



## DELAYS TO DIAGNOSIS AND MANAGEMENT OF UPPER TRACT UROTHELIAL CARCINOMA: THE NEED FOR A NEW PATHWAY

William Taylor, Nathan Ingamells, Sean Morris, Kesavapillai Subramonian  
Queen Elizabeth Hospital Birmingham, UK

Corresponding Author: [wstjtaylor@doctors.org.uk](mailto:wstjtaylor@doctors.org.uk)

Submitted: May 11, 2019. Accepted: June 1, 2019. Published: July 8, 2019.

---

### ABSTRACT

#### Background and Objective

Upper tract urothelial carcinoma (UTUC) is rare in comparison to urothelial carcinoma of the bladder or renal cell carcinoma. UTUC may present with loin pain, hematuria or alternatively can be identified as an incidental finding on imaging. There are often delays to diagnosis as hematuria clinics are efficient for bladder and renal cancer but less effective for UTUC. The diagnosis and treatment of UTUC is more challenging, as it often requires 2 operations and multiple MDT discussions. Diagnosis must be certain to avoid unnecessary radical surgery.

We found that our patients were experiencing significant delays to definitive surgery. Our patients currently follow the pathway for bladder and renal cancer, as there is no UTUC pathway at or trust or published in the literature. We audited our diagnostic pathway to see how we could tailor the pathway to be more effective for patients with UTUC. This will ensure that more patients will meet the NHS 62-day targets.

#### Materials and Methods

A retrospective review of patient's management pathway from December 2008 to December 2018. Patients were identified by the pathological code for UTUC.

#### Results

A total of 62 patients underwent nephroureterectomy during a 10-year period. 48 patients were analyzed. The median waiting time for hematuria clinic from referral was 21 days, a further 73 days to ureterorenoscopy and biopsy, and then 14 days to definitive nephroureterectomy. Only one patient met the NHS 62-day treatment target.

Our waiting times are comparable with other published international series. We have implemented a new UTUC pathway to streamline the diagnosis and management of UTUC. Some patients with UTUC will still have inevitable delays as diagnosis can be very challenging but this new pathway should improve the patient journey and reduce the waiting times significantly.

**Keywords:** *Upper tract urothelial carcinoma, transitional cell carcinoma, nephroureterectomy, ureteroscopy, management pathway*

Upper tract urothelial carcinoma (UTUC) is rare in comparison to urothelial carcinoma of the bladder. From 90–95% of urothelial carcinoma occurs in the bladder with just 5–10% occurring in the upper tracts.<sup>1</sup> In 17% of UTUC there is a concomitant bladder tumour.<sup>2</sup> The British Association of Urological Surgeons database shows that definitive treatment with nephroureterectomy is carried out in relatively low volume when compared to nephrectomy or resection of bladder tumour. In 2012 just 863 nephroureterectomies were carried out in the UK in 119 centres by 220 consultant surgeons. On average each surgeon carried out just 3 nephroureterectomies, with each unit contributing 6 in that year.<sup>3</sup>

At the time of presentation 15–25% of UTUC is muscle invasive.<sup>4</sup> 7% of UTUC are metastatic at presentation.<sup>1</sup> This is similar to urothelial cancer of the bladder where 75% is non-muscle invasive and 25% is muscle invasive at presentation.<sup>5</sup> Early diagnosis and treatment is therefore imperative in order to obtain the best survival outcomes for our patients.

UTUC commonly presents with hematuria but can also present with loin pain or as an incidental finding on imaging for other presenting complaints. Edwards et al set out a prospective analysis of their hematuria clinic in 2006.<sup>6</sup> They reviewed 4020 patients with visible or non-visible hematuria. Also, 18.9% of the patients with visible hematuria had an underlying malignancy compared to 4.8% of patients with non-visible hematuria. They identified 13 cases of UTUC, which is 2.6% of the overall patients diagnosed with a urological cancer. 10 (77%) of the UTUC were diagnosed on ultrasound scan. 3 patients were diagnosed after a normal ultrasound scan but an abnormal intravenous urogram. All 60 renal cell carcinomas were diagnosed on ultrasound scan. Bladder and renal cancers were all diagnosed on the day of the hematuria clinic. This study shows that if the IVU is not carried out on the day of the hematuria clinic there will be a delay in diagnosis of UTUC in 23% of cases. Computed tomography (CT) urogram has now replaced IVU and is carried out in the majority of hospitals hematuria pathways.<sup>7</sup>

UTUC can be identified with positive urine cytology. Viswanath et al reviewed the use of urine cytology in their unit and identified 3 patients out of a total 1000

who had positive urine cytology with a diagnosis of UTUC.<sup>8</sup> All 3 of these patients, however, would have been diagnosed radiologically at the hematuria clinic. The benefit of positive cytology is to aid the further management of the patient. If urine cytology is positive, flexible cystoscopy is normal and imaging shows a likely UTUC then an MDT can decide to omit ureterorenoscopy and biopsy and offer definitive treatment with nephroureterectomy or segmental resection of the ureter.<sup>9</sup>

In our unit we found that patients were experiencing significant delays to nephroureterectomy and so we set up an audit to assess whether these were isolated cases or if we needed to set up a separate UTUC pathway to improve the diagnosis and management delays.

## METHOD

A retrospective review of patients who had undergone nephroureterectomy for UTUC between December 2008 and 2018. Patients were identified by pathological code for UTUC. Their notes were reviewed to assess their patient journey and identify delays in their pathway. Patients were excluded if they had not received definitive treatment or if the details of their patient journey were not possible to obtain.

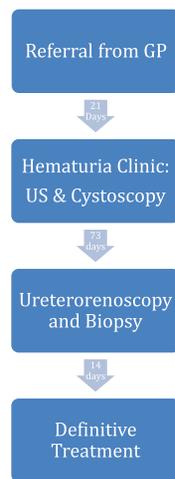
## RESULTS

A total of 61 patients had nephroureterectomy during the study period. There were 13 patients excluded because their full details were not available or if they had received their investigations at another trust and had been referred just for definitive surgery. A total of 48 patients were therefore analyzed.

The median waiting time to hematuria clinic was 21 days. Waiting time to ureterorenoscopy was a further 73 days and then a further 14 days to definitive surgery. The overall median time from referral to nephroureterectomy was therefore 108 days (Figure 1).

A total of 6 (12.5%) patients went straight to nephroureterectomy after MDT decision based on the imaging and positive cytology results. There were 42 patients who underwent ureterorenoscopy and attempted biopsy, 34 patients who underwent ureterorenoscopy had a biopsy taken, and 8 patients who did not have a biopsy as it was not possible to reach the mass due to external compression of the

**FIG. 1** Current diagnostic pathway median waiting times. Median 108 days from GP referral to definitive treatment.



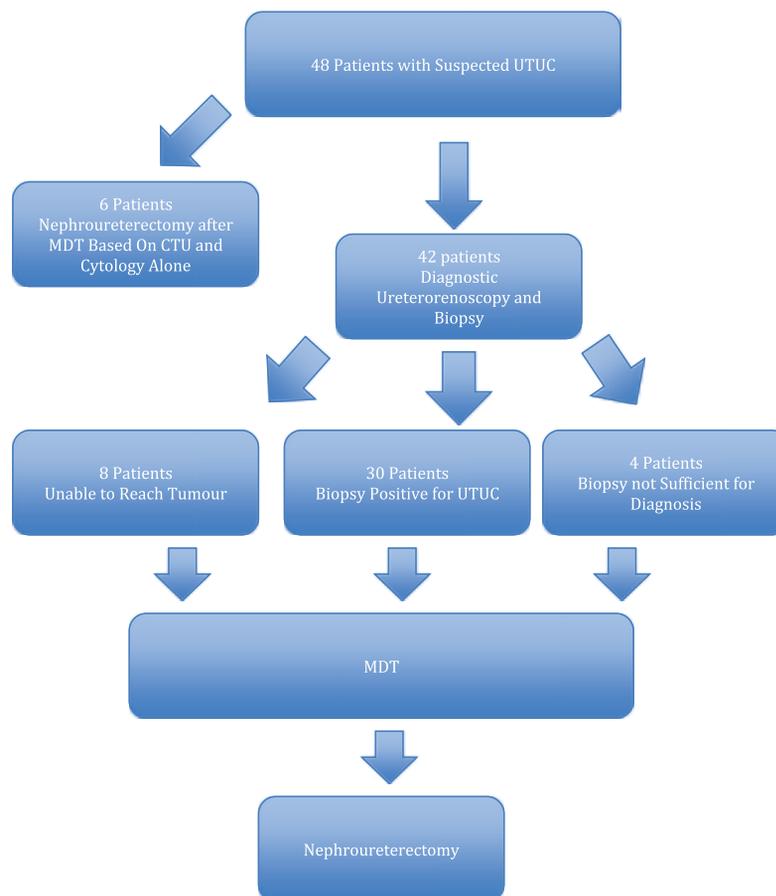
ureter. A total of 30 out of 34(88%) patients had a biopsy taken at ureterorenoscopy that was satisfactory for a diagnosis of UTUC (Figure 2). Selective urine cytology from the ureter was sent for analysis 11 of 28 (39%) samples was diagnostic of UTUC.

## DISCUSSION

### *Ureterorenoscopy Complexities*

Ureterorenoscopy is a difficult procedure to perform in patients with UTUC. Ureteroscopic biopsy correlates well with post nephroureterectomy histology.<sup>10</sup> Our series showed that in 8 of 42 (19%) patients we were unable to reach the tumour due to lymph node compression of the ureter or by the ureteric oedema that the tumour had created. Of these cases 75% were carried out or supervised by non-endourology urologists.

**FIG. 2** The investigation and management of 48 patients with suspected upper tract urothelial carcinoma after computed tomography urogram.



The quality of the specimen for the pathologist is notoriously poor when taken ureteroscopically as the biopsy forceps are so fine. Al-Qahtani et al performed a small study comparing the piranha biopsy forceps to the BIGopsy forceps.<sup>11</sup> They concluded that the BIGopsy had better yields than the piranha forceps. There was one (5%) case however where neither type of forceps could obtain tissue adequate enough for a diagnosis. Tissue for diagnosis was obtained in 7 of 20 patients with piranha and 17 patients with the BIGopsy forceps. This was a small study and we use the piranha forceps and have a much better diagnostic yield with our technique. The piranha forceps are frontloading rather than the back loading BIGopsy forceps. Frontloading enables them to be placed as late as possible which enables the working channel to be used for just irrigation giving a much clearer view with the inevitable bleeding that is encountered after the biopsy. This enables multiple biopsies to be taken more easily in our practise. Our series obtained tissue diagnostic for UTUC in 30 of 34 (88%) patients. In the 4 patients whose biopsy was not diagnostic only one was taken by an endourologist, trainees took 2 and a urology consultant took one.

If more biopsies are taken there is a greater possibility of tissue diagnosis.<sup>12</sup> Ureteroscopic biopsy has been proven to be reliable for stage and grade but there is a false negative rate and so multiple biopsies are essential to ensure that tissue has been taken that is representative of the mass and does not give false reassurance to the urologist.<sup>13</sup>

### ***The Benefit of Selective Urine Cytology***

The literature shows that urine cytology can be positive in around 70% of cases although these rates are variable.<sup>10</sup> Our series had a much lower diagnostic rate of just 39%. Unfortunately, the cytology was not positive in any of our cases where the ureteroscopic biopsy was negative and therefore did not help with diagnosis in our series. Nonetheless the literature shows it can be a very useful tool and given that it is easily collected at ureterorenoscopy should be included in our protocol to try to ensure that our patients have the best chance of tissue diagnosis prior to nephroureterectomy.

### ***Delay to Definitive Surgery***

There are delays in our diagnostic pathways. Only one patient met the NHS 62-day treatment target. The main delay was from hematuria clinic to the ureterorenoscopy. One reason for this was delay to CT and CT reporting and then the report being acted on by the clinician. There were also delays associated with the MDT. Our median time to definitive surgery from receipt of referral letter from the GP was 108 days. The literature uses different definitions of time to surgery and is usually measured as the time from diagnosis to definitive surgery. This makes comparisons between different studies difficult.

Nison et al performed a review of a large collaborative database to assess whether patients having ureterorenoscopy and biopsy had an adverse oncological outcome as a result of the wait for ureterorenoscopy and increase in length of their pathway.<sup>14</sup> Their database assessed the patient pathways of 542 patients. 170 had ureterorenoscopy and biopsy prior to nephroureterectomy and 342 went straight to nephroureterectomy. Their definition of time to surgery was from the date of imaging diagnosis of UTUC to the day of definitive surgery. The average wait for definitive surgery was 79.5 days for the ureterorenoscopy group and 44.5 days for patients progressing straight to nephroureterectomy. In their series there was no survival disadvantage of the increase delay to surgery even in patients with muscle invasive disease.

Sundi et al performed a retrospective review of 240 patients with non-metastatic UTUC.<sup>15</sup> They divided their patients into 2 groups. An early surgery group of 186 patients, defined as definitive surgery within 3 months of diagnosis and a late surgery group of 54 patients who waited more than 3 months or definitive surgery. Their five-year cancer-specific survival data was similar, 72% for early surgery and 71% for delayed surgery group.

Our delay is therefore significant in that almost all patients miss the NHS 62-day treatment targets but the literature shows that our unit is comparable to other units internationally. The delays our patients are facing are therefore similar to the delays faced by patients abroad. They are a result of UTUC being very difficult to diagnose, as it is rare in comparison to urothelial

cancer of the bladder for which the hematuria clinic is primarily designed. An advantage of the patient undergoing delay to nephroureterectomy and having a ureterorenoscopy first is that their tumour can be fully assessed endoscopically and potentially treated endoscopically if it is low grade, small and in a favourable location.<sup>16</sup> If the patient eventually fails endoscopic management and requires nephroureterectomy, they do not suffer worse oncological outcomes as a result of this delay.<sup>17,18</sup> This also ensures both the urologist and the patient that if the biopsy result shows high grade or a high stage then nephroureterectomy is an appropriate treatment. Patients should undergo radical nephroureterectomy if they do not have a malignant lesion. Diagnosis even with CT, ureterorenoscopy, cytology and biopsy can be challenging. Hong et al performed 244 radical nephroureterectomies and in their series 7 (2.9%) were benign histologically despite their investigation's findings.<sup>19</sup>

### ***Hematuria Clinic***

Hematuria clinic is excellent at diagnosing bladder and renal cancer. In most hematuria clinics the patient will receive an ultrasound and flexible cystoscopy, which will identify both of these diagnoses.<sup>6</sup> Patients who have an abnormal ultrasound can be counselled for a potential diagnosis of UTUC and be booked for an urgent ureterorenoscopy pending the results of the CT urogram. MDT and follow-up results clinic could also be booked for these patients to ensure that there is no delay to definitive surgery. If this shows a ureteric calculus then they may still require an urgent ureterorenoscopy for management of their obstructing stone. If the CT urogram shows an extra-renal pelvis or a pelvic ureteric junction obstruction then the patients can be reassured, booked for potential further investigations or discharged. Their theatre space can be used for another urgent patient. These patients should therefore experience little diagnostic delay. The patients who will still continue to experience delay are the group who have a normal ultrasound but their CT urogram shows an UTUC. This will be a very small number of patients each year in each unit (3 per 4020 patients with hematuria 0.07%).<sup>6</sup> This group of patients will only not experience a delay if they receive a CT urogram and it's reported on the

day of hematuria clinic. This would be a significant amount of extra work for the radiology department and is one reason that this has not been adopted in many hospitals. Many clinicians prefer ultrasound prior to CT as different phases can be requested if a tumour is found and a staging CT chest can also be added saving appointment time for the patient and CT scanner time.

### ***How We Have Changed Our Service***

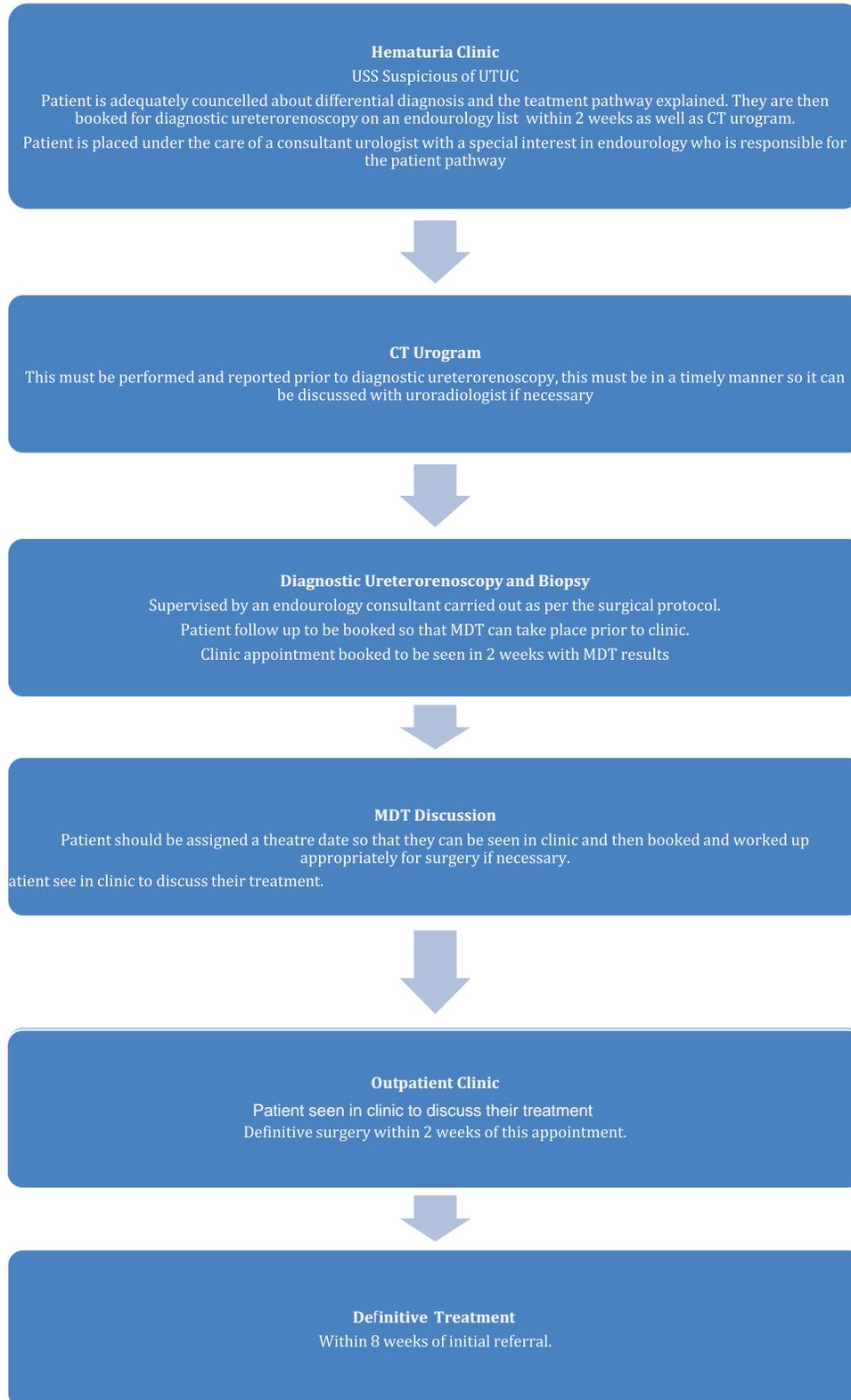
We have now set up a new pathway for the urgent diagnosis of UTUC in our unit (Figure 3). When a patient has an abnormal ultrasound scan at hematuria clinic suspicious for UTUC with a normal flexible cystoscopy they are added to an endourology theatre list for diagnostic ureterorenoscopy and biopsy within 2 weeks. Their care is transferred to a consultant with an interest in endourology who oversees the pathway. A CT urogram is performed prior to this and reported before surgery. Their name is put on the MDT list for discussion after the ureterorenoscopy to discuss the histology and management. A follow-up appointment is booked for the week following MDT where they can be assessed and counselled for definitive surgery. The pathway is 8 weeks and will allow the majority of patients to meet the NHS 62-day treatment target.

### **CONCLUSION**

UTUC is a difficult malignancy to diagnose as it is uncommon and often requires further investigations after hematuria clinic to obtain a tissue diagnosis. Our patients did experience delays to diagnosis and treatment but they are similar to other published international series. We have set up a new treatment pathway, which will help more patients meet the NHS 62-day treatment target. We hope that this leads to an improvement in oncological outcomes as well as improved patient satisfaction.

There will still be a small group of patients with a normal ultrasound scan who have UTUC. The diagnosis times may improve for these patients if in the future we performed CT urograms on all high-risk patients on the day of the hematuria clinic. Currently this is not possible in our unit but may be possible in the future. We will re-audit our pathway in the future and ensure that at least 60% achieve the 62-day target.

**FIG. 3** UTUC diagnosis and management pathway.



## GRANT SUPPORT

There was no grant support for this manuscript.

## REFERENCES

1. Soria F, Shariat SF, Lerner SP et al. Epidemiology, diagnosis, preoperative evaluation and prognostic assessment of upper-tract urothelial carcinoma (UTUC). *World J Urol* 2017 Mar 1;35(3):379–87.
2. Cosentino M, Palou J, Gaya JM et al. Upper urinary tract urothelial cell carcinoma: location as a predictive factor for concomitant bladder carcinoma. *World J Urol* 2013 Feb 1;31(1):141–5.
3. Connolly SS, Rochester MA, Baus. Nephroureterectomy surgery in the UK in 2012: British Association of Urological Surgeons (BAUS) Registry data. *BJU Internat* 2015 Nov;116(5):780–90.
4. Margulis V, Shariat SF, Matin SF et al. Upper tract urothelial carcinoma collaboration. outcomes of radical nephroureterectomy: a series from the upper tract urothelial carcinoma collaboration. *Cancer* 2009 Mar 15;115(6):1224–33.
5. Comp erat E, Larr e S, Roupret M et al. Clinicopathological characteristics of urothelial bladder cancer in patients less than 40 years old. *Virchows Archiv* 2015 May 1;466(5):589–94.
6. Edwards TJ, Dickinson AJ, Natale S et al. A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven hematuria clinic. *BJU Internat* 2006 Feb;97(2):301–5.
7. Cauberg EC, Nio CY, de la Rosette JM, et al. Computed tomography-urography for upper urinary tract imaging: is it required for all patients who present with hematuria? *J Endourol* 2011 Nov 1;25(11):1733–40.
8. Viswanath S, Zelhof B, Ho E et al. Is routine urine cytology useful in the hematuria clinic? *Annals Royal Coll Surg Engl* 2008 Mar;90(2):153–5.
9. Potretzke AM, Knight BA, Potretzke TA, Larson JA, Bhayani SB. Is ureteroscopy needed prior to nephroureterectomy? An evidence-based algorithmic approach. *Urology* 2016 Feb 1;88:43–8.
10. Williams SK, Denton KJ, Minervini A, Oxley J, Khashtgir J, Timoney AG, Keeley FX. Correlation of upper-tract cytology, retrograde pyelography, ureteroscopic appearance, and ureteroscopic biopsy with histologic examination of upper-tract transitional cell carcinoma. *J Endourol* 2008 Jan 1;22(1):71–6.
11. Al-Qahtani SM, Legraverend D, de Medina SGD et al. Can we improve the biopsy quality of upper urinary tract urothelial tumors? Single-center preliminary results of a new biopsy forceps. *Urologia internationalis* 2014;93(1):34–7.
12. Guarnizo E, Pavlovich CP, Seiba M et al. Ureteroscopic biopsy of upper tract urothelial carcinoma: improved diagnostic accuracy and histopathological considerations using a multi-biopsy approach. *J Urol* 2000 Jan 1; 163(1):52–5.
13. Vashistha V, Shabsigh A, Zynger DL. Utility and diagnostic accuracy of ureteroscopic biopsy in upper tract urothelial carcinoma. *Arch Pathol Lab Med* 2013 Mar;137(3):400–7.
14. Nison L, Roupr et M, Bozzini G, et al. The oncologic impact of a delay between diagnosis and radical nephroureterectomy due to diagnostic ureteroscopy in upper urinary tract urothelial carcinomas: results from a large collaborative database. *World J Urology* 2013 Feb 1;31(1):69–76.
15. Sundi D, Svatek RS, Margulis V et al. Upper tract urothelial carcinoma: impact of time to surgery. In: *Urologic Oncology: Seminars and Original Investigations*. Elsevier; 2012.
16. Shiraiishi K, Eguchi S, Mohri J, Kamiryoy Y. Role of ureteroscopic biopsy in the management of upper urinary tract malignancy. *Internat J Urol* 2003 Dec;10(12):627–30.
17. Boorjian S, Ng C, Munver R et al. Impact of delay to nephroureterectomy for patients undergoing ureteroscopic biopsy and laser tumor ablation of upper tract transitional cell carcinoma. *Urology* 2005 Aug 1;66(2):283–7.
18. Gadzinski AJ, Roberts WW, Faerber GJ, et al. Long-term outcomes of immediate versus delayed nephroureterectomy for upper tract urothelial carcinoma. *J Endourol* 2012 May 1;26(5):566–73.
19. Hong S, Kwon T, You D et al. Incidence of benign results after laparoscopic radical nephroureterectomy. *JSL: J Soc Laparoendoscop Surg* 2014 Oct;18(4).