Prognostic significance of cystoscopy findings following neoadjuvant chemotherapy for muscle-invasive bladder cancer

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Introduction: *To evaluate the potential significance of cystoscopy findings following neoadjuvant chemotherapy (NAC) as prognostic indicator in patients undergoing radical cystectomy for muscle-invasive bladder cancer (MIBC).*

Materials and methods: *Patients who received NAC prior to radical cystectomy for MIBC were analyzed. Patients were divided into two groups according to cystoscopy performed after two cycles of NAC: responders and non-responders. Univariate analysis was performed to analyze associations between observed response to chemotherapy and pT stage, pN stage and tumor downstaging. Logistic regression modeling was fitted to evaluate predictors for extravesical disease and pathologic downstaging. Kaplan-Meier analysis was used to evaluate disease specific survival.*

Results: *We identified 101 patients who received neoadjuvant chemotherapy prior to radical cystectomy. According to the cystoscopy findings, 60 patients (59%) were identified as responders to NAC. Stage pT0 at cystectomy was confirmed in 22 patients (36.5%) in the responder group versus only 1 patient (2.5%) in the non-responder group. Univariate analysis showed statistically significant association between response to chemotherapy observed on cystoscopy and pT stage as well as tumor downstaging. Multivariate regression modeling revealed that cystoscopy findings were an independent predictor of extravesical disease and pathologic downstaging. There was a distinct survival benefit in NAC responder group ($p < 0.001$). Cox proportional hazard model identified cystoscopy findings as an independent predictor of survival (OR 0.38, 95% CI 0.20-0.74, $p = 0.004$).*

Conclusions: *Observed response to NAC on follow up cystoscopy is associated with favorable pathological outcomes and is a significant predictor of survival in patients undergoing radical cystectomy for MIBC.*

Key Words: cystectomy, downstaging, cystoscopy, bladder cancer, neoadjuvant chemotherapy

Introduction

Bladder cancer is the 11th most commonly diagnosed cancer and the 14th leading cause of cancer deaths worldwide.[1] The standard management for organ-confined muscle-invasive bladder cancer (MIBC) is radical cystectomy with pelvic lymphadenectomy.[2-4] However, 30%-50% of patients with apparently organ confined muscle-invasive disease have undiagnosed micrometastases at the time of cystectomy.[3] Nearly half of patients develop metastases and ultimately die from bladder cancer despite aggressive local therapy.[2-5]

Integration of systemic chemotherapy with surgical management was proposed as an attempt to control micrometastases and improve survival. Several randomized trials have evaluated the use of neoadjuvant chemotherapy prior to radical cystectomy versus cystectomy alone.[6] A meta-analysis of these

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trials demonstrated a 5 year survival advantage with the addition of neoadjuvant chemotherapy to local treatment (from 45% to 50%).[7]

Despite level 1 evidence showing the benefit of neoadjuvant chemotherapy (NAC), this approach for the management of MIBC has not been universally adopted. In addition to the modest survival advantage and considerable toxicity, it has been argued that administration of NAC precludes or delays the standard surgical treatment, especially in patients who don't respond to the chemotherapeutic regimen.[8] Therefore, predicting outcomes and assessing the value of chemotherapy in this population is critical.

Chemotherapy-induced pathologic downstaging at cystectomy following NAC has been correlated with improved overall survival.[6,9,10] In particular, patients who achieved downstaging to pT0 had 5 year disease-specific survival ranging from 85% to 92%.[10-13] Hence, pathologic downstaging and the ability to achieve pT0 following NAC is considered an endpoint to assess the efficacy of the chemotherapeutic regimen and predict survival.

We sought to evaluate the potential significance of cystoscopy findings following NAC as a predictor of favorable pathologic outcomes and pathologic downstaging as well as a prognostic indicator in patients undergoing radical cystectomy for MIBC.

Materials and methods

After approval of the institutional review board and utilizing our prospectively maintained database, we analyzed patients who received NAC for MIBC between 1998 and 2011. All patients underwent an initial transurethral resection of bladder tumor (TURBT) at our institution with the intent of complete resection. Residual tumor size, multiplicity and location were documented at the end of the procedure if present. Pertinent cystoscopic images were saved in our database image managing system for future utilization. Clinical staging was based on examination under anesthesia, imaging and the TURBT pathology. The decision to administer NAC was determined by the clinical extent of the disease, patients' ability to tolerate combination chemotherapy and patients' preferences. NAC regimen, doses and schedules were adjusted as deemed necessary by the medical oncologists.

Outpatient flexible cystoscopy was performed routinely after the second cycle of NAC to evaluate the therapeutic response. Both pre-treatment TURBT and follow up cystoscopies were performed by the same surgeon. Operative reports as well as saved cystoscopic images for the pre-chemotherapy TURBT were reviewed at the time of follow up cystoscopy. Patients were divided into two groups according to the cystoscopy findings; responders (patients who had decreased tumor volume or no evidence of tumor) and non-responders (patients who had no change in tumor volume or tumor volume progression). All patients underwent radical cystectomy and standard pelvic lymphadenectomy following completion of NAC. The choice of urinary diversion was based on surgeon and/or patient preference.

Extensive gross and microscopic evaluation was performed for radical cystectomy specimens. In particular, residual macroscopic tumor or identifiable scar from prior transurethral resection were sampled and examined thoroughly. In addition, several sections were sampled from various anatomic sites within the bladder, urethra, and ureters for accurate staging.

In addition to cystoscopy findings after the second cycle of NAC, other patient data were collected, including age, sex, smoking history, diversion type, chemotherapy regimen, number of cycles, clinical T stage, presence of hydronoephrosis, pT stage, pN stage, lymphovascular invasion and tumor downstaging. Clinical staging was based on transurethral resection pathology and radiology reports. Tumor downstaging was defined as a pathological stage less than the corresponding clinical T stage. Endpoints included tumor downstaging, pathologically confirmed extravesical disease (greater than pT2) and disease specific survival.

Statistical analysis

Univariate analysis with the Pearson chi-square was done to analyze associations between cystoscopy findings (responders versus non-responders) and pT stage (pT2 or greater and greater than pT2), pN stage (N0 and greater than N0) and tumor downstaging.

Logistic regression modeling was fitted to evaluate predictors for extravesical disease and pathologic downstaging. Covariates in the extravesical disease model were age, smoking history, cystoscopy findings (responders versus non-responders), pN stage (N0 and greater than N0). Covariates for pathologic downstaging model were age, gender, smoking history, cystoscopy findings, chemotherapeutic regimen and number of chemotherapy cycles.

A Kaplan-Meier estimator curve with the log rank test and a Cox proportional hazard model were used to test whether observed response to chemotherapy predicted overall survival. All statistical analysis was done with SPSS 19 with 2-tailed $p < 0.05$ considered significant.

Results

Between 1998 and 2011, 746 patients underwent radical cystectomy and urinary diversion by one surgical team. After exclusion of patients who didn't receive NAC and patients with known metastatic disease who received salvage chemotherapy, we identified 101 patients who received neoadjuvant chemotherapy prior to radical cystectomy. Table 1 lists patients' characteristics.

Overall, 78 (77%) patients were male and 23 (23%) were female. Median age was 67 years. There were 69 patients (68%) with cigarette smoking history.

Eighty-five patients (84%) received gemcitabine and cisplatin (GC) (+/- paclitaxel) while 16 patients (16%) received a combination of methotrexate, vincristine, adriamycin and cisplatin (MVAC). The median number of cycles received was 3 (range, 2 cycles-6 cycles). The number of cycles completed was as follows: 37 patients completed two cycles, 51 patients completed three cycles, 10 patients completed four cycles, and 3 patients completed six cycles prior to radical cystectomy.

TABLE 1. **Overall patient demographics**

Age median (IQR)	67 (59-67)
No. gender (%)	
Male	78 (77)
Female	23 (23)
No. smoking history (%)	
Yes	69 (68)
No	32 (32)
No. clinical stage (%)	
≤ T2	96 (95)
≥ T3	5 (5)
No. hydronephrosis (%)	
Yes	18 (17.8)
No	83 (82.1)
No. pathologic T stage (%)	
T0	23 (22)
TIS	9 (9)
T1	8 (8)
T2	21 (21)
T3	29 (29)
T4	11 (11)
No. lymph nodes status (%)	
Positive	24 (23)
Negative	77 (77)
No. chemotherapy protocol (%)	
Gemcitabine/cisplatin	85 (84)
MVAC	16 (16)

IQR = interquartile range; MVAC = methotrexate, vincristine, adriamycin and cisplatin

Pathological staging confirmed that 61 patients (51.4%) had localized disease (pT2 or less) while 40 patients (39%) had extravesical disease (pT3 or more) at cystectomy. Twenty-four patients (23%) had pathologically confirmed lymph node metastasis.

Based on the cystoscopy findings after the second cycle of chemotherapy, 60 patients (59%) were identified as responders while 41 patients (41%) were identified as non-responders. Median age was 63 among the responder group versus 72 years among the non-responders. There was no statistically significant difference between the two groups in terms of age, sex, body mass index (BMI), smoking history, clinical T stage, chemotherapy regimen and number of chemotherapy cycles administered, Table 2.

Tumor downstaging

There was evidence of tumor downstaging in the responder group. Forty-five patients (75%) in the responder group had pathologically confirmed localized disease (T2 or less) versus 16 patients (39%) in the non-responder group. Stage pT0 at cystectomy was confirmed in 22 patients (36.5%) in the responder group versus only 1 patient (2.5%) in the non-responder group. Among patients with cT2/T3 disease, 35 patients (63%) had pathologically confirmed non-muscle invasive disease (Ta, Tis,T1) at cystectomy in the responder group versus 8 patients (20%) in the non-responder group.

Overall pathologic downstaging at cystectomy was observed in 41 patients (69%) in the responder group versus 11 patients (26%) in the non-responders. Among patients with clinically localized disease (T2 or less), 39 patients (40%) had pathologic downstaging in the responder group versus 10 patients (10.4%) in the non-responder group.

Univariate analysis established statistically significant association between cystoscopy findings (responders versus non-responders) and pT stage as well as tumor downstaging (each $p < 0.01$), Table 2.

Multivariate regression modeling revealed that cystoscopy findings were an independent predictor of extravesical disease (OR, 0.23, CI 0.05 to 0.98 $p = 0.04$), Table 3.

After accounting for age, gender, smoking history, lymph node positivity, chemotherapy regimen and number of cycles, cystoscopy findings were also identified as an independent predictor of pathological downstaging (OR, 7.79, CI 2.75 to 22.048 $p = < 0.01$), Table 3.

TABLE 2. **Univariate analysis**

	Responders n (%)	**Non-responders n (%)**	**p value**
Age median (IQR)	63 (59.2-70.0)	70 (63.0-77.0)	0.346
Body mass index median (IQR)	28.5 (24.3-31.0)	25.7 (23.3-28.8)	0.071
Gender			0.285
Male	48 (80.0)	30 (73.0)	
Female	12 (20.0)	11 (27.0)	
Clinical stage			0.196
≤ T2	56 (93.3)	40 (97.5)	
≥ T3	4 (6.7)	1 (2.5)	
Hydronephrosis			0.105
Yes	10 (16.6)	8 (0.19)	
No	50 (83.4)	33 (80.4)	
Chemotherapy protocol			0.053
Gemcitabine/cisplatin	49 (83)	36 (65)	
MVAC	10 (17)	6 (35)	
Mean number of cycles	2.9 ± 0.95	2.6 ± 0.69	0.132
Pathologic T stage			< 0.001
T0	22 (36.5)	1 (2.5)	
Tis	9 (15.0)	0	
T1	7 (11.5)	1 (2.9)	
T2	7 (11.5)	14 (34.0)	
T3	13 (22.0)	16 (39.0)	
T4	2 (3.5)	9 (22.0)	
Lymph nodes			0.172
Positive	12 (21.5)	12 (32.5)	
Negative	44 (78.5)	25 (67.5)	
Pathologic downstaging			< 0.001
Yes	41 (69.5)	11 (26.4)	
No	19 (30.5)	31 (73.6)	
Total	**60 (59.4)**	**41 (40.6)**	

IQR = interquartile range; MVAC = methotrexate, vincristine, adriamycin and cisplatin

Survival analysis:

Over a mean follow up of 28 months (range 6 months-196 months), 11 patients (18.3%) experienced recurrence and/or metastasis in the responder group versus 18 patients (44%) in the non-responder group. The mean time to recurrence was 14 months in the responder group versus 7.5 months in the non-responder group, Table 4.

A Kaplan-Meier survival curve with log rank test revealed that patients with observed cystoscopic response to chemotherapy had better survival rates than non responders. The 3 year and 5 year DSS were 71.4% and 48.3% for the responder group versus 19.9% and 10.5% for non-responder group respectively (p = < 0.001 each), Table 4, Figure 1. There were no disease-specific deaths in the subset where a pT0 response was attained. Cox proportional hazard modeling revealed that observed response to chemotherapy was an independent predictor of survival (OR 0.38, 95% CI 0.20 to 0.74, p = 0.004), Table 5.

Discussion

NAC has been proposed in the setting of MIBC to potentially eradicate the primary lesion and control micrometastasis before the patient is subjected to a major surgical procedure with a perioperative complication rate of approximately 30%-40%.[14]

TABLE 3. **Multivariate analysis of extravesical disease and pathologic downstaging predictors**

Covariate	OR (95% CI)	p value
Extravesical disease		
Age	1.06 (0.90-1.13)	0.03
Gender	1.00 (0.61-1.64)	0.15
Smoking history	0.98 (0.97-1.00)	0.11
Cytoscopy findings (responder versus non-responder)	0.23 (0.05-0.98)	0.04
pN stage (N0 versus > N0)	11.78 (2.36-58.59)	0.01
Pathologic downstaging		
Age	1.07 (0.70-1.66)	0.22
Gender	0.16 (0.04-0.58)	0.01
Smoking history	0.86 (0.55-1.35)	0.790
Cystoscopy findings (responder versus non-responder)	7.79 (2.75-22.05)	< 0.001
pN stage	0.29 (0.09-0.937)	0.04
Chemotherapy protocol (GC versus MVAC)	1.36 (0.81-2.29)	0.92
Number of cycles	1.97 (0.60-1.56)	0.958

GC = gemcitabine/cisplatin; MVAC = methotrexate, vincristine, adriamycin and cisplatin

TABLE 4. **Survival outcomes**

Outcome	Responders n (%)	Non-responders n (%)	p value
Recurrence/metastases			0.02
Yes	11 (18.3)	18 (44)	
No	49 (81.7)	23 (56)	
Months to recurrence	14.1+/-10.6	7.5 +/-9.2	0.09
Time to death	21.7 +/- 17.5	11.8+/-11.1	0.03
Deaths			< 0.001
Yes	17 (28.3)	33 (80.5)	
No	43 (71.7)	8 (19.5)	
% 3 year DSS	71.4%	19.9%	< 0.001
% 5 year DSS	48.3%	10.5%	< 0.001

DSS = disease-specific survival

TABLE 5. **Cox proportional hazard model of survival predictors**

Covariate	Hazard ratio (95% CI)	p value
Age	1.24 (0.93-1.67)	0.056
Gender (males versus female)	1.38 (1.06-1.80)	0.479
Cystoscopy findings (responder versus non-responder)	0.38 (0.201-0.744)	0.004
pT stage (T2 or less versus greater than T2)	4.281(1.94-9.415)	< 0.001
Pathologic downstaging (yes versus no)	2.01 (1.37-2.96)	< 0.001
pN stage (N0 versus greater than N0)	1.61 (1.21-2.14)	0.001

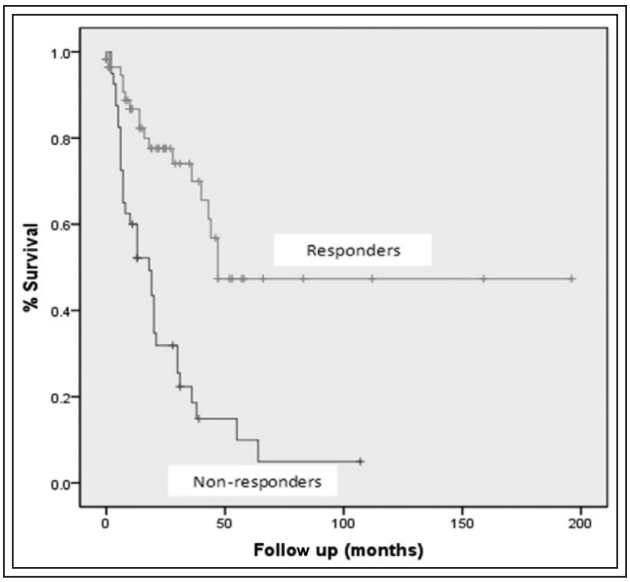

Figure 1. Cancer-specific survival in patients stratified by their observed response to chemotherapy

Several randomized trials investigated the role of NAC prior to radical cystectomy. The SWOG 8710 trial reported on 307 patients with MIBC randomly assigned to radical cystectomy with or without three cycles of neoadjuvant MVAC.[6] Among patients who received NAC, 14% improvement in overall 5 year was observed. In addition, stage pT0 at the time of cystectomy among those who received NAC was significantly higher (38%) than the cystectomy-only group (15%). More recently, long term results of the international multicenter BA06 30894 trial were reported.[15] In this trial, 976 patients were randomized to receive or not receive three cycles of cisplatin, methotrexate, and vinblastine (CMV) NAC prior to definitive therapy (cystectomy or radiotherapy). With a median follow up of 8 year, median overall survival was significantly increased in the chemotherapy arm from 37 to 44 months corresponding to an increase in 10 year survival from 30% to 36%.

A meta-analysis of 11 clinical trials of neoadjuvant chemotherapy in MIBC published by the Advanced Bladder Cancer meta-analysis collaboration showed a 5% absolute survival benefit at 5 years ($p = 0.003$).[7] Patients who received cisplatin-based combination chemotherapy regimen had a 50% survival at 5 years compared to a 45% survival of those who do not receive NAC.

Pathologic response to chemotherapy is probably the most important predictor of survival following NAC. The 5 year survival, in patients with muscle invasive disease, achieving tumor downstaging to pT0 or pTa/T1 with NAC, was 75%. Patients with residual muscle-invasive TCC after neoadjuvant therapy had a 5 year survival of only 20%.[16] In a retrospective analysis of the SWOG 8710 study, Sonpavde et al[9] reported that the quality of pathologic response (pT0 versus pTa, pT1 or CIS versus pT2+ disease) correlated with overall survival.[9] Similarly, recent data from analysis of the Nordic cystectomy trial reported a 5 year absolute risk reduction of 31% in overall survival in patients with pT0 who received NAC compared to controls.[10] Therefore, chemo-induced downstaging was considered as a surrogate for efficacy and increased survival following NAC and radical cystectomy.

Despite evidence to support the use of NAC, this approach is often not adopted. Controversy exists regarding its need and benefits in patients with clinically organ confined bladder cancer. Data from the National Cancer Database revealed that only 9% of patients with MIBC were treated with NAC from 2003 to 2007 in accredited cancer programs.[17]

A major argument against NAC is the delay in the surgical therapy, especially in patients who may respond suboptimally to chemotherapy. In line with this hypothesis, early identification of non-responders, predicting their outcomes and assessing the value of chemotherapy in this population is of most importance.

We utilized outpatient cystoscopy to identify non-responders to NAC early during the course of treatment. We investigated cystoscopy findings after the second cycle of NAC as a predictor of extravesical disease, pathologic downstaging and DSS. Our findings suggest that observed cystoscopic response to chemotherapy is associated with favorable pathology, significant tumor downstaging at cystectomy and subsequently improved survival. Identified responders had significantly higher percentage of pathologically confirmed localized disease and higher incidence of pathologic downstaging at cystectomy; 75% versus 39% and 69% versus 26% respectively.

Our data are consistent with previous reports, where stage pT0 was reported in 14%-38% following NAC for MIBC.[10-13] Overall, in our series, 22% of patients achieved tumor downstaging to pT0 at cystectomy. Moreover, we noted a significantly higher percentage of pT0 stage among responders compared to non-responders; 36.5% versus 2.5%. This correlated with significant better survival rates in the responder group.

The optimal number of NAC cycles remains questionable. It has been postulated that a more cycles will lead to better outcomes.[15,18] In this setting, the practical application of our findings is evident.

Patients identified as responders based on cystoscopy after two cycles of NAC may be encouraged to proceed with additional chemotherapy courses. On the other hand, non-responders should be counseled for either a salvage regimen or earlier cystectomy. This results in avoiding unnecessary treatment with additional side effects and potential delay in the definitive surgical therapy.

Schrier et al investigated the reduction in tumor vascularization using fast dynamic contrast-enhanced MRI to predict the response to chemotherapy in urothelial bladder cancer.[19] They postulated that persistence of early enhancement indicates either no or partial response. More recently, Yoshida et al, demonstrated the superiority of diffusion-weighted MRI examination over T2-weighted and T1-contrast enhanced imaging for monitoring therapeutic response.[20] However, the value of MRI was only demonstrated in metastatic and unresectable bladder cancer. Cost, technical considerations and interobserver variability have been significant limitations for its routine use.

Several molecular markers have also been investigated as predictors for the response to chemotherapy. The relationship between p53 mutation and response to chemotherapy has been controversial.[21] Bellmunt et al, reported that mRNA expression levels of repair cross-complementing 1 (ERCC1) gene are related to cisplatin resistance in metastatic urothelial bladder cancer.[22] Genome wide gene expression profiling was also utilized to identify a gene signature that would predict sensitivity to MVAC therapy.[23] However, none of these markers to date have been adopted in clinical use.

The strengths of our study include direct access to all medical records and prospective collection of data which allowed for accurate documentation of all relevant information. However, although the database was prospectively maintained, our study has inherent limitations in its retrospective design and is subsequently exposed to potential biases. Both pre-treatment TURBT and follow up cystoscopy were performed by the same surgeon. Furthermore, operative reports as well as saved cystoscopic images for the pre-chemotherapy TURBT were reviewed at the time of follow up cystoscopy. Therefore, errors related to subjective cystoscopic evaluation of the response to chemotherapy are believed to be minimal. Our study is limited by its retrospective nature and lack of pathologic and imaging confirmation of the cystoscopic response. Any shortcomings related to accuracy of clinical staging, variance of chemotherapy regimens as well as number of cycles are supposed to be equal in both study groups.

To our knowledge, this is the first study to analyze the significance of observed cystoscopic response to NAC as a predictor of favorable pathologic outcomes and survival after radical cystectomy. In the absence of reliable imaging modalities or molecular markers to predict and assess the response to chemotherapy, we suggest outpatient cystoscopy to be performed routinely after the second cycle of NAC. Cystoscopy findings are to be considered a surrogate for the therapeutic response. In addition to the important prognostic significance, findings provide guidance in patient counseling regarding modification of the chemotherapeutic regimen.

Conclusion

Observed response to NAC on follow up cystoscopy is associated with favorable pathologic outcomes and is a significant predictor of survival in patients undergoing radical cystectomy for MIBC. In the absence of reliable imaging modalities or molecular markers to predict and assess the response to chemotherapy, this correlation may have implications for preoperative patient counseling and modification of management strategies for patients with MIBC. □

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