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ORIGINAL ARTICLE

Associating liver partition and portal vein ligation for staged hepatectomy in patients with primary liver malignancies: A systematic review of the literature

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Summary

Purpose: *Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) represents a revolutionary new surgical technique and one of the most promising advances in liver surgery over the last decade, which provides rapid and effective growth of liver remnant volume, allowing surgical resection of hepatic lesions initially considered unresectable. The aim of this review was to address from a critical point of view, the impact of this novel procedure conducted for primary liver malignancies, on tumor biology itself and thus on short and long-term outcomes, as disease free survival and overall survival.*

Methods: *The present study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Identification of eligible studies was performed through a systematic search of the literature using Medline/PubMed, Scopus, Cochrane, Google Scholar, and clinicaltrials.gov databases. The end date of the literature search was set to 30th November 2018. The following keywords were used for the search: "Associating Liver Partition and Portal Vein Ligation for Staged hepatectomy", "ALPPS", "Portal Vein Embolization (PVE) And In Situ Split", "Portal Vein Ligation (PVL) And In Situ Split".*

Results: *The 28 studies enrolled in the present analysis incorporated 136 patients who were subjected to ALPPS due to primary liver malignancy. R0 resection status has been documented in 20 studies estimated to be 97.24%. 30-day mortality was 9.55%. Concerning 30-day morbidity graded according to Clavien-Dindo classification, interestingly 7 studies stated no postoperative complications, neither minor (I-II) nor major (III-V). As for the oncological outcomes, median follow up was 10 months (range 0-36), recurrence rate was 36%, disease free survival ranged from 1 to 36 months with a median of 6 months and overall survival ranged from 1 to 36 months with a median of 11 months.*

Conclusions: *ALPPS offers a reasonable chance of complete resection in patients with unresectable primary liver tumors. Optimal selection of patients, gaining the surgical experience of carrying out this technique and its impact on short and long-term results are issues that still remain under debate while waiting for the final outcomes of the multicenter registries with larger number of cases.*

Key words: *ALPPS, portal vein embolization, in situ split, portal vein ligation*

Introduction

Surgical resection is the best option for prolonged survival in patients with primary [1] or secondary liver tumors [2], especially if extrahepatic tumor manifestation is absent. Due to the im-

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pressive development of intra- and perioperative management within the past 3 decades, even major hepatectomies can be performed with acceptable morbidity and mortality [3]. However, "resectability" of primary or metastatic liver cancer is not clearly defined, with one of the major limiting factors for performing extensive liver resections to be the remaining liver volume, referred to as future liver remnant (FLR) [4,5]. In case of normal liver function, FLR of 25-30% is considered to be sufficient to maintain liver function after resection. For patients with hepatic dysfunction (eg liver fibrosis due to cirrhosis, cholestasis, macrosteatosis) or earlier liver injury (eg, due to chemotherapy), a higher FLR of approximately 40% is advised [6].

Several methods have been developed to increase resectability in patients undergoing major hepatic resections. The first technical option representing a major breakthrough in liver surgery is the concept of portal vein occlusion in the tumor-bearing liver lobe, conceived by Makuuchi, in 1990 [7]. The fundamental underlying principle behind this approach is to generate atrophy of the tumor-bearing lobe with subsequent hypertrophy in the contralateral lobe by diverting the portal venous flow into the liver section that is expected to remain, via either surgical portal vein ligation (PVL) or radiological portal vein embolization (PVE) [8]. Recent studies demonstrate that portal occlusion increases the FLR between 10-46% within 2- 8 weeks interval and with an achievable R0-resection rate of 70-100% in selected cases [9]. However, some patients display tumor progression after PVE, which can be critical, especially among those with borderline resectable or oncologically aggressive tumors. It is still vague whether this is just a matter of time (from portal vein occlusion to operation) or is due to growth stimuli to the tumor by the induced liver regeneration.

The abovementioned concerns led Rene Adam to propose the so called "two-stage hepatectomy", an alternative procedure performed in case of bilateral disease, in 2000 [10]. This approach implies that one liver lobe is initially cleared of tumors with a combination of direct resection plus local ablative therapies, followed by a period of recovery of approximately 4-6 weeks. Subsequently, after hypertrophy of the tumor-free lobe, tumor removal is completed by resection of the larger tumor mass in the contralateral liver lobe. The main drawback of "two-stage hepatectomy" however, is that not all patients are applicable for liver resection due to insufficient liver regeneration process and the most feared complication following major hepatectomies: "postophepatectomy liver failure" (PHLF) [9,11].

Although the mechanisms behind the failure of liver regeneration are ambiguous, research in the field combined with established surgical experience has aided the development of a new surgical procedure to promote an accelerated liver regeneration, opening up the benefits of liver resection to wider populations of patients undergoing extensive liver resections [5]. Following and reinterpreting the intuition of Pichlmayr, who first introduced in situ split in liver transplantations [12], Schlitt in Germany, performed the first "In situ split transection associated to portal vein ligation" in a young patient affected by Klatskin's tumor, in 2007 [13], followed by the first scientific report by Baumgart in 2011 [14] and popularized by Santibañes and his colleagues. Schnitzbauer et al. describe the preliminary experience with respect to 25 cases performed in 5 German centers and thereby introduce, for the first time, a new strategy to deal with extensive tumor burden [15-17]. In this initial experience, a high morbidity rate (68%) and a significant mortality rate (12%) were reported, whereas an impressive, rapid FLR volume hypertrophy and low rates of postoperative liver failure were observed. Soon after, an international registry was created to collect data on a voluntary basis from many centers around the world, which currently counts more than 1000 cases, the so called "The ALPPS Registry Group" [18,19].

The purpose of this systematic review is to evaluate the safety and feasibility of the novel approach, also known as associating liver partition and portal vein ligation in staged hepatectomy (ALPPS) [20] in primary liver malignancies.

Methods

Search strategy and data sources

The present study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Identification of eligible studies was performed through a systematic search of the literature using Medline/PubMed, Scopus, Cochrane, Google Scholar, and clinicaltrials.gov databases. The end date of the literature search was set to 30th November 2018. The reference list of the selected studies was manually assessed for the detection of potentially relevant articles. The following keywords were used for the search: "Associating Liver Partition and Portal Vein Ligation for Staged hepatectomy", "ALPPS", "Portal Vein Embolization (PVE) And In Situ Split", "Portal Vein Ligation (PVL) And In Situ Split". Two authors (EM and DM) independently performed the literature search, the study selection and the data extraction. The consensus from all authors resolved potential discordances in methodology, selection of articles and statistical analysis.

Table 1. Characteristics of the included studies

Study. First author [Ref]	*Study design*	*Country*	*Year of publication*	*Study period*	*Total number of patients (n)*	*Number of patients with PLM (n)*	*Gender, (male: female ratio)*	*Histology of primary tumor*
Schlitt et al [31]	Case series	Germany	2017	2007-2010	9	3	NR	1PHCC: 2IHCC
Alvarez et al [32]	Case series	Argentina	2012	2011-2012	15	2	1:1	PHCC: HCC
Cavaness et al [41]	Case report	USA	2012	2012	1	1	1:0	HCC
Knoefel et al [33]	Case series	Germany	2012	2009-2011	22	7*	NR	1:3:5:2 (HCC:PHCC: IHCC: GC)
Brustia et al [34]	Case series	France	2013	2012-2013	6	1	1:0	HCC
Ratti et al [35]	Case series	Italy	2013	2012	8	3	2:1	2 PHCC: 1 GC
Chia et al [36]	Case report	China	2014	2014	1	1	1:0	HCC
Nadalin et al [37]	Case series	Germany	2014	2010- 2013	15	10	NR	5 PHCC: 4 IHCC: 1 HCC
Troja et al [20]	Case series	Germany	2014	2009-2014	5	1	0:1	IHCC
Herman et al [38]	Case series	Brazil	2015	2011-2014	7	1	1:0	IHCC
Oldhafer et al [39]	Case report	Germany	2015	2015	1	1	1:0	IHCC
Vicente et al [40]	Case series	Spain	2015	2011-2014	9	1	0:1	IHCC
Vivarelli et al [41]	Case series	Italy	2015	2013-2014	9	5	0:5	3 PHCC: 1 IHCC: 1 HCC
Tsui et al [41]	Case series	Germany	2016	NR	2	2	0:2	GC
Bjornsson et al [42]	Case series	Sweden	2016	2012-2015	10	8	5:3	1 PHCC: 3 IHCC: 4 HCC
Cheung et al [43]	Case report	China	2016	2015	1	1	NR	HCC
Papamichail et al [44]	Case report	United Kingdom	2016	2015	1	1	1:0	HCC
Romic et al [45]	Case report	Croatia	2016	2015	1	1	0:1	HCC
Torres et al [46]	Case report	Brazil	2016	2016	1	1	1:0	HCC
Varma et al [47]	Case report	India	2016	2016	1	1	1:0	HCC
Chan et al [48]	Case series	China	2017	2013-2016	25	13	11:2	HCC
Ha et al [49]	Case report	Saudi Arabia	2017	2017	1	1	1:0	IHCC
Pineda- Solis et al [50]	Case report	USA- Canada	2017	2016	1	1	0:1	IHCC
Sanei et al [51]	Case series	India	2017	2013-2014	5 (4 drop out)	2	1:1	HCC
Chia et al [52]	Case series	Singapore	2018	2014-2016	13	7 (2 drop out)	8:1	HCC
Uribe et al [53]	Case series	Chile	2018	2013-2015	11	1	1:0	HCC
Vennarecci et al [54]	Case study	Italy	2018	2012-2017	24	18	NR	17 HCC: 1 CC
Wang et al [25]	Case study	China	2018	2013-2017	45	41 (4 drop out)	40:5	HCC
Total: 28	16:10:2		2012-2018	2007-2017	250	136		1:13:10:102:3:7

TPLM: primary liver malignancy, NR: not reported, IHCC: intrahepatic cholangiocarcinoma, PHCC: perihilar cholangiocarcinoma, HCC: hepatocellular carcinoma, GB: gallbladder carcinoma, NEN: neuroendocrine neoplasm. * Selected only the ISLT group with no prior PVE

Table 2. Patient characteristics

Study. First author [Ref]	*Mean age, yrs (range)*	*Tumor size, (cm), median*	*Primary tumor location*	*Type of liver resection*	*Postoperative day of 2nd stage operation, (N), range*	*Neoadjuvant chemo/ radiotherapy*	*Preoperative treatment*
Schlitt et al [31]	NR	NR	Right Lobe	R Trisectionectomy	NR	0	PHCC:PBD-IHCC:PVE-IHCC:None
Alvarez et al [32]	68 (59-77)	NR	Hilum: Right Lobe	R Trisectionectomy	7	0	Bilateral PBD:0
Cavaness et al [54]	57	3.4	Right Lobe	R Trisectionectomy	4	0	0
Knoefel et al [33]	NR	NR	Right Lobe	R Trisectionectomy	6 (4-8)	0	4 PVE: 7 None
Brustia et al [34]	46	NR	Right Lobe	R Hepatectomy	10	0	0
Ratti et al [35]	65.6 (60-72)	NR	2 Hilum: Gallbladder	R Trisectionectomy + Seg 1	12:8:6	0	1 PBD: 2 None
Chia et al [36]	55	18	Right Lobe + Seg 4	R Trisectionectomy	14	0	0
Nadalin et al [37]	NR	NR	Right Lobe	R Trisectionectomy: 1 R Trisectionectomy + Seg 1	NR	0	2 PBD: 7 None: 1 PVE
Troja et al [20]	72	NR	Right Lobe	Mesohepatectomy (Segs 3,4,5)	NR	0	0
Herman et al [38]	58	NR	Right Lobe	R Trisectionectomy	7	0	0
Oldhafer et al [39]	46	NR	Right Lobe	R Trisectionectomy	11	0	0
Vicente et al [40]	62	NR	Right Lobe	R Trisectionectomy	13	0	0
Vivarelli et al [21]	60.4	NR	Right Lobe	R Trisectionectomy	NR	0	2 PBD: 4 None:
Tsui et al [41]	63.5 (57-70)	NR	Gallibladder	Mesohepatectomy (Segs 3,4,5)	8 (7-9)	12 cycles: 0	0
Bjornsson et al [42]	70.5	9.45	Right Lobe	R Trisectionectomy	NR	0	4 PVE: 4 None
Cheung et al [43]	55	14	Right Lobe	R Trisectionectomy	10	0	0
Papamichail et al [44]	68	13	Right Lobe	R Trisectionectomy	14	0	TACE
Romic et al [45]	64	NR	Right Lobe	R Trisectionectomy	13	0	TACE
Torres et al [46]	57	19.4	Right Lobe	R Trisectionectomy	15	0	0
Varma et al [47]	52	12.8	Right Lobe	R Trisectionectomy	15	0	0
Chan et al [48]	60 (50-80)	7.5 (3-16)	NR	NR	7	NR	NR
Ha et al [49[	65	NR	Right Lobe	R Trisectionectomy	10	NR	NR
Pineda- Solis et al [50]	44	NR	Confluence Of Hepatic Veins	Monosegment ALPPS (Remnant Seg 6)	10	Cisplatin, 5-FU,Epirubicin (8 cycles)+ 50 GY Radio	0
Sanei et al [51]	48	NR	Right Lobe	R Trisectionectomy	9	0	0
Chia et al [52]	64.2 (54.4-69.8)	8.1 (5.2-13.2)	8 Right Lobe:1 Bilobar	R Trisectionectomy	7 (7-10)	NR	NR
Uribe et al [53]	70	NR	NR	R Trisectionectomy	10	NR	NR
Vennarecci et al [24]	NR	7 (3-20)	Right Lobe	HCC: 14 R hepaectomy R Trisectionectomies (11 partial ALPPS: 6 classic ALPPS)	NR	17 None: 1 CC Capecitabine, Cisplatin	17 None: 1 CC PBD
Wang et al [25]	52 (24-67)	13 (6-22)	NR	23 R Trisectionectomies: 4 R hemihepatectomy: 11 Extended R	NR	NR	NR

NR: not reported, PBD: previous biliary drainage, PVE: portal vein embolization

Table 3. Short term outcomes of the included studies

Study. First author [Ref]	*Operative time, (min) range 1st: 2nd Stage*	*Mean EBL, (mL) 1st: 2nd Stage*	*Mean FLR,* Pre-Stage 1, (ml)	*Mean FLR, Post- Stage 1, (ml)*	*FLR Hypertrophy, %, mean*	*Complications, (Clavien- Dindo Classification) (55)*	*Length of Hospital stay, (days), mean*	*30 day* mortality, (%)
Schlitt et al [31]	NR	NR	280 (190-370)	502 (275-729)	NR (35-90%)	100 %II	NR	0 (0 %)
Alvarez et al [32]	NR	NR	348.5 (285-412)	531 (521-541)	57% 931-83%)	None, (0%)	20	0 (0 %)
Cavaness et al [54]	NR	NR	200	405	100%	None, (0%)	17	NR
Knoefel et al [33]	NR	NR	293	477	63%	GI Bleeding (II): Bile Leak, Anastomotic Leak, ARDS, Ascites, Wound Infection (71%)	NR	0 (0 %)
Brustia et al [34]	240:180	NR	470	674	43%	Bile Leak (IIIb)	43	0 (0 %)
Ratti et al [35]	NR	NR	NR	NR	70 %(29.1-112.5 %)	GI Bleeding (II): Abscess, MOF (IV): Sepsis, PHLF A	18.3, (3- 30)	1 (30 %)
Chia et al [36]	231:198	500:700	383	532	10.5%	PHLF B (II)	27	0 (0 %)
Nadalin et al [37]	NR	NR	NR	NR	NR	NR	NR	3 (30 %)
Troja et al [20]	NR	NR	NR	NR	NR	Death (V)	34	1 (100 %)
Herman et al [38]	NR	NR	NR	NR	82%	None, (0%)	15	0 (0 %)
Oldhafer et al [39]	NR	NR	NR	591	103 %	Ascites (II)	20	0 (0 %)
Vicente et al [40]	NR	NR	NR	NR	110 %	Bile Leak (IVa)	36	0 (0 %)
Vivarelli et al [21]	NR	NR	332.6 (192-552)	570 (395-684)	88.4 %, (24- 160 %)	Sepsis, PHLF (V)	21.8, (15- 27)	1/5 (20 %)
Tsui et al [41]	NR	NR	527 (387-667)	849.5 (668-1031)	63.6 %(54.6-72.6 %)	Pneumonia, ARDS (V) 50%	20, 50%	0(100%), 1(50%)*
Bjornsson et al [42]	NR	NR	NR	NR	NR	100% (< IIIb)	NR	0 (0 %)
Cheung et al [43]	NR: 277	NR: 3200	302	399	29%	Ascites (II)	25	0 (0 %)
Papamichail et al [44]	NR	NR	274	460	68%	Arterial Bleeding (IIIa), PHLF	84	0 (0 %)
Romic et al [45]	NR	NR	NR	NR	90%	None (0%)	NR	0 (0 %)
Torres et al [46]	175: 246	600: 1200	NR	NR	NR	Ascites (II)	28	0 (0 %)
Varma et al [47]	NR	NR	251	423	69%	None (0%)	22	0 (0 %)
Chan et al [48]	385:156	500:350	292 (181.9-524.0):	519.7 (360.0-795.7)	11.5% (3.2- 23.4%)	Adhesive Inte- stinal Obstruction (9 %)	17.5 (12- 25)	0 (0 %)
Ha et al [49]	NR	NR	360	520	44%	None (0 %)	19	0 (0 %)
Pineda- Solis et al [50]	NR	800:NR	NR	NR	32%	Abscess, ARDS (IVa), 100%	31	0 (0 %)
Sanei et al [51]	NR	NR	NR	NR	NR	Pulmonary embolism (V): Pleural effusion (IIIa), PHLF (II), 100%	NR	1:2 (50 %)
Chia et al [52]	306(278-470): 126(104-171)	500 (450-900): 200 (100-500)	381.0 (280.0-422.0)	535.5 (365.5- 588)	According to histology	Minor 42.9, Major 14.2 (57.1%)	NR	0 (0 %), 1, (11.1%)*
Uribe et al [53]	NR	NR	NR	NR	NR	0 (0 %)	NR	0 (0 %)
Vennarecci et al [54]	HCC: 228 (120-349): 190(120-270)	NR	NR	NR	NR	1 HCC (5.6%): PHLF (V), 1 CC PHLF (V) (100%)	NR	1/ 17 HCC, 1/1 CC*
Wang et al [25]	273 (120 – 485): 215 (90 – 480)	300 (50 – 1600: 400 (50 – 5000)	342 (221 – 488)	510 (384 – 712)	NR	I: 8 (19.5), II: 15 (36.6), III: 6 (14.6), IV: 3 (7.3), V: 3 (7.3)	12 (6 – 28)	4/45 (8.8%), 5/45 (11.1)*

EBL: estimated blood Loss, NR: not reported, PHLF: post hepatectomy liver failure [WHAT'S THE MEANING OF THE ASTERISK?]

Table 4. Long terms outcomes of the included studies

Study. First author [Ref]	*Follow up (months), mean- range*	*Adjuvant* Chemo/radio-therapy (%)	*R0 Resection, n (%)*	*Recurrence, n (%)*	*Disease free survival* (months), median	*Overall survival* (months), median
Schlitt et al [31]	(0-14)	NR	3 (100%)	30%	6	14
Alvarez et al [32]	2:0	NR	2 (100%)	NR	2: NR	2: NR
Cavaness et al [54]	NR	NR	NR	NR	NR	NR
Knoefel et al [33]	NR	NR	NR	NR	NR	NR
Brustia et al [34]	NR	NR	NR	NR	NR	NR
Ratti et al [35]	NR	NR	3 (100 %)	NR	NR	NR
Chia et al [36]	2	NR	1 (100%)	NR	2	2
Nadalin et al [37]	NR	2 (20%)	8 (80 %)	3 (30%)	NR	NR
Troja et al [20]	1	NR	1 (100 %)	NR	1	1
Herman et al [38]	25	NR	NR	1 (100%)	6	25
Oldhafer et al [39]	2.5	Yes	NR	1 (100%)	1.5	2.5
Vicente et al [40]	NR	NR	1 (100 %)	NR	NR	NR
Vivarelli et al [21]	18.29 (0.69-29.53)	NR	5 (100 %)	2 (40%)	14.7 (0.69-29.53)	19.89 (0.69-29.53)
Tsui et al [41]	NR	NR	2 (100 %)	NR	NR	NR
Bjornsson et al [42]	11.06 (3.7 -21.0)	NR	7/8 (87.5 %)	3/8 (37.5 %)	5.1 (0.0-21.0)	9.85 (3.7 -21.0)
Cheung et al [43]	10	NR	1 (100 %)	0 (0 %)	10	10
Papamichail et al [44]	9	0	1 (100 %)	1 (100 %)	6	9
Romic et al [45]	12	NR	1 (100 %)	0 (0 %)	12	12
Torres et al [46]	3	NR	1 (100 %)	0 (0 %)	3	3
Varma et al [47]	14	Sorafenib, TACE	1 (100 %)	1 (100 %)	6	14
Chan et al [48]	NR	NR	NR	NR	NR	NR
Ha et al [49]	20	Yes	NR	0 (0 %)	20	20
Pineda- Solis et al [50]	3	NR	1 (100%)	0 (0 %)	3	3
Sanei et al [51]	(0-34)	NR	NR	0 (0 %)	17, (0-34)	17, (0-34)
Chia et al [52]	NR	NR	7 (100%)	NR	NR	NR
Uribe et al [53]	36	NR	1 (100%)	0 (0 %)	36	36
Vennarecci et al [24]	10 (2-54)	NR	18 (100%)	6/17 HCC (35.3 %)	HCC 24 (60%)	HCC 24 (38.5%)
Wang et al [25]	16.0 (0.1 – 46.9).	NR	41 (100%)	17/45 (37 %)	12(47.6%) 36:(43.9%)	12(64.2%) 36:(60.2%)

NR: not reported

Inclusion criteria

All appropriate prospective and retrospective studies, as well as case reports addressing outcomes of patients with primary liver malignancies who underwent ALPPS were considered eligible for inclusion. Only articles published in the English language were included. Letters to the Editor were included if they were judged to contain novel information or original opinions. Studies that reported at least two postoperatives outcomes (operative time, estimated blood loss, FLR, morbidity, mortality, complications, R0 resection status, and recurrence or survival rates) were included.

Exclusion criteria

Exclusion criteria included (1) abstracts, reviews, or expert opinions; (2) reports on ALPPS conducted for benign lesions or metastatic neoplasms to the liver with primary sites other than liver; (3) ALPPS conducted on humans <18 years old; (4) articles found to be reporting on a redundant patient population from another article by the same author. In this case, only the more comprehensive article containing the larger patient cohort was included; (5) animal studies; and (6) ALPPS variants, ALPPS conducted by means of minimal invasive techniques or emergency ALPPS.

Results

Study characteristics

The successive steps of the selection process are depicted in Figure 1. A total of 28 studies incorporating patients who underwent the originally described ALPPS for a primary liver malignancy (PLM) were considered eligible (Table 1). Sixteen studies were small case series (67 patients out of 171 patients), 10 studies were case reports (10 patients out of 10) and the remaining 2 studies were single-centre studies of higher patient volume (59 patients out of 69). The included studies reported and analyzed peri- and postoperative outcomes of 250 patients who underwent ALPPS for all indications between 2007-2017, incorporating 136 patients who were subjected to ALPPS due to primary liver malignancy. The indices analyzed were tabulated in four structured tables as follows: study characteristics (Table 1), patient characteristics (Table 2), perioperative details and outcomes (Table 3) and long-term outcomes (Table 4).

Patient and tumor characteristics

In summary, 250 patients from 28 studies worldwide underwent ALPPS for liver malignancy. Among patients who underwent ALPPS, a total of 136 were submitted to ALPPS for primary liver malignancy, with histological distribution of: cholangiocarcinoma (CC) in 1 patient, intrahepatic cholangiocarcinoma (IHCC) in 10 patients, perihilar cholangiocarcinoma (PHCC) in 13 patients, hepatocellular carcinoma (HCC) in 102 patients, gallbladder carcinoma (GC) in 3 patients and unknown histology in 7 patients. Patient age ranged from 24 to 83 years. Male to female ratio was 30:19, with 7 studies not providing information on gender. The primary tumor size ranged from 3 to 22 cm. A right trisectionectomy was performed in the majority of the cases (92%, n=113), followed by a right hepatectomy (15%, n=19), a monosegment ALPPS (0.8%, n=1), and a meso-hepatectomy (2.4%, n=3); detailed information on 10 procedures were not to be reported. The second stage operation was performed when the FLR was estimated to be adequate, ranging from the 4th to the 15th postoperative day from first stage operation. In addition, neoadjuvant chemoradiotherapy was administered in only 2.2% (n=3) of PLM patients in the total cohort, while perioperative adjuncts in the form of preoperative biliary drain (PBD), PVE or TACE were offered in 8, 10 and 2 patients, respectively (Table 2).

Perioperative and long-term outcomes

Analysis of perioperative outcomes for patients who underwent LSR revealed a median operative time of 240 min during the 1st stage procedure (range 175-385), followed by a median operative time of 206.5 min during the 2nd stage procedure (range 126-349). Additionally, median EBL at the 1st stage procedure was 500 ml (range 300-800) and 550 ml (range 200-3200) at the 2nd stage procedure. Median FLR prior to 1st stage procedure was 332.6 ml (range 200-527) and median post 1st stage procedure FLR was 510 ml (range 389-849.5).

Median FLR hypertrophy prior to 2nd stage operation was 68% (range 10.5-110). Length of total hospital stay ranged from 12 to 43 days and 30-day mortality was 9.55% (n=13 patients). Complications according to Clavien-Dindo classification system are presented in Table 3. Of note, 7 studies reported no postoperative complications, neither minor (I-II) nor major (III-V).

R0 resection status was documented in 20 studies, estimated to be 97.24% (n=106/109 patients). At a median follow up of 10 months (range 0-36), the recurrence rate was approximately 36% (n=36/99 patients). Median disease-free survival was 6 months (range 1-36) and median overall survival 11 months (range 1-36) (Table 4).

Discussion

We conducted a systematic literature review to evaluate the perioperative, short- and long-term outcomes of patients diagnosed with borderline resectable or unresectable primary liver malignan-

cies treated with ALPPS. Our primary goal was to reassess the indications to ALPPS, to select the best pool of candidates to this approach, obtaining an expansion of surgical candidates while maintaining an acceptable morbidity rate that should be comparable with other strategies for hypertrophy of FLR. To the best of our knowledge, this is the first systematic review published in the literature analyzing ALPPS in primary liver malignancies.

The 28 studies enrolled in the present analysis were small case series (n=16), case reports (n=10) and only 2 studies were single-centre studies of higher patient volume. A total of 26 multicenter series reporting larger number of cases were excluded from the analysis. The rationalization behind this methodology was the observation of diffuse overlap with other series published by the same center or other centers, which not always differ in hypothesis and aim, thus differ in time intervals, as well as high dropout rate of cases due to scarce data. The very same patients already published multiple times in single-center series, are then sometimes part of multicenter series both inside and outside of ALPPS registry reports, a clear duplication bias [14,15]. An additional portion of 10 multicenter series reporting larger number of cases were also excluded from the analysis due to substantial lack of sufficient data concerning primary liver malignancies such as epidemiology, intraoperative and postoperative outcomes [16-19].

The 28 studies enrolled in the present analysis incorporated 136 patients who were subjected to ALPPS due to primary liver malignancy. The second stage operation was performed when the FLR was estimated to be adequate and ranged from the 4^{th}-15^{th} postoperative day from the first stage operation, with drop out of 6/142 patients (4.22%). R0 resection status has been documented in 20 studies estimated to be 97.24% in 106 patients out of 109. Thirty-day mortality was 9.55% (13 patients). Further information on the exact diagnosis of each deceased is lacking, though it appears to take place in HCCs, GCs and CCs, with a slight predominance on CCs. In the Troja et al. study [20], the deceased patient was Jehovah's Witness and refused blood transfusion. Concerning 30-day morbidity graded according to Clavien-Dindo classification, interestingly 7 studies state no postoperative complications, neither minor (I-II) nor major (III-V). Vinarelli et al. [21] documents 100% septic phenomena in all 3 preoperative biliary drainages in CCs, that led to one death.

As for the oncological outcomes, the median follow up was 10 months, (range 0-36), recurrence rate was 36% (36 patients of 99), disease-free survival ranged from 1 to 36 months (median 6) and overall survival ranged from 1 to 36 months (median 11). The abovementioned outcomes seem comparable with the outcomes of multicenter studies. Considering the non existence of learning curve [22] due to small number of patients (especially in the case of CC surgical management) leading to bias worrisome results and on the other hand the lack of prospective randomised trials (RCTs) with large volume cases and long and thorough follow up leading to selection bias in favor of better published outcomes, we propose to re-evaluate the expansion of ALPPS indications gradually to patients with primary liver malignancies (especially since chemotherapy does not have a central role in their management), at least until proven otherwise from the outcomes of the ongoing RCTs. Gaining experience in managing primary liver malignancies with ALPPS procedure may lead to promising results as stated in the Ligro Trial [23], where superiority of ALPPS versus 2-stage hepatectomy seems now well established for the treatment of colorectal liver metastatic disease. This consideration is further encouraged by the short and long term outcomes of the two single center studies [24,25] which demonstrate significant benefit with this approach. Perihilar cancer requiring major hepatectomy and biliary resection was reported as a relative contraindication to ALPPS, because of extremely high morbidity and mortality rates. The 90-day mortality of biliary tumors, perihilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, and gallbladder cancer were 27, 13 and 33%, respectively in the international ALPPS registry [26].

Applications of this proposal concerning the treatment of unresectable cholangiocarcinoma displays many advantages: Surgeons can avoid preoperative PVE that predetermines the side of the liver to be resected (i.e. the embolized liver lobe). This modality leaves relative freedom in the strategy of resection, intensive cleaning of the FLR can be performed without the fear that a small FLR will result as a consequence of this radical procedure considering the diseased hemiliver left in place acts as an auxiliary liver to assist the FLR during the first week after the partition [27].

Now that the initial experimental phase has passed, ALPPS faces criticism from the scientific community since high rates of operative morbidity and mortality, as well as high recurrence rates, have been documented in the first case series. Regarding worrisome oncological outcomes, the most likely important question still unanswered is whether higher tumor resectability is latterly translated into improved survival [3]. Morbidity after ALPPS is reported to be 16-64%, and mortality 12-23%.

The major forms of morbidity include bile leakage and sepsis, and the major cause of mortality is post-hepatectomy liver failure (PHLF) of about 15-30% in the literature [3]. Somehow, a cause of this liver decompensation might be related to the potential consequences of the portal hyperflow to the FLR. The liver hemodynamic situation after the first stage of ALPPS is quite similar to that of liver graft when important previous portal hypertension exists or when a splittered graft is transplanted, receiving an over-portal flow respect to its size [34]. This condition is known as ''small for size'' syndrome due to sinusoidal congestion and endothelial dysfunction from portal overflow [35].

Finally, we must deem the place of ALPPS itself. There is no doubt that these complex procedures must only be undertaken by experienced surgeons in high-volume centres, and patient selection should be by means of a multidisciplinary team effort. Model for end-stage liver disease (MELD) and portal hypertension are two crucial factors in the decision making for surgical resection, especially when major liver resection or the ALPPS procedure are contemplated [28,29]. The careful management of these patients during the postoperative course of both surgical procedures is crucial to achieve success [30].

Several limitations need to be considered when interpreting the results of the present study. The main limitation was the absence of prospective randomized controlled trials and the inclusion of mainly retrospective case studies. Moreover, most ALPPS studies were performed with a relatively small number of patients leading to a heterogeneous patient cohort over a short observation period.

Conclusions

In conclusion, the present systematic review provides evidence that ALPPS offers a reasonable chance of complete resection in patients with unresectable primary liver tumors. ALPPS still faces criticism due to its high rates of operative morbidity and mortality, as well as its relatively high recurrence rates. Regarding the oncological outcomes, the most important question still unanswered is whether higher tumor resectability is latterly translated into improved survival. Optimal selection of patients, gaining the surgical experience of carrying out this technique and its impact on short and long-term results are issues that still remain under debate while waiting for the final outcomes of the multicenter registries with larger number of cases.

Conflict of interests

The authors declare no conflict of interests.

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