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Urologic Oncology: Seminars and Original Investigations 41 (2023) 295.e9–295.e17

UROLOGIC ONCOLOGY

Clinical-Bladder cancer

Biodynamic prediction of neoadjuvant chemotherapy response: Results from a prospective multicenter study of predictive accuracy among muscle-invasive bladder cancer patients

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Received 16 August 2022; received in revised form 8 November 2022; accepted 22 November 2022

Abstract

Background: Biodynamic signatures (temporal patterns of microscopic motion within a 3-dimensional tumor explant) offer phenomic biomarkers that are highly predictive for therapeutic response.

Objective: By utilizing motility contrast tomography, which provides a simple, fast assessment of motion patterns in living tissue, we evaluated the predictive accuracy of a biodynamic drug response classifier in muscle-invasive bladder cancer (MIBC) patients undergoing neoadjuvant chemotherapy (NAC).

Design, Setting, and Participants: One hundred five consecutive bladder cancer patients suspected of having MIBC were screened in a multi-institutional prospective observational study (NCT03739177) from July 2018 to June 2020, of whom, 30 completed NAC and radical cystectomy.

Intervention(s): Biodynamic signatures from treatment-naïve fresh bladder tumor specimens obtained after transurethral resection were measured in living tumor fragments challenged by standard-of-care cytotoxins. Patients received gemcitabine and cisplatin or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin per institutional guidelines and were followed through radical cystectomy.

Outcomes Measurements and Statistical Analysis: A 4-level classifier was developed to predict pathologic complete response (pCR) vs. incomplete response utilizing a one-left-out cross-validation protocol to minimize over-fitting. Area under the curve evaluated predictive utility.

Results: Thirty percent (9 of 30) achieved pCR. Utilizing the 4-level classifier, biodynamically "favored" (scoring $\geq$ 3) and "strongly favored" (scoring 4) regimens accurately predicted pCR at rates of 66.7% (4 of 6 patients) and 100% (4 of 4 patients), respectively. Biodynamically "favored" scores predicted pCR with 88% sensitivity and 95% negative predictive value, $P < 0.0001$. Only 5.0% (1 of 20 patients) achieved pCR from regimens scoring 1 or 2, indicating poor to no response from NAC. Area under the receiver operating curve was 96% (95% Confidence Interval: 79%–99%, $P < 0.0001$). Future direction involves validating this model prospectively.

Principal Conclusions: Biodynamic scoring accurately predicts response in MIBC patients receiving NAC and holds promise to substantially improve the scope of appropriate management intervention.

Research support provided by Animated Dynamics, Inc., Purdue University National Science Foundation Grant CBET-1911357.

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https://doi.org/10.1016/j.urolonc.2022.11.017
1078-1439/

Keywords: Bladder cancer; Targeted therapy; Neoadjuvant chemotherapy; Biomarkers

Abbreviations: AUC, area under the curve; GC, gemcitabine and cisplatin; MCT, motility contrast tomography; MIBC, muscle invasive bladder cancer; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; NAC, neoadjuvant chemotherapy; pCR, pathologic complete response; pIR, pathologic incomplete response; TURBT, transurethral resection of bladder tumor

1. Introduction

Motility contrast tomography (MCT) is a marker-free, non-destructive imaging modality that provides a fast and simple quantitative assessment of the patterns of motion in living tissue. Utilizing Doppler spectroscopy to quantify microscopic intra- and extra-cellular motion within a 3-dimensional living tissue explant (tumor specimen), patterns of motion over time (biodynamic signatures) may be able to serve as novel phenomic biomarkers [1−3]. When combined with existing genomic studies, these clinically-relevant biodynamic phenotypes may serve as surrogates to assess and predict treatment response and personalize oncologic care (Fig. 1). Several pre-clinical studies have demonstrated that a biodynamic assay, applied to tumor biopsy specimens as they are challenged by various cytotoxins, offers high predictive value for in vivo drug effect and allows the capability to monitor drug effects in real time [4−6]. This study is the first large-scale application of biodynamic response prediction in a multi-center clinical setting for muscle-invasive bladder cancer (MIBC).

Although neoadjuvant chemotherapy (NAC) has level 1 evidence supporting its use [7], its adoption has not become universal for multiple reasons. Many clinicians find it difficult to accurately pre-determine the true benefit of NAC, and thus, the majority of patients, ultimately, do not receive chemotherapy [8]. As we gain more knowledge on the impact of bladder cancer's molecular subtypes, determining the appropriate candidates for NAC is becoming clearer, although this process can be lengthy and fails to differentiate between different treatment regimens [9]. Currently, there is no predictive tool to determine the best candidates for NAC.

The primary objective of this study was to explore the clinical utility and predictive accuracy of a biodynamic signal in effort to determine the benefit of 2 standard-of-care NAC regimens (gemcitabine and cisplatin [GC] or methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC] for patients with (MIBC). We hypothesized that by comparing prospectively collected ex vivo biodynamic signatures of bladder tumors to confirmed pathologic response, we could develop a classifier that accurately predicts in vivo drug effect.

2. Materials and methods

2.1. Patient population

Treatment-naïve adult bladder cancer patients who were either suspected to have localized de-novo MIBC or confirmed MIBC and needed either a diagnostic transurethral resection of bladder tumor (TURBT) or repeat TURBT for debulking purposes were prospectively enrolled in a multi-center observational study at 4 bladder cancer centers across the United States (Vanderbilt University Medical Center, Nashville, TN; Indiana University Health, Indianapolis, Indiana; Community Health Network, Indianapolis, Indiana; Banner MD Anderson Cancer Center, Gilbert, AZ). Patients who were ineligible to receive standard-of-care NAC were excluded from enrollment. Participants were recruited by each investigator in a consecutive series from July 2018 to June 2020. *Patient ethnicity was not considered due to the sample size*. The ultimate chemotherapy and surgical plan were left to the discretion of the medical team and were not influenced by this study. Institutional review board approval was obtained at each of the participating sites.

2.2. Treatment regimen

Two standard-of-care chemotherapy regimens were evaluated: 1) GC and 2) dose-dense MVAC. Similar dosing regimens were used between centers.

2.3. Specimen collection

A biodynamic assay was performed for all enrolled patients within 24 hours of their TURBT. TURBTs were performed in their standard fashion, and a minimum of 80 mg of tumor (approximately 1−2 loops) were isolated for the study. *The index lesion was always sampled as were any additional concerning multifocal tumors.* Fresh (unfixed) treatment-naïve living bladder tumor specimens were delivered overnight via standardized chilled specimen collection kits to a central laboratory (Animated Dynamics, Inc., Indianapolis, IN) where they were divided into at least 36 tumor fragments, preserving the tissue microenvironment and keeping living cells intact and viable (confirmed by the biodynamic motility contrast metric measured on each sample prior to MCT).

Specimens were analyzed using MCT for approximately 5 hours prior to application of challenge drugs, followed by at least 12 hours of drug-effect measurement. *Biodynamic signatures were developed for all patients, but only the profiles from patients who proceeded with NAC were considered in development of the classifier*. For each patient, the biodynamic assay examined all combination therapies, component monotherapies, and negative controls (culture medium + 0.1% dimethyl sulfoxide). Concentration of each

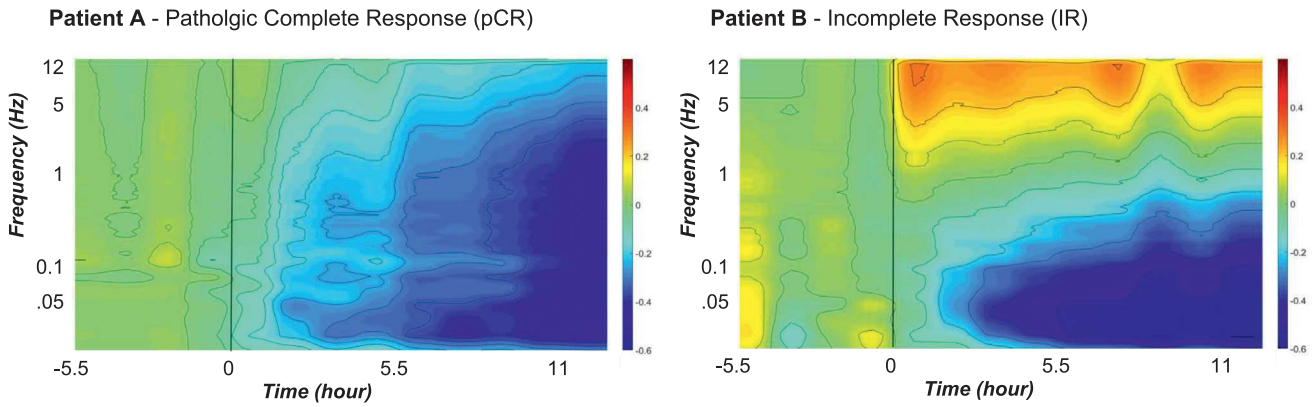

Fig. 1. Biodynamic time-frequency spectrograms. Ex vivo response to GEMCIS treatment for tumor biopsies from 2 patients: Patient A achieved pathologic complete response (pCR) vs. Patient B who had an incomplete response (IR). The horizontal axis follows the 18-hour time course of the biodynamic profiling test, and the vertical axis is the Doppler frequency associated with intracellular motions. The 5.5-hour baseline period is followed by application of the GEMCIS treatment at time t = 0 and 12.5 hours of drug-response monitoring. The vertical color scale is from -0.6 to +0.6 representing the fractional change in Doppler spectral density. Positive (red) values indicate enhanced kinetic activity, and negative (blue) values suppressed kinetic activity. Patient A shows broad motion suppression across all frequencies in response to the drug, which correlates with tumor cell death. In contrast, patient B exhibits strong high-frequency enhancement, indicative of decreased pharmacologic effect.

combination and monotherapy were previously established by dose-response studies conducted to tailor the biodynamic assay for bladder cancer tumors and therapies [10]. Five to six replicates of each combination therapy, monotherapy, and negative control were tested to accommodate tumor heterogeneity and sampling variance, producing an averaged high-content dataset for each challenge agent (each representing a unique "biodynamic signature"). The 6 replicates provide a sampling across spatial tumor heterogeneity yielding a high likelihood that at least several of the

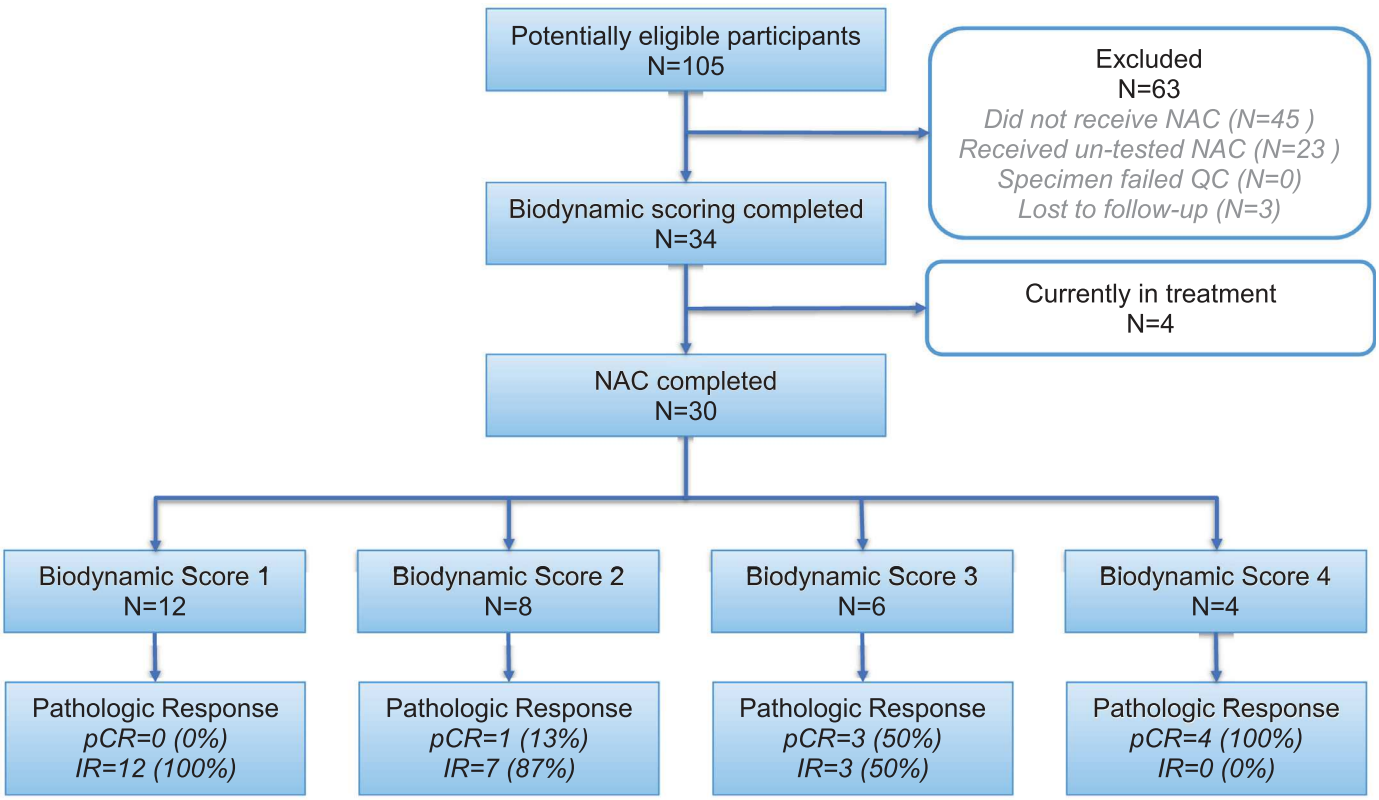

Fig. 2. Study Flow diagram. This study had 105 potentially eligible participants of whom 30 completed the NAC protocol. Patient outcomes are assessed as pathologic complete response (pCR: ypT0 N0) and incomplete response (IR: ypT > 0 or pN > 0). Biodynamic scores are in a range of 1 to 4, with 1 being the lowest likelihood of achieving pCR and 4 having the highest likelihood of achieving pCR. The percentages of patients achieving pCR or IR are given within each biodynamic score.

samples give a biologically relevant response. DNA-based specimen provenance testing was performed by a third-party reference laboratory to rule out occult transposition or contamination of study specimens among patients. All patients, caregivers, and research assistants were blinded to biodynamic signatures. Enrollees received unguided standard-of-care therapy per institutional guidelines and were subject to the discretion of the treating physician. All patients were followed through final surgical intervention (radical cystectomy).

2.4. Development and validation of a biodynamic classifier

Central review of post-NAC pathology reports characterized all outcomes as either a pathologic Complete Response (pCR) or an Incomplete Response (IR), with pCR being defined as the absence of any residual tumor in the resected organ or lymph nodes (i.e., ypT0 pN0) [10]. To develop the biodynamic classifier, an ensemble multinomial logistic regression machine-learning model was trained against the binary outcome classification using ridge regularization to reduce over-fitting. A Leave-One-Out cross-validation protocol successively left out each patient to use as a test subject as the classifier is retrained each time on the remaining patient data. The prediction quoted for each patient is from separately-trained classifiers. Biodynamically predicted response was converted to discrete biodynamic scores of 1, 2, 3, or 4 (the Onco4D® score), with 4 representing the highest probability of a pCR. Biodynamic patterns with a score of 4 tend to show broad-frequency inhibition caused by suppressed metabolism, while patterns with a score of 1 tend to show activation of cellular dynamics, possibly reflecting active response of the cells to counteract the toxins, with behavior for scores of 2 and 3 falling in between. Details of the principles of biodynamic analysis and the data workflow can be found in the Supplemental Packet.

2.5. Statistical analysis

The primary goal of the study was to develop and assess the statistical significance of the biodynamic classifier's utility for predicting a patient's pCR to various chemotherapy regimens. Calculation of area under the receiver operating curve (AUC) was conducted to evaluate predictive utility of the model. The AUC plotted the true positive rate (sensitivity) against the false positive rate (1 − specificity) for all possible cutoff values of the test (for this model: 1, 2, 3, or 4) with possible values ranging from 0.5 (no predictive ability) to 1.0 (perfect predictive ability) [11−14]. The literal interpretation of AUC in this context was the probability that the biodynamic score of a therapy drawn at random from all actual pCR results was higher than the biodynamic score of a therapy drawn at random from all therapies that did not result in pCR. Pre-study power analysis estimated that completion of the protocol by at least 20 patients would be necessary to observe a representative mix of clinically relevant subtypes and common neoadjuvant therapies in order to detect statistically significant predictive utility for each therapy with a 5% one-sided significance level and a power of 95% [15]. As no reference standard currently exists to predict chemotherapy response in this setting, predictive utility and null hypothesis were defined as an AUC > 50% (the AUC of a hypothetical test that randomly predicts pCR or IR). All statistical analyses were performed using NCSS 11 Statistical Software (2020) [16]. The study was conducted in accordance with Standards for the Reporting of Diagnostic Accuracy Studies [17].

3. Results

Of 105 potentially eligible participants, 30 completed NAC and radical cystectomy (GC = 20, dose-dense MVAC = 10) and were included in the final analysis. Altogether, 45 did not receive NAC, 23 received a regimen other than GC or MVAC, 3 were lost to follow-up and/or passed away prior to cystectomy, and 4 are currently in treatment (Fig. 2). Median age was 68 with 60% ($n = 18$) male (Table 1). The pCR rate after radical cystectomy (ypT0) was 30.0% (9/30) while all other patients were deemed to have an IR. pCR was higher in the MVAC

Table 1
Demographic and clinical characteristics of participants.

Patient characteristic	No. (%) of GC patients ($N = 20$)	No. (%) of MVAC patients ($N = 10$)	No. (%) of total patients ($N = 30$)
Age			
Median	69	63	68
Range	45−79	56−72	45−79
Gender			
M	13 (65%)	5 (50%)	18 (60%)
F	4 (20%)	4 (40%)	8 (27%)
Not disclosed	3 (15%)	1 (10%)	4 (13%)
Weeks of follow-up			
Median	23	18	22
Range	14−45	14−24	14−45
Enrollment site			
A	13 (65%)	5 (50%)	18 (60%)
B	4 (20%)	4 (40%)	8 (27%)
C	2 (10%)	1 (10%)	3 (10%)
D	1 (5%)	(0%)	1 (3%)
Pathologic response			
pCR	4 (20%)	5 (50%)	9 (30%)
IR	16 (80%)	5 (50%)	21 (70%)
Post NAC tumor stage			
ypT0	4 (20%)	4 (40%)	8 (27%)
ypT < 2	7 (35%)	4 (40%)	11 (37%)
ypT ≥ 2	13 (65%)	6 (60%)	19 (63%)
Post NAC node status			
Positive	7 (35%)	3 (30%)	10 (33%)
Negative	13 (65%)	7 (70%)	20 (67%)

GEMCIS = Gemcitabine + Cisplatin; IR = pathologic incomplete response; MVAC = methatrexate + vinblastine + doxorubicin (Adriamycin) + cisplatin; NAC = neoadjuvant chemotherapy; pCR = pathologic complete response (ypT0 pN0).

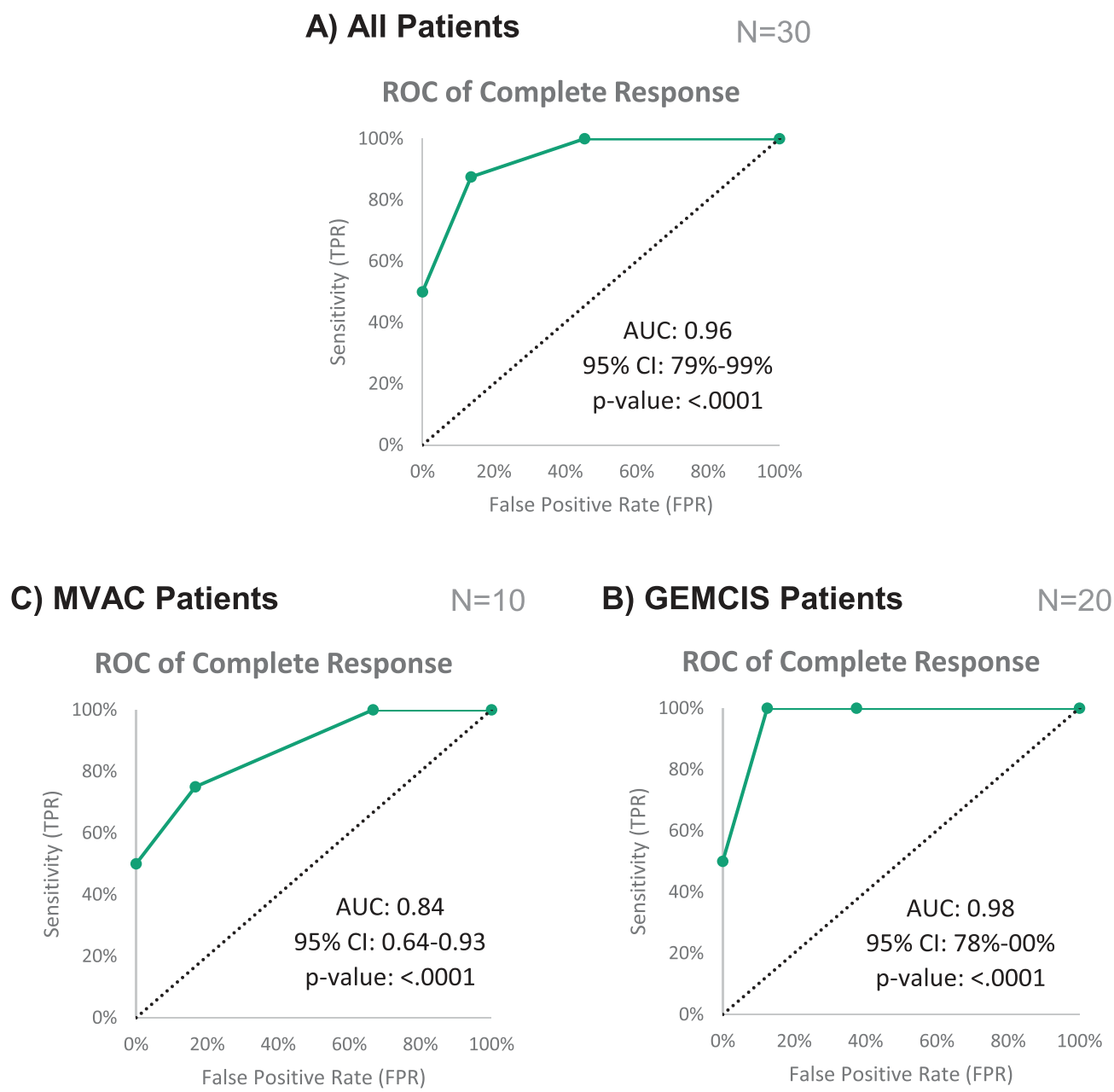

Fig. 3. Receiver Operating Curves (ROC) for (A) all patients, (B) those receiving GC, and (C) those receiving MVAC.

(50%, 5 of 10) vs. GC (20%, 4 of 20) group, although both were in range with previously published rates. 33% (10 of 30) were node positive at the time of cystectomy (all of which were classified as an IR). No adverse events were reported in relation to the study.

The predictive utility of the biodynamic classifier (AUC > 50%) was significant for the overall cohort and both chemotherapy subtypes ($P < 0.0001$ for all) [Fig. 3]. The classifier produced an AUC of 96% when applied to all 30 patients (95% CI: 79%–99%, $P < 0.0001$) and ranged from 84% for MVAC (95% CI: 0.64–0.93, $P < 0.0001$) to 98% for GC (%95 CI: 0.78–1.00, $P < 0.0001$). When translated into a scoring rubric, a biodynamic cutoff score ≥ 3 resulted in a test sensitivity of 88% and specificity of 86% for all patients (Table 2). The negative predictive value was 95% (range 83%–100%). Among the 4 patients with a biodynamic score of 4, all 4 achieved a pCR (100%), in contrast to the 0 of 12 (0%) with a score of 1 and 1 of 8 (13%) with a score of 2 (13%) [Fig. 4]. In other words, 19/20 (95%) with a score of 1 or 2 had an IR to chemotherapy. Further detail into descriptive statistics stratified by biodynamic score and chemotherapy subset are presented in Table 2.

4. Discussion

As we continue to transition into the era of personalized medicine, improving our understanding of pharmacologic resistance as it pertains to oncologic care is of paramount

Table 2
Descriptive statistics stratified by biodynamic score and chemotherapy subtype.

Cutoff score/ cohort	*N*	pCR Prev	T+	F+	F-	T-	TPR	TPR (Sens)	TNR (Spec)	FPR	PPV	NPV	ACC	AUC	95% CI	*P*-value
Biodynamic score of 4																
All patients	30	27%	4	0	4	22	50%	100%	50%	0%	100%	85%	87%	96%	79%–99%	<0.0001
By NAC regimen:																
GEMCIS	20	20%	2	0	2	16	50%	100%	50%	0%	100%	89%	90%	98%	78%–100%	<0.0001
MVAC	10	40%	2	0	2	6	50%	100%	50%	0%	100%	75%	80%	88%	36%–98%	0.0005
Biodynamic score of ≥3																
All patients	30	27%	7	3	1	19	88%	86%	13%	14%	70%	95%	87%	96%	79%–99%	<0.0001
By NAC regimen:																
GEMCIS	20	20%	4	2	0	14	100%	88%	0%	13%	67%	100%	90%	98%	78%–100%	<0.0001
MVAC	10	40%	3	1	1	5	75%	83%	25%	17%	75%	83%	80%	88%	36%–98%	0.0005
Biodynamic score of ≥2																
All patients	30	27%	8	10	0	12	100%	55%	0%	45%	44%	100%	67%	96%	79%–99%	<0.0001
By NAC regimen:																
GEMCIS	20	20%	4	6	0	10	100%	63%	0%	38%	40%	100%	70%	98%	78%–100%	<0.0001
MVAC	10	40%	4	4	0	2	100%	33%	0%	67%	50%	100%	60%	88%	36%–98%	0.0005
Biodynamic score of ≥1																
All patients	30	27%	8	22	0	0	100%	0%	0%	100%	27%		27%	96%	79%–99%	<0.0001
By NAC regimen:																
GEMCIS	20	20%	4	16	0	0	100%	0%	0%	100%	20%		20%	98%	78%–100%	<0.0001
MVAC	10	40%	4	6	0	0	100%	0%	0%	100%	40%		40%	88%	36%–98%	0.0005

ACC = diagnostic accuracy; AUC = area under the receiver operating curve (ROC) using the binormal approach; CI = confidence interval; F- = false negative; F+ = false positive; GEMCIS = gemcitabine + cisplatin; MVAC = methotrexate + vinblastine + adriamycin + cisplatin; N = number of evaluable outcomes accrued through 6/15/20; NAC = neoadjuvant chemotherapy; NPV = negative predictive value; pCR Prev = pathologic complete response prevalence; PPV = positive predictive value; P-value = probability associated with the Z-score for testing the hypothesis that AUC is > 0.5; T+ = true positive Onco4D® predictions; T- = true negative; TNR = true negative rate (specificity); TPR = true positive rate (sensitivity).

importance. With both tumor heterogeneity and inherent or acquired resistance affecting the use as well as efficacy of chemotherapy regimens for bladder cancer, [18,19] accurately predicting chemo-sensitivity prospectively and prior to treatment for urothelial cell carcinoma of the bladder remains essential but currently difficult. This is the first study to develop a predictive assay to assess chemo-sensitivity for urothelial cell carcinoma of the bladder in real time by utilizing MCT, the only diagnostic platform capable of quantifying the phenotypic effects of chemotherapy deep inside a contextually-relevant 3D microenvironment. This study offers a potentially novel avenue to predict chemotherapy response in bladder cancer and assess which patients are most likely to benefit from GC or dd-MVAC. While prospective validation studies are needed, we feel this study is important for the following reasons.

First, phenotypic predictability in 3-D configuration bypasses many of the current limitations in personalized medicine. Although genetic profiling has been utilized to identify therapeutic targets and efforts to draw from Big Data resources to statistically predict drug response are ongoing, the complexity of gene networks still present an arduous challenge in predicting actual tumor phenotype [9,20,21]. In MIBC, gene expression and molecular subtyping have predominantly sought to identify cisplatin-resistant tumors retrospectively rather than differentiate between chemotherapy regimens [22]. Furthermore, utilizing genetics alone to predict chemotherapeutic response fails to factor in unknown variables such as microenvironment and epigenetic effects, which can impact downstream phenotypic response and also fails to factor in genomic differences between the TURBT and radical cystectomy specimen [23,24]. A clinical trial of GC vs. dd-MVAC designed to prospectively evaluate the ability of a gene-expression profiling algorithm utilizing co-expression extrapolation to predict pathological response failed to show significant prognostic ability in the individual treatment arms [25]. In addition, previous efforts to assess phenotype directly by culturing cells from patient tumors have been constrained by 2-dimensional culture methods and a lack of demonstrated efficacy for clinical use [26]. Tumor phenotype is highly dependent upon the 3-dimensional structure of the tumor and its interaction with the *milieu intérieur* [27,28]. MCT allows for chemotherapeutic drug responses to be determined from intact and living 3-dimensional bladder tumor fragments. Its relatively short assay time, which can be applied to intact living tissue within 24 hours of collection, is another advantage that allows for minimal phenotypic and/or genomic drift given the limited number of cell cycles that can occur between TURBT resection and assay completion. Previous work with tumor biopsies, spheroids, and xenografts has shown MCT to be a highly accurate predictor of drug response [2,3].

Second, the high negative predictive value of the classifier (ranging from 75% to 100%) may aid in counselling patients in an objective manor. For patients whose bladder tumor is biodynamically contraindicated for a given therapy (biodynamic score of 1 or 2), this tool may enable medical oncologists to consider an alternative regimen, as the regimen with the low biodynamic score has a very low chance of achieving a pCR. The study implications are greatest for helping choose between GC and MVAC and potentially exploring clinical trials in the neoadjuvant space with agents such as checkpoint inhibitors. Both GC and MVAC

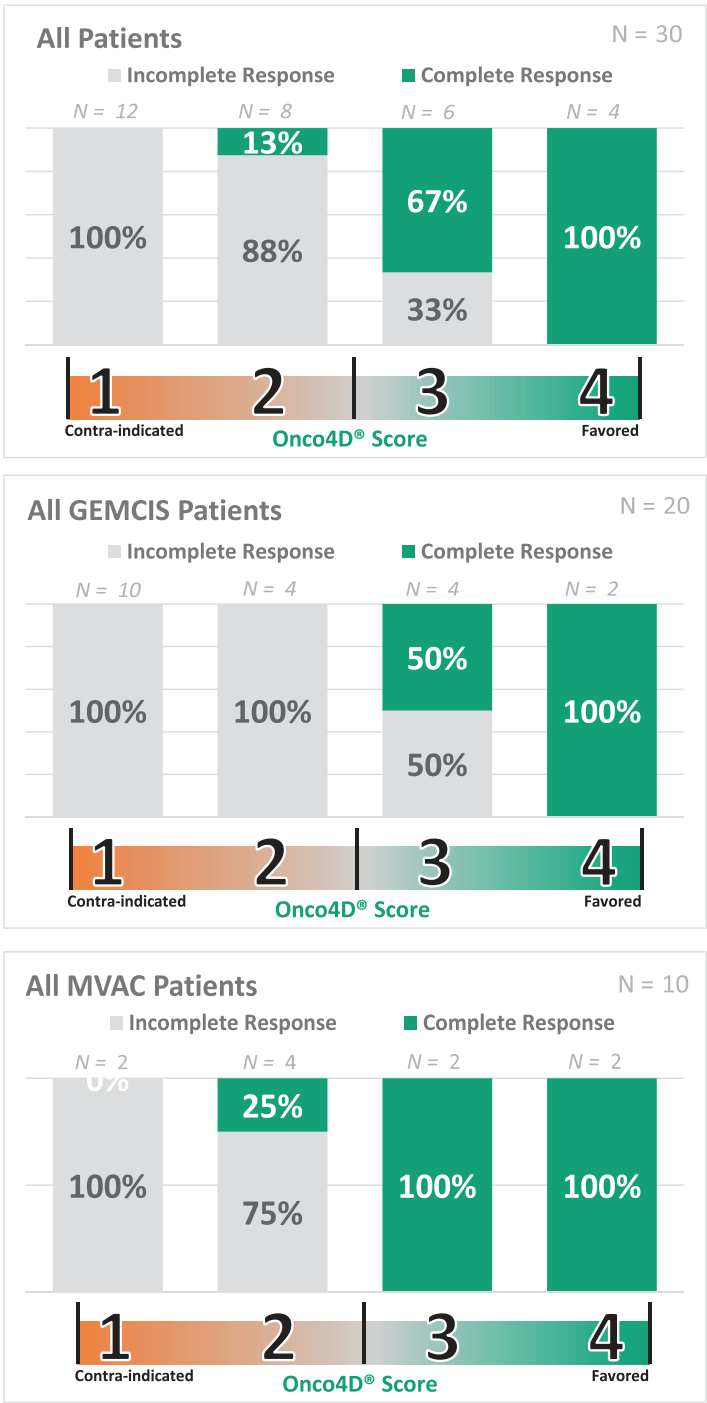

Fig. 4. Response distribution for the overall cohort and both GC and MVAC chemotherapy subsets, all of which achieved statistical significance ($P < 0.0001$).

are routinely given in the NAC setting without any objective data points (such as targetable genomic markers) to help inform a personalized choice between the 2. Our phenotypic profiling of the predictive response to both these agents may allow for oncologists to significantly improve patient care by 1) reducing the NAC failure rate by avoiding ineffective therapies, 2) avoiding potentially unnecessary cardiotoxicity of anthracyclines (doxorubicin) when GC is likely to yield superior performance, and 3) avoiding unnecessary nephrotoxicity with cisplatin agents when both regimens are unlikely to yield a durable response to treatment. pCR rates for GC and MVAC were equivalent when those regimens exhibited the most favorable biodynamic signature (biodynamic score = 4). The pCR for dd-MVAC was higher when the regimen exhibited a score of 3 or higher vs. GC (100% vs. 66.7%), but prospective validation studies are needed to better elucidate any difference here.

Third, given the high sensitivity and negative predictive value of the biodynamic signatures, a low biodynamic score for both GC and MVAC may argue in favor of either prompt radical cystectomy or clinical trial agents as opposed to the currently favored NAC pathway. This biodynamic assay could also be used for newer agents that will enter the neoadjuvant therapy pipeline, including checkpoint inhibitors, to further personalize therapy [29,30].

Despite the strengths of this study, several limitations should be acknowledged. First, now that the biodynamic score classifier has been created, it must be validated prospectively. Second, given this is an observational study, estimating how providers will modify clinical decision-making once they are aware of the biodynamic scores is only speculative currently. To address this issue, an outcome registry study is planned to measure the impact of biodynamic guidance on treatment patterns and evaluate longer-term endpoints such as disease-free and overall survival. Notably, the hypothesis that administering NAC to only those with a predicted pCR will portend a survival benefit remains unproven. In this regard, this prediction tool may be more efficacious in predicting who should endure NAC given its potential side effects. Third, although this study focused on evaluating complete response, there may be a role for assessing partial response, most notably ones that result in disease downstaging. It is also possible that some patients had their entire tumor removed at time of TURBT, thus inflating pCR rates. Nevertheless, this is unlikely, as all those with pCR had evidence of radiographic and/or grossly confirmed localized disease after TURBT and before starting NAC. Furthermore, as with any neoadjuvant study, partial response may be influenced by many factors including the initial clinical stage, rigor, and number of resections. Fourth, as there is increasing interest in trimodal therapy for bladder preservation, this biodynamic prediction tool should be assessed in its ability to predict response to bladder sparing techniques. *Fifth, differential analysis of individual foci within a multifocal tumor was beyond the scope of this study, but represents a potential avenue for future research. IR, for example, may actually reflect complete response for the subset of foci with a certain biodynamic phenotype, implying that individually tailored combination therapies might more effectively address highly heterogenous disease. Sixth, because patients in this study were followed only through cystectomy, predictive value of the classifier with respect to*

adjuvant chemotherapy response and disease-free survival has not been assessed. Seventh, correlation of node status with biodynamic phenotype was not possible given sample size constraints, but would be of potential interest in a larger future study. Finally, with several prospective, randomized, phase III studies comparing NAC with chemoimmunotherapy or combination immunotherapy being planned [31], future directions for this classifier involve updating it as new standard therapies for the treatment of MIBC are established.

5. Conclusions

Biodynamic scoring is a novel tool to predict response in MIBC patients receiving NAC, offering clinicians a simple scoring rubric that provides robust specificity and negative predictive probability for chemotherapy response. Downstream, biodynamic analysis may improve personalized medicine in bladder cancer by offering new data to better personalize pharmacotherapeutic selection among standard-of-care regimens, with or without future genomic biomarkers. Biodynamic phenotypes have the potential to fill a notable void in MIBC where targetable genetic biomarkers do not yet exist or still have unproven benefit. Future studies are needed to validate the scoring tool prospectively.

Originality

These contents represent the original work of the authors, and no part of the manuscript is under consideration, in press, published, or reported elsewhere.

Additional information

The full study protocol entitled "Onco4D® Biodynamic Chemotherapy Selection for Bladder Cancer Patients" is available on clinicaltrials.gov (identifier NCT03739177).

Conflict of interest

Certain authors (DN, JT, AN, TM) have an economic interest in Animated Dynamics, Inc. which holds an exclusive license from Purdue University to market biodynamic imaging technology.

Acknowledgments

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2022.11.017.

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