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Editorial

The prime time for management of hepatocellular carcinoma in Hong Kong

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In this issue of *Clinical and Molecular Hepatology*, the article 'the Hong Kong perspective of clinical management of HCC' written by Hui et al.[1] represented a timely piece of summery on the real-life practice of management of hepatocellular carcinoma (HCC). In the past decade, we have witnessed remarkable advances on the surveillance, diagnosis, and treatment of HCC, which lead to changes in clinical practice and result in improved outcomes of patients.[2] Due to the high disease burden and the mature healthcare system, Hong Kong is one of the earliest places in the world to adopt multidisciplinary care for HCC and to initiate research on HCC.

As highlighted in the review paper,[1] the management of HCC has undergone a rapid development, and this is leading to another wave of practice-changing studies. For surveillance of HCC, the use of alpha-feroprotein (AFP) and abdominal ultrasound (US) is well-known to be associated with improved early detection, curative treatment receipt and survival in patients with cirrhosis.[3-5] However, as compared to other screening strategies, such as breast cancer with mammogram with a sensitivity of 77 to 95%,[6] colorectal cancer with faecal immunochemical test with sensitivity of 79%,[7] nasopharyngeal cancer with EBV-DNA with sensitivity of 97.1%,[8] the sensitivity of combined AFP and US of approximately 60% for HCC is relatively lower. Recently, circulating cell-free DNA has gained popularity as a screening test for early detection of multiple cancers with encouraging results.[9,10] In a phase II case-control study involving 401 patients, a multi-target HCC blood test panel using three methylated markers, in combination with AFP and sex, showed a sensitivity of 82% for early-stage HCC detection with a specificity of 87%.[9] In addition, the Circulating Cell-free Genome Atlas study has recently reported the performance of a plasma cell-free DNA screening test using a panel of >100,000 informative methylation regions, with an overall sensitivity of 67.3% in a pre-specified set of 12 cancer types, including liver cancer. It is anticipated that cell-free DNA will be an important tool for surveillance in the near future.[11]

Hui et al.[1] depicted the real-life practice in diagnosis of HCC in Hong Kong, which is mainly based on non-invasive tests

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with contrast-enhanced imaging to identify the characteristic features of HCC. This is largely compatible with the recommendation of international guidelines.[12,13] However, there has recently been a swing back to obtain tissue diagnosis during work-up for HCC for two reasons. First, there is a growing recognition of alternative entities of liver malignancies including the intrahepatic cholangiocarcinoma (CC) and combined HCC-CC, which frequently require pathological diagnosis for confirmation.[14] In fact, a recent large retrospective analysis in UK has shown that around 10% of advanced-stage liver disease would receive an incorrect diagnosis based on non-invasive radiological criteria.[15] Second, given the increasing number of targeted therapy and immunotherapy for HCC, molecular subtyping of HCC is important to develop predictive biomarkers and the pursual of personalized treatment for HCC.

Following diagnosis of HCC, treatment of curative intent could be achieved by liver resection, ablation, or transplantation for early-stage disease.[1] However, as noted by Hui et al.[1], recurrence rates occurred in over 70% for patients following hepatectomy. Conventionally, effective adjuvant treatment has been lacking for HCC. This deadlock is expected to be broken in 2023 by the IMbrave050 study, which is a clinical trial randomizing 662 patients with HCC who had undergone curative resection or ablation, to receive adjuvant atezolizumab plus bevacizumab for up to 12 months, or no intervention.[16] According to a recently announced press release, the prespecified interim analysis showed that patients in the experimental arm had statistically significant improvement in recurrence-free survival (RFS).[16] The results are expected to be presented in major conferences in early half of 2023.

For intermediate-stage disease, transarterial chemoembolization (TACE) remains a standard treatment.[1] However, TACE as the only recommended treatment in this heterogeneous group has recently been challenged. On one hand, systemic therapy is increasingly considered a better alternative for selected high-burden intermediate-stage HCC. In fact, in the latest 2022 updated version of treatment recommendation based on BCLC staging, TACE is no longer recommended as treatment for intermediate-stage disease when patients have high-burden HCC (e.g., extensive bilobar liver involvement, diffuse, infiltrative HCC).[17] In a proof-of-concept retrospective propensity score-matched study, the use of lenvatinib in intermediate-stage "up-to-7" out HCC was associated with improved OS (37.9 months vs. 21.3 months, $P<0.01$), progression-free survival (PFS) (16.0 months vs. 3.0 months, $P<0.001$) and objective response rate (ORR) (73.3% vs. 33.3%, $P<0.001$) as compared to TACE.[18] The study also showed that hepatic function deteriorated with repeated TACE (baseline ALBI score from -2.66 to -2.09, $P<0.001$) but was maintained in the group treated with lenvatinib (baseline ALBI score from -2.61 to -2.61, $P=0.254$).[18] The use of more aggressive systemic therapy with atezolizumab plus bevacizumab in the intermediate-stage HCC is currently underway by ongoing randomized study (NCT04803994). On the other hand, the addition of systemic therapy to TACE could improve the outcome of intermediate-stage HCC. According to the TACTICS-L study, a phase II single-arm study, the combination of lenvatinib with TACE in intermediate-stage unresectable HCC patients was associated with a ORR up to 88.7% with complete response seen in 66.1% of patients.[19] The median PFS was 28.3 months, which had already approached the expected OS of intermediate-stage HCC based on available scientific evidence.[17] The randomized study from China also suggested that the addition of lenvatinib to TACE could improve both ORR, PFS and OS of both intermediate- and advanced-stage HCC.[20] The above data unanimously suggest that systemic therapy has an important role in intermediate-stage HCC.

As mentioned by Hui et al.[1], immunotherapy or immunotherapy containing regimes are increasingly advocated as their efficacy has been demonstrated in a number of landmark trials such as IMbrave150, CheckMate040 and HIMALAYA.[21-23] As a result, immunotherapy is recommended in both the first-line and subsequent-line settings according to local and international guidelines.[1,17] For all phase III clinical trials testing immunotherapy in advanced-stage HCC, patients with Child-Pugh A liver function were mostly recruited. However, a significant proportion of patients with Child-Pugh B liver function with advanced disease are frequently seen in the clinic at presentation. Recently, data has emerged that single agent nivolumab for Child-Pugh B unresectable HCC could be safe and effective, and thus now being incorporated

Abbreviations:

HCC, hepatocellular carcinoma; AFP, alpha-feto protein; US, ultrasound; CC, cholangiocarcinoma; RFS, recurrence-free survival; TACE, transarterial chemoembolization; PFS, progression-free survival; ORR, objective response rate

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into the latest Hong Kong consensus statement.[1] The CheckMate040 study (cohort 5), a phase I/II study testing single agent nivolumab in patients with advanced HCC and Child-Pugh B cirrhosis, was published.[24] It demonstrated clinically meaningful stabilization of liver function, and improved OS compared to historical cohort treated with sorafenib (7.6 months vs. 2.5–5.4 months).[24] Although in the CheckMate040 study, patients with Child-Pugh B7 liver function had similar OS compared to those with Child-Pugh B8 liver function, a couple of retrospective real-world studies have shown that patients with Child-Pugh B7 liver function derived more benefits from nivolumab than Child-Pugh B8.[25,26] Therefore, nivolumab could represent a potential treatment option in advanced HCC with Child-Pugh B7 liver function if it is validated in a larger cohort of patients.

Overall, "the Hong Kong perspective of clinical management of HCC" written by Hui et al.[1] is a timely piece of summary of the key advancements and real-life practice of HCC management in recent years in Hong Kong. Emerging breakthroughs are budding in all fronts of HCC management, including surveillance, diagnosis, and management of different stages of disease. We eagerly await these exciting results to come, and it will be the prime time for HCC in the coming years.

Authors' contribution

The authors contribute equally in the drafting and editing of the manuscript.

Conflicts of Interest

S.L. Chan is the advisory for Astra-Zeneca, MSD, Eisai, BMS and Roche. S.L. Chan received research fund from MSD, Bayer, Eisai, Ipsen and SIRTEX. S.L. Chan received Honoraria from Bayer, Astra-Zeneca, Eisai, Roche and MSD. S.L. Chan is the speaker for MSD, BMC, Astra-Zeneca, Eisai, Roche, Ipsen, SIRTEX and Hutchmed.

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