



Adverse events during neoadjuvant chemotherapy for muscle invasive bladder cancer – a Swedish retrospective multicentre study of a clinical database

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Background: Adverse events (AEs) during neoadjuvant chemotherapy (NAC) for muscle invasive bladder cancer (MIBC) are known but insufficiently reported. Clinical implications include affected cardiac, pulmonary, urinary, vascular and haematological organ systems. The main purpose was to evaluate the incidence and severity of AEs for ascertaining possible clinical significance. Further investigating possible effects of AEs on downstaging outcomes—downstaging is considered a surrogate marker for overall survival (OS).

Methods: A retrospective evaluation of AEs during ongoing NAC for MIBC patients analysing individual patient data in a clinical database. We identified 687 cystectomies between 2009–2020 at four Swedish urological centres. Inclusion criteria were cT2–4aN0M0 in 261 NAC patients undergoing radical cystectomy (RC). Medical files were reviewed and AEs were assessed and graded, including detailed measurements by the Common Terminology Criteria for Adverse Events (CTCAE) v.5. Data were retrospectively analysed in SPSS statistics 27.0 with Spearman rank-order correlation coefficient and Mann-Whitney U-test (MWU).

Results: A total of 251/261 patients [95% confidence interval (CI), 93–98%] experienced AEs during NAC pre-RC (mean two AEs/patient). In total, 208 (80%) patients received methotrexate, vinblastine, adriamycin (doxorubicin) and cisplatin (MVAC). In the total cohort, 200 (76.6%) received all pre-planned NAC-cycles. Most common AEs were anaemia (88.9%), thrombocytopenia (44.8%) and acute kidney injury (40.6%). Patients with prematurely terminated cycles had higher AE-grades ($P=0.042$ MWU). A correlation between higher AE-grades and decrease in downstaging existed, in the entire cohort (-0.133 ; $P=0.033$) and in patients undergoing all pre-planned NAC-cycles (-0.148 ; $P=0.038$). Anaemia and acute kidney injury were individually associated with decreased downstaging (-0.360 , $P=0.025$ and -0.183 , $P=0.010$, respectively).

Conclusions NAC in MIBC poses a significant risk for AEs before RC with clinical implications. For instance, patients terminating chemotherapy prematurely, have higher AE-grades and decreased downstaging. Further, acute kidney injury and anaemia are individually associated with decreased downstaging. We propose that early detection and prevention of AEs may increase downstaging of the primary tumour.

Keywords: Bladder cancer; neoadjuvant therapy; adverse effects; cystectomy

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Introduction

Bladder cancer is the 10th most common cancer and the 13th most deadly cancer in the world. It is approximately four times more common in men than women. North America, Southern and Western Europe are the nations with the highest rates of bladder cancer (1). At diagnosis, muscle invasive bladder cancer (MIBC) accounts for 25–30% of the patients. The standard curative treatment in Sweden and Europe for MIBC is neoadjuvant chemotherapy (NAC) pre-radical cystectomy (pre-RC) for medically fit patients. Its purpose is to eradicate systemic micro metastatic disease when tolerability of chemotherapy is expected to be better pre-RC (2). NAC pre-RC has shown a significant survival benefit with reduction in mortality compared to RC only (3,4). NAC patients also had increased tumour downstaging, where pathological complete response (pCR; pT0N0M0 stage) include better overall survival (OS) and recurrence-free survival. Tumour downstaging refers to pathological tumour-node-metastasis (pTNM) less than clinical tumour-node-metastasis (cTNM) in the primary tumour (5,6), downstaging being considered a surrogate marker for OS. The standard neoadjuvant regimen is a cisplatin-based combination. In Sweden, high-dose intensity methotrexate, vinblastine, adriamycin (doxorubicin) and cisplatin (HD-MVAC) is recommended. The HD-MVAC is less toxic and more efficacious. Gemcitabine-cisplatin (GC) is an alternative. If a patient is ineligible for cisplatin, the combination of carboplatin-gemcitabine (Carbo-Gem) can be given as second-line treatment (2). It is known that the platinum compounds serve a great risk of side effects. Potential organ systems that may be affected are cardiac, pulmonary, urinary, vascular and haematological (7). Evaluation of the side effects and complications during ongoing NAC is not well investigated and insufficient. In a Finnish registry study from 2019, 229 patients who underwent NAC pre-RC were analysed for adverse events (AEs) during ongoing chemotherapy. The AEs were reported by Common Terminology Criteria for Adverse Events (CTCAE) (8). A total of 124 patients (54%) had some form of AE. The only variable significantly associated with AE was the number of cycles, severe AEs occurred already around the first cycle (9). Furthermore, AEs have previously been described in randomized controlled trials (10–13). A Swedish study on the national registers from 2020 analysed short-term complications on perioperative variables up to 90 days post-RC in MIBC patients with NAC. The results showed no increased risk of short-term

complications (14). The Swedish national register for cystectomy and urinary bladder cancer is lacking variables for analysing AEs during the time of NAC pre-RC. Thus, limitations such as possible lacking variables in national registers (9,14), lacking variables during NAC before major surgery (14) and few published studies on AE-incidence during NAC before surgery, presents a knowledge gap on AE-incidence and AE-severity grades. Therefore, as our main purpose, we intended to evaluate if the AEs would be more frequent than in previous studies, with the addition of including a more detailed analysis of independent patient data from a clinical database. Our preconceived hypothesis of patients affected in the study population was 75%. In addition, a second aim was to explore the hypothetical correlation of AEs on tumour downstaging, a research field which has, to our knowledge, not yet been investigated and reported of. Negatively affected downstaging in NAC-MIBC patients may have clinical implications, downstaging being a surrogate marker for OS. We present the following article in accordance with the STROBE reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-78/rc>).

Methods

Ethical information

Ethical permission was acquired from Regional Ethics Board, Etikprövningsnämnden (EPN) Umeå, Sweden: Dnr 2013/463-31M. The study was retrospective and therefore no informed consent was required according to EPN. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Study design and patient group

This retrospective multicentre study of a clinical database included patients from four Swedish cystectomy centres which were Norrlands universitetssjukhus (NUS), länsjukhuset Sundsvall/Härnösand, Västmanlands sjukhus (Västerås) and Universitetssjukhuset Linköping (region Östergötland). Inclusion criteria were patients with MIBC (cT2–4aN0M0) who received NAC pre-RC between the years 2009–2020. During that period, 687 patients with reliable and retrievable data regarding potential NAC, underwent cystectomy at the four mentioned centres. A total of 261 patients enrolled for evaluation, for details see the flowchart (*Figure 1*).

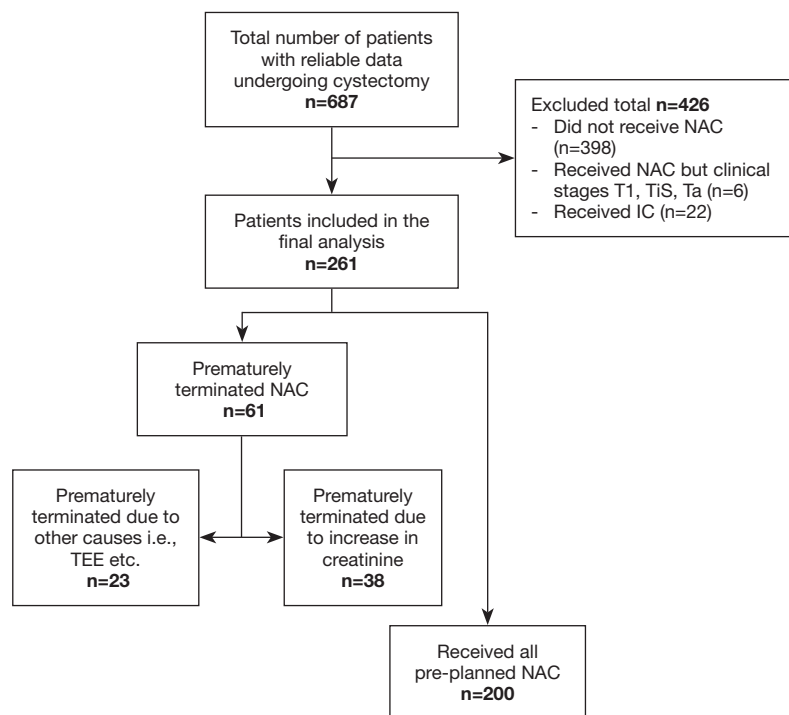


Figure 1 Flowchart displaying the exclusion and inclusion process resulting in 261 patients included in final analysis. NAC, neoadjuvant chemotherapy; IC, induction chemotherapy; TEE, thromboembolic event.

Study procedure

All data was collected retrospectively from medical records and compiled into a Microsoft Excel database. To reduce selection bias, patients with RC regardless of indication were derived from surgical lists in the participating centres. The final cohort included 261 patients of which 200 received all pre-planned number of NAC-cycles with a minimum of three cycles. Sixty-one patients terminated NAC prematurely with less than three cycles. Extracted data included age, gender, Charlson Comorbidity Index (CACI), NAC regimen, number of cycles, AEs during NAC pre-RC, clinical tumour-node-metastasis (cTNM) and pathological tumour-node-metastasis (pTNM). NAC regimens were documented in four groups: HD-MVAC, Carbo-Gem, methotrexate/vinblastine/epirubicine/cisplatin (MVEC) and other regimens including GC. The AEs were reported by the CTCAE v.5, a five-grade severity scale of AEs associated with the use of a medical treatment. The CTCAE scale is divided into 26 groups representing different organ systems. Disorders are further subdivided into specific AEs with individual grades. Grade 0 i.e., no AE, grade 1 and 2 indicating minor to moderate

AE, grades 3–4 indicating more severe or life-threatening consequences, and grade 5 death related to AE. Instructions on division between grades were stated within the source: either based on clinical events or lab-values. Baseline of lab-values in grades: upper or lower limit of normal (ULN or LLN) was specified from the same source as the CTCAE, the US department of health, National Institutes of Health (NIH), and lastly from NUS, Sweden (8). The grading within each AE is specified in *Table 1*. Further, downstaging outcomes were divided into four grades: progressive disease (PD; pN+, pT4b), stable disease (SD; pT2–4aN0M0), partial response (PR; pTa, pTis, pT1N0M0) and complete response (CR; pT0N0M0). For downstaging analysis, every patient was represented in their highest individual CTCAE grade, despite might having had several AEs. Furthermore, every AE was analysed individually. The two NAC sub-groups (all pre-planned NAC and prematurely terminated NAC group) were compared with each other for differences in downstaging outcome.

Statistical analysis

Baseline clinical characteristics were presented as mean with

Table 1 Grading within individual AEs by the CTCAE v.5 scale with baseline of upper or lower limits of normal

AE	Lab	Measure	Baseline value	Grade 1	Grade 2	Grade 3	Grade 4
Acute kidney injury	Creatinine	µmol/L	100 (men) 90 (women) (ULN)	>ULN-1.5×ULN	>1.5-3.0×ULN	>3.0-6.0×ULN	>6.0×ULN
Chronic kidney disease	eGFR-creatinine	mL/min/1.73 m ²	60 (LLN)	60-<LLN	30-59	15-29	<15
Anaemia	Haemoglobin	g/L	140 (men) 120 (women) (LLN)	100-<LLN	80-<100	<80	†
Thrombocytopenia	Platelet count	10 ⁹ /L	150 (LLN)	75-<LLN	50.0-<75.0	25.0-<50.0	<25.0
Leukopenia	White blood cell	10 ⁹ /L	4.5 (LLN)	3.0-<LLN	2.0-<3.0	1.0-<2.0	<1.0
Neutropenia	Neutrophil count	10 ⁹ /L	1.8 (LLN)	1.5-<LLN	1.0-<1.5	0.5-<1.0	<0.5

†, no value for staging was provided in the CTCAE, life threatening situation was suggested. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; eGFR, estimated glomerular filtration rate; ULN, upper limit of normal; LLN, lower limit of normal.

standard deviation or median with interquartile range (IQR) for continuous variables and frequencies and percentages for categorical variables. Confidence interval (CI) for the proportion of patients with AEs was constructed with Clopper-Pearson method. We treated the AE-grades and downstaging as ordinal variables. We used the Mann-Whitney U-test (MWU) to evaluate the relationship between AE-grades and two-category group variables. Spearman rank-order correlation was used to evaluate the relationship between different AE-grades and downstaging. Patients with missing data were case wise dropped from analysis. All used tests are two-sided with a significance level of 5%. The data was statistically evaluated in SPSS Statistics 27.0 for Mac (IBM Corporation, Armonk, NY, USA).

Results

Of the 261 patients with MIBC intended for NAC, 200 received all pre-planned cycles and 61 patients terminated NAC prematurely with less than three cycles. Of those 61 patients, 38 patients terminated due to AEs with acute kidney injury with an increase in creatinine. Twenty-three patients terminated due to other causes including but not limited to thromboembolic event (TEE) [1], TEE in peripheral inserted central catheter (PICC) [2], septic infection [5], febrile neutropenia [4], urinary tract obstruction with sepsis [1], chest pain without heart failure [1], unspecified fever [2], general fatigue [2], tumour progression [1] or other causes [4]. See *Figure 1*, describing the selection of the study cohort. Of the 261 patients, 78.2% were men (mean age 68 years). The mean number of NAC-cycles was 2.8 in the entire cohort. 1.5 when

NAC was terminated prematurely. A total of 208 patients (80%) received HD-MVAC/MVAC, 20% received another regimen. In total, 1.9% received both MVAC and another regimen. Baseline characteristics are shown in *Table 2*. All 261 patients underwent RC. Independent of grade, 251 patients had some form of AE which comprises of 96.2% (95% CI, 93-98%). Follow-up regarding AEs was done individually in each patient during NAC, within the period of diagnosis to RC, in average 3.7 months. *Table 3* presents the different AEs and overall distribution and differences between sub-groups of prematurely terminated cycles: less than three and all pre-planned cycles, three or more reported by the CTCAE scale. The most common AE was anaemia with 232 patients (88.9%) followed by thrombocytopenia (44.8%). Acute kidney injury due to increase in creatinine was seen in 40.6%. And chronic kidney disease in 11.1%. TEEs were seen in 24 patients (9.2%), febrile neutropenia was seen in 27 (10.3%). Eleven patients (4.2%) had urinary tract obstruction on different levels (e.g., hydronephrosis, ureteral dilation) and 10 (3.8%) had septicaemia. Five patients (1.9%) developed cardiac failure and two patients had liver failure (0.8%). A significant relationship existed between higher AE-grades and number of NAC-cycles. Patients who had less cycles due to premature termination had higher AE-grades, compared to patients with all pre-planned cycles ($P=0.042$ MWU) (*Figure 2*). No significant relationship existed between higher AE-grades and HD-MVAC/MVAC, compared to other regimen ($P=0.218$ MWU). Descriptive distribution of the highest AE-grade per patient on the entire cohort, and downstaging outcome, is presented in *Table 4*. Ten patients had no AE (3.8%), 98

Table 2 Baseline characteristics on the study cohort (n=261)

Variables	Values
Gender, n (%)	
Male	204 (78.2)
Female	57 (21.8)
Age (years), mean (standard deviation)	68 (7.0)
CACI, median [IQR]	5 [4, 5]
NAC regimen, n (%)	
HD-MVAC/MVAC	208 (79.7)
Other	53 (20.3)
Carbo-Gem	19 (7.2)
HD-MVEC	14 (5.4)
Other	20 (7.7)
NAC-cycles, mean (standard deviation)	
Total	2.8 (0.9)
≥3	3.2 (0.5)
<3	1.5 (0.6)
cT-stage, n (%)	
T2	169 (64.4)
T3	77 (29.5)
T4a	15 (5.7)
Downstaging (pTNM), n (%)	
CR (pT0N0M0)	84 (32.2)
PR (pTa, pTis, pT1N0M0)	45 (17.2)
SD (pT2–4aN0M0)	81 (31.0)
PD (pN+, pT4b)	51 (19.5)

CACI, Charlson Comorbidity Index; IQR, interquartile range; NAC, neoadjuvant chemotherapy; HD-MVAC, high-dose intensity methotrexate, vinblastine, adriamycin (doxorubicin) and cisplatin; MVAC, methotrexate, vinblastine, adriamycin (doxorubicin) and cisplatin; Carbo-Gem, carboplatin-gemcitabine; HD-MVEC, high-dose methotrexate/vinblastine/epirubicine/cisplatin; cT, clinical tumor; pTNM, pathological tumour-node-metastasis; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3 Distribution of AEs within patients who received NAC

CTCAE grade	NAC-cycles <3 (n=61)	NAC-cycles ≥3 (n=200)	All patients (n=261), n (%)
Acute kidney injury			
No event	18	137	155 (59.4)
Grade 1	23	50	73 (28.0)
Grade 2	19	10	29 (11.1)
Missing	1	3	4 (1.5)
Chronic kidney disease			
No event	44	188	232 (88.9)
Grade 2	14	12	26 (10.0)
Grade 3	3	0	3 (1.1)
TEE			
No event	57	180	237 (90.8)
Grade 2	0	2	2 (0.8)
Grades 3–4	4	18	22 (8.4)
Urinary tract obstruction			
No event	59	191	250 (95.8)
Grade 2	1	7	8 (3.1)
Grades 3–4	1	2	3 (1.1)
Septic infection			
No event	56	195	251 (96.2)
Grades 3–4	5	5	10 (3.8)
Febrile neutropenia			
No event	52	182	234 (89.7)
Grades 3–4	9	18	27 (10.3)
Heart failure			
No event	59	197	256 (98.1)
Grade 2	2	3	5 (1.9)
Liver failure			
No event	60	199	259 (99.2)
Grade 2	1	1	2 (0.8)
Anaemia			
No event	10	19	29 (11.1)
Grade 1	36	133	169 (64.8)
Grade 2	13	43	56 (21.5)
Grades 3–4	2	5	7 (2.7)

Table 3 (continued)

Table 3 (continued)

CTCAE grade	NAC-cycles <3 (n=61)	NAC-cycles ≥3 (n=200)	All patients (n=261), n (%)
Thrombocytopenia			
No event	31	113	144 (55.2)
Grade 1	16	62	78 (29.9)
Grade 2	4	10	14 (5.4)
Grades 3–4	10	15	25 (9.6)
Leukopenia			
No event	45	152	197 (75.5)
Grade 1	1	8	9 (3.4)
Grade 2	7	17	24 (9.2)
Grades 3–4	8	23	31 (11.9)
Neutropenia			
No event	51	173	224 (85.8)
Grade 2	3	3	6 (2.3)
Grades 3–4	7	24	31 (11.9)

CTCAE grades 1–4 with 0 cases are excluded from display. NAC, neoadjuvant chemotherapy; CTCAE, Common Terminology Criteria for Adverse Events; TEE, thromboembolic event.

patients had a maximum of grade 1 (37.5%), 68 patients had AE grade 2 (26%) and 81 patients had severe grades 3–4 (31%). Due to missing data, four patients could not be classified into any specific grade. No patient had AE grade 5, i.e., death due to AE pre-RC. The Spearman correlations between downstaging and highest AE-grade were calculated on patients within the cohort with varying NAC-cycles (Table 5). There was a significant correlation in the entire cohort (-0.133 ; $P=0.033$) and in patients who received all pre-planned NAC-cycles (-0.148 ; $P=0.038$). No significant correlation existed between highest AE-grades and downstaging when patients received less cycles due to early termination (-0.021 ; $P=0.874$). Correlation between individual AEs and downstaging on patients who received all pre-planned NAC-cycles, demonstrated a significant correlation between downstaging and anaemia, and between downstaging and acute kidney injury due to increased creatinine (-0.160 , $P=0.025$ and -0.183 , $P=0.010$, respectively; Table 6). There were no significant correlations between the other AEs and downstaging individually. A significant relationship between downstaging and number of NAC-cycles existed: three or more

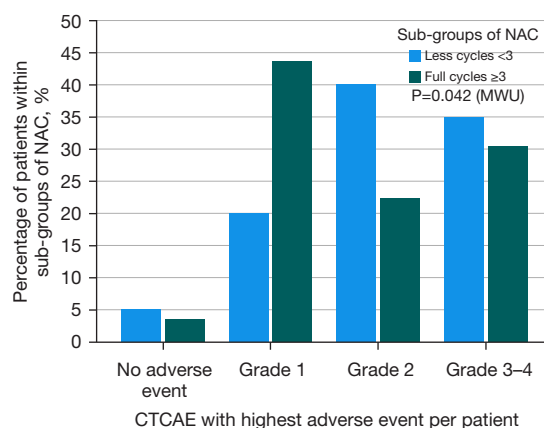


Figure 2 Significant relationship between sub-groups of NAC and grade by CTCAE. Patients with less than three NAC-cycles had a higher percentage of higher AEs grades 2–4, compared to patients with full NAC-cycles; three or more, who had lower grades 2–4 ($P=0.042$ MWU). NAC, neoadjuvant chemotherapy; CTCAE, Common Terminology Criteria for Adverse Events; MWU, Mann-Whitney U-test; AE, adverse event.

Table 4 Distribution of highest CTCAE grade per patient in groups of downstaging outcome (entire cohort)

CTCAE grades	PD (n=51)	SD [n=79 (2 [†])]	PR [n=44 (1 [†])]	CR [n=83 (1 [†])]
No AE	2	2	1	5
Grade 1	13	32	18	35
Grade 2	16	19	10	23
Grades 3–4	20	26	15	20

[†], patients excluded from downstaging outcome due to missing grade with missing creatinine value. CTCAE, Common Terminology Criteria for Adverse Events; AE, adverse event; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

($P=0.002$ MWU; Figure 3A) and between downstaging and MVAC, compared to other regimen ($P=0.006$ MWU; Figure 3B). No significant relationship existed between downstaging and prematurely terminated NAC due to increased creatinine ($P=0.051$ MWU; Figure 4A), however a significant relationship between downstaging and prematurely terminated NAC due to other causes existed ($P=0.029$ MWU; Figure 4B). No correlations between the highest AE-grades and the clinical variables of CACI and cT-stage existed ($P=0.123$ and $P=0.635$, respectively; Table 7).

Table 5 Correlation analysis between downstaging and the highest individual grade by CTCAE

Groups within patient cohort	Spearman correlation coefficient (95% CI)	P value
AE-grades in entire cohort (n=261)	-0.133 (-0.245 to -0.020)	0.033*
AE-grades in cohort all pre-planned NAC-cycles (n=200)	-0.148 (-0.283 to -0.016)	0.038**
AE-grades in cohort NAC-cycles <3 (n=61)	-0.021 (-0.281 to 0.218)	0.874

*, when AE grade decrease, downstaging will increase (in entire cohort). **, when AE grade decrease, downstaging will increase (in cohort who received all pre-planned). CTCAE, Common Terminology Criteria for Adverse Events; AE, adverse event; NAC, neoadjuvant chemotherapy; CI, confidence interval.

Table 6 Correlation analysis between downstaging and individual AEs in patients with all pre-planned (NAC-cycles, n=200)

AEs	N (%)	Spearman correlation coefficient (95% CI)	P value
Acute kidney injury	63 (31.5)	-0.183 (-0.308 to -0.040)	0.010*
Anaemia	181 (90.5)	-0.160 (-0.307 to -0.014)	0.025**
Chronic kidney disease	12 (6.0)	0.026 (-0.132 to 0.184)	0.718
Septic infection	5 (2.5)	-0.049 (-0.160 to 0.069)	0.493
Febrile neutropenia	18 (9.0)	0.090 (-0.056 to 0.223)	0.208
TEE	20 (10.0)	0.047 (-0.095 to 0.178)	0.516
Urinary tract obstruction	9 (4.5)	0.002 (-0.142 to 0.137)	0.979
Thrombocytopenia	87 (43.5)	-0.072 (-0.220 to 0.081)	0.316
Leukopenia	48 (24.0)	-0.088 (-0.221 to 0.052)	0.220
Neutropenia	27 (13.5)	-0.001 (-0.138 to 0.140)	0.986
Cardiac failure	3 (1.5)	-0.110 (-0.138 to 0.140)	0.125
Liver failure	1 (0.5)	-0.048 (-0.070 to -0.047)	0.504

*, significant correlation between downstaging and acute kidney injury. When acute kidney injury decrease, downstaging increase. **, significant correlation between downstaging and anaemia. When anaemia decrease, downstaging increase. AE, adverse event; NAC, neoadjuvant chemotherapy; TEE, thromboembolic event; CI, confidence interval.

Discussion

We present detailed analysis of individual data in this Swedish population-based study, where a total of 96.2% had NAC-induced AEs. This finding contrasts with other retrospective studies, here displaying a higher incidence of AEs. However, Salminen *et al.* reported a rate of 54% in total, of which 32% were in higher grades 3–4, and a majority receiving GC. Haematological AEs were the most prevalent (9). We report similar rate of highest AE-grades 3–4 of 31%, when majority received HD-MVAC. The difference in results between our study and Salminen *et al.* might be due to the different chemotherapy regimens and the difference in data collection. However, the AEs analysed by CTCAE severity scale are comparable. Despite the data

derived from the Finnish national cystectomy register, they presented noticeably higher rates of AEs compared to data from the Swedish national cystectomy register. However, the data was reported differently: from day of RC up to 90 days in the Swedish register, compared to the Finnish which reported AEs during ongoing NAC (9,14). Our study derived data during ongoing NAC, from individual medical records and may explain why our rates were higher than others, including AEs of grades 1–2. Additionally, Blick *et al.* had only available chemotherapy toxicity data on 34 of 80 patients and reported AEs in 26.5% patients treated with HD-MVAC. Neutropenia was the most frequently toxicity observed (15). Furthermore, 85% of patients suffered of at least one AE in a retrospective study from 2017 where gastrointestinal effects together with haematological were

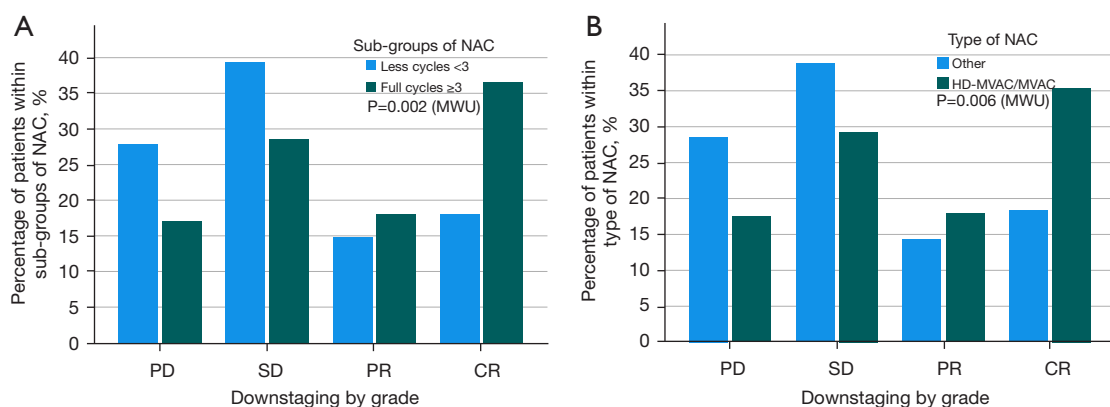


Figure 3 (A) Significant relationship between downstaging and number of NAC-cycles. Patients with less than three cycles had decreased downstaging due to higher percentage of PD and SD, compared to patients with full cycles; three or more ($P=0.002$ MWU); (B) significant relationship between downstaging and type of NAC regimen. Patients who received HD-MVAC/MVAC had higher percentage of PR and CR, compared to patients who received other NAC ($P=0.006$ MWU). NAC, neoadjuvant chemotherapy; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; MWU, Mann-Whitney U-test; HD-MVAC, high-dose intensity methotrexate, vinblastine, adriamycin (doxorubicin) and cisplatin; MVAC, methotrexate, vinblastine, adriamycin (doxorubicin) and cisplatin.

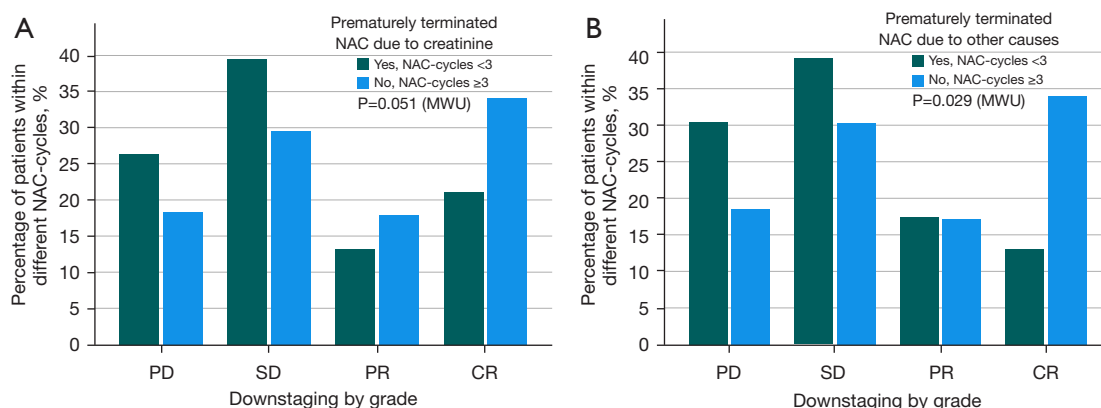


Figure 4 (A) No significant relationship between downstaging and prematurely terminated NAC, due to acute kidney injury with increase in creatinine, in patients with less than three or all pre-planned cycles ($P=0.051$ MWU); (B) a significant relationship between downstaging and prematurely terminated NAC due to other causes ($P=0.029$ MWU). Patients who did not terminate had higher percentage of CR. NAC, neoadjuvant chemotherapy; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; MWU, Mann-Whitney U-test.

the most common aside from fatigue (16). However, in a prospective phase II study from 2014 with 44 patients who received HD-MVAC, 82% experienced minor AEs and 12% more severe complications which comprises a total of 94% patients, similar to our study. Myelosuppression was the most common AE and no renal toxicities grade 3 or 4 was seen (17). In a large RCT, 32.5% patients receiving cisplatin, methotrexate and vinblastine (MVC) had haematological World Health Organization (WHO) grade 3 or 4 AEs. No

grade 3 or 4 renal toxic effects occurred (11). In addition, a meta-analysis presenting data of AEs from three studies reported granulocytopenia in 41.85% patients as the most prevalent (3). Comparison of efficacy of GC versus MVAC in NAC has been evaluated and no differences between the two modalities have been observed. There were equal rates of pathological and survival outcomes (18,19). Yet, the studies mentioned previously seem to favour GC in the aspect of AEs. Comparable to the previous

Table 7 Correlation analysis between the highest individual grade of CTCAE and individual clinical variables (based on the entire patient cohort)

Variables	Spearman correlation coefficient (95% CI)	P value
CACI	0.096 (−0.028 to 0.204)	0.123
cT-stage		0.635
T2, T3 and T4a	0.030 (−0.082 to 0.140)	

No significant correlation was seen. CTCAE, Common Terminology Criteria for Adverse Events; CACI, Charlson Comorbidity Index; cT, clinical tumour; CI, confidence interval.

studies, haematological AE was the most frequently seen complication in our study—anaemia in 88.9% of the patients. It is known since before that the platinum compounds increase side effects in the haematological system (7). The only variable with a significant relationship to higher AE-grades was the number of NAC-cycles. Patients who terminated prematurely with less cycles had higher AE-grades 2–4, indicating that patients who do not tolerate chemotherapy may be affected with severe complications earlier. Of those who tolerated all pre-planned cycles, a higher number of AEs grade 1 existed, indicating that minor AEs may be less likely to cause termination, as to be expected. They also had AEs grades 3–4, indicating that not all severe AEs may require early termination, or some severe AEs occur later in treatment, potentially as a cumulative effect of NAC or the cancer itself (*Figure 2*). However, Salminen *et al.* presented how patients received severe AEs (grades 3–4) already after one NAC-cycle (9). In our study, MVAC did not seem to affect the AE-grades more than other regimens ($P=0.218$ MWU). No correlation between higher AE-grades and CACI was visible, meaning a higher CACI-score did not suggest risk for side effects. Thus, the CACI-score cannot serve as a robust proxy for predicting AEs. The same absence of correlations between cT-stages and AEs were observed as well (*Table 7*).

Secondly, we wanted to investigate possible effects of AEs on downstaging outcomes. Correlation analysis displayed that when AE-grades decrease, downstaging increase (*Table 5*). Thus, suggesting that high AE-grades may have a negative impact on downstaging. Patients terminating NAC early had higher AE-grades compared to patients who received all pre-planned cycles (*Figure 2*). We suggest that lower AE-grades, possibly by early detection, treatment

and prevention of AEs, may result in less prematurely termination of NAC. Patients with all pre-planned NAC-cycles had increased downstaging (*Figure 3A*). Increased downstaging was also seen amongst patients who did not need to terminate NAC prematurely due to other causes, such as TEE etc. (*Figure 4B*). Downstaging being considered a surrogate marker for OS (5), we suggest that active prevention of AEs including severity grades, might benefit patients with MIBC and increase downstaging of the primary tumour. To the best of our knowledge, similar findings have not been published previously.

Furthermore, anaemia and acute kidney injury were individually associated with decreased downstaging for patients receiving all cycles. Since no other AE had an individual significant correlation with downstaging, anaemia and kidney injury are supposed to have an important role in the outcomes and possibly constitute priority areas. These observations have not been explored and presented before.

The major limitation in our study was a relatively small cohort. We have however identified the available patients from our collaborative centres who received NAC during the years 2009–2020. Another limitation could be that AE grades 3–4 were used as one compound grade during statistical calculations. This was due to some data in variables only registered as grades 3–4, and therefore not possible to separate. Both grades are however graded as severe according to CTCAE scale. The study is also of a retrospective nature. However, it was concluded in a recent study that retrospective and prospective study designs can yield results with similar accuracy, regarding collected data (20). The strength in this report may be in the details in which every patient was reviewed in their individual medical record with biochemical data. It is possible that more information on AEs was obtained this way, compared to using an existing register. In the Swedish cystectomy register, data such as anaemia and kidney injury during NAC is not compiled and therefore undetected and unreported. This study differs in design compared to a previous Swedish study, where the focus on AEs lay in the post-RC period 90 days, on variables according to the Clavien-Dindo classification (13). We collected AEs adjacent to NAC, pre-RC, to minimize influence on complications from radical surgery. We recorded a significantly larger number of AEs, including minor ones, from multiple organ systems, compared to other retrospective registry studies or RCTs. We argue that this type of collection contributed to the number of AEs and that MVAC was not seen as significantly related to higher

AE-grades compared to other regimens including GC, and MVAC therefore not primarily contributing to the severity grade of AEs. However, we cannot exclude that MVAC did not increase the number of AEs more than other regimens in this study. Five of seven Swedish University Hospitals have chosen to use MVAC instead of GC, thus a minority of Swedish patients receive GC.

Conclusions

NAC in MIBC poses a significant risk for AEs pre-RC with many clinical implications, and CACI-score cannot serve as a robust proxy for predicting AEs. Patients terminating chemotherapy prematurely, had higher AE-grades and decreased downstaging. Further, acute kidney injury and anaemia were individually associated with a decreased downstaging. We propose that early detection and prevention of AEs may increase downstaging of the primary tumour.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ethical permission was acquired from Regional Ethics Board, Etikprövningsnämnden (EPN) Umeå, Sweden: Dnr 2013/463-31M. The study was retrospective and therefore no informed consent was required according to EPN. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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