

Current position of ALPPS in the surgical landscape of CRLM treatment proposals

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Author contributions: Donati M and Oldhafer KJ equally contributed to the present work; Donati M wrote the article; Donati M and Oldhafer KJ collaborated on design and conception; Donati M and Stavrou GA completed literature research, data collection and wrote the table; Stavrou GA made the first language and style revision; Donati M and Oldhafer KJ made the final critical review of article.

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Received: April 12, 2013 Revised: July 21, 2013

Accepted: August 17, 2013

Published online: October 21, 2013

Abstract

The Authors summarize problems, criticisms but also advantages and indications regarding the recent surgical proposal of associating liver partition and portal vein ligation (PVL) for staged hepatectomy (ALPPS) for the surgical management of colorectal liver metastases. Looking at published data, the technique, when compared with other traditional and well established methods such as PVL/portal vein embolisation (PVE), seems to give real advantages in terms of volumetric gain of future liver remnant. However, major concerns are raised in the literature and some questions remain unanswered, preliminary experiences seem to be promising. The method has been adopted all over the world over the last 2 years, even if oncological long-term results remain unknown, and benefit for patients is questionable. No prospective studies comparing traditional methods (PVE, PVL or classical 2 staged hepatectomy)

with ALPPS are available to date. Technical reinterpretations of the original method were also proposed in order to enhance feasibility and increase safety of the technique. More data about morbidity and mortality are also expected. The real role of ALPPS is, to date, still to be established. Large clinical studies, even if, for ethical reasons, in well selected cohorts of patients, are expected to better define the indications for this new surgical strategy.

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Key words: Portal ligation; *In situ* split; Liver resections; Colorectal metastases; Liver metastases

Core tip: The recent publication by Regensburg's Group on the new technical possibility of associating liver partition and portal vein ligation for staged hepatectomy for the surgical managing of bilateral colorectal liver metastases, generated a great debate and a burst of publications about preliminary experiences from many groups all over the world. As one of the first groups in Germany to adopt this technique, in the present article we clarify some aspects of our experience in the light of published data and raised concerns.

Donati M, Stavrou GA, Oldhafer KJ. Current position of ALPPS in the surgical landscape of CRLM treatment proposals. *World J Gastroenterol* 2013; 19(39): 6548-6554 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v19/i39/6548.htm> DOI: <http://dx.doi.org/10.3748/wjg.v19.i39.6548>

INTRODUCTION

The progressive enlargement of surgical indications to colo-rectal liver metastasis (CRLM) resection of the last 20 years has led to a redefinition of resectability criteria^[1]. Nowadays no limits due to number of lesions and

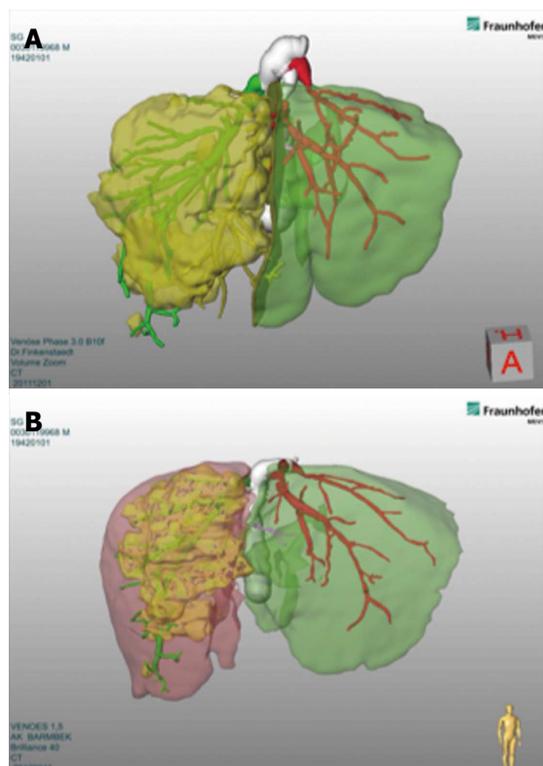


Figure 1 Example of strategy using a semi-automated 3D volumetry system. Hepavision® MEVIS. A: 3D volumetry before associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): future liver remnant (FLR) 26%; B: Two weeks after ALPPS volumetry of FLR: 43% (increase of 65%).

location are of value as in the past^[2]. The main problem for resectability criteria of CRLM is due to volume of future liver remnant^[3], in fact, postoperative liver failure is one of the biggest risk and a significant complication after extended hepatectomy^[4]. Some techniques were established such as portal vein ligation (PVL) and portal vein embolisation (PVE) with well known advantages and limits. Also 2 stage combined strategies were developed to overcome resectability problems due to bilobar location of metastases and two-staged hepatectomy has been reported as an efficient strategy for oncological outcomes and has been adopted by many liver centers^[5,6]. A real novelty on 2 staged surgical procedures that has recently been proposed, is the advent of associating liver partition and PVL for staged hepatectomy (ALPPS)^[7]. The technique was first performed by Schlitt *et al.*^[8] of Regensburg in 2007 and first presented to a German Congress in 2010. After that the technique spread all over the world^[9]. This is rapidly gaining great interest from the surgical community leading to debate^[10] and even proposals for a reinterpretation of methods^[10-12], and giving a new hope to a large number of patients traditionally judged unresectable^[13]. Despite an “explosion” of publications and case reports in the literature during the last 2 years, a lot of questions remain concerning safety and effectiveness of this method^[14]. Given the large amount of surgical experience world wide^[15], and the critical appraisals of some surgical groups, in the present article we would like to summarize the main sur-

gical aspects, open questions and express our point of view on this method in the light of our preliminary experience^[16] and other published data, in the era of two-stage treatment of CRLM^[17].

TECHNICAL ASPECTS AND DEVELOPMENT

The first aim of introducing this technique by Regensburg's group was to enhance liver hypertrophy after portal ligation increasing the ischemia effect on future liver remnant (FLR)^[16]. The concept on which this technique is based seems to be an old finding^[18], but of course revisited and reinvented or recombined in the light of new problems of CRLM surgery^[19]. The assumption is that any closure of the right portal branch is followed by a reactive perfusion of “deportalized” liver, from contralateral one, through the intrahepatic branches and collaterals presents between the 2 lobes^[20]. This aspect was recently confirmed by a clinical study^[21].

The technique consists in an association of classical right portal branch ligation together with liver parenchyma surgical split. The split could be conducted following the falciform ligament line (splitting segment 2-3 from the rest of the liver) as originally described^[7], or even atypically adding 4b segment as previously shown in our video^[22]. To split the liver avoiding manipulation and obtaining a better bleeding control, such as a clear anatomic line of parenchymal transection, we usually perform an anterior approach^[23]. Between the right and left split hemilivers a plastic sheet or bag should be positioned in order to avoid cicatrization with the disappearance of the resection line. In addition some atypical resection of additional metastases (1 or 2) in the future liver remnant must be performed. We have extended the indication to ALPPS also for bilateral CRLM with little FLR (< 30%) or even < 40% with damaged liver parenchyma; and during the first step of the procedure we resect metastases on FLR. Other groups used more restricted indications reserving ALPPS only for patients without metastases on FLR^[7].

In the original description the Authors waited for about 8-10 d before performing the 2nd step of specimen removal^[7]. Other Authors usually wait 7 d^[24], while our group usually performs the 2nd step after 12 d. A computed tomography (CT) scan after 1st step, in 7-10 d, is mandatory in order to evaluate volumetric gain. We routinely use 3D-reconstruction and Volumetry performed by MEVIS® system using Hepavision® software^[22] (Figure 1). The key role of CT-volumetry with 3D-reconstructions for this novel method was later confirmed by another study^[25]. This technique showed that the speed of hypertrophy and also the percentage of volume gain were more enhanced than with classical methods such as PVE or PVL^[7].

Some technical variants were quickly introduced by some surgeons. Some authors, in fact, proposed the laparoscopic approach^[11,26], citing some advantages of lapa-

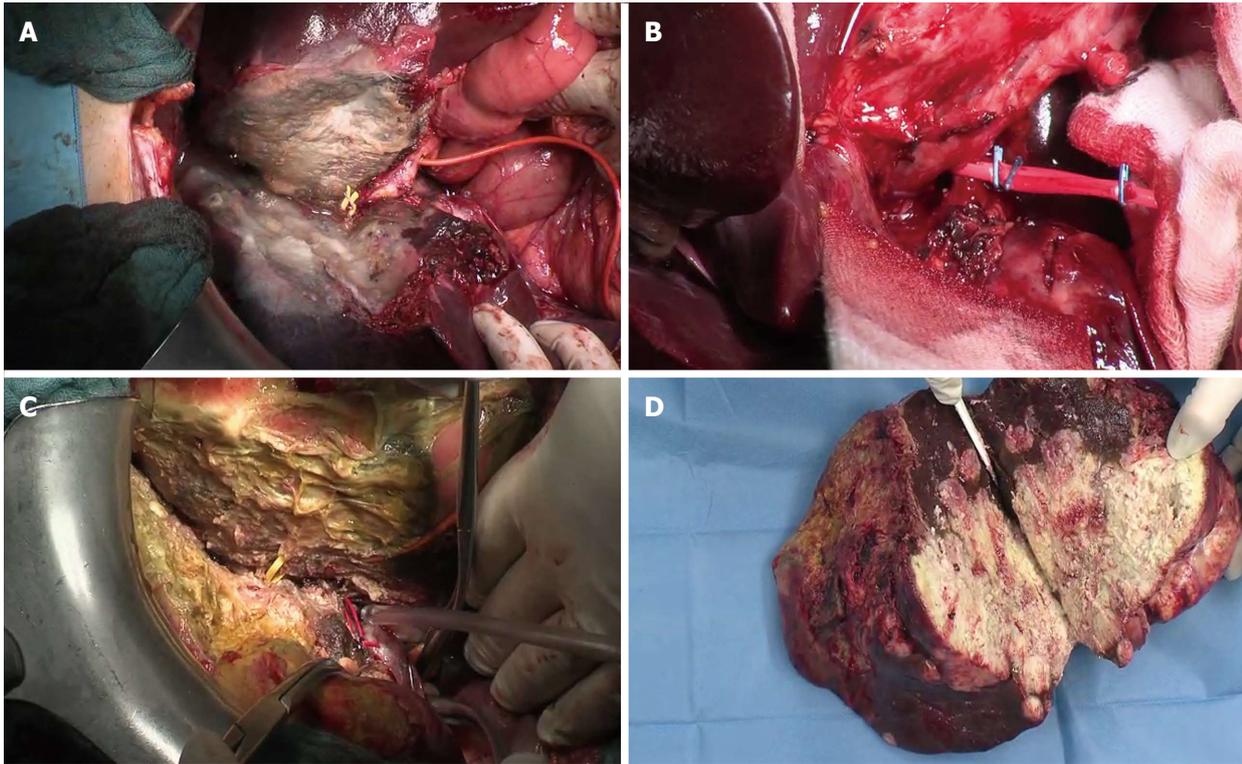


Figure 2 Intraoperative images of associating liver partition and portal vein ligation for staged hepatectomy in our center. A, B: 1st Step procedure with apposition of colored loop (red for the right hepatic artery, yellow for the right hepatic duct) and of T-drainage. C, D: Easy identification of loops during the second step and opened specimen of R0-resection of colo-rectal liver metastasis.

roscopy in avoiding adhesions thus making the 2nd step easier^[27]. Even if ALPPS was developed for extended right hepatectomy, 3 main strategies were recently standardized to use ALPPS not only for right hepatectomies but even for extended left hepatectomies^[28].

We proposed the following technical modifications in addition to referred routine use of 3D-reconstruction in order to improve the safety of the procedure: (1) Do not use the plastic bag or sheet but interpose only a fibrillar mesh (Figure 2A); (2) Use of a colored plastic loop to leave *in situ* for the 2nd step (yellow for right biliary duct and red for hepatic artery) in order to find it very easily and quickly during the challenging 2nd step (Figure 2B and C); and (3) Routine use of T-drain in order to reduce the risk of biliary leak and biomass (main referred surgical complication after preliminary reports (Figure 2B and C). Additionally we enhanced the significance of complete liver mobilization (apparently in contradiction with the anterior approach!) as previously described as a preliminary maneuver of surgical step 1, that in this technique, in our opinion, is of value not only for a complete manual and ultrasonography exploration of both lobes, but also to enhance the ischemia effect, avoid collateralisation through ligaments' vessels and increase the hypertrophy effect of ALPPS. On the other hand some surgeons criticized^[10,15] the technique, questioning: complexity of procedure, high risk of 2 very close big operations, additional morbidity and reported mortality, and uncertainty of long-term oncological results. If detractors have made

some logical considerations about the proposed method, also enthusiasts of ALPPS have been engaged in reporting positive results^[11,16,17]. It should be underlined that some of the most talented surgeons use ALPPS^[9], testifying to the potential of this technique, trying to find the best indications (Table 1).

We have also expressed some considerations related to our preliminary data in a previous article^[16], however, the ideas and criticisms raised during this last year convinced us to introduce, in this debate, some other considerations.

PUBLISHED EXPERIENCE

First of all it should be taken into consideration that ALPPS is mainly indicated for patients that have to undergo a right trisegmentectomy. This extended liver resection is known to be at particular risk of postoperative liver failure^[4], the combination in a 2 staged procedure is forced in these patients by a judgment of not resectability with other established 2 stage surgical strategies^[29-31]. Therefore this cohort of patients is "*per se*" a group of very sick patients with advanced disease, traditionally not resectable CRLM and therefore destined for palliative treatment. The novelty of this method is the percentage gain of patients to resectability. Thus we are convinced that the questionable additional risk related to the technique could be acceptable in the light of resectability gain. Doubtless, also other one stage combined proposed

Table 1 Associating liver partition and portal vein ligation for staged hepatectomy: an overview of worldwide experience

Author	Cases (n)	Hypertrophy (range)	Days of interval (range)	Morbidity	Mortality
Schnitzbauer <i>et al</i> ^[7]	25	74% (21-192)	8 (4-8)	64%	12%
Conrad <i>et al</i> ^[11]	1	44.80%	9	0%	0%
Robles Campos <i>et al</i> ^[12]	1	57%	7	0%	0%
Dokmak <i>et al</i> ^[15]	8	70% (5-147)	7	87.50%	25%
Donati <i>et al</i> ^[16]	8	80% (66-200)	10 (7-21)	-	-
Knoefel <i>et al</i> ^[17]	7	63%	6 (4-8)	57.20%	14.20%
Machado <i>et al</i> ^[26]	8	88% ¹	9	0%	0%
Machado <i>et al</i> ^[27]	1	159%	21	0%	0%
Hahn <i>et al</i> ^[37]	1	94%	9	0	0
Sala <i>et al</i> ^[49]	10	82% (31-140)	7	40%	0%
Andriani ^[50]	2	-	30	0%	0%
Torres <i>et al</i> ^[51]	1	-	-	-	-
Li <i>et al</i> ^[52]	9	87.20%	13	22.20%	22.20%

¹Data referred only to one case.

strategies could be taken into account in selected groups of patients^[32]. However, very aggressive chemotherapeutic regimens, in many cases, are nowadays forcing surgeons to find new technical solutions, sometimes delaying radical treatment in order to achieve patients' safety. We also think that the potential of ALPPS was wrongly judged by some eminent colleagues only because it was tested on very challenging indications (duodenocephalopan-creatotomy and extended hemihepatectomy for biliary tract tumors)^[15] leading to high morbidity and mortality rates. We expressed our opinion that the main indication for ALPPS seems to be for CRLM in selected patients, as stated in other papers^[16]. In patients affected by bilateral CRLM, the proposed method regained resectability also in apparently not resectable patients, increasing safety of resection and lowering risk of postoperative liver failure, enhancing, in a very short time (average about 7 d), the great hypertrophy potential of liver parenchyma. Undoubtedly ALPPS, compared to traditional PVE or PVL, allows a tremendously quick FLR growth (22% *vs* 3% growth the day after the procedure)^[16]. Of course our previous considerations should be considered in the light of no published long-term oncologic results. In consideration of the right moment to resect after split, this aspect should be carefully taken into account in patients submitted to several cycles of neoadjuvant chemotherapy. As we demonstrated in a previous publication, a long wait (about 4 wk) after split can allow a volumetric gain of 200%, but with the disadvantage of a more difficult second surgical step^[23]. It is foreseeable that with the rapid diffusion of new neoadjuvant chemotherapeutic regimens (chemo first approach), the need for ALPPS, as a safe alternative strategy to the classic 2 stage approach, will increase; in fact, more patients are gaining, and will gain, resectability due to partial or sometimes full response to new chemotherapeutic protocols^[33,34]. Thus a multidisciplinary approach of CRLM^[35], starting with aggressive neoadjuvant regimen, under indications of institutional tumor boards, will push more patients to ALPPS. On the other hand, ALPPS makes the resection safer after neoadjuvant chemothera-

py, reducing the risk of postoperative liver failure.

OPEN QUESTIONS

Even with the big enthusiasm for this technique and surge in the number of centers adopting it over the last 2 years, even in an episodic manner, leading to a lot of case reports^[36-38], some considerations must be made. First of all we should consider that the method has not yet been tested in an evidence based manner, only preliminary experience is available, publishing dishomogeneous data. Even the technique has not yet been standardized. The big question is if oncologic long-term results are acceptable, if a gain, in terms of quality of life and time gained, could balance the big risk of complications and mortality. Whether the stimulation of liver hypertrophy could also accelerate tumor progression is also an open question still debated since the time of classic PVE, PVL techniques^[39]. Recently, Van Gulik's group has shown how tumor progression could clearly be stimulated by PVE only^[40], reporting the objections about the short time-frame of ALPPS among speculations, because the same phenomenon is observed in PVE and PVL^[41]. Even a study by Pamecha *et al*^[42] first experimentally and then confirmed by Maggiori *et al*^[43], showed a clear tumor progression after PVE so that about one third of patients cannot undergo the second step after embolization because of tumor progression. Obviously one could speculate that if ALPPS allows a bigger and quicker liver regeneration, the same stimulation could realize an intensive and quicker tumor progression. An early recurrence was occasionally reported among disomogeneous published experiences^[7], but more data are expected in the next years and of course also results of international register.

If CRLM is to be considered the best indication in other tumours (for example Neuroendocrine tumor metastases) with slower biology and tumor progression, patients could benefit from such a method, this remains one of the main questions. Thus the great advantage of volumetric gain must be taken with the above mentioned

open questions before establishing the method in clinical practice. The method remains very challenging and not only for liver surgeons, but for extremely skilled liver centers and must be approached in a multidisciplinary manner. More effort must be made to reduce the morbidity and mortality associated with ALPPS.

Of course it must be taken into consideration that some other established methods of obtaining FLR hypertrophy are less risky and whenever possible should be the first choice in planning staged surgical strategies^[44]. Nevertheless, also if PVE is, to date, the most used technique and considered the standard procedure to enhance FLR, about 30% of patients never undergo complete resection because of insufficient hypertrophy or tumor progression on FLR. Furthermore, as in a recent systematic review the two stage hepatectomy with traditional strategies has shown an certain morbidity, that appears comparable with the morbidity of ALPPS (17% after first step and 40% after the second one)^[6]. Therefore, in well selected cases, in limit-cases, or when PVE failed to gain volumetric enhancement of FLR^[17,45], sometimes ALPPS seems to be the only reasonable-feasible option to achieve resectability. The additional morbidity and mortality referred in the bigger reports respectively up to 44% and 12% could be accepted as additional risks only in the light of “no other choices”, even if we need more scientific studies to confirm this. Furthermore, it should be taken into account that reported high mortality rates are referred to very initial experiences in very small groups of patients, in which also 1 death strongly influences overall mortality rates. However, also 3rd referral hepatobiliary centers need a learning curve to optimize the procedure. Some proposed technical details could reduce the “surgical risk” also shortening the time of the second procedure^[15]. Due to ethical limits to clinical experimentation and the difficulty in recruiting a reasonable group of highly selected patients, an online world register was created (see international register: www.alpps.net). Some detractors of ALPPS have recently published a study comparing traditional PVE efficacy and safety compared with published data on ALPPS, concluding to be in favour of traditional and well established strategies^[46]. However, despite confirming that PVE and similar techniques are still the standard of care, the referred study suffers from some BIAS in comparison, therefore conclusions are not well addressed by the study and a definitive conclusion cannot be made. The challenge of the ongoing study will be, despite the BIAS of patient collection from many different centers, to establish some kind of evidence of safety (as declared by many authors and criticized by others), usefulness (long-term oncologic results), best indications, and in our opinion also guidelines to standardize the preoperative flow-chart, surgical timing and steps. It is foreseeable that ALPPS could gain a position also among feasible surgical strategies for the complex scenario of Klatskin tumours^[47,48] in order to extend the resectability rate as we stated in a previous article^[16], and as confirmed by recently reported experiences^[35,49]. Despite all the potential of this technique, to

date the scientific evidence should be still considered as a phase 1 clinical trial; we believe that the method, in consideration of all the above mentioned open questions at the moment, should be adopted only by extremely well-trained and experienced Hepatobiliary Surgical Centres.

CONCLUSION

The problems on the table are many and the technique needs to be defined, maybe first on acceptable indications and long-term results, in order to achieve the current position of ALPPS not only in the surgical management of CRLM, but also in its greater potential to treat other liver tumours. Therefore, in conclusion, we think that the ALPPS proposal should be considered the “real novelty” in the CRLM surgical landscape of the last 3 years and despite the enthusiastic view to “change the face of liver surgery” as suggested by other Authors^[10], we prefer to say that it is foreseeable that such a method will gain, after the physiological period of experimentation and publication of the first large clinical studies, an important position among the surgical strategy options for the surgeon managing bilateral colorectal liver metastases, even maybe for a restricted and well-selected subgroup of patients.

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L- Editor A **E- Editor** Ma S





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ISSN 1007-9327



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