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Overcome intraoperative difficulties of ALPPS procedure: a single-center outcomes and technical experience

Anh The Pham, PhD, Cuong Manh Truong, MD*, Phuong Huy Trinh, MD

Backgrounds/aims: Recently, the ALPPS (Associating liver partition and portal vein ligation for staged hepatectomy) has become widely known to achieve hepatic resection by rapid future liver remnant hypertrophy, but it comes with intraoperative difficulties, followed by increased complications. This study aimed to report the outcomes of an oncology center in a low-income and middle-income country with ALPPS in patients with liver tumors and its technical variants, which were invented to overcome intraoperative difficulties of the ALPPS procedure.

Patients and methods: A retrospective analysis of patients undergoing ALPPS from September 2022 to December 2023 was performed.

Results: A total of 25 patients underwent the ALPPS procedure: 21 procedures for hepatocellular carcinoma (HCC), 3 combined hepatocellular-cholangiocarcinoma (cHCC-CCA), and 1 for small cell neuroendocrine carcinoma (SNEC). The mean postoperative stay was 29.6 ± 9.3 days (range 16–58 days). After stage 1, we counted 8 complications, all of grade II; after stage 2, the number of complications was decreased to 3:2 were of grade I and 1 were of grade IIIB. 3 (12%) patients failed to proceed to ALPPS stage 2. After a median follow-up of 9 months (range 2–25), disease recurrence has been recorded in 3 patients (12%), while 1 patient (4%) died, affected by HCC. The entire group's 2-year overall survival (OS) and disease-free survival (DFS) were 83.3% and 82.5%, respectively.

Conclusion: The ALPPS procedure is an approach for large liver tumors with small future liver remnant with acceptable OS and DFS in a low-income and middle-income country.

Keywords: ALPPS, HCC, hepatic resection, technical variants

Introduction

Post-hepatectomy liver failure (PHLF) remains a significant and potentially life-threatening complication following major liver resections. Accurate assessment of the future liver remnant (FLR) volume is critical in this context, as insufficient volume post-resection is directly linked to the development of PHLF[1,2]. The Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) procedure offers a unique advantage by inducing rapid FLR hypertrophy within a shorter timeframe between stages than other techniques. This is particularly relevant in cases involving portal vein tumor thrombosis (PVTT) or hepatic vein thrombosis (HVT). Despite its potential benefits, the application of ALPPS for hepatocellular carcinoma (HCC) remains controversial due to its higher reported complication rates compared to alternative methods for FLR hypertrophy.

HIGHLIGHTS

- The Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) has recently garnered recognition for facilitating hepatic resection through expedited hypertrophy of the future liver remnant (FLR). Despite its efficacy, the procedure is not without its challenges, presenting intraoperative complexities and an elevated risk of postoperative complications.
- The present study delineates the outcomes of implementing ALPPS and its technical modifications devised to mitigate the aforementioned intraoperative challenges in a cohort of 25 patients with hepatic neoplasms at an oncology center in a low-income to middle-income nation. The findings suggest that ALPPS is a viable strategy for managing extensive hepatic tumors accompanied by a diminutive FLR, yielding satisfactory overall survival (OS) and disease-free survival (DFS) rates.
- Nonetheless, these preliminary observations necessitate further corroboration from more extensive, multicentric studies to ascertain their applicability across diverse clinical settings.

Department of Hepatobiliary and Pancreatic Surgery, Vietnam National Cancer Hospital, Hanoi, Vietnam

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

**Corresponding author. Address: Department of Hepatobiliary and Pancreatic Surgery, Vietnam National Cancer Hospital, 30 Cau Buou Street, Hanoi 12500, Vietnam. Tel.: +84 987 811 995. E-mail: cuongsur@gmail.com (C. M. Truong).*

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However, in low- and middle-income countries (LMICs) like Vietnam, where portal vein embolization (PVE) is not widely adopted, ALPPS presents a valuable option for patients with insufficient FLR volume who would otherwise be ineligible for resection. Surgeons performing the ALPPS procedure often encounter a multitude of technical difficulties. This paper presents our initial experience with ALPPS for liver tumors, focusing on outcomes and the technical modifications we have implemented to address these challenges.

Methods

This article has been reported in line with the PROCESS criteria[3].

Our procedures adhered to the Declaration of Helsinki. This article was registered on "ResearchRegistry.com" with an identifying number.

This is a retrospective study. Between September 2022 and December 2023, 25 patients underwent two-staged hepatectomy with the ALPPS procedure, representing 0.93% of 2686 liver resections performed over 6 years of activity. We performed 21 procedures for HCC, 3 for combined hepatocellular-cholangiocarcinoma (cHCC-CCA), and 1 for small cell neuroendocrine carcinoma (SNEC).

All patients had locally advanced liver tumors and Child-Pugh A grade of liver function. No extrahepatic metastasis was found. One patient had a compression of tumor to the middle hepatic vein. The presence of tumor thrombosis in a major branch of PV, tumors involving the confluence of hepatic veins and inferior vein cava (IVC), or suprahepatic IVC, was considered as exclusion criteria for the procedure.

The goal of the study was to report the 90-day mortality, disease-free survival (DFS), overall survival (OS), liver function tests, postoperative complications (POC), length of hospital stay, FLR volumes and increase in FLR volume after the first stage was recorded.

All patients diagnosed with locally advanced liver cancer underwent a multidisciplinary team review. This team comprised hepatologists, liver surgeons, interventional radiologists, anesthetists, and oncologists. Preoperative radiological evaluation with volumetric computed tomography (VCT) or MRI was mandatory for all patients to exclude the presence of extrahepatic disease. A VCT scan was also performed before stage 1 of the ALPPS procedure to assess the FLR volume. Notably, a liver remnant-to-bodyweight ratio (LBWR) of at least 0.8 was deemed necessary to proceed with stage 2 surgery. Following stage 1, a repeat VCT scan of the liver was conducted starting from the postoperative day (POD) 13. To quantify the FLR volume increment, researchers employed the formula: %FLR volume increase = (vol1 – vol0)/vol0 × 100, where vol0 represents the baseline FLR volume and vol1 represents the FLR volume measured after stage 1.

Informed consent was obtained from all patients before the procedures.

Detailed descriptions of the standard ALPPS surgical techniques are available in the published literature[4]. ALPPS involves two stages. The first surgical procedure involves ligating the right portal branch and partitioning the two hemilivers parenchymal. The second step of the procedure is usually performed around 14 days after the first stage for these cases with sufficient FLR and without extrahepatic metastases. The tumoral hemiliver is removed by sectioning the right hepatic artery, the biliary duct, and the systemic venous pedicle. This manuscript focuses on the specific technical variations employed at our center to address intraoperative challenges encountered during the ALPPS procedure. PHLF was graded according to Belghiti's 50-50 criteria[5]. POC were categorized using the Clavien–Dindo classification. Tumor recurrence assessment utilized a combination of clinical examination, laboratory parameters, and radiological imaging modalities such as MRI, computed tomography (CT) scan, and PET scan.

Descriptive statistics were employed to summarize patient characteristics. The Kaplan–Meier method was used to estimate patient survival curves. All statistical analyses were performed using the SPSS software (version 21.0, SPSS Inc.).

Ethical issues: This study was conducted with the informed consent of all participating patients and received the requisite ethical approval from the Scientific Council of our hospital, including experts from relevant specialties: oncologists, gastroenterologists, hepatobiliary surgeons, radiologists, and pathologists.

Results

Between September 2022 and December 2023, in our institution, 25 patients underwent two-staged hepatectomy with the ALPPS procedure.

Preoperative characteristics

Preoperative characteristics of the study patients were shown in Tables 1, 2. The group's median age at the moment of surgery was 53.2 ± 12.2 years (range 30–73). Ninety-six percent of patients were men. The median BMI was 24 kg/m^2 (range 20–29). Nineteen patients (76%) were affected by HBV infection, while no patient was positive for HCV. The median value of AFP was 77.4 ng/ml (range 2.43–125 000). The preoperative median CEA and CA 19-9 levels were 3.3 ng/ml (2.3–56.3) and 15.1 U/ml (4.9–240.8), respectively.

Table 1

Preoperative characteristics of the study patients

Variable	ALPPS
	n = 25
Male/female	24/1
Age, years (range)	53.2 ± 12.2 (30–73)
BMI (range)	24 (20–29)
Preoperative diagnosis	
HCC	23
cHCC-CCA	2
Preoperative tumor markers	
AFP (range)	77.4 (2.43–125 000)
CEA (range)	3.3 (2.3–56.3)
CA 19.9 (range)	15.1 (4.9–240.8)
Preoperative viral status	
HBV, n (%)	19 (76)
HCV, n (%)	0

ALPPS, Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy; cHCC-CCA, combined hepatocellular-cholangiocarcinoma; HCC, hepatocellular carcinoma. AFP, Alpha-fetoprotein. CEA, Carcinoembryonic Antigen. CA 19-9, Carbohydrate Antigen 19-9. HBV, Hepatitis B virus. HCV, Hepatitis C virus.

Table 2

Preoperative characteristics of tumor of the study patients

Variable	
HCC	23
No. nodules (range)	1 (1–3)
Size of largest lesion (cm)	17
Right lobe + segment 4	4
Right lobe	19
Left lobe nodes	4
Middle hepatic vein involvement	8
cHCC-CCA	2
No. nodules	1
Size of largest lesion (cm)	9.6
Right lobe	2

cHCC-CCA, combined hepatocellular-cholangiocarcinoma; HCC, hepatocellular carcinoma.

Liver volumetry

VCT showed an average preoperative FLR of 336.9 ± 61.4 cm^3 calculated radiologically among patients of the whole group (Fig. 1). The mean preoperative FLR/ BW ratio was 0.77 ± 1.09%. After a median time of 14.28 ± 1.34 days since the first stage, VCT showed a mean FLR of 590.8 ± 98.7 cm^3 in the whole group with a mean FLR/ BW ratio of 0.98 ± 0.13%. The mean percentage of FLR increase was 83.3 ± 36.7% in the entire group (Fig. 2).

Intraoperative data (Table 3)

After a mean time from stage I of 14.3 days (range 13–19 days), 3 patients failed to proceed to stage 2 for different reasons: 1 had liver failure, 1 had IVC tumor thrombosis, and 1 had left liver metastases due to tumor progression. In 22 (88%) patients of ALPPS stage 2, right hepatectomy and right trisectionectomy accounted for 86.4% and 13.6%, respectively. A pringle maneuver was performed in all cases to reduce blood loss during liver parenchymal transection. The hanging maneuver was performed in 5 patients (20%) (Fig. 3). Routine double drain placement was put for all cases in stage 1. Left lobe metastasectomy was performed for 4 cases in stage 1 without increasing intraoperative complications. Four patients who were suspected of lymph node metastasis due to preoperative CT scan or intraoperative observation were performed lymphadenectomy, including those at the hepatoduodenal ligament, along the common hepatic artery, and within the retro-pancreatic space. Plastic bag cover was used for 3 first cases (Fig. 4). One patient with HCC had middle hepatic vein compression and had undergone middle hepatic vein ligation near the confluence of hepatic veins and IVC to prevent metastasis. For the first phase, the mean operative time was 164.6 ± 34.7 min (range 95–220), while the mean duration for the second stage was 130.2 ± 25.9 min (range 80–170) for the overall record. Mean blood loss during stages I and II of the ALPPS procedure were 230.2 ± 42.9 ml (range 100–600) and 162.3 ± 22.3 ml (range 100–280), respectively. No relaparotomy was required after both stages of ALPPS.

Postoperative outcomes (Table 3)

The mean postoperative stay was 29.6 ± 9.3 days (range 16–58 days). After stage 1, we counted 8 complications, all of grade II; after stage 2, the number of complications was decreased to 3:2 were of grade I and 1 were of grade IIIB. The mean postoperative stay was 29.6 ± 9.3 days (range 16–58 days). Postoperative pathology results found 3 cases of cHCC-CCA and 1 case of SNEC, treated with adjuvant chemotherapy. After a median follow-up of 9 months (range 2–25), disease recurrence has been recorded in 3 patients by HCC progression, treated with transarterial chemoembolization (TACE). One patient died of PHLF within 90 days from surgery (90-day mortality = 4%). 2-year OS and DFS for the entire group were 83.3% and 82.5%, respectively (Fig. 5).

Discussion

The introduction of the ALPPS procedure has marked a significant advancement in the field of liver surgery. However, a substantial body of existing research has primarily concentrated on the procedure's specific patient indications, technical considerations, and feasibility. Notably, these studies have also emphasized the potential drawbacks associated with ALPPS, including a high incidence of complications and mortality.

With the increasing adoption of image-guided liver hypertrophy techniques like PVE and hepatic vein embolization (HVE), the use of the ALPPS procedure is gradually declining in favor of these more contemporary approaches. However, for developing nations with limited access to such advanced technologies, ALPPS

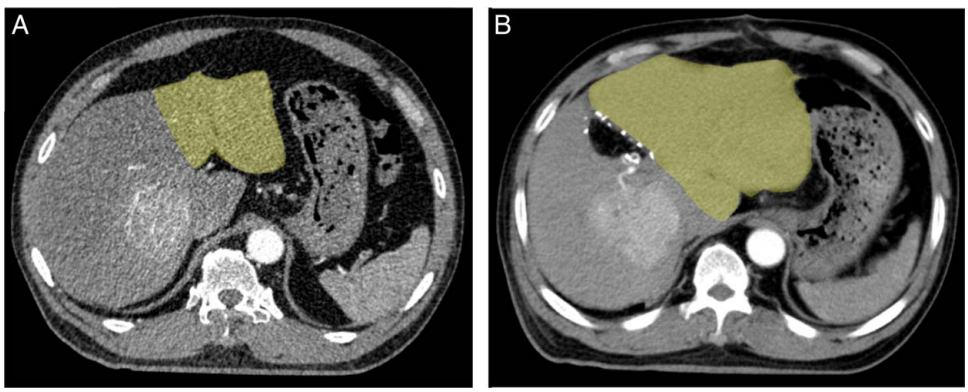

Figure 1. (A) Preoperative computed tomography (CT) image (RLV/BWR: 0.54%). (B) 14th postoperative day CT image (RLV/BWR:.0.93%). The yellow part shows the hypertrophy of left hemiliver.

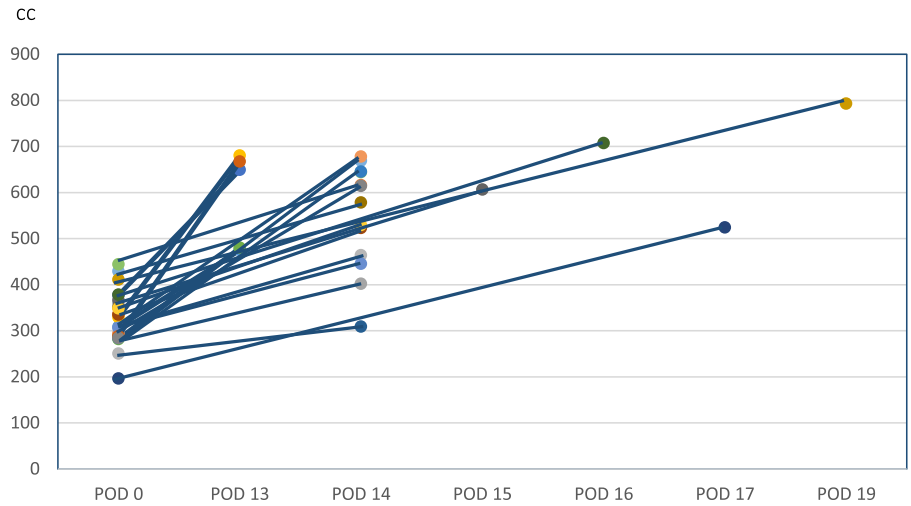

Figure 2. Future liver remnant increase between the Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS)-1 and ALPPS-2 procedures.

remains a valuable tool for expanding surgical options in patients with advanced-stage HCC. In this context, meticulous patient selection based on appropriate indications, thorough risk factor evaluation, and implementation of a standardized, precise surgical technique are crucial to minimizing the associated drawbacks[6].

Our study presents a unique series of 25 ALPPS procedures, with a high proportion performed for HCC. This emphasis on HCC reflects the dual nature of our center as both a national oncology center and a specialized facility for HCC treatment. Furthermore, HCC presents several clinical scenarios that make ALPPS a particularly attractive strategy: (1) Portal vein involvement: HCC often manifests as localized tumors with portal vein invasion. This precludes portal embolization, a key component of the classic two-stage hepatectomy. (2) Inadequate FLR Generation: In some cirrhotic livers, portal embolization fails to achieve a sufficient FLR volume necessary for resection. (3) Aggressive Neoplasms: Occasionally, massive and rapidly progressing HCC tumors leave insufficient time for the traditional two-stage approach.

As our experience demonstrates, ALPPS offers a viable option for resecting tumors that would otherwise be unresectable. These tumors might only be treatable with palliative or medical therapies according to BCLC guidelines. The introduction of ALPPS has thus expanded the indications for liver resection in HCC, allowing a more significant number of patients to benefit from curative surgical intervention.

Despite its potential benefits, long-term outcomes associated with ALPPS remain a concern. Studies have reported high complication rates ranging from 59 to 64% and mortality rates between 12 and 16%. Compared to classic two-stage hepatectomies, the higher morbidity and mortality associated with ALPPS raise questions about its overall feasibility[7,8]. Elderly patients (over 60 years old) are considered at higher risk for complications and death due to their diminished regenerative capacity compared to younger patients. Additionally, the need for blood transfusion and an extended operative time (>300 min) during the first stage procedure have been identified as independent risk factors for poor outcomes[9,10]. Research suggests a partial liver transection (above the middle hepatic vein) can achieve adequate hypertrophy. Compared to a total transection reaching the inferior vena cava, this approach offers similar results while potentially minimizing complications related to improper raw surface management (e.g. bile leaks and bleeding)[11]. Furthermore, a combination of partial hepatic transection with minimal liver mobilization using the "hanging maneuver" and an anterior approach may further minimize the impact of the first stage and facilitate faster patient recovery. This technique can reduce operative time and blood loss, decreasing the need for transfusions and ultimately lowering morbidity and mortality rates[12]. While ALPPS offers a valuable tool for expanding surgical options, careful patient selection and optimization of surgical techniques are crucial to mitigate the associated risks and improve long-term outcomes.

Our study corroborates previous findings that early morbidity and mortality rates following ALPPS are somewhat higher than those typically reported for major liver resections. Several contributing factors are likely at play, including the ALPPS procedure's inherent complexity, underlying cirrhosis, and locally advanced disease within the patient population. These observations are consistent with data from the international ALPPS registry, which documented an overall 90-day mortality rate of 8.8% among 320 patients, with postoperative liver failure identified as the leading cause of death in 75% of cases. Encouragingly, our series demonstrates a favorable profile regarding postoperative complications, operative times, blood loss, and the need for perioperative blood transfusions. These findings suggest that, within our institution, the ALPPS procedure has not only been successfully implemented but has also achieved a level of standardization that translates into improved patient outcomes.

Our experience has led to the adoption of several technical modifications aimed at reducing intraoperative complications during the ALPPS procedure:

(1) Minimizing adhesions: whenever feasible, we prioritize mobilizing the liver during stage 1 to minimize adhesion formation during stage 2. However, in large tumors or involvement with the diaphragm, where liver mobilization

Table 3

Operative data, postoperative complications, and clinical outcome of the study patients

Variable	ALPPS
Surgery	*n* = 22
Right hepatectomy	19
Right trisegmentectomy	3
Stage 1	*n* = 25
Operative time (mean, min)	164.6 ± 34.7 (95–220)
Blood loss (mean, ml)	230.2 ± 42.9 (100–600)
Intraoperative blood transfusion	0
Stage 2	*n* = 22
Operative time (mean, min)	130.2 ± 25.9 (80–170)
Blood loss (mean, ml)	162.3 ± 22.3 (100–280)
Intraoperative blood transfusion	0
Left lobe metastasectomy	4
Mobilization of right hemiliver	14
Hanging maneuver	5
Pringle maneuver (%)	100
Plastic bag use	3
Lymphadectomy	4
R0 resection (%)	100
Relaparotomy rate (%)	0
ALPPS efficacy (%)	88
Postoperative complications	8 + 3 = 11
Liver failure after step 1	4
Liver failure after step 2	2
Clavien I–II	7 + 2
Clavien IIIA	1
Clavien IIIB	0
Clavien IV	1
Clavien V	0
Postoperative stay (step 1 + 2) (mean, days)	29.6 ± 9.3 (16–58)
Adjuvant chemotherapy	4
30-day mortality (%)	0
90-day mortality (%)	4
Recurrence rate (%)	12
2-year overall survival (%)	83.3
2-year disease-free survival (%)	82.5
Follow-up (median, months)	9 (2–25)

ALPPS, Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy.

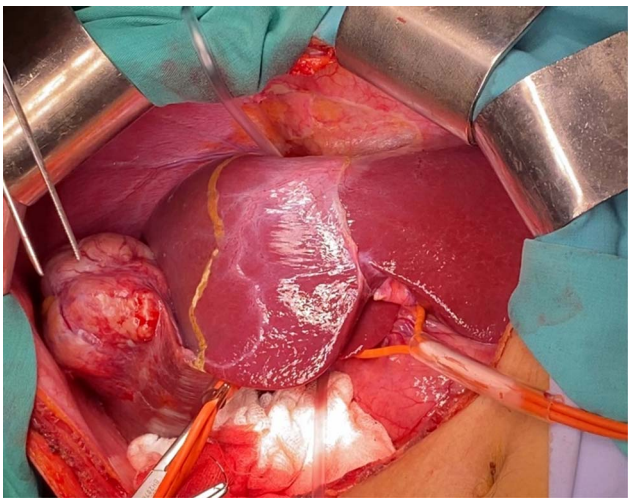

Figure 3. Liver hanging maneuver.

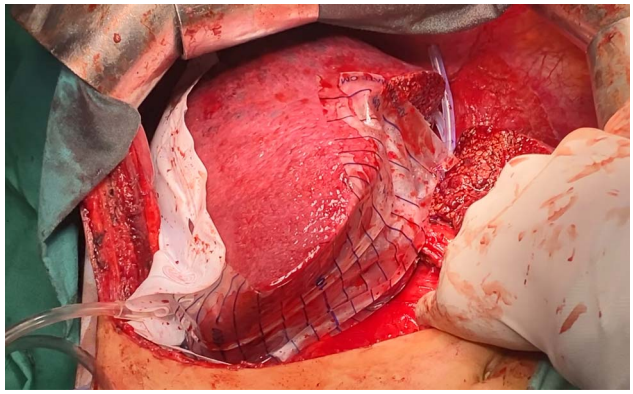

Figure 4. A plastic bag was used to prevent the adhesions in Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) stage 2.

risks tumor rupture, we employ a "non-touch" technique using an anterior approach without mobilizing the right hemiliver.

(2) Eliminating plastic bag covers: we have found plastic bag covers unnecessary for preventing adhesions. They may even contribute to fluid accumulation at the transection plane at stage 2 of the ALPPS procedure (Fig. 6). In some cases, a major medical complication arising after the first stage of the ALPPS procedure can significantly delay the re-operation. With the presence of a plastic bag, this delay can have several detrimental consequences. Existing fluid collections within the abdomen may enlarge over time, potentially leading to further complications. As collections persist, the risk of abscess formation increases. The presence of an abscess or any significant infection significantly elevates the patient's risk of developing sepsis, a life-threatening systemic inflammatory response. Besides, if the patient is not eligible for ALPPS stage 2, the plastic bag still requires a second surgery to remove it.

(3) Facilitating stage 2 dissection: the two drains placed in the right subhepatic fossa during stage 1 are now retracted along the posterior space of the right liver to the back of the right Glissonean pedicle for "hanging up" (Fig. 7). This technique facilitates the dissection process during stage 2.

(4) Standardized Glissonean pedicle division: we consistently transect all components of the right hepatic pedicle together using a vascular stapler during stage 2. This includes the right portal vein, previously isolated and ligated with sutures during stage 1. This combined approach minimizes the risk of damage to the left Glissonean pedicle, particularly the left hepatic bile duct, which could develop adhesions during the interval between stages.

Three patients experienced disease recurrence within one year following ALPPS surgery. Unfortunately, one patient succumbed to liver failure. These findings highlight the potential need for adjuvant therapy strategies to improve long-term survival rates. Postoperative adjuvant chemotherapy was administered to patients whose post-surgical pathology results revealed cHCC-CCA and SNEC. A monthly monitoring regimen was implemented for patients diagnosed with HCC. Enhanced TACE,

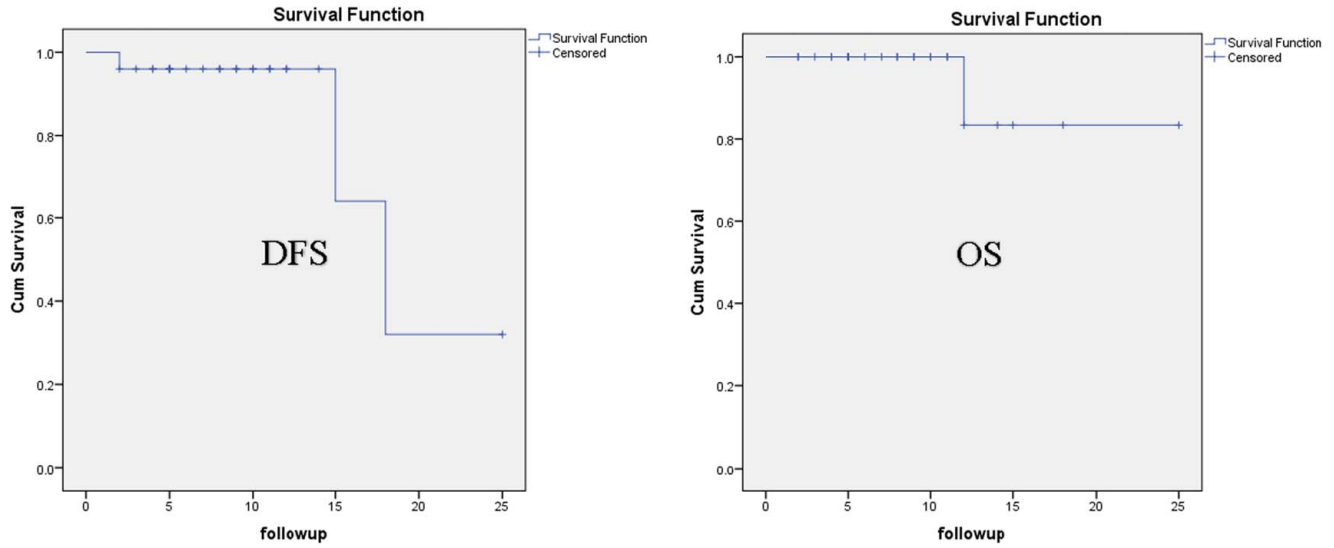

Figure 5. Two-years overall survival (OS) and disease-free survival (DFS).

radio-frequency ablation (RFA), re-surgery, or systemic therapy may be a targeted treatment approach if new lesions are identified.

Our study included only one patient with macrovascular invasion (MVI). Therefore, whether ALPPS offers any clinical advantage for this specific patient subgroup remains unanswered[13,14]. Retrospective surgical studies have suggested potential survival benefits in MVI cases. For instance, Kokudo *et al.*[15] reported a correlation between the extent of portal vein tumor thrombus (PVTT) and survival, with progressively shorter mean survival times observed for more advanced stages. However, more recent research presents contrasting findings. A French study retrospectively reviewed patients with HCC and MVI (predominantly with major portal vein thrombosis vp3/vp4) who were treated with either surgical resection or sorafenib (a targeted therapy medication). This study found that overall survival rates for patients undergoing surgical resection were comparable to those receiving sorafenib, with a notable 16% 90-day mortality rate in the surgical group[16].

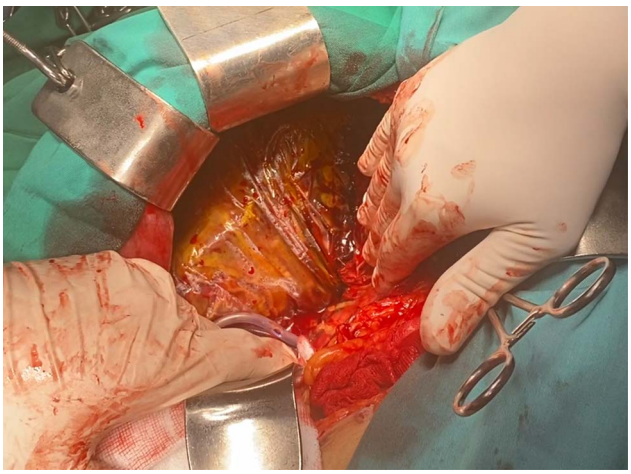

Figure 6. Bile fluid accumulation at the transection plane in Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) stage 2.

Our study demonstrated favorable 2-year OS and DFS rates of 83.3% and 82.5%, respectively, for the entire patient cohort. While these results exceed those reported by some previous studies[17–19], limitations exist. The relatively small sample size and short follow-up period restrict the generalizability of our conclusions.

These observations require external validation through more extensive studies to confirm their generalizability. While ongoing refinements in surgical technique can likely reduce the incidence of intraoperative complications, limitations exist in the present study. This was the first time we performed this technique without experience choosing a method to control tumoral hemiliver after phase 1. This led to using a plastic bag to cover it without predicting possible complications. In some cases, the lack of liver volume is not too much, and the remnant liver can be hypertrophied by TACE combined with PVE. However, due to a lack of embolization material at that time and some patients refused that method, the ALPPS procedure was performed as an alternative. The most frightening complication after the ALPPS stage 1 is liver failure, which demands plasma and albumin transfusion, causing a significant economic burden for poor patients, so it is a limitation of postoperative treatment in LMICs. Moreover, the small sample size restricts the generalizability of the findings. Finally, the follow-up period cannot provide definitive data on long-term oncological outcomes. Prospective studies with larger patient cohorts and extended follow-up periods are necessary to definitively assess the role of ALPPS in managing HCC, particularly in LMIC settings.

Conclusion

In HCC patients with insufficient remnant liver volume for hepatectomy, ALPPS presents a viable, effective, and oncologically sound surgical intervention. This procedure is particularly pertinent in medical facilities lacking the requisite infrastructure and resources to access PVE or in cases in which PVE does not

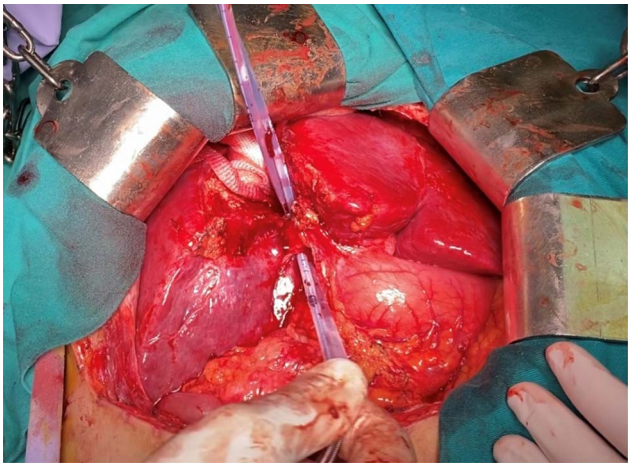

Figure 7. Hanging right Glissonean pedicle by 2 drains in Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) stage 2.

result in an adequate increase in the remnant liver volume. However, it is imperative to acknowledge that ALPPS is associated with a significant complication profile. Thus, it necessitates execution in specialized healthcare institutions equipped with advanced capabilities for managing potential liver insufficiency post-operatively.

Ethical approval

All procedures performed in this study involving human participants were by the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent

Written informed consent was obtained from the patients for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Informed consent. Informed consent was obtained from the study patients.

Patient perspective

This study was conducted with the informed consent of patient and received the requisite ethical approval from the Scientific Council of Vietnam National Cancer Hospital. The council comprises expert representatives from relevant specialties, including hepatobiliary surgeons, radiologists, oncologists, gastroenterologists, and pathologists. Their comprehensive review and endorsement ensured adherence to the highest ethical standards throughout the research process. Our procedures adhered to the Declaration of Helsinki.

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None.

Author contribution

Conceptualization: A.T.P., C.M.T. Data curation: all authors. Methodology: all authors. Visualization: all authors. Writing—original draft: C.M.T. Writing—review and editing: A.T.P., C.M.T.

Conflicts of interest disclosure

The authors declares no conflicts of interest.

Research registration unique identifying number (UIN)

This article has been reported in line with the PROCESS criteria. Our procedures adhered to the Declaration of Helsinki. This article was registered in "ResearchRegistry.com" with identifying number being "researchregistry10158".

Guarantor

Anh The Pham.

Data availability statement

None.

Provenance and peer review

None.

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