How close are we to establishing standards of lymphadenectomy for invasive bladder cancer?

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Abstract: Radical cystectomy and lymphadenectomy is an accepted standard of care for muscle-invasive bladder cancer. Although the absolute limits of lymphadenectomy have not been standardized a growing body of evidence supports an improvement in nodal staging and survival from an extended lymphadenectomy. The benefit has been reported for both node negative and node positive patients. This review focuses on lymph node mapping, factors that influence total lymph node count and the optimal number of lymph nodes that should be removed at lymphadenectomy.

Keywords: urinary bladder neoplasm, lymph node excision, anatomic template

Introduction

Performing a pelvic lymphadenectomy at the time of radical cystectomy for invasive bladder cancer is considered important. Improved locoregional disease control and pathologic nodal staging are irrefutable benefits of pelvic lymphadenectomy, although, the survival benefit has not been uniformly accepted. Accumulating evidence is providing substantial support to the therapeutic benefit of lymphadenectomy in bladder cancer patients but the anatomic extent of lymph node dissection remains controversial.

The lack of consensus or standardization of lymphadenectomy is present in both the academic and community setting. A population based analysis of 1,698 patients who underwent a radical cystectomy in the United States reported that 40% of patients had no lymph nodes removed and the rest had a wide range of lymph nodes removed [Konety *et al.* 2003]. Even in the setting of a cooperative group clinical trial, that included many academic medical centers, 9% of patients had no lymph nodes removed, 37% had a limited lymph node dissection, and 54% had a standard lymph node dissection [Herr *et al.* 2004].

For the purpose of our review we will standardize the definition of different anatomic templates of lymphadenectomy described in the literature. A limited lymphadenectomy (LLN) includes removal of the external and obturator lymph nodes, standard lymphadenectomy (SLN)

includes a LLN and removal of the internal iliac lymph nodes, and extended lymphadenectomy (ELN) includes a SLN and removal of the common iliac and presacral lymph nodes. Also a super-extended lymphadenectomy has been used and refers to an ELN and the removal of any additional lymph nodes above the aortic bifurcation.

The varying surgical approaches to lymphadenectomy are not just limited to the anatomic extent of dissection (quantity) but also the thoroughness (quality) of dissection as illustrated by widely differing node counts within a defined anatomic template. Single center experiences have reported median lymph node counts of 9 and 14 within a SLN [Herr *et al.* 2002; Poulsen *et al.* 1998]. Even when lymph node submission is packaged, median lymph node counts vary, as one group reported a median lymph node count of 12 (within the anatomic boundaries of a SLN) in a group of patients who underwent an ELN) and another 26 within the same template [Abol-Enein *et al.* 2004; Bochner *et al.* 2004]. The variation in lymph node count is not just restricted to the lower limits of pelvic lymphadenectomy but also ELN. Groups have reported median lymph node counts of 23, 25, and 39 when the dissection is confined to an ELN with packaged nodal submission [Abol-Enein *et al.* 2004; Bochner *et al.* 2004; Poulsen *et al.* 1998].

Many factors can affect the total number of lymph nodes recovered at lymphadenectomy

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and may explain some of the differences among institutions. The anatomic extent of dissection, the manner by which lymph nodes are submitted for pathologic analysis and the techniques used by the pathologist to identify lymph nodes are measurable and have been studied. A less measurable factor – thoroughness of dissection – is also likely important but difficult to study.

Establishing standards for the extent of lymphadenectomy that affects prognosis has been done for gastric [Siewert *et al.* 1998], breast [Mathiesen *et al.* 1990], and colorectal cancer [Caplin *et al.* 1998] and are integrated in the UICC classification of these cancers [Sobin and Wittekind, 1997]. Efforts to establish similar standards in bladder cancer are underway and this review presents a historical perspective and current state of the science of the role of pelvic lymphadenectomy in bladder cancer.

Pelvic lymphadenectomy – autopsy studies and historical perspective

Colston and Leadbetter described cadaveric dissections of individuals with neoplastic growth in the bladder who had metastases to pelvic lymph nodes only and it was suggested that potentially curative surgical resection may have been possible [Colston and Leadbetter, 1936]. Jewett and Strong in another cadaveric study of 107 cases confirmed that lymph node involvement may be the sole site of metastasis in 30–40% of patients with bladder cancer. The authors also reported the correlation between depth of bladder tumor penetration and the extent of lymph node involvement. The autopsy findings also formed the basis of the first widely accepted staging system for bladder cancer – the Jewett–Marshall staging system [Jewett and Strong, 1946]. In 1950 Kerr and Colby first reported on two surviving node positive patients who underwent a pelvic lymphadenectomy at the time of radical cystectomy [Kerr and Colby, 1950]. These findings influenced the suggestion of routinely performing a pelvic lymphadenectomy and wide surgical resection of the bladder to reduce local relapse and improve survival. In the same year Leadbetter and Cooper presented the surgical boundaries and approach of an extended lymphadenectomy based on understanding of the lymphatic drainage of the bladder and prostate [Leadbetter and Cooper, 1950]. The anatomical boundaries described by these authors in 1950 are identical to the boundaries being followed for extended lymphadenectomy today.

Whitmore and Marshall reported lymph node metastases in 55 of 230 patients with bladder cancer and only two (4%) patients were long-term survivors [Whitmore and Marshall, 1962]. Two decades later Skinner reported his experience of extended lymphadenectomy and reported a much higher rate (30%) of survival of patients with lymph node metastases [Skinner, 1982]. A considerable amount of literature has accumulated since 1982 supporting the therapeutic benefit of lymphadenectomy in some patients with nodal metastases but there is a lack of consensus on what lymph nodes should be removed.

Lymphatic drainage of the bladder

In order to better understand the locoregional spread of bladder cancer, a clear understanding of the lymphatic drainage of the bladder and pelvis is necessary. Leadbetter and Cooper significantly contributed to the understanding of the lymphatic drainage of the bladder. The lymphatic drainage of the bladder was described as 6 distinct areas:

- (1) The visceral lymphatic plexus within the bladder wall – arising in the submucosa and extending into the muscular layer of the organ.
- (2) The intercalated lymph nodes – that are juxta-vesical lymph nodes located within the perivesical fat arranged into anterior, lateral and posterior groups.
- (3) Pelvic collecting trunks – that are medial lymph nodes to the external iliac and hypogastric lymph nodes.
- (4) Regional pelvic lymph nodes – that include the external iliac, hypogastric and sacral lymph groups.
- (5) Lymphatic trunks leading from the regional pelvic lymph nodes.
- (6) Common iliac lymph nodes – proposed to be the secondary echelon of metastases, intermediate between the pelvic and aortocaval lymph nodes [Leadbetter and Cooper, 1950].

Mapping of regional lymph node metastases

The presence of lymph node metastases at the time of diagnosis of invasive bladder cancer is common. In a large cohort of 1,054 patients with urothelial carcinoma of the bladder, treated at a single institution, lymph node metastasis was identified in 246 patients (23%), most with extra-vesical tumor extension [Stein *et al.* 2001]. An analysis of 4,252 patients treated at multiple centers similarly reported that 943 patients (22%)

had lymph node metastases at radical cystectomy [Bruins and Stein, 2008].

Recognizing the complex nature of the lymphatic drainage of the bladder, lymphatic cross-over, lack of a sentinel lymph node and the possibility of skip metastasis results in an unpredictable distribution of lymph node metastases. Both retrospective and prospective anatomic maps of the distribution of lymph node metastases in bladder cancer patients have been described.

Whitmore and Smith were some of the earliest to report that the two most common sites of lymph node metastases were the obturator/hypogastric and external iliac lymph nodes, in 74 and 65% of lymph node positive patients respectively [Smith and Whitmore, 1981]. In 2004 several mapping studies of nodal metastases were published with the first being a retrospective study by Vazina and colleagues. Forty-three patients with lymph node metastases underwent at least an ELN and 22 patients had lymph node metastases at more than one site. Almost all of the patients who had organ-confined disease had lymph node metastases confined to the boundaries of a SLN, although, patients with non-organ confined disease commonly had disease outside of the boundaries (i.e. more proximal) of a SLN, including the common iliac and para-aortic lymph nodes. The authors stressed the importance of bilateral pelvic lymphadenectomy as well as reporting skip metastases in one patient (common iliac lymph node involvement without distal pelvic node involvement) [Vazina *et al.* 2004].

A carefully detailed prospective lymph node mapping study was reported by Leissner *et al.* and included six institutions. The majority of patients underwent a super-extended lymphadenectomy and the lymph nodes were removed as 12 separate anatomic packets. A total of 599 lymph nodes involved by tumor were identified in 81 patients and 55% of the metastases were distributed within a SLN. The obturator lymph nodes were the most common site (26%) followed by the external iliac (16%) and deep obturator/hypogastric (13.2%). The remaining lymph node metastases involved the common iliac (19%), presacral (8%), and lymph nodes above the aortic bifurcation (17%). Of the patients with lymph node metastases in any of the lymph nodes in a SLN, 57% also had involvement of the common iliac and 31% above the aortic bifurcation [Leissner *et al.* 2004]. Abol-Enein *et al.* in

the same year presented a similar mapping study of 200 patients that included 48 patients (24%) with nodal metastases. A total of 388 positive nodes were removed and the anatomic distribution of metastases and conclusion by the authors was similar to the Leissner study [Abol-Enein *et al.* 2004].

Our unpublished institutional data on 120 patients who underwent an ELN identified 36 patients (30%) with node positive disease. Of the patients with node positive disease the perivesical LN were involved in 24%, external iliac 38%, obturator 56%, internal iliac 47%, common iliac 32%, and presacral 24%. Fifteen patients had a solitary lymph node metastasis, including 4 (27%) outside of a SLN and of the 25 patients with ≤ 5 lymph nodes involved by tumor 8 (32%) had disease outside of a SLN.

A substantial body of evidence exists to support a thorough bilateral pelvic lymphadenectomy to include the common iliac and presacral lymph nodes if the goal is to eradicate all nodal disease within the true pelvis.

Can patients with nodal disease be cured by pelvic lymphadenectomy?

Several approaches have been used to quantify node positive disease and whether it correlates with survival. A useful means of stratifying node positive disease is the pN classification according to the tumor-node-metastasis (TNM) system, which distinguishes N1 (metastasis in a single lymph node, ≤ 2 cm in greatest dimension), N2 (metastasis in a single lymph node, 2–5 cm in greatest dimension; or multiple lymph nodes, none > 5 cm in greatest dimension) and N3 (metastasis in a lymph node, > 5 cm in greatest dimension) disease [Sobin and Wittekind, 1997]. In a series of 193 node positive patients the 5-year disease specific survival was 44.2% in N1 patients, 26.6% in N2 patients and no N3 patient survived beyond three years supporting that this staging system is useful for prognostication [Vieweg *et al.* 1999].

Another approach used in determining the burden of lymph node involvement by tumor is counting the number of involved lymph nodes. Lerner *et al.* retrospectively reviewed 591 patients treated with curative pelvic lymphadenectomy with en bloc radical cystectomy and reported that six or more positive nodes increased the risk of disease progression and death from disease

[Lerner *et al.* 1993]. Mills *et al.* similarly analyzed 83 node positive patients and assessed the impact of number of positive nodes, extracapsular extension, and size of nodal metastasis on recurrence-free and overall survival. On univariate analysis the 26 patients with a single positive node did not have better survival when compared with the 57 patients with <5 positive nodes (21 and 19 months respectively). On multivariate analysis less than 5 positive nodes, received adjuvant chemotherapy, and absence of extracapsular extension were associated with more prolonged survival [Mills *et al.* 2001].

The largest reported node positive series to date is that of Stein *et al.* who described the outcome of 244 patients. The authors categorized the node positive patients into those with ≤ 8 ($n=193$, 79%) and >8 ($n=51$, 21%) nodes involved by tumor. Patients with ≤ 8 positive nodes had significantly higher 5- and 10-year recurrence-free survival of 41 and 40% respectively compared to 10% in those with >8 positive nodes. On both univariate and multivariate analysis the number of LNs involved (≤ 8 versus >8) proved to be statistically significant for recurrence-free and overall survival [Stein *et al.* 2003]. Steven and Poulsen also reported that patients with ≤ 5 nodes involved by tumor had a more favourable recurrence-free survival (50 versus 13%) when compared to patients with more than 6 positive nodes [Steven and Poulsen, 2007]. Therefore tumor burden defined as the number of lymph nodes involved by tumor is useful for prognostication.

Total number of lymph nodes removed

Contemporary studies suggest that a minimum number of lymph nodes needs to be removed at radical cystectomy to optimize oncologic outcome and accuracy of nodal staging. Each of the reported studies has been retrospective in study design and most have been single institution experiences. Leissner *et al.* reported that removing 16 lymph nodes at radical cystectomy was necessary to detect nodal metastases and was also associated with improved disease-free and cancer-specific survival [Leissner *et al.* 2000]. Similarly Herr *et al.* retrospectively studied 322 patients and confirmed an improved survival for not only patients with nodal metastases but also patients without nodal metastases when a minimum of nine lymph nodes were removed at radical cystectomy [Herr *et al.* 2002]. A population-based study using the SEER

(Surveillance, Epidemiology and End Results program) data supported the findings of the single-institution studies. The removal of 10–14 lymph nodes, regardless of primary tumor stage, resulted in improved oncologic outcomes. Importantly the study highlighted the lack of standardization of lymphadenectomy in bladder cancer patients as only 22% of 1,698 patients had ≥ 10 lymph nodes removed suggesting that many more patients may have benefited from a more thorough lymphadenectomy [Konety *et al.* 2003]. Another study similar in design also used the SEER registry but only evaluated the 1,260 patients with node positive disease. A multivariate analysis controlling for patient demographics, tumor characteristics and year of diagnosis confirmed the number of positive nodes and total number of lymph nodes removed were independent predictors of survival. An inverse association was reported between the total number of lymph nodes removed in node positive patients and risk of death when analyzed by quartiles. Removal of more than 10 lymph nodes was associated with improved survival [Wright *et al.* 2008].

The independent prognostic value of the number of lymph nodes removed at radical cystectomy was substantiated in a randomized cooperative group trial (Southwest Oncology Group, 8710) that reported improved survival in patients receiving neoadjuvant chemotherapy prior to radical cystectomy. A multivariate model adjusted for neoadjuvant chemotherapy, age, pathologic stage and node status showed that removing at least 10 lymph nodes was associated with increased survival (hazard ratio, 0.51; $p=0.0001$) [Herr *et al.* 2004].

A more recent study also supported the concept that removing more lymph nodes improves oncologic outcome but concluded that no minimum lymph node count could be established but rather it is a continuous variable (the probability of survival continued to rise as the number of lymph nodes removed increased). This conclusion was based on a regression model controlling for age, co-morbidity, and tumor stage [Koppie *et al.* 2006].

Collectively, these retrospective studies provide insight regarding the minimum number of lymph nodes that need to be removed to favorably affect survival. However the outcomes should be interpreted carefully as the number of lymph nodes removed at radical cystectomy is

influenced by several factors including the extent of lymphadenectomy (quantity of surgery), how the lymph nodes are submitted by the surgeon for pathologic evaluation, the technique used by the pathologist to identify and analyze the lymph nodes, and the thoroughness of lymphadenectomy (quality of surgery). Related factors such as age and body mass index may also influence lymph node count, although the influence is probably limited and presently not well defined. Importantly a recent article confirms an increased awareness among surgeons treating bladder cancer patients that removing more lymph nodes affects oncologic outcomes. During the period 1988–2004 the SEER registry indicates the mean number of lymph nodes removed increased by 2.6 and the percentage of patients undergoing any form of lymph node dissection increased by an average of 19% [Hellenthal *et al.* 2009].

Poulsen *et al.* retrospectively reported the outcome data for 194 nonrandomized patients who had a standard (68 patients) or extended (126 patients) lymph node dissection. The median numbers of total lymph nodes removed were 14 and 25, respectively, supporting the influence of the limits of lymphadenectomy on lymph node count. The 5-year recurrence-free survival in organ confined bladder cancer was 64% in the standard and 85% in the extended lymphadenectomy groups. The authors also noted a decreased pelvic and distant metastasis rate (2 and 10%) in patients who underwent an extended dissection when compared with a limited dissection (7 and 21%) [Poulsen *et al.* 1998]. Another study similarly supported the extent or quantity of lymphadenectomy, defined by anatomic template of lymphadenectomy and not by node count, influences outcome. Dhar *et al.* reported a retrospective comparative study between two institutions with a differing approach to lymphadenectomy. One group routinely performed a limited and the other an extended lymphadenectomy. Not unexpectedly the median number of retrieved lymph nodes was considerably higher in the extended group, 22, when compared to the limited group, 12. Despite the methodological flaws of a retrospective and nonrandomized study design the extended group had improved disease-free and cancer-specific survival and this was demonstrated in both node positive and node negative patients [Dhar *et al.* 2008].

Besides anatomical extent of dissection, whether the lymph nodes are submitted as separate packets or *en bloc* influences total lymph node count. Bochner *et al.* prospectively reported that packaging lymph nodes increased the total lymph node count from 21 to 40 when compared to *en bloc* submission within the same anatomic template [Bochner *et al.* 2001]. Importantly another study noted that the manner of lymph node submission only influences total number of lymph nodes identified by the pathologist but not the percentage of patients with lymph node metastases [Stein *et al.* 2007].

The specific technique of lymph node identification and evaluation may influence total lymph node count but this concept has not been studied in detail in bladder cancer. In general the pathologist identifies lymph nodes by visualization and palpation under bright light. The more laborious and costly method of fat-clearing, immunohistochemistry or molecular techniques are not widely employed.

Lymph node density

Combining two prognostic variables known to influence survival – total number of lymph nodes removed and the number of lymph nodes involved by tumor – as one variable, Stein and colleagues and Herr simultaneously reported the concept of lymph node density [Herr, 2003; Stein *et al.* 2003]. Lymph node density is defined as the number of lymph nodes involved with tumor divided by the total number of lymph nodes removed. Stein *et al.* analyzed 244 patients with node positive disease and reported a lymph node density of less than 20% was associated with a better recurrence-free survival (5- and 10-year recurrence-free survival of 44 and 43%, respectively) when compared with a lymph node density of greater than 20% (5- and 10-year recurrence-free survival of 17%). On multivariate analysis pathologic T stage, number of positive lymph nodes, lymph node density and adjuvant chemotherapy were independently predictive of recurrence-free and overall survival [Stein *et al.* 2003]. Herr also reported the prognostic significance of a lymph node density of 20% [Herr, 2003].

Kassouf *et al.* published an analysis of pooled data from two comprehensive cancer centers in the United States that included 248 patients with nodal metastases following radical cystectomy. On univariate analysis non organ-confined

disease, higher pN stage, more than two positive lymph nodes, removing fewer than 12 lymph nodes, a lymph node density of greater than 20%, positive surgical margin, local recurrence, and not receiving adjuvant chemotherapy were associated with worse disease specific survival. However on multivariate analysis a lymph node density of >20% and not pN stage or number of lymph nodes involved by tumor was predictive of decreased disease specific survival and the authors concluded that lymph node density is superior to TNM nodal status in predicting disease specific survival for patients with lymph node positive disease after radical cystectomy [Kassouf *et al.* 2008].

Lymphadenectomy and locoregional disease control

Efforts to reduce local recurrence rates in bladder cancer are important as this is considered a lethal event. Herr and colleagues reported that removing more lymph nodes at radical cystectomy leads to improved local disease control in both node negative and node positive patients. Specifically it was suggested that removing more than 11 lymph nodes was necessary to reduce local recurrence rates [Herr *et al.* 2002]. An analysis of surgical variables that affected patient outcome in a cooperative group trial similarly reported an association between extent of lymphadenectomy and local recurrence rates. In this study removing fewer than 10 lymph nodes was associated with a higher risk of local disease relapse and even on multivariate analysis this remained an important predictive factor of local recurrence [Herr *et al.* 2004]. The presented data support the notion that a more extensive lymph node dissection or ELN is more likely to remove metastatic nodal disease leading to improved locoregional disease control.

Is the benefit of lymphadenectomy a staging benefit or true survival benefit

Since removing more lymph nodes at radical cystectomy is associated with a survival advantage in both node negative and node positive patients it is reasonable to suggest that an ELN may be associated with improved survival when compared with a more limited lymphadenectomy. However, one needs to question whether this survival advantage is due to more accurate nodal staging or a therapeutic benefit of the lymphadenectomy, or possibly both. It is possible that more accurate staging enriches the group of node positive patients with patients with low

volume nodal disease and the node negative group with fewer patients with node positive disease thereby increasing the survival in both groups (Will Rogers phenomenon).

Although different explanations for the survival benefit of more extensive lymph node dissections (ELN) have been proposed there is no convincing evidence, to date, as to what contributes the most. Nevertheless there is enough evidence to suggest that an ELN is associated with improved survival.

Conclusion

Evidence accumulated from single institutions, cooperative group trials and population-based cancer registries support the need to routinely perform a lymphadenectomy at the time of radical cystectomy. Lymphadenectomy improves locoregional disease control, accuracy of pathologic nodal stage and survival. However, the number of lymph nodes that need to be removed or anatomic extent of lymphadenectomy that results in improved oncologic outcomes is not fully known. Current evidence supports routinely performing an extended lymphadenectomy for invasive bladder cancer but it is based on retrospective nonrandomized studies. Only a prospective surgical study can help clarify the true impact of lymphadenectomy and establish surgical standards. It is possible that a more thorough lymphadenectomy (super extended lymphadenectomy) may lead to better oncologic outcomes in node positive patients.

Conflicts of interest statement

None declared.

References

- Abol-Enein, H., El-Baz, M., Abod El- Hameed, M.A., Abdel-Latif, M. and Ghoneim, M. (2004) Lymph node involvement in patients with bladder cancer with radical cystectomy: A patho-anatomical study – a single center experience. *J Urol* 172: 1818–1821.
- Bochner, B.H., Cho, C., Herr, H.W., Donat, M., Kattan, M.W. and Dalbagni, G. (2004) Prospectively packaged lymph node dissections with radical cystectomy: evaluation of node count variability and node mapping. *J Urol* 172: 1286–1290.
- Bochner, B.H., Herr, H.W. and Reuter, V.E. (2001) Impact of separate versus en bloc pelvic lymph node dissection on the number of lymph nodes retrieved in cystectomy specimens. *J Urol* 166: 2295–2296.

- Bruins, H.M. and Stein, J.P. (2008) Risk factors and clinical outcomes of patients with node-positive muscle invasive bladder cancer. *Expert Rev Anticancer Ther* 8: 1091–1101.
- Caplin, S., Cerottini, J.P., Bosman, F.T., Constanda, M.T. and Givel, J.C. (1998) For patients with Dukes' B (TNM Stage II) colorectal carcinoma, examination of six or fewer lymph nodes is related to poor prognosis. *Cancer* 83: 666–672.
- Colston, J.A. and Leadbetter, W.F. (1936) Infiltrating carcinoma of the bladder. *J Urol* 36: 669–689.
- Dhar, N.B., Klein, E.A., Reuther, A.M., Thalmann, G.N., Madersbacher, S. and Studer, U.E. (2008) Outcome after radical cystectomy with limited or extended pelvic lymph node dissection. *J Urol* 179: 873–878.
- Hellenthal, N.J., Ramirez, M.L., Evans, C.P., deVere White, R.W. and Koppie, T.M. (2009) Trends in pelvic lymphadenectomy at the time of radical cystectomy: 1988–2004. *J Urol* 181: 2490–2495.
- Herr, H.W. (2003) Superiority of ratio based lymph node staging for bladder cancer. *J Urol* 169: 943–945.
- Herr, H.W., Bochner, B.H., Dalbagni, G., Donat, S.M., Reuter, V.E. and Bajorin, D.F. (2002) Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. *J Urol* 167: 1295–1298.
- Herr, H.W., Faulkner, J.R., Grossman, H.B., Natale, R.B., de Vere white, R., Sarosdy, M.F. *et al.* (2004) Surgical factors influence bladder cancer outcomes: A cooperative group report. *J Clin Oncol* 22: 2781–2789.
- Jewett, H.J. and Strong, G.H. (1946) Infiltrating carcinoma of the bladder: relation of depth of penetration of the bladder wall to incidence of local extension and metastases. *J Urol* 55: 366–372.
- Kassouf, W., Agarwal, P.K., Herr, H.W., Munsell, M.F., Spiess, P.E., Brown, G.A. *et al.* (2008) 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* 26: 121–126.
- Kerr, W.S. and Colby, F.H. (1950) Pelvic lymph node dissection and total cystectomy in the treatment of carcinoma of the bladder. *J Urol* 63: 842–851.
- Konety, B.R., Joslyn, S.A. and O'Donnell, M.A. (2003) Extent of pelvic lymphadenectomy and its impact on outcome in patients diagnosed with bladder cancer: analysis of data from the Surveillance, Epidemiology and End Results Program data base. *J Urol* 169: 946–950.
- Koppie, T.M., Vickers, A.J., Vora, K., Dalbagni, G. and Bochner, B.H. (2006) Standardization of pelvic lymphadenectomy performed at radical cystectomy: can we establish a minimum number of lymph nodes that should be removed? *Cancer* 107: 2368–2374.
- Leadbetter, W.F. and Cooper, J.F. (1950) Regional gland dissection for carcinoma of bladder: a technique of one-stage cystectomy, gland dissection, and bilateral ureteroenterostomy. *J Urol* 63: 242–260.
- Lerner, S.P., Skinner, D.G., Leiskovsky, G., Boyd, S.D., Groshen, S.L., Ziogas, A. *et al.* (1993) The rationale for *en bloc* pelvic lymph nodes dissection for bladder cancer patients with nodal metastasis; long-term results. *J Urol* 149: 758–765.
- Leissner, J., Hohenfellner, R., Thüroff, J.W. and Wolf, H.K. (2000) Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. *BJU Int* 85: 817–823.
- Leissner, J., Ghoneim, M.A., Abol-Enein, H., Thüroff, J.W., Franzaring, L., Fisch, M. *et al.* (2004) Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. *J Urol* 171: 139–144.
- Mathiesen, O., Carl, J., Bonderup, O. and Panduro, J. (1990) Axillary sampling and the risk of erroneous staging of breast cancer. *Acta Oncol* 29: 721–725.
- Mills, R.D., Turner, W.H., Fleischmann, A., Markwalder, R., Thalmann, G.N. and Studer, U.E. (2001) Pelvic lymph node metastases from bladder cancer: Outcome in 83 patients after radical cystectomy and pelvic lymphadenectomy. *J Urol* 166: 19–23.
- Poulsen, A.L., Horn, T. and Stevens, K. (1998) Radical cystectomy: Extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to bladder wall. *J Urol* 160: 2015–2020.
- Siewert, J.R., Böttcher, K., Stein, H.J., Roder, J.D. and the German Gastric Carcinoma Study Group. (1998) Relevant prognostic factors in gastric cancer. *Ann Surg* 228: 449–461.
- Skinner, D.G. (1982) Management of invasive bladder cancer: a meticulous pelvic node dissection can make a difference. *J Urol* 128: 34–36.
- Smith, J.A. and Whitmore Jr, W.F. (1981) Regional lymph node metastasis from bladder cancer. *J Urol* 126: 591–593.
- Sobin, L.H. and Wittekind, C. (1997) *Urinary bladder. International Union against Cancer (UICC): TNM: Classification of Malignant Tumors*, Wiley-Liss: New York, pp. 187–190.
- Stein, J.P., Lieskovsky, G., Cote, R., Groshen, S., Feng, A.C., Boyd, S. *et al.* (2001) Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1054 patients. *J Clin Oncol* 19: 666–675.
- Stein, J.P., Cai, J., Groshen, S. and Skinner, D.G. (2003) Risk factors for patients with pelvic lymph node metastases following radical cystectomy with *en bloc* pelvic lymphadenectomy: concept of lymph node density. *J Urol* 170: 35–41.
- Stein, J.P., Penson, D.F., Cai, J., Miranda, G., Skinner, E.C., Dunn, M.A. *et al.* (2007) Radical cystectomy with extended lymphadenectomy: evaluating separate

package versus en bloc submission for node positive bladder cancer. *J Urol* 177: 876–881.

Steven, K. and Poulsen, A.L. (2007) Radical cystectomy and extended pelvic lymphadenectomy: survival of patients with lymph node metastasis above the bifurcation of the common iliac vessels treated with surgery only. *J Urol* 178: 1218–1223.

Vazina, A., Dugi, D., Shariat, S.F., Evans, J., Link, R. and Lerner, S.P. (2004) Stage specific lymph node metastasis mapping in radical cystectomy specimens. *J Urol* 171: 1830–1834.

Vieweg, J., Gschwend, J.E., Herr, H.W. and Fair, W.R. (1999) The impact of primary stage on survival in patients with lymph node positive bladder cancer. *J Urol* 161: 72–76.

Whitmore, W.F. and Marshall, V.F. (1962) Radical total cystectomy for cancer of the bladder: 230 consecutive cases five years later. *J Urol* 87: 853–868.

Wright, J.L., Lin, D.W. and Porter, M.P. (2008) The association between extent of lymphadenectomy and survival among patients with lymph node metastases undergoing radical cystectomy. *Cancer* 112: 2401–2408.

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