ORIGINAL ARTICLE

Two-stage hepatectomy (R0) with portal vein ligation—towards curing patients with extended bilobular colorectal liver metastases

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Abstract

Background and aims Patients with bilobular colorectal liver metastases (CRLM) experience poor prognosis, especially when curative resection cannot be achieved. However, resectability in these patients is often limited by low future remnant liver volume (FRLV). The latter can be enhanced by a two-stage liver resection, using portal vein ligation to induce liver hypertrophy. The aim of this prospective pilot study was to evaluate safety, secondary resectability, and time to recurrence of two-stage hepatectomy with portal vein ligation (PVL) and complete surgical clearance of the FRLV in patients with bilobular CRLM.

Materials and methods Out of 24 patients (63±8.26 years) with extended bilobular CRLM (metachronous $n=10$, synchronous $n=14$), 18 received preoperative 5-FU-based chemotherapy combined with oxaliplatin or irinotecan. Staging included thoracoabdominal computed tomography and ^{18}F-fluorodeoxyglucose-positron emission tomography scans. First-stage procedure consisted of PVL, resection of all CRLM in the FRLV, and radiofrequency ablation (RFA) of CRLM situated near the future resection plane.

Results During first-stage procedure, 7× RFA, 4× non-anatomical resections, and 4× bisegmentectomies were performed additionally to PVL. FRLV/body-weight ratio increased from 0.4% to 0.6% within 55 days (median) after PVL. Second-stage hepatectomy was performed in 19 patients without tumor progression. R0 resection was possible in 14 patients. During a median follow-up of 17 months, intrahepatic recurrence occurred in two, and extrahepatic recurrence in nine out of 14 patients.

Conclusion Two-stage hepatectomy with PVL and complete surgical clearance of FRLV is safe even after intensified systemic chemotherapy resulting in a curative resection rate of 58.3% (73.7% of re-explored cases).

Keywords Bilobular colorectal liver metastases · Two-stage hepatectomy · Portal vein ligation · Insufficient future remnant liver volume · Liver hypertrophy

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Introduction

Liver resection is the only potentially curative treatment option of colorectal cancer metastases (CRLM). It has become the standard of care even in patients with multiple metastases, resulting in 5-year survival rates of 37–50% in specialized centers [1, 2]. However, in case of bilobular involvement, patients experience a poorer outcome, with 5-year survival rates of only 20% [3]. As this still is beneficial when compared to intensive systemic chemotherapy alone [4], surgical approaches are recommended even in this

challenging subgroup of patients, provided that curative resection appears achievable. Unfortunately, 70–80% of patients presenting with multiple and/or bilobular CRLM are not resectable at the time of diagnosis [5]. In patients without extrahepatic spread, unresectability is mainly due to an insufficient amount of future remnant liver volume (FRLV) [6], which, in the absence of chronic liver disease, can be estimated as less than 30% of the initial total liver volume [7] or a FRLV to body weight ratio of <0.5% [8]. It has been demonstrated that secondary resectability in these cases can be achieved by either preoperative chemotherapy, portal vein occlusion, or both. While preoperative chemotherapy leads to an effective downsizing of CRLM [9], portal vein occlusion, performed as surgical ligation (PVL) or as interventional embolization (PVE), induces significant hypertrophy of the FRLV [10]. Portal vein occlusion thereby allows extended two-stage hepatectomy without transient liver failure [11]. In our experience, neither preoperative chemotherapy nor the number of metastases influence tumor-related overall survival when curative resection can be achieved (Fig. 1a,b). Additionally, Shaw et al. [12] reported 5-year survival rates of 44% after second hepatectomy for recurrent CRLM. Adam et al. [13] even described a 5-year survival rate of 32% after third hepatectomy. Although these data are encouraging and seem to justify aggressive multidisciplinary approaches, there is still no consensus on what the optimal oncological strategy should be.

The present prospective pilot study on 24 patients with bilobular CRLM describes an intensive multimodal treatment concept, including preoperative chemotherapy and two-stage hepatectomy with portal vein ligation (PVL) and complete surgical clearance of the FRLV. The paper focuses on feasibility, safety, and surgical and preliminary oncological outcome.

Materials and methods

All interventions were performed according to established surgical procedures and actual guidelines for the treatment of colorectal and hepatobiliary diseases by the German Society of Surgeons.

Between April 2005 and November 2007, 24 patients with a mean age of 63 ± 8.26 (range 42–76) years and presenting with bilobular CRLM were selected for a two-stage liver resection with PVL. All data were collected prospectively. The characteristics of the 24 patients are summarized in Table 1. Seven female and 17 male patients were included in the study. Primary tumor location was colon and rectum in 12 patients each. One patient received neoadjuvant radiochemotherapy before rectal resection, and eight patients were treated by chemotherapy in an adjuvant
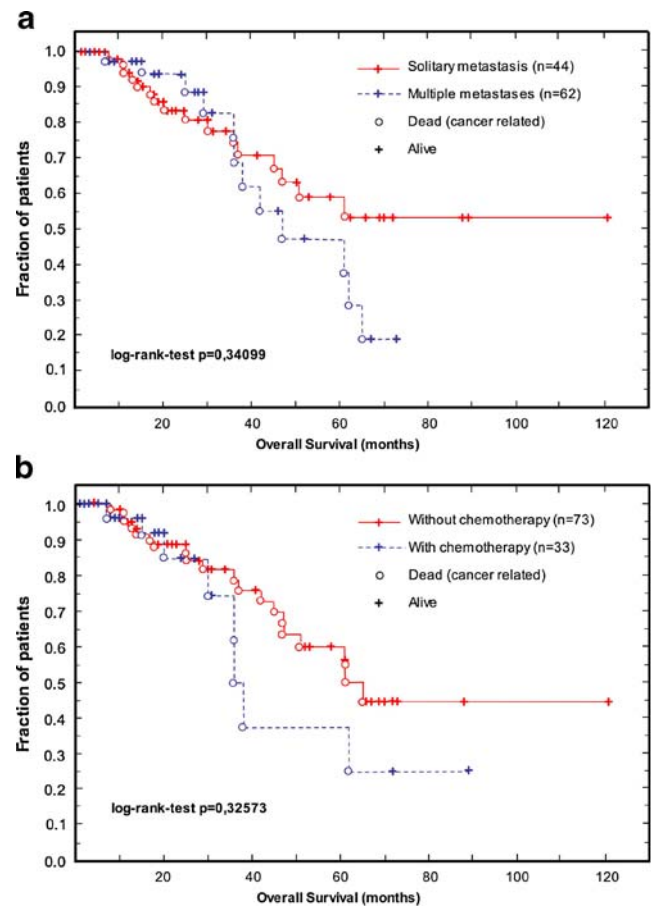
Fig. 1 **a** Kaplan–Meier-plot on overall survival after salvage resection of colorectal liver metastases with curative intent ($n=106$). Patients were stratified based on number of metastases but irrespective of preoperative and adjuvant treatment (University Medical Center Goettingen, Department for General and Visceral Surgery 2001–2007). **b** Kaplan–Meier plot on overall survival after salvage resection of colorectal liver metastases with curative intent ($n=106$). Patients were stratified according to preoperative treatment (chemotherapy versus no chemotherapy) irrespective of number of metastases, resection type, or adjuvant treatment (University Medical Center Goettingen, Department of General and Visceral Surgery 2001–2007)

setting after resection of the primary tumor. CRLM were synchronous in 14 patients (time between primary cancer resection and diagnosis of CRLM <3 month) and metachronous in ten patients, with a median disease-free survival between primary tumor resection and diagnosis of CRLM of 20 (range, 8–183) months.

Three patients had been included in our study because of intrahepatic recurrence. Two of these had undergone previous curative non-anatomic liver resection. The third patient had been treated by systemic chemotherapy with 5-fuorouracil, folinic acid, and oxaliplatin for synchronous CRLM, resulting in complete remission based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria [14] but presented with intrahepatic recurrence 22 months later.

Table 1 Patient characteristics

	Number	Percent
Patients	24	100
Sex		
Female	7	29.2
Male	17	70.8
Weight (kg)[a]	85.9±16.8	
Primary cancer		
Colon	12	50
Rectum[b]	12	50
Primary tumor stage		
UICC I	0	0
UICC II	5	20.8
UICC III	5	20.8
UICC IV	14	58.4
Systemic therapy of primary cancer		
5FU/FA + RT 50,4 Gy (neoadjuvant)	1	4.2
5-FU/FA ± Oxaliplatin (adjuvant)	8	33.4
Detection of hepatic metastases		
Synchronous[c]	14	58.4
Metachronous	10	41.6

UICC Union international contre le cancer, *5-FU* 5-fluorouracil, *FA* folinic acid, *RT* radiotherapy, *SD* standard deviation

[a] Mean ± SD

[b] TNM/UICC classification (up to 16 cm above anocutaneous verge as measured by rigide rectoscopy)

[c] Less than 3 months between resection of primary tumor and diagnosis of intrahepatic metastases

Eighteen (75%) patients received preoperative chemotherapy with oxaliplatin or irinotecan; six (33%) of them were treated additionally with the vascular endothelial growth factor antibody, bevacizumab. According to RECIST criteria, eight of the 18 patients (44.4%) showed stable disease or even partial response, while in ten patients (55.6%), progressive disease confined to the liver was observed (Table 2). However, in the latter, resectability had never been assessed by an experienced hepatobiliary surgeon before, but at restaging prior to our study, curative resection seemed to be achievable despite intrahepatic tumor progression. At the time of referral to our institution, the median preoperative Karnofsky performance index was >80%.

Preoperative evaluation included thoracoabdominal computed tomography (CT) scan with special regard to portal vein anatomy, as well as 3-dimensional volumetry, and also ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET). All data were preoperatively reviewed by a multidisciplinary team (hepatobiliary surgeon, medical and surgical oncologist, radiologist, and specialist in nuclear medicine). Figure 2 shows the design of our pilot study. The aim of the intensive preoperative imaging conducted was to rule out disseminated intrahepatic CRLM, which we considered as contraindication for primary surgical exploration, and to identify extrahepatic tumor spread. The latter was not considered as contraindication to liver resection when curative resection seemed to be achievable simultaneously to first-stage hepatectomy or during prior separate surgery. Patients with unresectable extrahepatic disease, namely with advanced local recurrence, disseminated pulmonary metastases, or peritoneal carcinomatosis were not eligible for this feasibility study.

First-stage hepatectomy

First-stage hepatectomy, as the key step in our multimodal therapy concept, was performed in all patients. After upper midline laparotomy with right subcostal (J-shaped) extension, complete exploration of the intraperitoneal cavity was performed. The liver was then evaluated with both bimanual palpation and intraoperative ultrasound to identify the intrahepatic metastatic pattern. Portal vein occlusion was performed at the side of main tumor load. To avoid extensive adhesions during second-stage hepatectomy, mobilization of the liver and especially hilar dissection were carried out most conservatively, with as minimal a division of the falciform ligament and diaphragmatic attachments as possible. Using a right lateral approach to the hepatoduodenal ligament, the main portal vein was then

Table 2 First-stage hepatectomy

|	Number	Percent
Preoperative chemotherapy for downsizing of CRLM		
None	6	25
FOLFOX/FOLFIRI	12	50
FOLFOX/FOLFIRI + Bevacizumab	6	25
Effect of preoperative chemotherapy[a]		
Stable disease/ partial remission	8	33.3
Progressive disease	10	41.7
Surgical procedures		
Right PVL	23	95.8
Left PVL	1	4.2
+ radio frequency ablation	7[b]	29.2
+ non-anatomical resection	4	16.6
+ bisegmentectomy segment II/III	4	16.6
+ resection of extrahepatic disease	1	4.2
Hospitalisation (days)[c]	12.3 ± 3.8 (8-28); 12	
Mortality	0	0
Morbidity	3	12.6
Wound infection	1	4.2
Cardiac arrhythmia	1	4.2
Urogenital infection	1	4.2

CTX chemotherapy, *CRLM* colorectal liver metastases, *PVL* portal vein ligation

[a] Relating to intrahepatic disease; based on RECIST-criteria [14]

[b] In two cases both RFA and non-anatomical resection were performed

[c] Mean ± SD (range); Median

Fig. 2 Algorithm for treatment of bilobular colorectal liver metastases applied in the study. After diagnosing bilobular CRLM, coexistence and extent of extrahepatic disease was evaluated and, if necessary, resected. During first-step hepatectomy, the site of main tumor load was identified with subsequent ipsilateral portal vein ligation or transection. CRLM in the future remnant liver lobe were resected completely if present. Those metastases situated near the future resection plane were treated by RFA to achieve local tumor control. Newly diagnosed extrahepatic disease was resected simultaneously. When restaging after liver hypertrophy showed no progression of disease, second-stage hepatectomy with major liver resection was performed. In case of progressive disease, the remaining CRLM were treated by RFA, followed by chemotherapy in palliative intention
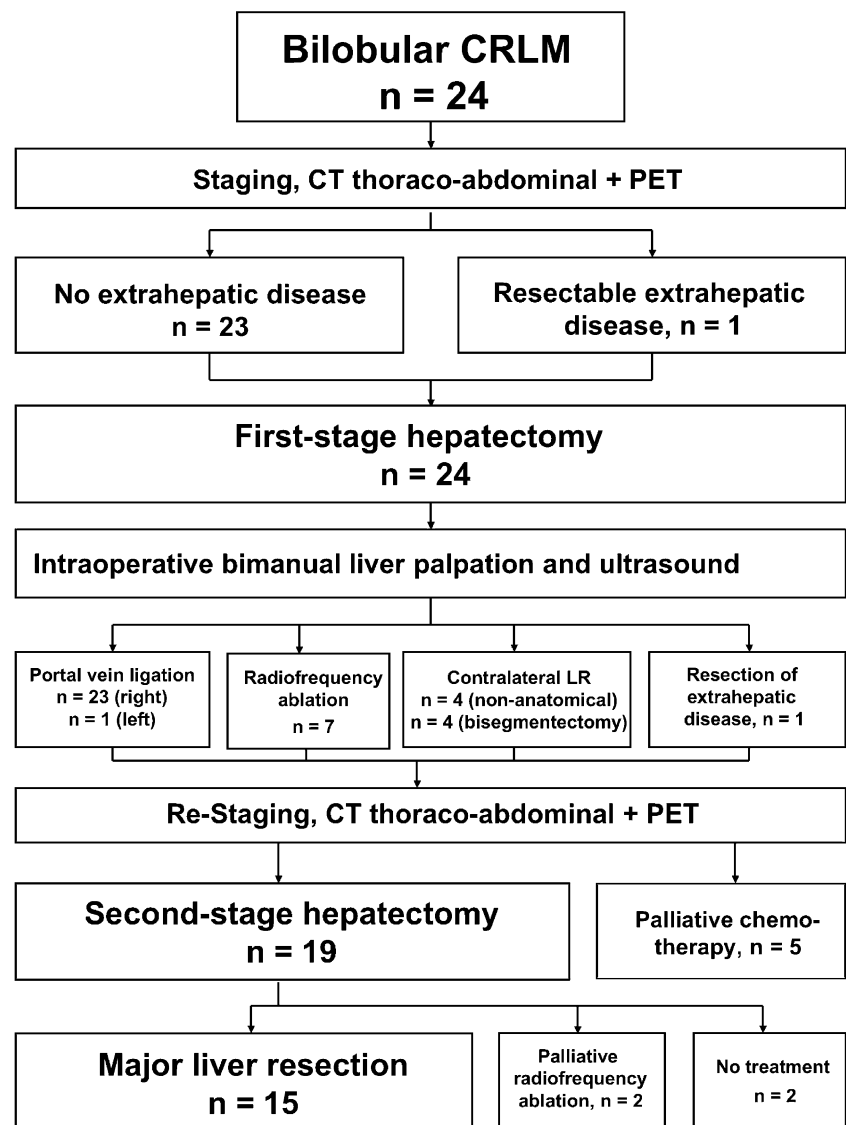

followed until its bifurcation into the left and right portal veins. To facilitate redissection during second-stage hepatectomy, the portal branch selected for occlusion was transected and oversewn using nonabsorbable sutures with the use of vascular clamps. In patients presenting with variant portal vein anatomy, namely a bifurcation of the main portal trunk into a right posterior and right anterior branch with the left portal vein arising from the latter, we modified our technique. A transection of the right posterior branch was performed as described, followed by ligation of the right anterior branch distal of the rise of the left portal vein (Fig. 3). Because CRLM have been reported to grow during liver regeneration following portal vein occlusion [15, 16], CRLM situated near the future resection plane were ablated by radiofrequency (RFA), suggesting that growth rate and metastatic potential during hypertrophy could thereby be reduced. This concerned metastases in S IVa/b, when right trisegmentectomy was planned, and

metastases in segment V/VIII when left trisegmentectomy was planned. CRLM in the lateral segments of the nonligated lobe were not treated by RFA but resected. In cases when only segments I and IV were unaffected by CRLM, right PVL was combined with bisegmentectomy of segment II/III.

Re-evaluation

Re-evaluation was performed routinely 6 weeks after first-stage hepatectomy and again consisted of thoracoabdominal CT scan with 3-dimensional volumetry and FDG-PET. All volumetric examinations were reviewed by the same experienced radiologist (G.S.). The second-stage procedure was cancelled when CRLM occurred in the future remnant liver or disseminated extrahepatic tumor spread was diagnosed. No chemotherapy was administered between first-stage and second-stage hepatectomy.
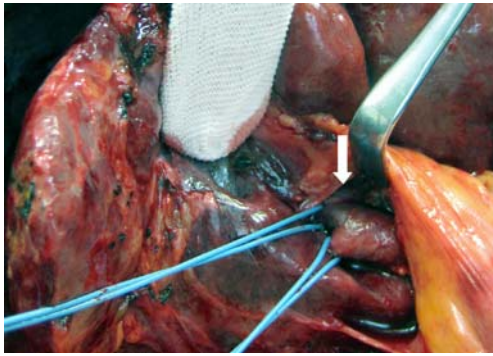
Fig. 3 Intraoperative situs with performed limited lateral dissection of the hepatoduodenal ligament in a patient with variant portal vein anatomy: the first bifurcation of the main portal vein (PV) divides the PV into a right posterior branch and right anterior branch (both indexed by *blue vessel loops*), the latter delivering the left portal vein (*white arrow*). Such anatomical variation is rare occurring in less than 15% of cases [42]. Transection instead of ligation of the portal vein branches during first-stage procedure results in technically easier complete dissection of the hepatoduodenal ligament during second-stage hepatectomy. It might be difficult to perform transection without liver dissection especially for the right anterior branch in the presence of variant portal vein splitting. Thus, in the displayed situation, we performed transection of the right posterior branch and ligation of the right anterior branch of the portal vein

Second-stage hepatectomy

Depending on the extent of liver resection during the first-stage procedure, we performed hemihepatectomy (in cases of previous bisegmentectomy) or trisegmentectomy during the second-stage hepatectomy. Liver parenchyma dissection was carried out without inflow occlusion. Lymph node dissection of the hepatoduodenal ligament was not performed routinely. In patients with resectable extrahepatic disease, this was resected simultaneously even if affecting the lung. According to our treatment paradigm, we cancelled the planned liver resection when new CRLM occurred in the FRLV and treated all detectable CRLM by RFA. The diagnosis of disseminated intra- or extrahepatic tumor spread resulted in termination of the operation. Postoperative liver failure was assessed according to Balzan et al. [17].

Histopathological examination was performed according to standard operating procedures.

Postoperative treatment

Previous immunohistochemical studies as well as analyses of serum titers of carcinoembryonic antigen (CEA) indicate its expression in >90% of colorectal cancer patients [18, 19]. In addition, diagnostic imaging studies with CEA-specific antibodies have shown selective and enhanced localization of colorectal cancer [20, 21]. Therefore, we performed immunohistochemical staining for CEA in all patients, and postoperative radioimmunotherapy with ^{131}I-labetuzumab [22, 23] was indicated on investigators' discretion when staining intensity was assessed as moderate or strong.

Follow-up

Patients were standardly followed up with a physical examination, liver biochemistry, CEA, and abdominal ultrasound every 3 months. Patients consenting to adjuvant radioimmunotherapy underwent thoracoabdominal CT and FDG-PET scans prior to radioimmunotherapy and afterwards, every 6 months. No patient was lost during the follow-up period until June 30, 2008.

Ethical considerations

All human interventions were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and have been approved by the regional ethical committee. All persons gave their informed consent prior to their inclusion in the study.

Statistics

The Kaplan–Meier survival estimates method was used to calculate overall survival, and significant differences were examined using the log-rank test. A difference was considered to be significant when the p value was less than 0.05. The analysis was performed using the statistical software Statistica (StatSoft, Tulsa, OK, USA).

Results

First-stage hepatectomy

In 23 (95.8%) of the cases, the right portal vein was ligated or dissected; in one patient, ligation of the portal branches was extended to segment IV. One patient underwent ligation of the left portal vein. Additional treatment to PVL consisted of RFA ($n=7$), non-anatomical resection ($n=4$), and bisegmentectomy of the left lateral segments II/III ($n=4$). In one patient, preoperative CT scan had shown a suspicious, FDG-PET-positive mass ventrocranial of the bladder, which could be identified intraoperatively as a local lymph node recurrence and could be completely resected. The mean hospital stay after first-stage procedure was 12.3±3.8 days with no mortality and a morbidity rate of 12.6% (Table 2).

Volumetric analysis

Table 3 gives a summary of the volumetric analysis. The median number of liver metastases detected by CT scan

Table 3 Volumetric data of the liver parenchyma

	Mean ± SD	Range	Median
No. of liver metastases before PVL (*n*)	3.1±2.3	1–7	2
Size of largest liver metastasis before PVL (cm)	4.3±2.9	0.9–11	4
TLV before PVL (ml)	1752.3±413.5		1613.5
FRLV before PVL (ml)	350.5±111		322
FRLV/body weight ratio before PVL	0.42±0.11		0.4
No. of liver metastases after hypertrophy (*n*)	4.2±3.3	1–10	4
Size of largest liver metastasis after hypertrophy (cm)	4.8±2.9	0.3–11	4.4
TLV after hypertrophy (ml)	1712.4±397.8		1610
FRLV after hypertrophy (ml)	475±171.4		419
time between PVL and re-evaluation (days)	57.9±18		55
ΔFRLV (ml)	123.2±106.7		114
ΔFRLV (%)	35.7±29.3		36.5
TLV/FRLV ratio	28±6.4		29
FRLV/body weight ratio	0.58±0.23		0.6

PVL portal vein ligation, *TLV* total liver volume, *FRLV* future remnant liver volume

before first-stage procedure was 2.0 (range, 1–7) with a median size of 4.0 cm (range, 0.9–11) for the largest metastases. Median FRLV had been measured as 322 ml with a FRLV/body weight ratio of 0.4. After PVL, the median number of CRLM increased to 4.0 (range, 1–10), coexistent with a slight increase in the median size of the largest metastasis to 4.4 (range, 0.3–11) cm. While total liver volume remained constant, FRLV increased to 419 ml after 57.9±18 days, representing a median volume gain of 36.5% and a FRLV/body weight ratio of 0.6 before second-stage hepatectomy.

Second-stage hepatectomy

Second-stage hepatectomy was performed in 19 (79.2%) of 24 patients (Table 4). Five patients were not eligible for surgical reexploration due to newly diagnosed disseminated pulmonary metastases (*n*=2) or progression of intrahepatic disease with new metastases in the FRLV (*n*=3). These five patients received systemic chemotherapy with palliative intent.

Nineteen patients were suitable for re-operation, but liver resection was cancelled in four patients due to occult progressive disease with peritoneal carcinomatosis (*n*=2), long-segment tumor infiltration of the future remnant left hepatic vein (*n*=1), or tumor involvement of FRLV (*n*=1). In the patient presenting with tumor infiltration of the left hepatic vein, curative resection would have been possible

by use of extracorporal bypass and vascular reconstruction techniques but was rejected due to an underlying cardio-vascular disease. In both patients with intrahepatic tumor progression, CRLM were treated by RFA during the second-stage procedure.

In 14 of 15 cases, the planned hemihepatectomy (after bisegmentectomy during the first-stage procedure (Fig. 4)) or trisegmentectomy could be performed. In one patient, the resection procedure had to be changed from right trisegmentectomy to central liver resection of segment V/VIII because of complete portal vein thrombosis. In two patients, CRLM were adherent to the diaphragm, so its partial resection was necessary to achieve tumor-free margins. In one additional patient, a pulmonary metastasis located in the right lower lobe was simultaneously resected via a transdiaphragmatic approach.

Re-operation was necessary in one case 6 days after curative second-stage hepatectomy due to biliary leakage. However, the patient died 28 days after right trisegmentectomy due to liver failure caused by left hepatic artery thrombosis. Mortality and morbidity rates of the second-stage procedure were 5.3% and 57.9%, respectively. Based on intensive histopathological examinations, curative resection could be achieved in 14 of 15 (93.3%) performed

Table 4 Second-stage hepatectomy

	Number	Percent[a]
Second-stage hepatectomy performed	19	79.2[b]
Liver resection	15	62.5[b]
Right trisegmentectomy (SIV-VIII)	13	68.4
Right hemihepatectomy (SV-VIII)[c]	1	5.3
Central liver resection (S V/VIII)	1	5.3
Surgical exploration, RFA	2	10.5
Surgical exploration, but no specific therapy	2	10.5
Multivisceral resection		
Diaphragm/ lung	3	15.8
Curative resection rate[d]	14	93.3
CEA expression of tumor cells strong or moderate[d]	15	100
Mortality	1	5.3
Morbidity[f]	11	57.9
Liver insufficiency[e]	3	15.8
Biliary leakage	4	21.1
Wound healing	1	5.3
Cardiopulmonal	4	21.1
Reoperation	1	5.3

[a] Percentage in correlation to number of patients re-explored
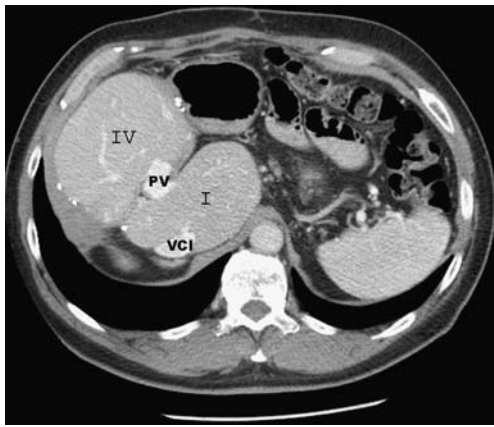[b] Percentage in correlation to number of patients in the study
[c] After bisegmentectomy S II/III at first-stage hepatectomy
[d] Only patients with liver resection during second-stage hepatectomy
[e] Defined by prothrombin time <50% and serum bilirubin >50 μmol/l on post-op day 5 [17]
[f] In patients with multiple complications, each is counted separately

Fig. 4 CT scan of the upper abdomen in portalvenous phase demonstrating enormous hypertrophy of segment I and IV after bisegmentectomy S II/III during first-stage hepatectomy, followed by standard right hemihepatectomy during second-stage hepatectomy. CT scan was performed 18 months after second-stage hepatectomy. *PV* portal vein, *VCI* inferior vena cava

liver resections. In all cases, immunohistochemical examination revealed a moderate ($n=1$) or strong ($n=14$) expression of CEA on the surface of tumor cells.

Follow-up

Follow-up was documented for the 13 patients with curative resection. Four patients received no adjuvant therapy following hepatic resection, while eight patients were enrolled in an adjuvant radioimmunotherapy protocol. Two months after R0-resection, one patient died of pulmonary embolism. During a median follow-up period

of 17 months, ten patients developed recurrent disease (Table 5) that, at the time of diagnosis, was multifocal in one, confined to the liver in one, and limited to the lung in six patients. Two additional patients presented with bone metastases after a disease-free survival of 5 and 6 months, respectively. Only one patient with a solitary pulmonary metastasis was suitable for surgical therapy and has been free of disease for 22 months, while in all other cases of tumor recurrence, chemotherapy or radiochemotherapy was applied. Three patients with recurrent disease died 14, 17, and 27 months, respectively, after second-stage procedure because of tumor progression. Two other patients with recurrent disease showed no progression under chemotherapy.

Discussion

This pilot study describes our experience with two-stage hepatectomy using portal vein ligation in patients with bilobular CRLM. These patients are associated with poor prognosis, and only if curative resection can be achieved, 5-year survival rates may reach 20% [3]. Therefore, every attempt should be made to convert initially unresectable to resectable patients which can be achieved by two-stage hepatectomy.

To induce hypertrophy of the FRLV, we favored surgical PVL instead of interventional PVE, although it has been reported by Broering et al. [24] to result in a significantly lower increase in liver volume. However, this conclusion should be restrained because the authors also showed a

Table 5 Follow-up

Patient No.	Time to recurrence[a]	Recurrence site	Treatment	Outcome at last observation	OS[b]	Status
1	4	Hepar, pulmo	CTX	PD	14	DOT
2P	1	Pulmo, osseous[c]	CTX	PD	27	DOT
3	2	Pulmo	CTX	PD	17	DOT
4P	6	Pulmo	CTX	PD	18	A
5	6	Osseous	RTX	PD	21	A
6	5	Osseous	RTX	PD	10	A
7	2	Pulmo	CTX	PD	7	A
8	3	Hepar, pulmo[c]	CTX	SD	17	A
9P	1	Pulmo	CTX	SD	17	A
10	–	–	–	NED	2	DOC
11P	–	–	–	NED	21	A
12	–	–	–	NED	12	A
13	7	Pulmo	Surgery	NED	29	A

CTX chemotherapy, *RTX* radiochemotherapy, *A* alive, *DOT* dead of tumor, *DOC* dead of other cause (pulmonary embolism), *P* progression under chemotherapy before liver resection, *PD* progressive disease, *SD* stable disease, *NED* no evidence of disease

[a] Time between second-stage hepatectomy and diagnosis of tumor recurrence (month), last observation 2008, 6, 30
[b] Time between second-stage hepatectomy and last observation
[c] Second side of recurrence under chemotherapy

significantly higher volume gain when portal vein branches to segment IV were occluded simultaneously, and this was done significantly more often in the PVE group. Furthermore, a recent publication by Aussilhou et al. [25] concluded that PVE and PVL result in comparable liver hypertrophy.

Compared to preoperative staging data, the surgical approach with PVL enhances sensitivity and specificity in the detection of CRLM using intraoperative ultrasound [26, 27]. It also allows combined PVL- and CRLM-directed therapy, even simultaneously with primary tumor resection without increasing morbidity or mortality rates [28, 29]. Although not as part of surgery for primary tumor, we performed liver resection up to bisegmentectomy and radiofrequency ablation together with PVL in eight and seven patients, respectively.

A number of studies have compared the efficacy of liver resection and RFA in the treatment of CRLM. They have demonstrated clearly that overall survival rates are higher, and local recurrence rates are lower in patients treated with resection [1, 30, 31]. Moreover, in cases where CRLM could not be resected completely, resection and RFA together did not significantly increase survival compared with RFA alone. Facing these results and remembering the categorical high risk of recurrence in patients with bilobular CRLM, RFA proves inappropriate for the treatment of CRLM in the nonligated hemi-liver.

Accordingly, the present series describes an aggressive two-stage hepatectomy concept with combination of PVL and complete surgical clearance of the nonligated hemiliver. Other authors [6] discussed that PVL combined with liver resection during first-stage hepatectomy may induce postoperative liver failure. In contrast, in our experience with 24 cases, no liver failure due to insufficient amount of liver volume occurred after the first-stage procedure, even though we performed bisegmentectomy of segments II/III in four patients (Table 2). In all patients, we observed a sufficient increase in FRLV using PVL with a mean interval of 57.9±18 days, and cancellation of second-stage hepatectomy was in no case based on insufficient hypertrophy.

Addressing oncological strategies, it has to be observed that there is still some controversy about whether chemotherapy, given between the two surgical procedures, is beneficial with regard to the curative resection rate. Severe sinusoidal injury has been observed in liver specimens after chemotherapy prior to liver resection [32–34], with some authors reporting an increased postoperative morbidity [33]—or even mortality rate [34]. Otherwise, intensive systemic chemotherapy with infusional 5-fluorouracil, folinic acid, and oxaliplatin or irinotecan have demonstrated response rates of up to 56% in primarily unresectable CRLM [35], resulting in curative resection rates of 12.5% [9], of which a high percentage will ask for two-stage procedures. Tumor

progression can be observed during liver hypertrophy not only in the nonligated [15] but also in the ligated lobe [16], which our data also demonstrate with regard to both number and size of CRLM (Table 2). Thus, there is a need for antitumor therapy between first- and second-stage hepatectomy, especially to control micrometastatic disease.

Besides systemic treatment, application of local chemotherapy has been studied in this context. Selzner et al. [36] treated 11 patients with PVL and intrahepatic arterial chemotherapy based on the antimetabolite, floxuridine. Although FRLV increased significantly 3 months after PVL, only six patients showed a partial response [14] to local chemotherapy, with an overall curative resection rate of only 36%. In a recently published study, Lygidakis et al. [28] also combined the surgical approach with three cycles of intra-arterial chemotherapy in 32 patients with synchronous bilobular CRLM. Two days after first-stage procedure including PVL, they started a complex transarterial chemotherapy schedule including oxaliplatin, irinotecan, mitomycin C, 5-fluorouracil, and calcium folinate, as well as the monoclonal antibody, bevacizumab. The chemotherapy was administered over 5 days with the next cycle following after 25 days. Major liver resection was performed 3 weeks after completing the third cycle of chemotherapy. Curative resection was possible in all patients, with a 2-year survival rate of 80%. Considering our number of five patients, though, that did not undergo second-stage hepatectomy based on intrahepatic (n=3) or pulmonary (n=2) progression, plus those four patients without major liver resection during second-stage procedure, a need for further studies on the appropriate management strategy in these patients becomes clear.

Curative resection could be achieved in 14 out of 19 re-explored patients (73.7%) even though we included patients with progression under chemotherapy and even patients with intrahepatic recurrence. In one of our patients, complete portal vein thrombosis required a switch in the operative resection strategy. Note that neither tumor progression, prothrombotic disorder, or infection was diagnosed in this case [37]. Instead of right trisegmentectomy, we performed central liver resection with curative intent. Although technically possible, we did not intend central liver resection initially because it is more complex, results in a wide resection plane which increases the risk for biliary fistula, and is associated with a longer parenchymal transection time as well as elevated intraoperative blood loss [38].

Patients with bilobular CRLM which are classified as mT4 according to Gayowski et al. [3] experience poor prognosis when compared to those having unilobular involvement. During early follow-up, we identified lung metastases in four patients already 1 (n=2) and 2 (n=2) months after curative liver resection (Table 5), respectively.

They have to be classified as occult metastatic disease at the time of restaging prior to second-stage hepatectomy. Thus, prolonging the interval between the two surgical procedures to 3 months seems to be reasonable because it would allow occult diseases to be disclosed. However, even though our follow-up period was short, only in two patients was the liver the first site of tumor recurrence, whereas other authors reported an intrahepatic recurrence rate of 48–75% during a comparable time frame [6, 39]. The low intrahepatic recurrence rate may result from our aggressive approach of resecting all CRLM in the FRLV.

Histopathological examination of the obtained liver specimens revealed moderate or even strong expression of carcinoembryonic antigen on the surface of tumor cells in all patients. As a result, postoperative radioimmunotherapy with ^{131}I-labetuzumab, as described previously [22, 23], has been offered to all patients resected curatively.

There is interdisciplinary consensus that only unresectable extrahepatic disease, unfit condition, and liver involvement of >6 segments excludes patients from liver resection for CRLM [40]. Therefore, the aim of the present study was to evaluate the outcome of consecutive patients fulfilling our inclusion criteria without preselecting them based on previous therapies and their response profiles. The underlying rationale of this study design is the definition of resectability as crucial end point in treatment concepts with curative intent [40]. However, as almost 75% of patients relapse after liver resection [41] within 2 years postsalvage resection of liver metastases, the observed and expected recurrence rate in our study population with already poor prognosis again argues for aggressive multimodal treatment prior to and especially postsalvage liver resection as well as for the establishment of reliable predictive clinical and molecular parameters that will allow patient stratification.

In conclusion, two-stage hepatectomy with portal vein ligation and complete surgical clearance of FRLV is a reasonable strategy in patients with bilobular, initially unresectable CRLM. The curative resection rate results in 73.7% of the re-explored cases. Further clinical trials are needed to evaluate whether antitumor therapy during liver hypertrophy may positively affect the curative resection rate by limiting the observed tumor progression after portal vein occlusion. Although not mandatory for volume gain, a second-stage procedure should be delayed by 3–6 months in cases of suspicious lesions found during restaging, in order to reduce unnecessary examinations in patients with unresectable and progressive disease. The described advances in the treatment of patients with bilobular CRLM have radically redefined what constituted an unresectable pattern of CRLM. Any patient with CRLM should be reviewed by a multidisciplinary team of experts, and resectability should be assessed by an experienced hepatobiliary surgeon before a decision on management is made. The treatment of tumor recurrence especially extrahepatic remains a future challenge.

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