

Hepatocellular carcinoma: one world, one cancer—different guidelines?

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Provenance: This is an invited Editorial commissioned by Editor-in-Chief Yilei Mao (Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China).

Comment on: Xie DY, Ren ZG, Zhou J, *et al.* Critical appraisal of Chinese 2017 guideline on the management of hepatocellular carcinoma. *Hepatobiliary Surg Nutr* 2017;6:387-96.

Submitted Jan 24, 2018. Accepted for publication Jan 29, 2018.

doi: 10.21037/hbsn.2018.01.05

View this article at: <http://dx.doi.org/10.21037/hbsn.2018.01.05>

Hepatocellular carcinoma (HCC) is a healthcare challenge in virtually all parts of the world. Therefore, it is no wonder that different guidelines have been developed reflecting expert consensus on the management of HCC in different regions, namely guidelines from the American Association for the Study of Liver Diseases (AASLD) for the USA (1,2), the Asian Pacific Association for the Study of the Liver (APASL) for the Asia-Pacific region (3), the European Association for the Study of the Liver (EASL) for Europe (4), and the Japan Society of Hepatology (JSH) for Japan (5,6). In 2018 an update of the EASL clinical practice guidelines (CPG) will appear.

China is a country with a large population of HCC patients due to a high prevalence of hepatitis B virus infection. Thanks to China's economic rise and the subsequent access to high quality healthcare, the management of HCC in China has reached the standard of developed countries. Therefore, the current update of the Chinese guidelines deserves a closer look.

Xie *et al.* have made the effort of reporting on the changes introduced by the update and comparing the Chinese with other international guidelines (7). Such an effort is particularly valuable, since the Chinese guidelines have not yet been published in English. While there are many commonalities between the different guidelines, Xie *et al.* report some striking differences.

The diagnostic approach to HCC is generally similar

between the various international guidelines: patients with chronic liver diseases and/or cirrhosis should undergo surveillance with alpha-fetoprotein (AFP) measurements and ultrasound (US) every 6 months in China and with or without AFP in the rest of the world. Nodules on US should be examined by one (size >2 cm) or two (size ≤2 cm) of the following methods: computed tomography (CT), magnetic resonance imaging (MRI), gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid-enhanced MRI (Gd-EOB-DTPA-MRI) or contrast-enhanced ultrasound (CEUS). That the latter two are recommended is a deviation from the AASLD (1,2) and EASL (4) guidelines which only recommend CT or MRI. However, the updated EASL CPG will also discuss CEUS. For inconclusive results, a biopsy is recommended unanimously.

Regarding the treatment of HCC, more differences between the Chinese and the other guidelines emerge: with the new version, the Chinese guidelines introduce their own staging system which contains four main (I–IV) and seven substages, and forms the basis for the proposed treatment algorithm. While there is mostly common ground between the Chinese and international guidelines for early HCC [left side of the Barcelona Clinic Liver Cancer (BCLC) staging system] with resection, ablation and transplantation being endorsed, the Chinese guidelines apply the University of California San Francisco criteria instead of the Milan criteria for the selection of HCC patients for transplantation. Moving to the right of the BCLC system,

the Chinese guidelines are distinguished by an extensive and unusual flexibility in the choice of treatment. In line with our recent review of the evidence for the various treatment options for intermediate HCC (8), the Chinese guidelines suggest an array of methods for more advanced HCC stages: resection remains an option as long as there is no vascular invasion or extrahepatic spread (equivalent to BCLC 0–B). Transarterial chemoembolization (TACE) is valid as long as liver function is CHILD A or B, and the performance status is >3 (equivalent to BCLC A–C). Systemic therapy is not restricted to sorafenib alone but includes FOLFOX, and is already proposed when ≥ 4 nodules are present (equivalent to BCLC B + C). Finally, radiotherapy can be considered for HCC with vascular invasion or extrahepatic spread (equivalent to BCLC C).

In conclusion, the Chinese guidelines' overall flexibility in the choice of treatment is a reflection of the currently available evidence and real-world practice. In this regard, the Chinese are closer to the JSH (6) than the AASLD (1) and EASL (4) guidelines. However, a trend towards flexibilization could be recently noticed in the update of the AASLD guidelines (2) which have ceased to favor TACE over other locoregional treatments for patients with intermediate HCC. It is therefore likely that the Western guidelines will further move in this direction until clearer evidence becomes available.

One aspect the Chinese and the other international guidelines have not yet implemented is the arrival of new kinase [lenvatinib (9) and regorafenib (10)] and checkpoint inhibitors [e.g., nivolumab (11) and pembrolizumab (12)]. In addition, at this year's ASCO Gastrointestinal (GI) Cancers Symposium, cabozantinib has been presented as another second line option. It is all but certain that these drugs will be included in the next updates, and it remains to be seen how flexible the Chinese guidelines will handle their use.

Demonstrated by the multitude of both basic and clinical research papers on HCC in recent years, China has become a big player in the HCC arena. This is supported by the country's size and the large number of HCC patients which allows to conduct clinical trials with high patient numbers. Therefore, there is ample reason to take the Chinese way of treating HCC patients seriously. While the new version of the Chinese guidelines adds new differences in comparison with the other international guidelines, reports such as the one from Xie *et al.* (7) facilitate learning from and exchange between different hepatological societies, which may yet lead to a convergence of guidelines in the future.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Foerster F, Galle PR. Hepatocellular carcinoma: one world, one cancer—different guidelines? *HepatoBiliary Surg Nutr* 2018;7(1):41-43. doi: 10.21037/hbsn.2018.01.05