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## Outcomes of staged hepatectomies for liver malignancy

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### Abstract

Liver malignancies are the fifth most common cause of death worldwide. Surgical intervention with curative intent is the treatment of choice for liver tumors as it provides long-term survival. However, only 20% of patients with metastatic liver lesions can be managed by curative liver resection. In most of the cases, hepatectomy is not feasible because of insufficient future liver remnant (FLR). Two-stage hepatectomy is advocated to achieve liver resection in a patient who is considered to not be a candidate for resection. Procedures of staged hepatectomy include conventional two-stage hepatectomy, portal vein embolization, and associating liver partition and portal vein ligation for a staged hepatectomy. Technical success is high for each of these procedures but variable between them. All the procedures have been reported as being effective in achieving a satisfactory FLR and completing the second-stage resection. Moreover, the overall survival and disease-free survival rates have improved significantly for patients who were otherwise considered nonresectable; yet, an increase in the morbidity and mortality rates has been observed. We suggest that this type of procedure should be carried out in high-flow centers and through a multidisciplinary approach. An experienced surgeon is key to the success of those interventions.

**Key words:** Staged hepatectomy; Portal vein embolization; Portal vein ligation; Colorectal liver metastasis; Hepatocellular carcinoma; Associated liver partition and portal vein ligation for staged hepatectomy

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**Core tip:** Surgical intervention with curative intent is the treatment of choice for liver tumors. A variety of techniques have been established to increase the possibility for resectability. Two-staged hepatectomy, with its distinguishing beneficial procedures, is one of the techniques that have been proposed to overcome this clinical challenge. In spite of higher perioperative morbidity and mortality associated with this procedure, the overall survival and disease-free survival rates have increased significantly. Patient

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selection through consensus by a multidisciplinary board panel is the mainstay to successful performance of this procedure.

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## INTRODUCTION

Liver malignancies are considered to be the fifth most common cause of death worldwide. Hepatocellular carcinoma (HCC) and colorectal liver metastasis are the main indications of liver resection in the Eastern and Western world, respectively<sup>[1]</sup>. Surgical intervention with curative intent is the treatment of choice for liver tumors, as it provides for long-term survival<sup>[2-4]</sup>.

Historically, only 20% of patients with metastatic liver lesions have had indications for management by curative liver resection. While in most of the cases, hepatectomy has not been feasible, due to insufficient future liver remnant (FLR)<sup>[5-7]</sup>. Recently, many options have become available to achieve liver resection with curative intent in those patients initially deemed to have nonresectable liver tumors. These include Portal vein embolization (PVE)/ligation, locoregional therapy, hepatic artery chemo-infusion, and systemic chemotherapy<sup>[8-13]</sup>. However, these options cannot provide curative resection in all cases, especially in patients with multiple bilobar lesions; in such cases, two-staged hepatectomy (TSH) has been advocated<sup>[14]</sup>.

This new approach is intended to resect the tumor completely in one lobe, with the remaining lobe to undergo resection later. The purpose of this staged resection is to minimize the risk of post hepatectomy liver failure by performing the second resection once liver regeneration is achieved. The second liver resection is curative, when restaging of the tumor after the first resection has excluded tumor progression or metastasis<sup>[14]</sup>.

Prior to 2000, staged hepatectomy was applied to the cases with advanced liver lesions. These were managed initially by laparotomy and portal vein ligation, followed by liver resection of the affected lobe at the later stage. Indeed, the first study on conventional TSH on bilobar liver metastasis from colorectal cancer was reported in 2000<sup>[11,14]</sup>.

We have based this review on our clinical and research experience to highlight the history of staged hepatectomy as well as the current practice, outcome and future direction of this surgical approach. We searched the Medline literature database from 1990 to 2018 using the search terms “staged hepatectomy”, “portal vein embolization”, “portal vein ligation”, “colorectal liver metastasis”, “hepatocellular carcinoma”, and “associating liver partition and portal vein ligation”.

## TYPES OF PROCEDURES

As aforementioned, treatment of malignant liver lesions with curative intent is preferred<sup>[15]</sup>. Since many patients have multiple liver lesions (which often preclude complete resection), multidisciplinary approaches have been proposed to achieve complete resection and decrease postoperative complications<sup>[14,15]</sup>.

The main principle of resectability is the preservation of an adequate FLR with in-flow, out-flow and biliary drainage capability while avoiding post hepatectomy liver failure. The FLR depends on the liver status and volume that can be studied preoperatively. Between 25% and 30% of total liver volume (TLV) in healthy liver is considered adequate. On the other hand, patients with either hepatic dysfunction or liver injury due to chemotherapy require FLR up to 40% of the TLV<sup>[8,16-18]</sup>. Multiple techniques have been described to augment the FLR; these are PVE/ligation, conventional TSH, and associated liver partition and portal vein ligation for staged hepatectomy (ALPPS).

### PVE/ligation

PVE/ligation is one of the strategies developed to increase the number of patients indicated for resection. It can be done radiologically through embolization of the



affected liver lobe's portal vein or surgically by ligating the portal vein with or without clearance of the FLR<sup>[19]</sup>.

In 1980s, Makuuchi *et al*<sup>[12]</sup> introduced PVE for the induction of FLR hypertrophy. This type of hypertrophy facilitates the removal of extensive liver tumors safely by mitigating the sudden rise in portal pressure that otherwise occurs during surgery. It also prevents perioperative liver dysfunction by increasing the FLR volume. This technique is considered an option in cases of multiple liver malignancy, allowing for the second curative liver resection after an appropriate time of regeneration<sup>[20-22]</sup>.

Four factors are important in deciding which patients will benefit from PVE. These are: ratio of FLR to TLV; extent of liver resection; baseline liver function; and, presence of systemic diseases that might affect the liver hypertrophy, such as diabetes mellitus<sup>[23]</sup>. Previously, patients with bilobar multiple metastases were not considered candidates for PVE. However, recent studies have confirmed that some of these patients can benefit from PVE in combination with TSH<sup>[24]</sup>. Patients who are contraindicated for PVE are summarized in Table 1<sup>[25,26]</sup>.

### TSH

TSH is a surgical strategy for bilobar liver metastasis, aiming to achieve a curative R0 resection. The main principle of this approach is a planned sequential liver resection that will facilitate complete metastasectomy in those cases in which a major resection in a single surgery would result in FLR insufficient for the patient's survival.

In the first stage, the less affected lobe that will be the FLR is cleared by wedge resections and/or controlled by ablation. Portal vein ligation may be performed during the procedure; otherwise, it can be performed later. The optimal interval time between the two stages has not yet been clarified<sup>[27]</sup>. Currently, the interval is calculated based on the FLR regeneration and the control of remnant liver tumors. During the regeneration waiting period, interval chemotherapy might be used to control tumor progression<sup>[28]</sup>.

The second stage is then performed, most commonly with hepatectomy of the contralateral lobe. The success of this method depends on the liver regeneration between the two stages, which allows for the second surgical step to be performed with a lower risk of post hepatectomy liver failure.

### ALPPS

A new innovative surgical technique for TSH is portal vein ligation and *in situ* splitting of the liver parenchyma. This new approach was developed by Schnitzbauer *et al*<sup>[29]</sup> from Regensburg, Germany. It is used for patients with marginally resectable or initially nonresectable liver tumors, either primary or metastatic, to induce a rapid increase in FLR<sup>[20,29]</sup>.

In ALPPS, the exact mechanism of the rapid liver regeneration is still not fully understood. Some pathophysiological mechanisms may explain this phenomenon. First, the portal vein ligation will lead to impairment of the bilateral portal flow and subsequently increase portal flow to the FLR; this will result in a redistribution of hepatotropic factors to the FLR. Second, a local regeneration stimulus is initiated after liver partitioning due to surgical trauma<sup>[30,31]</sup>.

In preoperative MRI or CT scan-based volumetric planning, both TLV and FLR are determined and calculated by the radiologist using integrated software techniques. Calculation of the FLR/remaining liver volume (RLV) to TLV ratio (RLV-TLV, expressed as a percentage of the TLV) and the RLV to body weight ratio (RLV-BWR, expressed as a percentage of the body weight) is carried out. The ALPPS procedure is considered when  $RLV/TLV < 25\%$  or  $RLV/BWR < 0.5\%$  in patients with a normal liver, and when  $RLV/TLV < 30\%$  and  $RLV/BWR < 0.8\%$  is found for patients with diseased liver then the procedure is required<sup>[32,33]</sup>.

ALLPS is a complex surgical procedure that consists of two major surgical stages and one interval phase.

In classical ALPPS, the stage 1 key steps are as follows: (1) Formal laparotomy and abdominal exploration to rule out any extrahepatic disease; (2) Complete liver mobilization, including ligation and division of the retrohepatic veins draining into the inferior vena cava and isolation of and encircling both the right hepatic vein and the middle hepatic vein with vessel loops; (3) Intraoperative ultrasonography to determine resectability and mark the partition plane; (4) Cholecystectomy; (5) If bilobular disease is present, complete tumor wedge resections of the FLR; and (6) Isolation of the right portal vein behind the common hepatic duct, followed by division of the portal supply of the diseased hemiliver. The partition of the liver parenchyma is continued until the retrohepatic vena cava is visualized. The right hepatic arterial in-flow and biliary drainage to the deportalized hemiliver are maintained during this first stage to preserve the liver synthetic function<sup>[34]</sup>.

During the interval phase, the patients are kept in hospital on close monitoring.

Table 1 Contraindications of portal vein embolization

	Contraindications	
	Absolute	Relative
Portal vein embolization	Overt clinical portal vein hypertension	Mild portal vein hypertension
	Extensive invasion of portal vein precluding safe catheter manipulation	Tumor extension to the FLR
		Biliary dilatation of the FLR
	Complete lobar portal vein occlusion	Extrahepatic metastatic disease
		Uncorrectable coagulopathy
		Renal insufficiency

FLR: Future liver remnant.

Within 7–10 d after the operation, a contrast-enhanced abdominal CT scan is performed. If adequate FLR (> 30%) has been achieved and the patient is stable, stage 2 of the procedure is scheduled. In stage 2, the diseased deportalized liver is removed by stapling through the hilar plate followed by stapling of the right hepatic vein and then the middle hepatic vein.

Due to the complexity and concerning outcome, classical ALPPS has been modified in many centers to achieve better results. In the associating liver tourniquet and portal vein ligation for staged hepatectomy, a tourniquet is used to compress the future transection plane between the liver lobe that is going to be resect and the FLR, in lieu of *in situ* splitting of the liver parenchyma. The main advantages of this new technique are reduction in operative time in the first stage and in blood loss. In addition, segment IV is not separated from the hilar bifurcation, thereby helping to avoid ischemic necrosis<sup>[35]</sup>.

The right ALPPS modification is used when the first stage consists of a left lateral sectionectomy, ligation of the right portal vein, and limited or non-anatomical multiple resections of the left, right anterior and caudate lobe lesions. *In situ* parenchyma splitting occurs along the right portal fissure. The second stage of this technique consists of completing the right posterior sectionectomy<sup>[36]</sup>.

In rescue ALPPS modification, the first stage consists of *in situ* parenchyma splitting between the right and left liver lobes along the main portal fissure, where the right portal vein has been already embolized radiologically. The second stage consists of completing the resection of the right hemiliver. This technique is considered when the patients are not candidates for the second stage of classical TSH due to insufficient regeneration<sup>[36]</sup>.

During the left ALPPS modification, the first stage consists of anatomical wedge or limited segmentectomy of the right anterior and posterior sections, left portal vein ligation, and *in situ* parenchyma splitting between the right and left lobes along the main portal fissure. The second stage consists of left hemihepatectomy with resection of segment 1<sup>[36]</sup>.

Hybrid ALPPS was proposed by Li *et al*<sup>[37]</sup> as non-touch technique to treat tumor infiltration of the right portal vein or biliary bifurcation as part of ALPPS. The first stage consists of *in situ* splitting of the hemiliver *via* an anterior approach, followed by right PVE at the first day postoperatively. The final step is completing the second stage of ALPPS. This modified ALPPS could be considered for patients with tumor infiltration of the right portal vein. However, the drawback of this technique is longer operative time in the second stage.

Partial ALPPS was reported by Petrowsky *et al*<sup>[38]</sup> in 2015. The partial ALPPS differs from classical ALPPS by the performance of partial partitioning (50% to 80%, depending on the hepatic veins and the tumor location). Some reports of partial ALPPS cases have shown zero mortality and favorable postoperative outcome, especially after the first stage.

Different types of monosegment ALPPS hepatectomy have been described by Schadde *et al*<sup>[39]</sup>. Additionally, a nomenclature was proposed based on the segment of the liver remnant, rather than the segments of resected liver. This variation of the ALPPS technique represents a substantial change to the traditional paradigm of liver resectability, which is defined as the removal of tumors with negative margins and preserving ≥ 2 contiguous liver segments along with their in-flow, out-flow and biliary drainage.

Generally, some modified techniques of the ALPPS procedure have been shown to reduce mortality and morbidity but, due to insufficient data, they are still under

evaluation in current practice.

## OUTCOMES

### Technical success

For TSH, 76% of patients become candidates for the second stage of the procedure<sup>[40,41]</sup>. However, some patients fail to complete the second stage due to many contributing factors, disease progression being the most common (13%-35%). Other factors are inadequate liver regeneration (0%-4%) and poor patient condition (3%)<sup>[42]</sup>.

Portal vein occlusion techniques are now routinely used in TSH to achieve microscopically negative resection. The PVE has a high technical success rate, approximately 100%; however, its technical failure has been mentioned in the literature<sup>[43,44]</sup>. The resection rate post-PVE in healthy liver can reach up to 85%, while in cirrhotic patients this rate is decreased to 70%. Failure of hypertrophy is rare but the degree of it is variable. The FLR hypertrophy ratio after PVE is 8%-25% in normal status liver. On the other hand, the FLR hypertrophy ratio is 6%-20% in cirrhotic livers<sup>[24,45]</sup>.

ALPPS has been reported to increase the FLR volume by 74% in a mean of 9 d. This short interval between the two stages is due to a rapid and effective hypertrophy, as compared to the vascular occlusion techniques. Many studies have demonstrated that 95%-100% of patients who underwent the first stage of ALLPS then completed the second stage. Importantly, this represents a viable treatment choice to patients with otherwise nonresectable tumors<sup>[20,46-48]</sup>. Furthermore, the R0 resection rate has been reported to be between 86% and 100%<sup>[20,46-48]</sup>.

Knoefel *et al*<sup>[49]</sup> compared the FLR hypertrophy of patients who underwent ALPPS, PVE, and combined procedures. The rates of FLR hypertrophy after PVE *vs* ALPPS were 43% and 63%, respectively. Moreover, the FLR hypertrophy in the ALLPS patients was achieved in 3 d. Currently, the international ALPPS registry shows a completion rate to second stage of around 100% on 553 patients from 84 centers around the world<sup>[50]</sup>.

In summary, the ALPPS procedure can be an appropriate option to overcome the two main limitations of PVE and TSH. Specifically, these are failure or lengthy time required to achieve adequate liver remnant and the high rate of patient drop-off from completing the second resection.

### Efficacy

As mentioned above, the majority of patients can complete the TSH. The remaining patients have a poor prognosis, with a median survival of 20.4 mo. The 3-year survival for patients who complete the second stage is 68% but only 6% for patients who do not. The 5-year survival rate is significantly different between the two groups, 49% and 0%, respectively<sup>[51-53]</sup>.

ALPPS is relatively a new technique, and has shown disease-free survival (DFS) ranging from 73% to 95% at the median of 6 mo. The 1-year DFS is between 46% and 60%<sup>[46,48,54,55]</sup>. Oldhafer *et al*<sup>[56]</sup> reported that 86% of ALPPS-treated patients developed tumor recurrence at a median time of 8 mo. Schadde *et al*<sup>[46]</sup> reported a 1-year recurrence rate in ALPPS of 54%, as compared to 52% for TSH. Cancer-free resection has also been compared between ALLPS and the portal vein occlusion techniques; in one study, 79% of the patients in the ALLPS arm showed cancer-free resection, as compared with 58% in the portal vein occlusion arm.

### Complications

Many complications have been reported for PVE, which are classified as percutaneous-related and PVE-related. The percutaneous-related complications are pneumothorax, vascular injury, and hemobilia. The PVE-related complications include non-target canalization and main portal vein thrombosis. Generally, PVE is a safe procedure, having 0% mortality and 2.2% morbidity<sup>[57]</sup>.

The main downside of ALLPS is the associated high morbidity and mortality. ALPPS has shown rates of overall and major complications that are higher than for the TSH procedure<sup>[58]</sup>. In particular, the postoperative complications reported range between 33% and 64%, as compared to the range of 16% to 25% in TSH<sup>[20,48,58]</sup>. The higher rate of infections and biliary leaks after the first stage of ALPPS compared to TSH can explain this<sup>[59]</sup>. The results of another comparison between the two procedures, carried out by Shindoh *et al*<sup>[60]</sup>, are summarized in Table 2.

The 90-d mortality of ALLPS and TSH was compared by Schadde *et al*<sup>[46]</sup>. He reported that at 15% in ALPPS and 6% in TSH. However, the 90-d mortality of ALLPS is variable in the literature. Schnitzbauer *et al*<sup>[20]</sup> reported a 12% 90-d mortality and



**Table 2 Comparison between associated liver partition and portal vein ligation for staged hepatectomy and conventional two-staged hepatectomy**

Complication	ALPPS	Conventional TSH
Major morbidity (Clavien-Dindo IIIA)	40%	33%
Bile leaks	24%	5.8%
Sepsis	20%	0%
Re exploration	28%	2.9%
Liver-related mortality	12%	5.8%

ALPPS: Associated liver partition and portal vein ligation for staged hepatectomy; TSH: Two-staged hepatectomy.

other series reported no 90-d mortalities.

### Disease-related outcomes

**Colorectal liver metastases (CRLM):** Colorectal cancer commonly metastasizes to the lung and liver. Resection is considered the best treatment of liver metastasis. TSH was introduced in 2000 as an effective surgical approach in bilobar CRLM<sup>[14]</sup>. Since then, it has served to increase the number of patients who can go for liver resection, with an acceptable mortality and morbidity. More recently, in 2012, ALPPS was introduced to treat patients who are borderline or nonresectable CRLM<sup>[20]</sup>.

In TSH, the reported 5- and 10-year survival rates are 40% and 30%, respectively<sup>[61]</sup>. The 1- and 2-year DFS rates were analyzed by Karoui *et al*<sup>[22]</sup> and reported to be 85% and 68%, respectively. However, more than 60% of these patients will have recurrence afterwards<sup>[61]</sup>. The reported 30-d mortality after TSH is 2.5% and the major morbidity rate is 19.6%<sup>[62]</sup>.

In comparison to TSH, ALPPS has shown inferior results. ALPPS registry for patients with CRLM has showed that 1- and 2-year DFS are 59% and 41%, respectively<sup>[55]</sup>. In total, 86% of the patients who underwent ALPPS for CRLM had a tumor recurrence, with a median time of 8 mo<sup>[56]</sup>.

**HCC:** Complete surgical resection is the only potentially curative intervention for HCC. Surgical resection improves the survival rate, increasing it to 9-13 mo from the no-intervention survival time of less than 3 mo.

TSH for HCC patients is not thoroughly investigated, as shown by the small body of literature, and hence no conclusion can yet be reached on its benefits in improving overall survival or DFS. On the contrary, ALPPS has been reported in HCC patients, particularly when there is vascular invasion. Torres *et al*<sup>[63]</sup> reported zero incomplete resection in HCC patients; a 1-year DFS of 87%, 90-d mortality of 12% and rate of high-grade complications (Clavien-Dindo complications IIIb or more) of 25%. Björnsson *et al*<sup>[64]</sup> reported no 90-d mortality in patients who underwent ALPPS for primary hepatobiliary malignancies (4 out of 10 patients had HCC). Two of the HCC patients were lost to follow-up, while two others had died within 6 mo with unclear reported cause of death. More studies are needed to draw a solid conclusion on the outcome of ALPPS in HCC patients.

## CONCLUSION

Staged hepatectomy procedures, including TSH, PVE and ALPPS, are currently well-established and accepted in practice in the field of liver malignancy treatment. Collectively, they have increased the number of patients who are eligible for liver resection from among those who otherwise are labeled as nonresectable. It has been demonstrated, as mentioned earlier, that this advancement has improved the DFS and overall survival as well.

The drawback of these extensive surgical interventions is the higher rate of complication and mortality. It is worth mentioning that these rates have improved from the time they were first advocated. This improvement is probably related to a better selection of patients who are accepted for these procedures. Moreover, the experience level of the healthcare center and its surgeons are paramount factors in these achievements.

We believe that these kinds of advanced intervention techniques and procedures should be carried out in high-flow centers through use of a multidisciplinary approach. More studies and reports are awaited to standardize the future practice and

to minimize the related adverse events.

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