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).

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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), 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
cDNA-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
cDNA 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
therapy, 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
deep 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
ewell 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
conjugates and other agents, are moving from mUC into
earlier disease settings (3). Therefore, the role of ctDNA as
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.

Acknowledgments

None.

Footnote

Conflicts of Interest: AA Lalani: honoraria/consulting from Bristol-Myers Squibb (BMS), grants and personal fees from Janssen, personal fees from Amgen, personal fees from Eisai, personal fees from NCCN, grants from Celgene, personal fees from Physicians Education Resource, personal fees from Onclive, personal fees from Research to Practice, other from Bayer, personal fees and other from Merc & Co., personal fees and other from Mirati Therapeutics, other from Oncogenex, personal fees and other from Pfizer, personal fees and other from Bristol-Myers Squibb, personal fees, non-financial support and other from Astra Zeneca, personal fees from Biocept, personal fees, non-financial support and other from Clavis Oncology, personal fees from EMD Serono, personal fees from Seattle Genetics, personal fees from Foundation Medicine, personal fees from Driver Inc., personal fees from QED Therapeutics, personal fees from Heron Therapeutics, personal fees from Janssen, other from Bavarian Nordic, other from Immunomedics, other from Debiopharm, personal fees from Glaxo Smith Kline, personal fees from Roche, personal fees from Genzyme, personal fees from Exelixis.

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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Cite this article as: Lalani AA, Pal SK, Sonpavde GP, Grivas P. Capturing recurrence in urothelial carcinoma: “more than meets the eye”. Transl Androl Urol 2019;8(Suppl 5):S524-S527. doi: 10.21037/tau.2019.12.06