The role of extended lymphadenectomy in bladder cancer was introduced by Donald Skinner some years ago, and caused some controversy at the time. Since then, it has been reported by other influential urologists as being of benefit to patients with this condition. In this issue, two of the mini-reviews are dedicated to a full description of this concept, giving a historical perspective, the rationale for the procedure, the technical aspects, and indicating important prognostic factors.

Lymphadenectomy for invasive bladder cancer: I. historical perspective and contemporary rationale

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INTRODUCTION

In the USA bladder cancer is the fourth most common cancer in men and the eighth most common in women, with TCC comprising nearly 90% of all primary bladder tumours. In 2004, it was estimated that 60 250 new patients were diagnosed with bladder cancer and 12 710 died from this disease [1]. Although most patients with bladder cancer present with superficial bladder tumours, 20–40% will either present with or subsequently develop muscle-invasive disease. Invasive bladder cancer is a lethal malignancy; if left untreated, >85% of patients will die from the disease within 2 years of diagnosis [2]. Despite an early and aggressive approach toward high-grade, invasive bladder cancer [3], nearly 25% of patients have pathological evidence of lymph-node metastases at the time of cystectomy [4–10]. These data underscore two important points about bladder cancer: (i) high-grade, invasive bladder tumours are potentially lethal; and (ii) significantly many patients at the time of definitive therapy have metastases to the regional lymph nodes.

The rationale for an aggressive treatment approach using radical cystectomy with an appropriate lymphadenectomy for high-grade, invasive bladder cancer is based on several important observations. First, radical cystectomy provides not only excellent local cancer control with the lowest pelvic recurrence rates, but also the best long-term survival [4]. This includes high-risk patients with pathological evidence of lymph-node metastases. Second, the morbidity and mortality of radical cystectomy has significantly improved over the past several decades. Radical cystectomy with an appropriate lymphadenectomy, although surgically more challenging, does not significantly increase the morbidity or mortality of the procedure. Third, TCC tends to be a tumour resistant to radiation therapy. In addition, radiation does not manage or control lymph-node metastases. Fourth, chemotherapy alone, or in combination with bladder-sparing protocols, have not shown equivalent long-term survival rates comparable to cystectomy [11]. Fifth, radical cystectomy provides accurate pathological staging of the primary bladder tumour (p stage) and regional lymph nodes. This allows

for the selective application of adjuvant therapy based on a precise pathological evaluation. Lastly, improvements in lower urinary tract reconstruction (particularly orthotopic diversion) have improved the quality of life of patients requiring bladder removal, eliminating the need for urostomy appliances, cutaneous stomas and the need for catheterization in most instances. Importantly, lymph-node metastases should not preclude appropriately selected patients from undergoing lower urinary tract reconstruction, even an orthotopic diversion [12]. For these reasons, radical cystectomy with a suitable lymphadenectomy has become a standard therapy for high-grade, invasive bladder cancer. In this review we evaluate the historical development and contemporary rationale for a lymphadenectomy in patients undergoing radical cystectomy.

A HISTORICAL PERSPECTIVE

The concept of a regional lymph-node dissection (LND) as a component in the surgical management of malignancies was first introduced into the American medical literature in 1886 by Halstead [13]. As a surgeon treating carcinoma of the breast, Halstead astutely noted a better survival in locally advanced breast cancer after applying a regional LND with mastectomy. This concept has become one of the important principles of oncological surgery; tumours tend to metastasize initially via the organ's primary lymphatics to the regional lymph nodes. The removal of the primary tumour and regional lymph nodes provide important staging and possibly therapeutic benefits.

The role of a lymphadenectomy in the treatment of bladder cancer has developed over the past several decades. The initial belief about advanced bladder cancer with gross lymphadenopathy was that of a uniformly fatal disease, and beyond the limits of surgical intervention. This notion was first challenged by Colston and Leadbetter [14] in 1936, after completing an autopsy study on 98 patients with bladder cancer. In that autopsy series, significantly many cadavers with bladder cancer were identified with limited metastatic disease restricted to the pelvic lymph nodes, and thought to be potentially amenable to surgical resection. A decade later, Jewett and Strong [15] published similar findings in another important autopsy series of 107 cases in which a percentage of cadavers with extravesical bladder tumours had metastatic involvement limited to the pelvic lymph nodes, the so-called 'cardinal site of metastasis'. This study correlated the incidence and the extent of lymph node involvement with the depth of penetration of the primary bladder tumour, referred to as 'an index of curability'. These pioneering observations helped form the foundation of the first widely accepted staging system for bladder cancer, the Jewett-Marshall staging system. Several contemporary radical cystectomy series have subsequently confirmed the correlation of the primary bladder tumour to the incidence of lymph-node metastasis [4–7,9,10].

The initial approach using an extended lymphadenectomy in six patients for bladder cancer was described in 1949 by Marshall and Whitmore [16]. These same authors subsequently reported 4-year follow-up data on 100 patients in 1956 [17]. The survival benefits of a pelvic lymphadenectomy in patients with bladder cancer should be first credited to Kerr and Colby [18]. In 1950, they reported survival in two node-positive patients undergoing radical cystectomy with a pelvic lymphadenectomy. In addition, the authors commented on their concerns of the high incidence of pelvic recurrence after a simple cystectomy. These observations prompted the routine application and inclusion of a lymphadenectomy with wide excision at the time of radical cystectomy. There was subsequently a decrease in pelvic recurrence, with improved survival [18]. These early experiences directed the modern surgical concept of a routine lymphadenectomy with wide surgical margins at the time of cystectomy to reduce local recurrences and improve the curability of the disease.

In 1950, Leadbetter and Cooper [19] also elegantly reported their experience detailing the surgical approach and boundaries of an extended lymphadenectomy in patients with bladder cancer, based on a better understanding of the lymphatic drainage of the bladder and prostate. This included: (i) proximally the distal aorta; (ii) laterally the genitofemoral nerve; (iii) distally the recurrent iliac vein (laterally), and the lymph node of Cloquet (medially). Although the specific boundaries or limits of a lymphadenectomy for bladder cancer continue to be debated today, the suggestion even in 1950 was that a more extended lymphadenectomy might be necessary to remove all potential lymph-node metastases, including the lymphatics at the level of the distal aorta and vena cava.

Nearly a decade later, Whitmore and Marshall [20] reported their clinical experience in 230 patients with bladder cancer undergoing surgical excision with lymphadenectomy. In this group, 55 patients were found to have D_1 (lymph node-positive) disease with two (4%) long-term survivors. The authors commented that they were unaware of any patient with histological evidence of nodal metastases who survived for >5 years, unless both the primary tumour and the metastases were excised. They concluded that 'for patients with only a few pelvic nodal metastases, radical cystectomy has provided some 5-year successful results - the only such of which we are aware.' Dretler *et al.* [21] subsequently updated this experience with lymphadenectomy in patients with bladder cancer undergoing cystectomy. That report confirmed the benefit of a lymphadenectomy, with better survival in node-positive patients, and was the first to specifically document no apparent increase in the morbidity and mortality associated with an extended LND at the time of radical cystectomy.

In 1982, Skinner [22] reported his pioneering surgical experience with the application of a 'meticulous', extended LND, with long-term survival in ≈30% of lymph node-positive patients. Controversy continues about the absolute extent (boundaries) of the LND in patients undergoing radical cystectomy for bladder cancer. Although it is thought that a 'standard' dissection (cephalad extent at the level of the common iliac bifurcation) provides adequate staging information, there is evidence to suggest that a more 'extended' (cephalad extent to include the common iliac vessels and possibly the distal aorta and vena cava) lymphadenectomy is beneficial in patients undergoing cystectomy for bladder cancer from a therapeutic standpoint, including those with node-positive and node-negative bladder disease.

LYMPHATIC DRAINAGE OF THE BLADDER

An anatomical understanding of the lymphatic drainage of the bladder is necessary when considering the specific sites of lymph-node metastases, as well as attempting to best define the required boundaries of an appropriate

lymphadenectomy. The primary contributions to the knowledge of vesical lymphatics have come from European sources and were well summarized by Leadbetter and Cooper in 1950 [19].

The lymphatic drainage from the bladder is accomplished by a system of lymphatic channels and lymph glands separated into six distinct areas: (i) the visceral lymphatic plexus within the bladder wall, initiating in the submucosa and extending into the muscular layer of the organ; (ii) the intercalated lymph nodes, which are juxtavesical lymph nodes located within the perivesical fat arranged into anterior, lateral and posterior groups; (iii) pelvic collecting trunks, which are medial lymph nodes to the external iliac and hypogastric lymph nodes; (iv) regional pelvic lymph nodes, which include the external iliac, hypogastric, and sacral lymph node groups; (v) lymphatic trunks leading from the regional pelvic lymph nodes to; (vi) the common iliac lymph nodes, those on the common iliac vessels, thought to be the secondary echelon of metastases, intermediate between the pelvic and the aortocaval lymph nodes [19].

Radical cystectomy series have confirmed that the most common sites of lymph node involvement are the obturator, hypogastric and external iliac lymph nodes. Smith and Whitmore [23] reported that these sites of nodal metastases were involved in 74% and 65%, respectively. This study also showed lymph-node metastases in 19% of cases to the common iliac lymph-node packet. This was one of the first anatomical lymph-node mapping studies in patients undergoing radical cystectomy that suggested the importance of an extended LND to remove all potential lymph-node metastases, including those along the common iliac vessels. The need to extend the LND to a higher (more cephalad) level remains controversial. Leadbetter and Cooper [19] initially commented that it was not necessary to include the aortocaval lymph nodes, as the surgical removal could not be done and should not be part of the cystectomy. Indeed, it was shown that an extended lymphadenectomy, including removal of the lymphatic tissue distal to the inferior mesenteric artery, can be safe [4,5]. Furthermore, there is pathological evidence to suggest that the lymph-node region extending from the aortic bifurcation to the level of the inferior mesenteric artery may be a common site of nodal metastasis that can be effectively removed surgically [5].

Similar to bladder cancer, prostate cancer preferentially metastasizes to the obturator/hypogastric and external iliac lymph nodes as the first site of lymph node spread [24,25]. In a canine study, the lymphatic drainage of the prostate was carefully evaluated based on the anatomy of the prostate [26]. Lymphatics of the prostate gland were found to drain primarily into the obturator and iliac lymph nodes and include the presacral lymph nodes. This finding, coupled with the fact that high-grade, invasive bladder cancer can involve the prostate [27], and knowing that mapping studies have documented presacral lymph-node metastases [5,9], underscores the importance of including removal of the presacral lymph nodes during the lymphadenectomy for bladder cancer.

Recently, the specific distribution of nodal metastases was prospectively evaluated in a multicentre study in which an extended lymphadenectomy was performed in all patients with bladder cancer [5]. This mapping study showed that positive lymph nodes were most common in the obturator spaces and adjacent to the iliac vessels. Interestingly, 16% of lymph-node metastases also included nodes above the aortic bifurcation, while 8% of nodal metastases involved the presacral region. Among patients with nodal metastases located within the limits of a 'standard' dissection (below the bifurcation of the common iliacs), a significant proportion also had nodal involvement at the level of the common iliac vessels and above the aortic bifurcation, at 57% and 31%, respectively. The authors noted that had the dissection been limited to the obturator spaces, 74% of all positive lymph nodes would have been left behind, and nearly 7% of the patients in this cohort would have been misclassified as node-negative. Furthermore, there were no isolated nodal metastases above the aortic bifurcation (with no nodal disease in the pelvis or along the common iliacs) in that study, suggesting that so-called 'skip lesions' are rare [5]. The significance of an extended lymphadenectomy was also corroborated in a study in which a third of patients with unexpected microscopic nodal involvement at the time of cystectomy had metastases to the common iliac lymph nodes [28].

A stage-specific lymph-node metastasis mapping study was recently reported by Vazina *et al.* [9]; 176 patients had an extended lymphadenectomy with radical cystectomy, in which 43 (24.4%) had pathological lymph node involvement. Although the most common sites of nodal metastases were the external iliac and hypogastric/obturator regions, 5.1% had presacral nodal involvement and 9% had disease above the common iliac bifurcation. Importantly, a third of patients with involvement of the common iliac lymph nodes also had involvement of the presacral region, supporting the importance of also removing these nodes. Interestingly, a 'skip metastasis' occurred in one patient with positive lymph nodes at or above the common iliac bifurcation with no involvement of the more distal pelvic lymphatics [9]. Collectively, these studies support the application of a more extended lymphadenectomy with the cephalad extent of dissection that includes the distal para-aortic and paracaval lymph nodes, and removal of the presacral nodal packet.

The need for a bilateral LND was also questioned, particularly in patients with a unilateral bladder tumour [29,30]. In the mapping study by Leissner *et al.* [5] bilateral lymph-node metastases were common even if the primary cancer was limited to the right or left hemisphere of the bladder wall. Mills *et al.* [31] evaluated lymph-node metastases in 83 patients with bladder cancer, after radical cystectomy, and found that 41% with a unilateral bladder tumour had contralateral nodal involvement. In a mapping study of 200 patients undergoing an extended lymphadenectomy, 24% were found to have node-positive disease and 39% of these had bilateral involvement [32]. These data suggest that a bilateral lymphadenectomy is important to remove all potential sites for nodal metastases at the time of cystectomy. In addition, in view of the diversity and potential for bilateral spread of nodal metastases, the concept of a sentinel-node lymphadenectomy may be difficult to apply, and not readily transferable to bladder cancer treated with radical cystectomy.

THE INCIDENCE OF BLADDER CANCER WITH LYMPH-NODE METASTASIS AT AUTOPSY

The incidence of lymph node-positive disease in autopsy studies suggests that lymph node involvement may be the sole site of metastases in 30–40% of patients with

TABLE 1 The incidence of lymph-node (LN) metastasis after radical cystectomy in contemporary series: correlation with the primary bladder tumour

Reference	Period	Total patients	N (%) LN metastases	Bladder tumour stage (TNM 1997), n (%)				
				P0, Pis, Pa, P1	P2a	P2b	P3	P4
Poulsen *et al.* [6]	1990–1997	191	50 (26)	2 (3)	4 (18)	7 (25)	33 (51)	4 (44)
Vieweg *et al.* [7]*	1980–1990	686	193 (28)	10 (10)	12 (9)	22 (23)	97 (43)	52 (41)
Leissner *et al.* [5]†	1999–2002	290	81 (28)	1 (2)	5 (13)	12 (22)	53 (44)	10 (50)
Stein *et al.* [4]	1971–1997	1054	246 (24)	19 (5)	21 (18)	35 (27)	113 (45)	58 (43)
Vazina *et al.* [9]‡	1992–2002	176	43 (24)	1 (4)	10 (16)		20 (40)	12 (50)
Abdel- Latif *et al.* [10]¶	1997–1999	418	110 (26)	3 (4)	4 (7)	29 (25)	59 (48)	15 (65)
Total		**2815**	**723 (26)**					

**six patients with Cis of prostatic ducts with lymph node-positive disease classified as Pis; †Multicentre trial; ‡P2a and P2b combined; ¶Includes squamous cell, adenocarcinoma and TCC of the bladder.*

bladder cancer. In 1931, Cunningham [33] collected data on 411 cases of bladder cancer that were evaluated by autopsy. Of these, 132 were from the Mayo Clinic, with 17% of the cases having regional lymph node involvement. Colston and Leadbetter [14] subsequently reported on 98 cases of carcinoma of the bladder at autopsy. Metastases were found in 56% of cases, while 25% had only pelvic or retroperitoneal lymph node involvement, a similar incidence documented in radical cystectomy series.

Jewett and Strong [15] studied the incidence of lymph node involvement in autopsy cases and were the first to correlate the depth of tumour invasion of the primary bladder tumour to the incidence of lymph-node metastases. In that study of 107 autopsies, there was no lymph node involvement in three cases in a group with mucosal infiltration only, in one of 15 (7%) with extension into the muscular layer, and in 52 of the 89 (58%) with extension into the perivesical tissues. Their early observation correlating lymph-node metastases with the depth of penetration of the primary tumour was subsequently confirmed in several large clinical studies of patients undergoing radical cystectomy [4–7,9].

It is reasonable to assume that the incidence of nodal metastases in patients undergoing radical cystectomy should be lower than in autopsy studies, as patients considered unresectable or inoperable are generally excluded from analysis. However, these autopsy studies suggest that: (i) significantly many patients with bladder cancer will have regional lymph-node metastases only; (ii) these lymph nodes can be removed with an appropriate lymphadenectomy; and (iii) the frequency of lymph node tumour metastases correlates to the degree or depth of invasion of the primary bladder tumour.

THE INCIDENCE OF BLADDER CANCER WITH LYMPH-NODE METASTASIS AFTER RADICAL CYSTECTOMY

The incidence of lymph-node metastases in patients undergoing radical cystectomy is ≈26% (Table 1) [4–7,9,10]. In the 2815 patients undergoing radical cystectomy with lymphadenectomy in the cited series, 723 (26%) were found to have lymph-node metastases. Furthermore, in support of Jewett's early observation, the correlation between the depth of invasion of the primary tumour and the incidence of lymph-node metastases is evident (Table 1). In the largest reported cystectomy series of 1054 patients [4], 246 (24%) had lymph-node metastases. The incidence of lymph-node tumour involvement correlated with increasing tumour stage, including 5% with superficial nonmuscle-invasive primary bladder tumours (P0, Pa, Pis, P1), 18% with superficial muscle-invasive tumours (P2a), 27% with deep muscle invasive tumours (P2b), 45% with extravesical tumours (P3), and 45% with P4 primary bladder tumours.

CONCLUSIONS

The routine inclusion of a regional lymphadenectomy with radical cystectomy for patients with invasive bladder cancer is based on a growing body of evidence, from early autopsy and animal studies to recent retrospective surgical series and multicentre prospective trials. Despite improvements in radiographic imaging, more than a quarter of patients with clinically organ-confined bladder cancer will be found to have lymph-node metastases. A properly performed lymphadenectomy provides not only prognostic information, but also a potential therapeutic benefit for these high-risk patients. It appears that an extended LND should include the distal para-aortic and paracaval lymph nodes, as well as the presacral nodes, known anatomical sites of lymph-node drainage from the bladder, and potential sites of lymph-node metastases in patients with bladder cancer. Although the limits (boundaries) of the LND remain controversial, developing data lends support for a more extended lymphadenectomy at the time of cystectomy in patients who are appropriate surgical candidates.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **LND**, lymph-node dissection.