# DISCUSSION

Clinical presentation of muscle-invasive TCC of the urinary bladder can be either de novo or progressive disease after a period of conservative management of non-muscle-invasive tumours by TURBT with or without additional BCG or intravesical chemotherapy. Approximately 80% of urothelial MIBC cases present de novo in whom invasion into the muscle layer is detected at the primary TURBT.[3]

Our prospective study aimed to investigate the difference of LN metastasis between de novo and progressive muscle-invasive TCC of urinary bladder, focusing on LN density parameter. We were only concerned to study LN malignant infiltration of both groups to clarify the actual need of neoadjuvant chemotherapy for either disease entity, de novo or progressive, urothelial MIBC before RC.

Both groups were comparable as regard age, sex, performance status and histopathologic stage and grade at RC. Results revealed that 34 patients (83%) exhibited de novo MIBC versus 7 patients (17%) presented as progressive which is comparable with published literatures.

There is still a controversy regarding which of better prognosis, de novo or progressive muscle-invasive TCC of the urinary bladder. Some studies mentioned better survival for progressive than de novo MIBC[26,29] while others showed better 5-year cancer specific survival for de novo invasive disease.[5] However, other studies concluded no statistically significant difference of CSS for both groups.[27,28]

In 2001, Vaidya et al.[26] found a 2-year survival rate of 49% for those with de novo invasive tumours and 79% for those with progression from less than $T_2$ at presentation.

However, in 2004, these data was challenged by Schrier et al.[5] who found a statistically significant decreased survival for patients with progressive tumours. In their retrospective series of 163 patients (89 de novo and 64 progressive), they came to a conclusion that treatment of high risk non-muscle-invasive tumours failing conservative therapy should not be delayed until invasion has occurred that's because their results revealed that the de novo group has a statistically significant better CSS than the progressive group ( 3- and 5-year survival rates of 67% and 55% respectively for patients with a de novo invasive tumour and 37% and 28% respectively for patients with a progressive invasive tumour).[5]

In 2004, May et al.[27] found the overall survival rate after 3 and 5 years was 59% and 50% for progressive tumours and 52% and 46% for de novo MIBC. They did not observe any statistically significant difference between these parameters, concluding that progressive tumours do not have a better prognosis than de novo invasive tumours.

In 2007, a published study from Turkey did not reveal a significant difference between the two groups (2-year CSS rate for the de novo and progressive groups of 75% and 72%, respectively).[28] However, 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 CSS rate of 54% and 43%, respectively).[28]

In 2012, data collected from 1,150 patients managed by radical cystectomy for urothelial carcinoma of the bladder from the Canadian Bladder Cancer Network, revealed

that lymph node invasion was more in patients with clinically muscle-invasive cancer de novo (213 patients - 28.82%) compared patients with progressive MIBC (67 patients - 20.06%).[29] Those authors concluded of that patients with non-muscle-invasive urothelial carcinoma of the bladder that progress to muscle invasion, requiring RC, appear to have better pathologic and clinical outcomes than patients presenting with clinically muscle invasive (T2 or higher) carcinoma de novo. This may be due to earlier diagnosis of invasive disease and thus better prognostic features and/or a difference in tumour biology.[29]

Our prospective study revealed that LN metastasis was identified more in the de novo than progressive urothelial MIBC. We had 9 patients (26.5%) and 1 patient (14.3%) were diagnosed pathologically to have LN metastases in group I and II, respectively. This, however, didn't achieve statistically significant difference ($p = 0.660$).

Progressive group included only 1 pN+ patient (14.3%) who initially presented with high grade non-papillary $pT_1$ and during follow up till progression to invasive disease, 7 times of high grade $pT_1$ were diagnosed on TURBTs specimens during course of the disease.

This progression and LN positive status can be explained by what was mentioned by El-Abbady et al.[30] They compared 16 patients with progressive with 20 patients who were diagnosed with de novo MIBC, all undergoing cystectomy. On meticulous histopathological examination they found that patients who underwent previous TURBTs had significantly more local spread of malignant cells into the bladder muscle as compared to patients with de novo muscle-invasive tumours. 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.

The concept of LN density for bladder cancer was first described in 2003 by Stein et al.[44] and Herr.[45] This nodal parameter takes into account two important prognostic factors; the LN tumor burden as well as the meticulousness of LND.

LN density has been stated to be superior to TNM nodal status in predicting disease-specific survival following RC.[55] Because the number of LN excised and pathologically examined may directly influence the TNM nodal status and the absolute number of positive LN, LN density is thought to be a superior in predicting prognosis than the number of reported LN.[55]

Various literatures have been published to study the prognostic value of LN density for bladder cancer patients (**Table IV**).

However, the prognostic utility of this concept lacks validation in a prospective fashion, and conclusions drawn from such retrospective studies are limited by several sources of misclassification and/ or selection bias.[55]

In 2003, Herr investigated the LN density (threshold value of 20%), and the number of positive LN (threshold value of 4) with respect to their effect on CSS.[45]

**Table (VI): Literature survey of published studies till 2011 on the prognostic value of lymph node density. (Reproduced from Bastian et al.[60] with modifications)**

| Study, year | Patient no. | Total no. of LN, median | Total no. of positive LN, median | Threshold value of the LN density | Results |
|---|---|---|---|---|---|
| Stein et al, 2003 [44] | 244 | 30 (1–96) | 2 (1–63) | <20 vs >20 | Significantly poorer RFS and OS above the threshold value (MRA) |
| Herr, 2003 [45] | 162 | 13 (2–32) | 3 (1–14) | <20 vs >20 | Significantly poorer CSS above the threshold value (MRA) |
| Konety et al, 2003 [53] | 361 | N/A | N/A | <25, 26–50, 51–75, >75 | No significantly poorer CSS above the multiple threshold values (MRA) |
| Abdel-Latif et al, 2004 [14] | 110 | 17.9 (mean) | 4.1 (mean) | <10, 10–20, >20 | No significantly poorer RFS above the multiple threshold values (MRA) |
| Fleischmann et al, 2005 [46] | 101 | 22 (10–43) | N/A | <20 vs >20 | No significantly poorer RFS above the threshold value (MRA) |
| Kassouf et al, 2006 [54] | 108 | 12 (1–58) | 2 (1–10) | <25 vs >25 | Significantly poorer RFS and OS above the threshold value (MRA) |
| Steven and Poulsen, 2007 [42] | 64 | 27 (11–49) | N/A | <20 vs >20 | Significantly poorer RFS and OS above the threshold value (URA) |
| Kassouf et al, 2008 [55] | 248 | 12 (2–58) | 2 (1–14) | <20 vs >20 | Significantly poorer CSS above the threshold value (MRA) |
| Wright et al, 2008 [56] | 1260 | 9 (1–48) | 2 (1–18) | <12.6, 12.6–25, 25,1–50, >50 | Significantly poorer CSS and OS above the multiple threshold values (MRA) |
| Wiesner et al, 2009 [57] | 46 | 33 (15–77) | 3 (1–28) | <11 vs >11 | Significantly poorer CSS above the threshold value (MRA) |
| Osawa et al, 2009 [58] | 60 | 12 (1–80) | 2 (1–12) | <25 vs >25 | Significantly poorer OS above the threshold value (MRA) |
| Bruins et al, 2009 [59] | 181 | N/A | 1 (1–2) | <4 vs >4 | Significantly poorer RFS and OS above the threshold value (MRA) |
| Bastian et al, 2011[60] | 477 | 12 (1–66) | 2 (1–25) | <20 vs >20 | Significantly poorer CSS above the threshold value (MRA) |

The author utilized the ratio between positive LN and the total number of LN to stratify patient prognosis. The author evaluated 162 cystectomy patients with positive LN. In a primary analysis, the author found that increasing numbers of LN evaluated were associated with more positive LN, confirming the hypotheses that a bigger sample would increase the chances of finding positive LN.[45]

Herr then examined LN ratio (number of positive LN/total number of LN in the specimen) and found that a 20% cut-off as an independent predictor of survival ($p = 0.002$) and local recurrence ($p = 0.01$).[45]

In the same year, Stein et al.[44] confirmed this association using the same 20% threshold (5-year recurrence-free survival, 44 vs 17%; $p < 0.001$).

Comparable results were presented by Kassouf et al.[55] In a multivariable analysis, only a higher LN density (threshold value of 20%) correlated with a significant worsening of CSS.[55]

In a univariate analysis conducted by Fleischmann et al.,[46] significant differences were found between patients with different LN densities (threshold value of 20%) in RFS and in overall survival. Stratification of the patients with respect to pN stage ($pN_1$ vs $pN_2$, likewise according to the 1997/2002 staging system) yielded no significant difference in the univariate analyses.

In 2011, a multivariate analysis exhibited a stronger effect of LN density on CSS compared to pN stage according to the 1997/2002 staging system.[60] They found that both LN density and pT stage have the strongest prognostic significance as regard mortality risk following RC. Patients at tumour stage $pT_2$ or lower with an LN density <20% exhibit a CSS of 56% after 5 years, while patients at tumour stage $pT_3$ or higher with an LN density >20% exhibit a 5-years CSS of 28%.[60]

In our study, mean and median 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%.

Neoadjuvant chemotherapy is recommended to patients with clinically operable, muscle-invasive $N_0$ $M_0$, urothelial BC before definitive surgery.[49]

Based on our study, it seems that patients with de novo MIBC appears to have a higher incidence of LN metastasis at time of RC and neoadjuvant chemotherapy could be recommended for this group. On the other hand, we advise for a larger study to prove such benefit for the progressive group.

# SUMMARY

Prognosis of patients with positive LN bladder cancer is affected by the extent of lymphadenectomy in RC, together with the LN density.

The aim of our series was to study the possible difference of LN metastasis in muscle-invasive TCC of urinary bladder; de novo versus progressive tumours, as regard LN density.

The study was designed as a prospective study in which clinical and histopathological information was gathered from 41 patients who presented with muscle-invasive TCC of the urinary bladder at Department of Urology, Alexandria Main University Hospital. All patients underwent, after full informed consent, RC with bilateral standard pelvic LN dissection.

Patients were divided into two groups, de novo and progressive. Each patient was subjected to the analysis of history, clinical evaluation, radiologic investigation (multiphasic CT+/- MRI) and histopathology of the cystectomy specimen and dissected LN, including LN density calculation.

The results were tabulated and analyzed. Both groups were comparable as regard age, sex, performance status and final pathologic staging after RC.

Thirty-four patients (83%) exhibited de novo MIBC versus 7 patients (17%) presented with progressive invasive lesions with median duration of 9.5 months between the resection of the first non-muscle-invasive tumour and $T_2$ disease diagnosis. The median number of retrieved LN was 15 (range: 4 – 36).

Of all patients, 10 patients (24.39 %) exhibited nodal metastasis (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, $p = 0.660$).

The median number of positive LN was 3 (range: 1-13). The mean and median 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 a cut-off value of 20%, which revealed an independent influence on cancer specific survival, 5 patients had LN density >20%.

We concluded that there is no statistical significant difference between de novo and progressive muscle-invasive TCC of urinary bladder as regard LN metastasis.