RESEARCH ARTICLE

NORTH AMERICAN ACADEMIC RESEARCH (NAAR) JOURNAL
2021 MARCH, VOLUME 4, ISSUE 3, PAGES 78-87
https://doi.org/10.5281/zenodo.4612958

Post Radical Nephroureterectomy Cystoscopic Surveillance and Usage of a Nomogram as a Predictor for Intravesical Recurrence

Aravind Raveendran[1], Qing Jun Meng[*], Yu Dong Tian[1], Lin Gang Cui[1], Teng Li[1], Yin Sheng Wei[1] , Yang Su[1]

[1*]Department of Urology,The First Affiliated Hospital Of Zhengzhou University, China

OPEN ACCESS

Accepted Mar 13,2021
Published Mar 17,2021

***Corresponding Author:**
Qing jun meng

DOI :https://doi.org/10.5281/zenodo.4612958

Pages: 78-87

Funding: none

How to cite this article (APA):
Qing Jun Meng Aravind Raveendran., Yu Dong Tian, Lin Gang Cui, Teng Li , Yin Sheng Wei & yang su(2021). Post Radical Nephroureterectomy Cystoscopic Surveillance and Usage of a Nomogram as a Predictor for Intravesical Recurrence. *North American Academic Research, 4(3)*, 78-87. doi:**https://doi.org/10.5281/zenodo.4612958**

Conflicts of Interest
There are no conflicts to declare.

ABSTRACT

Aim:Intravesical recurrence post radical nephroureterectomy (RNU) is a frequent event requiring intense cystoscopic surveillance. This study includes cystoscopic surveillance and usage of variable predictors for intravesical recurrence after radical nephroureterectomy. The current investigation objective was to recognize intravesical recurrence indicators and build up a tool to allow risk delineated methodology supporting patient advising for cystoscopic surveillance and post-operative intravesical MMC administration. Methods: We did a retrospective analysis of 324 patients with UTUC (Upper Tract Urothelial Carcinoma). Patients' demographic data, including age, gender, etiology, tumor size, previous bladder cancer, tumor location (renal pelvic or ureter), were reported. All the patients reported above were followed up for a mean period of 36 months. Computed tomography (CT), ultrasound imaging, cystoscopy, urine cytology, ureteroscopy tests were performed for each patient included in the study. The data set was divided into a development cohort of recurrent and non-recurrent patients). Multivariable and Univariable were addressed to intravesical recurrence after RNU. Predictive accuracy was quantified. Result:With a median follow-up of 36 months, intravesical recurrence occurred in 59 patients. IVR after RNU was noted in 59 patients after a median follow-up of 36 months. The probability of intravesical recurrence is 28.6%.The recurrent bladder tumors were managed with endoscopic resection and intravesical chemoimmunotherapy following the standard protocol. The recurrent bladder tumors showed the following characteristics: 3.4%, 3.4%, 8.5%, 37.3%, and 47.5% of tumors were in Ta, T1, T2, T3, and T4stages, respectively. One patient underwent radical cystectomy after a refractory muscle-invasive bladder tumor, and contralateral UTUC developed. Two patients had partial cystectomy after multiple endoscopic resections of T1 tumor, and intravesical chemotherapy failed. For 59 patients who developed bladder recurrence, the optimal cut-off point of early recurrence was determined to be six months after surgery (p=0.042). End-stage renal disease history and surgical margin positive patient has later bladder recurrence. After multivariable analysis, advanced concurrent bladder staging, tumor location, hydronephrosis, cytology, histology, lymph node, grade,

pre- bladder cancer, and age involvement were all significantly associated with intravesical recurrence (p values ≤0.05). The nomograms were exceptionally precise for foreseeing intravesical recurrence in the external validation.Conclusions: Intravesical recurrence after RNU is a typical event in patients with UTUC. We created nomograms that depict intravesical recurrence after RNU with sensible exactness. Such nomograms could improve clinical decision-making concerning cystoscopic surveillance planning and post-operative intravesical recurrence.

Keywords: Urinary tract urethral cancer ; Radical nephroureterectomy; Intravesical recurrence; Cytoscopic surveillance; Nomograms ;

Introduction

Upper tract urothelial carcinoma (UTUC) consists of renal pelvic and ureteral urothelial carcinoma (UC). Unlike bladder UC, UTUC contributes to 5–10% of all urothelial tumors, with an estimated annual incidence of 1–2 cases per 100,000 population in the United States [2]. About 60% are currently invasive at the time of diagnosis, and approximately 40% of patients die because of recurrence after radical nephroureterectomy (RNU) [1]. RNU with excision of the bladder cuff is the gold standard for the treatment of non-metastatic UTUC. Given that disease recurrence and progression rates are high, especially in patients with invasive or locally advanced UTUC, a better understanding of prognostic factors could help determine the appropriate therapeutic strategy and follow-up [2]. Tumor recurrence is common, especially intravesical recurrence (IVR). A meta-analysis showed that IVR incidence was 29%, with a median time of 22.2 months (range 6.7–56.5 months) [4]. Previous studies have proposed the predictor of IVR, but the definite pathophysiology of bladder recurrence remains unclear.

Two theories have been introduced to explain the possibility of frequent urothelial cancer recurrence. Firstly, implantation of a monoclonal origin tumor cell after intraluminal seeding [5] or field-cancerization theory [6] or both. Therefore, accurate prediction of IVR is necessary to identify the best candidates. The high capacity of UTUC for tumor seeding has brought into question the oncological safety of laparoscopic radical nephroureterectomy (LRNU) and open flank, especially in advanced tumors. This evaluation aims to associate the efficacy of cystoscopic surveillance and variable predictors for intravesical recurrence post-radical nephroureterectomy.

Advanced UTUC carries a poor prognosis with five-year cancer-specific survival (CSS) rates of less than 50% in patients with pT3 tumors, 5–10% in pT4 tumors, and 35% in pN+ disease. These compare to a pace of more than 80% in organ-confined UTUC [7,8]. Postoperative recurrences after Radical nephroureterectomy (RNU) are common and can occur at different sites: locoregional (20%), bladder (30%), distant (10–20%), and contralateral upper tract (2–6%) [9-13].Recently, nomograms predicting locoregional, intravesical, and distant metastatic recurrence based on clinicopathological variables have been developed using large, retrospective, multi-institutional data [7,8,10]. However, the anatomic and temporal and patterns of recurrence next to RNU have not been defined.

To date, only the Canadian Urological Association (CUA) and European Association of Urology (EAU) and

have guidelines on postoperative surveillance of UTUC [7,14,15]. The EAU recommends two surveillance pathways for "invasive" and "non-invasive" tumors [7]. The Canadian Urological Association (CUA) proposes three surveillance protocols based on tumor grade, pathological T stage, and pathological node status.[15] Given the emergence of data regarding the cost and potential morbidity and pathological prognostic variables related to surveillance, it is reasonable to tailor surveillance to patients at contrasting risk of recurrence. Our goal is to build up a post-RNU surveillance protocol dependent on repeat designs in an enormous, multi-institutional cohort of patients.

Materials and methods

Patient's evaluation

We were obtaining informed consent from 324 patients involved in this retrospective study. It was validated by the ethics committee of the first affiliated hospital of Zhengzhou University. Of these, 206 patients were available for follow-up, and 118 patients were excluded due to the follow-up's unavailability. From January 2012 to December 2019,127, male patients and 79 female patients were available for post-operative follow-up. Of those, 43 males and 16 females were diagnosed with bladder recurrence (BR) through the American joint committee on Cancer (AJCC) TNM system. Tumor classified as PTA, pt1, pt2, pt3, pt4.

Patients' demographic data were collected on the variables including age, tumor location, pre-bladder cancer, concurrent bladder, hydronephrosis, serum, histology, lymphovascular, staging, lymph node, cytology, and grade. All the patients reported were followed up for a mean period of 36 months.

Intervention Procedures

We use cystoscopy to glance at the interior of the bladder. Efflux from every ureter ought to be noticed for the presence of blood. Posterolateral walls of the bladder and the dome and are examined. The rest of the bladder should be reviewed for bladder diverticulum, bladder stones, sessile or papillary bladder lesions, erythematous patches, or trabeculation. Before eliminating the scope, the bladder ought to be drained. 64-slice CT is used to evaluate the recurrence and metastasis, and we also use urine cytology and biomarkers as liquid measurements.

Statistical Analysis

Data were analyzed using the SAS software version 9.4 and R software, indicating $p< 0.05$ are statistically significant.

Table 1 Patient characteristics

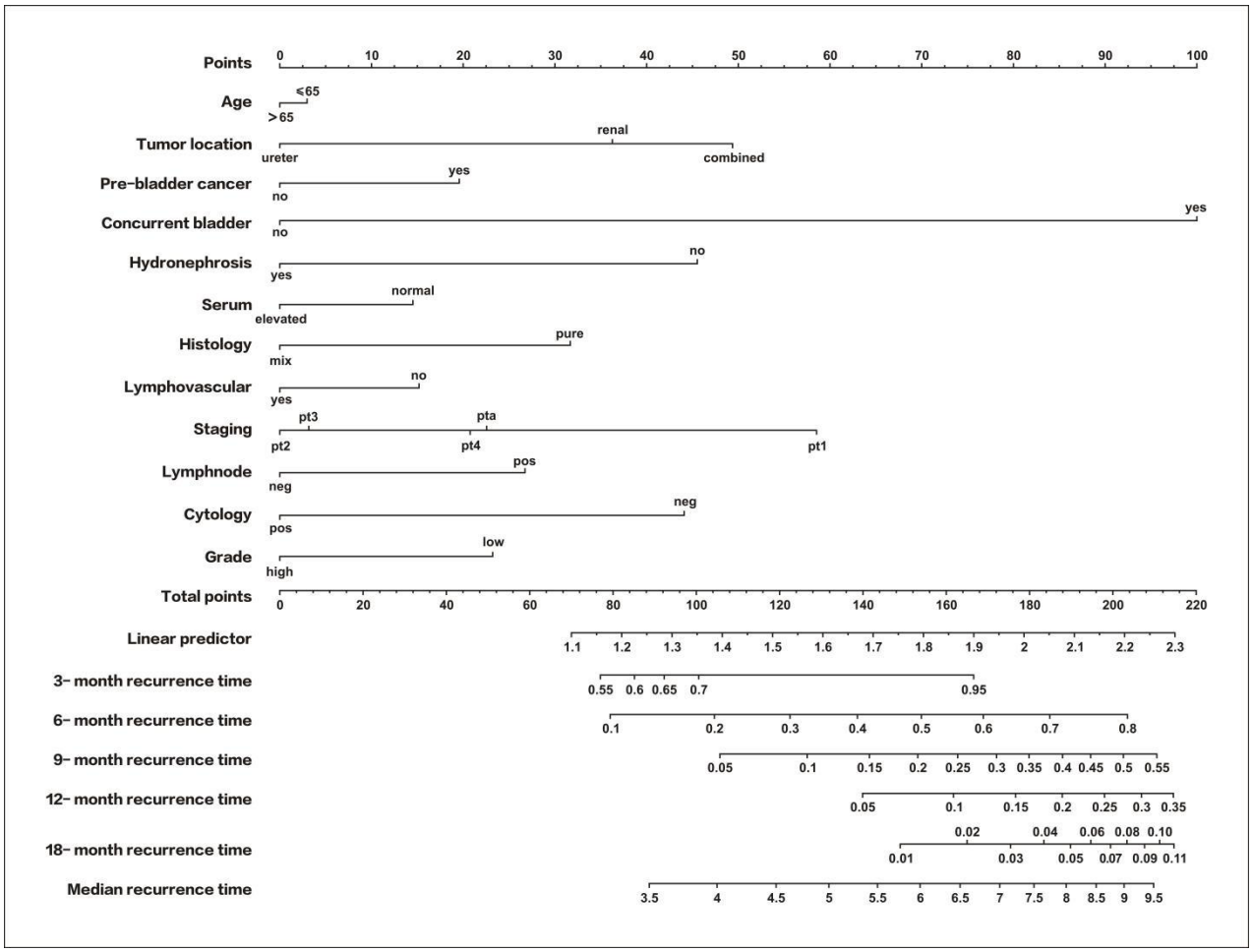
Variables	*parameters*	*non recurrent*	*recurrent*	*total patients*	*P*
Age	N	147	59	206	0.7731
	Mean(SD)	64.9(12.39)	65.4(11.12)	65.1(12.02)	
	Median	67.0	66.0	67.0	
	Min,Max	13, 85	29, 87	13, 87	
Median follow-up	N	147	59	206	<0.0001

	Mean(SD)	28.1(7.56)	33.3(5.82)	29.6(7.46)	
	Median	32.0	36.0	32.0	
	Min,Max	12, 36	12, 36	12, 36	
Tumor location	combined	0	3	3	0.0350
	renal	80	29	109	
	ureter	67	27	94	
Pre- bladder cancer	no	142	57	199	1.0000
	yes	5	2	7	
Concurrent bladder cancer	no	146	56	202	0.0308
	yes	1	3	4	
Urinary cytology	negative	89	36	125	1.0000
	positive	58	23	81	
Hydronephrosis	no	75	28	103	0.7581
	yes	72	31	103	
Serum creatinine level	elevated	38	18	56	0.4939
	normal	109	41	150	
Histology	mix	15	15	30	0.0081
	pure	132	44	176	
Lymphovascular invasion	no	131	46	177	0.0467
	yes	16	13	29	
Pathological stage	T2	29	5	34	<.0001
	T3	29	22	51	
	T4	31	28	59	
	Ta-1	58	4	62	
Pathological Grade	High	52	56	108	<.0001
	Low	95	3	98	
Lymph Node	negative	142	56	198	0.6915
	positive	5	3	8	

Table 2 Variables of pre and post nephroureterectomy

Variables	*95%CI*	*HR*	*P value*
Age (<65 y as referent)			
≥65 y	0.75-1.31	0.9931	0.961
Gender (female as referent)			
Male	0.66-1.15	0.8693	0.331
Tumor location (renal pelvis as referent)			
Ureter	0.74-1.29	0.9791	0.881
Both	0.18-1.80	0.5666	0.335
Bladder cancer history (no as referent)			
Yes	0.47-2.13	1.0000	1.000
Concurrent bladder cancer (no as referent)			
Yes	0.25-1.82	0.6754	0.438
Hydronephrosis (no as referent)			
Yes	0.74-1.28	0.9713	0.834
Serum creatinine (normal as referent)			
Elevated	0.70-1.30	0.9540	0.764
Urine cytology (negative or NA as referent)			
Positive	0.76-1.33	1.0041	0.977
Histology (pure urothelial as referent)			
Mixed type	0.54-1.17	0.7912	0.239
Lymphovascular invasion (no as referent)			
Yes			
Pathological stage (Ta as referent)	0.56-1.24	0.8366	0.375
T1			
T2	0.61-1.65	1.0000	1.000
T3	0.56-1.50	0.9193	0.736
T4	0.40-1.04	0.6489	0.074
Pathological grade (low as referent)	0.38-0.97	0.6068	0.035
High			
Lymph node (negative or NA as referent)	0.39-0.73	0.5329	0.000
Positive			
	0.45-1.86	0.9153	0.806

Figure 1 Nomogram for prediction of cancer specific survival of UTUC



Results

This is a retrospective study, initially involving 324 patients. Of these, 206 patients were available for follow-up, and 118 patients were excluded due to the follow-up's unavailability. The data set was divided into a development cohort of recurrent and non-recurrent patients.

We investigated the role of multiple variables in **Table 1** in the recurrence of UTUC. First, tumor location was found to be important in this regard (p=0.0350), further we checked the pathological stage, and it was found to be significant (p<0.0001). We then found lymphovascular invasion to be significant in recurrence (p<0.0467). Also, histology (p<0.0081) and pathological grade (p<0.0001) were found to be significant in recurrence of UTUC. All other variables are found not statistically significant.

Table 2: It reveals variables of pre and post nephroureterectomy. The tumor stage was <T2 in 63 (30.5%) patients and ≥T2 in 143 (69.4%) patients. Histology with the infiltrating type (66.4%) and high-grade tumors (75.6%) were predominant. Concomitant carcinoma in situ (CIS) in 6.9%, renal vein invasion in 1.4%, and surgical margin positive in 2.8% of patients are found.

Intravesical recurrence after RNU is a typical event in patients with UTUC. Nomograms depict intravesical recurrence after RNU with sensible exactness. Such nomograms could improve clinical decision-making with respect to cystoscopic surveillance planning and post-operative intravesical recurrence.

Figure1: Nomograms are commonly used tools to estimate prognosis in oncology and medicine. In the nomogram, it is clear that concurrent bladder has the greatest influence on predicting cancer-specific survival of UTUC, followed by staging, tumor location, hydronephrosis, cytology, histology, lymph node, grade, pre- bladder cancer, and age. Thus, the concurrent bladder is the variable that has the most influence on predicting cancer-specific survival of UTUC. At the same time, 'age' is the variable that has the least influence on predicting cancer-specific survival of UTUC. Here 'cancer-specific survival of UTUC' is our study variable and the rest are our predictive variables.

IVR after RNU was noted in 59 (28.6%) patients after a median follow-up of 36 months. The recurrent bladder tumors were managed with endoscopic resection and intravesical chemoimmunotherapy following the standard protocol. The recurrent bladder tumors showed the following characteristics: 3.4%, 3.4%, 8.5%, 37.3%, and 47.5% of tumors were in Ta, T1, T2, T3, and T4 stages, respectively. One patient underwent radical cystectomy after the development of refractory muscle-invasive bladder tumor and contralateral UTUC. Two patients had partial cystectomy after multiple endoscopic resections of T1 tumor, and intravesical chemotherapy failed. For 59 patients who developed bladder recurrence, the optimal cut-off point of early recurrence was determined to be six months after surgery ($p=0.042$). End-stage renal disease history and surgical margin positive patient has later bladder recurrence.

Discussion

UTUC is a rare disease and accounts for only 5% of urothelial carcinomas. The outcomes of patients with UTUC are heterogeneous and thus are difficult to predict. Given the low incidence of the disease, data regarding clinicopathologic predictors of outcomes are sparse. Recently, multi-institutional collaborative studies have identified several potential outcome predictors following RNU for UTUC [3,4]. Accurate estimation of treatment success, complications, and long-term morbidity is essential for physicians and their patients to make informed medical decisions regarding managing their disease. To this end, we and others have developed prognostic tools such as nomograms to obtain the most accurate and reliable predictions of outcomes. Based on the impact, each factor is taken into account that influences the outcome. These prediction tools can provide predictions that are both evidence-based and individualized.

In light of these predictors, we have had the option to make a post-RNU risk-based surveillance protocol. Besides, we included the temporal and anatomic patterns of recurrence for each risk group to direct recurrence and timing of analytic modalities, just as a repeated risk at various anatomic areas. Our outcomes likewise emphasize the significance of the initial surveillance cystoscopy at the three-month postoperative time point, given the clear risk of early bladder recurrence, particularly without postoperative intravesical chemotherapy, which was not utilized in any of our patients [16].

Our investigation affirms the high-risk of intravesical recurrence in moderate and high-risk patients and high-risk loco-local/metastatic recurrence in high-risk patients. Surgery alone doesn't have all the earmarks of being satisfactory in patients with high-risk illness, and multimodal therapy should be thought of. Given the way that decreases in renal function following RNU traditionally precludes an enormous extent of patients from adjuvant chemotherapy [17,18] and that there is new proof for adjuvant chemotherapy in this populace [19]. Strong consideration ought to be given to whether neoadjuvant/adjuvant chemotherapy may benefit patients with high-risk features. The constraint with this methodology is that the meaning of "high-risk" depends on postoperative pathological parameters. Some have endeavored to anticipate high-risk illness dependent on tumor grade on endoscopic biopsy and endoscopic tumor appearance and area.

This investigation is restricted by the shortfall of patients who went through renal-conserving management, including segmental ureterectomy and endoscopy. Extra limits incorporate the short mean follow-up and the low number of events beyond two years, making it hard to propose concrete suggestions beyond this period. Besides, we didn't catch whether recurrence was analyzed on imaging only or regarding the symptomatic presentation. The initially diagnosed recurrence was thought of, and metachronous metastases at other anatomic sites were excluded from the investigation. At long last, understanding management and surveillance were heterogeneous across centers, and patients accepting adjuvant chemotherapy were not excluded.

The disadvantage of routine surveillance is the potential for bogus positive outcomes presenting the patient to pointless invasive confirmatory studies. Regarding metastatic UTUC, it isn't realized whether detecting a systemic recurrence early by surveillance versus detection when symptomatic results in improved chemotherapy results. In bladder cancer, survival results are not distinctive for those with asymptomatic versus symptomatic recurrences [20,21]. However, this thought ought not to subvert the significance of surveillance, as some urothelial recurrences are curable.

Conclusion

Bladder recurrence (28.6% in 3 years) was common in UTUC after RNU, and early bladder recurrence (within six months) was associated with more relapsing high-risk non-muscle-invasive bladder cancer. Preoperative ureter manipulation was recognized as an independent factor related to early recurrence. These patients may require more severe observation to go through prophylactic intravesical chemotherapy after nephroureterectomy.

References

1. Roupret M, Babjuk M, Comperat E, et al. European Association of urology guidelines on upper urinary tract urothelial carcinoma: 2017 update. Eur Urol. 2018;73(1):111–122. doi:10.1016/j.eururo.2017. 07.036
2.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;35(3):379–387. doi:10.1007/s00345-016-1928-x

3. Li CC, Chang TH, Wu WJ, et al. Significant predictive factors for prognosis of primary upper urinary tract cancer after radical nephroureterectomy in Taiwanese patients. Eur Urol. 2008;54(5):1127–1134. doi:10.1016/j.eururo.2008.01.054
4. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin. 2011;61:212–36.
5. Xylinas E, Colin P, Audenet F, et al. Intravesical recurrence after radical nephroureterectomy for upper tract urothelial carcinomas: predictors and impact on subsequent oncological outcomes from a national multicenter study. World J Urol. 2013;31:61–8.
6. O'Brien T, Ray E, Singh R, et al. Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: a prospective, multicentre, randomised clinical trial of a single postoperative intravesical dose of mitomycin C (the ODMIT-C Trial). Eur Urol. 2011;60:703–10.
7. Margulis V, Youssef RF, Karakiewicz PI, et al. Preoperative multivariable prognostic model for predicting non-organ-confined urothelial carcinoma of the upper urinary tract. J Urol. 2010;184:453–8. doi: 10.1016/j.juro.2010.03.142. [PubMed] [CrossRef] [Google Scholar]
8. Yates DR, Hupertan V, Colin P, et al. Cancer-specific survival after radical nephroureterectomy for upper urinary tract urothelial carcinoma: Proposal and multi-institutional validation of a postoperative nomogram. Br J Cancer. 2012;106:1083–8. [PMC free article] [PubMed] [Google Scholar]
9. Xylinas E, Kluth L, Passoni N, et al. Prediction of intravesical recurrence after radical nephroureterectomy: Development of a clinical decision-making tool. Eur Urol. 2014;65:650–8. doi: 10.1016/j.eururo.2013.09.003. [PubMed] [CrossRef] [Google Scholar]
10. Tanaka N, Kikuchi E, Kanao K, et al. Metastatic behavior of upper tract urothelial carcinoma after radical nephroureterectomy: Association with primary tumour location. Ann Surg Oncol. 2014;21:1038–45. doi: 10.1245/s10434-013-3349-z. [PubMed] [CrossRef] [Google Scholar]
11. Cha EK, Shariat SF, Kormaksson M, et al. Predicting clinical outcomes after radical nephroureterectomy for upper tract urothelial carcinoma. Eur Urol. 2012;61:818–25. doi: 10.1016/j.eururo.2012.01.021. [PubMed] [CrossRef] [Google Scholar]
12. Li WM, Shen JT, Li CC, et al. Oncologic outcomes following three different approaches to the distal ureter and bladder cuff in nephroureterectomy for primary upper urinary tract urothelial carcinoma. Eur Urol. 2010;57:963–9. doi: 10.1016/j.eururo.2009.12.032. [PubMed] [CrossRef] [Google Scholar]
13. Novara G, De Marco V, Dalpiaz O, et al. Independent predictors of contralateral metachronous upper urinary tract transitional cell carcinoma after nephroureterectomy: Multi-institutional dataset from three European centres. Int J Urol. 2009;16:187–91. doi: 10.1111/j.1442-2042.2008.02201.x. [PubMed] [CrossRef] [Google Scholar]
14. Roupret M, Babjuk M, Compérat E, et al. European Association of Urology guidelines on upper urinary tract urothelial carcinoma: 2017 update. Eur Urol. 2018;73:111–22. doi: 10.1016/j.eururo.2017.07.036. [PubMed] [CrossRef] [Google Scholar]
15. Kapoor A, Allard CB, Black P, et al. Canadian guidelines for postoperative surveillance of upper urinary tract urothelial carcinoma. Can Urol Assoc J. 2013;7:306–11. doi: 10.5489/cuaj.1578. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
16. O'Brien T, Ray E, Singh R, et al. Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: A prospective, multicentre, randomized clinical trial of a single postoperative intravesical dose of mitomycin C (the ODMIT-C Trial) Eur Urol. 2011;60:703–10. doi: 10.1016/j.eururo.2011.05.064. [PubMed] [CrossRef] [Google Scholar]
17. Raman JD, Lin YK, Kaag M, et al. High rates of advanced disease, complications, and decline of renal function after radical nephroureterectomy. Urol Oncol. 2014;32:47.e9–47.14. [PubMed] [Google Scholar]
18. Xylinas E, Rink M, Margulis V, et al. Impact of renal function on eligibility for chemotherapy and survival in patients who have undergone radical nephro-ureterectomy. BJU Int. 2013;112:453–61. doi: 10.1111/j.1464-410X.2012.11649.x. [PubMed] [CrossRef] [Google Scholar]
19. Birtle AJ, Chester JD, Jones RJ, et al. Results of POUT: A phase 3, randomized trial of perioperative chemotherapy vs. surveillance in upper tract urothelial cancer (UTUC) J Clin Oncol. 2018 doi: 10.1200/JCO.2018.36.6_suppl.407. Epub ahead of print. [CrossRef] [Google Scholar]
20. Strope SA, Chang SH, Chen L, et al. Survival impact of follow-up care after radical cystectomy for bladder cancer. J Urol. 2013;190:1698–703. doi: 10.1016/j.juro.2013.05.051. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

21. Volkmer BG, Kuefer R, Bartsch GC, Jr, et al. Oncological follow-up after radical cystectomy for bladder cancer — is there any benefit? J Urol. 2009;181:1587–93. doi: 10.1016/j.juro.2008.11.112. [PubMed] [CrossRef] [Google Scholar]

Author: Aravind Raveendran
MBBS at Zhengzhou University
3rd year urology, Postgraduate student
Zhengzhou university, Zhengzhou, Henan, China