Lymph node expression of cytokeratin 7 and 20 in extended lymph node dissection with radical cystectomy for muscle-invasive disease: value in pathologic staging, treatment strategies, and outcomes

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Background
Precise staging of lymph node (LN) status is an important clinicopathological prognostic parameter following radical cystectomy.
Aim
The aim was to assess tumor recurrence in patients with T2 transitional cell carcinoma undergoing radical cystectomy with extended pelvic lymphadenectomy.
Patients and methods
A total of 80 patients underwent bilateral extended lymphadenectomy during radical cystectomy that reached up to the aortic bifurcation and sentinal LN. This was a multicenter study among Urology Departments of Ain Shams University Hospital, Theodor Bilharz Research Institute, and Saint Louis University Hospital. Comparison was based on classification of patients into two groups: cytokeratin 7 and 20 (CK7 and CK20) positive and negative.
Results
In this study, the authors used both CK7 and CK20 for evaluating the metastatic and micrometastatic burdens in LNs, and these markers were correlated with the primary bladder and its nodal metastases. After displaying the results, we evaluated the markers as follows: CK7 sensitivity is 100%, whereas specificity is 65% and showed 48.8% positive predictive value and 100% negative predictive value, with overall accuracy of 73.8%. CK20 has a sensitivity of 100%, whereas specificity is 65% and showed 48.8% positive predictive value and 100% negative predictive value, with overall accuracy of 73.8%.
Conclusion
The use of molecular markers provides a better and proper nodal staging but what is thought to be a disadvantage is the exaggerated sensitivity sometimes gives false-positive results.

Keywords:
cytokeratin, dissection, lymph node, pathologic staging, radical cystectomy, muscle-invasive disease, treatment strategies

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Introduction

Radical cystectomy with lymphadenectomy represents the standard treatment for muscle-invasive bladder cancer T2–T4a, NO, Nx, and MO. Lymphadenectomy is included as a part of the surgical procedure to control locoregional disease and to potentially improve cancer-specific survival. Survival after radical cystectomy is usually predicted by the pathologic tumor stage status of surgical margins and the involvement of lymph nodes (LNs) [1].

Although earlier studies have already demonstrated a prognostic benefit of extended lymphadenectomy as compared with limited lymphadenectomy, the anatomically adequate extent of LN dissection to obtain reliable staging results is still controversial [2].

Precise staging of LN status is an important clinicopathological prognostic parameter following radical cystectomy. Nodal involvement identifies a high-risk group that has the worst oncological outcomes and many benefit from adjuvant systemic therapies [3].

Removal of involved LNs theoretically can improve survival, as it decreases overall tumor burden and allows the immune system and chemotherapeutics to target a smaller number of cancer cells potentially with greater efficacy [4].

The benefits of pelvic lymphadenectomy (PLND) in removing micrometastatic disease appear to be significant in BC. Furthermore, the removal of grossly negative but microscopically involved LN may have a therapeutic benefit [3].

Wright *et al.* [5] in 2008 evaluated the long-term survival in patients with bladder cancer who underwent cystectomy and PLND with removal of at least one LN and no distant metastases. They found an increased number of LNs removed to be associated with improved survival in LN-positive patients, and this finding supports performing a more extended lymphadenectomy at the time of cystectomy.

Leissner *et al.* [6] in 2000 showed that extended pelvic lymphadenectomy (EPLND) significantly improved the prognosis of patients with invasive bladder cancer in both node-negative and node-positive patients when a greater number of LNs were resected. They set a cutoff of greater than or equal to 16 LNs to be removed in clinically LN-negative patients for a significant increase in 5-year tumour-free survival from 63 to 85% in patients with tumor confined to the bladder wall (pTis, pT1, and pT2), from 40 to 55% in pT3 tumors, and from 25 to 53% in patients with at most five positive LNs. They concluded that EPLND presents a potentially curative procedure in patients with nodal metastases.

Abol-Enein *et al.* [7] in 2004 evaluated the locoregional distribution of positive pelvic LNs in 200 consecutive patients undergoing radical cystectomy. The authors also attempted to identify the probability of LN clearance with increasing wide fields of node dissection. In their investigation, extended pelvic lymphadenectomy included the lymphatic tissue up to the inferior mesenteric artery (IMA), and the common, external, and internal iliac regions. A mean number of 50.6 LNs were retrieved per patient, with 48 (24%) patients exhibiting positive nodes. More than one-third of these patients (39.6%) demonstrated bilateral involvement; a single positive LN was identified in 22 (45.8%) patients. The authors demonstrated that close to 80% of all positive nodes could be cleared completely from the field of PLND including all lymphatic tissues along the common, external, and internal iliac regions. Metastases outside the true pelvis were only detected in multinodal disease, and these metastatic deposits were always associated with metastases at the obturator fossa and/or the internal iliac region. Therefore, the authors concluded that standard lymphadenectomy in bladder cancer should always include all lymphatic tissues in the true pelvis; LN dissection might be extended up to the IMA if frozen section examination exhibits positive LNs in the sentinel region of the true pelvis.

EPLND includes LNs between the aortic bifurcation and common iliac vessels (proximally), the genitofemoral nerve (laterally), the circumflex iliac vein and LN of Cloquet (distally), and the internal iliac vessels (posteriorly), including the obturator fossa and the presacral LNs anterior to the sacral promontory. An extended dissection may also extend superiorly to the level of the IMA. Importantly, the PLND along the external iliac vessels is completely circumferential, whereas the proximal dissection along the common iliac and great vessels includes anterior and lateral nodal tissues. Standard PLND differs in its cranial boundary which is limited to the level of the common iliac bifurcation. A limited PLND involves the LNs in the obturator fossa [7].

The cytokeratin (CK) family consists of at least 20 types of cytoplasmic intermediate filaments found in epithelial cells. Expression of these cytoskeletal proteins is determined by cell type, stage of development, and differentiation. Abnormal expression of CK has been found in various forms of neoplasia and other diseases.

Cytokeratin 20 (CK20), a low-molecular weight CK, is specifically expressed in the superficial and in some of the intermediate cells of the normal urothelium. Abnormal expression of CK has been found in various forms of neoplasia and other diseases.

Cytokeratin 7 (CK7) is another intermediate filament that is found in urothelial neoplasia of the urinary bladder. Immunohistochemical staining of CK7 and CK20 has been shown to be a helpful diagnostic aid in differentiating the origin of carcinomas, including urothelial carcinoma of urinary bladder. It is anticipated that the pattern of CK7 and CK20 expression in metastatic urothelial carcinoma is similar to its primary counterpart. As a result,

immunohistochemical staining of metastatic tumor of the LN may help in determining the origin of the primary tumor. However, limited information is available about the pattern of CK7 and CK20 expression in LN metastases of urothelial carcinoma [8].

The study by Jiang *et al.* [9] included 26 patients with LN metastases who underwent radical cystectomy and bilateral lymphadenectomy for bladder carcinoma. Immunohistochemical staining for CK7 and CK20 was performed on formalin-fixed paraffin-embedded tissues containing primary cancers and LN metastases. There was a concordant expression of CK20 in the primary cancer and its matched LN metastasis. Twelve (46%) cases showed positive CK20 immunoreactivity in the primary tumor and its matched LN metastases, whereas 14 (54%) cases were negative for CK20 in both the primary tumor and LN metastasis. All cases showed positive CK7 immunoreactivity in the primary cancers and matched LN metastases. They concluded that CK20 and CK7 immunoreactivity is reliably observed in metastases from bladder cancer when the primary tumor expresses both of them.

Aim

An open prospective study was done to assess tumor recurrence in patients with T2 transitional cell carcinoma (TCC) undergoing radical cystectomy with EPLND. Comparison was based on classifying the patients into two groups: CK7 and CK20 positive and negative.

Patients and methods

Traditionally radical cystectomy is recommended for patients with muscle-invasive bladder cancer T2–T4a, N0, Nx, and MO.

Other indications include high-risk and recurrent superficial tumors.

In our study, all patients indicated for radical cystectomy underwent bilateral extended lymphadenectomy after being consented and were preoperatively evaluated by the following: transurethral resection of the tumor with confirmed pathological analysis, full laboratory workup, and abdominal and pelvic computed tomography (CT) to exclude any radiologically seen LNs or visceral metastasis.

After histopathological examination of the removed bladder specimen, only what proves to be T2 TCC were reevaluated by histopathological analysis and immunohistochemical examination of the removed LNs by the markers CK20 and CK7.

We collected the results of 80 patients who were matched with number of positive LNs, number of negative LNs, and the presence of micrometastasis using CK7 and CK20 in LNs, with their correlation with the primary bladder tumor, and the patients were followed for 5 years in both urology and oncology clinics according to the European Urology Guidelines.

A total of 80 patients underwent bilateral extended lymphadenectomy during radical cystectomy that reached up to the aortic bifurcation and sentinal LN. This was a multicenter study among Urology Departments of Ain Shams University Hospital (Egypt), Theodor Bilharz research Institute (Egypt), and Saint Louis University Hospital (France).

IRB approvals were validated in each institute for the multicenter study.

Histopathological study

Tissues from radical cystectomies and lymphadenectomy were fixed in 10% buffered formalin and were embedded in paraffin and processed routinely to formalin-fixed 5 nm tissue sections.

The following stains were done as follows: hematoxylin and eosin-stained slides were used to evaluate the pathological diagnosis of all radical cystectomy and lymphadenectomy and to assess urothelial carcinoma (TCC) cases for pathological grades according to the WHO and pathological tumor stage in accordance with WHO classification for tumors by TMN (tumor, LN, and metastasis) staging [10]. Immunohistochemistry of CK20 and CK7 antibodies (5 μm) were be collected from formalin-fixed paraffin-blocks on microscopic slides coated with (3-amino propyl)triethoxysilane (Sigma, Agilent Dako, Santa Clara, California, USA). Antibody-mediated detection of CK20 and CK7 was performed using the standard streptavidin–biotin peroxidase complex method. Following deparaffinization and rehydration, antigen retrieval was performed by microwaving in 10 mmol/l citrate buffer, pH 6.0. Nonspecific antibody binding was prevented by preincubation with 100 μl blocking serum for 30 min at room temperature. Sections were incubated overnight with the primary antibodies: CK 20 and 7 at the optimal working

dilution of 1 : 100 and 1 : 100, respectively. After thorough washing in blocking buffer, the bound antibodies were detected with biotinylated second antibody, followed by streptavidin alkaline phosphatase conjugate. We used substrate chromogen mixture (Histostain-SAP Kit, alkaline phosphatase red; Zymed Lab-Sa System, Agilent Dako, Santa Clara, California, USA), and sections were counterstained with Mayer's hematoxylin before mounting.

Statistical analysis

Results are expressed as number (percentage). Comparison between categorical data [*n* (%)] was performed using χ^2-test or Fisher exact test if cell count was less than 5. κ agreement test was used to measure the association between LN pathology and CK7 and CK20.

Statistical Package for the Social Sciences (SPSS) (IBM, Chicago, IL, USA) computer program (version 19 windows) was used for data analysis. *P* value less than or equal to 0.05 was considered significant.

Results

All patients' data and inclusion criteria are displayed in Tables 1–6.

CK7 and CK20 expression in LNs are displayed in Figs 1–3.

Discussion

The optimal anatomic boundaries of an appropriate lymphadenectomy remain unclear because of conflicting data regarding the anatomic distribution and the pattern of LNs metastases in patients with bladder cancer.

To define the optimal extent of lymphadenectomy during cystectomy, Abol-Enein *et al.* [11] performed

Table 1 Post-TURB T pathology of the studied group

	N (%)
Urothelial tumor T2	80 (100.0)

Table 2 Preoperative computed tomography findings of the studied group

	N (%)
Enlarged LN	6 (7.5)
Not enlarged LN	74 (92.5)

LN, lymph node.

Table 3 Lymph node, cytokeratin 7, and cytokeratin 20 pathology of the studied group

	N (%)
Lymph node pathology	
Negative	60 (75.0)
Positive	20 (25.0)
Cytokeratin 7	
Negative	39 (48.8)
Positive	41 (51.2)
Cytokeratin 20	
Negative	39 (48.8)
Positive	41 (51.2)

Table 4 Association between lymph node pathology and cytokeratin 7 expression in the studied group.

	Lymph node pathology		κ value	*P* value
	Negative (*n*=60)	Positive (*n*=20)		
Cytokeratin 7				
Negative (*n*=39)	39 (65.0)	0	0.481	0.001
	TN	FN		
Positive (*n*=41)	21 (35.0)	20 (100.0)		
	FP	TP		

κ=0.4–0.6, moderate agreement. FN, false negative; FP, false positive; TN, true negative; TP, true positive. $P \leq 0.05$, significant.

Table 5 Association between lymph node pathology and cytokeratin 20 expression in the studied group

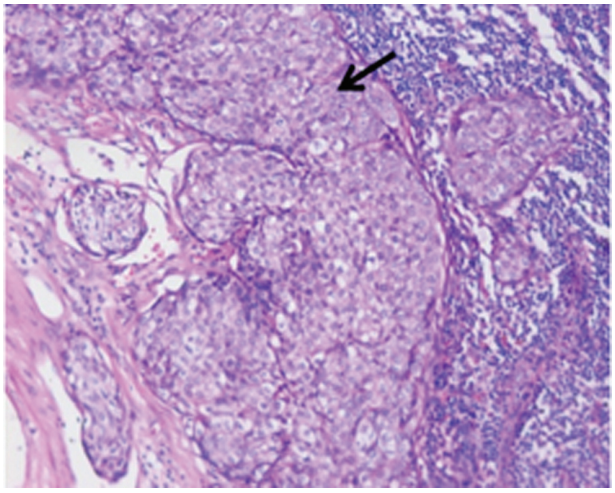
	Lymph node pathology [*n* (%)]		κ value	*P* value
	Negative (*n*=60)	Positive (*n*=20)		
Cytokeratin 20				
Negative (*n*=39)	39 (65.0)	0	0.481	0.001
	TN	FN		
Positive (*n*=41)	21 (35.0)	20 (100.0)		
	FP	TP		

κ value=0.4–0.6 (moderate agreement). FN, false negative; FP, false positive; TN, true negative; TP, true positive. $P \leq 0.05$, significant.

Table 6 Diagnostic indices of cytokeratin 7 and cytokeratin 20 in studied group

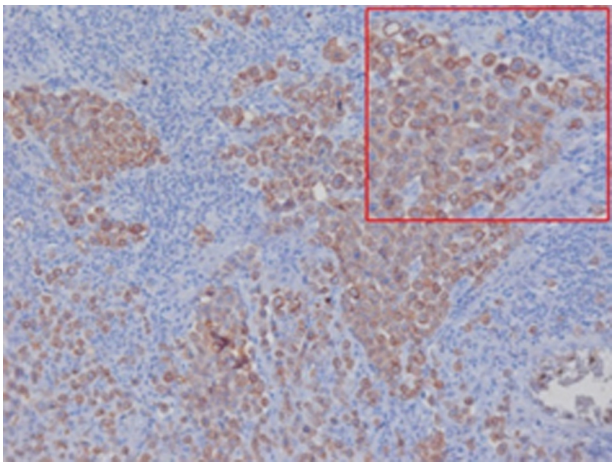
	Cytokeratin 7 (%)	Cytokeratin 20 (%)
Sensitivity	100.0	100.0
Specificity	65.0	65.0
Positive predictive value	48.8	48.8
Negative predictive value	100	100
Accuracy	73.8	73.8

Figure 1



Lymph node section showing groups of urothelial cells with high-grade metastasis in lymph node (hematoxylin and eosin, ×200).

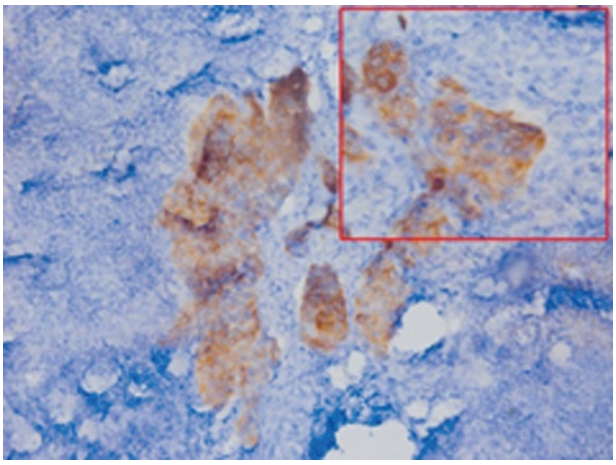
Figure 2



Lymph node section showing positive deposits of malignant urothelial cells positive for cytokeratin 7 (immunohistochemistry, DAB, CK7, ×200).

a prospective pathoanatomic single-center study with a total of 200 patients who underwent RC and extended lymphadenectomy up to the level of origin of the IMA. Of the patients, 48 (24%) had positive nodes, including eight patients with ≤pT2

Figure 3



Lymph node section showing positive deposits of malignant urothelial cells positive for cytokeratin 20 (immunohistochemistry, DAB, CK20, ×200). DAB, 3,3-Diaminobenzidine.

disease. The authors found that extrapelvic nodal metastasis was always associated with involvement of the obturator and/or internal iliac nodes, suggesting that there were no cases in which the primary drainage regions were skipped and disease landed in only secondary nodal sites. Thus, the authors defined the end pelvic site composed of the internal iliac, external iliac, and obturator groups of LNs as the sentinel regions.

In contrast, Leissner *et al.* [2] who conducted an analysis of LNs at 12 different anatomic sites in 290 patients did not identify a well-defined sentinel LN site. The authors defined three lymphadenectomy levels: level 1 comprised all lymphatic tissue below the common iliac bifurcation, level 2 comprised the lymphatic tissue above the common iliac bifurcation and below the aortic bifurcation, and level 3 was defined as the lymphatic tissue above the aortic bifurcation up to the IMA. The dissection field had a cranial border at the level of the IMA, a lateral border at the genitofemoral nerve, and a caudal border at the pelvic floor. The separate regions were paracaval right, interaortocaval, para-aortal left, lateral to common iliac artery right and left, lateral to external iliac artery right and left, presacral, obturator space right and left, and deep obturator space right and left. Eighty-one (27.9%) patients had positive LNs, including 18 (6.2%) patients with ≤pT2 disease. In 20 of 290 patients (6.9%), nodal metastases involved only level 1, and in 20 of 290 patients (6.9%), nodal metastases were located only at level 2. Positive LNs at only level 3 were not encountered. In conclusion, to achieve an accurate LN staging, it would be necessary to dissect up to the aortic bifurcation.

Vazina *et al.* [12] studied 176 consecutive patients (pT1–pT4) who underwent RC and lymphadenectomy. LN metastases were found in one (3.6%) patient with pT1, 10 (15.6%) patients with pT2, 20 (40%) patients with pT3, and 12 (50%) patients with pT4. In patients with stage ≤pT2, LN metastases were found exclusively in the pelvic region, except in two (3%) patients with positive common iliac and aortic bifurcation LNs. Of patients with pT3 or pT4, 16% had LN metastases outside the boundaries of a true pelvic LN dissection (nodal involvement of the common iliac nodes and at or above the aortic bifurcation). A skip lesion was detected in one patient with positive nodes at or above the common iliac bifurcation.

Tarin *et al.* [13] evaluated 591 patients who underwent RC with mapping pelvic LN dissection, and LN involvement was identified in 114 (19%) patients. Stratified by tumor stage <pT2, pT2, pT3, and pT4, LN involvement was identified in 18 (6%) patients, 16 (18%) patients, 68 (40%) patients, and 12 (60%) patients, respectively. Of the node-positive group, seven (6%) patients had LNs involved only above the common iliac bifurcation (skip lesions). As skip lesions are very rare, this phenomenon may be the result of missed positive LNs in the true pelvis or of a specimen-labeling error.

In our multi-center prospective study, we included 80 patients with T2 urothelial bladder tumor with no neoadjuvant chemotherapy given in order to evaluate the nodal metastatic and micrometastatic burden with standard histopathological examination and immunohistochemically staining with CK7 and CK20 to detect micrometastases in negative LNs examined by histopathology, and also the primary bladder tumor is stained with the same markers to confirm the correlation between the primary tumor and its nodal metastases.

We standardized the boundaries of extended lymphadenectomy between aortic bifurcation and common iliac proximally, the genitofemoral nerve laterally, the circumflex iliac vein and LN of Cloquet distally and the internal iliac vessels posteriorly including the obturator fossa and the presacral LNs anterior to the sacral promontory.

To respect these boundaries, the total operative time increased by 90 min, with no significant operative complications, and the total number of removed LNs varied from 16 to 18 LNs, with average blood loss of 500 ml.

The medical and occupational histories were included in the study of results.

The results of removed LNs at the level between the aortic bifurcation and common iliac vessels in our study group were negative in 60 (75%) patients and positive in 20 (25%) patients by standard histopathology examination.

So for further detection of micrometastasis burden in the all the removed LNs were examined by immunohistochemical markers.

CK20, a low-molecular weight CK, is specifically expressed in the superficial and in some of the intermediate cells of the normal urothelium. Abnormal expression of CK has been found in various forms of neoplasia and other diseases.

CK7 is another intermediate filament that is found in urothelial neoplasia of the urinary bladder. Immunohistochemical staining of CK7 and CK20 has been shown to be a helpful diagnostic aid in differentiating the origin of carcinomas, including urothelial carcinoma of urinary bladder. It is anticipated that the pattern of CK7 and CK20 expression in metastatic urothelial carcinoma is similar to its primary counterpart. As a result, immunohistochemical staining of metastatic tumor of the LN may help in determining the origin of the primary tumor.

The study by Jiang *et al.* [9] was performed on 26 patients with LN metastases who underwent radical cystectomy and bilateral lymphadenectomy for bladder carcinoma. Immunohistochemical staining for CK7 and CK20 was performed on formalin-fixed paraffin-embedded tissues containing primary cancers and LN metastases. There was a concordant expression of CK20 in the primary cancer and its matched LN metastasis. Twelve (46%) cases showed positive CK20 immunoreactivity in the primary tumor and its matched LN metastases, whereas 14 (54%) cases were negative for CK20 in both the primary tumor and LN metastasis. All cases showed positive CK7 immunoreactivity in the primary cancers and matched LN metastases. They concluded that CK20 and CK7 immunoreactivity is reliably observed in metastases from bladder cancer when the primary tumor expresses both of them.

Wang *et al.* [14] found that 89% (17 out of 19) of urothelial carcinomas were positive for CK20.

Chu *et al.* [15] reported recently that only 7 of 24 urothelial carcinomas (29%) were positive for CK20.

Moll *et al.* [16] found that 97% of the urothelial carcinomas in a series of 24 cases were CK20 positive.

In contrast to these studies, the number of the patients in our study is more significant, and both markers (CK7 and CK20) were used in staining both of the primary bladder tumor and all of the removed LNs to establish the correlation between the primary bladder tumor and its nodal metastasis.

The results of CK7 showed that among the 60 patients with negative LNs by standard histopathology above the common iliacs, 39 (65%) of them were CK7 negative and 21 (35%) of them were CK7 positive.

In the 20 patients with positive LNs by standard histopathology, the CK7 was positive in all of them.

The results of CK20 showed that in the 60 patients with negative LNs by standard histopathology above the common iliacs, 39 (65%) of them were CK20 negative and 21 (35%) of them were CK20 positive.

In the 20 patients with positive LNs by standard histopathology, the CK20 was positive in all of them.

CT of the abdomen and pelvis is used as a routine procedure for the preoperative staging assessment of muscle-invasive bladder cancer. However, this CT has limited accuracy to detect LN metastasis.

Paik *et al.* [17] retrospectively reviewed 82 consecutive patients with muscle-invasive bladder tumors who underwent preoperative staging CT of the abdomen, and they found that LN metastases were accurately determined in four (4.9%) patients. Ficarra and colleagues evaluated the data of 156 patients, where 45 (28.8%) of whom had pathologic LN involvement. This involvement was foreseen with pelvic CT in only 19 patients. Tritschler and colleagues reported an accuracy of 54% for CT in predicting LN metastases.

Kibel *et al.* [18] demonstrated a positive predictive value (PPV) of 78%, a negative predictive value (NPV) of 91%, sensitivity of 70%, and specificity of 94% for fluorodeoxyglucose positron-emission tomography/CT in the detection of positive LNs. Vargas and colleagues recently evaluated the diagnostic performance of MRI, 11C-acetate positron-emission tomography/CT, and contrast-enhanced CT for bladder cancer staging and found that the three imaging modalities displayed similar levels of accuracy.

In our study, all the patients were evaluated prior surgery with contrast-enhanced CT, and only six (7.5%) of them showed pelvic enlarged LNs, whereas the remaining showed no suspicious LNs, so like all these studies, CT has a very limited role in determining the nodal metastatic burden.

Wright *et al.* [5] evaluated the long-term survival in patients with bladder cancer who underwent cystectomy and PLND with removal of at least one LN and no distant metastases. They found an increased number of LNs removed to be associated with improved survival in LN-positive patients, and this finding supports performing a more extended lymphadenectomy at the time of cystectomy.

Hollenbeck *et al.* [19] in 2008 evaluated the outcome of patients with bladder cancer after cystectomy and PLND in relation to the number of LNs removed at different hospitals. They found that high LN counts tend to have higher survival rates after cystectomy for bladder cancer. However, this effect was modest and in large part was explained by confounding patient and hospital factors.

Still, growing evidence indicates that EPLND in patients with bladder cancer may confer a survival benefit not only for node-positive patients but also apparently for node-negative patients. Poulsen and colleagues demonstrated that an EPLND is beneficial in patients with organ-confined, LN-negative disease. The 5-year recurrence-free survival rate was 90% in patients with organ-confined and LN-negative disease in the EPLND group versus 71% in the standard PLND group ($P<0.02$). Moreover, EPLND reduced the rate of pelvic and distant metastases.Leissner *et al.* [2] showed that EPLND significantly improved the prognosis of patients with invasive bladder cancer in both node-negative and node-positive patients when a greater number of LNs were resected. They set a cutoff of greater than or equal to 16 LNs to be removed in clinically LN-negative patients for a significant increase in 5-year tumor-free survival from 63 to 85% in patients with tumor confined to the bladder wall (pTis, pT1, and pT2), from 40 to 55% in pT3 tumors, and from 25 to 53% in patients with at most five positive LNs. They concluded that EPLND presents a potentially curative procedure in patients with nodal metastases.

Herr *et al.* [20] analyzed the data of 322 patients with muscle-invasive bladder cancer who underwent radical cystectomy and bilateral PLND. They found a statistically significant survival benefit in node-positive patients with at least 11 LNs examined

(P=0.004). Interestingly, patients with node-negative disease also had a significantly better survival rate if eight or more LNs were identified by the pathologist in the surgical specimen (P<0.001).

Dhar *et al.* [21] compared recurrence pattern and survival in two consecutive series of preoperatively staged N0M0 patients treated with radical cystectomy and limited PLND (336 patients; Clevland Clinic, Clevland, Ohio, USA) and EPLND (322 patients; University of Bern, Bern, Switzerland) without adjuvant therapy. They found significantly higher recurrence rates in pT3pN0 patients with limited PLND with a median of 12 nodes resected (23% 5 years recurrence-free survival) versus those undergoing more EPLND with a median of 22 nodes resected (57% 5 years recurrence-free survival; P<0.0001). The 5-year recurrence-free survival rates for pT3pN0–2 patients were 19 and 49%, respectively (P<0.0001). Again, these data strongly support the benefit of extended bilateral PLND at cystectomy in node-positive and node-negative patients.

All of these promising results must be interpreted with caution. It is still not clear whether the benefit in survival is owing to the potentially curative removal of pelvic LN metastases in node-positive patients and removal of histologically not detected micrometastases in LN-negative patients or owing to the Will Rogers phenomenon which states that a patient with fewer tumor-negative LNs removed is more likely to still have undiscovered LNs harboring micrometastases than a patient with more negative LNs removed. The node-negative patients with an EPLND are more likely to be 'real' node-negative patients, and the risk of harboring occult metastases with a consecutive worse survival is lower than in patients with a smaller number of LNs resected. However, stage migration from node negative to node positive is more likely in the EPLND population with a very limited tumor burden only, leading to a better outcome in the node-positive population of the extended rather than the limited PLND population.

In our study, the patients were followed in both urology and oncology clinics for 5 years, and the outcome was as follows: three (3.75%) patients died within the 5 years from nononcological etiologies, and five patients were mananged for operation-related complications, as one patient developed pyelonephritis, two patients with intestinal obstruction, one patient with uretero-ileal anastomosis, and one patient with pulmonary embolism.

Conclusion

Precise staging of LN status is an important clinicopathological prognostic parameter following radical cystectomy. Nodal involvement identifies a high-risk group that has the worst oncological outcomes and many benefits from adjuvant systemic therapies.

Clearly extending the field of PLND will increase the number of LNs removed and the chances of identifying positive nodes.

An inadequately performed lymphadenectomy may underestimate the true disease burden and the need for potentially therapeutic adjuvant treatment.

A bilateral PLND that includes the external and internal iliac nodes to the common iliac bifurcation and complete dissection of the obturator fossa should provide adequate surgical nodal staging in most patients.

The use of molecular markers provides a better and proper nodal staging but what is thought to be a disadvantage is the exaggerated sensitivity sometimes gives false positive results.

In our study, we used both CK7 and CK20 for evaluating the metastatic and micrometastatic burdens in LNs, and these markers were correlated with the primary bladder and its nodal metastases.

After displaying the results, we evaluated the markers as follows:

CK7 has a sensitivity of 100% whereas specificity is 65% and showed 48.8% PPV and 100% NPV, with overall accuracy of 73.8%.

CK20 has a sensitivity of 100%, whereas specificity is 65% and showed 48.8% PPV and 100% NPV, with overall accuracy of 73.8%.

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Conflicts of interest

There are no conflicts of interest.

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