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Original Article

Impact of the extent of lymph node dissection on survival outcomes in clinically lymph node-positive bladder cancer

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Objective

To determine the oncological impact of extended pelvic lymph node dissection (ePLND) vs standard PLND (sPLND) during radical cystectomy (RC) in clinically lymph node-positive (cN+) bladder cancer (BCa).

Patients and Methods

In this retrospective, multicentre study we included 969 patients who underwent RC with sPLND (internal/external iliac and obturator lymph nodes) or ePLND (sPLND plus common iliac and presacral nodes) with or without platin-based peri-operative chemotherapy for cTany N1-3 M0 BCa between 1991 and 2022. We assessed the impact of ePLND on recurrence-free survival (RFS) and the distribution of recurrences (locoregional and distant recurrences). The secondary endpoint was overall survival (OS). We performed propensity-score matching using covariates associated with the extent of PLND in univariable logistic regression analysis. The association of the extent of PLND with RFS and OS was investigated using Cox regression models.

Results

Of 969 cN+ patients, 510 were 1:1 matched on propensity scores. The median (interquartile range [IQR]) time to recurrence was 8 (4–16) months, and median (IQR) follow-up of alive patients was 30 (13–51) months. Disease recurrence was observed in 104 patients in the ePLND and 107 in the sPLND group. Of these, 136 (27%), 47 (9.2%) and 19 patients (3.7%) experienced distant, locoregional, or both distant and locoregional disease recurrence, respectively. When stratified

by the extent of PLND, we did not find a difference in recurrence patterns ($P > 0.05$). ePLND improved neither RFS (hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.70–1.19; $P = 0.5$) nor OS (HR 0.78, 95% CI 0.60–1.01; $P = 0.06$) compared to sPLND. Stratification by induction chemotherapy did not change outcomes.

Conclusion

Performing an ePLND at the time of RC in cN+ patients improved neither RFS nor OS compared to sPLND, regardless of induction chemotherapy status. Pretreatment risk stratification is paramount to identify ideal candidates for RC with ePLND as part of a multimodal treatment approach.

Keywords

cN+, induction chemotherapy, lymph node-positive, radical cystectomy, template, urinary bladder neoplasms, urothelial cancer

Introduction

Radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND) is the standard-of-care treatment for muscle-invasive bladder cancer (MIBC) [1,2]. PLND has been shown to improve lymph node (LN) staging accuracy and long-term survival compared to RC alone [1,3]. Indeed, pathological LN status is an important predictor of survival outcomes and may determine the indication for adjuvant treatment [1,4].

The oncological impact of the extent of PLND remains controversial. While retrospective studies suggested improved survival outcomes for extended PLND (ePLND) [3], a recent randomized controlled trial (RCT; NCT01215071, LEA AUO) failed to show an oncological benefit of performing an ePLND compared to standard PLND (sPLND) in patients with locally resectable T1G3 bladder cancer (BCa) or MIBC (T2-T4aM0) [5]. In that trial, one-quarter of the included patients had positive LNs at RC (pN+), which may have limited the potential benefit of ePLND, given the favourable prognosis of pN0 disease [5]. According to available evidence, disease-free survival, specifically for pN+ patients, is superior after ePLND compared to sPLND [6].

Most of these data focus on patients without clinical evidence of LN metastasis. The oncological benefit of performing an ePLND in patients with clinically LN-positive (cN+) BCa remains poorly investigated [7]. Up to 50% of LN metastases lie beyond the anatomical boundaries of an sPLND template, and cN+ is the strongest risk factor for pN+, suggesting that cN+ patients are most likely to benefit from an ePLND [8–11]. In this study, we investigated whether ePLND would improve recurrence-free survival (RFS) and overall survival (OS) in patients with cN+ BCa, compared to sPLND, at the time of RC.

Patients and Methods

Study Population

This was an institutional review board-approved (reference number 1480/2022, Medical University Vienna), multicentre, observational study by the CLIPOLY (Clinically Positive Lymph Nodes) study group. Data collection was approved by the local ethics committees at all participating institutions. We retrospectively identified patients with cTany N1-3 M0 BCa who underwent RC with either sPLND or ePLND between 1991 and 2022. We excluded all primary metastatic (cM1) patients, patients with missing TNM stage or follow-up data, and patients who received peri-operative radiotherapy or immunotherapy (Fig. S1). Peri-operative systemic treatment consisted of platin-based combination chemotherapy.

Patient Characteristics and Covariates

Baseline characteristics and covariates included age at surgery, sex, smoking history, Charlson comorbidity index, chronic kidney disease stage based on the estimated GFR, hydronephrosis at staging, the staging modality prior to treatment, clinical T- and N-stage, type of urinary diversion, variant histology and concomitant carcinoma *in situ* at transurethral resection of bladder tumour, as well as receipt of induction chemotherapy. cN status was assessed via CT, MRI, or positron emission tomography (PET)-CT. Pelvic LNs larger than 8 mm in maximum short-axis diameter were considered metastatic.

Surgical and pathological variables comprised surgical approach, pathological T- and N-stage, total LN count, number of positive LNs, LN density, and receipt of adjuvant chemotherapy. A specialized uropathologist performed the pathological evaluation at each centre. Classification of histopathological stages followed the most recent American Joint Committee on Cancer TNM staging system.

At RC, the choice of the extent of PLND was at the surgeon's discretion. PLND templates were defined according to the European Association of Urology (EAU) guideline recommendations [1]. The sPLND template included the removal of the internal iliac, external iliac and obturator LNs, whereas the ePLND template consisted of the sPLND field as well as common iliac and presacral nodes.

Study Endpoints and Outcomes

The primary objective was to assess the impact of ePLND on RFS and the anatomical distribution of recurrences compared to sPLND. The secondary endpoint was OS. Survival endpoints were defined as the time from RC to recurrence or death from any cause. We defined locoregional recurrences as any tumour recurrence or progression within the surgical field of both sPLND and ePLND, the small pelvis, urethra, and the anastomotic regions. Tumour occurrence in the upper urinary tract was considered a new primary tumour. All other tumour manifestations were considered distant recurrences. Follow-up was performed according to contemporary guideline recommendations and started at the date of RC [1]. Patients were censored at their last follow-up or time of death.

Statistical Analysis

First, we stratified patients according to the PLND template or induction chemotherapy status and assessed differences in baseline variables between groups using descriptive statistics. Data on continuously coded variables were tested for normal distribution with the Shapiro–Wilk test for normality. Continuously coded variables with non-normal distribution were compared using the Wilcoxon rank sum test. Categorical variables were compared using the chi-squared or Fisher's exact test, as appropriate.

Second, to account for selection bias and the lack of randomization, we relied on a propensity-score (PS) approach. Using univariable logistic regression, we calculated crude odds ratios to estimate the effect of confounders on the treatment approach (sPLND vs ePLND). Subsequently, statistically significant confounders were used for 1:1 PS matching to the nearest neighbour using logistic regression and a calliper size of 0.2 [12]. Covariate balance between the unmatched and matched cohorts was compared using standardized mean differences (Fig. S2).

Third, after PS matching, the impact of PLND templates on survival outcomes was tested using univariable and multivariable Cox proportional hazards regression. Survival curves were plotted using the Kaplan–Meier method and compared using a log-rank test. We stratified subgroups according to whether patients received induction chemotherapy. To evaluate the impact of PS matching on RFS and OS, we repeated univariable and multivariable Cox regression analysis in the unmatched cohort as a sensitivity analysis.

Statistical analysis was performed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and P-values <0.05 were taken to indicate statistical significance.

Results

Baseline Characteristics and Pathological Outcomes

We identified 969 cN+ patients with cTany N1-3 M0 BCa who underwent sPLND or ePLND (Fig. S1). Prior to PS matching, age at RC, smoking history, Charlson comorbidity index, chronic kidney disease stage, pretreatment imaging modality, clinical T and N stage, urinary diversion, and receipt of induction chemotherapy were predictive of the type of PLND on univariable logistic regression analyses and were therefore used as variables for PS matching (Table S1).

After PS matching, we obtained 255 patients in each PLND group. Table 1 shows the differences in pathological outcomes after PS matching. In total, 201 patients (39%) had pathological tumour stage ≥T3, and 208 (41%) received induction chemotherapy. Of the 218 patients (43%) who had (y)pN0 disease on final pathological examination, 99 (33%) did not receive induction chemotherapy. Patients who underwent ePLND had more LNs removed compared to those who underwent sPLND (median 24 vs 16, respectively; $P < 0.001$). When stratified by induction chemotherapy status, the number of positive LNs was lower (median 0 vs 1; $P < 0.001$) in patients who received induction chemotherapy.

Induction chemotherapy consisted of cisplatin-based combination chemotherapy in 194 patients (93%), whereas 7% ($n = 14$) received a carboplatin-based regimen. The median number of cycles administered was 4 (interquartile range [IQR] 3–4). Overall, 71 patients (14%) received adjuvant combination chemotherapy with no difference (14% vs 14%) between the PLND groups. The majority of patients ($n = 63$ [89%]) received cisplatin-based adjuvant chemotherapy, while eight patients (11%) received carboplatin-based adjuvant chemotherapy.

Recurrence Sites

With a median (IQR) time to recurrence of 8 (4–15) months, 211 patients experienced disease recurrence. A detailed overview of tumour recurrence localization is presented in Table 2. Overall, 104 patients (49.3%) in the ePLND and 107 (50.7%) in the sPLND group experienced disease recurrence. In total, 136 patients (27%) experienced distant disease recurrence, 47 patients (9.2%) experienced locoregional disease recurrence, and 19 patients (3.7%) experienced both distant and locoregional disease recurrence. In nine patients (1.8%) disease recurrence was detected but the exact localization was not available. When stratified by the extent of PLND, we did not find a difference in recurrence patterns. However, the rate of local recurrences was higher in the sPLND group (27% vs 17%; $P = 0.2$). In seven patients

Table 1 Outcomes of 510 propensity-score matched patients who underwent radical cystectomy with standard or extended pelvic lymph node dissection with or without induction chemotherapy for clinically lymph node-positive bladder cancer.

	Overall	PLND template			Induction chemotherapy		
	***N* = 510**	**Standard *N* = 255**	**Extended *N* = 255**	***P* value**	**RC alone *N* = 302**	**IC plus RC *N* = 208**	***P* value**
CCI, *n/N* (%)				0.7			0.4
0–2	107/510 (21)	50/255 (20)	57/255 (22)		58/302 (19)	49/208 (24)	
3–4	136/510 (27)	69/255 (27)	67/255 (26)		85/302 (28)	51/208 (25)	
≥5	267/510 (52)	136/255 (53)	131/255 (51)		159/302 (53)	108/208 (52)	
Imaging prior to IC or RC, *n/N* (%)				0.7			**<0.001**
Conventional	470/510 (92)	234/255 (92)	236/255 (93)		289/302 (96)	181/208 (87)	
PET	40/510 (7.8)	21/255 (8.2)	19/255 (7.5)		13/302 (4.3)	27/208 (13)	
Clinical N-stage, *n/N* (%)				0.7			0.9
cN1	306/510 (60)	155/255 (61)	151/255 (59)		181/302 (60)	125/208 (60)	
cN2	174/510 (34)	87/255 (34)	87/255 (34)		102/302 (34)	72/208 (35)	
cN3	30/510 (5.9)	13/255 (5.1)	17/255 (6.7)		19/302 (6.3)	11/208 (5.3)	
Clinical T-stage, *n/N* (%)				0.7			0.9
≤cT2	309/510 (61)	152/255 (60)	157/255 (62)		184/302 (61)	125/208 (60)	
≥cT3	201/510 (39)	103/255 (40)	98/255 (38)		118/302 (39)	83/208 (40)	
Induction chemotherapy	208/510 (41)	102/255 (40)	106/255 (42)	0.7	NR	NR	NR
Surgical approach, *n/N* (%)				0.4			**<0.001**
LRC	15/510 (2.9)	10/255 (3.9)	5/255 (2.0)		2/302 (0.7)	13/208 (6.2)	
Open RC	434/510 (85)	214/255 (84)	220/255 (86)		283/302 (94)	151/208 (73)	
RARC	61/510 (12)	31/255 (12)	30/255 (12)		17/302 (5.6)	44/208 (21)	
PLND template, *n/N* (%)				NR			0.7
Standard	255/510 (50)	NR	NR		153/302 (51)	102/208 (49)	
Extended	255/510 (50)	NR	NR		149/302 (49)	106/208 (51)	
Urinary diversion, *n/N* (%)				0.4			0.074
Incontinent	381/510 (75)	195/255 (76)	186/255 (73)		217/302 (72)	164/208 (79)	
Continent	129/510 (25)	60/255 (24)	69/255 (27)		85/302 (28)	44/208 (21)	
Pathological T-stage, *n/N* (%)				0.2			**<0.001**
<(y)pT2	193/510 (38)	106/255 (42)	87/255 (34)		99/302 (33)	94/208 (45)	
(y)pT2	116/510 (23)	55/255 (22)	61/255 (24)		62/302 (21)	54/208 (26)	
≥(y)pT3	201/510 (39)	94/255 (37)	107/255 (42)		141/302 (47)	60/208 (29)	
Pathological N-stage, *n/N* (%)				**<0.001**			**<0.001**
(y)pN0	218/510 (43)	94/255 (37)	124/255 (49)		99/302 (33)	119/208 (57)	
(y)pN1	99/510 (19)	63/255 (25)	36/255 (14)		61/302 (20)	38/208 (18)	
(y)pN2	143/510 (28)	83/255 (33)	60/255 (24)		105/302 (35)	38/208 (18)	
(y)pN3	50/510 (9.8)	15/255 (5.9)	35/255 (14)		37/302 (12)	13/208 (6.2)	
Number of lymph nodes removed, median (IQR)	19.0 (16.0)	15.5 (14.0)	24.0 (17.0)	**<0.001**	19.0 (15.0)	19.0 (18.0)	0.9
Unknown	10	9	1		2	8	
Number of positive lymph nodes, median (IQR)	1.0 (3.0)	1.0 (2.0)	1.0 (3.0)	0.08	1.0 (3.0)	0.0 (1.0)	**<0.001**
Unknown	11	10	1		2	9	
Lymph node density, median (IQR) %	5.0 (17.2)	7.1 (20.0)	2.8 (15.4)	**0.009**	7.7 (22.4)	0.0 (9.8)	**<0.001**
Unknown	10	9	1		2	8	
Positive soft tissue surgical margins, *n/N* (%)	36/508 (7.1)	21/254 (8.3)	15/254 (5.9)	0.3	21/301 (7.0)	15/207 (7.2)	>0.9
Adjuvant chemotherapy, *n/N* (%)	71/510 (14)	36/255 (14)	35/255 (14)	0.9	62/302 (21)	9/208 (4.3)	**<0.001**

Wilcoxon rank sum test; chi-squared test; Fisher's exact test. CCI, Charlson comorbidity index; IC, induction chemotherapy; IQR, interquartile range; LRC, laparoscopic radical cystectomy; PET, positron emission tomography; PLND, pelvic lymph node dissection; RARC, robot-assisted radical cystectomy; RC, radical cystectomy.

(1.4%) a new primary tumour of the upper urinary tract was detected.

Survival Analysis

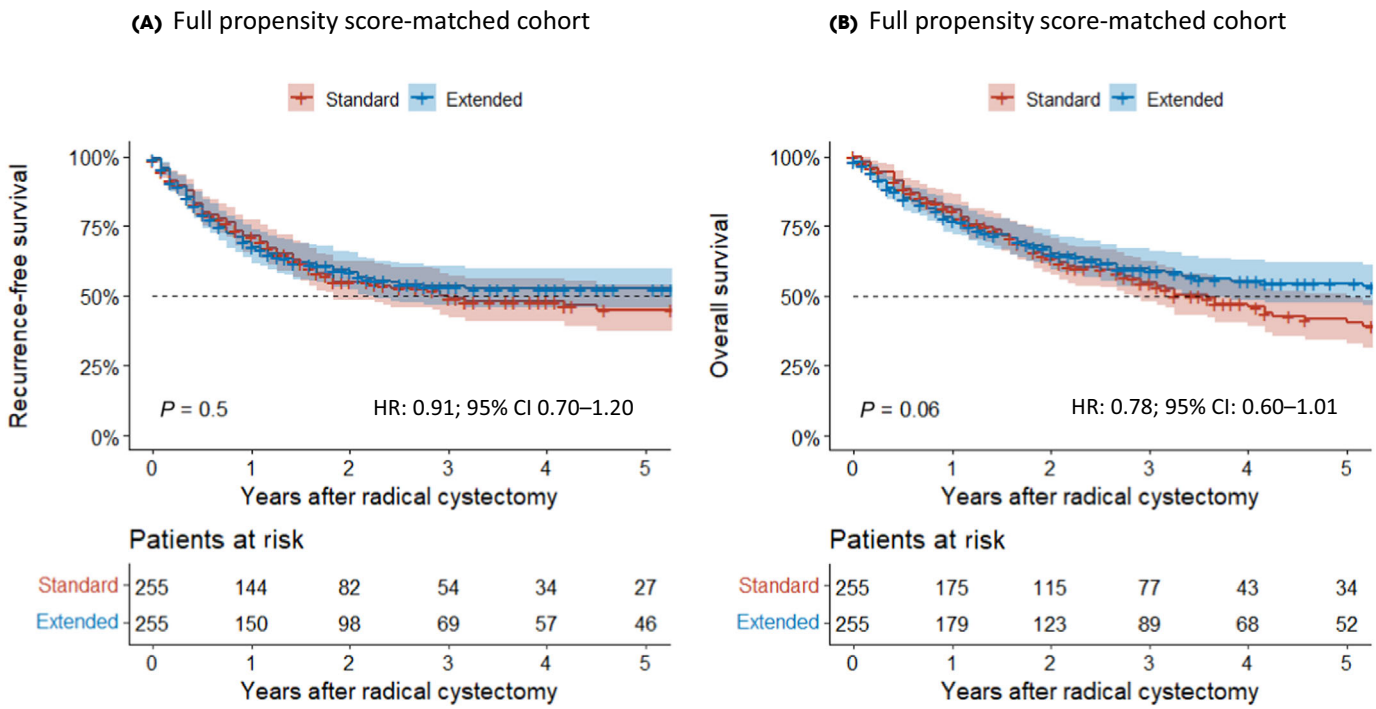
The median (IQR) follow-up of alive patients was 30 (13–51) months and 226 patients died. PS-adjusted Kaplan–Meier analysis did not show an association between ePLND and RFS (hazard ratio [HR] 0.91, 95% CI 0.70–1.20; $P = 0.5$) compared to sPLND (Fig. 1A). This was confirmed in multivariable analysis (HR 1.03, 95% CI 0.76–1.39; $P = 0.9$) adjusting for the effects of confounders (Table 3). The 3-year RFS rate was 53.3% (95% CI 46.8–60.7) in the ePLND and 49.1% (95% CI 42.1–57.2) in the sPLND group. ePLND was not associated with OS in univariable (HR 0.78, 95% CI 0.60–1.01; $P = 0.06$ [Fig. 1B]) or multivariable analyses (HR 0.81, 95% CI 0.61–1.09; $P = 0.2$ [Table 3]). The 3-year OS rates were 59.1% (95% CI 52.7–66.2) in the ePLND group and 54.8% (95% CI 48.1–62.4) in the sPLND group.

Table 2 Localization of tumour recurrences in 211 propensity score-matched patients who experienced a recurrence after radical cystectomy with standard or extended pelvic lymph node dissection for clinically lymph node-positive bladder cancer.

	Recurrences	PLND template		
	***N* = 211 *n*/*N* (%)**	**Standard *N* = 107 *n*/*N* (%)**	**Extended *N* = 104 *n*/*N* (%)**	***P* value**
Distant recurrence and new primary tumour	1/211 (0.5)	1 (0.9)	0 (0)	0.5
Unknown	8/211 (3.8)	3 (2.8)	5 (4.8)	
Locoregional and distant recurrence	19/211 (9.0)	9 (8.4)	10 (9.6)	0.9
Unknown	9/211 (4.3)	4 (3.7)	5 (4.8)	
Locoregional recurrence	47/211 (22)	29 (27)	18 (17)	0.2
Unknown	9/211 (4.3)	4 (3.7)	5 (4.8)	
Distant recurrence	135/211 (64)	64 (60)	71 (68)	0.3
Unknown	9/211 (4.3)	4 (3.7)	5 (4.8)	
Localization of all distant recurrences*	155/211 (73)	74 (69)	81 (78)	0.2
Osseous	25/211 (12)	16 (15)	9 (8.7)	
Unknown	12/211 (5.7)	3 (2.8)	9 (8.7)	
Lymphatic	74/211 (35)	38 (36)	36 (35)	
Unknown	14/211 (6.6)	5 (4.7)	9 (8.7)	
Visceral*	77/211 (36)	38 (36)	39 (38)	
Unknown	12/211 (5.7)	3 (2.8)	9 (8.7)	
Lung	37/211 (18)	17 (16)	20 (19)	
Liver	32/211 (15)	16 (15)	16 (15)	
Peritoneal	11/211 (5.2)	7 (6.5)	4 (3.8)	
Brain	5/211 (2.4)	3 (2.8)	2 (1.9)	
Other†	12/211 (5.7)	8 (7.5)	4 (3.8)	

**Multiple locations per patient possible. †Adrenal, inguinal, larynx, mediastinum, omentum, pararenal (not specified), pleural, retroperitoneal (not specified), retrostomal. Chi-squared test; Fisher's exact test. Bold values indicate p-value <0.05. PLND, pelvic lymph node dissection.*

Fig. 1 Recurrence-free survival (**A**) and overall survival (**B**) in 510 propensity score-matched patients who underwent radical cystectomy with pelvic lymph node dissection with or without cisplatin-based induction chemotherapy for cTany N1-3 M0 bladder cancer. HR, hazard ratio.



In subgroup analyses of patients who underwent induction chemotherapy followed by RC or RC alone, we did not identify a survival difference when stratified by the extent of PLND (Fig. 2A–D). Median RFS and OS estimates for the entire cohort, patients who received induction chemotherapy, and those who did not are shown in Table S2.

Table 3 Multivariable Cox proportional hazard models predicting recurrence-free survival and overall survival in 510 propensity score-matched patients who underwent radical cystectomy with standard or extended pelvic lymph node dissection for clinically lymph node-positive bladder cancer.

	Recurrence-free survival			Overall survival		
	HR	95% CI	*P* value	HR	95% CI	*P* value
PLND template (ref. standard)	1.03	0.76, 1.39	0.9	0.81	0.61, 1.09	0.2
Smoking history (ref: no)	1.21	0.85, 1.73	0.3	1.62	1.15, 2.30	**0.006**
CCI (ref: ≤2)						
3–4	1.97	1.22, 3.20	**0.006**	1.86	1.13, 3.05	**0.014**
≥5	1.70	1.12, 2.57	**0.013**	2.40	1.56, 3.69	**<0.001**
Hydronephrosis (ref: no)	1.19	0.86, 1.64	0.3	1.01	0.73, 1.38	>0.9
Imaging prior to IC or RC (ref: conventional)						
PET	2.44	1.45, 4.09	**<0.001**	0.82	0.44, 1.51	0.5
Pathological N-stage (ref: [y]pN0)						
(y)pN1	1.11	0.69, 1.77	0.7	1.16	0.76, 1.76	0.5
(y)pN2	2.53	1.74, 3.69	**<0.001**	1.88	1.31, 2.71	**<0.001**
(y)pN3	3.22	1.90, 5.46	**<0.001**	2.32	1.39, 3.86	**0.001**
Pathological T-stage (ref: ≤[y]pT1)						
(y)pT2	2.06	1.33, 3.20	**0.001**	1.87	1.26, 2.78	**0.002**
≥(y)pT3	3.63	2.47, 5.35	**<0.001**	2.81	1.95, 4.05	**<0.001**
Urinary diversion (ref: incontinent)	0.83	0.58, 1.17	0.3	0.72	0.51, 1.02	0.067
Soft tissue surgical margins (ref: negative)	1.92	1.09, 3.38	**0.023**	2.10	1.22, 3.60	**0.007**
Induction chemotherapy (ref: no)	1.16	0.82, 1.63	0.4	1.08	0.79, 1.49	0.6
Adjuvant chemotherapy (ref: no)	0.79	0.51, 1.20	0.3	0.78	0.52, 1.15	0.2

Bold values indicate p-value <0.05. CCI, Charlson comorbidity index; CI, confidence interval; HR, hazard ratio; IC, induction chemotherapy; PET, positron emission tomography; PLND, pelvic lymph node dissection; RC, radical cystectomy.

In sensitivity analysis in the unmatched cohort, ePLND was not associated with RFS in univariable (HR 0.92, 95% CI 0.76–1.12; $P = 0.4$) and multivariable analyses (HR 1.00, 95% CI 0.76–1.32; $P > 0.9$ [Fig. S3 and Table S3]). ePLND was associated with OS in univariable (HR 0.82; 95% CI 0.68–0.99; $P = 0.04$) but not multivariable analyses (HR 0.80, 95% CI 0.61–1.04; $P = 0.1$).

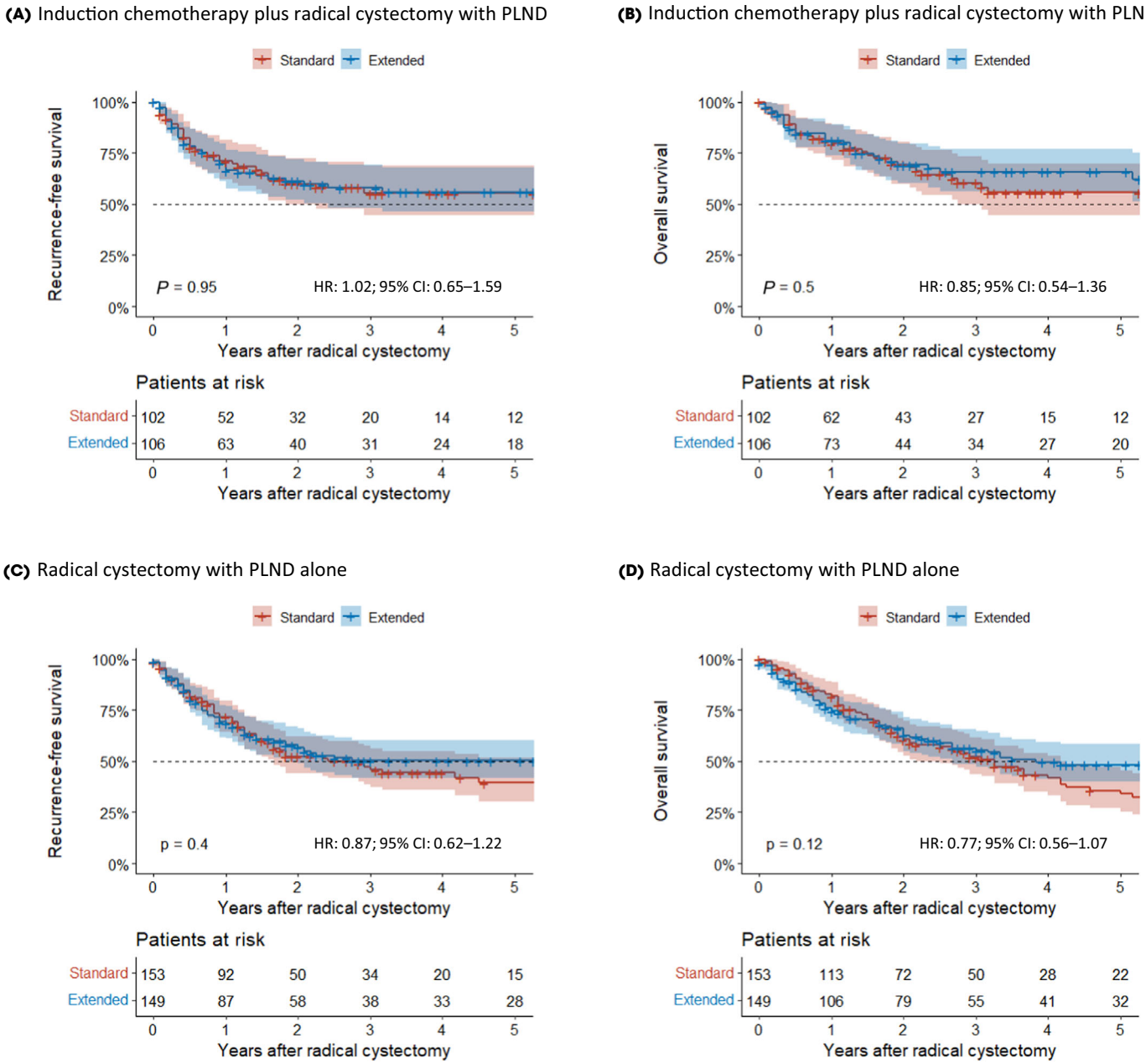
Discussion

In this study, we did not find an oncological benefit to performing an ePLND vs sPLND at the time of RC in a PS-matched cohort of cN+ BCa patients, regardless of whether induction chemotherapy was administered. Regarding our primary objective, both RFS and the anatomical distribution of recurrences did not differ between PLND templates. Our findings are consistent with those of two recent phase III RCTs assessing the impact of the PLND template in (non-metastatic) BCa; however, several differences in the patient population and study design warrant further discussion [5].

Our cohort consisted of patients with cN+ disease, excluding all cN0 patients, which were included in the LEA AUO trial [5]. In addition, while our sPLND template was identical to the 'limited' PLND template in the LEA AUO trial, the ePLND template in the same trial was more extensive than our ePLND as it included all LNs up to the inferior mesenteric artery [5]. Retrospective studies suggested that extending PLND beyond the ePLND template does not significantly improve survival in non-metastatic and cN+ disease, despite the possibility of isolated solitary retroperitoneal LN metastasis [3,7,13,14]. As more than 90% of lymphatic landing sites of the bladder are located in the surgical field up to the aortic bifurcation, we adhered to the PLND template definitions in the EAU guidelines and excluded the super-ePLND template [1,8]. In the LEA AUO trial, only one-quarter of patients had pN+ disease at RC, which was expected from the clinical stage entry criteria and 50% of metastases were exclusively located in the sPLND template [5]. Further differences include the randomization process (RCT vs PS matching) and pN+ rates.

We found that induction chemotherapy does decrease the likelihood of ypN+ but does not affect the impact of ePLND vs sPLND on outcomes. Neoadjuvant chemotherapy was not given in the LEA AUO trial [5]. A growing body of evidence suggests that cN+ patients benefit from peri-operative systemic therapy, but the optimal sequencing remains unclear as many cN+ patients end up with pN0 [15–18]. An aggressive approach combining induction chemotherapy with ePLND may improve survival outcomes by locally and systemically eradicating locoregional lymphatic metastases. Indeed, we found that the ypN0 rate was higher in the induction chemotherapy cohort and the ePLND cohort. On the other hand, subgroup analysis of patients who received induction chemotherapy and those who did not, revealed no survival difference when stratified by the extent of PNLD. The SWOG 1011 trial (NCT01224665) assessed the oncological impact of the extent of PLND (sPLND vs ePLND) on survival outcomes. Despite an increased LN yield and higher pN stage at final pathology in the ePLND group, there was no significant benefit in disease-free survival or OS compared to the sPLND group [19]. Since 57% of patients in the SWOG 1011 trial were treated with neoadjuvant

Fig. 2 Recurrence-free survival and overall survival in 510 propensity score-matched patients who underwent radical cystectomy with pelvic lymph node dissection (PLND) with (**A**, **B**) or without cisplatin-based induction chemotherapy (**C**, **D**) for cTany N1-3 M0 bladder cancer. HR, hazard ratio.



chemotherapy, the results of the anticipated subgroup analysis (neoadjuvant chemotherapy: yes vs no) are eagerly awaited [19]. Until then, our results suggest that the receipt of preoperative chemotherapy has a more significant impact on survival outcomes in cN+ patients than the extent of PLND, possibly by eliminating LN and other metastases using a systemic approach [20]. Additionally, we found no difference in the number of distant metastases between PLND groups, again suggesting that delivery of peri-operative systemic therapy may outweigh the benefits of an ePLND in cN+ disease. As such, median survival estimates for RFS and OS were generally longer in the subgroup of patients who received induction chemotherapy compared to those patients who did not.

Given the absence of level I evidence regarding cN+ disease, and that RCTs may not always reflect clinical practice, large-scale, multicentre studies are necessary to fill evidence gaps. We provide real-world data partially controlled for selection bias through statistical modelling, including PS matching and multivariable analysis. Future research should focus on the

substratification of cN+ disease to evaluate the benefit of performing an ePLND in a subgroup of patients with an increased risk of LN invasion at RC but a moderate risk of distant metastasis (e.g., pT2). These patients may benefit from a multimodal treatment approach, including induction chemotherapy and RC with ePLND with a moderate risk of additional peri-operative morbidity [5].

Our study findings must be interpreted within the limitations of the retrospective study design, especially regarding staging and the risk of selection bias [21]. Indeed, 33% of patients who did not receive induction chemotherapy had pN0 disease at RC, implicating that preoperative imaging was inaccurate. This finding has to be interpreted keeping the Will Rogers phenomenon in mind. Indeed, false-positive cN+ (pN0) patients have a more favourable long-term prognosis compared to the 'true' cN+ population. Yet, the evidence regarding the best modality for preoperative LN staging for BCa is limited and inconclusive [22]. Interestingly, staging with fluorodeoxyglucose PET/CT may lead to clinical nodal upstaging in 18% of MIBC patients staged with both conventional CT as well as fluorodeoxyglucose PET/CT, and results in higher concordance rates between cN and pN status [23]. However, although fluorodeoxyglucose PET/CT is increasingly used for staging BCa, it is not devoid of false-positive results and is limited in assessing response to preoperative systemic treatment [24–26]. Moreover, PET/CT is not yet available as a standard staging tool in many healthcare systems. Therefore, we accounted for different staging modalities in our multivariable analyses. Currently ongoing trials, such as a phase II trial (NCT05137262) comparing dose-dense methotrexate, vinblastine, doxorubicin and cisplatin induction chemotherapy with or without durvalumab in cN+ urothelial carcinoma of the bladder, or the phase II INSPIRE study (NCT04216290), perform pretreatment LN biopsies to reduce the number of false-positive LNs. However, pretreatment LN biopsy has not yet been implemented as a standardized diagnostic procedure in the treatment pathway of cN+ BCa in many centres. Therefore, we did not routinely perform biopsies prior to surgery. Interestingly, in a single-centre cohort with cN+ patients, the outcomes of those with biopsy-proven disease were similar to those with a clinical suspicion for node-positive disease [7].

Further limitations include the lack of randomization regarding the choice of the PLND template, which may have depended on the local protocol at each participating institution, the preoperative extent of node-positive disease, and receipt of or response to induction chemotherapy. In addition, we were not able to account for all existing preoperative risk factors such as lymphovascular invasion or the patient's medical history (primary vs progressive tumour), which may have influenced the surgeons' choice regarding the appropriate PLND template.

Our study is also limited by the absence of centralized radiological and pathological assessment and a standardized LN submission technique. The latter has been shown to affect LN yield but has no impact on long-term RFS or OS [27]. In addition, we were not able to control for the accuracy of PLND performed by each surgeon. However, in our study, the median number of LNs removed was 16 and 24 for sPLND and ePLND, respectively. This LN yield lies above previous cut-offs associated with OS in cN+, pN0, and pN+ disease, suggesting that, despite including numerous different surgeons, PLND was appropriately performed across centres [28,29]. Furthermore, we did not capture adverse outcomes associated with the extent of PLND. However, based on prior level I evidence, there was no difference in major complication rates between sPLND and ePLND, while a higher rate of lymphoceles within 90 days postoperatively was seen for the latter [5]. Similarly, preoperative chemotherapy does not increase RC and/or PLND morbidity [30]. Next, ePLND was associated with OS in sensitivity analysis, but this association was not significant in multivariable analysis. Lastly, our study is limited by the study period ranging from 1991 to 2022.

In summary, our study provides the first head-to-head comparison regarding the standard of care for PLND in patients with cN+ BCa. ePLND at RC improved neither RFS nor OS compared to sPLND, regardless of the use of induction chemotherapy. Our data do not support performing ePLND in unselected cN+ patients. Further stratification of cN+ disease is necessary to identify ideal candidates for RC with ePLND as part of a multimodal treatment approach.

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Disclosure of Interests

None.

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Appendix

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Abbreviations: BCa, bladder cancer; EAU, European Association of Urology; ePLND, extended pelvic lymph node dissection; HR, hazard ratio; IQR, interquartile range; LN, lymph node; MIBC, carcinoma invading bladder muscle; OS, overall survival; PET, positron emission tomography; PS, propensity score; RC, radical cystectomy; RCT, randomized controlled trial; RFS, recurrence-free survival; sPLND, standard pelvic lymph node dissection.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Flowchart showing the selection of patients treated with radical cystectomy and standard or extended pelvic lymph node dissection (PLND) with or without induction chemotherapy (IC) for cTanyN1-3 M0 bladder cancer.

Fig. S2. Pre-matching (triangles) and post-matching (circles) standardized mean differences between standard and extended pelvic lymph node dissection groups.

Fig. S3. Recurrence-free survival and overall survival in 969 unmatched patients who underwent radical cystectomy with pelvic lymph node dissection with or without cisplatin-based induction chemotherapy for cTany N1-3 M0 bladder cancer.

Table S1. Baseline characteristics of 969 patients who underwent radical cystectomy with standard or extended pelvic lymph node dissection for clinically lymph node-positive bladder cancer and univariable logistic regression analysis assessing the association of each covariate with the pelvic lymph node dissection template.

Table S2. Median survival in months and interquartile range for recurrence-free and overall survival in 510 propensity score-matched patients undergoing radical cystectomy with standard or extended pelvic lymph node dissection with or without prior induction chemotherapy for clinically lymph node-positive bladder cancer.

Table S3. Multivariable Cox proportional hazard models predicting recurrence-free survival and overall survival in 969 patients who underwent radical cystectomy with standard or extended pelvic lymph node dissection for clinically lymph node-positive bladder cancer.