Editorial from the ACHBPT

Advanced nonmetastatic hepatocellular carcinoma: curative surgery may be an option

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In this multicentric retrospective study (1), the authors aimed to compare surgery versus Sorafenib (SOR) for the treatment of advanced nonmetastatic hepatocellular carcinoma (HCC).

Data were collected from two Italian registries, between 2008 and 2019. Inclusion criteria were patients treated by SOR or hepatic surgery (SURG) for HCC with segmental portal invasion and/or deteriorated general condition [Eastern Cooperative Oncological Group Performance Status (ECOG-PS) grade 1 to 3] corresponding to Barcelona Clinic Liver Cancer stage C (BCLC-C), excluding extrahepatic metastasis and main portal trunk invasion. Primary endpoint was overall survival (OS) analysis while secondary endpoint was recurrence-free survival (RFS) for SURG group and progression-free survival (PFS) for SOR group. A total of 478 patients were analyzed. From the ITA.LI.CA registry (23 centers), 175 patients were analyzed for HCC treated with SOR and from the HE.RC.O.LE.S registry (30 centers) 303 patients were analyzed for resected HCC. Treatment decision was taken locally at each center at a multi-disciplinary meeting. In order to balance patient differences, authors used an inverse probability weighting (IPW) and created two pseudo-population groups with similar baseline characteristics.

OS at 1, 3, and 5 years was 83.6%, 68.1%, and 55.9% for SURG and 42.3%, 17.8%, and 12.8% for SOR [hazard ratio (HR) =4.092; 95% confidence interval (CI): 3.197–5.286; P<0.001]. RFS was 24 months in SURG and PFS was 5 months in SOR (HR =4.175; 95% CI: 2.282–7.641; P=0.006). Analysis was also conducted in two sub-groups of patients: patients with portal invasion and ECOG-PS 0 and patients without portal invasion but ECOG-PS >0. In all cases, surgery offered the best OS at 1, 3 and 5 years. After using Cox logistic regression in the weighted cohorts, elevated Charlson comorbidity score and SOR treatment were identified as significant predictors of decreased OS while SOR treatment was the only significant predictor of decreased PFS.

The aim of this study was to evaluate the potential benefit of surgery for selected HCC classified as BCLC-C, currently eligible only for systemic treatment. Given the shift from palliative to curative strategy, the implication in clinical practice is essential.

According to the Barcelona criteria, advanced HCC is defined as HCC with portal invasion and/or metastatic progression and/or ECOG-PS 1–2; and its treatment relies on systemic therapy as recommended in the latest European guidelines (European Association for the Study of the Liver 2018) (2). The presence of one of these criteria therefore directly assign the patient to a palliative management strategy, even if the prognosis of these patients can be very different. In current practice, some of the BCLC-C HCC patients are proposed for surgical resection if there is no metastatic spread and liver function is preserved. As

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it is ethically questionable to conduct a prospective study randomizing patients to a curative or palliative strategy, the authors performed a retrospective study on data collected prospectively from two Italian registries.

Despite the prospective collect of data, the authors still excluded 26 patients for missing data on outcome variables. Concerning baseline characteristics table, it is confusing to see 270 patients of the SURG group classified according to Child-Pugh (CP) cirrhosis score although only 162 patients had a diagnosis of cirrhosis and 80 patients presented a steatosis. Incoherencies can also be found in portal vein thrombosis (PVT) classification for 243 patients in the SURG group: 66 patients presented a segmentary thrombosis, 51 patients presented a second-order thrombosis and 81 patients presented a first order portal vein branch thrombosis while 45 patients were not accounted for.

Authors in this study observed that patients in SURG group presented fewer comorbidities and less severe liver disease than SOR group, which constituted the main bias of OS assessment. Also, SOR treatment and management of adverse effects has evolved in the past few years, with better selection of patients who can benefit from this treatment. Patients were included over a long period (2008 to 2019) with 37.1% of SOR patients presenting a poor (CP-B cirrhosis) liver function and thus probably taking less benefit of modern SOR treatment than expected.

Although an IPW method was used to adjust patient baseline characteristics, the long inclusion period remains an essential bias.

Despite the aforementioned biases (long period inclusion, retrospective design and population differences), the higher 5-year OS of the SURG group, compared with SOR group emphasizes the importance of considering surgical resection when feasible.

Currently, the development of immunotherapy has replaced SOR in the first-line treatment of advanced HCC, offering a significant benefit compared to SOR in OS (19.2 *vs.* 13.4 months, HR =0.66, P<0.0009) and PFS (6.9 *vs.* 4.3 months, HR =0.65, P=0.0001) (3). It would be thus interesting to compare surgery to immunotherapy regimes currently used.

In conclusion, the authors demonstrated the feasibility of surgical resection for selected BCLC-C patients, with a significant benefit in terms of OS and PFS compared to SOR. This benefit was observed for patients classified as BCLC-C for vascular invasion reason or for altered ECOG-PS. In the absence of metastatic spread or portal trunk invasion, curative surgical resection, when feasible, may be considered as a first-line treatment in selected patients with BCLC HCC patients.

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