Editorial

Development of conversion therapy for advanced hepatocellular carcinoma

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Although the number of hepatocellular carcinoma (HCC) patients is decreasing due to the development of hepatic anti-virus therapy, it remains a leading cause of cancer-related death worldwide. The recent development of systemic or locoregional therapy for advanced or unresectable HCC has enabled advanced HCC to be downstaged, and reports of conversion therapy have increased; however, many clinical and scientific subjects rely on the therapeutic strategies of advanced HCC. There is a need to assess the evidence and develop clinical guidelines for conversion therapy for HCC; therefore, the Chinese Expert Consensus on Conversion Therapy for Hepatocellular Carcinoma (2021 Edition), consisting of 16 statements, has been developed for clinical practice (1). This consensus addresses treatment strategies for both technically and oncologically unresectable HCCs. We applaud Chinese establishment of this comprehensive and cutting-edge consensus on the treatment of advanced HCC.

Conversion therapy involves converting unresectable HCC into resectable HCC and then surgically removing the tumor; therefore, the definition of resectability is critical. In this consensus statement, the resectability of HCC is characterized by two components: technical and oncological. Technically unresectable is the inability to achieve R0 resection, which includes factors such as the patient's general condition, liver function, and remnant liver volume, whereas oncologically unresectable is technically resectable but with inferior therapeutic efficacy in comparison to other non-surgical treatments. In technically or oncologically unresectable tumors, surgically unresectable China Liver Cancer Staging (CNLC) stage Ia (single nodule less than 5 cm), Ib (single nodule greater than 5 cm or two to three nodules less than 3 cm), and IIa (two to three nodules greater than 3 cm) HCC, and surgically resectable CNLC stage IIb (four or more nodules) and IIIa (tumor with vascular invasion) HCC are all potentially resectable HCC. Therefore, more active conversion strategies are needed for these potentially resectable HCCs, such as high-intensity and multimodality therapy, to achieve tumor shrinkage and downstaging in a short period or to increase the size of the remaining liver, allowing for radical resection. It is important to note that conversion and neoadjuvant therapy overlap in patients with potentially resectable HCCs. Groups eligible for neoadjuvant therapy should be distinguished from the unresectable ones through a classification. In Japan, Yoh *et al.* proposed "Borderline resectable", a classification of resectability, which considers technical difficulties, risk of postoperative liver failure, and oncological disadvantages (2).

Systemic (drug) therapy is critical in achieving conversion therapy as it has made remarkable progress for HCC in recent years. Clinical data for systemic therapy show that targeted therapy combined with immunotherapy—lenvatinib, pembrolizumab, and bevacizumab combined

with atezolizumab, bevacizumab analogs, sintilimab, and apatinib combined with camrelizumab (3-6)—are associated with more than 20% objective response rates (ORRs) in the treatment of unresectable HCC; however, the best systemic therapy for achieving conversion therapy for potentially resectable or initially unresectable HCC patients remains unknown. In conversion therapy, the depth of reduction (which affects the likelihood of tumor shrinkage and downgrading), speed (which affects the time to response), duration of tumor response, and organ-specific tumor response are important factors in determining treatment strategies. While it is critical to consider the characteristics of each drug and therapeutic regimen and tailor their use to tumor conditions, additional prospective studies will be required to select the best therapeutic regimen. It is also critical to safely perform surgery after an appropriate withdrawal period for each drug.

In conversion therapy, treatment strategies for portal vein tumor thrombus (PVTT) may be the most required ones. Based on data from a nationwide survey conducted by the Japan Liver Cancer Study Group, Kokudo *et al.* indicated that liver resection for HCCs, with PVTT limited to the first-order branch, is linked to a longer survival outcome compared to other non-surgical treatments (median survival time compared with liver resection group and non-surgical treatment group: 2.87 *vs.* 1.10 years, P<0.001) (7). Both hepatic vein tumor thrombus (HVTT) and PVTT are classified as advanced (CNLC grade IIIa) but potentially resectable HCCs. Kokudo *et al.*, through a retrospective analysis of data gathered in a Japanese nationwide survey, reported that in HVTT without inferior vena cava invasion, the liver resection group had a better median survival time than the non-hepatic resection group in a propensity score–matched cohort (3.42 *vs.* 1.81 years, P=0.023) (8). However, liver resection for PVTT or HVTT can be technically challenging, necessitating a major hepatectomy; recurrence-free survival is shorter than the cases without PVTT or HVTT. On the contrary, shrinking tumor thrombus with systemic or locoregional therapy makes liver resection less difficult and may improve prognosis (9).

Locoregional therapies include hepatic artery infusion chemotherapy (HAIC), selective internal radiation therapy, radiotherapy, and trans-arterial chemoembolization (TACE), and their role has been described primarily as conversion therapies for HCC with PVTT. In particular, HAIC for intermediate or advanced HCC has made great progress in China. A multicenter randomized control trial (RCT) in China found that the ORR of HAIC treatment in HCC patients with PVTT was significantly higher than that of sorafenib (mRECIST criteria, 27.6% *vs.* 3.4%, P=0.001) (10). Another RCT study compared the efficacy of HAIC and sorafenib combination therapy and sorafenib monotherapy in patients with HCC and PVTT, and the results showed that the ORR in the former group was significantly higher than the latter. HAIC is considered an effective treatment for PVTT, and downstaging allows for conversion therapy.

Improving future liver remnant (FLR) volume insufficiency is critical in performing radical resection of potentially resectable HCC, as well as tumor shrinkage and downstaging with multimodal treatments. In patients with insufficient FLR, associated liver partition and portal vein ligation for staged hepatectomy (ALPPS), and portal vein embolization (PVE) use is suggested for increasing the FLR volume. PVE has been used safely in clinical trials for a long time; however, after PVE, FLR hyperplasia takes a relatively long time, and more than 20% of patients lose the chance of surgery due to tumor progression or insufficient FLR hyperplasia (11). On the contrary, ALPPS can increase FLR faster than PVE, but it carries a high risk of perioperative complications (12), and the indications for ALPPS must be carefully determined. Modified ALPPS techniques such as associating liver partial partition and trans-ileocecal portal vein embolization for staged hepatectomy by Sakamoto *et al.* have also been reported to lower the complications (13).

Liver resection after tumor shrinkage and downstaging is the major factor in conversion therapy; however, radical liver resection is not the aim of the treatment for advanced or unresectable HCCs. The true purpose is to enhance the long-term prognosis of advanced or unresectable HCC. Shindoh *et al.* reported in selected patients with advanced HCC that conversion surgery after lenvatinib treatment may provide significant survival benefits over non-surgical treatments (14). According to the results of the Japanese multicenter prospective study assessing the efficacy of lenvatinib to achieve conversion surgery for initially unresectable HCC (LENS-HCC trial, jRCT s031190057) reported in ASCO-GI 2022, out of the 49 patients enrolled, 27 were eligible for conversion surgery with R0 resection, and the 1-year overall survival rate after conversion surgery was 75.9%. Now, the multicenter prospective study assessing the efficacy of atezolizumab and bevacizumab combination therapy to achieve conversion surgery for initially unresectable HCC is currently underway in Japan (UMIN000046634). However, non-surgical treatment alone such as anti-angiogenic drugs or molecular targeted therapy

combined with immunotherapies may allow patients to achieve long-term tumor control and survival. According to this statement, multi-disciplinary teams are important in selecting and implementing the appropriate treatment based on the tumor condition.

Liver transplantation could be a crucial treatment option in HCC patients with Child C liver function. In Japan, a new 5-5-500 rule (nodule size ≤5 cm in diameter, nodule number ≤5, and alpha-fetoprotein value ≤500 ng/mL) has been used for determining liver transplantation indication for HCC since 2019, due to compare survival rates of patients within Japan and Milan criteria (5 year-survival rates: 75.8% *vs.* 75.3%) (15). Bridging therapy for transplantation can be prioritized in the new anti-cancer drugs era for HCC; however, the description of liver transplantation for HCC can be very limited. It may be desirable to determine liver transplantation indication in the revised consensus.

More prospective clinical trials are required to determine the best treatment for tumor conditions and indications for conversion therapy. It is hoped that conversion therapy for advanced or unresectable HCC will be further developed as more evidence is gathered from the clinical practice.

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