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# Lymph node density in muscle-invasive transitional cell carcinoma of the urinary bladder; *De novo* versus progressive disease

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## ABSTRACT

**Objective:** The prognosis of bladder cancer patients with positive lymph node (LN) disease is affected by both the extent of lymphadenectomy and LN density retrieved during radical cystectomy. This study aimed at assessing the differences in LN metastasis between patients who presented primarily with muscle-invasive transitional cell carcinoma of the bladder "*de novo* disease" versus "progressive disease." The latter is defined as patients who progressed to muscle-invasive bladder cancer (MIBC) following prior conservative management of a non-muscle-invasive disease.

**Methods:** Data were prospectively collected from consecutive 41 radical cystectomies that were divided into two groups: Group I included *de novo* MIBC cases and Group II included progressive MIBC cases.

**Results:** The median age was 60 years (44-75). Thirty-four patients exhibited *de novo* disease versus 7 patients who presented as progressive MIBC with a median duration of 9 months between the resection of the first non-invasive tumor and the diagnosis of progressive MIBC (range: 6-56 months). The median number of retrieved LNs in both groups was 15 LNs (range: 4-36). Ten patients (24.39%) had positive pathological LN disease; distributed as 9 patients in Group I and 1 patient in Group II. The median LN density of LN-positive patients was 15.73% (6.46 % in Group I, 28.57% in Group II). Five patients had LN density >20%.

**Conclusion:** Although non-muscle-invasive urothelial bladder tumor may progress to muscle-invasive disease, it still carries less aggressive course than *de novo* MIBC based on differences in LN metastasis and density.

**Keywords:** Bladder cancer, lymph node density, non-muscle-invasive bladder tumor, progressive muscle-invasive bladder tumor

## Introduction

Urinary bladder cancer (BCa) is the most common urinary tract malignancy, with transitional cell carcinoma (TCC) being the most common pathologic subtype. Approximately, 15% of patients who present with muscle-invasive bladder cancer (MIBC) have a history of non-muscle-invasive cancer.[1] However, most of the diagnosed cases of MIBC (80% to 90%) present *de novo* (i.e., without history of non-invasive disease).[1]

Radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND) remains the gold standard treatment of MIBC,[2] which comprises 25% of BCa patients.[3] Approximately, 25% of patients, who undergo RC for clinical N0M0 disease, present with LN-positive disease according to pathologic staging.[4] The goal of PLND during the radical surgery is to remove the regional LN, particularly the typically affected sites.[4,5]

Herr[6] and Stein *et al*.[7] first described the concept of lymph node (LN) density for BCa, which is the number of LNs containing metastatic deposits divided by the total number of nodes removed and examined. It takes into account two important prognostic factors; the LN tumor burden and the meticulousness/extent of the LN dissection.[8]

Recently, it has been stated that extranodal extension in LN-positive patients, who underwent RC for urothelial MIBC, is an independent predictor of both cancer recurrence and cancer-specific mortality.[9] This finding, together with final histopathological results and the extent of LN removal, may help with clinical decision of enrollment of such patients in trials of adjuvant therapy together with tailored follow-up post RC.[9]

The aim of our series was to study the possible differences of LN metastasis in muscle-invasive TCC of urinary bladder between *de novo* and progressive MIBC disease.

## Methods

The study was designed as a prospective consecutive study in which clinical and histopathological data were gathered from 41 patients who presented to our tertiary center with muscle-invasive TCC of the urinary bladder between May 2013 and November 2014. All patients underwent RC with bilateral standard PLND after full informed consent. This study was reviewed and approved by the research ethics committee of the Alexandria University. Each patient was subjected to detailed history taking (BCa risk factors, previous transurethral resection [transurethral resection of bladder tumor (TURBT)], and intravesical therapy), clinical examination, laboratory workup, performance status assessment, radiological evaluation (multiphasic computed tomography ± magnetic resonance imaging), and bimanual examination under anesthesia. Patients who received neoadjuvant chemotherapy were excluded from the study.

Patients were divided into two groups:

- Group I *de novo* MIBC: Included 34 patients who presented primarily with muscle invasive TCC of the bladder.
- Group II progressive MIBC: Included 7 patients who progressed to MIBC following prior history of conservative treatment for non-muscle-invasive disease (NMIBC). All patients underwent RC after stage pT2 disease had been documented pathologically from the specimen collected at the last TURBT.

High volume surgeons (3 surgeons) performed RC and bilateral standard PLND. The cystectomy specimen and dissected LNs were sent in separate labeled bottles to a single experienced uropathologist. Pathologic evaluation fulfilled the following points: BCa stage, grade, pathologic subtype, total number of retrieved LNs, and number of positive LNs, if any. LN density was calculated using the following formula: Number of positive LNs times 100 divided by the total number of removed LNs.

## Results

Our series included 41 patients with mean age of 58.90 ± 7.10 years (44-75). Table 1 describes the demographic criteria and performance status of both studied groups. Thirty-four patients (83%) exhibited *de novo* MIBC Group I. Group II included 7 patients (17%) who started with NMIBC disease and progressed to MIBC. Both groups were matched for age, sex, and Karnofsky performance status. In Group II, the median and mean duration between the resection of the first non-invasive tumor and the diagnosis of stage ≥T2 disease was 9 and 17.85 ± 16.64 months, respectively (range 6-56 months).

The initial tumor grade and stage in the progressive group were low-grade papillary pT1 in one patient, high-grade non-papillary pT1 in 5 patients, and extensive dysplasia with carcinoma *in situ* in another patient. All patients with progressive MIBC received at least one course (6 doses) of intravesical Bacillus Calmette-Guerin therapy. However, none of them received maintenance doses.

Fifteen patients (15/34) were staged as pT2 in Group I versus 4 patients (4/7) in Group II. Nineteen patients (19/34) in Group I were staged as >pT2 versus 3 patients (3/7) in Group II. The mean number of overall retrieved LNs was 16.70 ± 8.72 (4-36). Group I showed 9 patients with positive LNs representing 21.95% (9/41) of the whole cohort. Four had single regional LN metastasis (pN1) while the other five were staged as (pN2). Group II showed only one patient who had nodal metastasis (Table 2). All positive LNs showed subcapsular sinusoidal involvement. Negative LNs showed reactive follicular hyperplasia and sinus histiocytosis.

The mean and median LN density of pN+ patients was 22.79% ± 21.78 and 15.73%, respectively (range: 4-70.6%). Using LN density with a cutoff value of 20%, which revealed an independent influence on cancer specific survival, 5 out of 10 pN+ patients displayed LN density >20%. Table 3 shows the comparison between the two studied groups according to total number of dissected LNs, tumor-positive LNs, and LN density. Table 4 illustrates pathological characteristics of patients with LN disease at cystectomy.

## Discussion

To the best of our knowledge, the current prospective study is the first to investigate the difference of LN density between *de novo* and progressive muscle-invasive TCC of the urinary bladder. We were only concerned to study LN malignant infiltration in both groups to clarify the actual need of neoadjuvant chemotherapy for either disease entity; *de novo* or progressive urothelial MIBC before RC.

Neoadjuvant chemotherapy is recommended in patients with clinically operable, muscle-invasive N0 M0, urothelial BCa before definitive surgery.[10] There are many advantages of neoadjuvant chemotherapy. It is delivered at the earliest time-point when the low burden of micrometastatic disease is expected. Tolerability of chemotherapy is expected to be better before cystectomy rather than after. Micrometastatic disease might respond to neoadjuvant therapy and reveal favorable pathologic status including negative LN status and negative surgical margins.[11-13] However, there are also potential disadvantages of neoadjuvant chemotherapy including that approximately 50% of clinically N0 M0 patients are without micrometastatic disease, thus receiving unnecessary treatment. Furthermore, the delay in RC may compromise outcomes in non-chemotherapy-responsive patients.[11-13]

**Table 1:** Demographic criteria and performance status (%) of both study groups

| Variable | Total (*n*=41) | Group I "*de novo*" (*n*=34) | Group II "progressive" (*n*=7) |
|---|---|---|---|
| Age (years) | | | |
| Range | 44.0-75.0 | 44.0-75.0 | 52.0-61.0 |
| Mean±SD | 58.90±7.10 | 59.21±7.57 | 57.17±3.25 |
| Median | 60.0 | 60.0 | 57.0 |
| Sex | | | |
| Male | 36 | 29 | 7 |
| Female | 5 | 5 | 0 |
| Performance status (%) | | | |
| Range | 80.0-90.0 | 80.0-90.0 | 80.0-90.0 |
| Mean±SD | 85.50±5.04 | 85.29±5.07 | 86.67±5.16 |
| Median | 90.0 | 90.0 | 90.0 |

SD: Standard deviation

**Table 2:** Comparison between the two studied groups according to pT and pN stages

| Variable | Total | Group I "*de novo*" | Group II "progressive" |
|---|---|---|---|
| pT stage | | | |
| $pT_2$ | 19 | 15 | 4 |
| $>pT_2$ | 22 | 19 | 3 |
| pN stage | | | |
| $pN_0$ | 31 | 25 | 6 |
| $pN_1$ | 4 | 4 | 0 |
| $pN_2$ | 6 | 5 | 1 |

pT: Pathological tumor, pN: Pathological nodal

**Table 3:** Comparison between the two studied groups according to total number of dissected LNs, tumor-positive LNs, and LN density

| Variable | Total | Group I "de novo" | Group II "progressive" |
|---|---|---|---|
| Total excised LNs | | | |
| Range | 4-36 | 4-34 | 7-36 |
| Mean±SD | 16.80±8.63 | 16.47±8.50 | 18.43±9.80 |
| Median | 15 | 16 | 15 |
| Tumor-positive LNs | | | |
| Range | 1.0-13.0 | 1.0-13.0 | 6.0 |
| Mean±SD | 4.50±4.38 | 4.33±4.61 | - |
| Median | 3.0 | 2.0 | - |
| LN density (%) | | | |
| Range | 4-70.6 | 4-70.6 | 28.57 |
| Mean±SD | 22.79±21.78 | 22.13±23.0 | - |
| Median | 15.73 | 6.46 | - |

LN: Lymph node, SD: Standard deviation

A population-based study of the effect of neoadjuvant chemotherapy on perioperative outcomes in BCa patients, treated with RC, revealed neoadjuvant chemotherapy, when compared to RC alone, is not associated with higher perioperative morbidity or mortality.[14] Our prospective study revealed significant difference in LN metastasis of *de novo* compared to progressive invasive tumors (26.5% and 14.3%, respectively). Based on this result, neoadjuvant chemotherapy may be considered as overtreatment for progressive invasive patients; however, a larger cohort study is recommended to justify such statement.

Many clinical studies evaluated the prognosis of patients with muscle-invasive TCC after RC. However, only few series studied the prognostic difference between *de novo* and progressive MIBC tumors. Still, patients with *de novo* and progressive MIBC are treated equally in normal daily practice where RC and bilateral PLND remain the gold standard. In 2001, Vaidya *et al.*[15] found a 2-year survival rate of 49% for those with *de novo* invasive tumors and 79% for those with progressive lesions. However, in 2003, these data were challenged by Schrier *et al.*[1] who found a statistically significant decreased survival for patients with progressive tumors (the 3- and 5-year survival rates are 67% and 55%, respectively, for patients with a primary invasive tumor and 37% and 28%, respectively, for patients with a progressive invasive tumor).

In 2004, May *et al.*[16] found the overall survival rate after 3 and 5 years was 59% and 50% for progressive tumors and 52% and 46% for *de novo* tumors. They did not observe any statistically significant difference between these parameters concluding that progressive tumors do not have a better prognosis than initially muscle-invasive tumors. In 2007, Türkölmez *et al.* could not reveal a significant difference between the two groups. Two-year cancer-specific survival rate for the *de novo* and progressive tumors was 75% and 72%, respectively. During follow-up, they mentioned that the decrease in the survival rate was greater in the progressive group although no statistical significance was observed (5-year cancer-specific survival rate of 54% and 43%, respectively).[17]

In 2012, Kotb *et al.* conducted a retrospective study on 1150 patients and concluded that patients with progressive MIBC had better clinical and pathological outcomes than patients

**Table 4:** Pathological characteristics of patients with LN disease at cystectomy

| Pathological stage | Patients with positive nodal status | Excised | Positive | LN density % |
|---|---|---|---|---|
| pT2a N2 | 1, *de novo* | 10 | 4 | 40 |
| pT2b N2 | 2, *de novo* | 17 | 12 | 70.6 |
| | | 31 | 2 | 6.46 |
| | 1, Progressive | 21 | 6 | 28.57 |
| pT3a N1 | 2, *de novo* | 15 | 1 | 6 |
| | | 18 | 1 | 5.5 |
| pT3b N1 | 1, *de novo* | 18 | 1 | 5.5 |
| pT3b N2 | 1, *de novo* | 14 | 5 | 35.7 |
| pT4a N1 | 2, de novo | 4 | 1 | 25 |
| | | 25 | 1 | 4 |

LN: Lymph node

presenting with *de novo* MIBC.[18] All aforementioned studies were retrospective. The current study is a prospective one, and it revealed that LN metastasis was readily more identifiable in the *de novo* MIBC. However, it is noteworthy that the group of progressive MIBC included a single pN+ patient who initially presented with high-grade non-papillary pT1 BCa.

The LN positive status was studied also by El-Abbady *et al*.[19] They compared 16 patients with progressive MIBC with 20 patients who were diagnosed with *de novo* MIBC, all undergoing cystectomy. On meticulous histopathological examination, they found that patients who underwent previous transurethral resections had significantly more local spread of malignant cells into the bladder muscle as compared to patients with *de novo* invasive tumors. Since they could demonstrate that intravesical pressure reaches pressures as high as 80 cm water, they suggested some malignant cells penetrate through the denuded urothelium during resection as a result of high intravesical pressures.

Various studies pointed to the prognostic value of LN density in MIBC. LN density is stated to be superior to TNM nodal status in predicting disease-specific survival following RC for BCa.[20] Because the number of nodes excised and pathologically examined may directly influence the TNM nodal stage and the absolute number of positive LNs, LN density is thought to be a superior prognostic factor that is less influenced by confounding from the number of reported LNs. We used a cutoff value of 20% for LN density to stratify pN+ patients into two groups, either >20% or <20%. Five patients had LN density >20%, and the only pN+ progressive case showed density of 28.57%.

## Conclusion

Although non-muscle-invasive urothelial bladder tumor may progress to a muscle-invasive disease, it still may carry less aggressive course rather than *de novo* MIBC based on the difference in risk of LN metastasis and density.

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