Editorial

Detection of circulating tumor DNA for advanced bladder cancer: where are we going?

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Bladder cancer (BC) is the ninth most common malignant disease and the thirteenth most common cause of cancer death worldwide. In 2012, 429,793 cases of BC were diagnosed and nearly 165,000 deaths were recorded globally (1). Urothelial carcinoma (UC) is the most common histologic subtype of BC, and represents nearly 90% of all cases (2). Around thirty percent of cases are diagnosed as muscle-invasive urothelial carcinoma (MIUC) and radical cystectomy (RC) remains the cornerstone of therapy (3). However, cancer-specific survival (CSS) after RC is relatively low, ranging from 72% at 5 years for patients with organ-confined disease, to 48–25% at 5 years in patients with extravesical extension or lymph node metastases. Around 50% of patients with clinical stages T2b–T4a will develop metastatic disease after two years of RC (4). This supports the use of neoadjuvant cisplatin-based chemotherapy (NAC) to achieve a better control disease and increase overall survival. NAC has demonstrated a 5% increase in 5-year cancer specific survival in MUIC compared to surgery alone (5). Interestingly, the 5-year CSS for patients who achieved pathological response (<ypT2) is 90%, in contrast to the 30–40% CSS for those who does not reach this degree of response (4,5).

To date, there are no biomarkers to predict these responses to NAC and most of the methods that we use to evaluate responses are based on clinical data and imaging procedures. Additionally, some patients will suffer toxicity, without any benefit. Therefore, the identification of reliable biomarkers to identify patients who will benefit from NAC is needed.

Several molecular biomarkers have been tested for prediction of response to NAC, including: regulators of apoptosis and cell survival (4-7), DNA repair genes (5-13), ERBB2 mutations (14) and gene expression signatures (15-17). Recently, immunological markers (18) and molecular subtypes of MIUC have been evaluated as potential biomarkers in patients treated with NAC (19).

DNA is continuously released into the bloodstream. In cancer patients, the majority of plasma DNA originates from healthy cells, whereas a minor fraction is related to the tumor (20). In 1989, Stroun *et al.* reported for the first time that the presence of circulating tumor DNA (ctDNA) originates from cancer cells (21). In 2008, Diehl *et al.* demonstrated that ctDNA reflect tumor response and progression after surgery and could be used as a marker for residual diseases and also as a prognostic factor (22).

In 2016, Birkenkamp-Demtröder *et al.* reported tumor DNA in blood and urine in patients diagnosed with MUIC and non-MUIC (23). In this retrospective pilot study, 12 patients initially diagnosed with non-MIUC were sequenced using next generation sequencing. Six patients were followed for 4–20 years developing later progression to MUIC or metastatic disease, and 6 patients had recurrence of non-MUIC during the following time of

7–20 years. ctDNA was detectable in plasma in 83% of the patients. Interestingly, higher levels of ctDNA in plasma were detectable from all patients with progressive disease. Recently, Christensen *et al*. evaluated droplet digital polymerase chain reaction (ddPCR) assays for hotspot FGFR3 and PI3KCA mutation detection in liquid biopsies (24). A total of 831 patients were included (363 with non-MUIC and 468 treated with RC). The authors reported, 36% of the non-MUIC and 11% of the patients treated with RC harboured at least one FGFR3 or PIK3KCA mutation. Furthermore, high levels of ctDNA were significantly associated with recurrence.

On the other hand, the same authors demonstrated early detection of metastatic relapse and indications of treatment response using ctDNA analysis (25). This exciting prospective study included 50 patients treated with NAC followed RC and 10 patients treated with first line chemotherapy for metastatic disease. All the patients were analyzed using a total of 84 specific tests, including PIK3Ca and FGFR3 mutation detection, detection of tumour and germinal DNA exons identifying a total of 61 genes. They found that ctDNA level after RC was detectable in 75% of the patients and survival analysis showed a significant association between clinical relapse and high ctDNA level. More important was that patients without relapse had no detectable ctDNA levels after RC. Interestingly, ctDNA levels decreased after two to five cycles of chemotherapy and were correlated with initial response by computed tomography.

This study provide an excellent clinical utility of ctDNA and demonstrate that ctDNA may reflect the presence of residual disease even in the absence of any other clinical evidence of disease and could be a useful tool for identify patients with higher risk of relapse when patients may benefit from changes in treatment schedules. In addition, ctDNA could facilitate to identify mechanisms of resistance related to emerging therapy such as PI3KCA alteration that leads resistance to FGFR inhibition in BC. Moreover, this finding provides a strong rationale to evaluate PI3K inhibitors in combination with FGFR inhibitors. This study is limited by the small cohort size, but the results are promising and could have a significant impact in our clinical practice.

A better understanding of the biology of ctDNA would aid the implementation of this approach. At the moment, most of the clinical trials in BC are testing ctDNA analysis for treatment monitoring. This will ensure, randomized trials comparing ctDNA guided decision-making against the analysis of the primary tumor.

Lastly, ctDNA could interrogate the heterogeneity of metastatic disease and the possibility to using it for screening is also fascinating and likely to be attractive in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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