의학석사 학위논문

림프절 비전이 근육침범 방광암으로 근치적 수술 전 신보조 항암요법을 받은 환자에서 술 후 병기감소와 임파전이의 예측

Prediction of down-staging and node-positive disease after neoadjuvant chemotherapy and radical cystectomy in patients with non-metastatic muscle invasive bladder cancer

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2018 년　2 월

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ABSTRACT

Radical cystectomy (RC) performed with total pelvic lymphadenectomy (PLND) is the golden standard for the treatment of non-metastatic muscle-invasive bladder cancer (MIBC). And neoadjuvant chemotherapy (NAC) improves pathologic down-staging and patient survival. But, it is not well established which patients show response to NAC prior to RC and what is the optimal range of PLND in this cohort remains controversial. In this study in which all patients received NAC and underwent extended PLND at the time of RC, we investigated the preoperative risk factors to predict major down-staging response or non-response after NAC and analyzed the location of lymph node disease to determine the optimal extent of PLND. All patients received NAC and underwent extended PLND during radical cystectomy (RC). Sixty-six clinical N0 MIBC patients who received NAC prior to RC from 1995 to 2016 were analyzed. The rate of major response and non-response after the RC and their peri-operative risk factors were evaluated by multivariate analysis. Major response was defined as absence of muscle-invasive disease and lymph node metastasis (pT1-0N0), and of non-response, defined as pathological node-positive disease (pN+). Of all subjects, median (IQR) age was 64.5 (IQR, 56.7–72.2) years, and 55 (83.3%) patients were male. Clinical T stages were ≤cT2 in 24 (36.4%), cT3 in 29 (43.9%), and cT4 in 13 (19.7%) patients. Tumor grade on transurethral resection of bladder tumor (TUR-BT) were low grade in 2 (3.0%), high grade in 63 (95.5%), and unknown in 1 (1.5%) patients. Median duration from initial TURBT to RC was 3.7 (3.0–4.3) months. During NAC, the overall chemotherapy response (OCR) assessed by imaging was 31.8% (complete remission, 2 patients;

partial response, 19 patients). Pathological T stages after RC were pT0 in 16 (24.2%), pTis in 6 (6.2%), pTa in (1.5%), pT1 in 6 (9.1%), pT2 in 8 (12.1%), pT3 in 25 (37.9%), and pT4 in 4 (6.1%) patients. The rate of pathological node-positive disease was 13.6% (pN1, 7 patients; pN2, 2 patients). Among patients with NAC response (OCR positive), only 2 (9.5%) had node positive diseases in the true pelvis. On multivariate analysis, clinical T stage ($\leq$cT2, odds ratio = 0.146, p = 0.003) was the only independent predictive factor for major response. There was no predictor for pathological node-positive disease (pN+). In patients with NAC plus RC, clinical T stage was an important predictor for the major down-staging response.

KEY WORDS

Bladder cancer; Neoadjuvant chemotherapy; Nodal involvement; Risk factors; Pathological outcomes

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INTRODUCTION

In the United States and Europe, urothelial carcinoma is the fourth most common tumor and represents a heterogeneous group of cancers[1]. Among them, urothelial carcinoma of the bladder (UCB) is the most common type and accounts for 95% of urothelial carcinomas[2]. According to the National Cancer Registry, the bladder cancer prevalence from 1998 to 2002 was 6.4 per 100,000 people, the highest among all urological cancers. As of 2012, the age-adjusted prevalence was 31.1 in males, 5.1 in females per 100,000, and was reported to be 16.3 in both[3, 4]. At the time of diagnosis, 20%~30% of BC has been was found to be muscle-invasive bladder cancer (MIBC)[5, 6], which is one of the most aggressive epithelial tumors and has an early systemic penetration rate. The 5-year survival rate mainly depends on the pathological stage and node status[7, 8] and most series have reported 5-year overall survival (OS) rates of 50 to 60%[9]. Radical cystectomy (RC) performed with total pelvic lymphadenectomy (PLND) is the gold standard for the treatment of MIBC after initial transurethral resection of bladder tumor (TUR-BT)[10-13]. Although this surgical approach induces complete tumor resection in a significant proportion of patients, MIBC patients are at high risk of distant recurrence after the surgery[14, 15], and despite the underlying radical surgery for local control, 50% of patients show extra-vesical extension and $\geq$25% of patients harbor lymph node (LN) metastases at the time of RC[16, 17].

International guidelines recommend the use of neoadjuvant chemotherapy (NAC) for patients with MIBC[14, 18]. A meta-analysis and randomized trials have shown a survival benefit for cisplatin-based NAC in patients with MIBC[19-21]. On the basis

of this evidence, it is strongly recommended that recent treatment guidelines consider cisplatin-based NAC prior to RC[12, 13]. Although NAC improves pathological down-staging and patient survival, the main response, defined as absence of muscle-invasive disease and LN metastasis (pT1-0N0), affects approximately only 40%[22]. Unresponsive patients are more likely to have no clinical benefit, are exposed to severe adverse effects, and experience a delay in surgical treatment[19-21]. However, it is not well established which patients are response to NAC prior to RC.

Regarding lymph node dissection(LND), Skinner et al.[23] were the first to report that a certain percentage of patients with LN-positive disease could achieve long-term survival with RC and PLND without systemic treatment, which emphasized the role of LND. The results of a subsequent series regarding the extent of LND, led to a strong recommendation for use of extended pelvic lymphadenectomy (ePLND) in all patients undergoing RC for MIBC to remove all metastatic tumor deposits completely[24]. Recently, the findings of a meta-analysis study showed that ePLND, compared with non-ePLND, provided a recurrence-free survival benefit not only for patients who had positive LN and pT3–4 disease but also for patients with negative LN[25]. Given that PLND is important in the management of patients under RC for MIBC and that ePLND can provide more accurate pathological stage and survival rates, the risks associated with ePLND should be carefully evaluated[26].

In this study, we aimed to identify preoperative factors predictive of good responders (down- staging) to NAC or of non-responders (node-positive diseases) by analyzing patients who received NAC prior to RC. We also investigated the location of LN disease after NAC to determine the optimal ePLND. We hypothesized that patients responsive to NAC are more likely to derive clinical benefit that the survival benefits

of NAC are more prominent than non-responders. Furthermore, we hypothesized that this responsive group can be provided a more limited range of PLND without adversely affecting therapeutic outcomes. These two issues are important to explore because they can give valuable information concerning not only proper candidate selection for NAC but also determination of the optimal range of PLND in the present era in which NAC and RC is considered standard therapy in patients with MIBC.

MATERIAL AND METHODS

Ethical Statements

This study protocol was approved by the institutional review board of the Asan Medical Center, Seoul, Republic of Korea. The need for informed consent was waived by the institutional review board because of the minimal risk for potential harm. All personal information was anonymized before analysis.

Patient Selection

The study population comprised 121 consecutive patients who underwent RC from May 1995 to December 2016 and received chemotherapy prior to RC with neoadjuvant intent in our institution. Of the 121 patients, 55 (45.5%) were excluded because of clinical node-positive disease (n = 40, 33.1%), not performing LND (n = 4, 3.3%), incomplete resection during RC (n = 2, 1.7%), non-UC (n = 5, 4.1%), incomplete cycles of planned chemotherapy (n = 3, 2.5%), and incomplete clinical data (n = 1, 0.8%). Therefore, 66 (54.5%) patients were analyzed in the current study (Figure 1).

Treatments and Pathologic Evaluations

All patients underwent computerized tomography (CT) scanning at initial diagnosis and immediately prior to RC. A median of 4 (range, 3–4) cycles of NAC were administered to patients prior to the RC. The most commonly used chemotherapeutic agents were the combination of gemcitabine and paclitaxel (GC) (n = 58, 87.9%), followed by dose-dense methotrexate + vinblastine + doxorubicin + cisplatin (MVAC)

(n = 6, 9.1%), and two patients used MVAC chemotherapy regimens (n = 2, 3.0%).

RC was routinely performed with ePLND, which included standard LND (from bifurcation of the common iliac vessels proximally, genitofemoral nerve laterally, obturator fossa posteriorly, medially up to the bladder and up to the deep circumflex iliac vein, and cloquet LNs in the hypogastric group distally) with extension up to the level of aortic bifurcation, including pre-sacral LNs[27, 28]. Excised specimens were processed according to the standard pathological procedure. The TNM staging of the tumor was classified according to the seventh revised recommendation of the American Joint Cancer Committee in 2010[29]. Tumor grade was assessed according to the World Health Organization 1973 and 2004 classifications[30]. For the analysis, grades ≤II and grade III in the 1973 classification were regarded as low and high grade in the 2004 classification. The presence of the described variant form in pathological reports, such as neuroendocrine differentiation, was also reviewed.

Statistical Analyses

Categorical variables are presented as frequencies and percentages, and continuous variables are expressed as the median and its interquartile range (IQR). Treatment responses to NAC were assessed by comparing the CT scans at two time points (initial diagnosis and after NAC) by using the recent version of the Response Evaluation Criteria in Solid Tumors (RECIST). RECIST offers four criteria, defined as follows: complete response (CR), disappearance of all target lesions (reduction in short axis to <10 mm); partial response (PR), reduction in the sum of target lesion diameters by ≥30%; progressive disease (PD), increase in the sum of the diameter of the target lesion by ≥20%; and stable disease (SD), when the change in the sum of

the diameters is not related to PD and PR[31].

The preoperative clinical TNM staging and postoperative pathological TNM staging were compared, and the proportions for patients who had down-staging with negative node (pT0-1N0) and patients who were node positive on final pathology (pN+) were assessed. To identify the risk factors for down-staging with node negative and node positive in the final pathological analysis, binary logistic regression analyses were performed. The potential preoperative risk factors assessed were clinical T stage, pathological T stage, tumor grade, presence or absence of the variant form by prior TUR-BT, and clinical response on NAC. All variables were assessed by univariate and multivariate analysis. All tests were two-tailed with a significance level of $p < 0.05$. All statistical analyses were performed by using a commercially available program (SPSS® version 21.0, IBM, Chicago, IL, USA).

RESULTS

The descriptive characteristics of the 66 patients with NAC prior to undergoing RC are shown in Table 1. The median age of the analyzed patients was 64.5 (IQR, 56.7–72.2) years for patients who underwent RC, and there were 55 (83.3%) males. Clinical T stages were cT2 in 24 (36.4%), cT3 in 29 (43.9%), and cT4 in 13 (19.7%) patients. Tumor grades on TUR-BT were low grade in 2 (3.0%), high grade in 63 (95.5%), and unknown in 1 (1.5%) patient. The median duration from the initial TUR-BT to RC was 3.7 (3.0–4.3) months.

During the RC, the median number of dissected nodes was 28.3 (19.0–33.2), and the rate of pathological node-positive (pN+) disease was 13.6% (pN1, 7 patients; pN2, 2 patients). Pathological T stage was observed in 16 (24.2%) patients with no remnant tumor (pT0), 6 (9.1%) patients with pTcis, 1 (1.5%) patient with pTa, 6 (9.1%) patients with pT1, 8 (12.1%) patients with pT2, 25 (37.9%) patients with pT3, and 4 (6.1%) patients with pT4. Down-staging with negative node (pT0–1N0) were observed in 29 (43.9%) patients (Table 1). There was a statistically significant decrease in T stage after NAC treatment (Figure 2, $p = 0.003$). When the clinical responses on NAC were assessed by comparing the CT scans at initial diagnosis and after the NAC (immediately prior to RC; Table 2), the overall chemotherapy response (OCR) rate of the underlying lesions was 31.8% observed in 21 patients (2 patients with complete remission [CR] and 19 patients with partial response [PR]). Three (12.5%) patients had pN + disease in clinical T2, 3 (10.3%) patients in T3, and 3 (23.1%) patients in T4. Only 2 (9.5%) patients showed pN + with OCR-positive

status after NAC, and all of them were clinical T3 stage. Table 3 shows the pattern of LN disease and down-staging according to the NAC responsiveness by the clinical T staging. Regarding down-staging in clinical node negative patients, 15 patients (62.5%) showed pathological T0 or T1 in clinical T2, it was 85.7% in patients with OCR positive. However, OCR did not have a statistically significant (p = 0.158) effect on the outcome prediction (Table 4).

Figure 3 shows a concise representation of the location of positive LNs. In this figure, two patients (E, F) showed pN2 located in the right common iliac artery station. Two patients (A, C) were OCR positive but showed LN-positive disease whose location was external and internal artery stations.

To identify the risk factors for down-staging with negative nodes on final pathology, binary logistic regression analyses were performed (Table 4). On multivariate analysis, clinical T stage (cT2; odds ratio [OR] = 0.146, $p = 0.003$) was the only independent predictive factor for pT0-1N0 on final pathology. However, pathological T stage ($p = 0.368$) muscle invasiveness, tumor grade ($p = 0.535$), presence of variant form ($p = 0.550$) during the prior TUR-BT, and the response to NAC ($p = 0.303$) were not independently associated with down-staging and negative nodes in the final pathological analysis (Table 4). When the risk factors for unfavorable pathological outcomes and node-positive disease on surgical pathology were assessed by similar methodology (Table 5), clinical T stage (≥cT3; $p = 0.182$), presence of variant form ($p = 0.296$) during the prior TUR-BT, and the response on NAC ($p = 0.384$) were not predictive of node-positive disease in the final pathological analysis (Table 5).

DISCUSSION

Grossmann et al.[32] demonstrated in the Southwest Oncology Group, one of the phase 3 clinical trials (S8710) about NAC, that the rate of residual disease (pT0) was significantly lower in patients who received preoperative MVAC chemotherapy than in those who did not receive NAC and had undergone cystectomy (38% vs. 15%; $p < 0.001$). The 5-year OS rate was higher in the group of pT0 patients than in the group of residual disease (no pT0) patients. In addition, although residual pT1 disease is not equivalent to pT0-Tis, the prognosis is worse[33]. Similar results were reported in a meta-analysis study by Petrelli et al.[10], who found that pT0N0M0 stage (complete pathological down-staging) was clearly associated with decreased risks of mortality and recurrence (55% and 81%, respectively) relative to those of any residual tumor disease. Pathological staging after RC is a major prognostic factor of OS in bladder cancer patients[34]. In particular, in patients receiving NAC, residual disease with persistent node-positive disease is one of the strongest prognostic factors for survival in patients who have undergone RC[35].

Among the patient groups showing postoperative pathological down-staging, CR was associated with better outcome in both the bladder and LNs than that in patients with positive node disease and any residual UCB[33, 36]. As mentioned previously, down-staging during the NAC has been considered a valid surrogate that correlates with outcomes in UCB[20, 37]. However, incorporation of NAC into clinical practice remains minimal[38], which suggests that certain subgroups benefit from preoperative NAC in patients undergoing RC. However, non-responders to NAC might be exposed to toxicity and experience a delay in surgical treatments, which In

our study, major responses after NAC and RC, which was defined as absence of muscle-invasive disease and LM metastasis (pT0-1N0), were observed in 43.9% of the patients (Table 1). These results are consistent with those of previous studies reporting a major response rate of 40%[22], which means that only approximately 40% of patients treated with NAC and RC are likely to show a survival benefit of NAC, and therefore, it is recommended that preoperative NAC be performed for these patients. On the other hand, 13.6% of our clinical node-negative patients were confirmed to have pathological node-positive disease in the final pathological examination despite preoperative NAC (Table 1). These non-responders did not show a survival benefit of NAC, and the treatment only delayed definitive local treatment. Therefore, these patients might have had better oncological outcomes when the immediate surgeries were performed than when the surgeries were delayed because of NAC.

Our results on the preoperative factors that predict major response or disease progression after NAC were clear. When the patient's clinical stage was low (cT2), the probability of major response by NAC tended to be higher (down-staging) and was also independent (OR = 0.146, $p = 0.003$; Table 4). In Canter's study (2010) of post-RC outcomes in patients with cT2 stage MIBC who did not receive NAC, 40% of the patients had pathological up-staging[39]. Our results showed pathological up-staging in only 5 (20.8%) out of 24 cT2 patients who received RC with NAC. However, the pathological findings previously identified in TUR-BT or the imaging response of NAC did not predict this at all (*P* range: 0.303–0.550; Table 3). The results of predicting non-responders (pN+) to NAC were similar (Table 3). Furthermore, there were no factors that could predict node-positive status in RC

patients after NAC. High clinical stage (≥cT3), variant forms in the pathological findings identified by previous TUR-BT, and clinical response to NAC also were not predictive factors (*P* range: 0.174–0.384; Table 4).

One of the interesting results in our series is that clinical responsiveness to NAC also failed to predict pathological down-staging and LN-positive disease. This finding largely can be attributable to the effect of TURB on the interpretation of CT findings after NAC. Especially in patients who had maximal TURB, there is no way to accurately assess the effect of NAC. One of the shortcomings in our study is that we could not factorize the effect of TURB in assessing responsiveness to chemotherapy. However, we think that practical TUBT could not be generalized in all MIBCs for which the tumor location and size varied widely. In this study, we think that the patients who underwent maximal TURB at the time of surgery were highly likely to be misinterpreted on their CT scans because of tissue reaction or inflammation related to the TURB effect. However, the NAC responsiveness in patients with minimal TURB in whom most of the tumor remained, should have predicted suitable candidates for NAC even though we could not perform subgroup analysis because of the heterogeneity of TURB and the small study group populations.

One definite finding from our study is that lower-stage patients with NAC responses can expect a lower pathological stage and a higher therapeutic effect. However, it is important to predict which patients with higher clinical stage will show a better response to NAC than the response by patients with lower clinical stage[40]. Our findings suggest that preoperative clinical data alone are not sufficient for deciding on customized or individualized treatment plans. Seiler et al. recently

reported that the response and survival benefit of cisplatin-based NAC in patients with muscle-invasive UCB was best in the basal genomic subtype group[41]. Thus, to identify UCB patients who are expected to have a real need for NAC and to have a good response to NAC in real clinical practice, the preoperative clinical parameters as well as the expression of genetic markers should be considered in the future. Additionally, effective radiological tactics are required to accurately measure the effect of NAC, including obtaining post-TURB CT to be compared with CT after NAC.

In our study, all patients underwent ePLND at the time of RC. The clinical impact of the number of LN dissected, the LN density, and ePLND were largely studied in patients with RC only[42]. However, the optimal range of PLND has not been addressed much in the literature in patients undergoing RC after NAC treatment[24, 27, 28]. Only 2 (9.5%) patients were node positive in the NAC response group in our series, and the locations were limited to the true pelvis that can be easily covered by the standard LND range. Even though the information obtained in the series is limited in this regard, the mapping study performed here will provide useful information for future studies because this may contribute to minimizing the complications caused by LND. In addition, the clinical impact of the removed number of nodes and density should be addressed differently in this cohort.

Our study had some limitations that should be considered. First, this was a retrospective study with a small sample size (n = 66). Second, we did not perform analyses for actual oncological outcomes, such as progression-free or OS, because of the relatively short-term follow-up durations. Almost all patients were administered NAC within the last few years. Lastly, genetic subtypes that have been recently

suggested, such as luminal or basal type, were not evaluated in our cohort.

CONCLUSIONS

A substantial proportion of the patients (43.9%) experienced major down-staging responses after NAC. However, the number was far less than that in the patients who only underwent cystectomy, and a significant proportion (13.6%) of the patients who received NAC still had LN-positive disease. Except for clinical T stage, there were no significant clinical factors predictive of major down-staging response and node-positive disease. To broaden our knowledge in this regard, development of more accurate methodology for assessing chemo-responsiveness is mandatory, and issues related to LND should be further addressed in the future.

Figure 1. Inclusion and exclusion criteria of the current study

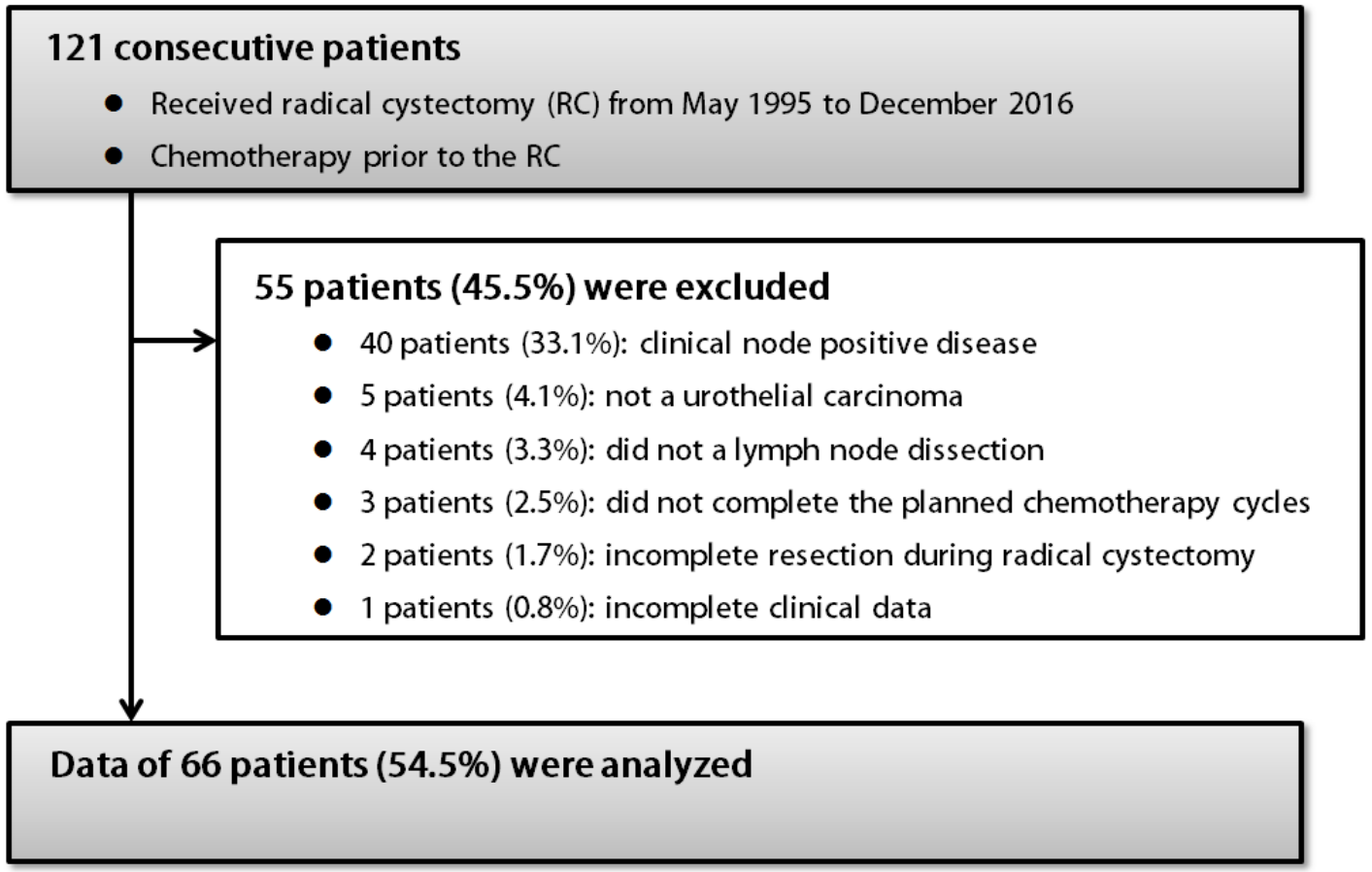


Table 1. General characteristics of analyzed subjects

	Median (IQR) or Number (%)
Number of patients	66
Patients characteristics	
Age (years)	64.5 (56.7–72.2)
Sex	
Male	55 (83.3%)
Female	11 (16.7%)
Duration from TUR-BT to RC (months)	3.7 (3.0–4.3)
Cycle of administered neoadjuvant chemotherapy	4.0 (3.0–4.0)
Chemotherapeutic agents	
GP	58 (87.9%)
MVAC	2 (3.0%)
DDMVAC	6 (9.1%)
Tumor-related parameters	
Clinical T stage	
≤cT2	24 (36.4%)
cT3	29 (43.9%)
cT4	13 (19.7%)
Pathological T stage (TUR-BT)	
≤pT1	3 (4.5%)
≥pT2	54 (84.8%)
pTx	9 (13.6%)
Tumor grade (TUR-BT)	
Low grade	2 (3.0%)
High grade	63 (95.5%)
Unknown	1 (1.5%)
Presence of variant from (TUR-BT)	16 (24.2%)

Pathological T stage	
pT0	16 (24.2%)
pTcis	6 (9.1%)
pTa	1 (1.5%)
pT1	6 (9.1%)
pT2	8 (12.1%)
pT3	25 (37.9%)
pT4	4 (6.1%)
Number of dissected nodes	28.3 (19.0–33.2)
Pathological N stage	
pN0	57 (86.4%)
pN1	7 (10.6%)
pN2	2 (3.0%)
pN3	0 (0.0%)
Response outcomes after neoadjuvant chemotherapy	
Down-staging with negative node (pT0-1N0)	29 (43.9%)
Node positive on final pathology (pN+)	9 (13.6%)

SD, standard deviation; IQR, interquartile range; TUR-BT, transurethral resection of bladder tumor; GP, gemcitabine and paclitaxel; MVAC, methotrexate + vinblastine + doxorubicin + cisplatin, DDMVAC, Dose-dense MVAC

Table 2. Treatment response to neoadjuvant chemotherapy determined by the Response Evaluation Criteria in Solid Tumors (RECIST)

	Total patients (N = 66)
RECIST criteria	
Complete remission	2 (3.0%)
Partial response	19 (28.8%)
Stable disease	41 (62.1%)
Progressive disease	2 (3.0%)

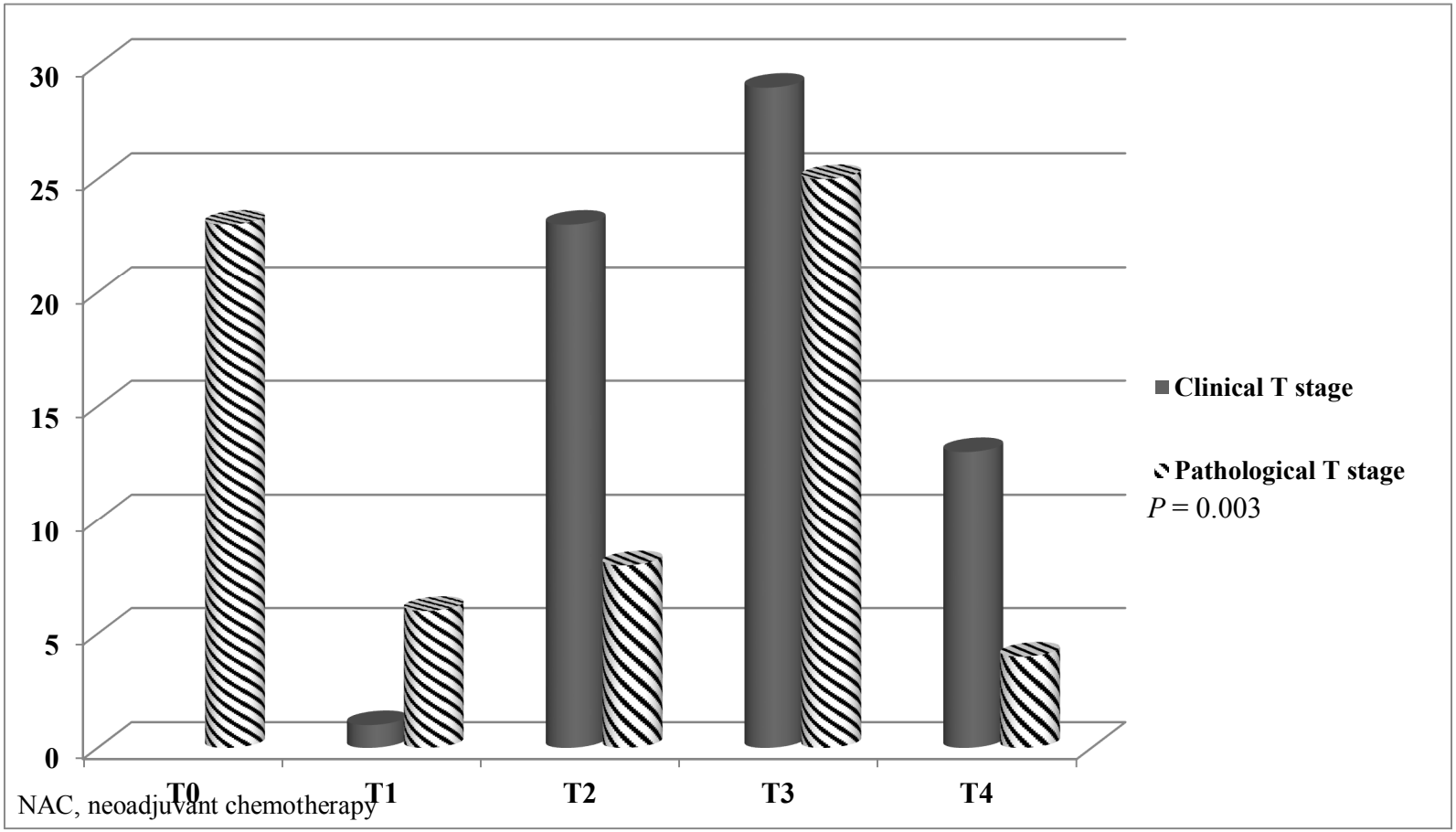
RECIST, Response Evaluation Criteria in Solid Tumors

Table 3. Pattern of lymph node positive (pN+) and down-staging according to response after neoadjuvant chemotherapy (NAC)

	NAC response		
	OCR (+) (n=21, 31.8%)	**OCR (-) (n=45, 68.2%)**	**Total, n 66**
Lymph node positive disease			
pN-, n (%)	**19 (90.5%)**	**38 (84.4)**	**57 (86.4%)**
pN+, n (%)	**2 (9.5%)**	**7 (15.6%)**	**9 (13.6%)**
Clinical T stage			
≤cT2, n (%)	**7 (29.2%)**	**17 (70.8%)**	**24**
pN+, n (%)	0 (0%)	3 (17.6%)	3 (12.5%)
pN-, n (%)	7 (100%)	14 (82.4%)	21 (87.5%)
cT3, n (%)	**9 (31.0%)**	**20 (69.0%)**	**29**
pN+, n (%)	2 (22.2%)	1 (5%)	3 (10.3%)
pN-, n (%)	7 (77.8%)	19 (95%)	26 (89.7%)
cT4, n (%)	**5 (38.5%)**	**8 (61.5%)**	**13**
pN+, n (%)	0 (0%)	3 (37.5%)	3 (23.1%)
pN-, n (%)	5 (100%)	5 (62.5%)	10 (76.9%)
Down-staging			
pT0T1, n (%)	10 (47.6%)	19 (42.2%)	29 (56.1%)
≥pT2, n (%)	11 (52.4%)	26 (57.8%)	37 (43.9%)
Down-staging			
≤cT2, n (%)	**7 (29.2%)**	**17 (70.8%)**	**24**
pT0T1, n (%)	6 (85.7%)	9 (52.9%)	15 (62.5%)
≥pT2, n (%)	1 (14.3%)	8 (47.1%)	9 (37.5%)
cT3, n (%)	**9 (31.0%)**	**20 (69.0%)**	**29**
pT0T1, n (%)	2 (22.2%)	9 (45.0%)	11 (37.9%)
≥pT2, n (%)	7 (77.8%)	11 (55.0%)	18 (62.1%)
cT4, n (%)	**5 (38.5%)**	**8 (61.5%)**	**13**
pT0T1, n (%)	2 (40.0%)	1 (12.5%)	3 (23.1%)
≥pT2, n (%)	3 (60.0%)	7 (87.5%)	10 (76.9%)

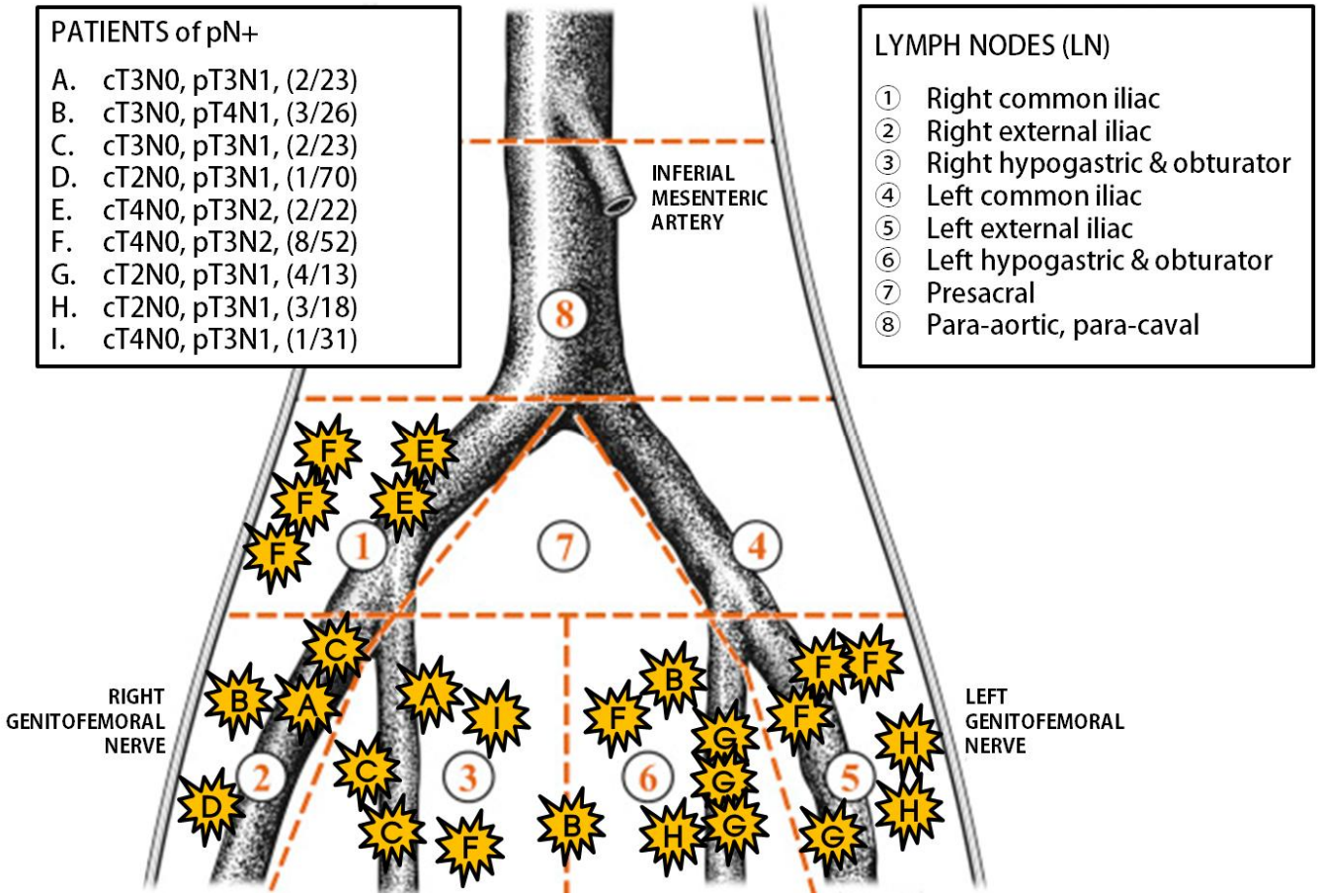
NAC, neoadjuvant chemotherapy; OCR , overall chemotherapy response(complete remission + partial response); pN+, Lymph node-positive disease; pN-, Lymph node-negative disease

Figure 2. Clinical T stage and pathological T stage after NAC treatment



NAC, neoadjuvant chemotherapy

Figure 3. Disposition of positive LN in patients with LN-positive disease after NAC plus RC



pN+, lymph node positive disease; LN, lymph node

Table 4. Risk factors for down-staging with negative node (pT0-1N0) on surgical pathology

	Univariate		Multivariate	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Clinical T stage (≤cT2)	0.181 (0.058–0.564)	0.003	0.146 (0.041–0.524)	0.003
TUR-BT stage (≤pT1)	0.431 (0.037–5.042)	0.502	0.295 (0.021–4.221)	0.368
Tumor grade (High grade)	0.375 (0.032–4.353)	0.433	0.270 (0.017–4.277)	0.535
Variant form (TUR-BT)	0.990 (0.318–3.079)	0.986	1.556 (0.356–6.629)	0.550
Response on neoadjuvant chemotherapy (CR or PR)	0.681 (0.439–3.522)	0.810	2.044 (0.524–7.972)	0.303

OR, odds ratio; CI, confidence interval; TUR-BT, transurethral resection of bladder tumor; CR, complete remission; PR, partial response

Table 5. Risk factors for node positive (pN+) on surgical pathology

	Univariate		Multivariate	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Clinical T stage (≥cT3)	4.324 (0.504–37.081)	0.182	4.529 (0.513–39.971)	0.174
Variant form (TUR-BT)	0.350 (0.040–3.037)	0.341	0.304 (0.033–2.826)	0.296
Response on neoadjuvant chemotherapy (CR or PR)	0.571 (0.108–3.021)	0.510	0.463 (0.082–2.620)	0.384

OR, odds ratio; CI, confidence interval; TUR-BT, transurethral resection of bladder tumor; CR, complete remission; PR, partial response

REFERENCES

1. Ploeg, M., K.H. Aben, and L. Kiemeney, *The present and future burden of urinary bladder cancer in the world.* World Journal of Urology, 2009. **27**(3): p. 289-293.
2. Munoz, J.J. and L.M. Ellison, *UPPER TRACT UROTHELIAL NEOPLASMS: INCIDENCE AND SURVIVAL DURING THE LAST 2 DECADES.* The Journal of Urology, 2000. **164**(5): p. 1523-1525.
3. Song, W. and H.G. Jeon, *Incidence of kidney, bladder, and prostate cancers in Korea: An update.* Korean J Urol, 2015. **56**(6): p. 422-8.
4. Koo, K.C., K.S. Lee, and B.H. Chung, *Urologic cancers in Korea.* Jpn J Clin Oncol, 2015. **45**(9): p. 805-11.
5. Reardon, Z.D., 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**(1): p. 165-70.
6. Leow, J.J., et al., *Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials.* Eur Urol, 2014. **66**(1): p. 42-54.
7. Sternberg, C.N., et al., *Chemotherapy for bladder cancer: treatment guidelines for neoadjuvant chemotherapy, bladder preservation, adjuvant chemotherapy, and metastatic cancer.* Urology, 2007. **69**(1 Suppl): p. 62-79.
8. Clark, P.E., et al., *Bladder cancer.* J Natl Compr Canc Netw, 2013. **11**(4): p. 446-75.
9. Winquist, E., et al., *Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis.* J Urol, 2004. **171**(2 Pt 1): p. 561-9.
10. Petrelli, F., et al., *Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy: a meta-analysis.* Eur Urol, 2014. **65**(2): p. 350-7.
11. Rosenblatt, R., et al., *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**(6): p. 1229-38.
12. Clark, P.E., et al., *Bladder Cancer.* Journal of the National Comprehensive Cancer

Network, 2013. **11**(4): p. 446-475.

13. Stenzl, A., et al., *The Updated EAU Guidelines on Muscle-Invasive and Metastatic Bladder Cancer.* European Urology, 2009. **55**(4): p. 815-825.
14. Gandaglia, G., et al., *The effect of neoadjuvant chemotherapy on perioperative outcomes in patients who have bladder cancer treated with radical cystectomy: a population-based study.* Eur Urol, 2014. **66**(3): p. 561-8.
15. Lavery, H.J., et al., *Pathological T0 following radical cystectomy with or without neoadjuvant chemotherapy: a useful surrogate.* J Urol, 2014. **191**(4): p. 898-906.
16. Madersbacher, S., et al., *Radical cystectomy for bladder cancer today--a homogeneous series without neoadjuvant therapy.* J Clin Oncol, 2003. **21**(4): p. 690-6.
17. Shariat, S.F., et al., *Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium.* J Urol, 2006. **176**(6 Pt 1): p. 2414-22; discussion 2422.
18. Booth, C.M., et al., *Patterns of referral for perioperative chemotherapy among patients with muscle-invasive bladder cancer: a population-based study.* Urol Oncol, 2014. **32**(8): p. 1200-8.
19. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration, *Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration.* Eur Urol, 2005. **48**(2): p. 202-5; discussion 205-6.
20. Grossman , H.B., et al., *Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer.* New England Journal of Medicine, 2003. **349**(9): p. 859-866.
21. International Collaboration of, T., et al., *International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial.* J Clin Oncol, 2011. **29**(16): p. 2171-7.
22. Zargar, H., et al., *Multicenter assessment of neoadjuvant chemotherapy for muscle-invasive bladder cancer.* Eur Urol, 2015. **67**(2): p. 241-9.

23. Skinner, D.G., *Management of invasive bladder cancer: a meticulous pelvic node dissection can make a difference.* J Urol, 1982. **128**(1): p. 34-6.

24. Leissner, J., et al., *Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study.* J Urol, 2004. **171**(1): p. 139-44.

25. Bi, L., et al., *Extended vs non-extended pelvic lymph node dissection and their influence on recurrence-free survival in patients undergoing radical cystectomy for bladder cancer: a systematic review and meta-analysis of comparative studies.* BJU Int, 2014. **113**(5b): p. E39-48.

26. Stein, J.P. and D.G. Skinner, *The role of lymphadenectomy in high-grade invasive bladder cancer.* Urol Clin North Am, 2005. **32**(2): p. 187-97.

27. Skinner, E.C., J.P. Stein, and D.G. Skinner, *Surgical benchmarks for the treatment of invasive bladder cancer.* Urol Oncol, 2007. **25**(1): p. 66-71.

28. Piotrowicz, S., et al., *Extent of lymphadenectomy in patients with bladder cancer undergoing radical cystectomy - a multi-institutional analysis.* Cent European J Urol, 2016. **69**(4): p. 323-326.

29. Edge, S.B., et al., *45. Urinary bladder*, in *AJCC cancer staging manual*, S.B. Edge, et al., Editors. 2010, Springer: New York. p. 497-506.

30. Lopez-Beltran, A., et al., *Tumors of the urinary system. Infiltrating urothelial carcinoma*, in *World Health Organization Classification of Tumours - Pathology and genetics of tumours of the urinary system and male genital organs*, J.N. Eble, et al., Editors. 2004, International Agency for Research on Cancer (IARC) press: Lyon. p. 93-109.

31. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-247.

32. Grossman, H.B., et al., *Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer.* N Engl J Med, 2003. **349**(9): p. 859-66.

33. Sonpavde, G., et al., *Quality of pathologic response and surgery correlate with survival for patients with completely resected bladder cancer after neoadjuvant*

chemotherapy. Cancer, 2009. **115**(18): p. 4104-9.

34. Advanced Bladder Cancer Meta-analysis, C., *Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis.* Lancet, 2003. **361**(9373): p. 1927-34.

35. D'Souza, A.M., et al., *Retrospective analysis of survival in muscle-invasive bladder cancer: impact of pT classification, node status, lymphovascular invasion, and neoadjuvant chemotherapy.* Virchows Arch, 2012. **461**(4): p. 467-74.

36. Kassouf, W., et al., *Outcome of patients with bladder cancer with pN+ disease after preoperative chemotherapy and radical cystectomy.* Urology, 2009. **73**(1): p. 147-52.

37. Teramukai, S., et al., *Evaluation for surrogacy of end points by using data from observational studies: tumor downstaging for evaluating neoadjuvant chemotherapy in invasive bladder cancer.* Clin Cancer Res, 2006. **12**(1): p. 139-43.

38. Porter, M.P., et al., *Patterns of use of systemic chemotherapy for Medicare beneficiaries with urothelial bladder cancer.* Urol Oncol, 2011. **29**(3): p. 252-8.

39. Canter, D., et al., *Clinicopathological outcomes after radical cystectomy for clinical T2 urothelial carcinoma: further evidence to support the use of neoadjuvant chemotherapy.* BJU Int, 2011. **107**(1): p. 58-62.

40. Galsky, M.D., J.P. Sfakianos, and B.S. Ferket, *Neoadjuvant Chemotherapy in Muscle-invasive Bladder Cancer: Are Things Now Getting Personal?* Eur Urol, 2017. **72**(4): p. 555-556.

41. Seiler, R., et al., *Impact of Molecular Subtypes in Muscle-invasive Bladder Cancer on Predicting Response and Survival after Neoadjuvant Chemotherapy.* Eur Urol, 2017. **72**(4): p. 544-554.

42. Ku, J.H., et al., *Lymph node density as a prognostic variable in node-positive bladder cancer: a meta-analysis.* BMC Cancer, 2015. **15**: p. 447.

국문요약

근치적 방광 절제술 (Radical cystectomy) 및 골반 림프절 절제술 (pelvic lymphadenectomy)은 근육 침윤성 방광암 (muscle-invasive bladder cancer) 치료의 표준 치료법이다. 그리고 림프절 전이를 보이지 않는 근육 침윤성 방광암 환자에서 신 보조 화학 요법 (neoadjuvant chemotherapy)은 병리학적인 병기 감소 (pathologic down-staging) 및 생존율을 향상시킨다. 그러나 어떤 환자가 근치적 방광 절제술 이전에 시행하는 신 보조 화학 요법에 효과적인 치료반응을 나타낼지에 대해서는 확립되어 있지 않다. 또한 이러한 항암제 투여 후 수술이 시행되는 환자에서 적절한 골반 림프절 절제술의 범위에 대해서는 알려진 바 없다. 본 연구에서는 근치적 방광 절제술 및 골반 림프절 절제술을 받은 환자에서 신 보조 화학 요법에 반응 후 항암치료의 반응 또는 무 반응을 예측할 수 있는 수술 전 위험 인자를 조사하고 림프절 절제 범위를 알아보고자 하였다. 1995 년부터 2016 년까지의 근치적 방광 절제술 및 술 전 신 보조 화학 요법을 받은 66 명의 임상적 림프절 전이가 없는 방광암 환자를 분석 하였다. 다변량 분석을 통해 근치적 방광 절제술 후 술 전 신 보조 화학 요법에 대한 주요 반응 및 비-반응의 비율과 병기진행의 위험 인자를 평가 하였다. 주요 반응은 병리학적 근육 침윤성 질환 및 림프절 전이가 없음(pT1-0N0)으로 정의되었다. 수술 시 환자 나이의 중앙값은 64.5 살 (IQR, 56.7-72.2) 이었으며, 55 명이

(83.3 %) 남성이었다. 임상적 T 병기는 24 명에서 (36.4%) cT2 이하, 29 명에서 (43.9 %) cT3, 13 명에서 (19.7%) cT4 였다. 방광 종양 절제술의 종양 등급은 2 명에서(3.0%) 저 등급, 63 에서 (95.5%) 고 등급, 1 명에서 (1.5 %) 미확인되었다. 초기 경요도방광종양 절제술(TUR-BT)에서 근치적 방광 절제술까지의 평균 기간의 중앙값은 3.7 개월 (3.0-4.3)이었다. 술 전 신 보조 화학 요법 전 후 영상으로 평가한 전체 화학 요법 반응은 (overall chemotherapy response) 31.8% 였다. (완전 관해: 2 명, 부분 관해: 19 명) 근치적 방광 절제술 후 병리학적 병기는 pT0: 16 명(24.2%), pTis: 6 명(6.2%), pTa: 1 명(1.5%), pT1: 6 명(9.1%), pT2: 8 명(12.1%), pT3: 25 명(37.9%), pT4; 4 명(6.1%)이었다. 술전 신 보조 화학 요법 무 반응은 (병리학적 임프절 전이 양성) 13.6 % 였다 (pN1: 7 명, pN2: 2 명). 술 전 신 보조 화학 요법에 대한 반응을 보인 21 명의 환자에서 2 명만이(9.5 %) 임프절 전이 양성 반응을 보였다. 양성 림프절 위치는 외장골동맥과 내장골동맥 부위였다. 다변량 분석에서 임상 T 병기는 술 전 신 보조 화학 요법의 주요 반응에 대한 독립적 인 예측 인자였다(≤cT2, OR=0.146, p=0.003). 술 전 신 보조 화학 요법의 무반응에 영향을 주는 예측 인자는 없었다. 술 전 신 보조 화학 요법에 대한 반응은 균일하지 않았다. 근치적 방광 절제술 및 골반 림프절 절제술을 받은 환자에서 임상 T 병기는 병기감소에 영향을 미치는 중요한 예측 인자였다. 본 연구에서 관찰된 흥미로운 점은 항암 반응 여부가 T 병기나 림프절 전이여부를 예측해내지 못하였다는 점이다.

TURB 시행 직후에 CT 를 촬영하여 항암 후 CT 와 비교하는 등 향후 항암 반응의 평가 방법에 개선이 필요함을 암시한다. 또한 본 연구에서 제시된 림프절 전이를 보이지 않는 근육 침윤성 방광암 환자에서 신 보조 화학요법 후 골반림프절 전이에 대한 위치 분석 (mapping study) (neoadjuvant chemotherapy)은 향후 이러한 환자에서 추가적으로 확립되어야 할 골반 림프절 절제범위, 더 나아가 절제 림프절 수의 임상적 의의에 대한 연구에 대해 중요한 단초를 제공해 준다.