Current Status of Lymphadenectomy During Radical Nephroureterectomy for Upper Tract Urothelial Cancer—Yes, No or Maybe?

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Abstract

While pelvic lymphadenectomy during radical cystectomy for bladder cancer is a well-established standard of care, the same does not hold true for upper tract urothelial carcinoma (UTUC). Indeed, a template-based lymphadenectomy is rarely, if ever, performed in conjunction with radical nephroureterectomy at most centres across the globe. While multiple studies have explored the staging and therapeutic role of lymphadenectomy in cases of UTUC, there remain large gaps in our understanding of the indications, extent and safety of this procedure as an adjunct to nephroureterectomy. This article elucidates the current knowledge on outcomes, benefits and complications of template-based lymphadenectomy during radical nephroureterectomy for UTUC. We also explore the current evidence-based guidelines on this controversial topic.

Keywords Lymphadenectomy · Radical nephroureterectomy · Urothelial cancer

Introduction

Upper tract urothelial carcinoma (UTUC) represents approximately 5–10% of all urothelial malignancies [1]. Radical nephroureterectomy (NU) with bladder cuff excision is the standard of care for non-metastatic UTUC and is well described in literature. Dentu and Albarran performed open nephroureterectomy (ONU) for UTUC in 1898 [2]. In this era of minimally invasive surgery, the approach to this procedure has evolved from an open to a laparoscopic to a robotic approach. While significant progress has been achieved in standardising the technical operative aspects, there remains a lack of consensus on the role and extent of lymphadenectomy as an adjunct to this procedure. This is indeed quite antagonistic to the status of lymphadenectomy during radical cystectomy for bladder cancer, in which it is regarded as an inseparable part of the procedure, and has been shown to impact survival [3].

Material and Methods

We performed a PubMed literature review using the keywords ‘upper tract urothelial carcinoma’, ‘nephroureterectomy’ and ‘lymphadenectomy’ in various combinations to screen the relevant abstracts in English language only. Selected full text articles were then procured and analysed to form the basis of this review (Table 1). An additional review of current guidelines was performed to summarise the current recommendations on the role of lymphadenectomy during radical nephroureterectomy for UTUC.

Results

Two of the authors searched the relevant articles individually. Original articles, meta-analysis and structured reviews published till 2017 were included. The final selection of the articles for this review was decided based on overall scientific content, nature of study, sample size, multi-centricity, duration of follow-up and uniqueness of the article.

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Table 1 Summary of representative studies on role of lymphadenectomy in cases of upper tract urothelial carcinoma

Study	Total NU	LND <i>N</i> (%)	Description of template-based dissection	LN positive out of LND (%)	Lymph node yield (median/mean)	Results	F/u months (median/mean)	Prognostic factors	Conclusion
Margulis et al. 2009 Multi-centric (UTUC collabora- tion) [4]	1363	590 (43)	No	9.9	2	28%—recurrences outside bladder 23%—cancer-specific deaths	51	Recurrence—grade, pT stage, LVI, N+, infiltrative growth CSS—age, grade, pT stage, N+, LVI sessile pattern	RNU—durable local control and CSS in localised UTUC Described prognostic factors— guide for adjuvant systemic therapy
Yang et al. 2014 [5]	6032	3243 (56.5)	NA*	NA*	NA*	LND group—advanced T stage and grade No difference in CSS between LND and non-LND group on overall analysis Subgroup—muscle invasive disease—LND group better CSS than non-LND	NA*	NR	Possible role of LND for CSS and RFS for muscle invasive UTUC
Komatsu et al. 1997 [6]	36	36 (100)	No	31	NR	Cause-specific survival at 5 years for N+ patients only 21% Recurrence rate (local + distal) 22.2%	55	pT3 stage with peripelvic and peritumoral fat infiltration	LND—therapeutic role guide for adjuvant chemotherapy
Roscigno et al. 2008 [7]	132	95 (72)	Yes	27	8	5-year CSS 62% 5-year CSS pN0 < pNx No significant difference between pNx and pN+ Relapse—76 (25.9%) Regional lymph node—most common site for relapse— 34/76	42	Extent of lymphadenectomy Number of nodes removed (cut off 6)	LND predictor for DFS, CSS in at least pT2 UTUC
Abe et al. 2010 Multi-centric [8]	293	152 (51.8)	Yes	14.4	6	IHC markers detects micro-metastasis in 14% of pN0 cases 5-year CSS pN+ (35%) < pNx (69%) < pN0 (77%) pT1 disease (<i>n</i> = 345) 5-year CSS for pN0, pNx—not significantly different pT2–pT4 disease (<i>n</i> = 813) 5-year CSS pN+ (33%) < pNx (58%) < pN0 (70%)	45	No LND—adverse factor for locoregional and distant relapse	Therapeutic role of LND—for clearing micro-metastasis
Roscigno et al. 2009 Multi-centric [9]	1130	552 (49)	Yes**	25.4	NR	5-year CSS pN+ (35%) < pNx (69%) < pN0 (77%) pT1 disease (<i>n</i> = 345) 5-year CSS for pN0, pNx—not significantly different pT2–pT4 disease (<i>n</i> = 813) 5-year CSS pN+ (33%) < pNx (58%) < pN0 (70%)	45	pN+—independent predictor of CSS For pT2–T4 disease pNx—bad prognosis pN0—good prognosis	LND—staging and prognosis Guidance for adjuvant chemotherapy
Brausi et al. 2007 [10]	82	40 (48.8)	Yes	40	11.5	LND, T stage, N stage—significant correlation with time of recurrence and overall survival	64.7	LND, T stage	Possible curative role of LND in infiltrative UTUC
Novara et al. 2007 Multi-centric [11]	269***	269 (100)	No	10	NR	21.2% cancer-related deaths	34	pT stage, pN stage, multifocality, concomitant MIBC, history of bladder TCC	pT, pN stage-independent pre- dictor of cancer-specific sur- vival
	2824	2077 (73.5)	No	11.6	NR		59.7	NR	

Table 1 (continued)

Study	Total NU	LND N (%)	Description of template-based dissection	LN positive out of LND (%)	Lymph node yield (median/mean)	Results	F/u months (median/mean)	Prognostic factors	Conclusion
Lughezzani et al. 2010 [12]						No difference in CSM rates between pN0 and pNx			No consensus regarding LND for UTUC
Adil et al. 2013 Multi-centric [13]	714	254 (35.5)	No	20	2	5-year CSS 81%—pN0 85%—pNx 47%—pN+	27	Extra nodal extension	LND advisable for palpable or radiologically enlarged nodes LN status—not an independent prognostic factor for CSS, OS, MFS on multivariate analysis
Burger et al. 2011 Multi-centric [14]	785	190 (24.2)	No	28.9	3	MFS, OS lower in pN+ cases No difference in CSS, RFS in pN0 versus pNx Locally advanced disease CSS, RFS—pN0 > pNx	34	Locally advanced disease	Locally advanced disease— LND potential role
Miyake et al. 1998 [15]	72	35 (48.6)	Yes	37.1	NR	No difference in survival between LND and no LND in total patient population LVI correlates with higher stage and grade Amongst patients without LVI, LND better survival than no LND	49	LVI—poor prognosis	LND—therapeutic role in cases without LVI Cases with LVI—no advantage of regional LND, LVI- war- rants aggressive systemic therapy
Kondo et al. 2010 [16]	209	109 patients of cN0 group— LND	78—complete LND 41—incomplete LND	19.2	10.8—complete LND group 4.4—incomplete LND group	Cancer-specific deaths 14%—complete LND group 29%—incomplete LND group Complete LND—impact on CSS in $\geq$ pT2 cN0	56.6—complete LND group 68—incomplete LND group	Complete template LND	Completeness of LND and not the number of lymph nodes removed—improves CSS in muscle invasive clinically node-negative UTUC
Fajkovic et al. 2012 Multi-centric [17]	2492	817 (32.8)	No	27.2	4	No difference with number of lymph nodes removed Extra nodal extension—49.5% Extra nodal extension— correlated with higher ECOG score and higher pT stage Lymph node density – 51.3% Extra nodal extension (MVA)— correlated with recurrence and CSM Lymph node density (30% cut off) (UVA) correlated with recurrence and CSM	33	Extra nodal extension	Addition of extra nodal extension to multivariable models improves predictive accuracy for estimating disease recurrence and CSM

*Not reported for the pooled data meta-analysis of individual articles which included predominantly 8 studies

**Not standardised due to multi-centric (13 centres) retrospective design

***19 concomitant radical cystectomy for MIBC

NR not reported, LND lymph node dissection, RNU radical nephroureterectomy, UTUC Collaboration upper tract urothelial carcinoma collaboration, CSS cancer-specific survival, DFS disease-specific survival, OS overall survival, MFS metastasis-free survival, RFS recurrence-free survival, LVI lymphovascular invasion, MIBC muscle invasive bladder cancer, TCC transitional cell carcinoma, IHC immunohistochemistry, UTUC upper tract urothelial carcinoma, UVA univariate analysis, MVA multivariate analysis, ECOG Eastern Cooperative Oncology Group

Discussion

Role of Lymphadenectomy in Staging

Lymphatic metastases in upper tract urothelial carcinoma are not uncommon, especially in high-grade and locally advanced tumours, and may be seen in up to 30–40% cases [18]. The M D Anderson group conducted a multi-institutional database evaluation which included 12 centres and 1363 patients who had a NU for UTUC [4] (Table 1). A total of 590 patients (43.3%) underwent lymphadenectomy in the same setting. Out of them, 135 patients (9.9%) had positive lymph nodes. Median lymph node yield was 2 (range 1–21) and median lymph node density was 50% (range 30–100%). They consistently found that lymph node positivity increased with stage of disease (< 1% for Ta/Tis, 2% for T1, 8% for T2, 17% for T3, 46% for T4). A similar association was also observed with the grade of the disease (low grade 2%, high grade 15%). It was also observed that lymph node positivity correlated with lymphovascular invasion, type of growth of tumour, presence of necrosis and concomitant carcinoma in situ. No correlation of lymph node positivity was seen with the location of the tumour. Other workers have reported a similar impact of tumour grade and stage on the probability of lymph node positivity during lymphadenectomy, with a greater predilection for lymph node involvement in invasive/high-grade tumours [5] (Table 1). There is little doubt that performance of lymphadenectomy in conjunction with NU for UTUC aids in assigning an accurate stage to the individual patient's disease state and helps in prognostication as well as in decision-making for adjuvant treatment.

Therapeutic Role of Lymphadenectomy

The therapeutic role of lymphadenectomy for UTUC has been a subject of debate. Two studies in early 1990s had evaluated the role of lymphadenectomy for UTUC. In 1997, Komatsu et al. reported a therapeutic benefit of lymphadenectomy in patients with lymph node-positive disease [6] (Table 1). They also found the lymph node status of the patient to be a useful indicator for requirement of adjuvant chemotherapy. In this small series of 36 patients with an average follow-up of 55 months, the cause-specific survival at 5 years for lymph node-positive patients was only 21%. Roscigno et al. found that lymphadenectomy has an emerging role in disease-free survival and cancer-specific survival (CSS) in muscle invasive UTUC treated surgically [7] (Table 1). Five-year cancer-specific survival in patients without lymphadenectomy (pNx) (48%) was significantly worse than patients with node-negative disease on pathology (pN0) (73%) (p value 0.001). Similarly, difference between 5-year CSS was not significant between pNx group (48%) and pN+ group (39%) (p value 0.476). Pathological nodal stage along with T stage was an

independent predictor of disease-free survival (DFS) and cancer-specific survival in this study. Also, number of lymph nodes removed and extent of lymphadenectomy were predictors for DFS and CSS. Abe et al. reported that avoiding lymphadenectomy in cases of UTUC increases chances of locoregional recurrence and distant metastases [8] (Table 1). They followed 293 patients of NU for UTUC, out of which 76 developed relapse. Most common site for relapse was the regional lymph nodes. They also found that immunohistochemistry analysis for anti-cytokeratin results in picking up micro-metastases in 14% patients which were earlier staged as pN0 via standard histopathological techniques. They emphasised the role of lymphadenectomy to eliminate these micro-metastases.

Roscigno et al. also conducted a multi-institutional study which included 1130 UTUC patients treated surgically in 13 centres worldwide [9] (Table 1). In this study, 36.5% patients had pN0 disease, 51.1% had pNx disease and 12.4% had pN+ disease. Pathological T stage varied from pT1–T4. Five-year CSS was lowest in pN+ cases followed by pNx followed by pN0 with statistical significance. This observation was applicable for pT2–4 disease, whereas in pT1 cases, the CSS was similar in pN0 and pNx patients. They recommended that lymphadenectomy should be considered to improve staging and guidance for adjuvant chemotherapy in cases where likelihood of pathological T stage is at least pT2.

Brausi et al. evaluated charts of 82 patients retrospectively which included T2–T4 UTUC operated for NU with or without lymphadenectomy [10] (Table 1). With a median follow-up of 64.7 months, they analysed the impact of status of lymphadenectomy (yes or no), T stage (T2 versus T3/4) and N stage (N0 versus Nx versus N+) on recurrence and survival. They concluded that status of lymphadenectomy and pathological T stage were independent predictors of survival and emphasised the curative role of lymphadenectomy in cases of infiltrative UTUC. Similar findings regarding the therapeutic role of lymphadenectomy have also been reported by other workers either in overall pathological T stage for UTUC [4, 11] or in muscle invasive UTUC [5] (Table 1).

In contrast, a review from the SEER database, which included 2824 patients from 1988 to 2004 concluded that there was no survival benefit of lymphadenectomy (pN0 versus pNx) in cases of UTUC [12] (Table 1). Cancer-specific mortality-free survival rates at 5 years for pN0 and pNx groups were equivalent at 81.2% and 77.8% respectively. The authors also emphasised a lack of defined landing zones and templates for lymphadenectomy in this situation. They concluded that the evidence for lymphadenectomy for all patients of UTUC is lacking and lymphadenectomy may have a role for high-grade and/or high-stage disease. In their opinion, lymphadenectomy is advisable for the patients with enlarged lymph nodes on palpation intra-operatively or on imaging preoperatively. Multivariate analysis of two multi-institutional databases

showed that status of lymph nodes was not an independent predictor for CSS [13, 14] (Table 1). However, on subgroup analysis of locally advanced cases after adjusting for age, gender, type of surgery, concomitant carcinoma in situ and lymphovascular invasion, the authors found that pN0 cases had better oncological outcomes than pNx patients [14]. Miyake et al. reported that the role of lymphadenectomy in patients with lymphovascular invasion (LVI) is limited, as the disease is already systematic in cases with LVI [15] (Table 1). While the final word on the therapeutic value of lymphadenectomy for UTUC is yet to be written, it does seem that there are certain subpopulations amongst all patients undergoing NU, which may derive additional benefits from it.

Trends in Lymphadenectomy

While the risks/benefits of lymphadenectomy are still being debated, the actual proportion of patients undergoing simultaneous lymphadenectomy during NU is very limited. In 2012, the Canadian Upper Tract Collaboration (CUTC) summarised different practice patterns zone wise across 10 institutions and included data of 1029 patients of UTUC [19]. Proportions of patients with pNx nodal stage were 69%, 80% and 70% across central, east and western regions of the country, respectively. They concluded that there was a great variability of practice patterns across different geographic areas, and this was primarily because of lack of standardised criteria for management of UTUC. In a large retrospective analysis of laparoscopic NU performed in Japan at 51 centres, only 451 out of 1003 patients underwent simultaneous lymphadenectomy (less than 50%) [20]. Failure to perform adequate lymphadenectomy does not seem to be influenced by the approach (open versus laparoscopic). In a comparative analysis of open versus laparoscopic nephroureterectomy, Liu et al. found that 59.6% and 55.8% patients undergoing open and laparoscopic NU did not undergo a simultaneous lymphadenectomy respectively [21].

Patterns of Spread and Recommended Templates for Lymphadenectomy

Kondo et al. have published their pioneering work on evaluation of lymph node metastases in cases of UTUC [16] (Table 1). In their series, the main area of spread for right renal pelvic tumours was to hilar nodes along with right paracaval and retrocaval space (Fig. 1). Left renal pelvic tumours primarily had metastasis to renal hilar nodes and paraaortic site (Fig. 1). Tumours of upper 2/3 of right ureter had a predilection to spread to paracaval, retrocaval and inter-aortocaval location (Fig. 2). Tumours of upper 2/3 of left ureter tended to spread to the paraaortic group (Fig. 2). They also observed that tumours of lower ureter spread to ipsilateral common iliac, external iliac, internal iliac and obturator lymph nodes (Fig. 3). To define regional nodes, the same group of workers considered the cut

Fig. 1 Schematic representation of lymphatic spread in pelvic tumours [16]. Right side—renal hilar, right paracaval and retrocaval site. Left side—renal hilar and paraaortic site

off for percentage probability of spread to the site as more than 30% [22]. They recommended that for completeness of lymphadenectomy, all primary sites should be resected as a part of radical nephroureterectomy.

Matin et al. have published their work on the templates of lymphadenectomy in UTUC [23]. They reported that for renal pelvic and proximal ureteric tumours on right side, dissection of hilum, paracaval, retrocaval and inter-aortocaval space addresses nearly all lymph nodes. In these cases, inter-aortocaval region is secondarily involved. Similarly on left side, hilar and paraaortic region constitutes the main lymph node template. For right-sided tumours, addition of inter-aortocaval packet to hilar, paracaval and retrocaval packet addresses almost 95.8%

Fig. 2 Schematic representation of lymphatic spread in tumours of upper 2/3 of ureter [16]. Right side—paracaval, retrocaval and inter-aortocaval site. Left side—paraaortic site

Fig. 3 Schematic representation of lymphatic spread in tumours of lower ureter [16]—ipsilateral common iliac, external iliac, internal iliac and obturator lymph nodes

lymph nodes (Fig. 4a). Similarly, for the left side, addition of inter-aortocaval group to paraaortic group addresses 90.2% lymph nodes (Fig. 4b). For right side mid ureteric tumours, inter-aortocaval and paracaval nodes would address the entire landing zone along with removal of the right common iliac group (Fig. 5a). For left side mid ureteric tumours, paraaortic, left common iliac and internal iliac group would be the ideal packet for dissection (Fig. 5b). Figure 5c, d represents templates for lower ureteric tumours. Addition of paracaval packet for right side and paraaortic packet for left side to extended pelvic lymph node dissection would cover all the drainage areas respectively for lower ureteric tumours. Confounders for this pattern of lymphatic spread would be those with previous history of chemotherapy or surgery (e.g. radical cystectomy) which alters lymphatic drainage. Kondo et al. proposed extending the templates of resection for improving completeness of lymphadenectomy [3]. In their opinion, for right pelvic tumours, inter-aortocaval nodes should be removed, and for lower ureteric tumours, presacral nodes should be removed for an extended template-based lymphadenectomy. Yee et al.

noted that imaging studies can miss almost 50% of lymph node spread [24]. This finding may contradict the traditional indication of lymphadenectomy performed for enlargement of lymph nodes on preoperative imaging only, thereby reinforcing the role of template-based dissection.

Prognostic Factors Related to Lymphadenectomy

Roscigno et al. have reported in their multi-institutional study that the minimum number of lymph nodes removed should be at least 8, to improve survival outcomes in UTUC [25]. However, Kondo et al. stress a greater role for template-based dissection vis-a-vis the number of nodes removed [3]. They advocate that a complete template-based lymphadenectomy is of prime importance to ensure improved survival outcomes in muscle invasive UTUC. As in cases of bladder cancer where a lymph node density of less than 20% is associated with better survival [26], Bolenz et al. reported that in UTUC as well, patients with lymph node density more than 30% had a greater risk of disease recurrence and cancer-specific mortality [27].

In a multi-institutional analysis of 2492 patients undergoing NU for UTUC, Fajkovic et al. evaluated the prognostic role of number of lymph nodes removed, number of positive nodes, lymph node density (LND) and presence/absence of extranodal extension (ENE) [17] (Table 1). Out of a total of 817 patients who underwent lymphadenectomy, 222 (27.2%) patients were identified to have lymph node metastases. One hundred ten (49.5%) patients in this series had ENE with LND of 51.3%. ENE was associated with a higher ECOG score and a higher pathological T stage. Presence of ENE and a LND > 30% was associated with higher chances of disease recurrence and cancer-specific mortality. Addition of ENE to pT stage and tumour architecture improved the ability to predict recurrence. Similarly, adding ENE to pT stage, age and tumour architecture improved prognostication of cancer-specific mortality.

Fig. 4 (reprint with permission) Representation of templates of lymphadenectomy for renal pelvic and proximal ureteric tumours [23]. **a** Right side—hilum, paracaval, retrocaval and inter-aortocaval site. **b** Left side—hilum and paraaortic site

Fig. 5 (reprint with permission) Representation of templates of lymphadenectomy for mid ureteric tumours [23]. **a** Right side—inter-aortocaval nodes, paracaval nodes, right common iliac nodes. **b** Left side—para-aortic, left common iliac and internal iliac group. Representation of templates of lymphadenectomy for lower ureteric tumours. **c** Right side—ipsilateral pelvic, paracaval packet. **d** Left side—ipsilateral pelvic, para-aortic packet

Similar findings relating to the impact of ENE on cancer-specific survival have also been reported by other authors [13].

Complications of Lymphadenectomy

There is a perception that incorporating template-based lymphadenectomy as a part of NU routinely is likely to negatively impact the safety profile of the latter. Most of the current data, however, does not support this perception. Kondo et al. compared outcomes of patients undergoing complete lymphadenectomy, incomplete lymphadenectomy or no lymphadenectomy as a part of NU for UTUC [3]. Operative time, estimated blood loss and hospital stay did not differ between these groups. Incidence of overall complications was higher in complete lymphadenectomy group but incidence of major complications by Clavien Dindo grade (3 or more) did not differ significantly. Rao et al. conducted the only prospective clinical trial for feasibility and safety of retroperitoneal lymph node dissection (RPLND) during NU for UTUC and included 20 patients (10 open, 4 laparoscopic and 6 robot assisted) [28]. Overall complications occurred in nine patients, out of which a major complication (Clavien grade IIIb) in the form chylous lymphatic leak requiring surgical

exploration occurred in one patient. This first ever prospective clinical trial to evaluate the side effect profile of lymphadenectomy in cases of UTUC found that RPLND in this setting is feasible with acceptable morbidity.

Impact of Minimally Invasive Surgery on Lymphadenectomy

After initial description of laparoscopic nephroureterectomy (LNU) by Clayman et al., the field of minimally invasive surgery has greatly evolved over the last two decades [29]. The main hurdle for lymphadenectomy during laparoscopy is the technical challenge associated with the procedure. There is a wide variability in the reported implementation of simultaneous lymphadenectomy during LNU (transperitoneal, retroperitoneal or hand assisted) [20, 21, 30]. During a minimally invasive approach, lymphadenectomy is performed predominantly for enlarged lymph nodes detected either on preoperative imaging or during surgery itself. Standardised templates of lymphadenectomy are not well described in these series. Multi-institutional analysis of 979 open RNU versus 270 LNU procedures showed that percentage of patients undergoing lymphadenectomy was significantly lesser in laparoscopy group (24.4%) as compared to the open cohort (42.4%) [30].

Table 2 Summary of guidelines for role of lymphadenectomy in cases of upper tract urothelial carcinoma

Guidelines	Statement	Strength rating	Grade of recommendation
EAU [35]	Despite the available literature, it is not possible to standardise the indications and extent of lymph node dissection		
	In case of high-risk tumours, lymph node dissection should be performed	Weak	–
NCCN [36]	Proposed templates for dissection—Retroperitoneal lymph node dissection on the side of affected ureter (right side—till the border of vena cava or right side of aorta; left side—border of aorta)		
	High-grade tumours or tumours which are large and/or invading into renal parenchyma should have regional lymphadenectomy along with radical nephroureterectomy with bladder cuff excision	–	2A
	Regional lymphadenectomy to be performed in cases of ureteric tumours which are high grade at the time of nephroureterectomy or distal ureterectomy	–	2A

Nonetheless, median lymph node yields in both groups were comparable [LNU—3 (range 1–31); open—4 (range 1–34)].

Simultaneous template-based lymphadenectomy during robot-assisted radical nephroureterectomy (RANU) still remains an unaddressed issue. Lymphadenectomy was performed with a good safety profile in 16/20 (Lee et al.) [31], 14/31 (Zarger et al.) [32] and 22/40 (Pugh et al.) [33] cases in major series of RANU reported till date. Average lymph node yield was 14.1, 9.4 and 11 in these series, respectively. With advent of multi-quadrant improved access, port in port configuration, miniaturisation of instruments and intuitive movements, access for lymphadenectomy especially pelvic lymphadenectomy is possible without repositioning or re-docking. We have described template-based simultaneous lymphadenectomy during RANU in a series of 11 patients without any major complications with a good lymph node yield [22.5 (range 7–47)] [manuscript provisionally accepted in *Indian Journal of Urology*] [34]. As elucidated in our manuscript, the use of the robotic platform is likely to emerge as a standard of care for this procedure by greatly facilitating template-based lymphadenectomy in this situation.

Guidelines

EAU guidelines mention that anatomical sites of lymphatic drainage are not completely defined for UTUC [35] (Table 2). There is limited role of lymphadenectomy in cases of Ta and T1 tumours because of lesser chances of lymph node positivity as compared to T2–T4 disease. Extent and indications of lymphadenectomy are yet to be standardised leading to weak recommendation for performing lymphadenectomy for high-risk tumours as per EAU guidelines [35] (Table 2). National Comprehensive Cancer Network (NCCN) guidelines recommend regional lymphadenectomy along with radical nephroureterectomy in cases of high-grade, larger tumours of renal pelvis with or without parenchymal invasion and ureteric tumours which are high grade at the time of nephroureterectomy or distal ureterectomy as per the indication (grade 2A) [36] (Table 2).

Conclusion

There is a growing amount of evidence towards recognising template-based lymphadenectomy as an important adjunct to surgical treatment for upper tract urothelial carcinoma—both for staging as well as therapeutic purposes. While gaps in knowledge remain, it can now be stated with a degree of certainty that this procedure has the potential to improve long-term outcomes in a proportion of patients suffering from this disease. Since template-based lymphadenectomy can be performed safely and expeditiously both by minimally invasive and open surgical methods, the time has come to consider this procedure as a regular part of the treatment paradigm for this disease.

Authors' contributions AS Tamhankar—Protocol development, data collection, data analysis, manuscript writing

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P Ahluwalia—Data collection, manuscript writing

G Gautam—Protocol development, data collection, manuscript writing

References

1. Tawfik ER, Bagley DH (1997) Upper-tract transitional cell carcinoma. *Urology* 50(3):321–329
2. Haupt G (2004) Editorial comment: transitional-cell carcinoma of the ureter. *J Endourol* 15:409
3. Kondo T, Tanabe K (2012) Role of lymphadenectomy in the management of urothelial carcinoma of the bladder and the upper urinary tract. *Int J Urol* 19(8):710–721
4. Margulis V, Shariat SF, Matin SF, Kamat AM, Zigeuner R, Kikuchi E, Lotan Y, Weizer A, Raman JD, Wood CG, the Upper Tract Urothelial Carcinoma Collaboration (2009) Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. *Cancer* 115(6):1224–1233
5. Yang D, Chen Q, Song X, Wang J, Che X, Zhu Z, Zheng W, Wang L (2014) Effect of lymph node dissection on the outcomes of upper tract urothelial carcinoma: a meta-analysis. *Expert Rev Anticancer Ther* 14(6):667–675
6. Komatsu H, Tanabe N, Kubodera S, Maezawa H, Ueno A (1997) The role of lymphadenectomy in the treatment of transitional cell carcinoma of the upper urinary tract. *J Urol* 157(5):1622–1624
7. Roscigno M, Cozzarini C, Bertini R, Scattoni V, Freschi M, Da Pozzo LF et al (2008) Prognostic value of lymph node dissection in patients with muscle-invasive transitional cell carcinoma of the upper urinary tract. *Eur Urol* 53(4):794–802

8. Abe T, Shinohara N, Muranaka M, Sazawa A, Maruyama S, Osawa T, Harabayashi T, Kubota K, Matsuno Y, Shibata T, Toyada Y, Shinno Y, Minami K, Sakashita S, Kumagai A, Takada N, Togashi M, Sano H, Mori T, Nonomura K (2010) Role of lymph node dissection in the treatment of urothelial carcinoma of the upper urinary tract: multi-institutional relapse analysis and immunohistochemical re-evaluation of negative lymph nodes. *Eur J Surg Oncol* 36(11):1085–1091
9. Roscigno M, Shariat SF, Margulis V, Karakiewicz P, Remzi M, Kikuchi E, Langner C, Lotan Y, Weizer A, Bensalah K, Raman JD, Bolenz C, Guo CC, Wood CG, Zigeuner R, Wheat J, Kabbani W, Koppie TM, Ng CK, Suardi N, Bertini R, Fernández MI, Mikami S, Isida M, Michel MS, Montorsi F (2009) Impact of lymph node dissection on cancer specific survival in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy. *J Urol* 181(6):2482–2489
10. Brausi MA, Gavioli M, De Luca G, Verrini G, Peracchia G, Simonini G et al (2007) Retroperitoneal lymph node dissection (RPLD) in conjunction with nephroureterectomy in the treatment of infiltrative transitional cell carcinoma (TCC) of the upper urinary tract: impact on survival. *Eur Urol* 52(5):1414–1418
11. Novara G, De Marco V, Gottardo F, Dalpiaz O, Bouygués V, Galfano A et al (2007) Independent predictors of cancer-specific survival in transitional cell carcinoma of the upper urinary tract: multi-institutional dataset from 3 European centres. *Cancer* 110(8):1715–1722
12. Lughezzani G, Jeldres C, Isbarn H, Shariat SF, Sun M, Pharand D, Widmer H, Arjane P, Graefen M, Montorsi F, Perrotte P, Karakiewicz PI (2010) A critical appraisal of the value of lymph node dissection at nephroureterectomy for upper tract urothelial carcinoma. *Urology* 75(1):118–124
13. Ouzzane A, Colin P, Ghoneim TP, Zerbib M, De La Taille A, Audenet F et al (2013) The impact of lymph node status and features on oncological outcomes in urothelial carcinoma of the upper urinary tract (UTUC) treated by nephroureterectomy. *World J Urol* 31(1):189–197
14. Burger M, Shariat SF, Fritsche HM, Martinez-Salamanca JJ, Matsumoto K, Chromecki TF, Ficarra V, Kassouf W, Seitz C, Pycha A, Tritschler S, Walton TJ, Novara G (2011) 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* 29(4):465–472
15. Miyake H, Hara I, Gohji K, Arakawa S, Kamidono S (1998) The significance of lymphadenectomy in transitional cell carcinoma of the upper urinary tract. *Br J Urol* 82(4):494–498
16. Kondo T, Hashimoto Y, Kobayashi H, Iizuka J, Nakazawa H, Ito F, Tanabe K (2010) Template-based lymphadenectomy in urothelial carcinoma of the upper urinary tract: impact on patient survival. *Int J Urol* 17(10):848–854
17. Fajkovic H, Cha EK, Jeldres C, Donner G, Chromecki TF, Margulis V, Novara G, Lotan Y, Raman JD, Kassouf W, Seitz C, Bensalah K, Weizer A, Kikuchi E, Roscigno M, Remzi M, Matsumoto K, Breinl E, Pycha A, Ficarra V, Montorsi F, Karakiewicz PI, Scherr DS, Shariat SF (2012) Prognostic value of extranodal extension and other lymph node parameters in patients with upper tract urothelial carcinoma. *J Urol* 187(3):845–851
18. Batata MA, Whitmore WF, Hilaris BS, Tokita N, Grabstald H (1975) Primary carcinoma of the ureter: a prognostic study. *Cancer* 35(6):1626–1632
19. Metcalfe M, Kassouf W, Rendon R, Bell D, Izawa J, Chin J et al (2012) Regional differences in practice patterns and associated outcomes for upper tract urothelial carcinoma in Canada. *Can Urol Assoc J* 6(6):455–462
20. Kamihira O, Hattori R, Yamaguchi A, Kawa G, Ogawa O, Habuchi T et al (2009) Laparoscopic radical nephroureterectomy: a multi-center analysis in Japan. *Eur Urol* 55(6):1397–1407
21. Liu JY, Dai YB, Zhou FJ, Long Z, Li YH, Xie D, Liu B, Tang J, Tan J, Yao K, He LY (2017) Laparoscopic versus open nephroureterectomy to treat localized and/or locally advanced upper tract urothelial carcinoma: oncological outcomes from a multicentre study. *BMC Surg* 17(1):8
22. Kondo T, Nakazawa H, Ito F, Hashimoto Y, Toma H, Tanabe K (2007) Impact of the extent of regional lymphadenectomy on the survival of patients with urothelial carcinoma of the upper urinary tract. *J Urol* 178(4 Pt 1):1212–1217
23. Surena FM, John PS, Patrick NE, Jonathan AC, Philippe ES (2015) Patterns of lymphatic metastases in upper tract urothelial carcinoma and proposed dissection templates. *J Urol* 194(6):1567–1574
24. Yee A, Cha E, Sfakianos J, Kim P, Friedman F, Sternberg I, Coleman J (2014) Can pre-operative CT identify positive lymph nodes in patients with upper tract urothelial carcinoma? *J Urol* 191(4):e917
25. Roscigno M, Shariat SF, Margulis V, Karakiewicz P, Remzi M, Kikuchi E, Zigeuner R, Weizer A, Sagalowsky A, Bensalah K, Raman JD, Bolenz C, Kassouf W, Koppie TM, Wood CG, Wheat J, Langner C, Ng CK, Capitanio U, Bertini R, Fernández MI, Mikami S, Isida M, Ströbel P, Montorsi F (2009) The extent of lymphadenectomy seems to be associated with better survival in patients with non-metastatic upper-tract urothelial carcinoma: how many lymph nodes should be removed? *Eur Urol* 56(3):512–518
26. Stein JP, Cai J, Groshen S, Skinner DG (2003) Risk factors for patients with pelvic lymph node metastases following radical cystectomy with en bloc pelvic lymphadenectomy: concept of lymph node density. *J Urol* 170(1):35–41
27. Bolenz C, Shariat SF, Fernandez MI, Margulis V, Lotan Y, Karakiewicz P et al (2009) Risk stratification of patients with nodal involvement in upper tract urothelial carcinoma: value of lymph-node density. *BJU Int* 103(3):302–306
28. Rao SR, Correa JJ, Sexton WJ, Pow-Sang JM, Dickinson SI, Lin HY et al (2012) Prospective clinical trial of the feasibility and safety of modified retroperitoneal lymph node dissection at time of nephroureterectomy for upper tract urothelial carcinoma. *BJU Int* 110(11 Pt B):E475–E480
29. Clayman RV, Kavoussi LR, Figenschau RS, Chandhoke PS, Albala DM (1991) Laparoscopic nephroureterectomy: initial clinical case report. *J Laparoendosc Surg* 1(6):343–349
30. Capitanio U, Shariat SF, Isbarn H, Weizer A, Remzi M, Roscigno M, Kikuchi E, Raman JD, Bolenz C, Bensalah K, Koppie TM, Kassouf W, Fernández MI, Ströbel P, Wheat J, Zigeuner R, Langner C, Waldert M, Oya M, Guo CC, Ng C, Montorsi F, Wood CG, Margulis V, Karakiewicz PI (2009) Comparison of oncologic outcomes for open and laparoscopic nephroureterectomy: a multi-institutional analysis of 1249 cases. *Eur Urol* 56(1):1–9
31. Lee Z, Cadillo-Chavez R, Lee DI, Llukani E, Eun D (2013) The technique of single stage pure robotic nephroureterectomy. *J Endourol* 27(2):189–195
32. Zargar H, Krishnan J, Autorino R, Akca O, Brandao LF, Laydner H, Samarasekera D, Ko O, Haber GP, Kaouk JH, Stein RJ (2014) Robotic nephroureterectomy: a simplified approach requiring no patient repositioning or robot redocking. *Eur Urol* 66(4):769–777
33. Pugh J, Parekattil S, Willis D, Stifelman M, Hemal A, Su LM (2013) Perioperative outcomes of robot-assisted nephroureterectomy for upper urinary tract urothelial carcinoma: a multi-institutional series. *BJU Int* 112(4):E295–E300
34. Tamhankar AS, Patil S, Ahluwalia P, Gautam G (2018) Robot assisted radical nephroureterectomy with extended template lymphadenectomy for upper tract urothelial carcinoma – an outcome analysis. *Indian J Urol* (provisionally accepted on 06.05.2018)
35. EAU Guidelines. Edn. Presented at EAU Annual Congress Copenhagen 2018 ISBN978-94-92671-01-1. URL <http://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/>
36. Spiess PE, Agarwal N, Bangs R, Boorjian SA, Buyyounouski MK, Clark PE et al. Bladder cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. URL www.nccn.org/content/15/10/1240 (Accessed 10.03.2017)