Editorial

Associating liver partition and portal vein ligation or combined transarterial chemo-embolisation and portal vein embolisation for staged hepatectomy for HBV-related hepatocellular carcinoma

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Many patients with hepatocellular carcinoma are diagnosed with large tumours at an advanced stage. In addition, conditions such as liver fibrosis, cirrhosis, portal hypertension, viral load, and portal vein thrombosis due to either non-neoplastic or portal vein tumour thrombus limit the indications for surgical management to a select subset of individuals (1). In fact, based on the American Association for the study of the liver (AASLD) and European Association for the study of the liver (EASL) guidelines surgical management is generally limited to patients with Barcelona Clinical Liver Cancer Criteria (BCLC) stage A disease (2). However, several centres of hepatobiliary surgical centers of excellence in East Asian countries have demonstrated the potential benefit of hepatic resection for patients with BCLC stage B and C disease. In turn, based data derived from these centers, new guidelines have been proposed that push expand operability criteria (3-5).

In considering the data, the principal aim of any multimodality treatment strategy should be to identify the subgroups of individuals and the specific individual patients who may benefit from surgical resection. Hepatic resection for patients with extensive disease can typically be defined into three categories: (I) single hepatic resection with or without modulation of functional liver remnant (FLR), (II) two stage or multistage hepatectomy usually with modulation of FLR and (III) parenchyma-sparing hepatic resection (6-8). In the late 1990s, a paradigm shift occurred with data demonstrating that these surgical approaches could achieve a complete resection with acceptable morbidity (9). In turn, multimodality treatment has increasingly focused on the prevention of postoperative liver failure secondary to an insufficient FLR complete (Ro) resection rather than tumour-related parameters such as size, number, or location (10-13).

In the current article, the authors compared 38 cases of associating liver partition and portal vein ligation

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(ALPPS) with 38 cases that combined transarterial chemoembolization (TACE) and portal vein embolisation (PVE) (14). Interestingly, the study demonstrated a difference in the overall survival among patients who did or did not undergo hepatic resection in the TACE + PVE cohort. In addition, factors associated with overall survival included ALPPS procedure, small tumour size and absence of severe liver fibrosis (14). The results served to emphasize the importance of the surgical treatment in addition to other modalities of therapy.

There are several questions, however, that require further clarification relative to selection criteria and definitions of inoperability. For example, one principal question that needs to be addressed is whether patients in the cohort of TACE & PVE included patients who refused a proposed ALPPS procedure, which may have biased the findings. Taking into account the potential operability of patients with HCC with concomitant PVTT, it would be interesting to know how intrahepatic metastases were defined and whether patients with PVTT were excluded from the study cohort. It has been reported that inclusion of segment IV promotes hypertrophy and consequently, increases resection rates (15). As such, further description of the PVE technique should be reported including what percentage of patients underwent occlusion of segment IV. The mean technical success rate of PVE has been reported to be 99.3% and the clinical failure rate, that is, failure to induce sufficient hypertrophy of the FRL to allow resection, is 3.9% (16).

Recently, Chan *et al.* (17,18) noted the negative impact that cirrhosis may have in the hypertrophy of the liver. The authors concluded that the higher drop-out rate in the cohort of PVE might be explained by the higher inclusion of cirrhotic patients (17,18). Of note, a recent network meta-analysis demonstrated that sequential hepatic venous embolisation could be a reliable alternative when either ALPPS or PVE fail to promote hypertrophy of the FLR (11). Considering the higher drop-out rate in the TACE & PVE cohort compared to ALPPS in the study by Li *et al.* (14), it would be important to know the exact of number of patients with cirrhosis in each cohort. Any difference in the cohorts could have explained the increased drop-out rate in the cohort of patients who underwent TACE & PVE. In addition, information as to whether the higher complications occurred in stage 1 ALPPS procedure or in stage 2 should be given.

There is an ongoing debate about the materials used for embolisation and the most adequate route of access (e.g., transjugular, transfemoral, trans-hepatic) (11,16). Another question is whether the NBCA can promote the increase of FLR fast enough before tumour progression. Perhaps using the less invasive method (PVE) is better, after taking into account the higher complication rate in the ALPPS cohort, as demonstrated in the present study (14,19).

Furthermore, patient level data reconstructed from the published Kaplan Meier plot demonstrated the robustness of the significant overall survival results using the survival-inferred fragility index (SIFI) (Bomze *et al.*, 2020). The SIFI was calculated by iteratively reassigning the median patient from the intervention to the control group until significance was lost. The calculated SIFI was 1 and 4 for overall survival among all patients with and without tumor resection in PVE groups, respectively (20). These findings indicate that the statistical conclusions rely on the outcomes of a few or a single patient. Fragile evidence in which a few patients could overturn the statistical significance suggest a higher uncertainty regarding the conclusions.

The decision as to whether a patient was fit to undergo surgery was based on judgement based on a combination of four factors: (I) the FLR, (II) indocyanine green clearance function test, (III) prealbumin and cholinesterase levels and (IV) 99m Tc-galactosyl serum albumin scintigraphy.

Implications for future research

To date, there is evidence that PVE, ALPPS and portal vein ligation trigger different molecular pathways related to the regenerative process. Therefore, further basic research is needed to understand better the molecular basis of the regenerative process. A better understanding of the underlying mechanism of regeneration may make it easier to choose the most adequate regenerative technique (10,11).

Recently, the first network meta-analysis demonstrated that sequential hepatic venous embolisation can be a reliable alternative in case of failure of hypertrophy of the FLR either by ALPPS or PVE. Therefore, high volume centres should use this new treatment option.

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