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ARTICLE

A population-based retrospective analysis on variation in use of neoadjuvant chemotherapy depending on comorbidity in patients with muscle-invasive bladder cancer undergoing cystectomy in Denmark in the period 2013–2019

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ABSTRACT

Introduction: The recommended treatment of localized muscle-invasive bladder cancer (MIBC) is cystectomy and neoadjuvant chemotherapy (NAC) for eligible patients. However, the percentage who receive NAC is varying.

Objective: The aim was to evaluate the variation in percentage of patients receiving NAC in Denmark since implementation in 2013, the potential influence of comorbidity on NAC administration, and the pathological outcome at time of cystectomy with and without NAC.

Methods: Patients were identified by cystectomy procedure codes and date of diagnosis in the period 2013–2019 in The Danish Bladder Cancer Database. Chi square test and Fisher's exact test were used to evaluate demographics and tumor-specific characteristics. Wilcoxon rank-sum test was used to compare Charlson Comorbidity Index (CCI) and compare age-adjusted CCI subgroups.

Results: Overall, 1032 patients age $\leq$75 years and tumor stage $\geq$T2 were included in the study; 594 patients (58%) received NAC. The percentage of NAC administration varied from 27% to 92%. Patients who received NAC had significantly less comorbidity estimated by CCI when compared to patients not receiving NAC. Of patients with MIBC who received NAC, 57% had complete response (CR) at cystectomy, whereas 29% of patients who did not receive NAC had CR at cystectomy ($p < 0.01$).

Conclusions: Patients with comorbidity estimated by high CCI score had a lower probability of receiving NAC. The probability of CR was twice as high in patients with MIBC treated with NAC compared to patients undergoing cystectomy alone. However, almost one third of patients with MIBC were tumor free at cystectomy despite no NAC administration.

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Introduction

Bladder cancer is a commonly diagnosed cancer in the western world. One out of four patients present with muscle-invasive bladder cancer (MIBC) at time of diagnosis, whereas the remaining patients present with non-muscle-invasive bladder cancer (NMIBC) [1,2]. Recommended treatment of localized MIBC is radical cystectomy (RC) in patients fit for surgery [3]. A randomized trial from 2011 and a meta-analysis study from 2005 have proven that administration of neoadjuvant chemotherapy (NAC) is associated with a survival benefit for patients undergoing radical cystectomy for MIBC [4,5]. Based on this evidence, guidelines recommend cisplatin-based NAC for treatment of eligible patients with MIBC before radical cystectomy [3,6]. This recommendation of NAC was introduced in the Danish guidelines in January 2013 whereas NAC was not used as standard in Denmark before that date [7]. In Denmark, eligible patients are defined as being age $\leq$75 years with normal renal function (glomerular filtration rate [GFR] > 60 ml/min by Tc-99m-DTPA clearance), performance status 0–1, and diagnosed with MIBC at transurethral resection of the bladder tumor (TURBT) [8]. The Danish national quality registry has set a standard of a minimum of 50% of patients potentially eligible for NAC are treated with NAC prior to radical cystectomy [9]. A minimum is set at 50% due to no available information on performance status or renal clearance in the Danish Bladder Cancer Database (DaBlaCa-Data).

A previous study has shown variation in the percentage of MIBC patients receiving NAC at the five cystectomy centers in Denmark ranging from 32% to 83% in the first three-year-period [10]. With this national study, we aim to evaluate the yearly variation in percentage of patients receiving NAC in Denmark within the first seven years since implementation in 2013. Moreover, we aim to investigate potential influence of comorbidities on NAC administration and finally, we will report the immediate pathological outcome at the time of cystectomy in patients with and without NAC.

Materials and methods

This study is a registry study based on data from DaBlaCa-Data [11]. We included patients undergoing cystectomy in Denmark in a 7-year-period from 1 January 2013 to 31

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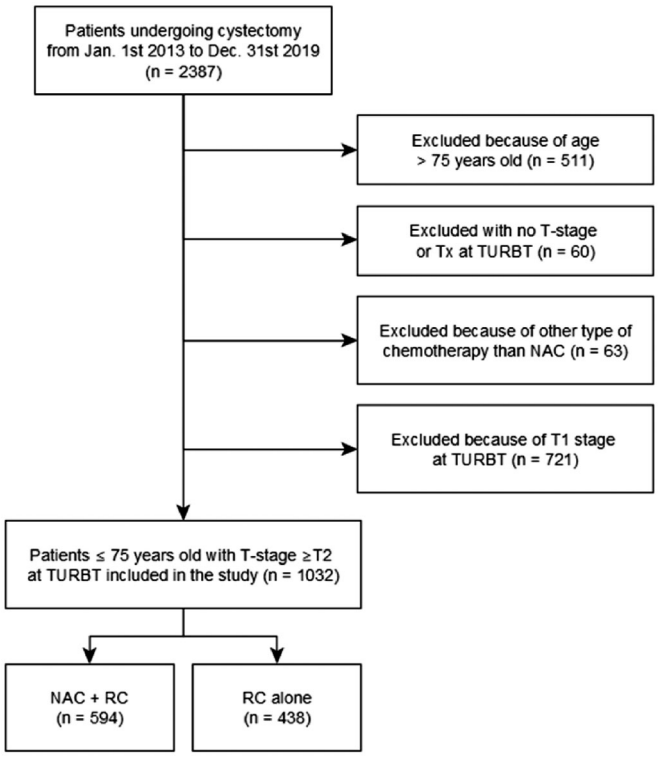

Figure 1. Flow chart of inclusion.

December 2019. All cystectomies in Denmark in this period were performed at five tertiary referral centers (Aarhus University Hospital (AUH), Aalborg University Hospital (AAUH), Odense University Hospital (OUH), Herlev Hospital, and Rigshospitalet, Copenhagen).

Patients were identified by cystectomy procedure codes and date of diagnosis [12]. Diagnosis was identified by WHO International Classification of Diseases version 10 (ICD-10) and NOMESCO Classification of Surgical Procedures (NCSP) was used for procedure codes gathered in the Danish National Patient Registry [13]. Patients receiving chemotherapy before cystectomy were identified through registration of a chemotherapy code preceding the cystectomy procedure code. To discriminate NAC from chemotherapy on other indications including downstaging for metastatic disease or clinical T4b, this is routinely registered manually in the database. Three patients had a chemotherapy code but no manual registration of having received NAC or chemotherapy for other reason. These patients were registered as having received NAC in this study. DaBlaCa-Data uses SNOMED codes registered by the pathologist at routine histopathological evaluation regarding T-stage of the TURBT and cystectomy specimens [14]. In patients without remnant tumor in the cystectomy specimen, no SNOMED code is registered regarding T-stage. Thus, patients without a T-stage at cystectomy are registered as T0.

All patients were registered with Charlson Comorbidity Index (CCI) score 0–9 prior to cystectomy [15]. Patients were grouped into five CCI categories: 0, 1, 2, 3, and ≥4. Age-adjusted Charlson Comorbidity Index (ACCI) score was subdivided into the same five groups. DaBlaCa-Data has no specific information on renal clearance at the time of cystectomy.

N-stage at cystectomy was reported as N0, N+, or Nx. Nx was classified as N0 in analyses in the current study as this covered patients where no metastases were registered in the removed lymph nodes.

Statistics and ethics

Statistical analyses were performed using Stata software version 16.1 [16]. Chi square test and Fisher's exact test were used to evaluate significant differences in demographic and tumor-specific characteristics in patients treated with NAC and RC compared to patients treated with RC alone. Wilcoxon rank-sum test was used to compare CCI and ACCI subgroups for patients who were treated with NAC and RC and RC alone, and patients treated with NAC and RC between the five cystectomy centers. Statistical significance was defined as $p < 0.05$.

Data retrieval from DaBlaCa-Data and analysis was approved by The Danish Clinical Quality Program – National Clinical Registries (RKKP). The project was registered on the internal list of research projects in Central Denmark Region approved by the Danish Data Protection Agency.

Results

Use of NAC

In total, 2387 patients underwent cystectomy for bladder cancer in Denmark in the period. We excluded 511 patients with age older than 75 years, 60 patients with no registered T-stage at neither TURBT nor cystectomy or Tx registered at TURBT, 63 patients who received chemotherapy on downstaging indication, and 721 patients with T1 stage at TURBT. Thus, 1032 patients who either received NAC or no chemotherapy before cystectomy were included in the study (Figure 1).

Table 1 lists the demographics of the study population. The median age was 67 years and the interquartile range was 62–72 years, and the male to female ratio was 2.2:1.

A total of 1032 patients were ≤75 years old and had MIBC (≥T2) at TURBT and were therefore potentially eligible for NAC. Of these, 594 patients (58%) received NAC.

The percentage of NAC administration varied from 27% to 92% of potentially eligible patients between the five centers in the period 2013–2019 (Table 2). In general; there was a staple percentage of patients receiving NAC at the individual centers except for a single center where a clear increase in NAC administration in the period was seen (Figure 2).

Comorbidity

Patients aged ≤75 years with MIBC at TURBT who received NAC before cystectomy had significantly less comorbidity estimated by both CCI and ACCI compared to the same category of patients undergoing cystectomy without NAC (Table 3). We found no statistically significant difference

Table 1. Demographics and tumor-specific characteristics for study patients with ≥T2 at TURBT undergoing RC with or without NAC.

Variable	Statistics	Total ($n = 1032$)	NAC + RC ($n = 594$)	RC alone ($n = 438$)	p Value
Gender					0.01
Male	n (%)	711 (69)	428 (72)	283 (65)	
Female	n (%)	321 (31)	166 (28)	155 (35)	
Age at diagnosis	Median, yr (IQR)	67 (62-72)	66 (61-71)	69 (64-73)	
Charlson Comorbidity score					<0.01
0	n (%)	665 (64)	414 (70)	251 (57)	
1	n (%)	150 (15)	84 (14)	66 (15)	
2	n (%)	133 (13)	70 (12)	63 (14)	
3	n (%)	40 (4)	16 (3)	24 (5)	
≥4	n (%)	44 (4)	10 (2)	34 (8)	
N-stage at cystectomy					0.02
N0	n (%)	824 (80)	492 (83)	332 (76)	
N+	n (%)	199 (19)	98 (16)	101 (23)	
Nx	n (%)	9 (1)	4 (1)	5 (1)	

NAC: neoadjuvant chemotherapy; RC: radical cystectomy; IQR: interquartile range; TURBT: transurethral resection of the bladder tumor.

Table 2. Proportion of cystectomy patients age ≤75 years at diagnosis and ≥T2 at TURBT receiving NAC in the period 2013–2019.

	2013		2014		2015		2016		2017		2018		2019		2013-2019
		%		%		%		%		%		%		%	%
Denmark, total	79/137	58	84/155	54	77/131	59	87/147	59	104/170	61	76/137	55	87/155	56	58
Rigshospitalet, Copenhagen	18/33	55	17/36	47	15/26	58	17/35	49	19/30	63	12/32	38	24/48	50	51
Herlev Hospital, Copenhagen	11/20	55	15/22	68	18/25	72	19/26	73	23/30	77	15/20	75	12/13	92	73
Odense University Hospital	21/30	70	19/32	59	9/15	60	14/22	64	20/41	49	23/36	64	22/38	58	61
Aarhus University Hospital	25/41	61	26/45	58	23/41	56	33/49	67	32/48	67	21/37	57	22/38	58	61
Aalborg University Hospital	4/13	31	7/20	35	12/24	50	4/15	27	10/21	48	5/12	42	7/18	39	39

TURBT: transurethral resection of the bladder tumor; NAC: neoadjuvant chemotherapy.

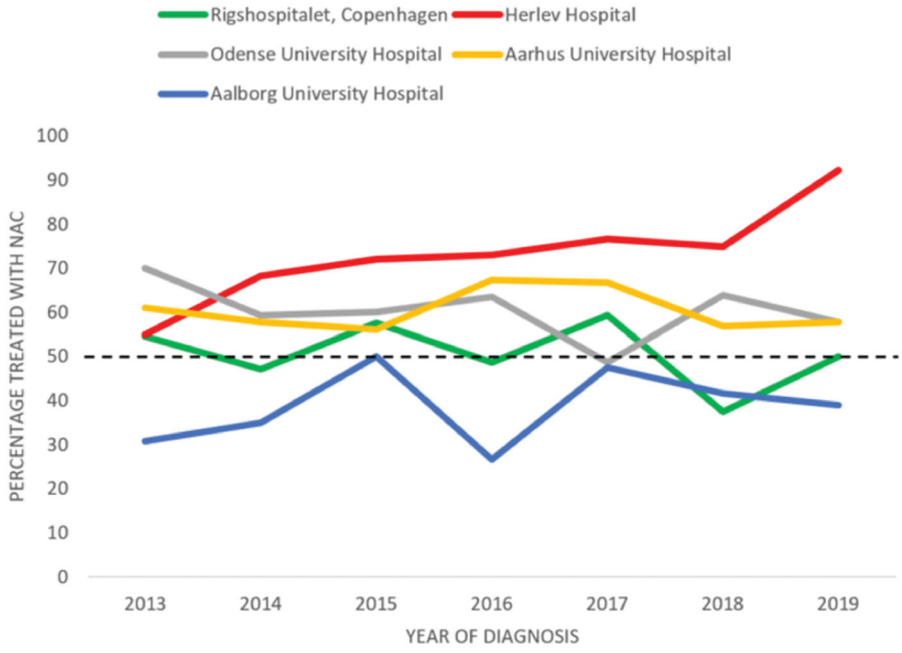

Figure 2. Percentage of NAC administration at the five Danish centers in the period 2013–2019.

regarding comorbidity when comparing patients treated at different centers in patients receiving NAC (Supplementary Tables S1 and S2).

Downstaging

A total of 57% (340/594) of the patients with MIBC at TURBT who received NAC had pathologically complete response at cystectomy whereas only 29% (126/438) of patients who did not receive NAC were T0 at cystectomy ($p < 0.01$) (Table 4). Moreover, 61% (363/594) of patients who received NAC were downstaged to < pT2 whereas only 33% (145/438) of patients who were not treated with NAC had < pT2 in the cystectomy specimen ($p < 0.01$).

N-stage at cystectomy

Of patients treated with NAC, 16% (98/594) were N+ at cystectomy whereas 23% (101/438) of patients not treated with NAC were N+ at cystectomy ($p = 0.01$). Of the patients with residual MIBC treated with NAC and RC, 71 of 231 patients (31%) were N+ at cystectomy. This was not statistically

Table 3. CCI and ACCI subgroups for patients age ≤75 years at diagnosis and ≥T2 at TURBT treated with RC and NAC or RC alone.

	Charlson comorbidity Index score subgroups					
	0	1	2	3	≥4	*p* Value*
CCI						
NAC + RC (*n* = 594)	414	84	70	16	10	
RC alone (*n* = 438)	251	66	63	24	34	<0.01
ACCI						
NAC + RC (*n* = 594)	23	87	208	170	106	
RC alone (*n* = 438)	9	32	106	145	146	<0.01

Period: 2013–2019.
CCI: Charlson Comorbidity Index score; ACCI: age-adjusted Charlson Comorbidity Index score; NAC: neoadjuvant chemotherapy; RC: radical cystectomy.

Table 4. Pathological outcome at cystectomy of patients with ≥T2 at TURBT.

	≤75 years at diagnosis		
	NAC + RC	RC alone	*p* Value*
Complete response	57% (340/594)	29% (126/438)	<0.01
NMIBC	4% (23/594)	4% (19/438)	0.71
Total downstaged	61% (363/594)	33% (145/438)	<0.01
MIBC	39% (231/594)	67% (293/438)	<0.01

*Chi^2 test.
TURBT: transurethral resection of the bladder tumor; NAC: neoadjuvant chemotherapy; RC: radical cystectomy; NMIBC: non-muscle-invasive bladder cancer; MIBC: muscle-invasive bladder cancer.

significantly different when compared to 94 of 293 patients (32%) with residual MIBC who were treated with RC alone that were N+ at cystectomy ($p = 0.74$).

Discussion

This study found a percentage of 29% of patients treated with RC alone to be T0 in the cystectomy specimen. When comparing patients treated with NAC before RC to patients treated with RC alone, almost twice as many were T0 at cystectomy following NAC (57% and 29%, $p < 0.01$). The percentage of patients treated with NAC varied from 27% to 92% during the study period. Overall, a stable percentage of patients receiving NAC at each individual center was seen, except for a single center where an increase in administration was seen. Patients treated with NAC had less comorbidity when comparing both CCI and ACCI between patients treated with NAC and RC and patients treated with RC alone.

Despite recommendations of NAC in guidelines, large variations in adherence have been reported: A SEER-based study reported that 15% of eligible patients received NAC in 2009 [17]. Zaid et al. [18] reported an increase of NAC utilization over time from 8% in 2006 to 21% in 2010. Hanna et al. [19] reported that 19% of patients with MIBC received NAC; this cohort was restricted to patients with a CCI of 0. A retrospective study of 94 patients in 2012–2014 reported a NAC utilization of 50% [20]. These studies seem to indicate an increase in the use of NAC.

The use of NAC for eligible patients with MIBC in Denmark was implemented on 1 January 2013. This unique strategy of simultaneous implementation at all five Danish cystectomy centers at the same date makes it possible to evaluate on national data since the time of implementation. Overall, the use of NAC has been successfully implemented in Denmark. Some variation in the percentage of MIBC patients receiving NAC is seen but according to Nielsen et al. [10] most patients not receiving NAC have a valid reason. Thus, they reported that of patients who did not receive NAC, 35% was due to GFR < 60 mL/min, high performance status (≥2) or other severe comorbidity.

However, complete TURBT also accounts for some of the cases of T0 in patients treated with NAC and RC and has previously been reported to be between 12% and 20% [21,22]. We found a statistically significant difference in patients without MIBC at cystectomy at RC between patients treated with NAC and RC or RC alone (61% and 33%, $p < 0.01$). This is similar to results found by Brant *et al.*; who reported that 62% of patients treated with NAC followed by RC and 20% of patients treated with RC alone were without MIBC at cystectomy [23]. Iyer et al. [24] found that 57% were without MIBC at cystectomy, although this study had only 46 evaluable patients. Zaid et al. [18] found that patients receiving NAC were significantly more likely to be without MIBC at RC (31.2% vs. 7.6%, $p < 0.01$).

A meta-analysis found a range from 9% to 46% of patients treated with NAC were downstaged to T0 at RC [25]. Grossman et al. [26] found that 38% of patients treated with NAC were T0 at RC and 15% treated with RC alone were T0 ($p < 0.01$). This is lower than our result (57% vs. 29%, $p < 0.01$).

A valid reason for no treatment with NAC could be considerable comorbidity. Our findings with significantly less comorbidity in patients treated with NAC compared to patients undergoing cystectomy without NAC support this hypothesis. Considerable comorbidity may also be associated with performance status >1 and impaired renal clearance.

This study uses a complete national dataset on patients undergoing radical cystectomy in Denmark 2013–2019 at time of the unique implementation of NAC on a national level. The limitations of this study are missing information on renal clearance, performance status, and histological subtype. DaBlaCa-Data is not yet able to identify patients with impaired renal function. In the future, the current standard of 50% of eligible patients receiving NAC should be increased when DaBlaCa-Data is able to consider renal clearance [9]. This study was also not able to consider patients who received NAC but did not complete RC.

Conclusions

Despite some variation in percentage of patients receiving NAC, we found a strong adherence to guidelines in this national study. Patients with comorbidity estimated by high CCI had a lower probability of receiving NAC at all centers. Moreover, we found that the probability of CR was twice as high in patients with MIBC treated with NAC compared to patients undergoing cystectomy alone.

Disclosure statement

Authors declare no conflicts of interest.

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