

Lymphadenectomy in upper tract urothelial carcinoma: Clinical insights and controversies (Review)

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Abstract. Upper tract urothelial carcinoma (UTUC), a relatively rare but highly malignant tumor arising from the renal pelvis and the urothelial layer of the ureter, accounts for 5-10% of all urothelial malignancies. The lack of specific early symptoms commonly results in a delayed diagnosis, with >60% of cases being diagnosed at an advanced stage of the disease. Lymph node involvement can critically affect the clinical outcomes, thus serving as a key prognostic indicator, guiding both staging protocols and treatment strategies. Lymphadenectomy, typically performed alongside radical nephroureterectomy, not only assists in evaluating the extent of the regional metastases, but also plays a critical role in

guiding both staging and treatment planning. Although several studies have suggested that a more extensive lymph node dissection (LND) can improve cancer-specific survival and disease-free survival rates, there is still no consensus on the optimal extent of dissection or a universally accepted surgical template. The present review aims to summarize the existing evidence on the efficacy of LND in UTUC, thus emphasizing its potential in staging, outcome prediction and possible survival benefits. The review also aims to address the challenges caused by inconsistent LND practices and the limited availability of robust prospective data. Furthermore, it discusses novel biomarkers that could improve patient classification, and proposes future research directions to improve the management of UTUC through more personalized and evidence-driven LND strategies.

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Abbreviations: UTUC, upper tract urothelial carcinoma; LND, lymph node dissection; RNU, radical nephroureterectomy; CSS, cancer-specific survival; DFS, disease-free survival; LNM, lymph node metastasis; EAU, European Association of Urology; NCCN, National Comprehensive Cancer Network; AUA, American Urological Association; CT, computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging; USPIO, ultrasmall superparamagnetic iron oxide; PDK, pyruvate dehydrogenase kinase; LVI, lymphovascular invasion; AUC, area under the curve; OR, odds ratio

Key words: upper tract urothelial carcinoma, lymph node dissection, prognostication, survival benefits, lymph node metastasis

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1. Introduction

Upper tract urothelial carcinoma (UTUC) is a rare yet clinically aggressive type of cancer, which arises from the transitional epithelium lining the renal pelvis (RP), ureters and proximal urethra (1). Distinct from bladder urothelial

carcinoma, UTUC is characterized by unique biological behaviors in terms of clinical presentation, anatomical localization and molecular alterations (2,3). Accounting for 5-10% of all urothelial cancer cases, this disease shows a high prevalence of nodal metastases at initial diagnosis, with lymph node involvement being recorded in 20-30% of cases (4). The frequent absence of early symptoms is considered a marked challenge in the management of UTUC, and commonly leads to late-stage diagnosis, with ~60% of cases being diagnosed at an advanced disease stage (5). In high-grade or locally invasive tumors, the lymph node metastasis (LNM) rate can increase to 30-40% (6). Therefore, LNM is considered a well-established predictor of poor survival outcomes (7).

The treatment approach for non-metastatic UTUC depends on the risk level of the tumor. For patients with low-risk (LR) UTUC, clinicians typically favor minimally invasive approaches, including kidney-preserving endoscopic procedures that maintain renal function. By contrast, high-risk (HR) UTUC typically necessitates a conventional treatment approach, including radical nephroureterectomy (RNU) combined with excision of the bladder cuff. This strategy aids in local disease management and can enhance cancer-specific survival (CSS) outcomes (1,8). It has been reported that in UC, LNM can commonly spread to nearby lymph nodes through the lymphatic drainage pathway (9). Therefore, systemic lymphadenectomy could exert both therapeutic and diagnostic roles by providing more accurate tumor staging, which in turn could improve treatment planning after surgery (10,11). This is particularly important for identifying patients who could benefit from additional therapies (1,12). However, there is still no consensus on the extent of lymph node dissection (LND) in patients with UTUC.

The present review aims to provide an integrative analysis of LND in the management of UTUC, highlighting its evolving clinical applications. The clinical relevance of LND in staging protocols and disease characterization, as well as its prognostic significance in predicting therapeutic efficacy and recurrence, are also discussed. Current controversies regarding surgical strategies and the technical demands associated with LND procedures are critically evaluated. Furthermore, the potential survival benefits associated with the extent of lymph node dissection are analyzed through both clinicopathological and molecular perspectives.

2. Pathophysiology and lymphatic drainage patterns

In UTUC, lymph nodes are the primary sites for metastasis. Understanding lymphatic drainage patterns is crucial for defining the extent of LND and improving the accuracy of staging and prognosis (13). The drainage variations by tumor location are illustrated in Fig. 1.

Although currently no standardized LND templates have been established by major guidelines, such as those provided by the European Association of Urology (EAU) and American Urological Association (AUA) (14-16), a foundational work by Akaza *et al* (17) was the first to propose a Tumor-Node-Metastasis framework for UTUC. Later, Kondo and Tanabe (9) refined this framework by mapping eight anatomical zones associated with tumor location, namely the RP, and the upper, middle or lower ureter,

bilaterally. Regional nodes were defined as those with a metastasis risk of >10%. Proximal segments correspond to areas lying above the inferior mesenteric artery (IMA), the mid-ureteral region spans from the IMA to the common iliac (CI) artery and the distal ureter (DU) extends to the ureteral meatus (9). This mapping laid the foundation for the widely referenced 'Kondo and Matin templates' (9,18,19). The LND templates based on the primary tumor location from the studies by Matin *et al* (18), Kondo *et al* (19) are illustrated in Fig. 2.

Lymph node status remains a critical prognostic indicator in UTUC. Therefore, previous studies indicated that node-negative (pN0) patients exhibited significantly superior 5-year disease-free survival (DFS) (84.5 vs. 43.6%; $P<0.001$) and CSS (78.3 vs. 33.2%; $P<0.001$) rates compared with node-positive (pN+) patients (9,20,21). These findings underscored the significant effect of nodal involvement in the onset of adverse effects and highlighted the importance of accurate nodal assessment in guiding adjuvant treatment decision, as evidenced by clinical trials, such as POUT (22).

Emerging evidence has also suggested that other clinical factors, such as age and gender, and biomarkers, including elevated fibrinogen, cystatin-C, C-reactive protein, neutrophil-to-lymphocyte ratio of >2.7, albumin-to-globulin ratio of <1.45, and preoperative anemia, can be also associated with LNM risk (13,14,23-28).

3. Clinical application and extent of LND in UTUC

Building on the anatomical principles established by the 'Kondo and Matin templates' (9,18,19), several clinical studies have evaluated the therapeutic outcomes of LND. Kondo *et al* (29) performed retrospective and prospective analyses via comparing the efficacy of systematic complete LND (CLND), incomplete or limited LND (ILND), and no LND (9,29-31). The results demonstrated that in patients with $\geq pT2$ disease, CLND could display superior CSS compared with ILND/no LND, and more particularly in patients with $pT3+$ tumors (5-year CSS, 73.2 vs. 43.7 and 47.3%, respectively) (9). For patients with $\geq pT2$ cN0M0 UTUC, CLND showed improved CSS compared with ILND (86 vs. 71%; $P=0.04$). Furthermore, CLND could independently predict both CSS and regional recurrence-free survival (RFS) in RP tumors (31). However, the survival benefits were less evident in distal ureteral tumors, possibly due to variations in the extent of lymph node dissection. By contrast, the population-based study by Lughezzani *et al* (8), and a multi-institutional study (32) reported no significant therapeutic survival benefits for LND, although in these studies the dissection templates were not specified.

Extended LND is increasingly recognized for its prognostic value. However, the majority of RNU procedures remove <8 lymph nodes (33). It has been reported that lymph node density, defined as the number of positive nodes to that of total nodes, can provide higher prognostic value compared with absolute lymph node counts. Therefore, a nodal density ratio of >30% was associated with higher recurrence [hazard ratio (HR), 1.8; $P=0.021$] and mortality (HR, 1.7; $P=0.032$) risks (34,35). Consistently, lymph node density of >20% could predict worse RFS (HR, 1.94) and

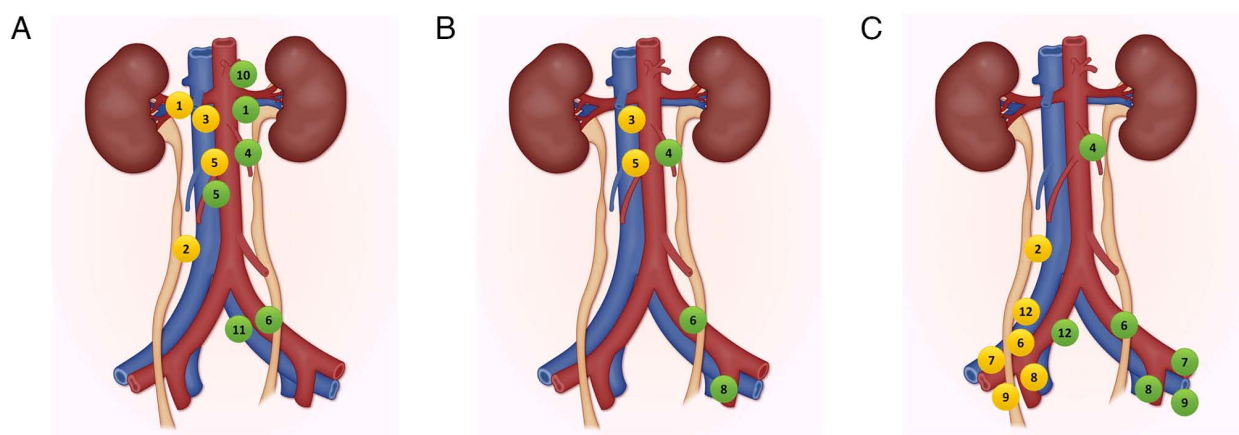


Figure 1. Regional lymphovascular drainage depending on the location of the primary tumors according to the studies by Matin *et al* (18) and Kondo and Tanabe (9). Regional nodal sites for the renal pelvis and the (A) upper ureter, (B) middle ureter and (C) distal ureter, with yellow circles representing the right side and green circles representing the left side. 1, renal hilar; 2, paracaval; 3, retrocaval; 4, paraaortic; 5, interaortocaval; 6, common iliac; 7, external iliac; 8, internal iliac; 9, obturator; 10, suprahilar; 11, aortic bifurcation; 12, presacral.

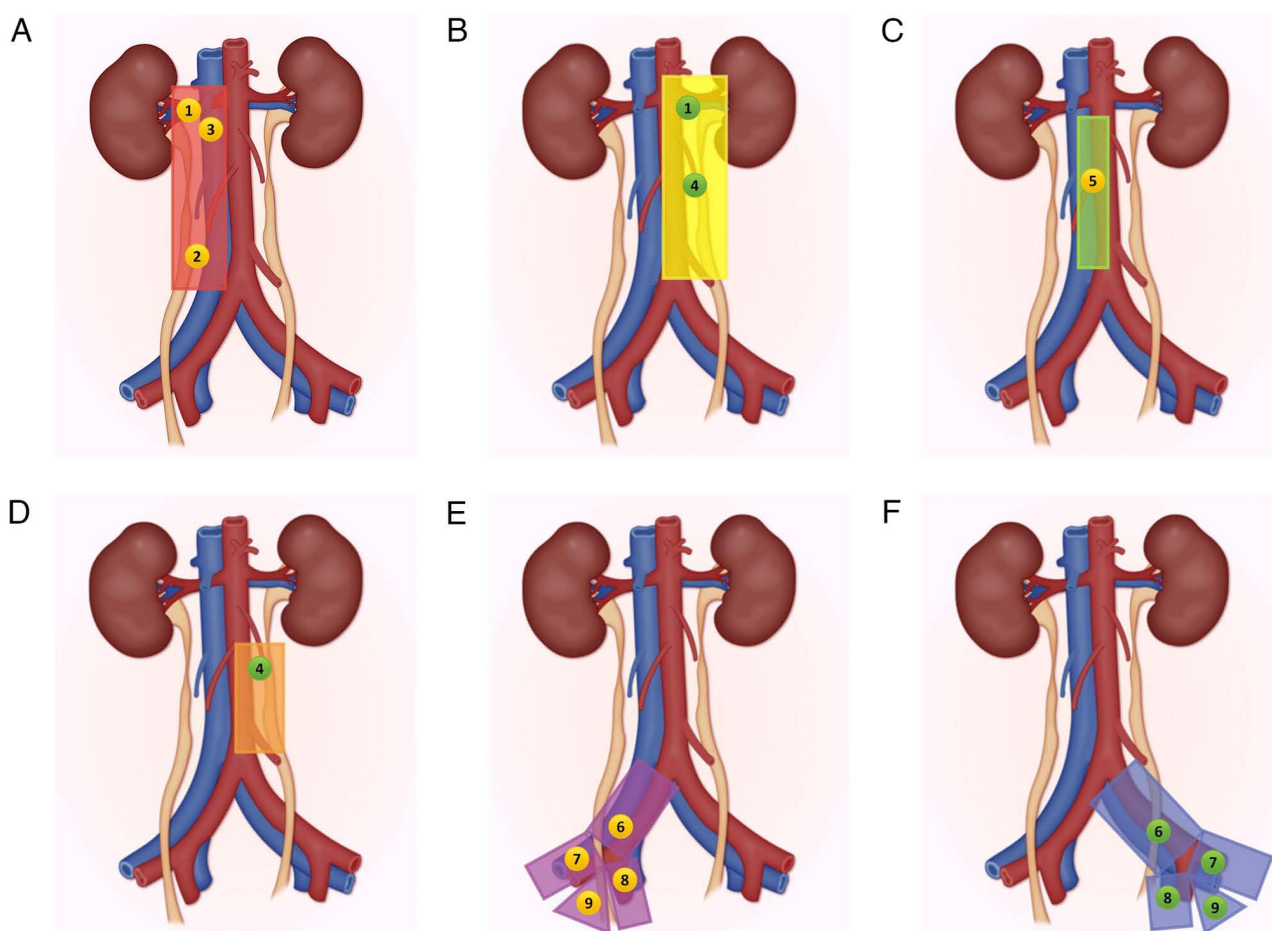


Figure 2. Templates for lymphadenectomy based on the primary tumor location according to the studies by Matin *et al* (18) and Kondo *et al* (19). (A) Right renal pelvis and upper ureter (red box: Renal hilar, paracaval and retrocaval LNs). (B) Left renal pelvis and upper ureter (yellow box: Renal hilar and paraaortic LNs). (C) Right middle ureter (green box: Interaortocaval LNs). (D) Left middle ureter (orange box: Paraaortic LNs). (E) Right distal ureter (purple box: Common iliac, external iliac, internal iliac and obturator LNs). (F) Left distal ureter (blue box: Common iliac, external iliac, internal iliac, obturator LNs). 1, renal hilar; 2, paracaval; 3, retrocaval; 4, paraaortic; 5, interaortocaval; 6, common iliac; 7, external iliac; 8, internal iliac; 9, obturator. LN, lymph node.

overall survival (OS; HR, 2.34) (20). The safety of LND has been also well-documented. Therefore, operative duration, estimated blood loss, and hospitalization period were comparable across CLND/ILND/no LND cohorts, with only

a minor increase in the incidence of complications reported in CLND (9,36,37).

Due to limited data, the optimal extent of LND in patients with UTUC remains still controversial. The widely

adopted 'Kondo and Matin template' (9,18) is based on small samples. Furthermore, the genomic differences in UTUC between Chinese and Western populations suggests that the application of LND templates should be region-specific. Notably, to date no studies have directly compared the effect of different LND extents on OS and PFS (38).

The conflicting conclusions between the studies by Kondo *et al* and Lughezzani *et al* could be due to critical methodological disparities. Firstly, there was heterogeneity in the surgical techniques applied. Therefore, Kondo *et al* employed a standardized template-based dissection protocol, including the dissection of interaortocaval (IAC) lymph nodes in right RP tumors. By contrast, the population-based analysis by Lughezzani *et al* lacked specified dissection templates, potentially leading to omission of HR nodal regions. Secondly, a patient selection bias was recorded. In the study by Kondo *et al* only patients with cN0 UTUC, who underwent meticulous CLND dissection were included. However, in the study by Lughezzani *et al* the patient cohort was more heterogeneous, encompassing both clinically node 0 (cN0) and cN+ cases, with variable extents of dissection, thus diluting any therapeutic effects. Thirdly, adjuvant therapy rates varied between the two studies. Therefore, >40% of patients in the study by Lughezzani *et al* received adjuvant chemotherapy (ChT) compared with only <15% in Kondo's cohort, thus potentially obscuring LND-specific survival benefits (8,9,11,30,31). These factors collectively indicated that the discrepancies in the survival rates could reflect limitations in study design rather than the intrinsic therapeutic value of LND. Future prospective trials should standardize dissection templates and stratify patients based on nodal risk to more accurately evaluate the therapeutic value of LND.

4. Prognostic significance of LND in UTUC

LNM is associated with adverse clinical outcomes and substantially decreased survival (39). Although evidence remains conflicting regarding the therapeutic value of LND, its potential in achieving definitive pathological staging of UTUC has been well documented. The majority of the available data has been derived from retrospective, single-institution studies, with several of them supporting the prognostic value of LND (12,29,40). These reports demonstrated that pN0 patients exhibited a superior CSS compared with pN+ patients, with 5-year CSS estimates of 56-85 and 0-39%, respectively. These findings indicated that accurate nodal evaluation via LND during RNU could enhance the postoperative risk classification and guide treatment decisions. Notably, two studies identified pNx status as an independent survival risk factor compared with pN0 status (29,41). By contrast, another study did not detect nodal status-related differences in survival endpoints (42). In addition, a population-based study that included 2,824 subjects revealed marked disparities in 5-year CSS, with rates of 34, 78, and 81% recorded for pN+, pNx and pN0 patients, respectively ($P < 0.001$). However, no prognostic significance was reported between the pN0 and pNx groups (43). Only two multicenter cohorts showed differences in CSS rates between the pN0 and pNx groups (12,44). Ouzzane *et al* (43) found no independent association between CSS and nodal status in adjusted models

(pN+ vs. pN0: HR, 1.6; 95% CI, 0.8-3.4; $P = 0.104$; and pNx vs. pN0: HR, 1.14; 95% CI, 0.7-1.9; $P = 0.592$). Subgroup analyses more consistently supported the prognostic value of LND in staging muscle-invasive or locally advanced UTUC (11,32,45). However, the findings of the aforementioned studies have not been verified by a multicenter study (43). Importantly, studies failing to demonstrate staging benefits commonly lack dissection protocol details, thus emphasizing the need for standardized LND templates.

Recent advances in immunotherapy have further underscored the critical role of LND in guiding systemic therapy decisions. According to the 2023 EAU guidelines, adjuvant nivolumab is now recommended for HR patients ($\geq pT3$ or pN+) who are ineligible for or decline platinum-based ChT, provided that their tumors express programmed death-ligand 1 (PD-L1) $\geq 1\%$ (15). This recommendation is based on proven survival benefits observed in the CheckMate 274 trial in patients with muscle-invasive UC (46). However, UTUC-specific data remain limited. Notably, LND remains indispensable for identifying nodal involvement (pN+ status), which directly determines eligibility for both adjuvant ChT and immunotherapy. While immune checkpoint inhibitors (ICIs) offer novel therapeutic insights, they do not alter the fundamental indications or extent of LND, a template-based dissection approach, which continues to be prioritized for accurate pathological staging and local disease control. Future studies should explore whether genomic differences, such as fibroblast growth factor receptor (FGFR) alterations, between Eastern and Western populations could affect immunotherapy responsiveness and necessitate region-specific LND templates (15).

5. Therapeutic strategies and controversies in patients with cN+ UTUC

For patients with cN+ UTUC commonly experiencing lymphatic dissemination, neoadjuvant platinum-based ChT prior to RNU/LND merits consideration. However, current guidelines lack UTUC-specific evidence to endorse this strategy, compared with the well-established protocols for bladder cancer (1,47). Regarding ChT timing in operable cN+ disease, the multicenter study by Shigeta *et al* (48) compared neoadjuvant vs. adjuvant approaches and found that preoperative ChT was associated with significantly improved 3-year DFS (58.2 vs. 37.1%; $P = 0.004$) and CSS (71.3 vs. 47.6%; $P = 0.002$) rates. Notably, selecting adjuvant therapy following RNU critically depends on the pathological findings of LND (49). A previous study suggested that initiating gemcitabine-cisplatin ChT within 90 days after surgery could improve DFS rate (HR, 0.45; 95% CI, 0.30-0.70; $P < 0.0001$) in patients with locally advanced UTUC (22). In metastatic UC, cisplatin-based ChT showed improved response rates compared with carboplatin-based ChT (50). However, as non-responders often switch to immunotherapy, selection bias persists (48). These findings reinforce managing cN+ disease as systemic malignancy requiring comprehensive treatment. Importantly, the majority of studies evaluating RNU by LND excluded cN+ patients, hindering natural history assessment and perpetuating debates regarding the therapeutic value of LND. Although the oncological effect of LND is modest in cN+ cases, accurate nodal staging remains vital for systemic

Table I. Stage classification for upper tract urothelial carcinoma: AJCC staging and proposed modifications.

Stage	AJCC staging (6th, 7th and 8th editions)	Modifications by Li <i>et al</i> (52)	Modifications by Abdel-Rahman (53)
I	T1N0M0	T1N0M0	T1N0M0
II	T2N0M0	T2N0M0	T2N0M0
III	T3N0M0	T3N0M0	T3N0M0
IV	T4/N+/M1	Low grade (G1-2): T4NxM0, TxN1-2M0, TxNxM1 High grade (G3-4): T4NxM0, TxN1-2M0, TxNxM1	IVA: T4/N+M0 IVB: T ₁₋₄ /N _{0/+} M1

Nx, regional lymph nodes cannot be assessed; N+, regional lymph node-positive; M1, distant metastasis is present; T4, tumor has invaded into adjacent organs; Tx, primary tumor cannot be assessed; AJCC, American Joint Committee on Cancer.

treatment planning (22,51). The current and proposed staging classifications are summarized in Table I (52,53).

6. Controversy of LND in UTUC

Current urological guidelines show considerable variability in their recommendations for LND in UTUC. According to the 2022 EAU guidelines, template-based LND should be considered over node-quantity-based approaches, thus emphasizing its potential survival advantages. Template-based LND has been associated with prolonged CSS time in muscle-invasive cases, reduced local recurrence rates, and improved outcomes in patients without clinical or pathological nodal involvement. Due to the difficulty in preoperatively diagnosing Ta and T1 tumor stages, the EAU strongly recommends concurrently performing template-based LND for all patients undergoing RNU (15). The 2023 AUA guidelines recommend LND during RNU or urethrectomy for HR UTUC, while in patients with LR UTUC, it can be performed under particular conditions, such as intraoperative detection of suspicious nodes, mid/distal ureteral tumors requiring template dissection, discordant biopsy/imaging features or when adjuvant therapy eligibility requires pathological nodal staging (16). The 2023 edition of the National Comprehensive Cancer Network (NCCN) guidelines recommends regional LND for high-grade, large, renal pelvic cancers that invade the renal parenchyma, and high-grade ureteral cancers (54). However, a more scientifically grounded LND template should be developed based on studies of LNM distribution and risk probability.

The standardized LND boundaries recommended by the EAU, NCCN and AUA guidelines are delineated in Table II (15,16,18,19). The EAU criteria integrate findings from three foundational studies, two of which provide precise anatomical resection templates (18,31,55). For malignancies involving the RP, upper ureter (UU) and mid-ureter (MU), Kondo's protocol mandates resection of the renal hilar (RH), paracaval (PC), retrocaval (RC) and IAC lymph nodes (31). By contrast, left-sided tumors necessitate RH and periaortic (PA) lymph node clearance. Lesions affecting the DU require the comprehensive dissection of ipsilateral CI, external iliac (EI), internal iliac (II) and obturator (Ob) nodal basins. Matin's approach differentiates primary and extended dissection zones, particularly for MU tumors, to

optimize the detection of metastasis (18). For right RP and UU tumors, RH/PC/RC dissections supplemented with IAC node dissection are recommended to enhance sensitivity. For left counterparts, RH/PA nodes with IAC inclusion are preferred. Right MU tumors need IAC, PC, and RC node dissection for residual disease, while left-sided cases include PA, CI and II nodes. Finally, for right-sided DU tumors, resection of CI, EI, II, Ob and PC nodes is warranted, while for left-sided DU tumors, the resection includes CI, EI, II, Ob and PA nodes (18).

According to the NCCN guidelines, the surgical management of the majority of MU neoplasms typically requires nodal dissection extending from the renal hilum to the branching of the inferior vena cava, including the precaval nodes, with concurrent removal of the CI, EI, Ob and pelvic arterial lymph nodes. For PA tumors, nodal resection should encompass the region between the renal pedicle and aortic division, incorporating the CI, EI, Ob and pelvic vascular nodes. In patients with DU tumors, complete unilateral excision of the CI, EI, Ob and pelvic arterial lymph nodes is required (54).

According to AUA recommendations, surgical management of pelvicalyceal malignancies should include unilateral dissection of the major vascular lymph node bundles spanning from the RH to the origin of the IMA. Tumors located to the upper two-thirds of the ureter warrant dissection of lymph nodes extending from the RH to the aortic bifurcation. However, tumors of the third distal ureter require removal of Ob and EI nodes, with optional dissection of the II and CI nodes. Emerging evidence has suggested that for cranial LNM metastasis, extended dissections based on clinical assessment should be considered (18,29,36,37,45,56-63).

Analysis of the Surveillance, Epidemiology and End Results database by Zhai *et al* (21) and Dong *et al* (64) suggested a potential survival benefit from LND in patients with cN0 UTUC, particularly in those with T3-4 disease, possibly due to the clearance of micrometastasis. However, to verify the effect of dissection extent on oncological outcomes, further studies are urgently warranted.

Given the ongoing debate regarding the efficacy of LND in UTUC, defining a reasonable dissection range is urgently needed. However, the current research on LND in UTUC remains limited, and the field is still in an exploratory state. Notably, no studies have directly compared the effects of different dissection ranges on clinical outcomes, such as OS

Table II. Lymph node dissection protocols in upper tract urothelial carcinoma: EAU, AUA and NCCN perspectives.

Guideline	Tumor location	Extent of LND	Lymph node groups	(Refs.)
EAU	RP, UU, MU and DU tumors (right-sided/left-sided)	- Right-sided/left-sided RP, UU and MU tumors: RH, PC, RC and IAC LNs/RH, and PA LNs. - Right-sided/left-sided DU tumors: Ipsilateral CI, EI, Ob and II LNs. - Right-sided/left-sided RP and UU tumors (Matin <i>et al</i>): Primarily RP, PC, RC LNs/RH and PA LNs, with additional IAC nodes on both sides to increase the chance of capturing all LNMs. - Right-sided/left-sided MU tumors (Matin <i>et al</i>): Primarily IAC LNs/PA LNs, with addition of PC, RC, CI and II nodes to remove remaining LNMs. - Right-sided/left-sided DU tumors (Matin <i>et al</i>): Primarily ipsilateral CI, EI, II and Ob LNs, with addition of PC and PA nodes to remove remaining LNMs.	RH, PC, RC, IAC, CI, EI, Ob, II and PA	(15,18,19)
AUA	Pyelocaliceal system (upper 2/3 of ureter, distal 1/3 of ureter)	- Tumors in the pyelocaliceal system: LNs of the ipsilateral great vessel extending from the RH to at least the inferior mesenteric artery. - Tumors in the upper 2/3 of the ureter: LNs of the ipsilateral great vessel extending from the RH to the aortic bifurcation. - Tumors in the distal 1/3 of the ureter: Ipsilateral pelvic LND, including at minimum the Ob and EI nodal packets. II and CI nodes may be removed in the appropriate clinical setting^a. Higher dissection^b may be considered based on cranial migration of LNM and clinician judgment.	RH, PA, CI, EI, Ob and II	(16)
NCCN	RP, UU, MU and DU tumors (left-sided/right-sided)	- Left-sided RP, UU and MU tumors: Regional LND includes PA LNs from the RH to the aortic bifurcation. Most MU tumors will also include CI, EI, Ob and hypogastric LNs. - Right-sided RP, UU and MU tumors: Regional LND includes PC LNs from the RH to the inferior vena cava bifurcation. Most MU tumors will also include CI, EI, Ob and hypogastric LNs. - DU tumors: Regional LND should include CI, EI, Ob and hypogastric LNs.	PA, CI, EI, Ob, hypogastric and PC	(54)

^aLymph node dissection may be adapted depending on the clinical stage, preoperative imaging (such as computed tomography or magnetic resonance imaging findings), or intraoperative findings, such as suspected or confirmed lymph node metastasis. ^bHigher dissection refers to extending the dissection to higher lymph node levels (for example, aortic bifurcation) in cases where lymph node metastases are suspected to migrate cranially, which may be considered based on tumor characteristics (size and stage) or clinician judgment. RH, renal hilar; PA, paraaortic; PC, paracaval; RC, retrocaval; IAC, interaortocaval; CI, common iliac; EI, external iliac; II, internal iliac; Ob, obturator; RP, renal pelvis; UU, upper ureter; MU, middle ureter; DU, distal ureter; LND, lymph node dissection; EAU, European Association of Urology; NCCN, National Comprehensive Cancer Network; AUA, American Urological Association.

and PFS. Although several anatomical templates for LND have been proposed, standardizing LND indications and techniques is challenging due to the retrospective and multicenter nature of the existing studies. In the majority of cases, the decision to perform LND is based on the

judgment of the surgeon, considering different factors, such as clinical presentation, tumor location and laterality. The patient outcomes from the reviewed studies according to the lymph node pattern are summarized in Table III (11,14, 20,30,32,40,41,45,56,59,61,65,66).

Table III. Summary of clinical outcomes and treatment approaches in upper tract urothelial carcinoma.

First author, year	Design	Year	Sample size, n	pN stage, n (%)	5-year DFS, %	5-year CSS, %	5-year OS, %	Median number of LNs removed (range)	LN density	Surgical approach, n (%)	Post-operative complications	Median follow-up (range), months	(Refs.)
Brown <i>et al</i> , 2006	Single institutional retrospective	2006	184	pN0, 89 (48); pNx, 71 (39); pN+, 24 (13)	47.4; 47.4; NS	78.0; 78.0; 37.6	70.3; 70.3; 33.9	NS	NS	Open, 158 (86); laparoscopic with open bladder-cuff excision, 26 (14)	NS	30.0	(65)
Kondo <i>et al</i> , 2010	Single institutional retrospective	2007	181	pN0, 139 (77); pNx/pN+, 32 (18)/10 (5)	NS	85.2; 15.5	NS	6.0 (2-30)	Mean, 3.7 (range, 0-16) (absolute number)	NS	NS	NS	(30)
Brausi <i>et al</i> , 2007	Multi-institutional retrospective	2007	82	pN0/pN+, 24 (29)/16 (20); pNx, 42 (51)	NS	NS	80.0; 30.0	NS	NS	Open transperitoneal, 74 (90); open flank, 8 (10) Open (98); Laparoscopic (2)	NS	64.7	(56)
Secin <i>et al</i> , 2007	Single institutional retrospective	2007	252	pN0, 105 (41); pNx 28 (11); pN+, 119 (48)	NS	56.0; 73.0; 0	NS	4.0 (2-10)	NS		NS	37.0	(40)
Roscigno <i>et al</i> , 2008	Single institutional retrospective	2008	132	pN0, 69 (52); pNx, 27 (20); pN+, 36 (28)	72.0; 39.0; 35.0	73.0; 48.0; 39.0	NS	8.0 (2-24)	NS	Open (100)	NS	42.0 (2-191)	(41)
Roscigno <i>et al</i> , 2009	Multi-institutional retrospective	2009	1,130	pN0, 412 (36); pNx, 578 (51); pN+, 140 (13)	71.0; 66.0; 29.0	77.0; 69.0; 35.0	NS	NS	NS	Open, 924 (82); laparoscopic, 206 (18) NS	NS	45.0 (1-250)	(45)
Lughezzani <i>et al</i> , 2010	Multi-institutional retrospective	2010	2,842	pN0, 1,835 (64); pNx 747 (26); pN+, 242 (9)	NS	81.2; 77.8; 34.2	NS	NS	NS		NS	43.0 (1-203)	(11)
Mason <i>et al</i> , 2012	Multi-institutional retrospective	2012	1,029	pN0, 199 (20); pNx, 753 (73); pN+, 77 (7)	90.9; 70.6; 80.0	72.1; 74.7; 29.8	NS	4.3 (mean)	Mean, 20%	Open, 583 (57); laparoscopic, 446 (43)	NS	19.8 (7.2-53.8)	(20)
Burger <i>et al</i> , 2011	Multi-institutional retrospective	2011	785	pN0, 136 (17); pNx, 595 (76); pN+, 54 (7)	71.6; 76.9; 21.3	79.0; 77.4; 26.7	NS	3.0 (2-6)	NS	Open, 715 (91); laparoscopic, 70 (9)	NS	34.0 (15-65)	(32)

Table III. Continued.

First author, year	Design	Year	Sample size, n	pN stage, n (%)	5-year DFS, %	5-year CSS, %	5-year OS, %	Median number of LNs removed (range)	LN density	Surgical approach, n (%)	Post-operative complications	Median follow-up (range), months	(Refs.)
Yoo <i>et al</i> , 2017	Single institutional retrospective	2017	418	pN0, 116 (29); pNx, 286 (68); pN+, 16 (3)	76.4; 73.4; 93.7	NS	80.2; 71.7; 12.5	7.0 (3-10)	NS	Open, 106 (37); minimal invasive, 180 (63)	NS	69.0	(60)
Ikeda <i>et al</i> , 2017	Multi-institutional retrospective	2017	404	pN0, 182 (45); pNx, 177 (45); pN+, 40 (10)	78.3; 61.9; 33.2	84.5; 73.3; 43.6	NS	6.0 (3-10)	NS	Open, 296 (74); laparoscopic, 103 (26)	NS	43.0 (17-89)	(59)
Inokuchi <i>et al</i> , 2017	Multi-institutional retrospective	2017	2,037	pN0, 955 (47); pNx, 859 (42); pN+, 223 (11)	NS	NS	69.3; 60.5; 30.0	6.0 (3-11)	NS	Open, 1,234 (60.5); laparoscopic, 787 (38.6)	NS	45.8 (21.8-75.9)	(14)
Li <i>et al</i> , 2021	Multi-institutional retrospective	2021	1,340	pN0, 278 (21); pNx, 1,004 (75); pN+, 58 (4)	NS	NS	NS	NS	NS	Hand-assisted, 741 (55); pure laparoscopic, 458 (34); robotic, 141 (11)	Clavien-Dindo >2: 80 patients (6%)	NS	(66)

n (%) values indicate number of patients receiving therapy (percentage of total sample size). NS, not specified; DFS, disease-free survival; CSS, cancer-specific survival; OS, overall survival; LN, lymph node.

7. Surgical outcomes and complications associated with LND in UTUC

Radical RNU can be performed using open, laparoscopic or robot-assisted techniques, with comparable oncological and safety outcomes (67,68). A study by Pearce *et al* (62) showed that patients undergoing LND had a 30% higher risk of postoperative complications compared with those without LND. However, no significant differences were observed in intraoperative complications among the different surgical approaches. Robot-assisted NU has been associated with the lowest postoperative complication rate, while open NU exhibits the highest rate, particularly for gastrointestinal and hemorrhagic complications ($P<0.001$).

In a previous study, Ishiyama *et al* (69) applied the Clavien-Dindo grading system (70) to evaluate postoperative complications in patients undergoing CLND compared with those in the no LND or ILND group, following propensity matching. The overall adverse event rates were comparable between the two groups (16.7 vs. 20.0%; $P=0.7385$). However, the incidence of lymphatic leakage was markedly increased in the CLND group (4.76 vs. 0.00%; $P=0.0231$). Notably, only one high-grade complication, namely Clavien-Dindo grade $\geq$ III, occurred in the CLND cohort. The analysis by Pearce *et al* (62) of 16,619 RNU patients, including 2,560 who underwent LND, revealed equivalent intraoperative complication rates between the two groups (4%) (62). Postoperative complications were more common in patients who were treated with LND (27-29%). However, statistical significance was not reached ($P=0.397$). Multivariable analysis revealed a 30% increased risk of surgical morbidity associated with LND [adjusted odds ratio (OR)=1.3]. Winer *et al* (63) revealed a dose-dependent association between the quantity of lymph nodes removed and 30-day postoperative complication rates (OR=1.18 for each additional five lymph nodes excised; 95% confidence interval, 1.05-1.32; $P=0.004$). However, no corresponding increase in high-grade complications (grade, $\geq$ III) was observed.

Furthermore, a randomized trial by Blom *et al* (71) demonstrated no significant differences in morbidity/mortality between different LND extents. However, patients in the LND group exhibited higher rates of blood loss of >1 liter (9.4 vs. 6.5%), thromboembolism (2.2 vs. 1.1%) and lymphatic drainage than the non-LND group. Consistent with other studies, Kondo *et al* (72) compared template-based LND with non-LND approaches and showed numerically higher, but not statistically significant, complication rates across different Clavien-Dindo grades. Procedure-specific events, including thigh numbness (2.6 vs. 0%) and lymphorrhea (5.2 vs. 1.1%), were more common in patients treated with LND compared with the non-LND group, especially in those undergoing pelvic LND. The overall complication rate was 14.2% (3.9% severe) in the LND group compared with 10.1% (1.1% severe) in the no-LND group. An earlier study by Kondo and Tanabe (9) also documented prolonged operation duration (323 vs. 288 min) and greater intraoperative blood loss (407 vs. 321 ml) in patients who underwent LND. It was therefore hypothesized that although LND could be associated with elevated risks of lymphatic and hemorrhagic complications, these could rarely affect clinical recovery.

8. Innovative approaches

Limitations of conventional imaging methods. Computed tomography (CT) imaging remains the first-line diagnostic tool for pretherapeutic evaluation of UTUC, with reported sensitivity and specificity rates of 92 and 95%, respectively (73). Research by Millán-Rodríguez *et al* (74), which included 93 upper tract urothelial tumors from 82 consecutive UTUC patients scheduled for nephroureterectomy, reported promising results for CT, with a sensitivity and specificity of 87.5 and 98%, respectively. Cross-sectional imaging, particularly CT, remains the cornerstone of clinical nodal staging of UTUC. However, a previous multicenter observational trial by Pallauf *et al* (75), encompassing 865 patients with UTUC who underwent RNU with LND, revealed that conventional imaging exhibited high specificity (91%) but low sensitivity (only 25%), thus resulting in limited detection reliability [area under the curve (AUC), 0.58]. Therefore, it was proposed that CT imaging should be primarily used to confirm, rather than to exclude, LNM.

Application and limitations of 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET)/CT in lymph node staging. Conventional imaging techniques, such as CT and PET, have limited precision in identifying the locations of LNM in UTUC (2,75-77). To enhance nodal staging accuracy, researchers are currently investigating biomarker-based approaches and multimodal imaging combinations. Among them, 18F-FDG/PET/CT imaging has shown emerging utility in identifying metastatic nodal involvement in both UTUC and bladder cancer (78-84). Although early studies indicated comparable detection accuracy between 18F-FDG/PET/CT and conventional magnetic resonance imaging (MRI) (82,84-86), accumulating evidence has supported the superiority of this hybrid modality over MRI, CT or PET alone. The strength of 18F-FDG/PET/CT stems from its capacity to detect metabolically active micrometastases (<2.0 mm), which can be undetectable by CT alone, thus enhancing the sensitivity of nodal staging (82,86). However, its limited specificity creates a challenge, particularly in distinguishing cancerous from inflammatory nodes (81). Several retrospective studies have assessed the utility of 18F-FDG/PET/CT for detecting preoperative LNM in UTUC and bladder cancer (78,79). A study published in 2020 reported a sensitivity rate of 82% and a specificity rate of 84% for preoperative nodal staging in UTUC using 18F-FDG/PET/CT (78).

In addition, a previous systematic review, which included three retrospective studies on the detection of LNM in UTUC, reported sensitivities of 82-95% and specificities of 84-91%, thus highlighting the prognostic value of 18F-FDG/PET/CT (81). A comparative analysis in bladder cancer demonstrated a higher sensitivity rate for 18F-FDG/PET/CT (78%) compared with that for CT (44%) for nodal assessment (87). A key limitation of 18F-FDG/PET/CT involves the interference from urinary excretion of the radio-tracer, which can reduce imaging clarity for nodal lesions adjacent to urinary structures (88). Choline PET/CT, which uses (11)C-choline, has also been explored for LNM detection in UTUC. A 2014 study showed high choline uptake in affected lymph nodes in patients with UTUC (89). Additionally,

Polom *et al* (90) attempted to detect sentinel lymph nodes using Technetium-99m injection during ureterorenoscopy and single-photon emission-CT/CT lymphangiography. While theoretically feasible, the method proved challenging due to significant technical constraints during Technetium injection.

Exploration of other imaging methods. Ultrasmall superparamagnetic iron oxide (USPIO) has gained increasing attention as a contrast agent in MRI. Metastatic lymph nodes, lacking macrophages, fail to absorb USPIO, thus resulting in minimal or absent T2-weighted imaging (WI) signal loss. By contrast, benign lymph nodes, which retain the normal activity of macrophages, absorb USPIO, eventually showing low T2WI signals, which aids in distinguishing metastatic nodes from non-metastatic nodes. Emerging evidence has suggested that USPIO-MRI can promote the identification of small nodal metastases, with reported sensitivity ranges of 65-92% and specificity levels of 93-98% (91,92). In an innovative approach, Birkhäuser *et al* (93) integrated diffusion-weighted imaging sequences with USPIO-MRI, achieving identification rates of 87 and 77% for lymph nodes of ≤ 8 and ≤ 3 mm in the short-axis diameter, respectively. The reading time was reduced from 32 to 9 min, with scanning performed 24-36 h post-administration (94). A previous meta-analysis also reported an overall sensitivity of 0.86 for USPIO-MRI in diagnosing pelvic LNM. However, its clinical application remains limited due to safety concerns and high costs (95).

Research into labeled monoclonal antibodies for urothelial neoplasms is ongoing (77). Among them, girentuximab-labeled PET/CT (89Zr-TLX250) has shown promising efficacy in staging renal cell carcinoma and breast cancer. TLX250 targets carbonic anhydrase IX, an enzyme which is significantly overexpressed in urothelial cancer cells (96). A phase I clinical trial is currently underway to assess the potential of 89Zr-TLX250 for imaging urothelial malignancies (87).

Imaging studies are increasingly integrated into preoperative protocols for predicting lymph node metastases in UTUC. A novel diagnostic model incorporating radiological parameters and histopathological characteristics, including pathological staging, lymphovascular invasion (LVI), lesion dimensions and pretreatment nodal status, demonstrated a predictive accuracy of 87.8% for detecting nodal metastasis (AUC=0.878; adjusted concordance index=0.887) (97).

9. Advances and barriers in molecular biomarkers for UTUC

Novel molecular classification frameworks for UTUC increasingly integrate genomic signatures and transcriptome analysis. Fibulin-2 (FBLN), a significant prognostic indicator, is strongly associated with diminished CSS rates and increased risk of metastasis in urothelial malignancies ($P<0.001$). It has been reported that FBLN is upregulated in advanced-stage tumors, also being associated with LNM and enhanced cell proliferation activity (93,98-106). The pyruvate dehydrogenase kinase (PDK) family, which is involved in mediating chemotherapeutic resistance and disease advancement in patients with bladder carcinomas (105-107), exhibits parallel pathobiological significance in UTUC. A previous study by Kuo *et al* (108) indicated that PDK3 upregulation was

significantly associated with aggressive clinicopathological features, including metastatic nodal disease, elevated tumor grade and unfavorable survival prognosis ($P<0.0001$).

Furthermore, other studies demonstrated that cartilage oligomeric matrix protein, another prognostic indicator, was associated with advanced T-stage, LNM, LVI, perineural infiltration, high-grade histology and increased mitotic rates (109-113). Metallothionein 2A was also associated with aggressive behaviors and advanced staging parameters in urothelial malignancies (114).

Laboratory-based biomarkers are also gaining increasing attention. Therefore, the de Ritis ratio (alanine aminotransferase/aspartate aminotransferase) showed prognostic potential in a previous study, since analysis of 135 cases of patients with a de Ritis index of ≥ 1.3 was strongly predictive of LNM ($P=0.0096$) (115,116). It has been reported that the systemic inflammatory status can affect metastasis, thus being considered as an additional prognostic tool (115,116). The systemic inflammation index (SII), defined as the number of neutrophils $\times$ platelet/lymphocyte count, serves as a low-cost prognostic tool (117-122). A study demonstrated that elevated SII values were associated with LVI positivity and poorer OS rates in UTUC (122). Kobayashi *et al* (123) incorporated SII >520 , Eastern Cooperative Oncology Group Performance Status >0 and clinical stage $\geq T3$ into a preoperative risk model to guide therapeutic decision-making.

The 2023 EAU guidelines recognize several emerging molecular biomarkers in UTUC. However, their integration into surgical decision-making remains limited. For example, DNA mismatch repair (MMR) deficiency, and particularly germline *MSH2/MSH6* mutations associated with Lynch syndrome (LS), were recorded in 9% of patients with UTUC, which was a markedly higher rate compared with that observed in bladder cancer (1%). Although LS screening is recommended for patients <60 years or with suggestive family history, its effect typically comes into practice for surveillance of metachronous cancers rather than in tailoring surgical approaches (124-130). PD-L1 expression ($\geq 1\%$) serves as a predictive biomarker for ICIs in metastatic UTUC, with pembrolizumab or atezolizumab recommended for cisplatin-ineligible PD-L1-positive patients. Adjuvant nivolumab can be considered for patients with HR ($\geq pT3/pN+$) cisplatin-ineligible UTUC post RNU. However, the aforementioned UTUC-specific survival benefits have not been fully investigated (51,131-133). Alterations in *FGFR2/3* guide later-line targeted therapy for platinum-refractory disease (erdafitinib). However, they do affect primary surgical approaches (134). While molecular subtyping (luminal and basal subtypes) holds prognostic potential, its clinical application in surgical planning is limited due to lack of validated treatment response associations (135).

Significant gaps remain in the integration of biomarkers into personalized surgery strategies. Kidney-sparing surgery (KSS) eligibility relies solely on clinical factors, such as tumor size, grade and focality, with no molecular predictors currently used to assess ipsilateral recurrence risk or progression to refine patient selection (136,137). LND templates are determined by tumor location and risk, without biomarkers predictive of occult micrometastasis. Furthermore, neoadjuvant ChT recommendations lack biomarkers, such as *ERCC2* mutations for platinum sensitivity, to identify non-responders, which

account for ~40% of all cases, risking delayed surgery without therapeutic benefits (138). For patients with LS-associated UTUC, molecular risk stratification, including particular MMR mutations (e.g., MLH1, MSH2, MSH6 and PMS2), does not guide prophylactic surgical interventions. Future efforts should be made to prospectively validate biomarkers in surgical trials, to develop integrated clinical-molecular prognostic models and to investigate biomarker-driven neoadjuvant therapies, such as FGFR inhibitors, to expand KSS eligibility. In summary, while biomarkers increasingly guide systemic therapy and genetic screening, their application in optimizing surgical management, including decisions on KSS candidacy, LND extent and utilization of neoadjuvant CHT, remains an unmet need in the evolution of UTUC precision medicine (55,136-138).

10. Conclusion and future perspectives

UTUC remains as a challenging oncological entity profoundly affecting a patient's survival and quality of life. The clinical utility of LND during RNU continues to be a subject of debate among urological specialists. While existing evidence supports the diagnostic value and possible therapeutic effects of LND, and particularly muscle-invasive and locally extensive disease, the optimal extent of dissection and its definitive effect on patient survival need further clarification. Although major guidelines vary between LND protocols, accumulating evidence increasingly supports the adoption of standardized anatomical templates to enhance diagnostic accuracy. Therefore, further high-quality studies are necessitated to establish consensus-driven practices. Advancements in functional imaging modalities, such as PET-CT/MRI, and molecular biomarker development, can promote tailored surgical planning. Ultimately, clarifying the therapeutic role of LND in the management of UTUC requires prospective multicenter trials to strengthen evidence-based protocols for optimizing outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HW, MD and ZT were responsible for conceptualization. ZT, CY, JW, YH and SF designed the literature search strategy,

screening criteria and evidence synthesis framework.. Formal analysis and data interpretation were performed by YH, SF, HL, DL, CG and JW. ZT, CY and JW helped write the original draft. HW, MD, ZT, CY, JW, YH, SF, HL, DL and CG reviewed and edited the manuscript. Visualization of figures/tables was performed by HL, DL, CG and JW. HW and MD supervised the study. HW and MD acquired funding. All authors have read and approved the manuscript. All authors have made substantial intellectual contributions, critically revised the manuscript for important content, and agree to be accountable for all aspects of the work. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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