Editorial

The impact of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) on liver tumors with unusual indications

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An associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been developed as a novel surgical technique for patients with insufficient future liver remnant volume even after portal vein embolization (PVE) ± hepatic arterial or venous embolization or conventional two-stage hepatectomy (TSH) (1-5). ALPPS was thought to be a breakthrough but high-risk procedure; however, it recently became a safer technique after the developing phase (1-3). Conversion surgery is strongly recommended for patients with initially unresectable liver tumors that are deemed resectable by systemic chemotherapy or hepatic arterial chemotherapy/embolization (6,7). The primarily targeted diseases are colorectal liver metastases (CRLM) and hepatocellular carcinoma (HCC). ALPPS is indicated for patients undergoing not only primary surgery but also conversion surgery.

ALPPS is highly invasive and requires a two-stage procedure; thus, indications must be rigorous. Various technical modifications have been proposed to improve the safety of the conventional ALPPS procedure, focusing on the method of liver resection, including mini-ALPPS, tourniquet ALPPS, ALPPS using radiofrequency or microwave ablation, and laparoscopic ALPPS (8). ALPPS does not replace other techniques, such as PVE followed by hepatectomy or conventional TSH, but may permit tumor resection for selected patients when other surgical options are unavailable (3). A recent randomized controlled trial (LIGRO trial) concerning CRLM showed significantly higher resection rates and better overall survival without increasing morbidity and mortality (5). ALPPS is well known to achieve rapid liver regeneration; however, functional liver regeneration assessed with functional volumetry with 99mTc-mebrofenin hepatobiliary scintigraphy is inadequate (9). Furthermore, the interval of 7–15 days between the two procedures in ALPPS might be too short to diagnose micrometastases to reveal themselves with radiological imaging (10).

An international ALPPS Registry was started in 2014 (2). HCC, cholangiocarcinoma (CCC), and CRLM have been the main diseases for the registration (2,3). Data from the ALPPS Registry (May 2019; https://ALPPS.net) included CRLM (64%), HCC (14%), intrahepatic CCC (7%), perihilar CCC (5%), neuroendocrine liver metastases (3%), and other liver tumors (7%) (3). Other liver tumors with unusual pathology were rarely observed; therefore, the advantages and disadvantages of ALPPS remained unknown. The most recent registration data showed 1,228 patients (http://www.alpps.net/?q=recruitment_status; 20th of February, 2020) treated with ALPPS. The ALPPS risk score had been created to avoid its futile use (4). Among 528 registered patients who underwent ALPPS, an unsuccessful outcome was observed in 47 (9%) patients. Age of ≥67 years [odds ratio (OR) =5.7] and tumor entity (OR =3.8 for biliary tumors) are the two independent futility predictors.

We sincerely congratulate Dr. Lai *et al.* for publishing

their study entitled "*Uncommon indications for associating liver partition and portal vein ligation for staged hepatectomy: A systematic review*" in *HepatoBiliary Surg Nutr* 2021 (11). To the best of our knowledge, this is the first systematic review that focuses on the role of ALPPS on unusual liver tumors. The authors investigated the MEDLINE, Scopus, and Cochrane Database based on the Preferred Reporting Items for Systemic Reviews and Meta-Analysis guidelines (12). The quality of the documents was investigated using the Newcastle-Ottawa Quality Assessment Scale, and studies with scores of >6 were defined as high-quality (13). Among the 486 articles screened for the inclusion criteria, 45 papers were selected. Reliable overlapping data was impossible to detect, mainly because the documents originated from international databases (11,14-17).

A total of 136 patients who are not generally indicated for ALPPS were summarized in this paper, including 41 (30.1%) neuroendocrine tumor (NET) metastases, 27 (20.0%) gallbladder cancer (GBC), 6 (4.4%) gastrointestinal stromal tumors (GIST), 6 (4.4%) primary benign liver disease, 4 (2.9%) other primary malignant liver diseases, 43 (31.6%) other secondary malignant liver diseases, and 9 (6.6%) pediatric cases (11). In all patients, the median interval to obtain sufficient hypertrophy between the first and the second ALPPS was short enough at 11 days (range, 6–28 days), which was comparable with widespread diseases including CRLM, HCC, and CCC.

Patients undergoing ALPPS for benign liver disease involved echinococcus, poliadenomatosis, Caroli disease, and cystic liver disease. Indications were limited, and some postoperative bile-duct injury has been reported. I agree with the authors that less aggressive interventional approaches should be preferred for benign liver diseases, including PVE ± hepatic arterial or venous embolization and radiation hepatectomy using Yttrium-90 microspheres (18).

The promising indications of ALPPS for malignant liver diseases are as follows: (I) a highly advanced but low-grade malignancy with low-frequency extrahepatic metastases, and (II) the existence of established effective chemotherapy. NET liver metastases mainly originate from abdominal organs, including the small bowel and pancreas. Therefore, curative primary lesion resection is essential. The largest study about ALPPS for NET was an ALPPS Registry study (17). In 27 patients, a neoadjuvant approach was conducted, of which 10 cases have somatostatin analogs, 8 have chemotherapy, 8 have locoregional therapies, 2 have peptide receptor radiotherapy, and 3 were without neoadjuvant therapy. ALPPS approach showed a good prognosis for patients with NET, with 1-year overall survival rates of 73–95% and 1-year disease-free survival rates of 73–83% (15,17). Liver transplantation (LT) is sometimes applied for patients with far-advanced NET. The 5-year overall survival rate was comparable in patients with LT and non-LT; however, the 5-year disease-free survival was higher in patients with LT (50% *vs.* 34%) (19). Nevertheless, the proper use of LT and ALPPS is unknown. Concerning GIST liver metastases, only six patients undergoing ALPPS have been reported. All three patients with survival data were alive for 6–37 months.

ALPPS was applied to 27 patients with GBC, mainly because of the widespread invasion to the liver parenchyma in the entire right liver and segment 4 with an estimation of a small future liver remnant. GBC is one of the highly malignant tumors, and neoadjuvant/adjuvant chemotherapy has not been established (20). Concomitant multiple liver metastases and massive lymph-node metastases should be a contraindication for extensive liver resection. We should be concerned with a strong bias because five patients were derived from an international study in an earlier period; however, 9 patients (60%) died within 90 days from the second ALPPS. ALPPS has not shown any survival benefits yet. Therefore, GBC is not a suitable disease category for ALPPS. Other patients receiving ALPPS for liver metastases other than CRLM, GBC, NET, and GIST were collectively evaluated in one group. The primary sites included four sarcomas, three melanomas, and various diseases. The follow-up period ranged from 2 to 40 months, but detailed recurrence data and prognosis were unknown. Nine pediatric patients undergoing ALPPS have been summarized as one case of benign focal nodular hyperplasia and eight cases of malignant liver tumors (six hepatoblastomas, one HCC, and one rhabdomyosarcoma). One patient with hepatoblastoma was alive at 55 months after the second ALPPS, but detailed treatment results were unknown.

ALPPS outcomes are improving on an annual basis; therefore, its timing and the number of experiences significantly impact the results. A prospective multicenter registry for these rare diseases is needed to clarify the usefulness of ALPPS. Further increase in the number of registered facilities is desirable. Finally, we strongly recommend ALPPS for highly advanced but localized low-grade liver malignancy, even in patients with unusual indications for ALPPS. Combination therapy with established effective chemotherapy is beneficial to complete ALPPS and achieve an excellent outcome.

Furthermore, as the authors recommended, ALPPS should only be performed in highly specialized centers where advanced hepatic resections are commonly performed, and interventional radiological procedures are routinely utilized as an alternative to promote hypertrophy of the future liver remnant.

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References

1. Tschuor Ch, Croome KP, Sergeant G, et al. Salvage parenchymal liver transection for patients with insufficient volume increase after portal vein occlusion -- an extension of the ALPPS approach. Eur J Surg Oncol 2013;39:1230-5.
2. Buac S, Schadde E, Schnitzbauer AA, et al. The many faces of ALPPS: surgical indications and techniques among surgeons collaborating in the international registry. HPB (Oxford) 2016;18:442-8.
3. Lang H, Baumgart J, Mittler J. Associated Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) Registry: What Have We Learned? Gut Liver 2020;14:699-706.
4. Raptis DA, Linecker M, Kambakamba P, et al. Defining Benchmark Outcomes for ALPPS. Ann Surg 2019;270:835-41.
5. Hasselgren K, Røsok BI, Larsen PN, et al. ALPPS Improves Survival Compared With TSH in Patients Affected of CRLM: Survival Analysis From the Randomized Controlled Trial LIGRO. Ann Surg 2021;273:442-8.
6. Beppu T, Miyamoto Y, Sakamoto Y, et al. Chemotherapy and targeted therapy for patients with initially unresectable colorectal liver metastases, focusing on conversion hepatectomy and long-term survival. Ann Surg Oncol 2014;21 Suppl 3:S405-13.
7. Yamamura K, Beppu T, Miyata T, et al. Conversion Surgery for Hepatocellular Carcinoma Following Molecular Therapy. Anticancer Res 2022;42:35-44.
8. Chan ACY, Lo CM. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS)-pushing the envelope in modulation of future liver remnant before major hepatectomy. Hepatobiliary Surg Nutr 2020;9:80-2.
9. Truant S, Baillet C, Deshorgue AC, et al. Drop of Total Liver Function in the Interstages of the New Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy Technique: Analysis of the "Auxiliary Liver" by HIDA Scintigraphy. Ann Surg 2016;263:e33-4.
10. Sparrelid E, van Gulik TM. Tumor progression in two-stage liver resections-is the shorter inter-stage period in associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) of benefit to the patient? Hepatobiliary Surg Nutr 2019;8:316-7.
11. Lai Q, Mennini G, Larghi Laureiro Z, et al. Uncommon indications for associating liver partition and portal vein ligation for staged hepatectomy: a systematic review. Hepatobiliary Surg Nutr 2021;10:210-25.
12. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777-84.
13. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-5.
14. Røsok BI, Björnsson B, Sparrelid E, et al. Scandinavian multicenter study on the safety and feasibility of the

associating liver partition and portal vein ligation for staged hepatectomy procedure. Surgery 2016;159:1279-86.
15. Schadde E, Ardiles V, Robles-Campos R, et al. Early survival and safety of ALPPS: first report of the International ALPPS Registry. Ann Surg 2014;260:829-36; discussion 836-8.
16. Truant S, Scatton O, Dokmak S, et al. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): impact of the inter-stages course on morbi-mortality and implications for management. Eur J Surg Oncol 2015;41:674-82.
17. Linecker M, Kambakamba P, Raptis DA, et al. ALPPS in neuroendocrine liver metastases not amenable for conventional resection - lessons learned from an interim analysis of the International ALPPS Registry. HPB (Oxford) 2020;22:537-44.
18. Bekki Y, Marti J, Toshima T, et al. A comparative study of portal vein embolization versus radiation lobectomy with Yttrium-90 micropheres in preparation for liver resection for initially unresectable hepatocellular carcinoma. Surgery 2021;169:1044-51.
19. Fan ST, Le Treut YP, Mazzaferro V, et al. Liver transplantation for neuroendocrine tumour liver metastases. HPB (Oxford) 2015;17:23-8.
20. Hu ZI, Lim KH. Evolving Paradigms in the Systemic Treatment of Advanced Gallbladder Cancer: Updates in Year 2022. Cancers (Basel) 2022;14:1249.

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