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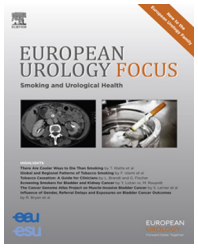

Review – Urothelial Cancer

Potential Benefit of Lymph Node Dissection During Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma: A Systematic Review by the European Association of Urology Guidelines Panel on Non–muscle-invasive Bladder Cancer

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Abstract

Context: The oncological efficacy of routine lymphadenectomy (lymph node dissection [LND]) at the time of radical nephroureterectomy (RNU) remains controversial.
Objective: To systematically review the available literature assessing the impact of LND in upper tract urothelial carcinoma (UTUC) patients.
Evidence acquisition: Embase, Medline, and Cochrane databases were searched for all studies comparing outcomes of patients undergoing RNU without LND versus any form of LND. We identified nine retrospective studies eligible for inclusion in this systematic review. We took cancer-specific survival (CSS) as the primary end point, and performed a narrative review and risk of bias assessment.
Evidence synthesis: Six studies compared outcomes of no LND versus LND. Three studies compared complete LND versus incomplete LND versus no LND. The incidence of pN+ in patients with high-stage (≥pT2) tumours ranged from 14.3% to 40%. Pre- and postoperative characteristics differed among the study groups, potentially biasing the results, as demonstrated by the risk of bias assessment, potentially favouring the LND group. Oncological outcomes such as cancer-specific, overall, recurrence-free, and metastasis-free survival were reviewed, demonstrating a survival benefit with LND in high-stage disease of the renal pelvis.

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Conclusions: Template-based and complete LND improves CSS in patients with high-stage (≥pT2) UTUC and reduces the risk of local recurrence. The impact of LND in ureteral tumours remains uncertain.
Patient summary: Studies comparing radical nephroureterectomy with or without the removal of nodes (lymph node dissection [LND]) were analysed. LND improves survival in patients with high-stage disease of the renal pelvis, if it is performed according to an anatomical template-based approach.

1. Introduction

Urothelial carcinoma (UC) affecting the urinary tract represents the fifth most common type of cancer [1]. Compared with bladder cancer (BC), upper tract UC (UTUC) is rare, representing 5–10% of UC cases [2,3]. Of patients with UC, 20–30% have lymph node (LN) involvement [4,5], and there is a relatively high risk of LN metastases in UTUC patients [6,7]. This risk increases with T stage [8], which is relevant because up to 60% of UTUCs are invasive at diagnosis compared with 25% of BCs [9].

In view of the possible survival benefit of lymph node dissection (LND) observed in muscle-invasive bladder cancer (MIBC) patients [10], one could hypothesise that routine lymphadenectomy (LND) at the time of radical nephroureterectomy (RNU) will improve survival in patients with UTUC. Indeed, the potential role of LND in the management of UTUC has been known for several decades, and LND at the time of radical RNU has been suggested as a therapeutic standard [11]. However, apart from a few reference centres, widespread implementation of LND continues to be low, and a recent Canadian study has reported that LND is performed in only 27% of cases [12]. This is explained, at least in part, by the low incidence of UTUC, scarce evidence-based data regarding LND in this setting, lack of standardisation of the technique, and most importantly, the absence of well-designed, prospective randomised trials. Consequently, any published studies tend to be restricted to a small number of groups.

In an attempt to address these issues, the European Association of Urology (EAU) Guidelines Panel on Non–muscle-invasive Bladder Cancer (NMIBC) proposed this systematic review. The review assessed the most contemporary data to obtain clinically relevant evidence to evaluate the role of routine LND and establish the benefit and harm of LND during RNU.

2. Evidence acquisition

2.1. Search strategy

A comprehensive search of the Embase, Medline, and Cochrane databases was performed and updated by an expert librarian (C.Y.) in December 2014 and February 2016, respectively.

The full search strategy used, according to a free text protocol applying only “humans” and “1995–2016” time-period filters, is presented in the Supplementary material.

2.2. Inclusion criteria

As recommended in the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines, we used the population, intervention, comparator, and outcome (PICO) approach to define study eligibility [13]. According to the PROSPERO registered protocol (DOI: 10.15124/CRD42015021966), studies were considered relevant to the current systematic review when they included adult patients (age >18 yr) diagnosed with UTUC and treated with RNU, with or without LND, in order to compare oncological outcomes.

The following types of studies were considered eligible for inclusion in our systematic review: (1) randomised controlled trials (RCTs) or quasi-RCTs; (2) in the absence of available RCTs, comparative non-randomised prospective or retrospective studies, comparing no LND versus any form of LND (complete or incomplete, as defined by the authors, ie, when following a defined template or not), in patients undergoing RNU for UTUC; (3) studies that defined LND as not performed (NoLND), incomplete (ILND), complete (CLND), and template based (T-BLND), considered by the authors as equivalent to CLND; (4) studies that included a minimum of 10 participants in each arm and a minimum follow-up of 1 yr to assess the primary outcome; and (5) studies that excluded patients with clinically positive LNs (cN+) or distant metastases (cM+).

No language restrictions were applied. The decision to include non-English language papers was made based on the English language abstract and screening of the full-text paper by a native speaker of the language of the paper.

Noncomparative studies, case reports, editorials, letters, review articles, and conference abstracts were not eligible and excluded during the systematic review process.

Finally, if two or more studies reported results of overlapping surgical series, the one with the largest sample was selected. The following exception was made, after discussion with the EAU NMIBC Guidelines Panel: when two or more different studies, using data from the same series, were clearly focused on different subanalyses and reported different outcomes.

2.3. Systematic review process

After duplicates were removed, three authors (J.L.D.E., T.S., and B.P.) completed an independent review of 3094 abstracts and selected 46 articles for separate full-text evaluation. In accordance with all the previously mentioned inclusion criteria, a final cross-checked selection was made

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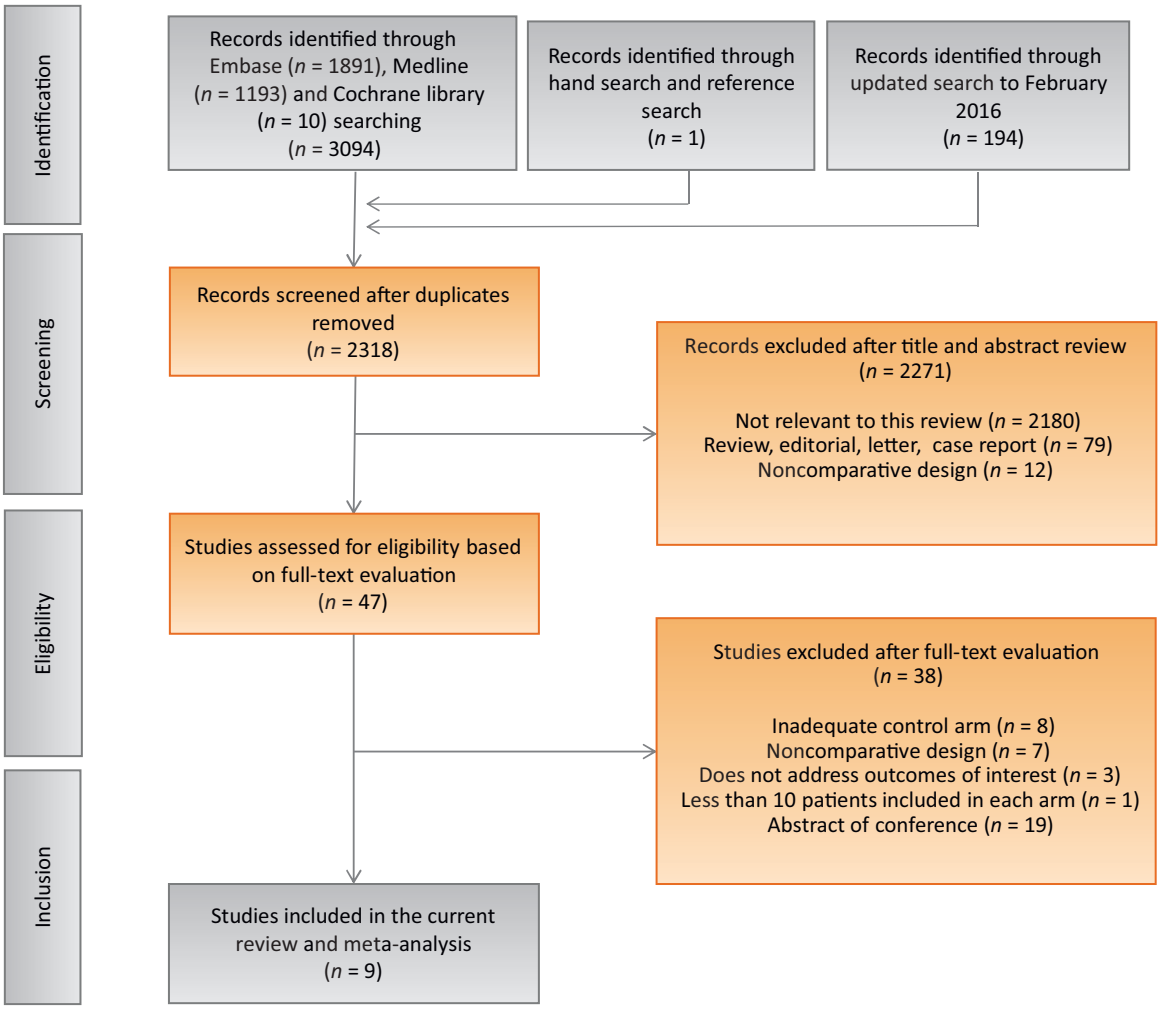

Fig. 1 – PRISMA flowchart UTUC PICO 3. PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analysis; PICO = population, intervention, comparator, and outcome.

of nine articles [14–22] published up to February 2016. Any disagreements about study inclusion were resolved by consulting the senior EAU guideline associate (H.M.B.), who supervised the systematic review process. The PRISMA flow chart depicting the process of the systematic literature search and selection of the included studies is shown in Figure 1.

The primary outcome was cancer-specific survival (CSS) at 1, 2, 5, and >5 yr. The secondary outcomes were: (1) overall survival (OS) at 1, 2, 5, and >5 yr; (2) recurrence-free survival (RFS) at 1, 2, 5, and >5 yr; (3) distant recurrence/progression-free survival (PFS) at 1, 2, 5, and >5 yr; and (4) adverse events or complications (as defined or reported by authors).

2.4. Data extraction

A standardised data extraction form was created a priori, to collect study level data comprising the study design, number of participants, objectives, extent of LND, dates of recruitment and follow-up, together with patient level data such as pre- and postoperative clinicopathological features. Relevant data were independently extracted by three authors (J.L.D.E., T.S., and B.P.), and their accuracy was cross checked. Each data extractor filled out forms for all relevant articles. Conflicts between paper reviewers were resolved by a fourth author (H.M.B.) looking back to these forms and to the original manuscript. Finally, relevant outcome data were extracted.

2.5. Data analysis

In the absence of RCTs, a narrative synthesis of included studies was performed, using descriptive statistics to summarise the extracted baseline characteristics data. Continuous outcomes were described using the median and interquartile range or the mean and standard deviation. Categorical outcomes were described using frequencies and percentages. Crude rates of relevant outcomes at available time points as well as unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were extracted. Two-sided statistical significance was set at a p value of <0.05 for all included studies.

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2.6. Risk of bias and confounding assessment

The risk of bias of each included study was assessed by three reviewers (J.L.D.E., T.S., and B.P.) working independently, and any disagreements were resolved by discussion or consultation with a senior reviewer (H.M.B.). Quality of the studies was assessed with the standard Cochrane Collaboration risk of bias tool, which comprises seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias [23]. The potential impact of the main confounders, identified a priori by the EAU NMIBC Guidelines Panel, was determined based on the current available literature. For each study, the reviewer assessed whether each prognostic confounder had been considered and, if necessary, controlled for in the analysis. The risk of confounding bias was high (red) if the confounder was not reported or not balanced among the treatment groups, without any adjustment in the statistical analysis. Alternatively, the risk of confounding bias was low (green) if the confounder was reported and balanced or adjusted for in the statistical analysis. Otherwise, the risk was considered to be unclear (yellow). Review Manager

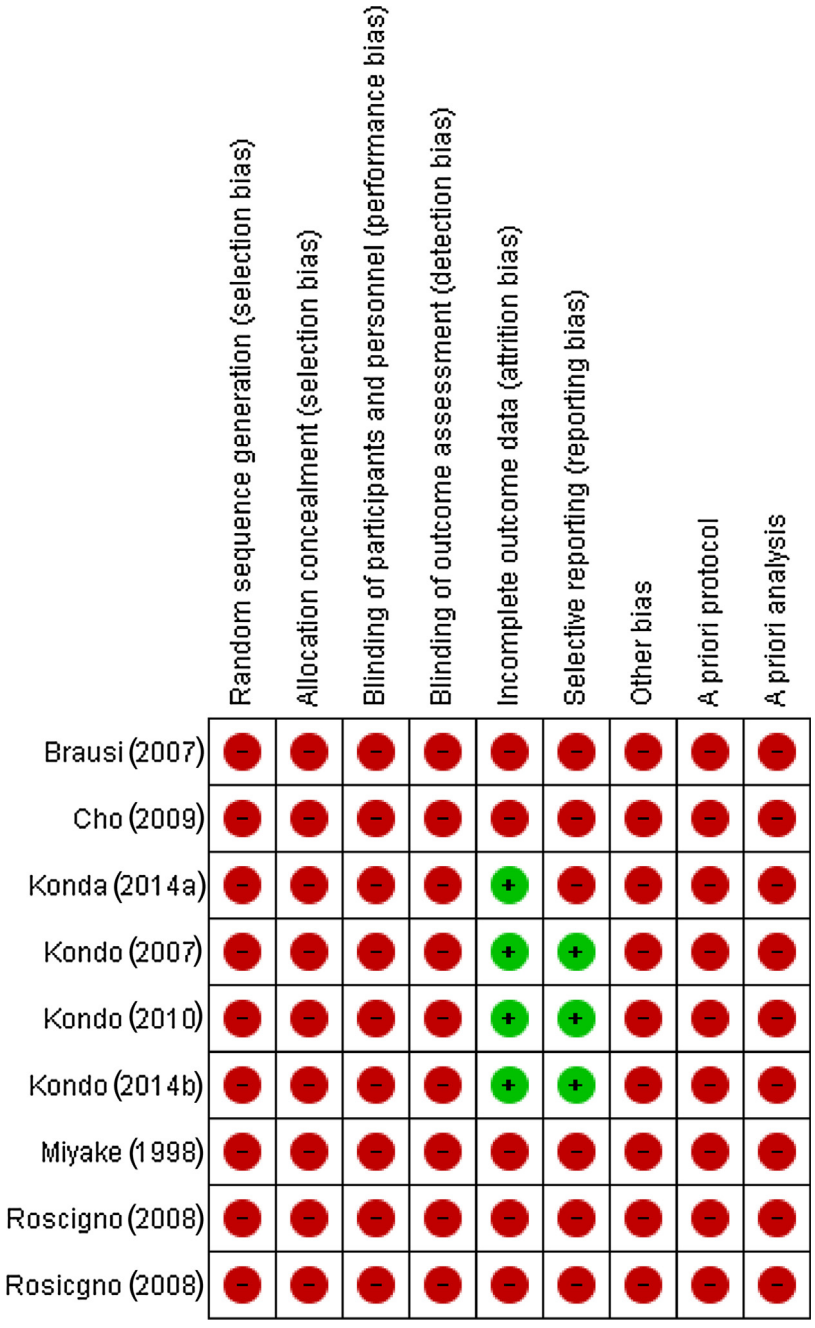

Fig. 2 – Risk of bias assessment. The risk of confounding bias was considered to be high (red) if the confounder was not reported or reported but imbalanced among the treatment groups without any adjustment in the statistical analysis. Alternatively, the risk of confounding bias was considered to be low (green) if the confounder was reported and balanced among the treatment groups, or imbalanced but adjusted for in the statistical analysis. In any other situation, the risk of confounding bias was considered to be unclear (yellow).

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version 5.3 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to present these results (Fig. 2).

3. Evidence synthesis

3.1. Overall characteristics and quality of included studies

Overall characteristics of the nine included publications are presented in Table 1. In the absence of RCTs, nine retrospective studies [14–22] were selected during the systematic search. Consequently, the potential impact of LND in the management of UTUC remains supported by level of evidence 3 [14–22] according to the 2009 Oxford scale. Three types of comparisons were reported: NoLND versus LND [14–19], CLND versus ILND versus NoLND [20,22], and CLND versus ILND [21]. Out of the nine included studies, four came from overlapping cohorts of patients but were included as they were clearly focused on different subanalyses and reported different outcomes [14,20–22]. Owing to the non-randomised retrospective design of the vast majority of the studies, a high risk of bias across all analysed domains was found. Furthermore, potential confounders were poorly addressed, with most items not being balanced or adjusted for, and hence falling into the high-risk (red) category.

3.2. LND versus NoLND

3.2.1. Baseline population characteristics

Pre- and postoperative characteristics of the patients included in the six studies comparing LND and NoLND [14–19] are shown in Table 2. There were three single-centre studies [15,18,19], two reported outcomes from two centres [14,17] and one from 13 centres [16], but only four mentioned consecutive enrolment [15–17,19].

Patients underwent open surgery in three series [15,17,19], with open or laparoscopic RNU in two [14,16], while the approach was not mentioned in one [18].

Follow-up was not reported in five of the six studies [15–19], and it showed a statistically significant difference in the other [14]. Age was not reported in two studies [15,17], and patients aged >75 yr were excluded from the LND arm in one study [14]. No study reported on race, body mass index (BMI), or smoking status, and only one reported on performance status [16]. One study [16] reported no previous MIBC and two reported concomitant BC in 18.3% and 8.3% of patients [17,19]. Use of adjuvant chemotherapy was mentioned in five studies [14–17,19], being used significantly more in the LND group in two of these [14,16].

Postoperative characteristics demonstrated significant differences in pT stage and grade in one study [16], with information lacking in three studies [15,17,18]. No study reported surgical margins. Only two studies described the presence of carcinoma in situ [16,19], with unequal distribution in one [16], which was a case with tumour necrosis [16].

3.2.1.1. Oncological outcomes. Survival outcomes in the six studies comparing LND and NoLND [14–19] are summarised in Table 3.

Brausi et al [17] reported a 40% rate of pN+ in ≥pT2 UTUC patients undergoing LND, with CSS rates of 44.8% and 81.6% in the NoLND and LND groups, respectively ($p = 0.007$). Roscigno et al [19] detected pN+ disease in 27% of ≥pT2 UTUC patients undergoing LND and reported 5-yr CSS rates of 48%, 73%, and 39% in NoLND (pNx), pN0, and pN+ patients, respectively, with actuarial 5-yr CSS rates of 67% and 40% in the LND and NoLND groups, respectively, LND appeared as an independent predictor of CSS ($p = 0.02$) after adjusting for age, tumour stage and grade, carcinoma in situ, lymphovascular invasion (LVI), chemotherapy, and year of surgery. These findings are supported by the largest of the six studies [16]. It reported pN+ disease in 2.2% and 16.4% of patients with pT1 and ≥pT2 UTUCs, respectively, and actuarial 5-yr CSS rates of 70%, 58%, and 33% in LND pN0, NoLND, and LND pN+, respectively, among invasive tumours. In contrast to pT1 disease, no difference was found between pN0 and pNx disease. Furthermore, among patients with pN0 tumours, the number of LNs removed was an independent predictor of CSS (HR = 0.934, $p = 0.015$) [16].

Kondo et al [14] further evaluated the role of LND. They reported 3-yr CSS rates of 89.8% versus 51.7% in a subset analysis of 56 patients with ≥pT2cN0M0 renal pelvis UTUC, when comparing LND versus NoLND (HR = 0.23, $p = 0.01$). However, this was not reproducible in ureteral tumours (HR = 0.99, $p = 0.99$). Contrary to these findings, Cho et al [15] detected pN+ in 14.3% of cN0 patients with ≥pT2 UTUC undergoing LND, and reported better local control and staging accuracy but no difference in survival ($p > 0.05$).

Regarding OS, Miyake et al [18] detected pN+ in 37% (12/34 cN0 and 1 cN1) of patients undergoing LND, with no pN+ disease in ≤pT1 stage or grade 1 tumours. There was only a significant difference in 1-, 3-, and 5-yr OS when comparing LND with NoLND in patients with no evidence of LVI (100%, 93%, and 86% vs 79%, 65%, and 50%, respectively, $p < 0.05$). Brausi et al [17] reported a median OS of 52.5 and 21.2 mo in the LND versus NoLND groups, which confirmed LND and T stage as independent predictors of OS ($p = 0.004$ and 0.008). No OS results were reported in one of the six studies [15], and an OS rate of 58% for the entire series was reported by two studies [16,19].

Assessing the impact on recurrence, Roscigno et al [19] reported actuarial 5-yr RFS rates of 64% and 37% in LND and NoLND patients, respectively (log-rank $p = 0.01$), with LND being an independent predictor of RFS ($p = 0.01$). Similarly, Brausi et al [17] reported actuarial 5-yr RFS rates of 64.3% and 46.3%, respectively ($p = 0.03$), with a prolonged time to recurrence from 18.5 to 51.2 mo.

Unadjusted and adjusted HRs for CSS and other oncological outcomes are reported in Table 4.

3.3. CLND/T-BLND versus ILND versus NoLND

3.3.1. Baseline population characteristics

Pre- and postoperative characteristics of patients included in the three studies [20–22] reporting oncological outcomes of CLND/T-BLND versus ILND versus NoLND are shown in Table 5.

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Table 1 – Overall characteristics of included studies assessing the role of lymphadenectomy in patients undergoing RNU for the management of upper tract urothelial carcinoma.

Study	Country	Study design	LoE	Consecutive recruitment	Number of centres	National registry	No. of patients, *n* (%)			Follow-up, median, *n* (range), mo			
							Overall	Control	Intervention	Overall	Control	Intervention	*p* value
Kondo et al ((2014) [20]	Japan	Retrospective	3	NR	2	No	180 (100)	NoLND 92 (51.1)	CLND 68 (37.7) ILND 20 (11.1)	NR	Median = 26.3 (1.0–225)	CLND Median = 47.1 (2.6–213) ILND Median = 38.1 (6.9–208)	0.01
Kondo et al ((2014) [14]	Japan	Prospective/ retrospective control	2b	NR	2	No	166 (100)	NoLND 89 (53.6)	T-BLND 77 (46.4)	NR	RP Median = 20.3 (1.0–102.5) U Median = 23.6 (1.1–95.0)	RP Median = 29.9 (1.0–78.4) U Median = 22.4 (1.1–77.9)	RP 0.006 U 0.99
Kondo et al ((2010) [21]	Japan	Retrospective	3	NR	2	No	119 (100)	ILND 41 (34.5)	CLND 78 (65.5)	NR	Median = 49.7 (3.2–221)	Median = 27.8 (1–203.1)	0.3
Cho et al ((2009) [15]	Korea	Retrospective	3	Yes	1	No	152 (100)	NoLND 89 (58.6)	LND 63 (41.4)	Median = 53 (6–214)	NR	NR	NR
Roscigno et al ((2009) [16]	Italy, Chile, France, Austria, USA, Germany, Japan, Canada	Retrospective	3	Yes	13	No	1130 (100)	NoLND 578 (51.2)	LND 552 (48.8)	Median = 45 (1–250)	NR	NR	NR
Brausi et al ((2007) [17]	Italy	Retrospective	3	Yes	2	No	82 (100)	NoLND 42 (51.2)	LND 40 (48.8)	Median = 64.7 (24–288)	NR	NR	NR
Kondo et al ((2007) [22]	Japan	Retrospective	3	NR	2	No	169 (100)	NoLND 88 (52.1)	ILND 36 (21.3) CLND 45 (26.6)	Median = 37.3 (1–209)	Median = 30.3 (0.3–209.1)	ILND Median = 47.2 (0.9–177.7) CLND Median = 51.8 (2.6–203.1)	NR
Miyake et al ((1998) [18]	Japan	Retrospective	3	NR	1	No	72 (100)	NoLND 37 (51.4)	LND 35 (48.6)	Median = 49 (7–116)	NR	NR	NR
Roscigno et al ((2008) [19]	Italy	Retrospective	3	NR	1	No	132 (100)	NoLND 37 (28.0)	LND 95 (72.0)	Median = 42 (2–191)	NR	NR	NR

LoE = level of evidence; NoLND = no lymphadenectomy; CLND = complete lymphadenectomy; ILND = incomplete lymphadenectomy; RNU = radical nephroureterectomy; T-BLND = template-based lymphadenectomy; NR = not reported.

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Table 2 – Pre- and postoperative characteristics of patients included in the studies comparing LND versus NoLND in patients undergoing RNU for upper tract urothelial carcinoma.

Study	Treatment group	Preoperative characteristics																			
		Patient characteristics								Tumour characteristics											
		Age (yr)		Gender		Performance score		Previous BCa		Location		Hydrone-phrosis		Multifocality		Size		cT stage		cN stage	
		n (range), yr	*p* value	*n* (%) (M/F)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%), cm	*p* value	*n* (%)	*p* value	*n* (%)	*p* value
Kondo et al (2014) [14]	Overall	NR	RP <0.001 U <0.001	112 (62.2)/54 (37.8)	RP 0.03 U 0.11	NR	NA	NR	NA	RP: 90 (54.2) U: 76 (45.8)	NR	NR	NA	NR	NA	NR	NA	NR	NA	cNo 166 (100)	N/S
	NoLND	RP Median = 76.8 (36–91) U Median = 75.7 (45–90)		RP 35 (67.3)/17 (36.7) U 18 (48.7%)/19 (51.3)		NR		NR		RP: 52 (58.4) U: 37 (41.6)		NR		NR		NR		NR		cN0 89 (100)	
	CLND	RP Median = 67.7 (51–83) U Median = 68 (46–86)		RP 33 (86.8)/5 (13.2) U 26 (66.7)/13 (33.3)		NR		NR		RP: 38 (49.4) U: 39 (50.6)		NR		NR		NR		NR		cN0 77 (100)	
Cho et al (2009) [15]	Overall	Median = 65 (25–86)	NR	103 (67.8)/49 (32.2)	NR	NR	NA	NR	NA	RP: 80 (52.6) U: 72 (47.5)	NA	NR	NA	Single 119 (78.3) Multiple 33 (21.7)	NA	<3 cm: 66 (43.4%) >3 cm: 86 (56.6%)	NA	NR	NA	cNo 152 (100)	N/S
	NoLND	NR		NR		NR		NR		NR		NR		NR		NR		NR		cN0 89 (100)	
	LND	NR		NR		NR		NR		NR		NR		NR		NR		NR		cNo 63 (100)	
Roscigno et al (2009) [16]	Overall	Median = 69.9 (27–94))	0.33	NR	NR	ECOG 0 = 786 (69.6) ECOG 1 = 279 (24.7) ECOG 2–3 = 65 (5.7)	0.208	MIBC = 0 (0)	N/S	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA
	NoLND	Median = 69.5 (31–94)		NR		ECOG 0 = 391 (67.6) ECOG 1 = 144 (24.9) ECOG 2–3 = 43 (7.5)		MIBC = 0 (0)		NR		NR		NR		NR		NR		NR	
	LND	pN0 Median = 69.1 (27–90) pN+ Median = 70 (29–92)		NR		ECOG 0 = 395 (71.6) ECOG 1 = 135 (24.5) ECOG 2–3 = 22 (4.0)		MIBC = 0 (0)		NR		NR		NR		NR		NR		NR	
Brausi et al (2007) [17]	Overall	Median = 67.7 (35–82)	NR	59 (72)/23 (28)	NR	NR	NA	15 (18.3%) Concomitant	NR	RP: 47 (57.3) U: 28 (34.2) RP + U: 7 (8.5)	NR	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA
	NoLND	NR		32 (76.2)/10 (23.8)		NR		NR		RP: 21 (50) U: 18 (42.9) RP + U: 3 (7.1)		NR		NR		NR		NR		NR	
	LND	NR		27 (67.5)/23 (32.5)		NR		NR		RP: 26 (65) U: 10 (25) RP + U: 4 (10)		NR		NR		NR		NR		NR	
Miyake et al (1998) [18]	Overall	Mean = 67 (45–82)	NR	54 (75)/18 (25)	NR	NR	NA	NR	NA	RP: 40 (55.6) U: 29 (40.3)) RP + U: 3 (4.2)	NA	NR	NA	NR	NA	NR	NA	NR	NA	cNx: 37 cN0: 34	NR
	NoLND	Mean = 67 (45–82)		27 (73)/10 (27)		NR		NR		RP: 21 (57) U: 15 (40) RP + U: 1 (3)	NR	NR		NR		NR		NR		cNx: 37 cN0: 0 cN+: 0	
	LND	Mean = 64 (47–82)		27 (79)/8 (21)		NR		NR		RP: 19 (54) U: 14 (40) RP + U: 2 (6)		NR		NR		NR		NR		cNx: 0 cN0: 34	

Table 2 (*Continued*)

Study	Treatment group	Preoperative characteristics																			
		Patient characteristics								Tumour characteristics											
		Age (yr)		Gender		Performance score		Previous BCa		Location		Hydrone-phrosis		Multifocality		Size		cT stage		cN stage	
		n (range), yr	*p* value	*n* (%) (M/F)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%), cm	*p* value	*n* (%)	*p* value	*n* (%)	*p* value
Roscigno et al (2008) [19]	Overall	Median = 67.0 (30–92)	0.19	NR	NA	NR	NA	11 (8.3) Concomitant	NA	RP/upper U 85 (64.4) Mid U 9 (6.8) Lower U 39 (29.5)	0.64	NR	NA	NR	NA	NR	NA	NR	NA	NR	NR
	NoLND	Median = 70.0 (46–92)		NR		NR		NR		RP/upper U 26 (70.3) Mid U 3 (8.1) Lower U 8 (21.6)		NR		NR		NR		NR		NR	
	LND	Median = 67.0 (30–88)		NR		NR		NR		RP/upper U 59 (62.1) Mid U 6 (6.3) Lower U 30 (31.6)		NR		NR		NR		NR		NR	

Study	Treatment group	Postoperative characteristics																			
		pT stage		pN stage		Grade		LVI		Concomitant CIS		LN removed		LN positive		Extracapsular extension		Neoadjuvant chemotherapy		Adjuvant chemotherapy	
		n (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (range)	*p* value	*n* (%)	*p* value	*n*, cm	*p* value	*n* (%)	*p* value	*n* (%)	*p* value
Kondo et al (2014) [14]	Overall	pT≤1 = 62 (37.3); pT2 = 27 (16.3); pT3 = 72 (43.4); pT4 = 5 (3)	RP 0.16 U 0.81	pN0 = 69 (41.6); pN+ = 11 (6.6); pNx = 89 (51.8)	RP < 0.001 U < 0.001	LG = 71 (42.8) HG = 95 (57.2)	RP 0.38 U 0.11	69 (41.6)	RP 0.38 U 0.05	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	RP = 4 U = 8	RP 0.30 U 0.02
	NoLND	RP pT ≤ 1 = 20 (38.5); pT2 = 4 (7.7); pT3 = 25 (48.1); pT4 = 3 (5.7) U pT ≤ 1 = 14 (37.8); pT2 = 7 (18.9); pT3 = 16 (43.2); pT4 = 0 (0)		RP pN0 = 0; pN+ = 3 (5.8); pNx = 49 (94.2) U pN0 = 0; pN+ = 0 (0); pNx = 37 (100)		RP LG = 20 (38.5) HG = 32 (61.5) U LG = 18 (48.6) HG = 19 (51.4)		RP 23 (44) U 11 (31)		NR		NA		NR		NR		NR		RP 1(2) U 1(3)	
	T-BLND	RP pT≤1 = 14 (36.8); pT2 = 6 (15.8); pT3 = 17 (44.7); pT4 = 1 (2.6) U pT≤1 = 14 (35.9); pT2 = 10 (25.6); pT3 = 14 (35.9); pT4 = 1 (2.6)		RP pN0 = 36 (94.7); pN+ = 2 (5.3) U pN0 = 33 (84.6); pN+ = 6 (15.4)		RP LG = 21 (55.3) HG = 17 (44.7) U LG = 12 (30.8) HG = 27 (69.2)		RP 13 (34) U 21 (54)		NR		RP Median 15 (4–32) U Median 14 (2–36)		NR		NR		NR		RP 3 (8) U 7 (18)	
Cho et al (2009) [15]	Overall	pT2 = 47 (30.9); pT3 = 98 (64.5); pT4 = 7 (4.60)	NA	pN0 = 54 (35.5); pNx = 89 (58.6); pN+ = 9 (5.9%)	NR	LG = 14 (9.2) HG = 138 (90.8)	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NA	NA	47 (30.9)	NA
	NoLND	NR		pNx:89 (100)		NR		NR		NR		0		0		NR		NA		NR	
	LND	NR		pN0 = 54 (85.7) pN+ = 9 (14.3)		NR		NR		NR		Median = 6 (1–35)		9/66 14.3%		NR		NA		NR	
Roscigno et al (2009) [16]	Overall	pT1 = 317 (28.1); pT2 = 269 (23.8); pT3–4 = 544 (48.1)	<0.001	pN0 = 412 (36.5); pNx =v578 (51.1); pN+ =v140 (12.4)	<0.001	LG = 291 (25.8) HG = 839 (74.2)	<0.001	349 (30.9)	<0.001	351 (31.1)	0.002	NR	NA	NR	NA	NR	NA	NR	NA	188 (16.6)	<0.001

Table 2 (*Continued*)

Study	Treatment group	Postoperative characteristics																			
		pT stage		pN stage		Grade		LVI		Concomitant CIS		LN removed		LN positive		Extracapsular extension		Neoadjuvant chemotherapy		Adjuvant chemotherapy	
		n (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (range)	*p* value	*n* (%)	*p* value	*n*, cm	*p* value	*n* (%)	*p* value	*n* (%)	*p* value
	NoLND	pT1 = 206 (35.6); pT2 = 144 (24.9); pT3–4 = 228 (39.5)		pNx = 578 (100)		LG = 193 (35.4) HG = 385 (66.6)		159 (27.5)		152 (26.3)		0		0		NR		NR		60 (10.4)	
	LND	pT1 = 111(20.1); pT2 = 125 (22.6); pT3–4 = 316 (57.3)		pN0 = 412 (74.6) pN+ = 140 (25.4)		LG = 98 (17.8) HG = 454 (82.2)		190 (34.4)		99 (36.1)		NR		NR		NR		NR		28 (23.2)	
Brausi et al (2007) [17]	Overall	pT2 = 47 (30.9); pT3 = 98 (64.5); pT4 = 7 (4.6)	NR	pN0 = 24 (29.3); pNx = 42 (51.2); pN+ = 16 (19.5)	NR	G2 = 44 (53.7) G3 = 38 (46.3)	NR	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NA	NA	NR	NA
	NoLND	pT2 = 26 (61.9); pT3 = 14 (33.3); pT4 = 2 (4.8)		pNx = 42 (100)		G2 = 34 (81) G3 = 8 (9)		NR		NR		0		0		NR		NA		3 (7.1)	
	LND	pT2 = 12 (30); pT3 = 22 (55); pT4 = 6 (15)		pN0 = 24(60); pN+ = 16 (40)		G2 = 10 (25) G3 = 30 (75)		NR		NR		Before 1999 Mean = 7.1 (5–10) After 1999 Mean = 11.5 (5–24)		NR		NR		NA		NR	
Miyake et al (1998) [18]	Overall	pTa = 11 (15.3); pT1 = 25 (34.7); pT2 = 18 (25); pT3 = 14 (19.4); pT4 = 4 (5.6)	NR	pNx = 37 (51.4); pN0 = 22 (30.6); pN+ = 13 (18.0)	NR	G1 = 12 (16.7) G2 = 33 (45.8) G3 = 27 (37.5)	NR	28 (38.9)	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA
	NoLND	pTa = 6 (16); pT1 = 13 (35); pT2 = 8 (22); pT3 = 8 (22); pT4 = 2 (5)		pNx = 37 (100)		G1 = 7 (18.9) G2 = 33 (43.2) G3 = 14 (37.8)		NR		NR		0		0		NR		NR		NR	
	LND	pTa = 5 (14); pT1 = 12 (34); pT2 =n 10 (29); pT3 = 6 (17); pT4 = 2 (6)		pN0 = 22 (62.9) pN+ = 13 (37.1)		G1 = 5 (14) G2 = 17 (49) G3 = 13 (37)		NR		NR		NR		NR		NR		NR		NR	
Roscigno et al (2008) [19]	Overall	<pT2 = 59 (45.5); pT2–3 = 73 (55.5)	0.91	pNx = 37 (28); pN0 = 69 (52.3); pN+ = 13 (19.7)		G2 = 75 (56.8) G3 = 57 (43.2)	0.77	51 (38.6)	0.11	45 (34.1)	0.31	NR	NA	NR	NA	NR	NA	NR	NA NR	10 (7.6)	NR
	NoLND	<pT2 = 17 (45.9); pT2–3 = 20 (54.1)		pNx = 37 (100)		G2 = 18 (48.6) G3 = 19 (51.4)		17 (45.9)		12 (32.4)		0		0		NR		NR		2 (5.4)	
	LND	<pT2 = 44 (44.2); pT2–3 = 53 (55.8)		pN0 = 69 (72.6); pN+n= 26 (27.4)		G2 = 57 (60) G3 = 38 (40)		34 (35.8)		33 (34.7)		Median = 8 (2–24)		Median = 2		NR		NR		8 (8.4)	

BCa = bladder cancer; CIS = carcinoma in situ; CLND = complete lymph node dissection; ECOG = Eastern Cooperative Oncology Group Scale of Performance Status; F = female; HG = high grade; ILND = incomplete lymph node dissection; LG = low grade; LND = lymph node dissection; LVI = lymphovascular invasion; M = male; MIBC = muscle-invasive bladder cancer; NA = not applicable; NoLND = no lymphadenectomy; NR = not reported; N/S = not significant; pN = pathological N stage; pT = pathological T stage; RNU = radical nephroureterectomy; RP = renal pelvis; T-BLND = template-based lymphadenectomy; U = ureter.

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Table 3 – Estimated cancer-specific, overall, and metastasis-free survival at the time points provided in the included studies comparing LND versus NoLND in patients undergoing radical nephroureterectomy for upper tract urothelial carcinoma.

Study	Treatment group	Cancer-specific survival						Overall survival						Metastasis-free survival					
		Cancer-specific death				Rate, %	*p* value	Overall death				Rate, %	*p* value	Metastasis				Rate, %	*p* value
		n (%)	*p* value	Time				*n* (%)	*p* value	Time				*n* (%)	*p* value	Time			
				n, mo	*p* value					*n*, mo	*p* value					*n*, mo	*p* value		
Kondo et al (2014) [14]	Overall	8 (4.8)	RP 0.07 U 0.55	NR	NA	NR	NA	32 (19.3)	NR	NR	NA	NR	NA	11 (6.6)	NR	NR	NA	NR	NA
	NoLND	RP = 11 (21) U = 4 (11)		NR	NA	3-yr CSS RP pT2–4: 51.7% 3-yr CSS U pT2–4 = 71.7%	RP $p = 0.01$ RP, T2–4 $p = 0.01$ U $p = 0.47$ U, pT2–4 $p = 0.99$	R P = 14 (26.9) U = 4 (10.8)	NR	NR	NA	3-yr OS RP pT2–4 = 48% 3-yr OS U pT2–4 = 71.7%	RP $p = 0.02$ RP, pT2–4 $p = 0.02$ U $p = 0.14$ U, pT2–4 $p = 0.57$	RP = 4 (8) U = 2 (5)	RP $p = 0.63$ U $p = 0.67$	NR	NA	NR	NA
	T-BLND	RP = 3 (8) U = 6 (15)		NR		3-yr CSS RP pT2–4: 89.8% 3-yr CSS U pT2–4 = 54.2%		RP = 5 (13.2) U = 9 (23.1)		NR		3-yr OS R P pT2–4 = 86.1% 3-yr OS U pT2–4 = 46.2%		RP = 3 (8) U = 2 (5)		NR		NR	
Cho et al (2012) [15]	Overall	55 (36.2)	NR	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA
	NoLND	NR	NA	NR	NA	5-yr CSS = 62.7%	0.9473	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA
	LND	NR		NR		5-yr CSS = 71%		NR		NR		NR		NR		NR		NR	
Roscigno et al (2011) [16]	Overall	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	5-yr OS = 58%	NR	NR	NA	NR	NA	NR	NA
	NoLND	NR	NA	NR	NA	5-yr CSS = 69%	0.23	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA
	LND	NR		NR		5-yr CSS = 66%		NR		NR		NR		NR		NR		NR	
Brausi et al (2007) [17]	Overall	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA
	NoLND	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA
	LND	NR		NR		NR		NR		NR		NR		NR		NR		NR	
Miyake et al (1998) [18]	Overall	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	3-yr OS = 71% 5-yr OS = 54%	NR	NR	NA	NR	NA	NR	NA
	NoLND	NR	NA	NR	NA	3-yr CSS = 65% 5-yr CSS = 50%	3 yr $p > 0.05$ 5 yr $p > 0.05$	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA
	LND	NR		NR		3-yr CSS = 73% 5-yr CSS = 50%		NR		NR		NR		NR		NR		NR	
Roscigno et al (2008) [19]	Overall	(54)	NR	NR	NA	5-yr CSS = 62%	NR	NR	NA	NR	NA	5-yr OS = 58%	NR	NR	NA	NR	NA	NR	NA
	NoLND	NR	NA	NR	NA	5-yr CSS = 40%	0.01	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NR
	LND	NR		NR		5-yr CSS = 67%		NR		NR		NR		NR		NR		NR	

LND = lymphadenectomy; NoLND = no lymphadenectomy; T-BLND = template-based lymphadenectomy; CSS = cancer-specific survival; OS = overall survival; RP = renal pelvis; U = ureter; NR = not reported; NA = not applicable; 3 yr and 5 yr = 3 yr and 5 yr time points.

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Table 4 – Unadjusted and adjusted HRs for CSS and other oncological outcomes.

	CSS			OS			RFS			MFS		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Unadjusted HRs												
Kondo et al (2014) [14]	0.23	0.05–0.77	0.01	0.28	0.07–0.81	0.01	0.39	0.12–1.04	0.06	NR	NR	NR
Cho et al (2009) [15]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Roscigno et al (2009) [16]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Brausi et al (2007) [17]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Miyake et al (1998) [18]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Roscigno *et al* (2008) [19]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kondo et al (2014) [20]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kondo et al (2010) [21]	0.55	0.24–1.25	0.15	NR	NR	NR	NR	NR	NR	NR	NR	NR
	0.3	0.11–0.77	0.01	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kondo et al (2007) [22]	0.55	0.27–1.11	0.09	NR	NR	NR	NR	NR	NR	NR	NR	NR
	0.50	0.21–1.23	0.13	NR	NR	NR	NR	NR	NR	NR	NR	NR
Adjusted HRs												
Kondo et al (2014) [14]	0.19	0.03–0.89	0.03	0.30	0.07–1.1	0.07	0.31	0.07–1.18	0.08	NR	NR	NR
Cho et al (2009) [15]	NR	NR	NR	NR	NR	NR	3.46	1.31–9.12	0.012	NR	NR	NR
Roscigno et al (2009) [16]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Brausi et al (2007) [17]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Miyake et al (1998) [18]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Roscigno et al (2008) [19]	2.098	NR	0.02	1.45	NR	0.01	1.45	NR	0.01	NR	NR	NR
Kondo et al (2014) [20]	NR	NR	NR	NR	NR	NR	0.17	0.04–1.07	0.06	NR	NR	NR
Kondo et al (2010) [21]	0.49	0.21–1.13	<0.09	NR	NR	NR	NR	NR	NR	NR	NR	NR
	0.24	0.08–0.67	<0.01	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kondo et al (2007) [22]	0.29	0.11–0.73	0.009	NR	NR	NR	NR	NR	NR	NR	NR	NR

CI = confidence interval; CSS = cancer-specific survival; HR = hazard ratio; MFS = metastasis-free survival; NR = not reported; OS = overall survival; RFS = recurrence-free survival.

Preoperative characteristics varied among the groups reported in the three studies. The studies were conducted in the same two institutions; therefore, they were included only after discussion with the EAU NMIBC Guidelines Panel and if the subject and outcomes of interest were different in each article. Consecutive enrolment is not mentioned, and no information is available regarding race, BMI, performance status, smoking, history of BC, or previous UTUC in any of the studies [20–22]. Differences in follow-up period were reported in one paper [20], with information lacking in the other two [21,22]. The study groups were not well balanced, with the exclusion of patients >75 yr of age from the treatment groups, which, alongside differences in potential comorbidities, presents a significant selection bias.

Regarding cT stage, comparable populations are included in two of three studies [20,21] and not reported in one [22]. All patients were clearly reported cN0 in one of three studies [20], with an equal contamination of both study arms (2%, $p = 0.94$) in one of three studies [21] and lacking information in another [22].

Postoperatively, no differences in pT stage or grade were reported in two studies [20,21], with no information regarding tumour necrosis or extracapsular invasion. Only one paper referred to differences in LVI [20]. Regarding the use of adjuvant chemotherapy, a significant difference in favour of the CLND group was reported in two studies [20,21].

3.3.2. Oncological outcomes

Survival outcomes in the studies comparing CLND versus ILND versus NoLND [20–22] are summarised in Table 6.

In 2007, Kondo et al [22] compared NoLND versus CLND and ILND. When focused on ≥pT3 tumours, there was no significant difference in survival between CLND and ILND, but survival in these two groups was superior to that of NoLND patients. However, multivariate analysis identified CLND as an independent prognostic factor. Later, Kondo et al [21] compared CSS between patients with ≥pT2, cN0, and cM0 UTUC undergoing CLND or ILND. They detected 15% of pN+ in the CLND group and reported a significant benefit with CLND (14% vs 29%, $p = 0.04$), even when adjusted by chemotherapy use and independent of the total number of LNs removed [21].

In the first study, although LN recurrence was similar among the three groups, distant metastasis was significantly higher in the NoLND group than in the CLND and ILND groups ($p = 0.04$) [22].

Overall, CLND appears as an independent prognostic factor for improved survival [20,21], while its performance did not appear to increase perioperative complications [22]. These studies did not report OS, although this outcome would be impaired by a selection bias because patients aged >75 yr were not routinely offered LND.

Unadjusted and adjusted HRs for CSS and other oncological outcomes are reported in Table 4.

3.4. Value of LND according to tumour location (renal pelvis vs ureter)

Two of the included studies assessed the value of LND according to tumour location (renal pelvis vs ureter) [14,20]. In the first study, Kondo et al [14] compared patients with LND versus those without LND stratifying their analysis in two subgroups according to tumour location: renal pelvis versus ureter. In renal pelvic cancer

Table 5 – Pre- and postoperative characteristics of patients included in the studies comparing CLND versus ILND and CLND versus ILND versus NoLND in patients undergoing RNU for upper tract urothelial carcinoma.

Study	Treatment group	Preoperative characteristics																			
		Patient characteristics								Tumour characteristics											
		Age, yr		Gender		Performance score		Previous BCa		Location		Hydrone-phrosis		Multifocality		Size		cT stage		cN stage	
		n (range), yr	*p* value	*n* (%) (M/F)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%), cm	*p* value	*n* (%)	*p* value	*n* (%)	*p* value
Kondo et al (2014) [20]	Overall	NR	<0.001	128 (71.1)/ 52 (28.9)	0.52	NR	NA	NR	NA	RP = 180 (100)	N/S	NR	NA	NR	NA	NR	NA	≤cT1 = 35 (19.4) cT2 = 68 (43.3) cT3 = 62 (34.4) cT4 = 7 (3.9)	0.48	cNo 180 (100)	N/S
	NoLND	Median = 75 (36–91)		62 (67.4)/ 30 (32.6)		NR		NR		RP = 92 (100)		NR		NR		NR		≤cT1 = 23 (25) cT2 = 39 (42.4) cT3 = 27 (29.3) cT4 = 3 (3.3)		cN0 92 (100)	
	CLND	Median = 67 (51–83)		51 (75)/ 17 (25)		NR		NR		RP = 68 (100)		NR		NR		NR		≤cT1 = 10 (14.7) cT2 = 27 (39.7) cT3 = 28 (41.2) cT4 = 3 (4.4)		cN0 68 (100)	
	ILND	Median = 68 (51–76)		15 (75)/ 5 (25)		NR		NR		RP = 20 (100)		NR		NR		NR		≤cT1 = 2 (10) cT2 = 10 (50) cT3 = 7 (35) cT4 = 1 (5.0)		cN0 20 (100)	
Kondo et al (2010) [21]	Overall	NR	0.59	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	≤cT1 = 15 (12.6) cT2 = 53 (44.5) cT3 = 46 (38.6) cT4 = 5 (4.2)	0.11	cN0 = 109 cN+ = 10	0.94
	ILND	Mean = 67.5 Median = 70.1 (44–90)		NR		NR		NR		NR		NR		NR		NR		≤cT1 = 7 (17) cT2 = 21 (51) cT3 = 12 (29) cT4 = 1(3)		cNx = 0 (0) cN0 = 38 (93) cN1 = 1 (2) cN2 = 2 (5) cN+ = 3 (7.3)	
	CLND	Mean = 66.4 Median = 67.5 (38–83)		NR		NR		NR		NR		NR		NR		NR		≤cT1 = 8 (10) cT2 = 32 (41) cT3 = 34 (43) cT4 = 4 (6)		cNx = 0 (0) cN0 = 71 (91) cN1 = 2 (2) cN2 = 5 (7) cN+ = 7 (9)	
Kondo et al (2007) [22]	Overall	Mean = 67.5 Median = 69.2 (38.7–85.5)		113 (67)/ 56 (33)	NR	NR	0.208	NR	NA	RP = 100 (59.2) U = 69 (40.8)	NA	NR	NA	NR	NA	NR	NA	≤cT1 = 39 (23.1) cT2 = 75 (44.4) cT3 = 60 (35.5) cT4 = 4 (2.4)	NR	NR	NA
	NoLND	Mean = 68.9 Median = 69.7 (39.8–85.5)		NR		NR		NR		NR		NR		NR		NR		≤cT1 = 27 (30.7) cT2 = 41 (46.6) cT3 = 18 (20.5) cT4 = 2 (2.3)		NR	
	CLND	Mean = 65.3 Median = 68.6 (38.7–80)		NR		NR		NR		NR		NR		NR		NR		≤cT1 = 7 (15.6) cT2 = 16 (35.6) cT3 = 21 (46.7) cT4 = 1 (2.2)		NR	
	ILND	Mean = 66.8 Median = 68.6 (46.8–77.6)		NR		NR		NR		NR		NR		NR		NR		≤cT1 = 5 (13.9) cT2 = 18 (46.6) cT3 = 21 (51.3) cT4 = 1 (2.8)		NR	

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Study	Treatment group	Postoperative characteristics																			
		pT stage		pN stage		Grade		LVI		Concomitant CIS		LN removed		LN positive		Extracapsular extension		Neoadjuvant chemotherapy		Adjuvant chemotherapy	
		n (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (range)	*p* value	*n* (range)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value
Kondo et al (2014) [20]	Overall	pT ≤ 1 = 54 (30.0); pT2 = 25 (13.9); pT3 = 89 (49.4); pT4 = 12 (6.66)	0.20	pN0 = 76 (42.2); pN+ = 16(8.9); pNx = 88 (48.9)	<0.001	LG = 95 (52.8) HG = 85 (47.2)	0.29	90 (50)	0.04	NR	NA	NR	<0.001	NR	NA	NR	NA	0 (0)	N/S	9 (5)	0.02
	NoLND	pT ≤ 1 = 30 (32.6); pT2 = 11 (11.9); pT3 = 44 (47.8); pT4 = 7 (7.60)		pN0 = 0 (0); pN+ = 4 (4.3); pNx = 88 (95.6%)		LG = 44 (47.8) HG = 48 (52.2)		45 (48.9)		NR		0		NR		NR		0 (0)		1 (1)	
	CLND	pT ≤ 1 = 22 (32.3); pT2 = 11 (16.2); pT3 = 32(47.1); pT4 = 3 (4.40)		pN0 = 63 (92.7); pN+ = 5 (7.3); pNx = 0 (0)		LG = 41 (60.3) HG = 27 (39.7)		30 (44.1)		NR		Mean 11.5 Median 11 (4–32)		NR		NR		0 (0)		7 (10)	
	ILND	pT ≤ 1 = 2 (10); pT2 = 3 (15); pT3 = 13 (65); pT4 = 2 (10)		pN0 = 13 (65); pN+ = 7 (35); pNx = 0 (0)		LG = 10 (50) HG = 10 (50)		15 (75)		NR		Mean 4.6 Median 3 (2–16)		NR		NR		0 (0)		1 (4)	
Kondo et al (2010) [21]	Overall	≤pT1 = 29 (24.4); pT2 = 22 (18.5); pT3 = 59 (49.6); pT4 = 9 (7.6)	0.24	pN0 = 98 (82.3); pN1 = 5 (4.2); pN2 = 16 (13.4)		NR	NA	NR	NA	NR	NA	NR	< 0.01		0.8	NR	NA	NR	NA	16/119 (13.44)	0.03
	ILND	≤pT1 = 12 (29); pT2 = 8 (20); pT3 = 19 (46); pT4 = 2 (5)		pN0 = 32(78); pN1 = 2 (5); pN2 = 7 (17)		NR		NR		NR		Mean = 4.4 Median = 4 (2–16)		Mean = 3 Median = 3 (1–7)		NR		NR		2 (5)	
	CLND	≤pT1 = 17 (22); pT2 = 14 (18); pT3 = 40 (51); pT4 = 7 (9)		pN0 = 66 (85); pN1 = 3 (4); pN2 = 9 (11)		NR		NR		NR		Mean = 10.8 Median = 9 (4–30)		Mean = 3.3 Median = 2.5 (1–14)		NR		NR		14 (18)	
Kondo et al (2007) [22]	Overall	≤pT1 = 45 (26.6); pT2 = 34 (20.1); pT3 = 89 (49.4); pT4 = 12 (6.7)	NR	pNX = 85 (50.3); pN+ = 18 (10.7); pN0 = 76 (44.9)	NR	NR	NA	NR	NA	NR	NA	NR	NR	NR	NR	NR	NA	NR	NA	35 (20.7)	NR
	NoLND	≤pT1 = 29 (33); pT2 = 17 (19.3); pT3 = 38 (43.2); pT4 = 4 (4.5)		pNX = 85 (96.6); pN+ = 3 (3.4)		NR		NR		NR		Mean = 0.04 Median = 0 (0–2)		Mean = 1.1 Median = 1 (1–2)		NR		NR		4 (16)	
	CLND	≤pT1 = 7 (15.6); pT2 = 9 (20); pT3 = 24 (53.3); pT4 = 3 (6.7)		pN0 = 39 (87); pN+ = 6 (13)		NR		NR		NR		Mean = 7.9 Median = 7 (4–30)		Mean = 4.1 Median = 3 (1–14)		NR		NR		3 (7)	
	ILND	≤pT1 = 9 (25); pT2 = 8 (22.2); pT3 = 17 (47.2); pT4 = 2 (5.5)		pN0 = 27 (75); pN+ = 9 (25)		NR		NR		NR		Mean = 4.4 Median = 4 (2–16)		Mean = 3.0 Median = 3 (1–7)		NR		NR		2 (6)	

BCa = bladder cancer; CIS = carcinoma in situ; CLND = complete lymph node dissection; ECOG = Eastern Cooperative Oncology Group Scale of Performance Status; F = female; HG = high grade; ILND = incomplete lymph node dissection; LG = low grade; LND = lymph node dissection; LVI = lymphovascular invasion; M = male; NA = not applicable; NoLND = no lymphadenectomy; NR = not reported; N/S = not significant; pN = pathological N stage; pT = pathological T stage; RNU = radical nephroureterectomy; RP = renal pelvis; T-BLND = template-based lymphadenectomy: U = ureter.

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Table 6 – Estimated cancer-specific, overall, and metastasis-free survival at the time points provided in the included studies comparing CLND versus ILND and CLND versus ILND versus NoLND in patients undergoing radical nephroureterectomy for upper tract urothelial carcinoma.

Study	Treatment group	Cancer-specific survival						Overall survival						Metastasis-free survival					
		Cancer-specific death				Rate, %	*p* value	Overall death				Rate, %	*p* value	Metastasis				Rate, %	*p* value
		n (%)	*p* value	Time				*n* (%)	*p* value	Time				*n* (%)	*p* value	Time			
				n, mo	*p* value					*n*, mo	*p* value					*n*, mo	*p* value		
Kondo et al (2014) [20]	Overall	37 (20.6)	NR	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	35 (19.4)	NR	NR	NA	NR	NA
	NoLND	23 (23.5)	0.05	NR	NA	2-yr CSS = 82% 5-yr CSS = 67.6%	2-yr CSS $p = 0.03$ 5-yr CSS $p = 0.03$	NR	NA	NR	NA	NR	NA	23 (25)	NR	NR	NA	NR	NA
	CLND	8 (12)		NR		2-yr CSS = 95% 5-yr CSS = 90.7%		NR		NR		NR		7 (10)		NR		NR	
	ILND	6 (30)		NR		2-yr CSS = 83.7% 5-yr CSS = 63.7%		NR		NR		NR		5 (25)		NR		NR	
Kondo et al (2010) [21]	Overall	23 (19.32)	NR	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA
	ILND	12 (29.16)	0.04	NR	NA	NR	3-yr CSS $p < 0.01$ 5-yr CSS $p < 0.01$	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA
	CLND	11 (14.1)		NR		NR		NR		NR		NR		NR		NR		NR	
Kondo et al (2007) [22]	Overall	33 (19.5)	NR	NR	NA	NR	NA	NR	NA	NR	NA	5-yr OS = 58%	NR	19 (11.3)	NR	NR	NA	NR	NA
	NoLND	20 (23)	NR	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA	14 (16)	NR	NR	NA	NR	NA
	CLND	6 (13)		NR		NR		NR		NR		NR		3 (7)		NR		NR	
	ILND	7 (19)		NR		NR		NR		NR		NR		2 (6)		NR		NR	

NoLND = no lymphadenectomy; CLND = complete lymphadenectomy; ILND = incomplete lymphadenectomy; CSS = cancer-specific survival; OS = overall survival; MFS = metastasis-free survival; RP = renal pelvis; U = ureter; NR = not reported; NA = not applicable; 2-yr, 3-yr, and 5-yr = 2, 3, and 5 yr time points.

≥pT2cN0M0, the 3-yr CSS favoured the T-BLND group over the NoLND group (89.8% and 51.7%, respectively; HR = 0.23, $p = 0.01$), while no difference in terms of survival was found between LND and NoLND in the subgroup of ureteral tumours (3 yr CSS: 54.2% vs 71.7%; HR = 0.99; $p = 0.99$). In 2014, the same group studied outcomes in a cohort of patients with cN0 renal pelvis UTUC [20]. They reported significant improvement in 2- and 5-yr CSS in the CLND (95% and 90.7%) versus ILND (83.7% and 63.7%) versus NoLND (82.0% and 67.6%) groups. In the latter study, in patients with ≥pT2, cN0 renal pelvic UTUC, there was a significant benefit in 2- and 5-yr RFS in the CLND group (87.4% and 84.3%) versus those in the ILND (80.0% and 66.0%) or NoLND (71.3% and 66.3%) group ($p = 0.03$) [20]. Hence, these two studies suggest that LND might be beneficial only in renal pelvis UTUC.

3.5. Discussion

UTUC has a poor prognosis, with a relatively high risk of LN metastases [6,7]. Comparable with the management of MIBC, LND at the time of RNU was suggested in the 1970s [11], but it has not been widely implemented outside a small number of highly specialised centres.

The European and Japanese guidelines give a level C recommendation to LND in patients with UTUC and invasive disease. According to the National Comprehensive Cancer Network Practice Guidelines in Oncology, LND should be performed in patients with high-grade disease, large tumours, and tumours invading renal parenchyma. The real incidence of pN+ in cN0 disease remains unknown. Two studies using novel cytokeratin antibody immunohistochemistry and quantitative reverse transcription polymerase chain reaction have reported pN+ rates of 10% and 14% among cN0 UTUC patients [24,25]. Although pN+ rate is low in ≤pT1, cN0 UTUC tumours [16], its incidence in patients with high-stage (≥pT2) tumours ranges from 14.3% to 40% [15–19,21].

Given the potential for lymphatic spread, one can assume that a major potential role for LND would be to improve staging accuracy. Indeed, early studies have demonstrated a significant survival advantage in pN0 compared with pN+ patients [19,26]. Roscigno et al [16] compared NoLND versus LND and reported actuarial 5-yr CSS that was significantly worse in pNx compared with pN0 patients (48% vs 73%, $p = 0.001$) and comparable with pN+ patients (48% vs 39%, $p = 0.476$). They concluded that LND is likely to provide better stratification of pN0 patients. The impact of LND on improved staging has been further demonstrated in a study by Abe et al. [24]. However, several other contemporary studies appear to contradict these results [8,27,28]. Nevertheless, lack of standardisation and information regarding the extent of LND, defined by Kondo et al only, clearly limited the later studies. The potential benefit of LND in staging is more important in higher-stage disease and also influenced by the extent of LND [16,19].

The potential impact of LND on survival is a controversial issue. The original report by Miyake et al [18] suggested a limited impact of LND, restricted to patients with no evidence of LVI. However, recently published data from other groups, supported by a large multicentre study [16], indicate a direct impact on CSS, although this benefit appears to be limited to ≥pT2 disease of the renal pelvis and when the LND is performed according to an anatomical template-based approach. An equally important unresolved question is whether the number of nodes removed correlates with such an impact. Roscigno et al [16] reported a cut-off of eight LNs to improve CSS, identifying the number of nodes as an independent factor for CSS. The impact of the number of nodes in cN0 disease has also been assessed in a contemporary study by Yoo et al [29] made public while revising the current manuscript. On multivariate analysis, the number of resected LNs and pathological T stage were significant predictors of LN metastasis. Interestingly, performance of LND was not associated with CSS or OS. In this retrospective study, the extension of the LND was not defined, and the authors conclude that the insufficient extension was responsible for those results [29]. Kondo et al [21] demonstrated that, in addition to the number of LNs removed, the anatomical template-based approach was responsible for such an impact, demonstrating improved CSS in high-stage disease, statistically significant between the NoLND and CLND groups, but not the ILND group. This was further evidenced by this group, demonstrating a beneficial effect of T-BLND on CSS and identified CLND as an independent factor for CSS in high-stage renal pelvic UTUC [14]. However, CLND did not show significant survival differences for tumours located in the ureter. The authors discussed several potential explanations for these findings. Ureteral tumours may simply represent a worse type of disease, with more aggressive behaviour. However, limitations or inaccuracies of the template used could have rendered the LND insufficient for tumours in this location. Kondo and Tanabe [30] reported that 14% of primary LN metastases were located in presacral nodes. At the time of reviewing the current manuscript, this group has published online (ahead of print) new results demonstrating a survival benefit of anatomical T-BLND for treatment of proximal ureteral tumours. Furthermore, recent findings by a multi-institutional mapping study have demonstrated that distal ureteral tumours are more likely to spread cranially than initially expected [31]. In view of these findings, one can speculate that LND may have an even greater beneficial impact on CSS in tumours of the distal ureter.

One important issue in the management of high-risk disease is the role of neoadjuvant and adjuvant chemotherapy. A recently published study compared 31 patients receiving cisplatin-based neoadjuvant chemotherapy with 81 historic controls. There was a significant increase in OS and CSS, with 5-yr rates of OS and CSS, with a 5-yr OS and CSS (80.2% and 90.1% vs 57.6%, $p = 0.204$ and 0.0015, respectively) [32]. The same group has also demonstrated the efficacy of sequential neoadjuvant chemotherapy with ifosfamide, doxorubicin, and gemcitabine, followed by cisplatin, gemcitabine, and ifosfamide in patients with locally advanced UTUC [33]. Those results agree with other studies, which were reported in the 2014 systematic review and meta-analysis by Leow et al [34]. Importantly, none of the

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studies included in our analysis has assessed this issue because either neoadjuvant therapy was never used or the information was lacking. As the included studies predated the recent trends towards a wider use of neoadjuvant chemotherapy in UTUC, the former hypothesis is more likely [34].

The use of adjuvant chemotherapy is more controversial and limited in many cases by postnephrectomy renal impairment and its minimal impact on survival [34]. Five studies comparing NoLND versus LND reported on the use of adjuvant chemotherapy [14–17,19], with significant differences in its use, favouring the LND group, in two studies [14,16]. Similarly, two studies comparing CLND versus ILND versus NoLND demonstrated a bias in favour of the CLND group [20,21]. Nevertheless, prospective evidence by Kondo et al [14] has demonstrated that adjuvant chemotherapy does not influence either CSS or RFS on univariate analysis in patients with renal pelvic UTUC. Moreover, most of the included studies adjusted for this possible confounder [19–21].

Another important issue for the widespread implementation of routine LND is the potential complications associated with such a procedure, which may cause morbidity and potentially mortality, as seen in other tumours. However, the evidence regarding such complications is scarce in the available literature. Only two papers refer to the potential complications of performing LND at the time of RNU. Brausi et al [17] reported no mortality within the first 30 d after surgery, while Kondo et al [14] did not find a significant increase in morbidity when comparing CLND versus NoLND in patients with renal pelvic or ureteral tumours. In that study, 90 d perioperative complications were reported in 13.2% of patients with renal pelvis disease, with 5.2% experiencing grade 3b complications. In ureteral tumours, the incidence of complications was 15.3%. The incidence of lymphorrhoea or chyle fistula was 5.2% in patients who underwent LND. T-BLND did not significantly increase the incidence of all grade complications during RNU in patients with renal pelvic or ureteral cancer. These findings agree with the incidence reported by Abe et al [35] using a similar template, and also by a laparoscopic and robotic approach [36]. These data regarding LND complications should be considered with caution given that their reporting was not in line with the current guidelines [37].

Regarding the potential morbidity of LND, it is important to emphasise that the included studies refer to open LND. The laparoscopic approach has been demonstrated to be safe [38], and it will be interesting to see the outcomes of larger laparoscopic and, in particular, robot-assisted LND. We should be prepared to accept some procedure-related morbidity as we do in the management of other malignancies, as long as there is an acceptable rate of complications and a clear overall benefit for the patient.

Another issue for discussion is the timing of LND. All the studies in our review referred to cases with LND at the time of RNU. However, this implies some potentially negative consequences. Longer operating time, with technical issues and difficulties, potentially results in less efficient dissection. Moreover, we are all familiar with the limitations of clinical staging, the risk of over- and understaging, and the risk of multifocality. Indeed, staging and definition of cN0/N+ disease were not standardised across studies and there was some contamination in some series [21]. More importantly, the finding of pN+ disease in low-stage tumours is rare (0–2.2%) [18,16]. These can result in an unnecessary LND for a low-stage tumour, in not performing LND for an understaged tumour, or using an insufficient template in a multifocal tumour. In this regard, one needs to take into account that some published outcomes are analysed based on pN status and not cN status, which could be even more clinically relevant in terms of the day-to-day practice guidance.

To the best of our knowledge, this study represents the most robust and up-to-date systematic review assessing the oncological effectiveness of NoLND versus CLND versus ILND in patients undergoing RNU for UTUC. However, the findings of this review are limited by the scarcity of published data, low quality of the published studies, and selection bias. Hence, an important drawback of the present systematic review is the inclusion of only nine series, including four coming from overlapping cohorts of patients. Another limitation of our systematic review is that the largest series from Roscigno et al [16] accounted for over 60% of all included patients. A further shortcoming is the primary end point chosen (CSS) that might be a matter of debate in such heterogeneous population. We decided to exclude studies with cN+ patients despite the existing controversies regarding the value of LN enlargement on preoperative imaging [39]. However, we believe that imaging findings might have guided the decision to perform LND or not in some series, and their inclusion would have introduced a major selection bias. Nevertheless, we attempted to provide at least a moderate level of evidence by including only comparative studies according to the Cochrane Collaboration principles.

The current systematic review highlights the lack of high-quality clinical evidence comparing oncological outcomes of LND at the time of RNU in UTUC patients. Pending large prospective randomised trials, we are responsible for gathering as much information as possible and sharing it with large ongoing international registries such as the Central Research Office of the Endourological Society UTU Registry and the National Cancer Data Base. Future analysis of these registries could then produce clinically relevant conclusions.

4. Conclusions

UTUC represents an infrequent malignancy that carries a poor prognosis, with a high risk of lymphatic spread and subsequent disease progression. The role of LND in UTUC remains controversial due to the lack of robust published evidence, standardisation, and prospective randomised trials. Based on available data, some conclusions can be drawn: the incidence of pN+ in cN0 $\geq$pT2 patients ranges from 14.3% to 40%. LND improves tumour staging. LND improves CSS in $\geq$pT2 UTUC tumours of the renal pelvis and the risk of regional LN metastases, while this benefit

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was not found in ureteral tumours. LND should be performed according to an anatomical template.

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Study concept and design: Dominguez-Escrig, Seisen, Peyronnet, Rouprêt, Bruins, Babjuk.
Acquisition of data: Dominguez-Escrig, Seisen, Peyronnet, Bruins, Yuan.
Analysis and interpretation of data: Dominguez-Escrig, Peyronnet, Seisen, Bruins, Rouprêt.
Drafting of the manuscript: Dominguez-Escrig, Seisen, Peyronnet, Rouprêt.
Critical revision of the manuscript for important intellectual content: Babjuk, Böhle, Compérat, Zigeuner, Sylvester, Burger, Mostafid, van Rhijn, Gontero, Palou, Shariat.
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Appendix A. Supplementary data

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