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The role of pelvic lymph node dissection as a predictive and prognostic factor in bladder cancer

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Abstract

The aim of this study was to evaluate the value of pelvic lymph node dissection (PLND) performed as a separate procedure in a consecutive Danish bladder cancer cohort and also to analyse if the number of lymph nodes excised had an impact on outcome. From 1992 to 1998, 339 cystectomy candidates were retrospectively reviewed. Based on a preoperative PLND, 248 patients (10% N+) underwent radical cystectomy and 91 (87% N+) underwent radio- or chemotherapy. The median follow-up was 6.3 years. PLND was able to separate N+ from N0 patients with a false-negative rate of 3% compared with the following cystectomy. Lymph node-positive patients treated with cystectomy ($n=24$) all died from their bladder cancer. Therefore, accurate pathological N classification before the treatment decision seems worthwhile. The median number of lymph nodes excised was six and the number of lymph nodes had an independent prognostic impact on survival. This underlines the need for guidelines for surgical lymphadenectomy and the pathological assessment of lymph nodes in bladder cancer.

Keywords: Bladder; Bladder neoplasm; Lymph nodes; Lymphadenectomy; Cystectomy

1. Introduction

Radical cystectomy and pelvic lymph node dissection has become the preferred standard treatment in the management of muscle invasive bladder cancer, but there is still an ongoing debate with regard to whether patients with lymph node metastasis should undergo a primary cystectomy or be offered other treatment modalities. Radical cystectomy and pelvic lymph node dissection appear to benefit a small number of node-positive patients, especially those with organ-confined tumours (⩽T3a) and involvement of only a single lymph node [1,2]. Recently, Herr reported [3] that a proportion of patients with grossly node-positive bladder cancer were cured with radical cystectomy and meticulous pelvic lymph node dissection. However, grossly enlarged nodes generally indicates a poor prognosis and cystectomy alone is unlikely to be curative. The main factors determining the outcome of patients with invasive bladder cancer patients are the pathological T and N classifications, established from the specimen after cystectomy [4]. The practice at the urological department of the Aarhus University Hospital in Denmark was to make a diagnostic preoperative pelvic lymph node dissection (PLND) and then offer the lymph node-negative patients radical cystectomy. Lymph node-positive patients were not considered curable by cystectomy and were referred to the oncological department to undergo radio- or chemotherapy.

Although radical cystectomy is routinely combined with pelvic lymphadenectomy, there is no consensus on the minimum number of lymph nodes to be excised or the extent of the lymph node dissection. Poulsen [5] extended the limits of pelvic lymph node dissection from the obturator fossa only to an area bounded proximally by the bifurcation of the aorta, laterally by the genitofemoral nerve, distally by the circumflex iliac vein and Cloquet's lymph node and posteriorly by the internal iliac vessels, including the presacral nodes and obturator fossa. By this extension, they found that the survival

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rate improved for patients with bladder cancer confined to the bladder wall. Leissner [6] concluded that extensive lymphadenectomy (⩾16 lymph nodes removed) enhanced the prognosis of bladder cancer patients undergoing cystectomy. Recently, Herr [7] concluded that resection and assessment of an adequate number of lymph nodes in cystectomy specimens increased the likelihood of proper staging and impacted on patient outcome.

The aim of this study was to evaluate the value of pelvic lymph node dissection (PLND) performed as a separate procedure in a consecutive Danish bladder cancer cohort that was considered suitable to undergo radical cystectomy. Furthermore, we wanted to analyse the number of lymph nodes excised and outcome with a specific emphasis on lymph node-positive patients.

2. Patients and methods

2.1. Patients

In a 7 year period (1 January 1992 to 31 December 1998), a total number of 339 patients with primary bladder cancer were considered suitable to undergo radical cystectomy. The patients were retrospectively followed from the time of pelvic lymph node dissection/cystectomy until death.

2.2. Clinical classification

The tumours were classified according to the International Union Against Cancer (UICC) 1992 classification system [8].

Before treatment, the clinical T classification (cT) was determined by cystoscopy, bimanual examination and biopsy findings. The clinical NM classification was evaluated using an ultrasonic scan of the abdomen and pelvis, chest X-ray and excretory urogram. In some cases, bone-scan, computed tomography (CT) scan or magnetic resonance imaging (MRI) were performed. All patients were considered Nx, M0.

2.3. Pathological classification

The pathological T classification (pT) was defined from the histopathological report. The pN classification was established using the specimen from either the PLND or cystectomy. The number and size of lymph nodes were palpated and determined visually by different pathologists. The lymph nodes detected were bisected and embedded for histopathological evaluation. Retrospectively, pN were separated into four categories: Nx if no lymph nodes were removed and examined or if unknown. If at least one lymph node was removed, pN category was classified as N0, N1 and N2, respectively.

2.4. Histopathological grading

All transitional cell carcinomas were classified according to the Bergkvist grading system [9].

2.5. Treatment

2 patients received neoadjuvant chemotherapy (cisplatin and methotrexate).

2.6. Pelvic lymph node dissection (PLND)

The strategy at the present institution was to perform a separate diagnostic lymphadenectomy in all muscle invasive transitional cell tumours and only then offer the lymph node-negative patients radical cystectomy. Lymph nodes were removed uni- or bilaterally from the obturator fossa, depending on the tumour localisation and size.

2.7. Radical cystectomy

Radical cystectomy involved the *en bloc* removal of the urinary bladder, prostate, seminal vesicles, proximal *vas deferens* and proximal urethra with a margin of adipose tissue and peritoneum in men. In women, the procedure involved removal of the urinary bladder, urethra, fallopian tubes, ovaries, uterus, varying portions of the anterior vaginal wall and surrounding fascia *en bloc*.

Lymph nodes from the obturator fossa were removed if this had not already been done at the previous staging operation.

2.8. Radiotherapy or chemotherapy

After a separate pelvic lymph node dissection, 91 patients were referred to the oncological department and treated with radiotherapy or chemotherapy.

2.9. Statistical analysis

At the end of registration (15 June 2002), the median follow-up of patients still alive was 6.3 years (range 3.4–10.4 years). Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 10.0 for windows program. Spearman's rank correlation coefficient was used to estimate the correlation of the number of lymph nodes examined, T classification and the number of positive lymph nodes. The survival functions were calculated for the endpoints disease-specific and overall survival by the method of Kaplan and Meier. The log rank test was used for comparison, and a test for trend with equal weighting was performed if more than two groups were compared. All time estimates were made using the date of PLND/cystectomy as the initial value.

Table 1
Clinical and pathological parameters related to PLND and therapy

	All *N* (%)	PLND		Therapy	
		Yes *N* (%)	No *N* (%)	Cystectomy *N* (%)	Rad/chemo. *N* (%)
All	339	240	99	248	91
Age (years)					
<60	95 (28)	63 (26)	32 (32)	71 (29)	24 (26)
60–69	168 (50)	125 (52)	43 (43)	125 (50)	43 (47)
>70	76 (22)	52 (22)	24 (24)	52 (21)	24 (26)
Gender					
Female	82 (24)	50 (21)	32 (32)	65 (26)	17 (19)
Male	257 (76)	190 (79)	67 (68)	183 (74)	74 (81)
Histopathological type					
Transitional cell carcinoma	319 (94)	237 (99)	82 (83)	230 (93)	89 (98)
Squamous cell carcinoma	10 (3)	1	9 (9)	9 (4)	1 (1)
Adenocarcinoma	5 (1)	0	5 (5)	5 (2)	0
Small cell carcinoma	4 (1)	2 (1)	2 (2)	3 (1)	1 (1)
Leiomyosarcinoma	1	0	1 (1)	1	0
Clinical T classification					
Ta, CIS	6 (2)	1	5 (5)	6 (2)	0
T1	54 (16)	7 (3)	47 (47)	52 (21)	2 (2)
T2	107 (32)	90 (38)	17 (17)	72 (29)	35 (38)
T3a	121 (36)	102 (43)	19 (19)	90 (36)	31 (34)
T3b	21 (6)	18 (8)	3 (3)	11 (4)	10 (11)
T4a	26 (8)	21 (9)	5 (5)	14 (6)	12 (13)
T4b	4 (1)	1	3 (3)	3 (1)	1 (1)
Malignancy grade[a]					
II	12 (4)	5 (2)	7 (9)	11 (5)	1 (1)
III	237 (74)	174 (73)	63 (77)	168 (73)	69 (78)
IV	70 (22)	58 (24)	12 (15)	51 (22)	19 (21)
Growth pattern					
Papillary	49 (14)	19 (8)	30 (30)	42 (17)	7 (8)
Solid	168 (50)	139(58)	29 (29)	119 (48)	49 (54)
Miscellaneous	25 (7)	21 (9)	4 (4)	16 (6)	9 (10)
Unknown	97 (29)	61 (25)	36 (36)	71 (29)	26 (29)
Carcinoma *in situ*					
CIS	133 (39)	90 (38)	43 (43)	94 (38)	39 (43)
Not CIS	179 (53)	131(55)	48 (48)	132 (53)	47 (52)
Unknown	27 (8)	19 (8)	8 (8)	22 (9)	5 (5)
Size					
<4 cm	112 (33)	78 (33)	34 (34)	83 (33)	29 (32)
⩾4 cm	119 (35)	92 (38)	27 (27)	84 (34)	35 (38)
Unknown	108 (32)	70 (29)	38 (38)	81 (33)	27 (30)
Pathological N classification					
N0	208 (61)	156 (65)	52 (53)	196 (79)	12 (13)
N1	46 (14)	41 (17)	5 (5)	9 (4)	37 (41)
N2	57 (17)	43 (18)	14 (14)	15 (6)	42 (46)
Nx	28 (8)	0	28 (28)	28 (11)	0

PLND, separate pelvic lymph node dissection; Rad/chemo, radiotherapy/chemotherapy.
[a] Only for transitional cell carcinoma.

A multivariate Cox proportional hazard analysis was used to evaluate prognostic parameters using death of bladder cancer and death of all causes as endpoints. Parameters were included in the model backward likelihood ratio. All P values were based on two-sided testing, and the level of statistical significance was 5%.

3. Results

The characteristics of 339 patients, considered as candidates for cystectomy, are listed in Table 1. The median age was 65 years (range 31–83 years).

3.1. Treatment strategy

The treatment pattern (Fig. 1) shows that 240 patients underwent preoperative PLND and 99 did not. At PLND, 80 patients (33%) were identified as lymph node-positive, a single patient underwent cystectomy in spite of a positive lymph node status, and therefore 79 patients were referred to the oncological department. Lymph node-negative patients underwent cystectomy, except for 12 patients (2 had cardio-pulmonary disease, 2 were discovered to have T4b tumours and 8 preferred radiotherapy for personal reasons). At cystectomy, 4 patients (of the 148) were reclassified as lymph node-positive, corresponding to a sensitivity of 97%. The 4 patients underwent PLND unilaterally, and the positive lymph nodes were identified at the contra-lateral side in all 4 cases. In the 'not PLND' group, all 99 patients underwent cystectomy without a preoperative staging operation. Nineteen had lymph node metastasis and 28 were classified as Nx (in 23 patients, no lymph nodes were removed and in 5 patients no information concerning lymph nodes were available). Thus, 248 underwent cystectomy and 91 patients were treated with radio- or chemotherapy.

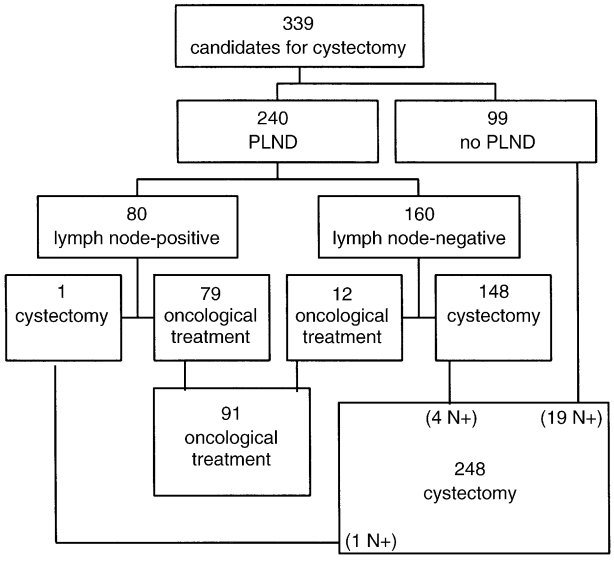

Fig. 1. Flow diagram showing the treatment pattern of 339 bladder cancer patients. PLND: separate pelvic lymph node dissection.

3.2. PLND

Table 2 illustrates the operation time, number of lymph nodes removed, N classification and side-effects following PLND. Forty-four side-effects occurred in 34 patients corresponding to a complication rate of 14%. No late morbidity after PLND was registered and there were no postoperative deaths.

3.3. Nodal metastasis according to clinical T classification and to the total number of lymph nodes removed

Table 3 shows the incidence of pathologically confirmed pelvic lymph node metastasis according to cT and number of lymph nodes excised for the 339 cystectomy candidates. Lymph node involvement increased with a more advanced T category ($P<0.001$). 10% of the lymph node-positive patients were identified among 60 superficial tumours (Ta, CIS, T1) and among the advanced non-organ-confined tumours (T3b-T4) 53% of the patients were classified as N+.

The median number of lymph nodes removed from all 339 patients was 6 (range 0–38). Using groupings of quartiles (1–3, 4–6, 7–11, $\geqslant$12), the overall percentage of patients with positive nodes decreased with an increasing number of lymph nodes removed.

Of the lymph node-positive patients, 17% was N2 and 14% N1. The distribution of N1 and N2 was not correlated to cT or the number of lymph nodes removed.

The exact number of lymph nodes excised was not described in the pathological report in 18% of the 339 cases.

3.4. Clinical T category

Table 1 shows the frequencies of the clinical T categories. From clinical estimates, 85% of the tumours were organ-confined ($\leqslant$T3a) and only 15% were not confined to the organs ($\geqslant$T3b). Fig. 2 demonstrates the highly statistically significant difference ($P<0.0001$) in the disease-specific survival rates. The more advanced the tumour, the poorer survival.

3.5. Pathological N category

The 5-year disease-specific survival for lymph node-positive patients was 8%, for N0 62% and for Nx 59% ($P<0.0001$) (Fig. 3). The survival difference between N1 and N2 was not significant ($P=0.08$).

All lymph node-positive patients treated with cystectomy ($n=24$) died of bladder cancer within 38 months.

The lymph node-positive patients referred to the oncological department, treated with radiotherapy or chemotherapy ($n=79$) had a 5 year disease-specific survival rate of 11% ($P=0.06$) (Fig. 4).

3.6. Survival

Cox proportional hazard regression analysis (Table 4) including 244 patients (with TCC tumours, known N classification and known number of lymph nodes removed) revealed clinical T-stage and pathological N-stage as independent prognostic factors. Furthermore, the number of lymph nodes excised showed an independent prognostic impact on survival. Patients who had only 1–3 lymph nodes excised had a significantly poorer survival rate than patients where more lymph nodes were removed. Using death of all causes as an endpoint gave similar results.

4. Discussion

A Danish bladder cancer cohort was followed retrospectively from the time of diagnosis until death. All 339 patients were candidates for cystectomy, but because of the standard procedure with preoperative PLND, only 248 were treated with cystectomy, whereas 91 were referred to the oncological department and underwent radio- or chemotherapy. 30% of the cohort was lymph node-positive (14% N1 and 17% N2) and they showed a poor prognosis that was independent of the treatment strategy.

4.1. Pelvic lymph node dissection as a preoperative method

Pelvic ultrasonography (UL), CT or MRI are disappointing modalities for identifying positive pelvic lymph nodes [10–12]. Ultrasonographic evaluation of pelvic nodes in cervical carcinoma showed a sensitivity of 67% and a specificity of 78% [10]. A retrospective review of 82 bladder cancer patients showed that CT evaluation of lymph nodes had a false-positive rate of 2% and a false-negative rate of 21% [11]. MRI technique performed on 55 bladder cancer patients resulted in no false-positives, but a false-negative rate of 15% [12]. Our study showed that separate PLND was a feasible method to identify lymph node-positive patients, and thereby separate patients into two highly significantly different prognostic groups, prior to treatment decision. Four false-negatives at PLND were identified (corresponding to a sensitivity of 97%) and no other non-invasive methods have a similar sensitivity. Pathologically-estimated false-positive lymph nodes could theoretically exist, but the number of cases are considered to be few. However, the procedure was invasive with a complication rate of 14%. Nevertheless, these were mainly minor complications without any long-term morbidity. Laparoscopic PLND has been shown to provide an adequate accuracy when staging patients with a decreased complication rate and hospital stay relative to open surgical procedures. However, although potentially attractive, such a procedure has also been shown to be time-consuming and require a significant learning curve [13].

Table 2
Operation time, number of lymph nodes, pathological N classification and complications after separate pelvic lymph node dissection in 240 bladder cancer patients

	All	Unilaterally	Bilaterally
No. of patients	240	170	70
Median operation time (min)		60 (15–200)	83 (27–195)
Median lymph nodes removed		5 (1–27)	10 (2–38)
Exact number of lymph nodes not described		22 (13%)	11 (16%)
Pathological N classification			
N0	160 (67)	109 (64)	51 (73)
N1	38 (16)	26 (15)	12 (17)
N2	42 (18)	35 (21)	7 (10)
Complications			
Total number of patients (%)	34 (14)	26 (15)	8 (11)
Wound infection	18	13	5
Cystitis/pyelonephritis	6	6	0
Re-exploration	7	4	3
Pneumonia	4	3	1
Sepsis	2	2	0
Pulmonary embolism	1	1	0
Reversible lesion of *n. obturatorius*	2	2	0
Haemorrhage requiring transfusion	2	2	0
Lesion of bladder (T4b)	1	1	0
Fistula	1	0	1

4.2. Treatment of lymph node-positive patients

Generally, patients with lymph node-positive bladder cancer are regarded as having a poor prognosis after radical cystectomy, although considerable variation in the 5 year survival rates are usually reported, ranging from 13 to 31% [14,15]. In Table 5, an overview of the incidence and survival of lymph node-positive patients following radical cystectomy are shown. Some authors have supported the use of aggressive surgical approa-

Table 3
Number of lymph nodes recovered and pathological lymph node classification after PLND and cystectomy in 339 patients related to clinical T classification

Lymph nodes recovered	Clinical T classification				
	N classification	Ta, CIS, T1 *N* (%)	T2, T3a *N* (%)	T3b, T4 *N* (%)	All stages *N* (%)
0	Nx	13	7	3	23 (100)
1–3	N0	5	15	3	23 (45)
	N1	1	10	5	16 (31)
	N2	0	4	8	12 (24)
	All	6	29	16	51
4–6	N0	9	36	5	50 (65)
	N1	1	5	3	9 (12)
	N2	0	13	5	18 (23)
	All	10	54	13	77
7–11	N0	8	31	6	45 (68)
	N1	0	9	1	10 (15)
	N2	0	10	1	11 (17)
	All	8	50	8	66
⩾12	N0	5	37	3	45 (74)
	N1	1	3	0	4 (7)
	N2	2	8	2	12 (20)
	All	8	48	5	61
Unknown	N0	11	30	4	45 (74)
	N1	0	6	1	7 (11)
	N2	1		1	4 (7)
	Nx	3	2	0	5 (8)
	All	15	40	6	61
Total	N0	38 (63)	149 (65)	21 (41)	208 (61)
	N1	3 (5)	33 (14)	10 (20)	46 (14)
	N2	3 (5)	37 (16)	17 (33)	57 (17)
	Nx	16 (27)	9 (4)	3 (6)	28 (8)
	All	60	228	51	339

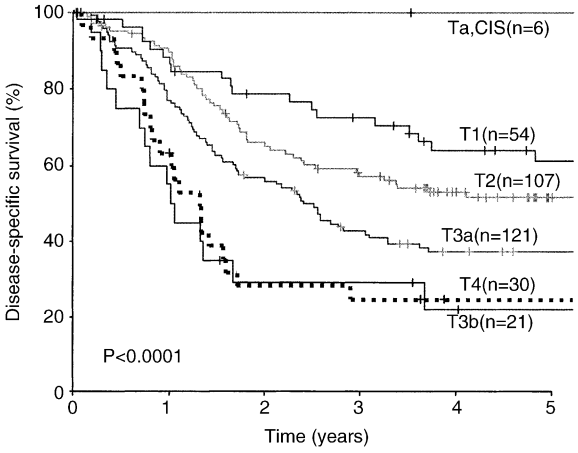

Fig. 2. Disease-specific survival in 339 bladder cancer patients related to clinical T-stage. CIS, carcinoma *in situ*.

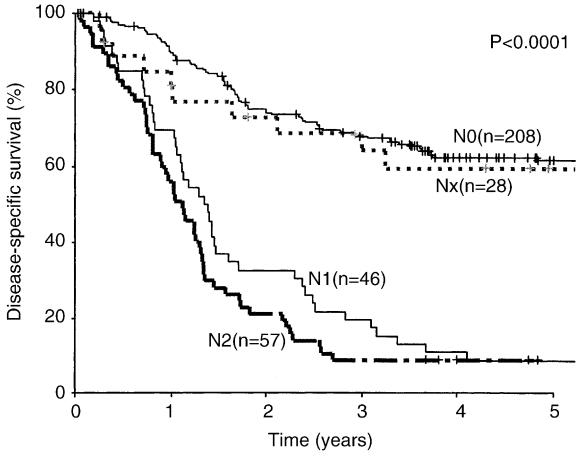

Fig. 3. Disease-specific survival in 339 bladder cancer patients related to pathological lymph node status.

ches for all bladder cancer patients, including lymph node-positive patients, and have shown very promising results [1,2,15]. The therapeutic value of meticulous PLND was evidenced by a similar outcome in those with node-negative disease and similar pT stage of the primary tumour [1,2]. However, this benefit rapidly disappeared when more than 1 lymph node was involved

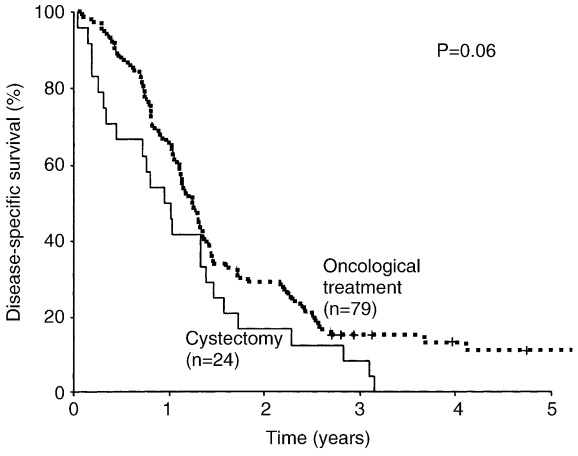

Fig. 4. Disease-specific survival of lymph node-positive patients treated with cystectomy or at the oncological department with radiotherapy or chemotherapy.

[2]. Recently, Herr and colleagues [3] showed 24% long-time survivors, among 84 bladder cancer patients with grossly lymph node-positive disease (N2, N3), who underwent radical cystectomy. However, the data must be interpreted with caution because several problems are encountered when comparing outcomes from different studies. Most of the studies in Table 5 were based on experiences at single institutions in which patient selection was controlled for. The exclusion criterions varied, but the number of patients selected at local hospitals before referral is unknown. From a geographical region Holmäng [16] studied in 1987 to 1988 all patients with muscle invasive bladder carcinoma, and found that more than 60% of the patients were considered unsuitable for radical cystectomy. Moreover, many patients with advanced bladder cancer were never referred to specialised units [17].

In the present series, a median of six lymph nodes was removed (five lymph nodes in unilateral PLND and 10 in bilateral PLND). The PLND in this study was diagnostic, and the extent of PLND was restricted to the nodes from the obturator fossa. In a comparative Danish study, the median number of lymph nodes removed from the obturator fossa was five [18]. However, in the majority of other studies, where the number of lymph

Table 4
Cox proportional hazards analysis using death of bladder cancer as an endpoint: analysis of 244 patients with well defined parameters (95 patients with non-TCC, unknown number of lymph nodes removed or Nx were excluded)

Variable	Patients *N*	Univariate analysis	Multivariate analysis	
		P value	*P* value	RR (95% Confidence intervals)
T classification		<0.0001	0.03	
Ta–T1	32			1
T2–T3a	173		0.7	1.1 (0.6–2.0)
⩾T3b	39		0.05	2.0 (1.0–4.0)
N classification		<0.0001	<0.001	
N0	158			1
N1	37		<0.001	4.2 (2.6–6.6)
N2	49		<0.001	6.3 (4.1–9.5)
Lymph nodes removed		0.02	0.03	
1–3	48	0.02		1
4–6	74		0.06	0.6 (0.4–1.0)
7–11	64		0.004	0.5 (0.3–0.8)
⩾12	58		0.28	0.8 (0.5–1.3)
Gender		0.9	0.3	
Male	191			1
Female	53		0.3	0.8 (0.5–1.3)
Age (years)		0.7	0.9	
<60	66			1
60–69	123		0.7	0.9 (0.6–1.5)
>60	55		0.8	0.9 (0.6–1.5)
Grade		0.9	0.8	
II	7			1
III	183		0.5	1.6 (0.4–6.7)
IV	54		0.5	1.6 (0.4–7.0)

nodes recovered was discussed, the number is far higher. Poulsen and colleagues recovered a mean of 14 lymph nodes in a limited lymphadenectomy and 25 in an extended lymphadenectomy [5]. Recently, Leissner and colleagues reported a median number of 13 lymph nodes. Based on post-mortem studies, Weingartner [19] recommended the removal of 20 lymph nodes as a guideline for pelvic lymphadenectomy, but he found large interindividual differences.

Beside the number of lymph nodes and the extent of PLND, the pathological assessment can also vary. Stein and colleagues [15] described the pathological practice as obtaining and examining multiple sections from the 'one stage PLND and cystectomy' specimen. Wilkinson showed that commonly used methods relative to examination of the surgical specimen could account for a greater than 30% false-negative interpretation [20], and by using lymph node revealing solution, the yield of normal and metastatic nodes of cystectomy specimens was enhanced significantly [21]. Thus, different surgical and pathological procedures, as well as patient selection, can account for large variations in the survival rates for lymph node-positive patients.

However, in spite of the aforementioned difficulties when comparing survival rates, the present outcome for lymph node-positive patients undergoing radical cystectomy, with no long-term survivors, seems inferior when compared with other published studies.

Table 5
Incidence and survival of lymph node-positive patients following radical cystectomy

Authors [Ref.]	Time period	Exclusion	Patients	PN+	Strata	5-year survival (%)
Roehrborn [28]	1971–1986	53 not TCC bladder cancer. Patients with advanced disease during exploration	280	42 (15%)	PN1 Pn2, 3	23[a] 18[a]
Pagano [29]	1979–1987	52 salvage cys 9 unknown	261	30 (11%)		4[a]
Lerner [1]	1971–1989	22 incurable	591	132 (22%)	<PT3 >PT3	50[a] 18[a]
Fosså [14]	1980–1990	Cohort of 534 271 had curatively intended radiotherapy. Patients who could not get curative treatment were excluded.	263	45 (17%)		13[a]
Malmstrom [30]	1985–1989	Of 325, only 275 underwent lymph node dissection	275	25 (9%)		≈1[a]
Poulsen [5]	1990–1997	Consecutive patients	194	51 (26%)		18[b]
Vieweg [2]	1980–1990	76 inadequate data	686	193 (28%)	<PT3 >PT3 pN1 pN2 pN3	51[a] 17[a] 33[a] 22[a] 0[a]
Bassi [31]	1982–1994	124 (pretreatment) 42 not bilat PLND	369	78 (21%)		15[a]
Cheng [32]	1980–1984	Consecutive patients Exclusion not mentioned	218	32 (15%)		18[a]
Leissner [6]	1986–1997	145 clinical follow-up not available, therefore survival data from only 302 patients	447	145 (32%), but only 79 were described	⩾16 ln <15 ln	35[c] 23[c]
Stein [15]	1971–1997	126 salvage cys 23 inoperable 46 distant metastasis 43 never free of disease	1054	246 (23%)		31[a]
Herr [3]	1980–1990	29 resection not possible	763	193 (25%), of these 84 N2, N3	N2, N3	≈26[c]
Mills [33]	1984–1997		452	83 (18%)		29%[a]
Knap	1992–1998	91 referred to oncological dept.	248	24 (10%)	N1, N2	0[c] 0[a]

cys, cystectomy; bilat, bilateral; dept., department.
[a] Overall survival.
[b] Recurrence-free survival.
[c] Disease-specific survival.

4.3. PLND as a therapeutic approach

Whether pelvic lymph node dissection has a curative effect in bladder cancer is still regarded as uncertain in many European countries [22]. The present study showed that the number of lymph nodes excised had an independent impact on survival. Retrospectively obtained information will necessarily be limited in its inaccuracy. In Denmark, there is no general practice to count the number of lymph nodes excised in bladder cancer, and it is important to note that the exact number was 'not described' in 18% of the patients. Therefore, many confounders can affect these results. On the other hand, the data available in this study could imply that the removal of many lymph nodes reflected a more complete cystectomy and PLND, with a wider margin of soft tissue around the bladder and thereby increased the likelihood of removing positive lymph nodes, including microscopic metastases, with an increasingly probability of curing the patient. In a retrospective study, Leissner [6] showed in an univariate analysis that bladder cancer patients with $\geqslant 16$ lymph nodes removed had a significantly superior tumour-specific survival rate and disease-free interval than those with $\geqslant 15$ lymph nodes removed. Poulsen and colleagues [5] prospectively followed 194 patients who underwent cystectomy and PLND (limited in 68 cases, extended in 126 cases). They suggested that extended limits of PLND improved the recurrence-free survival rate for patients undergoing radical cystectomy, but only for the subgroup with bladder cancer confined to the bladder wall. No advantage was found for tumours that were no longer confined to the organs or lymph node-positive patients. The overall prevalence of lymph node metastasis was higher in the extended dissection group compared with the limited group, and in an editorial comment Harry W. Herr mentioned that stage migration was the most likely explanation for the improved survival with an extended pelvic lymph node dissection in patients with organ-confined disease. Recently, Herr and colleagues [7] showed that the number of lymph nodes examined had an impact on local recurrence and survival for lymph node-positive as well as lymph node-negative patients, and suggested at least nine lymph nodes be excised. Convincingly, all 21 survivors (of 64 patients) with stage pN+ disease had at least nine lymph nodes detected.

4.4. Other treatment modalities for lymph node-positive patients

In this cohort, the lymph node-positive patients treated with radio- or chemotherapy had a non-significantly superior survival rate compared with lymph node-positive patients treated with radical cystectomy. Even though some departments achieve better outcomes for cystectomy cohorts, approximately 50% of patients with muscle invasive bladder cancer and the majority of lymph node-positive patients still die of their disease. Therefore, not all patients benefit from an aggressive surgical approach. The development of new chemotherapeutic agents and the increased use of chemotherapy have contributed to the improved survival of patients with metastatic bladder cancer [23]. Recently, results with Gc (gemcitabine/cisplatin) and MVAC (methotrexate/vinblastine/doxorubicin/cisplatin) regimens have shown long-term survival rates of 15–20% for patients with locally advanced or metastatic bladder cancers without visceral metastasis [24,25]. Furthermore, promising bladder preserving protocols with survival rates comparable with cystectomy cohorts [26,27] have been published. Therefore, treatment modalities other than cystectomy could be considered and appropriate patient selection, as well as accurate disease classification, before cystectomy would be worthwhile.

5. Conclusions

30% of this bladder cancer cohort, all considered suitable to primary cystectomy, was lymph node-positive (14% N1 and 17% N2). PLND was a feasible preoperative method to separate lymph node-positive from lymph node-negative patients, with a calculated sensitivity of 97% and an even higher specificity. It was possible to separate two significantly different prognostic groups, before making the final treatment decisions. Cystectomy with PLND restricted to the obturator fossa was an insufficient treatment for lymph node-positive patients, and there was a trend towards a better outcome for lymph node-positive patients undergoing radio- or chemotherapy.

Analysing published survival rates of N+ patients treated with cystectomy, selected patients with a few positive lymph nodes seemed to benefit from radical cystectomy and meticulous PLND, whereas most N+ patients had limited survival rates. Therefore, identification of N+ patients before making the final treatment decisions could be worthwhile.

The number of lymph nodes removed had an independent prognostic impact. This underlines the need for guidelines concerning surgical lymphadenectomy as well as the pathological assessment of lymph nodes in bladder cancer.

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