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REVIEW ARTICLE

Staged resection of bilobar colorectal liver metastases: surgical strategies

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Abstract
Background Radical resection is the treatment of choice for colorectal liver metastases (CLM). Unfortunately, only about 20 % of patients present with initially resectable disease, in most cases due to bilobar disease. In the last two decades, major achievements have been made to extend surgical indications to patients with bilobar CLM, such as two-stage hepatectomy with or without portal vein occlusion and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS).
Purpose The purpose of this review article was to summarize current surgical approaches and their safety and efficacy for patients with initially unresectable bilobar CLM.
Conclusion In selected patients, two-stage hepatectomy and ALPPS are efficient and safe to convert unresectable to resectable CLM. Further studies are required to evaluate long-term outcome of these procedures.

Keywords Colorectal cancer (CRC) · Two-stage hepatectomy (TSH) · Portal vein embolization (PVE) · Portal vein ligation (PVL) · ALPPS · In situ splitting

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide in both males and females [1]. About 25 % of CRC patients present with synchronous liver metastases [2]. Additional 25–50 % subsequently develops metachronous liver disease [3, 4]. Surgery is considered to be the only curative therapy and achieves 5-year overall survival rates of up to 50 % [5]. The indications for liver resection have been extended markedly within the past two decades. While patients with more than three liver metastases were considered to be unresectable at the beginning of the 1990s [2], there is currently no numerical limit regarding resectability of liver metastases [6–9]. Thanks to advances in neoadjuvant therapy, more patients have become resectable. 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 [10]. Despite the advances in systemic and surgical therapy, some patients with bilobar liver disease are not amenable to resection within a single operation due to insufficient volume of the future liver remnant (FLR) [11, 12]. In the last decades, several strategies have been developed to convert unresectable to resectable disease in patients with bilobar CRC liver metastases.

We here reviewed three different surgical approaches of staged liver resection for the treatment of bilobar CRC liver metastases: staged liver resection with portal vein embolization (PVE), staged liver resection with portal vein ligation (PVL), and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS).

Two-stage liver resection with portal vein embolization

In the first stage of hepatectomy, a complete clearance of the metastases located in FLR, usually the left liver, is performed, either through anatomical or atypical resections. No significant difference was found in oncological outcome between anatomical and atypical resections for colorectal liver metastases [13, 14]. For this reason, parenchymal-sparing resections are commonly preferred. Radiofrequency ablation (RFA) can also be combined with liver resection to treat metastases in unfavorable locations, such as a central metastasis [10]. Using intraoperative ultrasound guidance, a RFA probe is placed into the lesion and a RFA generator delivers energy, which causes irreversible changes in the target cells including protein denaturation and coagulative necrosis [15]. Although RFA, as a single therapy, shows an inferior long-term outcome than hepatectomy per se [16], the combination of liver resection and ablation can maximize the amount of liver parenchyma preserved after resection without worsening the long-term survival [14].

A PVE is performed to achieve hypertrophy of the FLR. Preoperative PVE was first described in 1986 in Japan in patients with hepatocellular carcinoma (HCC) [17]. Nowadays, PVE is usually performed through a percutaneous transhepatic ipsilateral approach using CT guidance. A variety of substances have been used for embolization, including histoacryl, lipiodol, gelfoam, and n-butyl cyanoacrylate (NBCA), none of which has been shown superior to another [18]. The most rapid increase in liver volume occurs within 3 weeks after PVE and then reaches a plateau phase of minimal regeneration [3].

About 4–6 weeks after PVE, the liver volume is evaluated to reassess resectability. After a sufficient growth of the FLR, the second-stage liver resection can be proceeded as (extended) hepatectomy. In case of significant involvement of segment IV in a planned right hepatectomy, a right PVE can be extended to segment IV branches with the aim to achieve better regeneration of the FLR [19–22]. Preoperatively, special attention needs to be directed to the extent of embolization and localization of embolization materials using the follow-up CT. Dissemination of embolization material to the bifurcation of the portal vein, the main portal vein, or even the left portal vein branch is important for planning of the operative procedure. Furthermore, inadequate embolization of a hepatic sector may require additional embolization sessions.

The second stage of resection is completed in 76–87 % of patients who undergo the first stage with subsequent PVE [23–25]. Univariate analysis showed that age over 70 years, male gender, larger lesions >5 cm, serum carcinoembryonic antigen level before PVE greater than 200 ng/ml, and three or more metastases in the FRL were significant factors predicting failure to achieve two-stage hepatectomy (TSH). Multivariable logistic regression analysis showed the presence of extrahepatic disease, three or more metastases in the FRL, and patient age above 70 years to be factors associated with the failure of staged resection [26, 27]. The main reasons for the non-completion of the second stage are tumor progression, followed by insufficient hypertrophy of the remnant liver and portal vein thrombosis of FLR. Earlier studies suggested that PVE may stimulate tumor growth and lead to reduced long-term survival [28–30]. Pamecha et al. believed that increased hepatic arterial blood flow followed by portal vein embolization may provide nutritional advantages for tumor growth, since liver metastases depend exclusively on arterial blood supply [31]. Data from international cancer centers showed that administration of chemotherapy between PVE and the second resection could prevent such tumor progression and was associated with improved long-term survival [32–34]. The initial concerns regarding potential detrimental effects of chemotherapy on liver hypertrophy were refuted in recent studies [35, 36]. In their study involving 100 patients, Covey et al. did not report any negative effects of chemotherapy on the hypertrophy response [37]. At present, combined PVE together with neoadjuvant chemotherapy can therefore be considered a safe and effective treatment strategy for resectable colorectal liver metastases (Fig. 1).

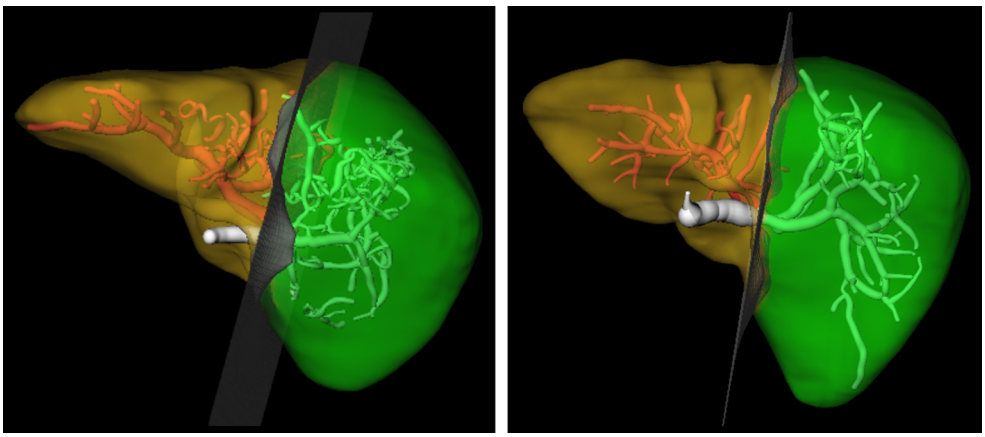

Fig. 1 Semi-automatic liver volume analysis before (*left*) and after (*right*) embolization of the right portal vein. Images are presented from the dorsal view. Liver volumes: before PVE, left hemiliver 650 cm^3; After PVE, left hemiliver 693 cm^3

To predict postoperative morbidity and mortality after liver resection for small FLR, Shindoh et al. presented a dynamic measure for volume analysis. They defined the degree of hypertrophy at initial volume assessment divided by number of weeks elapsed after PVE as the kinetic growth rate (KGR). KGR was shown to be a better predictor of postoperative morbidity and mortality than conventional measured volume parameters (sFLR volume and degree of hypertrophy) [38]. Postoperative serum bilirubin and international normalized ratio are indicators of hepatic insufficiency and should be used to define complications after liver resection [39].

Two-stage liver resection with portal vein ligation

Portal vein occlusion may also be achieved by surgical ligation during a first-step laparotomy. As in PVE, PVL uses the benefit of diversion of portal flow to the FLR to achieve liver hypertrophy. During the first stage, enucleation of the liver metastases in FLR is performed with subsequent extraparenchymal ligation of the liver that is planned for resection using a nonabsorbable suture. Four to eight weeks later, after hypertrophy of the disease-free FLR, a second step consisting of a (extended) hepatectomy is planned to completely clear the remaining liver metastases [40, 41]. PVL was shown to be able to induce hypertrophy of the future liver remnant. In comparison, PVE is the more effective technique to increase the future liver remnant, possibly due to lack of portal occlusion in distal branches of the portal vein [42–44]. In line with this theory, Wilms et al. emphasized collaterals between occluded and non-occluded liver segments as the underlying cause of inferior regeneration in the PVL group [44].

Two-stage liver resection without portal vein occlusion

The use of portal vein occlusion is not always required. If the future liver remnant is large enough and does not show signs of severe liver injury, portal vein occlusion may be omitted [10, 11]. A prolonged waiting period between the two hepatectomies is often necessary to achieve regeneration of the remaining liver before R0 resection can be attempted by second-stage hepatectomy [27]. Most of these patients had synchronous liver metastases and therefore had a resection of the primary colorectal cancer concomitant to the liver resection [10].

Associating liver partition and portal vein ligation for staged hepatectomy

In 2012, Schnitzbauer et al. introduced the ALPPS approach as a novel two-stage technique for patients with bilobar colorectal liver metastases [45].

During the first stage, the hemiliver planned for resection is completely mobilized from the inferior vena cava (IVC). After complete resection of all metastases in the FLR, the portal vein of the hemiliver to be resected is divided and total (up to inferior vena cava) or partial (up to the middle hepatic vein) parenchymal transection is performed. The hepatic artery and the bile duct are not divided within the first operation (Fig. 2). At the end of the first operation, the diseased hemiliver is physically separated from the FLR by being wrapped in a plastic bag or by a plastic sheath placed between the cut surfaces [46] (Fig. 3). After sufficient liver volume increase is confirmed by CT about a week later (Fig. 3), the second stage can be carried out. The plastic covering is removed; the hepatic artery is ligated and transsected. The bile duct and the venous drainage into the IVC are divided. After removal of the diseased hemiliver, the remaining lobe is then fixed to the ventral abdominal wall to prevent malrotation [45].

ALPPS has been shown to increase the resectability rate by lowering the rate of surgical dropout [47]. The short interval between the first and second resection indeed presents the most significant advantage of ALPPS (Fig. 4). The short interval may prevent tumor progression and there should be

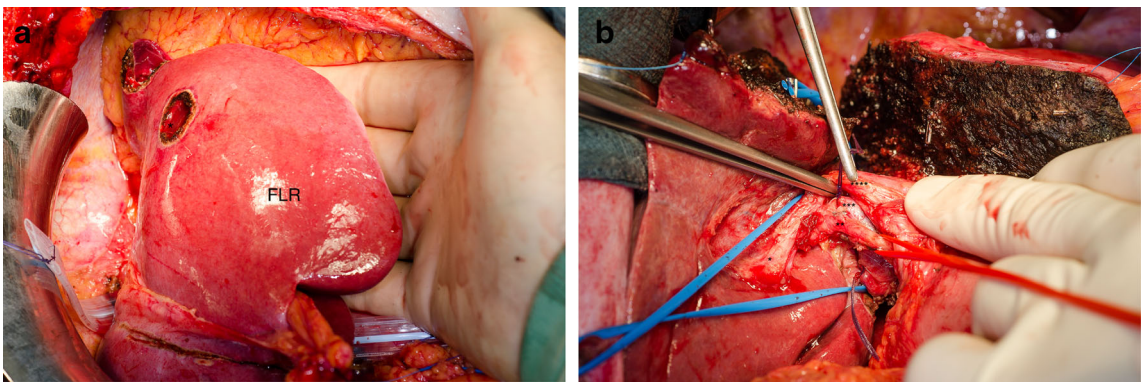

Fig. 2 Intraoperative anatomy after first stage operation of ALPPS. **a** The *asterisk* denotes the resection bed of single liver metastasis in FLR. **b** The *single asterisk* indicates the pedicle (*blue vessel loop*). *Two asterisks* indicate the right liver artery (*red vessel loop*); *three asterisks* indicate the right portal vein (ligatur); and *four asterisks* indicate the bile duct

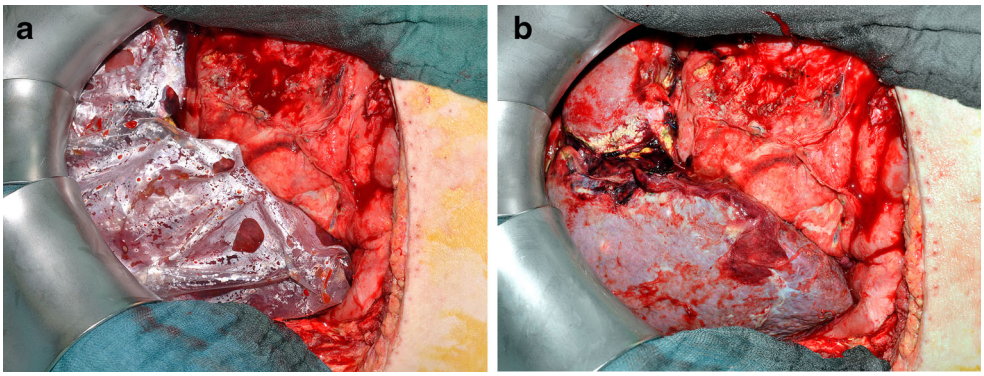

Fig. 3 Intraoperative anatomy at the beginning of second-stage operation of ALPPS. **a** Before removal of the plastic sheath. **b** After removal of the plastic sheath

fewer adhesions in the second-stage resection [48]. A recently published analysis of the ALPPS International Registry showed that only 2 % of the patients did not reach second-stage surgery [49].

A further advantage of ALPPS is the rapid and strong hypertrophy response of the FLR. As a FLR volume increases by 43 % in a mean of 27 days following PVE, the liver volume increases by a mean of 63 % within 3 days after ALPPS [50–52]. The enhanced hypertrophy observed after ALPPS may be explained by physical transection of the liver parenchyma, preventing formation of collaterals between the left (lateral) and right lobes [45] (Fig. 2). Therefore, in patients who have insufficient hypertrophy after PVE, ALPPS can still be considered as a "rescue approach."

Despite the efficiency and high feasibility of ALPPS, concerns remain regarding the safety of the procedure. In the initial series, a morbidity and mortality of 68 and 12.5 % were reported [45]. In the large multicenter experience in Brazil, similar morbidity and mortality rates of 59 and 12.8 %, respectively, were reported [53]. In a recent analysis of the ALPPS registry, the mortality rate was 8 % and the rate of grade IIIa or higher complications was 36 % for the subpopulation of patients with colorectal liver metastases [49]. In a small single-center study including six patients, Petrowsky et al. suggested that partial ALPPS (>50 % of the transection surface) is safer and achieves similar hypertrophy with no mortality [54]. These results were recently confirmed by a larger study on 21 patients [46]. Oncological data on long-term survival after ALPPS is limited due to its recent introduction and low numbers of patients. However, the existing figures on 1- and 2-year OS provided by Schadde and Alvarez (88–74 % and 78–63 %) [46, 49] as well as the 1-year DFS (67 %) [46] are encouraging when compared to the MD Anderson CRLM two-stage cohort with a 3-year survival of 67 % [23].

Discussion

This review describes various surgical approaches for patients with bilobar colorectal liver metastases. After clearance of the FLR, there are different strategies for induction of hypertrophy. Portal vein occlusion by PVE or PVL is a therapeutic option to induce hypertrophy within 4 to 6 weeks. Staged resections with PVE or PVL have been proven to be feasible and safe [4]. Staged resection can be achieved with long-term survival similar to that observed in patients with initially resectable liver metastases [23]. There is limited data comparing

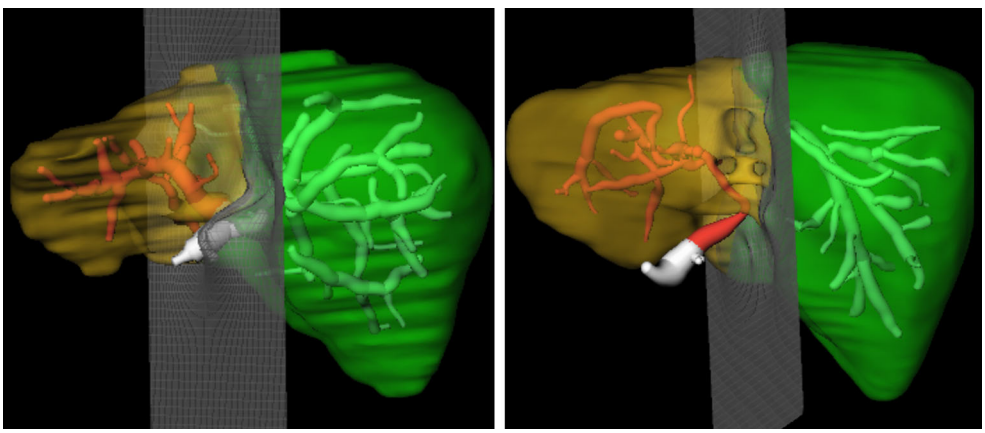

Fig. 4 Semi-automatic liver volume analysis before (*left*) and after (*right*) the first step of ALPP S (in situ split). Images are presented from the dorsal view. Liver volume: before in situ split, left hemiliver 279 cm^3; After in-situ-split: left hemiliver 428 cm^3

Table 1 Perioperative and survival outcomes after completion of two-stage hepatectomy

Study	Patients (*n*)	Interval PVE (%)	Feasibility (%)	Morbidity (%)	Mortality (%)	Median follow-up (months)	3-year DFS (%)	5-year DFS (%)	3-yearOS (%)	5-year OS (%)
Turrini [55]	34	100	71	20	6	40	24	14	59	35
Tsim [25]	36	95	87	33	0	19,5	27	NR	50	NR
Narita [27]	61	92	76	54	0	30	17	11	59	32
Muratore [56]	36	58	77	44	0	38.3	10	NR	65	NR
Brouquet [23]	47	70	72	49	6	50	20	20	84	64
Jamal [26]	44	56	52	48	0	31	NR	NR	68	42
Bowers [57]	32	72	82	56	4	12	NR	NR	28	NR
Tsai [58]	35	4	78	26	6	NR	NR	NR	58	NR
Wicherts [12]	41	20	69	59	7	24	26	13	60	42
Pamecha [31]	11	14	79	27	0	43	NR	NR	70	50
Tanaka [59]	22	0	92	23	0	NR	NR	NR	33	NR
Reißfelder [10]	33	67	NR	27	2	28	33	12	57	33

PVE to PVL. However, there is evidence for a more pronounced hypertrophy response after PVE due to the more effective occlusion of distal portal vein branches that prevent shunting between the right and left portal vein. In addition, dissection of the hepatoduodenal ligament for PVL within the first operation may cause adhesions that render the second operation more difficult. However, at present, both approaches may be recommended.

A two-stage hepatectomy procedure with or without portal vein occlusion has been shown to allow a curative resection in up to 20 % of initially unresectable patients. However, approximately 20–30 % of these patients cannot complete the second-stage resection because of tumor progression [12, 24], [58]. It is not clear, if the routine use of chemotherapy between the first and second-stage hepatectomy can lower tumor progression and dropout rates. Data from international cancer centers showed that administration of chemotherapy between PVE and the second resection could prevent such tumor progression and was associated with improved long-term survival [32–34]. Muratore et al. presented results that the routine administration of chemotherapy does not guarantee lower tumor progression rates after PVE [56]. Although Fischer et al. demonstrated that chemotherapy after PVE does not impair liver hypertrophy [32], chemotherapy still induces alterations of the parenchyma and reduces liver function [61–63]. Prospective controlled studies are needed to confirm these findings.

Since 2012, the so-called in situ splitting or ALPPS was introduced as a novel and innovative therapy for patients with bilobar CLM for rapid and effective induction of liver hypertrophy. Despite high rates of R0 resections with only very few patients not amenable for completion surgery, concerns remain regarding the safety of the procedure as demonstrated by high morbidity and mortality rates [45, 49, 53]. However, as experience with the ALPPS procedure increases, selection criteria may be developed to prevent this procedure in patients with high risk for perioperative complications. In addition, further refinements of the procedure such as partial ALPPS may help to decrease morbidity and mortality rates [46]. Furthermore, long-term survival and safety do not exist yet. The existing data on oncological survival is sparse but encouraging. Survival data after ALPPS is not inferior to that after conventional two-stage hepatectomy [46, 49]. Thus, based on current data, ALPPS should be preserved as “rescue procedure” if PVE or PVL cannot achieve a sufficient liver hypertrophy. (Tables 1 and 2).

Table 2 Perioperative and survival outcomes after ALPPS

Study	Patients (*n*)	Feasibility (%)	Morbidity (%)	Mortality (%)	Median follow-up (months)	1-year DFS (%)	2-year DFS (%)	1-year OS (%)	2-year OS (%)
Schadde [49]	56	98	40	9	NR	NR	NR	73	59
Nadalin [60]	15	97	66.7	28.7	17	NR	NR	NR	NR
Torres [53]	39	95	59	13	NR	NR	NR	NR	NR
Schnitzbauer [45]	25	98	44	12	6	NR	NR	NR	NR
Alvarez [46]	29	97	53	6.6	17	67	40	78	63

In conclusion, several strategies have been developed for treatment of bilobar liver metastasis so far. Staged resections with PVE or PVL have been proven to be feasible and safe. For ALPPS, a novel and innovative therapy for rapid and effective induction of liver hypertrophy, concerns remain regarding the safety of the procedure. Therefore, it is primarily recommended for patients with insufficient hypertrophy after PVE. Refinements of patient selection criteria together with increasing experience with this procedure are likely to further reduce morbidity. Also, additional data on patients' long-term outcome are required before this procedure can be recommended as the primary approach in patients with bilobar colorectal liver metastases and an inadequate future liver remnant.

Compliance with ethical standards

Conflicts of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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