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ORIGINAL RESEARCH

Safety and Efficacy of Liver Venous Deprivation Following Transarterial Chemoembolization Before Major Hepatectomy for Hepatocellular Carcinoma

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Objective: This study aimed to evaluate the safety and efficacy of liver venous deprivation (LVD) following transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC).

Methods: Between January 2021 and December 2022, HCC patients indicated for hepatectomy with initial insufficient future liver remnant (FLR) underwent LVD after TACE to induce preoperative liver hypertrophy.

Results: Twenty-seven HCC patients with a median age of 55 years underwent LVD. No TACE or LVD procedure-associated complications occurred, except for 1 case presenting with grade A liver failure after LVD (then recovered after 7 days). The FLR volume was 29.3% (interquartile range [IQR] = 7.5) and 48.9% (IQR = 8.6) of the total liver volume before and after LVD, respectively ($p < 0.001$). The degree of hypertrophy and FLR hypertrophy rate were 14.8% (IQR = 8.4) and 55.2% (IQR = 36.7), respectively. All 27 patients demonstrated sufficient FLR after LVD (24 patients at three weeks post-LVD, one at six weeks, and two at ten weeks), but only 21 patients accepted surgery. Postoperative histopathology showed 16 patients with cirrhosis and five with mild fibrosis (F1, F2). One patient presented with severe intraoperative bleeding due to damage of left hepatic vein and developed grade C liver failure, then died on day 32 postoperation.

Conclusion: LVD following TACE seems to be a safe, effective, and feasible method of inducing significant FLR regeneration in HCC, even in well-selected cirrhotic livers. Comparative studies with a large patient population and multicenter data are needed for further evaluation.

Keywords: hepatic vein embolization, hepatocellular carcinoma, liver hypertrophy, liver resection, liver venous deprivation, portal vein embolization

Introduction

After major liver resection, postoperative liver failure due to insufficient liver remnant volume remains the leading cause of death.[1] Portal vein embolization (PVE) is the most widely accepted way to induce hypertrophy of the future liver remnant (FLR) before major hepatectomy for treating hepatocellular carcinoma (HCC), which mainly occurs in chronic liver disease. However, after PVE, patients usually need to wait about 6–8 weeks before surgery, and up to 20–30% of patients cannot benefit from hepatectomy due to insufficient growth of FLR or tumor progression.[2–4] Additional hepatic vein embolization (HVE) in patients with inadequate FLR hypertrophy after PVE has also shown promising results.[5] However, this method requires a long waiting time with two different interventions.[5] In the last decade, the associated

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liver partition and portal vein ligation for staged hepatectomy (ALPPS) technique has been applied to increase FLR volume regarding PVE; however, the high mortality rate remains the drawback.[6–8]

Recently, liver venous deprivation (LVD; simultaneous PVE and HVE) has been applied to replace PVE, showing a more significant increase in liver hypertrophy and shortening of the waiting time for surgery.[9–12] However, reports of the use of this technique have been mostly for treating colorectal cancer liver metastases (CRLM) or biliary tumors, which generally occur in noncirrhotic livers.[9,11–13] Data on the use of this procedure for cirrhotic livers appear only sporadically in the literature.[10] Therefore, this study aimed to evaluate the safety and efficacy of the LVD following TACE for patients with HCC.

Materials and Methods

Study Population

Between January 2021 and December 2022, 27 patients with HCC indicated for hepatectomy with initial insufficient FLR volume (FLR < 25% of total liver volume [TLV] in normal liver or <40% of TLV with underlying liver diseases) underwent LVD to induce preoperative liver hypertrophy. An underlying liver disease was suspected if the patient had portal hypertension (esophageal varices and/or platelet count <100,000/mm^3 with splenomegaly), histopathology showing cirrhosis (F3/F4), or a metabolic syndrome or received eight or more cycles of chemotherapy. Our Institutional Review Board of Hanoi Medical University approved this study (Ref: 627/GCN-HDDDNCYSH-DHYHN, dated April 20, 2022). The Hanoi Medical University Review Board waived the patient or guardian consent requirement because the study was retrospective and involved analysis of anonymized image data. Our retrospective study was conducted adhering to the guidelines set forth in the Declaration of Helsinki.

Hepatocellular Carcinoma Control

All patients with HCC received transarterial chemoembolization (TACE) prior to LVD to control their tumors. TACE was performed through the femoral approach under local anesthesia. Celiac and superior mesenteric arteriograms were performed using a 5-Fr Yashiro catheter (Terumo, Tokyo, Japan) to evaluate tumor(s), feeding arteries, and the patency of the portal vein. The small microcatheter (from 1.8-Fr to 2.0-Fr) was inserted into the feeding arteries as selectively as possible to maximize tumor control and minimize liver damage. Patients could receive the conventional TACE (cTACE) or drug-eluting bead TACE (Deb-TACE). We preferred to use Deb-TACE for large, well-defined HCCs.

In case of using cTACE, 10 mg of epirubicin (Farmorubicina; Pfizer Italia, Nerviano, Italy) dissolved in 0.5 mL of non-ionic contrast media was mixed with 2 mL of lipiodol before super-selective injected into the feeding arteries. The total volume of the emulsion was adjusted depending on the size and number of tumors. A maximum of 150 mg epirubicin were permitted, but we normally used no more than 100 mg of epirubicin and 20 mL of lipiodol for per cTACE session.

In case of using Deb-TACE, DC bead 100–300 μm and/or 300–500 μm (DC bead, Biocompatibles UK Ltd, UK) loaded with epirubicin. Each vial of DC bead® was loaded with 75 mg of epirubicin. No more than two vials and 150mg of epirubicin per session were used.

For huge tumors, we prioritized embolizing all tumoral arteries near the FLR to avoid tumor spread during waiting for surgery. Two to three mL of lipiodol were selectively injected into the arteri(es) feeding the FLR. At the end of segmental feeding arteries were subsequently temporarily embolized by Gelatin Sponge until near stasis. Cone-beam CT was immediately obtained after finishing the embolization to ensure no malignant lesions in the FLR.

Liver Venous Deprivation

The LVD procedure would be carried out in several weeks after TACE. In patients with high tumor burden or high risk of tumor progression, if there was no post-TACE liver dysfunction on clinical and paraclinical examination, the LVD procedure could be early performed in one week to reduce the waiting time.

The patient underwent conscious sedation and local anesthesia. PVE was always performed before HVE in the same intervention. For PVE, the ipsilateral approach was preferred; the contralateral approach was used only when the ipsilateral approach was not favorable. For HVE, the transhepatic approach was preferred to the transjugular approach.

The latter was used only when the target hepatic vein could not be accessed through the liver parenchyma (eg, when the HCC was too large).

The peripheral branch of the portal vein was accessed with an angiocatheter (16G × 5.25; Angiocath™ BD, Sandy, UT, USA) under ultrasound guidance. In case of the HVE procedure using transhepatic approach, the peripheral branch of each targeted hepatic vein was accessed with an Angiocath 16G needle under ultrasound guidance (and then it was left in place and locked by a Luer Lock cap) before doing PVE. In case of the HVE procedure using transjugular approach, the right internal jugular vein was punctured permitting to catheterize the targeted hepatic vein(s).

Portography was performed through a 5-Fr catheter. Next, the portal branches supplying the future resected liver were embolized using a mixture of n-butyl-2-cyanoacrylate (NBCA) and lipiodol (at a ratio of 1:3 to 1:6) through a 2.7-Fr microcatheter. Tract embolization was performed with the same mixture of NBCA and lipiodol.

After completing PVE, a 7Fr or 8Fr sheath was inserted into each target hepatic vein. Right hepatic vein and accessory right hepatic vein(s) (if present) were embolized in patients scheduled for right hepatectomy. Right & middle hepatic veins and accessory right hepatic vein(s) (if present) were embolized in patients scheduled for extended right hepatectomy. An Amplatzer Vascular Plug (AVP) II (80–100% oversizing) was used to occlude each hepatic vein at least 2 cm from the vena cava. In the transhepatic approach, the peripheral branch of the embolized hepatic vein and needle tract were embolized with the same mixture.

Serum aspartate aminotransferase, alanine aminotransferase, and bilirubin levels and blood count were obtained one day after LVD. The patient was discharged the next day if no complications were found.

Abdominal CT was performed before and three weeks after LVD and repeated every 3–4 weeks thereafter if there was insufficient FLR growth or until surgery was no longer indicated. TLV (excluding tumor volume) and FLR volume were measured. The FLR volume as a percentage of TLV (%FLR) was calculated as FLR/TLV × 100%. The degree of hypertrophy (DH) was calculated as the difference between post-LVD and pre-LVD %FLR. The FLR hypertrophy rate was defined as the ratio of the change in FLR volume after LVD to the initial FLR volume (%). The main portal trunk diameter before and after LVD was also measured.

In cases with insufficient FLR after LVD, TACE was performed at week four from LVD and repeated every four weeks to control the tumors while waiting for the FLR growth. Surgery was indicated when sufficient FLR and no contraindications were found.

The Clavien–Dindo classification was used to classify postoperative complications if present. Hepatobiliary complications were defined according to the "50–50 criteria", with jaundice, encephalopathy, postoperative ascites, and/or grade C liver failure defined according to the International Study Group of Liver Surgery (ISGLS) definitions.[1]

Statistical Analysis

All statistical analyses were performed using SPSS 23.0 software (SPSS Inc., Chicago, IL, USA). Qualitative and continuous variables were described as percentages and medians (with interquartile ranges [IQRs]). Quantitative variables were compared using the Mann–Whitney *U*-test or Wilcoxon signed rank test. *P*-values < 0.05 were considered significant.

Results

Our study included 27 patients (21 men and 6 women) with a median age of 55 (IQR = 18) years. Their preoperative characteristics are summarized in Table 1. All patients had a history of chronic hepatitis B. Twenty-five patients had a Child–Pugh score of 5 and 2 patients a score of 6, of whom one had an ECOG status of 1. The median of the largest tumor diameter at the time of diagnosis was 65 mm (IQR = 39). Six patients refused surgery or biopsy; therefore, we cannot confirm whether or not they showed cirrhosis on pathology. Of the 21 patients undergoing surgery, sixteen presented with cirrhosis (F3/F4) on pathology, and the five remaining patients presented with liver fibrosis grade F1 or F2.

The characteristics of the CT images before and after LVD are summarized in Table 2. All cases underwent TACE before LVD (1–4 weeks). No liver dysfunction was found after TACE. In one case, partial splenic embolization was performed concurrently with the first TACE due to splenomegaly and decreased platelet count (66,000/mm^3). Two weeks after the procedure, the platelet count returned to normal (179,000/mm^3), and LVD was performed. At the first CT after

Table 1 Patients' Clinicopathological Characteristics Prior to Liver Venous Deprivation

Characteristic	N = 27
Age (years) (median; IQR)	55.0; 18.0
Gender Male (n; %) Female (n; %)	 21; 77.78 6; 22.22
Hepatitis Hepatitis B (n, %) Hepatitis C (n, %)	 27 0
BSA (m^2) (median; IQR)	1.66; 0.17
BMI (kg/m^2) (median; IQR)	22.0; 3.7
ECOG status = 1	1
MELD score (median; IQR)	7; 2
Child–Pugh score: 5 6	 25 2
Liver fibrosis on histopathology F0–1–2 (n, %) F3–4 (n, %)	(N = 21) 5 (23.81%) 16 (76.19%)
Serum total bilirubin level before LVD (μmol/l) (median; IQR)	13; 6.6
Platelet count ($\times 10^3/mm^3$) (median; IQR)	242; 135

Abbreviations: BMI, body mass index; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; MELD, model for end-stage liver disease.

Table 2 Parameters Related to Liver Volume (N = 27)

Characteristic	Before LVD	After LVD	p*
TLV (mL) (median; IQR)	1319.3; 413.8	1330.7; 414.2	0.149
FLR (mL) (median; IQR)	412.0; 92.3	652.8; 112.7	< 0.001
%FLR (%) (median; IQR)	29.3; 7.5	48.9; 8.6	< 0.001
Portal trunk diameter (mm) (median; IQR)	13.0; 1.6	14.0; 2.3	0.031

Note: *Wilcoxon signed rank test.
Abbreviations: FLR, future liver remnant; %FLR, FLR volume as a percentage of TLV; IQR, interquartile range; LVD, liver venous deprivation; TLV, total liver volume.

LVD, most cases showed sufficient FLR for liver resection except for three cases of cirrhosis. These cases underwent additional TACEs; they then gained sufficient FLR for right hepatectomy (one patient at six weeks and two patients at ten weeks after LVD). The %FLR increased significantly from 29.3% before LVD to 48.9% after LVD ($p < 0.001$). The DH and FLR hypertrophy rate were 14.8% (IQR = 8.4) and 55.2% (IQR = 36.7), respectively. In all cases, PVE was performed through an ipsilateral approach. For HVE, transhepatic access was available for 17 patients, while right transjugular access was available for the remaining 10 cases, with the median duration of the procedure being 49 (IQR = 10.5) minutes for the former and 64 (IQR = 32.3) minutes for the latter (Mann–Whitney *U*-test, $p = 0.021$). After LVD, one case showed grade A liver failure and recovered after seven days. Then, right hepatectomy was performed for this case at week 5 after LVD without postoperative liver failure (Figure 1).

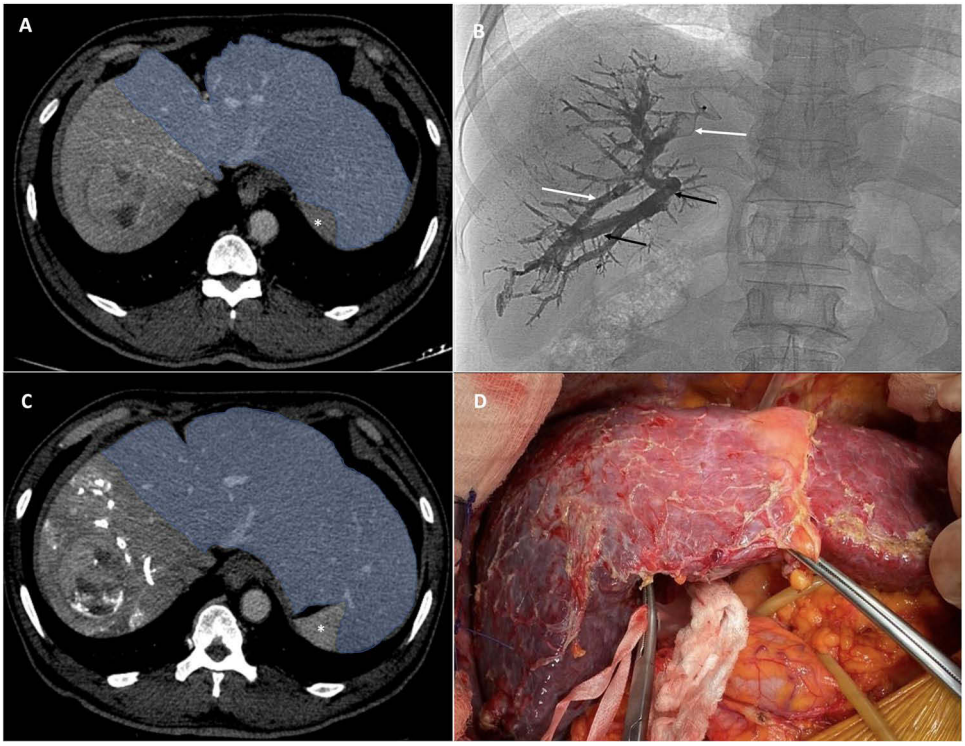

Figure 1 A 60-year-old male patient with single mass hepatocellular carcinoma of 6 cm in the right lobe and cirrhosis (Child–Pugh score = 5 points). (**A**) Axial computed tomography (CT) scan at the time of diagnosis; FLR volume was 457 mL, %FLR = 34.6%; *Spleen. (**B**) A single shot at the end of liver venous deprivation (LVD) showing embolized right portal vessels with glue (black arrows), Amplatzer vascular plugs and glue positioned on the right and hepatic vein (white arrows). After LVD, the patient presented an acute grade A liver failure (according to the International Study Group of Liver Surgery definitions) then recovered after seven days. (**C**) Axial CT scan at three weeks after LVD showing changes in FLR volume (655 mL) and %FLR (49.2%); *Spleen. (**D**) Intraoperative image showing good FLR regeneration. The patient then underwent right hepatectomy at week 5 after LVD without postoperative complications.

The relationship between cirrhosis and liver hypertrophy is shown in Figure 2. Although the cirrhosis group had a smaller initial %FLR than the non-cirrhosis group (the difference was not statistically significant, p >0.05), after LVD, the %FLR was similar between the two groups (p>0.05). There was no difference statistically significant in DH and FLR

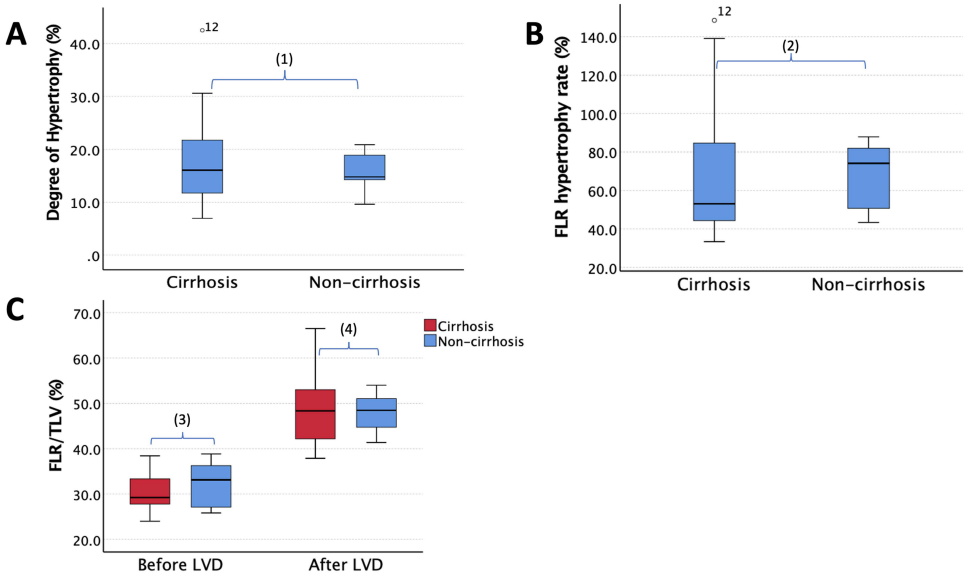

Figure 2 Volumetric analysis in the cirrhotic (n = 16) and non-cirrhotic group (n = 5). The degree of hypertrophy (**A**), the future liver remnant (FLR) hypertrophy rate (**B**), and the FLR volume as a percentage of total liver volume (TLV) (**C**) before and after liver venous deprivation (LVD). Values are given as median and interquartile range. (1), (2), (3) and (4): p > 0.05 (Mann–Whitney *U*-Test).

Table 3 Parameters Related to Surgery (N = 21)

Characteristic	Value
Liver resection (n; %)	21 (77.8)
Extended right hepatectomy (n; %) Right hepatectomy (n; %)	2 (9.5) 19 (90.5)
Duration of surgery (minutes) (median; IQR)	230.0; 118.0
Intraoperative transfusion (n; %)	1 (9.5)
Vascular/biliary reconstruction (n; %)	1 (9.5)
Postoperative complications (≥ IIIa Clavien–Dindo) (n)	1 (9.5)
Hepatobiliary complications (n; %)	1 (9.5)
In-hospital days (median; IQR)	12; 4
90-day mortality (n; %)	1 (4.76)
R0 resection margin at histology (n; %)	21 (100)

hypertrophy rate between cirrhotic and non-cirrhotic groups ($p > 0.05$). It is noted that three patients in the cirrhotic group presented delayed obtaining the target FLR (one at six weeks and two at ten weeks).

The intra- and postoperative data are summarized in Table 3. After LVD, all 27 patients had sufficient FLR volume for hepatectomy. However, only 21 patients were operated on, of whom 19 received a right liver hepatectomy and two received a right extended liver hepatectomy. The five remaining cases refused liver resection and continued treatment with TACE. One patient undergoing surgery showed excessive intraoperative bleeding due to injury to the left hepatic vein during removal of the middle hepatic vein. This patient had an operation time of 627 minutes and required a transfusion of 12 blood units. The patient then presented acute liver failure grade C (according to ISGLS) and was kept in the intensive care unit, then died on day 32 postoperation. No other major postoperative complications were found.

Discussion

After PVE, arterial blood flow increases to the embolized lobe due to the hepatic arterial buffer response.[14] In addition, the lobe is also perfused by peripheral portoportal collaterals behind the embolization position. When combined with HVE, congestion occurs in the hepatic sinusoid, resulting in reduced blood flow from the arterial source (reduction in the hepatic artery buffering response) and decreases blood supply from the intrahepatic portal venous collaterals.[5,9] The latter results in greater damage to the embolized liver lobe (but does not induce liver necrosis) and stimulates greater hypertrophy in the contralateral lobe.[9]

To date, many studies have shown that LVD is safe and effective against CRLM or cholangiocarcinoma, where it mainly occurs in the normal liver, but few have reported its efficacy against HCC, which often occurs in a setting of underlying liver disease (steatosis, fibrosis, or cirrhosis).[9–12] The ability of the chronic liver to regenerate is lower than that of the normal liver, and hepatic damage after embolization tends to be associated with the risk of liver failure. In addition, major hepatectomy is not usually indicated for patients with impaired liver function and/or portal hypertension. In this study, patients with a serum bilirubin level of < 2 the normal upper limit and no significant portal hypertension underwent LVD. To the best of our knowledge, this is the first study evaluating the application of LVD in patients with HCC and cirrhosis.

Because HCC is a highly angiogenic cancer, with angiogenesis playing an essential role in tumor growth and spread, tumor control before liver hypertrophy is necessary. Hayashi et al evaluated the growth of HCC after PVE without TACE and showed that the tumor growth rate acceleration was 2.65-fold.[15] In our study, TACE was always performed before LVD for all patients, and the super-selective technique was used as much as possible to minimize liver damage. We had no patients presenting liver dysfunction after TACE. That permitted us to early perform LVD just at least one week after

TACE in some patients. In contrast, repeat TACE was necessary to control the tumor and increase the likelihood of non-embolized liver hypertrophy in patients with insufficient FLR growth after LVD. In this case, TACE was crucial for further promote liver regeneration. As a result, all of our patients achieved the desired increase in liver volume up to 10 weeks after LVD, and none showed tumor progression during the waiting time.

Our results—a median DH of 14.8%, FLR hypertrophy rate of 55.2%, and %FLR increase from 29.3% to 48.9% after LVD, with the longest waiting time was only 3 weeks (except for three patients who needed to wait for 6 and 10 weeks)—are impressive. Compared to the findings of PVE in previous studies, the outcomes of LVD in our study are better for patients with HCC and cirrhosis. Farges et al recorded a DH of 9% after PVE in the cirrhosis group compared to 16% in the non-cirrhosis group.[16] Sun et al's study achieved a mean increase in %FLR of 31.1±16.1% in the cirrhosis group compared to 45.6±47.3% in the non-cirrhosis group ($p < 0.331$) after 4–6 weeks of PVE.[17] Ogata et al compared DH between PVE and TACE + PVE groups (additional TACE preceding PVE by 3–4 weeks) and showed a mean increase in %FLR of 8% and 12%, respectively ($p = 0.02$).[18] In our study, all five patients in the non-cirrhosis group showed very good results for liver regeneration at the first assessment (after 3 weeks), while in the cirrhosis group, the hypertrophy rate seemed to be slower), with three cases with a prolonged waiting time and requiring additional TACEs, although this difference was not statistically significant ($p > 0.05$). Laurent et al compared LVD and PVE groups, mainly of non-cirrhosis patients, and showed an increase in FLR of 62% and 29%, respectively ($p < 0.0001$).[11] Similarly, Le Roy et al found that the biembolization group (PVE + HVE) showed a higher hypertrophy rate compared to the PVE group (51.2% versus 31.9%, $p = 0.018$); biembolization was considered to be an independent factor affecting FLR, FLR hypertrophy, and FLR/BW ratio.[10]

The transjugular approach for HVE seems to be easier for accessing the target hepatic vein than the transhepatic approach owing to the direct view of the vein through liver parenchyma. Therefore, the intervention time of the former is usually longer than that of the latter. Some authors argue that better liver hypertrophy is obtained when the transhepatic approach is used because it can block the main hepatic vein (by AVP) and the intrahepatic veno-venous collateral branches (by NBCA).[9,11] Our results do not show a statistically significant difference between the two groups ($p > 0.05$). However, the accessing of the hepatic vein through liver parenchyma seems to make the postinterventional pain more severe. This worsening of the pain may be explained by the higher amount of glue required (to embolize the peripheral branches of the hepatic veins and embolization tract, which was not applied when using the transjugular approach), which caused an inflammatory reaction in the embolized lobe and the liver capsule around the puncture tract (Figure 1). The use of new-generation materials with less inflammatory reaction may reduce this undesirable effect.

Concerns about worsening portal hypertension symptoms after LVD due to the postintervention increase in the portal trunk diameter ($p < 0.001$) clearly demonstrate the change in portal venous pressure. Nevertheless, these changes did not result in manifestations of significant portal hypertension (thrombocytopenia, ascites, portal vein thrombosis, or gastro-intestinal bleeding due to varices hemorrhage) after LVD.

Le Roy et al found that intraoperative blood loss was higher in the LVD group than in the PVE group.[10] These authors explained this finding due to venous collaterals between the embolized and non-embolized liver, leading to more bleeding during parenchyma transection.[10] In our study, surgeons noted the presence of venous collaterals in the parenchyma, causing more easy bleeding than usual. However, this did not significantly interfere with the surgical procedure and no significant intraoperative blood transfusion related to this phenomenon was noted.

Our study has some limitations. First, the small sample was not very representative. Future studies should be conducted with larger sample sizes and a randomized controlled comparison with other methods of liver regeneration, such as PVE, ALPPS, radiation lobectomy, etc. Second, as mentioned above, the assessment of the impact of LVD on portal hypertension against the background of liver disease did not yield conclusive results, although no significant changes were recorded. Therefore, further evaluations are needed in future studies.

Conclusion

In summary, our results show that LVD is a safe, effective, and feasible method of liver hypertrophy before surgery for patients with HCC. This technique is expected to help increase the percentage of resectable HCC, even in well-selected cases of cirrhosis. Further comparative investigations with large study populations and multicenter data are necessary.

Data Sharing Statement

The datasets generated and/or analysed during the current study are not publicly available due to privacy concerns but are available from the corresponding author on reasonable request.

Ethical Approval

The institutional review board of Hanoi Medical University approved our research (Ref: 627/GCN-HDDDNCYSH-DHYHN dated 20 Apr 2022).

Informed Consent

The Hanoi Medical University Review Board waived the patient or guardian consent requirement because the study was retrospective and involved analysis of anonymized image data.

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Than-Van Sy and Le Thanh Dung contributed equally to this article as co-first authors.

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Disclosure

The authors declare no conflict of interests.

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