Impact of adjuvant chemotherapy on patients with lymph node metastasis at the time of radical cystectomy

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Introduction: *Radical cystectomy (RC) remains the gold standard treatment for patients with muscle-invasive bladder cancer. Unfortunately, a significant proportion of patients will have lymph node involvement at the time of RC. We set out to determine the impact of adjuvant cisplatin-based chemotherapy (AC) in a cohort of lymph node positive patients following RC.*

Patients and methods: *We reviewed our RC database and isolated patients with lymph node positive disease at the time of RC. Univariate and multivariable analysis was performed to identify predictors of poor outcome in patients receiving AC. Overall survival (OS), disease specific survival (DSS) and recurrence free survival (RFS) were calculated for those patients who received AC compared to those who did not.*

Results: *Of the 316 patients, we identified 85 patients with metastatic lymph node involvement at the time of RC. Fifty-five (65%) of these patients received AC. Median follow up was 46 months. On multivariable analysis lymph node positive patients receiving AC had significantly improved OS, DSS and RFS compared to patients who did not receive AC ($p = 0.031$, $p = 0.028$, $p = 0.004$). The delivery of AC conferred the greatest recurrence-free, disease-specific, and overall survival advantages to those with lymph node densities (LND) of < 20% with ($p = 0.016$, $p = 0.011$, $p = 0.007$, respectively).*

Conclusion: *AC administered to patients with known lymph node metastasis conferred a significant survival advantage compared to observation. Furthermore, a LND of < 20% predicts of a more favorable response to AC. Further studies in larger patient populations are warranted to reveal the exact impact of AC in this subset of patients.*

Key Words: bladder cancer, radical cystectomy, adjuvant chemotherapy, lymph node metastasis

Introduction

Bladder cancer is the second most common genitourinary malignancy in the United States with approximately 70,530 new cases and over 14,000 deaths expected in 2010.[1] Radical cystectomy (RC) with pelvic lymphadenctomy remains the gold standard treatment for patients with muscle invasive bladder cancer, and in experienced hands provides excellent local tumor control.[2] The disease-specific variables that have proven to provide prognostic value for urothelial carcinoma include tumor stage, tumor grade, and the presence of lymph node metastases.[3]

Prospective randomized trials have shown neoadjuvant cisplatin-based chemotherapy to be superior to RC alone with regard to overall survival for patients with muscle-invasive bladder cancer.[4-6] Neoadjuvant chemotherapy is now considered by

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many urologists and oncologists as standard of care for patients with muscle-invasive disease.[7] The evidence for adjuvant chemotherapy (AC) for bladder cancer is far less compelling due to smaller trials often lacking appropriate design or statistical power.[8-12] In spite of level 1 evidence favoring neoadjuvant chemotherapy, a significant majority of patients proceed to RC in the United States without chemotherapy.[13] The reasons for this apparent underutilization is unknown, but is likely multifactorial. Until neoadjuvant chemotherapy is more readily accepted by both patients and practitioners, AC will likely continue to have a role in the treatment of patients with extravesical and node positive bladder cancer. The purpose of our study was to further define the impact of AC in patients with lymph node positive bladder cancer to better define its therapeutic benefit.

Patients and methods

We reviewed our prospectively maintained RC database from 1988 to 2003. This database consists of 383 consecutive patients who underwent RC and pelvic lymph node dissection by a single surgeon. The indications for RC in all cases was muscle-invasive bladder cancer diagnosed by transurethral resection, or high grade Ta, T1 or carcinoma in situ refractory to repeat transurethral resection and intravesical immunotherapy or chemotherapy. Preoperative evaluation included chest x-ray, serum laboratory studies and abdominal and pelvic cross sectional imaging in all cases. Of the 383 patients 25 were excluded from the study for receiving neoadjuvant chemotherapy or radiation, 7 for receiving non-platinum based chemotherapy, and 30 for pathologic cell type other than urothelial carcinoma. Five patients were excluded from the analysis because they started but did not finish an adjuvant chemotherapy regimen and they had incomplete data at the time of analysis. The remaining 316 patients served as the final cohort for further analysis.

Radical cystectomy was performed with en bloc excision of the bladder, prostate and seminal vesicles in males and en bloc excision of the bladder, uterus, ovaries, anterior vagina and urethra in females. All patients underwent a bilateral pelvic lymph node dissection from the bifurcation of the common iliac vessels cranially, the genitofemoral nerve laterally and the node of Cloquet distally. Lymph node packets were sent separately for pathologic analysis. Lymph node template packets generally consisted of right and left obturator, external iliac, common iliac and a single pre-sacral packet. Pathology specimens were examined according to our institution's protocol under the direction of a genitourinary pathologist. All lymph node packets were submitted and analyzed separately. Tumors were staged according to the 2002 AJCC staging manual and graded according to the 1973 WHO classification system. Lymph node density (LND) was calculated as the number of positive nodes divided by the total number of nodes removed and multiplied by one hundred.

Follow up was performed according to our institution's protocol. Patients were seen postoperatively every 4 months for the first 2 years, every 6 months until year five, and then annually there after. Patients were monitored with a physical exam, general labs, chest x-ray and urine cytology with each visit. Upper tract monitoring was performed with either intravenous urogram or loopogram depending on the patients' serum creatinine on a yearly basis. Abdominal and pelvic cross sectional imaging was also performed on a biannual basis. Abnormal surveillance imaging or a positive cytology prompted further work up as necessary. Follow up was calculated from date of cystectomy to last date of contact, death or recurrence. AC regimens included methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) or combination gemcitabine/cisplatin. Chemotherapy regimens were administered at the discretion of the treating medical oncologist.

Clinical and pathologic features were analyzed to determine their overall significance on patient prognosis and recurrence. Specific variables analyzed included chemotherapy status, presence or absence of lymph node metastasis, lymph node density, clinical presentation (gross hematuria, microhematuria or other), gender, diversion type, pathologic stage and blood loss. The effect of AC was assessed in patients with node positive disease.

Univariate and multivariable Cox regression analysis were used to determine the significance of the clinical and pathologic variables with regard to overall survival, recurrence free survival and disease specific survival. Survival probabilities were estimated using Kaplan-Meier curves and compared using the log rank test. Significance for all statistical tests was set at $p = 0.05$. Statistical analysis was performed using Stata, version 9.1(StataCorp LP 1996-2007, College Station, Texas, USA).

Results

Of the 316 evaluable patients, 255 (80.7%) were men and 61(19.3%) were women. The mean age of the study population was 65.6 years (range: 37-83). Median follow up was 46 months (range: 3-223). Overall, 85 patients (26.9%) had lymph node metastasis on final pathology. Fifty-five (65%) of the lymph node positive patients received adjuvant cisplatin-based chemotherapy and 30 (35%) received no additional

TABLE 1. **Clinical and pathologic features of 85 lymph node positive patients**

	Adjuvant chemotherapy	No chemotherapy	p value
Age	61.9	71.3	**< 0.0001**
Sex			
Male	45 (82%)	22 (73%)	p = 0.359
Female	10 (18%)	8 (27%)	
Diversion type			
Non-continent	29 (53%)	26 (87%)	**p = 0.002**
Continent	26 (47%)	4 (13%)	
Pathologic stage			
P0/Pis/P1	6 (11%)	3 (10%)	p = 0.932
P2	9 (16%)	4 (13%)	
P3/P4	40 (73%)	23 (77%)	
Total nodes	16.9	16.6	p = 0.911
Lymph node density			
< 20%	28 (51%)	17 (57%)	p = 0.610
> 20%	27 (49%)	13 (43%)	

therapy. The mean number of nodes sampled for the entire cohort was 16.66 (range: 5-56), 16.46 for those not undergoing chemotherapy and 17.2 for those who received AC (p = 0.59). Twenty-eight (51%) of the patients who received AC had a LND of < 20% while 27 (49%) patients who received AC had a LND of > 20%. There was no statistical difference in gender, diversion type, blood loss or presentation between patients who received AC and those who did not. Clinical and pathologic data for the 85 patients stratified by chemotherapy status is presented in Table 1. There was a linear association between pathologic stage and the presence of lymph node metastases. Specifically, the risk of lymph node involvement was found to be 7.6% in patients with non muscle-invasive disease as compared to 59.1% in those with pT4 disease.

On univariate analysis, node status, pathologic stage, age and adjuvant chemotherapy were all statistically significant adverse predictors of RFS, DSS and OS. The two and five year RFS rates for lymph node positive patients who received AC were 47.4% and 35.0% respectively compared to 36.4% and 18.2% for those who did not receive AC (p = 0.03, Figure 1a). This RFS advantage was strongest for patients with a LND of < 20%. In this subset of patients two and five year RFS in AC patients was 59.6% and 43.1% respectively, compared

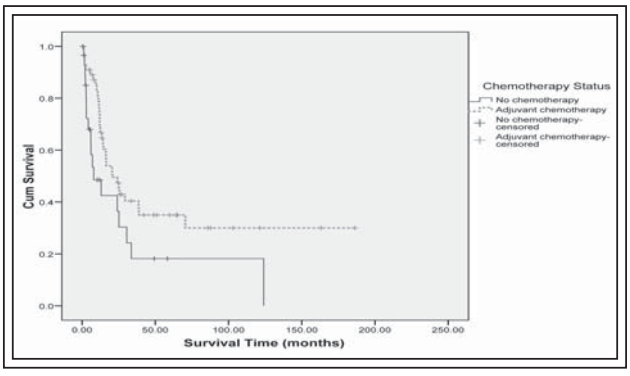

Figure 1a. Kaplan-Meier curve for RFS in lymph node positive patients based adjuvant chemotherapy status (total n = 85, AC group n = 55, no chemotherapy group n = 30, p = 0.03).

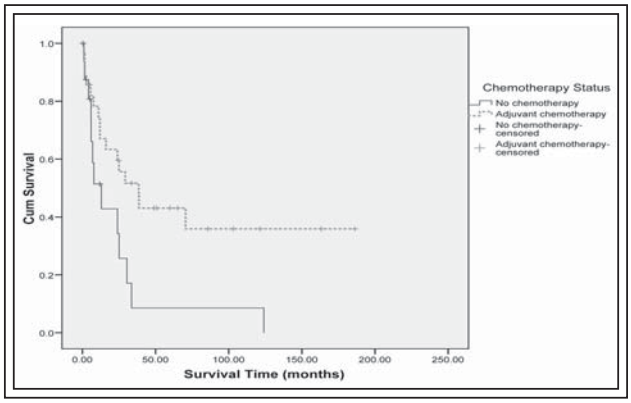

Figure 1b. Kaplan-Meier curve for RFS in lymph node positive patients with a lymph node density of < 20% based on adjuvant chemotherapy status (total n = 45, AC group n = 28, no chemotherapy group n = 17, p = 0.016).

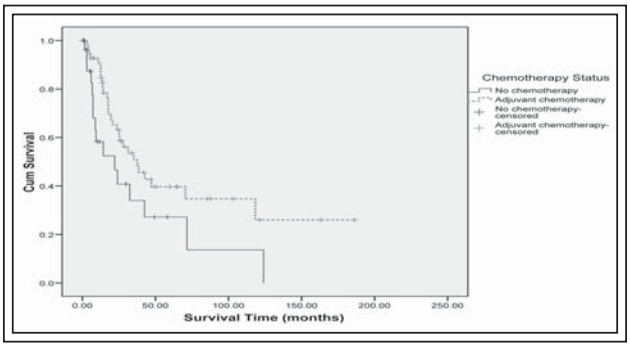

Figure 2a. Kaplan-Meier curve for DSS in lymph node positive patients based adjuvant chemotherapy (total n = 85, AC group n = 55, no chemotherapy group n = 40, p = 0.041).

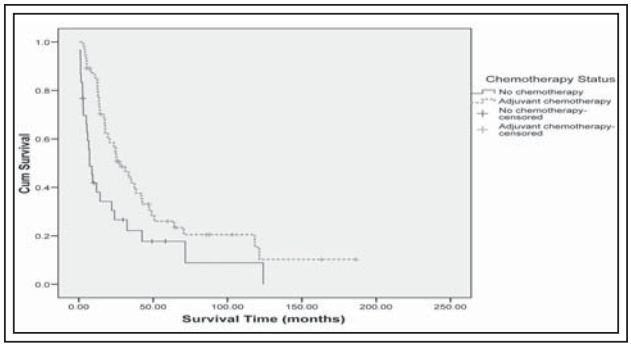

Figure 3a. Kaplan-Meier curve for OS in lymph node positive patients based adjuvant chemotherapy status (total n = 85, AC group n = 55, no chemotherapy group n = 30, p = 0.006).

to 34.3% and 8.6% for those who did not undergo AC (p = 0.016, Figure 1b). The RFS rates in patients with LNDs of > 20% did not differ significantly based on AC status (p = 0.40). Furthermore, lymph node positive patients who received AC had statistically significant (p = 0.041) improved two and five year (63.1% and 39.7%) DSS rates compared to patients who did not receive AC (46.6% and 27.2%), Figure 2a. This improvement in DSS was again even more pronounced in lymph node positive patients with LNDs of < 20%. In this subset of patients, two and five year DSS rates for those who received AC was 74.1% and 55.6% compared to 49.5% and 20.6% in those who did not receive AC (p = 0.011), Figure 2b. Finally, patients with lymph node positive disease who received AC had significantly improved overall survival rates with two and five year rates of 56.5% and 26.0% compared to 30.4% and 17.7% for those who did not receive AC (p = 0.006), Figure 3a. AC had its greatest impact on patients with LNDs of < 20% with two and five year overall survival rates of 71.3% and 38.9% for those who received AC compared to 35.3% and 14.7% for those who did not receive AC (p = 0.007), Figure 3b. As with RFS, an overall survival benefit for AC was lost in patients with LNDs of > 20 (p = 0.21).

Table 2 tabulates the results of our multivariable analysis. Age (HR 1.03, 95%CI 1.00-1.05, p = 0.04), lymph node positive disease (HR 1.91, 95%CI 1.18-3.11, p = 0.009) and pathologic stage (HR 4.0, 95%CI 2.36-6.78, p < 0.001) were all statistically significant predictors of worse RFS in the entire cohort. In patients with lymph node positive disease, those who underwent AC had significantly improved RFS rates on multivariable analysis compared to those who did not receive AC (HR 0.434, 95%CI 0.20-0.93, p = 0.03). Similarly, when examining the entire cohort, lymph node positive disease (HR 2.51, 95%CI 1.50-4.19, p < 0.001) and pathologic stage (HR 4.17, 95%CI 2.37-7.34,

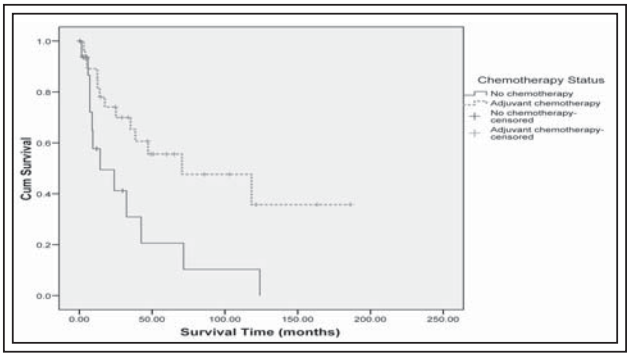

Figure 2b. Kaplan-Meier curve for DSS in lymph node positive patients with a lymph node density of < 20% based on adjuvant chemotherapy status (total n = 45, AC group n = 28, no chemotherapy group n = 17, p = 0.011).

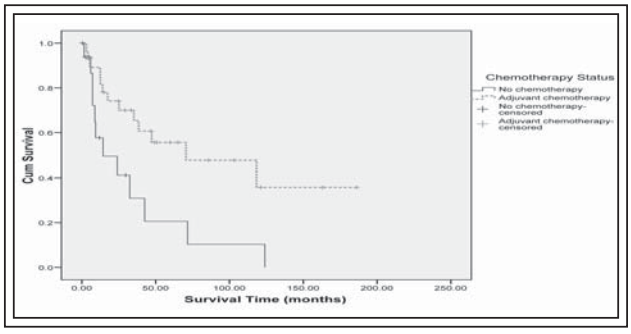

Figure 3b. Kaplan-Meier curve for OS in lymph node positive patients with a lymph node density of < 20% based on adjuvant chemotherapy status (total n = 45, AC chemotherapy group n = 28, no chemotherapy group n = 17, p = 0.007).

TABLE 2. **Multivariable analysis for RFS, DSS and OS for lymph node positive patients (n = 85)**

	RFS (HR, 95% CI, p value)	DSS (HR, 95%CI, p value)	OS (HR, 95%CI, p value)
Age	1.00, 0.96-1.04, 0.988	0.995, 0.95-1.04, 0.828	0.995, 0.96-1.03, 0.785
Sex			
Female[a]	-	-	-
Male	0.913, 0.46-1.82, 0.796	0.708, 0.34-1.48, 0.36	0.729, 0.39-1.35, 0.315
Diversion type			
Non-continent[a]	-	-	-
Continent	1.263, 0.61-2.62, 0.530	1.027, 0.49-2.17, 0.944	0.942, 0.51-1.75, 0.849
Stage			
P0/Pis/P1[a]	-	-	-
P2+	2.54, 0.77-8.4, 0.125	2.66, 0.79-8.8, 0.111	2.23, 0.87-5.70, 0.094
Lymph node density			
< 20%	-	-	-
≥ 20%	1.275, 0.69-2.35, 0.437	1.54, 0.82-2.94, 0.182	1.64, 0.97-2.76, 0.66
Chemotherapy			
No chemotherapy[a]	-	-	-
Chemotherapy	0.434, 0.20-0.93, 0.031	0.421, 0.19-0.91, 0.028	0.403, 0.22-0.75, 0.004

[a]reference category

p < 0.001) were significantly associated with poorer DSS on multivariable analysis. In the subset of 85 lymph node positive patients, AC was a statistically significant predictor of improved DSS on multivariable analysis (HR 0.421, 95% CI 0.20-0.91, p = 0.028). The protective effect of AC with regard to DSS was lost in lymph node positive patients with LNDs of > 20% (p = 0.95). Finally, age (p = 0.003), pathologic stage (p < 0.001) and lymph node positive disease (p < 0.001) were statistically significant predictors of decreased overall survival among the entire cohort of patients. Among patients with lymph node positive disease, patients who received AC had significantly higher overall survival rates than patients who did not receive AC, when controlling for the effects of age, sex, diversion type, pathologic stage and nodal density (HR 0.403, 95% CI 0.22-0.75, p = 0.004).

Discussion

Well designed clinical trials have clearly shown the benefit of neoadjuvant chemotherapy for patients with muscle-invasive bladder cancer.[4-6] Unfortunately, neoadjuvant chemotherapy continues to remain under-utilized in this patient population.[13] The exact reasoning for this apparent discrepancy is unknown, but there are likely multiple factors, both patient and physician related, which affect the decision to administer neoadjuvant chemotherapy. Physicians may be reluctant to offer neoadjuvant chemotherapy to patients without clinical evidence of extravesical or lymph node positive disease in an attempt to limit the number of patients "over treated" with chemotherapy. Due to the current insensitivity of clinical staging tools, this approach results in a significant proportion of patients having their disease upstaged at the time of RC. In fact, a recent study by McLaughlin et al reported a 62% rate of pathologic upstaging at the time of RC in patients with clinically staged T2 bladder cancer.[14] Furthermore, as many as 25% of patients will have evidence of lymph node metastasis at the time of RC.[2,15] Given this data, there is no question that neoadjuvant chemotherapy is currently under utilized in the management of muscle-invasive bladder cancer.

The evidence for AC in the setting of locally advanced and node positive bladder cancer is less compelling than that of neoadjuvant therapy. In light of the current under utilization of neoadjuvant chemotherapy, we sought to further establish the role of AC in patients with lymph node metastasis at the time of RC. Our data shows a statistically significant improvement in RFS, DSS and OS in node positive patients who received cisplatin based AC when controlling for other known predictors of outcome. Lymph node positive patients who received AC demonstrated improved two and five year RFS, DSS and OS rates when compared to lymph node positive

patients who did not. LND has been shown to be an independent predictor of prognosis in patients with muscle invasive bladder cancer following RC.[16,17] In our cohort, AC had its greatest impact in lymph node positive patients with LNDs of < 20%. In this subset of patients AC significantly improved the two and five year RFS, DSS and OS rates compared to patients who were observed. RFS, DSS and OS were not significantly different in lymph node positive patients with LNDs of > 20% regardless of chemotherapy status.

The prognosis for patients with locally advanced and node positive urothelial cancer at the time of RC remains poor. AC has the benefit of upfront surgical treatment without delay in patients with muscle invasive bladder cancer. AC has the additional benefit of basing treatment decisions on pathologic findings, delivering chemotherapy to higher risk patients while minimizing the number of patients potentially over treated with chemotherapy.[18] Additionally, current practice patterns highlight the fact that a significant percentage of patients are proceeding to RC without neoadjuvant chemotherapy and therefore AC will likely continue to play an important role in the treatment algorithm of these patients in the future.

There are few randomized trials in the literature to define the role of AC in patients with bladder cancer. Most of the trials that have been performed have been small, making it difficult to ascertain the exact benefit of AC.[8-12] Two trials have shown survival benefits for patients receiving AC after RC. Skinner et al randomized high risk patients (pT3-4 or node positive) to four cycles of cisplatin, cytoxan and doxorubicin versus observation following RC. A statistically significant survival advantage was noted in the AC group (4.3 years versus 2.4 years) compared to the observation group.[8] Stockle et al also randomized high risk patients following RC to three cycles of methotrexate, vinblastine, doxorubicin and cisplatin versus observation alone. This study was terminated early due to significant improvement in three year disease free survival in the AC arm (63% versus 13%).[12] Follow up data in this cohort of patients demonstrated a significant benefit in lymph node positive patients with regard to disease progression.[9] A recent meta-analysis of 491 patients from six different trials suggested a 25% relative reduction in risk of death from AC compared to that of patients observed after RC.[19]

In our cohort, we observed a survival benefit for patients who received AC which was more pronounced with lower nodal burdens following RC. This information would prove useful in identifying patients that would most likely benefit from chemotherapy in the postoperative setting. It also highlights the importance of a meticulous pelvic lymph node dissection at the time of RC and the need for careful processing and reporting of nodal tissue as this information may not only direct future therapy with regard to AC protocols, but is also useful in counseling patients about prognosis and potential response to chemotherapy.

This study has several limitations including its retrospective design, lack of randomization and the small number of node positive patients who underwent AC. Given the lack of randomization, there is likely selection bias in lymph node positive patients who underwent chemotherapy as evidenced by the significant proportion of older patients in the non-chemotherapy group. Patients received chemotherapy from a number of different oncologists from several centers without standardization of AC regimens. This fact also made it impossible to calculate time from RC to AC administration and exact dosage of chemotherapy as this data was often not available. Given these significant limitations, it is difficult to draw definitive conclusions regarding the impact of AC in patients with node positive disease at the time of RC. It does appear in this retrospective study that patients with LND < 20% who undergo cisplatin-based AC do experience better outcomes. This study highlights the need for larger prospectively designed trials in patients with high risk features after RC to further define the role of AC.

Conclusion

Adjuvant cisplatin-based chemotherapy appears to be associated with a significant improvement in RFS, DSS and OS rates in patients with lymph node positive urothelial cancer following radical cystectomy. Patients with lower nodal metastasis burdens (< 20%) at the time of RC appear to benefit the most. Larger, prospective trials are needed to further define the role of AC in patients with high risk pathologic features. □

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