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

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

**Materials and Methods:** From institutional data (January 2010 through December 2012) we identified 215 patients treated with radical cystectomy for bladder cancer. 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 patients treated with cystectomy after controlling for factors precluding the use of neoadjuvant chemotherapy.

**Results:** Of the 215 patients identified 127 (59%) were eligible for neoadjuvant chemotherapy. After additional consideration of 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, the development of quality metrics for this essential therapy depends on correct identification of the cystectomy population being assessed. Even with referral of all appropriate patients for medical oncology evaluation, use of chemotherapy would likely not exceed 50% of patients in nationally representative cystectomy data.

**Key Words:** drug therapy; neoadjuvant therapy; eligibility determination; urinary bladder neoplasms; quality indicators, health care

**Abbreviations and Acronyms**

ASA® = American Society of Anesthesiologists®

CIS = carcinoma in situ

CrCl = creatinine clearance

NAC = neoadjuvant chemotherapy

Accepted for publication January 24, 2014.

Supported by the Washington University Institute of Clinical and Translational Sciences Grants UL1 TR000448 and KL2 TR000450 from the National Center for Advancing Translational Sciences. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Study received institutional review board approval.

Nothing to disclose.

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In 2013 it was estimated that 72,570 new cases of bladder cancer would be diagnosed and 15,210 patients would die of their disease.[1] Approximately a third of patients diagnosed with bladder cancer would have T2 N0 M0 or greater disease. The overall survival of patients with localized muscle invasive disease treated with cystectomy without neoadjuvant chemotherapy is 62% and 50% at 5 and 10 years, respectively.[2] However, strong evidence supports an overall survival advantage (5% absolute

0022-5347/14/1921-0043/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2014.01.098
Vol. 192, 43-49, July 2014
Printed in U.S.A.

improvement in overall survival) with the use of neoadjuvant chemotherapy.[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 use of NAC remains low, ranging from 1.2% to 17% in national and institutional data sets.[6–8]

The true proportion of patients eligible for NAC is currently poorly defined. As such, efforts to establish the use of NAC as a quality metric, defined as a tool to help measure or quantify health care processes, outcomes, patient perceptions and organizational structure,[9] are limited. To establish NAC as a quality measure for patients undergoing radical cystectomy, we must also understand the barriers to its receipt. Therefore, we identified 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 before radical cystectomy.

## MATERIALS AND METHODS

Institutional review board approval from the Washington University Human Subjects Review board was obtained before 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 St. Louis for cancer arising from the 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 bladder cancer. Histological diagnosis was determined by most recent transurethral bladder tumor resection before radical cystectomy or before chemotherapy in patients who received preoperative chemotherapy. All histological samples were read or rereviewed at our institution. Evaluation for extent of disease (lymph nodes larger than 1 cm, soft tissue metastasis and bone metastasis) was performed using preoperative cross-sectional imaging.

### Primary vs Neoadjuvant Chemotherapy

Primary chemotherapy was defined as treatment for metastatic disease (based on clinical staging) followed by salvage cystectomy. In contrast, NAC was aligned with the inclusion criteria in the SWOG (Southwest Oncology Group) study (preoperative treatment with chemotherapy for patients with clinical TNM stage T2N0M0 to T4aN0M0).[10]

### Identification of Cohorts

We identified the population of patients who were candidates for chemotherapy before surgical intervention. Disease specific exclusions from preoperative chemotherapy were 1) 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). The remaining patients, including those with small cell histology, metastatic urothelial disease at presentation and urothelial histology, including mixed variants, of clinical classification T2 or greater that is locoregionalized, were considered eligible for preoperative chemotherapy.

In addition, based on eligibility for chemotherapy and clinical classification, we organized the population into 4 nested groups of patients who received cystectomy, including 1) patients eligible for NAC, 2) patients with primary urothelial cancer eligible for preoperative chemotherapy (clinical classification T2 or greater) including primary or NAC, 3) patients with primary urothelial cancer and 4) patients with cancer arising from the bladder.

### Identification of Patient Level Barriers to NAC

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. The patient level factors identified included patient refusal of chemotherapy, symptoms preventing delay in cystectomy for administration of chemotherapy, medical oncologist evaluation of patient overall medical status and renal function assessment (based on the Modification of Diet in Renal Disease formula). The creatinine value was recorded at the time of medical decision making by urology visit or, if referred, by the medical oncology visit. At our institution CrCl 45 ml per minute or greater was used as an approximate cutoff for the receipt of cisplatin. We then grouped the reasons for lack of chemotherapy as patient preference or patient symptoms/medical status.

### Determination of Eligibility for NAC

Using the number of patients referred to medical oncology who did vs did not receive NAC as our starting point, we calculated the proportion eligible for NAC who would have received treatment (cisplatin and carboplatin based) had all received referral to medical oncology. We then determined the maximum proportion of patients in each of the 4 groups undergoing cystectomy who would have received chemotherapy had referral to medical oncology been provided.

### Statistical Analysis

Logistic regression analyses examining patient age, race, gender, ASA physical status classification system and CrCl 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

A total of 215 patients undergoing radical cystectomy were identified based on our inclusion criteria. A subset of 127 was eligible to receive NAC (table 1). Almost 75% of the patients were male and median age was 69 years (range 38 to 89). Most