Playing Play-Doh to Prevent Postoperative Liver Failure

The “ALPPS” approach

Eduardo de Santibañes, MD, PhD,* and Pierre-Alain Clavien, MD, PhD†

The safe removal of extensive tumor load in the liver has been one of the main focuses of laboratory and clinical research for hepato-biliary surgeons over the past 3 decades.1 The first breakthrough is credited to Masatoshi Makuuchi, who in 1980s, introduced the concept of the portal vein embolization (PVE) of the right portal branch to induce hypertrophy of the left side of the liver, enabling a safer removal of large or multiple tumors, mostly located in the right hemiliver and segment IV.2 This technique was rapidly adopted by many to prevent liver failure after a variety of extensive right-sided hepatectomies.1,3 The next advance, about a decade later, was presented by surgeons at Hôpital Paul Brousse in Paris, France, with the introduction of sequential operations, referred to as “2-stage hepatectomy” to stepwise remove multiple liver tumors, with the aim of allowing the liver to regenerate between both procedures.4 Additional PVE was also used in a few patients. Soon after, Daniel Jaek and his colleagues from Strasbourg, France, developed another 2-stage approach for bilateral (predominantly right) tumor involvement. Using routine right PVE, after the initial removal of tumors located in the left hemiliver, the resulting hypertrophy of the left part of the liver (free of tumor) allowed a safer curative right or extended-right hemihepatectomy.5 Finally, the group from Zurich modified this approach by applying concomitant right portal vein ligation with wedge resections of all left-sided tumors during the first surgery, followed a few weeks later by an extended right hepatectomy.6 This modification was based on evidence that portal vein ligation triggers a similar or better regenerative response than PVE6,7 and could be safely applied, even in combination with partial hepatectomies of the left hemiliver. In a few patients with intact primary neuroendocrine or colorectal tumors, Belghiti and colleagues have also used portal vein ligation along with resection of the primary tumor.8 In many patients, those developments led to the successful removal of multiple, often bilateral, liver lesions otherwise felt to be unresectable. The drawback, however, was the need for long intervals between the 2 surgeries. The earlier techniques, without the use of selective portal vein occlusion, required a delay of 2 to 13 months before completing the second hepatectomy.4 The majority of patients in whom this approach failed, did so because they had developed disease progression in the meantime.4 With the advent of PVE, this period was dramatically shortened to 2 to 4 months,5 and with concomitant portal vein ligation to about 4 weeks.5 Other shortcomings included the insufficient hypertrophy of a putative remnant liver, preventing curative resection or, if performed, leading to postoperative failure due to “small for size” syndrome.3 In Figure 1, we show the development of the various types of staged hepatectomies.

The article in this issue of *Annals of Surgery* by Schnitzbauer and coworkers call out ref. 9 introduces a novel concept representing one of the most promising advances in oncological liver surgery so far. Contrary to many surgical innovations, this one was somehow developed by chance. In 2007, Dr Hans Schlitt from Regensburg, Germany, was planning an extended right hepatectomy in a patient with perihilar cholangiocarcinoma, but he realized intraoperatively that the future cholestatic liver remnant was too small to sustain the patient postoperatively. He took a good, but uncommon surgical decision, by performing only a selective hepatico-jejunostomy on the left biliary system. For the optimal positioning of the hepatico-jejunoostomy, he had to divide the liver parenchyma along the falciform ligament, thereby completely devascularizing segment IV, that is, an *in-situ* split as performed for pediatric liver transplantation. Finally, he ligated the right portal vein to induce hypertrophy of segments II to III. Out of curiosity, he performed a CT scan on postoperative day 8 and, to his surprise, found that the left liver had grown enormously. He decided to proceed with the removal of the diseased liver. The patient, who had been at risk of liver failure a week prior, tolerated the removal just fine.

After this successful case, Dr Schlitt deliberately applied this approach in a patient with extensive colorectal liver metastases and in another patient with a large cholangiocarcinoma. The enthusiasm for this approach was then shared with other surgeons, mostly from Germany, who used...
Many of these patients had extensive exposure to chemotherapy earlier. First, the new strategy elegantly addresses the most feared complication following major hepatectomies: “postoperative liver failure”. The diseased right hemiliver, left in place, acts as an auxiliary liver to assist the future liver remnant for the first and critical week after resection. In the meantime, cases and technical aspects were also reported by the group from Buenos Aires, Argentina. Schnitzbauer et al describe here the initial experience with respect to 25 cases performed in 5 German centers and thereby introduce, for the first time, a new strategy to deal with extensive tumor load that could change the face of liver surgery for many reasons (Figure 1). First, the new strategy defies this classic concept. Schnitzbauer et al report a 74% volume increase of the remnant liver in a mean of 9 days. We were able to confirm a consistent rapid increase in the size of the left liver within 1 week after the first surgery, and furthermore, we observed an even more dramatic increase in regeneration within a week after the removal of the diseased liver. In healthy livers, the maximum peak of regeneration is achieved at 2 weeks. The current technique defies this classic concept. Schnitzbauer et al describe in one patient features of hyperplasia in the histological examination of the remnant liver at the time of the second operation. We observed features of hepatocyte apoptosis in the diseased liver, and enhanced markers of hepatocyte proliferation in the remnant liver. We must assume that the combination of portal vein ligation, with a large inflammatory injury, and the absence of cross portal circulation between the 2 parts of the liver, by completely transecting the parenchyma has a profound effect on liver regeneration. The precise mechanisms behind this spectacular regenerative response, however, still need to be explored.

FIGURE 1. Strategies for safer removal of large or multiple liver tumors. A) Percutaneous portal vein embolization (PVE) of the right branch of the portal vein to induce hypertrophy of the contralateral left hemiliver, enabling safer right hemi-hepatectomy B) The two stage hepatectomy with sequential removal of different parts of the liver to enable regeneration of the liver between the two procedures. C) Two stage hepatectomy with removal of tumors usually in the left hemiliver followed by PVE, usually of the right branch of the portal vein, to induce hypertrophy of the left hemiliver. The second hepatectomy consists of a right hemi-hepatectomy. D) Two stage hepatectomy combining, in the 1st stage, removal of tumors in the left hemiliver and ligation of the right portal vein followed by removal of the right hemiliver during the second stage. E) The new approach presented in the issue of Annals of Surgery by Schnitzbauer et al. combining in-situ split usually between the left lateral sector and segment IV with ligation of the right portal vein followed by a right or extended right hepatectomy during the second operation. Removal of tumors in the left lateral sector can also be included in the first stage of the operation. We propose the acronym “ALPPS” to describe this novel approach: “Associating Liver Partition and Portal vein ligation for Staged hepatectomy”. Tumors are highlighted in yellow. The shaded areas indicate the removed part of the liver.
In most cases, the second hepatectomy has been a major challenge approached with earlier techniques of 2-stage hepatectomy, mostly related to the long interval between the 2 operations and the development of challenging adhesions. This initial series by Schnitzbauer et al, despite a shorter interval between the 2 operations, reports significant morbidity and 10% mortality (3/25). It is expected that increased experience with this procedure will lower the rate of complications.

Finally, laboratory tests that estimate liver reserve before liver resection may become obsolete as the “deportalized” auxiliary liver can be left in place during the critical regenerative phase of the future remnant liver, just like rubber boots in the operating room became unnecessary with less blood loss.

The novelty of this technique is the in-situ split, as labeled by the authors, leading to liver partition, which we believe, will likewise become standard in many specialized centers in the near future. Therefore, it is important to generate a self-explanatory and well-accepted denomination for this procedure. We propose the acronym “ALPPS” for Associating Liver Partition and Portal vein Ligation for Staged hepatectomy.

Some aspects of this demanding procedure require further discussion. The authors report waiting times between both surgeries of up to 28 days. However, in our opinion, the second step can usually be completed by postoperative day 7. Criteria other than volume would be welcome, especially to assess the function of the putative remnant liver. This might be particularly relevant in patients presenting steatosis, steatohepatitis, sinusoidal obstructive syndrome, or fibrosis. The raw surface of the diseased liver, being partially ischemic after the first step, might be associated with a higher risk of biliary leaks. With this in mind, the Buenos Aires group has wrapped the whole diseased-ischemic liver in a hermetic plastic bag with a drain inside it. This potentially prevents a chole-peritoneum and facilitates rapid completion of the liver resection. In their work, the German surgeons selected patients with a tumor-free left lateral section (segments II–III) for this approach. In contrast, we also removed tumors from the putative remnant liver, without the concern of ending this procedure with a small-for-size syndrome, because the contra lateral diseased lobe will act as an auxiliary liver.13 This technique should probably not be restricted for right trisectionectomy (segments IV–VIII ± segment I), but also for left trisectionectomy (segments I–V + segment VIII) and other atypical resections.

These complex procedures must be undertaken exclusively by experienced HPB surgeons in a high-volume center, and by means of a multidisciplinary team effort. The management of these patients during the postoperative course of both surgical procedures is crucial to achieve success. Further development of this procedure will require consensus regarding anesthesiology recovery, hemodynamic monitoring, management, antibiotics, early enteral/parenteral nutrition, and other issues to achieve the best results.

This novel strategy raises hope to cure patients during a single hospital stay from severe liver disease that might otherwise be judged unresectable by means of a 2-stage surgical approach. This technique readresses the current management of locally advanced liver malignancies and opens a new chapter in the history of liver surgery. The question of how well this new approach works in cirrhotic patients or after heavy chemotherapy has yet to be determined. Thanks to Dr Schlitt’s finding, many liver surgeons will be busy with this question for a long time.

Considering the 5 stages of the new surgical procedures “IDEAL” (Innovation, Development, Exploration, Assessment, and Long term), as proposed by the Balliol group17,18 the current multicenter pilot study fits with the first-stage “Innovation,” in which it involved highly selected patients and very few surgeons, and in which proper ethical approval is often problematic. This article clearly brings this new approach to the next step of “Development” involving more surgeons, more patients, a learning curve, and possible future randomized controlled trials, for example by comparing the ALPPS with earlier strategies, omitting the in-situ part.

REFERENCES