Editorial

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Liquid biopsy? A recent breakthrough in noninvasive bladder cancer surveillance

Approximately 70% to 75% of patients with urothelial carcinoma of the urinary bladder are diagnosed with nonmuscle invasive disease, including Ta and T1 tumors or carcinoma *in situ*. Of these patients, more than 50% experience tumor recurrence, and 10% to 15% experience disease progression. Considering the invasiveness and the cost of cystoscopic examination during several years of follow-up, simple and noninvasive detection methods such as the use of molecular biomarkers through transcriptome, proteome, epigenome, or metabolome analysis are imperatively needed [1].

Recently, liquid biopsy based on the circulating nucleic acids of tumor cells, such as analyses of circulating tumor DNA (ctDNA), circulating RNA, or microRNAs, has received enormous attention as a potential tool for real-time monitoring of disease status in cancer patients [2]. Of these, ctDNA is single- or double-stranded DNA released from primary tumors, circulating tumor cells, or metastatic tumors into the bloodstream of patients with malignancies [2]. Because ctDNA contains the same genomic alterations as the original tumor cells, researchers have great interest in using ctDNA as a tool for the diagnosis and surveillance of cancer [2]. Additionally, liquid biopsy based on ctDNA detection has the advantages of being noninvasive, being simple to acquire, having higher specificity, and having better sensitivity for application in real-world clinical practice.

For instance, a group from Johns Hopkins University presented a novel technology (digital polymerase chain reaction, or digital PCR) for detecting very low amounts of ctDNA and identifying its genomic alterations in 640 patients with various types of malignancies, such as colorectal, gastric, pancreatic, and breast cancers [3]. A group from Stanford University also reported an ultrasensitive platform for quantifying ctDNA in 17 patients with non–small-cell lung cancer (NSCLC) by using deep sequencing technology (CAPP-Seq) [4]. The authors noted that CAPP-Seq could detect ctDNA in 100% of patients with NSCLC. In addition, ctDNA levels were shown to be significantly correlated with tumor burdens or treatment responses, allowing this biomarker to be used for early response measurement [4].

In bladder cancer, Birkenkamp-Demtroder et al. [5] recently established a novel noninvasive surveillance tool for patients with nonmuscle invasive bladder cancer (NMIBC) by using ctDNA in blood and urine samples based on next generation sequencing (NGS) and digital PCR technologies. This is a very impressive concept study. It was published in *European Urology* in July of this year. The study consisted of 377 samples collected from 12 patients with NMIBC throughout their disease courses between 1994 and 2015 [5]. First, cancer-specific genetic signatures were determined by sequencing tumor and matched germline DNAs. Second, PCR was used to validate tumor-specific genomic variants. Sanger sequencing was applied to further define the specific breakpoints of genomic variants. Finally, droplet digital PCR (ddPCR) was designed to detect tumor-specific genomic alterations by using plasma and urine samples consecutively collected from patients with NMIBC. Of note, patients with progressive tumors had higher levels of ctDNA prior to disease progression than did patients with disease recurrence, while no patients who were disease-free showed detectable ctDNA in blood or urine samples. To the best of my knowledge, this is the first report to highlight that plasma and urine ctDNA can be used as a surveillance marker during long-term follow-up in NMIBC patients through NGS and ddPCR technologies.

For Korean patients with bladder cancer, Dr. Kim's laboratory [6] has recently proved that the amounts of *TopoIIA* ctDNA in urine are remarkably higher in bladder cancer patients than in noncancer controls or hematuria patients. Moreover, patients with muscle invasive bladder

cancer had higher *TopoIIA* ctDNA levels in urine than did patients with NMIBC [6]. Although this was a pilot study requiring large-scale prospective validation, it paves a new diagnostic avenue for bladder cancer patients with the use of ctDNA based on liquid biopsy.

Despite the highly attractive concept of liquid biopsy for detecting ctDNA, several pitfalls exist, including the lack of consensus in technical standardization of preferable sample type, suitable storage conditions, ideal candidate molecules, and optimal detection techniques [7]. Nevertheless, we anticipate that liquid biopsy focusing on ctDNA in plasma and urine will be routinely used in various clinical settings, including identification of risk for recurrence and progression in NMIBC patients, as well as monitoring treatment response in patients with advanced or metastatic bladder cancer.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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