



Enlarged and uncommon indications for ALPPS—where do we stand?

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Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been introduced in 2012 as an innovative surgical option that offers patients curative resection in otherwise nonresectable tumors. Considering the high morbi-mortality rates and poor oncologic outcome in the early experience, indications of ALPPS have been restricted to young patients with colorectal liver metastases (CRLM) following the first report on the international ALPPS registry (1). ALPPS further gained in safety after the first International ALPPS Meeting held in 2015 (2) in Hamburg, which prompted surgeons to better patient selection by chemotherapy (3), technical refinements toward less invasive ALPPS procedures (4), and better inter-stage decision making (5). In a recent comparative study (6), ALPPS showed higher resection rates than liver venous deprivation [LVD; i.e., radiological simultaneous portal vein embolization (PVE) and hepatic vein embolization] as an alternative. Regarding long-term outcomes, the randomized controlled trial LIGRO compared ALPPS *vs.* two-stage hepatectomy showing a significantly longer median overall survival (46 *vs.* 26 months) for ALPPS on intent-to-treat analysis (7). Thus, the oncological outcomes after ALPPS appear promising.

This process has enabled validating ALPPS as a safe and beneficial surgical option when appropriately used. Following the opening of the International ALPPS registry,

the number of patients receiving ALPPS has been increasing over time, with more than 1,200 cases reported in the registry so far (8). These studies published in 159 journals were written by 2,157 authors from 694 organizations in 43 regions. To date most of ALPPS studies have been published for the treatment of CRLM, hepatocellular carcinoma, and intrahepatic cholangiocarcinoma (ICC).

Regarding locally advanced ICC, the largest series published by Li *et al.* (9,10) came from the ALPPS registry. Among 102 patients, 99 completed the second stage, with R0 resection obtained in 87 (85%). The 90-day mortality rate of 20.8% reported in that study was high in comparison with that observed for conventional major hepatectomy or ALPPS performed for non-primary liver cancer. One possible explanation for this observation was the high complexity of surgery in ICC patients undergoing ALPPS (i.e., trisectionectomy in 78.7% of cases, biliary reconstruction in 35.6% and complex vascular reconstruction in 12.1%). Once again, better patient selection and improvement in inter-stage management contributed to a significant decrease in mortality over time (7% in the last 2 years). Despite the 90-day mortality, the comparative survival analysis demonstrated superior long-term outcomes of the ALPPS procedure over chemotherapy alone.

In a recent systematic literature review, Lai *et al.* (11)

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aimed identifying the best indications of ALPPS for uncommon liver pathologies. Overall 45 studies from 18 countries were selected including 136 ALPPS with such uncommon indications, namely 41 (30.1%) patients with neuroendocrine tumor (NET) metastases, followed by 27 (20.0%) gallbladder cancer (GBC), 9 (6.6%) pediatric tumors, 6 (4.4%) gastrointestinal stromal tumors (GISTs), 6 (4.4%) patients with benign primary liver disease, and eventually 4 (2.9%) and 43 (31.6%) patients with malignant primary or secondary liver disease, respectively. Those uncommon liver pathologies did not exceed 10% of the overall ALPPS cases, with only two countries having done more than 10 cases, i.e., Germany and Brazil. Of note only few modified ALPPS techniques were applied in the study population [12 (8.8%) partial ALPPS, 5 (3.7%) tourniquet ALPPS, 5 (3.7%) radiofrequency-assisted ALPPS, and 4 (2.9%) laparoscopic ALPPS], which could have significantly influenced the results.

In that study, robust data were reported mainly for NET metastases, which originated from the small bowel in 10 cases, pancreas in 9, and duodenum, lung, and ovary in one case each. The main indication for ALPPS in this setting was the bilobar pattern of liver metastasis and insufficient future remnant liver volume. Long-term results were reportedly good with 1-year overall survival rates ranging from 73% to 95%. By contrast, very poor results were observed for GBC, what could be feared because patients requiring an extended right hepatectomy for this aggressive tumor type are mostly at an advanced stage of the disease. There was no perioperative chemotherapy among the 27 reported cases, with the exception of neoadjuvant chemotherapy in two. The 90-day mortality rate after the second stage of ALPPS was as high as 60%. As a potential bias, five of these cases of deceased patients came from an international study specifically dedicated on early death after ALPPS. There were only 4 cases of ALPPS for benign primary liver disease, i.e., echinococcus, poliadenomatosis, Caroli disease, and cystic liver disease, with good postoperative outcome.

In conclusion, ALPPS for bilobar NET metastases was reportedly safe, with satisfactory long-term results. Nevertheless, ALPPS indication in NET cases may be challenged by liver transplantation as a valid alternative treatment. On the contrary, the results observed for the treatment of GBC are poor, though subjected to possible population selection biases. Regarding the other uncommon pathologies, the survival benefit of ALPPS and its impact on patient's quality of life still need to be clarified through

multicenter registry studies and in comparison with alternatives like PVE or LVD, liver transplantation, chemo- or radio-embolization, or systemic therapies.

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