Original Article

Effects of tumor size and location on survival in upper tract urothelial carcinoma after nephroureterectomy

Shreyas S. Joshi*, Laura L. Quast[1], Sam S. Chang, Sanjay G. Patel[2]

Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN, [1]Department of Urologic Surgery, University of Iowa Carver College of Medicine, Iowa City, IA, [2]Department of Urology, University of Oklahoma Health Sciences Center, Norman, OK, USA

*E-mail: ssjoshimd@gmail.com

ABSTRACT

Introduction: Upper Tract Urothelial Carcinoma (UTUC) is a rare disease with few prognostic determinants. We sought to evaluate the impact of tumor size and location on patient survival following nephroureterectomy for UTUC.

Materials and Methods: Data on 8284 patients treated with radical nephroureterectomy for UTUC in the United States between 1998 and 2011 were analyzed from the National Cancer Data Base. Univariable survivorship curves were generated based on pT stage, pN stage, grade, tumor size, and tumor site (renal pelvis vs. ureter). A Cox proportional hazards model was used to evaluate the effect of age, comorbidity, T stage, lymph node involvement, tumor site, and tumor size on survival.

Results: The median follow-up time was 46 months. A majority of the patients were male (55.4%) with a tumor size of ≥3.5 cm (52.0%) and pT stage <T2 (47.8%). The overall 5 years survival overall survival (OS) for the entire cohort was 51.6%. When stratified by tumor size <3.5 cm or ≥3.5 cm the 5-year OS was 45.9% and 58.5%, respectively. On multivariable analysis controlling for age, Charlson comorbidity index, grade, and tumor stage, tumor size ≥3.5 cm was independently predictive of worse OS (odds ratio: 1.13 [95% confidence interval: 1.02–1.26], $P = 0.023$).

Conclusions: Using the largest series of patients with UTUC undergoing nephroureterectomy, we demonstrated a worse survival in patients with larger tumor sizes (≥3.5 cm) but no difference in survival based on tumor location while controlling for other pathologic characteristics. Incorporation of tumor size into perioperative risk modeling may help with patient stratification and provide further prognostic information for patient counseling.

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is a rare disease representing 5% of all urothelial malignancies, with an incidence of 2.08 cases per 100,000 person years in the United States.[1] UTUC is generally an aggressive disease, and it is estimated that at diagnosis, 60% of UTUCs are invasive, compared to 15%–25% of urothelial carcinoma of the bladder.[2] Due to its rarity, clinical decision-making surrounding treatment of UTUC is largely extrapolated from the existing literature for urothelial carcinoma of the bladder.

To better understand the nature of UTUC, perioperative predictive models have been developed to predict invasive, and non-organ confined disease spread, recurrence-free survival (RFS), and cancer-specific survival (CSS).[3-5] While tumor stage and grade are consistently important in prognosis, tumor size and location have been less thoroughly studied, though recent retrospective studies have found that tumors >3 cm in size are associated with worse recurrence-free and CSS, and overall survival (OS).[6-8] Furthermore, there is controversy within the literature with regards to the impact of tumor location (renal pelvis vs. ureter) on survival outcomes. Whereas several studies of smaller cohorts appear to indicate that tumor location

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/iju.IJU_216_17

Received: 03.07.2017, **Accepted:** 29.08.2017

Financial support and sponsorship: Nil

Conflicts of interest: There are no conflicts of interest.

is predictive of postoperative outcomes,[9-12] other groups failed to show such a correlation.[13-15] The analysis of the largest prospective cohort of UTUC patients to date (the UTUC Collaboration) did not find tumor location to be of prognostic import.[16,17]

In this study, we utilized the National Cancer Data Base (NCDB) to better understand the impact of tumor size and tumor location on survival and to provide risk factor prognostic information for patients with UTUC. We hypothesize that larger tumor size and renal pelvis tumor location are associated with worse survival. Consideration of tumor size and location in addition to other patient and pathologic characteristics may allow for more precise risk stratification of patients with UTUC with the potential to identify patients who may benefit from more timely and aggressive surgery, as well as consideration of neoadjuvant chemotherapy (NAC).

MATERIALS AND METHODS

Data were obtained from the NCDB participant user file. The NCDB is a national database of oncologic outcomes for more than 1500 Commission on Cancer accredited facilities in the United States and Puerto Rico, representing 70% of all cancer cases in the United States. De-identified individual patient data are linked with demographic, pathologic and survivorship data for analysis.

Inclusion criteria

We identified 8,284 patients treated for UTUC in the United States between 1998 and 2011 with localized disease (cN0/cNx, cM0) for urothelial carcinoma (ICD-0-3 codes: 8120/3) with the location in the renal pelvis or ureter (C65-C68). All patients were treated with radical nephroureterectomy (RNU), with or without bladder cuff excision, and had no prior malignancy. Bladder cuff excision was not recorded; hence, the cohort includes a mix of these surgical variants.

Patient demographic data

Cohort demographic variables included age, sex, race/ethnicity, Charlson comorbidity index (CCI), location of treatment by region, year of treatment, and treatment center type. Race/Ethnicity data were categorized as white/black/other/unknown. The confidence interval was divided into groups as no comorbidities, CCI = 1, and CCI >1. Regions of the treatment within the United States consisted of Northeast, South/Southeast, Midwest, and West. Years of treatment were stratified into 1998–2000, 2001–2003, 2004–2006, and 2007–2011. Treatment center types included community cancer programs, comprehensive community programs, academic/research program, and other. Community cancer and comprehensive community programs differ in the number of cases they treat, at 100–500 new cases to over 500 cases, respectively. Academic/research programs treat over 500 new cases per year and also train resident physicians in at least four areas.

Pathologic data

Primary clinical variables included tumor size (<3.5 cm or ≥3.5 cm), tumor grade (low/high), tumor stage (pT0/T1/T2/T3/T4), pN stage (pN0/N+, Nx), and primary site (renal pelvis, ureter). Tumor size of 3.5 cm was selected as this was the median tumor size in the group.

Statistical analysis

Primary outcome variables included OS and 5-year survival after nephroureterectomy for UTUC. Univariable survival analysis was performed using the Kaplan Meier method and compared using the log rank test. Multivariable survival analysis was performed using a Cox proportional hazards model to evaluate the effect of age, comorbidity, T stage, lymph node involvement, tumor site, tumor grade, and tumor size on 5-year OS. Statistical analysis was conducting using STATA software, version 9.0 (Stata Corporation, College Station, TX, USA). Statistical significance was set *a priori* at $P < 0.05$.

RESULTS

Basic demographics

A total of 8284 patients met inclusion criteria with median follow-up time of 46 mo. The incidence of UTUC increased with age with 56.7% of patients being older than 70 years of age. The cohort was skewed toward the male gender (55.3% male, 44.6% female). One-third (32.6%) of patients had no comorbidities based on CCI. Treatment location was well distributed among regions within the United States with a majority of patients being treated at academic and comprehensive community programs. The number of patients with tumor size < 3.5 cm was almost equal to the number of those with tumor size ≥ 3.5 cm (48.0% vs. 52.0%) with an interquartile range of (2.3–5.0 cm). The majority of patients had high-grade tumors (82.0%), pN0 (68.3%), and a tumor location in the renal pelvis (68.0%). A larger proportion of patients presented with pT3 disease (31.2%) than pT0/Ta/TIS (24.2%) or pT1 (23.6%) disease [Table 1].

Survival analysis

The 5-year survival for the entire cohort was 51.6%. The 5-year OS decreased with each successive increase in pT stage. The 5-year survival was worse for pN + versus pN0 (14.8% vs. 55.8%, $P < 0.0001$), high grade tumors versus low grade tumors (48.4% vs. 74.3%, $P < 0.0001$), and tumor size ≥ 3.5 cm versus < 3.5 cm (45.9% vs. 58.5%, $P < 0.0001$). Having a tumor located in the ureter had similar 5-year OS as tumors in the renal pelvis (51.8% vs. 51.5%, $P = 0.817$) [Table 2]. Kaplan Meier survival curves are demonstrated in Figure 1 for pathologic characteristics.

Multivariable survival analysis demonstrated that increasing age ($P < 0.001$), increasing comorbidity ($P < 0.001$), larger

Table 1: Patient and demographic characteristics for patients with 5-year survival data

Patient characteristics (*n*=8284)	Frequency (*n*)	Percentage of total
Cohort		
Age		
<50	448	5.4
50-59	1082	13.1
60-69	2057	24.8
70-79	2984	36.0
>80	1713	20.7
Sex		
Male	4587	55.4
Female	3697	44.6
Race		
White	7703	93.0
Black	297	3.6
Other	199	2.4
Unknown	85	1.0
CCI		
No comorbidities	2699	32.6
CCI=1	910	11.0
CCI >1	308	3.7
Unknown	4367	52.7
Location of treatment		
Northeast	1709	20.6
South/Southeast	2328	28.1
Midwest	2359	28.5
West	1888	22.8
Center type		
Community cancer program	872	10.5
Comprehensive community program	4680	56.5
Academic/research program	2299	27.8
Other	433	5.2
Tumor size (cm)		
<3.5	3189	48.0
≥3.5	3450	52.0
Tumor grade		
Low grade	913	11.0
High grade	6792	82.0
Unknown	579	7.0
T stage		
pT0/Ta/Tis	2001	24.2
pT1	1953	23.6
pT2	1127	13.6
pT3	2583	31.2
pT4	620	7.5
pN stage		
N0	5656	68.3
N+	760	8.1
Nx	1958	23.64
Tumor location		
Renal pelvis	5630	68.0
Ureter	2634	32.0

CCI=Charlson Comorbidity Index

tumor size (P = 0.043), high grade tumors (P < 0.001), and increasing pT stage are associated with worse OS outcomes [Table 3]. Tumor location was not independently predictive of survival.

DISCUSSION

The rarity of UTUC has made it difficult to ascertain the prognostic value of several important disease variables. The NCDB database contains the largest cohort of such patients to date, from which we were able to analyze survival outcomes from 8284 patients who underwent radical nephroureterectomy for UTUC. We demonstrate that while controlling for age, comorbidity, tumor grade, pT stage, and pN stage, tumor size ≥3.5 cm was associated with worse OS. Location of the tumor (renal pelvis vs. ureter) did not have an impact on survival.

Table 2: Univariate 5-year survival by pathologic characteristics

By variable	5-year overall survival (%)	95% CI	
		Lower limit (%)	Upper limit (%)
5 year survival for patients with upper tract UCC			
All patients	51.6	50.5	52.7
T stage			
pT0/Ta/Tis	75.6	73.6	77.6
pT1	65.8	63.5	68.0
pT2	54.2	51.0	57.2
pT3	31.6	29.7	33.5
pT4	9.3	7.1	11.8
pN stage			
N0	55.8	54.5	57.2
N+	14.8	12.1	17.7
Nx	52.1	49.7	54.4
Tumor grade			
Low grade	74.3	71.2	77.1
High grade	48.4	47.2	49.7
Tumor size (cm)			
<3.5	58.5	56.7	60.3
≥3.5	45.9	44.1	47.6
Primary site			
Renal pelvis	51.5	50.1	52.9
Ureter	51.8	49.8	53.8

CI=Confidence interval, UCC=Urothelial cell carcinoma

The role of tumor size as a prognostic factor for survival after RNU has been controversial. Some studies showed that a tumor diameter of 3.0 cm or above is a risk factor for poor RFS after RNU, and Pieras *et al.* showed that tumor size can be used as a prognostic factor for bladder recurrence.[7,18] Conversely, others have shown that tumor size did not have an effect on CSS or recurrence.[6,19] The variation in findings is, in part, due to limitations in sample sizes. A larger cohort by Shibing *et al.* analyzing 795 patients from several centers did find that tumor size >3.0 cm was an independent predictor of worse RFS, CSS, and OS.[8]

Our study, which represents the largest such retrospective cohort, had a median tumor size of 3.5 cm, similar to the median of 3.0 cm found in other cohorts. As such, a cutoff of 3.5 cm was chosen. Our findings suggest that tumor size can be used as a predictor of 5-year survival, with rates of 58.5% for ≤3.5 cm versus 45.9% for those larger than 3.5 cm.

Another controversy in UTUC is whether tumor location (renal pelvis vs. ureter) affects survival and recurrence. Here again, the existing literature is conflicting. Two smaller single-institution studies showed that carcinoma of the proximal ureter has worse prognosis.[11,20] Another study showed that ureteral tumors have worse RFS and CSS on multivariable analysis.[21] However, a large number of other

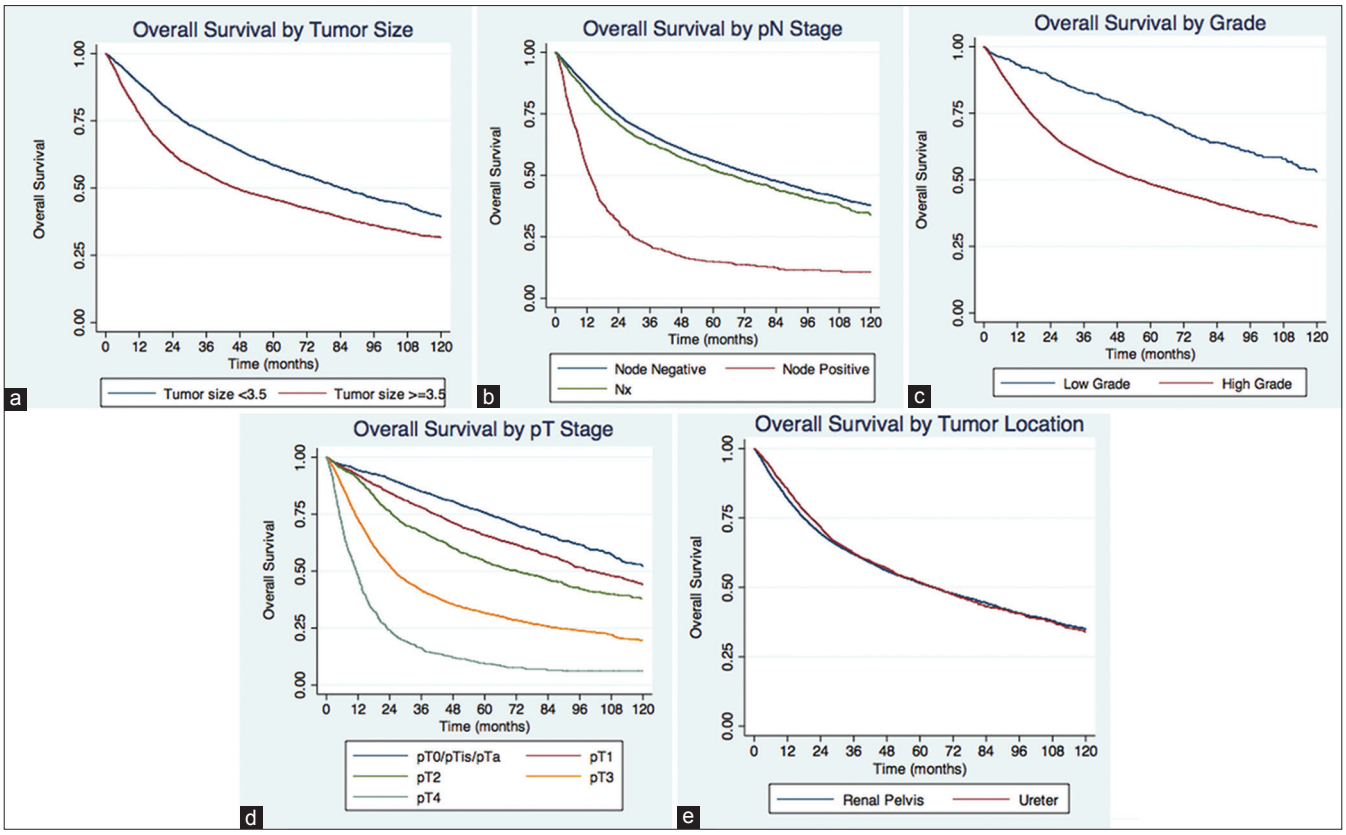

Figure 1: Survivorship (*n* = 8,284) by tumor size *P* Log Rank <0.0001 (a), N stage *P* Log Rank <0.0001 (b), grade *P* Log Rank <0.0001 (c), T stage *P* Log Rank <0.0001 (d), and tumor site *P* Log rank = 0.817 (e)

studies show that tumor location does not affect survival outcomes after surgery.[1,5,13,14,16,22] In the present study, we confirm that there is no statistically significant survival difference between patients with tumors primarily in the renal pelvis or in the ureter.

Identification of prognostic factors in UTUC is crucial to inform treatment strategies. The appropriate use of perioperative chemotherapy in UTUC might be better guided through an understanding of which patients are likely to have more aggressive disease characteristics. Adjuvant chemotherapy (AC) for UTUC, for example, has had varied success. Multiple studies have shown that AC has little or no effect on overall or CSS.[23,24] Moreover, RNU itself may block patients from receiving AC; some studies have shown a 25%–30% reduction in patient eligibility due to loss of estimated glomerular filtration rate.[24,25] For these reasons, NAC is becoming the gold standard for treatment of UTUC. And although prior evidence for the efficacy of NAC in UTUC came from extrapolating data demonstrating NAC effectiveness in bladder cancer, an important recent retrospective review by Porten *et al.* evaluating NAC for UTUC showed better overall and disease-specific survival for patients receiving NAC.[26] Based on our current understanding, it is difficult to know which patients will benefit most, if at all, from chemotherapy. Identifying pre- and post-operative clinicopathologic factors may, therefore, help to develop a risk-adapted approach to patient selection. Unfortunately, the use of perioperative chemotherapy was not widespread during the period in our study; and the patients in our NCDB cohort did not have sufficiently robust perioperative chemotherapy data to make conclusions.

This study has some important limitations. Retrospective data collection brings with it innate weaknesses. As with most retrospective clinical datasets, the data are affected by selection bias and confounding by indication to treat. Surgeons do not all use the same standardized criteria to decide whether or not to perform lymphadenectomy, and lymphadenectomy templates differ, all of which may impact survival outcomes. Indeed, there is biological plausibility that more aggressive lymph node dissection may improve survival following RNU, though no definitive evidence yet exists.[27] Furthermore, as UTUC is predominantly a disease of the elderly, competing comorbid illness likely plays an important role in the long-term outcomes, though this was controlled to the best of our ability using the comorbidity index. Finally, our dataset did not include measurements of lymphovascular invasion and tumor architecture, which have been found to be prognostic factors in other studies.[4,16]

CONCLUSIONS

Using the largest series of patients with UTUC having undergone RNU, we demonstrated worse survival in patients

Table 3: Cox proportional hazards model for mortality risk at 5 years

Variable	Hazard ratio	95% CI	*P*
Multivariate survival analysis			
Age			
<50	Reference		
50-59	1.23	0.85-1.78	0.27
60-69	1.83	1.30-2.56	<0.001
70-79	2.58	1.86-3.59	<0.001
>80	3.89	2.79-5.42	<0.001
CCI			
No comorbidities	Reference		
CCI=1	1.39	1.24-1.57	<0.001
CCI >1	1.95	1.65-2.31	<0.001
Tumor size (cm)			
<3.5	Reference		
≥3.5	1.13	1.02-1.26	0.023
Tumor grade			
Low grade	Reference		
High grade	1.43	1.17-1.76	<0.001
T stage			
pT0/Ta/Tis	Reference		
pT1	1.17	0.97-1.41	0.11
pT2	1.47	1.20-1.80	<0.001
pT3	2.93	2.48-3.45	<0.001
pT4	6.70	5.42-8.28	<0.001
pN stage			
N0	Reference		
Nx	1.04	0.93-1.17	0.46
N+	1.72	1.46-2.03	<0.001
Primary site			
Renal pelvis	Reference		
Ureter	1.09	0.97-1.22	0.16

CI=Confidence interval, CCI=Charlson Comorbidity Index

with larger tumor sizes (≥3.5 cm) and no difference in survival based on tumor location after controlling for other clinical and pathologic characteristics. Incorporation of tumor size into perioperative risk models may provide important prognostic information for patient counseling and selection regarding perioperative chemotherapy. We also confirm in this study that tumor location (renal pelvis vs. ureter) does not affect survival. Further prospective studies are needed to confirm the clinical and prognostic value of tumor size.

REFERENCES

1. Raman JD, Messer J, Sielatycki JA, Hollenbeak CS. Incidence and survival of patients with carcinoma of the ureter and renal pelvis in the USA, 1973-2005. BJU Int 2011;107:1059-64.
2. Rouprêt M, Babjuk M, Compérat E, Zigeuner R, Sylvester RJ, Burger M, *et al.* European Association of Urology guidelines on upper urinary tract urothelial cell carcinoma: 2015 update. Eur Urol 2015;68:868-79.
3. Rouprêt M, Hupertan V, Seisen T, Colin P, Xylinas E, Yates DR, *et al.* Prediction of cancer specific survival after radical nephroureterectomy for upper tract urothelial carcinoma: Development of an optimized postoperative nomogram using decision curve analysis. J Urol 2013;189:1662-9.
4. Cha EK, Shariat SF, Kormaksson M, Novara G, Chromecki TF, Scherr DS, *et al.* Predicting clinical outcomes after radical nephroureterectomy for upper tract urothelial carcinoma. Eur Urol 2012;61:818-25.
5. Favaretto RL, Shariat SF, Savage C, Godoy G, Chade DC, Kaag M, *et al.* Combining imaging and ureteroscopy variables in a preoperative multivariable model for prediction of muscle-invasive and non-organ confined disease in patients with upper tract urothelial carcinoma. BJU Int 2012;109:77-82.
6. Milenkovic-Petronic D, Milojevic B, Djokic M, Sipetic-Grujicic S, Milojevic IG, Bumbasirevic U, *et al.* The impact of tumor size on outcomes in patients with upper urinary tract urothelial carcinoma. Int Urol Nephrol 2014;46:563-9.
7. Espiritu PN, Sverrisson EF, Sexton WJ, Pow-Sang JM, Poch MA, Dhillon J, *et al.* Effect of tumor size on recurrence-free survival of upper tract urothelial carcinoma following surgical resection. Urol Oncol 2014;32:619-24.
8. Shibing Y, Liangren L, Qiang W, Hong L, Turun S, Junhao L, *et al.* Impact of tumour size on prognosis of upper urinary tract urothelial carcinoma after radical nephroureterectomy: A multi-institutional analysis of 795 cases. BJU Int 2016;118:902-10.
9. Tai YS, Chen CH, Huang CY, Tai HC, Wang SM, Pu YS. The effect of tumor location on oncologic outcomes in patients with upper urinary tract urothelial carcinoma stratified by pathologic stage. Urol Oncol 2016;34:4.e19-25.
10. Park J, Ha SH, Min GE, Song C, Hong B, Hong JH, *et al.* The protective role of renal parenchyma as a barrier to local tumor spread of upper tract transitional cell carcinoma and its impact on patient survival. J Urol 2009;182:894-9.
11. Park S, Hong B, Kim CS, Ahn H. The impact of tumor location on prognosis of transitional cell carcinoma of the upper urinary tract. J Urol 2004;171(2 Pt 1):621-5.
12. van der Poel HG, Antonini N, van Tinteren H, Horenblas S. Upper urinary tract cancer: Location is correlated with prognosis. Eur Urol 2005;48:438-44.
13. Isbarn H, Jeldres C, Shariat SF, Liberman D, Sun M, Lughezzani G, *et al.* Location of the primary tumor is not an independent predictor of cancer specific mortality in patients with upper urinary tract urothelial carcinoma. J Urol 2009;182:2177-81.
14. Milojevic B, Djokic M, Sipetic-Grujicic S, Milenkovic-Petronic D, Vuksanovic A, Bumbasirevic U, *et al.* Upper urinary tract transitional cell carcinoma: location is not correlated with prognosis. BJU Int 2012;109:1037-42.
15. Favaretto RL, Shariat SF, Chade DC, Godoy G, Adamy A, Kaag M, *et al.* The effect of tumor location on prognosis in patients treated with radical nephroureterectomy at Memorial Sloan-Kettering Cancer Center. Eur Urol 2010;58:574-80.
16. Margulis V, Shariat SF, Matin SF, Kamat AM, Zigeuner R, Kikuchi E, *et al.* Outcomes of radical nephroureterectomy: A series from the upper tract urothelial carcinoma collaboration. Cancer 2009;115:1224-33.
17. Raman JD, Ng CK, Scherr DS, Margulis V, Lotan Y, Bensalah K, *et al.* Impact of tumor location on prognosis for patients with upper tract urothelial carcinoma managed by radical nephroureterectomy. Eur Urol 2010;57:1072-9.
18. Pieras E, Frontera G, Ruiz X, Vicens A, Ozonas M, Pizá P. Concomitant carcinoma *in situ* and tumour size are prognostic factors for bladder recurrence after nephroureterectomy for upper tract transitional cell carcinoma. BJU Int 2010;106:1319-23.
19. Hisataki T, Miyao N, Masumori N, Takahashi A, Sasai M, Yanase M, *et al.* Risk factors for the development of bladder cancer after upper tract urothelial cancer. Urology 2000;55:663-7.
20. Akdogan B, Dogan HS, Eskicorapci SY, Sahin A, Erkan I, Ozen H. Prognostic significance of bladder tumor history and tumor location in upper tract transitional cell carcinoma. J Urol 2006;176:48-52.
21. Wu Y, Dong Q, Liu L, Han P, Wei Q. The impact of tumor location and multifocality on prognosis for patients with upper tract urothelial carcinoma: A meta-analysis. Sci Rep 2014;4:6361.
22. Williams AK, Kassouf W, Chin J, Rendon R, Jacobsen N, Fairey A, *et al.* Multifocality rather than tumor location is a prognostic factor in upper tract urothelial carcinoma. Urol Oncol 2013;31:1161-5.
23. Hellenthal NJ, Shariat SF, Margulis V, Karakiewicz PI, Roscigno M, Bolenz C, *et al.* Adjuvant chemotherapy for high risk upper tract

urothelial carcinoma: Results from the upper tract urothelial carcinoma collaboration. J Urol 2009;182:900-6.
24. Yafi FA, Tanguay S, Rendon R, Jacobsen N, Fairey A, Izawa J, *et al*. Adjuvant chemotherapy for upper-tract urothelial carcinoma treated with nephroureterectomy: Assessment of adequate renal function and influence on outcome. Urol Oncol 2014;32:31.e17-24.
25. Kaag MG, O'Malley RL, O'Malley P, Godoy G, Chen M, Smaldone MC, *et al*. Changes in renal function following nephroureterectomy may affect the use of perioperative chemotherapy. Eur Urol 2010;58:581-7.
26. Porten S, Siefker-Radtke AO, Xiao L, Margulis V, Kamat AM, Wood CG, *et al*. Neoadjuvant chemotherapy improves survival of patients with upper tract urothelial carcinoma. Cancer 2014;120:1794-9.
27. Kundu SD, Eggener SE. Retroperitoneal lymph nodes in transitional cell carcinoma of the kidney and ureter. Adv Urol 2009:181927.

How to cite this article: Joshi SS, Quast LL, Chang SS, Patel SG. Effects of tumor size and location on survival in upper tract urothelial carcinoma after nephroureterectomy. Indian J Urol 2018;34:68-73.