Role of lymph node dissection in the management of upper tract urothelial carcinomas: a meta-analysis

Runqi Guo†, Yuze Zhu†, Gengyan Xiong, Xuesong Li, Kai Zhang* and Liqun Zhou*

Abstract

Background: Lymph node dissection (LND) is not routinely performed during radical nephroureterectomy (RNU) in upper tract urothelial carcinomas (UTUC) and the role of LND has been controversial. We aim to investigate whether patients with LND had improved survival in UTUC patients.

Methods: We performed a systematic literature search of PubMed, Embase, and Cochrane library for citations published prior to January 2016, describing LND performed among UTUC patients and conducted a standard meta-analysis of survival outcomes.

Results: Eleven eligible studies containing 7516 patients satisfied the inclusion criteria. Pooled HRs for cancer-specific survival (CSS) and recurrence-free survival (RFS) were 1.17 (P = 0.18) and 1.33 (P = 0.19) respectively. However, the patients in the LND group had more advanced tumour stages and grades (P < 0.001). Further subgroup analysis showed that among muscle-invasive UTUC patients, the pooled HR for CSS and RFS were 1.10 (P = 0.42) and 0.92 (P = 0.72) respectively. Besides, no difference was found in CSS and RFS between pN0 and pNx individuals in overall populations and in patients with muscle-invasive UTUC, while pN+ patients had significantly worse prognosis when compared to pN0 patients.

Conclusions: LND during RNU allows more accurate staging and prediction of survival, but it remains uncertain whether LND independently improves survival in patients with UTUC. However, standard use of LND should be further investigated in a multi-center, prospective evaluation to obtain a definitive statement regarding this matter.

Keywords: Lymph node dissection, Recurrence, Survival, Upper urinary tract, Urothelial carcinoma

Background

Urothelial carcinomas are the fourth most common tumors [1]. However, upper tract urothelial carcinomas (UTUC) are comparatively uncommon compared to bladder cancer and occupy only 5–10% of urothelial carcinomas [2, 3]. Approximately 30% of patients suffered from muscle-invasive UTUC at presentation and the incidence of lymph node metastasis ranges from 30% to 40% at surgery [4, 5].

Radical nephroureterectomy (RNU) with bladder cuff resection and regional lymph node dissection (LND) is the backbone of management [3, 6, 7]. Generalizing results from previous bladder cancer researches [8–13], it seems reasonable to believe that LND in conjunction with RNU may provide not only utile staging and prognostic information but also a therapeutic benefit in selected patients with UTUC. Nevertheless, the therapeutic benefit of LND in improving survival remains controversial [14–16].

For these reasons, we systematically reviewed the published studies and performed a meta-analysis of studies in which data were reported for the treatment of LND to assess whether patients who achieved LND had improved cancer-specific survival (CSS) or recurrence-free survival (RFS) compared with patients who did not achieve LND, as a means for providing data for standardizing the indication of LND and assisting in creating a better management strategy for UTUC.
Methods
Search strategy
We systematically reviewed PubMed, Embase, and Cochrane library for citations published prior to January 2016, describing LND performed among patients with UTUC. The search strategy included the terms: lymphadenectomy or lymph node excision or lymphatic metastases, and upper tract urothelial neoplasms or upper tract urothelial cancer or transitional cell carcinoma of the upper urinary tract. Two authors independently reviewed article titles and abstracts for eligibility, and divergences were settled by consensus.

Inclusion and exclusion criteria of trials
Studies were included if they met all the following criteria: (1) prospective randomized studies or well-designed non-randomized controlled experiments; (2) studies analyzing the relationship between LND and UTUC prognosis; (3) clearly described outcome assessment by representing it in CSS or RFS; (4) sufficient survival information with hazard ratios (HR) and corresponding 95% confidence interval (CI), or Kaplan–Meier curves comparing survival among pathologic subgroups that were stratified according to LN status (pN0, negative node; pNx, skipping LND; pN+, positive node) or between LND and NLND; and (5) demographics and pathologic characteristics of patients were stratified according to LN status or according to the presence or absence of LND. Studies were excluded if they met one of the following criteria: (1) the article was a review or meta-analysis; (2) No available data could be able to extracted from the previously published studies; (3) the article deal with recurrent UTUC, metastatic carcinoma, previous or concurrent invasive bladder tumors or neoadjuvant chemotherapy; and (4) (potentially) overlapping study populations were reported for the same outcome.

Data extraction
All studies identified were independently reviewed by two reviewers. Titles and abstracts were screened for initial inclusion and final agreement on study inclusion was made by discussion and consensus with other authors. Two reviewers extracted data from all the included studies independently. Divergences were settled through consensus.

Quality assessment
The quality of the cohort studies was evaluated using the modified Newcastle-Ottawa Scale, which met the demands of this study [17]. This scale assesses risk in three domains: patient selection, comparability of LND and NLND groups and assessment of outcome (Table 1). To compare the two cohorts, we concentrated on the following variables that had been identified as independent predictors in previous multivariate studies: age, gender, tumor grade and tumor stage [18–21]. Each study was assessed by two reviewers independently. Any divergences were settled by discussion or through arbitrament by a third reviewer if no agreement could be reached.

Data analysis and synthesis
We use log HR and the variance as the summary outcome measure from all trials in the meta-analysis. For each trial, HR with the 95% CI of the survival rate was derived and calculated using either the fixed-effects model or the random-effects model [22]. Chi-square test was used to assess the heterogeneity between studies. For P values less than 0.1, the assumption of homogeneity was deemed invalid. Therefor, we calculated pooled estimates using random effects modeling, which provides more conservative estimates than fixed effects modeling when heterogeneity was present.

Publication bias is considered as a concern for meta-analyses. In our study, publication bias was assessed by funnel plots and Egger’s regression [23]. Review manager version 5.3 (Cochrane Collaboration, Oxford, UK) was used for data analysis. A P value of less than 0.05 was considered statistically significant.

Table 1 Newcastle-Ottawa quality assessment scale

| Check list | Selection |
| --- | --- |
| How representative was the control group (lymph node dissection) in comparison with the general elderly population for transitional cell carcinoma of the upper urinary tract? (if yes, one point; no point, if the patients were selected or selection of group was not described) | Group comparable for the grade of tumor, clinical TNM staging system (if yes, two points; one point was assigned, if one of these two characteristics had differences; no star was assigned, if the two groups differed) |
| How representative was the research group (non-lymph node dissection) in comparison with the elderly population for transitional cell carcinoma of the upper urinary tract? (if data from the same community as the control group, one point; no point, if drawn from a different source or selection of group was not described) | Group comparable for age, gender (if yes, two points; one star was assigned, if one of these two characteristics had differences; no point was assigned, if the two groups differed) |
| Assignment for treatment: any detail report? (if yes, one point) | Comprehensively evaluated the outcome? (yes, one point for information ascertained by record or International Classification of Diseases; no point, if this information was not reported) |
| Adequacy of follow-up (one star, if follow-up > 90%) | Adequacy of follow-up (one star, if follow-up > 90%) |
Results
Study identification and quality assessment
A total of 658 studies were identified. After excluding duplicates, 144 articles remained, 127 of which were excluded: 106 were apparent irrelevant studies, 4 were case, series/case reports, and 17 were letters/reviews/comments. 17 were reviewed in depth, and a full examination of the text was performed. Five studies were excluded because of insufficient outcome and one was excluded due to potentially overlapping study populations. At last, 11 studies involving 7516 UTUC patients were included into this meta-analysis [14, 15, 16, 24–30, 31] (Fig. 1) (Table 2).

The quality assessment of included cohort studies was performed using the modified Newcastle-Ottawa Scale. Studies that scored > 7 were considered as having low risk of bias, scores of 5–7 indicated moderate risk of bias, and scores of < 5 indicated high risk of bias, and the total scores are shown in Table 3. Most studies were deemed to be of moderate risk of bias and we only scored 3 of 11 studies as having low risk of bias. Commonly identified concern was the comparability of LND and NLND groups, especially regarding tumor grade and TNM staging.

Meta-analysis results
Cancer-specific survival
Of the 10 studies that referred to CSS, there was significant heterogeneity among them ($I^2 = 80\%$, $\chi^2 = 45.96$, $P < 0.00001$). Thus, a random-effects model was used to calculate the pooled HR and corresponding 95% CI. No statistically significance was found between the LND group and the NLND group (HR = 1.17, 95% CI: 0.93–1.48, $P = 0.18$) (Fig. 2 A1). Besides, patients with pN0 did not have better CSS compared with those with pNx (HR = 0.99, 95% CI: 0.81–1.22, $P = 0.95$) with significant heterogeneity ($I^2 = 94\%$, $\chi^2 = 35.97$, $P < 0.00001$) (Fig. 2 A2), while patients with pN+ showed poor CSS compared with those with pN0 (HR = 3.38, 95% CI: 1.94–5.89, $P < 0.00001$) with significant heterogeneity ($I^2 = 93\%$, $\chi^2 = 71.90$, $P < 0.00001$) (Fig. 2 A3).

To explore the source of apparent heterogeneity, we compared the differences in tumor stage and tumor grade between the groups, thereby demonstrating the features between the groups using Chi-square tests and Fisher’s exact tests for categorical variables (Table 4). The results showed that there was remarkable significant difference in tumor stage and tumor grade between the LND group and NLND group ($P < 0.001$), which might have significant association with the heterogeneity.

Recurrence-free survival
Significant heterogeneity was observed in the four studies that focused on RFS ($I^2 = 89\%$, $\chi^2 = 26.57$, $P < 0.00001$), hence we utilized the random-effects model. The pooled HR for RFS was 1.33 (95% CI: 0.87–2.06, $P = 0.19$), which indicate that LND was not associated was better RFS in patients with UTUC (Fig. 2 B1). Meanwhile, in consideration of pN0/pNx, no significant difference in RFS between pN0 and pNx was found (HR = 0.98, 95% CI: 0.62–1.55, $P = 0.93$) and there was significant heterogeneity among them ($I^2 = 85\%$, $\chi^2 = 19.82$, $P = 0.0002$) (Fig. 2 B2). In contrast, pN+ showed poor RFS compared with those pN0 (HR = 3.46, 95% CI: 2.00–5.97, $P < 0.0001$) with significant heterogeneity ($I^2 = 78\%$, $\chi^2 = 13.95$, $P < 0.003$) (Fig. 2 B3).

Subgroup analysis
We performed subgroup analysis according to pT statuses, among patients with muscle-invasive UTUC. Data for CSS in patients with muscle-invasive UTUC were reported in four studies, and there was heterogeneity among those studies ($I^2 = 63\%$, $\chi^2 = 8.04$, $P = 0.05$); hence, we utilized the random-effects model. However, no statistically significance was found between the two groups (HR = 1.10, 95% CI: 0.88–1.37, $P = 0.42$) (Fig. 2 C1).

Additionally, the results of the subsequent analyses showed no difference in RFS between the LND group and the NLND group among muscle-invasive UTUC individuals (HR = 0.92, 95% CI: 0.58–1.46, $P = 0.72$) and there was relatively high heterogeneity in this subgroup ($I^2 = 88\%$, $\chi^2 = 16.48$, $P = 0.0003$) (Fig. 2 C2).

Furthermore, among the patients with muscle-invasive UTUC, no significant difference between pN0
| Study | Type of study | Gender | Patients (n) | Follow-up median (month) | Median age (year) | Node status (overall) / LND or NLND | Extent of LND | Node status | Tumor location | Pathologic tumor stage | Tumor grade | Outcome |
|-------|---------------|--------|--------------|--------------------------|------------------|-----------------------------------|--------------|------------|----------------|------------------------|-------------|---------|
| Kondo T et al 2014 [31] | Prospective | Male 112 Female 54 | 166 | 23.7 | 72.4 | pN0 69 pNx 86 pN+ 11 | Renal pelvis tumor: LN from the renal hilar to the inferior mesenteric artery. Tumor of upper 2/3 ureter: LN from the renal hilar to the aortic bifurcation. Tumor of lower 1/3 ureter: the ipsilateral pelvic LN | Renal pelvis 90 Ureter 76 | pST1 62 pT2 27 pT3 72 pT4 5 | Low 71 High 95 | CSS |
| Ouzzane A et al 2013 [16] | Retrospective | Male 484 Female 228 | 714 | 27.0 | 70.0 | pN0 204 pNx 460 pN+ 50 | NA | Renal pelvis 388 Pelvis+ureter 90 Multifocal 236 | pTa/Tis 107 pT1 168 pT2 74 pT3 224 pT4 39 | G1 71 CSS, RFS G2 244 G3 399 |
| Mason RJ et al 2012 [15] | Retrospective | Male 654 Female 375 | 1029 | 19.8 | 68.6 | pN0 199 pNx 753 pN+ 77 | NA | Renal pelvis 538 Pelvis+ureter 213 Ureter 250 | pTa/Tis 108 pT1 463 pT2 160 pT3 244 pT4 54 | Low 340 CSS, RFS High 689 |
| Burger M et al 2011 [30] | Retrospective | Male 542 Female 243 | 785 | 34.0 | 68.0 | pN0 136 pNx 595 pN+ 54 | Hilar & regional LN adjacent to ipsilateral great vessel | NA | pTa 165 pTa 10 pT1 196 pT2 148 pT3 222 pT4 44 | G1 100 CSS, RFS G2 226 G3 459 |
| Abe T et al 2010 [29] | Retrospective | Male 195 Female 98 | 293 | NA | 69.2 | pN0 130 pNx 141 pN+ 22 | Tumor of renal pelvis tumor & upper 2/3 ureter: Hilar & regional LN adjacent to ipsilateral great vessel Lower ureteral tumor: ipsilateral pelvic LN | Renal pelvis 157 Pelvis+ureter 24 Ureter 112 | pTa/Tis 53 pT1 66 pT2 56 pT3 101 pT4 17 | Low 185 High 108 | RFS |
| Lughezzani et al 2010 [14] | Retrospective | Male 1666 Female 1158 | 2824 | 43.0 | 72.0 | pN0 1835 pNx 747 pN+ 242 | NA | Renal pelvis 1913 Ureter 911 | pT1 867 pT2 500 pT3 584 pT4 873 | G1 156 CSS G2 935 G3 1234 G4 499 |
| Rosigno M et al 2009 [28] | Retrospective | NA | 1130 | 45.0 | 69.1 | pN0 412 pNx 578 pN+ 140 | Renal pelvis and proximally ureteral tumor: LN from the renal hilar to the inferior mesenteric artery Mid and lower ureteral tumors: LN from the renal hilar to the bifurcation of the common iliac artery and ipsilateral pelvic LN | NA | pT1 317 pT2 269 pT3 4544 | Low 291 High 839 | CSS |
| Kondo T et al. 2007 [27] | Retrospective | Male 113 Female 56 | 169 | 37.3 | 67.5 | LND 81 NLND 88 | Renal pelvis tumor: LN from the renal hilar to the inferior mesenteric artery Tumor of upper 2/3 ureter: LN from the renal hilar to the aortic bifurcation | Renal pelvis 100 Upper ureter 9 | ≤pST1 45 pT2 34 pT3 79 pT4 9 | NA CSS |
| Study                      | Type of study | Gender | Patients (n) | Follow-up median (month) | Median age (year) | Node status (overall)/ LND or NLND | Extent of LND | Tumor location | Pathologic tumor stage | Tumor grade | Outcome |
|---------------------------|---------------|--------|--------------|--------------------------|-------------------|----------------------------------|--------------|----------------|----------------------|-------------|---------|
| Secin FP et al. 2007 [26] | Retrospective | Male 166 Female 86 | 252 | 37.2 | 69.0 | pN0 105 pNx 119 pN+ 28 | NA | Tumor of lower 1/3 ureter: ipsilateral pelvic LN | Midureter 20 Lower ureter 40 | NA | pTa 71 pTis 12 pT1 46 pT2 35 pT3 72 pT4 8 | G1 64 G2 38 G3 143 | CSS |
| Brausi MA et al 2007 [25] | Retrospective | Male 59 Female 23 | 82 | 64.7 | LND 67.8 NLND 67.1 | LND 40 NLND 42 | Renal pelvis and upper ureteral tumor: LN from the renal hilar to the inferior mesenteric artery Mid ureteral tumors: LN from the renal hilar to the bifurcation of the common iliac artery Lower ureteral tumor: ipsilateral pelvic LN | Renal pelvis 47 Pelvis+ureter 7 Ureter 28 | pT2 38 pT3 36 pT4 8 | G1 44 G2 38 | G3 | CSS |
| Miyake H et al. 1998 [24] | Retrospective | Male 53 Female 19 | 72 | 49 | LND 64 NLND 67 | LND 35 NLND 38 | Renal pelvis and upper ureteral tumor: LN from the renal hilar to the inferior mesenteric artery Mid ureteral tumor: LN from the renal hilar to the bifurcation of the common iliac artery Lower ureteral tumor: ipsilateral pelvic LN | Renal pelvis 40 Pelvis+ureter 3 Ureter 29 | pTa 11 pT1 25 pT2 18 pT3 14 pT4 4 | G1 12 G2 33 | G3 37 | CSS |

LND Lymph node dissection, NLND Non-LND, NA Not available, pN+ Positive lymph node, pN0 Negative lymph node, pNx Not undergo lymph node dissection, CSS cancer-specific survival, RFS recurrence-free survival
and pNx was found in CSS and RFS (HR = 0.97, 95% CI: 0.64–1.47, P = 0.87; and HR = 0.97, 95% CI: 0.64–1.47, P = 0.87, respectively) and there was significant heterogeneity ($I^2 = 94\%$, $Chi^2 = 35.97$, $P < 0.00001$; and $I^2 = 89\%$, $Chi^2 = 18.80$, $P < 0.00001$, respectively) (Fig. 2 C3 & 2C4). However, patients with pN+ showed poor CSS and RFS in comparison with those with pN0 (HR = 3.27, 95% CI: 2.83–3.78, P < 0.00001; and HR = 2.10, 95% CI: 1.05–4.20, P = 0.0002, respectively) (Fig. 2 C5and C6).

**Publication bias**

The publication bias was detected using a funnel plot of the meta-analysis result. The basic symmetry of the funnel plots suggested that there was no obvious publication bias (Fig. 3). The Egger’s test for CSS and RFS did not show any evidence of publication bias.

**Discussion**

Radical cystectomy with pelvic LND for muscle-invasive bladder cancer is relatively standardized because it improves tumor staging and survival of patients [32, 33]. However, potential benefit of LND during RNU on survival for UTUC is still controversial [15, 30]. On the basis of the latest European guidelines on UTUC, LND should be performed in conjunction with RNU not only for better tumor staging but also for prognosis improvement [3]. Nevertheless, this recommendation is only Level III evidence. Thus, we reviewed the published studies and conducted a meta-analysis to clarify the prognostic value of LND in patients with UTUC.

In the present research, 11 studies were eligible and the HRs of cumulative survival rates were summarized quantitatively. Our analysis revealed that pN+ patients had significantly worse prognosis when compared to pN0 patients. The same results were observed when restricting the analyses to patients with muscle-invasive carcinomas, who should, anyway, be systematically considered for staging LND in light of this growing body of data.

However, no difference was found in survival or disease recurrence when comparing pN0/pNx individuals and the LND/NLND groups. The sample size of the included studies could explain these results. Most of the early years studies include small numbers of patients (less than 200), while larger series (more than 1000) with more events only emerged recently. Besides, the decision to perform LND was left to the discretion of the surgeon, it is possible that those NLND patients had less aggressive disease than LND patients, and that a true benefit to LND does exist. An increased risk of cancer-related death is usually related to higher tumor stage and grade. In this comparison, there was no significant difference in CSS and RFS between the LND group and the NLND group, which may reversely suggest the possible therapeutic value of LND for patients with more aggressive tumors. Nevertheless, the results remained no significant difference when controlling for tumor stage.

Conversely, in a review by Kondo and Tanabe [34], it was highlighted that when the regional nodes were completely dissected, the patients with the advanced stage had significantly higher survival compared with those without LND.

Interestingly, pNx was not associated with poor CSS and RFS in patients with muscle-invasive carcinomas and in overall population. Several explanations may account for our results. First, pNx individuals were most likely identified by their surgeons as low risk for nodal metastases. It is also possible that pNx individuals may harbor micrometastatic lymph node deposits, which could be either destroyed or removed during the surgery, without being identified as pN1 by the pathologist. Furthermore, the lack of standardized anatomical limits

**Table 3** Assessment for quality of included studies

| Study                  | Selection | Comparability | Outcome assessment | Score |
|------------------------|-----------|---------------|--------------------|-------|
| Kondo T et al 2014 [31]| 1         | 2             | 1                  | 7     |
| Ouzzane A et al 2013 [16]| 1         | 1             | 0                  | 7     |
| Mason RJ et al 2012 [15]| 1         | 1             | 0                  | 6     |
| Burger M et al 2011 [30]| 1         | 1             | 0                  | 6     |
| Abe T et al 2010 [29]  | 1         | 1             | 0                  | 7     |
| Lughezzani et al 2010 [14]| 1         | 1             | 0                  | 7     |
| Roscigno M et al 2009 [28]| 1         | 1             | 0                  | 6     |
| Kondo T et al 2007 [27]| 1         | 1             | 2                  | 8     |
| Secin FP et al 2007 [26]| 1         | 1             | 1                  | 7     |
| Brausi MA et al 2007 [25]| 0         | 1             | 2                  | 8     |
| Miyake H et al 1998 [24]| 1         | 1             | 2                  | 8     |
and indication for the LND could account for our results: some patients certainly had very limited dissection and unsuitable for tumor location, leading to a wrong histological report of pN0 stage even though they had nodal metastasis not including in the LND.

It is noteworthy that 49.0% RNU patients were staged as pNx in our studies. In 2009, Roscigno et al. pointed out that patients with pN0 disease had a better prognosis than pNx disease in patients with muscle-invasive carcinomas [28]. It is conceivable that, despite a higher pNx rate at tertiary care centers, the extent of LND in those in whom it was performed was substantially greater than the LND extent in the community. Under this premise, a more important stage migration towards

![Forest plot comparing survival and subgroup analysis of different pT statuses.](image)

**Table 4** Chi-square tests for two groups

| Variable | LND (n, %) | NLND (n, %) | P value |
|----------|------------|-------------|---------|
| **Tumor stage** | < 0.001 | | |
| ≤T1 | 1210 (31.3) | 1684 (46.2) | |
| T2 | 722 (18.7) | 637 (17.5) | |
| T3 | 1204 (31.2) | 990 (27.2) | |
| T4 | 726 (18.8) | 335 (9.2) | |
| **Tumor grade** | < 0.001 | | |
| Low grade or ≤ G2 | 1610 (35.4) | 1281 (34.2) | |
| High grade or > G2 | 2936 (64.6) | 1682 (65.8) | |

LND lymph node dissection, NLND non LND and indication for the LND could account for our results: some patients certainly had very limited dissection and unsuitable for tumor location, leading to a wrong histological report of pN0 stage even though they had nodal metastasis not including in the LND.

It is noteworthy that 49.0% RNU patients were staged as pNx in our studies. In 2009, Roscigno et al. pointed out that patients with pN0 disease had a better prognosis than pNx disease in patients with muscle-invasive carcinomas [28]. It is conceivable that, despite a higher pNx rate at tertiary care centers, the extent of LND in those in whom it was performed was substantially greater than the LND extent in the community. Under this premise, a more important stage migration towards
true pN0 status may have occurred at tertiary care centers than in the current population-based series [14]. Taken together, our findings suggest that pNx individuals have no better prognosis than pN0 individuals.

Without standardized criteria for who should receive LND and how extensive LND should be, comparisons between series proved to be challenging. It was reported that the patients with incomplete LND in showed lower survival than those with complete LND, which reached statistical significance. Five-year CSS in the patients with pT2 or higher and pT3 or higher was 77.9% and 73.2% in the patients with complete LND, but just 54.0% and 43.7% in those with incomplete LND and 59.0% and 47.3% in those with NLND [34].

The most important finding of our study is that LND patients had no worse prognosis than NLND patients, especially in those with muscle-invasive carcinomas. According to a recent review, carrying out LND for UTUC is unlikely to be time-consuming and to increase the risk of major complications [34]. Although the current quality of evidence is generally not high, which may lead to biased and uncertain results, it might still suggest that the role of LND in UTUC is of importance, as UTUC is likely to simulate the biological behavior of bladder cancer because of the same histology among the two diseases.

Limitation should also be considered. First, the sources of the publications were limited, thus potentially introducing inevitable publication bias. Second, although 11 eligible studies involving 7516 patients were included in this meta-analysis, most of them were retrospective studies and the sample sizes of some selected studies are small, which might render the results less reliable. Third, marked heterogeneity of studies was seen in pooled-analysis of CSS and RFS. Furthermore, 7 of the 11 included studies provided the extent of LND, but the indication and extent of LND were not standardized. Last but not the least, as the included studies spanned a 10-year interval, the year in which the surgery occurred could be associated with different survival rates due to better imaging, earlier diagnosis and improved perioperative strategies of care. In the future, the role of LND should be further examined by validating templates of regional lymph nodes, and by prospective studies with larger numbers of patients. Then, we will discuss whether LND can be a standard treatment for UTUC.

Conclusions
LND during RNU allows more accurate staging and prediction of survival, but it remains uncertain whether LND independently improves survival in patients with UTUC. However, standard use of LND should be further investigated in a multi-center, prospective evaluation to obtain a definitive statement regarding this matter.

Abbreviations
CI: Confidence interval; CSS: Cancer-specific survival; HR: Hazard ratios; LND: Lymph node dissection; RFS: Recurrence-free survival; RNU: Radical nephroureterectomy; UTUC: Upper tract urothelial carcinomas

Acknowledgements
This work was supported by grants from the Collaborative Research Foundation of Peking University Health Science Center and National Taiwan University, College of Medicine (BMU20120316), Natural Science Foundation of Beijing (7152146) and the Clinical Features Research of Capital (No.Z151100004015173).

Ethic approval and consent to participate
The study was not primary research involving humans or animals but was a secondary analysis of human subject data available in the public domain.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Authors’ contributions
GRQ participated in data collection and management, data analysis and manuscript writing. ZYZ participated in data analysis and manuscript writing. XGY participated in data collection and manuscript writing. LXS participated in project development, critical revision and manuscript editing. ZK participated in project development, critical revision and supervision. ZLQ participated in project development, critical revision and supervision. All the authors approved the final manuscript.
Competing interest
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 11 October 2016 Accepted: 13 March 2018
Published online: 10 April 2018

References
1. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2009). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015; 65:5–29.
3. Roupért M, Babjuk M, Compérat E, Zigeuner R, Sylvester RJ, Burger M, et al. European Association of Urology guidelines on upper urinary tract urothelial carcinoma: 2015 update. Eur Urol. 2015;68:686–79.
4. Corrado F, Ferri C, Mannini D, Corrado G, Bertoni F, Bacchini P, et al. Transitional cell carcinoma of the upper urinary tract: evaluation of prognostic factors by histopathology and flow cytometric analysis. J Urol. 1991;145:1159–63.
5. Schatteman P, Chatzopoulos C, Assemacher C, De Visscher L, Jorion JL, Abdel-Latif M, Abol-Enein H, El-Baz M, Ghoneim MA. Nodal involvement in pelvic lymphadenectomy performed at radical cystectomy: can we establish its impact on outcome in patients diagnosed with bladder cancer. Eur Urol. 2010;58:517–23.
6. Donnell MA. Extent of pelvic lymphadenectomy and node dissection. J Urol. 2002;167:1295–8.
7. Leissner J, Hohenfellner R, Thüröff JW, Wolf HK. Lymphadenectomy in patients with transitional cell carcinoma of the bladder: significance for staging and prognosis. BJU Int. 2000;85:17–23.
8. Herr HW, Bochner BH, Babjuk M, Donat SM, Reuter VE, Bajorin DF. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. J Urol. 2002;167:1295–8.
9. Konety BR, Joslyn SA, O’Donnell MA. Extent of pelvic lymphadenectomy and its impact on outcome in patients diagnosed with bladder cancer: analysis of data from the surveillance, epidemiology and end results program data base. J Urol. 2003;169:946–50.
10. Abdel-Latif M, Abol-Enen H, El-Baz M, Ghoneim MA. Nodal involvement in bladder cancer cases treated with radical cystectomy: incidence and prognosis. J Urol. 2004;172:85–9.
11. Lennsen S, Scharf R, Dallaglio G, Bocher BH, Blazer V, et al. Laparoscopic nephroureterectomy for upper urinary tract transitional cell carcinoma: results of a Belgian retrospective multicentre survey. Eur Urol. 2007;51:1633–8.
12. Cornu JN, Rouprêt M, Babjuk M, Compérat E, Zigeuner R, Sylvester RJ, et al. NCCN Clinical practice guidelines in oncology: bladder cancer. Including upper tract tumors and urothelial carcinoma of the prostate. Version 2.2015, National Comprehensive Cancer Network Web site http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed May 2015.
13. Kondo T, Hara I, Takagi T, Kodama Y, Hashimoto Y, Kobayashi H, et al. Impact of lymphadenectomy in urothelial carcinoma of the upper urinary tract: multinstitutional relapse analysis and immunohistochemical re-evaluation of negative lymph nodes. Eur J Surg Oncol. 2010;36:1085–91.
14. Burger M, Shariat SF, Feltcheck HM, Martinez-Salamanca JL, Matsumoto K, Cromedick TF, et al. No overt influence of lymphadenectomy on cancer-specific survival in organ-confined versus locally advanced upper urinary tract urothelial carcinoma undergoing radical nephroureterectomy: a retrospective international, multi-institutional study. World J Urol. 2011;29:465–72.
15. Holmer M, Bendahl PO, Davidson T, Gudjonsson S, Månsson W, Liedberg F. Extended lymph node dissection in patients with urothelial cell carcinoma of the bladder: can it make a difference? World J Urol. 2009;27:521–6.
16. Kondo T, Tanabe K. Role of lymphadenectomy in the management of urothelial carcinoma of the bladder and the upper urinary tract. Int J Urol. 2012;19:710–21.