Did the International ALPPS Meeting 2015 Have an Impact on Daily Practice? The Hamburg Barmbek Experience of 58 Cases

Gregor A. Stavrou^{a, b} Marcello Donati^{a, c} Mohammad H. Fard-Aghaie^a Martin Zeile^{b, d}
Tessa M. Huber^a Axel Stang^{b, e} Karl J. Oldhafer^{a, b}

^aGeneral and Visceral Surgery, Surgical Oncology, Asklepios Hospital Barmbek, Hamburg, Germany;

^bSemmelweis Medical Faculty, Campus Hamburg, Hamburg, Germany;

^cDepartment of Surgery, Vittorio-Emanuele University Hospital Catania, Catania, Italy;

^dDiagnostic and Interventional Radiology, Asklepios Hospital Barmbek, Hamburg, Germany;

^eMedical Oncology, Asklepios Hospital Barmbek, Hamburg, Germany

Keywords

ALPPS · In-situ split · Liver · Two-stage

Summary

Background: ALPPS (associating liver partition and portal vein ligation for staged hepatectomy) was introduced only 10 years ago and has gained wide acceptance as a variation of staged procedures in liver surgery. It has been criticized for its high morbidity and mortality, which all centers reported in their initial series. **Methods:** After a world expert meeting in Hamburg in 2015 where all experts in the field met to discuss this method, caveats were extracted and formulated. We researched our complete prospective ALPPS database to see if the recommendations had any impact on outcome. **Results:** In total, we performed 58 ALPPS procedures in our center. 33 patients were operated on before, 25 after the meeting. Results in terms of morbidity and mortality were significantly better after the meeting, as were patient selection and strategy. **Conclusion:** In our own center's experience, the implementation of the meetings' recommendations and the information gathered through this valuable exchange had a dramatic impact on results. Having performed 58 ALPPS procedures in total, we can now conclude that ALPPS has become much safer in our hands since the 2015 meeting and that morbidity and mortality are no longer the issue to be discussed. Future research must focus on oncologic outcomes in these patients.

© 2017 S. Karger GmbH, Freiburg

Introduction

The first in-situ split procedure performed by Hans Schlitt in Regensburg in 2007 was adopted 10 years later as a new method to face extensive liver disease requiring staged procedures by many centers in Germany and worldwide [1–13].

After the first German multi-institutional series was published in 2012 [3], the HPB (hepato-pancreato-biliary surgery) community was excited, fascinated, and yet somewhat shocked by the high morbidity and mortality (M&M) that the new method – today referred to as ALPPS (associating liver partition and portal vein ligation for staged hepatectomy) [14] – had shown to produce. Many in the conservative arm of the HPB community advocated the immediate stop of the use of this procedure [8, 15–22]; however, others realized the potential of the new strategy once HPB surgeons had overcome the initial learning curve, and proposed a unique approach to this newly introduced method with the founding of the international ALPPS registry (www.alpps.net). With this, a platform was given to all to study actual results and to learn and further develop the method. With all the known flaws and limitations of such registries, it still remains a unique dataset. At the time when laparoscopic cholecystectomy was introduced, no one had thought of setting up a registry. Even laparoscopic bowel or liver surgery was started without monitoring; registries were implemented 10 years after the use of these techniques had become widespread. The ALPPS registry has been extensively studied and has produced helpful results so far including the understanding of pitfalls [23–26].

In February 2015, an International Expert Meeting on ALPPS took place in Hamburg (www.alpps.co), bringing together all

known experts in this field as well as prominent critics to discuss all aspects of the procedure over 2 days. The aim of the meeting was to reach a consensus on how the procedure could be advanced according to key recommendations of the meeting [27]. The involvement of our center with ALPPS started in 2011 [28] after a personal communication with Hans Schlitt. The purpose of this study is to show our experience over 6 years divided into a pre- and post-meeting period. With 58 ALPPS procedures performed in total, this appears to be one of the largest series worldwide.

Methods

Using our institution's prospective database for all ALPPS cases, we performed a complete workup of all patient data. We divided the identified 58 patients into 2 subgroups – before and after the 2015 ALPPS Meeting in Hamburg. We then analyzed technique, outcome, morbidity, and mortality, and provided follow-up for the first group.

From 03/2011 to 03/2017, 1,016 liver resections were performed in our department. A hypertrophy concept for staged procedures was used in 136 patients (3 classic 2-stage hepatectomies with portal vein ligation, 75 portal vein embolizations (PVE), 58 ALPPS), representing 13% of our total collective. As for colorectal liver metastases (CRLM), it is important to mention that all our patients received four cycles (more in a few cases) of modern chemotherapy (FOLFOX/FOLFIRI or later FOLFOXIRI) combined with antibodies (cetuximab/bevacizumab) to gain systemic control upfront, and also that stable disease or partial remission was a selection criterion for eligibility for an ALPPS approach.

Results

ALPPS 03/2011 to 02/2015 (Pre-Meeting Period)

A total of 33 ALPPS procedures were performed in this first period. Indications varied. ALPPS was mainly performed for CRLM ($n = 22$). Bilobar disease was present in 12 cases. A 'liver first approach' was used in 2 patients. Non-CRLM indications ($n = 11$) were hepatocellular carcinoma (HCC), cholangiocellular carcinoma (CCC), gastrointestinal stromal tumor, and other metastases. Mean age was 66.6 years with a mean Charlson comorbidity index of 9. 5 patients underwent ALPPS after PVE failed to induce hypertrophy ('rescue ALPPS'). Mean standardized future liver remnant (sFLR) volumes were 20% before step 1 (volume of additional atypical resections in the FLR was not measured) and 34% before step 2, with an absolute mean growth of 79%. In this period, we had already adopted a longer interval between steps, resulting in a mean period of 22 days.

Resections finally completed resulted in right hepatectomy plus multiple atypical resections in the FLR in 2 cases, extended right hepatectomy in 19 cases, and extended right hepatectomy plus atypical resections in the FLR in 10 cases. During step 1, we performed full transection with a liver hanging maneuver in the anterior approach and taping of structures as previously reported [29] (fig. 1); in 3 patients, a partial ALPPS procedure was performed.

Of the 33 patients, 31 entered into step 2, while 2 patients died after step 1 (a 78-year-old gentleman with CCC suffered cardiac

Fig. 1. Intraoperative photograph of an ALPPS step 1 from the early era. Performed as a full parenchymal transection down to the vena cava using the anterior approach with a liver hanging maneuver as well as adding Launois' maneuver and tagging of anatomical structures (red tag around right hepatic artery).

Fig. 2. Intraoperative photograph of an ALPPS step 1 from the post-meeting period. Performed as a partial (50%) parenchymal transection down to the level of the middle hepatic vein and tagging of anatomical structures (red tag around right hepatic artery).

failure on postoperative day (POD) 2 and could not be resuscitated; the other 73-year-old gentleman with HCC and nutritive-toxic Child A cirrhosis developed acute chronic liver failure as well as consecutive multiple organ failure after step 1 and died). No other patients manifested severe complications after step 1. Patients going on to step 2 suffered complications greater than Clavien-Dindo Grade IIIa in 27%. 5 patients were lost after step 2, accounting for an overall mortality of 20 and 15%, respectively, after completion of both steps.

The 5 patients lost after step 2 suffered liver failure. In 3 patients, the cause of liver failure was a small-for-size syndrome: 1 patient had a pre-step 2 sFLR of 22%, another patient had transient liver failure according to the International Study Group of Liver Surgery (ISGLS) definition [30] with a bilirubin level of 2.2 mg/dl pre-step 2; the third patient likely had a general problem with liver regeneration because his liver failed to show a hypertrophic response in spite of a technically good PVE with the sFLR only growing to 25.5% even after ALPPS step 1. The other 2 patients presented with liver failure provoked by cholestasis and cholangitis: Unfortunately, in 1 patient with gallbladder carcinoma, FLR volumetry was inappropriately performed and his sFLR was later corrected to be 19%. The other patient suffered septic multiple organ failure. He had undergone ALPPS as a rescue procedure for CRLM.

After a 4-month stay in the intensive care unit due to severe aspiration pneumonia following resection of a stenosing sigmoid primary cancer, he refused chemotherapy, and surgery was left as the only option for his liver metastases. Even though the liver remnant had shown good hypertrophy, the patient was in severely impaired general condition and developed cholangitis and liver failure after step 2.

At this time, there were no restrictions for the use of ALPPS, although it was not performed for Klatskin tumors. Comorbidities and age were not seen as criteria based on which a patient considered fit for conventional liver resection would have been denied the procedure. Volumetry of the liver remnant was introduced in that period, but it was not standardized and had technical difficulties and sometimes produced suboptimal results. ALPPS procedures were performed by the same 3 surgeons with hepatobiliary specialist training.

ALPPS 03/2015 to 03/2017 (Post-Meeting Period)

A total of 25 ALPPS procedures were performed in the post-meeting period. This does not resemble an increase in the use of the ALPPS concept since the total number of liver resections/year increased to over 200 in this era. CRLM was the main indication for ALPPS in the majority of cases ($n = 19$). In 6 selected patients, other indications were approved (liver metastases from neuroendocrine tumor, solitary fibrous tumor of hemangiopericytoma type, duodenal cancer, CCC, 2 Klatskin tumors). All patients with CRLM suffered bilobar disease, therefore a 'liver first approach' was utilized more often with 9 cases in total [31]. With 52.6 years, the mean age was significantly lower, as was the Charlson comorbidity index at 7.

Mean sFLR volumes were 19.75% before step 1 (volume of additional atypical resections in the FLR was not measured) and 30.58% before step 2, with an absolute mean growth of 59%. Again, the interval between steps was longer at 24 days. Resections finally completed resulted in right hepatectomy plus multiple atypical resections in the FLR in 1 patient, extended right hepatectomy in 5 patients, and extended right hepatectomy plus atypical resections in the FLR in 14 patients. 1 monosegment 7 reverse ALPPS was included. In this period, during step 1, we performed partial (50%) liver transection with preservation of the middle hepatic vein and without mobilizing the right liver in 20 patients (fig. 2). Hybrid ALPPS – a combination of parenchymal transection of 50% with tumor clearance in the FLR and a right PVE 1 week later – was done in 3 patients; only in 1 patient we managed to go on to step 2. In 2 patients with Klatskin tumors, right + segment 4 PVE was followed by laparoscopic parenchymal transection as a rescue procedure for insufficient FLR growth.

Of the 25 patients, only 21 went on to step 2. Reasons for drop-out (16%) were slow hypertrophy and rapid progress of disease while waiting for step 2 in 2 patients. Of the remaining 2 patients, 1 patient with insufficient hypertrophy after hybrid ALPPS received a 'rescue' right hepatic vein embolization (HVE) after waiting for months; and the other patient with Klatskin tumor, who had undergone laparoscopic hybrid partial ALPPS as step 1, repeatedly

refused to go on to step 2 despite good hypertrophy because his clinical condition was excellent and cholestasis was well controlled. Overall, severe morbidity defined as greater than Clavien-Dindo Grade IIIa occurred significantly less with 16%. We did not lose any patient directly due to ALPPS; however, 1 patient who failed to demonstrate hypertrophy of the FLR after step 1 underwent 'rescue PVE' of a newly developed segment 4 portal collateral followed by 'rescue right HVE', which eventually produced adequate hypertrophy. He was able to undergo right trisectionectomy 4 months after step 1; however, he developed an unexplained 40 °C fever and died of septic multiple organ failure on POD 14. Hence the accurate overall mortality was 4% in the post-meeting period. Results are summarized in table 1.

Discussion

Is an expert meeting able to have an impact on the daily routine and practice of a new method? If IDEAL (Idea, Development, Exploration, Assessment, Long-term Follow-up) guidelines [32] on how to reach a formal consensus on a new method are explored, probably not. Still, this expert meeting on ALPPS can be considered extraordinary because it fostered discussions between leaders in the field and gave way to new variations, insights, and experiences across the world. It also included all prominent voices expressing their concerns about the use of this method, cautioning the community to realize the need for some change to enable better results. The meeting's extracts were published in *Annals of Surgery* in 2016 [27].

Taking on board what we learned in the ALPPS meeting, we aimed for a better selection of patients. This is reflected in the fact that patients treated after the meeting were significantly younger and had less comorbidities. Meticulous planning of the operation based on diagnostic imaging is important as well as an interest and expertise in volumetry for calculating the sFLR [33–36]. This was implemented in our center in a way that only 1 radiologist with a special interest in HPB radiology, who also performed PVE himself, was in charge of volumetric analysis. From a technical point of view, we opted for a decrease in trauma during step 1 as proposed by de Santibañes et al. [37] and adopted partial ALPPS aiming at 50% parenchymal transection with preservation of the middle hepatic vein. Derived from the principle of formation of new portal collaterals as an obstacle in the progress towards hypertrophy in our PVE patients [38], we deliberately took time during step 1 to ensure the division of all possible segment 4 portal collaterals coming from the left portal branches as identified by intraoperative ultrasound. The preparation in the hepatoduodenal ligament was minimized to a direct access to the portal vein for its transection as well as tagging of the right hepatic artery. Before the ALPPS meeting, we used the liver hanging maneuver and anterior approach in step 1; now hanging is no longer used. However, we still avoid mobilization of the right liver during step 1.

Looking at our data, we can conclude that we succeeded in enabling sufficient growth in the FLR to go on to step 2 in most pa-

Table 1. Summary of patient characteristics and data about the ALPPS collective in both the pre- and post-meeting period

	Before meeting (n = 33)	After meeting (n = 25)
Mean age, years	66.6	52.6
Charlson comorbidity index, n	9	7
Colorectal liver metastases, n		
No	11	6
Yes	22	19
Bilobar, n	12	19
Liver first, n	2	9
Right hepatectomy (RH) + atypical resection S2/3, n	2	1
Extended right hemihepatectomy, n	19	5
Extended RH + atypical resection S2/3, n	10	14
Monosegment ALPPS, n	0	1
Partial ALPPS, n	3	25
No mobilization technique, n	2	20
Hybrid ALPPS, n	0	5
Step 1 only, n	2	4
Dropout before Step 2, n	2	4
Reason for dropout	2 deaths	2 progress 1 rescue hepatic vein embolization (HVE), 1 patient refused step 2
Morbidity > IIIa, %	27	16
Mortality, %	20 overall 15 in completed ALPPS	4 overall n = 1 lost after HVE (4 months after step 2)
Standardized future liver remnant (sFLR) before Step 1 (mean), additional resections in FLR not measured, %	20	19.75
sFLR before Step 2 (mean), %	34	30.5
Hypertrophy, %	79	59
Interval Step 1/2 (mean), n	22	24

tients. Giving that the starting sFLR was equivalent in the 2 groups (below 20%) before step 1, patients did not experience the same amount of growth with partial ALPPS (79 vs. 59%) in their FLR; nevertheless, there was enough volume to go on to step 2. The effectiveness of partial ALPPS was also studied multi-institutionally with the results leading to the same conclusion [39].

Gaining systemic control of the tumor upfront in patients with CRLM seems logical in these borderline resectable cases. Stable disease or partial remission seems a good criterion to select patients eligible for an ALPPS approach. We have not seen any impairment in hypertrophy even in partial ALPPS after chemotherapy, which corroborates the published data [40]. Hence we believe that 3–4 cycles of neoadjuvant chemotherapy are adequate prior to surgery, allowing good tumor control without impairing liver regeneration.

From the beginning, it was our policy to not strictly follow the ‘9-day’ dogma between the 2 steps, and this has not changed in the post-meeting period. However, with a cautious view on liver function assessment, we now wait slightly longer before step 2 to ensure normal liver function – lessons learned from the ALPPS meeting and from experiences published by the registry [24, 41]. From current data based on all kinds of liver function assessment tests (e.g.

HIDA scan), we now know that volume does not immediately equal function [42, 43]; hence we have learned to be cautious in that regard. It could be argued that a 3-week waiting time between steps for patients with CRLM comes close to the waiting period after PVE [20, 44]. However, this is not really the point; our patients with CRLM all suffered bilobar disease and had pre-step 1 sFLRs of far below 20%. Even with a perfect result after PVE, it would be unlikely that a patient could go on to step 2 after 3 weeks.

Undoubtedly, step 2 surgery after partial ALPPS is technically much more challenging compared to step 2 after full ALPPS, especially after a longer waiting period. For this reason, we adhere to the principle of the same 2 surgeons with experience in ALPPS being in charge in the operating theatre for both step 1 and 2, with an independent assessment of the anatomy being carried out by each surgeon before transection of structures. Where Launois’ maneuver is feasible, it enables transection far away from the left hilar structures with a stapler device, which has proven to be a good method in our practice. Our experience with hybrid ALPPS [45] has been inconclusive so far. We opted for this method in CRLM patients requiring extensive resection of metastases in the FLR in whom we felt portal occlusion would be too invasive at this point.

Of 3 patients with CRLM undergoing this procedure, 2 could not proceed to step 2 because of insufficient hypertrophy and disease progression. To accept a dropout rate of 4/25 patients with respect to their individual regenerative capacity of the liver was a new aspect for us in the post-meeting period. Still, a dropout rate of 16% is half that reported for PVE cases. On the other hand, we have found a new concept for the treatment of Klatskin tumors, as we still see ALPPS as an option in selected cases [46]. In 2 Klatskin tumor patients (Bismuth IIIa type), PVE extended to segment 4 was followed by laparoscopic partial ALPPS because hypertrophy of the sFLR was insufficient. After this, both patients had sufficient hypertrophy to go on to step 2. 1 patient refused step 2 surgery while the other received R0 clearance of his tumor without any complications. Next to the initially reported 'rescue ALPPS' after PVE failure [5], with advances in interventional technique and center experience, we can now also provide 'rescue PVE' for some new portal collaterals that form after step 1 as well as 'rescue HVE' if the FLR volume does not increase enough. We do not see PVE, 2-stage hepatectomy, and ALPPS as concurring methods for treating the same patients – they are rather variations of the same theme to treat selected patients who are at the far end of the resectability spectrum. Looking at this issue from the M&M perspective, ALPPS has proven to produce good results while maintaining an M&M comparable to large PVE series. The 5–6% mortality rate after PVE or 2-stage hepatectomy [19, 21, 47], and also our 4% mortality rate of ALPPS in the new era, highlight the fact that we are treating patients suffering from extensive disease with palliative chemotherapy as the only other option. This is consistent with data from the ALPPS registry, where mortality was 8% in total and 5% in patients suffering from CRLM and being <60 years of age [26]. With these complex oncologic strategies and technically even more complex surgeries, it is unlikely that we will ever reach a 0% mortality rate [48]. In this respect, we have to keep in mind that even palliative chemotherapy has a 90-day mortality of 5.5% according to large series [49]. The community should therefore come together more frequently and share their experience within special meetings as was done for ALPPS to further develop clinical strategies.

Since we seem to have conquered the problem of M&M 10 years after the ALPPS procedure was first performed, one big question remains: Does our strategy make sense oncologically? Our group was the first to advise caution on this issue after early recurrences

were noted [50]. Still, if patients go through tumor clearance of the liver once, they have better survival, which we know from multiple series. And this is also true for patients treated with ALPPS [51, 52]. The difference is that with ALPPS disease-free survival may be lower than with conventional 2-stage hepatectomy, but survival maybe comparable [53, 54]. With all the advances in modern combination chemotherapy, it looks like survival on chemotherapy for CRLM is just reaching over 20 months in selected groups of patients [55, 56], but these data are very complex and include patients who successfully underwent surgery after chemotherapy. We know that patients after ALPPS can live longer than those not receiving ALPPS [52, 54], and survival data from larger series are to be awaited. However, unfortunately, there is currently no study comparing surgical approaches ad extremis with palliative chemotherapy in a prospective way.

Conclusion

From our single center experience of 58 cases (33 pre- and 25 post-meeting), we can conclude that the Hamburg international ALPPS meeting had a tremendous impact on our practice of ALPPS. We have succeeded in reducing severe complications to 16% and have not lost any patients within 90 days of step 1 or 2. From a technical point of view, we have managed to implement partial ALPPS as an effective alternative that is equally effective in producing the required hypertrophy. The results achieved with partial ALPPS may not be exactly the same compared to complete ALPPS but are enough to proceed to the step 2 operation.

M&M should no longer be the main focus of discussion in ALPPS. To answer the question of oncologic benefit for the patients, we propose a randomized trial in patients with bilobar CRLM, with randomization to palliative chemotherapy alone or to staged surgical procedures including ALPPS after induction chemotherapy.

Disclosure Statement

The authors declare no conflict of interest.

References

- Baumgart J, Lang S, Lang H: A new method for induction of liver hypertrophy prior to right trisectionectomy: a report of three cases. *HPB (Oxford)* 2011;13:71–72.
- Lang SA, Loss M, Schlitt HJ: 'In-situ split' (ISS) liver resection: new aspects of technique and indication (Article in German). *Zentralbl Chir* 2014;139:212–129.
- Schnitzbauer AA, Lang SA, Goessmann H, et al: Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg* 2012;255:405–414.
- Hahn O, Dudás I, Pajor P, et al: ALPPS (associated liver partition and portal vein ligation for staged hepatectomy) – faster and more significant liver hypertrophy (Article in Hungarian). *Magy Seb* 2013;66:21–26.
- Knoefel WT, Gabor I, Rehders A, et al: In situ liver transection with portal vein ligation for rapid growth of the future liver remnant in two-stage liver resection. *Br J Surg* 2013;100:388–394.
- Li J, Girotti P, Königsrainer I, Ladurner R, Königsrainer A, Nadalin S: ALPPS in right trisectionectomy: a safe procedure to avoid postoperative liver failure? *J Gastrointest Surg* 2013;17:956–961.
- Torres OJ, Fernandes Ede S, Oliveira CV, et al: Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): the Brazilian experience. *Arq Bras Cir Dig* 2013;26:40–43.
- Dokmak S, Belghiti J: Which limits to the 'ALPPS' approach? *Ann Surg* 2012;256:e6, author reply e16–17.
- Machado MAC, Makdissi FF, Surjan RC: Totally laparoscopic ALPPS is feasible and may be worthwhile. *Ann Surg* 2012;256:e13, author reply e16–19.
- Sala S, Ardiles V, Ulla M, Alvarez F, Pekolj J, Santibañes E: Our initial experience with ALPPS technique: encouraging results. *Updates Surg* 2012;64:167–172.

- 11 Robles Campos R, Paricio PP, Conesa AL, Hernández CM, Pérez RG, Quiñonero MF: A new surgical strategy for multiple bilobular liver metastases: right portal occlusion and tourniquet in the parenchyma section line (Article in Spanish). *Cir Esp* 2012;90:191–196.
- 12 Guglielmi A, Ruzzenente A, Conci S, Valdegamberi A, Iacono C: How much remnant is enough in liver resection? *Dig Surg* 2012;29:6–17.
- 13 De Santibañes E, Alvarez FA, Ardiles V: How to avoid postoperative liver failure: a novel method. *World J Surg* 2011;36:125–128.
- 14 De Santibañes E, Clavien P-A: Playing Play-Doh to prevent postoperative liver failure: the 'ALPPS' approach. *Ann Surg* 2012;255:415–417.
- 15 Tanabe KK: Are we thinking? A commentary on 'Is partial-ALPPS safer than ALPPS? A single-center experience'. *Ann Surg* 2015;261:e93.
- 16 Tanabe KK: Commentary on 'Can we improve the morbidity and mortality associated with the associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) procedure in the management of colorectal liver metastases?'. Commentary on ALPPS: march of progress. *Surgery* 2015;157:204–206.
- 17 Rohatgi S, Harrison EM, Powell JJ, Wigmore SJ: ALPPS: adverse outcomes demand clear justification in an era of improving survival for colorectal liver metastases. *World J Surg* 2014;39:1848–1849.
- 18 Figueras J, Belghiti J: The ALPPS approach: should we sacrifice basic therapeutic rules in the name of innovation? *World J Surg* 2014;38:1520–1521.
- 19 Kokudo N, Shindoh J: How can we safely climb the ALPPS? *Updates Surg* 2013;65:175–177.
- 20 Shindoh J, Vauthey J-N, Zimmitti G, et al: Analysis of the efficacy of portal vein embolization for patients with extensive liver malignancy and very low future liver remnant volume, including a comparison with the associating liver partition with portal vein ligation for staged hepatectomy approach. *J Am Coll Surg* 2013; 217:126–133.
- 21 Aloia TA, Vauthey J-N: Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): what is gained and what is lost? *Ann Surg* 2012;256:e9, author reply e16–19.
- 22 Narita M, Oussoultzoglou E, Fuchshuber P, et al: What is a safe future liver remnant size in patients undergoing major hepatectomy for colorectal liver metastases and treated by intensive preoperative chemotherapy? *Ann Surg Oncol* 2012;19:2526–2538.
- 23 Buac S, Schadde E, Schnitzbauer AA, Vogt K, Hernandez-Alejandro R: The many faces of ALPPS: surgical indications and techniques among surgeons collaborating in the international registry. *HPB (Oxford)* 2016; 18:442–448.
- 24 Schadde E, Raptis DA, Schnitzbauer AA, et al: Prediction of mortality after ALPPS stage-1: an analysis of 320 patients from the International ALPPS Registry. *Ann Surg* 2015;262:780–786.
- 25 Ratti F, Schadde E, Masetti M, et al: Strategies to increase the resectability of patients with colorectal liver metastases: a multi-center case-match analysis of ALPPS and conventional two-stage hepatectomy. *Ann Surg Oncol* 2015;22:1933–1942.
- 26 Schadde E, Ardiles V, Robles Campos R, et al: Early survival and safety of ALPPS: first report of the International ALPPS Registry. *Ann Surg* 2014;260:829–836, discussion 836–838.
- 27 Oldhafer KJ, Stavrou GA, van Gulik TM: ALPPS – where do we stand, where do we go? Eight recommendations from the first International Expert Meeting. *Ann Surg* 2016;263:839–841.
- 28 Donati M, Stavrou GA, Basile F, Gruttadauria S, Niehaus KJ, Oldhafer KJ: Combination of in situ split and portal ligation: lights and shadows of a new surgical procedure. *Ann Surg* 2012;256:e11–12, author reply e16–19.
- 29 Stavrou GA, Donati M, Niehaus KJ, et al: In-Situ-Split der Leber kombiniert mit Pfortaderligatur. Ein neuer Ansatz um die Resektabilität bei kolorektalen Lebermetastasen zu steigern. *Z Gastroenterol* 2012;50:K376.
- 30 Rahbari NN, Garden OJ, Padbury R, et al: Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery* 2011;149:713–724.
- 31 Donati M, Stavrou GA, Stang A, Basile F, Oldhafer KJ: 'Liver-first' approach with ALPPS: the natural combination of two new concepts in liver surgery. *Surg Oncol* 2016;25:278–280.
- 32 McCulloch P, Altman DG, Campbell WB, et al: No surgical innovation without evaluation: the IDEAL recommendations. *Lancet* 2009;374:1105–1112.
- 33 Truant S, Boleslawski E, Sergeant G, et al: Liver function following extended hepatectomy can be accurately predicted using remnant liver volume to body weight ratio. *World J Surg* 2015;39:1139–1201.
- 34 Truant S, Oberlin O, Sergeant G, et al: Remnant liver volume to body weight ratio $\geq 0.5\%$: a new cut-off to estimate postoperative risks after extended resection in noncirrhotic liver. *J Am Coll Surg* 2007;204:22–33.
- 35 Vauthey JN, Chaoui A, Do KA, et al: Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery* 2000;127:512–519.
- 36 Vauthey J-N, Abdalla EK, Doherty DA, et al: Body surface area and body weight predict total liver volume in Western adults. *Liver Transpl* 2002;8:233–240.
- 37 De Santibañes E, Alvarez FA, Ardiles V, Pekolj J, de Santibañes M: Inverting the ALPPS paradigm by minimizing first stage impact: the Mini-ALPPS technique. *Langenbecks Arch Surg* 2016;401:557–563.
- 38 Zeile M, Bakal A, Volkmer JE, et al: Identification of cofactors influencing hypertrophy of the future liver remnant after portal vein embolization – the effect of porto-portal collaterals on the embolized liver volume. *Br J Radiol* 2016;89:20160306.
- 39 Linecker M, Kambakamba P, Reiner CS, et al: How much liver needs to be transected in ALPPS? A translational study investigating the concept of less invasiveness. *Surgery* 2017;161:453–464.
- 40 Hasselgren K, Malagó M, Vyas S, et al: Neoadjuvant chemotherapy does not affect future liver remnant growth and outcomes of associating liver partition and portal vein ligation for staged hepatectomy. *Surgery* 2017;161:1255–1265.
- 41 Linecker M, Stavrou GA, Oldhafer KJ, et al: The ALPPS risk score: avoiding futile use of ALPPS. *Ann Surg* 2016;264:763–771.
- 42 Sparrelid E, Jonas E, Tzortzakakis A, et al: Dynamic evaluation of liver volume and function in associating liver partition and portal vein ligation for staged hepatectomy. *J Gastrointest Surg* 2017;21:967–974.
- 43 Serenari M, Collaud C, Alvarez FA, et al: Interstage assessment of remnant liver function in ALPPS using hepatobiliary scintigraphy. *Ann Surg* 2017;DOI: 10.1097/SLA.0000000000002150.
- 44 Pandanaboyana S, Bell R, Hidalgo E, et al: A systematic review and meta-analysis of portal vein ligation versus portal vein embolization for elective liver resection. *Surgery* 2015;157:690–698.
- 45 Li J, Kantas A, Ittrich H, et al: Avoid 'All-Touch' by hybrid ALPPS to achieve oncological efficacy. *Ann Surg* 2016;263:e6–7.
- 46 Donati M, Stavrou GA, Gulik TM, Oldhafer KJ: Associating liver partition and portal vein ligation for staged hepatectomy for Klatskin tumours: hinc sunt leones! *ANZ J Surg* 2015;85:3–4.
- 47 Adam R, Imai K, Castro Benitez C, et al: Outcome after associating liver partition and portal vein ligation for staged hepatectomy and conventional two-stage hepatectomy for colorectal liver metastases. *Br J Surg* 2016; 103:1521–1529.
- 48 Dokmak S, Férrière FS, Borscheid R, Cauchy F, Farges O, Belghiti J: 2012 Liver resections in the 21st century: we are far from zero mortality. *HPB (Oxford)* 2013;15: 908–915.
- 49 Renfro LA, Goldberg RM, Grothey A, et al: Clinical calculator for early mortality in metastatic colorectal cancer: an analysis of patients from 28 clinical trials in the Aide et Recherche en Cancérologie Digestive Database. *J Clin Oncol* 2017;35:1929–1937.
- 50 Oldhafer KJ, Donati M, Jenner RM, Stang A, Stavrou GA: ALPPS for patients with colorectal liver metastases: effective liver hypertrophy, but early tumor recurrence. *World J Surg* 2014;38:1504–1509.
- 51 Schadde E, Ardiles V, Slankamenac K, et al: ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumors compared with conventional-staged hepatectomies: results of a multicenter analysis. *World J Surg* 2014;38:1510–1519.
- 52 Lang SA, Loss M, Benseler V, Glockzin G, Schlitt HJ: Long-term results after in-situ split (ISS) liver resection. *Langenbecks Arch Surg* 2015;400:361–369.
- 53 Lang H: ALPPS for colorectal liver metastases. *J Gastrointest Surg* 2017;21:190–192.
- 54 Björnsson B, Sparrelid E, Rosok B, et al: Associating liver partition and portal vein ligation for staged hepatectomy in patients with colorectal liver metastases – intermediate oncological results. *Eur J Surg Oncol* 2016; 42:531–537.
- 55 Stintzing S, Miller-Phillips L, Modest DP, et al: Impact of BRAF and RAS mutations on first-line efficacy of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab: analysis of the FIRE-3 (AIO KRK-0306) study. *Eur J Cancer* 2017;79:50–60.
- 56 Heinemann V, Weikersthal von LF, Decker T, et al: FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014;15:1065–1075.