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Collaborative Review – Bladder Cancer

The Impact of Lymphadenectomy and Lymph Node Metastasis on the Outcomes of Radical Cystectomy for Bladder Cancer

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Abstract

Context: The presence of lymph node metastases and the extent of lymphadenectomy have both been shown to influence the outcome of patients with muscle-invasive bladder cancer.

Objective: Current standards for detection of lymph node metastases, lymph-node mapping studies, histopathologic techniques, and risk factors in relation to lymph node involvement are discussed. The impact of lymph node metastases and the extent of lymphadenectomy on the outcome of patients treated with radical cystectomy are analyzed.

Evidence acquisition: A systematic literature review of bladder cancer and lymph nodes was performed searching the electronic databases Pubmed/Medline, Cochrane, and Embase. Articles were selected based on title, abstract, study format, and content by a consensus of all participating authors.

Evidence synthesis: Lymph node status is highly consequential in bladder cancer patients because the presence of lymph node metastases is predictive of poor outcome. Knowledge of primary landing sites of lymph node metastases is important for optimum therapeutic management. Accurate pathologic work-ups of resected lymph node tissue are mandatory. Molecular markers could potentially guide therapeutic decisions in the future because they may enable the detection of micrometastatic disease. In current series, radical cystectomy with an *extended* lymphadenectomy seems to provide a clinically meaningful therapeutic benefit compared with a *limited* approach. However, the anatomic boundaries of lymph node dissection are still under debate. Therefore, large prospective multicenter trials are needed to validate the influence of extended lymph node dissection on disease-specific survival.

Conclusions: An extended pelvic lymph node dissection (encompassing the external iliac vessels, the obturator fossa, the lateral and medial aspects of the internal iliac vessels, and at least the distal half of the common iliac vessels together with its bifurcation) can be curative in patients with metastasis or micrometastasis to a few nodes. Therefore, the procedure may be offered to all patients undergoing radical cystectomy for invasive bladder cancer.

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1. Introduction

Carcinoma of the bladder represents the fourth most common cancer in men and the eighth most common malignancy in women in the United States [1].

About 30% of patients present with a muscle-invasive disease at the time of diagnosis. If untreated, 85% of these patients will die from the disease within 2 yr of diagnosis [2]. Approximately 25% of patients with stages T1–T4 N0 M0 bladder cancer who undergo radical cystectomy (RC) and pelvic lymph node dissection (PLND) are found to have lymph node metastases [3–8].

2. Evidence acquisition

The basis for this article was a systematic literature review. The electronic databases Pubmed/Medline, Cochrane, and Embase were searched using these keywords: *bladder cancer/carcinoma, radical cystectomy* and/or *cystectomies, lymph node, lymph node dissection,* and *lymphadenectomy*. From Medline/Pubmed, 886 references were obtained; 34 references were obtained from Cochrane; and 971 references were obtained from Embase. Sixty-five articles were then selected based on content, abstract, and study format. Randomized trials with high levels of evidence were selected primarily, and well-designed control studies and comparative studies were also included. All of the selected articles were approved by a consensus of all participating authors.

3. Evidence synthesis

3.1. *Preoperative assessment of lymph node status*

Presence or absence of lymph node involvement has been shown to be predictive of outcome in patients who undergo RC and PLND. Today, pretreatment assessment of lymph node status is mainly based on imaging techniques like computed tomography (CT) and magnetic resonance imaging (MRI) with contrast enhancement, both of which are recommended by current guidelines [9].

The major shortcoming of this standard routine is the lack of accuracy and the evident discrepancy between clinical and pathologic staging for currently used CT and MRI devices [9–14]. Major studies have shown that patients who were staged N0 preoperatively proved to have positive lymph nodes at histology in approximately 25% of cases [5,15–19].

One of the reasons for the impaired detection of lymph node metastases is the fact that these techniques are mainly based on morphologic estimations such as size and shape of enlarged lymph nodes and, therefore, are not sufficient to detect very small metastases.

To overcome these deficiencies, several new techniques are currently being studied. One of these approaches uses positron emission tomography (PET), which allows noninvasive determination of various processes in vivo (energy and membrane metabolism, tissue perfusion, etc) [20]. Information regarding metabolic activity could support detection of lymph node metastases that are morphologically inconspicuous. Different protocols have been reported that used radiotracers like ^{18}F-fluorodeoxyglucose (FDG) or ^{11}C-choline in patients with muscle-invasive disease [20,21]. Although some small studies indicate that PET-CT may have a role in detection of nodal and distant metastases [20], larger clinical studies are needed to clarify the value of PET for this purpose.

Recently, the combination of CT and single photon emission computed tomography (SPECT) showed the potential to optimize preoperative anatomic localization of sentinel nodes in a small group of patients [22]. The number of sentinel nodes detected was markedly increased by using these two techniques in combination compared with conventional planar lymphoscintigraphy; however, SPECT cannot solve the problem of false-negative lymph nodes [23]. According to Liedberg et al, the rate of false-negative results may be as high as 20% [24]. In their review article, Bellin et al recently reported the use of ultrasmall superparamagnetic iron oxide (USPIO) particles [25]. USPIO is a lymph node–specific contrast agent for intravenous magnetic resonance lymphography. This technique showed a high sensitivity and specificity for diagnosing lymph node metastases in different urologic cancers.

Although encouraging initial reports on new techniques can now be found in the literature base, it will take time to validate the results before these new approaches can be integrated into clinical routine. Currently available standard imaging techniques are still not accurate enough to predict organ-confined tumors or pathologic node-negative disease in patients with invasive bladder cancer.

3.2. *Lymphadenectomy and distribution of lymph node metastases*

3.2.1. *Lymphadenectomy*

Mills et al [26] describe a *standard* lymphadenectomy (LAE) as a pelvic LAE that involves the removal of all

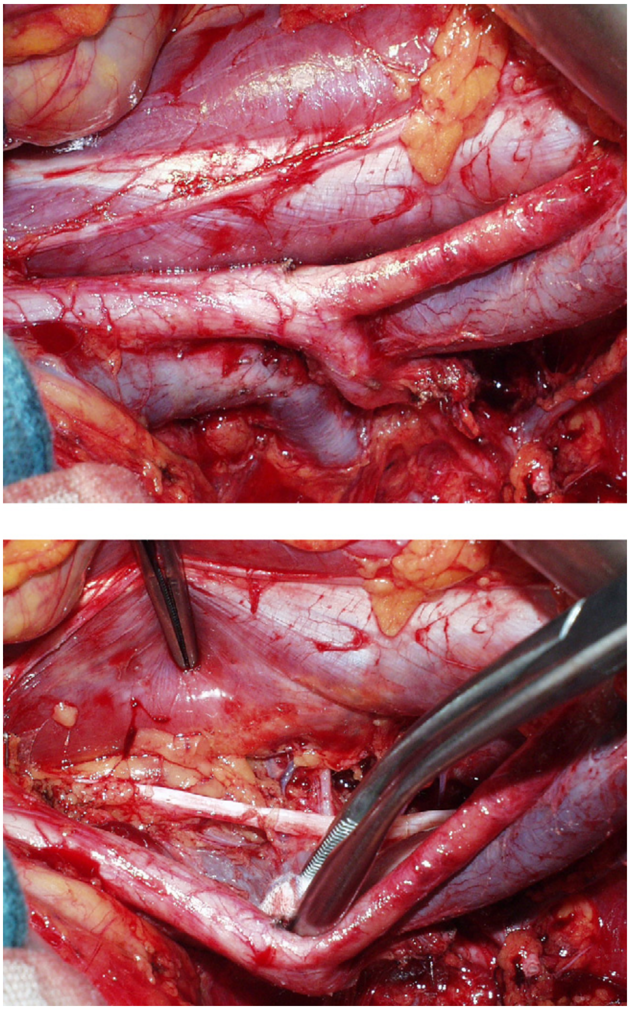

Fig. 1 – Meticulous pelvic lymph node dissection along the common, external, and internal iliac vas, including the lymph node tissue along the obturator nerve (picture by J. Gschwend).

nodal tissue up to and including the common iliac bifurcation, including the internal iliac (plus presacral), obturator fossa, external iliac, and distal common iliac (Fig. 1). The authors also recommend removal of tissue over the common iliac bifurcation up to the point where the ureter crosses the iliac vessel (as part of the external iliac area). The nodes medial to the ureter, (ie, around the proximal half of the common iliac artery/aortic bifurcation) are spared to avoid injury to the hypogastric nerves.

Stein et al [27] define an *extended* LAE as including all lymph nodes in the boundaries of the aortic bifurcation and common iliac vessels (proximally), the genitofemoral nerve (laterally), the circumflex iliac vein and lymph node of Cloquet (distally), the hypogastric vessels (posteriorly) including the obturator fossa, the presciatic nodes bilaterally, and the presacral lymph nodes.

3.2.2. *Localization of lymph node metastases*

Lymph node mapping studies help to define common landing sites of lymph node metastases [3,6,28,29]. Recently, a prospective multicenter study evaluated the pattern of lymphatic spread in 290 patients who underwent RC and extended PLND [4]. Lymph nodes were examined from 12 well-defined anatomic sites. The percentage of metastases at different sites ranged from 14.1% (right obturator nodes) to 2.9% (right paracaval nodes above the aortic bifurcation). Sixteen percent of lymph node metastases were detected above the aortic bifurcation, and 8% were detected in the presacral region. The authors concluded that if the dissection had been limited to the obturator sites, 74% of positive lymph nodes would have been left behind and about 7% of patients would have been understaged as lymph-node negative.

Vazina et al evaluated 176 patients (pT1–pT4) who underwent RC and PLND [6]. Of the 43 lymph node–positive patients, the percentage of metastases at different sites were as follows: aortic bifurcation (4%), common iliac nodes (right side: 5.7%; left side: 8%), presacral nodes (5.1%), pelvic nodes (right side: 12%; left side: 14%), perivesical nodes (2.8%), and pelvic nodes not specified (5.7%). Thirty-three percent of patients with involvement of the common iliac lymph nodes also showed positive nodes in the presacral region.

Abol-Enein et al evaluated 200 patients who underwent extended PLND [28]. The removed lymph nodes (median: 51 nodes per patient) were labeled according to the anatomic location of dissection. In 48 patients (24%), histopathologically positive lymph nodes were detected; 39% of these cases presented with bilateral lymph node involvement. Therefore, the authors advocated mandatory bilateral endopelvic dissection. This recommendation is supported by most of the current series [5,7,30].

Because no skipped lesions outside the small pelvis were found in this data set, the authors concluded that negative lymph nodes in the endopelvic region indicated that a more proximal dissection was not necessary.

El-Sahzli et al analyzed the role of extended LAE to the lower para-aortic area [31]. One skipped lesion was reported in a single patient (1 of 32 patients). The authors explained this observation referring to Shvetsov et al [32], who described lymphatic connections between the external iliac lymph nodes and aortic and lumbar nodes of the opposite side in 3% of cases.

Inevitably, there may be some overlap between areas of lymph node dissection that may complicate the accurate anatomic assignment of a removed lymph node and, therefore, the comparison between different studies. A node in the bifurcation of the common iliac artery, for instance, may be classified as common, internal, external, or obturator, depending mainly on the surgeon's estimation. This should be taken into account in the interpretation of all mapping studies. Collectively, these studies present debatable data regarding the spread of lymph node metastases in bladder cancer. However, these data indicate that a lymph node dissection encompassing only the nodes along the external iliac vessels and the obturator fossa would not be sufficient in a large number of cases.

Because skipped lesions are described only in rare cases, PLND is recommended at least along the external iliac vessel, along the obturator fossa, and on either side along the internal iliac vessels, including all nodes around the bifurcation of the common iliac artery (ie, at least up to where the ureters cross the common iliac artery).

3.3. *Possible benefits from an extended lymph node dissection*

If pelvic recurrence occurs after RC, the prognosis of patients gets very poor even with subsequent therapy, emphasizing the need for optimum local control at the time of initial treatment. Data of pelvic recurrence after RC are presented by Dhar et al [33]. All involved patients were initially clinically staged with organ-confined disease before RC. Some 130 patients who underwent limited bilateral pelvic LAE who later developed pelvic recurrence (defined as any radiographic soft-tissue density of $\geq$2 cm at or below the bifurcation of the aorta) were analyzed. The median time from RC to pelvic recurrence was 7.3 mo. Of the 130 patients, 128 (98.5%) died, with a 4.9-mo median survival length from the time of pelvic recurrence. Pelvic recurrence was found in 2.1% of pT1pN0 tumors, in 6.3% of pT2apN0 tumors, in 32.6% of pT2bpN0 tumors, in 45.6% of pT3apN0 tumors, in 76.0% of pT3bpN0 tumors, and in 66.7% of pT1–4 pN+ tumors.

Leissner et al showed that, for patients undergoing extended lymph node dissection, survival for both lymph node–negative and lymph node–positive patients improved, with a reduced local recurrence rate when a greater number of lymph nodes were removed [30]. It was shown that, when >16 lymph nodes were removed, the 5-yr recurrence-free survival rate increased from 63% to 85% in organ-confined tumors, from 40% to 55% in pT3 tumors, and from 25% to 53% in patients with up to (at most) five positive lymph nodes.

Poulsen et al [34] demonstrated that an extended lymph node dissection is beneficial in patients with organ-confined, lymph node–negative disease. There was a 5-yr recurrence-free survival rate of 90% in patients with organ-confined disease and without lymph node metastasis in the extended PLND group versus a rate of 71% in the standard PLND group ($p < 0.02$). Furthermore, an extended PLND reduced the pelvic and distant metastases rate in these patients.

Although these results seem very promising at first glance, they must be interpreted with caution. The Will Rogers phenomenon [35] must be remembered when analyzing prognosis outcomes in such series. A patient with only a few negative nodes removed may still have undiscovered positive nodes and thus may have a poor outcome. If many nodes are analyzed and classified negative, the likelihood of leaving behind undiscovered positive nodes is reduced, which results in a better prognosis for extended PLND.

Recently two series were evaluated that included patients with limited PLND (336 patients) and extended lymph node dissection (322 patients) [36]. All cases were staged preoperatively as N0 M0, and no patients received adjunct therapy. The 5-yr recurrence-free survival rate of patients with lymph node–positive disease was 7% for limited dissection and 35% for extended PLND. The 5-yr recurrence-free survival rate for pT2 pN0 cases was 67% for limited PLND and 77% for extended PLND, and the respective percentages for pT3 pN0 were 23% and 57% ($p < 0.0001$). The 5-yr recurrence-free survival rate for pT2 pN0–2 was 63% for limited PLND and 71% for extended PLND; for pT3pN0–2 cases the respective figures were 19% and 49% ($p < 0.0001$).

Collectively, these retrospective data suggest that limited PLND along the external iliac vessels and the obturator fossa only are associated with suboptimal staging and poorer outcome for patients with node-positive and node-negative disease. Extended PLND may allow for more accurate staging and for removal of undetected micrometastases. This could improve survival of patients with histopathologic lymph node–positive and –negative disease. Results from the German randomized multicenter study comparing an extended PLND versus limited PLND along with cystectomy are awaited.

Although an extended LAE may have beneficial effects on tumor treatment, the risks associated with an extended PLND must be carefully evaluated. The risk for elderly patients and especially for patients with comorbidities needs to be taken into account in all therapeutic decisions. Broessner et al analyzed whether an extended LAE would increase the morbidity in patients undergoing RC [37]. In this study, a cohort of 46 patients undergoing an extended LAE was compared with a matched group of 46 patients undergoing a standard LAE. For the extended LAE group, the operation time was found to be around 60 min longer compared with the limited approach. No significant difference in perioperative mortality, early complications, or the need for blood transfusions between the two groups was observed. The authors concluded that despite a prolonged operation time, an extended LAE appears not to increase the complication rate during or after (within 30 d after) surgery.

Also, in their retrospective analysis, Poulsen et al reported no significant impact of the extent of the LAE regarding mortality or lymphocele formation [34]. This observation is supported by Leissner et al, who report that lymphoceles and lymphedema were observed in 2% of patients with <16 lymph nodes removed and in 1% of patients with ≥16 lymph nodes removed [30]. The results of a multicenter prospective trial confirm the longer operation time (about 60 min) for an extended approach, whereas none of the participating centers observed any significant adverse side effects related to the extended LAE [4]. These studies collectively suggest that the morbidity associated with an extended LAE is comparable to a more limited approach; however, the risk of a longer operation time and associated complications needs to be respected for every patient individually.

In the current series, RC with an appropriate *extended* LAE extending at least up to where the ureter crosses the common iliac vessels seems to provide a clinically meaningful therapeutic benefit compared to a *limited* approach. Large prospective multicenter trials are needed to validate the influence of more extended PLND on disease-specific survival.

3.4. *Pathologic techniques for accurate lymph node assessment*

To obtain accurate data, PLND specimens need to be labeled according to the anatomic location of dissection and sent in separate portions (vials) to pathology. Stein et al demonstrated that the submission of 13 separate nodal packets increased the total number of lymph nodes removed and analyzed compared with en bloc submission [38]. Clinical observations such as an indurated lymph node or the number of lymph nodes palpated or the total number of lymph nodes seen should be reported to the pathologist.

To improve the identification of even small lymph nodes, several solutions other than formalin have been tested, such as the lymph node revealing solution (LNRS) of Koren et al [39] or similar recipes [40]. Tissue that is degreased using an LNRS allows for better discrimination of nodes, resulting in an increased lymph node yield and improved nodal staging when used in combination with conventional examination.

This procedure affects the mean size of newly detected lymph nodes, since visibility is improved. After exposure to LNRS, lymph nodes of <4 mm are detected in comparison to nodes of nearly 8 mm in conventional fixative. Consequently, the number of lymph nodes detected was doubled in this series [39].

An isolated node should be cut in 3-mm thick sections (recommended for accurate assessment of diameter, volume, extranodal growth, etc), and should be inspected for macrometastasis (usually >2 mm).

All lymph nodes should be embedded in sections of 3-mm thickness per capsule. Regarding further evaluation of lymphatic tissue using immunohistochemical analysis in clinical routine, Liedberg et al [41] and Yang et al [42] have stated that this method did not significantly improve the detection of micrometasases in excised lymph nodes.

In summary, a standardized and thus reproducible processing method for lymph nodes is essential. The pathologist should be informed accurately about the clinicians' findings and estimations. Fractioning and labeling of resected lymph nodes helps to improve quality and to raise lymph-node yield. To further support current evidence, it would be timely for the pathologist to report number of lymph nodes and total number in relation to number of metastatic lymph nodes as well as the extension of tumor cells beyond the lymph node structure.

3.5. *Molecular staging*

Molecular staging techniques are not in routine clinical use yet, but they aim to improve pathologic staging by detecting micrometastases in pelvic lymph nodes. Recently, the expression of cytokeratin 19 (CK19) and uroplakin II (UPII) was evaluated for prediction of the presence of lymph node metastases [43]. In this study, 760 lymph nodes of 40 patients who underwent RC and PLND were assessed. Histopathology detected 29 positive lymph nodes in six patients; however, positive expression of CK19 indicated the presence of a total of 49 positive lymph nodes and expression of UPII a total of 98 positive lymph nodes. The authors found that patients with micrometastases detected by these biomarkers had a statistically lower disease-specific survival rate compared with patients without micrometastasis, regardless of the presence of pathologically positive nodes.

Retz et al investigated mucin 7 (MUC-7) expression in the detection of micrometastasis in histopathologically normal lymph nodes [44]. MUC-7 proved to be positive in 46 of 160 (29%) histologically classified normal lymph nodes (pN0) from 17 bladder cancer patients.

Recently, Marín-Aguileria et al analyzed the expression of five genes to identify micrometastasis in lymph nodes using quantitative real-time polymerase chain reaction [45]. The combined expression of two genes (*FXYD3* and *KRT20*) was able to differentiate between positive lymph nodes and normal controls with 100% sensitivity and specificity. The expression of both genes indicated positive lymph nodes in 20.5% of patients with histologically negative lymph nodes.

Collectively, these studies demonstrate that biomarkers could enable the detection of micrometastases in about 20–30% of histopathologically negative lymph nodes. This represents a potential way to further optimize histopathologic staging. In contrast, the influence of micrometastases detected by such methods on patient outcome has not been sufficiently evaluated.

Despite the fact that results from prospective or randomized studies investigating the impact of molecular lymph nodes staging in bladder cancer patients are not available, there is strong evidence that molecular staging of lymph node tissue does more accurately detect micrometastatic node disease and that it may also predict prognosis. Although the biologic potential of metastases detected by molecular techniques is not known, it can be assumed that removal of *normal* nodes may be beneficial to some patients.

3.6. Different aspects of lymph node involvement as prognostic factors

Besides established prognostic factors like pathologic stage and tumor burden [3,5,30,46], there are other published prognostic factors that include different aspects of lymph node involvement.

3.6.1. Number of removed lymph nodes

Several studies indicate that the number of lymph nodes removed has prognostic significance in both lymph node–positive and lymph node–negative patients [4,47].

Different factors affect the actual number of lymph nodes removed and/or examined.

3.6.1.1. Surgical approach. A standard LAE as described by Fleischmann et al [48] obtains a mean of 23 nodes per patient, whereas an extended LAE (up to the inferior mesenteric artery) delivers a mean of 51 nodes per patient [28]. Many major series with a PLND at least up to the common iliac vessels [4–6,8,28,34,48] confirm an average yield of examined lymph nodes between 22 and 51 nodes per patient.

3.6.1.2. Physiologic variation. An anatomically based standard for pelvic LAE, published by Weingaertner et al [49], demonstrated substantial interindividual differences with a range of 8–56 removed lymph nodes per patient in the pelvic region (mean: 22.7 ± 10.2). The presence of such interindividual variances is supported by the findings of Fleischmann et al [48].

3.6.2. Pathologic work-up

As shown above, sending the nodal packages separately or using the degreasing solutions alone could double the number of detected and examined lymph nodes [39]. The accuracy (sections per block, etc) in the work-up of lymphatic tissue and the use of additional techniques may also play a major role.

Leissner et al [30] and Herr et al [50] found an effect of the number of nodes examined on survival, but these results could not be confirmed by Stein et al [46] when using the same template. Fleischmann et al [48] removed a mean of 23 pelvic lymph nodes in their series using the standard dissection approach. Interestingly, by grouping the patients in quartiles by the number of nodes examined, the authors could not demonstrate any significant differences in recurrence-free and overall survival rates. The authors suggested that a consistent radical LAE with equal accuracy and extent in each group led to equal outcomes irrespective of the absolute number of nodes removed explained by the interindividual variances.

As a guideline, removal of $\geq$20 lymph nodes per patient should be the aim. This value reflects the mean number of nodes that are removed during a meticulous pelvic LAE and is supported by Weingaertner's autopsy study [48,49].

For the performance of LAE, not only is the number of removed nodes important but the primary landing sites of lymph node metastases, as shown above, also need to be taken into account.

3.6.2.1. Number of positive nodes. Several studies have demonstrated that the absolute number of positive nodes affects patient outcome and survival. Different studies defined a cut-off level of five, six, and eight positive lymph nodes [5,17,46]. Subgroup analyses for all of these studies have shown a significantly better outcomes for patients with smaller absolute numbers of involved lymph nodes.

3.6.2.2. The concept of lymph node density. Lymph node density (LND) is defined as the ratio of positive lymph nodes to the total number of examined lymph nodes in percentage. LND reflects tumor burden in relation to the extent and quality of lymph node dissection. Stein et al evaluated the clinical outcome and risk factors for progression in 1054 patients [5]. Patients with LND ≤20% had a 43% chance of 10-yr recurrence-free survival compared with only 17% when LND was >20%.

Similar results were reported by Cheng et al, who examined 133 patients [51]. LND ≤20% was correlated with better disease-specific survival than LND >20%.

Kassouf et al compared the utility of LND with TNM nodal status in predicting disease-specific survival [52]. The 5-yr disease-free survival rate was 54.6% for patients with LND ≤20% versus 15.3% for patients with LND >20%. In this analysis, only LND >20% predicted decreased disease-specific survival.

It should be mentioned that if the extent of PLND increases, the likelihood of finding more negative (or positive) lymph nodes will increase, which would affect the LND. Physiologic differences in the total number of pelvic lymph nodes among individuals must also be taken into account [49]. This reason is why different authors recommend defining LND not simply as a percentage but rather in relation to the extent of PLND [26].

3.6.2.3. Extracapsular extension of pelvic lymph node metastasis. Fleischman et al analyzed the influence of extracapsular extension of pelvic lymph node metastases on patient prognoses [19]. This study evaluated 101 patients who underwent RC and extended PLND with curative intent who were diagnosed postoperatively with lymph node–positive disease. On average, 22 lymph nodes per patient were removed, with a median result of 2 positive nodes per patient. Some 59 patients (58%) were detected with extracapsular extension of lymph node metastases. The authors demonstrated that patients with extracapsular extension have significantly decreased recurrence-free survival (12 mo vs 60 mo) and overall survival (16 mo vs 60 mo) compared with those patients with intranodal metastases. According to multivariate analyses, extracapsular extension of lymph node metastases was the strongest negative predictor for recurrence-free survival in this data set.

In conclusion, provided that the PLND is representative (>20 nodes removed), then prognosis depends on the volume of metastases, the number of positive nodes, the ratio of positive nodes to total nodes, and the extent of extracapsular extension.

3.7. *Current TNM classification*

The presented data have highlighted the value of LAE not only as an important staging procedure but also as a procedure with therapeutic impact. The currently used TNM classification (2002) accounts for lymph node involvement only in a very basic way. Vieweg et al [8] demonstrated significant differences for disease-specific survival between patients with pN1, pN2, and pN3 disease. The 5-yr survival among groups was 44.2% in pN1 and 26.6% in pN2 disease. There were no survivors in the pN3 group after 3 yr of follow-up. Fleischmann et al, however, could not detect significant differences in recurrence-free and overall survival between the subgroups pN1 and pN2 [48]—a result that was also demonstrated by previous studies by Vieweg et al and by Roehrborn et al [53,54]. Herr et al [55] found no independent influence of different N stages in multivariate analyses for survival and local recurrences. The question, therefore, remains whether this classification needs to be adjusted to include factors such as LND, extracapsular growth, and number of removed lymph nodes.

The actual TNM system does not seem ideal for clinical purposes because it fails to incorporate various prognostic aspects of lymph node involvement. Inclusion of the number of positive nodes, the total number of nodes removed, and the presence or absence of extracapsular extension should be considered. A template of the exact location of removed lymph nodes should also be part of the system.

3.8. *Impact of lymph node involvement on long-term results following radical cystectomy*

A variety of studies have demonstrated that there is a chance of long-term survival in patients with lymph node–positive disease. Table 1 summarizes results of six large studies of patients treated with RC. In the selected six studies, 4133 patients were involved and a positive lymph node status was found in 23% of cases. Data from these analyses highlight that those patients with lymph node–positive disease had a mean 5-yr recurrence-free survival of 30% (20.9–35%) [5,15–19].

3.8.1. Radical cystectomy in patients with clinically positive lymph node disease

Herr et al analyzed the outcome of patients with grossly node positive bladder cancer after PLND and RC [56]. Included in this study were 83 patients treated with surgery alone (no neoadjuvant or adjuvant chemotherapy), presenting N2–3 disease, and with a follow-up of up to 10 yr. Twenty patients

Table 1 – Long-term survival outcome of patients with muscle-invasive bladder cancer treated with radical cystectomy with lymph node–positive (LN+) and lymph node–negative (LN−) disease

Study	No. of patients	No. of LN+ patients	LN+ survival, %	LN− survival	
				Organ-confined, %	Non–organ-confined, %
Stein et al [5]	1054	246			
5-yr RFS			35	–	–
10-yr RFS			34	–	–
pT0			–	86	–
pTis			–	89	–
pTa			–	74	–
pT1			–	78	–
pT2			–	–	87
pT3a			–	–	76
pT3b			–	–	61
pT4			–	–	45
5-yr OS			31	–	–
10-yr OS			23	–	–
Gschwend et al [15]	686	193			
5-yr DSS			31.2	66.7	
10-yr DSS			27.7	61.7	
5-yr OS			25	57.0	
10-yr OS			20.9	40.8	
Madersbacher et al [18]	507	121			
5-yr RFS			33	73	56
10-yr RFS			–	58	49
5-yr OS			26	62	49
Lerner et al [17]	591	132			
5-yr PFS			29	NR	NR
10-yr PFS			20	–	–
Hautmann et al [16]	788	142			
5-yr RFS			20.9	–	–
T2a			–	82.5	–
T3a			–	61.9	–
T2b			–	–	61.9
T3b			–	–	53.1
10-yr RFS			14.6	NR	NR
Fleischmann et al [19]	507	124			
5-yr RFS			32	NR	NR
5-yr OS			30	–	–

RFS = recurrence-free survival; PFS = progression-free survival; DSS = disease-specific survival; OS = overall survival; NR = not reported.

(24%) survived, and 64 patients (76%) died of the disease. Although this single study deals with a highly selected patient cohort, it appears that some patients with grossly node-positive bladder cancer have a chance of cure with RC through pelvic lymph node dissections. However, based on more recent results, inductive or preoperative chemotherapy, if feasible, would be preferable.

4. Conclusions

There is ample evidence from many centers that patients with metastases or micrometastases to a few pelvic lymph nodes have a chance of survival of approximately 30%, provided that the diseased nodes are removed. Evidence from the literature suggests that the template for PLND should at least include the regions of the external and internal iliac vessels together with the obturator fossa and should encompass the distal part and the bifurcation of the common iliac vessels on both sides. Whether a more extensive and/or cephalad LND is beneficial for the patients and outweighs its potential risks (eg, damage to autonomic nerves, possible surgical complications, prolonged surgical time) must actually be addressed on prospective randomized trials.

Author contributions: Alexander Karl had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Montorsi, Studer.
Acquisition of data: Karl.

Analysis and interpretation of data: Carroll, Gschwend, Knüchel, Stief, Montorsi, Studer.
Drafting of the manuscript: Karl.
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