Mini-Review

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Associating liver partition and portal vein ligation (ALPPS): Taking a view of trails

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Summary **Associating liver partition and portal vein ligation (ALPPS) is introduced as a modified two-staged hepatectomy for advanced liver malignancies, which requires extended hepatectomy with very small future remnant liver volume. It is characterized by rapid and large growth of future remnant liver and potential of widening the indication of curative resection with extended major hepatectomy for liver malignancies. It showed, however, much higher morbidity and mortality than extended hepatectomy after portal vein embolization. Here, we review the literatures and examine the role of ALPPS in Japan, where zero mortality after hepatectomy is highly expected.**

Keywords: ALPPS, Japan, hepatectomy, liver malignancies, liver volume, portal vein embolization

1. Introduction

The ultimate goal for liver surgeons in performing hepatectomy for hepatobiliary malignancies is complete resection of tumors with zero mortality. The morbidity and mortality after liver resection are associated with insufficient remnant liver volume and its function. Therefore, several methods to increase the future remnant liver volume before major hepatectomy, including portal vein embolization (*1*), ligation (*2*), sequential arterial and portal vein embolizations (*3*), and two-staged hepatectomy (*4*), were introduced. These techniques, however, usually required 2-8 weeks interval before completing the entire clearance of tumor burden in the liver and the risk of tumor progression during the period might be critical especially among the patients with borderline resectable tumors or oncologically aggressive tumors (*5,6*).

In 2011, Baumgart and colleagues reported *in situ* liver splitting through the umbilical ligament with concomitant right portal vein ligation, achieving future liver remnant (FLR) hypertrophy in 9 days in two-stage right trisectionectomy (*7*). A multi-institutional study was immediately started and 25 patients with marginally resectable liver malignancies were included (*8*). In the first operation, surgical exploration, right portal vein ligation and *in situ* splitting of the liver parenchyma along the falciform ligament were performed. Limited resections for tumors in future remnant liver were performed if necessary. Then after a median interval of days (range: 5-28 days) waiting period, the right trisegmentectomy was completed as second operation. The volume of the left lateral lobe was increased in a median volume ratio of 74% (range: 21%-192%), which is rather larger comparing with the increasing volume ratio of 10-20% in several weeks after portal vein embolization (PVE). The morbidity ratio was, however, up to 68% and 14% of the patients were died within a short follow-up period of 180 days in median (range: 60-776 days) after surgery (*8*).

This new technique is named as "associating liver partition and portal ligation for staged hepatectomy (ALPPS)" and several authors demonstrated successful cases with the similar procedures (Table 1). Most of all the following studies showed 60% or more increment of remnant liver volume and 100% R0 resection rate. Nevertheless, the postoperative short-term outcome is not satisfactory showing that high incidence of morbidity (mostly over 50%), postoperative liver failure (around 20%), and in-hospital mortality was up to 10-20%. An international registry study, in which 56 institutions from all over the world took part, showed the result of analyzing 202 patients (141 patients with

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Table 1. Review of literature on ALPPS

Items	Year	*n*	Diagnosis	Liver Regeneration* (%)	Interval (days)	Morbidity (%)	Hepatic Insufficiency (%)	Sepsis (%)	Bile leakage (%)	In-Hospital Mortality (%)
Schnitzbauer	2012	25	HCC 3 Mets 16	74	9	64	-	20	24	12
Sala	2012	10	HCC 1 Mets 7	82	7	40	20	-	-	0
Alvarez	2013	15	HCC 1 Mets 13	78	7	53	20	-	20	0
Li	2013	9	Mets 3	87	13	16	22	22	22	22
Schadde	2014	48	HCC 3 CRLM 26	74	-	-	-	-	9.3	15
Knoefel	2013	7	-	65	6	71	0			0
Gauzolino (variations)	2013	4	CRLM 4	27.8	7	75	0	-	25	0
Robles (ALTPS)	2014	22	HCC 1 Mets 20	63	11	63	23	-	23	9
Ratti	2014	6	CRLM 3	58.3	7.5	50	0	-	-	17
Gall (RALPP)	2015	5	CRLM 5	62.3	21.8	20	0	0	0	0

HCC: hepatecellular carcinoma, Mets: metastatic liver tumors, CRLM: colorectal liver metastases, ALTPS: tourniquet in the umbilical fissure and right portal vein occlusion, RALPP: radio-frequency-assisted liver partition with portal vein ligation. * Liver regeneration ratio is showed as the ratio of increased volume to the future remnant liver volume before first operation.

colorectal liver metastases) who underwent ALPPS from 2012-2013 (*9*). Median future remnant liver volume ratio was increased from 21% to 40% for standardized future liver remnant (sFLR) within a median of 7 days. Ninety-day mortality was 9%. Severe complications including mortalities (Clavien-Dindo ≥ IIIb) occurred in 27% of patients.

Although this procedure is discussed vigorously in famous journals of surgery, the practical advantage of ALPPS is still under debate because it showed a high morbidity and mortality rate and the oncological benefits of the aggressive resection are not proven.

2. Problems of ALPPS

The ALPPS is potentially effective procedure for patients who requires super extended liver resection to achieve curative resection of extensive liver malignancies. The most notable phenomenon is the rapid liver hypertrophy. Schadde *et al*. calculated the speed of liver hyperatrophy during the waiting period before final hepatectomy and showed that the extrapolated growth rate was 11 times higher in ALPPS (34.8 cc/day; interquartile range 26-49) compared with PVE/PVL (3 cc/day; IQR2-6; $p = 0.001$). Attention should be paid, however, to the difference of waiting periods between ALPPS (1-2 weeks) and PVE/PVL (4-8 weeks) in order not to overestimate the impact of ALPPS on liver hypertrophy. The kinetic growth curve of liver regeneration is always convex upward.

The enlarged volume of liver is not always parallel to the increment of liver function, as is often the case with recipients of living-donor liver transplantation who show considerably enlarged transplanted liver graft and are suffering persistent liver insufficiency with hyperbilirubinemia. The effect of inflammation in the ischemic and congestive area in the part of liver with vascular modulation can induce the edema of liver.

An experimental model using mice gave important information about the mechanism of accelerated hypertrophy in ALPPS (*10*). In the experiment, the mice which underwent either transection or PVL alone received plasma from ALPPS-treated mice or the mice which were subjected to splenic, renal, or pulmonary ablation instead. Injury to other organs or ALPPS-plasma injection combined with PVL induced liver hypertrophy similar to ALPPS. This result supports the hypothesis that liver damage after the first procedure of ALPPS raises inflammatory signals and promotes the liver hypertropthy.

It might be misunderstood that no ischemic area except for a small part of transected segment IV or limited resections are remained in the first operation. Portal flow in veno-occlusive area (congestive area), however, becomes hepatofugal (*11*) and the congestive area can theoretically change to ischemic when the portal vein was occluded. The process of liver splitting along the Rex-Cantlie's line or right side of falciform ligament is always accompanied with division of hepatic venous tributaries and congestive area appears.

Therefore, larger area than expected can change to be necrotic after the first operation accordingly and such complete devascularized area may become a source of severe sepsis (*12*). The occurrence of bile leakage in ALPPS is reported up to around 20%, which is much higher than that in ordinary hepatectomy (< 5%) (*13*). As several authors commented that bile leakage was associated with sepsis, it is possible that bile leakage in ALPPS reflects a large area of liver parenchymal necrosis, because the dark red colored discharge from the necrotic area in liver usually contains high levels of bilirubin.

Although complete resection of liver malignancy by ALPPS procedure is safely achieved, the long-term benefit of aggressive surgical treatment is still unclear, especially for the patients with multiple bilobar colorectal liver metastases or hilar cholangiocarcinoma progressing into the peripheral biliary tree.

3. Modification of ALPPS

According to the original procedure of ALPPS, most of the procedures were performed in the first operation and the right liver and ischemic segment IV put in the plastic bag was removed in second operation. Several modifications of the first operation to lower invasive procedure were proposed aiming at reducing the damage and obtaining better patient's condition with same rapid liver hypertrophy before second operation. Robles *et al*. introduced a liver tourniquet ligation method instead of splitting liver. A tourniquet was positioned around Rex-Cantlie's line between the right and middle hepatic veins used in the hanging maneuver and it was knotted tightly on a groove 1 cm deep which was made along the Rex-Cantlie's line. They showed 61% (33-189%) increasing of FLR after 7days and liver failure ratio was 23% and two of included 22 patients were died after the second operation (*14*). Machado *et al*. reported that total laparoscopic right portal vein ligation combined with *in situ* splitting is feasible (*15*). Gall *et al*. reported 5 cases of radio-frequency ablation along Rex-Cantlie's line instead of splitting liver. This procedure showed better liver regeneration ratio than PVE (64.3% *vs*. 24.8%) and no mortality among all the included 5 cases. Petrowsky *et al*. showed improved postoperative morbidity and mortality and similar rapid future remnant liver hypertrophy by modifying the liver splitting procedure, *i.e*., by switching from complete transection to a well-defined partial transection (> 50% of the transection surface). They hypothesized that sparing complete liver splitting can reduce the liver injury after the first operation by rescuing the "deportalized" part of the liver from congestion and ischemia (*16*).

4. ALPPS in Japan

Several high volume centers in Japan adopt ALPPS as an option of aggressive treatment for advanced colorectal liver metastases. It is difficult, however, to find a sign of the prevailing tide of ALPPS. The high mortality rate up to 10-20% in ALPPS cannot be easily accepted in Japan because the mortality rate of hepatectomy is reported less than 2% in a nationwide surveillance program and most of high volume center perform hepatectomy with nearly zero mortality (*17*). Furthermore, there is little limitation for performing portal vein embolization. A few institution indicated liver partition for patients who had insufficient volume increase and impaired liver function after portal vein embolization as an extension of ALPPS (*18*).

As Kokudo *et al*. pointed out that the ALPPS procedure can be said as a clinical study still under phase I (*19*), the most important issue is to modify this procedure safer and to establish indication criteria to select the cohort of patients who have best risk-benefit balance to adopt this procedure.

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