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Dear Editors,

We are pleased to submit the revised version of our article entitled "**CURRENT STRATEGIES TO INDUCE LIVER REMNANT HYPERTROPHY BEFORE MAJOR LIVER RESECTION**", for publication in the World Journal of Hepatology. Reviewers' questions and concerns are addressed in the text below. The manuscript has been modified to take into account the remarks of the reviewers as science editor and Company editor-in-chief comments. We hope that in his current form our manuscript will meet the requirements of this journal.

We look forward to hearing from you,

Yours faithfully

Hadrien Tranchart

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The author summarized current strategies to induce liver remnant hypertrophy before major liver resection. This is a valuable paper for HPB surgeon. I have two suggestions about this review. First, the format of the references is not satisfactory. Second, the author should make a table of the mechanism, efficacy, indication,and disadvantages of these strategies.

Response:

We thank the reviewer for these comments that have significantly improved our manuscript.

The format of the references was modified as required.

A table summarizing indications, advantages and disadvantages of these strategies was added to the manuscript.

Finally, we have reviewed the whole text trying to avoid any syntax error.

Revised manuscript (marked-up copy)

CURRENT STRATEGIES TO INDUCE LIVER REMNANT HYPERTROPHY BEFORE MAJOR LIVER RESECTION

Short title: Preoperative liver hypertrophy

Manuscript type: Review

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ABSTRACT

Hepatic resection is the gold standard for patients affected by primary or metastatic liver tumors~~,~~ but is hampered by the risk of post-hepatectomy liver failure. Despite recent improvements, liver surgery still requires excellent clinical judgement in selecting patients for surgery and, above all, efficient pre-operative strategies to provide adequate future liver remnant. The aim of this article is to review through literature the rational, the preliminary assessment, the advantages as well as the limits of each existing technique for preparing the liver for major hepatectomy.

Core tip: Hepatic resection is the gold standard for patients affected by liver tumors but is hampered by the risk of post-hepatectomy liver failure. We herein review through literature the rational, the preliminary assessment, the advantages as well as the limits of each existing technique for preparing the liver for major hepatectomy.

Key words: liver regeneration; major hepatectomy; liver insufficiency; future liver remnant; portal vein embolization.

INTRODUCTION

Hepatic resection is the gold standard for patients affected by primary or metastatic liver tumors~~,~~ but is hampered by the risk of post hepatectomy liver failure (PHLF). Indeed, PHLF is considered the most frightening complication in liver surgery, representing a major source of severe morbidity and mortality[1]. Despite recent improvements, liver surgery still requires excellent clinical judgement in selecting patients for surgery and, above all, efficient pre-operative tools to ~~leave an~~ provide adequate future liver remnant (FLR).

The liver has a unique capacity of preserving its volume thanks to regeneration. The atrophy-hypertrophy phenomenon is a prime example of liver's pathophysiologic (atrophy) and restorative (hypertrophy) response to injury[2]. It occurs whenever there is ~~an~~ impairment of bile or blood flow: the liver reacts with ~~an~~ atrophy of the region concerned and with ~~a~~ compensatory hypertrophy of the less or not impaired regions, resulting in characteristic gross deformity of the organ and, in some instances, in ~~a~~ rotation of the liver around a virtual hilar axis[3]. The mechanisms that induce cellular division are complex and based on different inflammatory cytokines. The Hepatic Grow Factor (HGF) seems to be the main mitogenic factor and its role has been established in liver regeneration[4].

The first case of *in vivo* human hepatic regeneration has been described by Pack et al. in 1962[5]. Starting from animal models in the first half of the 20th century, it was recognized that liver regeneration could also be induced by portal vein ligation (PVL)[6]. In 1986, the first cases of percutaneous transhepatic portal vein embolization (PVE) were performed before liver resection in the setting of hepatocellular carcinoma[7], and few years later Makuuchi et al.[8] reported the utility of PVE in promoting FLR hypertrophy prior to hepatic resection in patients with hilar cholangiocarcinoma. Since those initial reports, preoperative PVE has been established as the standard procedure for obtaining FRL hypertrophy, increasing

~~candidacy~~ eligibility of patients for major hepatectomy as well as improving postoperative outcomes and safety. However, concerns regarding insufficient increase of FLR and/or concomitant tumoral progression after PVE have led to development of recent alternative techniques to push further the limits of liver surgery.

The aim of this article is to review the techniques available for preparing the liver for ~~a~~ major hepatectomy, as well as to depict their advantages and limitations.

LIVER REGENERATION

Liver's unique capacity for regeneration was first recorded in the legend of Prometheus in Greek mythology and it represents the basis of the treatment of many liver diseases. Regeneration of the liver is a pathophysiological process, embracing both hypertrophy (increase in cell size or protein content in the prereplicative phase) and hyperplasia (increase in cell numbers). Both ~~these~~ events can take place independently[9]. The mechanisms of liver regeneration have mainly been studied after extensive hepatectomy. The players of regeneration following the different techniques exposed in this article are thought to be similar to those after hepatectomy, but the precise mechanism remains unknown. Basically, the regeneration process is a cytokine- and growth-factor-mediated pathway. The main cytokine-mediated pathways include members of the innate immune system, tumor necrosis factor (TNF)α and interleukin (IL)-6, and growth-factor-mediated pathways are regulated by HGF and transforming growth factor (TGF)α[10]. It is a multi-step process, starting from the "priming" of hepatocytes, the moment they acquire replicative capacity, followed by the proliferative step in which an adequate cell mass is attained, and a termination stage in which liver cell proliferation is ended once the necessary functional mass has been reached[11]. Proliferation of hepatocytes advances from periportal to pericentral areas of the lobule, as a wave of mitoses[12]. Proliferation of biliary epithelial cells occurs a little later than hepatocytes. The particularity of liver regeneration is that replacement of the lost hepatic mass is not mediated by a selected stem cells proliferation but it entirely depends on mature adult hepatocytes and other hepatic cell types. Concerning time interval, as far as we know, normal liver weight is reestablished within 8-15 days in humans[13].

POST HEPATECTOMY LIVER FAILURE (PHLF)

Although morbidity and mortality after liver surgery improved over the past 10 years, PHLF is still reported in up to 8%, ranging from 1.2% to 32%, and depending on patient's condition and functional reserve of the liver before resection[1]. Different definitions of PHLF are available. In 2011, the International Study Group of Liver Surgery (ISGLS) defined PHLF as "a post-operatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased International Normalized Ratio (INR) and concomitant hyperbilirubinemia on or after postoperative day 5"[14]. It is worth pointing that severe PHLF is associated to a ~~high~~ mortality rate of 54%.

A related syndrome that results in a transient but sometimes fatal form of liver failure has been described following liver transplantation (LT) but also after extensive liver resection. This is the so-called Small For Size Syndrome (SFSS). In 2005, Dahm et al. defined SFSS as graft to recipient weight ratio < 0.8% alongside two of the following for three consecutive days; bilirubin > 100 mmol/l, INR > 2 and encephalopathy grade 3 or 4[15]. Behind the definition, SFSS is a clinical syndrome characterized by post-operative liver dysfunction, prolonged cholestasis and coagulopathy, portal hypertension and ascites. It can lead to a higher rate of hemorrhage, sepsis and gastrointestinal bleeding[16]. The key point of

SFSS is the presence of portal hypertension and intra-hepatic portal congestion as the underlying cause of liver failure[17].

PREDICTION OF PHLF RISK

Despite improvements in surgical and postoperative management, parameters determining the degree of possible hepatectomy remain largely uncertain. Different patient related and surgical factors have to be considered to decrease PHLF incidence. Surgical factors include extent of resection and volume of FLR, duration of ~~peri~~intraoperative liver ischemia during portal pedicle clamping, duration of surgery and need for blood transfusion. The risk of PHLF is highly influenced by the quality of ~~the~~ underlying liver parenchyma. The type of underlying liver parenchyma is frequently assessed by preoperative liver biopsy, but noninvasive methods, as liver stiffness, are now available. For example, liver stiffness measurement by transient elastography (Fibroscan) predicts persistent hepatic decompensation in patients undergoing resection for hepatocellular carcinoma[18].

It is generally admitted that minimal functional liver mass needed for adequate postoperative liver function is estimated to be 20-25% in patients with normal liver parenchyma whereas those with chemotherapy-induced liver injury require FLR volume of approximately 30%, while those with cirrhosis at least a 40% minimal functional liver mass[19]. Therefore, standardized FLR volume can be easily evaluated by a tridimensional computed tomography (CT) reconstruction method, as FLR/estimated total liver volume[20]. Estimated total liver volume is generally calculated using a formula based on body surface area[21].

In addition to volume, estimation of FLR function is an important factor. Typical biochemical parameters, as liver function tests, albumin, and clotting factors must be evaluated. The old but effective Child-Turcotte-Pugh (CTP) score, which was introduced in

1964, still represents a simple system for grading liver function[22]. The model for end-stage liver disease (MELD) score, which is mainly used in liver transplantation, can also predict survival rate of cirrhotic patients to better select ideal candidates for surgery[23]. A recent study also showed that mean serum level of hyaluronic acid can be a useful tool, especially when liver biopsy is not feasible[24].

Dynamic tests of liver function can also be used. The most famous is ~~the~~ indocyanine green (ICG) clearance. ICG is a water soluble, inert, fluorescent tricarbocyanine dye with protein binding close to 95% (mainly, alpha1- and beta-lipoproteins and albumin), a hepatic extraction rate above 70%, and is almost completely excreted in its unchanged form by the liver. ICG elimination can be expressed as ICG plasma disappearance rate (ICGPDR) or retention rate at fifteen minutes (ICGR15), reflecting liver function. The use of ICG test for patient selection has been shown to decrease postoperative mortality[25].

In recent years, there have been several attempts to assess hepatobiliary MRI as a tool to predict liver dysfunction. Since it was first described in 1991 by Weinmann et al.[26], MRI has been showed to provide both global and segmental liver function information, and postoperative remnant liver function thanks to the measurement of liver signal intensity in the hepatobiliary phase.

Liver function evaluation by nuclear medicine techniques is also more and more used. Dynamic 99mTc-mebrofenin hepatobiliary scintigraphy has been used to provide quantitative information on total and regional liver function. The hepatic uptake of 99mTc-mebrofenin is similar to the uptake of organic anions such as bilirubin[27]. This technique efficiently estimates the risk of postoperative liver failure especially in patients with uncertain quality of liver parenchyma[28]. The 99m Tc-GSA is another recently proposed agent that is not affected by hyperbilirubinemia and can be used for liver function assessment in cholestatic patients[29]. Finally, the LiMAx test allows a real time *in vivo* determination of liver Cytochrome P450 1A2 (CYP1A2) activity. The CYP1A2 is not influenced by cholestasis or drugs and is ubiquit~~arian~~ous in liver parenchyma. Intravenous administration of 13C methacetin, a substance exclusively metabolized by CYP1A2, with continuous real-time breath analysis represents the base of LiMAx test[30].

PORTAL VEIN EMBOLIZATION (PVE)

Since the first report in 1986, PVE has progressively become the gold standard for inducing liver hypertrophy with satisfying safety and efficacy[31]. Initially described by laparotomy, the portal system access is now obtained by percutaneous puncture of the portal vein. According to operator's preference, an ipsilateral or contralateral approach can be chosen, in reference to the segment bearing the tumor. The ipsilateral approach has the main advantage of protecting the FLR from injury[2] whereas the contralateral approach facilitates embolization[32]. No matter the approach chosen, PVE is performed in a retrograde manner (**Figure 1**). Many embolic materials have been used for PVE without significant differences in terms of hypertrophy. Embolic materials include fibrin glue, N-butyl-2-cyanoacrylate (NBCA) and ethiodized oil, gelatin sponge and thrombin, coils, microparticles (eg, polyvinyl alcohol (PVA) particles or tris-acryl gelatin microspheres) and absolute alcohol[33]. A non-absorbable material is generally used. However, interesting results were reported with the use of an absorbable powder material (Gelfoam® powder, Pfizer, New York, USA) that lasts approximately 2 weeks, leading to temporary PVE. In the animal model, this method showed an efficient and stable liver regeneration[34]. These results were confirmed in a limited preliminary series in clinical practice[35] and a prospective study is undergoing (EMBORES study, NCT02945059). One of the advantages of temporary PVE is that it could theoretically be repeated several times to boost all the more liver hypertrophy, as it has been suggested in an animal model[36].

PVE is successively performed in more than 90% of cases[37]. CT-scan with volumetric evaluation is generally performed between 4 and 8 weeks after embolization. PVE induces a FLR hypertrophy than can reach 40%[37], with a low 2% morbidity rate and no mortality in the vast majority of studies[37-39]. PVE is considered an efficient method, allowing successful hepatectomy in more than 70% of cases[37, 38, 40].

Contraindications to PVE are extensive portal thrombus and important portal hypertension[41]. Another potential limit of PVE is the risk of tumor growth during the 4 to 8 weeks separating PVE and liver surgery. Besides, several authors suggested that PVE itself could promote tumor growth within the embolized liver[42-45]. Among others, these reasons have led to the development of alternative strategies.

PORTAL VEIN LIGATION (PVL) AND TWO-STAGE HEPATECTOMY (TSH)

As it requires a surgical procedure with portal pedicles dissection, PVL is nowadays mainly indicated in the setting of two-stage hepatectomy (TSH) for the treatment of bilobar liver disease[46, 47]. In the TSH strategy, the first surgical step includes tumoral clearance of the FLR (usually by parenchymal spearing resections or locoregional treatment like radiofrequency ablation) and concomitant PVL that allows FLR growth. In the second step, after liver regeneration (approximately 4 to 8 weeks after), major liver resection is performed (usually ~~a~~ right or right extended hepatectomy) (**Figure 2**). Similarly, PVL can be interesting for management of patients presenting synchronous colorectal metastases or neuroendocrine tumors[47]. The first surgical step associates colorectal resection with PVL, followed by major liver surgery in the second procedure. However, ~~even in those two-steps procedures,~~ many centers have adopted PVE (performed by percutaneous approach after FLR clearance or colorectal resection) for two-step procedures, ~~which avoids~~ avoiding portal pedicle dissection and facilitat~~es~~ing the second procedure[48].

It was initially suggested that PVE resulted in ~~a~~ superior FLR growth compared to PVL[49] as in theory PVE allows distal portal obstruction which decreases the possibility of intrahepatic collateral development. Several studies demonstrated that results are globally similar[50, 51]. In fact, the debate concerning efficiency of PVL compared to PVE is no longer relevant. PVL requires a surgical procedure and can appear as an alternative to PVE only when a two-step~~s~~ surgery is planned. In other cases, percutaneous PVE is clearly a simpler and better tolerated approach.

ASSOCIATING LIVER PARTITION AND PORTAL VEIN LIGATION FOR STAGED HEPATECTOMY (ALPPS)

The aim of this alternative strategy, described by Schnizbauer et al. in 2012[52], is to induce rapid and massive liver hypertrophy, allowing to perform liver surgery in a short period of time in patients with initially very limited FRL volume. The first step of the ALPPS procedure consists in performing PVL and an *in situ* spliting of the liver parenchyma, leaving the hepatic artery, bile duct, and hepatic vein intact until the subsequent operation. This first surgical step can be associated with ~~a~~ tumoral clearance of the FRL. During the second operation (that can be performed one to two weeks later) the remaining hepatic artery, bile duct, and hepatic vein are divided and the liver specimen is extracted (**Figure 3**).

The first report demonstrated a morbidity rate of 44% and a mortality rate of 12%[52], and triggered an intense debate about the safety of this procedure, limiting its promotion worldwide. The morbi-mortality rate decreased with experience but remains high, with approximately 40% of major postoperative complications and 9% of mortality[53]. Nevertheless, the ALPPS technique induces more than 65% of FLR growth in approximately 7 days[52-55] and the second procedure is feasible in more than 90% of cases [56]. The main advantage of the ALPPS procedure is rapid increase of FLR volume in a short interval and therefore a shorter interval between the two stages. Although volumetric results of this technique are impressive, several authors suggested that FLR volume hypertrophy is not correlated to its functional improvement [57, 58] which could partly explain high morbidity of the procedure. Besides, concerns have been raised by some authors regarding potential poorer oncological results comparing to the classical TSH[59]. The results of a metanalysis comparing ALPPS to TSH showed that extent of FLR increase was not different between the two groups[60]. Time needed to reach final liver volume was shorter in ALPPS than in the TSH approach[60]. In this metaanalysis, ALPPS was associated with higher incidence of major and overall morbidity and mortality compared to TSH[60]. However, in a recent randomized controlled trial, Hasselgren et al.[61] observed similar morbidity between ALPPS and classical TSH and an improved survival in the ALPPS group.

To decrease complication rate, a variety of technical modifications have been proposed such ~~us~~ as partial-ALPPS, mini-ALPPS, tourniquet-ALPPS, hybrid-ALPPS, microwave ablation assisted ALPPS and radiofrequency ablation assisted ALPPS. Huang et al. suggested in a systematic review that a partial ALPPS technique in which only partial parenchymal sparing is performed during the first surgical step could achieve lower morbidity and mortality rates, reaching the same FLR hypertrophy rate as ALPPS in non-cirrhotic patients[62].

SEQUENTIAL TRANS ARTERIAL EMBOLIZATION (TAE) AND PORTAL VEIN EMBOLIZATION (PVE)

Although PVE remains the gold standard for FLR hypertrophy, two concerns persist with this approach: an insufficient contralateral hypertrophy, particularly in patients with underlying liver disease (steatosis, fibrosis or cirrhosis), and the eventuality of tumor progression while waiting for the non-embolized liver to hypertrophy. In particular, portal flow interruption may induce a compensatory increase in arterial blood flow of ~~the~~ embolized segments and result in a paradoxically growth of tumors vascularized by arterial blood flow. In this context, it has been postulated that addition of transarterial embolization (TAE) or transarterial chemoembolization (TACE) would produce more rapid and extensive FLR growth (by obtaining obliteration of intrahepatic arterioportal shunts) and may help to counteract the stimulating effect on tumor growth[63]. Therefore, hepatocellular carcinomas, which are tumors particularly vascularized by arterial blood flow and developed generally in an underlying pathological liver parenchyma, are the main target of this combined strategy[64].

During TAE, a catheter is directly inserted *via* either common femoral or left radial artery and an intra-arterial injection of a combination of microspheres and PVA particles is performed in the arterial branches of the segments to be resected. During TACE, an intra-arterial injection of a cytotoxic drug is performed such as doxorubicin, epirubicin, idarubicin, mitomycin C, or cisplatin, that is emulsified in ethiodized oil (Lipiodol® Ultra-Fluid, Guerbet). This is followed by intra-arterial injection of an embolic agent, such as gelatin sponge, PVA particles, or microspheres[65] (**Figure 4**). TACE can also be performed using recently developed drug-eluting beads (DEB) that allow to slowly release chemotherapeutic agents, and to increase ischemia intensity and duration[65].

A sequential approach, with a time interval of few days, is recommended to limit the risk of nontumoral liver ischemic necrosis[66] and TAE is mostly performed before PVE [66, 67]. Although the number of patients reported in studies that evaluated this approach are limited, observed FLR hypertrophy is generally superior to that observed after isolated PVE. For example, Yoo et al.[68] reported a statistically significant increase of 7.3% and 5.8% of FLR (over the total liver volume) for sequential TACE/PVE and isolated PVE, respectively.

An important elevation of transaminases is generally observed after this sequential approach without important clinical consequences. In the largest series reporting this approach, Peng et al.[64] reported 29 procedures without deaths and only one complication and 27 patients (93%) underwent subsequent hepatectomy. Post-hepatectomy morbidity and mortality among those patients was 27.5% and 6.9%, respectively.

Theoretical contraindications of this method include extensive portal thrombus, important portal hypertension or previous biliary surgery (biliodigestive anastomosis) which exposes the patient to hepatic abscess formation after arterial embolization.

LIVER VENOUS DEPRIVATION (LVD)

This technique consists in performing conventional PVE and ipsilateral hepatic vein obstruction (**Figure 5**). By associating hepatic vein embolization, the aim is to eliminate any residual portal vein flow and reduce hepatic artery inflow which can further encourage liver regeneration. Initially described as a sequential approach in which hepatic vein embolization is secondarily performed in case of insufficient FLR growth after PVE, it was demonstrated that both procedures (portal and hepatic vein embolizations) can be performed simultaneously[69, 70]. This novel approach is particularly interesting as it allows ~~a~~ important liver regeneration with ~~a~~ good tolerance. Although no study comparing ALPPS to LVD is available, it has been suggested that LVD could overcome the limits of ALPPS, abolishing the necessity of two major surgical interventions in a close sequence.

Firstly, PVE is performed as previously described. For hepatic vein embolization, a vascular plug is placed in the proximal part of the hepatic vein to avoid migration of embolization agent. The vein is then embolized with a mixture of ethiodized oil and NBCA[71]. The term "extended LVD" is used for concomitant embolization of the right and middle hepatic vein with the right portal branch[57].

The results of this approach on FLR increase are superior to those observed after isolated PVE. In a recent large comparative study, Laurent et al. observed a FLR volume increase of 28.9% after PVE compared to 61.2% after LVD ($P < 0.0001$)[71]. In this study, the LVD allowed to perform ~~the~~ surgery in 86.4% of patients and no PHLF were reported. Kobayashi et al.[72] observed similar results with a superior FLR hypertrophy after LVD compared to PVE (35% vs. 24%, $P = 0.034$). Besides, the tolerance of LVD seems to be similar to the tolerance of isolated PVE[71, 72].

RADIATION LOBECTOMY (RL)

This recent approach is derived from transarterial radioembolization with yttrium-90[73]. In RL, ~~a~~ radioembolization of both the tumor and the non-tumoral liver parenchyma that will be secondarily resected is performed, which requires higher radiation doses[74, 75]. This technique allows concomitant tumoral control and FLR increase. One major advantage of this approach is that it could be proposed to patients with portal vein thrombosis[75].

The procedure is well-tolerated [74] with transient moderate adverse events. Results in terms of FLR volume growth are very similar to those observed after PVE. Vouche et al.[74] reported 45% of FLR hypertrophy and observed a correlation between the presence of a portal vein thrombosis and FLR growth. However, series reporting major liver resection after RL are scarce[76, 77]. Andel et al.[77] recently reported 10 major hepatectomies in patients that were initially treated with RL for insufficient functional FLR. The RL allowed a 41% increase of FLR volume with 84% of FLR function increase (evaluated on scintigraphy). All resections were performed without major intraoperative problems. Only one patient presented a serious complication not directly related to the liver surgery and other complications were mild.

CONCLUSIONS

Careful initial evaluation of FLR volume and function is crucial before planning major liver resection. When required, several approaches are now available to decrease the risk of PHLF (**Table 1**) and thus postoperative mortality. Although PVE remains the gold standard, recent techniques that are derived from PVE might play an increasingly important role in future years.

Article highlights:

- Portal vein embolization (PVE) has progressively become the gold standard for inducing liver hypertrophy with satisfying safety and efficacy.

- Portal vein ligation (PVL) is nowadays mainly indicated in the setting of two-stage hepatectomy (TSH) for the treatment of bilobar liver disease as it requires a surgical procedure with portal pedicles dissection.

- Associating liver partition and PVL (ALPPS) is an alternative strategy to induce rapid and massive liver hypertrophy, allowing to perform liver surgery in a short period of time in patients with initially very limited future liver remnant (FLR) volume.

- In patients with hepatocellular carcinoma, sequential trans arterial embolization (TAE) and PVE produce rapid and extensive FLR increase and may help to counteract the stimulating effect on tumor growth.

- Liver venous deprivation (LVD) associates conventional PVE and ipsilateral hepatic vein obstruction. This novel approach is particularly interesting as it allows important liver regeneration with a good tolerance.

- During radiation lobectomy (RL), a radioembolization of both the tumor and the non-tumoral liver parenchyma that will be secondarily resected is performed. This approach could be proposed to patients with portal vein thrombosis.

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FIGURES AND TABLES LEGENDS

Figure 1

~~Right portal vein embolization using contralateral (A) or ipsilateral (B) approach.~~

Right portal vein embolization using: A: contralateral; B: ipsilateral approach (authors' own work).

Figure 2

~~Two-stage hepatectomy procedure starts with tumoral clearance of the future liver remnant with concomitant right portal vein ligation (A), allowing left liver growth (B), and ends with right hepatectomy (C).~~

Two-stage hepatectomy procedure starts with tumoral clearance of the future liver remnant with: A: concomitant right portal vein ligation; B: allowing left liver growth; C: ends with right hepatectomy (authors' own work).

Figure 3

~~Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure starts with in situ splitting of the liver parenchyma with concomitant right portal vein ligation (A) and ends with right hepatectomy (B).~~

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure: A: starts with *in situ* splitting of the liver parenchyma with concomitant right portal vein ligation; B: ends with right hepatectomy (authors' own work)

Figure 4

~~Sequential trans arterial embolization (1) and portal vein embolization of the right liver (2).~~

Sequential embolization: A: trans arterial embolization; B: and portal vein embolization of the right liver (authors' own work)

Figure 5

~~Right liver venous derivation associates right portal vein embolization (1) and ipsilateral hepatic vein embolization (2) in a sequential or concomitant approach.~~

Right liver venous derivation associates in a sequential or concomitant approach: A: right portal vein embolization; B: and ipsilateral hepatic vein embolization (authors' own work)

Table 1

Indication, advantages, and disadvantages of existing approaches to induce liver remnant hypertrophy before major liver resection.

TABLE 1. Indication, advantages, and disadvantages of existing approaches to induce liver remnant hypertrophy before major liver resection.

Approach	**Indication**	**Advantage**	**Disadvantage**
Portal vein embolization (PVE)	Insufficient future liver remnant (FLR) volume	Percutaneous approach	Contraindicated in patients with extensive portal thrombus and important portal hypertension Could promote tumoral growth within the embolized liver
Portal vein ligation (PVL) and two-stage hepatectomy	Insufficient FLR volume and treatment of bilobar liver disease	PVL is performed during the first surgical step (tumoral clearance of the FLR)	Surgical procedure Morbidity
Associating liver partition and PVL for staged hepatectomy	Insufficient FLR volume +/- treatment of bilobar liver disease	Liver surgery is performed in a short period of time (15 days) First surgical step (PVL and *in situ* splitting of the liver parenchyma) can be associated with a tumoral clearance of the FLR	Surgical procedure Morbidity
Sequential trans arterial embolization and PVE	Insufficient FLR volume in patients with hepatocellular carcinoma	Percutaneous approach May help to counteract the stimulating effect of PVE on tumor growth	Sequential approach (two procedures) is recommended to limit the risk of nontumoral liver ischemic necrosis Contraindicated in patients with extensive portal thrombus, important portal hypertension or previous biliary surgery (biliodigestive anastomosis)
Liver venous deprivation	Insufficient FLR volume	Percutaneous approach	Contraindicated in patients with extensive portal thrombus and important portal hypertension Could promote tumoral growth within the embolized liver
Radiation lobectomy (RL)	Insufficient FLR volume	Percutaneous approach Concomitant tumoral control and FLR increase Can be proposed to patients with portal vein thrombosis	Data reporting liver resection after RL are scarce