

Answer to the reviewers

Reviewer 1:

- **“Paper will be interesting for readers. To my taste, the causes of insufficient PVE should be added: PV recanalization, portal collaterals etc.”**

We added the following paragraph in the discussion:

“The causes of insufficient volume growth of FLR after PVE are known: technical failure during the procedure (impossibility of cannulating the portal system due to altered portal anatomy), portal vein recanalization, portal collateral development and poor quality of hepatic parenchyma. In our study, 5 patients had chemotherapy before PVE, which induced histopathological damages (steatosis, sinusoidal obstruction syndrome and cholestasis), and affected the capacities of the liver to regenerate after PVE.”

- **Was it impossible to perform repeated PVE?**

In our study, there were no cases of portal vein canalization. Therefore, we did not perform repeated PVE. In our study, the main cause of insufficient volume growth of FLR after PVE was the poor quality of hepatic parenchyma caused by chemotherapy.

- **Why you did not use additional hepatic artery embolization? Impossible or ineffective?**

In our center, sequential arterial embolization and PVE is not performed as standard procedure by our interventional radiology experts.

- **Some missprints: P.5, Paragraph 2: unresecable. P.5: "In situ" with capital letter.**

The misprints have been corrected.

Reviewer 2:

- Why authors performed cholecystectomy at first step?

Cholecystectomy was performed at first step in order to place the transcystic stent for biliary drainage.

- In case of metastases located in the FLR, wedge resections or thermoablations were performed during ALPPS-1. Did the mets were not present before PVE? If they didn't it is a clear tumoral progression and contraindicates surgery. If present before PVE why authors didn't performed a two-stage hepatectomy?

Two patients had wedge resection and/or thermoablation during ALPPS-1.

The first patient had a thermoablation during ALPPS-1. First, she had an indication of a two-stage hepatectomy: she had a previous left lateral lobectomy and we planned to perform, after PVE, a right lobectomy. The thermoablation of the segment IV lesion was scheduled during PVE but it was not performed, because it was too difficult to clearly identify the lesion.

Moreover, the parenchymal liver analysis revealed 30% of steatosis and sinusoidal obstruction syndrome. We decided to perform ALPPS procedure because of the combination of insufficient future liver remnant and poor quality of the liver. During ALPPS-1, the metastasis in segment IV (which remained stable) was thermoablated.

The second patient had a wedge resection and a thermoablation during ALPPS-1. He had two metastases in the left lobe, which were stable after chemotherapy. We decided to perform ALPPS procedure instead of two-stage hepatectomy because the future liver remnant was very small after PVE (Future liver remnant to body weight ratio of 0,55 after PVE) and we expected a more important growth with ALPPS procedure than with two-stage hepatectomy.

- Parenchyma partition was partial o classical ALPPS?

The parenchymal partition was classical ALPPS.

We added "*We performed a complete parenchymal split*" in the surgical procedure section.

Reviewer 3:

- **In total, how many patients had portal vein embolization in the authors' center during the study period?**

During the study period, 48 PVE were performed.

- **How many ALPPS procedures were performed in the author's centre during the study period? The number of 7 patients with 'failed' PVE seems high to me as the study period was only 2 years.**

During the study period, 7 ALPPS were performed. All 7 procedures were rescue ALPPS. In our center, considering the high complication rate of ALPPS procedure in literature, ALPPS procedure was performed only as rescue, in case of insufficient volume growth of FLR after PVE.

- **In total how many liver resections were performed during this time period at the authors' center ?**

In our center, a total of 189 liver resections were performed between January 2014 and December 2015.

- **When was embolization of segment 4 considered necessary?**

Segment 4 embolization was considered necessary when a right trisegmentectomy was indicated. In case of technical failure during the procedure, segment 4 was not embolized.

- **In the method section, nothing is mentioned on how the selection for the literature review was made.**

We added the following paragraph in the method section:

“Literature review was performed using PubMed, Google Scholar and the Cochrane Library Central. Articles reported were written in English and ALPPS procedures were limited to humans. The mesh terms were: « ALPPS », « Associating liver partition and portal vein ligation for staged hepatectomy », « Portal vein embolization », « rescue ALPPS », « salvage ALPPS ».”

- **For comparison with the literature, volumetric measurements should be made on CT scans at the different time points on the 7 patients.**

It seems to us that we have addressed this particular point in Table 4, which summarizes the volumetric data relative to each of our 7 patients.

- **I urge the authors to please refrain from the wording ‘excellent results’ on page 12, as the mortality is 1/7 (14%)**

The word “excellent” was deleted.

This following section was added, as requested by the editor:

COMMENTS

Background

Hepatic surgery appears as the best curative option for patients with primary or secondary malignant tumors of the liver. The main complication after major hepatectomy is liver failure. Several studies have shown that the size of the future liver remnant (FLR) is a key element as it is directly correlated to the postoperative liver function.

Several strategies have been developed to lower the risk of postoperative liver failure, such as portal vein embolization (PVE). The aim of this technique is to decrease the portal blood flow to the ipsilateral liver, inducing atrophy of the ipsilateral liver and hypertrophy of the contralateral liver. In 2012, a new surgical technique has been developed, “Associating Liver Partition and Portal vein ligation for Staged hepatectomy” (ALPPS). This procedure induces rapid and extensive hypertrophy of the FLR in two steps. Several studies have described high perioperative morbidity and mortality. Therefore, some authors have suggested that ALPPS should be performed only as a “rescue”, after failed PVE.

Research frontiers

Considering the high perioperative morbidity and mortality of ALPPS procedure, the current hotspots in this research field is the necessity of a better selection of patients and the necessity to minimize complications, and more specifically biliary complications.

Innovations and breakthroughs

Yet, very few data relative specifically to the rescue ALPPS have been published as most of the existing articles do not focus on this particular indication. Most papers describe series of 1 to 3 cases and only 4 studies report small cohorts (9 to 11 patients). Therefore, the size of our cohort (7 patients) is consistent with the number of cases developed in literature.

Moreover, biliary complications are the main cause of morbidity after ALPPS, and they are much more frequent than with ordinary hepatectomies (5%). Our study suggests that the use of a biliary drainage during the interval phase seems a promising technique to reduce biliary complications. To our knowledge, this is the first publication describing the use of a systematic biliary drainage between ALPPS-1 and ALPPS-2.

Applications

The results of our study suggest that in the future, ALPPS procedure should be performed only as a “rescue”, in case of insufficient liver hypertrophy after PVE. Rescue ALPPS could allow previously unresectable patients to reach surgery. It provides an opportunity for complete resection in cases otherwise eligible only to palliative treatments.

Terminology

ALPPS (Associating Liver Partition and Portal vein ligation for Staged hepatectomy) procedure was performed in two steps (ALPPS-1 and ALPPS-2), separated by an interval phase. During ALPPS-1, the surgeon performs a transection of the hepatic parenchyma. In our study, ALPPS-2 was performed within 7 to 9 days after ALPPS-1. During ALPPS-2, the right liver is removed, after having ligated the remaining artery, bile duct and hepatic veins.