient FLR volume, preoperative portal vein embolization[22] or associating liver partition and portal vein ligation procedure[4] was performed to induce hypertrophy of the FLR and enable safe resection.

Surgical procedure and postoperative management

Following laparotomy or laparoscopy, the peritoneal cavity was examined to exclude peritoneal deposits. Intraoperative ultrasound of the liver was performed to identify the exact location of CRLM and their proximity to portal pedicles and hepatic veins and thus guide resection. Total or selective hepatic vascular exclusion was performed for major parenchymal transections, as needed.[23] Major hepatectomy was defined as resection of 3 or more continuous liver segments according to the Couinaud classification.[24]

Following hepatectomy, patients were monitored for postoperative complications according to the institutional standards. Postoperative morbidity was defined as any complication within 90 days after surgery and was graded according to the classification of Clavien and Dindo.[25] Major morbidity was defined as any complication $\geq$3a grade and postoperative mortality as grade 5. All patients were assessed again postoperatively at the multidisciplinary tumor board to discuss the need for any additional treatment versus tumor surveillance alone according to international guidelines.[26]

Histologic evaluation

Resected specimens were subjected to histologic evaluation to confirm the diagnosis of CRLM and determine the resection margin status. R1 resection was defined as the microscopic presence of tumor cells within 1 mm from the transection line, whereas R0 resection was defined as complete tumor resection with no tumor cells within 1 mm of the resection margin as previously described.[18]

Evaluation of tumor recurrence

Tumor recurrence was defined as the first tumor relapse after curative-intended hepatectomy for CRLM. For this study, cross-sectional imaging performed during the scheduled long-term oncologic surveillance after hepatectomy was reviewed by a radiologist in each center, blinded to the clinical outcomes, to identify the presence and location of recurrent disease. Cross-sectional imaging after surgery was scheduled every 3 months in the first 2 years and then every 12 months.

For this manuscript, the following definitions of recurrence location were used: true local recurrence at the liver resection margin defined as hepatic local recurrence (H-LR), intrahepatic recurrence not at the resection margin defined as hepatic nonlocal recurrence, and extrahepatic recurrence. The definition of any recurrence included all patients with recurrent disease at any intrahepatic and/or extrahepatic site, excluding patients with H-LR only. H-LR was defined as recurrent disease within 1 cm from the transection line in cross-sectional imaging.

Statistical analysis

Quantitative and qualitative variables were expressed as medians (range) and frequencies (percentage). Comparisons between groups were analyzed with the χ^2 or Fisher exact test for categorical variables and the Mann-Whitney *U* test for continuous variables, as appropriate. To identify factors associated with R1 resection, the following parameters were analyzed in univariate analysis: administration of preoperative chemotherapy, extent of hepatectomy, major versus minor liver resection, open versus laparoscopic hepatectomy, use of parenchyma-sparing resection, 90-day overall postoperative morbidity, 90-day major postoperative morbidity, 90-day postoperative mortality, and administration of postoperative chemotherapy. All factors with $P < .100$ in univariate analysis were then entered in a logistic regression model with backward elimination. Using the Kaplan-Meier method, OS was calculated from the date of resection to the date of death or last follow-up. Comparisons between survival rates were performed using log-rank tests. Multivariate analysis was performed to identify factors that are independently associated with OS using a Cox regression model with backward elimination by entering all parameters with $P < .100$ in the univariate analysis. *P* values < .05 were considered statistically significant. Statistical analyses were performed using the SPSS software package, version 25 (IBM, Armonk, NY).

Results

Patient characteristics

During the study period, 345 patients underwent liver resection for CRLM with curative intent in both centers. Histologic surgical margins were positive for tumor cells (R1) in 63 patients (18%) and negative in 282 patients. Close proximity to large vessels that could not be sacrificed for tumor-free margins were found in 30 out of 63 R1-resected patients (48%).

R1 resection was associated with worse OS compared with R0 resection (3-year OS: 40% vs 71%; $P < .0001$, Fig 1). Additionally, R1 resection correlated with more major resections (60.3% vs 45.0%; $P = .028$), less minimal-invasive hepatectomies (6.3% vs 25.5%; $P = .001$), increased postoperative morbidity (63.5% vs 41.1%; $P = .001$), and mortality (9.5% vs 2.5%; $P = .018$, Table I). In multivariate analysis, open hepatectomy (odds ratio 5.0, 95% confidence interval [CI] 1.4–10.0; $P = .006$) and postoperative morbidity (odds ratio 2.2, 95% CI 1.2–3.9; $P = .007$) were independently associated with R1 resection (Table I).

Tumor recurrence

Tumor recurrence was identified in 154 patients (45%) after a median follow-up time of 34 months. Median time to recurrence was 18 months. Characteristics of patients stratified according to the location of recurrence (H-LR versus any recurrence) are summarized in Table II. Clinicopathological parameters were not different between the 2 groups. Margin status was not associated with the location of recurrence, both intra- and extrahepatic ($P = .748$, Table III). H-LR was not detected more frequently after R1 resection than after R0 resection (17.9% vs 13.5%; $P = .555$). For a better understanding of how the location of CRLM affected the site of recurrence following R1 resection, we divided the R1 cohort among patients with recurrence ($n = 28$, Table III) in centrally located CRLM with proximity to large vessels (R1c, $n = 16$ [57%]) and subcapsular, superficially located (R1s, $n = 12$ [43%]) CRLM. There was no association between the location of CRLM and the incidence of recurrence ($P = .288$, Table III) after R1 resection.

Location of recurrence and overall survival

OS was not different between H-LR only and other combination of intrahepatic recurrence (hepatic nonlocal recurrence ± H-LR) (3-year OS: 78% vs 55%; $P = .436$, Fig 2). OS was also not different when comparing patients with H-LR only and patients with any recurrence (intrahepatic and/or extrahepatic) (3-year OS: 78% vs 64%; $P = .454$, Fig 3).

We additionally performed univariate and multivariate analysis to identify factors associated with OS following hepatectomy for CRLM including both H-LR versus other sites of recurrence versus no recurrence and R1 versus R0. The results are summarized in Supplementary Table S1. The multivariate analysis indicated that the site of recurrence was not associated with OS, whereas R1 status independently predicted worse OS (hazard ratio 2.1, 95% CI 1.3–3.4; $P = .003$).

Survival analysis according to the treatment for the recurrent disease showed that local therapy (repeat hepatectomy or ablation) for intrahepatic recurrence improved OS compared with palliative chemotherapy or best supportive care irrespective of whether intrahepatic and/or extrahepatic recurrence was present. Patients with intrahepatic recurrent disease undergoing local hepatic therapy had a significantly better 3-year OS compared with patients not able to receive repeat hepatectomy or ablation (85% vs 39%; $P < .0001$, Fig 4). In patients with intrahepatic and concomitant extrahepatic disease, the survival difference in favor of local liver-directed treatment did not reach statistical significance (3-year OS: 67% vs 59%; $P = .152$).

Discussion

This multi-institutional study demonstrated that R1 margin status was not associated with H-LR following curative-intended hepatectomy for CRLM. In contrast to R1 status, H-LR was not associated with worse OS. Our current study supports the hypothesis that R1 resection is more of a surrogate factor for advanced disease and not a determinant of recurrence pattern, as it was associated with the extent of resection and surgical postoperative outcomes but not the location of recurrent disease.

Previous studies have investigated the impact of histologically positive resection margins on recurrence probability and long-term survival after resection for CRLM. However, many of these studies are older than 10 years and thereby cannot assess the latest

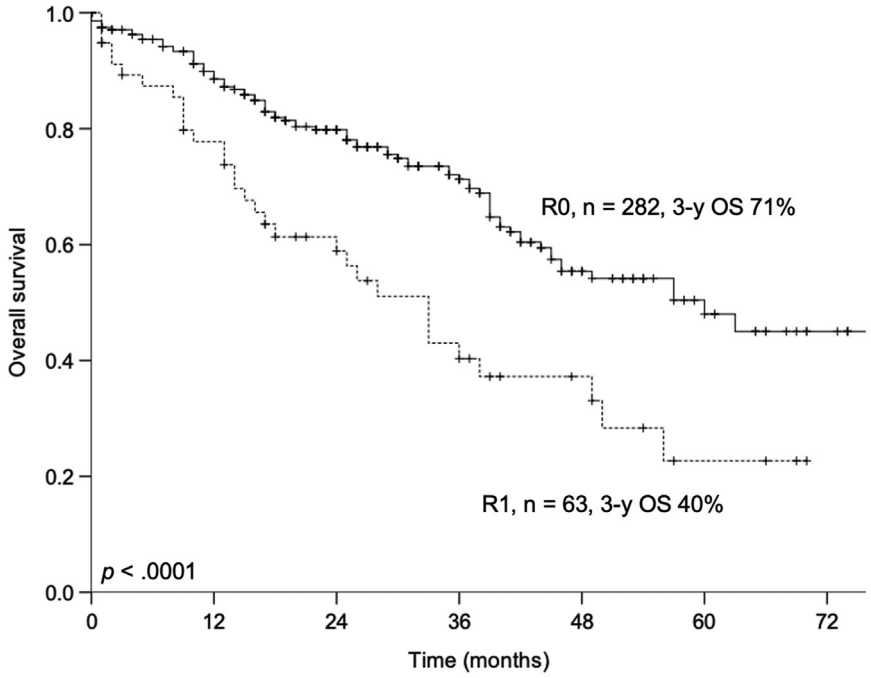

Fig 1. Overall survival according to margin status after liver resection for CRLM ($n = 345$). *CRLM*, colorectal liver metastases.

advances in systemic therapy and liver surgery.[16,17,19,27] Studies that proposed R1 resection as a predictor of worse outcome did not assess its impact on local recurrence at the resection margin.[16,17,19] The only study so far that also distinguished between recurrence at the surgical margin and recurrence elsewhere in the liver showing a significant association between R1 status and H-LR was performed in 2005.[19] In this study, no preoperative chemotherapy was reported and adjuvant chemotherapy regimens belonged to an era before the establishment of modern cytotoxic agents and monoclonal antibodies.[8,9] The benefits of perioperative chemotherapy with FOLFOX have been known since the European Organisation for Research and Treatment of Cancer study.[8] Within this setting, adjuvant systemic therapy after neoadjuvant chemotherapy and hepatectomy for CRLM may improve disease-free survival. Additionally, this study probably did not include any patients treated within the framework of modern parenchymal-sparing concepts, which have been increasingly implemented in our practice. In a more recent study, positive surgical margins were not associated with increased marginal recurrence despite more frequent intrahepatic recurrence.[27] In addition, multiple indicators supporting surgical margins as a surrogate factor of advanced disease were identified in this study, such as the association of R1 status with

Table I
Univariate and multivariate analysis of factors associated with R1 resection in 345 patients who underwent liver resection for CRLM

	R0 ($n = 282$)	R1 ($n = 63$)	UV	MV*	
			P	*P*	OR (95% CI)
Preoperative chemotherapy, *n* (%)	157 (55.7)	31 (49.2)	.351		
PVE, *n* (%)	23 (8.2)	10 (15.9)	.060	NS	
ALPPS procedure, *n* (%)	2 (0.7)	1 (1.6)	.455		
Surgical technique, *n* (%)			.188		
Right hepatectomy	65 (23.0)	15 (23.8)			
Left hepatectomy	22 (7.8)	8 (12.7)			
Extended right hepatectomy	35 (12.4)	11 (17.5)			
Extended left hepatectomy	6 (2.1)	4 (6.3)			
Left lateral hepatectomy	17 (6.0)	1 (1.6)			
Wedge resection	102 (36.2)	18 (28.6)			
Bisegmentectomy	35 (12.4)	6 (9.5)			
Major liver resection, *n* (%)	127 (45.0)	38 (60.3)	.028	NS	
Open hepatectomy, *n* (%)	210 (74.5)	59 (93.7)	.001	.006	5.0 (1.4–10.0)
Parenchymal-sparing resection, *n* (%)	139 (48.4)	25 (37.9)	.121		
90-d postoperative morbidity, *n* (%)	116 (41.1)	40 (63.5)	.001	.007	2.2 (1.2–3.9)
90-d major postoperative morbidity, *n* (%)	68 (24.1)	20 (31.7)	.209		
90-d postoperative mortality, *n* (%)	7 (2.5)	6 (9.5)	.018	NS	
Postoperative chemotherapy, *n* (%)	99 (35.1)	19 (30.2)	.454		

ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; *CI*, confidence interval; *CRLM*, colorectal liver metastases; *MV*, multivariate analysis; *NS*, not significant; *OR*, odds ratio; *PVE*, portal vein embolization; *UV*, univariate analysis.

* Logistic regression multivariate analysis included all variables with $P < .100$ in univariate analysis.

Table II
Clinicopathological data of 345 patients who underwent liver resection for CRLM according to tumor recurrence location

Variable	H-LR ($n = 22$)	Any recurrence* ($n = 132$)	No recurrence ($n = 191$)	All patients ($n = 345$)	*P*
Sex, *n* (%)					.944
Female	7 (31.8)	43 (32.6)	65 (34.0)	115 (33.3)	
Male	15 (68.2)	89 (67.4)	126 (66.0)	230 (66.7)	
Age, y, median (range)	68 (47–77)	61 (26–83)	65 (25–89)	64 (25–89)	.067
Age >65 y *n* (%)	12 (54.5)	52 (39.4)	93 (48.7)	157 (45.5)	.182
BMI, kg/m^2, median (range)	24.45 (18–35)	25.25 (17–46)	25.18 (17–43)	25.05 (17–46)	.607
BMI >30 kg/m^2, *n* (%)	4 (18.2)	21 (15.9)	36 (19.7)	61 (18.1)	.759
ASA physical status, *n* (%)					.088
1	0 (0.0)	3 (2.3)	3 (1.6)	6 (1.7)	
2	14 (63.6)	68 (51.5)	83 (43.5)	165 (47.8)	
3	6 (27.3)	59 (44.7)	103 (53.9)	168 (48.7)	
4	2 (9.1)	2 (1.5)	2 (1.0)	6 (1.7)	
Diabetes, *n* (%)	5 (22.7)	14 (10.6)	33 (17.3)	52 (15.1)	.153
Hypertension, *n* (%)	7 (31.8)	50 (37.9)	84 (44.0)	141 (40.9)	.586
Coronary heart disease, *n* (%)	1 (4.5)	7 (5.3)	17 (8.9)	25 (7.2)	1
Pulmonary disease, *n* (%)	1 (4.5)	7 (5.3)	17 (8.9)	25 (7.2)	1
Renal disease, *n* (%)	8 (0.0)	6 (4.5)	18 (9.4)	24 (7.0)	.595
Location of primary tumor, *n* (%)					.674
Right hemicolon	6 (27.3)	27 (20.5)	40 (20.9)	73 (21.2)	
Left hemicolon/sigmoid	8 (36.4)	45 (34.1)	71 (37.2)	124 (35.9)	
Rectum	8 (36.4)	60 (45.5)	80 (41.9)	148 (42.9)	
Synchronous CRLM, *n* (%)	14 (63.6)	81 (61.4)	94 (49.2)	189 (54.8)	.839
Size of largest CRLM >50 mm, *n* (%)	7 (33.3)	39 (32.5)	47 (25.7)	93 (28.7)	.940
Solitary CRLM, *n* (%)	8 (36.4)	41 (31.3)	69 (36.3)	118 (34.4)	.637
Preoperative chemotherapy, *n* (%)	16 (72.7)	87 (65.9)	85 (44.5)	188 (54.5)	.529
T stage of primary, *n* (%)					.190
1	0 (0.0)	8 (6.6)	8 (4.6)	16 (5.1)	
2	2 (9.1)	12 (9.9)	22 (12.8)	36 (11.4)	
3	17 (77.3)	66 (54.6)	115 (66.9)	198 (62.9)	
4	3 (13.6)	35 (28.9)	27 (15.7)	65 (20.6)	
N stage of primary, *n* (%)					.091
0	12 (54.6)	39 (31.7)	69 (40.1)	120 (37.9)	
1	7 (31.8)	47 (38.2)	56 (32.6)	110 (34.7)	
2	3 (13.6)	37 (30.1)	46 (26.7)	86 (27.1)	
3	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)	
UICC stage of primary, *n* (%)					.631
1	1 (4.6)	11 (8.4)	20 (10.9)	32 (9.5)	
2	3 (13.6)	11 (8.4)	28 (15.2)	42 (12.5)	
3	3 (13.6)	29 (22.1)	37 (20.1)	69 (20.5)	
4	15 (68.2)	80 (61.1)	99 (53.8)	194 (57.5)	
Tumor grading of primary, *n* (%)					.704
G1	1 (6.7)	5 (5.6)	2 (1.5)	8 (3.3)	
G2	13 (86.6)	71 (79.8)	119 (85.6)	203 (83.5)	
G3	1 (6.7)	13 (14.6)	18 (12.9)	32 (13.2)	
Length of ICU stay, d, median (range)	2 (0–9)	1 (0–7)	1 (0–51)	1 (0–51)	.147
Duration of hospital stay, d, median (range)	9.5 (5–37)	10 (2–109)	10 (2–87)	10 (2–109)	.855
90-d complications, *n* (%)	14 (63.6)	49 (37.1)	93 (48.7)	156 (45.2)	.019
90-d major complications, *n* (%)	6 (27.3)	25 (18.9)	57 (29.8)	88 (25.5)	.392
90-d mortality, *n* (%)	0 (0.0)	1 (0.8)	12 (6.3)	13 (3.8)	1
Anatomical resection, *n* (%)	15 (68.2)	83 (62.9)	118 (61.8)	216 (62.6)	.632
Major resection, *n* (%)	13 (59.1)	62 (47.0)	90 (47.1)	165 (47.8)	.292
Minimally invasive hepatectomy, *n* (%)	4 (18.2)	17 (12.9)	55 (28.8)	76 (22.0)	.506
Positive resection margins, *n* (%)	5 (22.7)	23 (17.4)	35 (18.3)	63 (18.3)	.555
Surgical technique, *n* (%)					.121
Right hepatectomy	9 (40.9)	29 (22.0)	42 (22.0)	80 (23.2)	
Left hepatectomy	3 (13.6)	8 (6.1)	19 (9.9)	30 (8.7)	
Extended right hepatectomy	1 (4.5)	20 (15.2)	25 (13.1)	46 (13.3)	
Extended left hepatectomy	0 (0.0)	6 (4.5)	4 (2.1)	10 (2.9)	
Left lateral hepatectomy	1 (4.5)	9 (6.8)	8 (4.2)	18 (5.2)	
Wedge resection	8 (36.4)	42 (31.8)	70 (36.6)	120 (34.8)	
Bisegmentectomy	0 (0.0)	18 (13.6)	23 (12.0)	41 (11.9)	
Need for intraoperative RBC transfusion, *n* (%)	4 (18.2)	32 (24.2)	37 (19.4)	73 (21.2)	.534
Length of operation, min, median (range)	239 (75–469)	262 (30–820)	237 (46–766)	249 (30–820)	.377
Surgical liver site infection, *n* (%)	4 (18.2)	5 (3.8)	16 (8.4)	25 (7.2)	.025
Postoperative chemotherapy, *n* (%)	9 (40.9)	70 (53.0)	39 (20.4)	118 (34.2)	.292

P: comparison between hepatic local recurrence (H-LR) and any recurrence.
ASA, American Society of Anesthesiologists; *BMI,* body mass index; *CRLM,* colorectal liver metastases; *H-LR,* hepatic local recurrence; *ICU,* intensive care unit; *RBC,* red blood cells; *UICC,* Union for International Cancer Control.
* Any recurrence incudes all recurrences except H-LR.

Table III
Association between margin status after liver resection for CRLM and site of tumor recurrence (n =154)

	R0 (n = 126)	R1 (n = 28)	R1c (n = 16)	R1s (n = 12)	P	P^*	$P^\dagger$
Site of recurrence, n (%)					.748	.516	.288
H-LR only	17 (13.5)	5 (17.9)	4 (25.0)	1 (8.3)			
Combined H-NLR + H-LR	9 (7.1)	3 (10.7)	2 (12.5)	1 (8.3)			
H-NLR only	17 (13.5)	4 (14.3)	3 (18.8)	1 (8.3)			
Extra- and intrahepatic recurrence	51 (40.5)	12 (42.9)	4 (25.0)	8 (66.7)			
Only extrahepatic recurrence	32 (25.4)	4 (14.3)	3 (18.8)	1 (8.3)			

P: comparison R0 versus R1.
CRLM, colorectal liver metastases; *H-LR,* hepatic local recurrence; *H-NLR,* hepatic nonlocal recurrence *R1c,* R1 central lesions; *R1s,* R1 superficial lesions.
* *P*: comparison R0 versus R1c versus R1s.
† *P*: comparison of R1c versus R1s.

CRLM size, bilateral tumor distribution, and the need for intraoperative red blood cell transfusion.[27] In our study, histologic detection of tumor cells at the level of transection did not significantly facilitate the development of more frequent H-LR or other intrahepatic recurrence. There was also no correlation between resection margin status and any intrahepatic or extrahepatic pattern of recurrence.

Another finding of our study revealed that H-LR was not associated with worse oncological outcome. OS in patients with H-LR was not significantly different compared with OS in patients with other intrahepatic or extrahepatic recurrence. Our results are supported by a recent study in which OS in patients with in situ intrahepatic recurrence did not differ from that of patients with de novo intrahepatic recurrence.[28] Our study validated this finding in a cohort of patients undergoing only hepatectomy, while the study from Lee et al also included patients treated with tumor ablation and those with extrahepatic metastases.[28] Similar to this study,[28] our patients benefitted from modern systemic therapy thus providing a homogeneous patient cohort for adequate evaluation of tumor recurrence patterns.

Our study population allowed for an analysis of the impact of liver-directed therapy for intrahepatic recurrence on long-term survival. Both repeat hepatectomy or ablation were compared with palliative chemotherapy or best supportive care and revealed to be beneficial. This finding has been recently confirmed by other studies, which showed superior outcomes in patients selected for surgery or ablation for intrahepatic tumor recurrence in comparison to patients treated with chemotherapy, chemoradiation, or best supportive care.[28,29] Repeat hepatectomy for recurrent CRLM has already been recognized as a safe and feasible procedure to improve oncologic outcome.[30] Five-year OS rates after repeat hepatectomy of up to 73% have been reported, and re-recurrence was significantly reduced if R0 could be performed, underlining again the role of positive surgical margins as a surrogate factor for unfavorable disease.[15] Furthermore, parenchymal-sparing resections (if deemed feasible owing to the extent and location of the CRLM) increasingly allow for repeat hepatectomies, as shown in our study.[31]

This retrospective study has several limitations. Firstly, preoperative chemotherapy was only administered in 54.5% of patients, which may have caused a certain inhomogeneity in the development of tumor recurrence. Previous studies have demonstrated an association between preoperative chemotherapy and recurrence patterns after resection for CRLM, such as a reduction of pulmonary recurrences.[21] However, preoperative chemotherapy was not

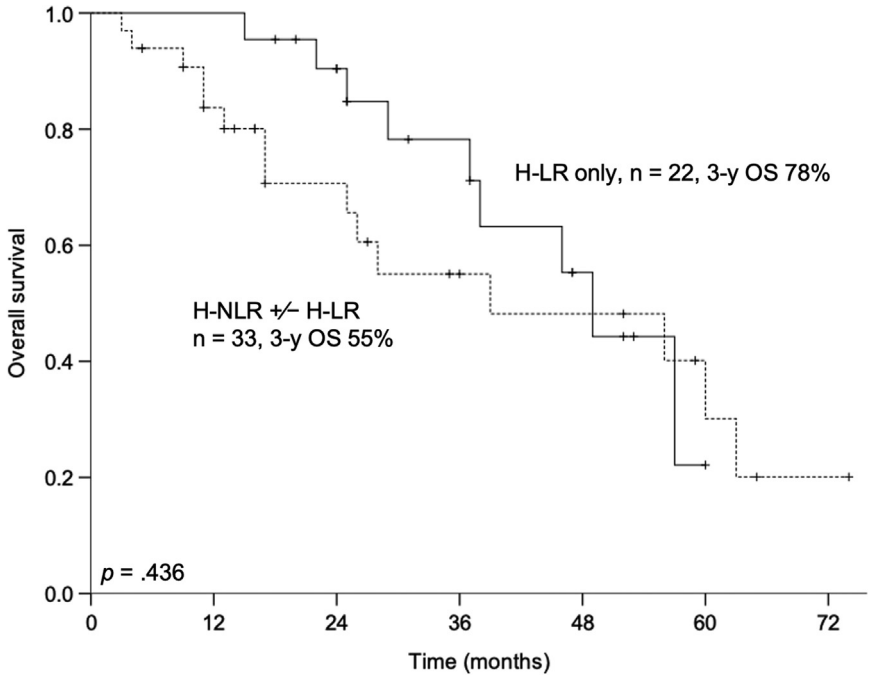

Fig 2. Overall survival after liver resection for CRLM according to the location of tumor recurrence in 55 patients with intrahepatic recurrence. *CRLM,* colorectal liver metastases; *H-LR,* hepatic local recurrence; *H-NLR*, hepatic nonlocal recurrence.

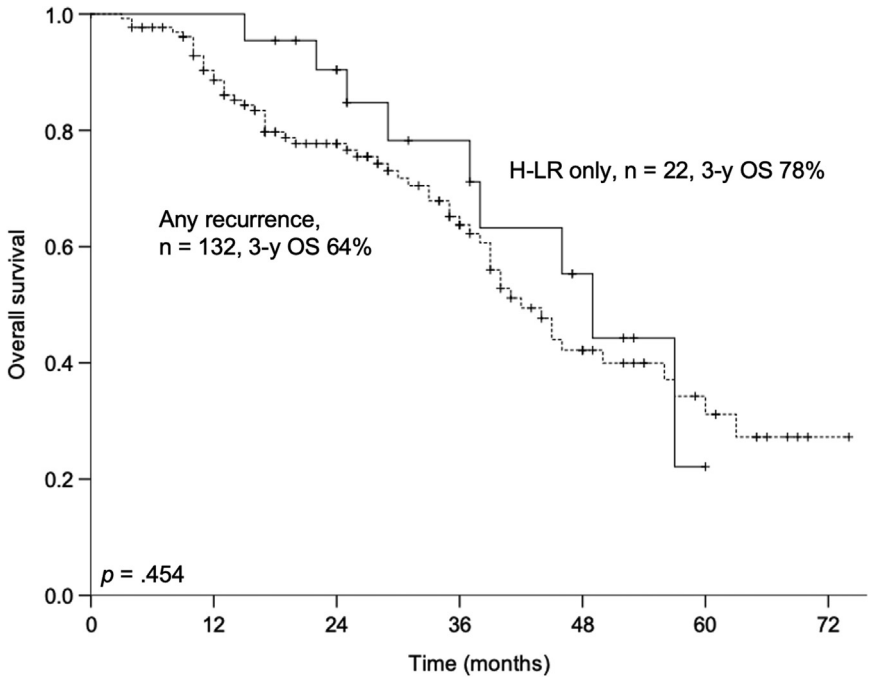

Fig 3. Overall survival after liver resection for CRLM according to the location of tumor recurrence in 154 patients with intra and extrahepatic recurrence. *CRLM,* colorectal liver metastases, H-LR, hepatic local recurrence.

significantly associated with H-LR versus any recurrence in our study. Furthermore, our study was limited by the lack of data concerning biomarkers such as somatic gene mutations[32] to validate our hypothesis that positive resection margins represent a surrogate factor of unfavorable disease biology. Positive *RAS* mutation status has been shown previously to be associated with positive resection margins[33] and to negatively influence survival after curative resection for CRLM.[20] Additionally, selection bias of patients with higher risk of recurrence in the R1 group was possible resulting in worse OS. This bias was made visible by the difference of major liver resections and laparoscopic procedures between R0 and R1 cases. Likewise, the R1 group demonstrated significantly higher postoperative morbidity and mortality rates that may have contributed to the decreased OS in this group. These results underline our hypothesis that R1 resection represents a surrogate factor for more advanced disease and probably unfavorable tumor biology requiring extended systemic and surgical treatment that may result in worse postoperative and long-term outcomes. In addition, our study (Supplementary Table S1) and

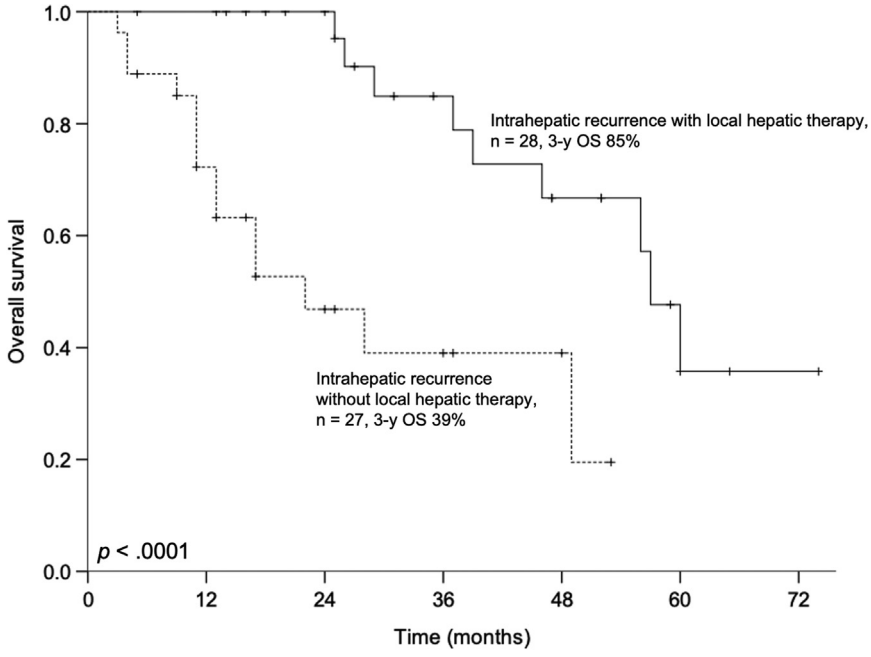

Fig 4. Overall survival after liver resection for CRLM according to the treatment of recurrence in 55 patients with intrahepatic recurrence. *CRLM,* colorectal liver metastases.

previous studies have shown the negative impact of postoperative morbidity on long-term survival after hepatetcomy for CRLM.[34,35] Finally, the number of patients included in our study was too small to stratify outcomes according to all sites of extrahepatic recurrence. However, fusion of bicentric data and thorough evaluation of follow-up imaging by specialized radiologists in each center contributed to precise evaluation of intrahepatic and extrahepatic recurrent disease.

In conclusion, our bicentric analysis indicates that R1 status is a surrogate factor for advanced disease and does not have a direct impact on the location of intrahepatic or extrahepatic tumor recurrence. H-LR is not associated with worse OS compared with other recurrences in the liver or elsewhere. Local treatment for intrahepatic recurrence may improve long-term survival in selected patients and therefore repeat hepatectomy and/or ablation should be considered in case of intrahepatic disease relapse. These findings justify (where possible) a parenchymal-sparing hepatectomy in the setting of CRLM, even if an R1 outcome is deemed very likely in the preoperative assessment.

Funding/ Support

The study has not received any financial support.

Conflict of interest/Disclosure

A. Andreou, S. Knitter, D. Kradolfer, M. H. Maurer, T. A. Auer, U. Fehrenbach, A. Lachenmayer, V. Banz, D. Candinas, and G. Beldi have no conflicts of interest or financial interests to disclose concerning the findings of this study. The following conflicts of interest regarding personal fees need to be disclosed: M. Schmelzle: Merck, Bayer, Erbe, Ethicon, Takeda, Olympus, Medtronic, Intuitive; W Schöning: Merck, Bayer, Ethicon; J Pratschke: Merck, Medtronic, Intuitive, Verb Surgical.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2020.11.024.

References

1. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg*. 2001;239:818–825.
2. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol*. 2009;27:3677–3683.
3. Brouquet A, Abdalla EK, Kopetz S, et al. High survival rate after two-stage resection of advanced colorectal liver metastases: response-based selection and complete resection define outcome. *J Clin Oncol*. 2011;29:1083–1090.
4. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg*. 2012;255:405–414.
5. Koh DM, Collins DJ, Wallace T, Chau I, Riddell AM. Combining diffusion-weighted MRI with Gd-EOB-DTPA-enhanced MRI improves the detection of colorectal liver metastases. *Br J Radiol*. 2012;85:980–989.
6. Shindoh J, Tzeng CW, Aloia TA, et al. Portal vein embolization improves rate of resection of extensive colorectal liver metastases without worsening survival. *Br J Surg*. 2013;100:1777–1783.
7. Melloul E, Hubner M, Scott M, et al. Guidelines for perioperative care for liver surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. *World J Surg*. 2016;40:2425–2440.
8. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet*. 2008;371:1007–1016.
9. Wong R, Cunningham D, Barbachano Y, et al. A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patients with poor-risk colorectal liver-only metastases not selected for upfront resection. *Ann Oncol*. 2011;22:2042–2048.
10. Mise Y, Aloia TA, Brudvik KW, Schwarz L, Vauthey JN, Conrad C. Parenchymal-sparing hepatectomy in colorectal liver metastasis improves salvageability and survival. *Ann Surg*. 2016;263:146–152.
11. DeMatteo RP, Palese C, Jarnagin WR, Sun RL, Blumgart LH, Fong Y. Anatomic segmental hepatic resection is superior to wedge resection as an oncologic operation for colorectal liver metastases. *J Gastrointest Surg*. 2000;4:178–184.
12. Vigano L, Capussotti L, Lapointe R, et al. Early recurrence after liver resection for colorectal metastases: risk factors, prognosis, and treatment. A LiverMetSurvey-based study of 6,025 patients. *Ann Surg Oncol*. 2014;21:1276–1286.
13. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol*. 2007;25:4575–4580.
14. Watanabe G, Mise Y, Ito H, et al. Repeat hepatectomy for early recurrence of colorectal liver metastases-prognostic impacts assessed from the recurrence pattern. *World J Surg*. 2020;44:268–276.
15. Andreou A, Brouquet A, Abdalla EK, Aloia TA, Curley SA, Vauthey JN. Repeat hepatectomy for recurrent colorectal liver metastases is associated with a high survival rate. *HPB (Oxford)*. 2011;13:774–782.
16. Figueras J, Burdio F, Ramos E, et al. Effect of subcentimeter nonpositive resection margin on hepatic recurrence in patients undergoing hepatectomy for colorectal liver metastases. Evidences from 663 liver resections. *Ann Oncol*. 2007;18:1190–1195.
17. Are C, Gonen M, Zazzali K, et al. The impact of margins on outcome after hepatic resection for colorectal metastasis. *Ann Surg*. 2007;246:295–300.
18. Andreou A, Aloia TA, Brouquet A, et al. Margin status remains an important determinant of survival after surgical resection of colorectal liver metastases in the era of modern chemotherapy. *Ann Surg*. 2013;257:1079–1088.
19. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg*. 2005;241:715–722:discussion 722–724.
20. Vauthey JN, Zimmitti G, Kopetz SE, et al. RAS mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. *Ann Surg*. 2013;258:619–626:discussion 626–627.
21. Buisman FE, Galjart B, van der Stok EP, et al. Recurrence patterns after resection of colorectal liver metastasis are modified by perioperative systemic chemotherapy. *World J Surg*. 2020;44:876–886.
22. Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey JN. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. *Br J Surg*. 2007;94:1386–1394.
23. Weiss MJ, Ito H, Araujo RL, et al. Hepatic pedicle clamping during hepatic resection for colorectal liver metastases: no impact on survival or hepatic recurrence. *Ann Surg Oncol*. 2013;20:285–294.
24. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg*. 2005;12:351–355.
25. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009;250:187–196.
26. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27:1386–1422.
27. de Haas RJ, Wicherts DA, Flores E, Azoulay D, Castaing D, Adam R. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? *Ann Surg*. 2008;248:626–637.
28. Lee AJ, Loyer EM, Kang HC, et al. Intrahepatic recurrence patterns predict survival after resection of colorectal liver metastases. *Ann Surg Oncol*. 2019;26:275–281.
29. Dupre A, Jones RP, Diaz-Nieto R, Fenwick SW, Poston GJ, Malik HZ. Curative-intent treatment of recurrent colorectal liver metastases: A comparison between ablation and resection. *Eur J Surg Oncol*. 2017;43:1901–1907.
30. Matsuoka H, Morise Z, Tanaka C, et al. Repeat hepatectomy with systemic chemotherapy might improve survival of recurrent liver metastasis from colorectal cancer-a retrospective observational study. *World J Surg Oncol*. 2019;17:33.
31. Matsumura M, Mise Y, Saiura A, et al. Parenchymal-sparing hepatectomy does not increase intrahepatic recurrence in patients with advanced colorectal liver metastases. *Ann Surg Oncol*. 2016;23:3718–3726.
32. Andreou A, Kopetz S, Maru DM, et al. Adjuvant chemotherapy with FOLFOX for primary colorectal cancer is associated with increased somatic gene mutations and inferior survival in patients undergoing hepatectomy for metachronous liver metastases. *Ann Surg*. 2012;256:642–650.
33. Brudvik KW, Mise Y, Chung MH, et al. RAS mutation predicts positive resection margins and narrower resection margins in patients undergoing resection of colorectal liver metastases. *Ann Surg Oncol*. 2016;23:2635–2643.
34. Leijssen LGJ, Dinaux AM, Kunitake H, Bordeianou LG, Berger DL. The impact of postoperative morbidity on survival in patients with metastatic colon and rectal cancer. *J Surg Oncol*. 2019;120:460–472.
35. Tanaka K, Kumamoto T, Nojiri K, Matsuyama R, Takeda K, Endo I. Impact of postoperative morbidity on long-term survival after resection for colorectal liver metastases. *Ann Surg Oncol*. 2016;23:929–937.