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# Propensity-matched analysis of patient-reported outcomes for neoadjuvant chemotherapy prior to radical cystectomy

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## Abstract

**Purpose—**To evaluate patient-reported outcomes (PROs) for bladder cancer patients undergoing neoadjuvant chemotherapy (NAC) prior to radical cystectomy (RC) using longitudinal data and propensity-matched scoring analyses.

**Methods—**155 patients with muscle-invasive bladder cancer scheduled for RC completed the European Organization for Research and Treatment of Cancer questionnaires, EORTC QLQ-C30, EORTC QLQ-BLM30, Fear of Recurrence Scale, Mental Health Inventory and Satisfaction with Life Scale within 4 weeks of surgery. A propensity-matched analysis was performed comparing pre-surgery PROs among 101 patients who completed NAC versus 54 patients who did not receive NAC. We also compared PROs pre- and post-chemotherapy for 16 patients who had data available for both time points.

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**Conflict of interest** The authors declare that they have no conflicts of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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**Results—**In propensity-matched analysis, NAC-treated patients reported better emotional and sexual function, mental health, urinary function and fewer financial concerns compared to those that did not receive NAC. Longitudinal analysis showed increases in fatigue, nausea and appetite loss following chemotherapy.

**Conclusion—**Propensity-matched analysis did not demonstrate a negative effect of NAC on PRO. Several positive associations of NAC were found in the propensity-matched analysis, possibly due to other confounding differences between the two groups or actual clinical benefit. Longitudinal analysis of a small number of patients found small to modest detrimental effects from NAC similar to toxicities previously reported. Our preliminary findings, along with known survival and toxicity data, should be considered in decision-making for NAC.

### Keywords

Patient-reported outcomes; Patient-centered research; Health-related quality of life; Bladder cancer

## Introduction

For patients with muscle-invasive bladder cancer (MIBC), cisplatin-based, neoadjuvant chemotherapy (NAC) given prior to radical cystectomy (RC) is associated with an overall survival benefit and is considered standard of care for patients who are eligible for such regimens [1–3]. Despite level 1 evidence, utilization of NAC has historically been low, perhaps due to concerns of overtreatment, tolerability and toxicity [4, 5]. Although comparisons of toxicity were measured in the randomized trials of NAC, we are not aware of any patient-reported outcomes (PRO) assessing comparative differences in health-related quality of life for those managed with or without NAC, or the longitudinal effects of NAC [6–9].

We therefore initiated a prospective PRO study for patients undergoing RC that included general and disease-specific measures [10]. The main objective of the overall study is to examine the impact of RC; therefore, a pre-surgical baseline assessment was performed on all patients. In conducting this study, we have also obtained pre-NAC data on a subset of patients. As such, the current study had two objectives: (1) perform a propensity-matched scoring analysis comparing post-NAC HRQoL prior to RC to that of patients who did not receive NAC; and (2) compare quality-of-life scores pre- and post-NAC.

## Methods

### Patient cohort

This study was approved by the institutional review board at Memorial Sloan Kettering Cancer Center. All patients with a diagnosis of bladder cancer who were scheduled for RC between September 2008 and July 2014 were approached in our urology clinic for enrollment in a prospective, longitudinal PRO study. Patients had to be ≥ 18 years of age, English speaking and able to provide informed consent. Patients were excluded if they were not able to follow up at our institution or had distant metastatic disease at diagnosis. All enrolled patients were asked to complete a baseline questionnaire within 4 weeks of the scheduled RC. If patients were recruited to the study prior to receiving NAC, they were

asked to complete questionnaires pre-NAC as well as post-NAC/pre-cystectomy. Receiving NAC was a shared decision between treating physician and patient.

**Patient-reported outcome variables—**The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQC30) version 3.0 is a validated instrument to measure the PRO in cancer patients [11]. It is a 30-item questionnaire with six functional domains: physical, role, emotion, social, cognition and global functioning. There are three symptom domains: fatigue, pain and emesis, and six single-item symptom questions measuring dyspnea, insomnia, appetite loss, diarrhea, constipation and financial concerns. A high score for a functional domain is considered a better level of functioning, whereas higher scores for a symptom domain or item are considered to be less favorable. A change in ten points or more over time is considered to be clinically significant [12].

The EORTC QLQ-BLM30 is a 30-item instrument designed for patients with MIBC and is intended for use as a supplementary module to EORTC QLQ-C30 [13]. There are seven domains: urinary symptoms, urostomy problems, bloating/flatulence, body image dissatisfaction, worry (future perspectives), catheter problems and sexual dysfunction. Higher scores reflect worse symptomatology. For the purposes of the present study, domains for urostomy problems and catheter problems were not relevant to patients, and thus were not included in our analysis.

We used three additional validated questionnaires to assess the psychological well-being of patients prior to RC. The Satisfaction with Life Scale is a five-item measure of global satisfaction with life [14]. Higher scores are indicative of more satisfaction. The Fear of Recurrence Questionnaire is a 22-item measure that was initially designed in breast cancer patients [15]. A higher total score reflects a higher fear of recurrence. The Mental Health Inventory is a 5-item questionnaire derived from the 38-item Mental Health Inventory Scale [16]. A higher total score reflects favorable mental health.

## Derivation of propensity scores

Because NAC was not a randomized treatment, but is a treatment that has certain clinical selection criteria, we used propensity scoring to account for differences between patients who did and did not receive NAC [17]. Propensity scores were created using logistic regression analysis to identify demographic and clinical variables associated with receipt of NAC [18]. Demographic variables included were age, gender, ethnicity, employment status and marital status. Clinical measures collected prior to enrollment included age-adjusted Charlson Comorbidity Index (CCI) [19], American Society of Anesthesiologists (ASA) score, receipt of intravesical therapy, receipt of pelvic radiotherapy, pre-operative glomerular filtration rate (GFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and receipt of NAC. Comorbidities were divided to categorize each condition per patient according to the CCI: cardiovascular disease, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease (COPD), peptic ulcer disease, diabetes, moderate to severe chronic kidney disease, hemiplegia, other hematological or solid cancer, chronic liver disease and

neurologic dysfunction. For our main analyses, we used the propensity score as a covariate, entered into regression models prior to testing the effects of NAC. We further considered an alternative approach to propensity adjustment, segmenting the sample into quintiles based on propensity scores. This allowed us to compare more tightly matched NAC and non-NAC patients within propensity quintiles. Some of the quintile groups were small using this approach, so we chose not to report it as a primary analysis. However, findings were suggestive of future research possibilities, as summarized in “Discussion”.

### Statistical considerations

SPSS v25.0.0 was used for all statistical testing [20]. Propensity scores were used as covariates for group comparisons and the standardized regression coefficients were calculated to represent the extent to which the two groups differed in standard deviation units. As this was an exploratory analysis of a subset of patients from our original protocol, we included all findings with exact statistical significance in both our longitudinal and propensity scoring analyses.

## Results

At baseline, 155 of 232 (67%) patients with MIBC completed the questionnaires prior to RC. 101 of 155 (65%) MIBC patients received NAC. Patient characteristics and comparisons of those who did and did not receive NAC are presented in Table 1. In terms of demographics, these groups were similar in all regards except for age. Compared to patients who did not receive NAC, patients who did receive NAC were younger (median 67 vs. 73 years old, $p < 0.001$). Although groups were similar in terms of age-adjusted comorbidity scores, we noted that the NAC group was less likely to have been diagnosed with chronic kidney disease (4% vs. 15%, $p = 0.016$) or with other malignancies (13% vs. 26%, $p = 0.041$), but were more likely to have been diagnosed with peptic ulcer disease (35% vs. 17%, $p = 0.018$). Eighty-seven of the 101 (86%) patients who underwent NAC treatment received gemcitabine and cisplatin.

### Propensity-matched scoring analysis

Propensity to receive NAC was associated with younger age [odds ratio (OR) = 0.934 per year, $p < 0.001$] and a trend toward not having received prior pelvic radiation (OR = 0.323, $p = 0.067$); however, all demographic and clinical variables used to derive propensity scores were used in the regression analysis.

Table 2 shows pre-surgery PRO for patients who did and did not receive NAC. The results of the linear regression analysis using propensity score as a covariate are presented in Table 3. Patients who received NAC reported better emotional function, fewer urinary symptoms and better scores on the Mental Health Inventory. There was also a trend toward fewer financial problems and lower levels of sexual dysfunction associated with NAC.

### Longitudinal analysis

Sixteen patients who received NAC completed both pre- and post-NAC questionnaires (Table 4). Patients who received NAC reported an increase in fatigue, nausea and appetite

loss. There was also a trend toward worse dyspnea and body image satisfaction, a decline in global health status, social function and financial problems.

## Discussion

In terms of toxicity of NAC, the Southwest Oncology Group 8710, which compared three cycles of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC), followed by RC to RC alone, found a 33% rate of grade 4 myelosuppression and 17% rate of gastrointestinal toxicity and no attributable deaths [7]. The International Collaboration of Trialists study assigned patients to three cycles of cisplatin, methotrexate and vinblastine or no chemotherapy prior to definitive treatment. They reported 16% grade 3 or 4 myelosuppression and common nausea despite antiemetics (percent not reported), and five patients (1%) died from toxicity. In the current study, nearly all patients in the NAC group received gemcitabine and cisplatin, which has been shown to have equivalent response rates with less toxicity compared to MVAC [21].

However, we believe that toxicity and PRO should be considered distinct end points. In fact, PROs are often more accurate than clinician-assessed toxicity [22, 23]. In analysis of both propensity-adjusted group differences and pre–post comparisons, NAC was found to have no detrimental effect on the majority of PRO items and domains measured, including physical function, pain, fear of recurrence and satisfaction with life.

Considering the lack of data on longitudinal PRO for neoadjuvant chemotherapy, we thought it was important to examine changes in the available 16 patients despite limitations in statistical power. We found that patients who received NAC reported statistically and clinically significant increases in fatigue, nausea and appetite loss as would be expected from reported toxicities. NAC was also associated with a trend toward worsening global health status, social function, dyspnea and body image. Ideally, a larger percentage of patients would have available pre- and post-NAC PRO data.

In our propensity scoring analysis, there was a positive association between receipt of NAC and emotional function, urinary symptoms, financial problems and mental health. However, these differences were small to modest and no differences were found in the majority of items measured. Although propensity matching controlled for age differences between the two groups, we acknowledge that in this non-randomized comparison, clinical selection criteria are very important and could introduce unmeasured confounding differences, such as unmeasured health conditions or health of sexual partners, which can explain the positive PRO effects of NAC. Alternatively, patients may feel encouraged about successfully completing chemotherapy and the positive association between NAC and improved survival.

In an exploratory analysis, we also performed a linear regression treating propensity as a categorical variable rather than as a linear covariate. Patients were divided into quintiles according to propensity, from least to most likely to receive NAC. Although limited by small sample sizes within groups, propensity matching in this way provided a tighter control, by forcing comparisons of NAC and non-NAC patients within each quintile. Regression analyses were repeated for all of the dependent variables listed in Table 3, controlling for

propensity group and testing propensity group by NAC interaction effects. The results demonstrated two distinct patterns. For variables related to physical symptoms, NAC patients tended to do worse than quintile-matched non-NAC patients on measures of specific symptoms, including diarrhea, constipation, nausea, fatigue and sexual interest. Alternatively, the impact of NAC on global and psychological variables depended upon each group's relative propensity to receive NAC. Specifically, receiving NAC was associated with better emotional functioning, less worry about recurrence and greater life satisfaction in the quintile second-most likely to receive NAC. In contrast, for patients in the second-least likely quintile, NAC was associated with worse mental health and more negative future perspective. The middle quintile showed mixed association between psychological outcomes and NAC, with worse role functioning but better emotional functioning. No group-specific effects were evident in either the first or the last propensity quintiles. Although further research is necessary, these analyses suggest that the quality-of-life effects of NAC could be predicted by more patient-centric criteria involving the patients' profile of demographic clinical characteristics.

This study has several limitations. We believe our overall response rate of 66% reflects the challenges of conducting a comprehensive PRO assessment prior to major surgery. Similar to other PRO studies, our results reflect the responses of patients who were willing and able to participate. It is important to note that not all patients are eligible to receive NAC and selection of patients incorporates multiple variables, some of which may not have been adequately captured. Although we performed a detailed propensity analysis of patient variables, we acknowledge that the non-randomized nature of treatment could have introduced biases not considered in the propensity scoring.

This is one of the first studies to compare PRO for NAC prior to RC. In the current study, we found small to modest detrimental PROs in our longitudinal analysis that mirrors known toxicities, but no negative PROs in our propensity-matched analyses. There may be specific subsets of patients for whom NAC has positive and negative impacts to PROs. Further follow-up will allow us to examine NAC effects post-operatively. We believe these preliminary findings further support the use of NAC in eligible patients. We emphasize that receipt of NAC should be a shared decision between health-care providers and patients, considering the clinical benefits and toxicity outcomes as well as PROs.

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**Table 1**

Patient characteristics

| | Neoadjuvant chemo-therapy | No neoadjuvant chemotherapy | *P* value |
|---|---|---|---|
| Number of patients | 101 | 54 | |
| Median age, yrs (IQ range) | 67 (60, 72) | 73 (67, 78) | < 0.001 |
| Gender | | | NS |
| Male | 72% | 83% | |
| Female | 28% | 17% | |
| Median BMI, kg/m$^2$ (IQ range) | 27 (25,31) | 28 (26, 30) | NS |
| Age-adjusted Charlson Comorbidity Index | | | NS |
| < 2 | 46% | 44% | |
| ≥ 2 | 54% | 56% | |
| Married | 76% | 65% | NS |
| Employed | 51% | 37% | NS |
| Caucasian | 95% | 98% | NS |
| GFR<60 | 29% | 52% | 0.004 |
| Number of cycles (missing $n = 11$) | | | |
| < 4 | 15 (17%) | | |
| 4 | 75 (83%) | | |

**Table 2**

Raw scores for patients who did and did not receive neoadjuvant chemotherapy

| Questionnaire | Domain/item | Patients who received neoadjuvant chem-otherarpy (NAC) | | Patients who did not receive NAC | |
|---|---|---|---|---|---|
| | | *n* | Mean (SD) | *n* | Mean (SD) |
| EORTC QLQ-C30 | Global health status | 101 | 72 (20) | 53 | 73 (19) |
| | Physical function | 101 | 90 (15) | 54 | 90(12) |
| | Role function | 101 | 83 (24) | 54 | 87 (23) |
| | Emotional function | 101 | 77 (18) | 53 | 75 (20) |
| | Cognitive function | 101 | 85 (18) | 53 | 90 (15) |
| | Social function | 101 | 74 (25) | 53 | 79 (24) |
| | Fatigue * | 101 | 26 (20) | 54 | 19 (15) |
| | Nausea/vomiting * | 101 | 6 (14) | 54 | 2 (5) |
| | Pain * | 101 | 10 (21) | 54 | 10 (19) |
| | Dyspnea * | 101 | 13 (19) | 54 | 11 (18) |
| | Insomnia * | 101 | 26 (26) | 54 | 27 (31) |
| | Appetite loss * | 101 | 13 (22) | 54 | 9 (19) |
| | Constipation * | 101 | 17 (23) | 53 | 12 (22) |
| | Diarrhea * | 101 | 7 (16) | 53 | 6 (17) |
| | Financial problems * | 101 | 14 (24) | 51 | 12 (25) |
| EORTC QLQ-BLM30 | Urinary symptoms * | 99 | 24 (19) | 54 | 35 (23) |
| | Future perspectives | 95 | 53 (26) | 43 | 45 (31) |
| | Bloating/flatulence * | 95 | 18 (18) | 43 | 17 (17) |
| | Body image satisfaction | 94 | 76 (26) | 42 | 80 (24) |
| | Sexual dysfunction * | 68 | 47 (22) | 38 | 52 (25) |
| Fear of Recurrence Scale | Fear of recurrence * | 99 | 78 (14) | 53 | 77 (15) |
| Mental Health Inventory | Mental Health Inventory | 100 | 22 (4) | 54 | 22 (5) |
| Satisfaction with Life Scale | Satisfaction with life | 98 | 26 (7) | 53 | 26 (6) |

* A higher score on these domains/items reflects worse quality of life

**Table 3**

Propensity-matched analysis

| Questionnaire | Domain/item | Standardized regression coefficient, ($\beta$) | *P* value | Interpretation |
|---|---|---|---|---|
| EORTC QLQ-C30 | Global health status | 0.08 | 0.390 | |
| | Physical function | 0.07 | 0.407 | |
| | Role function | − 0.03 | 0.730 | |
| | Emotional function | 0.31 | 0.001 | NAC associated with better emotional function |
| | Cognitive function | − 0.04 | 0.680 | |
| | Social function | 0.10 | 0.289 | |
| | Fatigue * | 0.06 | 0.523 | |
| | Nausea/vomiting * | 0.10 | 0.281 | |
| | Pain * | − 0.10 | 0.268 | |
| | Dyspnea * | 0.03 | 0.785 | |
| | Insomnia * | − 0.11 | 0.251 | |
| | Appetite loss * | 0.03 | 0.736 | |
| | Constipation * | 0.14 | 0.141 | |
| | Diarrhea * | 0.04 | 0.684 | |
| | Financial problems * | − 0.17 | 0.075 | |
| EORTC QLQ-BLM30 | Urinary symptoms * | − 0.23 | 0.008 | NAC associated with fewer urinary symptoms |
| | Future perspectives | 0.30 | 0.001 | NAC associated with better future perspectives |
| | Bloating/flatulence * | − 0.10 | 0.272 | |
| | Body image satisfaction * | 0.08 | 0.406 | |
| | Sexual dysfunction * | − 0.18 | 0.075 | |
| Fear of Recurrence Scale | Fear of recurrence * | − 0.13 | 0.154 | |
| Mental Health Inventory | Mental Health Inventory | 0.20 | 0.027 | NAC associated with better Mental Health Inventory |
| Satisfaction with Life Scale | Satisfaction with life | 0.84 | 0.351 | |

* A higher score on these domains/items reflects worse quality of life

**Table 4**

Results of patients who completed assessment pre- and post-chemotherapy

| Questionnaire | Domain/item | Patients with available data, n | Pre-chemo-therapy, mean (SD) | Post-chemo-therapy, mean (SD) | Mean difference | 95% CI for difference | *P* value | Interpretation |
|---|---|---|---|---|---|---|---|---|
| EORTC QLQ-C30 | Global health status | 15 | 75 (23) | 61 (19) | − 13 | − 28 to 1 | 0.07 | |
| | Physical function | 16 | 85 (20) | 77 (23) | − 8 | − 21 to 6 | 0.2 | |
| | Role function | 16 | 74 (38) | 63 (28) | − 11 | − 30 to 7 | 0.2 | |
| | Emotional function | 16 | 80 (16) | 78 (22) | − 2 | − 13 to 9 | 0.7 | |
| | Cognitive function | 16 | 88 (16) | 82 (22) | − 5 | − 15 to 4 | 0.3 | |
| | Social function | 16 | 77 (27) | 63 (29) | − 15 | − 30 to 1 | 0.06 | |
| | Fatigue * | 16 | 21 (30 | 43 (24) | 22 | 7 to 37 | 0.008 | Fatigue increased |
| | Nausea/vomiting * | 16 | 2 (6) | 19 (28) | 17 | 3 to 30 | 0.02 | Nausea increased |
| | Pain * | 16 | 16 (29) | 11(29) | − 4 | − 12 to 3 | 0.3 | |
| | Dyspnea * | 16 | 8 (19) | 21 (24) | 13 | − 2 to 27 | 0.08 | |
| | Insomnia * | 16 | 21 (24) | 25 (23) | 4 | − 5 to 13 | 0.3 | |
| | Appetite loss * | 16 | 6 (13) | 23 (26) | 17 | 2 to 31 | 0.03 | Appetite loss increased |
| | Constipation * | 16 | 19 (30) | 31 (23) | 13 | − 8 to 33 | 0.2 | |
| | Diarrhea * | 16 | 4 (11) | 4 (11) | 0 | − 6 to 6 | 1 | |
| | Financial problems * | 16 | 29 (34) | 23 (32) | − 6 | − 13 to 1 | 0.08 | |
| EORTC QLQ-BLM30 | Urinary symptoms * | 15 | 21 (18) | 19 (20) | − 2 | − 12 to 7 | 0.6 | |
| | Future perspectives | 11 | 46 (32) | 47 (30) | 1 | − 14 to 16 | 0.9 | |
| | Bloating/flatulence * | 12 | 22 (24) | 17 (19) | − 6 | − 23 to 12 | 0.5 | |
| | Body image satisfaction | 12 | 84 (31) | 75 (32) | − 9 | − 19 to 1 | 0.06 | |
| | Sexual dysfunction * | 9 | 50 (27) | 56 (28) | 6 | − 15 to 27 | 0.5 | |
| Fear of Recurrence Scale | Fear of recurrence * | 16 | 87 (46) | 79 (15) | − 8 | − 28 to 12 | 0.4 | |
| Mental Health Inventory | Mental Health Inventory | 16 | 23 (4) | 23 (5) | 0 | − 2 to 1 | 0.8 | |
| Satisfaction with Life Scale | Satisfaction with life | 16 | 29 (7) | 27 (8) | − 2 | − 5 to 1 | 0.3 | |

* A higher score on these domains/items reflects worse quality of life