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REVIEW

Role of associating liver partition and portal vein ligation for staged hepatectomy in colorectal liver metastases: A review

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Abstract

Colorectal cancer is the third most common cancer in the Western world. Approximately half of patients will develop liver metastases, which is the most common cause of death. The only potentially curative treatment is surgical resection. However, many patients retain a to small future liver remnant (FLR) to allow for resection directly. There are therefore strategies to decrease the tumor with neoadjuvant chemotherapy and to increase the FLR. An accepted strategy to increase the FLR is portal vein occlusion (PVO). A concern with this strategy is that a large proportion of patients will never be operated because of progression during the interval between PVO and resection. ALPPS (associating liver partition and portal vein ligation for staged hepatectomy) is a new procedure with a high resection rate. A concern with this approach is the rather high frequency of complications and high mortality, compared to PVO. In this review, it is shown that with ALPPS the resection rate was 97.1% for CRLM and the mortality rate for all diagnoses was 9.6%. The mortality rate was likely lower for patients with CRLM, but some data were lacking in the reports. Due to the novelty of ALPPS, the indications and technique are not yet established but there are arguments for ALPPS in the context of CRLM and a small FLR.

Key words: Colorectal liver metastases; Associating liver partition and portal vein ligation for staged hepatectomy; Portal vein embolization; Neoadjuvant chemotherapy; Liver surgery

Core tip: Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has emerged as a new method for patients with comprehensive liver metastases and a small future liver remnant. This review is an attempt to clarify the role of ALPPS in the context of colorectal liver metastases (CRLM). In this review, it is shown that the resection rate was 97.1%. The mortality rate was 9.6%. However, ALPPS is a new procedure, and the indications and diagnoses for which ALPPS is most suited are not yet clear. There are indications that ALPPS is particularly suited to the context of CRLM.

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LIVER METASTASES IN COLORECTAL CANCER

Rate, survival

Colorectal cancer (CRC) is the third most common cancer in the Western world. approximately half of the patients with CRC will develop liver metastasis (CRLM), which is the main cause of death in patients with CRC[1]. Resection is the only treatment with curative potential, and it is warranted if radical resection can be achieved, leaving a sufficient future liver remnant (FLR) and if the patient's physiological status is acceptable for surgery(2)[2,3].

For primary resectability, the FLR should be at least 20% in patients without intrinsic liver disease or who have not received neoadjuvant chemotherapy[1,3-5]. After chemotherapy, the FLR should be at least 30%[1,5] and at least 40% in patients with cirrhosis[1]. Postoperative liver function is dictated by volume, circulation and degree of fibrosis[3,4]. The frequency of upfront resectable CRLM is unfortunately only approximately 20%[4]. The remaining 80% are defined as non-resectable at presentation. Primary non-resectable metastases occur when the FLR is too small for resection or the location of the metastasis interferes with the main vascular or biliary structures of the liver. These patients are usually treated with chemotherapy to down-size the metastatic burden and to convert the disease into a situation that is amenable to surgical treatment. With this strategy, up to 50% of the patients have become resectable after downsizing[2].

Radical resection of liver metastases have an up to 58% 5-year survival rate and a 10-year survival rate of up to 36%[3,4,6-8] compared to 5%-10% with chemotherapy alone[4]. The disease-free 5-year survival rate was 22%, and 10-year disease-free survival rate was 19%[8] after surgical resection. Negative prognostic factors include, for example, bilobar metastases and the diagnosis of liver metastasis within 12 mo from the diagnosis of the primary tumor. The prognostic value of the size of the metastasis was not clear[9].

More than half of patients operated on for CRLM will progress with new liver metastases after resection; however, the 5-year survival rate after reresection was comparable to the survival rate after the first liver resection for CRLM[3].

Regardless of whether the patient undergoes down-sizing oncological treatment or not, patients with an FLR close to or less than the lower limit constitute a special challenge to the liver surgeon. Some of these patients can be operated on up front in one stage, while others require augmentation of the FLR.

Increasing the size of the FLR can be achieved with portal venous embolization (PVE) or portal venous ligation (PVL). One of these methods, portal vein occlusion (PVO), is often combined with two-stage surgery and has been a mainstay of treatment for patients with small FLRs.

PVE is technically feasible in almost 99% of patients, with a low risk of complications. FLRs increase by a median of 40%-62% after a median of 34-37 d. After PVE, 72.2%-80% of patients can proceed to surgery. Up to 20%-27.8% have progression of metastasis and are therefore not resectable. The complication rate after resection was 57.7%, and the 90-day mortality was 8.6%[2,10].

PVL and two-stage resection result in an FLR increase by a median of 30%-43.1% after a median of 37-57.9 d. The resection frequency is 62.5%-87% with 93.3% radical resection. Postoperative complications occurred in 25%-57.9%, and the reported mortality rate was 5.3%-10%[11-13]. Over the median follow-up of 17 mo, 66.7% experienced recurrence[13].

One major concern with PVO and resection is that the growth rate is usually slow and there is a risk of tumor progression. These factors have resulted in a 52%-80% resection rate[2,10,14-17].

PVO in CRLM induces growth of the FLR but can also induce progression of metastases in both embolized and non-embolized liver tissue. The risk of progression is most likely decreased with chemotherapy, and the risk can probably be further reduced with bevacizumab[2,18,19].

A concern with PVO and two-stage hepatectomy is that the growth of the FLR is variable and, in some cases, might be insufficient. A rather large number of patients will never be resected with this traditional approach; therefore, the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) approach could be an option for rescue in patients failing PVE/PL or as a direct method in patients with small FLRs.

The first ALPPS treatment was conducted in 2007[20]. This new method of treating an extensive tumor burden in the liver has not been standardized and has varied in both technical and anatomical approaches. The common technical principle for ALPPS is two-step resection. During the first procedure, there is parenchymal dissection of the liver (*in situ* split) between the lateral and medial sectors of the left hemi-liver, combined with ligation of the right portal vein, as well as of the portal branches to segments 4A and 4B. During the second procedure, the right artery and bile duct are transected, and the diseased hemi-liver is resected. Other combinations, involving isolation of part of the liver (by *in situ* split) with intact portal blood flow from parts of the liver that only have arterial blood flow, have been described. Because this is a novel treatment, the indications have yet to be

Table 1 Diagnoses and number of patients with each diagnosis

Diagnosis	Number
CRLM	68
Liver metastasis	39
CCA including Klatskin	32
HCC	8
Gallbladder cancer	2
Sarcoma	2
Malignant epithelioid hemangioendothelioma	1
Cystic liver disease	1
Metastatic ovarian cancer	1
Metastatic gastric cancer	1
GIST	1
Barrett-Ca	1

CRLM: Colorectal liver metastases; CCA: Cholangiocarcinoma; HCC: Hepatocellular carcinoma; GIST: Gastrointestinal stromal tumor.

defined and opinions vary. ALPPS has been used as a salvage procedure after failed PVO, as well as up front in patients with extensive liver metastasis or primary tumors.

ALPPS could be indicated when the FLR is smaller than 20%-30% of healthy liver or smaller than 30%-40% after chemotherapy, in cholestasis or when the FLR/BWR is smaller than 0.5 or 0.8, respectively[20-23]. The interval between step one and step two varies from 7.5 d[24] to at most 40 d[25].

Some reports have suggested that the current role of ALPPS is for rescue in patients with insufficient growth of the FLR after PVO. The procedure can be performed as a parenchymal transection or as portal ligation and parenchymal transection[26-28].

Concerns have been raised about the safety of ALPPS, given the rather high frequency of complications reported initially and the unknown long-term oncological results[29-34]. Another concern has been that the function of the FLR might not be correlated with the volume[35]. Concerns have also been raised regarding the risk with tumors close to the right portal vein and that dissection in close proximity to the tumor could possibly jeopardize the oncologic results[36]. An argument for two-stage hepatectomy and PVO is that it is a well-known procedure and that the longer interval is beneficial for de-selecting patients with more aggressive tumors who likely will not benefit from surgery[30,34].

This review was conducted to evaluate the role of ALPPS, so far, in the context of CRLM.

Search

A search in the PubMed database was undertaken, using the following search terms: ALPPS, associating liver partition and portal vein ligation in staged hepatectomy, and *in situ* split. The same reports were found *via alpps.net*, and using the same search terms, 129 reports were found. The search was conducted on September 29, 2014. Reports not about ALPPS were excluded, as were case reports. Reports with three or more patients were selected, resulting in 9 reports[20,21,24,25,37-41]. Some patients appeared in more than one report, and in such cases, the latest report was included.

RESULTS

A total of 160 patients who were operated on using the ALPPS procedure were identified in 9 published reports, and they consisted of 91 men and 66 women, age 20-83 years old[20,21,24,25,37-41]. The most frequent diagnosis was colorectal liver metastases (n = 71), followed by primary liver tumors (n = 40) and liver metastasis without a specified primary tumor (n = 39), which were almost equally frequent. Two reports included ALPPS performed in the context of only CRLM[25,40], while the others included mixed diagnoses. Two patients with CRLM did not proceed to the second operation because of disease progression[24], and another two patients did not proceed to the second operation due to fatal complications[37]. These 4 patients are included in the review. Three patients with CRLM were not included in the review although they completed both operations because they were not described in the paper[25]. A total of 68 patients with CRLM are therefore included in this report (Table 1).

Neoadjuvant chemotherapy

Most of the included papers were unclear regarding whether chemotherapy was administered as neoadjuvant or as down-sizing treatment; therefore, we used the term *neoadjuvant*. Sixty-four patients received neoadjuvant chemotherapy, and 33 of these patients were specified to be patients with CRLM. Of all of the patients with CRLM, 78.6% received chemotherapy. For patients with CRLM the most common regimen was FOLFOX (n = 16), combined with monoclonal antibodies for 5 patients; 2 patients received cetuximab, and 3 received patients bevacizumab. Five patients received FOLFIRI, combined with cetuximab (n = 1) or bevacizumab (n = 3). In one report (5 patients with CRLM), the chemotherapy regimen was not specified, and in one report, the number of patients who received neoadjuvant chemotherapy was not specified (26 patients with CRLM)[20,21,24,25,38,40,41]. In three reports, the number of cycles were specified within the range of 1-38 cycles, for a median of 8 cycles[20,24,41]. No reports clearly specified that neoadjuvant chemotherapy was performed to down-size. Two reports stated the numbers and sizes of metastases[25,39] (Table 2).

Indications for ALPPS and preoperative FLR

Indications were expressed either in terms of volume[20,41] or in the assessment of an otherwise unresectable tumor[25,37]. ALPPS was deemed indicated when the FLR/TLV was less than 25%, the FLR/BWR was less than 0.5 in patients with a healthy liver, or the FLR was less than 30%. After chemotherapy or

Table 2 Age, sex and American Society of Anesthesiologist physical status classification system of patients in the included papers, number of patients with colorectal liver metastases and chemotherapy

Ref.	Age (median and range)	Sex	ASA	Number of patients with CRLM	Neoadjuvant chemotherapy
Schnitzbauer *et al*[20]	63 (32-75)	14 M, 11 F		14	11 CRLM (7 folfox, 1 folfox + cetuximab, 1 folfox + bevacizumab, 1 xeliri + cetuximab, 1 xelox), 1 gastric cancer (flot3)
Torres *et al*[37]	57.3 (20-83)	22 M, 17 F		7	Not specified
Oldhafer *et al*[25]	65 (52-81)	4 M, 3 F			2 (folfox + bevacizumab, folfiri + bevacizumab/HD-5FU)
Ratti *et al*[24]	61 (45-72)	6 M, 2 F	7 ASA 2, 1 ASA 3	5	5 CRLM (folfiri + bevacizumab, folfox + bevacizumab, folfiri + cetuximab, folfiri, folfox + cetuximab)
Nadalin *et al*[21]	67 (43-80)	7 M, 8 F	10 ASA 2, 3 ASA 5	5	5 CRLM (4 folfox, 1 folfiri)
Ielpo *et al*[38]	58.5 (56-63)	2 M, 4 F		5	5 CRLM, regimen not specified
Schadde *et al*[39]	57 (48.5-65)	29 M, 19 F	40 ASA 1-2, 8 > 2	26	28, diagnosis and regimen not specified
Gauzolino *et al*[40]	52.5 (49-67)	3 M, 1 F		4	2 oxaliplation, 2 irinotecan
Troja *et al*[41]	65 (38-72)	4 M, 1 F		2	1 CRLM (folfiri + bevacizumab), 1 (imatinib/sunitinib, 1 cisplatin/5-FU)

CRLM: Colorectal liver metastases; CCA: Cholangiocarcinoma; HCC: Hepatocellular carcinoma; GIST: Gastrointestinal stromal tumor; ASA: American Society of Anesthesiologist physical status classification system; M: Male; F: Female.

in patients with fibrosis or cholestasis, the limit was higher, at 30%-40%[21]. There were no differences in the requirements for the volume of the FLR depending on diagnosis[34-38].

Volumetry

The volume of the FLR was mostly expressed in terms of percentage of the TLV; in one report, the quotas for the FLR and BWR were stated, and in some reports, the values for the pre- and postoperative FLR were not reported. The preoperative median volume of the FLR ranged between 22% and 27.8%, and the lowest reported volume ranged between 13.1% and 19%. The postoperative median volume of the FLR ranged between 33% and 46.9%. The median increase in FLR ranged between 65% and 110.3%. The interval between step 1 and step 2 ranged from 6 to 40 d, with a median interval of 6-15.3 d (Table 3)[20,21,24,25,37-41].

Surgical technique

All of the procedures were conducted as open surgery, except for two patients in whom both steps were conducted laparoscopically[37]. Common principles during the first step are examination of the abdominal cavity to exclude metastases and intra-operative ultrasound of the liver. Thereafter, identification of the portal vein, hepatic artery and bile duct is undertaken. The right portal vein is divided, and the hepatic artery and bile duct are marked with vessel loops to ensure identification during step 2. The liver parenchyma is then transected.

The differences in technique regard, in essence, how mobilization of the liver is conducted. The hanging maneuver during mobilization has been described in tree papers[21,25,40]. There have also been differences in whether the hepatic veins are transected during the first step. Transection of the middle hepatic vein was described in two papers[21,37], whereas dividing the minor retrohepatic veins was described in two[24,25] and transection of the minor hepatic veins was described in one paper[24]. Whether the portal vein, hepatic artery and bile duct to segment 4 were transected depended on whether resection, as extended right hemihepatectomy or not, was conducted, which was described in all of the papers. How parenchymal dissection was conducted was specified in three papers. The transection was described as total or nearly total in two papers[37] and complete in one[25]. To prevent adhesion between the two hemi-livers, a plastic bag[20,25,40], a collagen[25] or silicon[21] sheet, a bioactive sealant[24] or omentoplasty[41] was used. The use of a drain after step 1 was described in four of the papers[21,24,37,38].

After evaluation with CT and when the FLR gained a sufficient volume, step 2 was conducted. The exact criteria for FLR size to perform step 2 were described in three papers[21,24,38]. The common principle was transection of right hepatic artery, bile duct and hepatic vein, and regarding this step, no significant differences were described.

Complications

How complications were reported varied, although the complications were mostly reported according to the Clavien-Dindo grading system[42]. It was not possible from all of the reports to determine which diagnoses had which grade of complications.

A total of 211 complications were reported in 157 patients. In some reports, all of the complications were reported, not only the highest grade according to the Clavien-Dindo score; in other reports, complications were stated if they occurred after step 1 or step 2. Of all of the patients with complications, 15 were specified as patients with CRLM. The total mortality rate was 9.6% (n = 15). Of these patients, 4 were specified as having CRLM. In some papers, the diagnoses with complications or that resulted in mortality were not specified (Table 4).

Radicality

Radicality, R0, was achieved in 101 patients and R1 in

Table 3 Pre- and postoperative volume of future liver remnant, increase of future liver remnant and time for increase

Ref.	Preoperative volume of FLR[1]	Postoperative volume of FLR[1]	Increase	Time
Schnitzbauer *et al*[20]	FLR/BWR 0.38 (0.25-0.49)	FLR/BWR 0.61	74% (21-192)	9 (5-28)
Torres *et al*[37]	-	-	83% (47-211.9)	14.1 (5-30)
Oldhafer *et al*[25]	23.8% (13.1-37.2)	36.7% (22.4-59.5)	65% (16-97)	13 (10-40)
Ratti *et al*[24]	22% (16-27)	33% (31-40)	-	7.5
Nadalin *et al*[21]	22.6% (15.7-29.2)	36.3% (30-59.2)	87.2% (23.8-161)	10 (8-16)
Ielpo *et al*[38]	-	-	95.5% (56-214)	15 (12-21)
Schadde *et al*[39]	23% (18-29%)	41% (34-47%)	77.4% (52.8-101.7)	-
Gauzolino *et al*[40]	31% (20-47)	43.5% (32-52)	-	-
Troja *et al*[41]	-	-	-	14 (14-21)

[1]The future liver remnant (FLR) is expressed as a percentage of the TLV.

Table 4 Number of patients in each report and distribution of postoperative complications

Ref.	Number of patients	Grade Ⅰ	Ⅱ	Ⅲ	Ⅳ	Ⅴ
Schnitzbauer *et al*[20]	25	12	13	6 Ⅲa, 8 Ⅲb	3 Iva, 5 Ⅳb	3[1]
Torres *et al*[37]	39	[2]	-	-	-	5
Oldhafer *et al*[25]	7	1[1]	4[1]	1[1]		
Ratti *et al*[24] after step 1	8		1		2	
After step 2				3 Ⅲa		1
Nadalin *et al*[21] after step 1	15	12 (Ⅰ/Ⅱ)		3 Ⅲa, 2 Ⅲb	2	
After step 2	15	16 Ⅰ/Ⅱ		5 Ⅲa, 4 Ⅲb	7	4
Ielpo *et al*[38]	6	3			2 Ⅳa	1[1]
Schadde *et al*[39]	48	[3]				
Gauzolino *et al*[40]	4	2		1 Ⅲb		
Troja *et al*[41]	5		3	1		1

[1]Patients with CRLM; [2]18 patients had significant morbidity; [3]After step 1: 21 complications, 7 with grade Ⅲb or higher; after step 2: 35 complications, 13 with grade Ⅲb or higher.

4 patients. In two reports, with a total of 45 patients, the radicality of resection was not specified.

Follow-up

Follow-up was reported from all of the centers except for two, with a total of 47 patients[24,37]. The median follow-up ranged between 3 and 17 mo (1-33 mo).

Over the follow-up, a total of 38 patients had recurrence, and of these patients, 9 were specified as patients with CRLM. Five patients died, and of these 5, 3 patients were reported as having CRLM. Of the 110 patients for whom follow-up was reported, 56 (50.9%) patients were still alive without recurrence[20,21,25,38-41].

In conclusion, ALPPS was performed in 157 patients, for a resection rate of 97.5%. Sixty-eight of these patients had CRLM, and they had a resection rate of 97.1%. Thirty-three (78.6%) of the patients with CRLM received neoadjuvant chemotherapy. The mortality rate was 9.6%. R0 was achieved in 96.2% of the patients in whom radicality was reported. During the follow-up, 38 patients experienced recurrence, and 5 died. Fifty-six patients survived without recurrence.

DISCUSSION

Drawing firm conclusions about the role of ALPPS in CRLM, based on the present literature, is complicated. Most of the reports regarding ALPPS have involved patients with other diagnoses, as well as those with CRLM, and all of the studies have been retrospective in nature. At times, patients with CRLM could not be separated from others when outcomes are presented. In addition, some of the patients were included in more than one report.

In the present review, it was found that 78.6% of the patients with CRLM received neoadjuvant chemotherapy. Nine (27%) patients also received antibodies, which could indicate that the treatment was administered for downsizing purposes. Firm conclusions about complication rates were not possible to draw because in some reports, more than one complication for each patient was recorded, and in other papers, complications after step 1 and after step 2 were recorded. In this review, the mortality rate was as high as 9.6%, which is higher than with PVO, which has a mortality rate of approximately 6%[39]. However, the resection rate for patients with CRLM is 97.1%, compared to approximately 60%-66% for PVO[13,39,43,44]. Thus, ALPPS seems to offer benefits in the form of more patients being able to undergo liver resection, with the cost of increased mortality. Currently, there is no reliable method to distinguish those patients who might not benefit from PVE; therefore, it is impossible to say whether the relatively high mortality occurred in a subgroup of patients who otherwise would not have been assessed as resectable.

Surgical treatment for CRLM has evolved from being a rare chance offered to the minority of patients to being a realistic treatment for many of these patients. One of the great challenges in this patient group consists of patients with small FLRs. Until recently, the only treatment modality offered to this sub-cohort was PVO with or without two-stage hepatectomy.

The recurrence rate was 24.2% during the follow-up, which was of variable length between reports, and some patients experienced recurrence shortly after ALPPS. In the report by Schadde *et al*[39], the recurrence rate after 1 year of follow-up for ALPPS was 54%, compared to 52% for PVO. The long-term results for ALPPS are not clear due to the novelty of the method. After two-stage hepatectomy and PVO, the 5-year survival rate was approximately 42%-50%[3]. However, the recurrence rate has been reported to be as high as 76.9% after only 17 mo of follow-up[13].

The role of ALPPS is not yet clear; perhaps it is most suitable for patients with CRLM, although in the present review, there were other diagnoses included. One argument for its suitability in CRLM is that it might be possible to downsize the tumor before resection for these patients, in combination with neoadjuvant chemotherapy[45]. One argument against ALPPS in the context of primary liver tumors is that these tumors often present with cholestasis, requiring biliary draining before surgery, which increases the risk of bacteria in the biliary tree, which can increase the risk of postoperative infections.

Not only is ALPPS performed for a patient group with advanced malignancy and marginal liver function, but the technique has also not been standardized, making interpretation of the limited results at hand uncertain. There are variants of ALPPS in which the right hemi-liver as well as the lateral sector of the left hemi-liver are removed, leaving only segments Ⅰ and Ⅳ as FLRs[46]. In addition, what have been described as "left ALPPS", "right ALPPS" and "rescue ALPPS" all offer different scenarios, compared to the original right trisectionectomy[40]. A variant of ALPPS that has been reported to have a lower frequency of complications and, at the same time, sufficient growth of the FLR is ALTPS (associated liver tourniquet and portal ligation for staged hepatectomy)[47]. Instead of dividing the liver parenchyma, a tourniquet is placed along the line of future resection to prevent blood from flowing from the FLR to the part of the liver that will be removed. There have also been cases in which the first stage was performed laparoscopically[48]. Regardless of the surgical technique used and the part of the liver that constitutes the FLR, concerns have been raised about the risk of tumor spread during the first operation, and it has been suggested that this risk could be decreased with the anterior approach[49].

One aspect about which data have been lacking is ablative therapies, such as radio-frequency ablation (RFA) and percutaneous ethanol infiltration (PEI), combined with ALPPS. In none of the included reports was local ablation described as a complement to resection. In addition, data combining local ablation in classical two-stage resection have also been scant. One possible explanation for this finding might be that resection is the procedure of choice for curative treatment and that local ablative treatment plays a larger role in patients assessed as non-operable. Local ablative therapies had a higher frequency of recurrence than resection[50,51].

It has yet to be established where on the surgical landscape for patients with small FLRs this procedure should be placed. One group of patients who might be especially suitable for ALPPS would be those with insufficient growth of the FLR after PVO (salvage ALPPS). There is, however, no defined interval for how long one should wait for the FLR to obtain sufficient volume. To be able to determine earlier whether the patient will obtain a sufficient FLR, the concept of kinetic growth rate (KGR) or degree of hypertrophy (DH) has been suggested[52]. Growth rate is a predictor of postoperative liver failure. Patients with low KGRs are unlikely to benefit from PVO only and could thus be candidates for ALPPS. Another group of patients who might be especially suitable for ALPPS are those with "extremely low" FLRs, who, given the boundaries of growth achieved with PVO, are unlikely to reach the limit deemed necessary for resection. This group has not been defined earlier, and it is likely that it includes patients who have been categorized as not resectable from the beginning and thus have not been offered PVO. Given that ALPPS seems to be able to achieve a greater increase in FLR size than PVO alone, this group could consist of patients with CRLM who had not been treatable earlier but now might be. Finally, the largest question that remains to be solved is whether PVO without *in situ* split of the liver can now be retired and whether ALPPS should be used up front for all patients with CRLM that require growth of the FLR.

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