Editorial

ALPPS versus portal vein embolization for hepatitis B virus-associated hepatocellular carcinoma: a delicate balance between volume and morbidity

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We have read with great interest the recent study published by Li *et al.*, entitled "*Associating liver partition and portal vein ligation for staged hepatectomy versus sequential transarterial chemoembolization and portal vein embolization in staged hepatectomy for HBV-related hepatocellular carcinoma: a randomized comparative study*" (1). The authors suggest that associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) achieves significantly better intermediate-term overall survival outcomes versus classic treatment with transarterial chemoembolization (TACE) + portal vein embolization (PVE) in patients with a hepatocellular carcinoma (HCC) that is not resectable at a time because of the risk of liver failure. The findings obtained by the Shanghai group provide valuable information in the ongoing debate in the hepatobiliary surgery community as to whether the morbidity associated with ALPPS is justifiable to obtain greater hypertrophy with a lower drop-out due to both insufficient volume of future liver remnant (FLR) and tumor progression.

There is proven evidence that ALPPS achieves a sufficient volume much faster for a staged hepatectomy than classic regeneration techniques (2). Since its appearance, the high morbidity and mortality rate associated with this surgical procedure has always been criticized. Today, the development of variants of the original technique (less aggressiveness in the first stage with the same hypertrophy capacity), advances in minimally invasive surgery, the learning curve, and better patient selection, have led to improved postoperative results associated with this procedure (3-6).

Other reasons why rapid hypertrophy techniques have been questioned is because different authors presented that the risk assumed for this greater aggressive procedure was not related to an improvement in long-term oncological outcome. This initial hypothesis has subsequently been refuted by different studies showing that increased resectability was indeed associated with improved survival (7,8). Special mention should be made of the randomized controlled trial LIGRO which obtained a higher estimated median survival for patients randomized to ALPPS (46 months) compared to two staged hepatectomy (26 months) in patients with colorectal liver metastases (9). These results have allowed the use of ALPPS to be extended mainly in the treatment of colorectal cancer liver metastases, which are its main indication against primary malignant liver tumors and non-colorectal liver metastases.

In the case of HCC and intrahepatic cholangiocarcinoma, the evidence on whether the use of ALPPS is justified remains unclear. These tumors are characterized by developing in patients with worse liver function and in livers with greater histological alterations (fibrosis, steatosis, cholestasis, or cirrhosis), which increases the risk of complications associated with the technique, the capacity for liver regeneration and, in general, the risk of postoperative liver failure. Therefore, with such tumors, it is even more important to make appropriate patient selections. Regarding an intrahepatic cholangiocarcinoma, the evidence is very limited, although a multicenter study of the international ALPPS registry concluded that ALPPS allowed obtaining a higher percentage of negative resection margin, and a 1-, 2-, and 3-year survival rates of 82.4%, 70.5%, and 39.6%, respectively, in patients with a single lesion and sufficient FLR (10).

The management of HCC that requires a major hepatectomy has classically been a matter of controversy (11). The first point of disagreement is to decide how much percentage of FLR is sufficient to avoid postoperative liver failure. While some authors advocate at least 35% or a 0.7 volume/weight ratio in patients with a healthy liver, others prefer at least 40–50% volume or 1.1 ratio in patients with chronic liver disease and/or portal hypertension. In addition to volume, liver function measured by indocyanine green clearance or scintigraphy is important for predicting the risk of liver failure and is routinely performed by some groups.

In patients with insufficient FLR, PVE with or without associated TACE has classically been the most widespread treatment (12). This treatment modality obtained a good resectability rate, but on many occasions the characteristics of the liver did not allow sufficient growth to perform a hepatectomy with safety. The appearance of ALPPS was a hopeful new treatment alternative that presumably would decrease the drop-out rate. Unfortunately, due to the high initial morbidity, the disproportionate risk of postoperative complications in patients with associated liver disease called into question its usefulness. While many centers discarded this alternative and continued with the use of PVE, other groups opted for ALPPS to increase the resectability rate (13,14). In 2021, Chan *et al.* in a retrospective study comparing ALPPS versus PVE for hepatitis-related HCC showed that ALPPS improved resection rate with comparable safety profile than PVE (15). One-hundred forty-eight patients with HCC (136 HBV) underwent FLR modulation (46 ALPPS; 102 PVE), and while only 1 ALLPS dropped out, 33 PVEs failed to proceed to resection (resection rate: 97.8% versus 67.7%). They suggested that an intraoperative ICG <40% at stage I was a good predictor of hypertrophy and a safe second stage although they stated that there was less evidence as to whether this increased resectability could be related to improved 5-year overall survival.

The comparative study developed by Li *et al.* presents as the most relevant finding a significant improvement in the 3-year overall survival of the ALPPS group (65.8%) compared to TACE + PVE group (42.1%). Thirty-seven patients (97.4%) in the ALPPS group and 25 patients (65.8%) in the TACE + PVE group were able to undergo staged hepatectomy, respectively (1). Of note, while there was no significant difference in the overall survival between patients who underwent resection in both groups, there was a significant difference in the overall survival between patients with or without resection in the TACE + PVE group. These better oncologic outcomes in those patients who manage to complete the second stage reopen the debate on whether ALPPS should be performed in patients with HCC with associated liver disease. The only disadvantage described by the authors is the higher percentage of complications in the ALPPS group, but these figures could have been reduced if the authors had performed some of the variants of the original technique or a better selection of candidates for surgery, avoiding patients older than 67 years or with a body mass index greater than 28.

In conclusion, standardization of the treatment of HCC requiring major hepatectomy with risk of liver failure remains a pending issue. The appearance of new treatment modalities such as preoperative radioembolization that allows treating the tumor while favoring the growth of the FRH, or dual embolization that seems to achieve greater regeneration than PVE, raise new questions to be solved. These techniques let us avoid the possible complications associated with first time ALPPS at the cost of a lower percentage of hypertrophy and resectability. Considering that both the LIGRO trial and the Li *et al.* study have described better survival outcome in the groups with higher resectability, it would be an option to consider the ALPPS variant in selected patients with HCC with associated liver disease.

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