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REVIEW ARTICLE – HEPATOBILIARY TUMORS

Systematic Review and Meta-Analysis of Feasibility, Safety, and Efficacy of a Novel Procedure: Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy

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ABSTRACT

Background. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a novel strategy to resect liver tumors despite the small size of the liver remnant. It is an hepatectomy in two stages, with PVL and parenchymal transection during the first stage, which induces rapid growth of the remnant liver exceeding any other technique. Despite high postoperative morbidity and mortality in most reports, the technique was adopted by a number of surgeons.

Materials and Methods. This systematic review explores current data regarding the feasibility, safety, and oncologic efficacy of ALPPS; the search strategy has been published online. A meta-analysis of hypertrophy, feasibility (ALPPS stage 2 performed), mortality, complications, and R0 (complete) resection was performed.

Results. A literature search revealed a total of 13 publications that met the search criteria, reporting data from 295 patients. Evidence levels were low, with the highest Oxford evidence level being 2c. The most common indication was colorectal liver metastasis in 203 patients. Hypertrophy in the meta-analysis was 84 %, feasibility (ALPPS stage 2 performed) 97 % (CI 94–99 %), 90-day mortality 11 % (CI 8–16 %), and complications grade IIIa or higher occured in 44 % (CI 38–50 %) of patients. A standardized reporting format for complications is lacking despite the widespread use of the Clavien–Dindo classification. Oncological outcome is not well-documented. The most common topics in the selected studies published were technical feasibility and indications for the procedures. Publication bias due to case-series and single-center reports is common.

Conclusion. A systematic exploration of this novel operation with a rigid methodology, such as registry analyses and a randomized controlled trial, is highly advised.

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) was first coined as an eponym for a new technique in liver surgery to perform trisectionectomies with marginal remnant liver volume in a two-stage surgical procedure by inducing hypertrophy of the left liver by right portal vein ligation (PVL) and parenchymal transection,[1] referred to as 'in situ splitting' in the original publication.[2] The technique induced more hypertrophy of the remnant liver in less time than portal vein embolization (PVE)[3] and PVL.[4] Even when compared with recent reports of highly selective portal branch embolization with microspheres promising hypertrophy of the future liver remnant (FLR) of more than 60 %[5] over several weeks, in ALPPS the liver remnant increases at an approximately tenfold increased growth rate in only 1 or 2 weeks.[6] The technique was adopted by a number of liver surgeons, but also led to debate due to a relevant morbidity and perioperative mortality.[5,7–9] This systematic review was performed to assess the published evidence for feasibility, safety, and oncological efficacy of ALPPS. We also discuss how far the consensus recommendations on surgical innovations, as developed by the Balliol group (the so-

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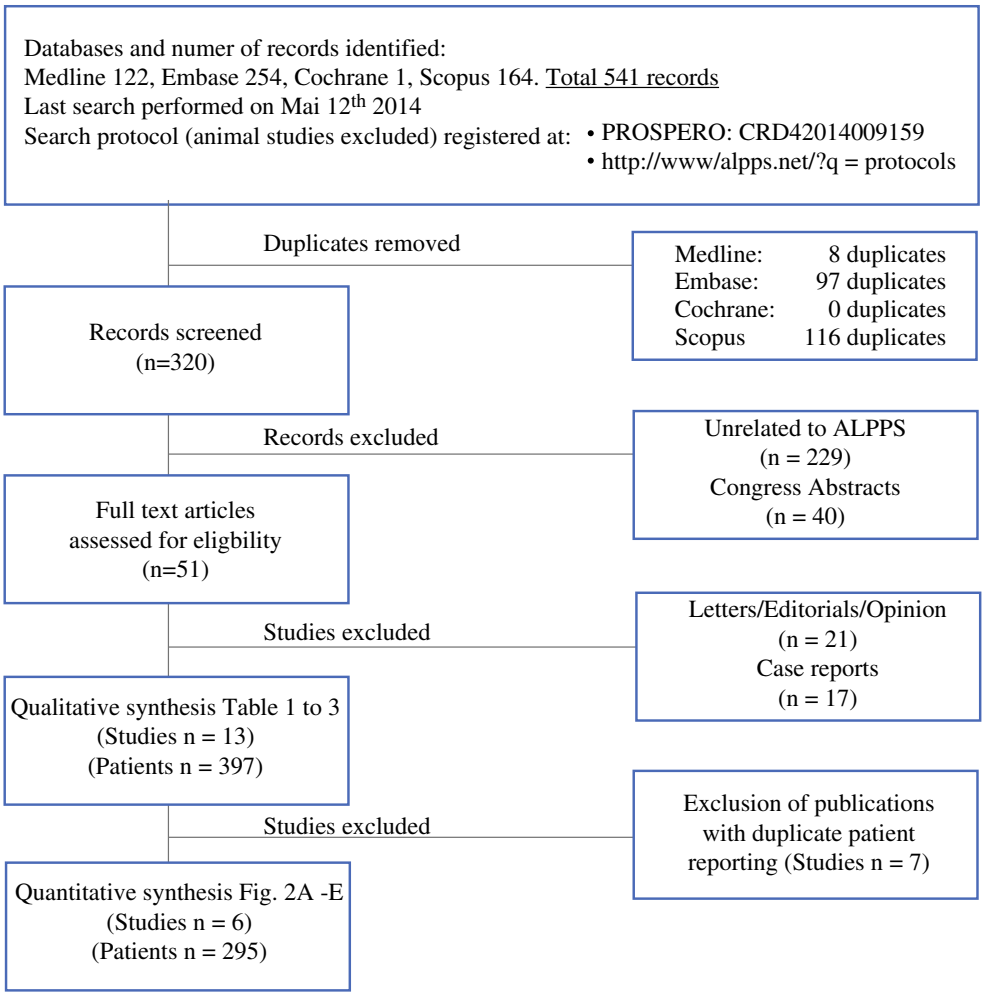


FIG. 1 Prisma flowchart of databases searched, strategy used, and exclusions performed. *ALPPS* Associating Liver Partition and Portal vein ligation for Staged hepatectomy

called Innovation Development Exploration Assessment and Long-term study [IDEAL] recommendations[10]), capture what happened when ALPPS was introduced in the surgical literature.

MATERIALS AND METHODS

Review Protocol and Registration

A systematic review protocol was developed and made available online (www.alpps.net) and on the international PROSPERO database (CRD42014009159).

Information Sources

A search of the databases Pubmed, Cochrane, EMBASE, and SCOPUS was performed. There were no language restrictions. Reference lists of relevant articles were reviewed and duplicates were removed. Studies unrelated to ALPPS, as well as abstracts, were excluded. Full-text articles were assessed for eligibility. All letters, editorials, and opinion articles, as well as case reports, were excluded. Studies reporting on up to three patients were classified as case reports. Manuscripts were tabulated in a qualitative synthesis and categorized into levels of evidence in accordance with the definition of the Centre of Evidence in Medicine in Oxford (http://www.cebm.net/index.aspx?o=1025). Patients were carefully screened for double reporting of patients and, after exclusion of those patients, a quantitative synthesis/meta-analysis was performed.

Study Selection and Data Collection Process

Figure 1 shows the study selection and data collection process. Data collection forms were used to extract data items from each included study.

Data Items and Summary Measures

Information on baseline descriptors of the patient populations undergoing ALPPS was extracted from the studies selected for analysis; age, tumor type, surgical approach (laparoscopic vs. open), preoperative chemotherapy, preoperative volumetry, and the time between stages and kinetic growth (in cc/day) were examined in each study. We also evaluated the indication to perform ALPPS as reported in the studies; ALPPS has either been reported in the context of liver tumors with FLRs too small for one-stage surgery ('marginally resectable') or as a salvage strategy after previous portal vein manipulation of some kind that did not result in adequate growth to proceed with the resection ('salvage'), such as f.e. PVE.

Data collection on outcomes was divided into three questions:

(1) How *feasible* is ALPPS? The first feasibility endpoint is hypertrophy of the liver remnant between stages. Centers were contacted to report their data as means with standard deviation rather than as a median, as is customary when undertaking a meta-analysis. As a second feasibility endpoint, the percentage of patients who achieved tumor removal in a stage 2 operation was chosen. The purpose of ALPPS is to remove the entire tumor load of a liver with extensive tumor burden within a short period of time. It is known that two-stage hepatectomies result in incomplete removal of tumor whenever stage 2 cannot be performed. We therefore defined *feasibilty of resection* as *performance of stage 2 with macroscopic removal of tumor*.

(2) How *safe* is ALPPS? The main safety endpoint was 90-day or in-hospital mortality. We choose both since 90-day mortality is not consistently reported. Overall complication rate and rate of complications grade IIIa and IIIb or higher were examined. Bias of the individual studies was categorized based on study design. The main discussion points and the virtues of each study were independently extracted by two authors (ES and AAS). Mortality and complications grade IIIa or higher were summarized in a meta-analysis.

(3) How *effective* is ALPPS in treating colorectal liver metastases (CRLM) oncologically? Data on complete (R0) versus incomplete resection (R1), overall survival (OS), and disease-free survival (DFS) were examined. Summary measures were only performed for completeness of resection due to the paucity of data for OS and DFS.

Statistics

Data are presented in parametric or non-parametric fashion depending on their presentation in the original publications. The software Comprehensive Meta-Analysis (Biostat, Englewood, NJ, USA) was used to generate the meta-analysis and forest plots using the random effects model.[11]

RESULTS

Study Selection

A literature search revealed a total of 51 full-text publications (Fig. 1). Twenty-one studies were excluded because they represented editorials, letters, and opinion pieces, and 17 contained case reports, which were also excluded. Thirteen studies were tabulated in a qualitative synthesis (see Tables 1, 2, and 3), with a total of 397 patients. Six studies could be evaluated in a quantitative synthesis after exclusion of seven publications reporting patients who were later included in larger reports. Of these, a quantitative meta-analysis could be performed on two to six studies, depending on available data.

Classification into Evidence-Level Groups

Of 13 studies, 10 were case-series, which were considered *evidence level 4* (Table 1). Two comparative studies have been published which include a total of 55 patients undergoing ALPPS. One study compares 7 patients with ALPPS with 15 patients with PVE,[12] and is classified as *evidence level 4* due to the small number of patients. The second study compares 48 patients with ALPPS with 86 patients undergoing PVE or PVL.[6] It constitutes *evidence level 3b* as it is an individual cohort study with a multivariate analysis to adjust for confounders. Analysis of the ALPPS registry, including 202 patients,[13] was classified as 'outcomes research' or *evidence level 2c*.

Characteristics of Patients and Feasibility of ALPPS

The most frequent indications for ALPPS were CRLM in 199 patients, followed by hepatocellular cancer (HCC) in 22 patients, perihilar cholangiocarcinoma (PHCC) in 21 patients, intrahepatic cholangiocarcinoma (IHCC) in 14 patients, gallbladder cancer (GBCA) in 7 patients, and non-CRLM (NCRLM) in 25 patients (Table 1). Indications were not reported for seven patients.[12] In all studies, ALPPS was used for initially non-resectable liver tumors; a salvage approach is additionally described in five studies. Overall, there were seven patients in whom laparoscopic ALPPS was reported.

The increase of liver volume can only be summarized in an analysis of two studies[2,13] because other groups did not report their mean increase of volume with standard deviations, even after individual requests. The summary

TABLE 1 Patient characteristics and feasibility of ALPPS

Study	Evidence level	Year of publication	Country	*N*	Age (years) [mean or median]	Tumor type, *n*	Indication to perform ALPPS	Surgical approach [open or lap]
Schadde et al.[13]	2c	2014	Multicenter	202	60	CRLM, 141 HCC, 17 PHCC, 11IHCC, 8 GBCA, 6 NCRLM, 19	Salvage + Marginally resectable	Open 197 Lap 5
Schadde et al.[6]	3b	2014	Multicenter	48[a]	57	CRLM, 26 HCC, 3 PHCC, 2 IHCC, 8 NCRLM, 7	Salvage + Marginally resectable	Open
Nadalin et al.[22]	4	2014	Germany	15	67	CRLM, 5 HCC, 1 PHCC, 5 IHCC, 4	Salvage 1Marginally resectable	Open
Ratti et al.[23]	4	2014	Italy	10[a]	8	CRLM, 5PHCC, 3	Marginally resectable	Open
Gauzolino et al.[24]	4	2013	France	4[a]	58	CRLM, 4	Salvage + marginally resectable	Open
Ielpo et al.[16]	4	2013	Spain	6[a]	58	CRLM, 5 PHCC, 1	Marginally resectable	Open
Knoefel et al.[12]	4	2013	Germany	7	NR for ALPPS	NR for ALPPS	Salvage + marginally resectable	Open
Li et al.[25]	4	2013	Germany	9[b]	67	CRLM, 3PHCC, 3 IHCC, 3	Marginally resectable	Open
Oldhafer et al.[15]	4	2013	Germany	7	66	CRLM, 7	Marginally resectable	Open
Alvarez et al.[26]	4	2012	Argentina	15[a]	54	CRLM, 10 HCC, 1 PHCC, 1 NCRLM, 3	Marginally resectable	Open
Torres et al.[27]	4	2012	Multicenter Brazil	39	57	CRLM, 32 HCC, 1 PHCC, 3 NCRLM, 3 Benign, 1	Marginally resectable	Open, 37 Lap, 2
Sala et al.[28]	4	2012	Argentina	10[a]	52	CRLM, 7 HCC, 1 PHCC, 1 NCRLM, 1	Marginally resectable	Open, 10
Schnitzbauer et al.[2]	4	2012	Multicenter Germany	25	63	CRLM, 14 HCC, 3 PHCC, 2 IHCC, 2 GBCA, 1 NCRLM, 3	Marginally resectable	Open

Study	Preop chemo number (%)	Volume before stage 1 (in cc) [median or mean]	Volume before stage 2 (in cc)	FLR or sFLR[c] before stage 1 [median or mean]	FLR or sFLR[c] before stage 2 [median or mean]	Increase (%) [median or mean]	Time, days [median or mean]	Kinetic growth (cc/day) [median or mean]	Feasibility (% stage 2 performed)
Schadde et al.[13]	NR	337	612	0.21 (sFLR)	0.40 (sFLR)	86 ± 52	10	30	197 (98)
Schadde et al.[6]	28 (58)	367	639	0.23 (sFLR)	0.41 (sFLR)	77	7	35	48 (100)
Nadalin et al.[22]	5 (33)	NR	NR	0.23	0.36	87	13	NR	15 (100)
Ratti et al.[23]	5 (63)	NR	NR	0.22 (sFLR)	0.33 (sFLR)	58	7.5	NR	6 (75)
Gauzolino et al.[24]	4 (100)	742	835	0.32	0.43	NR	NR	NR	4 (100)
Ielpo et al.[16]	5 (83)	NR	NR	NR	NR	110	15	NR	6 (100)
Knoefel et al.[12]	NR for ALPPS	293	477	0.18	0.26	65	6	22	7 (100)
Li et al.[25]	3 (30)	NR	NR	NR	NR	87	13	NR	9 (100)
Oldhafer et al.[15]	2 (29)	424	532	0.23	0.37	65	13	NR	7 (100)
Alvarez et al.[26]	9	403	706	0.27	0.47	78	6	NR	15 (100)
Torres et al.[27]	Some	NR	NR	NR	NR	83	14	NR	37 (95)
Sala et al.[28]	6	408	733	0.28	0.44	82	7	NR	10 (100)
Schnitzbauer et al.[2]	12 (48)	310	536	0.38	0.61	76 ± 40	9	NR	25 (100)

TABLE 1 continued

Summary measures									
N studies	Years	*N* of studies		*N* of patients	*N* of patients	*N* of studies	*N* of patients	% Hypertrophy (mean ± SD)	Feasibility (% with stage 2 performed)
13	L2: 1 L3: 1 L4: 11	2012–2014	Multicenter: 4 Single-center: 9 Total: 13	295	CRLM, 199 HCC, 22 PHCC, 21 IHCC, 14 GBCA, 7 NCRLM, 25 NR, 7	Marginally res. 12 Salvage 5	Open, 288 Lap, 7	See Fig. 2a	See Fig. 2b

ALPPS Associating Liver Partition and Portal vein ligation for Staged hepatectomy,*NR* not reported, *CRLM* colorectal liver metastasis, *iHCC* intrahepatic cholangiocarcinoma, *HCC* hepatocellular carcinoma, *pHCC* perihilar cholangiocarcinoma, *GBCA* gallbladder cancer, *NCRLM* non-colorectal liver metastases, *FLR* future liver remnant, *sFLR* standardized future liver remnant, *lap* laparoscopic, *preop* preoperative, *chemo* chemotherapy, *SD* standard deviation

[a] Denotes that patients have been reported in the ALPPS registry report[13] and are therefore not included in the summary measure in order to avoid double-counting of patients

[b] Denotes that patients in this study were included in the report by Nadalin et al.[22] and are therefore not included in the summary measures and Forest plots

[c] sFLR (FLR volume divided by standardized total liver volume according to the Vauthey-formula[14] is given in this column when it is reported, otherwise FLR divided by the actually measured total liver volume is reported

increase of only two studies was 84 %, with a confidence interval (CI) of 78–91 % (Fig. 2a).

The majority of studies reported a waiting interval between stages of approximately 1 week. FLR proportion to total liver volume or standardized FLR (sFLR) prior to stage 1 is around 0.20, and around 0.40 prior to stage 2. A meta-analysis was not performed for the size of the FLR because all studies reported medians. sFLR, as calculated according to a well-established methodology in liver surgery,[14] is used by only 3 of 13 reports.

Completion of ALPPS in stage 2 may be summarized in an analysis of six studies. Four of these studies reported 100 % progression to stage 2, but in the meta-analysis their results have to be weighted accordingly.In the meta-analysis their feasibility therefore does not equal 100 %. In summary, the feasibility rate (percentage of stage 2 performed) was 97 % (CI 94–99 %) [Fig. 2b]. Data on outcomes patients not undergoing stage 2 were only available from the registry analysis for 4 patients overall. Two patients had CRLM—one patient died perioperatively after stage 1, and one patient died from tumor progression 6 months after stage 1. A third patient with primary angiosarcoma of the liver could not undergo stage 2 and died from tumor progression after 6 months, while a fourth patient with PHCC died from tumor progression after 3 months.

Safety of ALPPS

A summary of the primary safety endpoint *90-day mortality* or *in-hospital mortality* is presented in Table 2 and Fig. 2c. The meta-analysis shows an 11 % mortality rate with a CI of 8–16 %.

The majority of studies, but not all, used a standardized reporting format for complications, such as the Clavien–Dindo classification. It is therefore difficult to clearly delineate complications reported in all studies. In the meta-analysis, 44 % of patients experienced complications grade IIIa or higher, with a confidence interval of 38–50 % (Fig. 2d).

Risk of Individual Study Bias

In the 13 selected studies, the most common bias found was related to single-center case-series (nine studies), retrospective analyses (two studies), followed by the reporting bias of a voluntary registry (one study), and lack of a control group (11 studies) (Table 2).

Study Topics

The most common topics in the selected studies published were the demonstration of technical feasibility to

TABLE 2 Safety of ALPPS

Study	Evidence level	Year of publication	Country	*N*	90-day mortality (%)	In-hospital mortality (%)	Overall complication rate, number of patients (%)	Highest major complication rate grade IIIa or higher (including V), number of patients (%)	Highest major complication rate grade IIIb or higher (including V), number of patients (%)	Main topic of the report	Main bias based on study design	Innovation
Schadde et al.[13]	2c	2014	Multicenter	202	19 (9)	18 (9)	NR	80 (40)	56 (28)	Safety indications	Reporting bias	Largest number 41 centers
Schadde et al.[6]	3b	2014	Multicenter	48[a]	7 (14.6)	7 (14.6)	35 (73) after stage 2	NR	7 (15) after stage 1 13 (27) after stage 2	Comparison with PVE/PVL	Retrospective	Multicenter Larger number Comparative design
Nadalin et al.[22]	4	2014	Germany	15	4 (29)	4 (29)	10 (67)	NR	NR	Indications	Single-center	Large series on PHCC
Alvarez et al.[26]	4	2013	Argentina	15[a]	0	0	9 (53)	5 (33)	4 (26)	Safety	Single-center	Large number without mortality
Ratti et al.[23]	4	2014	Italy	8[a]	1 (13)	1 (13)	3/6 (50)	2/6 (33)	2/6 (33)	Indications	Single-center	Comparison of ALPPS for CRLM and PHCC
Knoefel et al.[12]	4	2013	Germany	7	NR	1 (14)	6 (86)	5 (71)	NR	Comparison with PVE/PVL	Single-center	First comparative study First report of salvage
Li et al.[25]	4	2013	Germany	9[b]	2 (22)	2 (11)	6 (66)	4 (44)	3 (33)	Indications	Single-center	Focus on IHCC and PHCC
Gauzolino et al.[24]	4	2013	France	4[a]	0	0	4 (100)	1 (25)	1 (25)	Technical	Single-center	Successful case in SOS[c] (1 patient) Four new types of ALPPS ('reverse')
Ielpo et al.[16]	4	2013	Spain	6[a]	1 (17)	1 (17)	3 (50)	3 (50)	3 (50)	Technical	Single-center	Concern about high morbidity

TABLE 2 continued

Study	Evidence level	Year of publication	Country	*N*	90-day mortality (%)	In-hospital mortality (%)	Overall complication rate, number of patients (%)	Highest major complication rate grade IIIa or higher (including V), number of patients (%)	Highest major complication rate grade IIIb or higher (including V), number of patients (%)	Main topic of the report	Main bias based on study design	Innovation
Oldhafer et al.[15]	4	2013	Germany	7	NR	0	6 (86)	1 (14)	6 (86)	Oncologic	Single-center	First report with focus on recurrence in CRLM
Sala et al. [28]	4	2012	Argentina	10[a]	0 (0)	0 (0)	4 (40)	2 (20)	2 (20)	Technical	Single-center	Series without mortality
Schnitzbauer et al.[2]	4	2012	Multicenter Germany	25	NR	3 (12)	16 (64)	14 (56)	NR	Technical	Reporting bias	Inaugural study Detailed reporting of complications Multicenter
Torres et al.[27]	4	2012	Multicenter Brazil	39	NR	5 (13)	NR	NR 'significant morbidity' 23 (59 %)	NR	Technical	Retrospective	Large number
Summary measures					See Fig. 2c			See Fig. 2d		Most common 1. Technical, 5 2. Safety, 2 2. Indications, 2 3. Comparative, 2 4. Oncological, 1	Most common 1. Single-center, 9 2. Retrospective, 2 3. Reporting bias, 2	

ALPPS associating liver partition and portal vein ligation for staged hepatectomy, *NR* not reported, *CRLM* colorectal liver metastasis, *iHCC* intrahepatic cholangiocarcinoma, *pHCC* perihilar cholangiocarcinoma, *PVE* portal vein embolization, *PVL* portal vein ligation, *SOS* sinusoidal obstruction syndrome

[a] Denotes that patients have been reported in the ALPPS registry report[13] and are therefore not included in the summary measures and Forest plots

[b] Denotes that patients in this study were included in the report by Nadalin et al.[24] and are therefore not included in summary measures and Forest plots

TABLE 3 Oncologic efficacy of ALPPS

Author	Evidence level	Year of publication	Country	*N*	Number of R0 resections (%)	OS at 1 year, %	OS at 2 years, %	Median survival, months	DFS at 1 year, %	DFS at 2 years, %	Median DFS, months	Median follow-up, months (range)	Critical oncological discussion points by authors
Schadde A et al.[13]	2c	2014	Multicenter	202	169/185 (9)	73 (mixed tumors)76 (CRLM)	59 (mixed tumors) 62 (CRLM)	25 (mixed tumors) NR (CRLM)	60 (mixed tumors) 59 (CRLM)	42 (mixed tumors) 41 (CRLM)	14 (mixed tumors) NR (CLRM)	9 (6–13)	OS and DFS In CRLM comparable to two-stage hepatectomy literature
Schadde B et al.[6]	3b	2014	Multicenter	48[a]	40 (83)	NR	NR	NR	22 (46 %) [mixed tumors]	NR	NR	NR	Recurrence of ALPPS comparable to PVE/PVL
Nadalin et al.[24]	4	2014	Germany	15	13 (86)	NR	NR	NR	NR	NR	NR	17 (1–33)	ALPPS should not be used for cholangiocarcinoma
Alvarez et al.[28]	4	2013	Argentina	15[a]	15[a] (100)	NR	NR	NR	11 (73 %), time point not specified	NR	NR	6 (0.5–14)	Not addressed
Ratti et al.[25]	4	2013	Italy	8[a]	6/6 (100)	NR	NR	NR	NR	NR	NR	NR	Not addressed
Knoefel et al.[12]	4	2013	Germany	7	NR	NR	NR	NR	NR	NR	NR	NR	Address reduced waiting time as oncological advantage
Li et al.[27]	4	2013	Germany	9[b]	9[a] (100)	NR	NR	NR	NR	NR	NR	NR	Postulates prospective trial to test oncological benefit
Gauzolino et al.[26]	4	2013	France	4[a]	4 (100)	NR	NR	NR	NR	NR	NR	3	Recommends CRLM only and careful selection
Ielpo et al.[16]	4	2013	Spain	6[a]	NR	100 (3/3)	100 (2/2)	NA	66 (2/3)	100 (2/2)	NA	11 (1–30)	Long-term follow-up needed
Oldhafer et al.[15]	4	2013	Germany	7	7 (100)	71 (5/7)	NR	NR	14 (at 11 months)	NR	8	15	High recurrence rate discussed critically
Sala et al.[28]	4	2012	Argentina	10[a]	10 (100)	NR	NR	NR	NR	NR	NR	6 (2–11)	Rapid recovery after ALPPS allows chemotherapy to be restarted
Torres et al.[27]	4	2012	Multicenter	39	NR	NR	NR	NR	NR	NR	NR	NR	Not addressed
Schnitzbauer et al. [2]	4	2012	Multicenter	25	24 (96)	NR (6-month survival 86 %)	NR	NR	68 (mixed tumor type)	NR	NR	6 (2–26)	Oncological questions are difficult to address due to heterogeneity of indications
Summary measures					See Fig. 2e								

ALPPS associating liver partition and portal vein ligation for staged hepatectomy, *NR* not reported, *NA* not applicable, calculation not performed due to small numbers, *OS* overall survival, *DFS* disease-free survival, *CRLM* colorectal liver metastasis, *PVE* portal vein embolization, *PVL* portal vein ligation

[a] Denotes that patients have been reported in other studies with a larger patient number and are therefore not included in the summary measure in order to avoid double-counting of patients

[b] Denotes that patients in this study were included in the report by Nadalin et al.[24] and are therefore not included in summary measures and Forest plots

induce rapid hypertrophy with ALPPS (five studies), followed by discussion of safety (two studies) and indications (two studies). In two studies, the main aim was to compare ALPPS with conventional methods to manipulate the portal vein (Table 2).[6,12] Several studies reported the difficulty to analyze survival when mixed indications are reported,[2,6] while only one study explicitly focused on oncological outcome.[15]

Oncologic Efficacy of ALPPS

Completeness of resection (R0) was achieved in 91 % of patients, with a CI of 87–94 % (Table 3 and Fig. 2e). OS and DFS were rarely reported adequately, with the exception of two studies,[13,16] and were therefore not evaluated in a meta-analysis. Some studies reported unconventional time points, such as 6[2] or 11 months[15] to evaluate survival, and numbers were too small to evaluate survival separately for different tumor etiologies. Despite this lack of data, 10 of 13 studies hypothesized on oncological issues in the discussion section of their reports.

DISCUSSION

This analysis shows that 2 years after the inaugural publication of the novel ALPPS technique of two-stage hepatectomy, the level of evidence supporting its use remains low (no study higher than 2c). Studies confirm the feasibility of 97 % for completion of both stages of resection, with the two most common biases of single-center and retrospective design. Perioperative mortality was 11 %, with a CI of 8–16 %, and complications grade IIIa or higher occured in 44 %, with a CI of 38–50 %. The main discussion point in the literature wae technical feasibility of the procedure. Only two studies systemically addressed median follow-up, median survival and median DFS.

This systemic review was limited due to the small number of original publications in a very recently-introduced technique. The reason for an early systematic review is to support, with data, the ongoing debate on the benefits of ALPPS in surgical oncology of the liver. Warnings about performing a randomized trial have been brought forward due to the lack of safety of ALPPS.[9] At the same time, the quality of studies published does currently not allow the establishment of solid evidence of safety and efficacy, as shown by this review. Centers performing ALPPS who are interested in publishing their individual experience should be encouraged to address standard data items in their publications which allow for an assessment of feasibility, safety, and oncologic efficacy, or, alternatively, enter their data into an easily accessible international database (www.alpps.net).

The tendency of surgical innovators to provide reports based on experience rather than systematically test a new procedure should be discussed in the context of the Balliol recommendations on surgical innovation. McCulloch et al. developed a paradigm for surgical innovation, and classified five stages of surgical innovation: (1) innovation; (2) development; (3) systematic exploration; (4) assessment; and (5) long-term study (abbreviated with the eponym "IDEAL").[10] The discovery of ALPPS was a surgical innovation and the paradigm ought to be applicable. While comparing the reality of surgical innovation in ALPPS with the IDEAL recommendations, we made four observations.

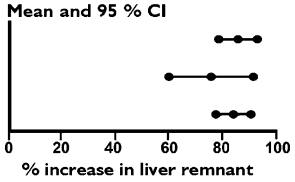
First, according to McCulloch et al., during the innovation stage (1) dramatic successes or failures were reported in single-digit case reports from individual centers. However, in the case of ALPPS, the inaugural publication was a multicenter report with a double-digit number of patients reported and detailed reporting of indications and complications. The inaugural study belongs to the 'development stage' (stage 2a) rather than the 'innovation stage' (stage 1), according to the Balliol paradigm. Interestingly, this inaugural report was followed by a wave of case reports and single-center-experience reports that characterize the 'innovation stage' (stage 1) in the Balliol paradigm. These studies do not contribute evidence beyond the level of the inaugural study, neither in the number of patients presented nor in systematic reporting of outcome data. Maybe due to the publication pressure in academic centers, individual center reports dominate over collaborative work in this field of surgical oncology. Letters are common and there is a wide divergence of opinion between supporters and critics without new data. Expert centers reported problems associated with ALPPS but their reports remain narrative.[7]

Second, according to the IDEAL paradigm, studies following the 'innovation stage' belong to the 'development stage', practiced by 'early adaptors'. At this stage, "few patients are being recruited, they are selected for specific characteristics".[17] In reality, ALPPS was performed for a wide range of indications and may have been overused as a magic bullet in high-risk patients with rapidly progressive malignancies. This 'expanded' development phase has made ALPPS known for its high risk of complications, and mortality has led to warnings by some about an 'immature procedure'.[9] This recoil may explain a temporary contraction in the number of procedures recorded in the ALPPS registry in 2013 (Schadde E, personal communication) and a general pessimism, which may be unjustified if a more homogeneous patient population is chosen.

The third observation is a hesitancy to enter the 'exploration phase' (stage 2b) after the development phase postulated by the IDEAL paradigm. In the exploration

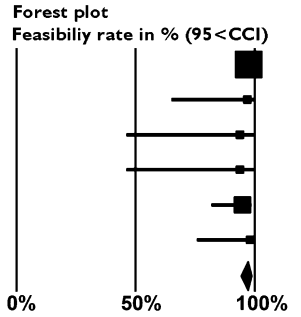
A **Meta-analysis of the increase of liver remnant after ALPPS in %**

Study Year	Mean %	Standard error	Variance	95% CI Lower	95% CI Upper	Relative weight of the study in %
Schadde A 2014	86	4	13	79	93	83
Schnitz-Lang 2012	76	8	64	60	92	17
Overall	**84**	**3**	**11**	**78**	**91**	



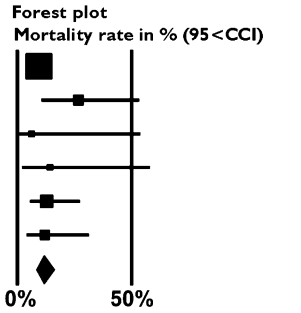
B **Meta-analysis of feasibility (ALPPS stage II performed)**

Study Year	Feasibility %	95% CI Lower	95% CI Upper	Relative weight of the study in %
Schadde A 2014	98	94	99	56
Nadalin 2014	97	65	100	6
Oldhafer 2013	94	46	100	5
Knoefel 2013	94	46	100	5
Torres 2012	95	82	99	22
Schnitzbauer-Lang 2012	98	76	100	6
Overall	**97**	**94**	**98**	



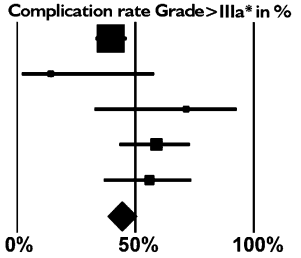
C **Meta-analysis of mortality after ALPPS**

Study Year	Mortality %	95% CI Lower	95% CI Upper	Relative weight of the study in %
Schadde A 2014	9	6	14	61
Nadalin 2014	27	10	53	10
Oldhafer 2013	6	0	54	2
Knoefel 2013	14	2	58	3
Torres 2012	13	5	27	15
Schnitzbauer-Lang 2012	12	4	31	9
Overall	**11**	**8**	**16**	



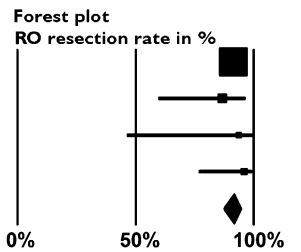
D **Meta-analysis of complication Grade > IIIa in % after ALPPS**

Study Year	Grade>IIIa %	95% CI Lower	95% CI Upper	Relative weight of the study in %
Schadde A 2014	40	33	47	73
Oldhafer 2013	14	2	58	1
Knoefel 2013	71	33	93	2
Torres 2012	59	43	73	15
Schnitzbauer-Lang 2012	56	37	74	9
Overall	**44**	**38**	**50**	



E **Meta-analysis of RO resection rate in ALPPS**

Study Year	RO resection %	95% CI Lower	95% CI Upper	Relative weight of the study in %
Schadde A 2014	91	86	15	82
Nadalin 2014	87	60	97	10
Oldhafer 2013	94	46	100	3
Schnitzbauer-Lang 2012	96	77	99	5
Overall	**91**	**87**	**94**	



◀**FIG. 2** Meta-analyses of various variables. Forest plots demonstrate adjusted event rates and 95 % CIs for each study and the relative weight of the study in the meta-analysis. **a** Meta-analysis of liver remnant increase in percentages is presented as a mean with standard error. **b** Meta-analysis of feasibility of ALPPS to complete stage 2 ALPPS. **c** Meta-analysis of mortality after ALPPS. **d** Meta-analysis of complications grade IIIa or higher according to the Clavien–Dindo classification. **e** Meta-analysis of R0 resection rate after ALPPS. *CI* confidence intervals, *ALPPS* associating liver partition and portal vein ligation for staged hepatectomy

phase, a larger patient population with clearly defined indications is treated by an early majority of surgeons. Recently, it has been argued that a randomized controlled trial (RCT) should not be performed until the safety of ALPPS has been established in a 'phase I process'.[9] This concern is understandable since, as this review shows, the majority of studies available today belong to the 'innovation phase' and present incomplete data, with the 'development phase' somewhat omitted. However, despite this concern, the IDEAL recommendations state that RCTs should be initiated before the plateau of the learning curve has been reached, since the rigid supervision of outcomes in a randomized multicenter trial is superior to individual practice in single centers. According to the Balliol statement, procedures not sufficiently evolved to warrant full evaluation may evolve further during the trial.[10] Additionally, there are now safety data available in the form of a registry.[13] Registries are recommended by the Balliol cooperation—additionally to RCTs–during the exploration phase. The recently performed registry analysis[13] can therefore be considered to be a first step in the 'exploration phase'. According to the Balliol statement, during the exploration stage enough reports have been published for the technology to be generally regarded as safe, and it is starting to lose its experimental character, although it is still novel.[17] Our meta-analysis shows a CI for mortality in mixed indications of 8–16 %. Mortality of ALPPS for CRLM is 8 % in the registry analysis and 5.1 % in patients with CRLM younger than 60 years of age.[13] This subset of patients was explored because a high mortality was observed for primary liver tumor indications in older patients. While conventional two-stage hepatectomy have primarily been performed in younger patients with CRLM (for example median age of 53 years (range 35–69) in the largest study[18]), ALPPS has been used by many as a magic bullet for older patients with primary liver cancers due to the allure of the 'auxiliary livery' left in place. Recently, a systematic review of the mortality of conventional two-stage hepatectomy for CRLM has been performed, with a range of 0–8 % and a mean of 3 %. As the authors admit, 3 % was not generated using weighing by meta-analysis. Studies included were a large series from Paul-Brousse Hospital, Paris, with a mortality of 7 %,[19] a large series from MD Anderson Cancer Center, with a perioperative mortality of 6 %,[18] and the series from John-Hopkins Hospital, with a perioperative mortality of 6 %.[20] Therefore, it appears that mortality of ALPPS is comparable to that of conventional two-stage hepatectomies, as long as comparable populations are actually compared. ALPPS for a population with strict inclusion criteria (CRLM, younger than 60 years of age) appears safe enough to be consider a randomized trial. One could also argue that only a randomized trial with strict inclusion criteria, under the strict surveillance of a Data Safety Monitoring Board ready to recommend that the trial be stopped if a too-high mortality rate occurs, may settle the controversy regarding the mortality of ALPPS.

Since the feasibility of two-stage hepatectomy to reach complete tumor resections is only 77 %,[21] and the feasibility of ALPPS is 97 %, an RCT with an oncological endpoint, such as for example 1-year DFS, should be seriously considered. The largest report with complete survival data of TSH in patients with CLRM shows a DFS of 39 % at 1 year.[18] Two other reports detail a median survival of 12 months or more but they are smaller and their populations differ from the population analyzed in the ALPPS registry analysis. If a difference of proportions of 20 % in DFS is assumed, together of a power of 0.8, approximately 110 (accounting for dropouts) subjects would have to be enrolled in each arm. The equipoise of ALPPS and conventional two-stage hepatectomies consists of the simple fact that ALPPS has a feasibility of 97 % with a CI of 93–98 %, as shown by this review. Consequently, two RCTs investigating ALPPS versus conventional two-stage hepatectomies were recently launched (clinicaltrials.gov-identifier: NCT01775267 and NCT01842971).

CONCLUSIONS

ALPPS appears to have a high feasibility of resecting primarily non-resectable liver tumors, and a mortality comparable to conventional two-stage hepatectomies. Data on oncologic outcomes are missing and have not been systematically reported by individual studies. The technique should not only be explored by further accrual of patients and analysis of registry data but also in an RCT of ALPPS versus two-stage hepatectomy for CRLM.

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