Editorial

Liver resection for hepatocellular carcinoma associated with hepatic vein invasion: is it time to reconsider the current treatment guidelines?

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Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is responsible for 70–90% of cases (1,2). The presence of macrovascular invasion such as portal vein tumor thrombus (PVTT) or hepatic vein tumor thrombus (HVTT) is known to be significantly associated with poor prognosis (3). The Barcelona clinic liver cancer (BCLC) staging system has been adopted and approved for guidance for HCC management by both the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Disease (AASLD) (4,5). According to this treatment guideline, HCC patients with macrovascular invasion are regarded as being at the advanced stage, and for whom the only proposed treatment option is sorafenib. However, the management of HCC with macrovascular invasion is complicated and still controversial.

Recently, Kokudo *et al.* retrospectively investigated the survival benefit of liver resection (LR) for HCC with HVTT using a data collected in a Japanese nationwide survey, by propensity-matched setting (6). The study included 1,021 Child-Pugh A HCC patients with HVTT without inferior vena cava invasion, and compared the survival of 540 patients who underwent LR and 481 patients who received other treatment. The median survival time (MST) in the LR group was 4.47 years, which was significantly longer than that in the non-LR group (1.58 years). After matching of 223 patients who underwent LR with 223 patients who received other treatment, the MST in the LR group was 1.61 years longer than that in the non-LR group (3.42 *vs.* 1.81 years, P=0.023). Among patients who underwent curative resection, the MST in patients without PVTT was significantly longer than that in patients with PVTT (5.67 *vs.* 1.88 years, P<0.001). Because of the rarity of the disease, available evidence concerning the treatment strategy for HVTT is limited. Therefore, this study will provide a strong body of evidence to support the value of LR for HCC with HVTT and the authors should be commended for their excellent large-cohort study based on a nationwide survey.

A previous single-institutional retrospective study published by the same group in the *Journal of Hepatology* in 2014 demonstrated that LR provided a better long-term outcome in HCC patients with microscopic and macroscopic HVTT when R0 resection was achieved (7). Other studies from China (8) and Italy (9) reported the efficacy of LR in selected patients (i.e., Vv1 or 2, *en-bloc* resection). The authors of these articles suggested that the presence of macroscopic vascular invasion including HVTT should no longer be considered an absolute contraindication for LR.

As mentioned above, sorafenib is the only choice of treatment for HCC patients with macrovascular invasion proposed by the BCLC system. Currently, sorafenib is regarded as a standard treatment for patients with advanced HCC (10). However, the MST in patients with advanced

HCC treated with sorafenib was 10.7 months, much less than the 4.5-year MST observed in the current paper (6) in patients with HVTT who underwent LR. These findings strongly suggest that, even if the existence of selection bias is considered, LR should be considered as the treatment of first choice in selected patients.

But who are these "selected patients"? In the current paper, number of tumors ≥3, PVTT (Vp2-3), gastroesophageal varices, and poor cancer cell differentiation were identified as independent poor prognostic factors for survival in patients with HVTT who underwent LR; these data may help to identify the "selected patients". HCC patients with macrovascular invasion including HVTT are a heterogeneous population with different disease behavior, and "selected patients" may benefit from aggressive surgical treatment. However, at this time, there are no established criteria. In addition, this study lacked several non-surgical treatments that have emerged recently as effective alternatives, such as targeted therapy, Y90 radioembolization, transarterial chemoembolization with drug-induced beads, and stereotactic radiation therapy. Because HCC with macrovascular invasion is an advanced stage of disease, LR in combination with these modalities should be considered to improve long-term outcome in these patients. Effective preventive agents after hepatectomy may also be needed. Furthermore, all patients should be evaluated in a multidisciplinary approach with experienced surgeons, hepatologists, oncologists, and interventional radiologists.

The time may have come to reconsider the treatment recommendations of the BCLC system, especially for advanced-stage HCC patients with macrovascular invasion. In addition, a worldwide consensus on the management of HCC with macrovascular invasion that is applicable for both Eastern and Western countries should be developed. International multicenter prospective registries or randomized controlled trials should be designed to establish the optimal treatment strategy in these patients.

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Footnote

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