ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2022 November 15; 14(11): 2088-2301

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Oncology

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RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xiang-Di Zhang*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jia-Ru Fan*.

NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
February 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5204/editorialboard.htm

PUBLICATION DATE
November 15, 2022

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World J Gastrointest Oncol 2022 November 15; 14(11): 2088-2096

DOI: 10.4251/wjgo.v14.i11.2088

ISSN 1948-5204 (online)

MINIREVIEWS

Portal vein embolization failure: Current strategies and future perspectives to improve liver hypertrophy before major oncological liver resection

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Specialty type: Surgery

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Baba H, Japan; Jackson T, United States; Zhu X, China

Received: August 4, 2022
Peer-review started: August 4, 2022
First decision: September 30, 2022
Revised: October 1, 2022
Accepted: October 31, 2022
Article in press: October 31, 2022
Published online: November 15, 2022

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Abstract

Portal vein embolization (PVE) is currently considered the standard of care to improve the volume of an inadequate future remnant liver (FRL) and decrease the risk of post-hepatectomy liver failure (PHLF). PHLF remains a significant limitation in performing major liver surgery and is the main cause of mortality after resection. The degree of hypertrophy obtained after PVE is variable and depends on multiple factors. Up to 20% of patients fail to undergo the planned surgery because of either an inadequate FRL growth or tumor progression after the PVE procedure (usually 6-8 wk are needed before surgery). The management of PVE failure is still debated, with a lack of consensus regarding the best clinical strategy. Different additional techniques have been proposed, such as sequential transarterial chemoembolization followed by PVE, segment 4 PVE, intra-portal administration of stem cells, dietary supplementation, and hepatic vein embolization. The aim of this review is to summarize the up-to-date strategies to overcome such difficult situations and discuss future perspectives on improving FRL hypertrophy.

Key Words: Portal vein embolization; Portal vein embolization failure; Rescue associating liver partition and portal vein ligation; Hepatic vein embolization; Liver venous deprivation; Segment 4 portal vein embolization

Core Tip: Portal vein embolization (PVE) is actually considered the standard of care for inducing volume augmentation of the future remnant liver. However, 20% of patients who have undergone PVE, reportedly never undergo curative resection, due to either insufficient future remnant liver (FRL) growth with an unacceptable risk of post-hepatectomy liver failure, or oncologic progression after PVE, while waiting for the adequate FRL hypertrophy (6-8 wk or more). The management of PVE failure is still highly debated, with different additional techniques that have been proposed, such as sequential transarterial chemoembolization followed by PVE, segment 4 PVE, intra-portal administration of stem cells, dietary supplementation, and hepatic vein embolization.

Citation: Cassese G, Han HS, Lee B, Cho JY, Lee HW, Guiu B, Panaro F, Troisi RI. Portal vein embolization failure: Current strategies and future perspectives to improve liver hypertrophy before major oncological liver resection. *World J Gastrointest Oncol* 2022; 14(11): 2088-2096
URL: https://www.wjgnet.com/1948-5204/full/v14/i11/2088.htm
DOI: https://dx.doi.org/10.4251/wjgo.v14.i11.2088

INTRODUCTION

The main goal of hepatic surgical oncology is to perform a R0 resection, by preserving a sufficient future remnant liver (FRL) to prevent post-hepatectomy liver failure (PHLF). Indeed, PHLF is still a major cause of mortality after major liver surgery[1]. To reduce the risk of PHLF it is necessary to preserve not only a sufficient amount of liver parenchyma, but also ensure adequate liver function[2]. Owing to advances in preoperative evaluation and optimization of the FRL, the postoperative mortality rate for major liver resections (≥ 3 segments) is currently showed to be less than 5%[3,4]. The FRL volume is the only factor that can be acted on, depending on the surgery and liver condition. An FRL ≥ 20% of the volume is considered safe in cases of healthy liver, ≥ 30% after chemotherapy, 40% in case of steatosis or cholestasis, and ≥ 50% in case of cirrhosis[5]. Prior to performing major hepatectomy, multiple patient factors should also be considered to optimize FRL growth, such as an age higher than 65 years, obesity or malnutrition, diabetes, chronic renal failure[4]. The degree of liver hypertrophy is also affected by many liver related factors, with the eventual presence of chronic liver disease or previous chemotherapy playing a fundamental role[6,7]. However, pooled data from a recent meta-analysis showed no difference in the degree of hypertrophy between patients receiving neo-adjuvant chemotherapy compared to patients who did not receive pre-procedural systemic treatment[8], despite a very high degree of heterogeneity in the studies included[9,10].

Portal vein embolization (PVE) is seen as the standard of care for inducing hypertrophy of the FRL. However, 20% of patients who have undergone PVE, reportedly never undergo curative resection, due to either insufficient FRL growth with an unacceptable risk of PHLF, or oncologic progression after the PVE procedure (6 wk or more before surgery)[11]. For patients with insufficient liver hypertrophy following PVE, adjunctive techniques such as hepatic vein embolization, segment 4 embolization, intra-portal administration of stem cells, dietary supplementation, and sequential transarterial embolization followed by PVE, have been proposed. However, evidence regarding the appropriate management of these patients after PVE failure is still lacking.

This review aims to summarize the up-to-date strategies available and future perspectives on the management of patients scheduled for major hepatic resection with insufficient FRL hypertrophy after PVE.

PVE: TECHNIQUE, INFLUENCING FACTORS AND LIMITATIONS

PVE was first described by Makuuchi *et al*[12] in 1984, in patients with cholangiocarcinoma (CCA) undergoing major hepatectomy[13]. However, the principle of contralateral liver lobe hypertrophy after hepatic vessel obliteration was first identified by James Cantlie 100 years before[14]. Currently, PVE is the standard of care procedure to obtain FRL hypertrophy in patients requiring major liver surgery, in case of marginal FRL. Reportedly, about 80% of patients are able to undergo the planned liver surgery

after 6-8 wk[15].

PVE is a technique of interventional radiology, carried out under local anesthesia. Three approaches have been classically reported for this procedure: trans-hepatic, trans-splenic and trans-ileocolic. The trans-hepatic technique involves percutaneous access to the portal branches. The trans-ileocolic technique consists of a mini-laparotomy to isolate and cannulate the ileocolic vein, to access the portal vein. As it is a more invasive procedure, it is used when interventional radiology is not feasible. The trans-splenic technique is more recent, providing the advantage of eliminating the risk of tumor seeding. This access was initially thought to have a higher risk of bleeding complications; however, such concerns have been addressed and this approach is being increasingly used[16]. In contrast, a meta-analysis by Abulkhir *et al*[17] found that FRL hypertrophy was significantly higher using the trans-hepatic technique. Recently, Yamao *et al*[18] described for the first time the round ligament approach, suggesting its usefulness in elective cases for which it is difficult to safely perform trans-hepatic or trans-ileocecal approaches. In their study on 50 patients undergoing major hepatectomy, the authors observed no morbidity, neither mortality, related to the round ligament approach. The median functional hepatic remnant rate before and after the procedure was 55.6% and 63.2%, respectively.

Response to PVE has been found to be an important predictor of PHLF. Abdalla *et al*[19] proposed a degree of hypertrophy (DOH) cutoff of > 5% in case of healthy liver and > 10% in cirrhotic patients, to safely perform a major hepatectomy. Chapelle *et al*[20] investigated the hypertrophic response after PVE using hepatobiliary scintigraphy (HBS) and found a cut-off value of 1.72%/min/m^2 of pre-PVE FRL-F for safe resection (81.3% sensitivity and 82.4% specificity). The increase in volume after PVE is not proportional to the increase in liver function (FRL-F), with a greater increase in FRL-F up to 3-4 wk after PVE procedure[21]. All previous studies agree that the smaller the FRL pre-PVE, the larger the FRL hypertrophy post-PVE[8,22,23].

PVE is contraindicated in cases of tumor invasion into the ipsilateral portal vein. A relative contraindication is portal hypertension since PVE may increase portal vein pressure and worsen the liver function and the clinical state[24].

Some previous studies suggested a negative impact of liver regeneration on long-term oncological outcomes, as regard to both disease-free survival (DFS) and overall survival (OS). Margonis *et al*[25] reported that a kinetic growth rate (KGR) higher than 1% could be related to an increased risk of recurrence. However, a meta-analysis focusing on the oncological outcomes of PVE showed that the procedure does not worsen the long term results of major liver surgery, without any higher risk in terms of hepatic recurrence, 3-year OS, and 5-year OS after PVE[26].

The true weight of most factors involved in PVE failure remains unclear, apart from the presence of the underlying liver disease. The main drawback of unresolved PVE: The 15%-25% rate of failure due to inadequate FRL hypertrophy or oncologic progression[11].

Risk factors for PVE failure

Several factors can influence the efficacy of PVE procedure. Regarding embolization materials that can be used for PVE, the combination of N-butil-cyanoacrylate (NBCA) with lipiodol is the most widely used, leading to reliable FRL hypertrophy with efficient embolization, and low rate of vascular recanalization[27]. Furthermore, recent reports showed similar results with resorbable materials, hypothesizing the advantage to prevent an accidental contralateral embolization[28]. A recent meta-analysis by Soykan *et al*[8] reported a significant difference in the degree of hypertrophy in favor of NBCA compared to the other agents. In the same study, other risk factors were investigated, and showed that sex and previous chemotherapy were not associated with a lower degree of hypertrophy, contrary to what has been previously reported. It is reported that five predictive factors for insufficient FRL growth: Age, FRL%, plasma indocyanine green detection rate (ICG-PDR), total bilirubin level, and a history of chemotherapy. A prediction formula was created using these parameters, and had a 100% sensitivity and 90.9% specificity for predicting an FRL < 20% after PVE. However, this finding has not been validated in larger cohorts.

MANAGEMENT STRATEGIES AFTER PVE FAILURE

Insufficient FRL augmentation after PVE is a difficult issue to overcome because of two reasons: The need to act quickly to avoid tumor progression and the need to prevent PHLF. Different strategies have been suggested without consensus. In Figure 1, the authors propose their algorithm, which is discussed below.

Segment 4 PVE

When right trisectionectomy is planned, additional embolization of segment 4 (S4) can be performed. The first encouraging experience with this procedure was published by Kishi *et al*[29], which showed a higher FRL hypertrophy, resulting in a median volumetric increase of 54% *vs* 26% after PVE alone, without affecting post-procedural morbidity or perioperative outcomes. Recently, a larger Scandinavian study showed similar results (median increase of 47% *vs* 38%, respectively; $P = 0.02$), but with a hetero-

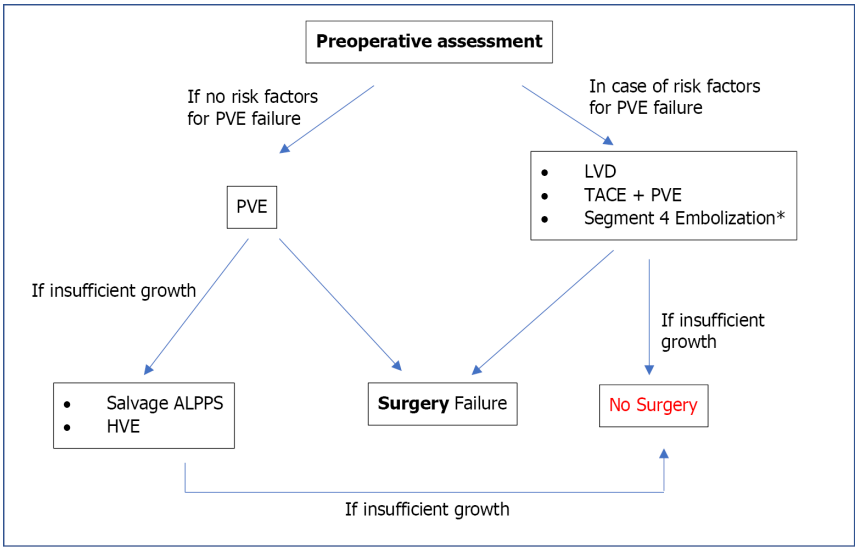

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Figure 1 Proposed algorithm for future remnant liver augmentation and portal vein embolization failure. The asterisk (*) represents only if right trisectionectomy is planned. PVE: Portal vein embolization; ALPPS: Associated liver partition with portal vein ligation for staged hepatectomy; LVD: Liver venous deprivation; TACE: Trans-arterial chemoembolization; HVE: Hepatic vein embolization.

geneous cohort, including patient with cirrhosis, CCA, and colorectal liver metastases (CRLM)[30]. Furthermore, the pre-PVE FRL was smaller in the S4 group (333 mL *vs* 380 mL; $P = 0.01$), which is associated with a higher DOH. A Japanese, propensity score-matched study in patients with biliary carcinoma also reported an improved FRL after PVE with S4 embolization[31]. In contrast, three other studies showed no significant differences between PVE alone and PVE with S4 embolization[22,32,33]. Studies have always considered the time interval needed to obtain FRL increase after S4 portal embolization similar to that after PVE, without the advantage of faster hypertrophy. Furthermore, when the scheduled surgery is not a right trisectionectomy, this technique is useless[34].

Hepatic vein embolization

Hepatic vein embolization (HVE) was introduced to obtain an additional increase in FRL after PVE failure. The first experience with sequential HVE after ipsilateral PVE was reported by Hwang *et al*[35] in 2004, in order to obtain an additional FRL hypertrophy in 42 patients. Another study reported an FRL augmentation rate of 28.9% after HVE (*vs* 13.3% after PVE alone), without significant complications[36]. The mechanism of action probably consists of a higher stress on the liver due to a major outflow obstruction, showing at the same time a protective effect of the residual arterial flow against any dangerous biliary ischemia. Similar outcomes were recently reported by Niekamp *et al*[37] in nine patients with CRLM who underwent salvage HVE following PVE failure. The standardized FRL increased from 16% to 26% after HVE and 22% after PVE ($P = 0.0005$). HVE was performed after a median of 40 d from PVE, and only four of the nine patients underwent hepatectomy. Thus, even though HVE is safer and more effective, the sequential association of PVE and HVE requires a long interval between them, without counteracting a possible progression of tumor disease. Hence, Guiu *et al* [38] published the first reports about the liver venous deprivation (LVD) technique, consisting in a simultaneous embolization of the hepatic vein(s) and ipsilateral portal vessels. LVD requires that both the ipsilateral portal and venous branch (+/− accessory veins) are occluded with an Amplatzer plug, placed approximately 1 cm from the ostium. NBCA is injected beyond the plug to close the intrahepatic part of the vein(s), as well as any collaterals. The extended LVD (e-LVD) is a variation of the technique in which the middle hepatic vein is also treated[39]. First data after 99 m-Tc mebrofenin hepatobiliary scintigraphy (HBS) reported a 66% improvement in FRL-F 7 d after e-LVD procedure. After 3 wk, the median volumetric gain was 63.3%, while the functional increase was 64.3%. Furthermore, subsequent studies have shown also safe perioperative and oncological results after the completion surgery[40-42]. Thus, preliminary studies have shown that LVD can induce a higher FRL hypertrophy than PVE, without adding additional periprocedural risks. However, to reach stronger conclusions, randomized studies comparing LVD and PVE are awaited (HyperLiv 01 and Dragon 1 are currently still ongoing).

In essence, HVE seems to be a safe salvage option after PVE failure, but carries the risk of tumor progression during the long waiting times. The LVD technique seems to be a better substitute for PVE, and aims to replace PVE owing to its higher and faster hypertrophic effects[43].

Salvage associating liver partition and portal vein ligation

Associating liver partition and portal vein ligation (ALPPS) was first described by Schnitzbauer *et al*[44] in 2012 as a novel two-staged hepatectomy, with the main advantage of remarkably reducing the delay between the first and second procedure. During the first stage, the lesions in the FRL are treated, and an anticipated line of resection is transected with ligation of the contralateral first order portal branch. After only 1-2 wk, completion surgery is performed after a sufficient FRL is confirmed using CT-based volumetry[45]. The reported successful rate for the completion surgery was 99%, while the traditional two staged hepatectomy reached only about 75%[46,47]. The shorter interval needed for FRL augmentation could significantly decrease the risk of tumor progression. Furthermore, the two surgeries could possibly be performed during the same hospitalization, affecting the costs and the organization. However, there has been concern regarding the effective increase in FRL-F. Olthof *et al*[48] showed a median increase of 29% in the FRL-F 7 d after ALPPS stage 1, compared to a volumetric increase of 78%, in a study involving patients with perihilar cholangiocarcinoma ($P < 0.01$). Similar results have been reported in patients with CRLM[49]. To this end, the efficacy of HBS in predicting PHLF after ALPPS was proven by Tomassini *et al*[50]; patients presenting with a daily gain in FRL-F of ≤ 2.7%/min/m^2 indicated a high risk of PHLF development, which requires re-discussion of the second stage. The ALPPS registry shows a mortality rate of 5% in a series which included only patients treated for colorectal liver metastasis aged < 60 years old[45]. The main disadvantage of this fast post-procedural hypertrophy is the risk for higher rates of perioperative morbidity and mortality[45].

ALPPS was proposed as a salvage procedure by Enne *et al*[51]. The study reported a mean FRL increase of 88% in 20 patients who underwent ALPPS after PVE failure, with an exceptional 100% success rate and no 90-d mortality. Similar results were reported by Sparrelid *et al*[49] in 11 patients with CRLM: A median FRL growth of 61.8%, with no 90-d mortality or high-grade complications (≥ 3b-complication according to Clavien-Dindo). Many variations of the original ALPPS procedure have been reported in the literature (mini ALPPS, partial ALPPS, radio-frequency-assisted liver partition with portal vein ligation, and Tourniquet modification), with the aim of reducing postoperative morbidity and bring some technical advantages. However, none of these ones have been proposed as salvage procedures. It may be beneficial to obtain data on this in the future. Additionally, Dondorf *et al*[52] reported the possibility of obtaining a significant further increase in FRL after additional ligation of the middle hepatic vein in combination with ALPPS (a sort of "surgical LVD"). Though higher morbidity and mortality were observed, they were most likely associated with the underlying liver conditions.

Although the actual role of salvage ALPPS is still debated, we believe that it can be considered a viable salvage option.

Sequential trans arterial chemoembolization and PVE

Herein, we present an option that can't be performed after PVE failure, but in addition to PVE when there are risk factors of failure, as proposed in our flow-chart. Indeed, the presence of an underlying chronic liver disease is a risk factor for poor hypertrophy after PVE. One of the reasons could be the presence of arterio-portal tumoral shunts, typical of hepatocellular carcinoma (HCC), which could counteract the hemodynamic effect of PVE. Sequential trans arterial chemoembolization (TACE) followed by PVE has been shown to achieve a higher DOH than PVE alone[53]. Ipsilateral PVE is performed 7-10 d after the initial TACE, once the blood parameters have normalized. The benefits of this dual technique include improved FRL hypertrophy relative to PVE alone and induction of an anti-tumor effect in the embolized lobe[54,55]. Ogata *et al*[54] reported a mean FRL increase in the TACEPVE group of 12% *vs* 8% for the PVE alone group ($P = 0.022$), with a DOH of 10% *vs* 5%, respectively ($P = 0.044$). In the same study, the TACE + PVE group had a higher complete tumor necrosis incidence (83.00% *vs* 0.05%; $P < 0.001$) and 5-year DFS (37% *vs* 19%; $P = 0.041$), owing to better local control of the HCC nodule. A limitation of this strategy is the consequent inflammation of the hepatic pedicle, which makes subsequent surgery more challenging. Furthermore, areas of residual segmental infarction were found within the non-cancerous liver on histopathology; thus, TACE should be performed carefully, since many of these patients have pre-existing liver dysfunction[55].

Intra-portal administration of stem cells

Fürst *et al*[56] first reported caries in six patients undergoing PVE with CD133 (+) bone marrow stem cells (BMSC) administration to improve FRL hypertrophy following PVE. In their study, a significantly higher mean increase in FRL volume was reported (77.3% *vs* 39.1%, $P = 0.039$). The time to surgery was also shorter in patients who received stem cell infusion (27 d *vs* 45 d, $P = 0.057$). Similarly, am Esch *et al* [57] showed a median absolute gain of 138.66 in the PVE-BMSC group compared to 62.95 mL in the PVE-alone group ($P = 0.004$). Post hoc analysis revealed better survival in the PVE-BMSC group ($P = 0.028$) than in the PVE-alone group ($P = 0.094$) and controls.

Despite the encouraging results, further issues need to be investigated prior to their routine use. Stem cells have been reported to stimulate tumor growth in murine models of CRLM[58,59]. Furthermore, the effectiveness of this technique in patients with chronic liver disease and prolonged chemotherapy remains unknown[60].

CONCLUSION

Owing to tremendous technological advances, appropriate FRL optimization can reduce the risk of PHLF. Although PVE is considered the standard of care for FRL volume augmentation, up to 20% of patients fail to undergo the planned surgery. An in-depth knowledge of all the risk factors for PVE failure can help us to choose the most effective procedure. In our opinion, LVD could replace PVE in the future, particularly in cases with negative predictive factors for FRL hypertrophy, once its validity has been confirmed. Other strategies, such as the combination of PVE and TACE or segment 4 embolization, can be carefully considered when appropriate. To date, after PVE failure, ALPPS is reportedly the most effective salvage procedure to obtain a volumetric gain with only a short delay, thus preventing tumor progression. However, prospective and large-scale studies on this challenging scenario are still needed.

FOOTNOTES

Author contributions: Cassese G, Han HS, Panaro F, and Troisi RI conceived and designed the study; Lee HW, Cho JY, Guiu B, and Troisi RI critically revised the manuscript; Cassese G and Lee B wrote the manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Country/Territory of origin: South Korea

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S-Editor: Chen YL
L-Editor: A
P-Editor: Chen YL

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