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EDITORIAL

How can we safely climb the ALPPS?

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R0 resection with zero mortality is the ultimate goal for hepatobiliary surgeons, especially for the treatment of extensive hepatobiliary malignancies. The safety of liver resection is dependent on the function of the future liver remnant (FLR), and an inadequate FLR volume is related to a significant increase in postoperative mortality and morbidity. Therefore, various criteria for the FLR volume have been proposed to secure the safety of major hepatectomies according to the extent of underlying injury in the liver [1–5]. However, these criteria for FLR volume often cause clinical dilemmas for surgeons in determining the surgical indications for patients with small FLR volumes because the safety of surgery and oncological radicality are, by nature, conflicting factors.

In the history of hepatobiliary surgery, there have been two outstanding approaches for the safe management of patients with very small FLR volumes. The first was the development of techniques that manipulate the portal blood flow to induce hypertrophy of the FLR. Initially achieved using portal vein ligation (PVL) [6–8], these techniques have evolved toward percutaneous portal vein embolization (PVE) [9–12]. Increasing evidence has suggested that hypertrophy of the FLR induced by portal flow modulation is associated with an improved safety of major hepatectomies [3, 10, 13]. In addition, dynamic volume parameters, such as the degree of hypertrophy [13] or the kinetic growth rate [14], are also very informative for estimating the histologic quality and functional reserve of the underlying liver. The second noteworthy approach was the "two-stage surgery" for the resection of multiple bilobar hepatic lesions. This sequential procedure was initially proposed by surgeons at the Hôpital Paul Brousse in Paris, France, with the expectation of allowing interim liver regeneration between the two sequential hepatic resections [15]. An oncological advantage of the two-stage approach has been reported in patients with extensive colorectal liver metastases [16], and this procedure used in conjunction with or without PVE has been adopted by numerous hepatobiliary centers. These two evolutional approaches have expanded the indications for surgery, and many patients with extensive liver tumors have benefited from surgery using these approaches. However, a remaining issue is that these approaches require at least several weeks to complete the entire clearance of the tumor burden within the liver. Some authors have suggested a risk of tumor progression during the waiting time after PVE [17, 18]. Therefore, the time lag between the preoperative intervention and resection can be critical, especially for the treatment of patients with borderline resectable tumors and/or oncologically highly aggressive tumors.

A recent notable paper in the field of hepatobiliary surgery was a case series introducing a new surgical procedure known as "ALPPS" (Associating Liver Partition with Portal vein ligation for Staged hepatectomy) that enables the rapid growth of the FLR [19]. The first stage of this procedure includes a right PVL and the in situ splitting of the liver along the umbilical fissure or the main portal fissure. Schnitzbauer et al. [19] reported that a 74 % volume increase was observed in the FLR at a median of 9 days after the first procedure. Immediately after its publication, this article triggered a large number of reactions from all over the world. Although the clinical outcomes demonstrated in this paper were very impressive and all the patients were able to proceed to a right

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Table 1 Reported outcomes of initial ALPPS experiences

	Institute	Years		Volume increase (%)	R0 resection (%)	Hepatic insufficiency (%)	Sepsis (%)	Bile leakage	Morbidity (%)	In-hospital mortality (%)
Schnitzbauer et al. [19]	Single	2012	25	74 (median)	100	–	20	24	64	12
Sala et al. [27]	Single	2012	10	82 (mean)	100	20	–	–	40	0
Alvarez et al. [22]	Single	2013	15	78 (mean)	100	20	–	20	53	0
Li et al. [28]	Single	2013	9	87 (median)	100	22	22	22	16	22
Clavien et al.*	Single	2013	13	–	100	15	23	–	–	23
Schadde et al.**	Multi	2013	47	–	79	–	–	–	–	15

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trisectionectomy very shortly after the first procedure, the morbidity rate (64 %) and the in-hospital mortality rate (12 %) were incredibly high, compared with those after a standard two-stage hepatectomy with percutaneous PVE (47 and 6 %, respectively) [20]. Subsequent reports from other institutions have shown similar outcomes, with the rapid growth of the FLR and high morbidity rates after surgery (Table 1). Of note, septic complications and bile leakage were observed in 20–25 % of the patients, and the in-hospital mortality rate was surprisingly high for this procedure. Considering these preliminary results, the safety of the ALPPS procedure remains questionable, and careful application is needed at this point in time, with the application of the procedure limited to experienced, high-volume hepatobiliary centers before encouraging this new technique to be performed worldwide.

Meanwhile, the reason for the rapid hypertrophy of the FLR observed with this procedure and the actual functional growth of the FLR are clinically important questions. Although the rapid growth of the FLR after the ALPPS procedure is very impressive, it remains difficult to compare the dynamic regeneration curve between ALPPS and a right + segment 4 PVE. As we reported previously, the hypertrophy of the FLR is negatively correlated with the pre-PVE FLR volume [18]. Because in situ splitting is usually performed along the umbilical fissure in the original ALPPS procedure, a very small portion of the liver (i.e., segment 2 + 3) will retain adequate inflow after the first procedure, similar to a right + segment 4 PVE [11, 21]. Thus, high-volume growth of the FLR can easily be expected in this setting. In addition, the initial volume evaluation is usually performed at 2–4 weeks after PVE, and the dynamic volume change during the very early phase after PVE remains unclear. Therefore, actual dynamic volume changes after ALPPS and right + segment four PVE should be first compared using animal models. Second, the mechanism explaining how the in situ splitting facilitates the regeneration of the FLR needs to be clarified. Because hepatic parenchymal transection is usually performed along the umbilical fissure (the segmental border between segment 3 and 4) or the main portal scissure (the boundary between the left and right hemilivers), it is incorrect to attribute the reason for the rapid growth of the FLR to the discontinuation of collaterals across these anatomical planes.

Recently, an international registry system for this procedure has been opened (http://www.alpps.net). This registry will contribute to the gathering of important clinical data and can be used as a basis for establishing adequate patient selection and improving the safety of this procedure. However, there seems to be several variations of the ALPPS procedure among the reported series (e.g., in situ splitting along the umbilical fissure vs. main portal fissure, ligation of the middle hepatic vein or not, ligation of the biliary tract or not, open approach vs. laparoscopic approach, etc. [22–27]). Technical standardization of the ALPPS procedure is needed before this registry system can be used to clarify the true safety of this procedure.

The ALPPS procedure is a potentially effective technique for patients with extensive tumors and very small FLR volumes. However, considering the several warnings that have been reported regarding high morbidity and mortality rates, it seems too early to compare this premature procedure with conventional, established approaches, such as PVE. To safely climb this newly found and challenging mountain, a Phase II randomized trial should be postponed until the current phase I process confirms the safety of the procedure by providing an acceptable morbidity/mortality rate compared with the current standard clinical practices.

Conflict of interest Both of the authors have no conflicts of interest to disclose.

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