A Comparison of Pitfalls after ALPPS Stage 1 or Portal Vein Embolization in Small-for-Size Setting Hepatectomies

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Keywords

ALPPS · Portal vein embolization, PVE · Liver resection · Small-for-size setting · Pre-completion pitfalls · Failure

Summary

Background: Portal vein embolization (PVE) followed by resection and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) are tools to enable liver resections in small-for-size settings. **Methods:** A systematic review of the literature and comparison of pitfalls between PVE and resection and after ALPPS stage 1 were performed. **Results:** Evidence levels were as low as 4 for both procedures. 20 publications were identified with reports on post-PVE or post-ALPPS stage 1 pitfalls. A total of 2,758 patients treated with PVE followed by resection and 698 patients undergoing ALPPS were analyzed. Pitfalls identified were failure to advance to resection (PVE: high (20%)/ALPPS: low (1%); $p = 0.0001$), tumor progression (PVE: high/ALPPS: low); insufficient hypertrophy (PVE: frequent/ALPPS: rare), and inter-stage liver failure (PVE: rare/ALPPS: frequent). However, in-house mortality was still very high after ALPPS (7 vs. 3%, $p = 0.0001$) in a pooled analysis. **Conclusion:** PVE is a well-established technique to induce hypertrophy in small-for-size settings. The weakness of PVE is that it may fail to advance to resection. Inter-stage liver failure in ALPPS triggers post-stage 2 mortality. Prolongation of the inter-stage interval to overcome liver failure or cancellation of the resection stage combined with adherence to defined indications has the potential to make ALPPS much safer and decrease mortality rates. Level of evidence is low for both techniques.

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Introduction

Portal vein embolization (PVE) was first described by Kinoshita et al. [1] and Makuuchi et al. [2] more than 30 years ago. Its establishment in modern liver surgery allowed surgeons to perform safe resections in small-for-size settings (surgically possible but functionally not) where the future liver remnant (FLR) increases in size in response to PVE and the patient does not show signs of disease progression. With the interventional embolization or surgical ligation of the portal vein, the FLR is stimulated, obtaining growth rates of 25–50% within 4–6 weeks [3]. In a second step, the tumor may be resected safely without driving patients into fatal post-hepatectomy liver failure, especially after extensive pre-resection chemotherapy [4, 5]. Until recently, PVE was an absolute sovereign and a monopolist with regard to enlarging the FLR. However, only 5 years ago, the group of Hans Schlitt established a new technique of 2-stage hepatectomy to induce FLR growth. The new technique combined portal vein ligation and parenchymal transection during the first stage of surgery, a short interval for FLR growth and regeneration (10 days), and the removal of tumor-bearing liver in the second step of surgery. The kinetic growth rates of the FLR were around 75% within 8–12 days after stage 1 surgery and were larger than any other report so far [6, 7]. Clavien and de Santibañes [8] established a now commonly used descriptive name for this new procedure: associating liver partition and portal vein ligation for staged hepatectomy, the so-called ALPPS procedure. However, just as most innovations suffer from initial throwbacks, the exploration phase of ALPPS also unveiled relevant morbidity in patients as well as unacceptable high mortality rates, especially in unselected patient cohorts and in certain indications such as perihilar cholangiocarcinoma [9–11]. Driven by the ALPPS registry, certain recommendations have been made concerning indications, surgical-technical modifications, and patient management, discussed and worded during the 1st international ALPPS consensus meeting in

Fig. 1. Flow chart of paper selection.

Hamburg in 2015 [12]. Nonetheless, the evidence level for ALPPS benefit is still low, with no prospective randomized controlled trials comparing PVE and ALPPS so far. Besides, blinded by the 100% feasibility rate and the tremendous rates of hypertrophy, almost nobody focused on what happened between stages 1 and 2 of ALPPS. This time period, in which the critical pathophysiological damage occurs, is very likely to determine the further course of patients after ALPPS stage 2. Therefore, a systematic review was performed to detect and compare the pitfalls occurring in the interval between PVE and subsequent resection and between ALPPS stage 1 and 2.

Methods

A PubMed/MEDLINE search was performed for the search terms '2-stage hepatectomy failure', 'portal vein embolization failure', 'portal vein embolization and hepatectomy', 'ALPPS', and 'in-situ split with portal vein ligation'. Doubles and non-suitable articles were excluded. The search was performed 2 times to minimize the risk of selection bias. Articles were included in the analysis when the abstract reported failure rates, complications, or pitfalls after PVE or ALPPS stage 1. In more detail, target information was extracted focusing on inter-stage pitfalls that predicted liver failure after stage 2 in ALPPS, and post-PVE factors hindering progress to subsequent resection. Failure in PVE was defined as an event that

did not allow advancement to resection, and in the ALPPS procedure, as critical factors that occurred between stages 1 and 2, discouraging advancement to stage 2. Data were presented in a descriptive manner using total numbers, proportions, and risk factors where available. A cumulative pooled outcome analysis of patients was performed to analyze failure rate and in-house mortality. Evidence levels for benefit in both PVE and ALPPS were determined using the latest Oxford Centre of Evidence-Based Medicine recommendations [13]. Statistical analyses were performed with Review Manager (RevMan) Version 5.2. (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2012).

Results

Number of Publications and Selection

A total of 1,693 publications were detected with the search terms described above until the cut-off date of June 2017. After exclusion of doubles, papers with an abstract or title not indicating the target topic, letters, case reports, as well as overviews and non-English articles, 57 papers remained. Of those, 37 were published before the year 2007 and were in large part analyzed in the meta-analysis by Abulkhir et al. in 2008 [3]. A total of 20 papers remained for analysis to compare ALPPS and PVE, focusing on pitfalls leading to failure of the intended treatment completion. Figure 1 displays a flowchart of the paper selection.

Evidence Levels for the Publications Analyzed

Evidence levels were generally low for the interventions dealt with in this review (PVE followed by resection or ALPPS). Of the 20 publications analyzed, 2 were systematic reviews of case series and case-control studies comparing the 2 techniques, 13 were case series, and 5 were case-control studies. There were no cohort studies. This accounted for an overall evidence level of 4 for both PVE and ALPPS, as the review by Abulkhir et al. [3] was not a meta-analysis of randomized controlled trials.

General Observations

Resection strategies using PVE or ALPPS are infrequently employed at a rate of approximately 8 times per year (range 3.2–15.6) in very selected high-volume hepatobiliary centers. Unfortunately, most centers do not provide the whole volume of their liver program. Therefore, the proportion of liver resections in small-for-size settings using ALPPS or PVE remains an educated guess. Nonetheless, the total numbers given above are likely to be representative.

Pooled Outcome Analysis of Failure and In-House Mortality Comparing ALPPS versus PVE Followed by Resection

Strikingly, the failure rate of PVE was considerably higher than that of ALPPS (fig. 2). A total number of 555 patients could not be resected after PVE whereas 1,956 were resected. In comparison, only 8 patients did not proceed to ALPPS stage 2, while 726 patients completed the treatment successfully. The difference was highly significant ($p = 0.0001$). However, the in-house mortality

Fig. 2. Forrest plot of failure to progress to resection – ALPPS procedure compared to PVE followed by resection.

Fig. 3. Forrest plot of in-house mortality – ALPPS procedure compared to PVE followed by resection.

after PVE was significantly lower than that after ALPPS (fig. 3). Here, we see a completely different picture. After PVE and resection, only 75 patients died and 2,273 survived. In contrast, after the ALPPS procedure, 60 patients died compared to 657 survivors. This difference was again highly significant ($p = 0.0001$).

Pitfalls Detected after PVE Hindering the Advancement to Resection

In the systematic review by Abulkhir et al. [3], the overall morbidity after PVE (including post-resection complications) was very low with 2.2% of all cases. Insufficient hypertrophy after PVE and disease progression were the most frequent reasons why resection was not performed. Besides, other authors described a worsening of comorbidities during the waiting time after PVE and a misinterpretation of resectability as additional factors. However, there were also factors directly related to PVE; nausea/pain, thrombosis in the mesenterico-portal veins, esophageal varicose bleeding, liver hematoma, and incomplete or wrong embolization were serious albeit rare PVE complications that could be hazardous for the patients.

Pitfalls Detected after ALPPS Stage 1 That Led to Adverse Outcome after Stage 2

Descriptions of inter-stage pitfalls after ALPPS remain rare. Truant et al. [14] performed the first systematic analysis. The authors described that the failure rate after ALPPS was 5% due to insufficient growth, portal vein thrombosis, and inter-stage death, and that a delay in the planned procedure beyond day 9 was seen in more than 50% of patients. Schadde et al. [15] described that inter-stage liver failure and an inter-stage MELD score >10 were highly predictive for mortality after stage 2. In detail, 21 of 28 patients with liver failure after stage 1 died within 90 days after stage 2, especially in the case of a MELD score >10 (odds ratio 3.9–4.9). Surgery-related fatal liver failure was finally confirmed in the publication by Linecker et al. [16]. Extracted data for all analyzed publications are displayed in table 1. Table 2 summarizes the findings described above.

Discussion

The technique of PVE followed by resection was developed over several decades and is a well-established tool in small-for-size settings in liver surgery [1]. ALPPS, in contrast, is the new kid on the block. It was published only 5 years ago, and the first procedure was performed 10 years ago [6]. PVE followed by resection was developed within a considerable timeframe without competition from any other procedure, and was properly assessed. That way, data from long-term studies were obtained. ALPPS revealed certain flaws in its beginning but was developed properly by the introduction of a registry which made the procedure safer. Nonetheless, this review showed that pre-resection pitfalls remain poorly reported in both PVE and ALPPS, and that the evidence level is low with publications of predominantly level 4 [13]. Strikingly, the failure to advance to liver resection was rather high in patients with PVE. The reasons for PVE failure are well analyzed and consistently described throughout the literature; however, they still contribute to a failure rate of approximately 20% of all procedures. Reports on ALPPS failure after the stage 1 operation are still very rare. Manuscripts focusing on reasons for failure after ALPPS have so far only been published by Truant et al. [14], Schadde et al. [15], and Linecker et al. [16]. ALPPS still results in a very high in-house mortality and thus also impairs the oncologic outcome of the patients; however, mortality has somewhat improved with better patient selection along with the adherence to the recommended avoidance of certain indications such as perihilar cholangiocarcinoma [11, 17].

In this review, the overall mortality for the ALPPS procedure was 7% compared to 3% after PVE followed by liver resection. This demonstrates that the implementation of correct indications for ALPPS is pivotal. Additionally, we learn that inter-stage complications must lead to a reconsideration of whether to delay or even stop the progression to stage 2. Since 21 of 28 patients with inter-stage liver failure died after completion of stage 2, manifestation of liver failure (International Study Group of Liver Surgery [4]) after stage 1 should be regarded as a contraindication for completing

Tab. 1. Overview of studies and extracted data from the literature

Author [ref.]	Journal	City	Year	Evidence level	Number of patients over time, n	Failure rate, % (n)	Reasons for failure and complications	Modality
Abulkhir [3]	Ann Surg	London	2008	review of case series and case-control studies	1,088	15	2.2% overall morbidity of PVE insufficient hypertrophy and progress as most frequent reasons for failure	PVE in mixed indications prior to major liver resection
Tsai [20]	HPB (Oxford)	Baltimore	2010	case series	45 in 14 years	22 (10)	progress (n = 7) poor ECOG status (n = 1) death before resection (n = 2)	PVE + CTx in CRLM
Massimino [21]	HPB (Oxford)	Portland	2012	case series	23 in 5 years	13 (3)	PVE complications (n = 7) pain/nausea (n = 2) SMV thrombosis (n = 1) liver hematoma (n = 1) wrong target vein (n = 2)	PVE in CRLM
Lam [22]	HPB (Oxford)	Sydney	2013	systematic review of case series and case-control studies	459	23 (107)	progress (n = 94) insufficient hypertrophy (n = 4) PVT (n = 4) death before resection (n = 2)	PVE + CTx+ablation (classic TSH concepts) in CRLM
Shindoh [23]	J Am Coll Surg	Houston	2013	case series	141	27.8 (40)	progress (n = 27) insufficient regeneration (n = 5) comorbidities (n = 8) incomplete embolization (n = 3) PVE complications (n = 2)	PVE in CRLM
Shindoh [18]	Br J Surg	Houston	2013	case-control study	265 139 PVE/ 126 primary resection	37 (51) in PVE	progress insufficient hypertrophy tumor load during laparotomy	PVE vs. conventional primary surgery in CRLM
Schadde [24]	HPB (Oxford)	Zurich	2013	case-control study	35 TSH vs. 163 conventional resections in 9 years	0% failure, only 9/35 with PVE	N.A.	N.A.
Schadde [17]	Ann Surg	Zurich	2014	case series	202	0	no analysis of inter-stage risk factors RBCT, OR time > 300 min., age > 60 years, and non-CRLM indication were risk factors of adverse outcome	ALPPS in mixed indications
Leung [25]	J Am Coll Surg	New York	2014	case series	153 in 13 years	N.A.	degree of hypertrophy and growth rate of <2.66% of total liver volume/week were predictive for liver failure after resection	PVE in CRLM

Table 1. Continued on next page

Table 1. *Continued*

Author [ref.]	Journal	City	Year	Evidence level	Number of patients over time, n	Failure rate, % (n)	Reasons for failure and complications	Modality
Shindoh [26]	J Gastrointest Surg	Houston	2014	case series	358 in 23 years	33 (118) without curative approach	progress (n = 19) irresectable (n = 25) insufficient regeneration (n = 13) comorbidities (n = 19) PVT (n = 8) PVE complications (n = 3) hematoma (n = 2) esophageal bleeding (n = 1)	PVE in mixed indications
Truant [14]	Eur J Surg Oncol	Lille	2015	case series	62	5 (3)	insufficient hypertrophy (n = 1) PVT (n = 1) death (n = 1) delayed > 9 d (n = 32)	ALPPS mixed indications
Schadde [15]	Ann Surg	Zurich	2015	case series	320	1.6 (5)	liver failure after stage 1 (ISGLS) MELD > 10 (risk factors for mortality after stage 2)	ALPPS in CRLM
Hernandez-Alejandro [27]	Surgery	London-Ontario	2015	case series	14 in 2 years	0	no complications reported	ALPPS in CRLM
Ratti [28]	Ann Surg Onc	Milan	2015	case-control study	48 36 TSH/12 ALPPS	6 (2) in TSH 0 in ALPPS	disease progression (n = 2)	TSH with PVE and ALPPS
Passot [29]	J Am Coll Surg	Houston	2016	case series	109 in 12 years	18 (20)	progress (n = 12) insufficient hypertrophy (n = 5) PVE-complications (n = 3)	PVE in CRLM
Sparrelid [30]	Langenbecks Arch Surg	Stockholm	2016	case series	11	100	insufficient hypertrophy following PVE	rescue ALPPS
De Santibañes [31]	Langenbecks Arch Surg	Buenos Aires	2016	case series	4	0	N.A.	ALPPS with PVE, no-touch anterior approach, partial parenchymal transection in mixed indications
Adam [32]	Br J Surg	Paris	2016	case-control study	58 41 TSH/17 ALPPS	36 (15) in TSH, 0 in ALPPS	similar complication rate but worse overall outcome in ALPPS	ALPPS vs. TSH with PVE in CRLM
Cieslak [33]	Surgery	Amsterdam	2017	case series	63	40 (18)	liver failure after surgery (3 fatal) insufficient hypertrophy (n = 4) surgery technically not feasible (n = 1) death before resection (n = 1)	PVE in CRLM
Linecker [16]	Surgery	Zurich	2017	case-control study	67 22 partial/22 matched/ 23 historic	0	surgery-related fatal liver failure grade C after stage 2 (n = 2)	ALPPS partial vs. full in CRLM

PVE = Portal vein embolization; ALPPS = associating liver partition and portal vein ligation for staged hepatectomy; CTx = chemotherapy; CRLM = colorectal liver metastases; SMV = superior mesenteric vein; PVT = portal vein thrombosis; TSH = 2-stage hepatectomy; N.A. = not available; RBCT = red blood cell transfusion; OT = operating time; ISGLS = International Study Group of Liver Surgery.

Tab. 2. Summary of key findings

	PVE and resection	ALPPS	Conclusion/recommendations
Technique used, n (over years)	>30	>10	ALPPS data still in phase of exploration (2b); however, recommendations indicate entry into assessment phase (3) of surgical innovations [34]
Evidence level	level 4 (low)	level 4 (low)	no randomized controlled trials, no direct comparison of the 2 techniques available
In-house mortality	acceptable	still too high	favoring PVE
Time interval before final resection	2–4 weeks	7–15 days	favoring ALPPS; however, time interval can be valuable for identifying patients that do not profit from progressing to final procedure for tumor biological reasons patients with ALPPS inter-stage complications may profit from a longer interval between stages favoring ALPPS
Failure rate (no progression to final resection)	very high	very low	
Progress	frequent	rare	may be a selection criterion and thus prevent postsurgical in-house mortality; OS of intention-to-treat analysis for PVE unclear
PVE complications	rare	N.A.	PVE = established procedure
Insufficient hypertrophy	frequent	rare	favoring ALPPS, especially as rescue ALPPS after failed PVE
Inter-stage liver failure	rare	frequent	favoring PVE; may lead to delay of ALPPS stage 2 making it a safer procedure
Inter-stage death	rare	rare	not a common problem
PVE = Portal vein embolization; ALPPS = associating liver partition and portal vein ligation for staged hepatectomy; OS = overall survival; N.A. = not available.			

ALPPS as outlined by Schadde et al. [15]. The stage 2 operation can either be cancelled or be performed only in the case of recovery from liver failure. This has 2 advantages: First, the rate of liver failure-associated mortality would be reduced, and second, although potentially conflicting with the rapid hypertrophy principle of ALPPS, a longer waiting time could improve biologic selection. If the failure to advance to stage 2 increased from the currently reported rate of 1% to 5 or even 10%, and if mortality rates were at the same time reduced to 3%, ALPPS would have the potential to be a more successful procedure than PVE. The overall number of patients with ALPPS failure would be much lower than that of those with PVE failure, resulting in better overall survival in an intention-to-treat setting due to the lower proportion of palliative treatment compared to patients with failure after PVE [18, 19].

The limitations of this analysis lie in the low level of evidence for both procedures. Double-checking all the included publications minimized the selection bias. However, the fact that only retrospective case series exist and the lack of head-to-head randomized controlled trials allowed only a descriptive comparison.

In conclusion, PVE is still the best option enabling safe liver resection in small-for-size settings. The pre-resection pitfalls after PVE are well described; however, failure to advance to liver resection after PVE leads 20% of patients to palliative treatment, resulting in a dramatic decrease in long-term oncologic survival. In patients with liver resection after PVE, however, the prognosis is still outstanding in this medically complex patient group. The outline of indications for ALPPS has much improved, but inter-stage problems are still poorly described. When inter-stage liver failure is avoided, the long-term prognosis after the ALPPS procedure is good. Either prolonging the inter-stage phase or cancelling the stage 2 procedure may allow the prevention of perioperative deaths in ALPPS, including an oncologically sound biologic selection.

Disclosure Statement

There are no conflicts of interest.

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