A Retrospective Analysis of the Effect on Survival of Time from Diagnosis to Neoadjuvant Chemotherapy to Cystectomy for Muscle Invasive Bladder Cancer

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Abbreviations and Acronyms

GC = gemcitabine and cisplatin

MIBC = muscle invasive bladder cancer

MVAC = methotrexate, vinblastine, doxorubicin and cisplatin

NAC = neoadjuvant chemotherapy

OS = overall survival

RC = radical cystectomy

TURBT = transurethral resection of bladder tumor

ypCR = complete pathological response after NAC

ypPR = partial pathological response after NAC

Purpose: We determine the impact of the timing of radical cystectomy from the diagnosis of muscle invasive bladder cancer on survival in patients also treated with neoadjuvant chemotherapy.

Materials and Methods: We performed a retrospective chart review of consecutive patients with muscle invasive bladder cancer who received neoadjuvant chemotherapy followed by cystectomy between 1996 and 2014 at a single institution. Cox proportional hazards regression models were used to investigate the effect of treatment time intervals on overall survival. Three treatment intervals were analyzed for survival impact, from diagnosis of muscle invasive bladder cancer to initiation of neoadjuvant chemotherapy, from initiation of neoadjuvant chemotherapy to cystectomy and from diagnosis to cystectomy. Other pretreatment and posttreatment clinicopathological parameters were also analyzed.

Results: Median time from the diagnosis of muscle invasive bladder cancer to radical cystectomy was 28 weeks. Cystectomy performed less than 28 weeks from the diagnosis did not result in significant improvement in overall survival outcomes (HR 0.68, 95% CI 0.28−1.63, p=0.388). Neither the timing of neoadjuvant chemotherapy initiation from diagnosis (median 6 weeks) nor the timing of cystectomy from neoadjuvant chemotherapy initiation (median 22 weeks) was associated with survival. Patient age, variant histology, extravesical and/or lymph node involvement (T3-4 and/or N1 or greater) were significantly associated with survival.

Accepted for publication November 9, 2015.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

* No direct or indirect commercial incentive associated with publishing this article.

† Financial interest and/or other relationship with Elsevier, Photocure SA, Heat Biologics and Theracoat Ltd.

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0022-5347/16/1954-0880/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2015.11.024
Vol. 195, 880-885, April 2016
Printed in U.S.A.

Conclusions: The timing of radical cystectomy in relation to muscle invasive bladder cancer diagnosis date does not significantly impact overall survival in patients with muscle invasive bladder cancer receiving neoadjuvant chemotherapy.

Key Words: urinary bladder neoplasms, neoadjuvant therapy, cystectomy, time factors

RADICAL cystectomy is the mainstay treatment for muscle invasive bladder cancer. However, surgery alone is associated with a suboptimal disease control rate and survival due in part to micrometastases. Due to its proven improvement in overall survival in randomized trials, cisplatin based combination chemotherapy given before cystectomy is recommended for patients with MIBC eligible to receive cisplatin.[1]

Several studies have evaluated various clinical factors for the prognosis of MIBC. Extravesical tumor stage (T3-4), advanced age, nonurothelial variant histology and a reduced number of lymph nodes removed have been established as poor prognostic factors for patients treated with radical cystectomy.[2–6] In addition, the timing of radical cystectomy has been proposed to be another prognostic factor for MIBC.[7–10] Several studies suggested that delay of cystectomy by more than 12 weeks from the diagnosis date is associated with inferior survival.[11] However, these studies were performed before the wide acceptance of cisplatin based neoadjuvant chemotherapy. Thus, these efforts mainly evaluated patients who were treated with surgery alone or mixed populations with small proportions of patients receiving various perioperative therapies. Investigations examining the relationship between time from diagnosis to cystectomy in patients treated with NAC are lacking. Therefore, we conducted the current study to determine the effect on survival of the timing of radical cystectomy from the diagnosis of MIBC in patients who received NAC.

MATERIALS AND METHODS

Patient Population

The Johns Hopkins Hospital institutional review board approved (N0:03-03-07-02d) bladder cancer database was queried to identify patients who received NAC and underwent radical cystectomy between 1996 and 2014. Patients with known clinical metastatic disease or noninvasive disease, with tumor with small cell histology, who received concurrent chemoradiation therapy and whose data were incomplete for analysis, were excluded from the study.

Clinical and Pathological Data Evaluation

Patient charts were reviewed for 1) baseline pretreatment characteristics including demographics, clinical stage, histology and previous intravesical therapy history; 2) intervals between diagnosis of MIBC at TURBT and the initiation of NAC and radical cystectomy; and 3) post-treatment and treatment clinical and pathological characteristics.

Study End Points

Tumor staging was analyzed by standard American Joint Committee on Cancer TNM criteria.[12] Complete pathological response after NAC (ypCR) was defined as the complete absence of any viable remaining urothelial carcinoma (including Tis, Ta, T1) on pathological examination of the cystectomy tissues. Partial pathological response after NAC (ypPR) was defined as the absence of any muscle invasive urothelial carcinoma on pathological examination of the cystectomy tissues. Pathological response rate (ypRR) was defined as the total percentage of patients achieving a ypCR or ypPR after NAC. Overall survival was defined as the duration of time from the diagnosis of MIBC to death from any cause. Survival status was verified using clinical records, physician reports, the Social Security Death Index website and by other means (ie obituary) for any patients lost to followup.

Statistical Analysis

Data were analyzed using SPSS® Statistics version 22. Chi-square testing was used to analyze categorical variables and Student's t-test was used to analyze continuous variables. Associations between variables and OS were analyzed by Cox proportional hazards regression for survival analysis, with data summarized by hazard ratios with 95% CIs. A level of significance was set at $p < 0.05$ for all analyses.

RESULTS

Study Population

Between January 1996 and August 2014, 314 consecutive patients received NAC followed by cystectomy at the Johns Hopkins Hospital. Reasons for patient exclusion are summarized in figure 1. A total of 201 patients comprised the final study group. The majority of patients (193, 96%) were treated between 2004 and 2014. During this same time 232 patients with MIBC were treated at our institution with cystectomy alone. The NAC study population was characterized by a mean patient age of 61.8 years (range 39 to 83) with the majority being male (159 of 201, 79%) and Caucasian (185 of 201, 92%). More than a third of patients had extravesical disease at diagnosis, with 57 (28%) and 14 (7%) patients with clinical T3 and T4 disease, respectively. There were

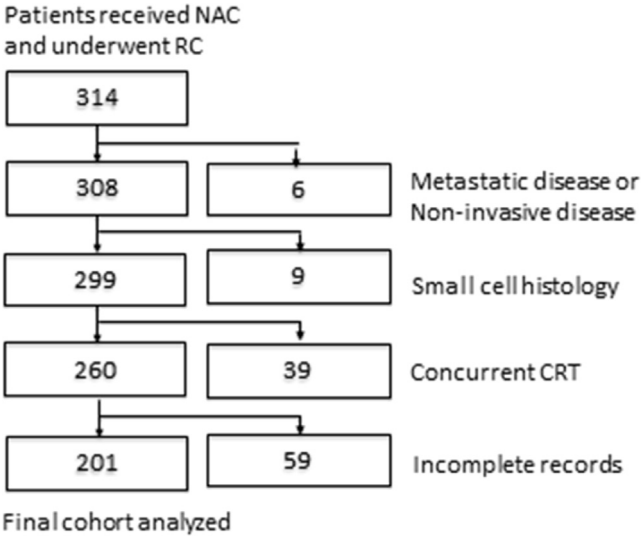

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram shows study cohort of 201 patients who received NAC and underwent RC for MIBC. *CRT,* chemoradiation therapy.

19 patients (9%) who had clinical evidence of lymph node involvement. Most tumors were pure urothelial carcinoma histology but 58 tumors (29%) had variant histologies including squamous and adenomatous differentiation, micropapillary and sarcomatoid variants. All tumors analyzed in this study were high grade. A minority of patients had previous intravesical bacillus Calmette-Guérin or chemotherapy for nonmuscle invasive disease (18 of 201, 9%).

Neoadjuvant Treatment Regimens

Gemcitabine and cisplatin was the most frequently administered chemotherapy regimen (in 168, 83.5%). Only 10 patients (5.0%) received a standard or dose dense MVAC regimen. Noncisplatin based regimens were used in 17 patients (9%), most of which were carboplatin based combinations. Median number of NAC cycles was 3.

Tumor Response

At cystectomy 44 (22%) patients achieved a complete pathological response (ypCR) and 58 (29%) patients achieved a partial pathological response (ypPR) with residual nonmuscle invasive disease (ypTa, Tis or T1) at cystectomy. Thus, the pathological response rate (ypRR) was 51%. Extravesical disease (ypT3,T4) and/or node positive disease (ypN 1 or greater) was found in 41 patients (20%).

Survival

Median followup was 24 months. Median OS was 43.2 months (95% CI 10.3–76.1). On univariable Cox regression analysis for overall survival age less than 62 years (HR 0.56, 95% CI 0.33–0.96, $p = 0.034$) and pure urothelial histology (HR 0.42, 95% CI 0.24–0.68, $p = 0.001$) were associated with statistically significant favorable survival. In contrast, less than 3 cycles of chemotherapy was associated with poor survival (HR 1.75, 95% CI 1.04–2.96). Similarly, patients with pathological extravesical disease (ypT3,T4) and/or node positive disease (ypN greater than 1) had significantly inferior survival outcomes compared to those with organ confined disease (HR 5.17, 95% CI 2.08–12.85, $p = 0.001$, table 1).

Association of OS and Treatment Intervals

Three treatment related intervals were analyzed for correlation with survival, including 1) from MIBC diagnosis on TURBT to the initiation of NAC, 2) from initiation of NAC to the radical cystectomy and 3) from MIBC diagnosis to radical cystectomy. Median durations of each interval were 42 days (6 weeks), 151 days (22 weeks) and 199 days (28 weeks), respectively. None of the treatment intervals was significantly associated with OS (table 2, fig. 2). Median survival for patients with cystectomy performed less than 28 weeks from TURBT diagnosis was not significantly different compared to a survival for patients with cystectomy performed beyond 28 weeks from TURBT diagnosis date (HR 0.68, 95% CI 0.28–1.63, $p = 0.388$). Similarly, the difference in median survival between patients who received NAC within 6 weeks from TURBT diagnosis date and those whose NAC was delayed beyond 6 weeks was not significant (HR 1.28, 95% CI 0.75–2.20, $p = 0.360$). Lastly, the timing of cystectomy from the initiation of NAC before and after 22 weeks did not have a significant impact on median survival (HR 1.12, 95% CI 0.47–2.60, $p = 0.801$).

Table 1. *Treatment related and posttreatment characteristics*

	No. (%)
Cisplatin based NAC:	
MVAC	10 (5.0)
GC	168 (83.5)
Other*	6 (3.0)
Noncisplatin based NAC	17 (8.5)
No. NAC cycles:	
Less than 3	114 (56.7)
3 or Greater	87 (43.3)
Pathological T stage:	
Complete response (ypT0)	44 (21.9)
Noninvasive disease (ypTa,Tis,T1)	62 (30.8)
Invasive disease:	
ypT2	23 (11.4)
yp3/4	77 (38.3)
Pathological N stage:	
ypN0	160 (79.6)
ypN≥1	41 (20.4)

* Carboplatin/paclitaxel, carboplatin/gemcitabine, cisplatin/gemcitabine/paclitaxel, cisplatin/paclitaxel, ifosfamide.

Table 2. *Cox regression of treatment time intervals*

	Days	HR (95% CI)	p Value
Diagnosis to NAC	Less than 42	1.28 (0.75–2.20)	0.360
NAC to RC	Less than 151	1.12 (0.47–2.60)	0.801
Diagnosis to RC	Less than 199	0.68 (0.28–1.63)	0.388

DISCUSSION

Several studies have evaluated the effect of the timing of radical cystectomy on clinical outcomes in patients with MIBC. A delay of surgery has been reported to be associated with a significantly higher incidence of nonorgan confined disease (pT3-4) and increase in the rate of lymph node metastases (pN+).[13–15] Chang et al reported that patients who underwent cystectomy after 90 days from diagnosis were more likely to have nonorgan confined disease (pT3 or greater) than those who underwent cystectomy within 90 days (81% vs 52%, p = 0.01).[13] Furthermore, such delay in cystectomy has been found to result in poor overall survival. In the report by Sanchez-Ortiz et al analyzing 189 patients with MIBC from 1987 and 2000, a surgery delay longer than 12 weeks from diagnosis was correlated with lower 3-year estimated survival compared with a shorter interval (HR 2.51, p = 0.006).[15] In a more recent report Mahmud et al evaluated 1,315 patients who had cystectomy in Canada from 1990 to 2002.[16] The authors found that delay of surgery by more than 12 weeks from the diagnosis was associated with poor OS (adjusted HR 1.2, p = 0.051). ICUD-EAU (International Consultation on Urological Diseases-European Association of Urology) 2012 guidelines state that delay of radical cystectomy in MIBC for more than 12 weeks after initial diagnosis is associated with reduced cancer specific survival based on the similar observation by Gore et al[17] from outcomes in cystectomy case analysis of the SEER (Surveillance, Epidemiology, and End Results)-Medicare database treated between 1992 and 2001.[18] However, these studies were performed before NAC became the standard of care for MIBC. Although the first study that demonstrated a survival benefit of NAC with MVAC regimen (SWOG 8710) was reported in 2003,[1] followed by supporting meta-analyses,[19–22] it is only recently that the use of NAC has been more frequently accepted.[23] Thus, it is not yet clear whether the association between timing of cystectomy and survival remains significant in patients with MIBC who receive NAC.

In this study we evaluated the impact of timing of cystectomy from diagnosis in patients who received NAC at our institution. Median time from diagnosis to cystectomy was 199 days (28 weeks). Interestingly our study did not reveal a significant correlation between longer time to cystectomy (more than 28 weeks) and overall survival. This finding is consistent with a recent single institution experience reported by Parker et al which evaluated the impact of RC timing on survival.[24] In their analysis of 72 patients with MIBC who underwent radical cystectomy after NAC, the mean time from diagnosis to RC was 173 days, which is similar to our experience of 199 days. When stratifying the cohort by time to RC (1 to 4, 5 and 6 months) there was no statistical difference in recurrence-free or cancer specific survival among the groups.

We also evaluated the individual impacts of the time between diagnosis to start of NAC and start of NAC to RC. Median length of each interval was 42 days (6 weeks) and 151 days (22 weeks), respectively. Neither period had an effect on OS. With 4 cycles of standard GC NAC requiring 12 weeks to administer, the median time from initiation of NAC to cystectomy of 22 weeks in our study implies a rough average estimate of 10 weeks from completion

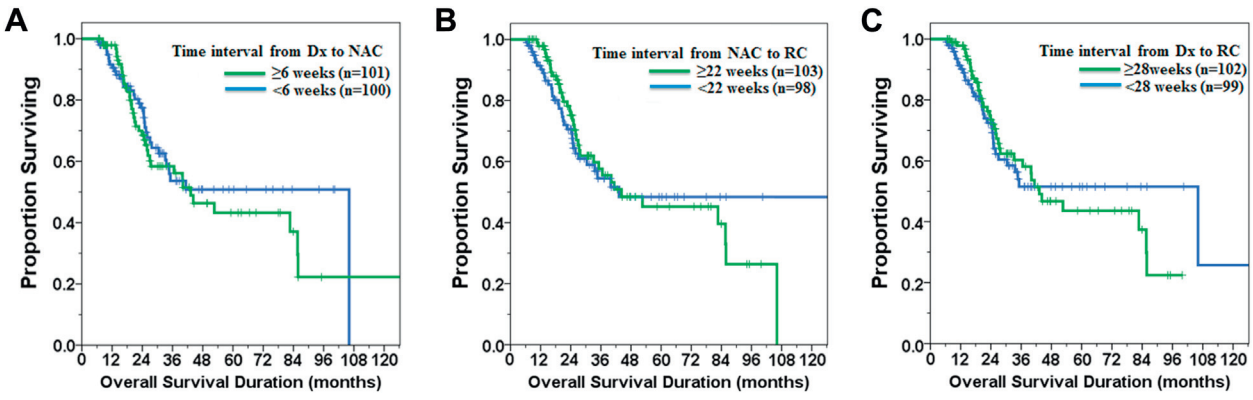

Figure 2. Kaplan-Meier estimated OS for each treatment interval. Timing of NAC initiation from diagnosis (*A*), RC from NAC initiation (*B*) or from diagnosis (*C*) was not associated with statistically significant difference in OS. Dx, diagnosis date from TURBT. *NAC*, initiation date of NAC. *RC*, date of RC.

of NAC to cystectomy. This time span is in agreement with a review evaluating the impact of the timing of cystectomy from completion of NAC on survival in patients with MIBC.[25] In this report cystectomy performed up to 10 weeks after the completion of NAC did not impact survival.[25]

In our study various clinical and pathological factors were also analyzed for their association with survival. The impact of variant histology on survival was highly significant, highlighting the need for the better characterization and development of new systemic regimens for those variant histologies. Younger patients (age less than 62 years) were associated with favorable survival in our study. However, we should not exclude patients from NAC if they have good functional status, as suggested by a recent report by Chau et al, which showed that elderly patients (age 70 or older) with good functional status and limited comorbidities diagnosed with MIBC receiving NAC achieved clinical outcomes similar to those of their younger counterparts.[26] In terms of posttreatment and treatment related factors, chemotherapy cycles less than 3 and pathological extravesical disease as well as lymph node involvement were associated with poor survival. This finding suggests that at least 3 total cycles of NAC are needed for the appropriate benefit and that the development of validated predictive markers to NAC regimen is warranted to select the patients who are likely to benefit from certain NAC regimens. This is an area of active investigation and various molecular markers of genes involved in DNA repair pathways (*ERCC2, ATM, RB1, FANCC*) have been proposed.[27–29] The COXEN (CO-eXpression ExtrapolatioN) algorithm is an example addressing this issue which is currently being prospectively validated in a clinical trial (NCT02177695).

To the best of our knowledge, our study is the first to analyze the impact of each treatment time interval on overall survival in patients with MIBC who received NAC. However, our study has several noteworthy limitations, such as inherent selection bias of retrospective review, relatively small sample size and a short followup time. Thus, the results should be interpreted with caution. Patients in our cohort are young (median age of 62) and mostly of Caucasian ethnicity with well preserved organ function. Thus, our study population may not represent average patients with MIBC. Of note, a large proportion of patients in our cohort received NAC by their treating community oncologists. The majority of patients received GC while only 5% of patients were administered an MVAC containing regimen. This reflects current practice where the GC regimen is widely accepted in the neoadjuvant setting due to its favorable safety profiles and efficacy comparable to that of MVAC shown in advanced urothelial carcinoma.[20] Furthermore, patients treated with NAC who had progression or toxicity that prevented cystectomy were not captured in our database. In our experience the frequency of this event is exceedingly rare (less than 5%). However, the absence of definitive data in our cohort is a limitation which highlights the need for prospective inclusion of such patients in future followup reports on this cohort. In our Kaplan-Meier survival plots the curves of cystectomy time 28 weeks or greater and less than 28 weeks from diagnosis overlap in the first 3 years then seem to diverge, suggesting a longer followup may result in a significant difference. Thus, our findings, which are consistent with recent small retrospective reviews from other institutions that showed no correlation between the timing of RC or NAC and survival, need to be validated in larger populations with longer followup. We continue to accumulate our data and plan to perform another analysis in the future.

CONCLUSIONS

An association between overall survival and the time between MIBC diagnosis and cystectomy was not observed in patients with MIBC receiving NAC in our single institution analysis. Our findings reinforce the role of NAC in patients with MIBC eligible for cisplatin. However, delays in treatment should not be legitimized based on our findings. Moreover, in patients not receiving NAC, time to cystectomy has been associated with survival outcomes. Thus, for patients not receiving NAC, prompt surgical intervention remains the standard of care.

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