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Patterns of Lymphatic Metastases in Upper Tract Urothelial Carcinoma and Proposed Dissection Templates

Surena F. Matin¹, John P. Sfakianos², Patrick N. Espiritu³, Jonathan A. Coleman², and Philippe E. Spiess²

¹Department of Urology, M.D. Anderson Cancer Center, Houston, TX, USA

²Department of Surgery, Urology Division, Memorial Sloan Kettering Cancer Center, New York, NY, USA

³Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center, Tampa, FL, USA

Abstract

Purpose—Information on patterns of lymph node metastases (LNM) for upper tract urothelial carcinoma (UTUC) is sparse. We investigate patterns of LNM in UTUC.

Materials/Methods—Retrospective multi-institutional study of 73 patients with N+M0 UTUC undergoing template lymphadenectomy during nephroureterectomy. Anatomic locations of tumor, number of lymph nodes removed, positive lymph nodes were analyzed and descriptive statistics performed.

Results—On right side: renal pelvis tumors (n=20) had LNM to the hilum (22.1%), paracaval (44.1%), retrocaval (10.3%) and interaortocaval (20.6%) regions. Proximal ureter tumors (n=10) had LNM to hilum (46.2%), paracaval (46.2%), and retrocaval (7.7%) regions. Distal ureter tumors (n=2) had LNM equally to paracaval and pelvic regions. On left side: patients with renal pelvis tumors (n=24) had LNM to hilar (50.0%), and paraaortic (30.0%) regions. Proximal ureter tumors (n=8) had LNM to hilar (36.4%) and paraaortic (63.6%) regions. Mid ureter tumors (n=5) had LNM to paraaortic (40%), common iliac (40%) and internal iliac (20%) regions. Distal ureter tumors (n=4) had LNM to paraaortic (33.3%), common iliac (33.3%), and external and internal iliac (16.7% each). Interaortocaval involvement from both sides as well as out-of-field LNM appeared to occur secondarily. Consolidated templates were constructed based on the available data.

Conclusion—UTUC has characteristic patterns of LNM dependent on the side and anatomic location of the primary tumor, including right to left migration and involvement of interaortocaval nodes in the setting of proximal disease. Standardized dissection templates should be prospectively evaluated in multi-center trials to assess for morbidity and potential clinical benefit.

Keywords

renal pelvis cancer; ureteral cancer; urothelial cancer; lymph node; surgery

Introduction

Similar to urothelial carcinoma of the bladder (UCB) upper tract urothelial carcinoma (UTUC) can follow routes of metastases to involve regional lymph nodes, an identified poor prognostic indicator that typically precedes the identification of visceral metastases. Data is sparse, however, regarding the patterns of lymphatic spread in UTUC though such information would prove useful when considering investigations of the potential role of lymphadenectomy. Prospective published literature on the extent and clinical benefit of lymphadenectomy in urothelial carcinoma has suggested a survival advantage for those with pathologically node-negative disease (pN0) and even for those with minimal lymph node positive disease (pN1) although such studies are mainly limited to UCB¹. Recent interest has been paid to extending these same concepts to UTUC in the setting of nephroureterectomy (NU) procedures and establishing standardized node dissection templates².

Retrospective data indicate a correlation between improved survival and lymphadenectomy performed during both open and minimally invasive procedures for NU³⁻⁶. However, complicating the ability to study patterns of lymphatic spread in UTUC is the relative rarity of disease and the wide anatomic variation of possible tumor involvement that may exist from renal pelvis to bladder. The vast arcades of vascular and lymphatic channels with associated nodal basins leading from these organ sites suggests a wide region for node dissection that could contribute to unacceptable increase in perioperative morbidity. Mapping studies to better understand the primary sites of involvement relative to tumor location would facilitate development of more risk-stratified and selective strategies. We sought to further investigate patterns of lymph node involvement (LNM) in patients managed surgically for UTUC with template LND performed at the time of NU and characterize the regions of LNM relative to primary tumor location as a means to describe patterns of spread and potentially inform the development of future studies of template dissection for this disease.

Patients and Methods

After institutional review board approval at all participating centers, we performed a retrospective chart review of prospectively maintained databases specific for patients with UTUC who underwent radical NU by a single surgeon each at one of 3 National Cancer Institute designated Comprehensive Cancer Centers. Patients included in the study had positive LNM identified from pathology specimens obtained from template node dissection performed at the time of NU or segmental ureterectomy between 2002 to 2013 at one of the 3 participating centers. Patients with a history of muscle invasive bladder cancer were included only if they had a disease-free interval greater than 2 years prior to surgery and subsequent UTUC developed in the renal pelvis or proximal ureter. Patients who received neoadjuvant chemotherapy were included only if preoperative biopsies confirmed LNM or if they had persistently positive nodes. Those with diffuse multifocal tumors were excluded. Tumor locations were annotated as renal pelvis (calyces to ureteropelvic junction), proximal ureter (lower extent inferior mesenteric artery), mid ureter (lower extent inferior margin of iliac vessels), and distal ureter. For the purposes of stratifying LNM by primary tumor

location 3 groups were evaluated by laterality: Renal pelvis +/- proximal ureteral, proximal and/or mid ureter only or distal ureteral tumors only. Patients with renal pelvic and proximal ureteral tumors underwent at minimum a template dissection of the ipsilateral great vessel. On the right side this includes: hilum to vena cava bifurcation, including paracaval (which includes precaval region) and retrocaval nodes; on the left side: hilum to origin of inferior mesenteric artery, including paraaortic nodes (which includes preaortic nodes). Additional dissection of interaortocaval and common iliac nodes were performed when suspicious nodes were identified in these regions on preoperative imaging or upon visual inspection intraoperatively. Tumors involving the mid ureter underwent paraaortic in addition to ipsilateral common and external iliac LND. Those with distal ureteral tumors underwent pelvic lymphadenectomy (common, external, internal iliac and obturator). For mid and distal ureteral tumors additional dissection (paracaval or paraaortic) was performed based on imaging, intraoperative inspection, or at the surgeon's discretion. Post-operative surveillance schedule included urine cytology, cystoscopy, with abdominal and chest radiographic imaging every 3–6 months the first 2 years then every 6–12 months. We assessed patient demographics, the location of the primary tumor, locations of lymph nodes metastasis; tumor and lymph node stage; and number of lymph nodes dissected.

Results

A total of 92 patients were identified. Nineteen patients were excluded due to multifocal tumor involvement (11) or muscle-invasive bladder disease within 2 years (8). The characteristics of the study cohort of 73 patients are presented in table 1. Three patients with biopsy proven LNM during pre-operative staging had N0 disease after preoperative chemotherapy, and 4 patients had a remote history (>2 years) of radical cystectomy, presenting with tumors in the renal pelvis or proximal ureter. These patients were included in the analysis.

Table 2 details LNM landing sites based on the location of the primary tumor, and these are anatomically represented in figures 1–2. On the right side, patients with renal pelvis tumors had high frequency LNM to the hilum, paracaval, retrocaval, and interaortocaval regions (table 2 and figure 1). However, only 1 of the 5 patients with interaortocaval LNM had no other sites of LNM, suggesting that in the majority of right renal pelvis tumors the interaortocaval area is affected secondarily. Proximal ureter tumors had LNM with equal frequency to the hilum and paracaval region, and less frequently in the retrocaval region (figure 1). There were no right mid ureter tumors. Right distal ureter tumors had LNM to the paracaval and pelvic regions with equal distribution (figure 2).

On the left side, patients with renal pelvis tumors had LNM found primarily in hilar, and paraaortic regions (table 2 and figure 1); interaortocaval LNM were infrequently found (2 of 23 patients) in both cases when other LNM existed in paraaortic areas, suggesting secondary involvement. Proximal ureter tumors had LNM exclusively to the hilar and paraaortic regions (figure 1). No cases of retroaortic LNM were identified. Mid ureter tumors had LNM of the paraaortic, common iliac, and internal iliac regions (figure 2). Left distal ureter tumors had LNM to the paraaortic, common iliac, and external and internal iliac regions

(figure 2). The 1, 2, and 5-year cancer-specific survival rates of the overall cohort were 69%, 49%, and 27%, respectively.

Given the similarity of LNM patterns for renal pelvis and proximal ureter tumors, a single consolidated dissection template was considered for each side (figure 3). For the right side, dissection of the hilum, paracaval, retrocaval, and interaortocaval region would capture nearly all LNM. For the left side, a hilar and paraaortic dissection would capture nearly all primary LNM. Given the more minimal numbers for mid and distal ureter tumors, we included data from the publication by Kondo et al⁹ in considering refining dissection templates based on available data. In that study 6 patients with mid ureteral (3 each side) and 4 distal ureter (2 each side) were reported. Figure 4 shows these putative templates based on the combined data. Notable for mid ureter tumors, significant proportion of LNM were identified in the interaortocaval and paracaval/retrocaval (right) and paraaortic (left) regions, suggesting cranial lymphatic drainage from the mid-ureteral location. Lymphadenectomy for distal ureter tumors which removes the typical pelvic templates (common, external and internal iliac, obturator) would remove the majority of LNM, but similarly, a proportion could remain adjacent to the ipsilateral great vessel (Figure 4).

Discussion

This study informs the primary landing sites of LNM contingent on the laterality and location of the primary tumor, allowing the initial development of anatomic dissection templates. To the best of our knowledge, only 2 published studies have evaluated patterns of LNM in UTUC. In 1975 Batata et al reported on the survival of ureteral cancer and in one of the earliest descriptions demonstrated the distribution of regional LMN metastases in 17 patients⁷. Komatsu et al described the range of primary sites for LNM of 11 patients⁸. Both studies were unable to account for tumor laterality and generalized the affected regions in the retroperitoneum, making it difficult to determine a pattern of LNM. In 2007 Kondo et al reported on the primary site of LNM in 42 patients of which 23 were pathologically confirmed, while the other 19 were clinically determined⁹. Until now, the study by Kondo et al.⁹ represents the most detailed description of primary LNM.^{4,9} They expanded the cohort to detail 67 patients to further support their lymph node schema, but they were unable to account for LNM from tumors of the left proximal ureter because no LNM occurred for tumors of that location in their cohort.¹⁰ Recent retrospective studies from that group have shown reduced local recurrences in those undergoing LND¹¹ and a prospective-registry study of patients undergoing LND showed improved survival to those who elected or were too old or ill for LND¹². While we show similar findings to their initial report and subsequent templates, notable differences and highlights are also evident. Apparent secondary involvement of interaortocaval nodes, more common from the right than the left, suggests that patients without any disease in the paracaval or retrocaval (for the right side) or paraaortic area (left side) may be able to have this region omitted, possibly guided by frozen section analysis at the time of surgery. Similarly, out-of-field lymph nodes (such as suprahilar, common iliac, aortic bifurcation, and others, Table 2) appeared to always occur when primary LNM were present in the hilar or paravascular areas. Also, upward migration of metastases to the paracaval and paraaortic regions from mid and distal ureteral tumors is a

novel finding from this study which requires further study with larger number of patients in a prospective study incorporating these sites of dissection.

The value in expanding our knowledge on determining patterns of LNM for UTUC is critical given current inaccuracy of clinical staging by either endoscopy or imaging, the latter which can miss LNM in nearly 50% of cases¹³. Currently lymphadenectomy performed at the time of radical NU remains the most accurate means to completely and accurately staging UTUC. Given the paucity of information regarding the patterns of lymphatic spread of UTUC, no standardized templates exist for LND, leaving the possibility of understaging or overtreatment. This is a major limitation to developing a reasonably accurate means for predicting nodal status as noted by the UTUC Collaboration.¹⁴ Several reports have offered compelling rationale for the therapeutic benefits of thorough LND in urothelial cancer. Herr et al. demonstrated that removal of over 10 nodes at the time of radical cystectomy improved survival for patients that appeared comparable to the benefits yielded from neoadjuvant chemotherapy, further corroborating retrospective data identifying a survival advantage associated with a larger number of nodes removed at LND.¹⁵ In a large retrospective series Stein et al reported a durable 34% 10-year recurrence-free survival in patients with LNM identified from LND at the time of cystectomy and later reported a survival advantage associated with greater than 15 nodes removed.¹ Additionally, a report from Koppie et al from a series of over 1100 UCB cases showed increasing nodal yields demonstrated a survival improvement regardless of LNM status and were unable to identify a limiting number of nodes beyond which there was no further benefit.¹⁶ These studies serve to underline the central importance of LND in the surgical management of urothelial cancer and the attention that should be paid to meticulous dissection templates.

The therapeutic benefit of lymphadenectomy for UTUC is less well studied though supported by recent reports as noted previously. Characteristics of LND, specifically the number of lymph nodes removed and the nodal density have been identified as prognostic factors for improved survival^{5,6}. A meta-analysis on the effect of LND on outcomes of UTUC showed improved survival, particularly for locally advanced tumors.¹⁷

Tremendous variation exists in surgical practices for performing LND in UTUC, even between surgeons at the same center. Nearly all studies that identified prognostic factors and survival impact from lymph node dissection for UTUC could not account for the anatomical extent of the lymphadenectomy. In a prospective study Kondo et al evaluated the association of anatomical extent of lymphadenectomy with survival outcomes using a standardized template for dissection. These hypothesis generating results suggest that extended template dissection is associated with improved survival for patients with pT2 or greater tumors of the renal pelvis, but not for tumors with ureteral involvement.¹² While an argument could be made that patients with lymphatic metastases would become eligible for adjuvant therapy, its utility is still controversial for advanced UTUC as studies have shown very limited to no significant survival benefit.¹⁸⁻²⁰ On the other hand, emerging data suggests a significant 5-year survival benefit with a neoadjuvant approach.²¹

There are several limitations to this retrospective study. Selection criteria for patients undergoing LND were not detailed and this may introduce bias in the sample in regard to

disease burden and other patient factors not captured, but this was not felt to be a major factor for the purposes of generating mapping data. Templates for dissection at the 3 institutions, while similar, may not have been identical in every case, and may have limited detection of nodal sites at some locations, or alternatively overemphasized LNM when more extended dissections were performed outside templates. Confounders include the use of chemotherapy, prior surgery (eg. cystectomy) and prior history of UCB – all of which could potentially impact the biology and anatomy of nodal metastases. The inclusion of those with a remote history of cystectomy may have added a bias in the anatomic landing sites, although in all cases tumors were located in the upper retroperitoneum and not likely to have had disruption of lymphatic channels by prior pelvic surgery. The inclusion of these cases was necessary to maximally represent LNM for this uncommon disease. We acknowledge these factors, however, the limitation of patient numbers (another factor) prevents detailed analysis of their putative impact. A greater number of patients with mid and distal ureter tumors from future studies would help provide a better understanding of lymphatic patterns and tailoring of dissection templates although further sub-dividing an already small number of cases in this rare disease should be avoided. Going forward, we recommend for all practitioners who perform lymphadenectomy to separate and annotate the pathologic specimens as precisely as possible in regards to the anatomic locations described using harmonized terminology in order to help inform future studies more accurately. In the meantime, this data provides support for practical lymphadenectomy dissection templates to be used during NU for UTUC.

Conclusion

UTUC has characteristic patterns of lymphatic spread dependent on the side and anatomic location of the primary tumor consistent with lymphatic drainage patterns identified from UCB and retroperitoneal lymphadenectomy procedures, including right to left migration, possible secondary involvement of interaortocaval nodes and other areas of intralymphatic spread in the setting of proximal disease. Standardized dissection templates based on tumor location to account for these patterns may help to improve LNM yield and should be prospectively evaluated, preferably in multi-center trials, to assess for morbidity and potential clinical benefit.

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Figure 1.

LNM locations and frequency of primary tumors of right (A) and left (B) renal pelvis in 20 (68 lymph nodes) and 24 patients (100 lymph nodes), and right (C) and left (D) proximal ureter in 10 (13 lymph nodes) and 8 patients (22 lymph nodes), respectively. Paracaval, anterior precaval and lateral paracaval regions. Para-aortic, anterior preaortic and lateral para-aortic regions. Copyright S.F. Matin 2015.

Figure 2.

LNM locations and frequency of primary tumors of left mid ureter (A), and right (B) and left (C) distal ureter in 5 (5 lymph nodes), 2 (2 lymph nodes) and 4 patients (6 lymph nodes), respectively. There was no right mid ureter tumor. Paracaval, anterior precaval and lateral paracaval regions. Para-aortic, anterior preaortic and lateral para-aortic regions. Copyright S.F. Matin 2015.

Figure 3.

Consolidated lymph node dissection templates for renal pelvis and proximal ureter tumors. On right side primary hilar, paracaval (anterior precaval and lateral paracaval regions) and retrocaval lymphadenectomy would capture 82.9% of LNMs (solid outline) while adding interaortocaval lymph node dissection (dashed outline) would increase rate to 95.8% (A). On left side primary hilar and para-aortic (anterior preaortic and lateral para-aortic regions) lymphadenectomy would capture 86.9% of LNMs while adding interaortocaval lymph nodes would increase rate to 90.2% (B). Copyright S.F. Matin 2015.

Figure 4.

Lymph node dissection templates for tumors of mid (A and B) and distal (C and D) ureter developed by combining data from publication by Kondo et al. ⁷ That study included 3 patients with right mid ureter tumors and LNMs to retrocaval and interaortocaval regions (A), and 3 with left mid ureter tumor with LNMs to para-aortic (anterior preaortic and lateral para-aortic) region (B). On right side primary dissection of interaortocaval nodes would capture 66.7% of possible LNMs (solid outline) while adding paracaval (anterior precaval and lateral paracaval) and retrocaval nodes would remove remaining 33.3% (dashed outline) (A). No LNMs were identified in common iliac region but they were likely dissected at ureteral resection. On left side para-aortic node primary dissection would remove 62.5% of LNMs (solid outline), and adding common iliac and internal iliac lymph nodes would increase rate to 100% (dashed outline) (B). Study by Kondo et al also included 2 right distal ureter tumors with LNMs to common iliac and obturator regions (C) and 2 left distal ureter tumors with LNMs to common and internal iliac regions (D). Extended pelvic template dissection would capture 75.0% of LNMs on right side (solid outline) while adding paracaval dissection would increase rate to 100% (dashed outline) (C). Primary pelvic dissection on left side would capture 83.3% of LNMs (solid outline) while adding para-aortic dissection would increase rate to 100% (dashed outline) (D). Copyright S.F. Matin 2015.

Table 1

Patient characteristics.

	n (%) or median (IQR)
Age	69 (61, 75)
Gender (male)	43 (59%)
Previous history of bladder cancer	29 (40%)
Received neoadjuvant chemotherapy	27 (37%)
Approach:	
Open	42 (57%)
Minimally invasive surgery	31 (43%)
Number of lymph nodes removed, total	13 (5,20)
Renal pelvis	15 (8.5, 21)
Proximal ureter	7.5 (2, 13)
Mid ureter	14 (1.5, 24)
Distal ureter	8 (2.5, 16.5)
Laterality	
Left	41 (56%)
Right	32 (44%)
Tumor location	
Renal pelvis	44 (60%)
Proximal ureter	18 (25%)
Mid ureter	5 (7%)
Distal ureter	6 (8%)
Tumor stage classification	
pT0/a/is/1	13 (18%)
pT2	9 (12%)
pT3	34 (46%)
pT4	17 (24%)
Tumor size, cm	3.6 (2.3, 6)

Table 2

Distribution of LNM landing sites based on location of the primary tumor.

Right	Renal pelvis (20 patients) 68 LNM	Proximal ureter (10 patients) 13 LNM	Mid ureter (0 patients)	Distal ureter (2 patients) 2 LNM
Hilar	15 (22.1%)	6 (46.2%)	--	--
Paracaval	30 (44.1%)	6 (46.2%)	--	1 (50%)
Retrocaval	7 (10.3%)	1 (7.7%)	--	--
Interaortocaval	14 (20.6%)*	--	--	--
External iliac	--	--	--	1 (50%)
Unspecified	2 (2.9%)	--	--	--

Left	Renal pelvis (24 patients) 100 LNM	Proximal ureter (8 patients) 22 LNM	Mid ureter patients) 5 LNM	(Distal ureter 4 patients) 6 LNM
Hilar	53 (53.0%)	8 (36.4%)	2 (40%)	--
Paraaortic	31 (31.0%)	14 (63.6%)	2 (40%)	2 (33.3%)
Interaortocaval	4 (4.0%)*	--	--	--
Suprahilar	1 (1.0%)*	--	--	--
Common iliac	1 (1.0%)*	--	--	2 (33.3%)
External iliac	--	--	--	1 (16.7%)
Internal iliac	--	--	1 (20%)	1 (16.7%)
Aortic bifurcation	1 (1.0%)*	--	--	--
Retrocrural	2 (2.0%)*	--	--	--
Unspecified/other	7 (7.0%)	--	--	--

* 7 lymph node metastases (LNM) associated with LNM in hilar, paracaval, or retrocaval sites.

* all in patients with lymph node metastases (LNM) in hilar or paraaortic lymph nodes.