available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Collaborative Review – Bladder Cancer

Lymphadenectomy for Bladder Cancer at the Time of Radical Cystectomy

Derya Tilki [a,b,*], *Maurizio Brausi* [c], *Renzo Colombo* [d], *Christopher P. Evans* [a], *Yves Fradet* [e], *Hans-Martin Fritsche* [f], *Seth P. Lerner* [g], *Arthur Sagalowsky* [h], *Shahrokh F. Shariat* [i], *Bernard H. Bochner* [j]

[a] *Department of Urology, University of California, Davis, Medical Center, Sacramento, CA, USA;* [b] *Department of Urology, Ludwig-Maximilians-University, Munich, Germany;* [c] *Department of Urology, Ausl Modena, Modena, Italy;* [d] *Department of Urology, University Vita-Salute, Milan, Italy;* [e] *Laval University, Québec City, Québec, Canada;* [f] *University of Regensburg, Caritas St. Josef Medical Center, Regensburg, Germany;* [g] *Baylor College of Medicine, Houston, TX, USA;* [h] *University of Texas Southwestern Medical Center, Dallas, TX, USA;* [i] *Weill Cornell Medical Center, New York, NY, USA;* [j] *Urology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA*

Article info

Article history:
Accepted April 19, 2013
Published online ahead of print on April 29, 2013

Keywords:
Bladder cancer
Lymphadenectomy
Systematic review

Abstract

Context: Although the importance of lymphadenectomy during radical cystectomy (RC) in high-risk non–muscle-invasive and muscle-invasive bladder cancer (BCa) is well accepted, the optimal extent of lymphadenectomy, number of lymph nodes (LNs) to be retrieved, and prognostic and therapeutic role of lymphadenectomy remain debated issues.
Objective: In this review, we summarize the existing data on the value of lymphadenectomy for staging and outcome of BCa patients undergoing RC and lymphadenectomy.
Evidence acquisition: A systematic Medline/PubMed literature search of peer-reviewed scientific articles published from 1998 and 2012, concerning the role of lymphadenectomy in BCa patients, was carried out. The terms and permutations used were *lymphadenectomy, bladder cancer/carcinoma, urothelial carcinomas, radical cystectomy, lymph node metastasis, lymph node dissection, bladder, recurrence*, and *survival*. Selective older articles were included.
Evidence synthesis: Bilateral pelvic lymphadenectomy is an integral part of RC for BCa. The literature regarding the role of lymphadenectomy in BCa patients in general is retrospective, nonstandardized, and of low-level quality in regard to evidence. Prospective randomized trials designed to define the optimal template of lymphadenectomy and its impact on oncologic outcome are advocated. Some of these studies are ongoing, and their completion and analyses are necessary to resolve controversies.
Conclusions: Many consistent and concordant observations, although of low level of evidence, document that the extent of lymphadenectomy may influence disease-free survival after RC independent of the status of LNs and the pathologic stage of BCa. Lymphadenectomy standardization at the time of RC to create evidence-based guidelines is essential for further improvement of surgical quality and BCa patient survival.

* Corresponding author. Department of Urology, University of California, Davis, Medical Center, 4860 Y Street, Suite 3500, Sacramento, CA 95817, USA. Tel. +1 916 734 2011.
E-mail address: derya.tilki@ucdmc.ucdavis.edu (D. Tilki).

http://dx.doi.org/10.1016/j.eururo.2013.04.036

1. Introduction

For patients with muscle-invasive bladder cancer (BCa) and patients with high-risk non–muscle-invasive BCa, radical cystectomy (RC) with bilateral pelvic lymphadenectomy provides accurate staging and adequate local and regional control [1–3]. Besides pathologic tumor stage (pT), lymph node (LN) status is the strongest prognostic factor in patients with BCa [1–3].

Although the importance of lymphadenectomy in management of muscle-invasive BCa is generally accepted [4], no consensus exists regarding the optimal extent of lymphadenectomy, the number of LNs to be retrieved, or the magnitude of the therapeutic benefit in patients with BCa undergoing RC [5,6]. This lack of consensus is mainly because of a lack of prospective randomized studies that compare limited lymphadenectomy with extended lymphadenectomy in BCa patients.

At present, the European Association of Urology and the American Urological Association guidelines do not offer clear recommendations about the field or extent of lymphadenectomy [7]. The International Consultation on Urological Diseases 2012 guidelines recommend that lymphadenectomy at RC remove all lymphatic tissue around the common iliac, external iliac, internal iliac, and obturator group bilaterally, since as many as one-third of all positive nodes are located around the common iliac artery (level of evidence 2b–3) [8].

We summarize the available data on pelvic lymphadenectomy, which have been obtained either retrospectively or nonrandomized prospectively. In addition, we give some insight into the status of two prospective randomized trials on extended lymphadenectomy compared with standard lymphadenectomy that are ongoing and yet to be published.

2. Evidence acquisition

A systematic literature review was performed searching the electronic databases PubMed/Medline. The search was performed using combinations of the following terms: *lymphadenectomy, bladder cancer/carcinoma, urothelial carcinomas, radical cystectomy, lymph node metastasis, lymph node dissection, bladder, recurrence*, and *survival.* A total of 2153 references were obtained. Sixty-three articles were selected based on title, abstract, study format, and content by a consensus of all participating authors. The majority of articles considered were published between 1998 and 2012. The literature regarding the role of lymphadenectomy in BCa patients in general is retrospective, nonstandardized, and of low-level quality in regard to evidence. Conclusions drawn from the studies are subject to significant biases inherent in observational studies of surgical procedures. Older studies were included selectively if historically relevant or if there were limited data in more recent publications. No evidence level 1 information from prospective randomized trials was available.

3. Evidence synthesis

3.1. *Current evidence*

3.1.1. *Lymphatic drainage from the bladder/anatomic boundaries of lymphadenectomy/distribution of positive lymph nodes*

Several studies of patients who underwent RC and lymphadenectomy have revealed that primary lymphatic drainage of BCa extends into the internal iliac, external iliac, obturator, and presacral LNs. Secondary drainage progresses into the common iliac LNs and then into the para-aortic, interaortocaval, and paracaval LNs [5,9,10].

The optimal anatomic boundaries of an appropriate lymphadenectomy remain unclear, partly because of conflicting data regarding the anatomic distribution and patterns of LN metastases in BCa patients [5,9,10]. Several contemporary mapping studies have been published.

To define the optimal extent of lymphadenectomy during cystectomy, Abol-Enein and colleagues performed 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 inferior mesenteric artery (IMA) [9]. Of the patients, 48 (24%) had positive nodes, including 8 patients with $\leq$pT2 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 endopelvic site composed of the internal iliac, external iliac, and obturator groups of LNs as the sentinel regions.

In contrast, Leissner et al., who conducted an analysis of LNs at 12 different anatomic sites in 290 patients, did not identify a well-defined sentinel LN site [5]. 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 patients (27.9%) had positive LNs, including 18 patients (6.2%) with $\leq$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. studied 176 consecutive patients (pT1–pT4) who underwent RC and lymphadenectomy. LN metastases were found in 1 patient (3.6%) with pT1, 10 patients (15.6%) with pT2, 20 patients (40%) with pT3, and 12 patients (50%)

with pT4. In patients with stage ≤pT2, LN metastases were found exclusively in the pelvic region, except in two patients (3%) 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 lymph node dissection (LND; nodal involvement of the common iliac nodes and at or above the aortic bifurcation) [10]. A skip lesion was detected in one patient with positive nodes at or above the common iliac bifurcation.

Tarin et al. evaluated 591 patients who underwent RC with mapping pelvic LND [11]. LN involvement was identified in 114 patients (19%). Stratified by tumor stage <pT2, pT2, pT3, and pT4, LN involvement was identified in 18 patients (6%), 16 patients (18%), 68 patients (40%), and 12 patients (60%), respectively. Of the node-positive group, seven patients (6%) had LNs involved only above the common iliac bifurcation (skip lesions) [11]. Since 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.

The pathoanatomic studies have two main limitations in common. First, it remains undetermined how many LNs are left behind and in which anatomic locations. Second, the area to which a removed LN is assigned may vary by surgeon.

The combination of lymphoscintigraphy and computed tomography (CT) can enhance preoperative anatomic localization of sentinel nodes in BCa and aid in the identification of sentinel nodes during surgery [12,13]. Roth and colleagues used multimodality single-photon emission CT (SPECT)/CT plus intraoperative γ probe to show the template of the bladder's primary lymphatic landing sites and found that extension of the lymphadenectomy to the common iliac region up to the ureteroiliac crossing would incorporate 92% of initial drainage sites. The authors found 4% of all technetium Tc 99m–positive LNs, or 12% of all Tc 99m–positive LNs along the external iliac vessels, in the fossa of Marcille (dorsolateral to the proximal external iliac vessels and dorsal to the junction of the ureters with the common iliac vessels). A limitation of the study is that LN tissue medial to the common iliac vessels, the lower para-aortic/paracaval nodes, and the presacral nodes was not routinely dissected because the authors assume that preservation of autonomic nerves may lead to better sexual and pelvic floor function postoperatively [14].

Analysis of the data of 40 patients with cystectomy and unilateral BCa using multimodality SPECT/CT plus intraoperative γ probe by the same group showed that crossover lymphatic drainage (positive LNs on the contralateral side) was a common phenomenon, and unilateral pelvic LND would have missed radioactive LNs in 40% of patients. However, the authors noted no lymphatic drainage to the contralateral internal iliac region, thus concluding that contralateral pelvic LND can be limited to the obturator fossa and external and common iliac regions when bladder tumors are strictly unilateral [15].

3.1.2. Nodal staging system

3.1.2.1. Historical perspective and development of the current nodal staging system. The current nodal staging system finds its origin in detailed anatomic studies from the early 20th century [16]. Colston and Leadbetter performed a landmark autopsy study on 98 cases of BCa in 1936 [17]. They described pelvic or retroperitoneal metastasis in 25% of the cases and postulated that LND might cure early locoregional disease [16]. Jewett and Strong described the first staging system of the local tumor in 1946 [18]. In 1950, McDonald described the concept of vascular and lymphatic invasion and showed that there was a direct relation to prognosis [19]. In the same year, Leadbetter and Cooper presented the surgical boundaries and approach of an extended lymphadenectomy, in which the common iliac LNs were identified as the secondary echelon of metastases, intermediating between the pelvic and aortocaval LNs [16]. Marshall presented a modification of the Jewett/Strong staging system in 1952, when he introduced a stage description for the definition of the extent of metastatic disease. He described two categories, in which continuous local, lymphatic, and distant tumor spread were merged: Stage D1 lesions were confined to the pelvis, including invasion of the pelvic walls, and stage D2 lesions were beyond the limits of the pelvis [20]. The aortic bifurcation was chosen arbitrarily instead of the sacral promontory to segregate the two stages when LNs were involved.

BCa was TNM-classified for the first time in 1974 by the Union Internationale Contre le Cancer (UICC)/Committee on TNM Classification. The new system included a separation, for classification of those tumors associated with metastases, to either regional nodes (N) or distant sites (M). At that time these distinctions were judged as having little practical importance because of serious limitations in the ability to detect early metastases, as well as the inability to influence prognosis once gross metastases were apparent [21].

In 1977, the American Joint Committee on Cancer (AJCC) published the first edition of its TNM staging system [22]. Through a collaborative effort, the recommendations in the publications of the UICC and the third edition of the AJCC's manual became identical after 1987. The definitions of the nodal stations and the changes in the pN substaging over the years are summarized in Table 1.

3.1.2.2. Preoperative node staging. CT of the abdomen and pelvis is used as a routine procedure for the preoperative staging assessment of muscle-invasive BCa [7]. However, this CT has limited accuracy to detect LN metastasis.

Paik et al. 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 4 patients (4.9%) [23]. Ficarra et al. evaluated the data of 156 patients, 45 (28.8%) of whom had pathologic LN involvement. This involvement was foreseen with pelvic CT in only 19 patients [24]. Tritschler and colleagues reported an accuracy of 54% for CT in predicting LN metastases [25].

Kibel et al. demonstrated a positive predictive value of 78%, a negative predictive value of 91%, sensitivity of 70%, and specificity of 94% for fludeoxyglucose positron emission

Table 1 – Overview of the development of N staging according to the American Joint Committee on Cancer's *Cancer Staging Manual*

	Edition 1 (1977)	Edition 2 (1983)	Edition 3 (1988)	Edition 4 (1992)/Edition 5 (1997)/ Edition 6 (2002)	Edition 7 (2009)
Definition of nodal stations	The regional lymph nodes are the pelvic nodes below the bifurcation of the common iliac arteries. The juxtaregional lymph nodes are the inguinal, common iliac, and para-aortic nodes.	The regional lymph nodes are the nodes of the true pelvis, whose anatomic boundaries are subtended by the arcuate line and planes involved. The fixed points of the pelvis are the pubic crest, pectineal line, medial border of ilium, ala of sacrum, and sacral promontory. Distant nodes are all others.	The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. Distant nodes are all others. Laterality does not affect the N classification. The significance of regional lymph node metastasis in staging bladder cancer lies in the number and size, not in whether unilateral or contralateral.	The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. The common iliac nodes are considered sites of distant metastasis and should be coded as M1. The significance of regional lymph node metastasis in staging bladder cancer lies in the number and size, not in whether metastasis is unilateral or contralateral.	The regional lymph nodes draining the bladder include primary and secondary drainage regions. Primary nodal regions drain into the common iliac nodes, which constitute a secondary drainage region. The relevant information from regional lymph node staging is obtained from the extent of disease within the nodes, not from whether metastases are unilateral or contralateral.
Nx	Minimum requirements cannot be met.	Minimum requirements to assess the regional nodes cannot be met.	Regional lymph nodes cannot be assessed.	Regional lymph nodes cannot be assessed.	Regional lymph nodes cannot be assessed.
N0	No involvement of regional lymph nodes.	No involvement of regional lymph nodes.	No regional lymph node metastasis.	No regional lymph node metastasis.	No regional lymph node metastasis.
N1	Involvement of a single homolateral regional lymph node.	Involvement of a single homolateral regional lymph node.	Metastasis in a single lymph node, $\leq$2 cm in greatest dimension.	Metastasis in a single lymph node, $\leq$2 cm in greatest dimension.	Single regional lymph node metastasis in the true pelvis.
N2	Involvement of contralateral, bilateral, or multiple regional lymph nodes.	Involvement of contralateral, bilateral, or multiple regional lymph nodes.	Metastasis in a single lymph node, $>$2 cm but $\leq$5 cm in greatest dimension, or multiple lymph nodes, none $>$5 cm in greatest dimension.	Metastasis in a single lymph node, $>$2 cm but $\leq$5 cm in greatest dimension, or multiple lymph nodes, none $>$5 cm in greatest dimension.	Multiple regional lymph node metastasis in the true pelvis.
N3	There is a fixed mass on the pelvic wall with a free space between the wall and the tumor.	There is a fixed mass on the pelvic wall with a free space between the wall and the tumor.	Metastasis in a lymph node $>$5 cm in greatest dimension.	Metastasis in a lymph node $>$5 cm in greatest dimension.	Lymph node metastasis to the common iliac lymph nodes.
N4	Involvement of juxtaregional lymph nodes.	Not defined.	Not defined.	Not defined.	Not defined.

tomography (PET)/CT in the detection of positive LNs [26]. Vargas et al. recently evaluated the diagnostic performance of magnetic resonance imaging (MRI), 11C-acetate PET/CT, and contrast-enhanced CT for BCa staging and found that the three imaging modalities displayed similar levels of accuracy [27]. In their analysis, MRI correctly staged 56% of patients (9 of 16), overstaged 38% (6 of 16), and understaged 6% (1 of 16). CT correctly staged 50% of patients (8 of 16), overstaged 44% (7 of 16), and understaged 6% (1 of 16).

LND remains the most accurate LN staging procedure.

3.1.3. Prognostic importance of lymph node status

LN status is a powerful predictor of cancer-specific survival (CSS). Different series of BCa patients treated with RC and lymphadenectomy have shown that up to 70–80% of patients with histologically LN-positive disease experience disease recurrence, compared with 30% of patients with histologically negative LNs and extravesical disease [28,29]. The International Bladder Cancer Nomogram Consortium studied data of 9064 patients who underwent RC and lymphadenectomy, including 1550 patients with LN-positive disease managed with surgery alone [30]. The authors have developed an international BCa nomogram that predicts recurrence risk after RC for BCa using information on patient age, sex, time from diagnosis to surgery, pathologic tumor stage and grade, tumor histologic subtype, and regional LN status. A series of nomogram models were constructed to include either total number of LNs removed, number of positive LNs, or ratio of positive LNs to total LNs removed (LN density). However, node status alone outperformed these node parameters and therefore was placed in the final nomogram model.

3.1.3.1. Role of number of lymph nodes removed. The LN count has been widely used as a surrogate for extent of lymphadenectomy and was shown to be an important prognostic factor in BCa patients [5,31–35]. While the benefit of lymphadenectomy for oncologic outcome was originally reported in LN-positive patients [36], its value in LN-negative cases has been shown as well in uncontrolled nonrandomized series [34].

In 1982, Skinner reported that lymphadenectomy can cure up to one-third of patients with LN metastases [36].

Leissner et al. studied 447 patients who underwent RC and correlated the number of LNs with clinical outcome [37]. Survival was analyzed using a threshold value of 16 LNs, because the correlation between the total number of LNs removed and the percentage of patients with positive nodes was strongest at this boundary. The authors found significant differences in the tumor-specific survival and the disease-free interval between patients with $\geq$16 LNs removed and patients with $<$16 LNs removed [37]. At 5 yr, 65% of the patients with $\geq$16 LNs removed were disease-free and alive, whereas only 51% of the patients with $<$16 LNs removed were tumor-free and alive. A limitation of the study was that one-third of cases were not followed.

Herr et al. analyzed data on 322 patients with muscle-invasive BCa who underwent RC and bilateral pelvic lymphadenectomy [33]. The authors evaluated the associations of the number of LNs retrieved with the local recurrence rate and survival outcome [33]. In both LN-negative and LN-positive cases, improved survival (40% and 30% improvements at 5 yr, respectively) was associated with a greater number of LNs examined. Herr and colleagues concluded that nine or more LNs should be studied to define LN status accurately.

In another study, Herr reports 5-yr overall survival rates of 33% in patients with 0–5 examined LNs, 44% with 6–10 nodes, 73% with 11–14 nodes, and 79% with $>$14 nodes [38].

May et al. studied the records of 1291 LN-negative BCa patients undergoing RC and reported that identification of a higher LN count is associated with an improved oncologic outcome [34]. In line with Leissner and colleagues, May et al. defined an LN threshold of $\leq$16 to be significantly associated with CSS. Patients with $<$16 and $\geq$16 removed LNs showed CSS rates after 5 yr of 72% and 83%, respectively.

While other groups also defined a minimum number of LNs between 9 and 16 to be removed to confer a survival benefit [31], Koppie et al. could not identify an optimal number of LNs sufficient for maximizing BCa outcomes when a limited or extended pelvic LND is performed during RC [39]. In their study, the probability of survival continued to rise as the number of LNs removed increased, up to a maximum of 24 nodes identified. However, lymphadenectomy was performed no higher than the IMA, so information beyond that level was not provided. A retrospective multicenter study suggested that 90% of patients with LN metastasis were identified when 45 nodes were counted by the pathologist, suggesting that a thorough anatomic node dissection and analysis of all potential node-bearing tissue by the pathologist may optimize the sensitivity for detection of node metastasis. The minimal limits of the node dissection in this study consisted of the genitofemoral nerve, bladder, bifurcation of the common iliac vessels, femoral canal, hypogastric vessels, and obturator fossa [31].

3.1.3.1.1. Biases from these studies. These retrospective studies include important limitations. Most important, the studies were not controlled for the extent of lymphadenectomy and were based on surgeon preference. Patients with significant comorbidities might have undergone limited lymphadenectomy more often compared with healthier patients. Koppie et al. demonstrated that older and sicker patients are less likely to have an LND, and if they do, they are more likely to have fewer LNs removed [39].

Thus, the patients who were selected to undergo more limited LND may have had greater comorbidities and inherently lower overall survival because of increased competing risks for mortality. This possibility suggests that overall survival as an end point is problematic and difficult to interpret in these studies. Also, since LN count has been used as a surrogate for extent of lymphadenectomy in most studies, the anatomic limits of lymphadenectomy were variable and comparisons difficult. Most studies involved multiple surgeons and differing handling of specimens; these characteristics have most likely influenced results, because the number of LNs dissected is largely dependent on the surgeon and LN packaging [38,40–43]. The pathologist was not identified as an independent variable associated with LN count, although this is theoretically possible [39]. (For further details, see sections 3.1.3.1.2 and 3.1.3.1.3.)

3.1.3.1.2. Surgical factors affecting lymph node counts. The number of retrieved LNs depends on the thoroughness, quality, and extent of lymphadenectomy. Fang et al. assessed the impact of an institutional policy requiring that a minimum number of 16 LNs be examined [42]. Specimens with <16 LNs were resubmitted (including any fat) to detect additional LNs. After policy implementation, the median number of LNs increased from 15 to 20. The percentage of cases with ≥16 LNs increased from 42.9% to 69.3%. The LN positivity rates did not change significantly, but the proportion of patients with LND <20% increased from 43.9% to 65.5%. Overall survival increased from 41.5% to 72.3% [42].

Bochner et al. prospectively evaluated RC cases to determine which factors may contribute to the variability in the number of reported LNs and found that only the extent of the LND influenced node yield significantly [40]. Minimally invasive approaches have been criticized for limiting the extent of lymphadenectomy. However, several studies have documented that adequate pelvic lymphadenectomy, which is comparable to that recommended for open surgery, can be performed safely with robotic assistance. LN retrieval appears not to be adversely affected with the use of minimally invasive surgery tools [44,45].

3.1.3.1.3. Nonsurgical factors affecting lymph node counts. The number of LNs retrieved is dependent not only on surgical factors but also on the careful examination by the pathologist. The pathologic processing technique may have an important effect on prognostic parameters such as LN yield. Bochner and colleagues evaluated the impact of separate compared with en bloc pelvic LND on the number of LNs retrieved in cystectomy specimens [41]. In their analysis, standard and extended lymphadenectomy en bloc specimens yielded a mean of 2.4 and 22.6 LNs, respectively, compared with 8.5 and 36.5 LNs retrieved from separate LN specimens. Stein et al. confirmed the effect of separate package compared with en bloc submission of LNs on LN counts. The authors found that the submission of 13 separate nodal packets at RC significantly increased the total number of LNs removed and identified a higher number of positive LNs compared with en bloc submission [46]. Based on the variations seen in reported LN counts, a distinct recommendation on number of LNs to be removed does not seem feasible.

3.1.3.2. Studies that try to control for biases: outcomes of limited compared with anatomically extended lymphadenectomy. Only limited data are available regarding the impact of a defined anatomically extended lymphadenectomy on clinical outcome in BCa patients. Poulsen et al. compared extended LND up to the aortic bifurcation and endopelvic LND only [47]. The authors found that the extended dissection reduced the 5-yr probabilities for pelvic and distant metastasis for patients with ≤pT3a disease.

To overcome some of the aforementioned limitations of earlier studies, Abol-Enein and colleagues performed a prospective nonrandomized single-center study evaluating the impact of performance of a defined extended lymphadenectomy on disease-free survival (DFS). The operative procedure was performed by only two high-volume surgeons to subdue an operator-dependent variable. Specimens from individual anatomic regions were sent separately and evaluated by a single uropathologist [48]. An intraoperative decision was made to perform an extended dissection based on status of the liver, body mass index, and performance status. The authors found that an anatomically defined extended lymphadenectomy up to the level of origin of the IMA, compared with a standard lymphadenectomy (endopelvic region composed of the internal iliac, external iliac, and obturator groups of LNs), was associated with better DFS for LN-positive BCa patients independent of other clinicopathologic features (5-yr DFS: 48.0% compared with 28.2%). The authors suggest that nodal disease identified by frozen section in the endopelvic region (standard lymphadenectomy) necessitates dissection up to the aortic bifurcation. The nonrandomized nature of the study limits conclusions regarding the survival benefit for the extended node dissection. These data suggest that some patients with nodal involvement can be cured by meticulous extended lymphadenectomy. The study is limited by the lack of randomization and no a priori prospective statistical assumptions [48].

Dorin and colleagues compared the distribution of LN metastases in 646 patients undergoing RC at the University of Southern California and at Oregon Health Sciences University using a uniformly applied extended LND template [49]. Twenty-three percent of the patients had LN metastases at the time of cystectomy. The authors found a difference in the median per-patient LN count between institutions, which may be due to the interindividual variability in number of pelvic LNs, but they found no significant interinstitutional differences in the incidence or distribution of positive LNs. Among LN-positive patients, 41% had positive LNs above the common iliac bifurcation. The authors concluded that adherence to meticulous dissection technique within an extended template might be more important than total LN count for achieving optimal oncologic outcomes [49].

Two contemporary retrospective comparisons of patients undergoing a limited LND compared with a more extensive LND [50] or *extended* LND (mid–common iliac) compared with a *superextended* LND (up to the IMA) [51] suggest that there may be superior survival probabilities associated with a more extensive LND for all patients undergoing RC.

However, these studies offer only low-level evidence, because they were nonrandomized, were retrospectively evaluated, and selected patients who underwent lymphadenectomy dependent on the surgeons' preference.

3.1.3.3. Outcomes based on number of positive lymph nodes and ratio of positive lymph nodes (lymph node density)

3.1.3.3.1. Outcomes based on number and location of positive lymph nodes. Stein et al. evaluated the clinical outcomes and risk factors for progression in patients with LN metastases following RC and bilateral pelvic lymphadenectomy [52]. The authors found that the total number of LNs involved with tumor was a significant prognostic variable. Patients with eight or fewer positive LNs had significantly higher survival rates compared with patients with more than eight positive LNs. Five-year and 10-yr recurrence-free survival (RFS) for patients with eight or fewer LNs was 41% and 40%, respectively, compared with only 10% RFS at 10 yr when more than eight LNs were involved with tumor [52]. Kassouf and colleagues found that the number of positive nodes was significantly associated with RFS on univariate analysis but was not statistically significant on multivariate analysis [53].

Jensen et al. analyzed 167 patients who underwent RC and extended LND to the level of the IMA. Forty-three patients (26%) had LN metastases. Female gender, advanced T stage, presence of LN metastasis, nonregional LN metastases (M positive), and number of positive LNs (one compared with more than one) were found to be significant adverse prognostic predictors in multivariate analysis [54].

Tarin et al. evaluated the effect of the location of regional pelvic nodal involvement on RFS and on CSS in 591 patients who underwent RC with pelvic LND [11]. The authors showed that patients with positive common iliac LN metastasis removed at the time of RC have a similar outcome when compared with patients with nodal disease limited to the true pelvis. The authors reported 5-yr RFS and CSS of 38% and 45% for pN1 disease, 35% and 31% for pN2 disease, and 25% and 42% for pN3 disease, respectively. After adjustment for age, gender, pathologic histology, stage, node density, location of positive nodes, perioperative chemotherapy, and grade, Tarin and colleagues found that the number of positive LNs (none, one, or two or more) was significantly associated with cancer-specific death, whereas the location of the positive LNs was not [11].

3.1.3.3.2. Lymph node density. *LN density* describes the ratio of positive LNs to the total number of retrieved nodes [55,56]. Reports on LN density have suggested a predicative importance; however, other studies have not demonstrated that LN density adds additional prognostic importance over information obtained from LN status alone or the number of positive LNs and number of total LNs retrieved alone.

Herr retrospectively studied LN density as a prognostic factor in BCa survival after cystectomy and found that cases with a ratio of >20% positive LNs after pelvic lymphadenectomy had a worse prognosis compared with cases with a ratio of ≤20% [55]. Stein et al. analyzed their results using LN density in a population of BCa patients who underwent an extended lymphadenectomy up to the aortic bifurcation and confirmed the prognostically relevant threshold of 20% [52]. However, the median number of nodes removed was 13 in the study by Herr [55] and 30 in the study by Stein et al. [52].

LN density has been the subject of several subsequent reports with a wide variation in the number of retrieved nodes and different threshold values of LN density [57–59]. Kassouf and colleagues reported the superiority of LN density compared with TNM nodal status in predicting disease-specific survival (DSS) after RC [57]. Wiesner et al. showed that LN density was an independent predictor of DSS in multivariate analysis [59]. May and colleagues confirmed LN density (ordinal scaled by 20%), but not pN stage, as an independent predictor of DSS in 477 patients with LN-positive BCa [58]. In contrast, Tarin et al. demonstrated no added prognostic advantage of LN density over LN status alone in their series of 591 patients who underwent extended lymphadenectomy [11]. Similarly, Jensen and colleagues evaluated the prognostic impact of LN variables in 167 patients undergoing RC and extended LND and found that stratification according to LN density had no prognostic value [54].

3.1.3.4. Extracapsular extension and nodal metastatic load. In a limited number of series, extracapsular extension (ECE) of LN metastases has been reported to be the strongest factor predicting prognosis in LN-positive patients. Mills and associates reported their experience with 83 LN-positive patients treated by cystectomy and pelvic dissection up to the bifurcation of the common iliac arteries and found capsular infiltration to be the only independently significant prognostic factor [6]. However, lymphadenectomy was limited to the pelvic LNs in their study. Fleischmann et al. analyzed a consecutive series of 507 patients and confirmed ECE of LN metastases as an independent factor predicting prognosis [60].

Fajkovic et al. sought to verify the independent prognostic value of extranodal extension (ENE) in a large, multi-institutional cohort of patients treated with RC for urothelial cancer of the bladder and to test whether ENE improved the accuracy of predictive models, including established clinical and pathologic predictors of cancer recurrence and mortality [61]. The authors found that ENE was a powerful prognosticator of oncologic outcomes, regardless of receipt of adjuvant chemotherapy or number of LNs removed.

Seiler et al. reviewed the data of 162 LN-positive patients and found that tumor stage, ECE of LN metastases, and total diameter of LN metastases were significantly correlated with overall survival, DSS, and RFS in univariate analysis [62]. However, on multivariate analysis, only ECE and primary tumor stage added independent prognostic information. Nevertheless, the level of evidence supporting ECE as a powerful prognostic factor is low.

3.1.3.5. Recommendations for adequate dissection for staging. The following recommendations are made for adequate dissection for staging:

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

- Dissection of the common iliac and presacral nodes may provide more accurate N staging among patients with node metastases according to the current TNM classification.
- It is unclear whether the cranial dissection limitation at the aortic bifurcation provides equivalent or better accuracy of N staging compared with a limitation at the ureteroiliac crossing.
- A preoperative or intraoperative tailoring of extent because of presumably organ-confined tumor stages seems to be insufficient because of a low predictive capacity of current clinical or intraoperative staging and the small but real risk of nodal involvement in early-stage ($\leq$pT2) disease.
- A distinct standard recommended number of LNs to be removed for adequate staging cannot be specified based on current evidence. An anatomic approach to the LND as previously noted should be used to guide the extent of the LND.

3.2. *Prospective randomized trials*

3.2.1. *General considerations*

There is no high-level evidence that defines the relationship between the extent of the lymphadenectomy and disease progression and survival. There is at least the possibility that the modest increase in operative time, potential increase in blood loss, and increase in dissection surface area may outweigh any derived survival benefit.

The importance of a randomized clinical trial to address this important surgical question is reflected in the experience in gastric and pancreatic cancer. In the landmark trial of gastrectomy, there was no recurrence-free or overall survival benefit from adding para-aortic node dissection to the standard D2 lymphadenectomy, yet there was a nonstatistically significant increased incidence of surgery-related complications in the extended node dissection group (p = 0.07) [63]. Similarly, extended LNDs for pancreatic head cancer have been conducted since the 1980s. A randomized clinical trial to assess the difference between a standard and an extended nodal dissection was initiated but closed after an interim analysis revealed poorer survival and increased morbidity in the extended nodal dissection group [64].

3.2.2. *Important issues in trial design*

The underlying hypothesis is that if disease is located in LNs above the bifurcation of the common iliac, removal of nodes in the extended template will improve sensitivity for detecting LN metastases, provide a more complete removal of regional LN metastases, improve locoregional control, and potentially lead to improved long-term survival.

The trials should allow for the administration of neoadjuvant chemotherapy as an established standard of care, and randomization should be stratified to balance the treatment arms. To optimize the potential benefits of an extended node dissection through improved nodal staging, patients with pathologic node metastasis and locally advanced pathologic tumor stage (pT3–T4) should be considered for adjuvant chemotherapy based on the increased risk of progression with RC alone. Failure to include this stipulation in the trial design could result in biased administration of adjuvant chemotherapy, influenced by the arm to which the patient was randomized, and lead to noninformative results. Surgeons should demonstrate equipoise in enrolling all eligible patients to provide an appropriate distribution of patients with N stages 1–3.

3.2.3. *Current phase 3 randomized studies*

The Association of Urogenital Oncology and the German Cancer Association have completed accrual to the first phase 3 trial addressing this important question in muscle-invasive BCa. The primary end point is progression-free survival, predicted to be 65% in the extended arm (up to the IMA) and 50% in the conventional arm (the internal iliac, external iliac, and obturator nodes) ($p < 0.05$; two-sided; power: 90%; 5 yr of follow up). The first analysis of progression-free and overall survival is ongoing (pers. comm., Juergen Gschwend).

Southwest Oncology Group (SWOG) 1011 (ClinicalTrials.gov identifier NCT01224665) follows a similar design but with slightly different assumptions and power calculations. The study was designed based on a review of the contemporary cystectomy literature, which included a mix of standard and extended node dissection. The investigators felt that a reasonable estimate of disease-free and overall survival associated with standard node dissection for patients with muscle-invasive BCa was 55% at 3 yr and 55% at 5 yr, respectively. A poll of centers of excellence suggested that a 10–12% improvement in 3-yr DFS (65–67%) for patients undergoing an extended lymphadenectomy would be meaningful and would establish extended node dissection as the standard of care in this patient population (SWOG 1011). The study investigators determined that powering a trial to show a benefit of 5–7% would require a significantly larger number of patients and would present significant challenges to obtaining National Cancer Institute approval and achieving accrual targets. The SWOG study has 85% power to detect a 28% reduction in the hazard rate of progression or death with extended LND compared with limited dissection (hazard ratio: 0.72). This corresponds to an improvement in 3-yr DFS from 55% to 65%, or alternatively, median DFS would be extended from 3.5 to 4.8 yr if the DFS distributions are exponential. The trial calls for accrual of 620 patients and randomization of 564 patients, as well as an expectation that 10% of enrolled patients will be ineligible for randomization at the time of surgery based on failure to meet the criteria for randomization.

Surgeon credentialing and ongoing quality assurance are critical to the success and equipoise of the trial. Surgeons are required to have performed 50 cystectomies in the previous 3 yr, and 30 cystectomies are required annually at each hospital. Each surgeon is required to submit operative and pathology reports, as well as intraoperative photographs documenting the completeness of both the standard and extended node dissection templates, to participate in the trial.

A vanguard group of experienced surgeons completed a proof-of-concept lead-in phase based on accrual of the first 100 patients before opening the trial to the larger urologic oncology surgical community. This trial was opened in August 2011 and had accrued 136 patients as of February 2013.

These two important clinical trials will provide a robust amount of pathologic material derived from primary tumors and LNs for translational research.

4. Conclusions

Bilateral pelvic lymphadenectomy is an integral part of RC for BCa. Lymphadenectomy, completed according to the extended template, provides optimal pathologic BCa staging. High technical quality of nodes dissected by the surgeon and examined by the pathologist is essential for optimal pathologic node staging. Many consistent and concordant observations, although of low level of evidence, document that the extent of lymphadenectomy may influence DFS after RC independent of the status of LNs and the pathologic stage of BCa. Standardizing the lymphadenectomy procedure at the time of RC to create evidence-based guidelines is essential for further improving surgical quality and BCa patient survival.

Author contributions: Derya Tilki 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: Tilki, Evans, Lerner, Bochner.
Acquisition of data: Tilki, Brausi, Colombo, Evans, Fradet, Fritsche, Lerner, Sagalowsky, Shariat, Bochner.
Analysis and interpretation of data: Tilki, Evans, Lerner, Bochner.
Drafting of the manuscript: Tilki, Evans, Fritsche, Lerner, Bochner.
Critical revision of the manuscript for important intellectual content: Tilki, Brausi, Colombo, Evans, Fradet, Fritsche, Lerner, Sagalowsky, Shariat, Bochner.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Tilki, Bochner.
Other (specify): None.

Financial disclosures: Derya Tilki certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

References

[1] Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001;19:666–75.
[2] Shariat SF, Palapattu GS, Karakiewicz PI, et al. Discrepancy between clinical and pathologic stage: impact on prognosis after radical cystectomy. Eur Urol 2007;51:137–51, discussion 149–51.
[3] Hautmann RE, Gschwend JE, de Petriconi RC, Kron M, Volkmer BG. Cystectomy for transitional cell carcinoma of the bladder: results of a surgery only series in the neobladder era. J Urol 2006;176:486–92, discussion 491–2.
[4] Burkhard FC, Roth B, Zehnder P, Studer UE. Lymphadenectomy for bladder cancer: indications and controversies. Urol Clin North Am 2011;38:397–405, v.
[5] Leissner J, Ghoneim MA, Abol-Enein H, et al. Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. J Urol 2004;171:139–44.
[6] Mills RD, Turner WH, Fleischmann A, Markwalder R, Thalmann GN, Studer UE. Pelvic lymph node metastases from bladder cancer: outcome in 83 patients after radical cystectomy and pelvic lymphadenectomy. J Urol 2001;166:19–23.
[7] Stenzl A, Cowan NC, De Santis M, et al. Treatment of muscle-invasive and metastatic bladder cancer: update of the EAU guidelines. Eur Urol 2011;59:1009–18.
[8] Gakis G, Efstathiou J, Lerner SP, et al. ICUD-EAU International Consultation on Bladder Cancer 2012: radical cystectomy and bladder preservation for muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2013;63:45–57.
[9] Abol-Enein H, El-Baz M, Abd El-Hameed MA, Abdel-Latif M, Ghoneim MA. Lymph node involvement in patients with bladder cancer treated with radical cystectomy: a patho-anatomical study—a single center experience. J Urol 2004;172:1818–21.
[10] Vazina A, Dugi D, Shariat SF, Evans J, Link R, Lerner SP. Stage specific lymph node metastasis mapping in radical cystectomy specimens. J Urol 2004;171:1830–4.
[11] Tarin TV, Power NE, Ehdaie B, et al. Lymph node-positive bladder cancer treated with radical cystectomy and lymphadenectomy: effect of the level of node positivity. Eur Urol 2012;61:1025–30.
[12] Liedberg F, Chebil G, Davidsson T, Gudjonsson S, Mansson W. Intraoperative sentinel node detection improves nodal staging in invasive bladder cancer. J Urol 2006;175:84–8, discussion 88–9.
[13] Sherif A, Garske U, de la Torre M, Thorn M. Hybrid SPECT-CT: an additional technique for sentinel node detection of patients with invasive bladder cancer. Eur Urol 2006;50:83–91.
[14] Roth B, Wissmeyer MP, Zehnder P, et al. A new multimodality technique accurately maps the primary lymphatic landing sites of the bladder. Eur Urol 2010;57:205–11.
[15] Roth B, Zehnder P, Birkhauser FD, Burkhard FC, Thalmann GN, Studer UE. Is bilateral extended pelvic lymphadenectomy necessary for strictly unilateral invasive bladder cancer? J Urol 2012;187: 1577–82.
[16] Leadbetter WF, Cooper JF. Regional gland dissection for carcinoma of the bladder: a technique for one-stage cystectomy, gland dissection, and bilateral uretero-enterostomy. J Urol 1950;63:242–60.
[17] Colston JA, Leadbetter WF. Infiltrating carcinoma of the bladder. J Urol 1936;36:669–89.
[18] Jewett HJ, Strong GH. Infiltrating carcinoma of the bladder: relation of depth of penetration of the bladder wall to incidence of local extension and metastases. J Urol 1946;55:366–72.
[19] McDonald JR, Thompson GJ. Carcinoma of the urinary bladder: a pathologic study with special reference to invasiveness and vascular invasion. J Urol 1948;60:435–45.
[20] Marshall VF. The relation of the preoperative estimate to the pathologic demonstration of the extent of vesical neoplasms. J Urol 1952;68:714–23.
[21] Skinner DG. Current state of classification and staging of bladder cancer. Cancer Res 1977;37:2838–42.
[22] American Joint Committee on Cancer Staging and End Results Reporting (1977, 1978). Manual for staging of cancer, rev. Chicago, IL: American Joint Committee on Cancer; 1978.

[23] Paik ML, Scolieri MJ, Brown SL, Spirnak JP, Resnick MI. Limitations of computerized tomography in staging invasive bladder cancer before radical cystectomy. J Urol 2000;163:1693–6.
[24] Ficarra V, Dalpiaz O, Alrabi N, Novara G, Galfano A, Artibani W. Correlation between clinical and pathological staging in a series of radical cystectomies for bladder carcinoma. BJU Int 2005;95: 786–90.
[25] Tritschler S, Mosler C, Straub J, et al. Staging of muscle-invasive bladder cancer: can computerized tomography help us to decide on local treatment? World J Urol 2012;30:827–31.
[26] Kibel AS, Dehdashti F, Katz MD, et al. Prospective study of [18F]fluorodeoxyglucose positron emission tomography/computed tomography for staging of muscle-invasive bladder carcinoma. J Clin Oncol 2009;27:4314–20.
[27] Vargas HA, Akin O, Schoder H, et al. Prospective evaluation of MRI, (1)(1)C-acetate PET/CT and contrast-enhanced CT for staging of bladder cancer. Eur J Radiol 2012;81:4131–7.
[28] Shariat SF, Karakiewicz PI, Palapattu GS, et al. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. J Urol 2006;176:2414–22, discussion 2422.
[29] Stamatakis L, Godoy G, Lerner SP. Innovations in radical cystectomy and pelvic lymph node dissection. Semin Oncol 2012;39: 573–82.
[30] Bochner BH, Kattan MW, Vora KC. Postoperative nomogram predicting risk of recurrence after radical cystectomy for bladder cancer. J Clin Oncol 2006;24:3967–72.
[31] Capitanio U, Suardi N, Shariat SF, et al. Assessing the minimum number of lymph nodes needed at radical cystectomy in patients with bladder cancer. BJU Int 2009;103:1359–62.
[32] Dhar NB, Campbell SC, Zippe CD, et al. Outcomes in patients with urothelial carcinoma of the bladder with limited pelvic lymph node dissection. BJU Int 2006;98:1172–5.
[33] Herr HW, Bochner BH, Dalbagni G, Donat SM, Reuter VE, Bajorin DF. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. J Urol 2002;167: 1295–8.
[34] May M, Herrmann E, Bolenz C, et al. Association between the number of dissected lymph nodes during pelvic lymphadenectomy and cancer-specific survival in patients with lymph node-negative urothelial carcinoma of the bladder undergoing radical cystectomy. Ann Surg Oncol 2011;18:2018–25.
[35] Wright JL, Lin DW, Porter MP. The association between extent of lymphadenectomy and survival among patients with lymph node metastases undergoing radical cystectomy. Cancer 2008;112: 2401–8.
[36] Skinner DG. Management of invasive bladder cancer: a meticulous pelvic node dissection can make a difference. J Urol 1982;128: 34–6.
[37] Leissner J, Hohenfellner R, Thuroff JW, Wolf HK. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder: significance for staging and prognosis. BJU Int 2000;85: 817–23.
[38] Herr HW. Extent of surgery and pathology evaluation has an impact on bladder cancer outcomes after radical cystectomy. Urology 2003;61:105–8.
[39] Koppie TM, Vickers AJ, Vora K, Dalbagni G, Bochner BH. Standardization of pelvic lymphadenectomy performed at radical cystectomy: can we establish a minimum number of lymph nodes that should be removed? Cancer 2006;107:2368–74.
[40] Bochner BH, Cho D, Herr HW, Donat M, Kattan MW, Dalbagni G. Prospectively packaged lymph node dissections with radical cystectomy: evaluation of node count variability and node mapping. J Urol 2004;172:1286–90.
[41] Bochner BH, Herr HW, Reuter VE. Impact of separate versus en bloc pelvic lymph node dissection on the number of lymph nodes retrieved in cystectomy specimens. J Urol 2001;166:2295–6.
[42] Fang AC, Ahmad AE, Whitson JM, Ferrell LD, Carroll PR, Konety BR. Effect of a minimum lymph node policy in radical cystectomy and pelvic lymphadenectomy on lymph node yields, lymph node positivity rates, lymph node density, and survivorship in patients with bladder cancer. Cancer 2010;116:1901–8.
[43] Sharir S, Fleshner NE. Lymph node assessment and lymphadenectomy in bladder cancer. J Surg Oncol 2009;99:225–31.
[44] Davis JW, Kamat AM. Lymphadenectomy with robotic cystectomy. Curr Urol Rep 2013;14:59–63.
[45] Lavery HJ, Martinez-Suarez HJ, Abaza R. Robotic extended pelvic lymphadenectomy for bladder cancer with increased nodal yield. BJU Int 2011;107:1802–5.
[46] Stein JP, Penson DF, Cai J, et al. Radical cystectomy with extended lymphadenectomy: evaluating separate package versus en bloc submission for node-positive bladder cancer. J Urol 2007;177:876–81, discussion 881–2.
[47] Poulsen AL, Horn T, Steven K. Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. J Urol 1998;160:2015–9, discussion 2020.
[48] Abol-Enein H, Tilki D, Mosbah A, et al. Does the extent of lymphadenectomy in radical cystectomy for bladder cancer influence disease-free survival? A prospective single-center study. Eur Urol 2011;60:572–7.
[49] Dorin RP, Daneshmand S, Eisenberg MS, et al. Lymph node dissection technique is more important than lymph node count in identifying nodal metastases in radical cystectomy patients: a comparative mapping study. Eur Urol 2011;60:946–52.
[50] Dhar NB, Klein EA, Reuther AM, Thalmann GN, Madersbacher S, Studer UE. Outcome after radical cystectomy with limited or extended pelvic lymph node dissection. J Urol 2008;179:873–8, discussion 878.
[51] Zehnder P, Studer UE, Skinner EC, et al. Super extended versus extended pelvic lymph node dissection in patients undergoing radical cystectomy for bladder cancer: a comparative study. J Urol 2011;186:1261–8.
[52] Stein JP, Cai J, Groshen S, Skinner DG. Risk factors for patients with pelvic lymph node metastases following radical cystectomy with en bloc pelvic lymphadenectomy: concept of lymph node density. J Urol 2003;170:35–41.
[53] Kassouf W, Leibovici D, Munsell MF, Dinney CP, Grossman HB, Kamat AM. Evaluation of the relevance of lymph node density in a contemporary series of patients undergoing radical cystectomy. J Urol 2006;176:53–7, discussion 57.
[54] Jensen JB, Ulhoi BP, Jensen KM. Evaluation of different lymph node (LN) variables as prognostic markers in patients undergoing radical cystectomy and extended LN dissection to the level of the inferior mesenteric artery. BJU Int 2012;109:388–93.
[55] Herr HW. Superiority of ratio based lymph node staging for bladder cancer. J Urol 2003;169:943–5.
[56] Herr HW. The concept of lymph node density—is it ready for clinical practice? J Urol 2007;177:1273–5, discussion 1275–6.
[57] Kassouf W, Agarwal PK, Herr HW, et al. Lymph node density is superior to TNM nodal status in predicting disease-specific survival after radical cystectomy for bladder cancer: analysis of pooled data from MDACC and MSKCC. J Clin Oncol 2008;26: 121–6.
[58] May M, Herrmann E, Bolenz C, et al. Lymph node density affects cancer-specific survival in patients with lymph node-positive urothelial bladder cancer following radical cystectomy. Eur Urol 2011;59:712–8.

[59] Wiesner C, Salzer A, Thomas C, et al. Cancer-specific survival after radical cystectomy and standardized extended lymphadenectomy for node-positive bladder cancer: prediction by lymph node positivity and density. BJU Int 2009;104:331–5.

[60] Fleischmann A, Thalmann GN, Markwalder R, Studer UE. Extracapsular extension of pelvic lymph node metastases from urothelial carcinoma of the bladder is an independent prognostic factor. J Clin Oncol 2005;23:2358–65.

[61] Fajkovic H, Cha EK, Jeldres C, et al. Extranodal extension is a powerful prognostic factor in bladder cancer patients with lymph node metastasis. Eur Urol. In press. http://dx.doi.org/10.1016/j.eururo.2012.07.026.

[62] Seiler R, von Gunten M, Thalmann GN, Fleischmann A. Extracapsular extension but not the tumour burden of lymph node metastases is an independent adverse risk factor in lymph node-positive bladder cancer. Histopathology 2011;58:571–8.

[63] Sasako M, Sano T, Yamamoto S, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med 2008;359:453–62.

[64] Farnell MB, Pearson RK, Sarr MG, et al. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery 2005;138:618–28, discussion 628–30.