Editorial Commentary

Capturing recurrence in urothelial carcinoma: "more than meets the eye"

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Urothelial carcinoma is the sixth most common cancer in the United States and is a significant source of mortality worldwide (1). Bladder urothelial carcinoma is a molecularly heterogeneous malignancy that typically presents as an exophytic tumour (or flat carcinoma *in situ*) confined to the mucosa or lamina propria (NMIBC); however, up to a third of patients have muscle-invasive (MIBC) and about 4% metastatic disease (mUC) at the time of diagnosis (2). While platinum-based chemotherapy has been the cornerstone of therapy for a long time, significant progress has been made recently in the treatment armamentarium of mUC, particularly with immune checkpoint and fibroblast growth factor receptor (FGFR) inhibition (3). For MIBC, neoadjuvant cisplatin-based chemotherapy has been shown to improve overall survival and thus is considered the standard of care prior to definitive locoregional therapy (4). Given the morbidity and mortality associated with mUC, optimizing early detection of recurrence after definitive therapy remains a very important, unmet need.

In the *Journal of Clinical Oncology*, Christensen and colleagues report their analysis of plasma cell-free DNA (cfDNA) to prognosticate outcomes and capture recurrence in patients with MIBC treated with neoadjuvant chemotherapy and cystectomy (5). Between 2013–2017, 64 patients were evaluable for recurrence, and had blood collected before and during chemotherapy as well as before and after cystectomy. With a median follow up of 21 months post cystectomy, 13 patients (20%) were noted to have recurrence. Utilizing techniques that employed unique patient-specific assays designed for 16 somatic mutations, the authors performed multiplex polymerase chain reaction next-generation sequencing on plasma cfDNA. A sample was considered positive for circulating tumor DNA (ctDNA) if two or more target variants were detected (6). Kaplan Meier curves were displayed for recurrence-free and overall survival (RFS and OS, respectively); however, hazard ratios (HR) of both univariate and multivariable analysis were provided in the supplementary appendix for RFS only.

Overall, the authors showed that patients with MIBC either with undetectable ctDNA at diagnosis, or those who 'clear' ctDNA during treatment, ultimately have better prognosis and lower chance of recurrence than those who continue to have positive ctDNA. These findings are reported at three clinically relevant time points. Firstly, patients who were found to be ctDNA-positive at diagnosis (prior to start of neoadjuvant chemotherapy) had an overall recurrence rate of 46% (11 of 24 patients), with HR for RFS of 29.1 (P=0.001). When incorporated with multivariable analysis of T stage at diagnosis (T1/T2 *vs.* T3/T4), N stage before cystectomy (N0 *vs.* N1/2/3), and pathologic downstaging (no *vs.* yes, defined as Ta, CIS, N0, or less after therapy), HR remained significant

at 11.6 (P=0.03). A provocative future clinical question is whether neoadjuvant chemotherapy could potentially be omitted in patients who are found to be ctDNA-negative at diagnosis? This is in the context that only one out of 35 patients who were ctDNA-negative experienced recurrence in this study. However, these findings should be interpreted with great caution given the small sample size, patient selection, potential confounders, need for larger studies and prospective validation. Guidelines recommend neoadjuvant cisplatin-based chemotherapy in fit patients with MIBC and definitive local therapy is indicated afterwards in the absence of metastasis (7). Ultimately, this study highlights the future potential for ctDNA to aid in differentiating stage and prognostication at diagnosis of MIBC and after initial therapy, given the high risk of micro-metastasis.

Secondly, patients who were found to be ctDNA-positive after chemotherapy and prior to cystectomy had an overall recurrence rate of 75% (6 of 8 patients), with HR for RFS of 12 (P<0.001); however, this did not remain significant in multivariable analysis [HR 2.4 (0.6–9.8), P=0.21]. All patients who were ctDNA-positive at that time point were later found to have ≥ ypT1N0 at cystectomy; similarly, all patients who were ultimately ypT0 were also found to be ctDNA-negative at that time point. This raises another important future clinical consideration: could patients found to be ctDNA-negative post neoadjuvant chemotherapy be spared from radical cystectomy? Alternatively, could bladder-sparing treatment be considered in this scenario? Increasingly in the multidisciplinary clinical care setting, considerations of radical surgery (after cisplatin-based neoadjuvant chemotherapy in fit patients) *vs.* trimodality therapy (TMT) are discussed in a patient-centered manner and in the context of institutional pathways and provider preferences. The study suggests a potential role for ctDNA to be further tested prospectively as an integrated (and possibly integral) biomarker in the context of treatment modality selection. Furthermore, the dynamics of ctDNA during chemotherapy was significantly associated with recurrence risk: recurrence rate was 29% in those who had positive ctDNA drop to undetectable with chemotherapy *vs.* 86% in those who remained ctDNA-positive post chemotherapy (P=0.023). Interestingly, the results did not demonstrate apparent association between recurrence and pathologic downstaging (P=0.23). This should be interpreted in the context that only 24 patients were included in this subset analysis, which necessitated Fisher's exact testing instead of Cox proportional hazards regression modeling, along with other potential confounders.

Thirdly, and perhaps most significantly, patients who were found to be ctDNA-positive during surveillance after cystectomy had an overall recurrence rate of 76% (13 of 17 patients), with HR for RFS of 131 (P<0.001) that remained consistent with multivariable analysis. Further, ctDNA analysis appeared to have a 'lead time' of 96 days compared to conventional imaging in terms of detecting recurrence. The authors reported an impressive sensitivity (100%) and specificity (98%) of serial surveillance ctDNA analysis to detect recurrence post cystectomy. This raises important questions and intriguing possibilities in the surveillance setting. What is the utility of adjuvant treatment in a patient who is already ctDNA-negative post operatively? There are several ongoing trials evaluating adjuvant immune checkpoint inhibition after definitive therapy for MIBC (NCT02450331, NCT03171025, NCT02632409, NCT02891161, NCT03244384). It is reasonable that ctDNA should be tested in the context of future adjuvant trials for validation, and to assess whether it may help refine selection of patients more likely to benefit from adjuvant therapy. It also remains to be clarified at what interval should ctDNA surveillance occur in relation to conventional imaging and clinical assessment. Further study on the rational timing of ctDNA testing (during neoadjuvant treatment, prior to definitive locoregional treatment, and on surveillance) should be considered in the context of practical, real world implementation—noting system level (costs) and patient level (inconvenience) issues. Indeed, only eight patients in this study had truly simultaneous radiographic imaging and plasma sampling collections.

Advances in the treatment of UC have developed from a deeper collective understanding along the disease spectrum from early to late disease state. The utility of non-invasive circulating biomarkers in screening, diagnosis, surveillance, prognostication, assessment of treatment response and understanding of resistance mechanisms continues to be an area of growing interest (8-10). With a high number of clinical trials evaluating augmentation to standard systemic therapy, development of plasma assays will need to be nimble and in consideration of the dynamic treatment landscape (11). For example, studies involving immune checkpoint inhibition, targeted therapies, antibody drug conjugates and other agents, are moving from mUC into earlier disease settings (3). Therefore, the role of ctDNA as well as the optimal assay/platform remains open to further inquiry in this rapidly evolving environment. Importantly, a variety of cfDNA panels that are being evaluated have differences in the gene tested, gene-sequencing

depth, bioinformatics assessment, reporting methods, etc. Moreover, there are emerging unique platforms for cfDNA testing in MIBC including circulating cell-free methylated DNA (cfmeDNA), which carries the advantage that methylation changes in cfDNA are stable and tissue-/tumor-specific (12). To truly inform practice, larger prospective validation is warranted to correlate changes in ctDNA and tumour tissue genomic alterations with robust clinical outcomes; results from the PREVAIL and ATLAS studies, for example, are thus eagerly anticipated (NCT03788746, NCT03397394). Relevant considerations include the percentage quantification of ctDNA as well as the detection of specific genomic alterations in ctDNA. Finally, evaluation of the host's urine is another promising avenue for non-invasive testing cfDNA and merits further clinical study, particularly in correlation with tumor tissue and plasma analysis (13). Ultimately, the rich, dynamic and complex biology of UC provides a fertile ground for drug development and a bright future for the potential of non-invasive biomarker testing. The goal is to facilitate the provision of timely, cost-effective, precision-driven, patient-centered care across the disease spectrum. In that context, the study by Christensen and colleagues provides both the promise and foundation for further testing of ctDNA across oncology trials.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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