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ORIGINAL ARTICLE

Comparison of various surgical approaches for extensive bilateral colorectal liver metastases

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Abstract
Purpose Tailored operative strategies have been proposed for patients with bilobar colorectal liver metastases (CLM). The aim of the study was to evaluate the long-term outcome, safety and efficacy, including cancer-specific survival, morbidity, and mortality, of three different surgical strategies for extensive bilateral CLM.
Methods This is a retrospective study of a prospective database of 356 consecutive patients, who underwent hepatic resection due to CLM between January 2003 and January 2009. Fifty-nine patients underwent three different therapeutic approaches: 22 patients with portal vein embolization (PVE) + staged resections, 11 patients with staged resections solely, and 26 patients with an extensive liver resection and simultaneous or subsequent radiofrequency ablation (RFA).
Results The three groups were comparable regarding their general patient characteristics. The overall morbidity and mortality rates were 27.1 and 1.7 %, respectively. There were no significant differences in morbidity, mortality, or survival between the three groups. The median survival of all patients was 48 months, with a recurrence-free survival of 30 months.
Conclusions The clearance of bilobar CLM can be achieved by various strategies, all of them providing an acceptable mortality rate and survival for the patients. Therefore, patients with bilobar liver metastases should receive a procedure tailored for their individual extent of disease.

Keywords Staged hepatic resection · Portal vein embolization · Radio frequency ablation · Mortality · Morbidity · Survival

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Introduction

Within the past two decades, hepatic resection has become well accepted for the treatment of selected patients with colorectal cancer (CRC) liver metastases. Liver resection with complete tumor clearance may achieve long-term survival with up to 50 % of patients surviving 5 years [1] and therefore, represents the treatment of choice and gold standard for patients with colorectal liver metastasis. In fact, resection and complete destruction of liver metastasis by local ablation are the only potentially curative treatment options. Advances in neoadjuvant therapy have rendered more patients resectable, together with the improved perioperative outcome of patients undergoing liver resection and have extended the indications and limits for surgical therapy of CRC metastases. At present, patients are generally considered eligible for surgery if there is no evidence of nonresectable extrahepatic disease, if the liver lesions are technically resectable, and if the functional residual liver volume is considered to be sufficient to prevent posthepatectomy liver failure.

Despite the advances in systemic and surgical therapy of metastatic CRC, patients who present with initially unresectable, extensive, and bilateral liver metastases still present a therapeutic challenge. In selected patients with bilobar CRC liver metastases, two-stage liver resection can be achieved safely with long-term survival similar to that observed in patients with initially resectable liver metastases

[2]. Due to an insufficient future liver remnant, a proportion of these patients remain unresectable even after moderate or good response to neoadjuvant (or "preoperative") chemotherapy [3]. For these patients with bilobar disease in whom a complete clearance of the liver is not feasible within a single hepatectomy, sequential procedures have been advocated [4]. In a staged resection approach, a portion of the metastatic disease is resected within an initial operation, which is followed by a period of time to allow hypertrophy of the remnant liver. Then, a second operation is performed to achieve macroscopic clearance. Such planned staged hepatectomies should be distinguished from unplanned repeat hepatectomies for recurrent disease [5]. Further approaches to avoid posthepatectomy liver failure in these patients include the use of portal vein embolization (PVE) [6, 7] or resection together with radiofrequency ablation (RFA) of remaining lesions [8]. Unfortunately, there is a limited data on the adequate management of patients with extensive bilobar colorectal liver metastases and it has thus remained unclear, if any of the above described treatment approaches are superior regarding patients' perioperative and oncological outcome [9–11].

The aim of the present comparative study was to assess three different operative strategies of staged liver resections within the same surgical center with special regard to the perioperative outcome and long-term survival of patients with diffuse, bilateral, colorectal liver metastases.

Patients and methods

Patients

This retrospective study of clinical data of patients with liver metastasis from CRC who received primary or repeat hepatic resection with curative intent at the Department of General, Visceral and Transplantation Surgery, University of Heidelberg from January 2003 to January 2009 were prospectively included in a database. This database contained information on preoperative assessment, surgical treatment, perioperative course, histopathology, and long-term follow-up. The diagnosis of metastatic CRC was confirmed by histopathologic assessment of the resected specimen. Only patients with liver metastases (syn- and metachronous) and no other tumor burden were included in the study. Diagnostic work-up and perioperative management followed the guidelines of the Department of General, Visceral and Transplantation Surgery and Department of Anesthesiology, University of Heidelberg and were described in detail elsewhere [12–15]. Some patients (n=33) in this study were included in other previous analyses [15, 13].

The majority of patients were followed at our outpatient clinic or the National Center for Tumor Diseases (NCT) at periodic intervals. Information on the remaining patients was obtained by written questionnaires. Additionally, the general practitioners of the included patients were contacted. Follow-up included data on date of recurrence and death and reason of death.

All patients involved in this study had bilobar metastases that were not resectable within one procedure. Therefore, patients with an extended hemihepatectomy or with simultaneous atypical resections were not included.

This study was accomplished according to the Helsinki Declaration, the principles of the Good Clinical Practice (ICH-GCP) guidelines (E6) and the Federal Data protection Act. The study was approved by the ethics committee of the University of Heidelberg.

Definitions

Potentially curative surgery was defined as complete (R0) resection of all liver metastases, regardless of size, number, distribution, or width of (negative) resection margin. In case of a RFA, R0 was defined if the coagulation border exceeded the metastasis border by at least 2 cm. The Brisbane 2000 terminology of hepatic anatomy and resections was used [16]. Tumor stage was classified according to the 7th edition of the TNM classification of the Union Internationale Contre le Cancer (UICC). Bile leakage and posthepatectomy liver failure was defined according to the ISGLS definitions [17, 18].

Surgical strategies for treatment of bilobar colorectal liver metastases

Three different surgical approaches for the treatment of bilobar CRC liver metastases were compared in the present study: staged liver resection without PVE, liver resection plus PVE followed by a second liver resection, and a liver resection plus radio frequency ablation (RFA). The decision for the individual therapeutic approach was made in a multidisciplinary board including surgical oncologists, medical oncologists, and radiologists.

In the first step, the localisation of the liver metastases was evaluated. The three criteria for a potential resectability were inflow (whether influencing portal vein and the hepatic arteries), outflow (whether influencing liver veins or bile ducts), and remaining parenchyma (more than 20–30 % remnant liver parenchyma). In general, patients with bilobar metastases were divided into synchronous and metachronous metastases.

Patients with colorectal cancer and synchronous bilobar liver metastases received the resection of the primary tumor concomitant with a minor resection of the liver to clear one side. Then, the second staged, resection of the liver was performed; most of the time a right hemihepatectomy. If the remnant left hemiliver was big enough, evaluated during the primary resection, the second resection was performed without an additional PVE.

Patients with metachronous metastases were treated the same way. They received a staged resection without PVE in case of a normal volume of the remnant hemiliver and a PVE if the remnant parenchyma was too small.

The decision for a resection and RFA was made if the patient had an additional small central liver metastasis and the expected parenchymal defect after a resection of the metastasis would be not in an adequate proportion to the remaining parenchyma (see also flow chart Fig. 1).

Staged liver resection without PVE This group included only patients with an a priori planned two-stage hepatic resection without PVE. The goal of the first-stage hepatectomy was to clear the planned remaining hemiliver (most commonly the left side) of all macroscopic disease. The second resection was performed within a period of 8 weeks and most frequently represented a right hemihepatectomy. Most of these patients had synchronous liver metastases and therefore had a resection of the primary colorectal cancer concomitant to the liver resection.

Staged liver resection plus PVE As a first step, these patients underwent metastasectomy of the left liver. After an interval of 2 to 3 weeks, PVE of the right portal vein was conducted to achieve hypertrophy of the left hemiliver. The second liver resection, exclusively a right hemihepatectomy, proceeded following sufficient growth of the remaining left liver 4 to 6 weeks after PVE [19]. During PVE, each patient received analgesic sedation with 1.25-mg midazolam and 75-mg pethidin. Percutaneous puncture of the portal vein was performed with a 20 cm, 22-G Neff-Needle (Cook, Bloomington, USA) using CT as guidance method. The side of the percutaneous approach was chosen respecting the vascular anatomy and localization of the tumor. A 0.46-mm platinum wire was inserted via the needle into the portal circulation retrogradely to place a 5F introducer sheath in the next step. The wire and the introducer sheath pusher were then removed under visualization of the correct positioning of the introducer sheath in the portal vein. After inserting a steerable 0.89-mm Terumo guidewire (Radifocus, Terumo, Somerset, USA), the introducer sheath was removed and a 5F pigtail catheter was placed in the main stem of the portal vein for photography. The target branches of the right portal vein were embolized using a 4F selective vertebralis type catheter. For the purpose of embolization a combination of Histoacryl and Lipiodol (1:4 ratio) was chosen. Technical success was defined as final occlusion of all right-sided vessels supplied by the portal vein including the feeding main portal branch. The segment four branches were not routinely occluded.

Liver resection plus radio frequency ablation (RFA) Patients in this group received a planned major liver resection in combination with RFA for unfavorably located bilobar CRC liver metastases. These patients had a central metastasis in one hemiliver and multiple metastases in the resected hemiliver. Three patients received an intraoperative RFA. A RFA probe was placed percutaneously (after the operation) or intraoperatively into the lesion and a RFA generator delivered energy. An alternating current caused ionic agitation and frictional heat, leading to irreversible changes in the target cells, such as protein denaturation, and coagulative necrosis [20]. Vascular perfusion essentially affects the volume and shape of ablation zones [21]. Perfusion-induced vascular cooling limits the efficiency of RFA by the so-called heat-sink effect [22].

The RFA were carried out using a monopolar radiofrequency system (model 1500X RF generator; AngioDynamics, Latham, USA). RF-electrode was used as a probe with internal saline infusion and a diameter of 6.4F, a shaft length of 25 cm, four arrays, plus active trocar tip, and a manually adjustable active tip length of 1 to 4 cm (StarBurst Talon; AngioDynamics, Latham, USA). As ablation parameters, an electrode power of 150 W and a target temperature of 105 °C were chosen. The active tip length of the probe and the ablation time were adapted individually to each patient and procedure.

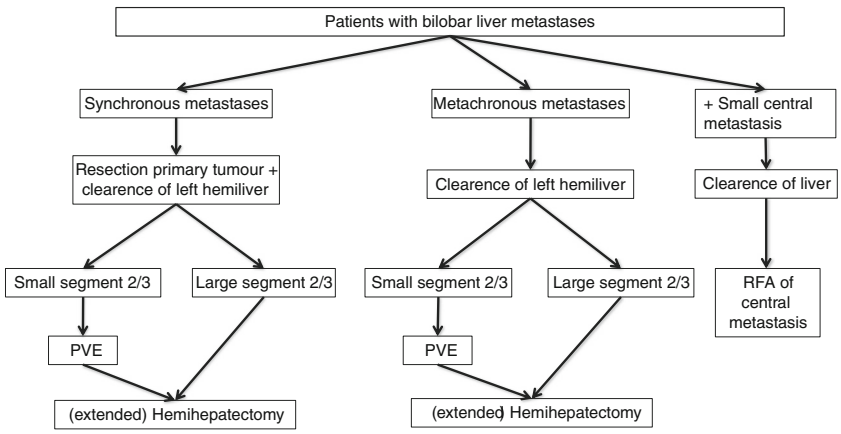

Fig. 1 Flow chart of the treatment options for bilobar liver metastases

Statistical analyses

Statistical computations were performed with JMP (SAS Institute, Cary, NC, USA) and SPSS (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as median (range) and were compared by using the Wilcoxon test, whereas categorical variables were presented as absolute and relative frequencies (count and percent) and compared using the Fisher's exact test or chi-squared test. Actuarial survival curve was calculated by the Kaplan-Meier method and differences between groups were calculated by the log–rank test. Statistical significance was defined as p value of <0.05.

Results

A total of 63 (17.6 %) patients (out of 356 patients) who underwent initiation of a staged resection or combined procedure (surgery plus RFA) of bilateral colorectal liver metastases during the study period were identified from our CRC liver metastases database. Four patients were excluded because they never received the second operation after PVE, so a total of 59 patients were eligible. There were 42 (71.2 %) men and 17 (28.8 %) women with a median age of 57 (26–80) years. The median BMI (kg/m^2) for all patients was 25.3 (20–35). The primary tumor was located in the colon in 25 (42.4 %) and in the rectum in 34 (57.6 %) cases. Most of the patients had synchronous metastases (n=41, 69.5 %), whereas the other patients were initially diagnosed at Union Internationale Contre le Cancer (UICC) stage III (n=11, 18.6 %), UICC stage II (n=4, 6.8 %) and UICC stage I (n=3, 5.1 %), respectively. Synchronous metastases occurred in 9 (81.9 %) patients with staged resections, in 16 (72.7 %) patients with PVE and a staged resection and in 16 (61.5 %) patients with resection and RFA, respectively. Metachronous metastases were detected 22.5 months (range 6–39) after the resection of the primary tumor in the staged resection group, after 8 months (5–18) in the PVE group and after 11 months (5–26) in the RFA group. The distribution of patients according to the Memorial Sloan Kettering Cancer Center (MSKCC)-score from 1 to 5 was 7 (11.9 %), 17 (28.8 %), 21 (35.6 %), 13 (22 %), and 1 (1.7 %), respectively. The median number of metastases was 4 (2–13). A total of 11 (18.6 %) patients had a staged resection without PVE, 22 (37.3 %) patients had a staged procedure with PVE, and 26 (44.1 %) patients had a liver resection plus RFA. In total, 41 patients received neoadjuvant chemotherapy. Thirteen patients had FOLFIRI (2 patients including bevacizumab) and 23 patients had FOLFOX. The lengths of therapy were three cycles for each patient. Further five patients had only 5-FU. The three groups were homogenously distributed in their general patient characteristics (Table 1). Patients with a staged resection had a time interval of 59± 12.4 days, while patients with an additional PVE had 53± 6.3 days between the two operations.

The overall morbidity rate for all operations was 27.1 % (n=16) and mortality rate was 1.7 % (n=1), respectively. There was no difference of the central venous pressure (CVP) between the groups (p=0.7) that could have been a reason for elevated intraoperative bleeding.

These selected patients with bilateral metastases had a median survival of 48 (31.7–64.2) months and a recurrence-free survival of 30 (26–33) months with a median follow-up of 28 (0–84) months. All patients received adjuvant chemotherapy after liver resection.

Staged liver resection

There were no significant differences in the perioperative outcomes between minor and major hepatic resections (Table 2). The blood loss was larger in patients with a minor liver resection (1,150 vs. 500 ml), though this difference was not statistically significant. This may be explained by the fact that 9 out of the 11 patients had a minor liver resection (synchronous liver metastases) first together with a colonic or rectal resection of the primary tumor. Patients with minor liver resections in combination with a synchronous bowel resection had two wound infections after the first operation, while the morbidity after the second liver resection included one grade A bile leakage, one grade A posthepatectomy liver failure, and one wound infection.

Liver resection plus PVE

The second operation was always the larger resection after successful PVE. This is reflected by the median operation time comparing the major with minor resection (230 vs. 145 min; p=0.03), the blood loss (1,200 vs. 250 ml; p=0.009) as well as the need for transfusion of packed red blood cells (PRBC) (4 vs. 0; p=0.007) and fresh frozen plasma (FFP) (4 vs. 0; p= 0.1). The overall morbidity rate was 22.7 % (n=10) for both operations. There were seven patients with bile leakage (grade A=2, grade B=5, grade C=0), and four patients with posthepatectomy liver failure (grade A=2, B=1, C=1), respectively. One patient with a grade C liver failure died during the postoperative course (see also Table 3).

Four patients underwent a PVE but never received a second operation (these patients were not included in the study). The reasons were tumor progression in two patients, insufficient hypertrophy of the remnant liver in one patient and partial thrombosis of the left portal vein after occlusion of the right portal vein and segment 4 portal vein in another patient.

Table 1 General characteristics of patients with PVE and liver resection, RFA and liver resection, or staged liver resection (n=59)

	Staged resection *N* (%) or median (range)	PVE + resection *N* (%) or median (range)	RFA + resection *N* (%) or median (range)	*p* value
n	11	22	26	
Age	56 (40–67)	57.5 (39–75)	57 (26–80)	0.74
Gender	11	22	26	0.92
Male	8 (72.7)	15 (68.2)	19 (73.1)	
Female	3 (27.3)	7 (31.8)	7 (26.9)	
BMI	25.2 (21–35)	25.1 (21–35)	25.1 (20–34)	0.80
ASA				0.45
2	6 (54.5)	12 (54.5)	15 (57.7)	
3	5 (45.5)	10 (45.5)	9 (34.6)	
4			2 (7.7)	
MSKCC score				0.03
1		1 (4.5)	6 (23.1)	
2	2 (18.2)	5 (22.7)	10 (38.5)	
3	6 (54.5)	7 (31.8)	8 (30.8)	
4	3 (27.3)	9 (40.9)	1 (3.8)	
5			1 (3.8)	
Number of metastases	4 (2–8)	4 (2–13)	3 (2–11)	0.48
UICC stage at diagnosis				0.86
1		1 (4.5)	2 (7.7)	
2	1 (9.1)	1 (4.5)	2 (7.7)	
3	1 (9.1)	4 (18.2)	6 (23.1)	
4	9 (81.9)	16 (72.7)	16 (61.5)	
Primary tumor location				0.28
Colon	7 (63.6)	8 (36.4)	10 (38.5)	
Rectum	4 (36.4)	14 (63.6)	16 (61.5)	
CEA				
≤200 ng/dl	9 (81.8)	19 (86.4)	24 (92.3)	0.69
>200 ng/dl	2 (18.2)	3 (13.6)	2 (7.7)	
Nodal status (of primary)				
Positive	7 (63.3)	17 (77.3)	18 (69.2)	0.81
Negative	4 (36.7)	5 (32.7)	8 (30.8)	
Size of metastases				
≤5 cm	6 (54.5)	10 (54.5)	16 (61.6)	0.48
>5 cm	5 (45.5)	12 (45.5)	10 (38.4)	
Preoperative chemotherapy				
Yes	9 (81.8)	14 (63.6)	18 (69.2)	0.56
No	2 (18.2)	8 (36.4)	8 (30.8)	
Recurrence	11 (100)	17 (77.3)	26 (100)	0.05
Tumor-related death	2 (18.2)	9 (40.9)	13 (50)	0.46
Recurrence-free survival (months)	28 (18.2–37.7)	28 (22.6–33.3)	36 (20.7–51.2)	0.06
Liver-specific disease-free survival (months)	26 (16.6–36.1)	27 (21.2–33.3)	36 (20.7–51.2)	0.057
Overall survival (months)	59 (13.2–104.7)	36 (27–44.9)	49 (37.4–60.5)	0.58

$p<0.05$ was considered to be statistically significant

PVE portal vein embolization; *RFA* radio frequency ablation; *BMI* body mass index; *ASA* American Society of Anesthesiologists; *MSKCC score* Memorial Sloan Kettering Cancer Center score; *UICC* Union Internationale Contre le Cancer; *CEA* carcinoembryonic antigen

Table 2 Perioperative data for staged liver resections (n=11)

	Minor resection *N* (%) or median (range)	Major resection *N* (%) or median (range)	*p* value
CVP (mmHg)	3.2 (1–7)	6.1 (1–8)	0.26
Operating time (min)	208 (110–390)	160 (116–398)	0.61
Blood loss (ml)	1150 (100–4,000)	500 (100–1700)	0.18
PRBC	0 (0–4)	0 (0–4)	0.66
FFP	0 (0–9)	0 (0–6)	0.85
Intensive care unit (d)	2 (1–3)	2 (1–4)	0.40
Morbidity	2 (18.2)	3 (27.3)	0.63
Bile leakage	0	1	
Liver failure	0	1	
Wound infection	2	1	
Mortality	0	0	

CVP central venous pressure; *PRBC* packed red blood cells; *FFP* fresh frozen plasma

$p<0.05$ was considered to be statistically significant

Liver resection plus RFA

In this group, 11 patients had hemihepatectomy (5 extended), 4 patients had a combined bisegmentectomy of segments 2/3 and 7/8, 2 patients had a combined bisegmentectomy of segments 2/3 and 6/7, 3 patients had multiple wedge resection (5 or more metastases), and 3 patients had a bisegmentectomy of segments 2/3 and an intraoperative RFA, respectively.

Operation time and the median blood loss were not significantly different to the other procedures. The median intraoperative central venous pressure (CVP) was 4 mmHg, comparable to the CVP of patients with PVE or a staged liver resection. Patients had a median stay at the intensive care unit (ICU) of 2 days. While six patients had a postoperative complication, no patient died. The most frequent complication was a postoperative bile leakage (grade A=2, grade B=3, grade C=0), followed by a wound infection and one patient developed a grade A posthepatectomy liver failure (see also Table 4).

Comparison of staged resection with or without PVE

Most of the perioperative parameters were not significantly different between the first two groups (staged resection vs. staged resection with PVE). However, the blood loss (p=0.03) and consecutive need of PRBC (p=0.002) was more than double in patients with a staged resection and PVE (see Table 5).

Overall and recurrence-free survival

The 1-, 3-, and 5-year overall survival rates for patients with a staged procedure were 88, 57, and 33 %, respectively. Disease-free survival rate was 90, 33, and 12 % at 1, 3, and 5 years. The recurrence rate of all patients was 91.5 %. The median survival was 48 months. Overall and disease-free survival rates of the 59 treated patients were not different compared with patients that underwent a single hepatectomy in the same study period [12].

Table 3 Perioperative data for PVE and liver resection (n=22)

	Resection before PVE *N* (%) or median (range)	Resection after PVE *N* (%) or median (range)	*p* value
CVP (mmHg)	6.5 (3–13)	4 (1–12)	0.007
Operation duration (min)	145 (82–335)	230 (152–390)	0.03
Blood loss (ml)	250 (20–900)	1,200 (400–6,000)	0.009
PRBC	0 (0–4)	4 (0–14)	0.007
FFP	0 (0–4)	4 (0–48)	0.10
Intensive care unit (d)	2 (1–4)	2 (1–31)	0.30
Morbidity	3 (13.6)	7 (31.8)	0.85
Bile leakage	2	5	
Liver failure	0	4	
Wound infection	1	1	
Mortality	0	1 (4.5)	0.49

$p<0.05$ was considered to be statistically significant

PVE portal vein embolization; *CVP* central venous pressure; *PRBC* packed red blood cells; *FFP* fresh frozen plasma

Table 4 Perioperative data for liver resection and RFA (n=26)

	Liver resection + RFA *N* (%) or median (range)
CVP (mmHg)	4.1 (0–15)
Operation duration (min)	210 (40–380)
Blood loss (ml)	650 (100–3,200)
PRBC	0 (0–6)
FFP	0 (0–4)
Intensive care unit (d)	2 (0–5)
Morbidity	6 (23.1)
Bile leakage	5
Liver failure	1
Wound infection	1
Mortality	0

RFA radio frequency ablation; *CVP* central venous pressure; *PRBC* packed red blood cells; *FFP* fresh frozen plasma

There was no difference of the overall and disease-free survival between the three groups with regard to the performed procedure (see Figs. 1, 2, and 3).

Furthermore, we tried to identify risk factors for a shortened survival of these patients. Table 6 depicts that no risk factor could be found in univariate analysis. In multivariate analysis of all factors with $p<0.3$ no risk factor could be found either (data not shown).

None of the included patients had reoperations because of recurrent tumor growth. In case of recurrent disease, patients received chemotherapy.

Discussion

The present study demonstrates that various individualized procedures for bilobar liver metastases are feasible, safe, and offer a good long-term survival for selected patients that were initially not resectable within one procedure. Furthermore, three different ways to achieve tumor clearance were compared and did not show any differences with regard to long-term survival.

There is clear evidence that selected patients with CRC liver metastases benefit from hepatic resection. It is now well accepted that curative (R0) resection of liver metastases, if technically feasible, improves survival irrespective of the number and size of the lesions, the width of the resection margin and involvement of major vascular structures [23, 24]. Advances in surgical technique and perioperative care such as PVE or RFA have permitted this more radical approach to the treatment of CRC liver metastases and extended the indications for surgical therapy. Patients with bilobar metastases are often regarded unresectable because the remnant liver parenchyma may not be sufficient and patients could suffer from posthepatectomy liver failure. A way to avoid this potential problem is a staged procedure in which one lobe (usually the left) of the liver is cleared of the metastases in the first operation. PVE is a therapeutic option to enlarge the remaining segments followed by the second resection within 4 to 6 weeks later [6, 7]. Another possibility to reach tumor clearance is the combination of liver resection and RFA [8] or just a staged "two-step" liver resection. In our study, all these different procedures to achieve tumor clearance in patients with bilobar liver metastases were compared (PVE + resection; resection + RFA; staged "two-step" resection).

Patients of all three groups had almost similar general characteristics and were comparable to the patient cohorts in previously published articles [25, 26]. These patients with initially unresectable liver metastases often had neoadjuvant chemotherapy to downstage the tumor burden in the liver. Two thirds of patients in our series received neoadjuvant chemotherapy, which is in accordance to the percentage described in other publications [4, 27]. None of the patients had chemotherapy in the interval (neither in the PVE group nor in

Table 5 Comparison of perioperative data for staged liver resection with or without PVE

	Resection + PVE major resection *N* (%) or median (range)	Staged resection major resection *N* (%) or median (range)	*p* value
CVP (mmHg)	4 (1–12)	6.1 (1–8)	0.54
Operation duration (min)	230 (152–390)	160 (116–398)	0.10
Blood loss (ml)	1,200 (400–6,000)	500 (100–1,700)	0.03
PRBC	4 (0–14)	0 (0–4)	0.002
FFP	4 (0–48)	0 (0–6)	0.12
Intensive care unit (d)	2 (1–31)	2 (1–4)	0.26
Morbidity	7 (31.8)	3 (27.3)	0.56
Bile leakage	5	1	
Liver failure	4	1	
Wound infection	1	1	
Mortality	1 (4.5)	0	

$p<0.05$ was considered to be statistically significant

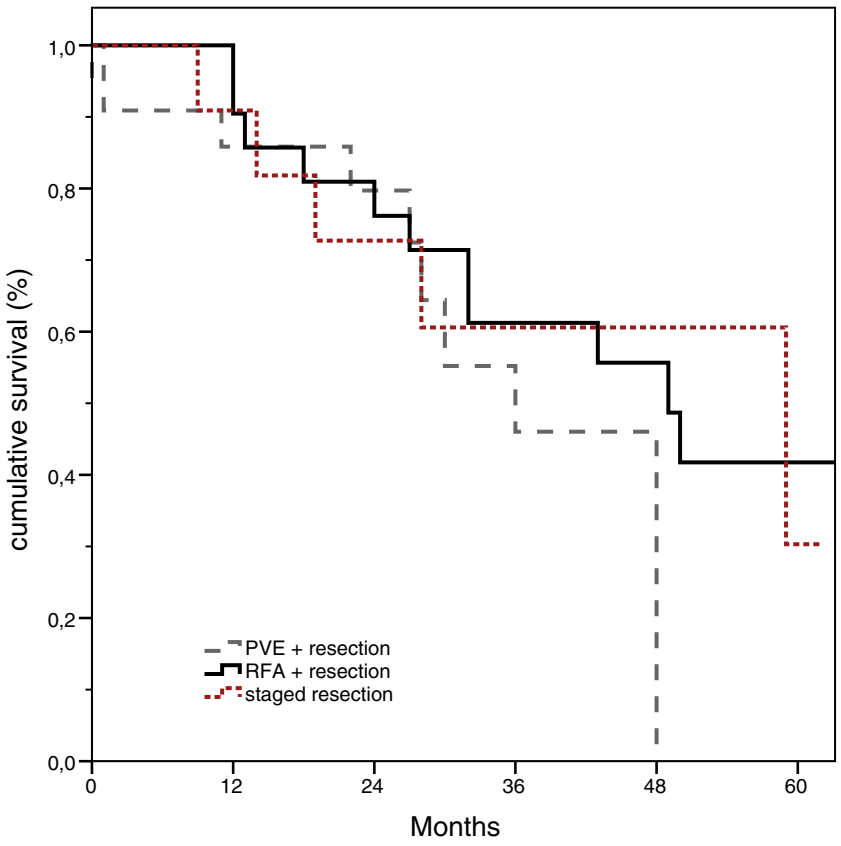

Fig. 2 Survival of patients with potentially curative resection of colorectal cancer liver metastases stratified for the three different resection groups

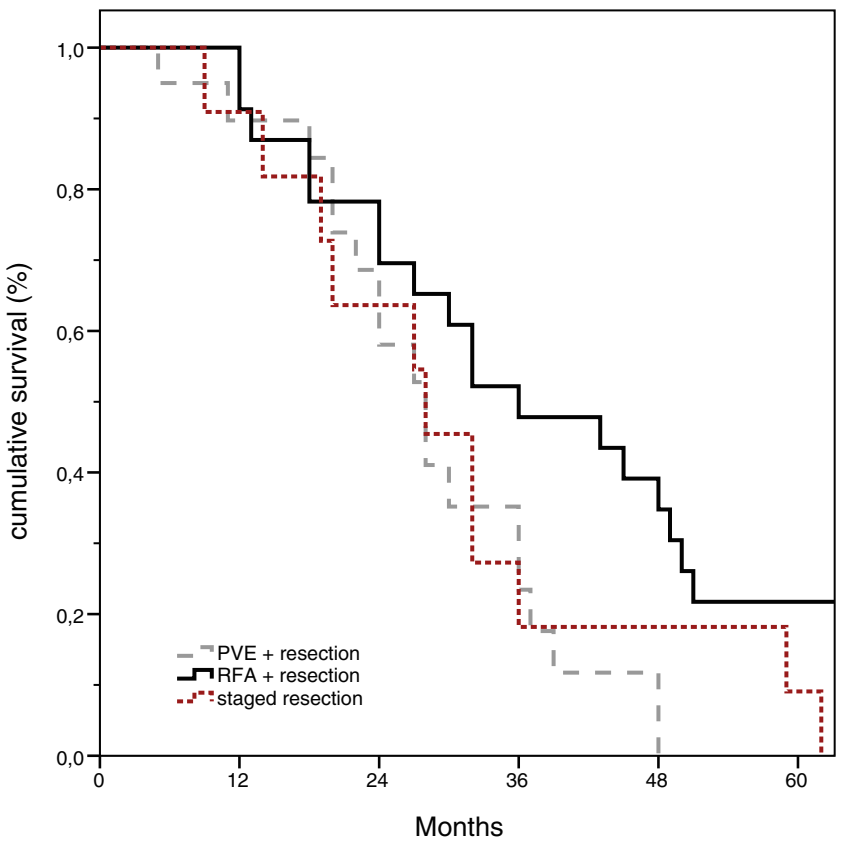

Fig. 3 Recurrence-free survival of patients with potentially curative resection of colorectal cancer liver metastases stratified for the three different resection groups

Table 6 Univariate analysis of factors associated with survival after an individualized procedure of liver resection for bilobar CRC metastasis

	Median survival (months, 95 % CI)	*p* value
Gender		
Male	48 (19.2–76.8)	0.91
Female	49 (23.4–74.5)	
ASA		
2	59 (35.7–82.2)	
3	36 (17.9–54.0)	0.25
4	12 (12–49)	
MSKCC score		
1	50 (19.6–80.3)	
2	49 (24.5–73.4)	
3	32 (25.5–62)	0.94
4	28 (26.0–29.9)	
5	43 (only 1 patient)	
MSKCC score		
≤2	50 (46.6–53.3)	0.51
>2	43 (23.7–62.2)	
Primary tumor		
Colon	43 (26.7–59.2)	0.21
Rectum	50 (19.6–80.3)	
CEA		0.29
≤200 ng/dl	50 (26.1–73.8)	
>200 ng/dl	43 (not reached)	
Node		
Positive	49 (21.9–76.0)	0.42
Negative	48 (20.7–75.2)	
Surgical approach		
Resection + PVE	36 (27.0–49.9)	
Resection + RFA	49 (37.4–60.5)	0.58
Staged resection	59 (13.2–104.8)	
Size of metastases		0.17
≤5 cm	49 (33.9–64.0)	
>5 cm	36 (22.0–49.9)	
Preoperative chemotherapy		
Yes	49 (24.7–73.2)	0.73
No	48 (37.7–58.2)	

the staged resection group) between the first and second resection [25, 28]. Although Goere et al. demonstrated that chemotherapy after PVE does not impair liver hypertrophy [28], chemotherapy still induces alterations of the parenchyma and reduces liver function [29, 30] Therefore, we abandoned interval chemotherapy with the known risk of possible tumor progression [31]. Indeed, 15 % of patients (n=2) in the PVE group showed tumor progression and could not undergo the planned procedure. However, it is not clear or proven that interval chemotherapy is really able to reduce this failure rate and dropout rates between the two surgical steps with or without PVE rather reflect the poor tumor biology with a selection of suitable patients for this staged procedure.

The retrospective design is a major limitation of the study that may have caused significant bias. One should note that although all patients had initially unresectable metastases (judged by an experienced liver surgeon) and the distribution and number of the metastases, as well as the general patient characteristics, were similar, the three groups were heterogeneous with regard to their oncologic disease. Therefore an individual approach had to be discussed for every patient in our interdisciplinary tumor board considering the tumor burden and location of the metastases. For example, patients with a liver metastasis close to a large intrahepatic vessel were not subjected to RFA + resection because of the blood cooling effect and the consecutive incomplete destruction of the liver lesion. However, it was the aim of the present study to compare the available treatment approaches and to detect potentially significant differences in long-term survival. To this end, this appears the most suitable approach to assess the oncological value of the evaluated treatments, as a prospective randomized trial comparing the different approaches appears hardly feasible and trials comparing these treatment options to systemic therapy without resection are unethical.

Another important aspect is the safety of all three procedures. The overall postoperative morbidity and mortality rates with 27.1 and 1.7 % in this cohort are equivalent to staged or single-stage hepatic resections in the literature [26, 15, 32]. This is especially worth mentioning as these patients had an extensive resection with a high morbidity risk. The comparison of the three groups revealed that patients treated with PVE and liver resection had the highest morbidity rate, although not significantly varying from the others. Even the groups with two resections (PVE or "two-step") have similar morbidity rates compared to single resections in the literature what legitimates the risk of a second operation to achieve tumor clearance. So, staged procedures in initially unresectable CRC liver metastases have a similar risk to gain a complication compared to normal, standardized liver resections. The low mortality rate of 1.7 % underlines the safety.

Bilobar CRC liver metastases are a well-known risk factor for tumor recurrence [12, 33]. Because of the extent of the disease, lower survival rates would be expected for these patients. However, our results confirm that all three strategies have the potential to offer a similar survival benefit for patients with advanced bilobar disease. This is in accordance with reports from others [26, 25] who could demonstrate the safety and survival benefit for patients with initially unresectable liver metastases. Nevertheless, the tumor recurrence rate remains high with 91.5 % in our cohort. But, regardless of the recurrence rate, these patients still have a benefit from the operation. The published survival rate of chemotherapy only in CRC liver metastases is around 31 months [34]. In this

study, the median survival rate is 48 months. It seems that a staged surgical procedure to obtain tumor clearance in CRC liver metastases is advisable whenever possible. Schnitzbauer et al. recently described a new surgical approach with a staged "two-step" procedure for initially unresectable metastases [35]. The authors described a combination of a small left liver resection, a right portal vein ligation and an in situ liver splitting in the first procedure. Within nine days after the first operation, the remaining liver tissue increased by 74 %. Then, in a second operation, the completion of the resection was performed. This procedure is a very interesting option as the time interval between the first and second resection is rather short and, meanwhile, tumor growth is unlikely. The morbidity and mortality rates were slightly elevated but tolerable with respect to the extended resection. The overall survival and recurrence rates after this surgical approach still need to be evaluated.

Conclusions

In summary, it seems that all three approaches are feasible with regard of oncological outcome and perioperative morbidity and mortality in this selected, not randomized patient cohort. There is no general pathway on how to treat patients with extended bilobar metastases. It is always an individualized concept and has to be decided by the location of the metastases, their relation to the vessels and the potential remaining liver parenchyma. Therefore, the treating oncologists and surgeons should always consider a tailored, multiple step approach to reach tumor clearance in these patients.

Conflicts of interest None.

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