The role of pelvic lymphadenectomy in non-muscle invasive bladder cancer

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Introduction: *We evaluated whether the extent of lymphadenectomy at the time of radical cystectomy for non-muscle invasive bladder cancer (NMIBC) impacts recurrence free survival.*

Materials and methods: *We conducted an IRB approved retrospective analysis of patients with clinical NMIBC who underwent radical cystectomy from 1990-2010. Patients were stratified based on extent of lymph node dissection using total lymph node yield as a surrogate indicator of lymph node dissection extent, with cut off analyses performed at 0, 8, 10, and 20 nodes removed. Analyses of recurrence free survival (RFS) were performed using log-rank analysis and multivariate Cox regression.*

Results: *One hundred and ninety-six patients with NMIBC met the inclusion criteria for this study, with no differences in RFS detected in those who had ≥ 10 nodes compared to < 10 nodes removed (p = 0.63). Upon multivariate analysis, ≥ 10 nodes removed (HR 1.00; p = 0.99) was not significantly associated with decreased RFS, while high grade tumor (HR 3.22; p = 0.05) and positive margin status (HR 3.87; p = 0.04) were. The median number of nodes removed was 8 (range 0-45), with no difference in RFS using this as a cut off point (p = 0.19). The removal of ≥ 20 nodes did not predict worse survival compared to < 20 nodes removed (p = 0.07).*

Conclusions: *Although the extent of lymphadenectomy has been associated with improved survival in patients undergoing radical cystectomy for muscle invasive bladder cancer, we were unable to detect an impact of lymph node dissection extent on RFS in patients with NMIBC. This finding emphasizes that when determining extent of lymph node dissection in radical cystectomy, one size does not fit all.*

Key Words: lymphadenectomy, NMIBC, bladder cancer

Introduction

Non-muscle invasive bladder cancer (NMIBC) (pTa, pT1, carcinoma in situ), a chronic disease with high rates of recurrence, accounts for 75% of new bladder cancer diagnosis.[1] In NMIBC, about 70% of patients present as pTa, 20% as pT1, and 10% with carcinoma in situ.[2] Primary treatment for NMIBC is transurethral resection of the bladder tumor (TURBT), which is often followed by intravesical chemotherapy or immunotherapy with mitomycin C or bacillus Calmette-Guerin (BCG).[3]

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Radical cystectomy is generally reserved for patients with high risk NMIBC who choose to receive early definitive surgical intervention, for those who have failed intravesical therapy, and for those who have progressed to muscle invasive disease.[4,5] It is widely accepted that radical cystectomy with a pelvic lymph node dissection provides excellent control and long term survival for patients with localized bladder cancer.[6-9] While patients with muscle invasive bladder cancer have been shown to have improved clinical outcomes when a more extensive dissection is performed, little is known about the interaction between extent of lymph node dissection and outcome for those with NMIBC.[10] Patients with treatment refractory NMIBC for whom radical cystectomy are indicated likely present with more aggressive phenotypes that may benefit from standard lymphadenectomy.[11] Additionally, patients with NMIBC have been shown to have a significantly lower incidence of positive lymph nodes.[12] Although anatomic extent of lymph node dissection has varied widely over the past two decades, currently a minimum of 10 lymph nodes removed has been suggested as the definition of an adequate

lymph node dissection for patient undergoing radical cystectomy for muscle invasive bladder cancer.[6,13] We therefore, chose to explore the outcomes of patients with NMIBC who have undergone a widely variable extent of lymph node dissection over the past two decades at our institution.

Materials and methods

A retrospective review of the institutional review board approved Columbia University urologic oncology outcomes program was conducted with the eligibility criteria limited to patients with clinical TNM stage Tis, Ta, or T1, N0, M0 urothelial bladder cancer. NMIBC is defined as being confined to the mucosa or invading the lamina propria but not yet invading the detrusor muscle. Clinical staging was based on TURBT pathology, exam under anesthesia, and preoperative imaging results. Staging was defined according to the 7th edition of the AJCC/UICC guidelines. Patients who received neoadjuvant, adjuvant, or no chemotherapy were included.

All surgeries were performed by 1 of 12 urologic surgeons from 1990-2010. There was no established template used during lymphadenectomy. The extent and boundaries of lymph node removal likely varied over time, were determined at the discretion of the surgeon, and were not always clear in the operative report. For the purposes of this retrospective review lymph node dissection was divided into two categories: removal of ≥ 10 lymph nodes, or removal of 0-9 lymph nodes.

The pathologic protocol for processing lymph nodes is as follows: the lymph nodes are identified by palpation of the submitted specimen, excised from the surrounding adipose tissue, and then enumerated. The remaining tissue undergoes microscopic review to identify non-palpable nodes. All pathological data utilized were not re-reviewed for purposes of this study. Postoperatively patients were followed using radiographic imaging, routine laboratory examination, physical exam and pathological analysis at the discretion of their physician.

Patients included in the study had at least 12 months of follow up post-cystectomy, with recurrence free survival (RFS) defined as the number of the months after cystectomy without disease recurrence. If there was no recurrence, RFS was defined as the time from cystectomy until the latest known visit as of May 2012. Kaplan-Meier survival curves were used to detect variation in RFS, and comparisons between groups were made by the log-rank test. Multivariate Cox hazard models were used to analyze factors associated with RFS, including age, race, clinical T stage, margin status, tumor grade, and number of nodes removed (< 10 versus ≥ 10 nodes). The same analyses were conducted for the median number of nodes removed (< 8 versus ≥ 8 nodes, 0 versus > 0 nodes, and < 20 versus ≥ 20 nodes). All p values reported are two sided and statistical significance is defined as $p \leq 0.05$. All analyses were performed with Stata 11.0 SE (StataCorp LP, College Station, TX, USA).

Results

A total of 196 patients met the inclusion criteria of clinical NMIBC and underwent radical cystectomy from 1990-2010 at our institution. Of these, 53 (27%) patients were upstaged (≥ pT2) upon final cystectomy pathology (cTis: 6/33, cTa: 3/32, cT1: 44/131), with 13 patients having node positive disease (pN+) upon pathologic staging at cystectomy. The overall positive margin rate was 8/196 (4.1%). The distribution of demographic and clinical characteristics between those with < 10 nodes and those with ≥ 10 nodes are shown in Table 1, with no significant differences between the two groups. The median follow up time was 75.0 months for those with <10 nodes and 54.6 months for those with ≥ 10 nodes.

Log-rank Kaplan Meier analysis yielded no differences in RFS regardless of nodal count (p = 0.63), Figure 1. Table 1 shows the multivariate Cox proportional hazards model, demonstrating that ≥ 10 nodes removed was not significantly associated with RFS (HR 1.00; 95% CI 0.51-1.95; p = 0.99). Positive margins on cystectomy pathology (HR 3.87; 95% CI 1.09-13.71; p = 0.04), Hispanic race (HR 3.86; 95% CI

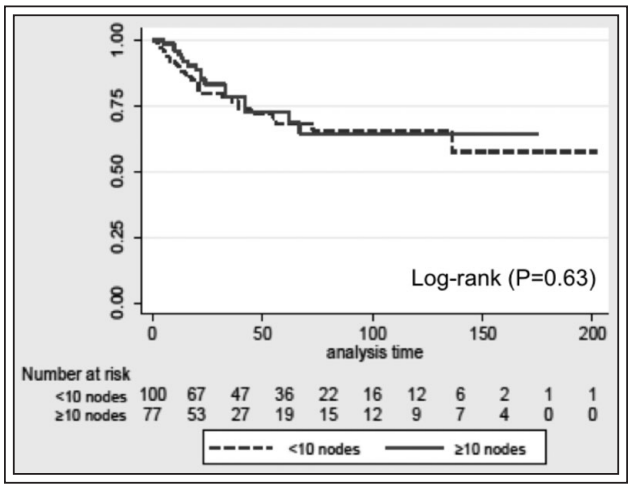

Figure 1. Kaplan-Meier survival analysis of recurrence free survival.

TABLE 1. **Multivariate Cox hazard analysis of factors associated with decreased recurrence free survival with < 10 nodes and ≥ 10 nodes removed**

	Hazard ratio (HR)	Confidence interval (CI)	p value
Age	1.02	0.98-1.05	0.35
Race (ref: White)			
Hispanic	3.86	1.51-9.84	0.005
Black	2.24	0.65-7.80	0.20
Other	1.36	0.31-6.03	0.69
Clinical T stage (ref: Ta)			
Tis	0.45	0.15-1.35	0.16
T1	0.41	0.19-0.86	0.02
Positive final margin	3.87	1.09-13.71	0.04
High grade	3.22	0.98-10.55	0.05
Number of nodes (< 10 versus ≥ 10)	1.00	0.51-1.95	0.99

1.51-9.84; p = 0.005), and high grade tumor (HR 3.22; 95% CI 0.98-10.55; p = 0.05) are significantly associated with decreased RFS. Clinical stage T1 (HR 0.41; 95% CI 0.19-0.86; p = 0.02) was associated with increased RFS.

Only 2/196 (1%) patients were treated with neoadjuvant chemotherapy, while 23/196 (11%) patients were treated with adjuvant chemotherapy. Since only 25 of the 196 patients received perioperative chemotherapy, models of the effect of chemotherapy on RFS would not be valuable or fully represent the role of chemotherapy in this small group.

The median number of nodes removed was 8 (range 0-45 nodes). When using 8 as a cut off value for number of nodes dissected, the log rank test showed no difference in RFS (p = 0.19). In a comparison of patients with > 0 nodes (n = 182) versus those with 0 nodes (n = 14) removed, log-rank test again revealed no differences in RFS (p = 0.16).

Twenty-one patients had ≥ 20 nodes removed, while 175 patients had < 20 nodes removed. Baseline characteristics of these two groups of patients are outlined in Table 2. No characteristics were significantly

TABLE 2. **Baseline characteristics of groups with < 10 versus ≥ 10 nodes removed and < 20 versus ≥ 20 nodes removed**

Characteristic	< 10 nodes	≥ 10 nodes	p value	< 20 nodes	≥ 20 nodes	p value
N	109	87		175	21	
Mean age (yrs)	68	68	0.80	68	67	0.72
Sex—no. (%)			0.57			0.40
Male	84 (77.1)	70 (80.5)		136 (77.7)	18 (85.7)	
Female	25 (22.9)	17 (19.5)		39 (22.3)	3 (14.3)	
Race—no. (%)			0.42			0.81
White	82 (75.2)	73 (83.9)		138 (78.9)	17 (80.9)	
Hispanic	11 (10.1)	7 (8.0)		17 (9.7)	1 (4.8)	
Black	9 (8.3)	3 (3.4)		10 (5.7)	2 (9.5)	
Other	7 (6.4)	4 (4.6)		10 (5.7)	1 (4.8)	
Clinical stage—no. (%)			0.52			0.05
Ta	20 (18.3)	12 (13.8)		32 (18.3)	0 (0)	
Tis	16 (14.7)	17 (19.5)		27 (15.4)	6 (28.6)	
T1	73 (67.0)	58 (66.7)		116 (66.3)	15 (71.4)	

TABLE 3. **Multivariate Cox hazard analysis of factors associated with decreased recurrence free survival with < 20 nodes and ≥ 20 nodes removed**

	Hazard ratio (HR)	Confidence interval (CI)	p value
Age	1.02	0.98-1.06	0.31
Race (ref: White)			
Hispanic	4.34	1.69-11.15	0.002
Black	2.46	0.73-8.32	0.15
Other	1.37	0.31-6.04	0.68
Clinical T stage (Ref: Ta)			
Tis	0.37	0.12-1.14	0.08
T1	0.36	0.17-0.77	0.01
Positive final margin	3.66	1.01-13.24	0.05
High grade	3.30	1.01-19.76	0.05
Number of nodes (< 20 versus ≥ 20)	2.70	0.98-7.37	0.05

different except for T stage, with no Ta patients in the ≥ 20 nodes dissected group (p = 0.05). Upon log-rank Kaplan Meier analysis, a dissection of ≥ 20 nodes did not predict a worse survival compared to those with < 20 nodes removed (p = 0.07). A multivariate Cox proportional hazards model shown in Table 3 demonstrated that ≥ 20 nodes removed was associated with an increased risk of cancer relapse even when controlling for stage (HR 2.70; 95% CI 0.98-7.37; p = 0.05). Hispanic race (HR 4.34; 95% CI 1.69-11.15; p = 0.002), positive final margin (HR 3.66; 95% CI 1.01-13.24; p = 0.05), and high grade tumor (HR 3.30; 95% CI 1.01-19.76; p = 0.05) were associated with decreased RFS. Clinical stage T1 (HR 0.36; 95% CI 0.17-0.77; p = 0.01) was associated with increased RFS.

Discussion

As there are no guidelines for the extent of lymphadenectomy when performing a radical cystectomy in patients with NMIBC, it is critical to understand how surgical factors may affect the outcome of disease. This study represents the first to analyze the impact of lymph node yield in clinically node negative NMIBC patients, and our results largely demonstrated that the extent of lymphadenectomy is not associated with RFS.

For patients with stage < pT3a bladder cancer without pretreatment, an extensive pelvic lymph node dissection from the external iliac vessels to the bifurcation of the aorta improves survival, likely because a more comprehensive dissection results in the excision of a greater number of lymph nodes.[14] This increases the sensitivity in detecting lymph node metastasis. However, the reason for the inability of lymph node yield to significantly predict survival outcome in our results can be explained by the differences in the patients included in this study, as we incorporated patients only with clinical NMIBC disease regardless of prior treatment status. Nodal yield is influenced by the surgical technique used, which likely varied according to the surgeon performing the radical cystectomy. Even despite equal anatomic clearance during lymphadenectomy by the same surgeons practicing at two different hospitals, each hospital reported significantly different nodal yields.[15] For instance, it is difficult to differentiate fatty lymph nodes from adipose tissue, indicating that there are fundamental differences in surgical specimen evaluation at pathology departments. These variations make it difficult to standardize lymph node yield, which means that number of lymph nodes removed should not be relied upon as a perfect surrogate to indicate extent of operation or surgical quality until standardized methods are agreed upon.15 Anatomic boundaries of dissection, while not perfect, seem to be a better indicator of therapeutic effectiveness compared to nodal yield.[16] Unfortunately, when conducting retrospective outcomes research in this area, total lymph node yield is the only measure of lymphadenectomy extent.

The decreased RFS of those with ≥ 20 nodes removed upon Cox hazard ratio analyses may be accounted for by the differences in clinical T staging at baseline, as no patients had Ta disease and ≥ 20 nodes removed. The relatively fewer subjects in the group that had ≥ 20 nodes removed (n = 21) also predisposes to Type I

error. Thus, it is likely that ≥ 20 nodes dissected truly represents a surrogate for more aggressive disease and a higher degree of concern by the operating surgeon.

As no differences in RFS were shown when using 0, 8, or 10 nodes as cut off points, our results indicate that lymph node yield may not have a direct impact on RFS in patients undergoing cystectomy for NMIBC. Furthermore, the lack of a significant difference in survival in 0 versus > 0 nodes removed brings into question whether or not a lymphadenectomy should be even required in patients with clinically node negative NMIBC. Other studies have demonstrated increased probability of survival when the number of lymph nodes removed increases, even though no minimum number of lymph nodes could be determined.[16] However, clinical factors such as tumor stage were not adjusted for, making it difficult to generalize these findings for NMIBC. Shariat et al found that in patients with clinical Ta-Tis disease, at least six lymph nodes need to be removed to achieve 90% confidence that the patient is node negative.[17] The minimum number needed for cT1 patients was 10 nodes. However, no long term survival analyses were performed, so these results cannot be extrapolated directly to survival outcomes.

There may be numerous contributing explanations for the inability to use lymph node yield as a predictor for survival in NMIBC. The likelihood of detecting metastatic lymph node disease increases with the number of lymph nodes examined in pT3 and pT4 disease, but not in lower disease stages.[18] Additionally, it has been found that up to 20% of cases classified as N0 are shown to have micrometastases in the lymph nodes after thorough re-examination of recovered lymph nodes.[19] If this is the case, then it is possible that some NMIBC patients did not have correct nodal staging on final pathology, thus underestimating the value of the lymph node dissection in removing disease.

The foremost limitation of this study is the lack of information related to preoperative planning or intraoperative decision-making by the surgeon to determine the extent of the node dissection performed. For instance, surgeons may have extended the lymphadenectomy for their patients thought to be at highest risk for nodal involvement. Although central pathology review was not performed, this reflects the real world variations in analysis of lymph nodes by pathologists at academic centers such as ours.

Conclusions

This study is the first to evaluate the value of lymph node dissection for clinical NMIBC node negative patients. While increased lymphadenectomy yield is an indicator of improved survival in muscle invasive disease, our results suggest that this surgical procedure offers no survival advantage for clinically node negative patients with NMIBC. While the urologic oncology community awaits the results of the SWOG S1011 randomized trial of "standard" versus "extended" lymph node dissection for muscle invasive bladder cancer, no such trial exists for NMIBC and is unlikely to be performed. To more fully address this question, other institutions will need to review and report on their patients NMIBC. The therapeutic extent of lymphadenectomy remains to be defined in clinical NMIBC, as it is clear that one size does not fit all. □

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