Editorial

Is the Barcelona Clinic Liver Cancer guideline for treating intermediate to advanced staged hepatocellular carcinoma still appropriate?

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Comment on: Zhao S, Zhang T, Dou W, *et al.* A comparison of transcatheter arterial chemoembolization used with and without apatinib for intermediate- to advanced-stage hepatocellular carcinoma: a systematic review and meta-analysis. Ann Transl Med 2020;8:542.

Submitted Nov 13, 2020. Accepted for publication Dec 07, 2020.
doi: 10.21037/atm-2020-132
View this article at: http://dx.doi.org/10.21037/atm-2020-132

Among several staging systems for prognostic classification and therapeutic strategy, Barcelona Clinic Liver Cancer (BCLC) staging system is widely accepted because it includes liver function and performance status as well as tumor stage in consideration of therapeutic strategy. According to the BCLC guideline, surgical resection, ablation, and transplantation are recommended for early stage hepatocellular carcinoma (HCC) (0 or A). For advanced stage HCC (C), systemic therapy is recommended for patients with preserved liver function (1,2). Chemoembolization is recommended for multinodular HCC with preserved liver function at an intermediate stage of HCC (B). With transarterial chemoembolization (TACE), survival of patients is expected to be prolonged compared to that of untreated patients (3,4). In addition to TACE, combination therapy with radiation or systemic therapy shows better outcome than TACE alone (5,6). However, incidence of gastroduodenal ulcers and levels of ALT and total bilirubin in patients receiving TACE plus RT are higher than those in the TACE alone group. TACE in combination with tyrosine kinase inhibitor is an effective treatment for TACE-refractory advanced HCC, although it has severe adverse effects that can be mitigated by lowering the dose (7). Immune checkpoint inhibitors also fail to meet predefined threshold for statistically significant long-term benefit (8).

As described above, stage B HCC comprises a highly heterogenous patient population. Therefore, it is challenging to choose the right strategy to treat each patient (9). TACE-based therapy does not provide clear long-term survival benefits. Although several targeted multi-kinase inhibitors have been introduced, safe and effective new drugs are rarely found. Due to recent improvement of surgical technique for hepatectomy along with understanding of HCC, surgical complications have been dramatically decreased. Even for patients with decreased liver function, limited anatomical resection or limited wedge resection with minimal invasive surgery can be safely applied. A recent systematic review of 50 studies including 14,808 patients who underwent hepatic resection to treat HCC large/multinodular HCC and 24 studies with 4,389 patients who underwent hepatic resection to treat HCC with macrovascular invasion has shown a positive role of hepatic resection (10). According to that review, median in-hospital mortality for patients with either type of HCC was significantly low, especially in Asian patients (2.7%). Overall 5-year survival rates for patients with large (>5 cm) or multinodular HCC was 42% for Asian patients. Another well-designed meta-analysis has reviewed high-quality studies including one randomized controlled trial (RCT), five propensity-score matching nonrandomized comparative trials (NRCTs), and 12 NRCTS that have compared survival outcomes of 1,986 patients after primary hepatectomy and TACE for stage B/C HCC. They found significant survival benefits of primary hepatectomy over TACE (hazard ratio: 0.59; 95% confidence interval: 0.51–

0.67; P<0.00001) (2). Based on a large multi-center study, Torzilli *et al.* (11) have reported that surgery in current practice is widely applied for patients with multinodular, large, and macrovascular invasive HCC, providing acceptable short- and long-term results and justifying an update of EASL/AASLD therapeutic guidelines. Ishizawa *et al.* (12) have reported very similar results, stating that neither multiple tumors nor portal hypertension are surgical contraindications for HCC. When primary hepatectomy and TACE are compared for BCLC B with high level of evidence, a randomized study (13) and a propensity score matched analysis (14) have shown remarkably better survival rate with primary hepatectomy (3-year survival rate of 51.5% with hepatectomy *vs.* 18.1% with TACE; 5-year survival rate of 43% with hepatectomy *vs.* 15% with TACE, both P<0.001). Recent development of minimal invasive hepatectomy has made hepatic resection more safe and less invasive. Its oncologic outcome is comparable with conventional open hepatectomy. Moreover, minimal invasive hepatectomy shows fast recovery with much improved surgical morbidity and mortality (15,16) with safe oncologic outcomes (17). Therefore, even with stage B HCC, surgical resection should be considered for selected patients.

Despite there are a lot of well-designed reports that show safety and good long-term outcome of hepatic resection in selected patients with stage B, EASL/AASLD guidelines based on BCLC classification still leave little room for hepatic resection. In the decision making to select the first choice of treatment, surgical resection or TACE for patients with BCLC B, there is a big discrepancy of preference between hepatic surgeons and hepatologists. On the basis of the regret threshold model, surgeons prefer surgery whereas hepatologists prefer TACE (18). Thus, there is a need for communications between surgeons and physicians to have a multi-disciplinary approach to treat stage B HCC.

Zhao *et al.* have shown the effectiveness of combination treatment of apatinib and TACE which provides better survival benefits for stage B HCC than TACE monotherapy (19). Apatinib, also known as YN968D1, is a tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor receptor-2 (VEGFR2, also known as KDR). It inhibits VEGF-mediated endothelial cell migration and proliferation, thus blocking new blood vessel formation in tumor tissues. Additive use of multikinase inhibitors after TACE is logically acceptable as described in the discussion of this study because repeated TACE can result in a certain resistance to chemotherapeutic agents due to TACE induced hypoxia and ischemia. However, available data have some weak points because each study has small sample numbers with short follow-up duration. In addition, most of selected studies were performed in China. In the forest plot of meta-analysis, less than half of studies have shown that TACE plus apatinib has significantly better long-term outcome than TACE alone. Moreover, there are adverse effects associated with apatinib, hypertension, hand-foot syndrome, and oral ulcer like other systemic therapy agents. Therefore, in the treatment of stage B HCC, treatment strategy should be selected very carefully considering both tumor characteristics and patients' performance. Nevertheless, in the era of precision medicine with targeted therapy, this treatment option will need more effective multidisciplinary approach to treat HCC. TACE combined with apatinib can be tried for curative treatment. We hope that this new modality of chemoembolization combined targeted therapy can extend the role of surgical resection in HCC.

In conclusion, primary hepatectomy may be the first considerable option for intermediate- and advanced-stage HCC of selected patients. When the tumor is unresectable, combination therapy with TACE plus radiotherapy, multi-kinase inhibitor, or immune checkpoints inhibitor can provide much better survival benefit than TACE or systemic therapy alone. The paradigm of sequential treatment of sorafenib followed by regorafenib, cabozantinib, various immunotherapy, and hopefully apatinib for advanced HCC maybe shifted in the near future.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure from (available at http://dx.doi.org/10.21037/atm-2020-132). The authors have no conflicts of interests to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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Cite this article as: Kang KJ, Ahn KS. Is the Barcelona Clinic Liver Cancer guideline for treating intermediate to advanced staged hepatocellular carcinoma still appropriate? Ann Transl Med 2021;9(1):1. doi: 10.21037/atm-2020-132