Enhancing bladder cancer care through the multidisciplinary clinic approach

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Introduction: *We report the impact of our 25-year multidisciplinary care delivery model experience on patients with muscle invasive bladder cancer treated at our National Cancer Institute (NCI)-designated Sidney Kimmel Cancer Center at Jefferson University. To our knowledge, our multidisciplinary genitourinary cancer clinic (MDC) is the longest continuously operating center of its kind at an NCI Cancer Center in the United States.*

Materials and methods: *We selected a recent group of patients with cT2-4 N0-1 M0 bladder cancer seen in the Sidney Kimmel Cancer Center Genitourinary Oncology MDC from January 2016 to September 2019. These patients were identified retrospectively. SEER-18 (Surveillance, Epidemiology, and End Results) database, November 2019 submission was queried to obtain patients with similarly staged disease diagnosed between 2015 and 2017. Completion rates of radical cystectomy, use of neoadjuvant therapies, and survival outcomes were compared between the two cohorts.*

Results: *Ninety-one patients from the MDC form this time period were identified; 65.9% underwent radical cystectomy and 71.8% received neoadjuvant therapy in the form of chemotherapy, immune checkpoint inhibition or a combination of the two – higher than reported national trends for neoadjuvant therapies. Progression of disease was seen in 24.2% of patients. A total of 8675 patients met inclusion criteria in the SEER database. Rates of radical cystectomy were significantly higher in MCD patients when compared to SEER derived data (65.9% vs. 37.7%, p =< 0.001). MCD patients had significantly better cancer-specific survival (mean 20.4 vs. 18.3 months p = 0.028, median survival not reached).*

Conclusion: *Our long term experience caring for patients with genitourinary malignancies such as bladder cancer in a uniform multidisciplinary team results in a high utilization of neoadjuvant therapies. When compared to a contemporary SEER-derived cohort, multidisciplinary patients were more likely to undergo radical cystectomy and had longer cancer-specific survival.*

Key Words: urinary bladder neoplasms, SEER program, delivery of health care

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Introduction

The coordination of optimal and efficient care to patients with urologic cancers is challenging. In 1996, the Sidney Kimmel Cancer Center at Jefferson University established a Genitourinary Oncology Multi-disciplinary Clinic (MDC) comprised of urologists, radiation and medical oncologists as well as with pathologists, radiologists, nurses, social workers and clinical researchers to help meet the complex needs

of patients requiring multimodality care. This model allows patients to be evaluated and presented with multiple appropriate management options within one appointment. The benefits to the patient are numerous; they are presented with comprehensive care by physicians who are able to work collaboratively in real-time within an efficient clinical setting. Care is all encompassing with psychosocial support, genetic counseling and clinical trial enrollment available to the patient when necessary.

We have already described our clinical model and the successful delivery of leading patient care to men with prostate cancer improves outcomes for stage III disease when compared to National Cancer Institute SEER-derived data.[1] In our 25-year experience working in a multidisciplinary team we have witnessed an evolution in the treatment approach to localized. While radical cystectomy (RC) has remained the standard of care, multimodality treatment with maximal endoscopic tumor resection followed by chemoradiation is an acceptable alternative for those who refuse or are unsuitable for RC. Furthermore, cisplatin-based neoadjuvant chemotherapy (NAC) is now considered standard of care for appropriate patients and the perioperative use of checkpoint inhibitors is being investigated.[2,3] Coordination between urologists, medical oncologists, and radiation oncologists to offer and administer these therapies in a timely manner is therefore imperative. We herein report on our experience treating patients with muscle invasive bladder cancer (MIBC) as we celebrate the 25th anniversary of our multidisciplinary genitourinary clinic at the Sidney Kimmel Cancer Center.

Materials and methods

In accordance with our institutional standard of care, patients with MIBC who are considering treatment are scheduled for evaluation in our MDC. Patient pathology, radiographic and clinical data are discussed at a weekly multidisciplinary tumor board, followed by a single patient encounter session with all providers on the same day. A retrospective review of patients referred to the MDC with a bladder cancer diagnosis was used to identify patients within our Cancer Registry with clinical stage II and IIIA (cT2-4, cN0-1, M0) bladder cancer who were evaluated between January 2016 and September 2019. All patients with urothelial carcinoma were included. Variant histology were cases excluded unless they were a component of a predominantly urothelial carcinoma. Patients who had undergone definitive treatment for MIBC prior to MDC evaluation and patients on clinical trials were also excluded. The electronic medical record was queried for demographics, staging studies, surgical and biopsy pathology as well as outcomes data for if and which NAT was used, if clinical trial participation occurred and survival data. Progression was defined as recurrent cT2 disease following chemoradiation or development of new nodal or metastatic disease following treatment with chemoradiation or cystectomy.

Survival outcomes were compared to the NCI Surveillance, Epidemiology, and End Results (SEER) Program for 2018. SEER-18, Nov 2019 submission was queried, representing 28% of the United States population.[4] Site code "Urinary Bladder", histology recode-broad groupings "8120-8139: transitional cell papillomas and carcinomas," and year of diagnosis "2015-2017" were used to identify cases. Cases were then further selected for patients with T2-4, N0-1, M0 (stage II and IIIA) disease. When only clinical staging was available, cN2/3 patients were excluded, however when pathological designation was present, pN2/3 patients were included to account for those upstaged at time of RC.

Descriptive data and Kaplan-Meier survival curves were derived using SPSS v. 25. Means were derived for continuous variables. Log rank test was used to compare overall survival and cancer specific survival curves. Chi-square analysis was used to compare RC rates and qualitative demographical data. This study was approved by the Thomas Jefferson institutional review board (# 19D.775) and a waiver of informed consent was granted. Patient satisfaction was analyzed from a simple blinded six-item questionnaire.

Results

We identified a representative sampling of 91 patients fitting our inclusion criteria treated at the MDC between January 2016 and September 2019 and with 8675 similar patients from SEER. Demographic information is listed in Table 1 and demonstrates a mean age of 72.1 yrs. Mean age was unable to be determined for SEER as individual ages were not recorded for patients older than 85. Our proportion of male and female patients does not differ significantly from SEER ($p = 0.309$), however there are significantly more patients who do not identify as Caucasian ($p = 0.001$) seen at our MDC.

Staging and treatment information for patients treated at our MDC is noted in Tables 2 and 3 respectively. The majority of patients had T2N0M0 disease, followed by T3N0M0 disease, which was similar to the SEER derived patients. Of the 64 patients who were considered candidates for cystectomy, 46

TABLE 1. **Demographics of MDC vs. SEER patients**

		MDC	SEER
Age at first appointment (mean)		72.1 years (43-90 years)	**
Sex			
(p = 0.309)	Male	64/91 (70.3%)	6504/8675 (74.9%)
	Female	27 (29.7%)	2171 (25%)
Race*			
(p =< 0.001)	African American	12 (13.2%)	616/8675 (7.1%)
	Caucasian	70 (76.9%)	7577 (87.3%)
	Asian/Indian	3 (3.3%)	405 (4.7%)
	Other/unknown	6 (6.6%)	77 (1%)

*statistically significant; **unable to calculate due to limitations of SEER database
MDC = multidisciplinary center; SEER = Surveillance, Epidemiology, and End Results

TABLE 2. **Staging and histological variations**

Stage (MDC) n = 91	
cT2N0M0	54 (59.3%)
cT2N1M0	3 (3.3%)
cT3N0M0	28 (30.8%)
cT4N0M0	4 (4.4%)
cT4N1M0	2 (2.2%)
Stage (SEER)** n = 8675	
T2N0M0	5885 (67.8%)
T2N1M0	220 (2.5%)
T3N0M0	1150 (13.3%)
T3N1M0	215 (2.5%)
T4N0M0	756 (8.7%)
T4N1M0	92 (1.1%)
T2(p)N2-3M0	48 (0.6%)
T3(p)N2-3M0	181 (2.1%)
T4(p)N2-3M0	128 (1.5%)
Variant histology (MDC) n = 91	
None	52 (57.1%)
Squamous	18 (19.8%)
Micropapillary	4 (4.4%)
Sarcomatoid	4 (4.4%)
Nested	2 (2.2%)
Plasmacytoid	2 (2.2%)
Neuroendocrine/ small cell	6 (6.6%)
Rhabdoid	1 (1.1%)
Glandular	2 (2.2%)

**includes clinical and pathological staging
MDC = multidisciplinary center; SEER = Surveillance, Epidemiology, and End Results

TABLE 3. **Treatment information for MDC patients**

Primary treatment n = 91	
Radical cystectomy	60 (65.9%)
Chemoradiation	19 (20.9%)
Supportive care/ transurethral resection only	5 (5.5%)
NAC only	3 (3.3%)
Aborted intraoperative cystectomy	1 (1.1%)
Other	3 (3.3)%
Neoadjuvant regimen n = 46	
ddMVAC**	17 (36.9%)
Gemcitabine/cisplatin	12 (26.1%)
Cisplatin/etoposide	3 (6.5%)
Gemcitabine/pembrolizumab	2 (4.3%)
Gemcitabine/cisplatin/ pembrolizumab	8 (17.4%)
Carboplatin/etoposide	1 (2.2%)
Intravesical gemcitabine/ systemic vivolumab	1 (2.2%)
Pembrolizumab	2 (4.3%)
Reason for NAT discontinuation	
Sepsis/infection	4 (11.1%)
Progression of disease	3 (6.5%)
Renal failure	3 (6.5%)
Poor tolerance	2 (4.3%)
Clinical trial closure/device removed	1 (2.2%)
Death	1 (2.2%)

**dose dense methotrexate, vincristine, adriamycin and cisplatin
MDC = multidisciplinary center; NAC = neoadjuvant chemotherapy; NAT = neoadjuvant therapy

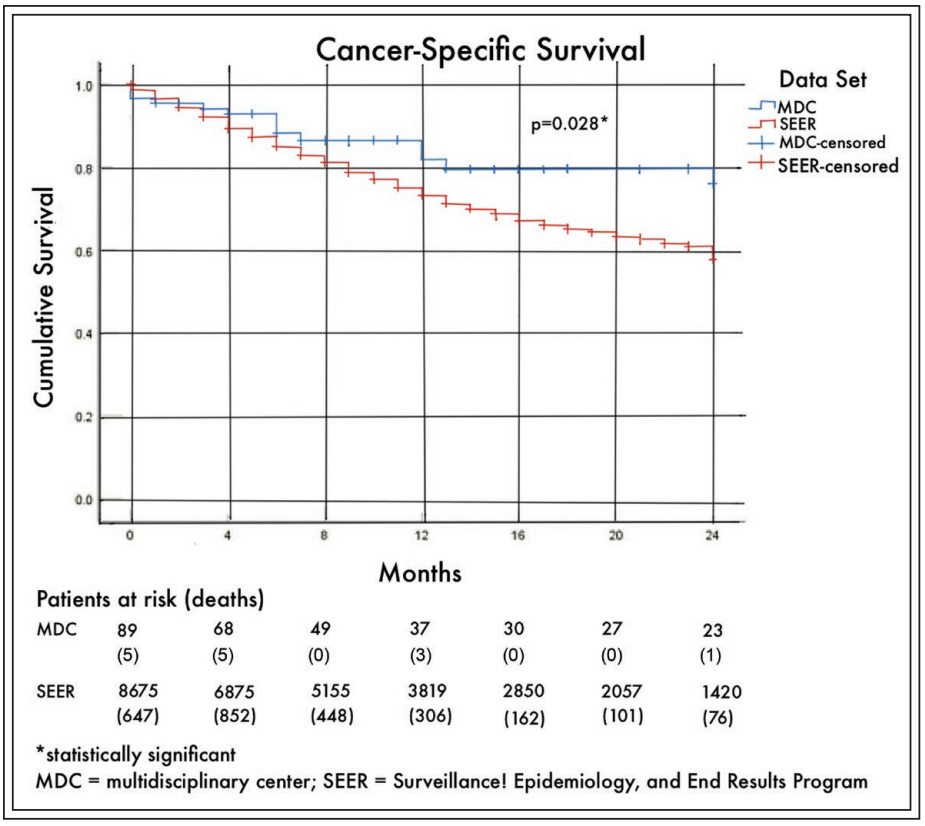

Figure 1. Cancer-specific survival (CSS) of MDC vs. SEER patients.

(71.8%) received NAT through MDC. Neoadjuvant therapy (NAT) consisted primarily of chemotherapy (n = 33/46, 71.7%) however immune checkpoint inhibition (ICI) monotherapy or combination chemotherapy and ICI were also utilized. Patients not treated with chemotherapy were typically cisplatin ineligible and treated as part of a clinical trial or at the discretion of the MDC team. The rate of clinical trial participation in our MDC was 12.1%. Three patients received NAC, but did not undergo cystectomy; one patient declined further intervention and two developed metastatic disease prior to surgery.

Cystectomy was performed in 65.9% of MDC patients compared to 37.8% (3278/8675) of matched cohort from SEER database (p =< 0.001). Nineteen of our patients were down staged at time of RC, all of which had received NAT. The ypT0N0 rate for MDC patients who completed therapy was 5/34 (14.7%). Downstaging after RC (</= pT1) was seen in 14/34 (41.1%) patients who completed therapy.

Median follow up was 8 months (range: 0-50). Of all patients, 22 (24.2%) experienced disease progression. There were 32 deaths (35.2%) in our cohort, 14 of which were cancer related (15.4%). Compared to the matched cohort from SEER, cancer-specific survival (CSS) was improved (mean 20.4 vs. 18.3 months, p = 0.028), Figure 1.

Discussion

The complexity of modern treatment for patients with MIBC mandates coordination between urologic, radiation, and medical oncologists. Multidisciplinary clinics have emerged as a strategy to simplify the process for patients and provide a forum for clinicians of different disciplines to evaluate and discuss patient care in real-time. Both RC and NAC have been underutilized on a national level, despite being a well-established standard of care. Previous national database analyses have reported RC rates of 18.9%-42.9%, which is comparable to the 37.8% RC utilization from this study's SEER cohort.[5,6] Our rates of RC utilization were significantly higher at 65.9%, ascribing to a better adherence to clinical guidelines.

While direct comparison of RC rates was possible with these data sets, the ability to compare other treatment information was otherwise limited. SEER does not collect information on NAT usage and direct analysis of radiation and chemotherapy as primary treatment was not performed due to questions regarding the sensitivity of this data within SEER.[7] Despite these limitations, it should be noted that systemic NAT utilization in this study is notably higher than previous published National Cancer Database rates of 20.8%-40%.[8,9] Recently, single institution data from Almassi et al reported a NAC of 57% from 2010-2015. From these results, and previous studies, it was theorized that this represents the upper limit of utilization due to cisplatin eligibility within the real-world population.[10] Our cisplatin-based NAT utilization slightly exceeds this, but is comparable, at 62.5% (40/64). In those patients who were ineligible for cisplatin-based NAT, the MDC approach allowed for clinical trial enrollment and early utilization of neoadjuvant ICI monotherapy following the reporting of PURE-1.[11] This increased our NAT usage to a total of 71.8%.

Progression of disease was seen in 24.2% of patients by 24 months. Of note, no patient with follow up longer than 24 months experienced disease progression. While it was not possible to directly compare this to SEER data, this number is not unexpected based on the typical pattern of early recurrence seen in bladder cancer. Long term disease-free survival after cystectomy has been quoted at 30%-80% depending on stage of disease, with the majority of recurrences occurring within the first 2-3 years.[10,12,13]

While overall survival did not differ between MDC patients and SEER database patients, there was a significant difference seen in CSS. Given the much higher rate of RC in the MDC cohort, and the known survival benefit of NAC, these results suggest that adherence to clinical guidelines observed may be an advantage our MDC model has over traditional siloed practice.[14]

Limitations of this study are related primarily to its retrospective nature. Although every effort was made to characterize long term follow up for patients, this was not always possible. Some patients ultimately sought definitive treatment at outside institutions after their MDC evaluation, but were still included in analysis if treatment information was available in the record. Limitations inherent to the reliability and variability of SEER data are also present. Prior to 2016, clinical and pathological staging was not differentiated within the SEER database. Once this designation was introduced, staging was changed to report either clinical or pathological staging, but not both. If a patient was down staged after NAC, only the highest clinical staging was reported in SEER, leading to a wide variety in reporting. Therefore, direct comparison of staging in this study was not possible. It should also be noted there was a high number of left-sided censorship for survival data in both the MDC and SEER cohorts, and therefore this data must be interpreted with caution.

Lastly, our cohort was heterogeneous in staging and histology. While most patients had cT2 disease, a large proportion had cT3/cT4 disease on staging and 5 patients had evidence of cN1 disease. Furthermore, the rate of identification of variant histology was high at 42.9%. This may account for the lower ypT0 rate as compared to historical data.[14,15] Data on the outcomes of patients with histological variants is mixed, but depending on the specific variant, tends to be similar or inferior to pure urothelial carcinoma.[16] It is important to note that the recent data from Almassi et al, with similar variant histology rates of 41%, also reported a lower than previously reported ypT0 rate of 22%.[10] Our study in conjunction with this data suggests that in high volume centers where variant histology is common, ypT0 rates may be lower than previously reported. While trimodal therapy with the goal of bladder preservation is becoming common in the management of MIBC, in the time period of this study no patients elected this approach.

Conclusions

A MDC model allows for the timely coordination amongst the disciplines necessary to provide timely, optimal care to patients with MIBC. This approach confers high rates of both NAT and RC utilization which appears to improve cancer specific survival over a cohort of patients found in SEER. Our study, in conjunction with others, suggests real-world benchmarks for NAT utilization.

Improvements in molecular characterization of bladder cancer predictive and prognostic biomarkers as well as the incorporation of new effective therapies with a better toxicity profile, such as immunotherapy, is changing the treatment paradigm for MIBC.[17]

The MDC model should be considered the optimal management model in order to provide the best care to patients with MIBC as these newer therapies become available. □

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