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OUTCOME OF BLADDER CANCER PATIENTS WITH pN+ DISEASE AFTER PREOPERATIVE CHEMOTHERAPY AND RADICAL CYSTECTOMY

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Abstract

Objectives—Persistent nodal disease in the surgical specimen (pN+) after preoperative chemotherapy for urothelial carcinoma (UC) is associated with poor prognosis. To improve our understanding regarding outcome of such patients, we performed a retrospective review of our experience.

Methods—Between 1993–2003, 857 patients underwent radical cystectomy for UC of the bladder, and 150 were found to be pN+. Of these, 37 were pN+ despite preoperative chemotherapy and form the basis of this report. Survival data were analyzed using Kaplan-Meier method and Cox regression analysis.

Results—The patients' median age was 66 years (range 39 to 85 years), and the median follow-up was 50 months (range 13.0 to 58.7 months). Clinical stages (at time of initiation of preoperative chemotherapy) were cT2 with lymphovascular invasion: 7, cT3b: 6, cT4a: 4, cT4b: 2, and cN+: 18. The 2-year overall (OS), disease-specific (DSS), and recurrence-free (RFS) survival rates were 20%, 29.2%, and 13.5%, respectively. Eleven (30%) patients received adjuvant chemotherapy after surgery; majority (73%) were platinum-based regimens. On multivariate analysis, surgical margin status, gender, and histology were significantly associated with OS, and histology and use of adjuvant chemotherapy were significantly associated with RFS.

Conclusion—Patients who have persistent nodal disease despite preoperative chemotherapy have a poor prognosis. A cohort of such patients may do well with adjuvant chemotherapy. Lymph node density and pT stage are not prognostic in patients with nodal metastasis after preoperative chemotherapy.

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“Take Home Message”: Although patients who have persistent nodal disease despite preoperative chemotherapy have a poor prognosis, our results suggest that a cohort of such patients may benefit from adjuvant chemotherapy.

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INTRODUCTION

Radical cystectomy and pelvic lymph node dissection (PLND) is the gold standard for muscle-invasive transitional cell carcinoma (TCC) of the bladder. Preoperative chemotherapy has been used in an attempt to improve outcomes. In a recent meta-analysis performed to examine the effect of neoadjuvant chemotherapy in the treatment of bladder cancer, platinum-based combinations of neoadjuvant chemotherapy showed a significant benefit to overall survival (OS) [combined hazard ratio of 0.87 (95% CI 0.78–0.98, $p=0.006$)]¹. A large prospective, randomized trial reported by Grossman et al recently confirmed these findings².

The risk of relapse in patients treated with chemotherapy followed by radical cystectomy is largely dependent on pathologic findings. In a study from M. D. Anderson Cancer Center, response to therapy (defined as $\leq pT2$ in the surgical specimen) was found to be highly prognostic with only 12% of these patients experiencing relapse³. Not surprisingly, 86.1% of patients who had node-positive disease in the surgical specimen experienced relapse and died of metastatic disease within 4.5 years. An analysis of the aforementioned prospective randomized SWOG study² confirmed that pathologic stage and nodal status were associated with survival in patients receiving neoadjuvant therapy, with 5-year survival for node-positive patients being as low as 9%⁴. Thus persistent nodal disease in the surgical specimen despite preoperative chemotherapy is associated with poor prognosis, and patients are often offered salvage chemotherapy only at time of disease progression for palliation. To improve our understanding of such patients, we performed a retrospective review of our experience with patients with bladder cancer who were treated with preoperative chemotherapy followed by cystectomy and had persistent viable tumor in the lymph nodes.

METHODS

An IRB (institutional review board) approved search was performed using our bladder cancer database. We focused on the period from 1993 to 2003 in order to provide a contemporary series of patients. During the period studied, 857 patients underwent radical cystectomy for TCC of the bladder at our institution, and 150 of them were found to have viable tumor in the lymph nodes at cystectomy. Of these, 37 patients had viable tumor in lymph nodes after receiving preoperative chemotherapy and form the basis of this report. Each patient had a pre-operative metastatic work-up that included blood tests, chest x-ray, computerized tomography (CT) of the abdomen and pelvis, and bone scan. All patients underwent a radical cystectomy with PLND and urinary diversion. All PLND were performed bilaterally. Over the past decade, our limits of PLND have gradually evolved to extend up to the level of the aortic bifurcation. The majority of lymph node dissections were sent to the pathologist en bloc and not in packets. There were no patients that were found to have intraoperative findings of grossly palpable nodes. Postoperative, patients were then followed with routine blood tests, chest x-rays, CT of the abdomen and pelvis, and bone scans (if indicated) to assess for recurrence of disease at predefined intervals.

Variables analyzed included age, sex, clinical stage, histology, lymphovascular invasion, type of urinary diversion, pathological stage, number of nodes excised, number of positive nodes, lymph node density (ratio of nodes involved to nodes removed), extranodal extension, presence of carcinoma in situ, margin status, and adjuvant chemotherapy. Survival data were analyzed using the Kaplan-Meier method, with log rank tests to evaluate associations between survival and the variables studied. Univariate Cox proportional hazards regression models were fit to the data. All potential prognostic factors with a p -value < 0.25 from the univariate analysis were then included in a saturated multivariate model, and backward elimination was used to remove factors from the model based on the likelihood ratio test. A p value of < 0.05 was considered statistically significant.

RESULTS

Overall

Baseline characteristics of the 37 patients with node positive disease after preoperative chemotherapy are listed in Table 1. Patients received preoperative chemotherapy for locally advanced bladder cancer – defined at our institution by the presence of 3-dimensional palpable mass (cT3b) on bimanual EUA (examination under anesthesia), invasion of adjacent organs (cT4), cT2 lesion with lymphovascular invasion (LVI) on transurethral biopsy specimen, or clinically evident pelvic node metastasis on abdominal imaging. Eighteen patients (49%) had clinically evident nodal metastasis (11 with cT2, 5 with cT3b, and 2 with cT4 lesions) whereas 19 patients (51%) had clinically negative nodes (7 with cT2 and LVI, 6 with cT3b, and 6 with cT4 lesions). Thirty (81%) patients received platinum-based preoperative chemotherapy, and seven (19%) were given non-platinum-based regimens (usually on various active protocols at the time). Patients received a median of 5 cycles of preoperative chemotherapy.

The patients' median age was 66 years (range 39 to 85 years). The median post-cystectomy follow-up for patients alive was 50 months (range 13.0 to 58.7 months), while the median follow-up for all patients was 13 months (range 1.5 to 59.6 months). The 2-year overall (OS), disease-specific (DSS), and recurrence-free (RFS) survival rates were 20%, 29.2%, and 13.5%, respectively. The median OS, DSS, and RFS survival durations were 13.0, 14.6, and 6.0 months, respectively (Figure 1a).

Survival by Clinical Features

In all, 21 (57%) patients had pure TCC, and 16 (43%) had TCC plus variant histology such as micropapillary TCC, 7; squamous carcinoma, 5; lymphoepithelial histology, 2; and glandular differentiation, 2. The presence of variant histology was significantly associated with shorter OS ($p=0.01$) and RFS ($p=0.036$) but not with DSS in the multivariate analysis. Of the 37 patients, 18 had clinically evident pelvic nodal metastasis (cN+) prior to cystectomy and hence received 'preoperative' chemotherapy compared to 19 patients who were clinically node negative (cN0) and received chemotherapy in the true 'neoadjuvant' setting. Clinically evident nodal metastasis was significantly associated with shorter DSS (13.5 vs 19.9 months, $p=0.02$, HR 2.84, CI 1.18–6.81), shorter RFS (4.9 vs 10.8 months, $p=0.022$, HR 2.58, CI 1.15–5.78) but not with OS in the multivariate analysis. Female gender was significantly associated with OS (HR 0.25, $p=0.006$). Age, history of superficial TCC, and the presence of lymphovascular invasion were not associated with OS, DSS, or RFS.

Stratification by Pathological Stage

The pathologic T-stage distribution at cystectomy was pT0: 1, pTis: 1, pT2: 5, pT3: 19, and pT4: 11 (Table 1). Thus, only 2 patients had no evidence of residual muscle-invasive disease in the resected specimen. Results of tests for associations of variables with survival in multivariate analysis are shown in Table 2. Of the 37 patients, 25 (68%) had recurrence of disease; 2 had pelvic recurrence, 13 had distant disease, and 10 had both. In the presence of positive nodes after preoperative chemotherapy, pT stage had no effect on OS, DSS, or RFS. Total number of nodes removed (median 13), number of positive nodes (median 2.5), and lymph node density (median 25%) did not correlate with OS, DSS, or RFS. Five (14%) patients had positive surgical margins on final pathology. The majority of patients with positive margins (4/5, 80%) died of disease and the status of surgical margins was significantly associated with OS ($p=0.003$), DSS ($p=0.001$), and RFS ($p<0.001$) on multivariate analysis. Presence of carcinoma in situ, extranodal extension, number of cycles of preoperative chemotherapy, type of urinary diversion, and post-operative performance status of all patients at decision regarding adjuvant therapy were not associated with OS, DSS, or RFS. Eleven (30%) patients received adjuvant chemotherapy for pN+ disease started after recuperation from radical cystectomy

(median duration of 2 months from surgery, range 1 to 3 months). The majority (73%) received platinum-based regimens, most commonly MVAC; all patients were given a different regimen than what they received preoperatively. In multivariate analysis, adjuvant chemotherapy was significantly associated with improved RFS ($p=0.02$, HR 0.29, CI 0.10–0.81) with a trend towards significance with prolonged OS ($p=0.08$, HR 0.44, CI 0.18–1.11) and DSS ($p=0.07$, HR 0.36, CI 0.12–1.07) (Table 2). Kaplan Meier analysis of median survival for those who received adjuvant chemotherapy versus those who did not was - OS: 16 vs 12.6 months, DSS: 59.7 vs 13.5 months, and RFS: 13 vs 4.7 months (Figure 1b–c). To assess whether patients treated with adjuvant chemotherapy versus those who did not were comparable, the two groups were analyzed. Patients who received adjuvant chemotherapy were younger (median age 52 vs 68 years, $p<0.01$) and understandably trended towards having better performance status ($p=0.06$). However, there was no significant difference between the 2 groups with regards to clinical stage ($p=0.47$), pathologic stage ($p=0.64$), lymph node density ($p=0.99$), concomitant variant histology ($p=0.72$), surgical margins ($p=0.28$), tumor downstaging ($p=0.39$).

DISCUSSION

Our results suggest that patients who have persistent nodal disease despite preoperative chemotherapy have a very poor prognosis. A cohort of such patients may benefit from adjuvant chemotherapy. Lymph node density and pT stage are not prognostic in patients with nodal metastasis after preoperative chemotherapy.

It is known that patients with nodal metastases have poor prognosis despite radical cystectomy and pelvic lymphadenectomy with 5-year overall survival in this subgroup of patients being approximately 25% to 35% and relapse rates as high as 66%^{5–7}. Neoadjuvant chemotherapy is now considered an integral part of multi-modality therapy for patients with bladder cancer, particularly those with clinical locally advanced disease such as those who have a three-dimensional mass on bimanual EUA (cT3b), invasion of adjacent organs (cT4), or lymphovascular invasion on cystoscopic biopsy^{2,3,8}. However, patients with persistent nodal disease in the cystectomy and PLND specimen after preoperative chemotherapy have a very poor prognosis³. There is a lack of data in the literature that attempts to identify prognostic variables to predict outcome and possibly influence future management for these patients. Based on the extremely high rate of recurrence observed in the setting of node positive disease following neoadjuvant chemotherapy, we have offered patients who wished to be aggressive additional adjuvant chemotherapy. Our report suggests that adjuvant therapy in these patients may prolong recurrence-free survival.

Although pathologic lymph node density, initially coined by the USC group, was later confirmed in our institution to be prognostic in patients undergoing upfront cystectomy^{5,9}, we found no significant association between number of positive lymph nodes, total number of lymph nodes, or lymph node density and OS, DSS, or RFS in this population where preoperative chemotherapy was administered. However, we still believe that the extent of node dissection should be similar in patients with upfront cystectomy versus those treated with neoadjuvant chemotherapy. Furthermore, unlike previous reports on surgical series involving cystectomy alone⁵, the extent of tumor in the primary site (organ-confined vs extravesical extension) was not predictive of survival in this subgroup of patients with nodal metastasis who were treated with preoperative chemotherapy.

Adjuvant chemotherapy following radical cystectomy has been previously studied in five randomized trials which studied patients who were considered to be at high risk either due to locally advanced pT stage (pT3 or pT4) or regional nodal metastasis (pN+)^{10–14}. In two of these trials, adjuvant chemotherapy did not appear to confer any benefit over observation.^{11, 13} The trials which did suggest a benefit for adjuvant chemotherapy compared with observation

alone included that by Friehe et al ¹², Skinner et al ¹⁴, and that from the University of Mainz ¹⁰. To date, the role of adjuvant chemotherapy in patients who have received prior chemotherapy and are still found to be pN+ at time of cystectomy has not been reported. In our analysis, those pN+ patients who received adjuvant chemotherapy had a significantly prolonged recurrence-free survival (13 versus 5 months) and a trend towards significance with prolonged overall survival (16 versus 13 months), and disease-specific survival (59.6 versus 13.5 months). Thus data seem to suggest that in a sub-group of patients with more aggressive disease – who are pN+ despite preoperative chemotherapy – adjuvant chemotherapy can be administered and select patients seem to do well. We do acknowledge, however, that it is impossible to definitively identify an optimal therapeutic strategy from a retrospective study. In addition to potential biases in the selection of patients for adjuvant chemotherapy, our results could have also been affected by the (relatively) small sample size of a single center study. Furthermore, even though performance status was not associated with OS, DSS, or RFS in the multivariate analysis, patients who received adjuvant chemotherapy trended towards having better performance status (p=0.06). Definitive recommendations will have to await results from prospective randomized trials addressing this issue.

CONCLUSION

Patients who have persistent nodal disease despite preoperative chemotherapy have a very poor prognosis. Our results suggest that a cohort of such patients may do well with adjuvant chemotherapy. Lymph node density and pT stage are not prognostic in patients with nodal metastasis after preoperative chemotherapy.

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References

1. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Lancet* 2003;361:1927–34. [PubMed: 12801735]
2. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, deVere White RW, Sarosdy MF, Wood DP Jr, Raghavan D, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003;349:859–66. [PubMed: 12944571]
3. Randall, Millikan CD.; Swanson, David; Sweeney, Paul; Ro, Jae Y.; Smith, Terry L.; Williams, Dallas; Logothetis, Chrostopher. Integrated Therapy for Locally Advanced Bladder Cancer: Final Report of a Randomized Trial of Cystectomy Plus Adjvant M-VAC Versus Cystectomy With Both Preoperative and Psotoperative M-VAC. *Journal of Clinical Oncology* 2001;19:4005–4013. [PubMed: 11600601]
4. Herr HW, Faulkner JR, Grossman HB, Natale RB, deVere White R, Sarosdy MF, Crawford ED. Surgical factors influence bladder cancer outcomes: a cooperative group report. *J Clin Oncol* 2004;22:2781–9. [PubMed: 15199091]
5. Stein JP, Cai J, Groshen S, Skinner DG. Risk factors for patients with pelvic lymph node metastases following radical cystectomy with en bloc pelvic lymphadenectomy: concept of lymph node density. *J Urol* 2003;170:35–41. [PubMed: 12796639]
6. Vieweg J, Gschwend JE, Herr HW, Fair WR. Pelvic lymph node dissection can be curative in patients with node positive bladder cancer. *J Urol* 1999;161:449–54. [PubMed: 9915424]
7. Abdel-Latif M, Abol-Enein H, El-Baz M, Ghoneim MA. Nodal involvement in bladder cancer cases treated with radical cystectomy: incidence and prognosis. *J Urol* 2004;172:85–9. [PubMed: 15201743]
8. Winquist E, Kirchner TS, Segal R, Chin J, Lukka H. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. *J Urol* 2004;171:561–9. [PubMed: 14713760]

9. Kassouf W, Leibovici D, Munsell MF, Dinney CP, Grossman HB, Kamat AM. Evaluation of the relevance of lymph node density in a contemporary series of patients undergoing radical cystectomy. *J Urol* 2006;176:53–7. [PubMed: 16753366]discussion 57
10. Stockle M, Meyenburg W, Wellek S, Voges G, Gertenbach U, Thuroff JW, Huber C, Hohenfellner R. Advanced bladder cancer (stages pT3b, pT4a, pN1 and pN2): improved survival after radical cystectomy and 3 adjuvant cycles of chemotherapy. Results of a controlled prospective study. *J Urol* 1992;148:302–6. [PubMed: 1635123]discussion 306–7
11. Bono AV, Benvenuti C, Reali L, Pozzi E, Gibba A, Cosciani-Cunico S, Comuzzi U, Anselmo G. Adjuvant chemotherapy in advanced bladder cancer. Italian Uro-Oncologic Cooperative Group. *Prog Clin Biol Res* 1989;303:533–40. [PubMed: 2675010]
12. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. *J Urol* 1996;155:495–9. [PubMed: 8558644]discussion 499–500
13. Studer UE, Bacchi M, Biedermann C, Jaeger P, Kraft R, Mazzucchelli L, Markwalder R, Senn E, Sonntag RW. Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. *J Urol* 1994;152:81–4. [PubMed: 8201695]
14. Skinner DG, Daniels JR, Russell CA, Lieskovsky G, Boyd SD, Nichols P, Kern W, Sakamoto J, Krailo M, Groshen S. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. *J Urol* 1991;145:459–64. [PubMed: 1997689]discussion 464–7

a

Figure 1. (A) Kaplan-Meier estimate of overall (OS), disease-specific (DSS), and recurrence-free (RFS) survival of all patients with positive nodes after preoperative chemotherapy. Kaplan-Meier estimate of recurrence-free survival (B) and disease-specific survival (C) in patients who received adjuvant chemotherapy versus those who did not.

Table 1

Clinico-pathologic characteristics of patients

	# of patients (%)
Number of patients	37
Median age (years)	66 (range 39 to 85)
Gender	
Male	28 (76)
Female	9 (24)
Clinical T-stage	
2 [*]	18 (49)
3b ¹	11 (30)
T4a ²	5 (13)
T4b ³	3 (8)
Clinical N-stage	
N0	19 (51)
N+	18 (49)
Histology	
TCC	21 (57)
TCC + other	16 (43)
Neoadjuvant chemotherapy	
Platinum-based	30 (81)
Other [†]	7 (19)
Pathological stage	
≤ T1	2 (6)
T2	5 (13)
T3	19 (51)
T4	11 (30)
Median # of positive nodes	2.5
Median # of nodes	13
Median lymph node density	25% (range 4% to 100%)
Extranodal extension	19 (51)
Lymphovascular invasion	26 (70)
CIS	12 (32)
Positive surgical margin	5 (13)
Adjuvant chemotherapy	
Yes	11 (30)
No	24 (64)
Unknown ¹	2 (6)

* 11 patients had cN+ and 7 had lymphovascular invasion on transurethral biopsy

¹ five patients had cN+,

² one patient had cN+,

³ one patient had cN+

[†] other: ifosfamide/adriamycin/gemcitabine in 4 patients, taxol/carboplatinum in 1, gemcitabine/adriamycin in 1, and gemcitabine/carboplatinum in 1 patient.

[!] These patients were lost to follow-up

Table 2

Univariate (A) and Multivariate (B) analysis of variables that predict overall, disease-specific, and recurrence-free survival.

(A)				
	# of patients	OS	DSS	RFS
Age		NS	NS	NS
<65	18			
≥65	19			
Gender		NS	NS	NS
Male	28			
Female	9			
Clinical N-stage		0.014	0.035	0.02
cN ₀	19			
cN ₁₋₂	18			
Performance status [*]		0.037	NS	NS
ECOG 0-1	23			
ECOG 2-3	12			
Histology		NS	0.033	0.01
TCC	21			
TCC + variant	16			
Pathologic stage		NS	NS	NS
≤ pT2	7			
> pT2	30			
Lymph node density		0.017	NS	NS
≤25%	18			
>25%	19			
Surgical margin status		0.001	0.001	0.001
Negative	32			
Positive	5			
Adjuvant chemotherapy [*]		0.034	0.028	0.001
No	24			
Yes	11			
(B)				
	# of patients	OS	DSS	RFS
Age		NS	NS	NS
<65	18			
≥65	19			
Gender		0.006	NS	NS
Male	28			
Female	9			
Clinical N-stage		NS	0.02	0.022

(A)	# of patients	OS	DSS	RFS
cN ₀	19			
cN ₁₋₂	18			
Performance status *		NS	NS	NS
ECOG 0-1	23			
ECOG 2-3	12			
Histology		0.012	NS	0.036
TCC	21			
TCC + variant	16			
Pathologic stage		NS	NS	NS
≤pT2	7			
> pT2	30			
Lymph node density		NS	NS	NS
≤25%	18			
>25%	19			
Surgical margin status		0.003	0.001	<0.001
Negative	32			
Positive	5			
Adjuvant chemotherapy *		NS	NS	0.02
No	24			
Yes	11			

* 2 patients had incomplete data

statistically significant (p < 0.05)

lymph node density is ratio of positive nodes to total number of nodes excised