A Multi-Institutional Analysis of Outcomes of Patients with Clinically Node Positive Urothelial Bladder Cancer Treated with Induction Chemotherapy and Radical Cystectomy

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Purpose: Selected patients with bladder cancer with pelvic lymphadenopathy (cN1-3) are treated with induction chemotherapy followed by radical cystectomy. However, the data on clinical outcomes in these patients are limited. In this study we assess pathological and survival outcomes in patients with cN1-3 disease treated with induction chemotherapy and radical cystectomy.

Materials and Methods: Data were collected on patients from 19 North American and European centers with cT1-4aN1-N3 urothelial carcinoma who received chemotherapy followed by radical cystectomy between 2000 and 2013. The primary end points were pathological complete (pT0N0) and partial (pT1N0 or less) response rates, with overall survival as a secondary end point. Logistic regression and Cox proportional hazard ratios were used for multivariate analysis of factors predicting these outcomes.

Results: The total of 304 patients had clinical evidence of lymph node involvement (cN1-N3). Methotrexate/vinblastine/doxorubicin/cisplatin was used in 128 (42%), gemcitabine/cisplatin in 132 (43%) and other regimens in 44 (15%) patients. The pN0 rate was 48% (cN1—56%, cN2—39%, cN3—39%, p=0.03). The complete and partial pathological response rates for the entire cohort were 14.5% and 27%, respectively. The estimated median overall survival time for the cohort was 22 months (IQR 8.0, 54). On Cox regression analysis overall survival was associated with pN0, negative surgical margins, removal of 15 or more pelvic nodes and cisplatin therapy.

Conclusions: Complete pathological nodal response can be achieved in a proportion of patients with cN1-3 disease receiving induction chemotherapy. The best survival outcomes are observed in male patients on cisplatin regimens with subsequent negative radical cystectomy margins and complete nodal response (pN0) with excision of 15 or more pelvic nodes.

Key Words: urinary bladder neoplasms, cystectomy, neoadjuvant therapy, survival

Abbreviations and Acronyms

GC = gemcitabine/cisplatin

KM = Kaplan-Meier

MVAC = methotrexate/vinblastine/doxorubicin/cisplatin

NAC = neoadjuvant chemotherapy

OS = overall survival

pCR = pathological complete response

pPR = pathological partial response

RC = radical cystectomy

UC = urothelial carcinoma

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In patients with muscle invasive bladder cancer neoadjuvant chemotherapy before radical cystectomy has been shown to be associated with improved survival.[1–5] However, most studies assessing the efficacy of NAC

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have excluded patients with clinically node positive disease (cN1-3). In patients with cN1-3 disease systemic chemotherapy may be seen as the primary therapy and RC as consolidation in those with a major response to the induction chemotherapy. Thus, there are few data available to assess outcomes in this group of patients. The 5% improvement in overall survival with NAC observed in the landmark meta-analysis of 2,688 patients included only 4% with cN1-3 disease.[3] Thus, the reported results may not necessarily extend to cN1-3 cases.

Patients with cN1-3 disease are generally treated with the same regimens as those with cN0 disease.[6] MVAC (methotrexate/vinblastine/doxorubicin/cisplatin)[2] and cisplatin/methotrexate/vinblastine[5] have been established as effective NAC regimens in prospective randomized phase III clinical trials, but gemcitabine/cisplatin has been widely adopted as the favored regimen based on the lack of detected survival difference and less toxicity compared to MVAC.[7] Several retrospective data sets have also shown comparable pathological complete response rates with GC and MVAC in the neoadjuvant setting.[8,9] Carboplatin based regimens are widely believed to be inferior to cisplatin based regimens,[10–13] but are nonetheless administered by some providers in the NAC setting with the belief that suboptimal NAC is better than no NAC.[9,14–17]

We recently reported real-world outcomes of NAC in cN0 cases in a large retrospective multi-institutional series.[9] The aim of the current study is to extend this analysis to cN1-3 cases, and assess clinicopathological and survival outcomes after GC, MVAC and other noncisplatin based chemotherapy regimens in the same multi-institutional series.

PATIENTS AND METHODS

Study Population

A total of 19 European and North American institutions contributed to this study. Institutional review board approvals were obtained. Patients with cT1N1-3M0 and cT2-4aN0-3M0 bladder cancer who were treated with chemotherapy and RC between 2000 and 2013 were identified. Only patients with pure UC or mixed UC with squamous and/or glandular differentiation were included in the study. For this analysis patients with cT1-4aN1-3M0 disease were selected. Lymph node status was determined by the treating physician based on imaging criteria without specific requirement for biopsy confirmation. Patients were grouped according to the chemotherapy regimen they received into MVAC, GC and "other." The "other" group included patients who received gemcitabine/carboplatin, other carboplatin based regimens and taxanes, but not cisplatin. Patients who received chemotherapy but did not subsequently undergo cystectomy were not captured. The primary end point was pathological response to induction chemotherapy. Partial pathological response was defined as down staging to nonmuscle invasive disease, pT1N0 or less, and complete pathological response was defined as pT0N0. Median overall survival was a secondary end point.

Analysis

Information relating to demographics, clinical staging, chemotherapy, surgery, histopathology and survival outcomes were analyzed for the study population. Chemotherapy data incorporated type of regimen and number of cycles. Surgical variables included the extent of pelvic lymphadenectomy (standard vs extended, as categorized by the treating urologist as well as the number of nodes removed and subsequently identified by the pathologist). Histopathology assessment encompassed histological classification, presence of carcinoma in situ, and surgical soft tissue margin status and pathological TNM staging based on the 2010 American Joint Committee on Cancer classification. Duration of followup was measured from the date of RC.

Statistics

Categorical variables were compared using the chi-squared test. For variables with nonnormal distribution data were presented as median (range or interquartile range) and groups were compared using the Mann-Whitney U-test. Multivariable logistic regression analyses of selected variables were used to define factors predicting pCR and pPR. Survival analysis was performed using Kaplan-Meier analysis and groups were compared using the log rank test. A multivariable Cox proportional hazards regression model for overall survival was used to assess hazard ratios, and included relevant clinical and pathological variables. The number of removed nodes was examined using the minimal p value approach at different cutoff points (10-15).[18] Using Kaplan-Meier analysis and the log rank test the lowest cut point at which OS was significantly different between the 2 groups was used to dichotomize the data for inclusion in the Cox model. Analyses were performed using SPSS® v21 software and significance was set at $p < 0.05$.

RESULTS

Of 1,618 patients with bladder cancer receiving chemotherapy 304 (19%) had clinically node positive disease (cN1-3). Data on pathological nodal status (pN0-3) were available for 248 (82%) of these 304 patients.

Baseline Characteristics

The median age of the 304 patients in our cohort was 64 years (IQR 58–71) and pure UC (92%) was the dominant histological subtype on final pathology (see supplementary table, http://jurology.com/). GC (43%) and MVAC (42%) were used at equivalent rates in the cohort. Gemcitabine/carboplatin was administered in 89% of the remaining other regimen group (15%). The median number of chemotherapy cycles administered was 4 and 44 (14%) patients received more than 4 cycles.

Table 1. *Logistic regression analysis of clinical and pathological predictors of pN0, complete and partial response to induction chemotherapy*

		pN0		pCR		pPR	
Variables in Equation	Category	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Gender:	M						
	F	0.84 (0.47–1.51)	0.56	0.49 (0.19–1.26)	0.14	0.61 (0.30–1.23)	0.17
Age:	65 or Less						
	Greater than 65	1.43 (0.85–2.39)	0.18	1.36 (0.66–2.79)	0.40	1.45 (0.81–2.59)	0.21
Clinical T stage:	T1-2						
	T3-4	1.03 (0.61–1.73)	0.92	1.43 (0.69–2.99)	0.34	1.02 (0.57–1.83)	0.96
Clinical node stage:	cN1						
	cN2-3	0.50 (0.30–0.84)	0.01	1.16 (0.56–2.39)	0.69	0.78 (0.43–1.40)	0.40
No. chemotherapy cycles:	1–3						
	4 or Greater	1.91 (1.06–3.45)	0.03	1.65 (0.68–4.02)	0.27	1.90 (0.93–3.86)	0.08
Chemotherapy regimen:	MVAC/GC						
	Other	0.84 (0.40–1.79)	0.66	1.05 (0.37–2.95)	0.93	0.56 (0.22–1.44)	0.23

Chemotherapy Regimen

Patients were distributed similarly in the 3 chemotherapy regimens with regard to age at diagnosis, gender, risk factors for UC (smoking and radiation history) and number of treatment cycles received. Overall a median of 4 cycles (IQR 3–4) was administered for each of the 3 regimens. The proportion of patients with clinical T3-T4a disease for each chemotherapy regimen was similar (MVAC 50%, GC 51%, other 49%). The proportion of clinical N2-N3 disease was also similar between the cisplatin and noncisplatin groups (49% vs 50%).

Pathological Outcomes

Pathological Complete and Partial Response. The unadjusted pCR (pT0N0) and pPR rates (pT1N0 or less) for the 248 patients with known T and N stage were 14.5% and 27%, respectively. pCR was only seen in patients with cN1-N2 disease. The unadjusted pCR rates for MVAC, GC and other regimens were 16%, 13% and 15%, respectively (p=0.89, see supplementary table, http://jurology.com/). The pPR rates for the 3 groups were 30%, 27% and 18% (p=0.64). On multivariable analysis none of the selected variables included in the equation were independent predictors of pCR or pPR (table 1).

Pathological Nodal Response. Complete pathological nodal response (pN0) was achieved in 48% of the cohort. Overall 56% of cN1 cases vs 39% of cN2 cases and 39% of cN3 cases were pN0 (p=0.03). OS was markedly improved in cN2-3 cases that became pN0 (45) compared to those that remained pathologically node positive (70) (table 2). Of the patients with pT0 bladder status 38% were found to have positive lymph nodes (pT0N+).

Survival Outcomes

Median followup for the entire cohort was 13 months (IQR 5.0, 28). Median followup after RC in patients alive at last followup was 20 months (IQR 6.0, 49). The estimated median OS for the cohort was 23 months (IQR 9.0, 176). Information on disease status was not available for 27 patients. During followup local recurrence or metastatic disease developed in 151 patients (55%). Overall 138 (50%) patients died during followup at a median of 10 months (IQR 4–19), of whom 122 (88%) died of bladder cancer. At last followup 19 (28%) pT0, 25 (23%) pN0 and 6 (18%) cases with pCR had died of disease. The estimated median OS for MVAC, GC and other regimens was 20, 24 and 19 months, respectively (p=0.25). Figure 1 demonstrates the KM curves for patients grouped by pathological staging, showing a median OS not reached (NR, mean 107), 45 (mean 83) and 14 (mean 52) months for patients with pT1N0 or less, pT2-4aN0 and pTxN1-3 disease, respectively (p <0.001). Table 3 summarizes median overall survival according to pathological T and N stage.

Median OS was longer for cN1 vs cN2-N3 cases, but this did not reach statistical significance (24 vs 17 months, p=0.23, fig. 2), and remained insignificant after controlling for age, gender, chemotherapy, number of cycles and clinical T-stage (HR 1.34, 95% CI 0.93–1.93, p=0.11). At the cutoff point of 15 lymph nodes removed, OS was significantly different between the less than 15 or 15 or greater groups (median 35 vs 16, p=0.01). This was the lowest point at which OS was significantly

Table 2. *Median months overall survival (IQR) according to nodal status*

	Clinical Node Status		
	cN1	cN2-3	cN1-3
Median pathological node status (IQR):			
pN0	71 (24–not reached)	84 (23–177)	84 (23–177)
pN1-3	13 (4–34)	16 (6–39)	14 (5–35)
pNx	24 (13–64)	11 (4–17)	13 (7–43)
p Value:			
pN0 vs pN1-3	<0.001	0.001	<0.001
pN0 vs pNx	0.07	<0.001	<0.001
pN1-3 vs pNx	0.06	0.24	0.69

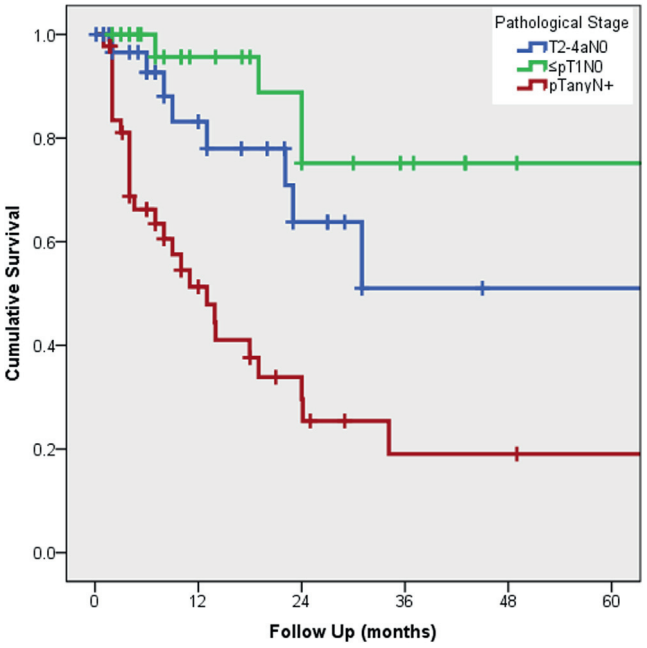

Figure 1. KM plot for OS and pathological response

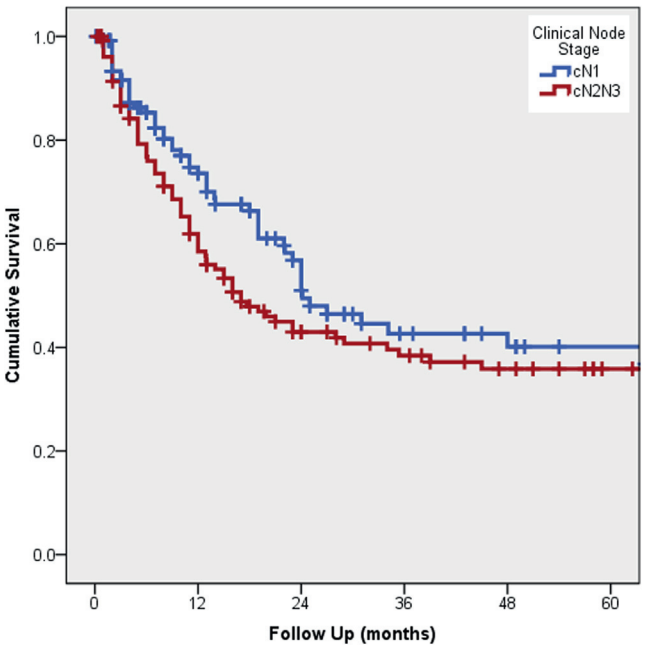

Figure 2. KM plot for OS and clinical nodal stage

different and at lower values (10 to 14) OS was not statistically different between the groups.

On multivariable Cox model OS was associated with complete pathological response in the nodes (pN0), the number of nodes removed, negative surgical margins and cisplatin chemotherapy (table 4). A difference in OS after GC vs MVAC was not observed (HR MVAC vs GC 0.91, 95% CI 0.57–1.47, p=0.71).

A second Cox proportional hazard analysis for OS was performed in which pCR replaced pT stage and number of positive lymph nodes. In the latter analysis pCR was significantly associated with improved OS (HR 0.41, 95% CI 0.19–0.92, p=0.03). Surgical margin and number of nodes removed (15 or greater) were also predictors of survival. Similar results were also observed when assessing pPR (HR 0.35, 95% CI 0.18–0.68, p <0.01). Number of nodes removed and surgical margin were again significant in the latter analysis.

Patients with Unknown Pathological Nodal Status

Pathological nodal status was unknown in 56 patients (pNx). Of the pNx cases 44% were cT3/4 and 61% were cN2-N3. Overall 82% received cisplatin chemotherapy with 79% receiving 4 or more cycles of treatment. The stages pT0Nx and pT≤1Nx were observed in 26% and 37% of this group, respectively. Median estimated OS for the patients with pNx disease was 13 months (7.0–64) (fig. 3). This was similar to the median survival for the pN+ cohort (13 vs 14, p=0.69) and lower than that of patients with pN0 disease (13 vs 84, p <0.001, table 2).

Table 3. *OS and pathological response*

Pathological Stage	No.	OS (IQR)	Mean (95% CI)
pT0N0	36	84 (71–not reached)	93 (54–94)
pT<2N0	66	NR (71–not reached)	107 (76–138)
pT≥2N0	53	45 (16–177)	83 (49–118)
pT0N1-3	22	16 (7–not reached)	35 (16–54)
pT<2N1-3	33	16 (4–not reached)	32 (17–47)
pT≥2N1-3	96	13 (5–34)	48 (24–72)

DISCUSSION

To our knowledge this is the largest series of patients with clinically node positive disease who

Table 4. *Cox proportional hazard model for predicting death from any cause*

Variables in Equation	Compared Categories	HR (95% CI)	p Value
Gender:	M		
	F	1.57 (0.98–2.51)	0.06
Age:	Less than 65		
	65 or Greater	1.03 (0.69–1.55)	0.88
Pathological T stage:	Less than pT2		
	pT2 or greater	0.76 (0.46–1.26)	0.29
Pathological margin:	Neg		
	Pos	2.96 (1.72–5.09)	<0.001
No. pos nodes:	Zero	Reference	
	Single	2.56 (1.47–4.47)	0.001
	2 or Greater	3.26 (1.98–5.36)	<0.001
No. nodes removed:	Less than 15		
	15 or Greater	0.55 (0.36–0.86)	0.01
No. chemotherapy cycles:	1–3		
	4 or Greater	1.17 (0.72–1.90)	0.54
Chemotherapy regimen:	MVAC/GC		
	Other	1.88 (1.06–3.34)	0.03

Overall 205 cases included in analysis.

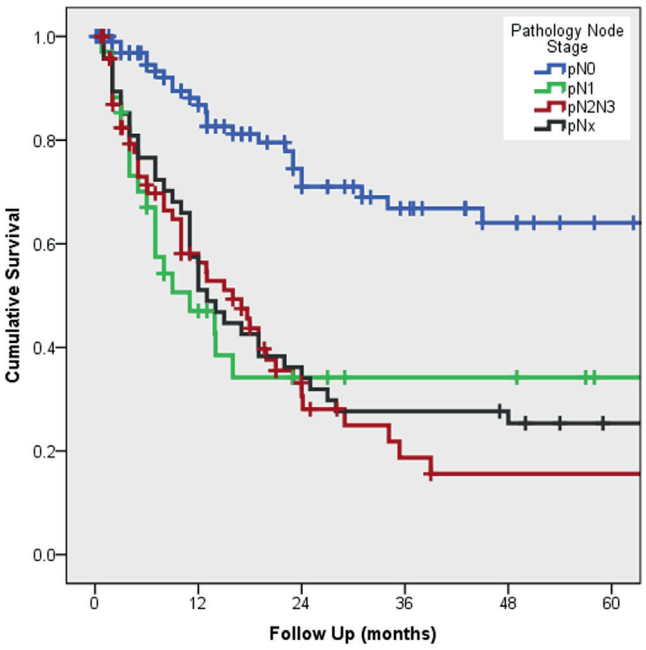

Figure 3. KM plot for OS and pathological nodal response

received induction chemotherapy and underwent RC. Our results demonstrated that 48% of cN1-3 cases were converted to pN0, and that down staging to pT0 occurred in 24% of cases. However, 38% of the pT0 cases had persistent nodal involvement so that the pCR rate for the entire cohort was only 14.5%. This is considerably lower than the pCR rate of 38% observed in prospective trials in cases of cN0 urothelial carcinoma,[2,19] and lower than the 23% pCR rate we observed in 935 node negative cases from the same institutions.[9]

Nieuwenhuijzen et al reported a pCR of 21% and median survival of 15.4 months in a single institutional series of 52 patients with cN1-3 disease who were treated with induction MVAC followed by RC.[20] The same group subsequently reported on 152 patients who were treated with preoperative MVAC (77%), GC (15%) and gemcitabine/carboplatin (8.6%) for nonorgan confined disease (75% cN1-3), 82% of whom underwent consolidative RC.[21] Median overall survival was 18 months, with a median OS of 13 months for patients with pN1-3 disease and 27 months for those with pN0 ($p < 0.001$). The authors concluded that complete pathological response to induction chemotherapy is an important prognostic indicator and suggested that surgery may be of little benefit for persistent node positive disease after chemotherapy. Our survival analysis suggests that complete nodal response and negative margins were associated with better OS.

Since cN1-3 bladder cancer is generally considered in the same context as metastatic disease, the optimal duration of systemic chemotherapy would traditionally be considered 6 cycles.[22] The current study does not address how many cycles are optimal, but it is noteworthy that the majority of patients (85%) in this cohort received 4 or fewer cycles of induction chemotherapy. We have not captured the intended number of cycles and any potential reduction in planned chemotherapy. Nonetheless, these results would suggest that patients with cN1-3 bladder cancer who are deemed suitable for radical cystectomy are being treated similarly to patients with cN0 disease receiving neoadjuvant chemotherapy. The literature on 6 cycles of chemotherapy is in the context of noncurative therapy, and it is reasonable to suggest that more than 4 cycles is unlikely to make a difference in patients being considered for potentially curative surgical extirpation. When we repeated the Cox regression analysis with different cutoff values for the number of cycles of chemotherapy, the cutoff of 6 or greater was not significant.

On multivariable analysis removal of 15 or more pelvic nodes was also associated with improved OS. This was the lowest number of nodes removed that influenced OS. In a group of patients with cT2-4N0M0 disease not receiving preoperative chemotherapy Herr previously demonstrated that removal of more than 10 nodes in patients with pN0 disease and 13 or more in those with pN+ disease were associated with improved OS.[23] This cutoff was also the minimum lymph node yield required in the SWOG p53-MVAC trial.[24] More important than establishing a cutoff for lymph node yield, our results highlight the need for bilateral pelvic lymph node dissection in this cohort of patients.

As biopsy confirmation was not required for cN staging, some cN1 cases may be over staged. However, overall survival between cN1 and cN2-3 cases was not statistically different. Additionally, in the current cohort 59 of 133 (44%) cN1 cases with known pathological nodal status were pN+. This is significantly higher than the 198 (21%) patients with pN+ disease reported in 929 with cN0 disease treated preoperatively with similar chemotherapy regimens from the same institutions participating in the current study ($p=0.001$).[9] Therefore, despite the deficiency of detailed information regarding the size, location and the criteria for clinical nodal staging in this cohort, the much higher pN+ rates among patients with cN1 disease from the same institutions suggests that the majority of the current cN1 group do represent a higher risk category than those with cN0 disease, and to some extent supports the consistency of the clinical staging methods used in this cohort. Nevertheless, we do accept staging inaccuracies as an important limitation in our results.

This retrospective study has a number of limitations, including the absence of randomization or standardization of chemotherapy administration at different participating sites, as well as selection bias in the choice of chemotherapy regimens. It is possible that a true difference in chemotherapy regimens with respect to pathological outcome and survival could be missed with this study design. We did not capture patients who received chemotherapy for cN1-3 bladder cancer but did not proceed to RC, so we are likely reporting on a favorable subset of patients with cN1-3 disease. We did not have centralized radiological and pathological review, and biopsy confirmation of nodal involvement was not obtained for all patients included in this study.

Furthermore, this study did not evaluate variations in chemotherapy dose and dose intensity per cycle, or any chemotherapy related toxicity, morbidity and mortality. We did have a number of missing data points that were excluded from the analysis. There were baseline differences between the chemotherapy regimens, which may constrain direct comparison, although we adjusted for those in the multivariate analyses. Certain risk factors such as performance status and medical comorbidities, the presence of hydronephrosis, cardiovascular status or renal function were not included in the data collection. The followup was relatively short, although most recurrences and deaths would be expected within 2 years.[25] Despite these limitations, these data provide important information about the natural history and prognostic factors of clinically node positive bladder cancer treated with induction chemotherapy and RC.

CONCLUSIONS

Induction chemotherapy in patients with clinically node positive disease is associated with a clinically significant pathological response. Complete pathological nodal response can be achieved, even in patients with cN2-3 disease, and this corresponds to improved survival. In patients with cN1-3 disease the best outcomes are seen in those receiving cisplatin based chemotherapy who have negative margins and complete nodal response at RC. No significant difference was observed between GC and MVAC regimens in treating these patients with cN1-3 disease before RC.

APPENDIX

The following collaborators contributed to this study:

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EDITORIAL COMMENT

This article describes outcomes in patients with clinical node metastases associated with muscle invasive cT2-cT4a urothelial bladder cancer. There is an important take home message that patients with cN1-3 disease are potentially curable and should be treated with therapeutic cisplatin based chemotherapy and radical cystectomy with a proper anatomical complete bilateral pelvic lymphadenectomy.

The findings add to a body of retrospective data providing a robust menu for prospective hypothesis testing. Studies in progress include SWOG 1314 (NCT02177695), with the primary aim of validating a predictive biomarker (COXEN) associated with response to NAC in patients receiving MVAC or GC. SWOG 1011 (NCT01224665) and the similarly designed German LEA trial (AB 25/02) will define the proper anatomical extent of the lymphadenectomy performed at the time of cystectomy. Many of the centers involved in the present study have made significant contributions to SWOG 1011 and hopefully are also engaged with SWOG 1314. We need to continue to develop innovative, prospective, multicenter trials so our patients can be treated based on the highest level available evidence.

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