Original research

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): A new strategy to increase resectability in liver surgery

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Abstract

Background: Partial hepatectomy with clear surgical margins is the main curative treatment for hepatic malignancies. The safety of liver resection, to a great extent, depends on the volume of future liver remnant. This manuscript reviews some important strategies that have been developed to increase resectability for patients with borderline volume of future liver remnant, particularly associating liver partition and portal vein ligation for staged hepatectomy (ALPPS).

Methods: To identify potentially relevant articles, we searched Medline and PubMed from January 2010 to December 2013 using the keywords “ Associating liver partition and portal vein ligation for staged hepatectomy”, “ALPPS”, “ portal vein embolization”, “ future liver remnant”, “ liver hypertrophy”, and “ liver failure”. A number of references from the key articles were also cited. There were no exclusion criteria for published information to the topics.

Results: Portal vein ligation (PVL) or embolization (PVE) are traditional approaches to induce liver hypertrophy of the future liver remnant (FLR) prior to hepatectomy in primarily non-resectable liver tumors. However, about 14 percent of patients fail to this approach. Adequate hypertrophy of the FLR using PVL or PVE generally takes more than four weeks. ALPPS can induce rapid growth of the FLR, which is more effective than by portal vein embolization or occlusion alone. Reportedly, the hypertrophy extent of FLR was 40%–80% within 6–9 days in contrast to approximately 8%–27% within 2–60 days by PVL/PVE. However, ALPPS was reported to have high operative morbidity (16%–64% of patients), mortality (12%–23% of patients) and bile leakage rates. Bile leakage and sepsis remain a major cause of morbidity, and the main cause of mortality includes hepatic insufficiency.

Conclusion: ALPPS has emerged as a new strategy to increase resectability of hepatic malignancies. Due to high morbidity and mortality rates of ALPPS procedure, the surgical candidates should be selected carefully. Moreover, there are very limited available evidence for its technical feasibility, safety and oncological outcome which are needed for further evaluation in larger scale of studies.

1. Introduction

Partial hepatectomy with clear surgical margins is the main curative treatment for primary liver cancer or colorectal liver metastasates [1]. However, size of future liver remnant (FLR) is one of the determining factors for resectability as postoperative liver failure is the most severe complication after partial hepatectomy. In general, patients without any underlying liver diseases can tolerate a FLR volume greater than or equal to 25% of the liver volume. Patients with chronic liver disease but without cirrhosis usually require a FLR of at least 30% while those patients with cirrhosis but without portal hypertension require a FLR of at least 40% [2,3]. Truant and her associates [4] recommend an estimated FLR to body weight ratio of greater than 0.5. Thus, for patients with borderline volume of FLR, surgeons have difficulty to choose either resection of the hepatic tumor with potential risk of postoperative liver failure (PHLF) or giving palliative treatment to the patient, such as using transcatheter arterial chemoembolization or local ablative therapy to avoid PHLF [5–7]. In recent years, some strategies, such as portal
vein ligation (PVL), portal vein embolization (PVE), have been developed to induce liver hypertrophy of the future liver remnant (FLR) prior to hepatectomy in primarily non-resectable liver tumors. Two staged liver resections have been developed to increase the resectability for those bilobar liver malignancies. Associating liver partition and PVL for staged hepatectomy (ALPPS) is a new 2 stage surgical strategies to increase size of FLR. It can induce rapid liver hypertrophy avoiding liver failure in most patients, so it can enable resection in patients with liver tumors previously considered unresectable. However, its safety and effectiveness remain unclear. In this article, we provide a systematic review of current status of ALPPS.

2. Traditional strategies to increase resectability

2.1. Preoperative portal vein embolization (PVE)

Makuuchi and his associates [8] first introduced the concept of PVE into clinical practice in the 1980s. For patients with large or multiple tumors located in right hemiliver and segment 4, the right portal branch was embolized to induce marked atrophy of the affected right liver and prominent hypertrophy of the contralateral left liver. There are many subsequent reports describing the efficacy of preoperative PVE in extended hepatectomies [9,10]. With advances in radiological intervention, PVE can now be safely carried out via one of the following two approaches, the contralateral and the ipsilateral approaches, using ultrasound-guided percutaneous transhepatic puncture under local anesthesia. PVE induces liver hypertrophy by increasing the production of hepatic growth factor (HGF) and transforming growth factor (TGF), along with redistribution of portal blood flow [11]. Complications after PVE include liver abscess, biliary fistula, main or branched portal venous thrombosis or even liver necrosis due to concomitant injury of hepatic artery [12]. The potential drawbacks are: firstly, obstructed bile ducts in the embolized liver segments may get infected and can develop into troublesome abscesses when resection is not carried out; secondly, enhanced tumor growth after PVE can be recognized. Changes in cytokines and growth factors, alterations in hepatic blood supply and enhanced cellular host response can promote local tumor growth after PVE; thirdly, patients showing slow growth of FLR or with persistently small FLR volume after 3 weeks of PVE are unlikely to exhibit further liver regeneration beyond this time point. Thus, further extension of the waiting time seems futile [13]; fourthly, small metastases in the FRL or peritoneal carcinomatosis can escape detection from medical imaging and are only detected during laparotomy. A meta-analysis published in 2008 on 37 studies carried out from 1990 to 2005 involving 1088 patients demonstrated that it took a mean of 29 days from PVE to surgery, with an 8% to 27% increase in FLR, and in 14% of patients resection was precluded after PVE due to disease progression or insufficient hypertrophy of the FLR [12].

2.2. Two-stage hepatectomy

The two-stage hepatectomy was pioneered by surgeons at the Hôpital Paul Brousse in the 2000s. The operation was designed when it was impossible to remove all malignant lesions in the liver in a single procedure [14]. The intention of the first hepatectomy was to keep the final FLR clear of all malignant lesions. During the waiting time to second operation, the FLR hypertrophies can be induced making the second hepatectomy feasible and potentially curative [15]. Under this principle, a variety of methods of two-stage hepatectomy were developed. Jaeck [16] routinely used right PVE which resulted in hypertrophy of the left liver after the initial removal of all the tumors located in the left liver (the FLR), allowing a safer curative right or extended-right hemihepatectomy. Clavien [2] modified the procedure by combining wedge resections of all the left-sided tumors in the FLR and concomitant right portal vein ligation in the first operation, and then followed by extended right hepatectomy a few weeks later. This modification is based on evidences that portal vein ligation triggers a similar or better regenerative response than PVE [17]. On this basis, Adam and his colleagues [15] combined ligature or/and absolute alcohol injection into the right portal vein at time of first operation involving resection of all the left sided malignant lesions in FLR. The ligature precluded any backflow of alcohol into the main/left portal vein as well as cavernous transformation of the ligated portal system. These improvements enormously shorten the interval between two hepatectomies. However, the major reason for failure of the two-stage hepatectomy is tumor progression during a too long waiting period for the FLR to hypertrophy or an insufficient volume increase after portal vein occlusion [18–20]. There are other disadvantages [21–23]: firstly, liver regeneration can be impaired or altered by prolonged use of some chemotherapeutic agents. Secondly, patients have to be carefully selected to slow tumor progression with well-differentiated tumors allowing a sufficient delay for regeneration of FLR. Thirdly, in addition to the fibrous adhesions after the first hepatectomy, the atrophy—hypertrophy complex related to the right portal ligation changes the dissection plane of the right hepatectomy, thus, making it potentially dangerous to perform the second hepatectomy.

3. The new strategy: ALPPS

3.1. The emergence of ALPPS

Professor Hans Schlitt from Regensburg, Germany, performed the first ALPPS in 2007. To a certain extent, this great procedure was invented by chance. Professor Schlitt planned to carry out extended right hepatectomy in a patient with hilar cholangiocarcinoma. He realized intraoperatively that the FLR was too small to sustain the patient’s life postoperatively. Hence, he made a good but uncommon surgical decision by performing only selective left hepatico-jejunostomy for palliation. For optimal positioning of hepatico-jejunostomy, he divided liver parenchyma along falciform liga-

3.2. The characteristics of ALPPS

ALPPS has recently been described as a new strategy to induce a rapid and large FLR volume increase. There are two important characteristics of ALPPS: rapid hypertrophy and fundamental auxiliary role undertaken by deportalized and diseased liver during time interval between in situ liver splitting (ISLS) and second operation. Although the arterialized liver containing tumor is
excluded and deprived of its portal blood supply, it still can act as an auxiliary liver to assist the growing FLR in metabolic, synthetic, and detoxifying functions until the contralateral liver has grown enough to entirely take up the physiological function \[27,28]. It is at this time that the depolarized part of liver can be removed with impunity. The reported mean interval between the first and the second operation was 7 days (range: 6–9 days). The evidence just depends on those cohort series in heterogenous group of patients. All these studies are mainly focused on hypertrophy rate, technical feasibility and safety.

PVL or PVE are traditional approaches to induce liver hypertrophy of the FLR prior to hepatectomy in primarily non-resectable liver tumors. However, these approaches fail in about 14 percent of patients. Adequate hypertrophy of FLR using PVL or PVE generally takes more than four weeks. Although the growth rate after PVE can be increased by portal CD113-positive stem cell application, this still cannot grow as fast as the FLR hypertrophy after ISLS. ALPPS can induce rapid growth of FLR, which is greater than that of reported with portal vein embolization or occlusion alone. Recent studies have confirmed marked hypertrophy of FLR by 40%–80% within 6–9 days or 22% per day after ISLS compared with approximately 3% after PVE \[29\]. In addition, Knoefel and his associates \[30\] demonstrated that ISLS can offer an opportunity for curative liver resection even after failed PVE with insufficient growth of FLR. ISLS leads to complete devascularization of segment 4 and prevents formation of vascular collaterals between left lateral section and remaining right sided liver, leading to portal flow deprivation to excluded segments 2 and 3 and redistribution of hepatotropic factors, resulting in accelerated liver hypertrophy \[31,22\]. Knoefel \[30\] showed that rapid growth of FLR after ISLS is a result of real parenchymal hypertrophy because there are only small differences on the density of FLR on CT images carried out before and 3 days after ISLS. Thanks to faster hepatocyte regeneration, drop-out rate of two-stage procedure becomes less. This waiting time interval can be critical, especially for patients with marginally resectable tumors or oncologically aggressive tumors \[33\]. Furthermore, ALPPS allows earlier postoperative chemotherapy.

3.3. Indications and contraindications of ALPPS

The indications of ALPPS include patients with FLR of less than 30% in normal livers or less than 40% in diseased livers resulting from cholestasis, macrosteatosis, fibrosis or pathologic changes associated with chemotherapy. Indications include marginally resectable or locally advanced unresectable liver tumors of any origin with an insufficient FLR either in volume or quality. The pathologies that commonly applied include colorectal liver metastases, hilar cholangiocarcinoma and hepatocellular carcinoma. In addition, major liver resection combined with synchronous resection of other organs, such as colorectal cancer and liver metastases, neuroendocrine pancreatic and intestinal tumors with massive liver metastases, are also potential indications. ALPPS is mainly applicable to those who needed extended right hepatic resection. The contraindications of ALPPS include unresectable liver metastases in the FLR, unresectable extrahepatic metastases, severe portal hypertension, high anesthetic risks, poor medical conditions for major surgery \[34\].

3.4. Operative steps in ALPPS

The morbidity and mortality rates after ALPPS have been reported by Torres and his associates \[35\] to be 59.0% and 12.8%, respectively. With the advances in surgical techniques, 0% operative mortality rates have been reported \[32,34–36\]. It is important to identify proper disease staging by intraoperative exploration and intraoperative ultrasound (IOUS). Dissection of the hepatoduodenal ligament and radical lymphadenectomy should be performed not only for oncological reasons. Clear identification of all hilar structures is necessary for such a complex procedure. The right liver is completely mobilized from the inferior vena cava (IVC). The right portal vein is ligated. It is of paramount importance to avoid any damage to hepatic artery of diseased liver and to the vasculobiliary structures of FLR. Hepatic parenchymal transection is carried out on right side of falciform ligament, separating liver segments 2 and 3 from the rest of liver. Cholangiography is routinely performed through cystic duct after liver parenchymal transection to detect any bile leak. At the end of the first operation, the hepatic pedicle of diseased liver, the hepatic veins, and the cystic duct are encircled with a black silk to facilitate their identification during second stage of the operation. The use of fibrin sealant on the raw surface or a plastic bag around the liver facilitates the second procedure by minimizing postoperative adhesions and avoiding bile peritonitis due to bile leak. Prophylactic antibiotics are given because of the presence of an ischemic diseased liver and a foreign body in the abdominal cavity. In the second stage of the operation, intra-operative ultrasound is used on the FLR to detect any tumor that may have been missed during the first operation. If new tumors are found, either resection or ablative therapy can be performed. Resection of the diseased liver is achieved using vascular staplers for the vasculobiliary structures. There are some important points on this operation: first, preoperative chemotherapy does not seem to influence the degree of liver hypertrophy \[32\]. Second, simultaneous surgery for primary tumor with ALPPS on synchronous liver metastases has been shown to be safe and effective in the first stage operation \[34\]. Third, total laparoscopic ALPPS has been reported \[35,37\] with effect of less adhesions during the second stage of operation \[35,37\]. Fourth, ligation of bile duct of the diseased liver does not improve the degree of liver hypertrophy, but increases morbidity and mortality due to bile leak with possible injury of right hepatic artery during dissection \[38\].

3.5. The modifications of ALPPS

In 2013, Gauzolino and his associates \[39\] presented 3 technical modifications of classical ALPPS: the left, the rescue and the right ALPPS modifications.

The left ALPPS modification: The first step consists of limited resection or anatomical segmentectomy of the right anterior and posterior sections, left PVL and ISLS between the right and left liver along the main portal fissure. The second surgical step consists of completing the left hemipatectomy with resection of segment 1.

The rescue ALPPS modification: The first step consists of ISLS between the right and left hemilivers along the main portal fissure; the right portal vein has already been “ligated” by radiological coils. The second surgical step consists of completing the right hepatectomy. This modification is limited to patients who are not candidates for the second step of “classical” two-stage hepatectomy because of insufficient liver hypertrophy after the conventional methods.

The right ALPPS modification: The first surgical step consists of a left lateral sectionectomy, ligation of the posterolateral branch of the right portal vein, multiple limited or anatomical resections of the left medial, right anterior section and caudate lobe. ISLS along the right portal fissure is facilitated by a right modified hanging maneuver positioning the lower end of hanging tape between the anterior and posterior right pedicles. The second step consists of completing the right posterior sectionectomy.
3.6. Drawbacks and controversies in ALPPS

ALPPS was reported to have high operative morbidity, mortality and bile leakage rates (Table 1). Morbidity after ALPPS was reported to be 16%–64% of patients, and the mortality rate was 12%–23% of patients. The main morbidity included bile leakage and sepsis, and the main cause of mortality included hepatic insufficiency. Another disadvantage of ALPPS is the use of foreign bodies such as plastic bags or sheets during the dissection of the hilar pedicle which is against the principle of the “no touch” oncological concept. ALPPS has been successfully carried out on a patient with hepatic fibrosis due to hepatitis C infection with portal vein thrombosis [41]. However, more studies are needed to evaluate the role of ALPPS in patients with hepatic fibrosis.

4. Conclusion

ALPPS is a new strategy to increase resectability of hepatic malignancies. Due to high morbidity and mortality rates related to ALPPS procedure, the surgical candidates should be selected carefully. Current evidence still appears too limited, its technical feasibility, safety and oncological outcome still need to be evaluated further in larger scale of studies.

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