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Original research

ALPPS for primary and secondary liver tumors

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HIGHLIGHTS

- ALPPS for hepatocellular carcinoma.
- ALPPS for locally advanced HCC with portal vein invasion.
- Future liver remnant growth after ALPPS in normal and cirrhotic livers.
- Technical and oncological feasibility of ALPPS in cirrhotic patients with HCC.

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ABSTRACT

Introduction: To report our experience on associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) in patients with liver tumors.
Methods: ALPPS is a surgical technique that allows hepatic resection after rapid liver hypertrophy.
Results: Thirteen operations were performed: 8 for hepatocellular carcinoma (HCC) with liver cirrhosis (LC) and 5 for colorectal liver metastases (CRLM, n = 3) and cholangiocarcinoma (CC, n = 2) in normal livers (NL). Of the 11 men (85%), the median age was 60 years (range 36–74). Six (75%) HCC patients had BCLC stage C and 2 (25%) had BCLC stage B disease. The median % future liver remnant (FLR) volume increase was 71.7% in patients with LC and 64.8% in NL (p = 0.44). Twelve patients achieved a sufficient FLR growth after the first stage (92.3% efficacy). Four right trisectorectomies and 9 right hepatectomies were performed. All patients completed the second stage (100% feasibility). R0 resection was achieved in all cases. The 90-day mortality rate was 23.1% (12.5% for HCC patients with LC vs 40% for CRLM and CC patients with NL, p = 0.13). After the first stage the overall morbidity rates were 62.5% and 80% (p = 0.61), whereas after the second stage they were 87.5% and 80% in patients with LC and NL respectively (p = 0.99). At a median follow-up of 15 months (range 1–27), the median DFS was 9 months (CI95% 6–12), and the 1yr-DFS was 42%. The median survival was 25 months (CI95% 10–40), and the 1-yr overall survival was 74%.
Conclusions: ALPPS induced a considerable and comparable FLR growth in HCC patients with liver cirrhosis and patients with CRLM and CC with normal liver parenchyma. HCC patients who underwent ALPPS had a high rate of macrovascular tumor involvement. A high rate of R0 resection is expected in properly selected patients.

1. Introduction

Liver resection provides a realistic chance of cure for primary and secondary liver tumors of the liver through incorporation into a multidisciplinary scheme of management. Over the last two years,

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there has been considerable debate on the application of ALPPS to induce hypertrophy of future liver remnant (FLR) in patients with locally advanced liver tumors for major liver resections [1–7]. ALPPS should be considered one recent advance in hepatobiliary surgical oncology and has expanded the indications of patients who may benefit from radical liver resection.

The initial experience suggested that increase in FLR in normal livers was more prominent and rapid with ALPPS when compared with techniques like portal vein embolization (PVE) or portal vein ligation (PVL) [8–12]. Unfortunately, ALPPS was reported to associate with high postoperative mortality and morbidity rates [1,2,6,8,10,13].

ALPPS can be performed for various locally advanced malignant liver tumors located in a healthy liver (e.g. colorectal liver metastases (CRLM) and cholangiocarcinoma (CC)). Its use for hepatocellular carcinoma (HCC) in a cirrhotic liver has been very limited [1,2,8,10,13]. The use of ALPPS has also been investigated in cirrhotic patients with large HCC with major vascular invasion and the preliminary clinical results were encouraging [14]. ALLPS has been reported to be feasible even in patients with underlying liver disease and it was able to induce a significant volume increase in FLR within a short time to allow completion of the two-step strategy of the ALPPS approach [14,15].

The aim of this study was to investigate the role of ALPPS in patients with primary and secondary liver tumors in liver cirrhosis (LC) or normal liver (NL) to compare the short-term clinical outcomes and volume increments in FLR.

2. Materials and methods

2.1. Patients

This is a retrospective and observational study. Data for all patients undergoing 2-stage hepatic resection with the ALPPS procedure for HCC (8), CRLM (3), and CC (2) at two different institutions between September 2012 and June 2015 were analyzed. Nine patients were operated at the San Camillo Hospital and 4 at the National Cancer Institute Regina Elena.

The patients were divided in two groups based on the underlying liver: Liver cirrhosis (LC) and normal liver (NL). The 90-day mortality, disease-free survival (DFS), overall survival, postoperative complications (POC), liver parameters, coagulation status, renal function, length of hospital stay, FLR volumes and increase in FLR volume after the first stage were compared between the 2 groups.

All patients with locally advanced liver cancers were discussed by a multidisciplinary panel of hepatologists, liver surgeons, interventional radiologists, anaesthetists and oncologists. Patients with LC were considered eligible for surgical resection if they had preserved liver function (serum bilirubin level < 1.5 mg/dl, INR < 1.3, and no signs of liver decompensation), oesophageal varices $<$ grade 1, platelets count $> 80 \times 10$/L and absence of ascites. Child-Pugh, Model for End-Stage Liver Disease and Eastern Cooperative Oncology Group score were calculated. No metabolism and/or hemodynamic tests were performed before surgery (i.e. Indocyanine Green Clearance Test, Hepatic Venous Pressure Gradient). Patients with hepatocellular carcinoma were stratified according to the BCLC staging classification. All patients underwent preoperative radiological evaluation with volumetric Computed Tomography (VCT) or Magnetic Resonance Imaging (MRI) to exclude extrahepatic disease and to assess FLR volumes. The presence of tumor thrombosis in a major branch of PV, hepatic veins or bile duct was not considered as an exclusion criteria for the procedure. Tumor recurrence was assessed by clinical examination, laboratory parameters and radiological examination (MRI, CT scan and PET scan).

Hematoxylin-eosin-stained slides and immunohistochemical analysis from surgical specimens were reviewed and fibrosis was scored according to the Metavir Scoring System. A score of 0–4 was given according to the degree of fibrosis: 0 (no fibrosis), 1 (mild fibrosis), 2 (moderate fibrosis), 3 (severe fibrosis), and 4 (cirrhosis).

2.2. Liver volumetry

For all patients a baseline FLR volume was measured before stage 1 by VCT scan. A FLR of 40% and a liver remnant to body weight ratio (BWR) $= 0.8\%$ was considered as the "gold standard" to perform a major hepatic resection in LC and a FLR of 30% and a liver remnant to body weight ratio (BWR) $= 0.5\%$ was considered as the "gold standard" to perform a major hepatic resection in NL without any attempts for PV embolization.

VCT scan of the liver was repeated after the first stage starting from postoperative day (POD) 6. For the 2 groups the difference between the FLR after the first stage and FLR at baseline was calculated (%FLR1 − %FLR0). Correlation between the FLR volume at the baseline (vol_0) and after the first stage (vol_1) was calculated by using the formula: %FLR volume increase $= (vol_1 - vol_0)/vol_0 \times 100$ to evaluate the FLR volume increment [9]. Liver resections and anatomy were defined according to the Brisbane Conference nomenclature and Couinaud's segmentation of the liver [16,17]. Grading of Post-Hepatectomy Liver Failure (PHLF) was defined according to the International Study Group of Liver Surgery (ISGLS) classification [18]. Postoperative complications (POC) were defined according to the Dindo-Clavien classification [19]. Informed consent was obtained from all patients before the procedures. The surgical techniques for ALPPS have been described elsewhere [14]. In all patients, liver parenchymal transection was performed using the anterior approach with hanging maneuver [20,21].

2.3. Statistical method

Descriptive statistics were used on the characteristics of patients. The Chi-square, Fisher exact and Mann–Whitney U-tests were used when comparing categories against categorical and continuous data, respectively. Comparison of measures obtained at different time points in the same patients was performed by the Friedman test. The Kaplan-Meier method was used to estimate survival curves and any differences between the subgroups were assessed by the log-rank test. All significance was defined at a $p < 0.05$. The SPSS software (SPSS version 21.0, SPSS Inc., Chicago, Illinois, USA) was used for all statistical evaluations.

3. Results

3.1. Patient demographics

Thirteen patients underwent ALPPS for HCC ($n = 8$), CRLM (n-3), and CC ($n = 2$). Eight patients with HCC were determined to have a grade 4 fibrosis or cirrhosis, which was related to HCV in 6 and to HBV in 2. Five patients with CRLM and CC were determined to have grade 0 fibrosis. Eight ALPPS procedures were performed in LC and 5 in NL. The median age of the patients at the time of surgery was 60 years (range 36–74). There were 11 men. The median BMI was 26.7 kg/m^2 (range 21–30).

Six (75%) patients had thrombotic involvement of a large vein or bile duct: right portal vein ($n = 2$), middle hepatic vein ($n = 2$) (Fig. 1), right hepatic vein + right portal vein ($n = 1$) and right hepatic bile duct ($n = 1$). Six (75%) patients had BCLC stage C disease with tumor thrombus and 2 (25%) had BCLC stage B disease. The median preoperative alpha-fetoprotein was 21,011 ng/ml (range 62.9–92,000). The cirrhotic patients were all classified as

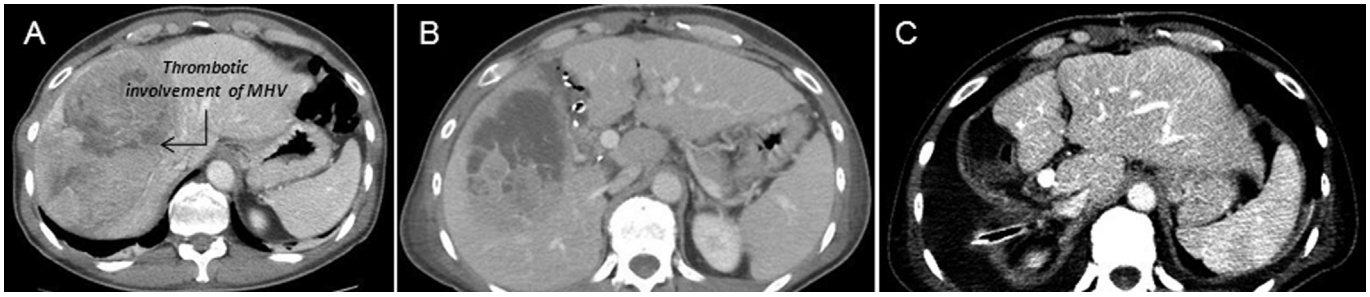

Fig. 1. A, Preoperative VCT scan of a fifty-two year old man with a large HCC of the right liver measuring 14 cm with thrombotic involvement of the middle hepatic vein (MHV) (black arrow). B, Post first-stage ALPPS CT scan showing parenchymal transection up to inferior vena cava. C, Post second-stage ALPPS CT scan performed before discharge showing hypertrophy of the FLR.

Child-Pugh A6 and the median preoperative MELD score was 8 (range 7–9). All patients affected by HCC were beyond the Milan criteria and were not eligible for liver transplantation (LTX). One patient had a previous left colectomy for sigmoid cancer (pT3 N2 G3).

The patients with CRLM had synchronous bilobar multiple metastases from colorectal cancer and all had undergone neo-adjuvant chemotherapy (Folfoxiri + Cetuximab (n = 1) or Folfox + Bevacizumab (n = 2)). The preoperative median level of carcinoembryonic antigen (CEA) was 130.6 U/ml (range 4.7–115). The previous colonic operations were: Hartmann operation (n = 1) and rectal anterior resection (n = 1). The median time from colorectal surgery to ALPPS procedure was 11 months.

Two patients had intrahepatic CC with normal preoperative serum bilirubin after preoperative biliary drainage. The preoperative median level of CA 19.9 was 235 U/ml (range 40–430). One patient received neoadjuvant chemotherapy with capecitabine. One patient had right portal vein involvement (Table 1).

3.2. Liver volumetry

The preoperative and postoperative FLR volume, FLT/TLV and FLR volume to BWR were comparable between the two groups (Table 2).

Twelve patients achieved a sufficient increase in FLR after the first stage (92.3% efficacy). One patient with LC never achieved a sufficient FLR hypertrophy. A comparable FLR volume gain was observed in patients with LC and NL. The FLR increased within one week from 23% to 44% in patients with LC and from 25% to 49% in patients with NL. The median %FLR volume increase was 71.7% in patients with LC and 64.8% in patients with NL within one week after the first stage.

3.3. Intraoperative data

All patients underwent a stage 2 operation after a median of 9 days (100% feasibility). There were 4 right trisectorectomies and 9 right hepatectomies.

Stage 1: the median operating time, median blood loss and intraoperative blood transfusions were comparable between the two groups (Table 3). Pringle maneuver was performed in 2 patients for an average of 25 min. Additional surgical procedures included FLR clearance of tumors in 3 patients with liver metastasis, biliodigestive anastomosis in 3 patients and simultaneous rectal anterior resection in one patient with CRLM. One patient with HCC received thrombectomy of the middle hepatic vein.

Stage 2: the median operating time, median blood loss and intraoperative blood transfusions were comparable between the two groups (Table 3). Additional surgical procedures included ileostomy for anastomotic leak of colorectal anastomosis (n = 1) and portal thrombectomy (n = 1). During hospitalization, 2 units of RBC were transfused in patients with LC and 6 units in patients with NL (Table 3). Total liver transection was performed in 11 patients (84.6%) and partial parenchymal transection in 2 (15.4%). Negative resection margins (R0) were achieved in 13 patients (100% oncological feasibility).

Table 1
Preoperative patient characteristics and outcomes.

Patient	Age	Gender	Etiology	Cancer diagnosis	N. lesions	Largest tumor (cm)	Portal vein thrombosis	Postoperative stay (days)	Recurrence site	Days to recurrence	Days to death
1	68	M	HCV	HCC	1	7	no	22	–	–	–
2	36	M	HBV	HCC	1	7.7	yes	22	–	–	357
3	74	M	HCV	HCC	1	9.7	yes	45	–	–	45
4	54	M	HCV	HCC	1	9.4	no	20	–	–	–
5	74	M	HCV	HCC	2	3.1	yes	22	Liver	180	450
6	52	M	HCV	HCC	1	14	yes	22	Liver	160	–
7	66	M	HBV	HCC	1	3,5	no	67	Liver	195	–
8	64	M	HCV	HCC	2	4,5	No	34	–	–	–
9	60	F	Primitive liver	CC	1	15	yes	66	–	–	81
10	48	M	Colrectal adc	CRLM	multiple	6	no	33	–	–	–
11	70	F	Colrectal adc	CRLM	2	5.6	no	31	liver	275	–
12	54	M	Primitive liver	CC	1	12	no	42	–	–	30
13	56	M	Colrectal adc	CRLM	7	4	no	26	Liver-lung	357	–

HCC: hepatocellular carcinoma; HBV: hepatitis B; HCV: hepatitis B; CC: colangiocarcinoma; CRLM: colorectal liver metastases; adc: adenocarcinoma.

Table 2
Liver volumes pre and post stage 1 and FLR volume increase.

Variable		ALPPS in LC group n = 8	ALPPS in NL parenchyma group n = 5	p value
		(Median and range)		
Time between step 1 and step 2	Days	8 (7–10)	10 (7–12)	p = 0.56
Preoperative				
FLR volume	cc	421 (304–655)	418 (209–645)	p = 0.83
FLR/TLV	%	23 (19–38)	25 (17–34)	p = 0.79
FLR/BWR		0.64 (0.39–0.73)	0.47 (0.34–0.73)	p = 0.24
After step 1				
FLR volume	cc	723 cc (450–1135)	689 (424–1006)	p = 0.49
FLR/TLV	%	44 (35–56)	46 (20–90)	P = 0.71
FLR/BWR		0.99 (0.67–1.6)	0.83 (0.4–1.3)	P = 0.37
% volume increase	%	71.7	64.8	P = 0.44

Table 3
Operative data and clinical outcomes.

		ALPPS in LC group n = 8	ALPPS in NL parenchyma group n = 5	P value
		(Median and range)x		
Stage 1				
Operative time	Min.	306 (228–400)	322 (275–430)	p = 0.66
Blood loss	cc	220 (100–550)	350 (250–850)	p = 0.03
RBC transfusion		0	0	
Stage 2				
Operative time	Min.	244 (150–525)	219 (173–320)	p = 0.19
Blood loss	cc	150 (100–250)	250 (150–330)	p = 0.03
RBC transfusion		0	0	
Total parenchymal transection	%	85	100	p = 0.94
ALPPS efficacy	%	87.5	100	p = 0.94
Plastic bag use	%	0	0	
Planned	%	85	100	p = 0.94
Complete resection (R0)	%	100	100	
Re-laparotomy rate	%	0	40	p = 0.20
ICU stay	Days	5 (2–8)	2 (1–35)	P = 0.66
Postoperative stay	Days	22 (20–67)	33 (26–66)	p = 0.28
90-day mortality	%	1 (12.5%)	2 (40%)	p = 0.51

3.4. Postoperative complications (POC) and laboratory findings

ALPPS was planned in 11 patients (84.6%) based on the preoperative VCT scan. In 2 (25%) patients with HCC, the decision to perform ALPPS was made at the time of surgery as intraoperative ultrasound showed disease progression requiring a right hepatectomy.

Overall, 47 POC were documented: 17 at the first stage and 30 at the second stage. After the first stage 76.5% were of grade I and 23.5% of grade II. POC of grade II happened more commonly in patients with LC than in those with NL (44.4% vs 0%, p = 0.08). After the second stage there was a significantly higher rate of POC of grade III–IV in patients with NL (p = 0.001) (Table 4). After the first stage the overall morbidity rates were 62.5% and 80% in patients with LC and NL respectively (p = 0.61), whereas after the second stage they were 87.5% and 80% in patients with LC and NL respectively (p = 0.99) (Table 4).

Laboratory findings including AST, GPT, total bilirubin, prothrombin time and creatinine after stages 1 and 2 are detailed in Table 5. According to the ISGLS definition, in cirrhotic patients a grade A PHLF was found in 1 patient while a grade C was found in 1 patient. In patients with NL a grade A PHLP was found in 1 patient while a grade C was found in 1 patient. Patients with LC and NL have comparable values of AST, ALT, Total bilirubin, INR and creatinine. After stage 1, AST and ALT significantly declined in both groups. After stage 2, ALT significantly declined in patients with LC whereas AST significantly declined in patients with NL.

Table 4
Postoperative complications according to severity grade (Dindo-Clavien).

Grade		%	ALPPS in LC group n = 8	%	ALPPS in NL parenchima group n = 5	%
Step 1						
I	13	76.5	5	55.6	8	100
II	4	23.5	4	44.4	0	0
III–IV	0	0	0	0	0	0
Sum	17	100	9	100	8	100
Step 2						
I	15	50	13	81.3	2	14.3
II	9	30	1	6.25	8	57.1
III–IV	6	20	2	12.5	4	28.6
Sum	30	100	16	100	14	100.0

Table 5
Postoperative laboratory findings. Values expressed as median and range are given up to POD 5 after stage 1 and POD 15 after stage 2.

	ALPPS in LC					ALPPS in NL				
	POD1	POD3	POD5	POD15	*p value*	POD1	POD3	POD5	POD15	*p value*
Step1										
Bilirubin	1.0 (0.3–9.0)	1.25 (0.50–5.90)	1.05 (0.6–6.4)	–	*0.28*	0.70 (0.60–1.0)	0.70 (0.60–1.30)	0.60 (0.40–0.70)	–	*0.37*
INR	1.56 (1.23–1.86)	1.43 (1.08–1.61)	1.38 (1.13–1.66)	–	*0.07*	1.20 (1.0–1.52)	1.27 (1.15–1.35)	1.25 (1.12–1.35)	–	*0.94*
AST	394.5 (73–3525)	166.5 (50–421)	72 (36–105)	–	*0.001*	318.5 (208–473)	84 (68–216)	30.5 (17–60)	–	*0.02*
ALT	329 (59–3379)	259.5 (99–1314)	132.5 (64–535)	–	*0.005*	402.5 (209–518)	299 (161–457)	127 (83–174)	–	*0.04*
Creatinine	0.75 (0.43–1.69)	0.73 (0.46–1.20)	0.74 (0.45–1.47)	–	*0.79*	0.85 (0.74–1.0)	0.70 (0.60–0.90)	0.80 (0.60–0.92)	–	*0.07*
Step2										
Bilirubin	1.80 (0.40–7.0)	1.20 (0.60–6.0)	1.87 (0.60–5.09)	2.0 (0.40–4.07)	*0.75*	1.68 (1.10–1.95)	1.98 (0.70–2.30)	1.57 (0.40–4.50)	1.31 (0.50–10.30)	*0.83*
INR	1.47 (1.31–1.99)	1.42 (1.29–1.84)	1.43 (1.27–1.75)	1.39 (1.09–1.55)	*0.12*	1.68 (1.15–2.55)	1.56 (1.18–1.85)	1.54 (1.21–1.73)	1.33 (1.12–1.43)	*0.07*
AST	94.5 (24–1544)	69.5 (29–101)	50 (26–88)	53 (37–106)	*0.07*	65 (45–1741)	44 (25–404)	20 (19–131)	37 (18–60)	*0.03*
ALT	125 (29–1088)	80 (24–232)	51.5 (19–118)	53 (32–93)	*0.001*	91 (39–889)	73 (23–522)	50 (32–305)	34.5 (18–67)	*0.09*
Creatinine	0.79 (0.49–1.87)	0.57 (0.30–1.03)	0.66 (0.4–1.1)	0.75 (0.46–1.30)	*0.34*	0.77 (0.47–0.97)	0.70 (0.39–1.09)	0.78 (0.4–1.1)	0.78 (0.26–0.93)	*0.62*

3.5. Outcomes

The 90-day mortality rate was 23.1% for the entire group. Three patients died: 1 (12.5%) patient with LC died of hepatic failure while 2 (40%) patients with NL died of sepsis, $p = 0.51$. Two patients died during follow-up: 1 for infection and 1 for HCC recurrence and progression.

The rate of relaparotomy was 15.4%. The median follow-up of the study cohort was 15 months (range 1–27). The median survival time was 25 months (CI95% 10.5–39.5) with a 1-yr overall survival of 74%. No difference was observed between the patients with LC and with NL ($p = 0.98$). The median DFS was 9 months (CI95% 4.1–13.9) with a 1yr-DFS of 42%. Disease recurrence was detected in 5 patients (3 in patients with LC vs 2 with NL, $p = 0.99$). All the data are summarised in Table 3.

4. Discussion

ALPPS is considered as one of the main surgical innovations in recent years in liver surgical oncology. This new surgical strategy has the main advantage of inducing pronounced and rapid increase of FLR within a short period of time [8–12]. This makes ALPPS an important surgical option to overcome the main limitations of the two-step classic strategy: 1) technically impossible when the tumor has invaded the right portal vein, 2) in patients with a high risk of tumor progression resulting in unresectability between the two steps and 3) in patients with FLR which may not hypertrophied enough to undergo major resections.

For the above mentioned reasons, ALPPS has raised interest amongst liver surgeons. However, the procedure has a relatively high morbidity rate which ranges from 59% to 64% and a high in-hospital mortality rate which ranges from 12 to 16% [13]. For these reasons the use of ALPPS has extensively been debated [22–31]. The experience with this procedure has now been increasing. It is becoming clear that the short-term outcomes can be improved with refinement in surgical technique, better patient selection and identifying risk factors so as to avoid adverse outcomes [1–15].

The initial technique as described by Schnitzbauer has been simplified in many aspects. The use of the “anterior approach” to avoid right liver mobilization to reduce adhesion formation and to avoid deployment of a plastic bag around the right liver has been reported [33]. The liver hanging maneuver (HM) has been combined with the anterior approach in patients with HCC with major vascular invasion. These important technical improvements facilitate splitting of the hemilivers down to the anterior wall of inferior vena cava, avoiding any “tumor manipulation” during hepatectomy and reducing intraoperative blood loss, perioperative blood transfusion, and operative time which ultimately result in improved postoperative and long-time oncologic outcomes [34]. Other technical modifications include: laparoscopic ALPPS, liver partition by thermal ablation, use of Tachosil for coverage of raw surface after liver parenchymal transection, and monosegment and partial-ALPPS [35,36].

This study confirms that the early morbidity and mortality rates after ALPPS are higher than that reported in the literature for major liver resections. A recent report from the international ALPPS registry showed an overall 90-day mortality rate of 8.8% in 320 patients who mainly had CRLM, and 75% of deaths were due to postoperative liver failure which was the predominant cause of death. A MELD score of more than 10 before stage-2 has been shown to be a predictive risk factor for adverse outcome [37]. Patients who are heavily pretreated with systemic chemotherapy for CRLM are also at a high risk of poor outcomes and a careful attention to the type and duration of systemic therapy is advisable

before ALPPS. In this study, of the 5 patients with CRLM and CC, 4 received neoadjuvant chemotherapy. These patients had a significant increase in FLR volume of 64.8% after liver partitioning. However, this increase was slightly inferior than that observed for patients with LC and that reported in a systematic review on ALPPS which found an average volume increase of 78%–91% [1]. A study from Kremer et al. recently showed that neoadjuvant chemotherapy significantly impaired FLR regeneration in ALPPS and reported a FLR volume increase of 59% post chemotherapy [38].

A study, from Oldhafer, reported an early tumor recurrence rate of 86% in patients who underwent ALPPS for CRLM despite R0 resection was achieved in all the patients and chemotherapy was administered in the perioperative phase [8]. However, in these patients a high tumor recurrence rate is expected since ALPPS is used in patients with extensive metastatic liver disease which has a poor oncologic prognosis. The ALPPS strategy could not change the natural history of the disease. The use of ALPPS in patients with CC is still controversial.

On the other hand using ALPPS on patients with HCC with a background of LC is completely different. First, cirrhotic livers have less regenerative capacity; second, HCC has a tendency to associate with neoplastic thrombosis of portal vein, hepatic vein or bile duct which has a poor prognosis [34,35]. Third, the most frequent pattern of HCC recurrence is within the liver. There are effective treatments (repeated hepatectomy, TACE, SIRT, RFA, RE) which can significantly prolong survival if the recurrence is detected early.

In a previous study ALLPS has been shown to be technically feasible and safe in HCC patients with cirrhosis and a significant volume increment of FLR can be induced in a short time to allow for completion of the two stage strategy [15].

ALPPS seems to be an attractive strategy in the following scenarios: 1) a conventional two-stage approach is not feasible due to invasion of a portal venous branch, 2) previous PVE or PVL has failed to induce enough hypertrophy of the FLR for a major hepatic resection, 3) in hepatic vein neoplastic thrombosis (HVNT) and/or portal vein neoplastic thrombosis (PVNT) with a risk of rapid progression into the cava-atrium and 4) in aggressive tumors where the classical strategy cannot be applied due to the risk of rapid tumor progression between the two stages.

In this study, ALPPS in HCC patients has the following drawbacks: in five patients PVNT and/or HVNT were present. PVNT prevents any radiological embolization to be carried out. The risk of HVNT with rapid progression to involve the vena cava and right atrium was high. In another two patients, unexpected rapid malignant disease progression was detected at the time of surgery, making right hepatectomy necessary. In this study, a large proportion (71.5%) of patients had neoplastic involvement of portal vein, hepatic vein or bile duct making the ALPPS a very attractive solution for such complex cases. All these patients with locally advanced disease underwent radical surgery.

HCC patients should be carefully selected to undergo ALPPS as the outcomes have not been well reported. There were only sporadical reports on ALPPS for HCC patients. A recent study from D'Haese JG et al. compared the outcomes of 35 HCC patients with 225 patients with CRLM. They found a significantly high perioperative mortality rate of 31% for HCC patients and concluded that the use of ALPPS remains prohibitive for most HCC patients, and ALPPS should be performed in a highly selected group of HCC patient who were younger than 60 years and had low-grade fibrosis [39]. Interestingly, they found a hypertrophy rate of 47% in patients with LC and showed that the hypertrophy rate of the FLR correlated well with the degree of liver fibrosis. Patients with low-grade fibrosis had extensive hypertrophy whereas those with LC had a minor degree of hypertrophy. These findings confirmed our findings that the FLR increased within one week from 23% to 44% and the median increase in FLR volume was 71.7% in patients with LC.

The present study involves eight HCC patients who were classified as BCLC stage B or stage C who should be treated with TACE or new therapeutic agents. However, the survival of HCC patients with major vascular invasion treated with sorafenib is about 10 months [40]. An aggressive surgical approach in patients with HCC and associated PVNT and/or HVNT yielded long term outcomes which were significantly better than those patients treated by sorafenib (47.4 vs 10.7 months) [41,42]. Furthermore, Wang et al. reported prolonged survival (19 months) in patients with HCC with inferior vena cava neoplastic thrombosis treated by surgery [43]. All these justify an aggressive surgical approach and support the use of ALPPS in HCC patients with BCLC stage B and C as survival is better compared to non-surgical treatment. Furthermore, even if tumor recurrence occurs, the majority can still be treatable. Thus, ALPPS can expand the indication and increase the number of patients to undergo major radical liver resections for HCC. These observations still require external validations to confirm. Although the results of the present study are interesting, this study has limitations. This is a retrospective study which included a small sample of patients. There is likely to have selection biases. In addition, a multivariate analysis for confounding variables was not performed and the majority of patients were operated recently without a sufficiently long follow-up for long term oncological results.

In conclusion, we report the operative results and short term outcomes of 13 patients who underwent ALPPS for locally advanced primary and secondary liver tumors. This study showed that ALPPS induced considerable and comparable FLR growths in HCC patients with LC and patients with CRLM and CC with NL. In HCC patients there was a high rate of macrovascular tumor involvement although a high rate of R0 resection is still expected.

Ethical approval

Ethical approval not requested.

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Author contribution

Giovanni Vennarecci: writing, study design, performed surgery.
Gian Luca Grazi: data collection, performed surgery.
Elisa Busi Rizzi: data collection.
Emanuele Felli: data collection.
Mario Antonini: performer surgery, data collection.
Giampiero D'Offizi: data collection.
Sperduti Isabella: data analisys.
Giuseppe Maria Ettorre: study design, performed surgery.

Conflicts of interest

None.

Guarantor

Giovanni Vennarecci.
Giuseppe Maria Ettorre.

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