Editorial

Hepatocellular carcinoma surveillance: the often-neglected practice

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Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer worldwide and as such represents a significant global health burden. The clinical societies dedicated to the study of liver diseases all recommend routine surveillance for those at risk. These societies include the Asian-Pacific, European, and American associations for the study of liver disease. The aim of surveillance is to prolong survival, which is to diagnose HCC when the patient remains eligible for potentially curative interventions including resection and transplantation. In a detailed review published recently, Kanwal and Singal discuss the evidence for HCC surveillance, evaluate current surveillance methods and point out new imaging and serological initiatives to improve on current method (1). Their review covers some familiar topics and point to new endeavors in improving the effectiveness of HCC surveillance. In regards to their review article, several important points need to be emphasized as follows.

Promotion of surveillance is the principle challenge

Worldwide, only small minorities of patients at risk for HCC undergo the recommended surveillance regimen. Japan and Korea remain the only two countries with a national surveillance program. Elsewhere, the utilization of regular ultrasound screening is low, with only 12–29% of patients diagnosed with HCC receiving regular (annual or biannual) ultrasound surveillance prior to diagnosis (2-4). The poor uptake in surveillance is likely due to a combination of factors including lack of knowledge of guidelines, suboptimal patient adherence to guidelines, healthcare provider bias (alcohol related liver disease) and logistical factors (3). It should be noted that increasing the uptake of surveillance for the at-risk population is much more beneficial than the incremental gain from improving on the current surveillance methods. As healthcare practitioners, we need to advocate for surveillance to our patients, our colleagues, and our public health authorities.

Improvements in ultrasound have increased early HCC detection

With the advent of harmonic and compound imaging in the mid-2000's, there has been significant increase in the sensitivity of the detection of early HCC (5). The meta-analysis quoted by Kanwal and Singal demonstrating an early HCC detection rate of only 47% by sonography utilized many studies from pre 2000's (6). However, when the results are analyzed by the decade of publication, there is a significant rise in the detection rate for each decade, rising to 62.2% for ultrasound alone in the 2010's (7,8). Other studies published over the last decade show that ultrasound alone or with AFP has sensitivity for the detection of early (curable) stage HCC between 69–88% (5,9-11). For example, in Qidong area of China, biannual ultrasound with AFP caught HCC in early stages in 80.1% of patients, most of whom had HBV-induced liver disease (12). A recent prospective multicenter trial from France of 1,671 patients with cirrhosis is quite instructive (13).

Patients with HCC who strictly followed the surveillance recommendations of ultrasound every 6 months were early stage [Barcelona Clinic Liver Cancer (BCLC) stage 0 & 1] in 86% of cases. They also had statistically higher overall survival. But even those who underwent surveillance less often had early stage tumor in 71% of cases. The cause of cirrhosis in this population was HCV in 79%. Therefore Kanwal & Singal's argument that detection rates may be lower in HCV cirrhosis populations does not hold. The bottom line is that current surveillance recommendations work for the significant majority of patients.

Slow growth rate of early tumor means surveillance gets multiple chances at its detection

Surveillance of HCC is believed to be effective because in the majority of cases, the progression of the tumor is of sufficiently slow rate and limited extent to allow curative therapies. HCC has a relatively long tumor volume doubling time, with a median of 76.8 days for Hepatitis B virus, 137.2 days for Hepatitis C virus and 99.8 days for non-viral hepatitis (14). The same study has calculated that for a single tumor to grow from 1 to 5 cm in diameter, the upper limit of "early HCC", it takes a median of 678.9 days. The long tumor volume doubling time allows ultrasound several opportunities to detect the tumor, if it is missed by the initial scan, before it reaches an intermediate or advanced stage (BCLC stage B, C and D). This improves ultrasound's effective sensitivity. It also explains why studies in which the effectiveness of US surveillance is measured always show better performance than in those when ultrasound is compared to a higher sensitivity modality, such as CT or MRI. In a proportion of patients, CT and MRI detect the tumor at a smaller size before ultrasound has the opportunity to detect it at a later date.

Other imaging means of surveillance are not cost-effective

Decreased specificity is the cost of increased sensitivity in HCC surveillance. The earlier one attempts to detect tumors, the more likely that a benign nodule is falsely called positive. After all, HCC in the majority of cases occurs with a background of nodular cirrhosis; there are many more benign nodules than malignant ones. False positives result in multiple costly investigations and enhanced follow-up. The decreased specificity, along with the upfront cost of CT or MRI, is what makes surveillance by these modalities not cost-effective (6). Finding low-risk nodules, so called LI-RADS 2 and 3, on CT and especially MRI scans is quite common in cirrhotic patients and should there be enhanced observation for these, the cost of surveillance would explode. Ultrasound on the other hand is often insensitive to these nodules. Other disadvantages to CT and MRI include limited access, contraindications to contrast, and patient-related factors preventing or reducing scan quality, such as claustrophobia, inability to suspend respiration, and language barriers. Ultrasound is relatively inexpensive, is widely available in all regions of the world and has no contraindications. Radiation is often listed as a disadvantage of CT, but in reality that risk is negligible in patients with cirrhosis in whom median survival is 12 years (15). Imaging based surveillance methods of the future need to overcome these challenges as well as that of cost-effectiveness.

Kanwal & Singal also discuss serological markers and their potential for use in surveillance in the future. Serological markers in theory may hold many advantages over imaging, including lower cost, higher specificity, ease of application to a wider population, and no contraindications. Unfortunately, AFP is only an adjunct marker and its contribution to ultrasound surveillance is quite incremental in the modern era, likely in the range of 6–8% improved sensitivity to ultrasound alone (7). Several biomarkers have been identified and tested in preclinical studies including DNA, messenger RNAs, non-coding RNAs, proteins and post-translational protein modifications, with some biomarkers progressing to phase 2 trials. Future research is needed into these biomarkers, but it may allow tailoring of surveillance techniques to those at higher/lower risk of developing HCC in the future (1).

In conclusion, Kanwal and Singal highlight the need for surveillance and the need to improve the uptake of surveillance in those at-risk of developing HCC. It is important to note that there has been a significant change in ultrasound technology over the last few decades and the sensitivity of the detection of HCC in studies published before the mid 2000's is not applicable to today's ultrasound surveillance. Better, more accessible surveillance tools are being developed. But in the meanwhile, far more effort is needed to identify at-risk patients and direct them to surveillance as recommended by current guidelines.

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Footnote

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