



Timing of treatment for muscle-invasive bladder cancer in the neo-adjuvant chemotherapy era

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Abstract: Muscle-invasive bladder cancer (MIBC) is a potentially lethal disease and radical cystectomy (RC) remains the gold standard for its treatment. Neoadjuvant chemotherapy (NAC) followed by RC can improve OS and is currently approved by international guidelines. In the setting of patients undergoing primary RC, several studies have shown that a delay from the time of diagnosis to surgery greater than 3 months could negatively impact oncological outcomes. It remains to be determined how timing impact patients undergoing NAC. Time to initiation of NAC represents an important time course which is poorly reported; two studies investigating it failed to demonstrate an association between delay of NAC and prognosis. After the completion of chemotherapy, there is no clear indication on how much recovery time is needed before performing surgery and how much delay is acceptable without affecting oncological outcomes. Single-center experiences suggest that surgery could be safely delayed up to approximately 10 weeks or that earlier RC does not affect perioperative morbidity. However, these results could not be reproduced by population-based studies. Even though lacking of evidence, is it not wise to reduce delays between each step in the treatment of MIBC?

Keywords: Delay; muscle invasive bladder cancer; neoadjuvant chemotherapy (NAC); radical cystectomy (RC)

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Introduction

Several trials investigated the role of neoadjuvant chemotherapy (NAC), these were summarized by a meta-analysis including 3005 patients which determined that platinum-based NAC provided a 5% improvement in 5-yrs OS and a 9% improvement in 5-yrs DFS (1). NAC has been implemented in guidelines (2,3). The most up-to-date meta-analysis concluded an 8% improved OS at 5 years (4). Furthermore, other putative advantages of NAC are a better tolerance to systemic therapy before a major surgical intervention; additionally, a potential down staging of tumor could be achieved allowing for a more complete resection and resulting in prognostic information. While

promising results are becoming available on the impact of immunotherapy, recent efforts were concentrated in predicting responders to NAC in order to avoid surgical delays for non-responders (5). It has been suggested that any delay in radical cystectomy (RC) could negatively affect oncological outcomes for patients with muscle-invasive bladder cancer (MIBC) (1-3). Several factors might play a role in such delay that can be related to the healthcare providers or to the patient. It is questionable whether the potential benefits of NAC could be negatively affected by the increasing potential causes of delays between each step of the multimodal treatment. In this paper we aim to review the current literature to investigate the effect of timing of

both RC and NAC.

Timing of upfront RC

Early studies investigating outcomes related to delay in cystectomy in the pre-NAC era were systematically reviewed by Fahmy *et al.* where every potential cause of delay was investigated: a trend toward better survival was reported with shorter delays from the onset of symptoms to physician referral, additionally delayed time to first TURBT influenced negatively the tumor dimensions (6). When analyzing the delay from TURBT to definitive treatment, most of the studies arbitrarily chose a cut-off of 90 days for delayed and non-delayed groups and there was a fair consensus indicating that patients undergoing delayed cystectomy had higher incidence of adverse pathological and oncological outcomes, namely: non-organ confined disease, lymph node metastasis (7,8), lymphovascular invasion (9), worse CSS (7) and OM (7,10). Subsequently the arbitrary endpoint of 12 weeks/90 days was confirmed by a retrospective analysis performed by Lee *et al.* in 2006 which explored all potential time points that could represent a cut-off for significant delay in RC, excluding the patients undergoing NAC. A significant OS advantage was found when RC was performed within 93 days from the diagnosis on the multivariate analysis ($P=0.04$), similarly a non-significant 10% increased CSM was reported ($P=0.08$). Interestingly RC delay did not predict local upstaging suggesting that extended time without treatment could impact survival through micrometastatic spread rather than local progression (11).

A SEER-Medicare study restricted to 441 subjects with T2N0M0 urothelial carcinoma reported similar results in this particular subgroup of patients. CSM and OM were increased with the delay of RC, namely with HR 2.0 ($P<0.01$) and HR 1.6 ($P<0.01$), respectively, for those delayed more than 12 weeks. No significant differences were found instead between patients undergoing RC within 4–8 weeks of TURBT and 8–12 weeks (12). Another population-based study from Canadian registries of 1,271 patients undergoing RC without any prior NAC or history of superficial aimed to discriminate the impact of direct and indirect referral to a urologist, where patients were considered indirectly referred if they had 5 or more encounters for symptoms related to BCa before their first urologic visit. Patients who were indirectly referred after first symptoms of bladder cancer experienced poorer survival (HR 1.29; 95% CI: 1.10–1.52), with woman experiencing significant longer delay in referral

($P<0.001$) (13).

A Turkish multi-institutional retrospective study on 396 patients undergoing RC + PLND for BCa without NAC reported that patients treated with RC within 3 months from the diagnosis of MIBC experienced improved DFS (22 *vs.* 10.8 months, $P<0.001$) and OS (26 *vs.* 13.9 months, $P<0.001$) compared to those treated after 3 months. Notably in this study no multivariate analysis was performed but interestingly approximately 40% of patients underwent RC stage lower than pT2 (14); this raises the question whether timing could be impactful also when RC is performed for NMIBC disease failing conservative treatment, in fact immediate cystectomy is recommended also after BCG-failure. In this context a cohort of 117 patients undergoing RC for recurrent NMIBC and treated with at least one induction course of BCG was analyzed by Haas *et al.* Within these patients 56 underwent at least one additional salvage intra-vesical therapy after NMIBC recurrence; this group did not experience significantly pathological upstaging to MIBC (21% *vs.* 19%) nor difference in OS ($P=0.58$) and CSS ($P=0.70$) compared to upfront RC after BCG failure. Although the multivariate model aimed to control for other risk factors (gender, age, multifocality, prostatic urethra involvement, carcinoma *in situ* and lymphovascular invasion) these results could not be used to state the non-inferiority of additional intra-vesical therapies for BCG failure compared to immediate RC because of the underlying selection bias for patients undergoing salvage treatment (15).

In order to investigate whether the worse prognosis of MIBC associated with female gender could be related to delays in surgery and referral of women, Williams *et al.* queried the SEER Database and showed that gender did not cause significant delay in RC, thus raising the question of what explains the differences in OS and CSS between genders (16).

Recently the question regarding the impact of timing of RC was extended to patients with variant histology on a retrospective cohort of 363 patients with cT2–T4 without history of intra-vesical therapy or NAC. In their multivariate model every month in delaying RC was associated with worse OS for patients with variant histology on pathology (HR =1.36, 95% CI: 1.11–1.65; $P=0.003$). A delay of 12 weeks or longer was associated with worse overall survival for both histologic variant and conventional urothelial carcinoma groups. Interestingly, there were no differences in RFS and variants detected at transurethral resection were not predictors of oncological

outcomes as the pathological evaluation was, confirming the pre-existing literature showing the low sensitivity of TURBT for detecting variants. Additionally, patients who underwent surgery with a delay greater than 8 weeks had a non-significant increase in extra-vesical disease (78.8% vs. 65.7%) while there were no differences in lymph-node metastases (29.4% vs. 27.8%) again suggesting a combination of advanced stage, hematological spread and micrometastases as potential factors for worse oncological outcomes (17).

Timing to NAC start

In the studies aforementioned, patients undergoing NAC were intentionally excluded to avoid confounding; however, presently, the proportion of patients undergoing NAC is not negligible and the start of chemotherapy becomes the first time point in the treatment. Theoretically the initiation of NAC could suffer fewer delays compared to surgery because of the reduced need of preoperative assessment and waiting list; however, other factors could healthcare and patient-related factors could cause a delay in treatment and need to be investigated. *Table 1* summarizes the reported finding of the main RCTs investigating NAC and justifying its use. Notably only one study by Kitamura *et al.* (26) specified in the methods that NAC began within 28 days from the diagnosis of MIBC, while other studies did not provide such information. The lack of information on this timing is absolutely evident and at this point only one study directly performed a comparison between different timing to NAC initiation and its related outcomes.

Results come from population-based study using data from the NCBDB database on 2,227 cT2-4N0M0 patients treated with NAC and RC; authors tested the impact of both time from diagnosis to NAC and RC on oncological outcomes. Overall median time to NAC and to RC was 39 days (interquartile range, 26–56 days) and 155 days (131–185 days), respectively. None of them was associated with OS, nor could a specific cut-off be found. In particular, among patients receiving NAC, a delay for RC ≥ 6 months was not associated with worse OS. These findings were confirmed also for both responders (30%) and non-responders to NAC. Interestingly time to NAC equal or greater than 8 weeks was associated with pathologic upstaging (OR 1.27, 95% CI: 1.02–1.59, $P=0.031$). In this population 25% of patients started NAC more than 8 weeks after the diagnosis and African-American origin, Government Insurance and treatment in an academic

facility were significantly associated with the risk of delayed treatment (32). In this unique and well conducted study, the short median time to initiation of NAC could have affected the ability to find any effect on survival, with sufficient power only to demonstrate pathological upstaging, whose effects on survival could become evident with longer follow-up.

Timing of NAC and then RC

In clinical practice there is debate on how much an invasive intervention such as RC should be delayed after NAC in order to maximize the patient's recovery and ability to tolerate surgery without affecting the oncological outcomes and there is general agreement that RC should be delayed for a period after the last dose of NAC in order to maximize the patient's blood counts and perhaps ability to tolerate surgery. In this context, RCTs investigating NAC provides more information on the time frame between RC and NAC (*Table 1*).

A population based study from the Netherlands including 1,782 patients reported that a delay in RC greater than 3 months was not associated with OS (HR 0.9; 95% CI: 0.45–1.82); notably 93% of the patients in the cohort underwent RC within 3 months thus limiting the number of patients with delayed treatment. Interestingly this study a separate subgroup analysis was performed for 105 patients who underwent neoadjuvant treatment (NAC =91, radiotherapy =14) and again failed to find association between timing to RC and OS (HR 0.9; 95% CI: 0.45–1.82). Investigation for the potential causes of delay in RC found that patients who were older than 75 years (OR 0.5; 95% CI: 0.32–0.77), treated in a university hospital (OR 0.34; 95% CI: 0.21–0.56) and being referred from another hospital for RC (OR 0.41; 95% CI: 0.26–0.69) were less likely to undergo RC within 3 months (33).

Alva *et al.* specifically investigated the impact of the timing of cystectomy delivery after NAC on survival in patients with MIBC in a collaborative, multidisciplinary cancer program at an academic tertiary care center using a cohort of 153 patients (6 of them did not receive platinum-based NAC). The median time to RC from the termination of NAC was <7 weeks (range, 1.7–179.6 weeks); age, NAC regimen, site of NAC delivery and clinical stage had no influence in time to RC. The authors performed an analysis on survival stratified on weekly intervals of time to RC from NAC termination: no differences in CSS and OS for those undergoing RC within 4 and 12 from the termination

Table 1 Main RCTs investigating efficacy of NAC

Study	Year	Regimen	Time from diagnosis to NAC	Intervention	Time from NAC to intervention
Wallace (18)	1991	Cisplatin	N/D	RT	10 days–3 week
Martinez-Piñeiro (19)	1993	Cisplatin	N/D	RC	3–4 weeks
Shiple (20)	1998	MCV	N/D	RT + cisplatin ± RC	N/D
Bassi (21)	1999	MVAC	N/D	RC	N/D
Sengeløv (22)	2002	Cisplatin + MTX	N/D	RT or RC	3–4 weeks
Osman (23)	2014	CG	N/D	RC	Surgery at mean 2 w after NAC (range, 10–21 days)/mean of 3 weeks after diagnosis (range, 17–30 days)
Grossman (24)	2003	MVAC	N/D	RC	RC in 17 days (median, 16 days; range, 1 to 55 days). Patients in the combination-therapy group underwent cystectomy a mean of 115 days after randomization (median, 113 days; range, 11 to 169 days)
Khaled (25)	2014	CG	N/D	RC or RT	10 to 21 days for RT, N/D for RC
Kitamura (26)	2014	MVAC	Within 28 days of randomization	RC	Within 28 days of randomization or after NAC end
ICT (27,28)	2011	MCV	N/D	RC or RT	N/D
Sherif (29)	2004	Cisplatin + adriamycin or MTX	N/D	RT + RC or RC	N/D
Plimack (30)	2014	AMVAC	N/D	RC	Median time from NAC start to RC =9.7 weeks
Choueriri (31)	2014	ddMVAC	N/D	RC	Median time from NAC end to RC =6 weeks (range, 4–12 weeks)

RCT, randomized clinical trial; NAC, neoadjuvant chemotherapy; RC, radical cystectomy; N/D, not described.

of NAC were found, thus suggesting this as a reasonable timing for surgery. More extreme time points were represented by too few patients for a reliable evaluation. When analyzing the potential causes for cystectomy delivery beyond 10 weeks (20% of the cohort), scheduling issues were the most reported factor (39%) (34).

Park *et al.* presented the results related to a retrospective cohort of 201 patients treated with NAC (mainly cisplatin based regimens) at the John Hopkins Hospital, with median follow-up of 24 months regarding three treatment intervals: OS for those receiving NAC within 6 weeks from TURBT was not different from NAC delayed after 6 weeks from TURBT (HR 1.28, 95% CI: 0.75–2.20, $P=0.360$), as it was for cystectomy performed before or after 28 weeks from the diagnostic TURBT (HR 0.68, 95% CI: 0.28–1.63, $P=0.388$) and for those who underwent RC before and after 22 weeks from the initiation of NAC (HR 1.12, 95% CI: 0.470–2.60,

$P=0.801$), interestingly however survival curves show a non-significant divergence after 3 years of follow-up that might have been captured with longer follow up (median follow up of 24 months) (35). Additionally in this single-center experience 56.7% of the population did not complete the 3 cycles of chemotherapy, this was found to be a predictor of poor survival but it is actually impossible to discriminate whether the unknown causing factors of incomplete NAC could impact the delay of treatment (36).

Another single-center cohort of 306 patients undergoing NAC for cT2–4,N0,M0 at the University of Texas MD Anderson Cancer Center was analyzed in order to identify the optimal recovery window of time between NAC and RC. With a median recovery window of 46 (range, 18–199) days, the time from the last day of NAC to RC was categorized in 21 days intervals; patients with a recovery window of 64–84 days had the highest median age.

Amongst the four recovery windows no differences were found in perioperative complications and overall morbidity ($P=0.735$) and in the multivariate model only age and surgical duration were predictors of major complications. A non-significant trend towards extra-vesical disease was found shorter recovery windows (between 18 and 63 days). Interestingly only a recovery window equal or greater than 85 days was a predictor of lymph node metastasis (OR 2.92, 95% CI: 1.20–7.09; $P=0.0180$). Overall these results suggest that early cystectomy is feasible does not impact on surgical complications. Hence, recovery time between NAC and RC may represent factor that can be modeled on the patient's characteristics and performance after NAC, with potential negative oncological impact if excessively prolonged (37).

Boeri *et al.* presented the Mayo Clinic experience on the effect of time from last cycle of NAC to RC on survival outcomes in a retrospective cohort of 226 patients with T2-4, N0, M0 pure urothelial MIBC undergoing at least 3 cycles of cisplatin-based NAC. A time to cystectomy greater than 10 weeks was associated with worse OS ($P=0.003$) and CSS ($P<0.001$) and this significant difference is maintained increasing the number of weeks of delay; regarding potential clinic-pathological causes of the delay the only factor found to be significant was the burden of comorbidities while the study lacked on information regarding treatment toxicity or logistic causes of delay (38).

A study on 1,509 MIBC patients from SEER database by Chu *et al.* recently reported that among patients younger than 80 years, mortality increased with delays in first-line RC beyond 12 weeks (HR 1.39; $P<0.05$) but this impact was not confirmed for patients older than 80 years ($P=0.67$). Within patients undergoing NAC (18%) no interaction was found between patient age and delay in RC. Overall delays in RC were associated with increased OM both in patient receiving NAC (HR 1.63; 95% CI, 1.06–2.52, $P<0.05$) and in those undergoing upfront RC (HR 1.34; 95% CI: 1.03–1.76, $P<0.05$). Associations between patient, provider, or health system factors and delay were not found (39).

Many patients are referred to an academic center for RC but some of them return to community oncology, before RC, to undergo NAC. This raises a potential issue of treatment coordination causing potential delays. Rose *et al.* analyzed the median number of days between the diagnosis and RC and this was found to be longer ($P=0.015$) when NAC was given in the community setting in comparison to when it was given in the same academic center that eventually performed the RC, but there were not differences in pathological response ($P=0.81$), DFS ($P=0.50$)

or OS ($P=0.20$). Given the comparable chemotherapy regimens, doses and complications, authors suggest that the main causes driving this delay in RC are related to poor transitions of care between academic and community setting. This 43-day delay in RC for those undergoing NAC at an outside facility however did not translate into clinical consequences, however these results should be read in light of a relatively small sample size (94 total patients) and follow-up (median less than 10 months) (40). In light of these results a large, multi-institutional tertiary care cohort of 3,957 patients undergoing RC was used to evaluate the association of distance to tertiary center and survival outcomes. In the overall cohort distance to the facility did not influence oncologic outcomes in tertiary center, also after adjusting for NAC use. Interestingly among patients eligible for NAC, those who lived at greater distance from the tertiary center were more likely to undergo NAC and experience shorter form diagnosis to RC; this could be explained by a referral bias that affects tertiary centers (41).

Discussion

Despite guidelines recommendation based on several RCTs and recent studies reporting that NAC is well tolerated by patients (42), the survival benefit on a population-based scale was not reproduced, especially in pT2N0 patients (43,44). Additionally, a theoretical possibility of adverse outcomes exists for patients who experience RC delay because of complications from NAC. These equivocal results might be influential into clinical practice leading to underutilization of NAC.

The appropriate timing of NAC initiation, subsequent recovery and surgery remains controversial and *Table 2* summarizes the main findings of the discussed studies. RCTs testing the survival outcomes of delay in treatment are clearly unethical, thus retrospective observational studies with major inherent selection bias are the only option to study this topic. Additionally, it is unlikely that novel trials are to be designed given the advent of immunotherapy

In this manuscript we reviewed current evidence regarding the definition of delay in each treatment step and its impact. Different single-institutional cohorts were reported with limitations mainly connected to the highly selected population in referral centers. On the other hand, administrative databases suffer of inherent confounding by possible coding inaccuracies, incomplete data entry and dependence on data codes that restrict the factors available for analysis. It is not surprising then that no uniform results

Table 2 studies investigating the effect of delay in BCa treatment

Study	Patient population	Definition of delay	Results
Sanchez-Ortiz <i>et al.</i> (7)	290 NMIBC and MIBC patients	12 weeks from TURBT to RC	Greater extravesical disease, nodal involvement and OS for delayed RC
Chang <i>et al.</i> (8)	153 MIBC patients	90 days from TURBT to RC	Greater extravesical disease in delayed RC
Hara <i>et al.</i> (9)	50 MIBC patients	3 months from TURBT to RC	Greater vascular involvement in delayed RC
Mahmud <i>et al.</i> (10)	1,592 patients undergoing RC	12 weeks from TURBT to RC	Lower OS for delayed RC
Lee <i>et al.</i> (11)	214 T2N0M0 patients	93 days from TURBT to RC	Lower OS for delayed RC
Gore <i>et al.</i> (12)	441 T2N0M0 patients	12 weeks from TURBT to RC	Lower OS and CSS for delayed RC
Turk (14)	396 NMIBC and MIBC patients	3 months from TURBT to RC	Lower OS and DFS for delayed RC
Haas (15)	117 NMIBC patients	One additional course of intravesical therapy before RC	No differences in upstaging and survival
Lin-Brandt (17)	363 MIBC patients	8 weeks from TURBT to variant histology	Worse OS for delayed RC in patients with variant histology
Audenet <i>et al.</i> (32)	2,227 cT2-4N0M0 patients treated with NAC and RC	8 weeks from TRUBT to NAC	Pathologic upstaging for delayed NAC
Bruins <i>et al.</i> (33)	1,782 RC patients, 91 NAC patients	3 months from TURBT to RC	No differences in OS for delayed RC
Alva <i>et al.</i> (34)	153 NAC patients	12 weeks from NAC termination to RC	No survival differences for RC performed between 4 and 12 weeks after NAC
Park <i>et al.</i> (35)	232 RC alone patients, 201 NAC patients	28 weeks from TURBT to RC, 22 weeks from NAC initiation to RC, 6 weeks from TURBT to NAC initiation	No difference in OS for the intervals evaluated
Mmeje <i>et al.</i> (37)	306 NAC patients	Different recovery windows from NAC termination to RC	No differences in complications and morbidity, increased risk of lymph node metastases for recovery time >85 days
Boeri <i>et al.</i> (38)	226 NAC patients	10 weeks from NAC termination to RC	Worse OS and CSS for delayed RC
Chu <i>et al.</i> (39)	1,238 primary RC, 271 NAC patients	12 weeks from diagnosis to RC, 11 weeks after the termination of NAC	Worse OS for delayed RC only in patients younger than 80 years, no interaction for patients receiving NAC

MIBC, muscle-invasive bladder cancer; NMIBC, non muscle-invasive bladder cancer; RC, radical cystectomy; CSS, cancer specific survival; DFS, disease-free survival; OS, overall survival; NAC, neoadjuvant chemotherapy.

are reported.

Without NAC, delayed RC is associated with worse survival outcomes that seem not directly related to local progression (11); this relationship might be related to micrometastatic spread and vascular invasion however there is lack of reported sites of tumor progression in studies evaluating RC delay. The action on micrometastases is indeed one of the proposed mechanisms of action of NAC. In light of this, it seems logical to acknowledge the importance of time to effective treatment, being it either

RC or NAC. 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. We reviewed how time to NAC start is poorly mentioned in NAC studies and only two studies (32,35) directly investigated the potential impact of this timing: the results of both studies show no significant impact on survival outcomes, although captured trends may potentially become significant with longer follow-up times. On the other hand it is possible that NAC, given the ability

to cure and prevent distant micro-spread of disease, might be able to “compensate” treatment delays as opposed to RC.

Provided the indication for NAC, guidelines recommend to proceed to RC in timely manner (2); the definition of timely is yet to be found. The contrasting results of the reviewed studies might be affected by the heterogeneity of included populations; some authors have included clinical N1 patients and those with mixed or variant histology in their series (34,37) or not receiving complete NAC (35). The different duration of proposed NAC regimens is another factor that might have influenced the overall timeline of patient treatments. There is however another and probably the most important bias present in the reviewed studies that is the almost complete absence data on patients who initiated NAC but did not undergo cystectomy because of either treatment-related toxicity or death, patient refusal, or disease progression.

The idea that late radical treatment could negatively impact the prognosis is common in other cancers such as breast (45), head and neck (46) and even intermediate/high risk prostate cancer (47). Despite the conflicting results that prevent to define a specific timeline of treatment for MIBC patients, delays seem a preventable and modifiable factor which is a result of a combination of scheduling preparatory visits, restaging evaluation, secondary opinion, recovery between treatment and preparation for surgical procedure. The lack of communication and information between healthcare providers and patients and within healthcare providers, particularly when different institutions are involved, could affect negatively outcomes of such a highly aggressive disease.

Conclusions

Multimodal treatment of MIBC with NAC followed by RC is encouraged but can cause delays that potentially affect the efficacy of treatments. Although high-level evidence supporting a direct relationship between treatment delay and prognosis is lacking, it is reasonable to invest any effort in reducing time to the initiation of the primary effective treatment (either RC or NAC) as well as reducing the interval between NAC and RC, as most of the described causes of delay are preventable and there is no evidence that early treatment can cause any harm.

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