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Defining the Potential of Neoadjuvant Chemotherapy Utilization as a Quality Indicator for Bladder Cancer Care

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Abstract

Purpose—Despite known survival benefits, overall use of neoadjuvant chemotherapy before cystectomy is low, raising concerns about quality of care. However, not all cystectomy patients are the eligible for this therapy. We sought to establish the maximum proportion of patients expected to receive neoadjuvant chemotherapy if all eligible patients received consultation with medical oncology.

Materials and Methods—From institutional data (January 2010 through December 2012) we identified patients treated with radical cystectomy for cancer arising from the urinary bladder (n = 215). After excluding patients not eligible for neoadjuvant chemotherapy, we fit models assessing patient disease and health factors affecting referral to medical oncology and receipt of neoadjuvant chemotherapy. Expected use of chemotherapy was then determined for increasingly broad groups of cystectomy patients after controlling for factors precluding use of neoadjuvant chemotherapy.

Results—Of 215 patients identified, 127 (59%) were eligible for neoadjuvant chemotherapy. After additional accounting for patient factors (patient refusal, health status, and poor renal function), maximum receipt of neoadjuvant chemotherapy increased from 42% to 71% as more restrictive definitions for the eligible patient cohort were used.

Conclusions—Substantial variability exists in the proportion of patients eligible for neoadjuvant chemotherapy based on the population identified. While there is substantial underuse of neoadjuvant chemotherapy, development of quality metrics for this essential therapy will be dependent on correct identification of the cystectomy population being assessed. Even with referral of all appropriate patients for medical oncology evaluation, utilization of chemotherapy would likely not exceed 50% of patients in nationally representative cystectomy data.

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Keywords

chemotherapy; neoadjuvant therapy; eligibility determination; bladder cancer; quality indicator

In 2013, it is estimated that 72,570 new cases of bladder cancer will be diagnosed and 15,210 patients will die of their disease¹. Approximately one-third of patients diagnosed with bladder cancer will have T2 N0 M0 or greater disease. The overall survival of patients with localized muscle-invasive disease treated with cystectomy without neoadjuvant chemotherapy (NAC) is 62% and 50% at 5 and 10 years respectively². However, strong evidence supports an overall survival advantage (5% absolute improvement in overall survival) for the use of neoadjuvant chemotherapy [ENREF 3](#)³. Consequently, established published guidelines recommend the use of cisplatin-based NAC for patients with locally advanced urothelial cancer of the bladder^{4, 5}. Despite the evidence and recommendations, contemporary utilization of NAC remains low, ranging from 1.2% to 17% in both national and institutional data sets⁶⁻⁸.

The true proportion of patients eligible for NAC is currently poorly defined. As such, efforts to establish use of NAC as a quality metric, defined as a tool to help measure or quantify healthcare processes, outcomes, patient perceptions, and organizational structure⁹, are limited. In order to establish NAC as a quality measure for patients undergoing radical cystectomy, we must also understand the barriers to its receipt. Therefore, we sought to identify disease and patient specific factors associated with underuse of NAC. To assist in development of NAC as a quality indicator, we then determined the maximum proportion of patients eligible for NAC prior to radical cystectomy.

Materials and Methods

Institutional Review Board approval from the Washington University Human Subjects Review board was obtained prior to conducting this study. We performed a retrospective cohort study that identified all patients at our institution who underwent radical cystectomy at Barnes-Jewish Hospital/Washington University in Saint Louis for cancer arising from the urinary bladder from January 2010 through December 2012. Patient information was obtained via review of medical data in the electronic medical record system. The clinical classification was determined from the pre- cystectomy histology and classification of the bladder cancer. Histological diagnosis was determined by most recent transurethral resection of the bladder tumor prior to radical cystectomy or prior to chemotherapy in patients who received pre-operative chemotherapy. All histological samples were read or re-reviewed at our institution. Evaluation for extent of disease (lymph nodes greater than 1 cm in size, soft tissue metastasis, and bone metastasis) was performed by preoperative cross-sectional imaging.

Primary chemotherapy vs. Neoadjuvant chemotherapy

Primary chemotherapy was defined as treatment for metastatic disease (based on clinical staging), followed by a salvage cystectomy. In contrast, NAC was aligned to the inclusion

criteria in the SWOG study¹⁰ (pre-surgical treatment with chemotherapy for patients with clinical tumor-node- metastasis (TNM) stage T2N0M0 to T4aN0M0).

Identification of cohorts

First, we identified the population of patients who were candidates for chemotherapy prior to surgical intervention. Disease specific exclusions from pre-operative chemotherapy included: 1) patients with clinical classification of diagnosis not eligible for chemotherapy (CIS, Ta, and T1) and 2) primary histology not responsive to chemotherapy (squamous, adenocarcinoma, sarcoma, and large cell). Remaining patients, including those with small cell histology, patients with metastatic urothelial disease at presentation and those with urothelial histology, including mixed variants, of clinical classification T2 that is loco-regionalized, were considered eligible for pre-operative chemotherapy.

Second, based on eligibility for chemotherapy and clinical classification, we classified patients into four nested groups of patients who received cystectomy: 1) patients eligible for NAC, 2) patients with primary urothelial cancer eligible for pre-operative chemotherapy (clinical classification T2) including primary or NAC, 3) patients with primary urothelial cancer, and 4) patients with cancer arising from the bladder.

Identification of the patient-level barriers to neoadjuvant chemotherapy

Patients eligible for NAC were assessed for referral to medical oncology and subsequent receipt of cisplatin- and carboplatin-based NAC. We evaluated the medical oncologist's notes to elucidate the barriers to the receipt of NAC. Patient-level factors identified included patient refusal of chemotherapy, symptoms preventing delay in cystectomy for administration of chemotherapy, the medical oncologist's evaluation of the patient's overall medical status, and renal function assessment (based on the Modification of Diet in Renal Disease formula). Creatinine value was recorded at the time of medical decision making, either by urology visit or, if referred, by the medical oncology visit. At our institution, a creatinine clearance ≥ 45 ml/min was used as an approximate cutoff for receipt of cisplatin. We then grouped the reasons for lack of chemotherapy as patient preference or patient symptoms/medical status in our analysis.

Determination of eligibility for neoadjuvant chemotherapy

Using the number of patients referred to medical oncology that did and did not receive NAC as our starting point, we calculated the proportion of patients eligible for NAC who would have received treatment (cisplatin- and carboplatin-based) had all patients received referral to medical oncology. We then determined the maximum proportion of patients in each of the four groups of cystectomy patients who would receive chemotherapy were referral to medical oncology provided.

Statistical Analysis

Logistic regression analyses examining patient age, race, sex, American Society of Anesthesiologists (ASA) physical status classification system, and creatinine clearance were performed to identify the factors acting as barriers to referral to medical oncology by

urologists as well as the barriers to the receipt of chemotherapy once patients were referred to medical oncology. Analysis was performed using R version 2.15.1 statistical software.

Results

215 patients receiving radical cystectomy patients were identified based on our inclusion criteria. A subset of 127 was eligible to receive NAC (Table 1). Almost 75% of our patients were male. The median age of our patients was 69 (min: 38, max: 89). Most patients had adequate renal function with only 10% of the entire cohort with a CrCl < 45 ml/min.

Identification of disease-specific cohorts

Figure 1 demonstrates the breakdown of patients eligible for chemotherapy based on histology, classification of disease and extent of disease. 127 of 215 (59%) of the entire cohort were eligible for NAC based on having at least T2 urothelial cancer localized to the bladder. Figure 2 demonstrates the cohort in four disease-specific groups and how current population-based and institutional data sets can identify them.

Identification of the patient-level barriers to neoadjuvant chemotherapy

With identification of patients eligible for NAC, 61 (48%) were not referred to medical oncology for assessment, thus acting as a rate limiting step in the provision of chemotherapy (Figure 3). There were no significant differences among the patients eligible for chemotherapy that were, or were not, referred to medical oncology (Table 2). The lack of difference between groups referred and not referred to medical oncology allowed greater justification to extrapolate our results to the entire cohort of patients eligible for chemotherapy.

Barriers to receipt of neoadjuvant chemotherapy after referral to medical

oncology—Among the 66 patients referred to medical oncology, 19 (29%) did not receive NAC. Of these patients 11 did not receive treatment due to patient preference and 8 did not receive treatment due to their overall health status, medical comorbidities or symptoms from their disease. Therefore, of the patients referred to medical oncology, 17% did not receive chemotherapy due to patient preference and 12% did not receive treatment due to medical status. Only age over 80 was associated with decreased use of NAC, and no patients with creatinine clearance less than 45 ml/min received cisplatin-based NAC (Table 2).

By applying the patient factors precluding NAC and the expected proportion of patients who could receive NAC to our patient population, we developed the distributions of patients shown in Figure 4a-d. Figure 4a demonstrates the projected maximum utilization of NAC for patients in the cohort who met clinical requirements (urothelial histology of clinical classification T2) for treatment. After accounting for patient refusal and medical factors, we found that 71% of patients (shown by the addition of the percentages in the red shaded areas in Figure 4) would have received any NAC, and 61% (percentage in the dark-red shaded area in Figure 4) would have received cisplatin-based chemotherapy if all patients receive referral to medical oncology. In figure 4b, patients with metastatic urothelial cancer were added to the patient population (dark-orange shaded area), resulting in decreased use of

NAC (61% overall and 52% cisplatin-based). Figure 4c examines all clinical classifications of primary urothelial cancer of the bladder, with overall and cisplatin-based NAC decreasing to 46% and 39% respectively. Finally, Figure 4d includes all patients undergoing radical cystectomy for cancer arising from the bladder. In this full patient population undergoing cystectomy, overall and cisplatin-based NAC use would decrease to 42% and 36% respectively. An additional 10% to 14% of patients would receive primary chemotherapy for metastatic disease and small cell histology at presentation for therapy.

Discussion

Depending on the population of cystectomy patients identified, between 56% and 71% of patients could be expected to receive chemotherapy before surgery. Maximum use of NAC would be between 42% and 71% of cystectomy patients. As in many studies, the major barrier to receipt of NAC was referral to medical oncology.

Evaluation of the referral patterns to medical oncology has been reviewed for other solid tumors. Reported rates of referral to medical oncology for non-urologic solid tumors range from 60- 70%¹¹⁻¹³. It is not as clear what the referral patterns to medical oncology are for patients with appropriate classification urothelial cancer of the bladder. Preoperative evaluation by a medical oncologist has been suggested as a quality indicator for patients undergoing cystectomy¹⁴. However, given the low incidence of utilization of NAC, it is likely most patients are not being referred for medical oncology evaluation. Similar to studies in the adjuvant setting¹⁵, our findings for barriers to the receipt of neoadjuvant cisplatin-based chemotherapy suggest the only patient factor precluding referral of appropriately classified urothelial cancer patients to medical oncology should be impaired renal function.

With the knowledge of the factors acting as barriers to the receipt of treatment that changes patient outcomes, we may better establish use of NAC as a quality metric.¹⁶ Evidence from multiple studies suggests the implementation of quality metrics do improve health care outcomes¹⁷⁻¹⁹, however, no quality metrics have been accepted for bladder cancer care. Cooperberg et al proposed quality measures for bladder cancer include avoiding delay in time to cystectomy beyond 3 months of diagnosis, performing an adequate lymphadenectomy as measured by nodal yield, and offering orthotopic diversion when appropriate²⁰. Given its proven benefits to overall survival, use of NAC would appear to be a suitable candidate for a quality metric. With the current low utilization of this therapy, it is important to be able to track the trends in utilization with current national patient databases and to accurately assess receipt of therapy.

The establishment and tracking of quality metrics in urologic oncology has lagged behind those of other surgical oncologic specialties. An excellent example of how quality metrics have been implemented and monitored involves breast cancer. The National Consortium of Breast Centers established 37 quality measures that a participating center may utilize and subsequently upload usage data to a central interactive website to allow for comparison among other sites. The goal of this centralized data organization was to increase the adoption of quality care and provide designations for centers as a quality breast center of

excellence (for increased public recognition). Collaborative efforts such as this may serve to improve outcomes for patients with bladder cancer.

Receipt of NAC has a potential role as a quality metric in urologic oncology. Figure 4 demonstrates how the eligibility for NAC varies depending on how the cohort is identified. Depending on the database utilized to define the cystectomy population, the percentage of patients eligible for NAC may change. Most administrative datasets lack sufficient information regarding tumor characteristics to provide detail regarding eligibility for NAC versus primary chemotherapy, or even to determine if chemotherapy is needed for any particular patient. **Due to use of pathologic staging, even SEER-Medicare data**, with accurate ascertainment of tumor status and the ability to determine chemotherapy use, cannot reliably differentiate patients who received primary chemotherapy and were down staged from patients who received NAC. Such limitations make institutional data required to accurately track NAC utilization. However, our results provide utilization rates that could be applied to administrative data. Using our results, if all patients were referred for assessment by medical oncology at appropriate clinical classifications, we would expect maximum chemotherapy utilization to be around 50% of patients in nationally representative data.

We acknowledge that there are inherent limitations of a retrospective institutional evaluation. The first limitation was that our population cohort was developed from single tertiary care center and limited to patients undergoing cystectomy. As such, patients may have higher grade and more extensive disease as well as a higher percentage of variant histologies of bladder cancer. However, due to these referral patterns, it is likely our projected eligibility for NAC is a conservative estimate. Related to limiting our cohort to cystectomy patients, we may have a potential for a selection bias as some patients may not be able to undergo cystectomy after NAC. Per the findings in the SWOG study¹⁰, NAC did not adversely affect a patient's chance of undergoing cystectomy. We also used a creatinine clearance of 45 ml/min as a cutoff for adequate renal function for the administration of cisplatin. This number is lower than other studies^{15, 21} ENREF 23 using 60 ml/min as a cutoff. Therefore, our medical oncologists' tolerance for giving cisplatin-based chemotherapy for a lower renal function may overestimate the eligibility for intervention at other centers, especially if patients go to cystectomy instead of receiving carboplatin based therapy. Additionally, we also do not suggest that the percentages we determined for use of chemotherapy are to be used as a quality measure. However, a lower percentage may be established as a benchmark for improvement, and our results provide guidance on tracking utilization of NAC in nationally representative data. Lastly, some question which patients truly benefit from NAC, implying that it should be reserved for patients with T3 or greater disease^{22, 23}.

Conclusion

Even with referral of all patients for medical oncology evaluation, utilization of NAC by all eligible patients prior to cystectomy is not possible. Our results suggest a maximum utilization in nationally representative cystectomy data would be 50% of patients even if all patients received referral to medical oncology when appropriate. Maximum use of NAC is influenced by patient disease characteristics, patient refusal of therapy, and medical

oncologists' evaluation of patient-level factors. However, the substantial underuse of chemotherapy prior to cystectomy illustrates the need for a benchmark level of utilization as a quality metric for bladder cancer care.

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References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin*. 2013; 63:11. [PubMed: 23335087]
2. Madersbacher S, Hochreiter W, Burkhard F, et al. Radical cystectomy for bladder cancer today--a homogeneous series without neoadjuvant therapy. *J Clin Oncol*. 2003; 21:690. [PubMed: 12586807]
3. Advanced Bladder Cancer Meta-analysis, C. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. *Eur Urol*. 2005; 48:202. [PubMed: 15939524]
4. Stenzl A, Cowan NC, De Santis M, et al. The updated EAU guidelines on muscle-invasive and metastatic bladder cancer. *Eur Urol*. 2009; 55:815. [PubMed: 19157687]
5. NCCN Clinical Practice Guidelines in Oncology. Bladder Cancer. National Comprehensive Cancer Network; 2013.
6. David KA, Milowsky MI, Ritchey J, et al. Low incidence of perioperative chemotherapy for stage III bladder cancer 1998 to 2003: a report from the National Cancer Data Base. *J Urol*. 2007; 178:451. [PubMed: 17561135]
7. Raj GV, Karavadia S, Schlomer B, et al. Contemporary use of perioperative cisplatin-based chemotherapy in patients with muscle-invasive bladder cancer. *Cancer*. 2011; 117:276. [PubMed: 20830767]
8. Porter MP, Kerrigan MC, Donato BM, et al. Patterns of use of systemic chemotherapy for Medicare beneficiaries with urothelial bladder cancer. *Urol Oncol*. 2011; 29:252. [PubMed: 19450992]
9. Services, C. f. M. M. Quality Measures. 2013:2013.
10. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med*. 2003; 349:859. [PubMed: 12944571]
11. Oliveria SA, Yood MU, Campbell UB, et al. Treatment and referral patterns for colorectal cancer. *Med Care*. 2004; 42:901. [PubMed: 15319616]
12. Luo R, Giordano SH, Freeman JL, et al. Referral to medical oncology: a crucial step in the treatment of older patients with stage III colon cancer. *Oncologist*. 2006; 11:1025. [PubMed: 17030645]
13. Earle CC, Neumann PJ, Gelber RD, et al. Impact of referral patterns on the use of chemotherapy for lung cancer. *J Clin Oncol*. 2002; 20:1786. [PubMed: 11919235]
14. Svatek RS, Rosenberg JE, Galsky MD, et al. Summary of the 6th annual bladder cancer think tank: New directions in urologic research. *Urol Oncol*. 2013; 31:968. [PubMed: 22300756]
15. Dash A, Galsky MD, Vickers AJ, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. *Cancer*. 2006; 107:506. [PubMed: 16773629]
16. Lohr KN, Schroeder SA. A strategy for quality assurance in Medicare. *N Engl J Med*. 1990; 322:707. [PubMed: 2406600]
17. Jha AK, Orav EJ, Li Z, et al. The inverse relationship between mortality rates and performance in the Hospital Quality Alliance measures. *Health Aff (Millwood)*. 2007; 26:1104. [PubMed: 17630453]

18. Cheng SH, Wang CJ, Lin JL, et al. Adherence to quality indicators and survival in patients with breast cancer. *Med Care*. 2009; 47:217. [PubMed: 19169123]
19. Hall BL, Hamilton BH, Richards K, et al. Does surgical quality improve in the American College of Surgeons National Surgical Quality Improvement Program: an evaluation of all participating hospitals. *Ann Surg*. 2009; 250:363. [PubMed: 19644350]
20. Cooperberg MR, Porter MP, Konety BR. Candidate quality of care indicators for localized bladder cancer. *Urol Oncol*. 2009; 27:435. [PubMed: 19573775]
21. Canter D, Viterbo R, Kutikov A, et al. Baseline renal function status limits patient eligibility to receive perioperative chemotherapy for invasive bladder cancer and is minimally affected by radical cystectomy. *Urology*. 2011; 77:160. [PubMed: 20709369]
22. Niegisch G, Lorch A, Droller MJ, et al. Neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer: which patients benefit? *Eur Urol*. 2013; 64:355. [PubMed: 23773558]
23. Culp SH, Dickstein RJ, Grossman HB, et al. Refining Patient Selection for Neoadjuvant Chemotherapy before Radical Cystectomy. *J Urol*. 2014; 191:40. [PubMed: 23911605]

Figure 1.
Patients who should not get chemotherapy versus those who should

Figure 2. Populations of patients receiving radical cystectomy. Each of the four groups is nested inside the prior larger group, and the relationship to available data sets to address use of chemotherapy is shown.

Figure 3.

Flowchart for actual number of cystectomies for urothelial cancer eligible for neoadjuvant chemotherapy

Figure 4. Additions of red shaded areas will determine utilization of neoadjuvant chemotherapy for patients for their respective four established cohort groups. Additions of red and orange shaded areas will determine maximum utilization of patients receiving neoadjuvant and primary chemotherapy for their respective cohorts

Table 1

Characteristic Information for the Identified Cohorts

	Original Cohort N (%)	Eligible for Neoadjuvant Chemotherapy N (%)
Total Patients	215	127
Sex		
Male	171 (79.5)	102 (80.3)
Female	44 (20.5)	25 (19.7)
Race		
White	205 (95.3)	118 (92.9)
Other	10 (4.7)	9 (7.1)
Age		
<60	48 (22.3)	25 (19.7)
60-70	64 (29.8)	35 (27.6)
70-80	75 (34.9)	48 (37.8)
80+	28 (13.0)	19 (15.0)
CrCl	(1 missing)	
<45	23 (10.7)	14 (11.0)
≥45	191 (88.8)	113 (89.0)
ASA		
2	79 (36.7)	44 (34.6)
3	128 (59.5)	80 (63.0)
4	8 (3.7)	3 (2.4)
Final Clinical Classification		
CIS	12 (5.6)	6 (4.7)
T0	35 (16.2)	23 (18.1)
Ta-Low	4 (1.9)	0 (0.0)
Ta-High	8 (3.7)	1 (0.8)
T1-High	13 (6.0)	2 (1.6)
T2	38 (17.7)	22 (17.3)
T3a	16 (7.4)	11 (8.7)
T3b	39 (18.1)	29 (22.8)
T4a	28 (13.0)	19 (15.0)
T4b	22 (10.2)	14 (11.0)

Table 2

Factors influencing both referral to medical oncology as well as receipt of neoadjuvant chemotherapy among patients referred to medical oncology

	Number Referred to Medical Oncology		P-value	Adjusted Model P-value		Number Receiving Neoadjuvant Chemotherapy		P-value	Adjusted Model P-value		Number Receiving Cisplatin-Based Neoadjuvant Chemotherapy		P-value	Adjusted Model P-value	
	No	Yes		No	Yes	No	Yes		No	Yes	No	Yes		No	Yes
Gender															
Male	49	53	0.997			15	38	0.860			19	34	0.234		0.587
Female	12	13				4	9				7	6			
Age															
<80	49	59	0.152			14	45	0.008			21	38	0.103		0.057
80+	12	7				5	2				5	2			
CrCl															
<45	5	8	0.466			5	3	0.038			8	0	0.002		***
>45	56	58				14	44				18	40			
ASA															
2	20	24	0.672			6	18	0.607			7	17	0.199		0.247
3 or 4	41	42				13	29				19	23			

*** CrCl was excluded from this model as no patients with CrCl < 45 received cisplatin-based chemotherapy