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**Editorial: ultrasound-based HCC Surveillance in the 21st century – authors' reply**

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The letter from Dr. Patel[1] raises some interesting points that are worthy of further discussion.

Surveillance ultrasound has the potential for high sensitivity and specificity as demonstrated in prospective cohort studies[2], although recent data have demonstrated a substantial gap between its efficacy and its effectiveness when implemented in clinical practice, including low sensitivity for early tumor detection[3] and suboptimal specificity leading to screening-related harms[4]. Our study adds to this literature suggesting subgroups of patients, including obese individuals, patients with nonalcoholic steatohepatitis (NASH), and those with Child Pugh B or C cirrhosis, may be particularly prone to suboptimal ultrasound quality and the potential for surveillance failure in detecting early stage hepatocellular carcinom[5].

Dr. Patel highlights that ultrasounds in our study were interpreted retrospectively based on stored hard copy images, resulting in an overestimation of the proportion of inadequate exams. Although we agree real-time performance of the exam by the interpreting radiologist may improve exam quality, this is unfortunately not standard practice in many parts of the world, including the United States. Instead, technologists typically perform ultrasounds using a set protocol, recording representative still images to document exam completeness, which are subsequently interpreted by radiologists at a later time. It is possible operator experience, specific technologist training, and real-time exam interpretation could overcome some of ultrasound's operator dependency and improve its performance for early HCC detection; however, these interventions are unlikely to overcome all of ultrasound's potential limitations, and some exams will still likely be compromised by poor visualization in obese patients and those with nodular, heterogeneous hepatic parenchyma[5].

Although alternative surveillance strategies may be needed long-term as HCC epidemiology shifts from hepatitis C to NASH-related cirrhosis, we agree with Dr. Patel that using multi-phasic CT and MRI in all patients with cirrhosis is likely not feasible given issues of cost, potential harms, and radiologic capacity. Further, the performance of CT and MRI for surveillance in patients prone to ultrasound failure, such as those with obesity, is unknown. Discovery of highly sensitive and specific serum biomarkers is an important effort in improving HCC surveillance performance, as some biomarker panels have shown potentially high sensitivity for early HCC detection.[6] However, we are still likely years away from sufficient validation for their routine use in clinical practice. In the interim, ultrasound, with or without alpha

fetoprotein (AFP), continues to be our primary HCC surveillance modality and efforts to maximize ultrasound effectiveness are critical.

**References**

1.  Patel D. Editorial: ultrasound surveillance of hepatocellular carcinoma in the 21$^{st}$ century. *Aliment Pharmacol Ther* 2016

2.  Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, Marrero JA. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. *Aliment Pharmacol Ther* 2009;30:37-47.

3.  Singal AG, Conjeevaram HS, Volk ML, et al. Effectiveness of Hepatocellular Carcinoma Surveillance in Patients with Cirrhosis. *Cancer Epidemiol Biomarkers Prev* 2012; 21: 793-9.

4.  Atiq O, Tiro J, Yopp AC, et al**.** An Assessment of Benefits and Harms of Hepatocellular Carcinoma Surveillance in Patients with Cirrhosis. *Hepatology* 2016; doi: 10.1002/hep.28895

5.  Simmons O, Fetzer DT, Yokoo T, et al. Predictors of Adequate Ultrasound Quality for HCC Surveillance in Patients with Cirrhosis. *Aliment Pharmacol Ther* 2016 doi: 10.1111/apt.13841

6.  Berhane S, Toyoda H, Tada T, et al. Role of the GALAD and BALAD-2 Serologic Models in Diagnosis of Hepatocellular Carcinoma and Prediction of Survival in Patients. *Clin Gastroenterol Hepatol* 2016; 14(6): 875-886.