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Liver venous deprivation versus associating liver partition and portal vein ligation for staged hepatectomy for colo-rectal liver metastases: a comparison of early and late kinetic growth rates, and perioperative and oncological outcomes

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A B S T R A C T

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Background: Different techniques have been developed to optimize the Future Liver Remnant (FLR). Associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) and liver venous deprivation (LVD) have shown the higher hypertrophy rates, but their place in clinical practice is still debated.

Methods: Thirty-two consecutive ALPPS and LVD procedures for CRLM performed between December 2015 and December 2019 were included. This retrospective study evaluated kinetic growth rates (KGR) as primary outcome, and perioperative and oncological outcomes as secondary endpoints.

Results: A total of 17 patients underwent LVD before surgery, whereas 15 underwent ALPPS. On early evaluation (7 vs 9 days, respectively), KGR did not differ between ALPPS and LVD cohort (0.8% per day vs 0.3% per day, $p = 0.70$; 23 cc/day vs 26 cc/day, $p = 0.31$). Late evaluation (21 vs 9 days) showed a KGR significantly decreased in the LVD group (0.6% per day vs 0.2% per day, $p = 0.21$; 20 cc/day vs 10 cc/day $p = 0.02$). Mean FLR-V increase was comparable in the two groups (60% vs 49%, $p = 0.32$). Successful resection rate was 100% and 94% in LVD and ALPPS group, respectively. The hospital stay ($p < 0.0001$) and severe complications rate ($p = 0.05$) were lower after LVD. One and 3-years overall survival (OS) were 72,7% and 27,4% in the ALPPS group, versus 81,3% and 54,7% in LVD group ($p = 0.10$). The Median DFS was comparable between both techniques (6.1 months and 5.9 respectively, $p = 0.66$).

Conclusions: LVD and ALPPS shows similar KGR during the early period following preparation as well as similar survival outcomes. Hospital stay and severe complications are lower after LVD.

1. Introduction

Liver resection is the cornerstone of treatment of colorectal liver metastases (CRLM) with low morbidity and mortality in highly experienced centers [1,2]. Surgical therapy can achieve 5-year survival rates higher than 50%, compared to only about 5% for patients medically treated [3]. Currently, the standard of surgical care is the Parenchymal-Sparing Hepatectomy (PSH). This strategy is a balance

between the potential to achieve a complete tumor resection with curative intent (R0 resection) and the preservation of as much liver parenchyma as possible [4]. Considering that up to 75% of patients develop a recurrence within 2 years [5], PSH showed to improve 5-years Overall Survival (OS) in case of recurrence (salvageability) [6]. The key point of such strategy is the possibility to repeatedly perform the hepatectomy, that can offer long-term disease control without increasing perioperative mortality and morbidity rates [7,8]. On the other hand,

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huge tumors or close vascular relationships could indicate major hepatectomies. The major limitation for performing extensive hepatectomies is the risk of post-hepatectomy liver failure (PHLF), that still remains the main cause of mortality after major liver resection [9]. In order to minimize the risk of PHLF, a correct preoperative work-up is mandatory by investigating both the quantity and the quality of the Future Liver Remnant (FLR). It is generally accepted that the volume of the FLR (FLR-V) must be higher than 25% of the volume of a normal liver, 30% of a liver with steatosis or after several chemotherapy cycles, and at least of 40% in case of cholestasis or cirrhosis [10].

With the intention of optimizing the FLR, several techniques have been developed to induce hypertrophy. Since its introduction in 1984, portal vein embolization (PVE) is generally considered the standard technique for inducing increase in FLR [11–13]. However, PVE is hampered by a substantial failure rate, with a 20% unsuitable rate for resection due to either insufficient FLR growth or tumor progression during the post-PVE period, that may be sometimes very long (6 weeks or more) to gain enough residual volume [14]. To overcome these limitations, associating liver partition and portal vein ligation (ALPPS), with also several modified versions, has been recently introduced. These techniques showed greater and faster hypertrophy than PVE, but at the cost of significantly higher morbidity and mortality [15,16].

In the past 5 years, a new interventional radiological technique has emerged: the liver venous deprivation (LVD). It has been proposed as an alternative radiological technique to induce hypertrophy of the FLR [17]. It consists in the simultaneous embolization of the portal vein and one or two hepatic veins, to increase the damage to the liver leading to an increase in hypertrophy of the contralateral parenchyma, with a reported kinetic growth rate of 16 ± 7 cc/day according to the first reports [17–19]. Recently, Guiu et al. reported the FLR volume increase rate after LVD is reduced from the 37,8% of the first 7 days to the 2% of the last 7 ones [20]. Thus, it seems unfair to compare KGR between LVD and ALPPS only after a long interval, as previously published in the only comparison article [21]. Yet, preliminary data reporting great early volume and functional FLR increase call for comparing LVD and ALPPS during this early period with the ultimate goal to operate the patient as early as possible to prevent further risk of tumor progression [22].

The aim of this retrospective study is therefore to compare, in patients with CRLM, the early and late FLR kinetic growth rate (KGR), perioperative and oncological outcomes following ALPPS vs. LVD before major hepatectomies in patients with CRLM.

2. Materials and methods

2.1. Study design

This is a tri-institutional retrospective observational study, conducted according to the STROBE guidelines (Strengthening and reporting observational studies in epidemiology) of the EQUATOR network [24]. Informed consent was obtained prior to both radiological procedures and surgery.

Consecutive patients who underwent LVD and ALPPS prior to right hemi-hepatectomy or extended right hepatectomy (tri-sectionectomy) for colorectal liver metastases between December 2015 and December 2019 in Montpellier University Hospital (for LVD procedures), Montpellier Institute of Cancerology and at the Division of HPB Minimally Invasive and Robotic Surgery at the Federico II University Hospital of Naples (for ALPPS procedures), were retrospectively analyzed. All cirrhotic patients were excluded, to reduce heterogeneity, since the role of LVD in cirrhotic patients is still not clear [23]. The presence of an underlying liver disease was based on the histo-pathologic results on the surgical specimen.

The therapeutic indications for all patients were discussed in a multidisciplinary oncology meeting. The decision to perform a liver augmentation procedure was based on FLR volume. The procedure was performed when the expected FLR was <25% in normal liver, <30% in

liver after chemotherapy, <40% in case of underlying liver disease (cholestasis or fatty degeneration).

An ALPPS procedure was indicated in case of right hemi-hepatectomy or tri-sectionectomy and a left lobe disease not susceptible of percutaneous therapy, and where LVD procedure was not available.

LVD procedure was performed at Montpellier University Hospital in case of right hemi-hepatectomy or tri-sectionectomy when the expected FLR volume and/or function were not sufficient, according to the center experience, within study protocols.

The follow-up policy after LVD and ALPPS was based on contrast-enhanced computed tomography (CT) at one and three weeks following LVD, and at 8–12 days after ALPPS stage one.

The indication to completion surgery was based on volume data, according to underlying liver parenchyma and patient condition, according to the aforementioned criteria.

2.2. Radiological procedure

The LVD technique has been described in detail elsewhere [17]. In summary, the right hepatic vein (and accessory when present) was cannulated under ultrasounds guidance. PVE was performed using the right transhepatic access. The right portal vessels were embolized using a compound of *n*-butyl cyanoacrylate and lipiodol (ratio 1: 6). The micro guidewire placed in the hepatic vein(s) was then used to deploy an oversized Amplatzer II vascular plug. The plug is placed at a distance of about 1.5 cm from the ostium of the inferior Vena Cava (IVC), in order to facilitate surgical ligation of the hepatic vein. Finally, all distal venous branches were embolized using a mixture of *n*-butyl cyanoacrylate and lipiodol (ratio 1: 6). Some patients also received an embolization of the middle hepatic vein, the so-called extended liver deprivation (eLVD) [18], depending on the baseline FLR and the type of surgery (resection of segment IV).

2.3. Surgical intervention

All patients included underwent a laparotomic right hemi-hepatectomy (segments 5–8), or extended right hepatectomy (S5-8, S4), with or without additional wedge resections in the left liver [25]. An intraoperative ultrasound was performed to confirm the surgical feasibility of the procedure and to guide the resection. The right hepatic artery and portal vein were systematically ligated and dissected before the parenchymal section with an anterior approach. The hepatic veins were closed and divided with a vascular staple; the Amplatzer plug was not found to be an obstacle to the surgical ligation of the hepatic vein. If necessary, Pringle's maneuver with intermittent clamping and right hepatic vein control was performed.

For ALPPS procedure the first stage was carried out by treating eventual lesions of the lobe to preserve, by resection or thermal ablation. Then the transection line was performed by an ultrasound cavitation device and the right branch of the portal vein was ligated. The second stage consisted in the division of the ipsilateral artery and bile duct and hepatic vein in order to complete the hepatectomy [26].

2.4. CT-volumetry

Multiphase contrast-enhanced CT was carried out during preoperative assessment and after LVD or ALPPS stage 1. The portal-venous phase was used for volumetric assessment. The liver was outlined on an axial scan in a semi-automated fashion with manual adjustment to ensure that all extra-hepatic structures were excluded in order to calculate the total liver volume (TLV; cc). The tumor volume (TV; cc) and FLRV (cc) were calculated by manual delineation according to Couinaud's functional segmentation of the liver, as described by Heymsfield [27,28]. For volumetric reconstructions in Montpellier University Hospital was used a PACS workstation (Carestream Vue PACS, Carestream Health), while

in Naples the Synapse Vincent (Fuji film Medical, Tokyo, Japan), was currently used for complex PSH procedures and volume calculation.

The volume share of the FRL (FRL-V; %) was calculated using from the manual reconstruction, according to the formula described by Vauthey et al. [29]: [1] FLR-V share = FRL-V/(eTLV- TV) x 100, where eTLV: = -794.41 + 1,267.28 x body surface area.

2.5. Hypertrophy parameters

To compare the hypertrophy responses, the kinetic growth rates (KGR) for FRLV share were calculated by dividing the point differences of the FRLV share between preoperative and interstage assessments by the number of days after PVE or ALPPS stage 1. KGR was analyzed as both percentage growth per day as well as cc growth per day, as follows: [3] KGR = (FLR_{interstage} - FLR_{baseline})/days [30]. The increase of the FRLV share was calculated using the following formula: [2] FLR increase = FLR_{interstage} - FLR_{baseline}/FLR_{baseline} x 100% [31].

Considering the long interval between radiological procedures and surgery, volumes were compared after the first post-procedural imaging and the last imaging made before surgery.

2.6. Post-operative follow-up

The Post-operative and follow-up data were analyzed. The Post-operative complications were classified according to the Clavien-Dindo classification [32]. PHLF, biliary leaks (BL) and post-hepatectomy hemorrhage (PHH) have been diagnosed and classified according to the International Study Group of Liver Surgery (ISGLS) [33–35]. Ascites was defined according to the International Ascites Club [36].

All patients were examined within one month after discharge from the surgery department and received clinical, biological and imaging evaluation every 3 months after discharge for the first two years according to oncological protocols. Then outpatients' controls were scheduled every 12 months if no relapse was found. In case of tumor recurrence, the case was re-examined by the Multi-Disciplinary Team (MDT) with the aim of carrying out curative treatment as much as possible.

2.7. Statistical analysis and endpoints

Continuous data are expressed as mean and standard deviation (SD) or median and interquartile range (IQR) depending on whether they have a normal distribution. Comparisons between groups were performed using student's T test or Wilcoxon's rank test, depending on the distribution of the variable.

Categorical data are expressed as associated frequencies and percentages. Comparisons between groups were performed using Pearson's Chi Square test.

The primary endpoint was KGR. Secondary outcomes were oncological outcomes and peri-operative results. All survival analyzes were performed using the Kaplan-Meier method to calculate the median and 95% CIs. Comparisons were made using the Log Rank test.

The Median follow-up was calculated using the inverse Kaplan-Meier methodology [37]. Statistical analysis was conducted using SPSS software (version 26.0).

3. Results

3.1. Patients and tumor characteristics

Overall, data regarding 32 patients from 3 centers were collected. The overall median follow-up was 36 months (CI 95% 8–52). Patients and tumors' characteristics are available in Table 1. Median diameter of the biggest lesion was slightly larger in ALPPS group, 50 mm vs 40 mm in LVD group, but without statistical significance (p 0.06), as well as for the median number of tumor nodules (6 vs 4, p = 0.24). The percentage

Table 1

Patients and tumor characteristics. SD: standard deviations; BMI: body mass index; IQR: inter-quartile range; RECIST: response evaluation criteria in solid tumors; CI: confidence intervals.

	ALPPS	LVD	p-value
Age, mean (SD)	59.2	58.7	0.91
Sex (male, %)	7 (35)	13 (65)	0.13
BMI, mean (SD)	26.4 (3.9)	25.9 (3.4)	0.91
Tumor size, median in mm (IQR ₂₅₋₇₅)	50 (40–101.5)	40 (21–52.5)	0.06
Tumor nodules, median (IQR ₂₅₋₇₅)	6 (5–10)	4 (1–4,5)	0.24
Mutated K-Ras, n (%)	6 (40)	6 (35)	0.54
Liver metastasis presentation, n (%)	11 (73)	14 (83)	0.53
-Synchronous	-3 (27)	-10 (71)	0.02
-Liver first approach	-8 (72)	-4 (29)	
-Colon first approach	4 (27)	3 (17)	
Metachronous			
Neoadjuvant	15 (100)	17 (100)	ns
Chemotherapy, n (%)			
Chemotherapy cycles before liver surgery, median (IQR ₂₅₋₇₅)	12 (8–15)	6 (4–14)	0.13
Preoperative chemotherapy schemes, n (%)	FOLFOX 1 (6) FOLFIRI 1 (6) FOLFIRI + CETUXIMAB 1 (6) FOLFOX + CETUXIMAB 1 (6) XELOX + BEVACIZUMAB 1 (6) FOLFIRINOX 1 (6) FOLFOXIRI + BEVACIZUMAB 0 (0) FOLFOX + BEVACIZUMAB 4 (24) FOLFIRI + BEVACIZUMAB 4 (24)	FOLFOX 1 (6) FOLFIRI 3 (17.5) FOLFIRI + CETUXIMAB 3 (17.5) FOLFOX + CETUXIMAB 0 (0) XELOX + BEVACIZUMAB 3 (17.5) FOLFOXIRI + BEVACIZUMAB 4 (24) FOLFIRI + BEVACIZUMAB 2 (12) FOLFIRI + BEVACIZUMAB 1 (6)	0.99 0.60 0.60 0.46 0.46 0.33 0.22 0.38 0.32
Response to preoperative chemotherapy according to RECIST criteria, n (%)	4 11	5 12	0.86
Partial Response Stable Disease			
Follow-up, median (CI 95%)	38 (31–43)	32 (16–46)	0.07

of patients treated by chemotherapy was equal (100%). In ALPPS cohort, 11 patients presented synchronous CRLM, while 4 had a metachronous presentation; in the LVD group they were 14 and 3, respectively (p = 0.52). Among the patient with synchronous presentation, 8 patients (72%) had undergone a colon first resection strategy in ALPPS group, compared to 4 in LVD group (29%, p = 0.02).

3.2. Volume analysis

Median pre-procedural tumor volumes were comparable between the two groups (83 cc in ALPPS vs 51 cc in LVD, p = 0.24). The mean pre-procedural FLRV-share was 29,7 in the ALPPS group vs 29,3 in the LVD one (p = 0.53). All LVD patients underwent volumetric evaluation after 7 days and after 21 days. ALPPS patients underwent first imaging follow-up after a median of 9 days (IQR 5). Early KGR did not significantly differ between both techniques (0.8% per day vs 0.3% per day, p = 0.70; 23 cc/day vs 26 cc/day, p = 0.31). On the contrary, late KGR was greater after ALLPS (20 cc/day vs 10 cc/day p = 0.02), with a lower difference in percentages (0.6% per day vs 0.2% per day, p = 0.27). The preoperative mean FLRV-share increase was comparable in the two groups

(60% vs 49%, 0.32). Data about volume analysis are shown in Table 2.

3.3. Peri-operative outcomes

The results were stratified according to liver volume augmentation procedure (LVD and ALPPS stage 1, Table 2) and surgical procedures (completion surgery and ALPPS stage I, Table 3) and surgical procedures (completion surgery and ALPPS stage I and II, Table 4). There was a significant difference in Length of Stay (LoS) in favor of LVD (3 vs 9 days, $p = 0.0001$). After ALPPS stage 1, two patients were not discharged, being hospitalized until second stage. When comparing first procedures, intra-procedural blood loss and post-operative major complications were in favor of LVD procedure. The only shown difference in favor of ALPPS stage 1 was the number of left lobe treatment, due to an higher number of bilobar disease in ALPPS group. Surgical results couldn't be compared between first procedures, since LVD is a radiological intervention while ALPPS stage I is a complex surgery. Thus, surgical outcomes were compared also between LVD completion surgery and ALPPS stage I, showing a lower operation duration in the completion surgery ($p = 0.05$), with similar blood losses and post-operative complications (Table 4a).

The successful resection rate was higher for LVD group ($p = 0.27$), where all patients underwent completion surgery, while one patient in ALPPS group failed because of complications after stage 1. Four patients received a right hepatectomy as ALPPS stage 2 surgery and 11 received a right tri-sectionectomy, whereas in LVD group 7 and 10 underwent these two procedures, respectively. The median delay before the hepatectomies was significantly inferior in ALPPS group 14 ± 13 vs 39 ± 31 ($p = 0.002$). The median LoS after the completion surgery was similar in the compared groups, as well as the total incidence of postoperative complications (6 vs 9, $p = 0.50$). The median intraoperative estimated blood losses were lower in ALPPS groups (150 ± 600 vs 600 ± 1000 , $p = 0.004$), as well as post operative hemorrhages (0 vs 7, $P = 0.005$), even if they were all grade A. Seven patients received intraoperative blood transfusions in LVD group, while only 2 during ALPPS stage 2 procedures ($p = 0.05$).

One patient died in the firsts 90 postoperative days in ALPPS group.

3.4. Survival analysis

In the ALPPS group 13 patients died during follow-up, with one death linked to stage 1 procedure. In the LVD group, 6 patients died

Table 2

Volumetric analysis. SD: standard deviations; IQR: inter-quartile range; TLV: Total liver volume; FLRV: Future liver remnant volume; KGR: kinetic growth rate.

	ALPPS	LVD	p-value
Pre-procedural Tumor Volume, Median (IQR ₂₅₋₇₅)	83 (44–186)	51 (35–121.5)	0.24
Pre-procedural FLRV-share %, mean (SD)	29.7 (16)	29.3 (6.8)	0.53
Early Evaluation			
Delay procedure-first imaging in days, median (IQR)	9 (5)	7 (0)	
TLV gain in cc, mean (SD)	308 (298)	290 (261)	0.83
FLRV share %, mean (SD)	40 (13)	34 (8)	0.11
FLRV increase %, mean (SD)	62 (36)	40 (38)	0.09
KGR %, mean (SD)	0.8 (0.9)	0.3 (1.7)	0.31
KGR in cc, mean (SD)	23 (15)	26 (25)	0.70
Late Evaluation			
Delay procedure-last imaging in days, median (IQR)	9 (9)	21 (0)	
TLV gain in cc, mean (SD)	306 (298)	183 (271)	0.24
FLRV share %, mean (SD)	41 (13)	39 (9)	0.69
FLRV increase %, mean (SD)	60 (34)	49 (29)	0.32
KGR %, mean (SD)	0.6 (0.9)	0.2 (0.2)	0.21
KGR in cc, mean (SD)	20 (15)	10 (8)	0.02

Table 3

First liver volume augmentation procedures. Comparison of the outcomes between ALPPS stage 1 vs LVD. IQR: Inter-quartile range.

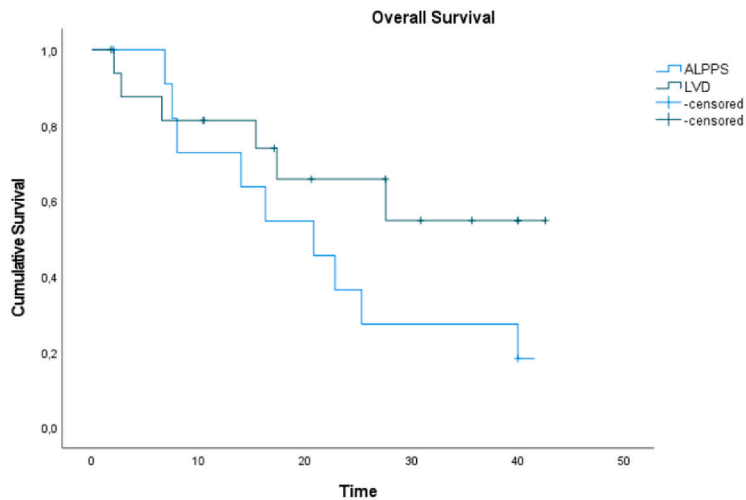
	ALPPS (n = 17)	LVD (n = 15)	p-value
Length of stay, median (IQR ₂₅₋₇₅)	15 (9–17)	3 (3–3)	<0.0001
Intra-procedural Complication, n (%)	1 (6)	1 (5.8)	0.47
Intra-procedural treatment of the left lobe	10 (67)	3 (17)	0.01
-wedge	9 (61)	0	0.0002
-microwave ablations	1 (6)	3 (17)	0.31
Post-procedural complications, n (%)	7 (46)	7 (41)	0.51
Clavien-Dindo ≥ 3 , n (%)	3 (20)	0	0.05

Table 4

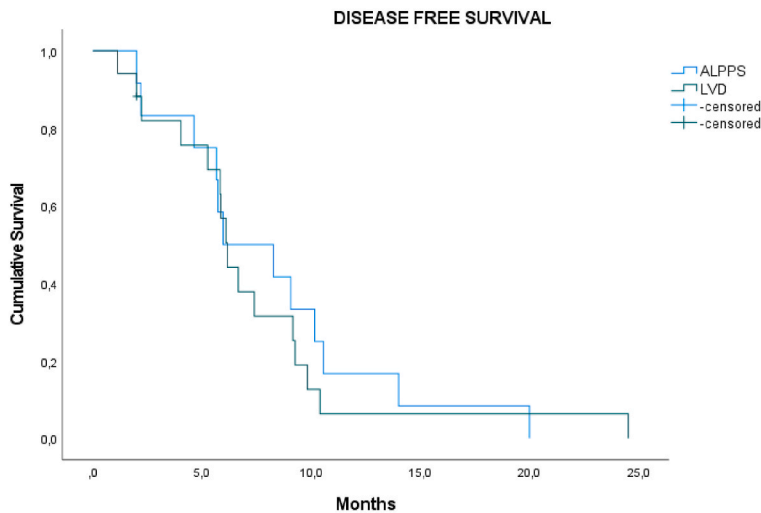
Surgical results. Comparison of intra- and post-procedural outcomes after (a) completion surgery of LVD group vs ALPPS stage 1 and (b) after completion surgeries of LVD vs ALPPS stage 2. PHLF: Post-hepatectomy liver failure; BL: biliary leaks; PHH: post-hepatectomy hemorrhage.

A			
	ALPPS stage I	Completion Surgery after LVD	p-value
Operation time in minutes, mean (SD)	342 (92)	288 (76)	0.05
Blood loss in ml, median (IQR ₂₅₋₇₅)	400 (300–650)	600 (300–1275)	0.14
Intraoperative Transfusions, n (%)	2 (12)	7	0.05
Post-procedural complications, n (%)	7 (46)	9 (52)	0.72
Clavien-Dindo ≥ 3 , n (%)	3 (20)	1 (5.8)	0.22
B			
	ALPPS stage II	Completion Surgery after LVD	p-value
Delay first procedure – completion surgery, median (IQR ₂₅₋₇₅)	14 (10–23)	39 (23–57)	0.002
Types of hepatectomy n (%)	4 (26)	7 (41)	0.38
-right hepatectomy	10 (74)	10 (59)	
-right trisectionectomy			
Hepatectomy not performed, n (%)	1 (6)	0	0.27
Duration operation time, mean (SD)	238 (36)	288 (76)	0.06
Blood loss, median (IQR ₂₅₋₇₅)	150 (100–700)	600 (300–1275)	0.004
Intraoperative Transfusions, n (%)	2 (12)	7 (41)	0.05
Length of stay, median (IQR ₂₅₋₇₅)	8 (7–15)	11 (8–13)	0.24
Post-operative complications, n (%)	6 (40)	9 (52)	0.50
PHLF	3 (40)	3 (17)	0.60
BL	1 (6)	1 (5.8)	0.72
PHH	0	7 (41)	0.005
Clavien-Dindo ≥ 3	4 (26)	1 (5.8)	0.13
90-days mortality	1 (6)	0	0.27
Hepatic Recurrence, n (%)	15 (100)	9 (52)	0.002

during the follow-up, without deaths related to the procedure. The OS at 1 year was 72,7% in the ALPPS group (CI 95% 59–85) and 81,3% in LVD group (CI 95% 72–90); 3-ys OS was 27,4% (CI 95% 18–36) and 54,7% (CI 95% 46–63) respectively, without statistically significant difference ($p = 0.10$) (Fig. 1). The Median DFS was comparable between both techniques: 6.1 months in the ALPPS cohort and 5.9 for LVD patients; $p = 0.66$) (Fig. 1). During follow-up, in the ALPPS group, 15 patients developed liver recurrence (100%), while in LVD group 9 patients (52.9%) ($p = 0.002$). Among LVD patients 6 developed pulmonary metastasis and 4 patients a peritoneal carcinomatosis. In the second group, a pulmonary metastatic progression occurred in two patients, two patients developed a lombo-aortic lymph node metastasis, one patient a peritoneal carcinomatosis.



	1-year OS	3-years OS	p-value
ALPPS	72.7%	27.4%	0.10
LVD	81.3%	54.7 %	



	1-year DFS	3-years DFS	Median DFS	p-value
ALPPS	16.7%	0%	6.1	0.66
LVD	6.3%	0%	5.9	

Fig. 1. a) Overall Survival and b) Disease Free Survival for ALPPS and LVD group.

4. Discussion

To our knowledge this is the first study that compares early and late KGR after ALPPS and LVD for colorectal liver metastases, and that deals with the oncological outcomes of the two techniques, with a median follow-up of 36 months.

Previously, Chebaro et al. published a multicentric comparison between these two procedures, including different indications [21]. This previous work was not focused on volumetric results, since it evaluated KGR at different and, thus, non-comparable time points, whereas previous literature showed that LVD presents very different kinetics during the post-procedural weeks [20]. Herein, early KGR did not significantly differ between both groups. Indeed, Guiu et al. previously showed

both higher volumetric and functional gain in the first days after LVD procedure [18]. In the same study, the majority of FLR functional growth after PVE was also obtained as early as 7 days after preparation in line with previous literature that had shown that the volumetric gain underestimates the functional gain [38,39]. In a recent paper comparing LVD to PVE, it has been claimed that LVD could trigger fast FLR regeneration and be considered as a “radiological ALPPS”, but unfair comparison of KGR have been reported so far since no early volumetric data were overlooked [40].

Another substantial difference with the previously published multicentric comparative study, was the high heterogeneity in LVD technique, with many patients that received only proximal occlusion, while our work deals with a standardized procedure, providing a careful

proximal and distal embolization in order to limit veno-venous collateral development in the resected liver in order to obtain a more effective growth. Such a difference could minimize heterogeneity in the results and explain another key difference in our outcomes: the 100% successful rate of LVD procedures, intended as the percentage of treated patient who were able to undergo liver surgery. In ALPPS group, one patient failed to undergo the hepatectomy because of a left hepatic vein thrombosis with hepatic decompensation and ascites, with post-operative complications that lead to death after 2 months. The result is coherent with previous experiences on ALPPS [41], that could let imagine an higher part of ALPPS treated patients failing to undergo the planned intervention, even if very good results were specifically reported in CRLM patients [42]. Such a high successful rate for LVD must be confirmed in further and wider studies, but it could be ascribed also to the low complication rate of the radiological procedure, as already widely reported in the literature, which may significantly reduce the risk of drop-out [43]. Indeed, the safety of the volume augmentation procedure appears to the authors to be a key issue in the comparison (the patients subjected to only one surgery), as well as the potential reduction of direct and indirect costs to be incurred for the health system. Thus, a further cost-effectiveness analysis will be also desirable in the future.

The median delay between LVD and completion of surgery was 39 days. This delay can be regarded as particularly long for a technique able to provide fast FLR increase, but so far LVD has been regarded as a PVE-like technique: the longer the waiting-time the greater the FLR augmentation. Thus, the introduction of this novel technique has been initially linked to a protocol aiming to 4–6 week interval before completion surgery, similar to PVE, the current standard of care. As suggested in a previous report, all the previously published results call for a strong reduction of this delay, and for applying an ALPPS-like strategy [20]. Further studies and efforts should focus on interval time reduction when applying LVD procedures, thanks to the excellent patients' tolerance and to the reported efficacy in terms of KGR [22,23].

Interestingly, intraoperative bleedings and transfusions, and post-hepatectomy hemorrhage (even if all grade A) were higher in the LVD group. These results could be partially explained by the significative venous congestion developed after LVD, together with the presence of veno-venous shunts after the hepatic vein occlusion [43], potentially leading to such an increase in the risk of intraoperative bleeding and post-operative hemorrhage. These hypotheses remain to be verified.

The fear of tumor progression while waiting after volume augmentation procedures is still a hot topic [44–46]. One of the most accredited theories considers increased arterial blood flow as the main possible cause of tumor progression, and this is because colorectal metastases are mainly nourished by it [47,48]. However, the enrolled patients didn't experience a tumor progression after LVD before the completion surgery, similarly to the ALPPS cohort. The 1-yr and 3-ys survival and disease-free recurrence rates were not statistically different between the two groups, despite the limiting factors of the study design and the small sample size. As regard to the comparison between the oncological outcomes, we must also underline how ALPPS patients in our study had a slightly larger median tumor size. However the difference didn't reach the statistical significance, and could be ascribed to the tendency to carry out a more aggressive and more morbid surgical procedure in cases with more advanced disease. Since we are in an initial phase of diffusion of the LVD procedure, it is almost impossible to have two cohorts perfectly equal from this point of view, if not by setting up a prospective randomized study, that could be stimulated precisely by our results.

A higher proportion of patients underwent a clearance of the left lobe after ALPPS during the first stage procedure: 11 patients received an intra-procedural treatment of the left lobe (9 additional resections and 2 thermal ablations). It must be underlined that LVD also gives the opportunity to percutaneously treat the left lobe. Simply, ALPPS patients had higher percentage of bilobar disease, indicating once again a different strategy for a more advanced disease. These data, together with

our results, confirm that the two techniques are basically not mutually exclusive but could be proposed by tailoring them specifically to case by case.

In our experience and according to the results of this study we believe that LVD could replace PVE in the future, both because it has shown an high safety and patients tolerance, and because it has excellent early KGR. On these assumptions is based the ongoing randomized trial of ultrafast FRL preparation comparing LVD and PVE, namely the HYPER-LIV 01. On the other hand, ALPPS can be a viable salvage option, as already proposed, after PVE failure [49], or in the case of a patient requiring extensive left lobe tumor clearance not feasible by percutaneous technique. Once more, the correct patient and procedure selection is the way.

This study has several limitations. Firstly, its retrospective nature and the relatively small sample size, can't lead to definitive conclusions. Because of the new introduction of LVD technique, despite the multi-center nature of the study, the small sample size could also have decreased the statistical significance of our results. However, our aim was to compare for the first time the different KGR after the two procedure and stimulate new further studies that would take into account the different KGR growth trends. The difference in the disease course among the two cohorts according to the previously published literature, is another limitation [50]. It could explain the approximately 28% of lower overall survival and the higher percentage of liver-only recurrence in the ALPPS group. However, since LVD is still in the initial phase of diffusion and ALPPS is not a risk-free procedure, we are convinced that our paper should be read as a promising first comparison of the volumetric data of the new radiological procedure with respect to the "surgical competitor", also in order to understand the different growth kinetics and the perioperative and long term outcomes. At the same time, there are also some strengths in this study. Montpellier University Hospital is the pioneer of LVD procedure, with a consolidated technical experience possibly leading to better outcomes and a lower learning curve effect. Initial data on the differences between ALPPS and LVD were obtained from centers with a lot of experience in ALPPS and little in LVD, furthermore mixing for different indications. Herein we have considered only CRLM patients, therefore without taking into consideration patients with cholestatic or cirrhotic livers, as the place of LVD and ALPPS in the management of cirrhotic patients remains unclear [19, 51]. Similarly, the good results of ALPPS in terms of safety and survival outcomes are in line with reports from experienced centers, that propose CRLM as the best indication [42].

In conclusion, despite its retrospective design and small sample sizes, this study shows very interesting results that may guide additional prospective studies, as well as help clinical practice for CRLM patients. LVD and ALPPS showed comparable daily KGR in the early period when performed in centers with high expertise and a perfected procedure. LVD allows a slightly higher successful resection rate than ALPPS, with a significantly lower LoS and severe postoperative complications. Additional randomized prospective studies are thus needed to adequately confirm such results.

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Declaration of competing interest

Nothing to declare.

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