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REVIEW

Therapeutic role of template-based lymphadenectomy in urothelial carcinoma of the upper urinary tract

Tsunenori Kondo, Toshio Takagi, Kazunari Tanabe

Tsunenori Kondo, Toshio Takagi, Kazunari Tanabe, Department of Urology, Tokyo Women's Medical University, Tokyo 162-8666, Japan

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Correspondence to: Tsunenori Kondo, MD, PhD, Department of Urology, Tokyo Women's Medical University, 8-1, Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. tkondo@kc.twmu.ac.jp
Telephone: +81-3-33538111
Fax: +81-3-33560293

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Abstract

Lymphadenectomy for urothelial carcinoma of the upper urinary tract has attracted the attention of physicians. The mapping study of lymphatic spread has shown that a relatively wide area should comprise the regional nodes for tumors of the right renal pelvis or the right upper two-thirds of the ureter. A prospective study showed that an anatomical template-based lymphadenectomy significantly improved patient survival in tumors of the renal pelvis. This benefit was more evident for patients with pT2 stage tumors or higher. The risk of regional node recurrence is significant reduced by template-based lymphadenectomy, which is likely to be associated with improved patient survival. The removal of lymph node micrometastases is assumed to be the reason for therapeutic benefit following lymphadenectomy. The number of resected lymph nodes can be used to assess the quality of lymphadenectomy, but not to determine the extent of lymphadenectomy. The guidelines currently recommend lymphadenectomy for patients with muscle-invasive disease, even though the current recommendation grades are still low. The present limitation of lymphadenectomy is the lack of standardization of the extent of lymphadenectomy and the randomized trials. Further studies are warranted to collect the evidence to support lymphadenectomy.

Key words: Lymphadenectomy; Lymph node excision; Urothelial carcinoma; Treatment outcome; Therapeutic uses; Diagnosis; Guideline

Core tip: The role of lymphadenectomy in urothelial carcinoma of the upper urinary tract had examined. A prospective study showed that anatomical template-based lymphadenectomy significantly improves patient survival in tumors of the renal pelvis. This benefit is demonstrated more clearly for patients with pT2 tumors or higher. The risk of regional node recurrence is significant reduced by template-based lymphadenectomy, which is likely to be associated with improved patient survival. The guidelines currently recommend lymphadenectomy for patients with muscle-invasive disease. Further studies are warranted to

collect the evidence to support lymphadenectomy.

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INTRODUCTION

About 20%-30% of patients with urothelial carcinoma develop lymphatic metastases, and thus, it is known to confer a high risk of developing lymphatic metastases[1,2]. Thus, controlling lymphatic spread may be an important strategy to improve patient survival. Lymphadenectomy may be a possible strategy for surgically treating cancer that spread to the lymph nodes. The standard surgical treatment for muscle-invasive bladder cancer is radical cystectomy[3]. Concomitant lymphadenectomy provides a better outcome than no lymphadenectomy, and an extension in the lymphadenectomy template may possibly result in higher patient survival[4,5]. Thus, guidelines currently recommend lymphadenectomy as an integral part of radical surgery for bladder cancer[3].

Most carcinomas arising from the upper urinary tract are pathologically urothelial carcinomas, which are similar to bladder cancer. It is well known that there is a high risk of metastases to the lymph nodes in urothelial carcinomas of the upper urinary tract (UCUT)[6,7]. Moreover, stage and grade migration toward more aggressive disease has been reported in UCUT[8]. Thus, one can speculate that controlling metastases to the lymph nodes is more important in UCUT.

In this review article, we summarize the current understanding of the role of lymphadenectomy in UCUT. Unfortunately, the evidence regarding lymphadenectomy in UCUT is small as compared with that for bladder cancer. A recent study by the cancer registry shows that lymphadenectomy is rarely performed[9]. In addition, patient survival did not improve with radical nephroureterectomy over a period of 18 years[10]. The role of lymphadenectomy needs to be discussed to improve the outcome of surgery.

THE HISTORY OF LYMPHADENECTOMY IN UCUT

The high incidence of lymphatic metastases in UCUT was reported as early as the 1970s[6,7]. Thus, the inclusion of lymphadenectomy as a standard procedure was suggested for radical nephroureterectomy indications[11]. However, the role of lymphadenectomy was not examined sufficiently until the 1990s because UCUT is a very minor disease among malignancies[12].

In the 1990s, 2 studies shed new light on the importance of lymphadenectomy. Komatsu *et al*[13] reported the outcomes of relatively wide lymphadenectomy. Lymph node metastases that were pathologically confirmed by lymphadenectomy (pN0), were not significantly associated with higher patient survival than those with pathologically confirmed lymphatic metastases (pN+). This result supports the use of lymphadenectomy for staging. Another study by Miyake *et al*[14] showed that lymphadenectomy improved survival in selected patients without lymph vessel invasion. However, the small number of patients in these studies precluded widespread discussion. Thereafter, no new information regarding the benefits of lymphadenectomy was available until 2007.

THE EXTENT OF LYMPHADENECTOMY

In the 1980s, some investigators examined the primary sites of lymphatic metastases in UCUT[7,15,16]. Their results showed that metastases spread primarily to the renal hilar, abdominal para-aortic, and paracaval nodes from the renal pelvis and to the abdominal ureter and the intrapelvic nodes from the distal ureter. Current descriptions in the Union for International Cancer Control TNM classification is are based on results reported more than 30 years ago[17]. However, the location or laterality of primary tumors was not taken into account when considering the anatomical extent of the regional nodes. Therefore, the aforementioned results could not be used to determine the extent of lymphadenectomy in clinical practice.

In 2007, we conducted more detailed mapping studies of lymph nodes. In this study, we examined 42 patients with lymph node metastases confirmed by pathological examination of surgical specimens or radiological methods[18]. Sites of primary nodal metastases were identified according to the location of the tumors, for example, the renal pelvis, the upper and middle ureter, and the lower ureter. Our results showed that primary metastatic sites were located in a larger area than previously thought for tumors of the right renal pelvis and the upper two-thirds of the right ureter. We reanalyzed the pattern of lymphatic metastases by increasing the number of the patients with lymph node metastases to 75, but the results were similar (Table 1)[19]. In tumors of the right renal pelvis, lymphogenous metastases spread primarily to the right renal hilar, paracaval, retrocaval, and interaortocaval nodes. Primary metastatic sites in right upper and middle ureter tumors also include the right renal hilar, retrocaval, and interaortocaval nodes. Tumors of the left renal pelvis or the left upper/middle ureter primarily metastasized to left renal hilar and para-aortic nodes. The lower boundary of the metastatic sites was at the level of the inferior mesenteric artery for tumors of the renal pelvis and at the aortic bifurcation for tumors of the upper and middle ureter. Primary metastatic sites for tumors of the lower ureter included the ipsilateral common iliac, external iliac, obturator, and internal iliac

Table 1 The incidence of primary nodal involvement in each lymph node sites according to the location of the tumor in urothelial carcinomas of the upper urinary tract

Location of the primary tumor (No. of patients with nodal metastasis)		Ipsilateral						Ipsilateral				
		Suprahilar	Ipsilateral renal hilar	Para-caval	Retro-caval	Interaorto-caval	Para-aortic	Common iliac	External iliac	Obturator	Internal iliac	Presacral
Right	RP (22)	-	14 (84%)	8 (36%)	9 (41%)	3 (14%)	-	-	-	-	-	
	UU (3)	-	1 (33%)	-	1 (33%)	2 (66%)	-	-	-	-	-	
	MU (5)	-	-	-	1 (20%)	4 (80%)	-	-	-	-	-	
	LU (7)	-	-	-	-	-	-	4 (57%)	1 (14%)	5 (71%)	2 (29%)	1 (14%)
Left	RP (25)	-	20 (80%)	-	-	1 (4%)	11 (44%)	-	-	-	-	
	UU (0)	-	-	-	-	-	-	-	-	-	-	
	MU (5)	-	-	-	-	-	5 (100%)	-	-	-	-	
	LU (8)	-	-	-	-	-	-	4 (50%)	2 (25%)	3 (38%)	1 (13%)	

R-RP: Right renal pelvis; R-UU: Right upper ureter; R-MU: Right middle ureter; R-LU: Right lower ureter; L-RP: Left renal pelvis; L-UU: Left upper ureter; L-MU: Left middle ureter; L-LU: Left lower ureter.

nodes. Our first study did not reveal presacral nodes as a primary site, but a revised study showed that 14% of patients had primary metastases to this site.

Based on these results, we thought that nodal sites at more than 10% risk of metastasis, for example, regional lymph nodes, should be dissected. The proposed anatomical extent of lymphadenectomy is shown in Figure 1[19]. The suggested template for renal pelvic cancer is very similar to that for renal cell carcinoma, which is based on several studies[20]. For the right kidney, the paracaval, retrocaval, and precaval nodes should be included from the adrenal vein to the level of the inferior mesenteric artery, and for the left kidney, the para-aortic and pre-aortic nodes should be included from the crus of the diaphragm to the inferior mesenteric artery[20]. Interaortocaval nodes should always be removed despite the laterality of tumors when extended Lymphadenectomy (LND) is sought, but this is different from our results in which dissection of interaortocaval nodes can be ignored for tumors of the left renal pelvis. The template for lower ureteral cancer is also similar to that proposed for bladder cancer[21,22].

Our nonrandomized prospective study showed the therapeutic benefit of lymphadenectomy for tumors of the renal pelvis, confirming the rationale of this template[23]. However, our prospective study did not support the therapeutic role in ureteral cancer tumors. It remains to be determined whether the currently proposed anatomical template of ureteral cancer is appropriate.

Recently, another multi-institutional mapping study was reported, where a similar pattern of lymphatic metastases was observed for renal pelvic cancer. However, tumors below the crossing of the common iliac artery were more likely to spread cranially than expected, with an incidence of 33%-40%[24]. This might suggest that the template we propose for lower ureteral cancer is not adequate to cover primary metastatic sites. Further studies are warranted to standardize the extent of lymphadenectomy for UCUT.

DOES LYMPHADENECTOMY BENEFIT ACCURATE STAGING?

One of the major roles of lymphadenectomy is to provide accurate staging of lymphatic metastases. Lymphadenectomy could allow better stratification of patients to determine the indication of adjuvant therapy. In bladder cancer, lymphadenectomy has a role in staging. Extended lymphadenectomy reportedly improves staging accuracy because the incidence of pathological node metastases is increased by extending the extent of lymphadenectomy[5,25-27].

Several studies have examined the benefits of staging in UCUT. Komatsu *et al*[13] reported the role of relatively wide lymphadenectomy in 1997. Their results showed significantly higher cancer-specific survival (CSS) in patients without lymphatic metastases (pN0) as confirmed by lymphadenectomy compared to those with pathological node metastases (pN+), suggesting a role for wide lymphadenectomy in staging[13]. Roscigno *et al*[28] reported results for a similar extent of lymphadenectomy as Komatsu *et al*[13]. They compared patient survival between 3 groups, including patients without lymphatic metastases as confirmed by lymphadenectomy (pN0), those with pathological node metastases (pN+), and those without lymphadenectomy (pNx). Five-year CSS was highest in pN0 patients, moderate in pNx patients, and lowest in pN+ patients (73%

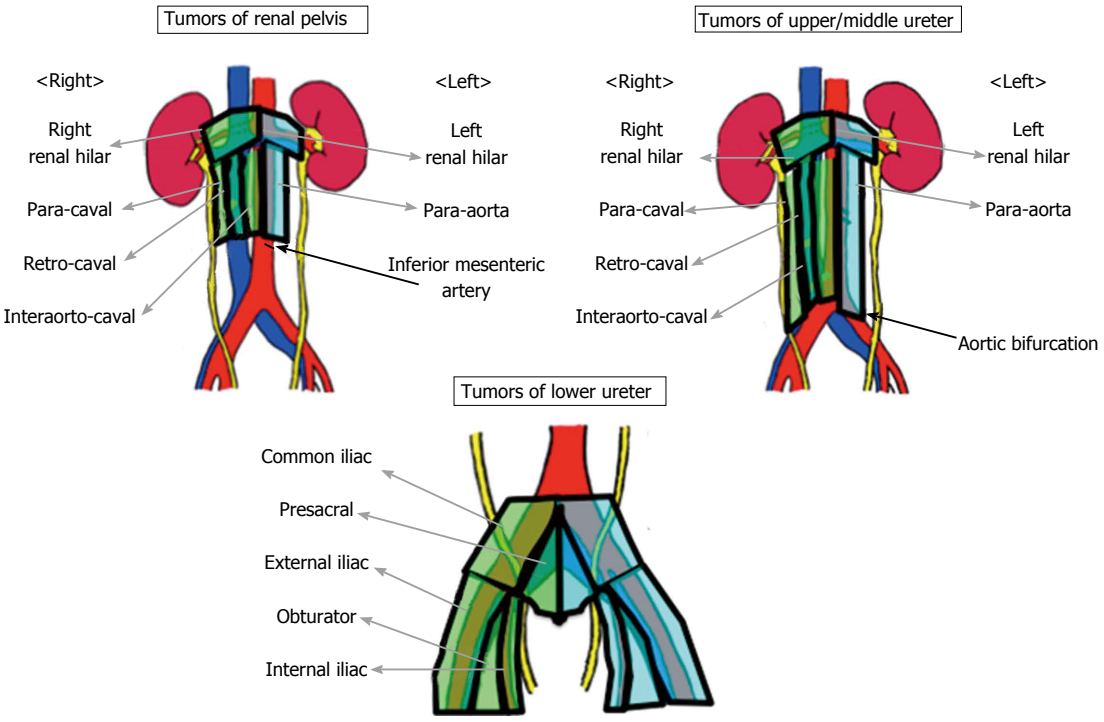

Figure 1 The extent of lymphadenectomy currently proposed for urothelial carcinoma of the upper urinary tract.

vs 48% *vs* 39%)[28]. Although there was no difference between pNx and pN0 patients (P = 0.476), the difference between pN0 and pNx patients was significant (P < 0.001). They concluded that lymphadenectomy is likely to provide better stratification of pN0 patients just like Komatsu *et al*[13].

Thereafter, several multi-institutional studies have been reported. The results are summarized in Table 2. Roscigno *et al*[29] conducted a multi-institutional study to further examine patient survival according to the lymph node status. CSS was stratified according to the nodal status in patients with a staging of pT1 or higher. Five-year CSS was 77% in pN0, 69% in pNx, and 35% in pN+. For patients with pT2 staging or higher, this difference was demonstrated more clearly (5-year CSS: 70% *vs* 58% *vs* 33%). Abe *et al*[30] also reported the results of a similar analysis. Recurrence-free survival was significantly higher in pN0 patients than in pNx patients with pT2 stage tumors or higher, but not in those with pT1. These 2 studies confirm the role of lymphadenectomy in stratifying patients with a favorable prognosis (pN0). This benefit is more prominent in those at the pT2 stage or higher. The extent of lymphadenectomy was described in these 2 studies, and they utilized a relatively wide template.

However, another 3 studies failed to demonstrate better stratification of pN0 by lymphadenectomy than that achieved without lymphadenectomy (pNx). On the other hand, these studies showed that lymphadenectomy could stratify patients with unfavorable prognosis by identifying pathological metastases to the lymph nodes (pN+)[31-34]. Lughezzani *et al*[31] collected the most number of patients by using for a population-based study by using a surveillance, epidemiology, and end results database. Lymphadenectomy could discriminate between pN+ patients with a poor prognosis, and pN0 or pNx patients. However, this benefit was limited to patients with a pT3 stage tumor or higher. Burger *et al*[32] also reported that stratification of pN+ patients with a significantly poor prognosis was observed only in locally advanced disease. Mason *et al*[33] also reported similar results to those by Lughezzani *et al*[31] and Burger *et al*[32]. Ouzzane *et al*[34] failed to demonstrate the benefit of staging in patients with a tumor of stage pT2 or higher, when examining 714 patients from multiple institutions in France. However, the extent of lymphadenectomy was not described in these 4 studies where the survival was similar between pN0 and pNx patients.

As mentioned above, there is a difference in the stratification of patients; pN0 stratification is better than pNx, and pN+ stratification is worse than pNx. One possible reason is the extent of lymphadenectomy. The latter 4 studies included all types of lymphadenectomy, whereas the first 2 studies had a relatively wide extent for dissection. We also examined the benefit of lymphadenectomy-based staging in our patient cohort. From 1988 to February 2015, we treated 314 nonmetastatic patients who underwent radical nephroureterectomy. Of these, 158 patients (53%) underwent lymphadenectomy, including 126 patients with lymphadenectomy based on the anatomical template (Figure 1, complete LND) and 42 where all regional sites were not dissected (incomplete LND). Our result was very similar to that reported by the others[29,30]. Five-year CSS, according to the status of lymph node metastases,

Table 2 Reports on staging benefit of lymphadenectomy in urothelial carcinoma of the upper urinary tract

Authors	Year	Institute	Template of LND	Subject	No. of patients	Results	Staging benefits	Ref.
Roscigno	2009	Multi	Not well described	≥ pT1	1130	5 yr-CSS: pN0 77% > pNx 69% (P = 0.032) > pN+ 35% (P < 0.001)	Yes	[29]
				≥ pT2	813	5 yr-CSS: pN0 70% > pNx 58% (P = 0.017) > pN+ 33% (P < 0.001)		
Abe	2010	Multi	Not well described	pT1	66	RFS: pN0 = pNx (P = 0.702)	Yes	[30]
				≥ pT2	227	RFS: pN0 > pNx (P < 0.001) = pN+ (P = 0.134)	in ≥ pT2	
Burger	2011	Multi	Not well described	Organ-confined	519	CSS: pN0 = pNx = pN+	Yes	[32]
							In locally advanced disease	
				Locally advanced	266	CSS: pN0 = pNx (P = 0.633) > pN+ (P < 0.001)		
Lughezzani	2010	Multi	Not described	pT1, pT2	1324	CSS: T1 pN0 = pNx (P = 0.4) = pN+ (P = 0.1)	Yes	[31]
						T2 pN0 = pNx (P = 0.8) = pN+ (P = 0.1)	In ≥ pT3	
				pT3, pT4	1382	CSS: T3 pN0 = pNx (P = 0.9) > pN+ (P < 0.001)		
						T4 pN0 = pNx (P = 0.3) > pNx (P < 0.001)		
Mason	2012	Multi	Not described	All patients	1029	OS: pN0 66.1% = pNx 66.0% (P = 0.617) > pN+ 22.3% (P < 0.01)	Yes	[33]
Ouzzane	2013	Multi	Not described	All patients	714	5 yr-CSS: pN0 81% = pNx 85% (P = 0.6) > pN+ 47% (P < 0.001)	Yes	[34]
							but in T1	
				≥ pT2	337	CSS: pN0 = pNx (P = 0.44) = pN+ (P < 0.15)		
TWMU	2015	Single	Well described	All patients	314	5 yr-CSS: pN0 84% > pNx 70% (P = 0.02) > pN+ 31% (P < 0.001)	Yes	-
				≥ pT2	212	5 yr-CSS: pN0 79% > pNx 59% (P < 0.007) > pN+ 31% (P < 0.004)		

LND: Lymphadenectomy; CSS: Cancer-specific survival; RFS: Recurrence-free survival; LNs: Lymph nodes; CompLND: Complete lymphadenectomy; DFS: Disease free survival; OS: Overall survival.

was 84.9% in pN0, 70.2% in pNx, and 31.5% in pN+ patients (Figure 2). The difference between the groups was statistically significant. This trend was demonstrated more clearly in patients with pT2 stage tumors or higher. Five-year CSS according to the status of lymph node metastases was 79.6% in pN0, 59.1% in pNx, and 31.5% in pN+ patients (Figure 2). Thus, we believe that the extent of lymphadenectomy influences the staging benefits.

Collectively, most studies agree that there are benefits from lymphadenectomy-based staging. In addition, this benefit is likely to be demonstrated more clearly in patients with advanced disease.

DOES LYMPHADENECTOMY IMPROVE SURVIVAL?

Retrospective study

In bladder cancer, extended lymphadenectomy where the cranial boundary of the template is at the level of aortic bifurcation has shown improvement in not only staging accuracy but also patient survival[4,5]. A therapeutic benefit of lymphadenectomy is expected in UCUT as well as bladder cancer because of histological similarity. However, no one had examined the role of lymphadenectomy in improving patient survival until 2007, except for Miyake *et al*[14] who showed that LND benefited only selected patients. The therapeutic benefits of lymphadenectomy are summarized in Table 3.

Three retrospective studies from single institutes were published in 2007. We identified an anatomical template of lymphadenectomy from the mapping study (Figure 1)[18]. Thus, we hypothesized that the extent of lymphadenectomy was an important factor that influences patient survival. In this study, we subclassified 169 patients into 3 groups, and compared the patient survival among groups[35]. The 3 groups include the patients for whom the regional nodes were all dissected [complete lymphadenectomy (CompLND)]; those in whom lymphadenectomy did not include all regional sites [incomplete lymphadenectomy (IncompLND)]; and those without lymphadenectomy (No-LND). CSS was lower in the No-LND group than in the CompLND or IncompLND groups, but the difference was not

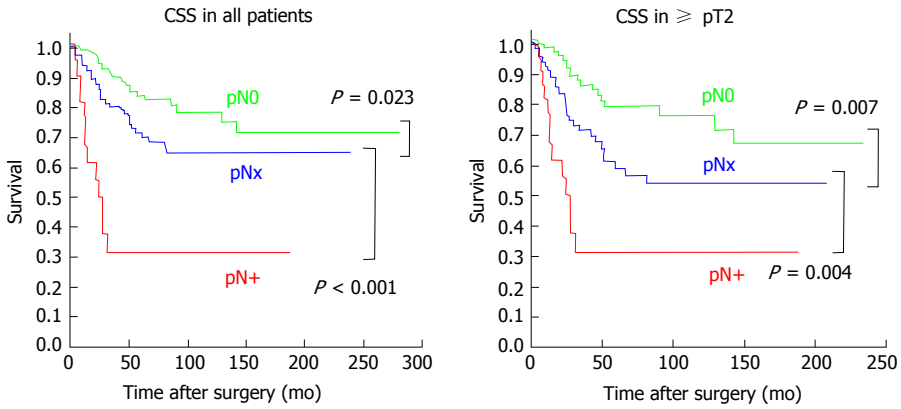

Figure 2 Benefit of staging lymphadenectomy by stratification of patients according to lymph node status in our institute. CSS: Cancer-specific survival.

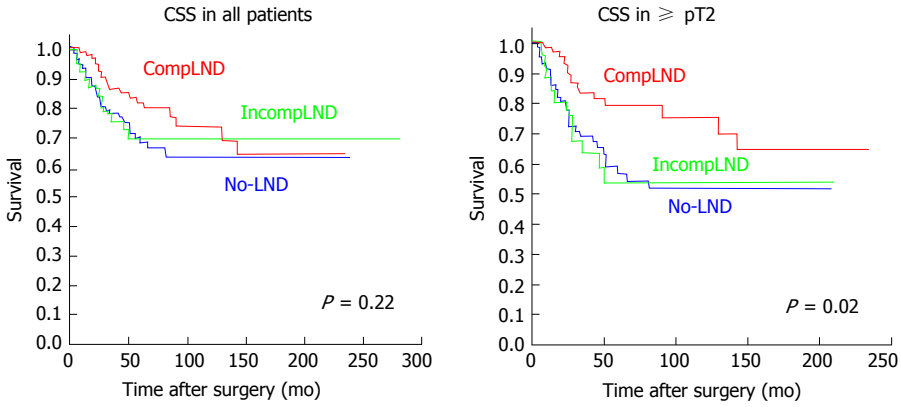

Figure 3 Therapeutic benefit of lymphadenectomy according to the extent of lymphadenectomy in our institute. LND: Lymphadenectomy; CSS: Cancer-specific survival.

statistically significant. However, for patients with pT3 stage tumors or higher, the survival rate increased incrementally from No-LND to IncompLND to CompLND. The difference between the CSS in the No-LND and CompLND groups, but not the IncompLND group, showed statistical significance. Multivariate analysis showed that CompLND was a significant independent factor for reducing the risk of cancer-specific mortality. Figure 3 shows the results from our current database, which includes 314 nonmetastatic patients, which is almost double that in our previous report. The results are similar to what we reported in 2007. A significant improvement in patient survival is observed in the CompLND group in patients with pT2 stage tumors or higher. In contrast, CSS in the IncompLND group was similar to that of No-LND even in patients with advanced stage cancer. Thus, our results suggest a therapeutic benefit of lymphadenectomy; however, lymphadenectomy should be performed based on the anatomical template.

Results from other retrospective studies have been reported. Brausi *et al*[36] reported the influence of relatively wide lymphadenectomy in 82 patients with pT2 stage tumors or higher. Lymphadenectomy included the following lesions: The para-aorta or vena cava between the renal hilum and the inferior mesenteric artery for tumors of the renal pelvis or the upper ureter; the para-aorta or vena cava between the renal hilum and the bifurcation of the common iliac artery for tumors of the mid-ureter; and the pelvic nodes on the ipsilateral side for lower ureteral tumors. The lymphadenectomy groups showed significantly higher disease-specific survival than those without lymphadenectomy in patients with pT2 stage tumors or higher (81.6% *vs* 44.8%, $P = 0.007$). Roscigno *et al*[28] also examined the influence of lymphadenectomy with an extent similar to that used by Brausi *et al*[36] on patient survival. Patients who underwent lymphadenectomy showed significantly higher CSS than those who did not undergo lymphadenectomy for advanced disease at the pT2 stage or higher (5-year CSS: 57% *vs* 40%, $P = 0.01$). These 2 studies from Italy also supported a therapeutic role for lymphadenectomy and emphasized the disadvantage of ignorance regarding lymphadenectomy.

Thereafter, multi-institutional retrospective studies were conducted to confirm the therapeutic benefit of lymphadenectomy. However, a major limitation of these multi-institutional studies is the lack of a standardized lymphadenectomy template among institutes and surgeons. Thus, we should carefully interpret these results. The largest study was reported by Roscigno *et al*[29], in which 1130 patients from 13 international

Table 3 Reports on therapeutic benefit of lymphadenectomy in urothelial carcinoma of the upper urinary tract

Authors	Year	Institute	Property	Template of LND	Subject	No. of patients	Survival results	Independent factors in Multivariate analysis?	Therapeutic benefit?	Ref.
Kondo	2007	Single	Retrospective	Clearly described	All patients	169	CSS: CompLND = IncompLND = No-LND (P = 0.06)	Yes: CompLND for CSS	Yes	[35]
					≥ pT3	88	CSS: CompLND > No-LND (P = 0.01)		In ≥ pT3	
Kondo	2012	Single	Retrospective	Clearly described	≥ pT2	191	5 yr-CSS: CompLND 77.9% > IncompLND 54.0% = No-LND 59.0% (P = 0.03)	Not determined	Yes	[23]
					≥ pT3	140	5 yr-CSS: CompLND 73.2% > IncompLND 43.7% = No-LND 47.3% (P = 0.01)		In ≥ pT2	
Brausi	2007	Single	Retrospective	Described	≥ pT2	82	DFS: RPLN 81.6% > No-LND 44.8% (P = 0.007)	Yes: RPLD for OS	Yes in ≥ pT2	[36]
Roscigno	2008	Single	Retrospective	Described	≥ pT2	132	5 yr-CSS: LND 57% > No-LND 40% (P = 0.01) pN0 72% > pNx 39% (P < 0.001)	Yes: LND and pN0 for CSS	Yes in ≥ pT2	[28]
					≥ pT2pN0	95	7 LNs > less than 7 (P < 0.001)	Yes: No. of LNs for CSS	Yes In ≥ 7 LNs removed	
Roscigno	2009	Multi	Retrospective	Not well described	≥ pT2	1130	5 yr-CSS: LND 66% = No-LND 69% (P = 0.23)	Yes: pN0 for CSS	No	[29]
Roscigno	2009	Multi	Retrospective	Not well described	≥ pT1pN0	412	5y-CSS: 8 LNs or more 84% > less than 8 73% (P = 0.038)	Yes: No. of LNs for CSS	Yes in ≥ 8 LNs removed	[37]
Abe	2010	Multi	Retrospective	Not well described	All patients	293	RFS: pN0 > pNx (P < 0.001) > pN+ (P = 0.004)	Yes: pNx of RFS	Yes	[30]
Burger	2011	Multi	Retrospective	Not well described	Organ-confined	519	CSS: pN0 = pNx	No	Yes but limited only in locally advanced disease	[32]
					Locally advanced	266	CSS: pN0 = pNx (P = 0.633)	Yes: pN0 for CSS in locally advanced		
Lughezzani	2010	Multi	Retrospective	Not described	All patients	2824	No; CSS is pN0 = pNx	No	No	[31]
Mason	2012	Multi	Retrospective	Not described	All patients	1029	OS: pN0 66.1% = pNx 66.0% (P = 0.617)	No	No	[33]
Ouzzane	2013	Multi	Retrospective	Not described	All patients	714	5y-CSS: pN0 81% = pNx 85% (P = 0.6) > pN+ 47% (P < 0.001)	No	No	[34]
					≥ pT2	337	CSS: pN0 = pNx (P = 0.44) = pN+ (P < 0.15)			
Kondo	2014	Multi	Prospective	Clearly described	Renal pelvis	90	≥ pT2 3 yr-OS: LND 86% > No-LND 48% (P = 0.01) 3 yr-CSS: LND 89% > No-LND 51% (P = 0.01) 3 yr-DFS: LND 77% > No-LND50% (P = 0.06)	Yes in CSS in > pT2	Yes in renal pelvic cancer in ≥ pT2	[23]
					Ureter	76	≥ pT2 3 yr-OS: LND 46% = No-LND 71% (P = 0.57) 3 yr-CSS: LND 54% = No-LND 71% (P = 0.99) 3 yr-DFS: LND 54% = No-LND 59% (P = 0.79)	No		

LND: Lymphadenectomy; LNs: Lymph nodes; CompLND: Complete lymphadenectomy; IncompLND: Incomplete lymphadenectomy; DFS: Disease-free survival; RPLD: Retroperitoneal lymph node dissection; RFS: Recurrence free survival; OS: Overall survival.

institutes were analyzed. Disappointingly, CSS was not significantly different between patients who underwent lymphadenectomy and those who did not (5-year CSS: 66% *vs* 69%, P = 0.23)[29]. Moreover, lymphadenectomy benefited pN0 patients. The number of lymph nodes removed significantly correlated with the improvement of CSS[37]. A

cutoff level of 8 lymph nodes improved CSS significantly (84% *vs* 73%, $P = 0.038$), and the number of lymph nodes removed was an independent factor for predicting CSS. Thus, it was suggested that lymphadenectomy should be performed to an adequate extent, which is in accordance with our principles for anatomical template-based lymphadenectomy[19,35].

Other studies were not a direct comparison between patients who did and did not undergo lymphadenectomy. They tried to find the therapeutic benefits of lymphadenectomy by comparing the survival of pN0 and pNx patients. This reflects the benefits of staging, but may also reflect therapeutic benefit. Abe *et al*[30] also reported improved CSS in pN0 patients compared to pNx patients with pT2 stage tumors or higher from multiple institutions. These studies also demonstrated that ignorance of lymphadenectomy (pNx) was an independent factor for predicting a poor patient outcome. Multivariate analysis by Burger *et al*[32] also showed an increased risk of recurrence and death in pNx patients with locally advanced disease. Thus, these 2 studies also support the therapeutic role of lymphadenectomy in patients with advanced disease.

However, 3 studies demonstrated no difference in patient survival between pN0 and pNx patients as mentioned in section 4[31,33,34]. In addition, multivariate analysis in a population-based study based on the surveillance, epidemiology, and end results database showed that omitting lymphadenectomy did not pose a disadvantage to patient survival[31]. They concluded that no therapeutic benefit was obtained from lymphadenectomy.

Thus, retrospective studies examining the therapeutic benefit of lymphadenectomy show large discrepancies among studies. One of the major reasons for this is the lack of standardization of the extent of lymphadenectomy. We need a prospective study to resolve this issue.

Prospective study

We conducted a prospective study in 2 Japanese institutes[23]. This study was initiated in 2006. At that time, we were not aware that the presacral lymph node was a regional node in lower ureteral cancer. Thus, dissection of presacral nodes was not necessary for inclusion in this study. In principle, template-based lymphadenectomy was performed at the time of radical nephroureterectomy in all patients irrespective of preoperative staging, except for patients over 75 years old or with significant comorbidities. Thus, this study was considered to be a nonrandomized prospective study. Lymphadenectomy was performed for 77 patients, while 89 patients did not undergo lymphadenectomy.

Figure 4 shows recurrence-free, cancer-specific, overall survival of patients. In patients with renal pelvic cancer, CSS and overall survival were significantly higher in the lymphadenectomy group compared to the no lymphadenectomy group, although the difference in recurrence-free survival was marginally significant. Multivariate analysis showed that template-based lymphadenectomy was a significant independent factor for reducing cancer mortality in patients with renal pelvic cancer. In contrast, lymphadenectomy did not improve patient survival in ureteral cancer. A similar trend was observed for patients with pT2 stage tumors or higher.

Thus, our bi-institutional, nonrandomized prospective study further supports a therapeutic benefit for lymphadenectomy in patients with renal pelvic cancer, but not in those with ureteral cancer. This study also confirms the rationale of using our anatomical lymphadenectomy template for renal pelvic cancer. Again, our prospective study failed to show the survival benefit of lymphadenectomy in ureteral cancer. However, our recent retrospective study shows that lymphadenectomy is also likely to improve survival in patients with upper/middle ureteral cancer, but not in those with lower ureteral cancer (prepared for submission). The template of lymphadenectomy for upper/middle ureteral cancer is similar to that for renal pelvic cancer. I believe that the benefit of lymphadenectomy will be confirmed in upper/middle ureteral cancer in the future. The reason why patients with lower ureteral cancer did not benefit from lymphadenectomy needs to be determined. Some possible explanations include an inadequate template and the higher malignant potential of lower ureteral cancer.

To the best of our knowledge, this is the only published prospective study that examines the role of lymphadenectomy. Another ongoing prospective study analyzed a preformed super-extended template[38]. They only reported the safety and feasibility of utilizing this template, not the patient survival. We definitely need a randomized trial to confirm the therapeutic benefit of lymphadenectomy.

Does lymphadenectomy reduce the risk of regional node recurrence?

There is a dearth of evidence to support the survival benefits of lymphadenectomy. One possible way of improving patient survival by lymphadenectomy may be the prevention of regional node recurrence.

Our prospective study shows significantly improved patient survival following anatomical template-based lymphadenectomy in renal pelvic cancer. In order to further examine the role of template-based lymphadenectomy, we analyzed how the extent of lymphadenectomy influences the recurrence pattern in renal pelvic cancer[39]. We collected the data of 180 patients with nonmetastatic (cN0M0) urothelial carcinoma of the renal pelvis from 2 institutions, and compared the sites of tumor recurrence between template-based lymphadenectomy, incomplete lymphadenectomy, and no lymphadenectomy. Recurrence in the regional nodes was significantly decreased in the complete template-based group (2.9%, 2/67) compared to the incomplete lymphadenectomy (18.1%, 4/22) and

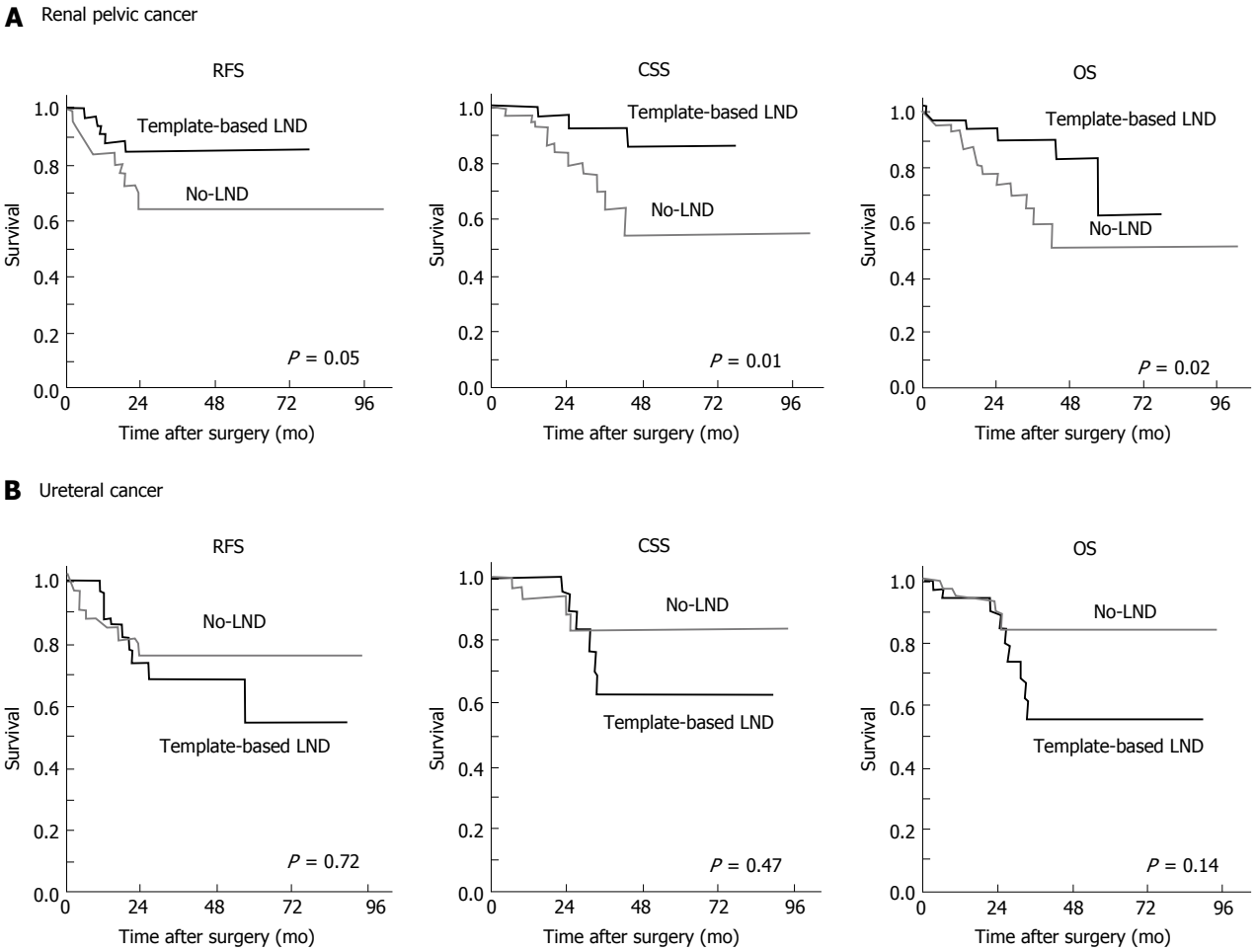

Figure 4 Patient survival in a non-randomized prospective study according to the location of the primary tumor. LND: Lymphadenectomy; CSS: Cancer-specific survival; RFS: Recurrence-free survival; OS: Overall survival.

no lymphadenectomy (10.9%, 10/91) groups (P = 0.03; Figure 5). We should emphasize that 75% (3/4) of regional node recurrences in the incomplete lymphadenectomy group were found outside the dissected sites. Complete lymphadenectomy was a predictive factor for a reduced risk of regional node recurrence. Thus, this study shows the role of template-based lymphadenectomy in reducing the risk of regional node recurrence in renal pelvic cancer, which may in turn be associated with improved patient survival. At the same time, our study suggests that the prevention of regional node recurrence by lymphadenectomy is attributed to the dissection of tumor microdeposits in the regional lymph nodes.

Abe *et al*[30] confirmed the above hypothesis by examining micrometastases to the lymph nodes using immunohistochemistry with an anticytokeratin antibody. They demonstrated that 14% of patients with no metastases, as diagnosed by regular hematoxylin-eosin staining, showed a positive immunohistochemical reaction for micrometastases. In addition, the majority of patients with micrometastases survived for a long time after lymphadenectomy.

We also examined lymph node micrometastases by examining the expression of urothelial carcinoma-specific markers in lymphadenectomy specimens using the quantitative reverse transcription-polymerase chain reaction[40]. We found that this technique detected micrometastases in about 10% of patients who had no metastases according to routine hematoxylin-eosin staining. Moreover, the prognosis of the patients was stratified well according to the metastatic status of the lymph nodes.

Collectively, these results show that the therapeutic benefit of lymphadenectomy is likely to be attributed to the surgical resection of microtumor deposits that spread to the lymph nodes in UCUT. Again, we should emphasize that the therapeutic benefit could not be obtained without anatomical template-based lymphadenectomy.

UNDERLYING ISSUES REGARDING LYMPHADENECTOMY

Minimum number of lymph nodes removed that influence patient survival

The number of lymph nodes removed is likely to be a good indicator for assessing the extent of lympha-

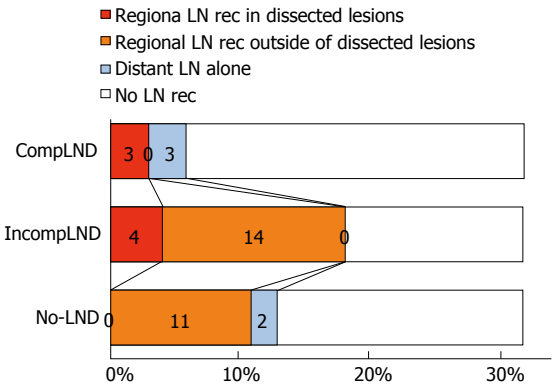

Figure 5 Recurrence pattern in regional nodes according to the extent of lymphadenectomy in patients with renal pelvic cancer. LND: Lymphadenectomy; LN: Lymph node.

denectomy in bladder cancer[41-43]. Reportedly, survival rates continued to rise as the number of resected lymph nodes increased[44]. The question is whether a minimum number of lymph nodes should be resected to influence patient survival in UCUT.

Roscigno *et al*[28] reported that a minimum of 7 lymph nodes should be removed to significantly improve survival in patients with pT2 stage tumors or higher. A multi-institutional study showed that the removal of 8 lymph nodes or more resulted in higher CSS compared to the removal of less than 8 lymph nodes in patients with ≥ pT1pN0[37]. In this patient cohort, the risk of cancer mortality continued to decrease as the number of lymph nodes removed increased, as in bladder cancer.

We also examined whether there is a minimum number of resected lymph nodes that can affect patient survival[45]. Our results showed that there was no cutoff value that significantly influenced patient survival (Figure 6). Eight lymph nodes were likely to be a minimum requirement for improving patient survival, but it was not a statistically significant value. In contrast, template-based lymphadenectomy was significantly associated with a higher CSS rather than incomplete lymphadenectomy where all regional sites were not resected. Thus, lymphadenectomy should be performed by following the anatomical template. We believe that the number of resected lymph nodes cannot be used to determine the extent of lymphadenectomy, but can be used for assessing the adequacy of lymphadenectomy.

Indication of lymphadenectomy

It is important to determine the indication of lymphadenectomy in UCUT. Patients who benefit from lymphadenectomy have been examined. According to studies that analyzed the benefit of lymphadenectomy (Table 2), this role is limited in patients with pT2 stage tumors or higher. The therapeutic benefit of lymphadenectomy is also more clearly demonstrated in patients with pT2 stage tumors or higher (Table 3). Thus, an indication for lymphadenectomy is assumed in patients with pT2 tumors or higher. This is also supported by the results showing the incidence of lymphatic metastases according to pathological stage. Our data shows that the incidence of lymph node metastases increases incrementally as the pathological stage becomes higher (Figure 7). The risk of lymphatic metastases was only at 1% in the patients with pT1 stage tumors or lower, whereas tumors at the pT2 stage show a 7% risk of lymph node metastases. This risk increases to 26% in pT3 tumors. It is reasonable to perform lymphadenectomy in patients with pT2 tumors or higher.

However, there is a major concern about accurate preoperative staging based on current radiological modalities. Although multidetector computed tomography might provide more accurate staging[46], it is likely to be very difficult to distinguish stage 1 from 2. In other words, invasion of the muscle layer of the renal pelvis or the ureter is very difficult to diagnose according to our results[47]. Some tumors clinically diagnosed as carcinoma in situ may upstage to the muscle-invasive diseases pathologically[48]. Thus, we currently consider all patients with an indication of nephroureterectomy as candidates for lymphadenectomy. We omit lymphadenectomy for patients of an advanced age or with severe comorbidity[47].

Association with neoadjuvant or adjuvant chemotherapy

The role of neoadjuvant therapy has been discussed recently since a majority of patients is unfit for cisplatin-based chemotherapy after nephroureterectomy because of the development of chronic kidney disease[49,50]. In addition, adjuvant chemotherapy has little effect on improving survival[51,52]. Thus, the role of neoadjuvant chemotherapy has recently attracted physicians' attention.

A recent retrospective study showed that cisplatin-based neoadjuvant chemotherapy significantly improved patient survival[53]. In addition, multivariate analysis showed that lymphadenectomies where more than 8 lymph nodes were resected were no longer a significant factor when neoadjuvant chemotherapy was included. Furthermore, it is difficult to draw a definitive conclusion from these results, which are from a single institute. However, further study is warranted to elucidate the association between the benefit of lymphadenectomy and neoadjuvant chemotherapy.

Adjuvant chemotherapy might enhance the therapeutic benefit of lymphadenectomy. Several studies examined the effect of adjuvant chemotherapy, but most failed to show an improvement in patient survival[51,52,54-56]. We examined the role of adjuvant chemotherapy in a retrospective study. Lymphadenectomy was a significant independent factor reducing the risk of cancer mortality, but adjuvant chemotherapy was not a significant factor, even in the univariate analysis (HR = 1.89, 95%CI: 0.677-5.43; $P = 0.222$)[35]. Our prospective study also showed that adjuvant chemotherapy does not influence either cancer-specific or disease-free survival on univariate analysis in patients with renal pelvic cancer[23]. Thus, these results suggest that the therapeutic benefit of lymphadenectomy

CSS according to the total No. of LNs removed in ≥ pT2

	NO. LNs	Cut-off value						
		5	6	7	8	9	10	11
5y CSS	< Cut-off	64.5	60.7	60.4	64.4	67.4	70.1	70.1
	≥ Cut-off	76.4	82.2	87.3	86.7	83.6	78.0	78.0
P-value		0.64	0.17	0.10	0.07	0.22	0.62	0.62

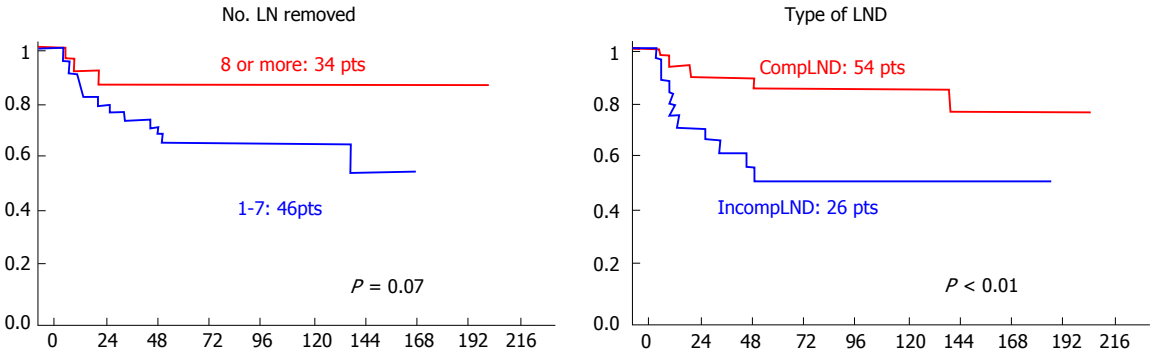

Figure 6 The influence of the number of lymph nodes removed on cancer-specific survival. LND: Lymphadenectomy; CSS: Cancer-specific survival; LNs: Lymph nodes.

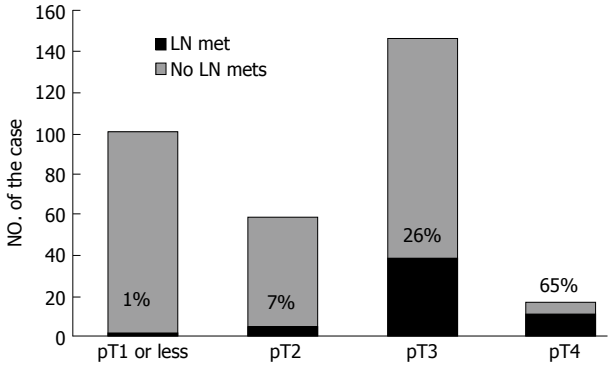

Figure 7 The incidence of lymphatic metastases according to the primary tumor stage. LN: Lymph node.

is independent, but not synergistic with adjuvant chemotherapy.

Is laparoscopic or robotic lymphadenectomy feasible?

Lymphadenectomy was performed using an open procedure for all the patients in our study. The median yield of lymph nodes from template-based lymphadenectomy was 15 in renal pelvic cancer and 14 in ureteral cancer for our prospective study[23]. This number is believed to be the current standard, but it was only 7 in the lymphadenectomy cohort before 2006[35].

Laparoscopic lymphadenectomy results were reported by Abe *et al*[57] showing that the median number of resected lymph nodes was 10. They recently reported the prospective results for their current laparoscopic lymphadenectomy procedure[58]. The median number of lymph nodes removed increased to 14, which is very similar to the number from our prospective study for open lymphadenectomy[23]. Thus, experienced surgeons can perform laparoscopic lymphadenectomy as effectively as an open procedure. However, a long learning curve will be required.

Very few results of robotic lymphadenectomy with nephroureterectomy have been reported. Pugh *et al*[59] reported that the median number of lymph nodes was 11. The mean number of resected lymph nodes was 14.1 according to Lee *et al*[60]. These results are very similar to those from our prospective study. Our opinion is that robotic lymphadenectomy may be feasible. The appropriate procedure can be determined by the surgeons' experience. However, we believe that an open procedure is the most reliable and the experience of surgeons is not likely to influence its quality.

What are the disadvantages of lymphadenectomy?

The disadvantages of lymphadenectomy in UCUT should also be considered. In our prospective study, we compared the incidence of complications in the template-based lymphadenectomy group to that of the no lymphadenectomy group (Table 4)[23]. Patients who undergo template-based lymphadenectomy show a higher incidence of complications at all grades as well as grade 3 or higher, but without a significant difference. More frequent complications in the lymphadenectomy group include numbness in the thighs and lymphorrhea. Lymphorrhea including chyle fistulas occur at a higher incidence and grade in those who undergo lymphadenectomy than those who do not (5.2% *vs* 1.1%). One patient required percutaneous drainage, but conservative management spontaneously resolved the problem in other patients. Numbness in the thigh may be associated with lymphadenectomy for pelvic nodes (2.5% *vs* 0%).

Rao *et al*[38] reported complications from a prospective study of super-extended lymphadenectomy that encompassed the area from the retroperitoneum to the pelvis. The morbidities in this study were transfusion (32%), ileus (5%), and chylous leakage (10%). Chylous leakage was managed with conservative treatment except for 1 patient for whom surgical intervention was

Table 4 Perioperative complications of the template-based lymphadenectomy and the no lymphadenectomy group

Template-based lymphadenectomy (77 patients)			No lymphadenectomy (89 patients)	
	Morbidity	*n*	Morbidity	*n*
	Grade 1		Grade 1	
	Numbness of thigh	2	Atelectasis	1
	lymphorrhea	1	Delirium	2
	Wound infection	1	Wound infection	2
	Grade 2		Lymphorrhea	1
	Chylous leakage	1	Subcutaneous hematoma	1
	Retroperitoneal abscess	1	Grade 2	
	Lymphorrhea	1	Anemia	1
	Gastric ulcer	1	Grade 4	
	Grade 3a		Intraoperative massive bleeding	1
	Lymphorrhea	1		
	Grade 3b			
	Rectal injury	1		
	Ureteral injury	1		
Incidence (all grades)		11		9
		14.20%		10.10%
Incidence (≥ grade 3)		3		1
		3.90%		1.10%

needed.

We also compared intraoperative bleeding and operation time in patients who underwent template-based lymphadenectomy or no lymphadenectomy. The lymphadenectomy group showed more intraoperative bleeding and longer operation times (407 mL *vs* 321 mL, 323 min *vs* 288 min), but there was no significant difference[19]. The length of hospital stay after surgery did not differ between groups. A randomized prospective study examining the role of lymphadenectomy in renal cell carcinoma showed no increase in complications from extensive lymphadenectomy compared to no lymphadenectomy (26% *vs* 22%)[61].

We performed lymphadenectomy in an open procedure with a retroperitoneal approach in all patients. Thus, we cannot comment on transperitoneal lymphadenectomy for UTUC. However, in the above randomized phase 3 trial for kidney cancer, all surgeries were done with a transperitoneal open procedure[61]. Thus, we believe that lymphadenectomy does not increase the risk of complications, irrespective of the approach used.

Thus, lymphadenectomy may result in a slight increase in complications including lymphorrhea or hemorrhage, but has no influence on patients' recovery from surgery. We should consider the complications of lymphadenectomy; however, they should not dissuade surgeons from performing lymphadenectomy except in patients with comorbidity or of an advanced age.

CURRENT RECOMMENDATIONS FOR LYMPHADENECTOMY IN THE 2015 GUIDELINES

Four guidelines are currently available for UCUT. The latest European Association of Urology guidelines (2015 version) recommend lymphadenectomy for cases of invasive disease[62]. The recommendation grade is still low at grade C. The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology Version 1.2015 state that lymphadenectomy should be a part of nephroureterectomy for high-grade tumors, or tumors that are large and invade the renal parenchyma[63]. The National Cancer Institute-Physician Data Query suggests that lymphadenectomy at the time of radical nephroureterectomy may offer prognostic information, but little, if any, therapeutic benefit[64]. The guideline of the Japanese Urological Association also supports the staging benefit, and recommends lymphadenectomy to improve survival in patients with advanced disease with suspected muscle invasion as a grade C recommendation[65].

Thus, the current recommendation grade for lymphadenectomy still remains low; however, our nonrandomized prospective study is not incorporated[23]. The role of lymphadenectomy is expected to be supported by guidelines at a higher level than at present, especially in renal pelvic cancer.

CONCLUSION

Herein, the current situation and issues of lymphadenectomy for UCUT have been summarized. There are some major problems underlying lymphadenectomy, including the lack of standardization of the extent of lymphadenectomy and a randomized prospective trial. However, we believe that lymphadenectomy is strongly recommended for tumors of the renal pelvis. Lymphadenectomy should follow the anatomical template. Further research is warranted to establish the role of lymphadenectomy in UCUT.

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