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Impact of Extended Lymph Node Dissection on Survival Outcomes in Patients With Bladder Cancer and Upper Tract Urothelial Carcinoma: A Multicenter Retrospective Study

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Purpose: To evaluate whether extended pelvic lymph node dissection (PLND) improves survival outcomes compared with standard PLND in patients with bladder cancer (BCa) undergoing radical cystectomy (RC), and to assess its potential benefits in patients with prior or concurrent radical nephroureterectomy (p/cRNU).

Materials and Methods: A multicenter analysis included 2202 patients with BCa undergoing RC with standard or extended PLND at 11 tertiary centers from 2003 to 2023. Following propensity score matching, 659 pairs (n=1,318), including 128 patients with p/cRNU, were analyzed. Recurrence-free survival (RFS) was the primary outcome, while overall survival (OS), cancer-specific survival (CSS), and readmission rates were secondary outcomes. Survival analyses performed using Kaplan-Meier methods and clustered Cox models.

Results: Extended PLND yielded significantly more lymph nodes than standard PLND (median: 27.0 vs. 17.0, p<0.001) but did not improve RFS, CSS, or OS in the overall cohort (all p>0.05). Extended PLND increased readmission rates (28.4% vs. 20.2%, p=0.001) and readmission risk (odds ratio, 1.57; 95% confidence interval [CI], 1.15–2.16, p=0.005). However, subgroup analysis revealed extended PLND significantly improved RFS in patients with p/cRNU (hazard ratio, 0.54; 95% CI, 0.38–0.77; p<0.001).

Conclusion: Extended PLND does not provide survival benefits for overall patient population and increases readmission risk but significantly improves RFS in patients with p/cRNU. Tailoring PLND extent based on upper tract disease status is recommended.

Key Words: Urinary bladder neoplasms, Lymph node excision, Upper tract urothelial carcinoma, Cystectomy, Survival

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INTRODUCTION

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is the established standard of care for muscle-invasive bladder cancer and high-risk non-muscle-invasive bladder cancer [1,2]. PLND during RC not only provides staging information but also potentially enhances oncologic outcomes by removing microscopic metastases [3]. Nevertheless, the optimal PLND extent—whether standard or extended—and its impact on oncologic outcomes remain a subject of debate [3-5]. Two recent randomized controlled trials (RCTs) (LEA AUO and SWOG S1011) reported no survival benefit of extended over standard PLND but noted higher morbidity [6,7]. However, these trials did not address a key clinical subgroup: patients with bladder cancer and prior or concurrent upper tract urothelial carcinoma (UTUC).

Urothelial carcinoma frequently exhibits multifocality along the urothelial lining, with UTUC developing in approximately 2%–4% of patients with bladder cancer [8]. Conversely, patients with UTUC carry a higher risk of developing bladder cancer, with approximately 17%–33% reportedly developing subsequent bladder cancer [9]. These patients often require radical nephroureterectomy (RNU) either prior to or concurrently with RC. Despite being a relatively common clinical scenario, the impact of PLND extent during RC on oncologic outcomes of patients with prior or concurrent UTUC has not been thoroughly investigated. Given the complex patterns of lymph node metastasis and potential therapeutic role of lymph node dissection (LND) in UTUC [10,11], the optimal PLND extent during RC may differ significantly in these specific patients.

To address this critical knowledge gap, this multicenter study aimed to (1) validate the findings of previous RCTs regarding PLND extent in real-world settings and (2) evaluate the potential subgroup-specific effects related to PLND extent.

MATERIALS AND METHODS

1. Study Population

This multicenter study utilized the Korean Bladder Cancer Study Group database, comprising 11 tertiary centers from October 2003 to December 2023. The Institutional Review Boards at each of the participating sites waived the requirements for informed consent due to the retrospective nature of the study. This study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline [12].

We included patients with clinical stage Tany Nany M0 bladder cancer who underwent RC with either standard or extended PLND. The exclusion criteria were patients with: nonurothelial carcinoma; incomplete follow-up or survival data; missing clinical TNM staging or PLND-related information; those who underwent limited or no PLND; incomplete data on prior or concurrent RNU (p/cRNU) status, urinary diversion type, pathological stage, or histological subtype; and missing readmission status.

2. Data Collection and Definitions

Data on the following clinicopathological characteristics were obtained: sex, age at surgery, body mass index, hypertension, diabetes mellitus, American Society of Anesthesiologists (ASA) physical status classification grade, histological subtype from transurethral resection of bladder tumor specimens, clinical T and N stages, RNU status,

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receipt of neoadjuvant chemotherapy (NAC), operation type (minimally invasive surgery vs open surgery), pathological T and N stages, pathological features of RC specimens (lymph node yield, number of positive lymph nodes, lymphovascular invasion, surgical margin status), and receipt of adjuvant chemotherapy. PLND extent was classified into (1) standard PLND, which included obturator, perivesical, external iliac, and internal iliac nodes up to the common iliac bifurcation, and (2) extended PLND, which included the standard template plus common iliac nodes and node-bearing tissue up to either the aortic bifurcation or inferior mesenteric artery. Dedicated radiologists at each institution determined the clinical lymph node status. Pathological staging followed the 8th edition of the American Joint Committee on Cancer TNM staging system [13].

Subgroup analyses were performed by stratifying the cohort according to p/cRNU status, NAC status, and histological subtypes. For patients with p/cRNU, additional data on the anatomical location of UTUC were requested from the centers and incorporated when provided as part of exploratory analysis.

3. Study Outcomes

The primary outcome was recurrence-free survival (RFS), defined as the time interval from RC to the first documented recurrence. The secondary outcomes were overall survival (OS), cancer-specific survival (CSS), and hospital readmission rates. OS and CSS were determined from the date of the RC to the date of death from any cause or cancer-specific death, respectively.

Disease recurrence was defined radiologically to include both locoregional recurrence (confined to the surgical bed or pelvic cavity) and distant metastasis (encompassing all other nonurothelial metastatic sites). Upper tract or urethral recurrence was classified as *de novo* urothelial cancer rather than disease recurrence. Postoperative readmissions were tracked from the date of discharge and stratified into 4 intervals: within 1 month, between 1 and 3 months, between 3 and 6 months, and between 6 and 12 months after discharge.

4. Statistical Analysis

We conducted 1:1 propensity score matching (PSM) using nearest-neighbor matching with a 0.25 caliper to reduce selection bias between the standard and extended PLND groups [14]. Survival analyses were conducted using Cox proportional hazards models with clustered robust variance estimators to account for interhospital variability. To identify factors associated with readmission, we performed multivariable logistic regression analysis. Subgroup analyses were performed using Kaplan-Meier method and the same Cox models with cluster effect adjustment.

All statistical analyses were performed using R ver. 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria), with 2-sided tests and a significance threshold of $p<0.05$.

Detailed statistical methods, including the software packages used for the analyses, are provided in the Supplementary Methods.

RESULTS

1. Patient Characteristics and PSM

Among 3,972 RC cases identified across 11 tertiary centers, 2,202 patients met our criteria (Fig. 1). Baseline characteristics of the entire cohort are summarized in Supplementary Table 1; with 175 patients (7.9%) underwent p/cRNU.

PSM yielded 659 matched pairs with balanced characteristics (all absolute standardized mean difference <0.1, $p>0.05$) (Supplementary Table 2, Supplementary Fig. 1). The median follow-up was 44.0 months (interquartile range [IQR], 16.0–72.0) in standard PLND and 47.0 (IQR, 17.5–72.0) months in extended PLND ($p=0.468$).

2. Clinicopathological Characteristics of the Matched Cohort

The clinicopathological features and surgical data of the propensity score-matched cohort are shown in Supplementary Table 3. In the matched cohort, 128 patients underwent p/cRNU, with comparable distributions of p/cRNU between the standard and extended PLND groups (5.8% vs. 6.5% and 4.2% vs. 2.9%, respectively). Continent

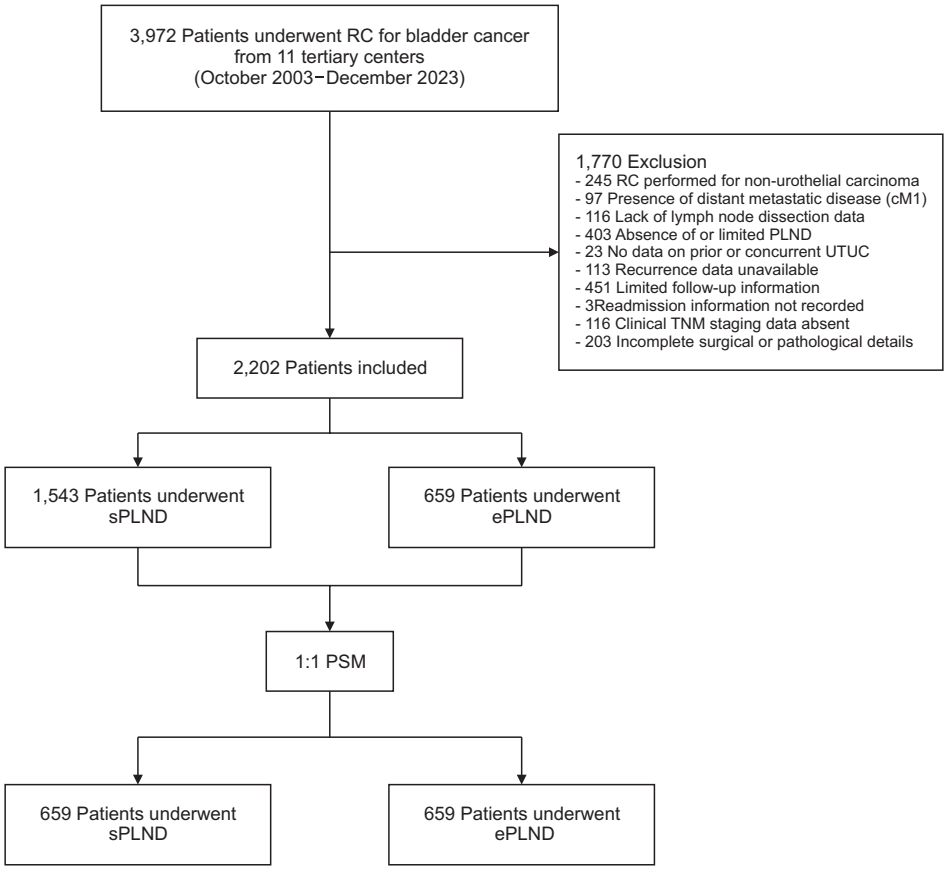

Fig. 1. Flow diagram of patient selection. RC, radical cystectomy; PLND, pelvic lymph node dissection; UTUC, upper tract urothelial carcinoma; TNM, Tumor-Node-Metastasis staging system; ePLND, extended PLND; sPLND, standard PLND; PSM, propensity score matching.

urinary diversion was significantly more common in the extended PLND group (50.8% vs. 33.7%, p<0.001). Pathological T stage distribution was similar between the 2 groups (p=0.083), whereas nodal-related patterns differed significantly. Extended PLND showed higher lymph node yield (27.0 vs. 17.0, p<0.001) and a greater proportion of pN3 stage disease (p<0.001), with slightly higher pathological N positivity (31.0% vs. 28.5%). Other factors, including the median number of positive nodes, lymphovascular invasion, surgical margin status, and rates of adjuvant chemotherapy, were similar between the groups.

3. Survival and Postoperative Outcomes

Five-year survival outcomes between extended versus standard PLND were: RFS (65.1% vs. 60.8%), CSS (68.3% vs. 70.8%), and OS (50.3% vs. 57.8%). Univariable and multivariable analysis confirmed that PLND extent was not significantly associated with RFS, CSS, or OS (all p>0.05) (Supplementary Table 4 and Table 1). Pathological stage ≥pT3 (vs.≤pT2) (HRs: 2.045, 2.450, 2.023) and nodal involvement ≥pN1 (vs.pN0) (HRs: 2.107, 2.146, 1.829) were significant predictors for RFS, CSS, and OS, respectively (all p<0.001).

Readmission rates were higher in the extended PLND group (28.4% vs. 20.2%, p=0.001) (Supplementary Table 5); such higher rates were consistently observed across all time periods. In the multivariable analysis, extended PLND emerged as an independent predictor of readmission (odds ratio [OR], 1.573; 95% CI, 1.147–2.157; p=0.005) (Supplementary Table 6).

4. Subgroup Analysis

In the matched cohort, extended PLND was performed in a similar proportion of patients between p/cRNU and non-p/cRNU subgroups (48.4% [62 of 128] vs. 50.2% [597 of 1,190], respectively; p=0.780) (Supplementary Table 7). Subgroup analyses revealed that extended PLND significantly improved RFS in patients who underwent p/cRNU, while no significant

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Table 1. Multivariable Cox regression analysis of survival outcomes in the matched cohort

Variable	RFS			CSS			OS		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age				1.020	1.012–1.027	<0.001	1.031	1.021–1.041	<0.001
BMI	0.975	0.944–1.007	0.124	0.970	0.907–1.038	0.379	0.975	0.929–1.022	0.290
p/cNUx	1.380	1.131–1.682	0.001	-	-	-	-	-	-
Continent (vs. incontinent)	0.889	0.754–1.049	0.165	0.909	0.724–1.140	0.407	0.834	0.752–0.925	<0.001
≥pT3 (vs. ≤pT2)	2.045	1.501–2.785	<0.001	2.450	2.026–2.964	<0.001	2.023	1.782–2.295	<0.001
≥pN1 (vs. pN0)	2.107	1.558–2.849	<0.001	2.146	1.548–2.975	<0.001	1.829	1.519–2.202	<0.001
Lymphovascular invasion	1.337	0.989–1.809	0.059	1.272	0.975–1.659	0.076	1.312	1.085–1.587	0.005
Positive surgical margin	0.991	0.890–1.103	0.864	1.339	0.960–1.868	0.086	1.126	0.886–1.431	0.332
ePLND (vs. sPLND)	0.870	0.655–1.156	0.337	1.126	0.787–1.610	0.516	1.329	0.966–1.829	0.080
Adjuvant CTx	1.260	0.516–3.079	0.612	0.957	0.416–2.202	0.917	-	-	-

RFS, recurrence-free survival; CSS, cancer-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; p/cNUx, prior or concurrent nephroureterectomy; pT, pathological tumor stage; pN, pathological nodal stage; ePLND, extended pelvic lymph node dissection; sPLND, standard pelvic lymph node dissection; CTx, chemotherapy.

differences were observed in CSS or OS in either subgroup (Fig. 2).

In the p/cRNU subgroup, while the standard PLND group showed a median RFS of 44.0 months (95% CI, 13.6–74.4), the extended PLND group did not reach median RFS during the study period (log-rank p=0.019) (Fig. 3A). After adjusting for cluster effects and other covariates, this association remained statistically significant (HR, 0.544; 95% CI, 0.382–0.774; p<0.001) (Table 2). However, in the non-p/cRNU subgroup, no statistically significant difference was observed between standard and extended PLND regarding RFS (log-rank p=0.453) (Fig. 3B).

Parallel subgroup analysis of the entire cohort revealed that extended PLND was associated with improved RFS in the p/cRNU subgroup (HR, 0.585; 95% CI, 0.370–0.926; p=0.022); but not in the non-p/cRNU subgroup (Supplementary Table 8, Supplementary Figs. 2 and 3).

For exploratory analysis, data on the UTUC location were available for 69 patients in the p/cRNU subgroup. Among them, 46 had ureteral tumors (with or without renal pelvis/calyx tumors), whereas 23 had tumors confined to the renal pelvis/calyx. The Kaplan-Meier analysis showed that extended PLND resulted in better RFS among patients with ureteral tumors, albeit without statistical significance (Supplementary Fig. 4A). Conversely, no difference in RFS was observed between extended and standard PLND among patients with renal pelvis/calyx tumors (Supplementary Fig. 4B).

In the subgroup analyses stratified by NAC status and histological subtypes, extended PLND showed no significant survival benefit over standard PLND regardless of NAC status or histological subtype (Supplementary Fig. 5).

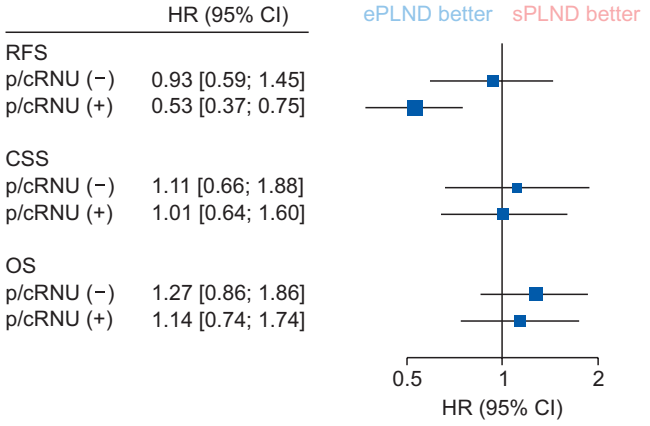

Fig. 2. Forest plot of hazard ratios for survival outcomes stratified by p/cRNU status. HR, hazard ratio; CI, confidence interval; p/cRNU, prior or concurrent radical nephroureterectomy; RFS, recurrence-free survival; CSS, cancer-specific survival; OS, overall survival; ePLND, extended pelvic lymph node dissection; sPLND, standard pelvic lymph node dissection.

DISCUSSION

This multicenter study validated recent RCT findings showing no OS benefit of extended PLND in RC, while uniquely demonstrating improved RFS with extended PLND in patients with p/cRNU. To our knowledge, this study represents the largest investigation regarding PLND extent during RC and evaluating the impact of RNU status on oncologic outcomes. These findings suggest that PLND extent may need to be tailored according to upper tract

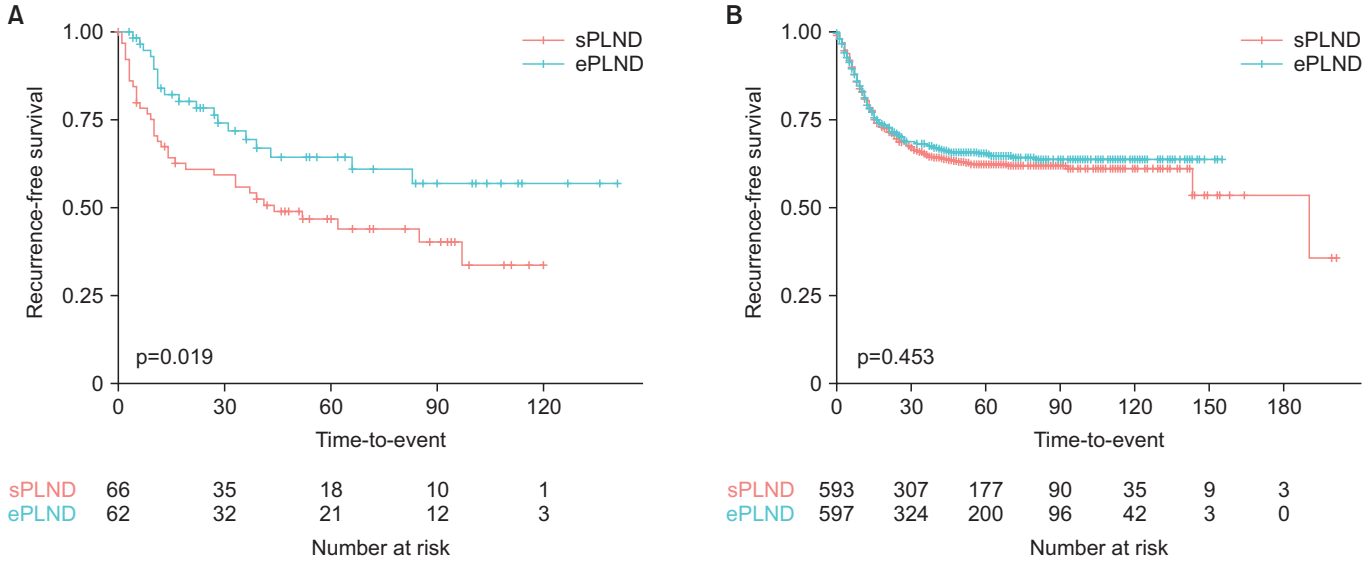

Fig. 3. Kaplan-Meier curves for recurrence-free survival stratified by p/cRNU status and PLND extent. (A) p/cRNU subgroup. (B) Non-p/cRNU subgroup. sPLND, standard pelvic lymph node dissection; ePLND, extended pelvic lymph node dissection.

Table 2. Multivariable Cox regression analysis of recurrence-free survival in the p/cRNU subgroup

Variable	Non-p/cRNU			p/cRNU		
	HR	95% CI	p-value	HR	95% CI	p-value
BMI	0.975	0.941–1.011	0.173	0.940	0.816–1.083	0.390
Continent (vs. incontinent)	0.839	0.710–0.991	0.039			
≥pT3 (vs. ≤pT2)	1.993	1.485–2.676	<0.001	2.087	1.084–4.017	0.028
≥pN1 (vs. pN0)	2.174	1.498–3.155	<0.001	1.173	0.657–2.092	0.590
Lymphovascular invasion	1.504	1.159–1.952	0.002	-	-	-
Positive surgical margin	1.030	0.790–1.344	0.825	-	-	-
ePLND (vs. sPLND)	0.936	0.726–1.206	0.608	0.544	0.382–0.774	<0.001
Adjuvant CTx	1.252	0.511–3.068	0.624	1.362	0.336–5.514	0.665

p/cRNU, prior or concurrent radical nephroureterectomy; HR, hazard ratio; CI, confidence interval; BMI, body mass index; pT, pathological tumor stage; pN, pathological nodal stage; ePLND, extended pelvic lymph node dissection; sPLND, standard pelvic lymph node dissection; CTx, chemotherapy.

disease status.

The quality of PLND in our study was comparable to that in previous studies, with median nodal yields of 17 and 27 in the standard and extended PLND groups, respectively. This 10-node difference reflects a clear technical distinction in dissection extent and supports the validity of our template definitions, suggesting that PLND was performed appropriately across multiple centers. Additionally, the aforementioned yield is consistent with established thresholds associated with the survival benefits of PLND [15-17].

Our primary analysis revealed that RFS, CSS, and OS were comparable between the standard and extended PLND groups, which aligns with the findings of the 2 pivotal RCTs. The LEA AUO trial enrolled 401 patients across German centers and reported no significant differences between the extended and standard PLND groups in 5-year RFS (65% vs. 59%; HR, 0.84; 95% CI, 0.58–1.22; p=0.36), CSS (76% vs 65%; HR, 0.70; p=0.10), and OS (59% vs. 50%; HR: 0.78; p=0.12) [6]. Similarly, the more recent SWOG S1011 trial, which included 595 patients, showed comparable 5-year disease-free survival (56% vs. 60%; HR: 1.10; 95% CI: 0.86–1.40; p=0.45) and OS (59% vs. 63%; HR: 1.13; 95% CI, 0.88–1.45) between the 2 groups [7]. Several methodological differences between these landmark trials and our study warrant discussion. The PLND template classification applied in our study was identical to that in the LEA AUO trial despite their use of the terminology "extensive" versus "limited" LND. Nevertheless, the LEA AUO trial excluded patients who received NAC.

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Furthermore, our study included patients with high-risk non-muscle-invasive bladder cancer, whereas the SWOG S1011 trial focused exclusively on patients with muscle-invasive bladder cancer (≥cT2). Despite methodological differences, all 3 studies consistently reported no survival benefit of extended PLND, highlighting the robustness of these findings.

Regarding subgroup analyses in specific bladder cancer populations, the SWOG S1011 trial demonstrated that PLND extent did not result in significant differences in disease-free survival or OS across various pre-specified stratification factors, including clinical T stage, pathological T or N stage, and NAC receipt status [7]. Previous observational studies have reported inconsistent findings regarding the impact of PLND in specific patient populations, with one study involving clinically node-positive patients showing no differential effect of PLND extent based on NAC status [18], while another revealed significantly varying effectiveness among histological subtypes, with greater benefits observed in patients with urothelial carcinoma, squamous cell carcinoma, and signet ring cell carcinoma [19].

Building on these findings, our subgroup analyses of NAC status and histological subtypes revealed that extended PLND did not provide significant survival benefits over standard PLND, with the only significant benefit observed in RFS among patients with p/cRNU (Supplementary Fig. 5).

The significant RFS improvement observed with extended PLND in p/cRNU patients complements existing evidence supporting the role of LND in UTUC management. While RCTs comparing LND approaches in RNU are lacking, retrospective studies demonstrate that template-based LND during RNU can achieve RFS rates of up to 86.8%, and systematic LND with ≥3 nodes removed improves OS (HR, 0.58; 95% CI, 0.39–0.89) [11,20]. These findings have influenced current clinical guidelines, which now recommend regional LND during RNU for patients with high-grade UTUC [1,2].

The complex lymphatic metastasis patterns of UTUC provide a biological basis for our findings. Right-sided renal pelvis and upper 2/3 ureter tumors primarily drain to the renal hilar, paracaval, and retrocaval nodes, whereas left-sided tumors drain to the renal hilar and para-aortic nodes. Especially, lower ureteral tumors—regardless of their laterality—commonly involve the common iliac, external iliac, internal iliac, and obturator nodes [10,21]. This intricate metastasis configuration elucidates the reason patients with UTUC may gain significant advantages from extended nodal dissection during RC, as demonstrated by our results. Furthermore, our explanatory analysis showed that patients with ureteral tumor involvement showed more favorable RFS with extended PLND compared with those with isolated renal pelvis/calyx tumors. This finding, though exploratory, further supports the potential value of extended PLND in patients undergoing RC after or concurrent with RNU.

Consistent with previous RCTs, our study demonstrated the association between extended PLND and increased morbidity, particularly higher readmission rates. The LEA AUO trial reported increased grade 3 lymphoceles in the extended PLND group [6], whereas the SWOG S1011 trial reported higher perioperative morbidity with a greater incidence of grade 3–5 complications (54% vs. 44%) in patients undergoing extended PLND [7]. Although our analysis was limited to readmission rates rather than specific complication data, the consistent pattern of increased morbidity across multiple studies underscores the importance of careful patient selection for extended PLND.

The key strengths of our study include its multicenter design, long-term follow-up, large sample size, and rigorous statistical methodology incorporating both PSM and cluster effect analyses, which enabled detailed subgroup evaluations. Nonetheless, our study has some limitations. First, our p/cRNU subgroup analysis was based on a relatively small sample size (n=128 for the matched cohort and n=175 for the entire cohort). Despite the small sample size in the p/cRNU subgroup, the substantial effect size (HR, 0.544; p<0.001) and biological plausibility of our findings underscore their relevance. Second, inherent to the retrospective study design, selection bias may exist despite PSM and multivariable analyses with cluster adjustment. Third, the lack of centralized outcomes and pathological assessments, detailed UTUC characteristics (such as location, grade, and stage), and standardized complication reporting system represent key areas for future research.

CONCLUSIONS

While extended PLND may not benefit overall patients with bladder cancer, it significantly improves RFS in patients with p/cRNU. This finding provides valuable guidance for surgical decision-making in patients with prior or concurrent upper tract diseases; nevertheless, careful patient selection is essential, given the increased morbidity. Future prospective studies should focus on validating these findings and defining the optimal PLND extent in this specific patient population.

NOTES

- **Supplementary Materials:** Supplementary Methods, Supplementary Figs. 1-5, and Supplementary Tables 1–8 are available at https://doi.org/10.22465/juo.255000320016.
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