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EDITORIAL

Circulating Tumor DNA Testing for Liver Cancer

Circulating tumor DNA (ctDNA) analysis represents a potential paradigm shift in personalized medicine. Unlike tissue biopsy, it constitutes a minimally invasive approach that allows for diagnostic, predictive, and prognostic marker detection, early and serial assessment of metastatic disease, therapy monitoring, and determination of clonal evolution. Because ctDNA reflects genetic and epigenetic alterations from primary cancers, it may be used for the surrogate analysis of cancer genomes via liquid biopsy, especially in those tumors for which biopsy specimens are difficult to obtain or unobtainable. Several studies have supported the potential utility of ctDNA as cancer biomarkers. Both the levels of ctDNA in the plasma or serum of cancer patients and cancer-specific genetic and epigenetic changes have been detected in ctDNA and have demonstrated potential diagnostic, prognostic, and predictive value.[1]

Hepatocellular carcinoma (HCC) is the third leading cause of cancer deaths worldwide.[2,3] Currently, diagnosis is based on imaging techniques and/or biopsy. Because the disease is frequently diagnosed at late stages, prognosis is poor for HCC patients, with a 5-year survival rate of only approximately 11%.[4] With the advent of large-scale genomic technologies, the complex mutation landscape of HCC has been largely defined[5,6] and has helped improve the treatment options for HCC patients. For instance, the multikinase inhibitor sorafenib has been shown to increase survival in patients with advanced HCC.[7,8] *HRAS*/*NRAS* mutation analysis of ctDNA has been applied in a phase 2 clinical trial to assess response to a mitogen-activated protein kinase kinase (MEK) inhibition.[4] Until now, however, a comprehensive characterization of ctDNA on HCC patients has not been conducted.

To evaluate the usefulness of ctDNA for the characterization of genomic alterations in HCCs, Ono et al[9] performed whole-genome sequencing on 46 HCC samples and matched normal lymphocytes from patients who underwent hepatectomy or liver transplantation and for whom preoperative and postoperative serial serum samples were available. Somatic alterations were detected in all 46 samples. For each tumor, the authors selected three somatic rearrangements and designed primers spanning their breakpoints for serum ctDNA polymerase chain reaction testing. They detected ctDNA in the preoperative serum of 7 of the 46 patients. In these patients, serum ctDNA positivity correlated with larger tumor size and higher α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) levels. The cumulative incidence of recurrence and extrahepatic metastasis within 2 years after hepatectomy were also found to be remarkably worse in ctDNA-positive patients than in the ctDNA-negative group. Further, ctDNA was found to be an independent predictor of microscopic vascular invasion of the portal vein, although no statistically significant difference in the cumulative survival rate was observed between ctDNA-positive and ctDNA-negative patients.

Ono et al[9] also quantified ctDNA by real-time polymerase chain reaction in serially sampled serum before and after surgery from ctDNA-positive patients and demonstrated that the serum ctDNA levels were increased with disease progression and reflected the response to treatments. Cell-free DNA was increased after a transcatheter arterial chemoembolization (TACE) procedure, with the highest level being detected 4 days after the procedure. In addition, the authors performed exome sequencing on the primary tumor, and they paired plasma ctDNA in one patient with HCC/cholangiocarcinoma and found that 83% of mutations detected in the primary tumor could also be identified in the plasma ctDNA. The remaining discrepancy is likely explained by the low sequencing depth, which provides insufficient sensitivity for the detection of low-frequency variants or tumor heterogeneity.

These data have important implications. First, it is apparent that ctDNA levels reflect the cancer progression and therapy effects on HCC and that the TACE procedure is capable of enriching ctDNA in cell-free DNA in blood. Second, these data demonstrate the potential utility of ctDNA as a biomarker for individualized management of hepatocellular carcinoma. With further validation, the determination of HCC genome profiles through ctDNA analysis may help guide individualized therapy selection and monitoring without requiring percutaneous biopsies.

LARISSA V. FURTADO
JEREMY P. SEGAL
Department of Pathology
University of Chicago Medical Center
Chicago, Illinois

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Correspondence
Address correspondence to: Larissa V. Furtado, MD, 5841 S. Maryland Avenue, Room N-305, MC 1089, Chicago, Illinois 60637. e-mail: lfurtado@bsd.uchicago.edu; fax: 773-834-3449.

Conflicts of interest
The authors disclose no conflicts.

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