Review Article

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ALPPS readdresses the management of advanced liver tumors

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ABSTRACT

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been developed to induce rapid liver hypertrophy of the future liver remnant (FLR) prior to hepatectomy in primarily non-resectable or marginally resectable liver tumors. In recent years, this novel strategy has aroused interests of many liver surgeons. Its indications have been broadened gradually with more and more reported cases. Modified ALPPS is also developed to reduce morbidity and mortality. The authors searched Medline and PubMed to identify related articles published in English, using terms: "ALPPS, associating liver partition and portal vein ligation for staged hepatectomy, in situ split, in situ splitting, liver partition". The authors summarized and analysed the superiority, indications, modifications, safety, mechanisms of regeneration of ALPPS was more effective than traditional portal vein embolization (PVE) or portal vein ligation (PVL). ALPPS obtained 80% volume increase of future liver remnant (FLR) within 7 days in contrast to 10%-46% within 2 to 8 weeks by PVE or PVL. ALPPS opens a chapter in the history of liver surgery and readdresses the management of advanced primary and metastatic liver tumors. The high morbidity and mortality associated with ALPPS could be decreased remarkably if we carefully select patients and carry out the operation with experienced surgeons. In addition, the safety, mechanisms and oncological outcome of ALPPS are still not clear, which need further research and randomized controlled trials.

Keywords: Associating liver partition, Advanced liver tumors, Future liver remnant, Liver regeneration, Modified ALPPS, Portal vein ligation for staged hepatectomy

INTRODUCTION

Radical hepatectomy with clear surgical margins remains the only potentially treatment for primary or metastatic hepatic cancer. However, postoperative liver failure is one of the greatest risks and serious complications following major hepatectomy due to future liver remnant (FLR) is too small in volume. A newly reported technique named associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) can induce adequate and rapid hypertrophy of the FLR, thereby

increasing the resectability in primarily non-resectable liver tumors.¹

THE EMERGENCE AND CHARACTERISTICS OF ALPPS

The first ALPPS case was performed by Dr Hans Schlitt from Germany in 2007 by chance, following Baumgart et al formally reported this novel approach as a series of 3 cases. And then, the acronym" ALPPS" was proposed by de Santibanes and Cla-vient to describe this technique.²

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In recent years, more and more cases have been reported (Table 1). ALPPS is characterized by rapid hypertrophy of FLR, high feasibility and auxillary role of dis-eased hemiliver during interval between two operations. Schnitzbauer et al described their initial experience with 25 cases, and they obtained 74% median volume increase within 9 days.1 Schadde et al reported 80% volume increase of the FLR within 7 days, which were concluded from 202 cases in multi-center.3 In sharp contrast, traditional approaches such as portal vein ligation (PVL) or portal vein embolization (PVE) only obtained 10%-46% volume increase within 2 to 8 weeks. The feasibility (ALPPS stage 2 performed) was 97%, and the R0 resection was 91% according to the meta-analysis on 295 ALPPS cases reported by Schadde et al.4 Furthermore. the diseased hemiliver which will be resected in subsequent operation acts as an auxillary liver during interval, and it still provides more than 60% of total liver function at 6 days after the in situ spitting (ISS), according to de Santibanes by means of assessing the uptake of 99m Tc HIDA.²

INDICATIONS AND CONTRAINDICATIONS OF ALPPS

The indications of ALPPS are broadened, but It is proposed to carefully assess FLR volume before operation. Patients with normal hepatic function can tolerate ap-proximately 30% of FLR volume, but more than 40% of FLR volume is recommended in patients with cirrhosis or previous liver injury. Truant et al proposed that FLR to body weight ratio more than 0.5% is considered to be safe. The patients who can't tolerate conventional hepatectomy could be the candidates for ALPPS while the contraindications are excluded. Poor medical conditions, unresectable liver metastasis tumor and extrahepatic metastasis tumor are considered to be the contraindications of ALPPS. The colorectal liver metastasis (CRLM) has been the most common and effective candidate for ALPPS in recent years.

On the one hand, some surgeons proposed that we should be more cautious in selecting the candidates. Li et al[7,8] recommended that patients with stented biliary sys-tem and cholestatic liver should be considered contraindications for ALPPS, because of the lower potential regeneration and high risk for intra-abdominal infection and bacteraemia. Meanwhile those patients are often diagnosed of hilar cholangiocarcinoma.

On the other hand, some surgeons applied this novel approach in many more other patients undergoing liver injury, major vascular invasion except for CRLM. Vennarecci et al applied ALPPS in 5 cases of hepatocellular carcinoma with liver cirrhosis and major vascular invasion. In addition, Bjornsson et al recommended that ALPPS is applicable to the elderly people. They had succeeded in two patients aged 77 and 80 respectively, while Chan et al reported their experience of ALPPS for a 6 years old girl with

hepatoblstoma. Furthermore, Tschuor et al suggested that ALPPS could apply in patients who underwent PVL/PVE with subsequent insufficient volume gain. 11,12

THE MODIFICATIONS OF ALPPS

The classical ALPPS is mainly applied for right trisectionectomy (or right hepa-tectomy), while left lateral lobe (or left hemiliver) was left in place as remnant liver. Gauzolino et al proposed 3 variations of ALPPS on the basis of the difference of liver transection line and remnant liver. The first one is "left ALPPS": Splitting along the main portal fissure and right hemiliver left as remnant liver. The second one is "rescue ALPPS": It is applied in patients who undergoes PVL or PVE with subse-quent insufficient liver hypertrophy. Parenchymal transection is as a rescue procedure for those patients, which is similar with Tschuor et al description. The third one is "right ALPPS": Splitting along the right portal fissure and left media, right anterior section, while caudate lobe (segment I,IV,V,VII) are left as remant liver. While de Santibanes et al reported a similar case using only segments I and IV as remnant liver. 13,14

The reason why ALPPS associated with high morbidity and mortality mainly owes to most of the liver transection. So many modifications of in situ splitting (ISS) have been developed to deal with the high morbidity and mortality. Robles et al proposed replacing the ISS with tourniquet, which also succeeded in occlusion of in-trahepatic collateral. 15 This technique was named "associating liver tourniquet and right portal vein ligation for staged hepatectomy-ALTPS". The tourniquet was placed around the parenchymal transection line, namely umbilical fissure for right trisec-tionectomy while cantile's line for right hepatectomy. They obtained 150% and 57% volume increase in two cases respectively. Then, they implemented the "modified ALTPS" in order to obey the oncological "non-touch" principle. The "modified ALTPS" include three steps as followed: placing the tourniquet around the liver transection line; percutaneous portal vein embolization (PVE) after first stage; completing the right trisectionectomy or right hepatectomy. These techniques avoid dissection of the hilum, and 77% volume increase is also achieved. Furthermore, Ro-bles, R et al applied this technique in 22 patients (Table 2), and the results were as following: interval between two operations was 11 days, median increase of FLR was 61%, and postoperative liver failure was 22.7%, while morbidity and mortality were 63.6% and 9% respectively, with 100% for 6 months overall survival (the two patients died postoperative were excluded).¹⁶

Gall et al proposed another modification of ISS named "Radio-frequency-assisted liver partition with portal vein ligation (RALPP)", they re-placed the ISS with a precise avascular area up to 1 cm by using in-line radio frequency.¹⁷ They applied this technique in 5 patients (4 patients was performed laparo-scopically), and found that

RALLP could significantly increase the FLR by a median of 62.3% within 21.8 days, while the morbidity and mortality were 20% and 0% respectively. None patients developed a postoperative bile leak and mortality at 90 days.

Some surgeons also applied laparoscope in ALPPS or its modifications for minimally invasion and less adhesion. Gall et al performed 4 RALLP cases laparoscopically, Machado et al completed a totally laparoscopic ALPPS and a partially laparoscopic ALPPS, while Cai et al applied laparoscope firstly in ALTPS for patients combined cirrhosis with HCC. 18-20

THE SAFETY AND SHORT-TERM OUTCOMES OF ALPPS

ALPPS associates with high morbidity and mortality. The reported cases demon-strate that morbidity ranges from 22% to 87%, while the mortality ranges between 0% and 28.7%. Shindoh et al comparing the efficacy of PVE with the ALPPS, the re-sults revealed that major morbidity of PVE was 33%, liver insufficiency was 12.5% and 90-day liver-related mortality was 5.8%. So they recommended that percutaneous PVE and interval surgery remained the standard of management for patients with low FLR volume.²¹ Furthermore, Schadde et al drawed conclusions from 202 cases that incidence of severe complications including mortalities (Clavien-Dindo >IIIb) was 27% while Ninety-day mortality was 9% (19/202).3 They also found that the red blood cell transfusion, ALPPS stage I operating time greater than 300 minutes, age more than 60 years, and non-CRLM were all Independent factors for severe complications. And the age, use of Pringle maneuver, and histologic changes implied less volume gain. At the same time, Schadde et al reported that the mortality were 11% (CI=8%-16%) and 44% (CI=38-50) respectively with complications grade IIIa or higher. On the contrary, Alvarez et al obtained 0% mortalities under modifications in highly selected patients, and the morbidity was decreased to 36% by Hernandez-Alejandro et al.^{4,22,23} Many surgeons payed special attention to the tumor recurrence and overall survival. Schadde et al compared 48 ALPPS cases with 83 conventional-staged hepatectomies cases, and found that the tumor recurrence at 1 year was 54% versus 52% for ALPPS and PVE/PVL, respectively (p=0.7). It is reported that the overall survival was all 100% with median follow up of 6, 6, 9 months respectively. While the overall survival at 1 and 2 years was 73% and 59% respectively according to Schadde et al report.

THE MECHANISMS OF LIVER REGENERATION INDUCED BY ALPPS

The rapid and adequate hypertrophy of FLR induced by ALPPS attribute to the ISS, which changes the hemodynamics of liver and induce up-regulation of cytokines in the FLR. This procedure associates liver partition with portal vein ligation. It succeeds in

occlusion of intrahepatic vascular collateral, and then the portal vein which is full of nutrition only supplies the remnant liver. Furthermore, the surgical trauma may also play a role. Those mechanisms might be explained by previous discovery. Furrer et al had found that the blood perfusion and accumulation of macrophages, particularly Kupffer cells of the FLR might play important role in rat liver regeneration after PVL or PVE.

Some animals models were also established with the purpose of exploring the possible mechanisms of liver regeneration. Yao et al succeeded in establishing a model of PVL+ISS in rats.²⁴ The rats were randomly assigned to three groups: PVL, PVL+ISS and sham operation, they obtained the results that the expression of ki-67 in hepatocyte in FLR and the HRR (hepatic regeneration rate) of PVL+ISS were higher than that of the PVL at 72h after surgery (p<0.01), and the hepatocyte injury in the PVL+ISS was more severe than that in the PVL, which was confirmed by liver bio-chemical and histopathology. They also found that both the mRNA levels and the proteins levels of cytokines such as TNF-,IL-6 et al in the FLR were higher in the PVL+ISS than the PVL. At last, they drew a conclusion that the up-regulation of cytokines in the FLR may play important role in this procedure.

Schlegel et al also developed the model of ALPPS in rats, the rats were randomly assigned to three groups: ALPPS, ISS and PVL.²⁵ Furthermore, part of PVL-treated mice were subjected to splenic, renal, or pulmonary ablation and plasma from ALPPS-treated mice was injected into mice after PVL. They found that the hypertrophy of FLR after ALPPS doubled relative to PVL, and the cytokines related to hepatocyte proliferation were 10 times higher than the controls.

Interestingly, injury to other organs or ALPPS-plasma injection combined with PVL induced liver hypertrophy similar to ALPPS, which seemingly implied that the local trauma or inflammatory reaction could promote hypertrophy of FLR.

THE OPEN QUESTIONS AND SOLUTIONS OF ALPPS

ALPPS opens a chapter in the history of liver surgery and readdresses the management of advanced primary and metastatic liver tumors. But as a newly reported technique, there are still many controversies which need further basically scientific and clinic research. Remaining controversies are as following:

The use of plastic bag

The plastic bag was designed initially to prevent adhesions and collect bile leak-age in early ALPPS cases, but Hernandez et al abandoned using the bag because it increased the potentially risk of infection. Furthermore, the second operation has to be performed with the

purpose of removing the bag regardless of the outcomes of stage 1. Chan et al proposed achieving parenchymal transection without prior right liver mobilization by using "anterior approach", which could reduce the adhesion formation so as to negate the use of plastic bag.

The proposition was agreed by Vennarecci et al, and the latter further proposed using the association of liver hanging maneuver (HM) with the anterior approach for preventing adhesion formation.^{26,27}

Whether the FLR hypertrophy accompany with liver function improvement

Knoefel et al proved that the hypertrophy of FLR after ISLT is a result of real parenchymal instead of liver edema by measuring the liver density, which there were

little differences in CT images from before and 3 days after ISLT. But that whether the FLR hypertrophy accompany with liver function improvement remains unclear.⁶

Whether ALPPS may further stimulate tumor progression

Whether the stimulation of FLR hypertrophy induced by up-regulation of cyto-kines could further accelerate tumor growth or progression[remains debated. While it was confirmed by Pamecha et al and Maggioriet et al that there was a clear tumor progression after preoperative portal vein embolization or ligation on patients or rat model respectively. ^{19,28} So it seems possible that ALPPS also induce rapid tumor progression which expected more researches.

Table 1: ALPPS reported in the past 3 years.

Author (years)	Case*	Diagnosis (n)	Interval (days)	FLR gain (%)	Complete surgery (%)	R0 resection (%)	PHL F(%)	Morbidity (%)	Mortality (%)	OS % (follow up months)
Schnitnitz bauer et al ¹	25	CRLM(14),h- CCA(2),i-CCA(2) HCC(3), others(4)	9	74	88	100	-	64	12	86 (6)
Li et al ⁵	9	CRLM(3),h-CCA(3), i-CCA(3)	13	87	100	100	22	22.2	-	-
Knoefel et al ⁶	7	NR	6	63	100	-	-	57.2	14.2	-
Alvarez et al ⁷	15	CRLM(10),h- CCA(1), HCC(1), others(3)	7	78.4	100	100	20	53	0	100 (6)
Sala et al ⁸	10	CRLM(7),h- CCA(1),HCC(1), others (1)	7	82	100	100	20	40	0	100 (6)
Torres et al ⁹	39	CRLM (32) , CCA (3) , HCC(1) , others (3)	14.1	83	95	100	2.5	59	12.8	-
Dokmak et al ¹⁰	8	NR	7	70	-	-	-	87.5	25	-
Schadde et al ¹¹	48	CRLM(26),h- CCA(),HCC(3), others (7)	-	77.4	-	-	12.5	72.9	15	-
Ratti et al ¹²	6	CRLM (3) , h- CCA (2) , Gallbladder cancer(1)	7. 5	-	100	100	-	66.7	16.7	-
Hernande z et al ¹³	14	CRLM(14)	7	93	100	86	-	36	0	100 (9)
Troja et al ¹⁴	5	NR	14	-	100	100	-	-	20	-
Oldhafer et al ¹⁵	7	CRLM(7)	13	13	65	100	-	85.7	0	-
Nadalin et al ¹⁶	15	CRLM(5),h-CCA(5), i-CCA(4) HCC(1)	13	87.2	100	86.7	-	66.7	28.7	66.7 (17)
Alvarez et al ¹⁷	30	CRLM(19),CCA(2), HCC(3)	6	89.7	97	93.1	-	53a	6.6	78(12) 63(24)

^{*} Case series with less than five patients were excluded. a grade ≥ Clavien-Dindo IIIa 43%, ≥ IIIb 31%

Table 2: ALPPS and its modifications in the past 3 years.

approach	Cases (n)	Diagnosis (n)	Interval (days)	FLR gain (%)	PHLF (%)	Morbidity (%)	Mortality (%)	OS % (followup months)
ALPPS ³	202	CRLM (141), HCC (17), h-CCA (11), i-HCC (8)	7	80	-	27ª	9	73(12)
ALPPS ⁴	295	CRLM (199), HCC (22), h-CCA (21), i-HCC (14)	-	84	-	44 ^b	-	59(24) 89(3)
ALTPS ²⁸	22	CRLM (17), HCC (1)	11	61	22.7	63.6	9	100 (6) ^c
RALLP ²⁹	5	CRLM (5)	21.8	62.3	0	20	0	100 (3)

Morbidity of severe complications including mortalities (Clavien-Dindo ≥IIIb); Morbidity of Clavien-Dindo ≥IIIa; The two patients died postoperative were excluded.

Oncological "non-touch" principle

That the mobilization of right liver and dissection of the hilum, even the pringle maneuver were essential for Classical ALPPS which was supposed to be an "all-touch" technique. So Li J et al proposed avoiding "All-Touch" by "Hybrid ALPPS", which consists of 3 steps: in-situ split using "anterior approach", right-PVE through interventional radiology; and complete 2-stage hepatectomy. Furthermore, the "Hybrid ALPPS" is so similar to the "modified ALTPS" which was stated above.

At last, further researches on ALPPS including randomized controlled trial were expected to explain the mechanisms of liver regeneration, tumor biology on a molec-ular and biochemical level, optimal definition of its indication, efficacy and safety of its modifications such as ALTPS, RALLP, laparoscopic ALPPS et al. And the online world register (www.alpps.net) was currently concentrating on exploring the ALPPS. The authors believe that ALPPS may replace the PVE/PVL as the first choice for the management of advanced liver tumors with small FLR, with highly selected patients and in experienced hands.

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