INTRODUCTION

Incidence and mortality of bladder cancer world-wide and in Egypt

Bladder Cancer (BC) is the most common malignancy of the urinary tract and the 7th most common cancer in men and the 17th in women.(1) It is the 9th most common cancer in the world, with 430,000 new cases diagnosed in 2012, being three times more common in males compared with females.(1) In the United States, BC is the 4th most common cancer in men and the 8th most common cancer in women, with transitional cell carcinoma (TCC) comprising nearly 90% of all primary bladder tumours. In the European Union, age standardised incidence rate (ASR) is 27 per 100, 000 for men and six per 100,000 for women.

The world global age standardised mortality rate is 3 for men versus 1 per 100,000 for women. In the European Union, age standardised mortality rate is 8 for men and 3 per 100,000 for women, respectively. (1) In 2012, BC was the 8th most common cause of cancer-specific mortality in Europe. (1)

The incidence of BC has decreased in some registries possibly reflecting decreased impact of causative agents, mainly smoking and occupational exposure.(2) The mortality has also decreased, possibly reflecting increased standard of care.(3)

In Egypt, the ASR is 21.48 per 100,000 for males and 5.55 per 100,000 for females.The mortality rate is 6.5 per 100,000 for both sexes, being 11.07 per 100.000 in males and 2.7 per 100.000 in females.(1)

Clinical presentation of TCC of the urinary bladder

Transitional cell carcinoma of the urinary bladder can present as a non-muscle-invasive or as a muscle-invasive lesion. Approximately 75% of patients present with non-muscle-invasive tumours (figure, which are either limited to the mucosa (T_a) or the lamina propria (T_1).(4) Although carcinoma in situ (Cis) is also be considered non-muscle-invasive, it tends to behave more aggressively and is often found in association with high grade non-muscle-invasive tumours.(4)

Approximately 15% of patients have progressive muscle-invasive bladder cancer (MIBC) who present initially with non-muscle-invasive disease. However, 80% to 90% of the diagnosed cases of MIBC present de novo, primary invasive BC, without prior history of non-muscle-invasive disease.(5)

Role of radical cystectomy for bladder cancer

Radical cystectomy (RC) with bilateral lymph node dissection (LND) is the gold standard for treatment of MIBC,(6) which comprises 25% of BC patients.(7)

The rationale for this surgical approach is based on several observations. First, RC provides the best long-term survival and excellent local cancer control, with the lowest pelvic recurrence rates, including patients with lymph node (LN) involvement.(8-16) Second, the morbidity and mortality of RC have improved over the past several decades, even with the application of a more extended LND.(17)

Table (I): TNM staging for urinary bladder cancer, 7th edition (2009).

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N - Lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M - Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Third, TCC is a radioresistant tumor, and radiation is not used to manage LN metastases.[17] Fourth, improvements in lower urinary tract reconstruction have improved the quality of life of patients requiring cystectomy.[17] Fifth, , chemotherapy alone, or in combination with bladder-sparing protocols, has not demonstrated equivalent long-term survival rates with those for RC.[17] Finally RC provides accurate pathologic staging of the primary bladder tumor and regional LN, which can serve as a basis for adjuvant therapy.[18] LN metastases found at the time of RC should not preclude patients from undergoing lower urinary tract reconstruction or even orthotopic diversion.[18]

Node-positive disease is identified in approximately 25% of patients who undergo RC for clinical N_0M_0 disease.[19]

As regard non-muscle-invasive TCC, If RC is indicated before pathologically confirmed progression into muscle-invasive tumour, immediate (immediately after NMIBC diagnosis) and early (after BCG failure) RC can be distinguished. [20]

There are several reasons to consider RC for selected patients with non-muscle-invasive BC including: [20,21]

1) The staging accuracy for T1 tumors by TURBT is low with 27-51% of patients being upstaged to muscle-invasive tumour at RC.

2) Some patients with non-muscle-invasive tumours experience disease progression in muscle-invasive.
3) Retrospectively, those patients with high risk non MIBC who undergo early rather than delayed cystectomy for tumour relapse, after initial treatment with TURBT and BCG, have a better survival rate.

Potential benefit of RC must be weighed against the risk, morbidity, and impact on quality of life. It is reasonable to propose immediate RC to those patients with non MIBC who are at highest risk of progression. [22-25]

These are: [22-25]

1) Multiple and/ or large (> 3 cm) T1, high-grade (G3) tumours.
2) T1, high-grade (G3) tumours with concurrent Cis.
3) Recurrent T1, high-grade (G3) tumours.
4) T1G3 and Cis in the prostatic urethra.
5) Micropapillary variant of urothelial carcinoma.
6) Nested variant of urothelial carcinoma.

Prognosis of de novo and progressive MIBC

Many clinical studies have been published on the prognosis of patients with muscle-invasive TCC who underwent RC. However, only a few studies have been published that have evaluated the prognostic difference between de novo and progressive tumours.

Patients with de novo and progressive MIBC are treated equally in normal daily practice in which RC and bilateral pelvic LND remain the gold standard.

Some studies mentioned better survival for progressive than de novo MIBC[26,29] while others showed better 5-year cancer specific survival (CSS) for de novo invasive disease.[5,28] However, other studies concluded no statistically significant difference of CSS for both groups.[27,28]

As regard the worse prognosis of progressive MIBC patients, one possible explanation was mentioned by Schrier et al.[5] Those authors suggest that in high risk non-muscle-invasive BC, both therapy-sensitive and insensitive cells coexist. Intravesical therapy may select resistant clones and more aggressive tumour cells may continue to grow and progress to MIBC.

Another interesting possible explanation was mentioned by El-Abbady et al.[30] that showed on meticulous histopathological examination of patients who underwent previous TURBTs, had significantly more local spread of malignant cells into the bladder muscle as compared to patients with de novo 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 pressure.

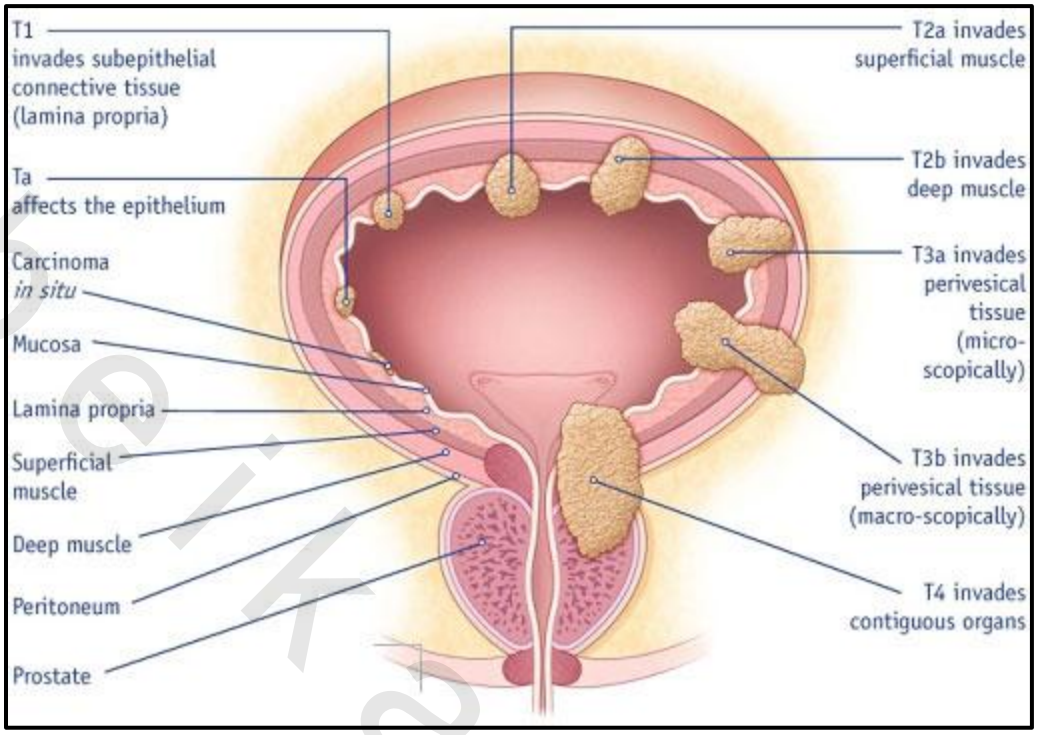

Figure (1): Schematic diagram of T staging of bladder cancer
(Quoted from: Internet, www.actiononbladdercancer.org)

Lymphatic drainage of urinary bladder

An anatomical understanding of the lymphatic drainage of urinary bladder is an obvious requirement when considering the specific sites of LN metastasis, as well as attempting to best define the absolute required boundaries of an appropriate lymphadenectomy.

Lymphatic drainage of the urinary bladder is accomplished by a system of lymphatic channels and LN separated into the following distinct areas:[31]

1) The visceral lymphatic plexus within the bladder wall, initiating in the submucosa and extending to the muscular layer of the bladder.

2) The intercalated LN, the juxtavesical LN located within the perivesical fat arranged into anterior, lateral and posterior groups.

3) Pelvic collecting trunks to the external iliac and hypogastric LN.

4) Regional pelvic LN, the obturator, external iliac, hypogastric, and presacral LN groups.

5) Lymphatic trunks leading from regional pelvic LN to common iliac LN on the common iliac vessels, thought to be the secondary site of metastasis, intermediate between pelvic and aortocaval LN.

Regarding the anatomy of LN groups of urinary bladder drainage, it includes the following [32] (figures 2, 3, 4):

1) **The obturator LN:** 1-2 in number in the obturator fossa in close relation to the obturator nerve and vessels.

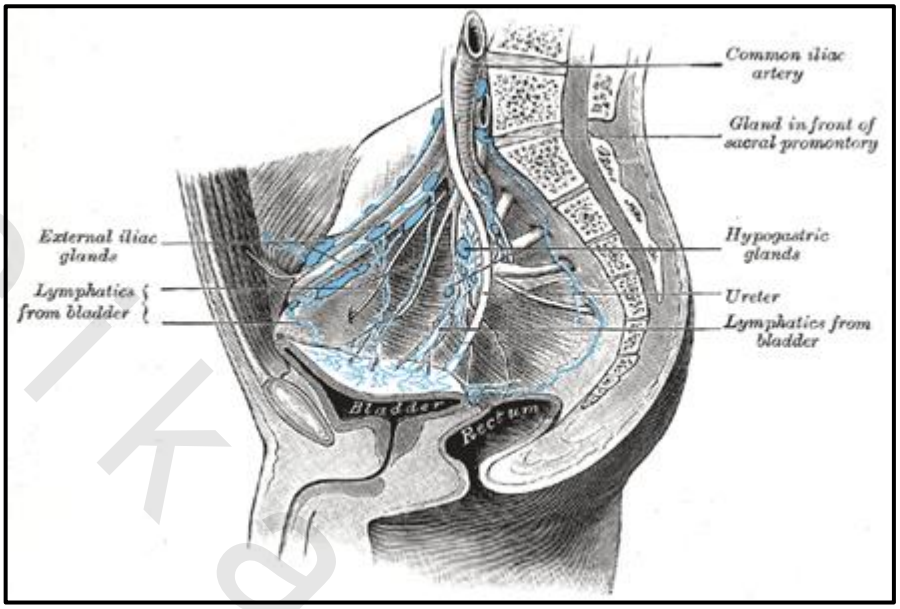

Figure (2): Lateral view of urinary bladder lymphatics.
(Quoted from: Internet, www.med.mun.anatomy).

2) **The External Iliac LN:** From 8-10 in number, lie along the external iliac vessels. They are arranged in three groups, one on the lateral, another on the medial, and a third on the anterior aspect of the vessel, the third group is, however, sometimes absent. Their principal afferents are derived from the inguinal and subinguinal LN, the deep lymphatics of the abdominal wall below the umbilicus and of the adductor region of the thigh, and the lymphatics from the glans penis, the membranous urethra, the prostate, the dome of the urinary bladder, the cervix uteri, and upper part of the vagina.

3) **The Hypogastric** *(internal iliac)* **LN:** Surround the hypogastric vessels, and receive the lymphatics corresponding to the distribution of the branches of the hypogastric artery (*i.e.*, they receive lymphatics from all the pelvic viscera, from the deeper parts of the perineum, including the membranous and cavernous portions of the urethra, and from the buttock and back of the thigh).

4) **The presacral LN:** Placed in the concavity of the sacrum, in relation to the middle and lateral sacral arteries; they receive lymphatics from the rectum and posterior wall of the pelvis. The efferents of the hypogastric group end in the common iliac LN.

5) **The Common Iliac LN**: From 4-6 in number and are grouped behind and on the sides of the common iliac artery, one or two being placed below the bifurcation of the aorta,

in front of the 5th lumbar vertebra. They drain chiefly the hypogastric and external iliac LN, and their efferents pass to the lateral aortic LN.

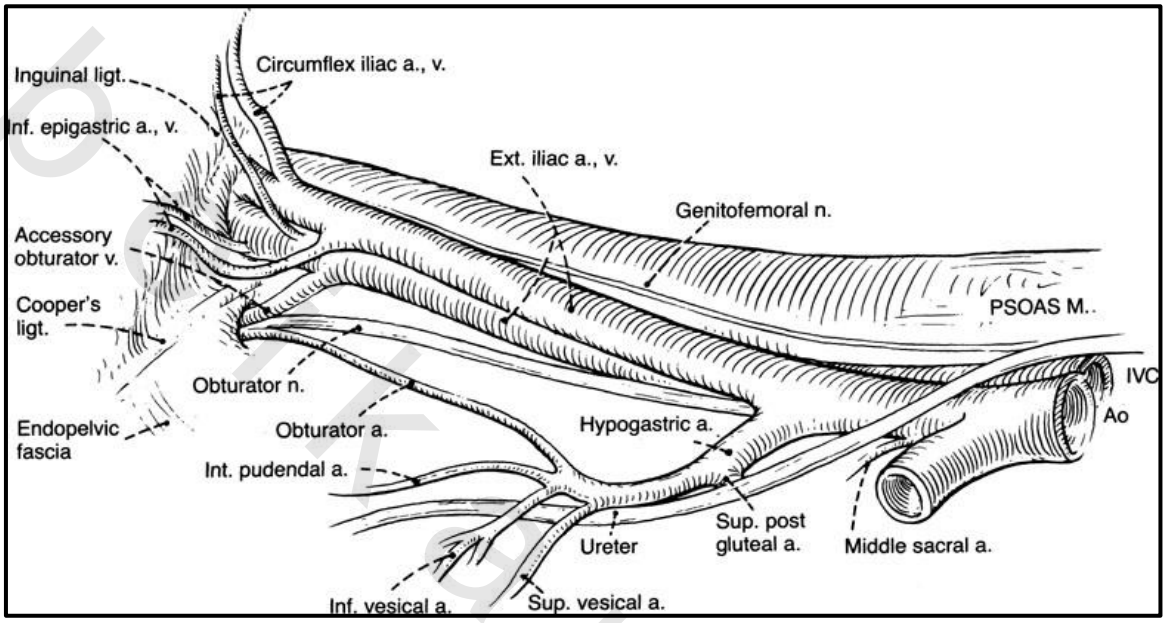

Figure (3): Anatomy of pelvic vessels and nerves.
(Quoted from: Internet, www.med.mun.anatomy)

The lymphatic vessels run alongside the principal blood vessels. Those of the parietes of the pelvis, which accompany the superior and inferior gluteal, and obturator vessels, follow the course of the hypogastric artery, and ultimately join the lateral aortic LN.[32]

Lymph node dissection for bladder cancer

LND is the most accurate means of determining regional LN involvement. It identifies patients who require adjuvant chemotherapy because of a high risk of relapse after surgery.[33,34] Meticulous LN dissection may cure some patients with positive LN.[10,14]

An extended lymphadenectomy must include all LN in the boundaries of the aortic bifurcation and common iliac vessels (proximally), the genitofemoral nerve (laterally), the circumflex iliac vein and LN of Cloquet (distally), the hypogastric vessels (posteriorly) including the obturator fossa, presciatic nodes bilaterally, and the presacral LN.[35] The extended dissection may also reach superiorly to the level of the inferior mesenteric artery.[35]The standard lymphadenectomy is more limited, with the cephalad extent generally beginning at the level of the common iliac bifurcation. The lateral and distal limits are similar to the extended dissection.[33]

Bladder cancer tends to invade progressively from its superficial origin in the mucosa to the lamina propria and sequentially into the muscularis propria, perivesical fat,

and contiguous pelvic organs, with an increasing incidence of LN involvement at each stage.[35] The incidence of LN involvement increases with this progression. LND is a diagnostic tool that provides staging information and risk assessment.[17]

Despite what is known regarding pelvic LND for BC, several issues continue to be debated, including the therapeutic benefit of this procedure in patients requiring cystectomy, the number of LN that should be removed, and the extent of the LND.

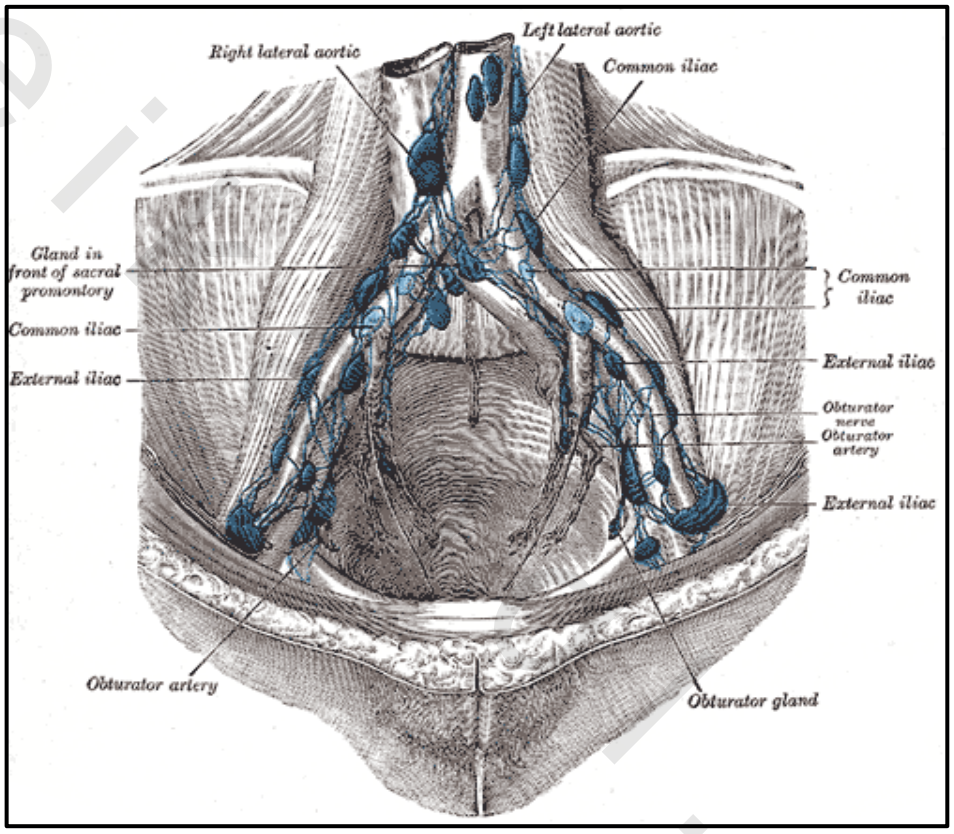

Figure (4): The LN groups of the pelvis.
(Quoted from: Internet, www.med.mun.anatomy)

Although a "standard" LND (cephalad extent at the level of the common iliac bifurcation) is believed to provide adequate staging information, there is evidence to suggest that a more "extended" LND (cephalad extent to include the common iliac vessels and possibly the distal aorta and vena cava) is therapeutically beneficial in node-positive patients undergoing cystectomy for BC.[17]

It is known that an extended LND, including removal of the lymphatic tissue up to the level of the inferior mesenteric artery, can be performed safely.[8,9] Furthermore, pathologic evidence is available to suggest that the LN region extending from the aortic bifurcation to the level of the inferior mesenteric artery may be a site of nodal metastasis that can be effectively removed surgically.[9,13,14]

Lymph node metastasis in bladder cancer

Several LN mapping cystectomy series have helped to define the extent of LND for BC. Results from an early RC series in 1981, one of the first anatomic LN mapping studies by Smith and Whitmore [(36)] in patients undergoing RC, have demonstrated that the two most common sites of LN involvement are the obturator and the external iliac LN. These sites of nodal metastases were involved in 74% and 65% of cystectomies respectively. They also demonstrated nodal metastases at the level of common iliac LN reaching 19%.

In 2004, a multicenter mapping study of the specific distribution of LN metastases was prospectively evaluated in which an extended LND was performed in all patients with BC. In this study positive LN were most common in the obturator spaces and adjacent to the iliac vessels, 16% to LN above the aortic bifurcation and 8% to LN on presacral region. Among patients with nodal metastases located within the limits of a "standard" dissection (below the bifurcation of the common iliacs), a significant proportion of patients also had nodal involvement at the level of the common iliac vessels and above the aortic bifurcation reaching 57% and 31%, respectively.[(9)]

The authors noted that, had the dissection been limited to the obturator spaces, 74% of all positive LN would have been left behind and nearly 7% of the patients would have been misclassified as node negative. They also noted that 10% of single-node metastases involved the common iliac LN only.[(9)]

The significance of an extended LND to include at least the common iliac groups was also corroborated in a study that found 33% of patients with unexpected microscopic nodal involvement at the time of cystectomy had metastases to the common iliac LN.[(37)]

In another mapping study conducted by Abol-Enein et al. on 48 node-positive patients who underwent an extended LND to the level of the inferior mesenteric artery, authors evaluated the probability of disease (node-positive) clearance with increasingly wider fields of dissection. If the LND included all lymphatic tissue in the pelvis (standard LND), the probability of node clearance was only 65%. This proportion increased to 79% when the LND was extended to the level of the aortic bifurcation and included the presacral nodes. However, if the LND did not extend to the level of the inferior mesenteric artery, 21% of the nodal tissue in this study would not have been removed, suggesting the importance of a more extended LND.[(14)]

Emerging data also suggest that the presacral LN should be removed in patients undergoing cystectomy for BC. The lymphatic drainage of the prostate, trigone, and posterior bladder includes the presacral LN. The possibility of prostate involvement in 20% to 40% of BC patients is another factor suggesting the importance of removing these LN. Drawing from the literature, presacral involvement is seen in approximately 6% of patients undergoing cystectomy for TCC of the bladder.[(17)]

The need for a bilateral LND has also been questioned, particularly in patients with a unilateral BC.[(38)] In the mapping study by Leissner et al.[(9)] bilateral LN metastases were commonly seen even if the primary cancer was limited to the right or left hemisphere of the bladder wall.

In a mapping study of 200 patients undergoing an extended LND, 24% were found to have node-positive disease and 39% of these patients had bilateral involvement. These data confirm that a bilateral LND is necessary to remove all potential sites for nodal metastases at the time of cystectomy.[14]

The number of LN assessed pathologically depends upon some factors that collectively contribute to determining the actual number of LN retrieved and the exact extent of LN tumour involvement: [17]

1) The extent of the LND, extended vs standard.

2) How the surgical specimen is actually submitted for pathologic evaluation.

3) The pathologist's diligence in searching and preparing the LN for histopathologic evaluation.

Table (II): Incidence of LN metastases following RC in contemporary series: correlation with primary BC stage (Reproduced from Stein et al.[17] with modifications).

Study	Patients No.	LN metastasis No. / %	Bladder tumour stage, No.				
			< pT2	pT2a	pT2b	pT3	pT4
Poulsen et al.[10]	191	50 (26%)	2	4	7	33	4
Vieweg et al.[11]	686	193 (28%)	10	12	22	97	52
Leissner et al.[9]	290	81 (28%)	1	5	12	53	10
Stein et al.[8]	1054	246 (24%)	19	21	35	113	58
Vazina et al.[13]	176	43 (24%)	1	10		20	12
Abdel-Latif et al.[14]	418	110 (26%)	3	4	29	59	15
Madersbacher et al.[41]	507	124 (24%)	2	26		64	32
Hautmann et al.[16]	788	142 (18%)	2	31		73	36
Cheng et al.[15]	120	38 (32%)	3	6		14	15

Information from both the surgeon and pathologist is important in determining the LN count and involvement of tumour. Unless standardized methods are agreed on by pathologists, the number of reported LN as an indicator of surgical quality and LN density as a prognostic factor should be used cautiously.[39]

Although the utilization of varying pelvic LND techniques has accounted for differences in the nodal assessment, there is still great variability in the literature even when considering the same boundaries for LN dissection. These differences have also been noted when the same surgeon or the same group of surgeons change the way they submit the LN packages or have their LN counts evaluated from different pathology groups.

Meijer et al. prospectively studied 174 patients with MIBC operated by the same group of surgeons at two different hospitals between 2007 and 2009 to search for differences in LN counts. While the two groups were comparable in respect to the use of neoadjuvant chemotherapy and pathologic T and N stage and the mean number of positive LN (1.21 vs 1.51; $p = 0.65$), a significant difference between the mean number of LN (16 vs 28; $p < 0.001$) was encountered.[39]

In another publication, Fang et al. reported a change in the median LN counts from 15 to 20 after initiating a policy where specimens with less than 16 LN identified were resubmitted for additional pathologic examination. The percentage of patients with positive LN in this study was not affected by the new policy (27.9 vs 27.2%; $p = 0.89$).[40]

In a report evaluating factors that contribute to the variability in the number of reported LN removed at cystectomy, only the extent of the LND was found to influence the nodal yield significantly.[37]

Although the exact number of LN that need to be removed at the time of cystectomy is unknown, it appears that extending the limits of the LND and submitting the LN in packets increase the number of LN evaluated.[41]

Node metastasis contralateral to the primary site of the tumor is common and thus mandates a bilateral LN dissection.[33] Metastasis to common iliac and more proximal LN in the absence of pelvic nodal metastasis is uncommon but can occur via the posterior lymphatic collecting ducts which may drain directly to the common iliac LN.[33]

Skip nodal metastasis was reported by Steven and Paulsen in a series of 336 patients undergoing extended node dissection.[42] But these were not seen in the series from Mansoura study where they mentioned that there is a sentinel region, which is the endopelvic region. They mentioned that there are no skipped lesions and negative nodes in the endopelvic region indicate that more proximal dissection is not necessary.[14]

Leissner et al. [12] mentioned survival for LN negative and positive patients is improved, with a reduced local recurrence rate, when a greater number of LN are removed. This finding was true for patients without LN metastases and for patients with five positive nodes or less.[12] If more than 16 LN were removed, the 5-year recurrence-free survival rate increased from 63% to 85% in organ-confined tumours, from 40% to 55% in pT3 tumours, and from 25% to 53% in patients with at most five LN metastases.[12]

Extending the boundaries of the LN dissection increases in the average number of LN removed from 14 in a standard dissection to 25 when the dissection was carried up to the bifurcation of the aorta. [19]

It was concluded that at least 10 to 14 LN should be retrieved as a minimal number of LN for adequate staging and prognostic evaluation of invasive BC.[38]

As regard the association of intravesical tumour location with metastases to the pelvic LN in TCC of the bladder, there is a recent study of 173 patients who underwent RC and bilateral pelvic LND for muscle-invasive or high risk non-muscle-invasive BC. [43]

Those authors found that 50 patients (28.9%) presented with LN metastases. They found that tumours located exclusively on the lateral bladder walls and tumours involving the lateral walls were highly correlated with LN positive disease. Posterior wall tumours were least associated with LN metastases compared with other tumour locations.[43]

LN density for bladder cancer

The concept of LN density for BC, that is the number of LN containing metastatic deposits divided by the total number of LN removed and examined, was first described in 2003 in two separate and independent reports by Stein et al.[44] and Herr.[45]

This concept takes into account two important prognostic factors; the LN tumour burden as well as the meticulousness of nodal dissection.[48]

The principle behind LN density came from the increasing number of publications demonstrating the impact of the total number of LN retrieved on prognosis and the discussion as to whether better staging would be completely responsible for this effect. The fact that the chances of finding one positive LN in a more extensive pelvic LND were greater than in limited dissection led the investigators to postulate that the significance of positive nodal disease would vary between patients with different node samples.[47]

In order to overcome this issue, Herr utilized the ratio between positive LN and the total number of LN to stratify patient prognosis. In 2003, 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. The author then examined LN ratio (number of positive LN /total number of LN in the specimen) and a multivariate analysis suggested 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%; $p < 0.001$).

Patients with LN positive disease following RC may be stratified into high risk groups based on the primary bladder tumour, pathological subgroup, number of LN removed and total number of LN involved.[44]

LN density, which is a novel prognostic indicator as described by Stein et al., may better stratify LN positive cases because this concept collectively accounts for the total number of positive LN (tumour burden) and the total number of LN removed (extent of lymphadenectomy).[44]

They recommended that future staging systems and the application of adjuvant therapies in clinical trials should consider applying LN density to help standardize this high risk group of patients following RC.[44]

In a univariate analysis conducted by Fleischmann et al., significant differences were found between patients with different LN densities (threshold value of 20%) in RFS and in overall survival, however on multivariate analysis only extranodal extension was the independent prognostic factor. [46]

Various cut-off values have been reported in the literature with regard to LN density but the a threshold value of 20%, as mentioned by most literatures, is presented as an instrument for stratifying patients on the basis of their distinct oncologic progression.[48]

Role of neoadjuvant chemotherapy for BC management

Neoadjuvant chemotherapy is recommended to patients with clinically operable, muscle-invasive N_0 M_0, urothelial BC before definitive surgery.[49] There are many advantages of neoadjuvant chemotherapy:[49-51]

1) It is delivered at the earliest time-point, when the low burden of micrometastatic disease is expected.

2) Tolerability of chemotherapy is expected to be better before cystectomy rather than after.

3) Hypothetically, patients with micrometastatic disease might respond to neoadjuvant therapy and reveal favourable pathologic status including negative LN status and negative surgical margins.

However, there are potential disadvantages of neoadjuvant chemotherapy: [49-51]

1) Approximately 50% of clinically N_0 M_0 patients are without micrometastatic disease and will receive unnecessary treatment.

2) Overtreatment may result from staging errors.

3) The delay in definitive surgery may compromise outcomes in non- chemotherapy-responsive patients.

A population-based study of the effect of neoadjuvant chemotherapy on perioperative outcomes in BC patients, treated with RC, revealed neoadjuvant chemotherapy, when compared to RC alone, is not associated with higher perioperative morbidity or mortality.[52]

The goal of this series data analysis was to study the natural history of MIBC, both de novo and progressive disease, as regard the LN density in LN positive patients.