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Is neoadjuvant chemotherapy for pT2 bladder cancer associated with a survival benefit in a population-based analysis?

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ABSTRACT

Background: Patients with organ confined muscle-invasive bladder cancer (MIBC) who are candidates for radical cystectomy (RC) should receive neoadjuvant chemotherapy (CHT). However, the most contemporary CHT use rates indicate low adherence to these guidelines. We tested contemporary neoadjuvant CHT rates and associated cancer-specific mortality (CSM) and overall mortality (OM) in pT2N0 MIBC patients treated with RC.

Materials and methods: Within the SEER database (2004–2015), we identified patients with pT2N0 MIBC patients who underwent RC. CHT administration rates were evaluated using estimated annual percentage changes (EAPCs) analyses. After inverse probability of treatment weighting (IPTW), Kaplan–Meier (KM) analyses and Cox regression models (CRMs) were used to test the effect of CHT vs no CHT on survival. Landmark analyses tested for immortal time bias.

Results: Of 3978 RC patients, 38.2% of patients received CHT. Between 2004 and 2015, CHT rates increased from 15.9% to 66.2% (EAPC: +14.2%; $p < 0.001$). IPTW-adjusted KM showed 10-year CSM-free survival rates of 78.9% for CHT vs 76.7% for no CHT patients ($p = 0.6$). Similarly, IPTW-adjusted KM showed 10-year OM-free survival rates of 54.6% for CHT vs 57.9% for no CHT patients ($p = 0.8$). In IPTW-adjusted MCRMs, CHT was not significantly associated with lower CSM (HR 0.97, CI 0.82–1.14; $p = 0.7$) or OM (HR 1.02, CI 0.90–1.16; $p = 0.7$). Virtually the same CSM and OM rates were recorded after landmark analyses.

Conclusions: CHT use in pT2N0 MIBC RC patients sharply increased over the study span. However, neoadjuvant CHT was not associated with better survival in this patient group.

1. Introduction

Radical cystectomy (RC) represents the standard of care for patients with pT2N0 muscle-invasive urothelial carcinoma of the bladder (MIBC) [1–3]. Patients who are candidates for RC should also receive neoadjuvant chemotherapy (CHT), if eligible. The neoadjuvant CHT recommendations originates from several randomized clinical trials (RCTs) that showed improved survival after cisplatinum-based regimens vs RC alone [4–7]. However, all such trials failed to demonstrate a clear survival advantage in the context of pT2 MIBC. Additionally, most such trials did not stratify according to pT2N0 vs more advanced stage [6,7] or did not provide stage specific HRs [4]. Moreover, a recent NCDB based analysis also failed to demonstrate a survival benefit of neoadjuvant CHT across all stages, including pT2N0 patients [8]. The equivocal nature of the evidence supporting improved survival after neoadjuvant CHT in pT2N0 patients resulted in low adoption of neoadjuvant CHT into clinical practice, as

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Table 1
Baseline characteristics of 3978 patients with organ confined node-negative (pT2N0) muscle-invasive urothelial carcinoma of the bladder treated with radical cystectomy, with or without neoadjuvant chemotherapy.

Variables		Overall (n = 3978)	CHT = Not administered (n = 2459, 61.8%)	CHT = Administered (n = 1519, 38.2%)	p value
Age at surgery (years)					< 0.001
	Median	68	69	66	
	Range	61–75	62–76	59–72	
Race, n (%)					0.008
	White	3608 (90.7)	2203 (89.6)	1405 (92.5)	
	African American	184 (4.6)	126 (5.1)	58 (3.8)	
	Other	186 (4.7)	130 (5.3)	56 (3.7)	
Gender, n (%)					0.3
	Male	3088 (77.6)	1895 (77.1)	1193 (78.5)	
	Female	890 (22.4)	564 (22.9)	326 (21.5)	
Marital status, n (%)					< 0.001
	Married	2589 (65.1)	1538 (62.5)	1051 (69.2)	
	Never Married	417 (10.5)	267 (10.9)	150 (9.9)	
	Previously Married	812 (20.4)	551 (22.4)	261 (17.2)	
	Unknown	160 (4)	103 (4.2)	57 (3.8)	
Year of surgery, n (%)					< 0.001
	2004-2009	1783 (44.8)	1388 (56.4)	395 (26)	
	2010-2015	2195 (55.2)	1071 (43.6)	1124 (74)	
Socio-economic status, n (%)					< 0.001
	High	1951 (49)	1332 (54.2)	619 (40.8)	
	Low	2027 (51)	1127 (45.8)	900 (59.2)	

CHT = Chemotherapy.

evidenced by 17% and 19% neoadjuvant CHT rates according to SEER-Medicare and NCDB-based analyses [8–11].

Our intent was to assess the most contemporary neoadjuvant CHT use rates and its efficacy in pT2N0 MIBC patients. Specifically, we hypothesized that neoadjuvant CHT rates have increased relative to the historical figures. Moreover, we postulated that such increase may have resulted in a survival benefit. To address these two endpoints, we assessed contemporary perioperative CHT administration rates in pT2N0 MIBC RC patients. Subsequently, we tested the association of between perioperative CHT versus no CHT and two mortality outcomes, namely cancer-specific mortality (CSM) and overall mortality (OM). We relied on the most contemporary version of the Surveillance, Epidemiology, and End Result (SEER) database.

2. Materials and methods

2.1. Data source and patient selection

The current study relied on the SEER database (2004–2015), which samples 26% of the United States and approximates the United States in terms of its demographic composition, as well as of its cancer incidence [12]. In the SEER database, we focused on men aged 18 years or older, diagnosed between 2004 and 2015 with histologically confirmed urothelial carcinoma of the bladder (UCB) (International Classification of Disease for Oncology [ICD-O-3] site code C67.0 to C67.9). We only considered patients with non-metastatic pT2N0 MIBC, who underwent RC with lymph node dissection (LND), with or without perioperative CHT.

CSM was defined according to the SEER mortality code. All non UCB-related deaths were considered as other-cause mortality. All autopsy or death certificate cases were excluded from the current study. Due to lack of target and dose specific information, external-beam radiotherapy (EBRT) patients were excluded from our analyses. Further exclusion criteria were: low grade disease, unknown tumor stage or grade and unknown number of lymph nodes examined. These selection criteria yielded 3978 assessable patients.

2.2. Statistical analyses and covariates

Descriptive statistics included frequencies and proportions for categorical variables. Medians and ranges were reported for continuously coded variables. The statistical significance of differences in medians and proportions was tested with Wilcoxon and chi-square tests.

To test CHT use rates and the association between perioperative CHT with mortality after RC, six specific steps were performed. First, we evaluated temporal trends in neoadjuvant CHT administration. Estimated annual percentage changes (EAPCs) were calculated with the least squares linear regression [13]. Second, we used a propensity score adjustment that relied on inverse probability of treatment-weighting (IPTW) to reduce the effect of potential selection bias [14]. Covariate balance was assessed using the standardized difference approach. Third, IPTW-adjusted Kaplan-Meier plots illustrated CSM and OM rates according to CHT use vs no use. Fourth, Cox regression models (CRMs) tested the effect of CHT on CSM and OM. Subsequently, six separate sets of models tested the effect of neoadjuvant CHT according to year of surgery (2004–2009 vs. 2010–2015), gender (male vs. female) and age category (≤ 70 vs. > 70 years old). Fifth, landmark analyses at 3-months tested for immortal time bias [14]. Finally, we performed power analysis [15] aimed to test whether the sample size available for analyses was sufficient to detect an absolute difference of 5% or 10% in CSM or OM at 10 years of follow-up, between CHT and non-CHT, for an $\alpha = 0.05$ and a $\beta = 0.1$.

In CRMs, adjustment variables consisted of age at diagnosis, year of surgery, gender, race (White, African American and other), socio-economic status (low, high) and marital status (married, unmarried, previously married, unknown). All statistical tests were two-sided with a level of significance set at $p < 0.05$. Analyses were performed using the R software (version 3.3.0; http://www.r-project.org/).

3. Results

3.1. General characteristics of the study populations

Overall, we identified 3978 patients with non-metastatic pT2N0 MIBC treated with RC between 2004 and 2015. Of these, 1519 (38.2%) underwent CHT and 2459 (61.8%) did not. CHT patients were younger (66 vs. 69 years old, $p < 0.001$), more frequently married (69.2 vs. 62.5%, $p < 0.001$) and more frequently White (92.5 vs. 89.6%, $p < 0.001$) compared to no CHT patients (Table 1). After IPTW adjustment, standardized differences of weighted comparisons between treatment groups were < 10% (Supplementary Fig. 1) .

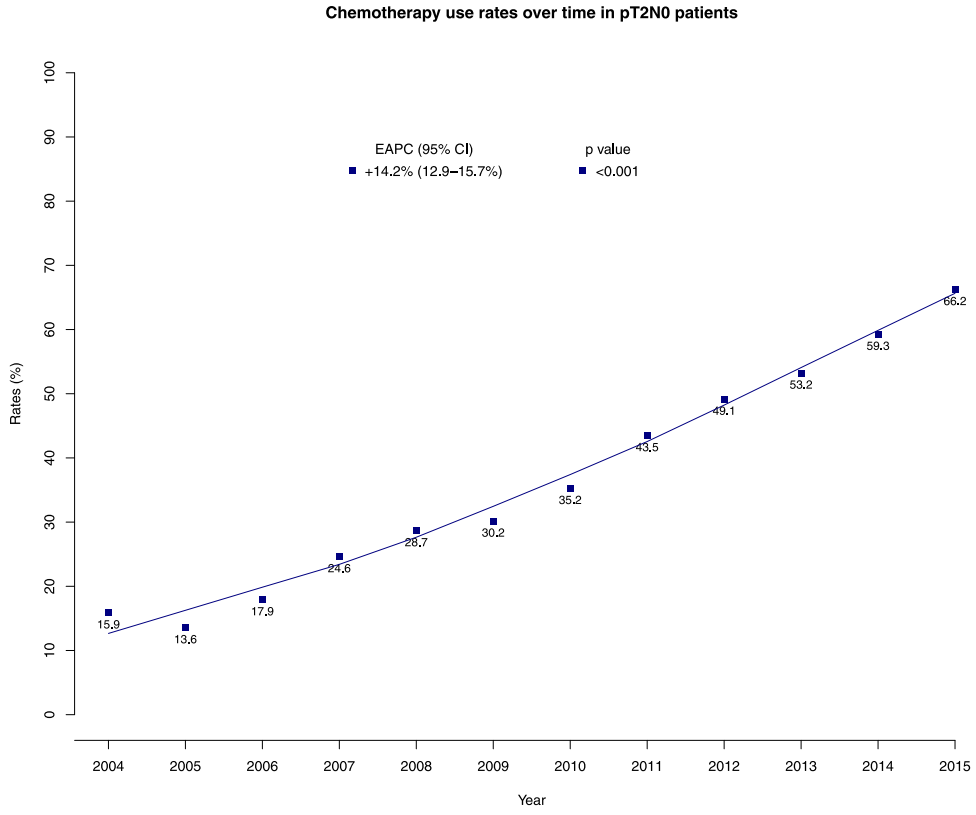

Fig. 1. Temporal trends of chemotherapy use over time in pT2N0 patients within the SEER database.

3.2. Annual trends and survival analyses

Overall, CHT administration rates increased from 15.9% to 66.2% (EAPC: +14.2%; p < 0.001) between 2004 and 2015 (Fig. 1). Before IPTW adjustment, neoadjuvant CHT was associated with lower CSM and lower OM rates. Specifically, 10-year CSM-free survival rates were 80.6% (CI: 77.2–84.1%) for CHT vs 75.6% (CI: 73.1–78.1%) for no CHT patients (p = 0.01) (Fig. 2a and b). Similarly, 10-year OM-free survival rates were, respectively, 60.3% (CI: 53.9–67.4%) for CHT vs 56.0% (CI: 52.9–59.2%) for no CHT patients (p < 0.001) (Fig. 2a and b).

After IPTW adjustment, neoadjuvant CHT was no longer associated with lower CSM and lower OM rates. Specifically, 10-year CSM-free survival rates in T2N0 patients were 78.9% (CI: 76.4–81.4%) for CHT vs 76.7% (CI: 73.8–79.8%) for no CHT patients (p = 0.6) (Fig. 2c and d). Conversely, IPTW-adjusted 10-year OM-free survival rates were 54.6% (CI: 50.2–59.4%) for CHT vs 57.9% (CI: 54.1–61.9%) for no CHT patients (p = 0.8) (Fig. 2c and d).

Similarly, after IPTW adjustment, in CRMs neoadjuvant CHT was also no longer associated with lower CSM (HR 0.97, CI 0.82–1.14; p = 0.7) and OM (HR 1.02, CI 0.90–1.16; p = 0.7) (Table 2). The results of IPTW-adjusted CRMs were confirmed in landmark analyses at 3 months for both CSM (HR 1.02, CI 0.86–1.20; p = 0.8) and OM (HR 1.06, CI 0.93–1.21; p = 0.3). Finally, power analysis revealed that our study was powered sufficiently to detect HR differences of 1.28 or more for both CSM and OM. Conversely, the current power of our analysis was 23% for detecting a HR of 1.1 and 8% for detecting a HR of 1.05.

3.3. Sensitivity analyses

Within the six sensitivity analyses, virtually the same findings as in the main analysis were obtained (Supplementary Table 1). Specifically, no difference in CSM and OM analyses that focused on different gender and age groups. Similarly, sensitivity analyses that focused on historical vs. contemporary patients demonstrated similar CSM rates with and without CHT administration. OM analysis also showed no effect of CHT in historical patients. However, when OM was analyzed in most contemporary patients, CHT administration was associated with HRs of 0.77 (p = 0.03) (Supplementary Table 1). However, this association disappeared in landmark analyses at 3 months that control for immortal time bias (HR 0.83, CI 0.65–1.05, p = 0.1).

4. Discussion

Patients with pT2N0 MIBC who are RC candidates should receive neoadjuvant CHT, if eligible [1]. Based on this international guideline recommendation, neoadjuvant CHT was adopted into clinical practice, albeit at a slowly increasing rate. For example, SEER-Medicare and NCDB data showed neoadjuvant CHT rates between 17 and 19% [8–11]. The suboptimal neoadjuvant CHT use rate may be related to equivocal survival benefits, when its efficacy was examined in pT2N0 patients. For example, Grossman et al. [4] reported a median survival of 105 vs 75 months (p = 0.05) to pT2N0 patients respectively treated with neoadjuvant CHT or no CHT. Nonetheless, these authors demonstrated a significantly higher efficacy, when neoadjuvant CHT was administered to pT3N0/N + patients (median survival 65 vs. 24 months). A similar lack of specific protective effect was reported by Sherif et al. [5]. Unfortunately, several other prospective trials of neoadjuvant CHT failed to report their results after stratification according to T and N stages [6,7]. In consequence, only two neoadjuvant CHT trials allow to formally distinguish the effect of neoadjuvant CHT vs. no neoadjuvant CHT between pT2N0 versus more advanced stage patients. However, both analyses where such distinction is possible demonstrate absence of statistically significant survival benefit of neoadjuvant CHT in pT2N0 patients [4,5]. Lack of benefits may represent an historical phenomenon and may be at least in part attributable to small sample sizes and selection biases. In consequence, we performed an observational study focusing on neoadjuvant CHT in a large cohort of pT2N0 MIBC patients treated with RC. We hypothesized that contemporary rates of CHT

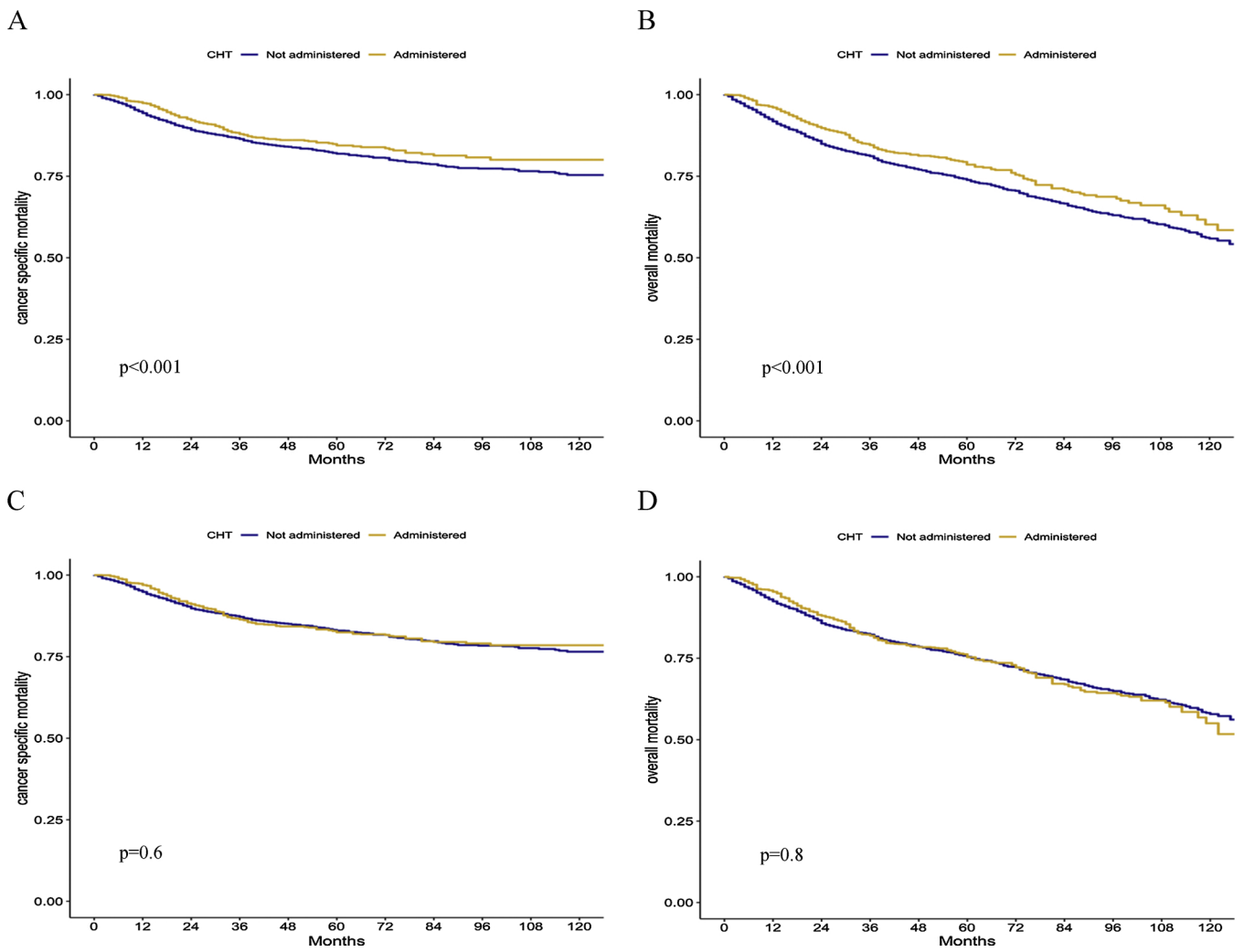

Fig. 2. Kaplan–Meier plot depicting CSM-free survival (a–c) and OM-free survival (b–d) of 3978 patients with pT2N0 muscle-invasive urothelial cancer of the bladder treated with radical cystectomy who received or not neoadjuvant chemotherapy, before (a and b) and after (c and d) inverse probability of treatment adjustment.

increased over time and that neoadjuvant CHT is associated with a clinically meaningful and statistically significantly lower OM and CSM. Our analyses revealed several noteworthy findings.

First, the rates of neoadjuvant CHT use were higher than in four previous reports [8–11]. Specifically, an increase of CHT administration rates from 32 to 56% between 2004 and 2015 was recorded. These observations are very encouraging with respect to adherence to perioperative CHT use guideline recommendations and indicate greater confidence in neoadjuvant CHT on behalf of involved clinicians.

Second, we tested the association between neoadjuvant CHT and CSM and OM endpoints. Our findings revealed statistically significantly lower CSM (80.6% vs. 75.6% 10-year CSM-free survival, $p = 0.01$) and OM (60.3 vs 56.0% 10-year CSM-free survival, $p < 001$) with neoadjuvant CHT administration in unadjusted analyses. However, after IPTW adjustment that aimed to decrease the effect of selection biases, the association between neoadjuvant CHT and lower CSM ($p = 0.6$) and OM ($p = 0.8$) disappeared. This residual lack of association between neoadjuvant CHT and lower mortality rates for both endpoints is indicative of selection biases that were likely operational. Subsequent analyses relied on IPTW adjustment, as well as on additional multivariable adjustment. Again, neoadjuvant CHT was not associated with lower CSM or OM. These findings further substantiated lack of association with lower mortality endpoints after most stringent statistical adjustment for various selection biases that may exist between neoadjuvant CHT and no neoadjuvant CHT patients. Taken together, our findings suggest absence of a potential survival benefit when neoadjuvant CHT is administered to pT2N0 MIBC patients.

Third, we relied on sensitivity analyses to test a potential association between neoadjuvant CHT and lower CSM and/or OM in specific patient subgroups, namely in males vs. female, in younger vs. older patients and in contemporary vs. historical patients. All sensitivity analyses were complemented with additional landmark analyses to control for immortal time bias. After controlling for immortal time bias, none of the sensitivity analyses revealed a statistically significant association between neoadjuvant CHT and one of the two tested endpoints (CSM and/or OM). In consequence, neoadjuvant CHT does not appear to be more effective in younger patients, in more contemporary patients or in either of the gender.

Fourth, it may be considered noteworthy that a difference in OM exists with respect to results addressing this endpoint within the subgroup of contemporary patients. Specifically, after multivariable and IPTW adjustment but prior to testing for immortal-time bias, the association between CHT and OM demonstrated a protective effect and was statistically significant. However, when 3-month landmark analysis was applied to this comparison (CHT vs no-CHT), the resulting OM effect was no longer statistically significant. It is of note that this methodology was uniformly applied in all survival analyses that addressed CSM and OM. This approach was based on the notion that immortal-time bias may result from consideration of immediate survival that is recorded after a specific procedure, in this case neoadjuvant CHT in RC patients,

Table 2
Multivariable Cox regression models predicting cancer-specific mortality and overall mortality of pT2N0 muscle-invasive bladder cancer patients treated with radical cystectomy, after inverse-probability of treatment weighting.

Variables		Cancer-specific mortality		Overall mortality	
		Hazard ratio (95% Confidence interval)	p-value	Hazard ratio (95% Confidence interval)	p-value
Chemotherapy					
	Not administered	Ref.		Ref.	
	Administered	0.97 (0.82–1.14)	0.7	1.02 (0.89–1.15)	0.8
Age at diagnosis		1.03 (1.02–1.04)	< **0.001**	1.03 (1.03–1.04)	< **0.001**
Gender					
	Male	Ref.		Ref.	
	Female	0.91 (0.74–1.11)	0.3	0.78 (0.66–0.92)	**0.003**
Race					
	White	Ref.		Ref.	
	African American	1.87 (1.36–2.57)	< **0.001**	1.80 (1.39–2.32)	< **0.001**
	Other	0.54 (0.33–0.89)	**0.02**	0.61 (0.43–0.87)	**0.006**
Year of surgery					
	2004–2009	Ref.		Ref.	
	2010–2015	0.81 (0.68–0.97)	**0.02**	0.79 (0.68–0.91)	**0.001**
Socio-economic status					
	High	Ref.		Ref.	
	Low	0.88 (0.74–1.04)	0.1	0.89 (0.78–1.02)	0.1
Marital status					
	Married	Ref.		Ref.	
	Never married	1.25 (0.95–1.65)	0.1	1.34 (1.08–1.66)	**0.007**
	Previously married	1.43 (1.16–1.75)	< **0.001**	1.57 (1.35–1.84)	< **0.001**
	Unknown	1.14 (0.71–1.81)	0.6	1.34 (0.95–1.89)	0.08

by virtue of favorable selection. Landmark analyses control for the systematic inflation of the survival benefit and should ideally be applied when a bias in survival can be operational. In the current manuscript, the application of landmark analyses indeed revealed an association between CHT and tested survival outcomes that decreased in magnitude and was no longer statistically significant, relative to results presented prior to landmark analyses. In consequence, the results of the landmark analyses indicate two important points: 1) an immortal-time bias was indeed operational in the population of contemporary patients; 2) after controlling for that bias, results no longer reached statistical significance. This methodology was applied in several previous survival analyses [14,16], even in smaller sample size analyses with more limited effect size. In these comparisons, the adjustment for immortal-time bias did not result in decreased magnitude of the protective effect or loss of statistical significance. In consequence, such methodology does not invariably eliminate the putative benefit of a treatment modality. However, its application in the current analysis did obliterate the beneficial effect of CHT on OM, as well as its significance and this result should be interpreted as final.

The cumulative interpretation of our observational results suggests that neoadjuvant CHT unlikely improves CSM and OM outcomes in pT2N0 MIBC patients. Although our analysis is observational in nature, it is in very close agreement with prospective studies that allowed subgroup analyses of neoadjuvant CHT in pT2N0 patients [4,5]. In those studies, pT2N0 patients derived no survival benefit from neoadjuvant CHT, as was the case in the current observational study. It should be of note that two of other prospective randomized trials of neoadjuvant CHT do not allow stratification of the results according to pT2N0 vs pT3 or higher stage. In consequence, a residual uncertainty persists regarding the efficacy of neoadjuvant CHT in pT2 patients. To address this uncertainty, unpublished data from previous clinical trials that specifically focus on pT2 patients without contamination with higher stages would be necessary to eliminate this uncertainty. Today, two or more decades after publication of the results or completion of these studies, it is unlikely that previously unreported data will be released into public domain. It is also quite unlikely that novel neoadjuvant CHT trials will be designed or completed. However, given the advent of immunotherapy and its promising role in MIBC, data examining neoadjuvant CHT relative to combination of neoadjuvant CHT, as well as neoadjuvant CHT relative to immunotherapy alone, may provide us with novel insight. Since such studies are already ongoing [17,18], contemporary neoadjuvant CHT efficacy results will become available within the upcoming years.

Our study is not devoid of limitations. First and foremost, our database lacks detailed information regarding CHT. Specifically, data on the exact timing of CHT administration are missing. However, both North American and European guidelines do not recommend adjuvant CHT in patients with pT2N0 at final pathology, if neoadjuvant CHT was previously administered. In consequence, no patients should have received adjuvant CHT in our analysis based on this premise. Moreover, the exact composition of CHT regimens was also not available in the current database. However, neoadjuvant CHT should only be used in patients platinum eligible, since non-platinum neoadjuvant CHT has no proven survival benefit [1]. In consequence, no patients should have received non-platinum based regimens according to these considerations. Second, the nature of the SEER database that relies on Consensus Stage assignment does not allow to discriminate between clinical and pathological UCB stage. In the setting of neoadjuvant CHT, its administration may result in partial or even complete responses. Patients with complete responses (pT0) are known to exhibit substantially better survival than those with no response (pT2). However, the proportion of pT0 patients after neoadjuvant CHT is marginal (between 7 and 10%) [19,20]. In consequence, the effect of complete response on cancer control will be equally marginal since it will only affect 7 to 10% of RC patients. Based on this consideration, we postulated that lack of ability to adjust for the effect of down-staging unlikely affected a considerable proportion of patients, i.e. no more than 10%. Additionally, lack of ability to discriminate between down-staged patients and those who have not been down-staged does not change the overall effect of CHT on the cohort of patients whose consensus stage was pT2, since down-staged and non-down-staged patients are included in this population. Therefore, the effect recorded in our analysis fully accounts for the beneficial effect of downstaging that may have occurred in some patients. In consequence, the only real limitation that is operational

within the current analysis consists of our inability to quantify CSM in the small fraction of patients that received neoadjuvant CHT and have shown a complete response. Third, it should also be emphasized that the SEER database does not provide performance status or renal function. In consequence, we could not exclude patients with poor performance status and/or poor renal function, who would usually not be offered cisplatinum-based perioperative CHT. Moreover, the SEER database does not allow adjustment for baseline comorbidities. This said, our analyses target OM, as well as CSM, and the results targeting both endpoints were virtually identical. In consequence, it is unlikely that comorbidities resulted in other-cause mortality that was differentially distributed between CHT and no CHT patients. Fourth, data regarding secondary cancer control endpoints, such as recurrence rates and progression-free survival, are unavailable in the SEER database and these represent additional weaknesses. Additionally, the SEER registry does not provide specific information on urinary diversion type and surgical approach (open vs. minimally invasive). Last but not least, the historical nature of our database does not allow the ascertainment of patients treated with immunotherapy.

5. Conclusions

CHT use in pT2N0 MIBC RC patients sharply increased over the study span. However, neoadjuvant CHT was not associated with better survival in this patient group.

Author contributions

Elio Mazzone had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial disclosures

Elio Mazzone certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

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Conflict of interest

None to declare.

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Appendix A. Supplementary data

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