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Early Detection of Metastatic Progression by Circulating Tumor DNA in Patients Undergoing Bladder-Preserving Trimodality Therapy

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Study Need and Importance: Radical cystectomy and trimodality therapy (TMT) are efficacious options for patients with muscle invasive bladder cancer (MIBC). Despite aggressive therapy, MIBC may be associated with a high risk of distant metastasis. Post-TMT surveillance with conventional imaging has inherent limitations for early detection of micrometastatic disease. The use of plasma circulating tumor DNA (ctDNA) as a potential biomarker for early detection of micrometastases in the post-TMT setting may aid in identifying patients who derive benefit from timely interventions. Limited data describe the clinical application of ctDNA in post-TMT surveillance.

What We Found: A total of 32 patients with MIBC and at least one post-TMT ctDNA measurement were stratified as ctDNA (+) or ctDNA (−). At a median follow-up of 181 days after first post-TMT ctDNA measurement, ctDNA (+) status was associated with worse metastasis-free survival (Figure) and recurrence-free survival. ctDNA (+) status correctly identified metastatic progression with 100% sensitivity and 93% specificity at 6 months post TMT. Finally, ctDNA-based detection preceded clinical identification of metastasis with a median lead-time of 138 days.

Limitations: This was a retrospective and single institution study with small sample size and a relatively short median follow-up. There was a lack of up-front standardization of serial ctDNA assessments before, during, and after TMT.

Interpretation for Patient Care: This hypothesis-generating study implies that plasma ctDNA positivity may serve as an early predictive marker for metastatic progression in patients treated with TMT. For ctDNA (+) patients, surveillance intensification may provide an opportunity for earlier detection of metastasis and initiation of salvage therapy.

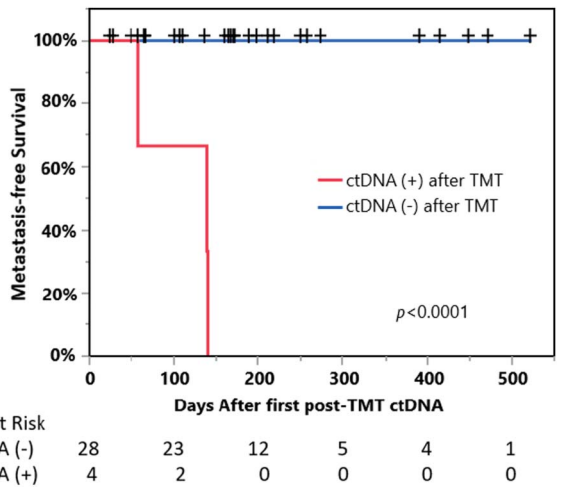

Figure. Positive circulating tumor (ct) DNA is associated with metastatic progression. Kaplan-Meier survival analysis of metastasis-free survival stratified by ctDNA status. TMT indicates trimodality therapy.

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Early Detection of Metastatic Progression by Circulating Tumor DNA in Patients Undergoing Bladder-Preserving Trimodality Therapy

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Purpose: Radical cystectomy and trimodality therapy (TMT) are efficacious treatments for muscle invasive bladder cancer. Novel methods for post-treatment surveillance are needed to detect recurrence. This study assesses the value of plasma circulating tumor DNA (ctDNA) for detection of post-TMT recurrence.

Materials and Methods: We performed a retrospective ctDNA analysis in 32 patients with at least one post-TMT ctDNA measurement before any disease recurrence. Patients were stratified as post-TMT ctDNA (+) or ctDNA (−) and assessed for metastasis-free survival and recurrence-free survival (RFS) using Kaplan-Meier and Cox regression methods.

Results: At a median follow-up of 181 days (range: 24-522) after the first post-TMT ctDNA measurement, 4 patients (12.5%) were ctDNA (+) and 28 patients (87.5%) were ctDNA (−); 3 of 4 ctDNA (+) patients developed radiographic evidence of

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Conception and design: Zhao, Grass, Yin, Jain.
Data acquisition: Zhao, Grass, Nakashima.
Data analysis and interpretation: Zhao, Grass, Yin, Khatri, Nakashima, Chadha, Chatwal, Zhang, Ionescu, Linscott, Li, Poch, Sexton, Yu, Spiess, Zemp, Gilbert, Manley, Jain, Torres-Roca, Johnstone, Yamoah.
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Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.
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metastasis. All 28 ctDNA (−) patients were without metastasis. ctDNA positivity correctly identified all metastatic progression with 100% sensitivity and 93% specificity at 6-month post-TMT ctDNA surveillance. Furthermore, ctDNA-based detection preceded clinical detection of metastasis with a median lead time of 138 days. ctDNA (+) status was associated with worse metastasis-free survival ($P < .0001$) and RFS ($P < .0001$). In univariable analysis, ctDNA (+) status was the only variable significantly associated with worse RFS (HR 3.53, 95% CI: 1.11-11.53, $P = .03$).

Conclusions: Plasma ctDNA is a potential biomarker for early detection of metastatic progression after TMT. Our hypothesis-generating findings provide a basis for larger studies to evaluate the utility of ctDNA-guided post-TMT surveillance.

Key Words: muscle invasive bladder cancer (MIBC), trimodality therapy (TMT), circulating tumor DNA (ctDNA)

Bladder cancer is the ninth most common cancer diagnosed globally, with an estimation of 84,870 new cases and 17,420 deaths occurring in 2025 within the United States.[1] Localized muscle invasive bladder cancer (MIBC) accounts for 25% to 30% of all newly diagnosed bladder cancers and carries a high risk of local and distant progression with a poor prognosis.[2] Consensus-based recommendations for localized MIBC include either neoadjuvant systemic therapy followed by radical cystectomy (RC) or bladder preservation with trimodality therapy (TMT), which combines maximal transurethral resection of the bladder tumor followed by concurrent chemoradiation.[2-4] Although there are no randomized controlled trials comparing the clinical outcomes of TMT to RC, multiple retrospective cohort-matched analyses have shown similar clinical outcomes between the 2 modalities in well-selected cases with TMT providing an additional benefit of functional organ preservation.[3,5]

Despite aggressive therapy with RC or TMT, MIBC is associated with an elevated risk of distant metastasis, which is the main contributor of bladder cancer-related mortality.[6] Currently, monitoring of treatment response following TMT consists of periodic cystoscopy, urine cytology, and cross-sectional imaging. Specifically, the identification of metastatic progression is through conventional imaging, which has inherent variability of measurements and detection thresholds for measurable tumor size.[7] Therefore, early recognition of impending metastatic progression before imaging detection remains a major clinical challenge for patients undergoing TMT.

The use of circulating tumor DNA (ctDNA) as a biomarker for cancer diagnosis and treatment guidance has demonstrated encouraging results in multiple cancer types, including bladder cancer.[8-11] Implementation of ctDNA-guided surveillance in conjunction with standard methods (eg, cross-sectional imaging and cystoscopy) after definitive treatment is particularly important for early detection of residual disease or micrometastases, which may aid in selecting high-risk patients who derive benefit from early therapeutic interventions.[12-14] In patients treated with perioperative systemic therapy and RC, recent studies demonstrated predictive value of ctDNA for early detection of metastatic progression with high sensitivity and specificity, and with a positive median lead time over radiographic imaging.[15-18] However, the predictive value of ctDNA-guided disease surveillance in the TMT setting is largely unknown.

We hypothesized that post-TMT ctDNA would demonstrate a predictive value for metastatic progression. For the first time, we have demonstrated that plasma ctDNA may be a useful biomarker for early detection of metastatic progression in MIBC patients undergoing TMT. Our results highlight the value of adding ctDNA-guided disease monitoring to standard surveillance methods and establish rationale for large validation studies to evaluate ctDNA as a monitoring tool for early detection of metastatic progression following TMT.

MATERIALS AND METHODS

Patient and Clinical Samples

Following institutional review board approval, we retrospectively reviewed the records of consecutive patients with localized MIBC who were treated with TMT between June 2020 and April 2024 at Moffitt Cancer Center and who had at least 1 post-TMT ctDNA evaluation before any disease recurrence at the time of data analysis in August 2024. The patient's clinicodemographic information and treatment characteristics were recorded. Blood samples were collected at scheduled clinic visits and plasma ctDNA levels were analyzed using the commercially available Signatera Assay (Natera Inc, Austin, TX) which uses tissue-based whole exome sequencing to identify 16 high-ranked clonal somatic variants for each patient. Plasma samples with at least 2 variants detected are defined as ctDNA (+).[11,15]

Patients diagnosed with MIBC who were eligible and elected for TMT or who refused RC were treated with maximal transurethral resection of the bladder tumor followed by concurrent chemotherapy and radiation. A total of 32 patients were included in this analysis. In addition to ctDNA assessment, all patients underwent surveillance protocols with cystoscopy and cross-sectional imaging at Moffitt Cancer Center according to the standard-of-care. Patients with suspicious intravesical or metastatic recurrences underwent biopsy as indicated.

Statistical Analysis

The cohort characteristics were presented with descriptive statistics. The median follow-up was determined with the reverse Kaplan-Meier (KM) method. Metastasis-free survival (MFS) and recurrence-free survival (RFS) were calculated from a prespecified landmark time point defined as the date of the worst post-TMT ctDNA assessment to the date of first event (clinical detection of metastasis for MFS or the composite of local recurrence and/or metastasis for RFS). Patients without observed events were censored at the last follow-up. A landmark analytic approach was used to ensure that only patients who remained recurrence-free at the time of ctDNA assessment were included in the time-to-event analysis, thereby avoiding guarantee-time bias. To assess the prognostic value of post-TMT ctDNA for MFS and RFS, we applied time-to-event methods including KM survival estimates and Cox proportional hazards modeling. Univariable Cox models were used to evaluate the association of ctDNA status and other clinical covariates with outcomes. Given the limited number of events, we did not perform multivariable modeling to avoid overfitting. For visual representation of follow-up, a swimmer plot was generated with time 0 anchored at the end of TMT (treatment completion), illustrating longitudinal surveillance from therapy completion. A significant result was delineated as a P-value $< .05$. All statistical analyses were performed with JMP Pro 16 software. The time-restricted sensitivity and specificity for ctDNA detection of metastatic progression were calculated at 6 months after the first post-TMT ctDNA surveillance.

Table 1. *Patient Demographic, Clinicopathologic, and Treatment Characteristics*

	N = 32	(%)
Patient characteristics		
Median age at diagnosis (range)	75 (48-93)	
Sex		
Female	8	25.0
Male	24	75.0
T category		
T2	24	75.0
T3	7	21.9
T4	1	3.1
N category		
N0	31	96.9
N1	1	3.1
Tumor histology		
Urothelial carcinoma	21	65.6
Urothelial with subtype histology	11	34.4
Hydronephrosis	8	25.0
LVI	6	18.8
CIS	3	9.4
Treatment characteristics		
NAC	9	28.1
Median radiation dose (range), Gy		
Bladder	55 (53-64.8)	100
Pelvic lymph node	40 (40-51)	96.9
Concurrent chemotherapy		
Cisplatin	16	50.0
Gemcitabine	15	46.9

Abbreviations: CIS, carcinoma in situ; LVI, lymphovascular invasion; NAC, neoadjuvant chemotherapy.

RESULTS

Patient Characteristics and General Clinical Outcomes

Baseline clinicopathologic and treatment characteristics for the 32 patients included in this study are summarized in Table 1. The cohort predominantly consisted of older adults with localized MIBC, most of whom were male and presented with cT2N0 disease. A substantial proportion had adverse features such as lymphovascular invasion, focal carcinoma in situ, or unilateral hydronephrosis. Nearly all patients received concurrent chemoradiation, most commonly with cisplatin or gemcitabine, and none received adjuvant systemic therapy.

In this cohort, 17 patients (53.1%) had both pre-TMT and post-TMT ctDNA evaluation, while 15 patients (46.9%) had ctDNA assessment only after TMT. The median time for the first post-TMT ctDNA measurement from the last day of TMT was 123 days (range 0-1268). The median number of ctDNA measurements was 2 (range 1-6). In patients with pre-ctDNA and post-ctDNA, 15 initially had negative pre-TMT ctDNA but 2 became ctDNA (+) following TMT. The other 2 patients had positive pre-TMT ctDNA, of whom 1 continued to have positive ctDNA after TMT and the other reverted to ctDNA (-). In patients with only post-TMT ctDNA, 1 had positive ctDNA. Therefore, 4 patients were categorized as ctDNA (+), while the other 28 patients were categorized as ctDNA (−) (Supplementary Table 1, https://www.jurology.com).

With a median follow-up of 181 days (range: 24-522) after the first post-TMT ctDNA measurement, 3 of 4 patients in the ctDNA (+) group developed radiographic evidence of metastasis, which included 2 lung and 1 lymph node metastases (Table 2). However, the other 28 patients categorized as ctDNA (−) all remained free of metastasis. No patient developed a local MIBC recurrence or required salvage cystectomy in both groups. Of note, there were 2 non-MIBC (NMIBC) recurrences, all being in the ctDNA (-) group with high grade

Table 2. *Clinical Outcomes Stratified by Post–Trimodality Therapy and Circulating Tumor DNA Status*

Outcomes	ctDNA (+) (n = 4)	ctDNA (−) (n = 28)
Metastatic progression	3	0
Site of metastasis		
Lymph node	1	0
Lung	2	0
MIBC recurrence	0	0
NMIBC recurrence	0	2

Abbreviations: ctDNA, circulating tumor DNA; MIBC, muscle-invasive bladder cancer; NMIBC, nonmuscle-invasive bladder cancer; TMT, trimodality therapy.
ctDNA (+) is associated with high risk of metastatic progression.
There were 2 NMIBC recurrences in the ctDNA (−) group.

histology (Supplementary Figure 1 and Supplementary Table 2, https://www.jurology.com). Of the patients who developed metastatic progression, 1 received salvage radiation and 2 received systemic therapy. Only one patient died from cancer-related death in the ctDNA (+) group at the time of analysis.

Plasma ctDNA Positivity Is Associated With Metastatic Progression After TMT

We found that ctDNA (+) classification during post-TMT surveillance was positively associated with metastatic progression. This is underscored by the finding that patients with ctDNA (+) categorization had worse MFS compared with the ctDNA (−) cohort (Figure 1; $P < .0001$). The KM estimated 1-year MFS in ctDNA (+) and ctDNA (−) group is 0% and 100%, respectively. Furthermore, a time restricted analysis at 6-month ctDNA surveillance after TMT identified metastatic progression with 100% sensitivity (3 of 4 patients) and 93% specificity (14 of 15 patients).

The timing of serial plasma ctDNA dynamics and metastatic detection relative to the last day of TMT are shown for all patients in a Swimmer plot (Supplementary Figure 2, https://www.jurology.com) as well as selected patients in the ctDNA (+) group (Figure 2A and 2B) and for a single representative patient in the ctDNA (−) group (Figure 2C). We noticed an early detection of ctDNA before clinical detection of metastatic progression in all 3 patients in the ctDNA (+) group with a lead time of 57, 138, and 139 days. For example, patient 7128 had detectable ctDNA at 94 days after TMT whereas observance of clinical metastatic progression was detected at 233 days after TMT; this was associated with a lead time of 139 days (Figure 2A).

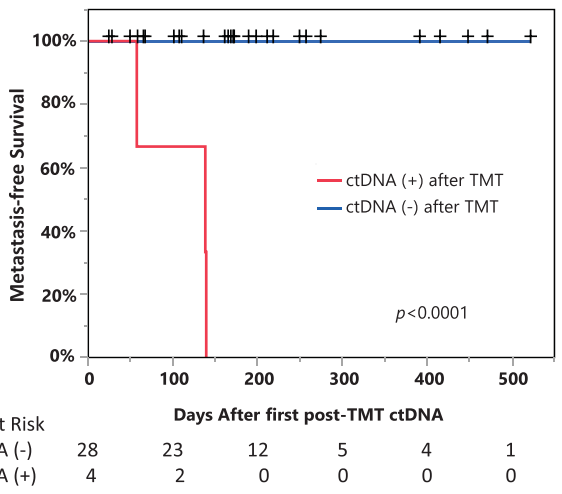

Figure 1. Positive circulating tumor (ct) DNA is associated with metastatic progression. Kaplan-Meier survival analysis of metastasis-free survival stratified by ctDNA status. TMT indicates trimodality therapy.

Plasma ctDNA Positivity Is Associated With Disease Recurrence After TMT

As previously mentioned, no patient had a local MIBC recurrence, but there were 2 NMIBC recurrences detected by cystoscopy and confirmatory biopsy. All the NMIBC recurrences occurred in the ctDNA (−) group. When taking into consideration both local and distant metastasis as a composite of RFS, ctDNA (+) categorization was associated with worse RFS ($P < .0001$) (Figure 3). The KM estimated 1-year RFS in ctDNA (+) and ctDNA (−) group is 0% and 92.8%, respectively. In univariable analysis, ctDNA (+) status (HR 3.53, 95% CI: 1.11-11.13, $P = .03$) was the only variable significantly associated with worse RFS after TMT (Table 3).

DISCUSSION

This study identified 2 novel and important findings for plasma ctDNA-based surveillance in patients undergoing TMT: (1) ctDNA may serve as an early predictive marker for metastatic progression and (2) ctDNA identifies metastatic progression with high sensitivity and specificity with a positive lead time compared with traditional radiographic assessment. Therefore, early detection of metastatic spread by ctDNA in the post-TMT setting may provide a window of opportunity for earlier initiation of salvage therapy to improve clinical outcomes.

Our study suggests that ctDNA positivity may serve as an early indicator of micrometastatic spread, as patients categorized as ctDNA (+) have an elevated risk of metastatic progression in contrast to those classified as ctDNA (−) who have a low risk of metastatic progression. Furthermore, this commercially available plasma ctDNA assay showed excellent clinical performance as it identified metastatic progression with 100% sensitivity and 93% specificity at 6-month post-TMT ctDNA surveillance with a median lead time of 138 days compared with radiographic evaluations. This TMT experience compares favorably to that described in the cystectomy literature as well. For example, in a retrospective study evaluating plasma ctDNA of 68 patients after RC, Christensen et al reported similar sensitivity (100%) and specificity (98%) to detect metastatic progression with a median lead time of 96 days.[15,16] Therefore, for patients with localized MIBC treated with either RC or TMT, plasma ctDNA analysis may serve as a predictive marker for metastatic progression.

While adjuvant immunotherapy has not yet been adopted in the TMT setting, it has become a standard of care following RC in patients with adverse pathological features and high risk of relapse.[19,20] Although the phase 3 IMvigor010 trial did not detect a benefit of adjuvant atezolizumab in patients with high-risk pathologic features after cystectomy compared to

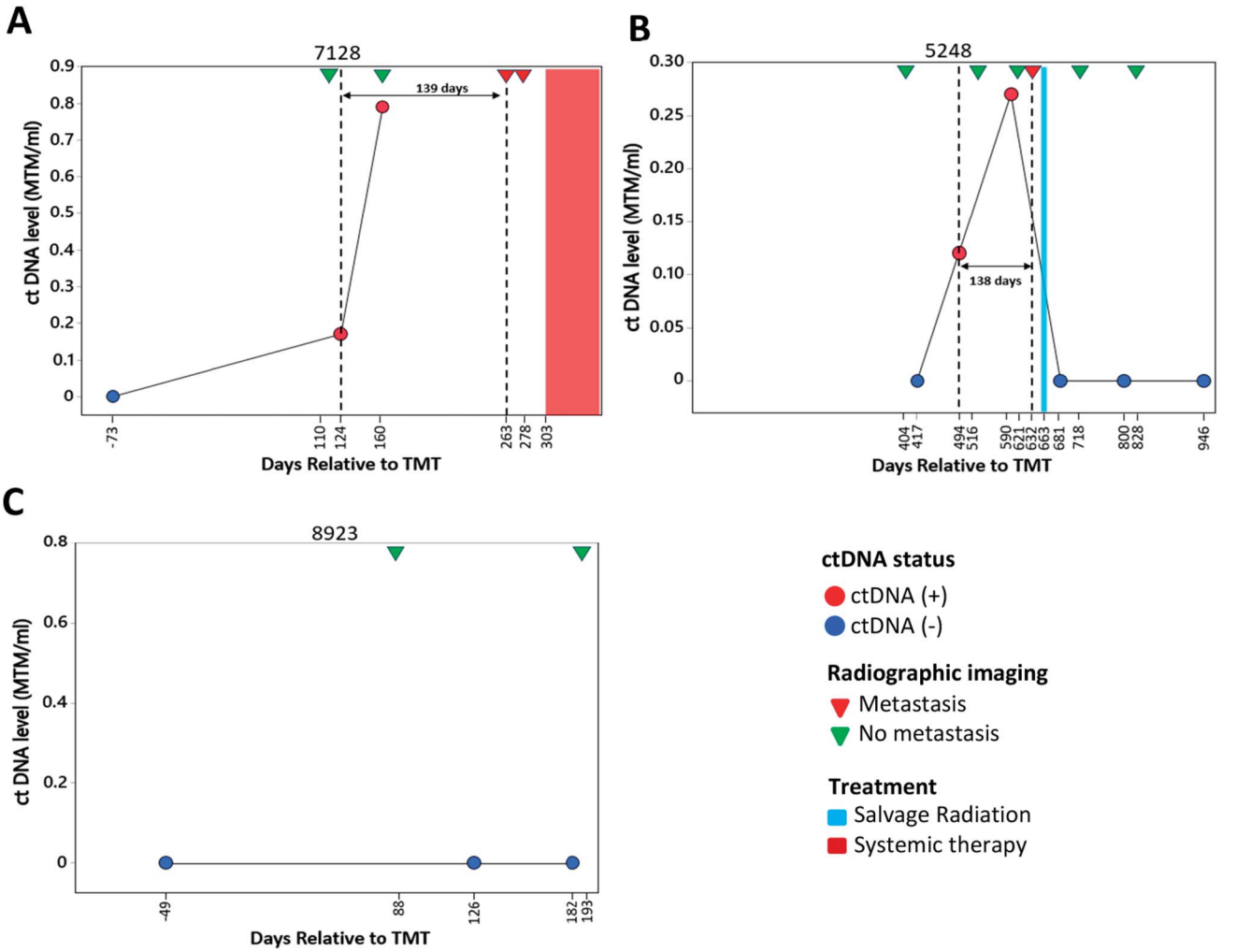

Figure 2. Dynamic circulating tumor (ct) DNA changes in individual disease courses. Representation of disease courses, imaging studies, applied treatments, and longitudinal ctDNA changes from 2 selected patients in the ctDNA (+) group (A and B). Days between dotted lines represent leading time between first post–trimodality therapy (TMT) ctDNA positivity and radiographic evidence of metastasis. C, Representation of disease course and ctDNA changes from 1 patient in the ctDNA (−) group. MTM indicates mean tumor molecules.

observation,[21] an ad hoc analysis by Powles et al demonstrated that disease-free survival and overall survival benefit were confined to the ctDNA (+) group treated with atezolizumab.[10,22] Notably, ongoing prospective IMvigor011 (NCT04660344) and MODERN (NCT05987241) trials are evaluating how post-cystectomy ctDNA can guide therapy escalation with immunotherapy.[9,23] Given the equipoise in outcomes between extirpative surgery and TMT, it may be assumed that adjuvant therapy escalation with immunotherapy in post-TMT patients with positive ctDNA would have similar benefits as those in the IMvigor010 subset. The experimental arm of the fully accrued SWOG 1806 trial (NCT03775265) evaluating TMT with atezolizumab includes concurrent dosing and an adjuvant component.[24] Thus, future translational studies evaluating ctDNA in this cohort will be of benefit to understand how ctDNA-based adjuvant therapy intensification may be applied in TMT. In addition, future studies may address whether TMT is suitable in patients planned for cystectomy but with clearance of their ctDNA following neoadjuvant systemic therapy or whether pre-TMT and post-TMT ctDNA dynamics should guide adjuvant therapy.

In our cohort, we did not observe any local MIBC recurrence; however, a total of 2 NMIBC recurrences were detected by routine cystoscopy and confirmatory biopsy. Interestingly, all NMIBC recurrences were observed in ctDNA (−) patients, suggesting that plasma ctDNA assays may not be sensitive nor specific for the detection of NMIBC recurrence in the post-TMT setting. This is not surprising given the bladder tumor burden is much less in the setting of post-TMT NMIBC relapse and likely does not increase the risk of lymphatic access, extravesical spread, or entrance of ctDNA into the circulation. Furthermore, NMIBC cells are likely shedding tumor DNA directly into the bladder

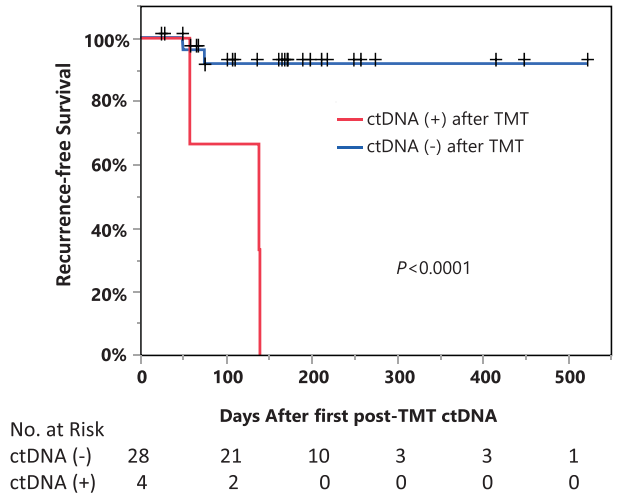

Figure 3. Positive circulating tumor (ct) DNA is associated with disease recurrence (local and distant). Kaplan-Meier survival analysis of recurrence-free survival stratified by ctDNA status. TMT indicates trimodality therapy.

lumen, which is more likely to be detected by approaches that employ urine tumor DNA (utDNA) rather than plasma ctDNA. Indeed, a growing body of evidence has shown the effectiveness of utDNA for early detection and post-treatment surveillance of NMIBC.[25-27] Therefore, adding utDNA to plasma ctDNA monitoring in the post-TMT setting may be complementary for early detection of both local recurrence and distant metastasis.

This study has several limitations to consider in addition to its retrospective nature. First, it is a single institution study with a small sample size and a relatively short median follow-up duration. This is underscored by the fact that no patients developed MIBC recurrence, and most patients (31 of 32) are alive at time of analysis. Thus, no conclusions can be drawn in regard to ctDNA positivity and localized MIBC relapses or survival in the post-TMT setting. Second, there was no up-front standardization of ctDNA assessment frequency which was influenced by patient referral patterns, tumor tissue availability, and patient willingness for ctDNA monitoring. Yet ctDNA evaluation frequently coincided with our institutional post-TMT surveillance protocol later into the study period. This is reflected in that only 17 of 32 patients (53%) had both pre-TMT and post-TMT ctDNA evaluations. Currently, the optimal cadence of ctDNA evaluation in the post-TMT setting is undefined; however, implementation of ctDNA monitoring has now paralleled standard post-TMT surveillance patterns in our practice. Furthermore, to assess the impact of dynamic ctDNA changes in the setting of TMT, standardized serial measurements should be performed before, during and after TMT, to complement cystoscopy and imaging studies. Finally, as ctDNA is an emerging biomarker in MIBC, the cost-effectiveness of this approach vs standard surveillance methods is an important consideration. Studies in other cancers have found that use of post-treatment ctDNA surveillance reduced cost compared with conventional imaging methods and use of ctDNA to guide adjuvant chemotherapy initiation led to no detriment in outcomes and was more cost efficient.[28,29] Similar studies in bladder cancer are warranted for the judicious use of ctDNA in optimizing clinical outcomes and balancing economic impacts.

CONCLUSIONS

We have found that plasma ctDNA positivity may serve as an early predictive marker for metastatic progression in patients with MIBC treated with bladder-sparing TMT. Plasma ctDNA identified metastatic progression with high sensitivity and specificity and a substantial positive lead time compared with radiographic imaging. Based on our findings, a potential workflow for ctDNA-guided post-TMT surveillance can be proposed. For ctDNA (+) patients, surveillance intensification by shortening the interval of imaging or changing the imaging approach (ie, switch from CT to positron emission tomography) may provide an opportunity for earlier detection of metastatic progression, which can be salvaged by metastasis-directed therapy (eg, ablative radiation, surgery) or earlier initiation of systemic therapy. Conversely, patients without detectable

Table 3. *Univariable Analysis for Recurrence-Free Survival*

Variable	Reference	Comparator	HR (95% CI)	*P* value
ctDNA	Negative	Positive	3.53 (1.11-11.13)	.03
Sex	Male	Female	1.22 (0.54-2.73)	.6
T stage	T2	T3/T4	0.78 (0.34-1.88)	.6
LVI	No	Yes	1.42 (0.56-3.56)	.5
CIS	No	Yes	2.29 (0.68-7.86)	.2
Urothelial with subtype histology	No	Yes	0.74 (0.34-1.57)	.4
Hydronephrosis	No	Yes	0.46 (0.20-1.08)	.1
Neoadjuvant chemotherapy	No	Yes	1.13 (0.52-2.47)	.8

Abbreviations: CIS, carcinoma in situ; ctDNA, circulating tumor DNA; LVI, lymphovascular invasion.
ctDNA (+) status is the only variable significantly associated with worse RFS.

ctDNA for a sustained period may have an opportunity to eventually reduce the intensiveness of imaging surveillance given their low risk of micrometastatic spread and continuation with complementary ctDNA monitoring. This could represent a path to reduce radiation exposure from diagnostic imaging and lessen the economic burden of bladder cancer care.[30]

This is among the first studies that have evaluated the utility of plasma ctDNA in the setting of TMT. Although these findings are hypothesis-generating and will require further assessment in pooled multi-institutional analyses and prospective studies before widespread implementation, the field of circulating biomarker assessment in patient selection and post-TMT surveillance is ripe for exploration.

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EDITORIAL COMMENTS

For patients with muscle-invasive bladder cancer undergoing trimodal treatment (TMT) with curative intent, surveillance with cystoscopy and cross-sectional imaging has several limitations. These include potential delays in detecting metastatic disease, inability to identify microscopic disease, and no optimal risk stratification to intensify or de-escalate surveillance based on patient-specific disease features. The advent of circulating tumor DNA (ctDNA) across many disease spaces, including urothelial bladder cancer, is potentially poised to change this.

Here, Zhao et al evaluate the role of ctDNA as an early predictive marker for metastatic recurrence after TMT in a small retrospective cohort.[1] Even within the limitations of the study, their findings are compelling: post-TMT ctDNA positivity was associated with a 75% metastatic progression rate vs 0% in the ctDNA-negative cohort. Importantly, ctDNA demonstrated 100% sensitivity and 93% specificity at 6 months, offering a median lead time of 138 days over imaging for detection of metastatic disease.

These findings raise important implications for the role of ctDNA in the surveillance of post-TMT patients, as positive ctDNA status is viewed as an indication of micrometastatic disease. While ctDNA status was not associated with intravesical recurrence (cTa-T2 cM0), the ability to diagnose M1 disease before surveillance imaging may prompt consideration for early systemic immunotherapy, paralleling the survival benefit from ctDNA-directed immunotherapy initiation observed among post-cystectomy patients in the IMvigor011 trial.[2]

Another important implication is whether a negative and sustained normal ctDNA in the first year of treatment allows for de-escalation of radiological surveillance, which may reduce cost burden and radiation exposure for this at-risk patient population. While a smaller retrospective evaluation with inherent limitations, this study is hypothesis generating and sets another stage for prospectively evaluating and integrating ctDNA into the care of our patients with bladder cancer.

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Circulating tumor DNA (ctDNA) has emerged as a promising tool to guide management of patients with muscle-invasive bladder cancer (MIBC). Thus far, it has largely been leveraged as an adjunct test after cystectomy for risk stratification of patients who may benefit from adjuvant therapy. We commend Zhao et al[1] on their study describing the prognostic role of ctDNA in the organ-sparing treatment setting. In their cohort of 32 patients who underwent trimodal therapy (TMT) for MIBC, they report 100% sensitivity and 93% specificity of ctDNA (+) status at 6-month post-TMT surveillance in identifying metastatic progression with a median lead time of 138 days compared with standard radiographic assessment.

Although limited in sample size, follow-up duration, and ctDNA assessment frequency, this study expands the utility of ctDNA in management of patients with MIBC and parallels the prognostic value observed in patients undergoing extirpative therapy. The recently published exploratory analysis of the IMvigor011 trial demonstrated worse overall survival in post-cystectomy ctDNA (+) patients compared with ctDNA (−) patients.[2] However, ctDNA (+) patients treated with adjuvant atezolizumab experienced improved overall survival and

disease-free survival vs those who received placebo.[2] There was no difference in outcomes between the treatment arms in the ctDNA (−) cohort, suggesting that patients with undetectable ctDNA may be able to avoid adjuvant therapy.[2] The ongoing MODERN (NCT05987241) and TOMBOLA (NCT04138628) trials aim to prospectively determine whether ctDNA can guide the decision to use adjuvant therapy, and in the MODERN trial, whether ctDNA (+) patients further benefit from an escalated combination therapy regimen.[3]

As the authors suggest, ctDNA status may guide post-TMT surveillance schedules and decision to use adjuvant therapy in the future; however, additional investigation, potentially modeled from pericystectomy trials, is needed to better characterize its use as a biomarker for patients treated with TMT.

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The authors provide evidence that plasma circulating tumor DNA (ctDNA) detects metastatic progression months before imaging among patients undergoing organ-preserving trimodality therapy (TMT) for muscle-invasive bladder cancer.[1] This extends the role of ctDNA from post-cystectomy surveillance to the organ-preservation setting and represents the largest series of ctDNA post TMT to date. Larger cohorts are sure to be published in the near future.

We are now truly "beyond the bladder." The future of muscle-invasive bladder cancer management lies not in local therapy alone, but with the incorporation of individual molecular data to quantify systemic risk. The landmark IMvigor011 trial—using the same tumor-informed ctDNA assay Signatera (Natera)—demonstrated clinically meaningful survival gains with ctDNA-directed adjuvant atezolizumab after radical cystectomy.[2] The parallel findings in this TMT cohort make it clear: tumor-informed ctDNA monitoring should be standard of care regardless of treatment strategy chosen for primary tumor management (radical cystectomy vs TMT).

The future is now. Treatment decisions can no longer rely exclusively on clinical staging frameworks developed in the 1980s and 1990s. It is time to upgrade to a DeLorean with a flux capacitor and incorporate advanced tools—such as up-front MRI of the bladder and ctDNA—to guide contemporary treatment decision-making. Ongoing trials such as the phase III NRG-GU015 (ARCHER; Phase III Adaptive Radiation and Chemotherapy for Muscle Invasive Bladder Cancer Trial) integrating real-time longitudinal ctDNA from Natera, the phase II SWOG S2427 (BRIGHT; Single Arm Phase II Study of Bladder Preservation with Immunoradiotherapy after a Clinically Meaningful Response to neoadjuvant Therapy in Patients with Muscle Invasive Bladder Cancer), and the completed phase III SWOG S1806 will further elucidate ctDNA's utility.[3] With perioperative enfortumab vedotin plus pembrolizumab achieving pathologic complete response rates of 64% in cisplatin-ineligible patients who underwent cystectomy (KEYNOTE-905/EV-304), the time for the US urologic community to embrace bladder preservation is now.[4]

Where we are going, there are no roads. Many questions have yet to be formally asked in the context of a prospective trial—let alone answered—but clinical and translational researchers across the world now have an exciting new set of tools that will undoubtedly allow us to treat our patients with more personalization and improve outcomes. Integrating bespoke ctDNA into practice today will improve outcomes tomorrow. Buckle up and welcome to the future.

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