Editorial

Improving the safety of associating liver partition and portal vein ligation for staged hepatectomy

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Liver resection is the only potential curative treatment option in patients with colorectal liver metastases (CRLM). Between 15–25% of the patients are primarily resectable, whereas in the majority of patients, the extent of and biological behavior of the disease, anatomical proximity to vital hepatic structures and insufficient future liver remnant (FLR) precludes resection. Modern chemotherapy has provided vast improvement by providing downsizing of tumors and various methods like portal vein embolization (PVE) and two stage hepatectomy have been established as standard practice in order to increase the number of patients that can be offered resection (1,2). Association liver partitioning and portal vein ligation for staged hepatectomy was first reported in a small case series from Germany in 2010, and was more formally published and described in 2012 as a novel technique to induce rapid volume growth of FLR (3). The method has, however, been regarded as controversial and evoked debates due to high procedure related morbidity and mortality rates, that does not seem to be merely related to lack of experience, since it has also been reported from experienced referral HPB centers (4,5). The mortality risk associated with associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) by far exceeds the standards commonly associated with liver resection for metastatic disease. Cause of perioperative death has in particular been attributed to liver failure and infectious complications.

In 2012, an international voluntary ALPPS registry was formed, enabling the collection of a significant part of the world experience on this procedure. Linecker and coworkers have recently published a paper evaluating the risk of futile outcome, defined as mortality within 90 days following ALPPS in the Annals of Surgery (6). The material consists of 528 cases from 38 centers. The number of deaths was 47 (9%) with 18 patients (38%) and 45 (96%) dying after 1 and 3 months respectively. Two additional patients died in hospital beyond 3 months. Based on this population, the authors have calculated the relative risk for futile outcome, divided into pre stage 1 factors and pre stage 2 factors. The risk scores were modeled on the basis of factors significantly related to lethal outcome within 3 months in multivariate regression analysis. For pre stage 1, non CRLM/non biliary tumors, biliary tumors and age above 67 years were found to be closely related with futile outcome and given risk points of 1, 2 and 3 respectively. Thus, the pre stage 1 risk score has a range of 0–5, and the model was able to predict 90 day mortality risk of 2,7%, 4,9%, 8,6%,15%, 24% and 37% based on scores 0, 1, 2, 3, 4 and 5 respectively. The incidence of major complications (Clavien-Dindo ≥3b) after stage 1 was 10% in the cohort. Patients with a futile outcome had significantly more interstage major complications (33% versus 7%) and a higher incidence of liver failure as defined by the International Study Group of Liver Surgery criteria (ISGLS). As one might anticipate, signs of organ dysfunction and/or failure during the interstage interval was predictive of mortality. Consequently, the variables for the pre stage 2 risk score were elevated bilirubin and creatinine

before stage 2 together with the pre stage 1 risk score itself and the presence of major interstage complication (≥3b). Risk points were calculated based on the regression coefficients in the model. The pre stage 2 risk score was able to predict 90 day mortality of 5%, 10%, 20% and 50% for scores of 3.9, 4.7, 5.5, and 6.9 respectively. The leading causes of 90 day mortality in the whole cohort was sepsis, (38%), liver failure (36%) and carcinogenic shock (11%).

The risk factors identified are plausible, and in concordance with clinical experience and the recent literature. Recent studies indicate that patients with biliary tumors are at a particular risk of complications and perioperative death when undergoing ALPPS surgery (7). A national audit among Italian centers demonstrated that elevated interstage bilirubin levels and an indication of biliary tumor were predictors of high mortality, and the authors suggested a moratorium on the ALPPS procedure for biliary tumors (8). Although it has been demonstrated in numerous publications that safe HPB surgery is feasible and safe in advanced age, there are accumulating evidence that there is a significant risk associated with elevated age when it comes to ALPPS (9,10). In the current study by Linecker, continuous age did not offer any advantage as compared with the cutoff value of 67 years.

The clinically most important message form this report is the suggestion that we can reduce the elevated risks associated with the ALPPS procedure by consideration of these factors and thereby improving patient selection. Furthermore, the results highlight the importance of liver and other organ dysfunction during the interstage course. The median time between stage 1 and 2 in this study was 10 days (8–14 days). The reported results could indicate that the interstage interval should not rely on volume hypertrophy of FLR alone, but that any significant aberration in liver or other vital organ function mandates a consideration of postponing the stage 2 procedure until organ dysfunction and complication have been resolved.

The fast gain in volume growth of the FLR has been the major attraction and marketing value of ALPPS, suggesting that this can solve the problem of a small FLR in many patients that would otherwise be deemed inoperable. The gold standard in most HPB departments is PVE/portal vein ligation (PVL) giving satisfactory hypertrophy of the FLR in 60–80% of the cases. An important question is what ALPPS can do for those failing on PVE. The LIGRO trail (https://clinicaltrials.gov/ct2/show/NCT02215577) running in Scandinavia will hopefully provide these data.

The mechanisms underlying the extraordinary hypertrophy seen by the ALPPS procedure are not fully understood, but a complex interplay between portal flow diversion and the release of growth factors and cytokines seems to be paramount to elicit this response (11). A major concern, however, is that there is no apparent linear relationship between volume increase of the FLR and functional reserve and in the report from Linecker and coworkers, the standardized FLR volume was not independently predictive of futile outcome, although the remnant volumes were significantly lower in the proportion of patients that died. This urges the need for a better understanding of the functional status of the FLR, particularly before the stage 2 procedure. Considering the causes of death in the current paper and in previously published studies, sepsis and liver failure seems to be the most prevalent conditions leading to lethal outcomes. It is likely, that the high incidence of sepsis observed, is closely related to liver dysfunction, since low liver volumes following resection are associated with impaired function of the reticuloendothelial system (12) and this may translate into higher infection rates in conjunction with liver surgery (13). Functional assessment of the liver remnant can be performed by a variety of approaches (14). Indocyanine green clearance test is the most widely used and performs better than clinical scoring systems, but cannot be applied for assessment of regional hepatic function. The Amsterdam group has studied 99mTc-mebrofenin hepatobiliary scintigraphy (HBS) and demonstrated that the technique can be used to study total and FLR function (15) and to assess the risk of post resection liver failure (16,17). HBS have recently also been applied similarly in the setting of ALPPS (18). A recent paper utilizing comprehensive functional measurements, suggests that dynamic chances in the FLR during the various stages of the ALPPS procedure are not synchronous. There seems to be an impaired functional reserve in the remnant liver, in spite of rapid volume growth after stage 1 and 2 of ALPPS, indicating that the functional recovery lags behind volume growth (19). As more and more centers are hopefully including objective functional assessment of the FLR, these findings can possibly be confirmed and lead to improved guidelines for how to improve the management of ALPPS patients.

The history of ALPPS is an illustration of how novel developments can have a somewhat unfortunate introduction into clinical practice. The early enthusiasm did lead to widespread use, without solid evidence for the mechanisms involved in rapid regeneration or for the risks

of the procedure. Thus, as with many other techniques and methods in clinical medicine, the early developments are often far from the IDEAL recommendations for surgical innovation (20). On this background, the founders of the international ALPPS registry and the authors of the ALPPS risk score should be complimented for their work to systematically collect the experiences with this procedure into prospective research databases and providing the surgical community with evidence based risk assessments that can improve the outcome of patients subjected to this operative procedure.

ALPPS is still in its early phase with regards to development, signified by the large number of alternative approaches that are being reported in the literature (21). When considering the published articles of the recent years, there seems to be a tendency towards less invasive surgical procedures for the stage 1 operation (22-24), and laparoscopic ALPPS have been described (25). Possibly, this could lead to lower incidence of interstage complications, thereby lowering the risk of mortality, but the evidence for this is still scarce. There is a substantial developmental work to be done with regards to improved patient selection, interstage management strategies as well as improved functional assessment of the liver remnant that must be done before we as a surgical community can claim that we have conquered the ALPPS and placed this method as a standard of care and part of the hepatobiliary surgical toolbox.

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Footnote

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