Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy in the Treatment of Colorectal Liver Metastases: Current Scenario

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Keywords

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Abstract

Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) has expanded the surgical armamentarium for patients with advanced and bilateral colorectal liver metastases. However, the enthusiasm that the medical fraternity had about ALPPS was hampered by a high mortality rate and early and frequent tumor recurrence. While surgical safety has improved, mainly due to technical refinements and a better patient selection, the oncological value in the face of early tumor recurrence remains unclear. The only randomized controlled trial on ALPPS versus two-stage hepatectomy (TSH) so far confirmed that ALPPS led to higher resectability with comparable perioperative complication rate, but oncological outcome was not measured. Robust

data regarding long-term outcome are still missing. TSH and ALPPS might be complementary strategies for the resection of colorectal liver metastases (CRLM) with ALPPS being reserved for patients with no other surgical option, that is, after failed portal vein embolization or those with an extremely small future liver remnant. In other words, ALPPS can be considered a supplementary tool and a last resort in the liver surgeon's hand to offer resectability in otherwise nonresectable CRLM. In these individual cases, and always embedded into a multimodal treatment setting, ALPPS may offer a chance of complete tumor removal and prolonged survival and even a chance for cure.

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Colorectal Cancer is the third most frequent cancer worldwide. Nearly half of the patients present either with liver metastases at the time of diagnosis or will eventually develop metastases during the course of the disease. Hepatic resection is currently the treatment of choice if a curative approach is intended offering 5-year survival rates of up to 50–60% depending on patient

selection. However, at the time of diagnosis, only a minority of about 15–30% of patients are candidates for upfront hepatic surgery [1–4]. Most often, multifocal intrahepatic tumor spread in both liver lobes, extensive tumor burden or diffuse extrahepatic metastases result in either technical or functional irresectability, or make a resection questionable from an oncologic point of view. On the other hand, although chemotherapeutic possibilities are steadily improving, patients not amenable to surgery hardly have a chance for long-term survival or even cure. In case of irresectable colorectal liver metastases (CRLM), the median overall survival ranges between 18 and 28 months in highly selected patient cohorts depending on several factors such as extent of liver involvement, presence of additional extrahepatic tumor, T and N stage, and molecular characteristics of the primary tumor as well as the individual response to modern systemic therapy including targeted therapy [5].

Over the past 3 decades, the therapeutic options for CRLM have steadily improved. The 2 most significant changes were the development of effective chemotherapy regimens and the introduction of preoperative liver volume modulation techniques. Thus, even patients with an extensive hepatic tumor load formerly deemed irresectable can now be offered a surgical approach and complete tumor removal with the chance of prolonged survival and even cure [3, 4, 6].

Several strategies have been developed to increase hepatic resectability. Two earlier milestones were the invention of portal vein embolization (PVE) to induce hypertrophy of the future liver remnant (FLR) and the introduction of chemotherapy in a down-sizing intention to achieve secondary resectability in patients with metastases initially considered irresectable [1, 7]. In 2000, two-stage hepatectomy (TSH) was introduced to enable the complete resection of bilateral multinodular hepatic metastases not amenable to resection in a single procedure, not even after effective downsizing chemotherapy [2]. However, the treatment of bilateral metastases in the setting of an estimated small FLR remained a big challenge. To cope with this problem, conventional TSH was further modified by combining tumor clearance of one hemi-liver with simultaneous contralateral portal vein ligation (PVL) or subsequent PVE to stimulate growth of the FLR [8]. The hypertrophy rates observed after 4–12 weeks following this approach usually range between 20 and 40% but can reach almost 60–70% in highly specialized centers. Reported survival data after TSH with and without PVE/PVL vary tremendously depending on patient selec-

tion criteria [9, 10]. The best results are comparable to outcome data after surgery for primarily resectable CRLM, with a 5-year-survival of about 30% and the best result being 64% if both steps are completed [11]. However, the risks inherent to this strategy are an ineffective liver hypertrophy on the one hand and a probable stimulation of growth of both the FLR and the tumor on the other hand. Thus, the time after stage 1 hepatectomy and PVE/PVL required to achieve sufficient hypertrophy of the FLR bears the risk of tumor progression. This has been shown in several studies where up to 25–38% of patients did not proceed to step 2, mainly due to a tumor progression and less often due to an insufficient volume gain [11–17]. Patients who fail to complete stage 2 hepatectomy have a poor survival similar or even worse than patients treated with chemotherapy alone [11–16]. These data underline the importance of the completion of the planned 2 stage procedure and the necessity of a complete tumor clearance.

In 2007, Prof. Hans J Schlitt [18] from Regensburg, Germany, performed, not necessarily on purpose, the first Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) procedure or, as it was and is still called in Germany the “in-situ split liver resection” in a patient with a hilar cholangiocarcinoma. This innovative concept to induce rapid hypertrophy of the FLR was soon adapted by many surgeons nationwide but was hardly recognized outside Germany [18]. In 2012, the first report of 25 cases from 5 German centers was published, including 14 patients with CRLM. In the inaugural paper, a rapid growth of the FLR with a median hypertrophy rate of 74% after 9 days and a 100% resection rate in patients with otherwise irresectable tumors were reported [19]. This first presentation of ALPPS attracted tremendous international interest and hepato-pancreato-biliary (HPB) groups from all over the world began to work in the field of ALPPS. Shortly thereafter, further reports confirmed the initial promising results and, in addition, it could be shown that ALPPS was effective even after the failure of PVE [20–26]. In an early retrospective analysis at 4 specialized HPB centers comparing data of ALPPS and extended hepatectomy following PVE/PVL, complete tumor resection was significantly better in ALPPS with similar survival rates. This was insofar remarkable, as ALPPS was mainly applied in cases with a higher tumor burden not amenable to conventional resection after PVL/PVE [27]. Although achieved in a non-matched comparison, this finding suggested at least an oncologic non-inferiority of ALPPS compared to extended hepatectomy after PVE/PVL. These data intrigued a growing in-

terest in ALPPS as a new and curative surgical treatment option also in patients with extensive colorectal hepatic tumor burden. Median hypertrophy rates of 160% (range 93–250%) in selected cases even permitted resections of all but one liver segment, the so-called monosegment ALPPS [28, 29]. In 2015, Schadde et al. [29] reported 12 cases of “monosegment ALPPS” without any postoperative mortality.

However, the early enthusiasm about ALPPS cooled off when a high mortality rate of 12% (3/25) in the initial series became apparent and quite a number of surgeons then raised their concerns regarding the safety of the ALPPS procedure [30–32]. It is important to note that in the initial report, the 3 patients who accounted for the postoperative mortality were patients with CRLM who had undergone preoperative chemotherapy. However, the high complication rate was attributed to the newness of the procedure and supposed to lower in the course of time with increasing experience. With regard to the indication, subsequent reports could show that for CRLM, which is by far the most frequent indication for an ALPPS procedure, the complication rates were lower than those for primary hepatobiliary malignancies [33]. Nevertheless, complication rates after ALPPS for CRLM still seemed to be higher than after conventional liver resection, this, however, not considering a selection bias in the ALPPS group of patients with more advanced disease who otherwise would have been treated either by palliative chemotherapy alone or by extended hepatectomy after PVE and PVL [34].

As for any new surgical procedure with increasing experience, there were several modifications to reduce morbidity and improve outcome. Improvements have been achieved by proper patient selection and in particular by refining the surgical technique mainly aiming at reducing post-stage 1 morbidity [35–39]. Main advances have been attributed to the preservation of the middle hepatic vein during first-stage hepatectomy, leading to the concept of an only partial hepatic transection named “partial ALPPS”. Most important, the transection of only 50–80% of liver parenchyma is associated with a significant reduction of perioperative morbidity but does not appear to compromise the extent of the hypertrophy induced [39–40]. Complete transection of the liver parenchyma during stage 1 is now left to those situations where tumor invasion into the FLR in between stages is to be avoided. Other modifications, such as the combination of partial ALPPS and PVE either simultaneous (“Mini ALPPS”) or subsequent, aimed to further limit post-stage-one morbidity by avoiding surgical manipulation of the hepatic hilum [35, 41].

Most recently, laparoscopic ALPPS was shown to further decrease the invasiveness of both stages [42].

All these technical refinements and an improved patient selection led to a stepwise reduction of the perioperative complication rate of ALPPS [34, 35, 43, 44]. In the second large publication from the ALPPS Registry, a mortality rate of 5% for CRLM after stage 2 has been reported, which came near the reported mortality after major conventional hepatectomy [45]. A recent single-center analysis reported a zero-mortality at 90 days in 17 ALPPS cases many of which were performed after extensive preoperative chemotherapy. The data confirm that even after chemotherapy there is a low perioperative complication and mortality rate possible in ALPPS [44]. Two most recent publications of the ALPPS Registry in 2016 and 2017 noted a continuous drop in risk-adjusted early mortality and morbidity [46, 47]. While a meta-analysis by Moris et al. [48] still accounted a higher morbidity and mortality in ALPPS but with no difference in liver-related mortality data of the first, and so far only randomized controlled trial (RCT), the most definite way to compare ALPPS versus TSH/PVE, showed no difference in the perioperative complication (Clavien-Dindo grade III–IV) and the 90-day-mortality rate. These data clearly suggest that with improved technical experience and patient selection, ALPPS should no longer be considered a much riskier operation than TSH [48, 49].

The second major concern in ALPPS is about its oncological benefit. The early enthusiasm about increasing resectability in patients with even extensive tumor burden was paralleled by reports about early and rapid growing tumor recurrence in many cases. The assumed pathological mechanism is the simultaneous massive stimulation of hepatocellular hypertrophy as well as growth of residual tumor cells in the FLR. However, clinical as well as experimental data are controversial and need further investigation. While some authors described an earlier tumor recurrence in admittedly very small series, the meta-analysis by Moris et al. [48] showed similar tumor recurrence rates for TSH and ALPPS [50]. However, since there is a great variability in indications and patient selection for TSH and ALPPS from center to center, it is most likely that comparability of data is limited. The only RCT comparing ALPPS and TSH did not analyze the oncological outcome and therefore cannot help to answer this question. We have to wait for further RCTs to evaluate whether ALPPS is associated with a higher or faster rate of tumor relapse.

One proposed benefit of ALPPS is the rapid regeneration of the liver compared to PVL/PVE. Indeed, the ki-

netic growth rates seen with ALPPS (about 22–35 mL/day) are almost tenfold higher than with TSH plus PVE (about 3–5 mL/day) [51, 52]. This difference is still difficult to explain but may be attributed to a systemic response to the additional parenchymal transection. Apparently, the degree of hypertrophy observed after ALPPS step 1 does not seem to be hampered by preoperative chemotherapy, but data are controversial [44, 53, 54]. Similarly, data regarding proliferation indices (Ki67 index) are contradictory in literature. While Fukami et al. [55] found an increase in Ki67 from 60 to 80% between step 1 and 2 in ALPPS, Joechle et al. [56] did not reveal any difference in Ki67 between ALPPS or conventional hepatectomy.

It still remains a matter of debate whether the enhanced liver recovery is a curse or blessing. Of note, some authors have argued that a slower hypertrophy rate may be beneficial not only because of the assumed lesser stimulus of tumor growth but also because of the longer waiting time in between steps allowing a better assessment of tumor growth and thereby a better patient selection.

Indeed, after PVE/PVL alone or in combination in the setting of TSH – with the latter having an even better chance to detect and remove small tumor deposits and metastases during step 1 – up to 24–41% of patients do not undergo stage 2 hepatectomy, mainly due to disease progression [12, 13, 16]. In an analysis by Narita of 80 intended and 61 performed TSH (dropout rate 24%), more than 2 CRLM detected in the FLR during step one were a negative predictor of not achieving the second step [16].

In ALPPS, the time interval in between step 1 and 2 is with usually only 7–14 days much shorter than in TSH. This interval is too short to detect newly developing tumors in the FLR. Thus, almost all patients are subjected to both stages and a high rate of formally complete resections is achieved. This was shown in both data of the ALPPS registry and also the recently published first RCT comparing ALPPS and TSH for FLR <30% (LIGRO trial). Resection rates were significantly superior in ALPPS versus TSH (92 vs. 57%, $p < 0.0001$) with comparable surgical margins and perioperative morbidity and mortality [49].

Compared to TSH, the detection of tumor progression after ALPPS has shifted from the interstage period to the post-stage 2 period, meaning that a substantial number of patients are subjected to the risks of stage 2 but already have micrometastases in the FLR. This is endorsed by a meta-analysis comparing ALPPS and TSH where despite a higher resectability rate in ALPPS, disease-free survival is the same in both groups [48].

Long-term oncologic data are almost missing. In an initial report of ALPPS, the 1- and 2-year OS was 76 and 63% for CRLM respectively [33]. However, these survival data need to be seen in the light of the high initial perioperative mortality of 9% and, even more important, considering that ALPPS patients might have had more extensive hepatic disease compared to patients undergoing other procedures. In a recent series from 2 high-volume centers, a 3-year overall survival of 50% was reported after 58 ALPPS for CRLM. In another admittedly small single-center analysis with 7 cases only, a 3-year survival of even 64% was reported [57, 58].

So far, only few series appeared comparing data of ALPPS and TSH, showing, crossly looked at, no survival difference [12, 59–61]. While Adam et al. [12] reported a significant difference in median survival (ALPPS 20 months, TSH 37 month), Ratti et al. [60] and Kambakamba et al. [61] found a similar 1-year survival (94 vs. 92%) and mean survival (24.7 ± 2.3 vs. 29.3 ± 5.1 months), respectively, with also no difference in 1-year disease-free survival in both series.

It is unique in all publications that patients undergoing stage 1 but not completing stage 2 have the worst prognosis, even worse than CTx only [11, 12]. This is probably owed to the delayed onset of chemotherapy and/or a reduced physical condition after stage 1 operation in this subset of patients. Having in mind the poor survival if stage 2 is not completed, it is not surprising that the question arises whether a dropout after the first stage of TSH is truly an advantage for better selection rather than a loss of chance for the patient [62]. In this match pair analysis, Vigano et al. [62] compared the results of TSH versus ultrasound-guided one stage hepatectomy (OSH) in 2 high-volume centers of liver surgery. The 2 main findings were the significantly higher dropout rate in TSH than in OSH (38.1 vs. 0%), and that the completion of resection was the only independent prognostic factor [62]. Consistently, survival curves after OSH and completed TSH were comparable. These findings could be an indicator that stimulation of hypertrophy in the presence of tumor – as in TSH – does not lead to an impaired outcome if complete tumor clearance can be achieved subsequently. On the other hand, these findings do not at all exclude that enhancement of hypertrophy promotes tumor growth – as suggested by experimental data where no progression of tumor growth was seen in ALPPS in a mouse model [63]. However, data are still controversial and require further investigation.

Certainly, we need to look at and compare the data of this study carefully, in particular with regard to the very

low R0-resection rates of 19% in OSH and of only 15.9% in TSH. It is noteworthy that the median number of nodules was 7 in both arms, with almost 30% of patients having more than 10 metastases, a situation where diffuse intrahepatic spread is the rule and where it is unlikely to achieve high rates of tumor-free survival, regardless of the surgical strategy applied. In this setting, it hardly matters that R0-resection rates are low, and it is not at all surprising that overall and disease-free survival are similar for OSH and completed TSH. In subsequent reports with higher numbers of patients, Torzilli et al. [17] could confirm that parenchymal sparing is safer than major hepatectomy with a tendency to result in an even better survival [64, 65].

The charm of this approach is – next to avoiding the morbidity of a second or (in case of PVE) a third operation/intervention – minimizing parenchymal loss but at the expense of a high risk of incomplete tumor resection. By doing so, the concept of OSH challenges the basic rules of surgery for CRLM. Although in recent years the potential benefit of an R1-resection has been pointed out – in particular in the setting of multifocal CRLM with good response to chemotherapy – R0-resection is still the standard goal of surgery for CRLM [66, 67]. In OSH for multifocal CRLM, however, R1-resection is widely accepted, the more as also the detachment of metastases from major vascular structures (R1 vascular margin) has been shown to be almost equivalent to R0 resection [68, 69].

In contrast to this, the goal in TSH is the achievement of an R0-resection, as it is also in ALPPS. In a recent analysis, the achievement of an R0 resection still was 1 prognostic factor. Importantly, a margin >1 mm is associated with improved overall survival, while a margin >1 cm is even associated with an improved disease-free survival [70]. Needless to say, in numerous metastases, a safety margin of 1 cm is hardly to achieve. In contrast, in limited numbers of metastases, even if extensive in size, a wider safety margin could be possible. A better oncologic result might even justify the loss of large amounts of parenchyma. Most recent data from the MD Anderson showing a 5-year survival of 35% after TSH versus 23% OSH in a retrospective analysis support this approach [71].

In order to achieve tumor-free resection margins (R0-resection) in TSH and ALPPS, complete tumor clearance of the FLR during step 1 is paramount. Thus, the number and size of metastases in the FLR seems to be of greater importance for the success of these procedures than the total tumor burden [72].

An exact and comprehensive characterization and documentation not only of lesion number, size, and distribution in the liver and the FLR but also of other factors such as kind and intensity of oncological pretreatment, molecular characteristics, etc. will help to enhance the comparative studies of our data. KRAS mutations have been shown to be associated with a worse survival after resection of CRLM in a preliminary report, in particular, also in ALPPS [73, 74]. A finding like this will sharpen our selection criteria and help to avoid most probably futile and high-risk surgery. Furthermore, these data form the basis for future trials to further compare OSH, TSH, and ALPPS in the management of bilateral CRLM.

In order to find the role of ALPPS, it is worthwhile considering how therapeutic options have changed for patients with CRLM [32, 75]. Next to improvements in surgical techniques, the development of effective chemotherapy along with targeted therapy led to much better response rates and tumor shrinkage. Nowadays, converting therapy is one of the cornerstones in the treatment of CRLM. Effective downsizing does not only in higher resectability rates but also result in more parenchymal sparing resections instead of major hepatectomies. There is no doubt that with advances in chemotherapy and biologicals, the need for major hepatectomies for CRLM has considerably reduced. It is now not uncommon that patients have numerous operations/interventions/ablations over years in combination with chemotherapy or followed by periods of chemotherapy. Importantly, all these interventions and procedures can be done with low morbidity, and nowadays, overall operative mortality rates after surgery for CRLM is below 2% in most specialized hepatobiliary centers. Of note, a randomized comparison with palliative chemotherapy only is not available so far and certainly will be difficult to achieve. A recent case-match study from the ALPPS registry compared otherwise irresectable “ALPPS patients” to historic controls receiving palliative chemotherapy and concluded a non-superiority in early oncological outcome in the ALPPS group [76]. It has to be pointed out, however, that with a median of 7 liver segments affected and a median of 4 lesions in the FLR, the disease in the surgical group was far advanced, most likely too advanced for a surgical approach. It is not possible to outsmart tumor biology, and thus these data have to be regarded as a failure of patient selection rather than of the concept of ALPPS.

These are the hallmarks against which ALPPS has to be measured, and it is in this context that ALPPS has to

be placed in. In view of this, it does not seem appropriate to consider ALPPS when an already “established” conventional surgical approach is feasible [18, 75, 77]. Thus, ALPPS is the last resort at the end of the spectrum in the treatment of CRLM, and here, where patients have no surgical alternative to ALPPS, its oncological outcome needs to be compared to modern palliative chemotherapy alone or in combination with locoregional therapy.

At our own institution, since the beginning of our ALPPS program in 2009, out of almost 800 liver resections for CRLM (nearly half of them for bilateral metastases, overall perioperative 90-day mortality rate below 1%), we performed 8 ALPPS, thus accounting for about 1% of all resections for CRLM only. ALPPS was done after a median of 7 months of chemotherapy (range 4–11 months) and all resections performed were exclusively right trisectionectomy, with additional excision of segment I ($n = 4$) and excision of 1–3 metastases out of the FLR ($n = 4$).

In conclusion, ALPPS has undoubtedly expanded the surgical armamentarium for patients with CRLM once deemed unresectable due to a high tumor load and a small FLRV, as shown in the so far first and only RCT on ALPPS versus TSH. However, the benefit of such an aggressive approach is still unclear. As always in oncologic surgery, biology is key and can be hardly overcome, in particular, not by surgery alone. This is in particular true in multifocal or diffuse intrahepatic disease. In order to place ALPPS in this context, we need to weigh what can be achieved and gained by surgery in a multimodal setting. Initial concerns regarding the safety of this novel procedure have triggered

tremendous efforts to reduce morbidity and to improve perioperative results. Due to technical refinements, mainly aiming at a reduction of post-stage 1 morbidity and at a better patient selection, overall morbidity and mortality rates have improved and are now comparable to major conventional liver resections. The oncological value in the face of early tumor recurrence in a substantial number of patients remains unclear, and the oncological outcome of patients with advanced bilateral liver metastases undergoing ALPPS does not seem better than that in patients after TSH. A valid comparison with TSH/PVE is missing, as the only RCT on ALPPS versus TSH did not take into consideration the oncological outcome. Clearly, ALPPS does not replace other surgical techniques but certainly ALPPS has its place in the armamentarium of experienced liver surgeons. As long as robust data regarding oncological outcome are missing standard TSH or preoperative PVE might be preferable. TSH and ALPPS might be complementary strategies for resection of CRLM with ALPPS being reserved for patients with no other surgical option, that is, after failed PVE or those with an extremely small FLR. In these individual situations, and always embedded into a multimodal treatment setting, ALPPS may still offer a chance of complete tumor removal and thus prolonged survival and even a chance for cure.

“Biology is King, selection of cases is Queen, and the technical details of surgical procedures are the Princes and Princesses....” [78]. We need to have this in mind when trying to define the role of ALPPS in the treatment of CRLM.

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