Viewpoint

Surveillance of hepatocellular cancer—why can't we do better?

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Hepatocellular carcinoma (HCC) has become a priority because of high case fatality and increasing incidence, especially in the United States. Because the best curative therapies are liver resection and transplantation, the Holy Grail of HCC is early identification. Finding smaller tumors allows for surgical intervention with better outcome and also allows time to wait for precious donor livers. In this recent article, Kanwal and Singal summarize the current best practices for HCC surveillance. They rightfully point out that the direct evidence for benefit of HCC surveillance has included only 2 large randomized controlled trials from Chinese patients with hepatitis B and multiple retrospective studies which inferred survival benefit (1,2). Singal *et al.* have also reported the systematic review of 47 studies which demonstrated that surveillance allowed for early tumor detection, improved receipt of curative therapy and better survival (3). This is truly as good as the data will ever be, as a randomized prospective controlled trial will never be performed in the future. Patients and physicians both would have difficulty with randomization to no surveillance with the available data which suggests benefits from surveillance.

The real problem with HCC surveillance lies in determining who should be screened and how we should do it. A decade or two ago, it was much easier to identify the population at risk because the majority of patients with HCC had viral hepatitis. Various professional societies like the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) have recommendations on who to screen including those with hepatitis B, by age and gender, hepatitis C, and cirrhotics. The standard surveillance tools have included liver ultrasound and serum alpha-fetoprotein. Tzartzeva *et al.* report the pooled sensitivity of US to be 84% and sensitivity to be 91% with a large meta-analysis of cohort studies (4). However, the accuracy of US can be affected by the difficulty of finding a tumor in a nodular liver and limited by operator dependence, obesity and body habitus. Although surveillance with contrast enhanced imaging may be more accurate than US, these modalities are constrained by the need for intravenous contrast and the cost. The authors do mention that an abbreviated MRI may be more cost effective and studies are underway to explore this. There are also ongoing studies that aim to enhance patient compliance with HCC surveillance. These may involve electronic medical record reminders to physicians and better systems to call back patients for testing.

In defining who should be screened, the highly effective antiviral agents for hepatitis B and the new direct acting antivirals for hepatitis C, have clearly changed the population at risk for HCC. Universal vaccination of hepatitis B, guidelines for who to screen for HBV and HCV, and treatment of viral hepatitis will continue to decrease viral hepatitis related HCC. Treated patients have undetectable virus, less progression to cirrhosis and a lower chance of developing HCC. The population increasingly diagnosed with HCC are those patients who have nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD) and metabolic syndrome as well as those patients who have hepatitis B or C who are unaware of their disease or are not treated for various reasons (substance abuse, poor compliance, lack of insurance, or psychosocial reasons). How will we reach these patients for HCC surveillance with the current tools that we have? Most of the patients who have NASH, NAFLD and metabolic syndrome are likely not seen in specialized liver centers who would be championing the cause for

HCC surveillance. These patients are likely followed by primary care physicians, cardiologists and endocrinologists who are managing diabetes, obesity, hyperlipidemia and complications of metabolic syndrome. Few of these clinicians will be thinking about NAFLD and NASH unless patients have other more obvious consequences of liver disease such as ascites, thrombocytopenia or variceal bleeding. A suspicious liver mass will then be incidentally found when imaging is done for the other complications or if a patient has abdominal pain or unexplained weight loss.

While there is little question that there is benefit from HCC surveillance, the real impact on HCC incidence and treatment in the next decade will be made when we can identify biomarkers that can be used easily by primary care physicians to diagnose NAFLD and NASH. Efforts will then also be needed to provide linkage to liver care once these patients have been identified. This will require education of primary care providers to perform these tests and appropriately refer these patients to specialized liver centers and physicians. There will likely also be the need for more liver specialists and liver centers to provide care and conduct HCC surveillance.

Even if in an ideal world, where we can identify small HCC on all patients will there be enough surgeons and donor livers to perform all of these liver resections and transplants to impact long-term survival? Perhaps, we can learn from some of our colleagues in Asian countries, like Japan, where there are comprehensive surveillance programs and 60–65% of HCC is detected at Barcelona Clinic Liver Cancer (BCLC) stage zero. Liver resections and ablation are done for small lesions with excellent results as deceased donors for transplant are very limited. Over 60% of their patients underwent resection or transplant and 5-year survival was 44% (5). This is in contrast to the US where detection at BCLC 0 was only 17% and 5-year survival was estimated at 11–15% (6,7). Asian countries likely have a higher population of viral hepatitis than the US so again, the paradigm may be different from the US. Our efforts to fight HCC must thus be multi-pronged and include not only optimal HCC surveillance techniques and processes but also better identification of the population at risk and ultimately more physicians who can directly treat patients with liver disease and HCC.

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Footnote

Conflicts of Interest: LL Wong is a speaker for Eisai.

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