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A delay ≥8 weeks to neoadjuvant chemotherapy before radical cystectomy increases the risk of upstaging

François Audenet, M.D.[a], John P. Sfakianos, M.D.[a], Nikhil Waingankar, M.D., M.S.H.P.[a], Nora H. Ruel, M.S.[b], Matthew D. Galsky, M.D.[c], Bertram E. Yuh, M.D., M.S.H.C.P.M., M.I.S.M.[d], Greg E. Gin, M.S., M.D.[e,f,*]

[a] *Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY*
[b] *Division of Biostatistics, City of Hope National Medical Center, Duarte, CA*
[c] *Department of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY*
[d] *Division of Urology and Urologic Oncology, City of Hope National Medical Center, Duarte, CA*
[e] *Division of Urology, VA Long Beach Healthcare System, Long Beach, CA*
[f] *Department of Urology, University of California, Irvine, Orange, CA*

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Abstract

Objectives: To investigate delays to neoadjuvant chemotherapy (NAC) and radical cystectomy (RC) and their effect on outcomes in a large national registry of patients with localized muscle invasive bladder cancer.

Patients and methods: Within the National Cancer Database (2004–2014), we identified 2,227 patients who underwent NAC and RC for cT2-T4aN0M0 urothelial carcinoma of the bladder. Times from diagnosis to treatments were tested for association with overall survival and pathologic outcomes, using Cox models, and restricted cubic splines regression.

Results: Median times from diagnosis to NAC and RC were 39 days (interquartile range: 26–56) and 155 days (interquartile range: 131–185), respectively. Time to NAC and time to RC were not associated with overall survival in the complete cohort, as well as in subgroups of responders and nonresponders to NAC. Overall, 916 patients (41%) were upstaged after RC, including 485 patients (22%) with positive lymph nodes. We identified delay to NAC ≥8 weeks as a significant cut-off point to predict the risk of upstaging in multivariable analysis (odds ratio: 1.27; 95% confidence interval: 1.02–1.59; $P = 0.031$). Black race, Medicaid insurance, and academic facilities were associated with a higher risk of delayed treatment.

Conclusion: After diagnosis of muscle invasive bladder cancer, NAC should be initiated as soon as possible and no more than 8 weeks to prevent upstaging. There is no evidence to support avoiding NAC due to concerns of delayed RC that was generated from surgery alone studies, as long as RC is performed within 7 months from initial diagnosis.

Keywords: Cystectomy; Delay; Neoadjuvant chemotherapy; Outcomes; Socioeconomic Factors; Urothelial carcinoma

1. Introduction

Bladder cancer is the fifth most common cancer in the United States with an estimated incidence of 81,190 in 2018 [1]. Approximately 25% of new cases present as muscle invasive disease, which is associated with a higher risk of developing metastasis and death. Studies have suggested that a delay in radical cystectomy (RC) is associated with a decrease in overall survival (OS) [2–5] and it is now recommended to perform radical surgery within 3 months from diagnosis [6]. However, after RC, the 5-year survival is only 50% [7]. In recent years, there has been a movement toward a multimodality treatment approach for patients with localized muscle invasive bladder cancer. Cisplatin-based neoadjuvant chemotherapy (NAC) in eligible patients

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*Corresponding author. Tel.: +1-714-456-6717; fax: +1-888-378-4358.
E-mail address: ggin1@uci.edu (G.E. Gin).

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is now recommended before RC, and is supported by large meta-analyses showing a 5% decrease in overall mortality [8]. Despite high level of evidence, the adoption of this strategy remains limited, with around 20% of patients effectively receiving NAC before RC in daily practice [9]. One of the hesitations in recommending NAC is that it may delay definitive therapy with RC, which may compromise patient outcomes [10]. However, it is unclear if the effect of delays on patient outcomes still holds true in the setting of NAC utilization. Care delays, care transitions, and access to cancer care are also becoming increasingly relevant in the debate over health care policy in the United States. In this study, we aimed to investigate in a large national registry of patients with bladder cancer, delays to NAC and RC and their effect on outcomes, using OS and pathological upstaging as primary endpoints.

2. Patients and methods

2.1. Data source

The National Cancer Database (NCDB) is a nationwide, facility-based, comprehensive cancer registry, established in 1989, that currently captures approximately 70% of all newly diagnosed malignancies in the United States annually, comprising more than 34 million unique cancer cases [11]. The NCDB draws data from over 1,500 Commission on Cancer accredited facilities in the United States for initial diagnosis and/or first course of treatment administered. The database is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons and has been previously described in detail [12].

2.2. Study population

From a population of 475,680 men and women who were diagnosed with bladder tumors between 2004 and 2014 (International Classification of Diseases-Oncology-3 codes C67.0–C67.9), we identified 17,942 individuals who were treated with RC for clinically localized cT2-T4aN0M0 urothelial carcinoma of the bladder. Of them, 2,780 patients (15%) received multiagent chemotherapy before RC. Patients who received radiotherapy or immunotherapy or any other treatment as part of the planned first course of therapy were excluded (n = 118). Patients with missing data for final pathology, follow-up or time to treatments were also excluded (n = 435). After application of these criteria, 2,227 patients who received NAC + RC for cT2-T4aN0M0 urothelial carcinoma of the bladder were eligible for analysis (Fig. 1).

2.3. Statistical analysis

Descriptive statistics were used to characterize the study population. Times to NAC and RC were defined as time from diagnosis to start of treatment. OS was defined as date of diagnosis to death. The median follow-up was estimated using the reverse Kaplan–Meier-based method, which is constructed by reversing "censor" and "event" to assess the length as well as the completeness of the follow-up [13]. Cox proportional hazards models were used to assess the association between delays to treatments and OS. Exploratory analyses were performed to determine if a cut-off point for the delay to treatment was associated with OS. We examined all delay intervals using deciles to divide the cohort into 2 populations at each time point. Log-rank analyses then detected any possible survival difference between the 2 populations. Time to treatment was also modeled using restricted cubic spline regression to predict the relative hazard of death [14]. We further divided the population into responders to NAC (≤pT1N0) and nonresponders (≥pT2 or pN+) to explore a potential association between delays to treatment and OS. Predictors of response to chemotherapy (≤pT1N0) and upstaging (pT stage higher than cT stage or positive lymph nodes on final pathology) were also investigated using univariable and multivariable logistic regression analyses. All analyses were conducted using R v3.4.4 (https://cran.r-project.org).

3. Results

3.1. Time to NAC ± RC and OS

The characteristics of the 2,227 patients included are listed in Supplementary Table S1. Overall, 78% of the patients were cT2. Median time from diagnosis to initiation of NAC and from diagnosis to RC were 39 days (interquartile range [IQR]: 26–56) and 155 days (IQR: 131–185), respectively (Fig. 2). The median time between initiation of NAC and RC was 112 days (IQR: 92–137). With a median follow-up of 45.7 months (IQR: 31.0–65.5), the 2-year and 5-year OS rates were, respectively, 69% (95% confidence interval [CI]: 67.3–71.2) and 49% (95% CI: 46.3–51.4). Using Cox proportional hazards models, time to NAC and time to RC as continuous variables were not associated with OS. Furthermore, using deciles to divide the cohort into 2 populations at each time point, no significant cut-off point in predicting worse OS was identified for time to NAC or RC, up to the ninth decile (83 days and 222 days, respectively). Restricted cubic splines Cox regression adjusted for age, Charlson score, prior history of cancer, pT, and pN stage did not show any significant increase in the relative hazard of death with increased time to treatments (Fig. 3). Especially, among patients receiving NAC, a delay for RC ≥6 months was not associated with worse OS (Supplementary Fig. S1).

3.2. Responders vs. nonresponders to NAC

Of the 2,227 patients included, 679 (30%) had a pathological response after NAC (≤pT1N0). These patients had a significantly better OS compared to nonresponders (median OS: 113 months [95% CI: 110-NA] vs. 32 months [95%

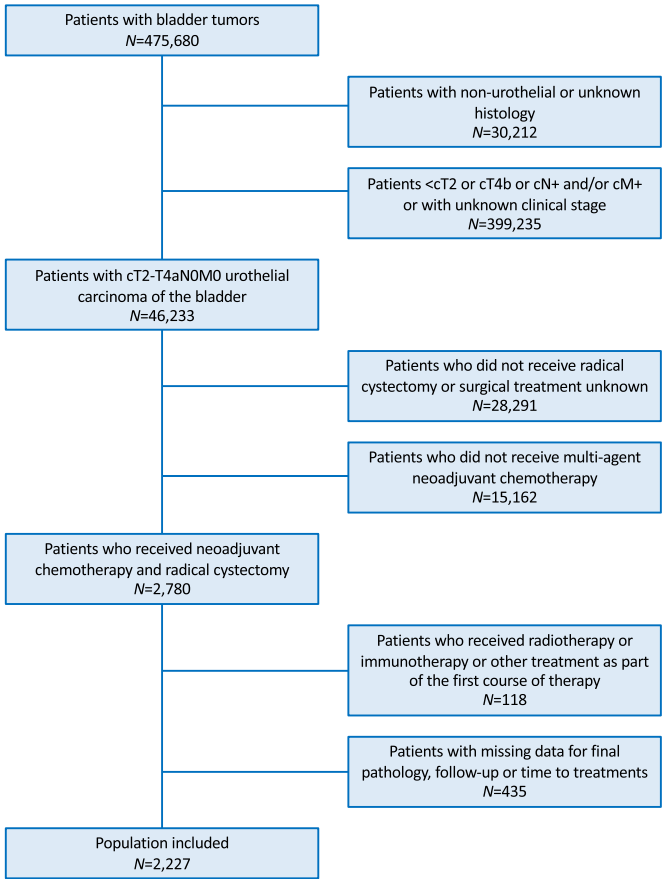

Fig. 1. Flowchart describing the selection of the patients who received neoadjuvant chemotherapy and radical cystectomy for cT2-T4aN0M0 urothelial carcinoma of the bladder in the National Cancer Database, 2004–2014.

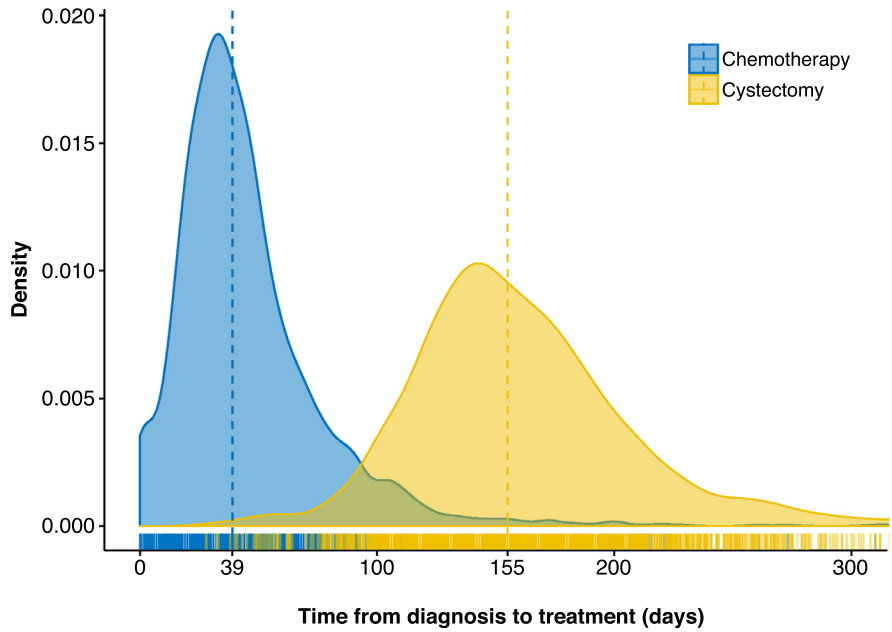

Fig. 2. Density plot representing the distribution of the time from diagnosis to neoadjuvant chemotherapy and radical cystectomy for patients with cT2-T4aN0M0 urothelial carcinoma of the bladder in the National Cancer Database, 2004–2014. Dashed lines represent the medians.

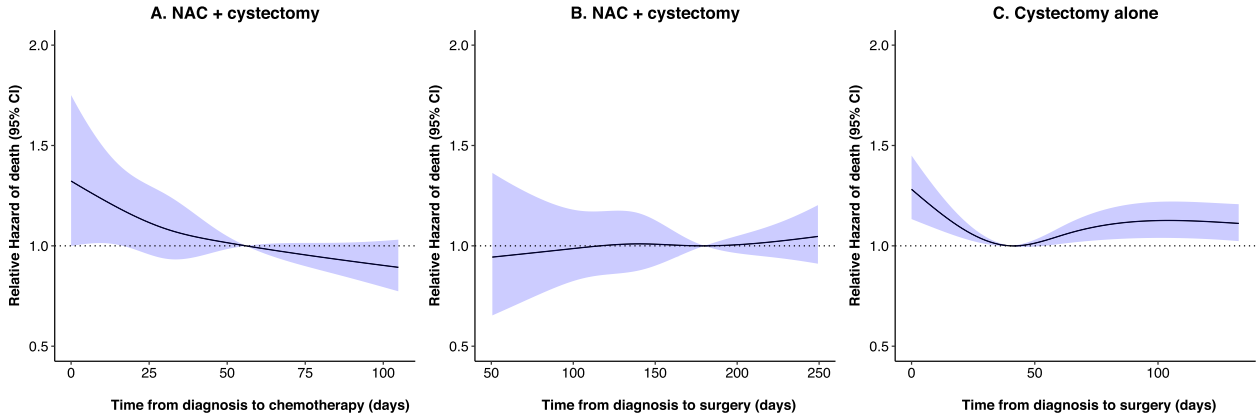

Fig. 3. Restricted cubic splines Cox regression adjusted for age, Charlson score, prior history of cancer, pT, and pN stage, predicting the relative hazard of death with time to treatment, for patients with cT2-T4aN0M0 urothelial carcinoma of the bladder treated with neoadjuvant chemotherapy + radical cystectomy in the National Cancer Database, 2004–2014 (A: reference = 56 days; B: reference = 180 days). As a control, we present the relative hazard of death depending on time to surgery in 7,578 patients with cT2-T4aN0M0 urothelial carcinoma of the bladder treated with radical cystectomy alone in the National Cancer Database, 2004–2014 (C: reference = 40 days).

CI: 29.3–35.8]; $P < 0.001$). In each subgroup (responders and nonresponders), time to NAC and time to RC as continuous variables were not associated with OS and no significant cut-off point was identified. Adjusted restricted cubic splines Cox regression did not show any significant increase in the risk of death with time to treatments (Supplementary Fig. S2). When looking at predictors of response to NAC, neither time to NAC nor time to RC was significantly associated with pathological response.

3.3. Predictors of upstaging on final pathology

Overall, 916 patients (41%) were upstaged after RC, including 485 patients (22%) with positive lymph nodes. Time to NAC and time to RC were not associated with OS in this subgroup. However, in univariate analysis, time to NAC as a continuous variable was associated with a higher risk of upstaging (odds ratio [OR]: 1.003; 95% CI: 1.00–1.005; $P = 0.034$; Supplementary Table S2). Using exploratory analyses with deciles, we identified 8 weeks as a significant cut-off point to predict the risk of upstaging (OR: 1.24; 95% CI: 1.03–1.50; $P = 0.021$) with all subsequent cut-off points remaining significant. This was confirmed by restricted cubic spline logistic regression (Fig. 4). In multivariable analysis, time to NAC ≥8 weeks was significantly associated with pathologic upstaging (OR: 1.27; 95% CI: 1.02–1.59; $P = 0.031$; Table 1).

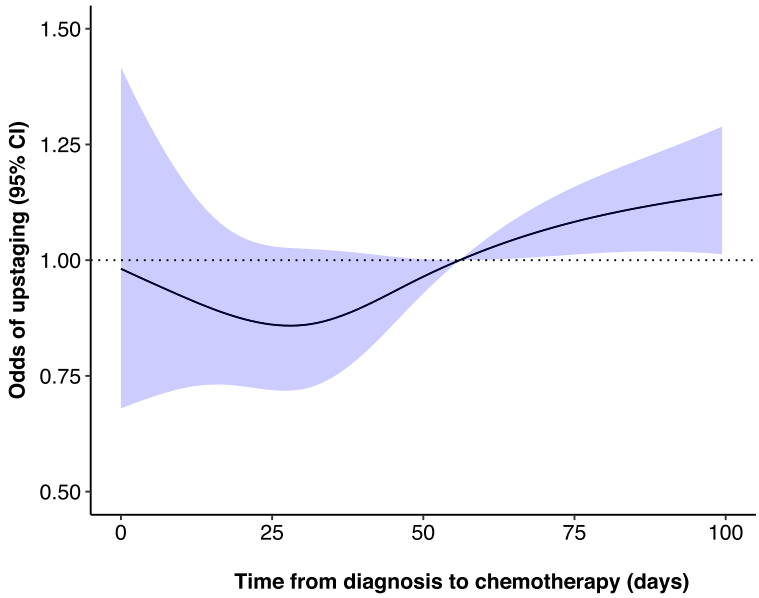

Fig. 4. Restricted cubic splines logistic regression predicting the odds of upstaging on final pathology with time to chemotherapy, for patients with cT2-T4aN0M0 urothelial carcinoma of the bladder treated with neoadjuvant chemotherapy + radical cystectomy in the National Cancer Database, 2004–2014 (reference = 56 days).

Table 1
Predictors of upstaging on final pathology for patients who underwent neoadjuvant chemotherapy + radical cystectomy for cT2-T4aN0M0 urothelial carcinoma of the bladder in the National Cancer Database, 2004−2014 (significant *P* values are in bold)

	Univariable		Multivariable	
Variables	OR [95% CI]	*P* value	OR [95% CI]	*P* value
Age	1.01 [1.00; 1.02]	**0.011**	1.01 [0.99; 1.02]	0.066
Gender				
Male	Ref.	Ref.	Ref.	Ref.
Female	1.07 [0.87; 1.30]	0.533	1.07 [0.87; 1.32]	0.501
Race				
White	Ref.	Ref.	Ref.	Ref.
Black	1.20 [0.82; 1.75]	0.358	1.20 [0.81; 1.77]	0.363
Other	0.68 [0.42; 1.06]	0.092	0.76 [0.47; 1.19]	0.240
Charlson comorbidity index				
0−1	Ref.	Ref.	Ref.	Ref.
≥2	1.52 [1.02; 2.28]	**0.041**	1.47 [0.98; 2.21]	0.064
Prior history of cancer				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.33 [1.07; 1.66]	**0.009**	1.28 [1.02; 1.60]	**0.031**
cT stage				
cT2	Ref.	Ref.	Ref.	Ref.
cT3-4	0.64 [0.51; 0.78]	**<0.001**	0.63 [0.51; 0.78]	**<0.001**
Time from diagnosis to chemotherapy				
<8 weeks	Ref.	Ref.	Ref.	Ref.
≥8 weeks	1.25 [1.03; 1.52]	**0.023**	1.27 [1.02; 1.59]	**0.031**
Time from diagnosis to surgery	1.00 [1.00; 1.00]	0.849	1.00 [1.00; 1.00]	0.353

CI = confidence interval; OR = odds ratio.

3.4. Predictors of delay in starting active treatment

Overall, 552 patients (25%) started NAC more than 8 weeks after diagnosis (median: 77 days [IQR: 65−96.2]). There was no significant difference in the clinical stage compared to patients with NAC started before 8 weeks (20% of cT3-T4 vs. 21%, $P = 0.304$). However, demographic characteristics were different between the 2 groups (Supplementary Table S3). In multivariable analysis, African-American origin (OR: 2.10; 95% CI: 1.37−3.19; $P < 0.001$), Medicaid or other government insurance (OR: 1.53; 95% CI: 1.00−2.30; $P = 0.046$), and treatment in an academic facility (OR: 1.24; 95% CI: 1.00−1.54; $P = 0.047$) were significantly associated with the risk of delayed treatment (Supplementary Table S4).

4. Discussion

In muscle invasive bladder cancer, delays of longer than 12 weeks to RC have been associated with pathologic upstaging [2,15] and decreased survival [4,5]. However, most of these studies were completed prior to the adoption of NAC. In this study, we explored if these effects continue to be significant in the setting of NAC. Using the NCDB, which represents the continuum of practice settings in the United States, our analysis showed that in patients who received NAC, time to RC up to 7 months after diagnosis was not associated with OS. Even in the group of patients who progressed under NAC (upstaging on final pathology), the time to RC was not significantly associated with OS. Similarly, 2 single institution studies have examined wait times to RC in the NAC setting and have not found any association with OS [16,17]. However, a monocentric study found that the recovery window between the end of NAC and RC should not exceed 12 weeks to prevent the risk of lymph node involvement [18].

The absence of association between delayed RC and OS among patients who received NAC could be explained by the fact that the effective treatment starts with the initiation of chemotherapy. Similar to prior studies on impact of care delays in RC-only patients, time to effective treatment seems to be an important prognostic factor. With a short median time from diagnosis to initiation of NAC (39 days), we were not able to demonstrate any effect on OS. However, a delayed treatment ≥8 weeks was significantly associated with upstaging on final pathology after RC. This could ultimately lead to higher cancer-related mortality and morbidity, given the possible need for further systemic therapy, and could become significant with longer follow-up. In our cohort, at least 23% of the patients with upstaging on final pathology did receive adjuvant chemotherapy. As it has been shown that adjuvant chemotherapy after NAC and RC may be associated with an OS benefit for patients with pT3/T4 and/or pN+ disease [19], this could potentially make differences in OS more difficult to demonstrate. Nonetheless, this finding strengthens the argument that a longer wait time to therapy may compromise cancer control. While the 8-week cut-off to NAC was significantly associated with the risk of upstaging, there is

likely no completely safe delay when treating invasive bladder cancer.

Waiting times for health services have recently been used as a metric to gauge quality of care delivery [20]. Particularly, delays in cancer treatment can affect patient satisfaction [21] and may have psychological consequences in addition to detrimental effects on oncological outcomes [22,23]. Identifying factors associated with treatment delays can inform health policy aimed at minimizing disparities in access to care. Several socioeconomic factors associated with care delays were identified in our study. Insurance status was independently associated with delays to NAC. Compared to private insurance, Medicaid and other government insurance were significantly associated with longer wait times. In other malignancies, insurance status has also been shown to be a predictor of care delay, more advanced stage at presentation and decreased survival [24–26]. We also found black race to be a significant predictor of delay to NAC, although there was no significant detrimental effect on OS. Time from diagnosis to initiation of NAC was significantly longer in academic facilities. Indeed, patient referrals to specialists and navigation through a new health system may contribute to these delays [27]. Patients may also seek second and third opinions for their care, adding on time to eventual treatment.

There are potential limitations to our analysis including the limitations inherent to retrospective studies, although no randomized trial is ethically feasible to address this question. One of the most important limitations is the lack of data regarding the type, dosing, or duration of NAC given. In the NCDB, chemotherapy is recorded as multi-agent or single-agent. We only included patients receiving multi-agent chemotherapy to primarily focus on the effect of cisplatin-based regimens. However, some of these individuals could still have received carboplatin-based regimens, as the exact regimens are unknown. Other limitations include inability to identify patients who received inadequate rounds or doses of chemotherapy or have impaired renal function, as suboptimal NAC is associated with poorer recurrence-free survival and OS [28]. Furthermore, clinical–pathologic stage discrepancy is remarkably common in bladder cancer [29]. Due to the lack of information available from the NCDB, we were unable to comment on factors such as imaging modalities or clinical examinations used to determine clinical stage or the extent of transurethral resection. After NAC, the time to RC is influenced by several factors both within and outside of the control of providers, including tolerability and adverse effects related to chemotherapy. In the literature, the most common reasons for delay were scheduling issues in 39% and adverse health status in 25% [16]. The lack of granularity provided through the NCDB does not allow exploration of these factors. Moreover, patients who started chemotherapy and rapidly progressed without receiving definitive treatment were not included. Finally, cancer-specific survival, time to recurrence, type of recurrence, and quality of life are also important outcomes not captured by the NCDB, thereby limiting our analysis to OS. However, cancer-specific survival is closely correlated to OS in bladder cancer, and we believe that OS can serve as a close surrogate.

5. Conclusion

This report represents, to our knowledge, the first large observational cohort study evaluating the effect of time to treatments in patients receiving NAC + RC. We found that time from diagnosis to surgery up to 7 months does not seem to affect OS in patients treated with NAC. However, a delay ≥8 weeks to start NAC was significantly associated with a higher risk of upstaging and lymph node positivity on final pathology. Consequently, given the aggressiveness of the disease, we should expedite referral of patients for NAC initiation as soon as possible and no more than 8 weeks after diagnosis. There is no evidence to support avoiding NAC due to concerns of delayed treatment that was generated from surgery alone studies, as long as RC is performed within 7 months from diagnosis.

Conflict of interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.urolonc.2018.11.011.

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