Editorial

Searching for common ground in a global disease

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There are few malignancies that present clinicians with as many challenges as the patient with hepatocellular carcinoma (HCC). The common occurrence of chronic liver disease with a cancer arising in the liver creates competing risks for outcomes with all treatments, both procedure and medical based. It is for this reason that patients are often best managed at centers with particular expertise in all aspects of this disease including hepatobiliary surgery and liver transplantation, hepatology, diagnostic and interventional radiology, and medical oncology (1). Over the past decades there has been robust research in all of these specialties on how best to approach patients with this disease. It has been the efforts of guideline committees to synthesize these data to provide clinicians with evidence based recommendations. While guidelines give broad recommendations, often treating clinicians must extrapolate how these will apply to the individual patient sitting in front of them. In addition, medical knowledge is always evolving and at times, there are gaps in research and expert consensus and personal experience is the best we can rely on. While there are numerous guidelines published representing regional expertise (2-4), what is reassuring is that generally there is more consensus than disagreement, and not surprisingly, the disagreement is in areas where data with high levels of evidence are lacking.

In the current updates to the Chinese Guidelines reviewed by Xie *et al.* (5), we see some updated recommendations that are generally in line with global consensus. Before we can discuss staging and treatment of HCC, we must first find and diagnose the disease. Surveillance for HCC in those at risk is perhaps the area that is most important in improving outcomes for our patients. While the level of evidence from large prospective randomized studies demonstrating a clear survival advantage with screening are lacking, it is a fact that the highest chance of cure is with smaller tumor burdens. Finding small tumors increases the availability of curative approaches such as resection, liver transplantation, and ablative approaches (6). Still, there is a tremendous under awareness of primary liver disease globally; half of the cases of HCC occur in China alone as result of widespread HBV infection. I would argue, the first step to finding HCC is identifying those patients at risk and therefore widespread screening for HBV needs to be implemented. As we have seen, well organized vaccination programs can dramatically reduce the incidence and mortality from HBV related HCC (7). This needs to be a priority in HCC guidelines. Once those patients at risk have been identified, global guidelines consistently recommend surveillance that includes some imaging modality, typically ultrasound (5). The use of tumor markers alone is discouraged but updated guidelines either recommend including them or leave them as optional (5). The frequency of performing these studies every 6 months is consistent with most global recommendations with the exception of the JSH guidelines which for patients characterized as "super-high-risk", the recommendation of US every 3–4 months and CT or MRI imaging every 6 months is recommended. While the JSH guidelines will likely find smaller HCCs, the benefit in changing outcomes versus less frequent approaches are not proven.

All guidelines consistently define a non-invasive diagnostic approach. The current updates to the Chinese guidelines broadens the imaging modalities used to make the diagnosis of HCC and removes a minimum size criterion. this is in contrast to AASLD and EASL guidelines that recommend a dynamic CT or MR imaging and a minimum size of ≥1 cm.

Perhaps the area that leads to the most variability globally is staging which will then effect treatment recommendations. In the extremes, there is generally a consensus. Patients with decompensated liver disease, often characterized by poor performance status (PS 3–4) and Child-Pugh C liver function have a limited life expectancy and supportive/palliative care is most appropriate. The exception would be those patents with a tumor burden deemed appropriate for transplant. While the current Chinese guidelines endorse UCSF criteria for transplant, globally it is accepted a patient within Milan criteria is still curable even in the setting of poor liver function (8). On the other extreme, are patients with well-compensated liver disease, good performance status and smaller tumors, with no vascular invasion for whom surgical resection is universally recommended. Unlike Western guidelines, the Chinese guidelines are less conservative in that they will recommend resection for patients with slightly elevated bilirubin levels and mild portal hypertension as long as their liver remnant is of adequate size based on indocyanine retention. Guidelines are consistent in recommending surgery over radiofrequency for resectable patients and reserving RFA when there are anatomical or medical contraindications to resection. It should be noted that there is a trend in Asia to offer RFA to larger tumors in as well (>3 cm).

Another area where there is general global consensus is for patient with clear extrahepatic spread. For patients with metastatic disease, preserved performance status (PS 0–2) and preserved liver function (CP A–B) guidelines consistently recommend systemic treatment. While for a decade, sorafenib has been the only agent to show an improvement in overall survival in this population in the front-line setting (9), recent data has demonstrated the multi-kinase inhibitor lenvatinib to be non-inferior (10) and now there are agents with proven survival advantages in the second-line setting including regorafenib (11) and cabozantinib (12). The Chinese guidelines maintain a role for systemic chemotherapy with FOLFOX though the data supporting its benefit is marginal (13).

It is in the patients that don't fit the above profiles that we start to see regional differences. One of the biggest questions for guidelines is in the medically fit patient, what tumor characteristics would preclude a surgical resection? Western guidelines tend to move away from resection in the setting of macrovascular invasion (MVI) defined as tumor thrombus seen on imaging. The justification being that the recurrence risk is high enough that survival advantages are lost. In contrast, the Chinese guidelines and others from Asia make a distinction between intrahepatic MVI and extrahepatic MVI, with the former being considered advanced and appropriate for systemic treatment which is the approach in the West. The difference between the two approaches for patients with intrahepatic MVI is somewhat philosophical- do we make guidelines that are geared towards the representative patients (the median, as in the West) or do we guide them by the tail-of-the curve. With the occurrence of less cirrhotic patients in China from HBV related HCC, more patients are physiologically resectable likely driving this more invasive approach, while Western guidelines shy away from surgical resection for tumors with intrahepatic MVI and significant multi-focality. Similarly, there is debate about the role of chemoembolization (TACE) in these patients with Western guidelines supporting systemic therapy over local-regional approaches in these patients. A randomized study of TACE versus systemic therapy is pivotal to answer this question. Recent randomized studies to establish a role for radioembolization in these patients have been negative (14,15). Similar studies with TACE are needed to definitely answer this question.

In summary, there are more consistencies between guidelines than controversy, and the Chinese guidelines should be discussed on the world-stage. Arguably, given the large number of patients with HCC in China as compared to other areas, China is very well-positioned to answer many of the critical questions in the management of HCC. The issue is, are they prepared to do so? A well-organized research effort in China with a commitment to answering some of the questions mentioned above that lack high-grade level 1 evidence could be of great value to the global community. This requires being open to trial designs which will challenge regional biases, but are ethical and appropriate because the answers are not supported by current prospectively generated data. If surgical resection is superior to other approaches for patients with intrahepatic macrovascular invasion, then prove it in a well-designed study. The patient resources and medical expertise exist in China to definitively answer important questions such as this. This approach in the end will continue to broaden the utility of the Chinese Guidelines in the global HCC community.

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Footnote

Conflicts of Interest: RS Finn has served as a consultant to Eisai, Bayer, Bristol Myers Squibb, Eli Lilly, Novartis and Pfizer.

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