Changes in neoadjuvant chemotherapy utilization in muscle invasive bladder cancer treatment: a tertiary center retrospective study

Katarzyna Gronostaj1, Anna Katarzyna Czech1, Jakub Fronczek2, Tomasz Wiatr1, Mikołaj Przydacz1, Przemysław Dudek1, Łukasz Curyło1, Wojciech Szczeklik2, Piotr Chłosta1

1Jagiellonian University Medical College, Department of Urology, Cracow, Poland
2Jagiellonian University Medical College, Department of Intensive Care and Perioperative Medicine, Cracow, Poland

Citation: Gronostaj K, Czech AK, Fronczek J, et al. Changes in neoadjuvant chemotherapy utilization in muscle invasive bladder cancer treatment: a tertiary center retrospective study. Cent European J Urol. 2020; 73: 13-18.

Introduction The year 2015 brought a major shift in the national health care system in Poland – the diagnosis and treatment of patients with malignant diseases became a priority. Close multidisciplinary collaboration was facilitated to optimize patients’ care. The aim of this study was to investigate temporal changes in neoadjuvant chemotherapy (NAC) utilization in patients who underwent radical cystectomy (RC) due to muscle invasive bladder cancer (MIBC) in a single academic center in Poland.

Material and methods Patients who underwent planned curative RC with bilateral pelvic lymph node dissection between January 2013 and December 2018 in a tertiary care center were included in the study. To assess the response to chemotherapy, tumor regression grades (TRGs) were included into the standard pathological examination of RC specimens.

Results Out of 183 patients enrolled into the study, 105 (57.4%) underwent NAC before RC. Only 1 (4%) out of 25 patients underwent NAC prior to RC in 2013. The percentage of patients who received NAC in subsequent years were: 4% (1/25) in 2013, 36% (9/25) in 2014, 55.3% (21/38) in 2015, 62.9% (21/35) in 2016, 83.9% (26/31) in 2017 and 89.7% (26/29) in 2018 (p-value for trend <0.001). Thirty patients (28.6%) had complete pathological response to NAC (TRG1), 50 patients (47.6%) showed strong response (TRG2) and 25 patients (23.7%) had weak or no response (TRG3).

Conclusions This study showed an increasing utilization of NAC amongst MIBC patients who underwent RC. Close multidisciplinary collaboration is the key to optimizing perioperative care of patients with MIBC.

Key Words: muscle invasive bladder cancer • neoadjuvant chemotherapy • tumor regression grade

INTRODUCTION

Muscle invasive bladder cancer (MIBC) is a deadly disease. A recent paper concerning the natural history of MIBC showed that 38% of untreated patients developed metastatic disease and 41% died because of the cancer up to 6 months after the diagnosis [1]. These data clearly emphasize the need for therapeutic intervention to increase the patient’s chances for survival. Current guidelines recommend cisplatin-based multidrug neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) for eligible MIBC patients [2]. Even though the improvement in survival from NAC in the treatment of MIBC is supported by level 1 evidence [3], data concerning the advantage of NAC outside of clinical trials are limited. What is even more bothering, a population-based study using a National Cancer Database failed to demonstrate the survival benefit of NAC [4]. Although these results should be interpreted with caution, they might, among other issues, be the reason why the real life
utilization of NAC is far from optimal. The largest reports published in the recent years showed that the percentage of patients treated with NAC oscillates around 20% [5, 6]. The situation varies between countries and centers and more encouraging reports with higher NAC usage were published [7, 8, 9]. NAC was first used in our institution in 2013 and its usage has been increasing. The year 2015 brought a major shift in the national health care system in Poland. Due to the introduction of a dedicated pathway of oncological treatment (‘oncological package’) the diagnosis and treatment of patients with malignant diseases became a priority. A close collaboration between urologists, medical oncologists, radiotherapists, and radiologists was facilitated by weekly tumor board meetings held to optimize patients’ care. To provide the assessment of response to chemotherapy, tumor regression grades (TRGs) were included into the standard pathological examination of RC specimens. TRGs, which reflect and quantify pathological response to NAC, were introduced by Fleischmann et al. in MIBC patients who underwent NAC followed by RC [10]. One exploratory study showed prognostic value of TRGs [10]. This finding was recently confirmed in an independent cohort [11]. The aim of the current study was to investigate the changes in NAC utilization over subsequent years and to present the pathological response to NAC in a single academic center in Poland.

Table 1. Patients’ characteristics, pre-treatment clinical staging and initial grading

| Variable                  | Statistics | All patients (n = 183) | RC only (n = 78) | NAC+RC (n = 105) | p (RC only vs. NAC +RC) |
|---------------------------|------------|-----------------------|-----------------|-----------------|------------------------|
| Age                       | Median IQR | 65.00 60.00–69.00    | 66.50 62.00–73.00 | 64.00 58.00–67.00 | 0.004                  |
| Gender (male)             | n (%)      | 124 (80.0) 60 (78.9) | 64 (81)        | 0.904            |
| BMI                       | Median IQR | 27.17 24.50–29.70    | 26.95 24.49–29.32 | 27.40 24.50–29.90 | 0.583                  |
| Smokers (current / former)| n (%)      | 108 (71.6) 42 (58.3) | 66 (83.5)      | 0.001            |
| Occupational exposure     | n (%)      | 26 (18.2) 14 (21.9)  | 12 (15.2)      | 0.134            |
| ASA score (%)             | n (%)      | 1 (0.6) 0 (0.0)      | 1 (1.3)        | 0.381            |
| CAD                       | n (%)      | 37 (23.9) 23 (30.3)  | 14 (17.7)      | 0.100            |
| CHF                       | n (%)      | 15 (9.7) 10 (13.2)   | 5 (6.4)        | 0.254            |
| Aortic stenosis           | n (%)      | 2 (1.3) 2 (2.6)      | 0 (0)          | 0.460            |
| PVD                       | n (%)      | 9 (5.8) 5 (6.6)      | 4 (5.1)        | 0.952            |
| DVT/PE                    | n (%)      | 2 (1.3) 1 (1.3)      | 1 (1.3)        | 0.001            |
| HT                        | n (%)      | 104 (67.1) 53 (69.7) | 51 (64.6)      | 0.060            |
| DM                        | n (%)      | 32 (20.6) 16 (21.1)  | 16 (20.3)      | 1.000            |
| COPD                      | n (%)      | 12 (7.9) 9 (11.8)    | 3 (3.9)        | 0.323            |
| CVE                       | n (%)      | 5 (3.2) 3 (4.0)      | 2 (2.5)        | 0.953            |
| Clinical T-stage          | n (%)      | 99 (54.1%) 42 (53.8%) | 57 (54.3%)    | 0.389            |
| T2-3a                     | n (%)      | 58 (31.7%) 22 (28.2%) | 36 (34.3%)    | 0.003            |
| T3b                       | n (%)      | 26 (14.2%) 14 (17.9%) | 12 (11.4%)    | 0.653            |
| Clinical N-stage          | n (%)      | 126 (68.9%) 44 (56.4%) | 82 (78.1%)    | 0.001            |
| N0                        | n (%)      | 57 (31.1%) 34 (43.6%) | 23 (21.9%)    | 0.653            |
| Grading LG/HG             | n (%)      | 127 (70.7%) 3 (3.8%) | 102 (98.1%)    | 0.001            |
| LG                        | n (%)      | 177 (97.3%) 75 (96.2%) | 73 (69.5%)    | 0.134            |
| G2                        | n (%)      | 65 (35.5%) 33 (42.7%) | 32 (30.5%)    | 0.323            |
| G3                        | n (%)      | 118 (64.5%) 45 (67.7%) | 73 (69.5%)    | 0.001            |

RC – radical cystectomy; NAC – neoadjuvant chemotherapy; IQR – interquartile range; n (%) – number (percentage); BMI – body mass index; ASA score – American Society of Anesthesiologists score; CAD – coronary artery disease; CHF – chronic heart failure; PVD – peripheral vascular disease; DVT/PE – deep venous thrombosis/pulmonary embolism; HT – hypertension; DM – diabetes mellitus; COPD – chronic obstructive pulmonary disease; CVE – cerebral vascular event; LG – low-grade; HG – high-grade
MATERIAL AND METHODS

Medical data of patients who underwent cystectomy between January 2013 and December 2018 in a single academic center was reviewed (n = 282). Only patients with MIBC who were scheduled for planned curative RC with bilateral pelvic lymph node dissection were included for further analysis. Exclusion criteria were: palliative (n = 23), urgent (n = 6) or benign (n = 7) indications for cystectomy, non-muscle invasive bladder cancer (NMIBC) (n = 22) or other than pure urothelial histology of bladder cancer (n = 14), other malignancies (n = 27) except localized adenocarcinoma of prostate.

After obtaining the study protocol approval from the local bioethics committee, the data was collected from hospital records. Transurethral resection of the bladder tumor (TURBt), physical examination, computed tomography (CT) or X-ray of chest and CT or magnetic resonance imaging (MRI) of abdomen and pelvis were used for clinical staging. The final pathology staging was determined according to the 2009 and 2017 TNM classification [12, 13]. TRGs were assessed following the previously described method [10]. TRG1 was assigned when there were no cancer cells, but only fibrosis in tumor bed and reflected complete pathological response to chemotherapy. TRG2 was defined as cancer cells present in less than 50% of tumor bed with predominant fibrosis and indicated strong response to NAC. TRG3 was assigned when there was cancer present in more than 50% of tumor bed and corresponded to weak or no response to NAC. TRGs were evaluated independently for bladder specimen and affected lymph nodes. In the case of varying results the final TRG was the higher (worse) TRG.

Table 2. Characteristics of neoadjuvant chemotherapy (NAC)

|          | Total NAC (completed) n = 105 (95) | PG (completed PG) n = 62 (56) | MVAC (completed MVAC) n = 10 (9) | ddMVAC (completed ddMVAC) n = 22 (21) | GemCarbo (completed GemCarbo) n = 11 (9) |
|----------|----------------------------------|-------------------------------|---------------------------------|-----------------------------------|----------------------------------------|
| 2013     | 1 (1)                            | 1 (1)                         | 0 (0)                           | 0 (0)                             | 0 (0)                                 |
| 2014     | 9 (7)                            | 3 (2)                         | 1 (1)                           | 0 (0)                             | 5 (4)                                 |
| 2015     | 21 (20)                          | 20 (19)                       | 0 (0)                           | 0 (0)                             | 1 (1)                                 |
| 2016     | 22 (20)                          | 19 (18)                       | 1 (1)                           | 0 (0)                             | 2 (1)                                 |
| 2017     | 26 (23)                          | 11 (9)                        | 4 (3)                           | 8 (8)                             | 3 (3)                                 |
| 2018     | 26 (25)                          | 8 (8)                         | 4 (4)                           | 14 (13)                           | 0 (0)                                 |

NAC – neoadjuvant chemotherapy; PG – cisplatin, gemcitabine; MVAC – methotrexate, vinblastine, adriamycin, cisplatin; ddMVAC – dose-dense methotrexate, vinblastine, adriamycin, cisplatin; GemCarbo – gemcitabine, carboplatin

Table 3. Tumor characteristics and neoadjuvant chemotherapy (NAC) response

| Variable | Statistics | NAC + RC (n = 105) | RC only (n = 78) | NAC completed (n = 95) | NAC uncompleted (n = 10) |
|----------|------------|-------------------|-----------------|-----------------------|-------------------------|
| Pathologic T-stage | | | | | |
| T0       | n (%)      | 26 (24.2)         | 4 (5.1)         | 24 (25.3)             | 2 (10)                  |
| Ta-1-Cis | n (%)      | 26 (24.2)         | 3 (3.8)         | 25 (26.3)             | 1 (30)                  |
| T2       | n (%)      | 25 (23.8)         | 19 (24.4)       | 23 (24.2)             | 2 (10)                  |
| T3-4a    | n (%)      | 28 (26.7)         | 52 (66.7)       | 23 (24.2)             | 5 (50)                  |
| Pathologic N-stage | | | | | |
| N0       | n (%)      | 82 (78.1)         | 44 (56.4)       | 77 (81.1)             | 5 (50)                  |
| N+       | n (%)      | 23 (21.9)         | 34 (43.6)       | 18 (19.9)             | 5 (50)                  |
| TRG1     | n (%)      | 30 (28.6)         | –               | 28 (29.5)             | 2 (20.0)                |
| TRG2     | n (%)      | 50 (47.6)         | –               | 46 (48.4)             | 4 (40.0)                |
| TRG3     | n (%)      | 25 (23.8)         | –               | 21 (22.1)             | 4 (40.0)                |

RC – radical cystectomy; NAC – neoadjuvant chemotherapy; TRG – tumor regression grade
Statistical analysis

Descriptive statistics on baseline variables are presented as median (interquartile range [IQR]) or count and percentage. Between-group differences were investigated using the Wilcoxon-Mann-Whitney, chi-squared or Fisher’s exact tests as appropriate. We performed the Cochran-Armitage test for trend in proportions of patients receiving NAC across subsequent years in the period of interest. A two-sided alpha level of 0.05 was used as a cut-off for declaring statistical significance.

Table 4. Basic characteristics, pre-treatment clinical staging, initial grading and chemotherapy used according to tumor regression grade group

| Variable                        | Statistics | TRG 1 (n = 30) | TRG 2 (n = 50) | TRG 3 (n = 25) | p    |
|---------------------------------|------------|----------------|----------------|----------------|------|
| Age                             | Median IQR | 62.5 (58–67)   | 64.5 (60–69)   | 63 (60–67)     | 0.322|
| Gender (male)                   | n (%)      | 21 (70.0)      | 45 (90.0)      | 19 (76.0)      | 0.068|
| BMI                             | Median IQR | 27.4 (26.8–29.5)| 27.5 (24.5–29.9)| 26.1 (23.4–30.8)| 0.882|
| Smoking status                  |            |                |                |                |      |
| Current smoker                  | n (%)      | 0 (0.0)        | 1 (2.0)        | 0 (0.0)        | 0.309|
| Non-smoker                      | n (%)      | 25 (83.3)      | 30 (60.0)      | 19 (76.0)      |      |
| Former smoker                   | n (%)      | 5 (16.7)       | 19 (38.0)      | 6 (24.0)       |      |
| Occupational exposure           | n (%)      | 4 (13.3)       | 4 (8.0)        | 6 (24.0)       |      |
| ASA score                       |            |                |                |                |      |
| 1                               | n (%)      | 0 (0.0)        | 1 (2.0)        | 0 (0.0)        | 0.142|
| 2                               | n (%)      | 25 (83.3)      | 30 (60.0)      | 19 (76.0)      |      |
| 3                               | n (%)      | 5 (16.7)       | 19 (38.0)      | 6 (24.0)       |      |
| CAD                             | n (%)      | 4 (13.3)       | 10 (20.0)      | 3 (12.5)       | 0.653|
| CHF                             | n (%)      | 0 (0.0)        | 5 (10.0)       | 6 (24.0)       | 0.229|
| Aortic stenosis                 | n (%)      | 0 (0.0)        | 1 (2.0)        | 0 (0.0)        | 1.000|
| PVD                             | n (%)      | 1 (3.3)        | 4 (8.0)        | 0 (0.0)        | 0.504|
| DVT/PE                          | n (%)      | 1 (3.3)        | 1 (2.0)        | 2 (8.3)        | 1.000|
| HT                              | n (%)      | 16 (53.3)      | 37 (74.0)      | 15 (62.5)      | 0.161|
| DM                              | n (%)      | 5 (16.7)       | 12 (24.0)      | 6 (25.0)       | 0.692|
| COPD                            | n (%)      | 2 (6.7)        | 1 (2.1)        | 1 (4.2)        | 0.809|
| CVE                             | n (%)      | 0 (0.0)        | 2 (4.0)        | 0 (0.0)        | 0.720|
| Clinical T-stage                |            |                |                |                |      |
| cT2-3a                          | n (%)      | 20 (66.7)      | 29 (58.0)      | 8 (32.0)       | 0.010|
| cT3b                            | n (%)      | 10 (33.3)      | 16 (32.0)      | 10 (40.0)      |      |
| cT4a                            | n (%)      | 0 (0.0)        | 5 (10.0)       | 7 (28.0)       |      |
| Clinical N-stage                |            |                |                |                |      |
| cN0                             | n (%)      | 30 (100.0)     | 41 (82.0)      | 11 (44.0)      | <0.001|
| cN+                             | n (%)      | 0 (0.0)        | 9 (18.0)       | 14 (56.0)      |      |
| Grading LG/HG                   |            |                |                |                |      |
| LG                              | n (%)      | 1 (3.4)        | 1 (2.0)        | 0 (0.0)        | 1.000|
| HG                              | n (%)      | 28 (96.6)      | 49 (98.0)      | 25 (100.0)     |      |
| Grading G1/G2/G3                |            |                |                |                |      |
| G2                              | n (%)      | 9 (30.0)       | 18 (36.0)      | 5 (20.0)       | 0.365|
| G3                              | n (%)      | 21 (70.0)      | 32 (64.0)      | 20 (80.0)      |      |
| Type of NAC                     |            |                |                |                |      |
| PG                              | n (%)      | 18 (60.0)      | 31 (62.0)      | 13 (52.0)      | 0.137|
| MVAC                            | n (%)      | 1 (3.3)        | 5 (10.0)       | 5 (20.0)       |      |
| ddMVAC                          | n (%)      | 9 (30.0)       | 10 (20.0)      | 2 (8.0)        |      |
| GemCarbo                        | n (%)      | 2 (6.7)        | 4 (8.0)        | 5 (20.0)       |      |
| NAC completed                   | n (%)      | 28 (93.3)      | 46 (92.0)      | 21 (84.0)      | 0.519|

TRG – tumor regression grade; RC – radical cystectomy; NAC – neoadjuvant chemotherapy; IQR – Interquartile range; n (%) – number (percentage); BMI – body mass index; ASA score – American Society of Anesthesiologists score; CAD – coronary artery disease; CHF – chronic heart failure; PVD – peripheral vascular disease; DVT/PE – deep venous thrombosis/pulmonary embolism; HT hypertension; DM – diabetes mellitus; COPD – chronic obstructive pulmonary disease; CVE – cerebral vascular event; LG – low-grade; HG – high-grade; PG – cisplatin; gemcitabine; MVAC – methotrexate, vinblastine, adriamycin, cisplatin; ddMVAC – dose dense methotrexate; vinblastine; adriamycin; cisplatin; GemCarbo – gemcitabine, carboplatin
RESULTS

Out of 183 patients enrolled into the study, 105 (57.4%) underwent NAC before RC. Patients’ characteristics, pre-treatment clinical staging and initial grading obtained from TURBt specimen are presented in Table 1. Except for younger age, higher percentage of positive smoking history and lower percentage of clinically suspicious lymph nodes in NAC+RC patients, the groups were similar (Table 1). The percentage of patients who received NAC in subsequent years were: 4% (1/25) in 2013, 36% (9/25) in 2014, 55.3% (21/38) in 2015, 62.9% (21/35) in 2016, 83.9% (26/31) in 2017 and 89.7% (26/29) in 2018 (Figure 1; p-value for trend <0.001).

NAC regimen details are presented in Table 2. Ten patients did not complete planned chemotherapy due to the treatment toxicity. All these patients received less than half of planned infusions. The decision concerning NAC termination was made by a medical oncologist. Ninety-four patients underwent cisplatin-based combination. The most popular schedule was cisplatin-gemcitabine (PG), however in the last two years of the analyzed period, ddMVAC (dose-dense methotrexate, vinblastine, adriamycin, cisplatin) was prescribed more often.

Final pathology results including histopathological response to chemotherapy are presented in Table 3. Nearly half of the patients who underwent NAC did not show muscle invasive disease in final surgical specimen. More than three-quarters of NAC patients showed either complete (TRG1) or partial (TRG2) pathological response to chemotherapy.

Patients characteristics, pre-treatment staging, initial grading, type of NAC used and tumor characteristics according to TRG group are presented in Table 4 and Table 5.

DISCUSSION

The study showed a major increase in NAC utilization since its introduction in 2013. In 2015, due to changes in the national health care system in Poland, tumor board meetings became mandatory, which resulted in the close collaboration between medical oncologists, radiotherapists, radiologists and urologists. One of the observed effects of this multidisciplinary cooperation was an increased accessibility to medical oncologist’s consults and subsequent rapid increase in NAC utilization. A similar phenomenon has been described before [14]. The percentage of NAC utilization reaching nearly 90% in 2018 is one of the highest reported up to date. To our best knowledge, only one study from Japan reported comparably high results [7]; however, in this study the predominant schedule of NAC was carboplatin-based. In the current study the NAC regimen was assigned at the discretion of a medical oncologist and the eligibility criteria for cisplatin-based chemotherapy were extended to patients with glomerular filtration rate over 50 ml/min, which might be one of the reasons for such high NAC utilization.

Data concerning the assessment of response to chemotherapy published to date was limited to complete (ypT0N0) or non-invasive (ypTa-T1-Tis N0) downstaging [15, 16, 17]. Introducing TRGs gave the possibility not only to quantify the response to NAC but also to assess the response to NAC in more advanced pathological stages. Over 75% of patients in our study had complete (TRG1) or strong (TRG2) pathological response to chemotherapy. Patients characteristics, pre-treatment staging, initial grading, type of NAC used and tumor characteristics according to TRG group are presented in Table 4 and Table 5.

| Variable | Statistics | NAC + RC (n = 105) | TRG 1 (n = 30) | TRG 2 (n = 50) | TRG 3 (n = 25) |
|----------|------------|--------------------|----------------|----------------|----------------|
| Pathologic yT-stage | | | | | |
| yT0      | n (%)      | 26 (24.8)          | 24 (80.0)      | 1 (2.0)        | 1 (4.0)        |
| yT1-Cis  | n (%)      | 26 (24.8)          | 6 (20.0)       | 20 (40.0)      | 0 (0.0)        |
| yT2      | n (%)      | 25 (23.8)          | 0 (0.0)        | 16 (32.0)      | 9 (36.0)       |
| yT3-4a   | n (%)      | 28 (26.7)          | 0 (0.0)        | 13 (26.0)      | 15 (60.0)      |
| Pathologic yN-stage | | | | | |
| yN0      | n (%)      | 82 (78.1)          | 30 (100.0)     | 41 (82.0)      | 11 (44.0)      |
| yN+      | n (%)      | 23 (21.9)          | 0 (0.0)        | 9 (18.0)       | 14 (56.0)      |

NAC+RC – neoadjuvant chemotherapy and radical cystectomy; TRG – tumor regression grade; n (%) – number (percentage)
included in the study. Moreover, not all the patients had a pre-treatment CT chest scan, only chest X-ray, which might be the cause of a potential understaging.

CONCLUSIONS

This study showed an increasing utilization of NAC amongst MIBC patients who underwent RC in tertiary academic center. The probable reason for that might be the shift in the national health care system facilitating regular tumor board meetings. The close multidisciplinary collaboration is the key to optimizing care of patients with MIBC.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

References

1. Martini A, Sfakianos JP, Renström-Kostela L, et al. The natural history of untreated muscle-invasive bladder cancer. BJU Int. 2020; 125: 270-275.

2. Witjes JA, Lebret T, Compérat EM, et al. Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Eur Urol. 2017; 71: 462-475.

3. Yin M, Joshi M, Meijer RP, et al. Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer: A Systematic Review and Two-Step Meta-Analysis. Oncologist. 2016; 21: 708-715.

4. Hanna N, Trinh QD, Seisen T, et al. Effectiveness of Neoadjuvant Chemotherapy for Muscle-invasive Bladder Cancer in the Current Real World Setting in the USA. Eur Urol Oncol. 2018; 1: 83-90.

5. Reardon ZD, Patel SG, Zaid HB, et al. Trends in the use of perioperative chemotherapy for localized and locally advanced muscle-invasive bladder cancer: a sign of changing tides. Eur Urol. 2015; 67: 165-170.

6. Liu W, Tian J, Zhang S, et al. The utilization status of neoadjuvant chemotherapy in muscle-invasive bladder cancer: a systematic review and meta-analysis. Minerva Urol Nefrol. 2020 [epub ahead of print] doi: 10.23736/S0393-2249.19.03648-8

7. Anan G, Hatakeyama S, Fujita N, et al. Trends in neoadjuvant chemotherapy use and oncological outcomes for muscle-invasive bladder cancer in Japan: a multicenter study. Oncotarget. 2017; 8: 86130-86142.

8. Nielsen N, Wrist Lam G, Fabrin K, Holt P, Thind PO, Jensen JB. Reasons why not all Danish patients with muscle invasive bladder cancer receive neoadjuvant chemotherapy before radical cystectomy. Scand J Urol. 2019; 53: 213-216.

9. Gronostaj K, Czech AK, Fronczek J, et al. Implementation of neoadjuvant chemotherapy in muscle invasive bladder cancer treatment in Poland: a single institution retrospective study. Cent European J Urol. 2019; 72: 100-105.

10. Fleischmann A, Thalmann GN, Perren A, Seiler R. Tumor regression grade of urothelial bladder cancer after neoadjuvant chemotherapy: a novel and successful strategy to predict survival. Am J Surg Pathol. 2014; 38: 325-332.

11. Gronostaj K, Czech AK, Fronczek J, et al. The Prognostic Value of Tumor Regression Grades Combined With TNM Classification in Patients With Muscle-Invasive Bladder Cancer Who Underwent Neoadjuvant Chemotherapy Followed by Radical Cystectomy. Clin Genitourin Cancer. 2019; 17: E1203-1211.

12. Sobin L, Gospodarowicz M, Wittekind C. TNM Classification of Malignant Tumours, 7th Edition. New York, NY: John Wiley & Sons; 2011, pp.262-265

13. Amin MB, Edge SB, Greene FL, Schilsky RL, Gaspar LE, Washington M. AJCC cancer staging manual. New York, NY: Springer, 2017.

14. Rehman S, Crane A, Din R, et al. Understanding avoidance, refusal, and abandonment of chemotherapy before and after cystectomy for bladder cancer. Urology. 2013; 82: 1370-1375.

15. Rosenblatt R, Sherif A, Rintala E, et al. Nordic UrothelialCancer Group.Pathologic-downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. Eur Urol. 2012; 61: 1229-1238.

16. Bhindi B, Frank I, Mason RJ, et al. Oncologic Outcomes for Patients with Residual Cancer at Cystectomy Following Neoadjuvant Chemotherapy: A Pathologic Stage-matched Analysis. Eur Urol. 2017; 72: 660-664.

17. Zargar H, Espiritu PN, Fairey AS, et al. Multicenter assessment of neoadjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol. 2015; 67: 241-249.