European Journal of Surgical Oncology 45 (2019) 1253–1259

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Contemporary use and survival after perioperative systemic chemotherapy in patients with locally advanced non-metastatic urothelial carcinoma of the bladder treated with radical cystectomy

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ARTICLE INFO

Article history:
Received 30 November 2018
Received in revised form
17 January 2019
Accepted 29 January 2019
Available online 3 February 2019

Keywords:
Locally advanced bladder cancer
Radical cystectomy
SEER program
Cancer-specific mortality
Chemotherapy

ABSTRACT

Background: Locally advanced muscle-invasive bladder cancer (MIBC) patients who are candidates for radical cystectomy (RC) should receive perioperative chemotherapy (CHT). However, the adherence to CHT guidelines is low. Thus, we tested contemporary CHT use rates and associated cancer-specific mortality (CSM) and overall mortality (OM) rates.

Materials and methods: Within the SEER database (2004–2015), we identified pT3N0/+ MIBC patients, who underwent RC, with or without perioperative CHT. Estimated annual percentage changes (EAPCs) analyses were used. After inverse probability of treatment weighting (IPTW), Kaplan–Meier (KM) analyses and Cox regression models (CRMs) tested the association of CHT on survival in the overall population (n = 3817), as well as after stratification according to stage, gender and age. Landmark analyses tested for immortal time bias.

Results: Overall, 44.3% of patients received CHT. Between 2004 and 2015, CHT administration rates increased from 32.1% to 55.6% (EAPC: +6.0%; $p < 0.001$). In CRMs, CHT was associated with lower CSM (HR 0.73, CI 0.65–0.81) and OM (HR 0.69, CI 0.62–0.76). In sensitivity analyses, CHT was also associated with lower CSM and OM in N0 patients (CSM: HR 0.76, 95% CI 0.65–0.88; OM: HR 0.69, 95% CI 0.60–0.79) and in N+ patients (CSM: HR 0.69, 95% CI 0.59–0.80; OM: HR 0.67, 95% CI 0.58–0.77), as well as according to gender and age. Landmark analyses confirmed the above results.

Conclusions: Perioperative CHT was associated with better survival and its rate of use increased in locally-advanced MIBC RC patients. The latter confirm one large observational study and several small prospective studies.

Introduction

Radical cystectomy (RC) represents the standard of care for patients with locally-advanced muscle-invasive urothelial carcinoma of the bladder (MIBC) [1,2]. Unfortunately, half of such patients harbour T3 and/or N+ disease. Neoadjuvant or adjuvant

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https://doi.org/10.1016/j.ejso.2019.01.218
0748-7983/

chemotherapy (CHT) is strongly recommended for such patients according to both the NCCN [3] and the EAU guidelines [1]. However, the level of evidence that these recommendations are based on is relatively low. Specifically, two large randomized trials have demonstrated a benefit of neoadjuvant cisplatinum-based CHT [4,5]. However, both randomized trials enrolled relatively small patient sub-groups with locally advanced MIBC. This limitation remained in the meta-analysis that examined the combined study findings [6]. As a result, the use of neoadjuvant CHT demonstrated marginal uptake (from 17% to 19%) according to population-based figures [7–10]. Similarly, several historical adjuvant CHT trials relied on sub-optimal CHT regimens, small patient populations and/or were affected by methodological limitations that undermined their findings [11–14]. Of available trials, the three most contemporary studies [15–17] suffered of poor patient enrollment, which resulted in early closure. Given the challenges of prior prospective trials of adjuvant CHT, it is unlikely that new studies will be designed and implemented. To address that evidence gap, Galsky et al. [18] relied on the Nation Cancer Database (NCDB) to assess overall survival (OS) after adjuvant CHT for pT3 and/or N+ MIBC and showed an association with better OS.

In search of additional data examining the potential benefit of neoadjuvant or adjuvant CHT in patients with pT3 or N+ MIBC, we evaluated the Surveillance, Epidemiology, and End Result (SEER) registry. Our intent was to examine the association between perioperative CHT and cancer-specific mortality (CSM), as well as overall mortality (OM).

Materials and methods

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 demographic composition, as well as of cancer incidence [19]. 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, locally advanced (pT3N0 or pT3N+) MIBC, who underwent RC with lymph node dissection (LND), with or without perioperative CHT. Since no specific data are available to determine the exact timing of CHT administration, either before or after RC, CHT use was defined as perioperative.

CSM was defined according to the SEER mortality code. All other 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 analyses. Further exclusion criteria were: low grade disease, unknown tumor stage or grade and unknown number of lymph nodes examined. These selection criteria yielded 3817 assessable patients.

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, five specific steps were performed. First, we evaluated temporal trends of CHT administration. Estimated annual percentage changes (EAPCs) were tested with the least squares linear regression [20]. Second, we used a propensity score adjustment that relied on inverse probability of treatment-weighting (IPTW), to minimize the effect of potential selection biases [21]. Covariates included in IPTW models were age at diagnosis, year of surgery, gender, race (White, African American and other), socioeconomic status (low, high), marital status (married, unmarried, previously married, unknown) and nodal stage (N0, N+). 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 in the overall population and in specific subgroups. First, two separate sets of models tested the effect of CHT in respectively pT3N0 and pT3N+ patients. Subsequently, separate sets of models tested the effect of CHT according to gender (male vs. female), as well as age category ($\leq$70 vs. > 70 years old). Fifth, landmark analyses at 3-months tested for immortal time bias [21]. Landmark analyses control for the systematic inflation of the survival benefit and should ideally be applied, when a bias in survival can be operational. 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 perioperative CHT in RC patients, by virtue of favourable selection. Lastly, we generated a graphical depiction of the current HRs relative to those reported within the previous observational study [18] and prospective trials [12–15,17] focused on adjuvant CHT in locally advanced MIBC RC patients [22].

In CRMs, adjustment variables consisted of age at diagnosis, year of surgery, gender, race (White, African American and other), socioeconomic status (low, high), marital status (married, unmarried, previously married, unknown) and nodal stage (N0, N+). All statistical tests were two-sided with a level of significance set at $p < 0.05$. Analyses were performed using the R software (version 3.5.1; http://www.r-project.org/).

Results

General characteristics of the study populations

Overall, we identified 3817 patients with non-metastatic locally advanced (T3N0 or T3N+) MIBC treated with RC between 2004 and 2015. Of these, 1692 (44.3%) underwent CHT. CHT-treated patients were younger (66 vs. 72 years, $p < 0.001$), more frequently married (66.4 vs. 60.9%, $p < 0.001$) and more frequently harboured N+ disease (48.0 vs. 29.6%, $p < 0.001$) compared to no CHT patients (Table 1). After IPTW adjustment, standardized differences of weighted comparisons between treatment groups were <10% (Supplementary Fig. 1).

Annual trends

Overall, CHT administration rates increased from 32.1 to 55.6% (EAPC: +6.0%; $p < 0.001$) between 2004 and 2015. CHT administration rates increased from 26.3 to 51.9% (EAPC: +8.3%; $p < 0.001$) (Fig. 1a) in pT3N0 patients vs 43.4–61.6% (EAPC: +3.6%; $p < 0.001$) in pT3N+ patients (Fig. 1b).

Survival analyses

Overall, IPTW-adjusted 10-year CSM-free survival rates were, respectively, 51.3% (CI: 48.2–54.5%) for CHT-vs 46.3% (CI: 42.9–49.9%) for no CHT-treated patients ($p = 0.01$) (Fig. 2a–b). Similarly, IPTW-adjusted 10-year OM-free survival rates were, respectively, 39.6% (CI: 36.4–43.1%) for CHT vs 32.1% (CI: 28.9–35.7%) for no CHT patients ($p < 0.001$) (Fig. 2a–b). In CRMs,

Table 1
Baseline characteristics of 3817 patients with locally advanced muscle-invasive bladder cancer treated with radical cystectomy, with or without perioperative chemotherapy.

Variables	Category	Overall (n = 3817)	CHT = Not administered (n = 2125, 55.7%)	CHT = Administered (n = 1692; 44.3%	p value
Age at diagnosis (years)					<0.001
	Median	70	72	66	
	IQR	61–77	64–79	59–73	
Race, n (%)					0.3
	White	3398 (89)	1883 (88.6)	1515 (89.5)	
	African American	229 (6)	139 (6.5)	90 (5.3)	
	Other	190 (5)	103 (4.8)	87 (5.1)	
Gender, n (%)					0.02
	Male	2782 (72.9)	1517 (71.4)	1265 (74.8)	
	Female	1035 (27.1)	608 (28.6)	427 (25.2)	
Marital status, n (%)					<0.001
	Married	2418 (63.3)	1294 (60.9)	1124 (66.4)	
	Never Married	412 (10.8)	232 (10.9)	180 (10.6)	
	Previously Married	877 (23)	540 (25.4)	337 (19.9)	
	Unknown	110 (2.9)	59 (2.8)	51 (3)	
Year of surgery, n (%)					<0.001
	2004–2007	1204 (31.5)	791 (37.2)	413 (24.4)	
	2008–2011	1291 (33.8)	725 (34.1)	566 (33.5)	
	2012–2015	1322 (34.6)	609 (28.7)	713 (42.1)	
SES, n (%)					<0.001
	High	1862 (48.8)	1102 (51.9)	760 (44.9)	
	Low	1955 (51.2)	1023 (48.1)	932 (55.1)	
Nodal stage, n (%)					<0.001
	N0	2377 (62.3)	1497 (70.4)	880 (52)	
	N1	1440 (37.7)	628 (29.6)	812 (48)	

IQR = Interquartile range; CHT = Chemotherapy; SES = Socio-economic status.

CHT was significantly associated with for lower CSM (HR 0.73, CI 0.65–0.81) and OM (HR 0.69, CI 0.62–0.76) (Table 2). The results were confirmed after landmark analyses at 3 months for CSM (HR 0.81, CI 0.72–0.90) and OM (HR 0.76, CI 0.69–0.84).

Similar findings were obtained in sensitivity analyses (Supplementary Table 2). Specifically, presence or absence of lymph node invasion resulted in virtually the same CSM and OM results, when CHT was administered. Similarly, virtually the same HRs were recorded in analyses stratified by gender or age (Supplementary Table 2). Our findings are also in agreement with previous prospective studies examining adjuvant CHT vs. no adjuvant CHT [12–15,17] in patents with locally advanced MIBC. Moreover, our results replicate those reported by Galsky et al. [18] that were based on the NCDB (Supplementary Fig. 2).

Discussion

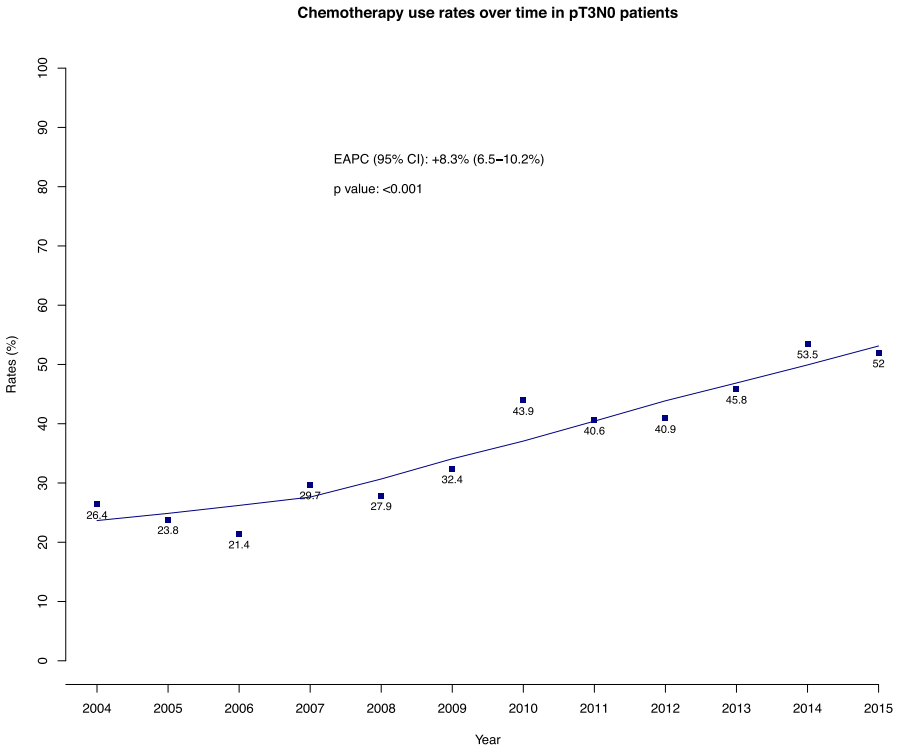
Patients with locally-advanced MIBC, who are RC candidates, should receive perioperative CHT in either neoadjuvant or adjuvant form, if their overall health status allows it [1]. Despite NCCN as well as EAU CHT guideline recommendations [1,3], the adherence to perioperative CHT was suboptimal [7–10,18,23]. Lower quality data that support CHT use may explain suboptimal administration rates. Galsky et al. [18] recently added to the weight of evidence supporting the use of adjuvant CHT in patients with locally-advanced MIBC, using an NCDB-based analysis. The current analysis represents a second large scale observational contribution to the evidence supporting the use of perioperative CHT in the setting of locally-advanced MIBC that relied on a different cohort, namely the SEER database. Our analyses yielded several interesting and novel findings.

First, the rates of CHT use were higher than in any previous report, where they ranged from 17 to 19% for neoadjuvant CHT and from 23 to 25% for adjuvant CHT. These historic observations apply to all RC patient subgroups, including those with N+ disease. In the current analyses, CHT use rates increased from 26 to 52% in pT3N0 patients vs. 43–62% in pT3N+ patients. These observations are very encouraging with respect to guideline adherence regarding perioperative CHT use in patients with locally-advanced MIBC. Unfortunately, the data format precludes a specific stratification between neoadjuvant and adjuvant CHT. Nonetheless, our findings do reflect the recommended administration of CHT either before or after RC in patients with locally-advanced MIBC, that is defined in the guidelines by the stage combination pT3N0 and pT3N+. These encouraging observations were made despite lack of data on renal insufficiency and poor performance status. Moreover, our rates are not restricted to any age cut-off and even include octogenarians and older patients. Use of restriction criteria based on absence of renal insufficiency, absence of poor performance status and age 70 or younger would have resulted in higher CHT adherence rates.

Second, we identified an association between perioperative CHT in locally advanced MICB patients and lower CSM and lower OM. Moreover, after multivariable adjustment for additional potential patient differences, statistically significantly lower CSM (HR 0.73, $p < 0.001$) and OM (HR 0.69, $p < 0.001$) rates were recorded in CHT patients. These observations suggest a beneficial role of perioperative CHT in locally-advanced MIBC RC patients and validate the existing prospective and observational data, where a similar survival benefits was reported. The data format precludes a strict stratification between neoadjuvant and adjuvant CHT administration. Nonetheless, all CHT study subjects received CHT either before or after RC, according to guideline recommendations. Despite the lack of formal stratification regarding the timing of CHT delivery, our findings are in agreement with the observational report of Galsky et al. [18] and in very close agreement with data from prospective trials. In consequence, our findings add to the body of evidence supporting the use of perioperative CHT in the setting of locally advanced MIBC patients treated with RC.

Third, sensitivity analyses were used to further test the association between perioperative CHT and the two separates mortality endpoints, namely CSM and OM. In sensitivity analyses that focused on pT3N0 vs. pT3N+ disease, lower CSM and OM rates were recorded in perioperative CHT patients, in both study subgroups. Moreover, the magnitude of the recorded HRs was virtually the same in both subgroups. The same findings were obtained in sensitivity analyses stratified according to gender (male vs female),

a



b

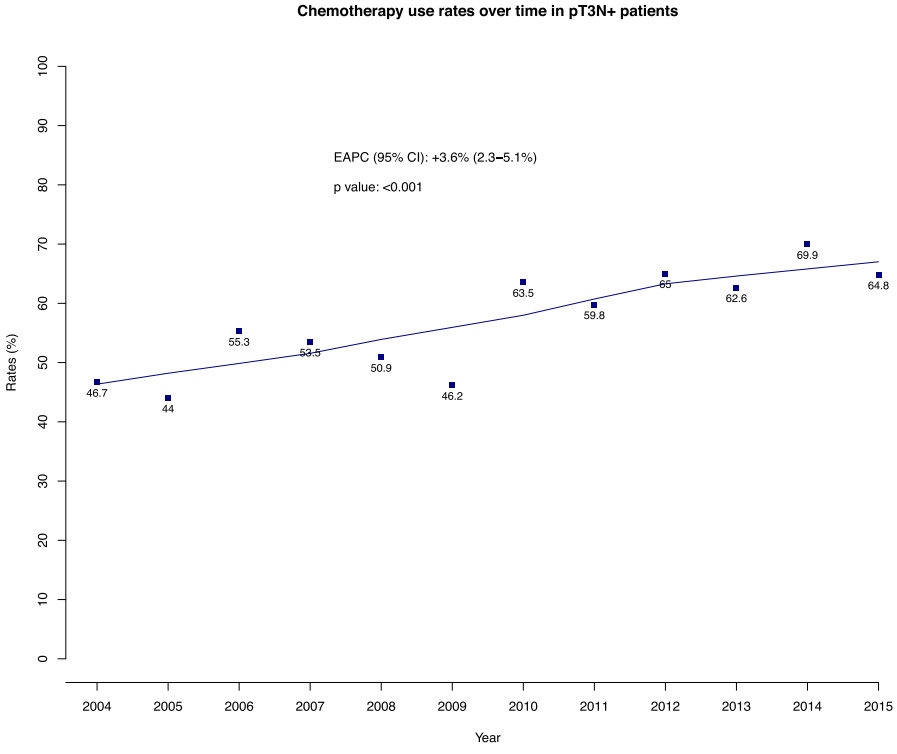


Fig. 1. Temporal trends of chemotherapy use over time within the SEER database, stratified according to nodal stage.

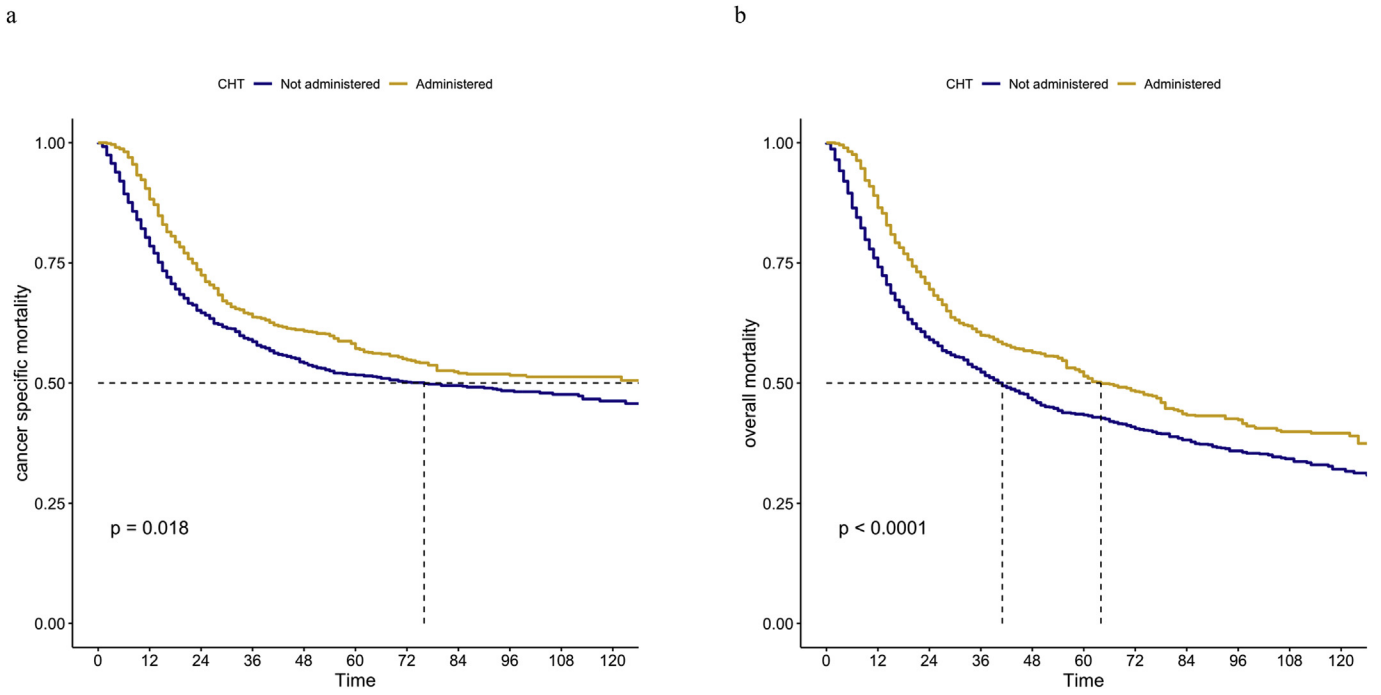


Fig. 2. IPTW-adjusted Kaplan–Meier plot depicting CSM-free survival (a) and OM-free survival (b) of 3817 patients with locally-advanced muscle-invasive urothelial cancer of the bladder treated with radical cystectomy who received or not perioperative chemotherapy, after adjustment for inverse probability of treatment weighing.

Table 2
Multivariable Cox regression models predicting cancer-specific mortality and overall mortality of muscle-invasive bladder cancer patients treated with radical cystectomy with or without perioperative chemotherapy, after inverse-probability of treatment weighting.

		Cancer-specific mortality			Overall mortality		
Variables		Number of events (%)	Hazard ratio (95% Confidence interval)	p-value	Number of events (%)	Hazard ratio (95% Confidence interval)	p-value
Chemotherapy							
Age at diagnosis	Not Administered	1260 (26.1)	Ref.		1842 (38.1)	Ref.	
	Administered	862 (24.1)	0.73 (0.65–0.89)	<**0.001**	1068 (29.8)	0.69 (0.62–0.76)	<**0.001**
	–		1.00 (0.99–1.01)	0.1	–	1.01 (1.00–1.01)	<**0.001**
Gender							
	Male	1556 (24.6)	Ref.		2188 (34.6)	Ref.	
	Female	566 (27.2)	1.02 (0.90–1.15)	0.8	722 (34.7)	0.91 (0.81–1.01)	0.1
Race							
	White	1896 (25.1)	Ref.		2600 (34.6)	Ref.	
	African American	133 (29)	1.04 (0.82–1.32)	0.7	184 (40.2)	1.09 (0.89–1.34)	0.4
	Other	93 (23)	1.02 (0.80–1.29)	0.8	126 (31.2)	0.95 (0.76–1.18)	0.7
Marital status							
	Married	1304 (24.2)	Ref.		1773 (32.9)	Ref.	
	Never Married	245 (27.1)	1.23 (1.04–1.47)	0.01	335 (37.1)	1.33 (1.14–1.55)	<0.001
	Previously married	499 (27.3)	1.16 (1.01–1.33)	0.03	704 (38.5)	1.22 (1.08–1.37)	<0.001
	Unknown	74 (25.4)	1.30 (0.94–1.80)	0.1	98 (33.7)	1.22 (0.90–1.64)	0.2
Socio-economic status							
	High	1048 (25.5)	Ref.		1458 (35.5)	Ref.	
	Low	1074 (25)	0.94 (0.84–1.04)	0.2	1452 (33.7)	0.93 (0.84–1.02)	0.1
Year of surgery							
	2004–2007	842 (32.7)	Ref.		1275 (49.5)	Ref.	
	2008–2011	811 (28.5)	0.99 (0.87–1.12)	0.9	1068 (37.5)	1.00 (0.90–1.12)	0.9
	2012–2015	469 (15.7)	1.05 (0.91–1.22)	0.5	567 (19)	1.02 (0.89–1.17)	0.1
Nodal stage							
	N0	1203 (19.1)	Ref.		1834 (29.2)	Ref.	
	N1	919 (43.5)	2.37 (2.13–2.64)	<**0.001**	1076 (50.9)	2.11 (1.91–2.32)	<**0.001**

as well as in those focusing on age (≤70 vs > 70 years old). Last but not least, the overall cohort, as well as all subgroups, were subjected to landmark analyses at 3 months. Taken together, the sensitivity analyses, as well as the landmark analyses, confirmed the robustness of the association between perioperative CHT and lower CSM and OM, regardless of the type of data stratification that was applied. This implies that in clinical practice presence or absence of lymph node invasion in patients with pT3 MIBC does not affect the expected protective effect of perioperative CHT. Similarly, pT3N0/N+ patients are expected to benefit of perioperative CHT to

similar extent regardless of their age or gender. Finally, our sensitivity analyses (Supplementary Table 1) were in virtually perfect agreement with the protective effect reported by Galsky et al. [18] within the NCDB. Similarly, very close agreement was recorded with historical prospective data depicting the effect of perioperative CHT in the same type of MIBC patients [12–15,17].

Although our analysis represents a retrospective assessment of CHT in locally advanced bladder cancer, which do not provide the same level of evidence as prospective designs, it does have several strengths. To the best of our knowledge, our analysis represents the most contemporary analysis of the effect of perioperative CHT on survival in patients with locally advanced MIBC. Only one similar study was reported by Galsky et al. [18]. It focused on a larger patient sample (n = 5653). However, all subjects were treated between 2003 and 2006 vs. 2004 and 2015 in the current analysis. Moreover, our cohort originates from eighteen SEER registries, distributed across the United States, with the intent of providing a large and informative sample, which offers similar generalizability to the NCDB analysis reported by Galsky et al. [18]. Our sensitivity analyses provided additional proof of generalizability and robustness. The SEER database also provided novel information that could not be obtained from NCDB analyses. Specifically, our findings corroborated the association between perioperative CHT with lower OM, as well as CSM. Hence, the current analysis provided more complex proof of the association between CHT and mortality, than when OS alone was reported.

Our study is not devoid of limitations. First and foremost, our data lacks detailed information regarding CHT timing. In consequence, our findings must be interpreted in the light of CHT being administered either prior to RC or after RC. Both settings reflect North American and European guidelines recommendations. However, our analyses cannot quantify whether one approach is better than the other. Additionally, we cannot quantify the proportion of patients that benefited of one or the other approach. Moreover, our database does not provide detailed information about the composition of CHT that was administered. A proportion of patients might have received non-platinum regimens, that in general are less effective than platinum-based regimens. In consequence, it is likely that restriction to patients who received platinum-based CHT might have resulted in even lower HRs than those reported in the current results section. Second, 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 not be offered cisplatinum-based perioperative CHT. Lack of exclusion of these two patient groups, poor performance status and/or poor renal function, has likely resulted in higher CSM and OM HRs than if those individuals were excluded. Third, the SEER database does not allow adjustment for baseline comorbidities. To maximally reduce this potential bias, we relied on IPTW that resulted in standardized differences of weighted comparisons between treatment groups <10%. However, it is possible that important differences persisted according to variables that are unavailable in retrospective databases, such as the SEER database. This said, our analyses target OM, as well as CSM, and both endpoints were virtually identical and, as further proof of validity, our findings are in agreement with those of previous retrospective analyses [18]. In consequence, it is unlikely that comorbidities resulted in other-cause mortality that was differentially distributed between CHT and no CHT patients. Fourth, the SEER database does not allow further adjustment for clustering at hospital or surgeon level. It is of note that the use of clustering methods had substantial impact on results of analyses involving morbidity endpoints, such as postoperative complications [24]. However, clustering showed relatively limited impact on short term mortality results, indicating that the between-surgeon or between-hospital variation are negligible when survival outcomes are considered [24]. In consequence, it is unlikely that clustering at surgeon or hospital level may modify in a meaningful fashion survival outcomes of RC patients treated or not with perioperative CHT recorded in the current analysis. Last but not least, the historical nature of our database does not allow the ascertainment of patients treated with immunotherapy.

Conclusions

The current observational data showed an important increase in CHT rates, as well as improved survival in patients with locally advanced MIBC. The latter confirm one large observational study and several small prospective studies.

Conflict of interest

Elio Mazzone, on behalf of all authors, 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 (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Authors' contribution

Mazzone, Elio: Project development, Data analysis, Manuscript writing/editing.
Nazzani, Sebastiano: Project development, Data analysis.
Knipper, Sophie: Data collection or management.
Tian, Zhe: Data collection or management, Data analysis.
Preisser, Felix: Data collection or management, Data analysis.
Gallina, Andrea: Supervision.
Soulières, Denis: Data collection or management.
Tilki, Derya: Supervision.
Montorsi, Francesco: Project development, Supervision.
Shahrokh, Shariat F.: Supervision.
Saad, Fred: Manuscript writing/editing.
Briganti, Alberto: Project development, Manuscript writing/editing.
Wisnivesky, Juan: Manuscript writing/editing, Supervision.
Karakiewicz, Pierre I.: Project development, Manuscript writing/editing, Supervision.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.01.218.

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 (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Formatting of funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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