AIM OF THE WORK

The aim of the work was to study the nature of LN metastasis in urothelial MIBC, both the de novo and the progressive disease, focusing on LN density parameter.

PATIENTS

The study was designed as a prospective study in which clinical and pathological information was gathered from 41 consecutive patients, presented with pathologically proven muscle-invasive TCC of the urinary bladder on TURBT before RC. Patients who received neoadjuvant chemotherapy were excluded from the study.

Classification of the patients

Patients were divided into two groups:

Group I ‘’de novo MIBC”: included 34 patients who presented with primary invasive TCC of urinary bladder, T2 or higher MIBC whether clinical and /or pathological.

Group II “Progressive MIBC”: included 7 patients who progressed to MIBC following prior history of conservative treatment for non-muscle-invasive tumors with TURBTs and BCG immunotherapy.

METHODS

Evaluation of the patients

After taking full informed consent, all patients in this study were subjected to the following:

1. Pre-operative evaluation:

A. History: including

- Personal and demographic data including; gender, age at presentation of muscle-invasive disease and hometown.
- Risk factors of BC including tobacco smoking and occupational hazards.
- Onset and mode of clinical presentation.
- Medical co-morbid conditions, if any.
- Past history of any surgical intervention.
- Detailed history of previously done TURBTs regarding time, number, frequency, histopathology of the resected tissues and intravesical chemotherapy or BCG.

B. Clinical assessment: included general examination, performance status (using Karnofsky performance status scale) and DRE.

C. Routine laboratory investigations and cardiac assessment: including

Complete blood count, fasting blood sugar level, serum creatinine level, blood urea nitrogen, serum albumin, liver enzymes, prothrombin time and activity, urine analysis, urine culture and sensitivity and serum total PSA.

ECG was done to all cases and ECHO was done when recommended.

D. Radiologic evaluation: including multiphasic CT and/or MRI of abdomen and pelvis, to assess local tumor staging and LN involvement.

2. Operative evaluation: including

a. Biamanual examination under general anesthesia for local tumour assessment.
b. All patients underwent RC, standard bilateral pelvic LND dissection and urinary diversion. The cystectomy specimen and resected LN were packed and sent in labeled separate bottles to the pathology laboratory.

3. Postoperative evaluation: including

A. Group description

Our series included 41 patients and were classified into two groups:

a. Group I: 34 patients with de novo muscle-invasive bladder tumours. This group included patients in whom invasion into the muscle layer was detected at the primary TURBT.

b. Group II: 7 patients with muscle-invasive tumours in whom progression from a non-muscle-invasive to muscle invasion had been identified. The diagnosis of non-muscle-invasive tumor was done by revision of the pathology reports of previous TURBTs.

B. Histopathology and LN examination: including

All histopathology reports were based on the 2009 TNM classification, 7th edition.

a. Cystectomy specimen: Including gross and microscopic description and reporting the tumour stage, grade, pathologic subtype and the safety margins.
b. LN examination: including

Pathologic LN dissection as the following steps:

1) Fixation overnight in formalin and search for the LN the next day.
2) Description of the number of LN, size of the largest node in each group.
3) Appearance; obvious involvement by the tumour.
4) All LN were submitted for microscopic examination.
5) Cross-sections of LN, including at least protion of capsule: one to three sections depending on size of the node.
6) Small LN (up to 3 mm in thickness after fat is removed) were submitted as a single piece.
7) Large LN were bisected and if necessary further sectioned into 2-3 mm slices.
8) Storage of the remainder in the formalin container properly identified as belonging to LN group.

LN reporting as following

1) The number of LN positive for metastatic disease and the total number of LN examined were reported.
2) The size of the largest metastasic LN.
3) **Calculation of LN density:** was calculated using the following formula: number of positive LN times 100 divided by the total number of removed LN.

Methods of statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Comparison between different groups regarding categorical variables was tested using Fisher's Exact test. The distributions of quantitative variables were tested for normality. For non-categorized variables, comparison between two independent populations was done using Mann Whitney test.

RESULTS

This study was carried out on 41 patients presented with muscle invasive TCC of the urinary bladder who underwent RC with standard bilateral pelvic LND. All available pre-operative, intra-operative, and post-operative data were collected, tabulated and analyzed. The following data were studied:

A. Age, sex and performance status

Both groups were comparable as regard age, sex and performance status **(Table III).** Median age of patients was 60 years at time of RC, 60 years and 57 years for group I and group II, respectively.

Thirty-six (88%) patients were males. All patients in group II were males while only 5 patients in group I were females.

Median performance status of all patients, using Karnofsky scale, was 90.

B. Clinical course of progressive group

Patients who presented with MIBC were divided into two groups according to clinical course whether de novo or progressive (Figure 5). Regarding progressive group, median and mean duration between the resection of the first non-muscle-invasive tumour and the diagnosis of stage T_2 disease was 9 and 17.85±16.64 months respectively (range: 6-56 months).

The initial tumour stage in the progressive group was low grade papillary pT_1 in 1, high grade non-papillary pT_1 in 5 and extensive dysplasia with Cis in 1 patient. All progressive patients received induction 6 doses of BCG, however, no single patient received maintenance BCG therapy due to either unavailability especially during the revolution events or unaffordable by other patients.

C. TNM staging and LN disease

The histopathologic characteristics after examination of the cystectomy specimen and excised LN of both groups are shown on table (III). Staging was based the TNM classification, 7^{th} edition. As regard tumour stage, 19 patients (46 %) were pT_2 while the remaining were $>pT_2$ disease.

Nodal staging revealed that 31 patients were free of LN metastasis (25 patients in group I and 6 patients in group II). Stage pN_1 was identified in 4 patients, all from group I, while pN_2 was diagnosed in 6 patients (5 patients from group I and 1 patient from group II).

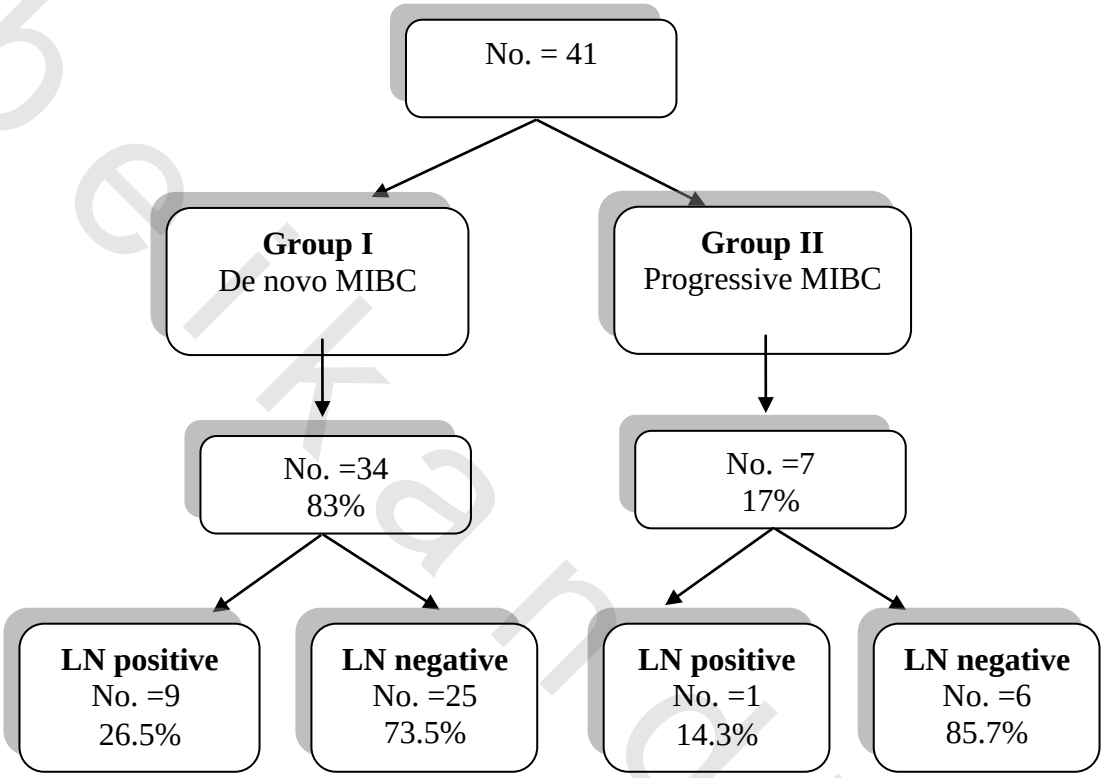


Figure (5): Study design.

Table (III): Clinical and histopathological description of both study groups.

variable	Total (No= 41)	Group I 'de novo' (No. = 34)	Group II ' progressive' (No.= 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
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
Total LN			
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
Tumour positive LN			
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	-

Mean and median number of retrieved LN in all patients was 16.80 ± 8.63 and 15 LN, respectively (range: 4-36 LN). Both de novo and progressive cases were comparable as regard total number of retrieved LN (mean number of retrieved LN was 16.47 ± 8.50 vs 18.43 ± 9.80, for group I and II respectively).

Of all series, only 10 patients (24.39 %) exhibited nodal metastasis where 9 out of 34 patients in de novo group and only 1 out of 7 patients in progressive group. Statistically, there was no significant difference between the two groups as regard LN metastasis (26.5% of de novo vs. 14.3% of progressive, p = 0.660). Examples of histopathological images of LN are shown on figures (6- 9).

Table (IV): Comparison between the two studied groups according to total number of dissected LN, tumor positive LN and LN metastasis.

Variable	Total (No. = 41)	De novo (No. = 34)	Progressive (No. = 7)	P value
Total number of dissected LN				
Median	15.0	16.0	15.0	0.627
Tumor positive LN	**(No. = 10)**	**(No. = 9)**	**(No. = 1)**	
Median	3.0	2.0	6.0	-
LN metastasis				
-ve	31 (75.6%)	25 (73.5%)	6 (85.7%)	0.660
+ve	10 (24.4%)	9 (26.5%)	1 (14.3%)	

Mean and median number of positive LN was 4.50±4.38 and 3, respectively (range: 1-12 positive LN). Detailed pathologic description of LN positive patients is shown on table (V).

LN density was calculated using the following formula: number of positive LN times 100% divided by the total number of removed LN. The mean and median l\LN density of pN+ patients was 22.79% ± 21.78 and 15.73%, respectively (de novo: 22.13% ± 23.0 and the only pN+ progressive case showed density of 28.57%). Using LN density with a cut-off value of 20%, which revealed an independent influence on cancer specific survival, 5 patients had LN density >20%.

Table (V): Pathological characteristics of patients with LN disease at cystectomy.

Pathological stage	LN+ patients No., group	No. of LN		LN density %
		Excised	Positive	
pT_{2a} N_2	1, De novo	10	4	40
pT_{2b} N_2	2, De novo	17	12	70.6
		31	2	6.46
	1, Progressive	21	6	28.57
pT_{3a} N_1	2, De novo	15	1	6
		18	1	5.5
pT_{3b} N_1	1, De novo	18	1	5.5
pT_{3b} N_2	1, De novo	14	5	35.7
pT_{4a} N_1	2, De novo	4	1	25
		25	1	4

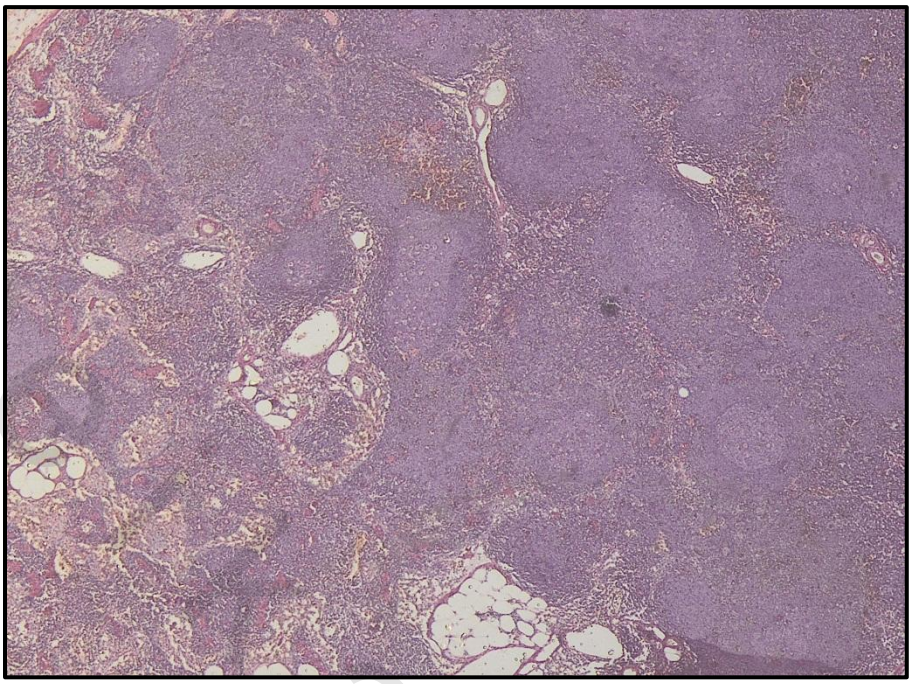


Figure (6): Histopathologic image of tumor free LN showing reactive lymphoid hyperplasia (H&E stain - x100)

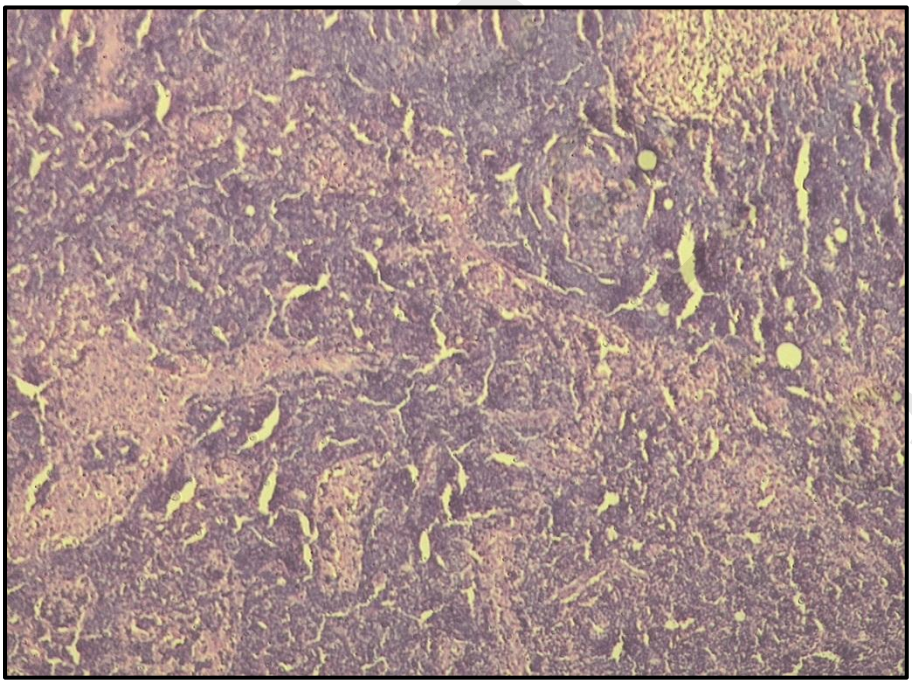
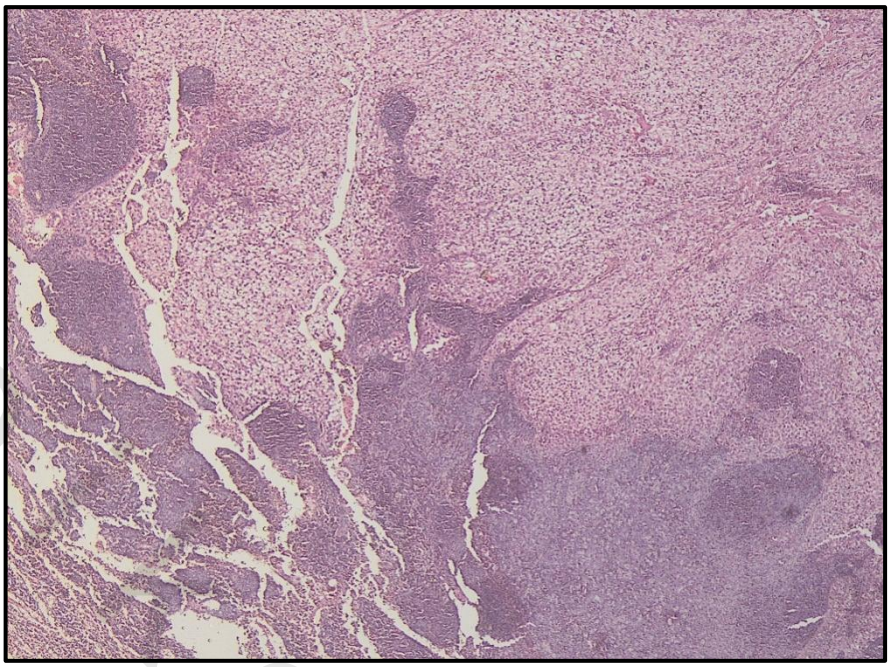
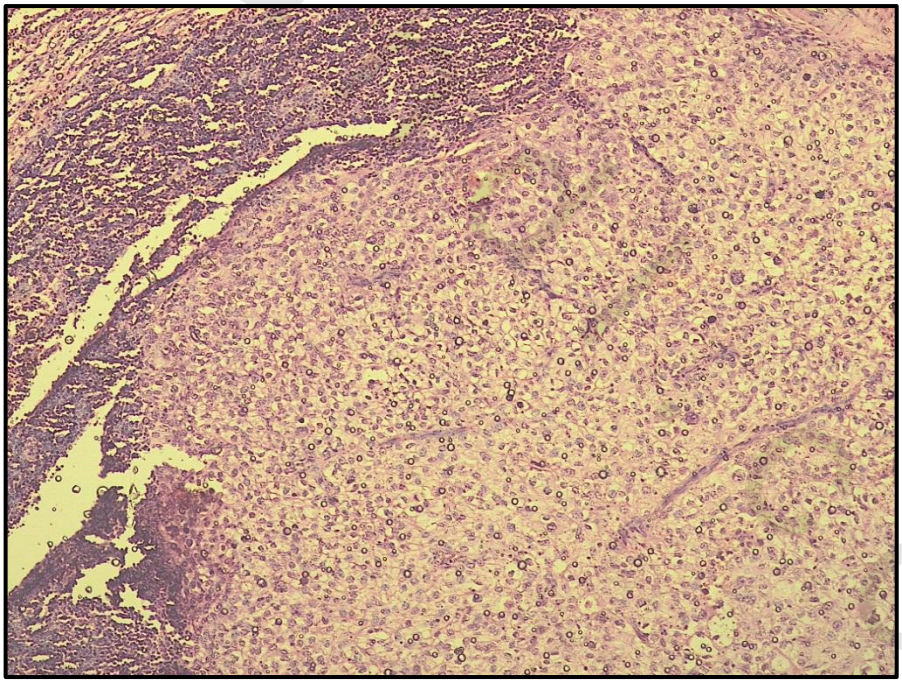


Figure (7): Histopathologic image of tumour free LN showing reactive sinus histiocytosis (H&E stain - x400).



a) Low power view (H&E stain- x100).



b) High power view. (H&E stain - x400).

Figure (8): Histopathologic images (a&b) of a LN showing near total replacement by diffuse cohesive sheets of carcinoma cells.

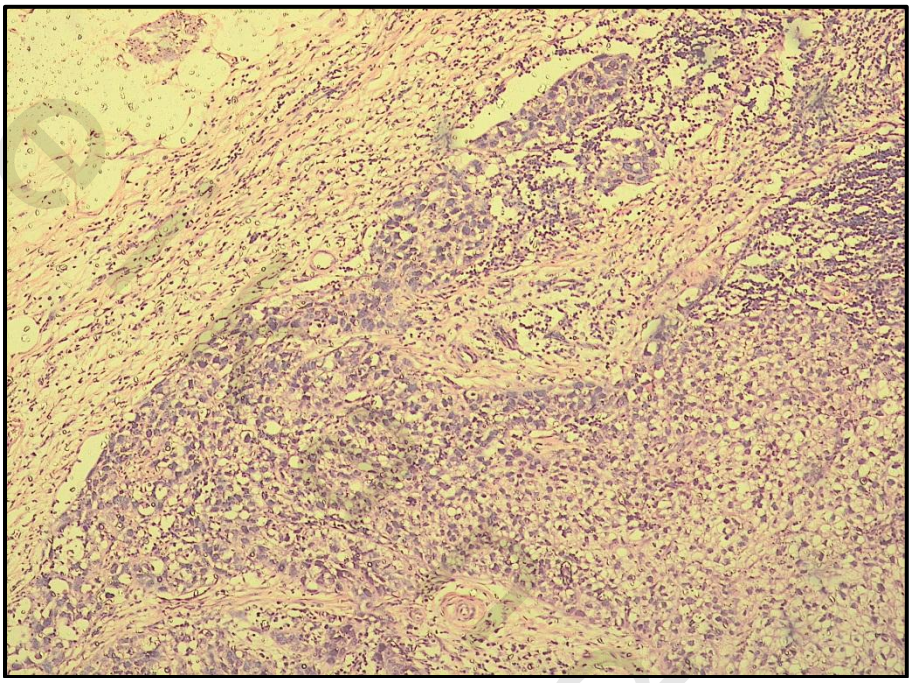


Figure (9): Histopathologic image of a LN showing malignant infiltration of perinodal fat and subcapsular sinuses (H&E stain-x400).