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8-armed octopus: Evaluation of clinicopathologic prognostic factors of urothelial carcinoma of the upper urinary system

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1. Introduction
Urothelial carcinomas (UC) can arise in any part of the urinary tract lined by urothelium; however, the majority of cases are located in the lower tract (bladder, urethra) (1,2). Upper urinary system urothelial carcinomas (UUSUC), including renal pelvis and ureteral tumors, are known to be rare tumors, which constitute approximately 5%–10% of all UCs. The natural history and prognosis of UUSUC differ from bladder cancer (3–6). Among UUSUC, 60% of cases are invasive at diagnosis while only 15%–25% of bladder tumors are invasive at initial diagnosis. Moreover, the prognosis of UUSUC is poor and five year recurrence-free and overall survival (OS) rates are reported as 28% and 23%, respectively (1,2,7–13).

There are many studies in the literature evaluating the factors affecting the prognosis of the UC but the data about the prognostic factors of UUSUC are limited (1, 7, 9, 12-16). In this study, we evaluated the effect of clinicopathological factors including age, sex, tumor grade, tumor stage, tumor necrosis, lymphovascular invasion (LVI), perineural invasion (PNI), lymph node metastasis (LNM), and distant metastasis on OS of UUSUC.

2. Materials and methods
A total of 74 cases diagnosed with UUSUC from three different centers between February 2000 and December 2017 were included in the study. In patients with suspicion of UUSUC, diagnosis was obtained radiologically by using...
computed tomography urography which has the highest diagnostic accuracy among all of the clinically available imaging techniques. Radical nephroureterectomy with bladder cuff excision was performed without compromising oncological principles. Avoidance of entry into the urinary tract during surgery was taken into consideration in order to prevent tumor seeding in both open and laparoscopic nephroureterectomy cases. Approach to distal ureter was either performed with open or endoscopic techniques. Lymph node dissection was performed in case of clinical or radiological suspicion for metastasis. The demographic and clinicopathological features such as age, sex, tumor localization, distant metastasis, and concomitant tumor development in the urinary system and OS were obtained from urology records. Hematoxylin-eosin–stained slides were revised and histological grade, stage, differentiation, PNI, LVI, necrosis, LNM, and the status of the surgical margins were noted. World Health Organization (WHO) 2016 classification of urinary tumors was used for tumor grading and staging (17).

### 2.1. Statistical analysis

The correlation between OS and disease-free survival (DFS) and age, tumor size, tumor grade, tumor stage, tumor differentiation, concomitant UC, surgical margin, PNI, LVI, necrosis, LNM, and distant organ metastasis were investigated using Kaplan–Meier method, and log rank analysis. Multivariate analyses of OS were performed using the Cox regression method. P < 0.05 was considered to be the level of statistical significance. The OS and DFS of all patients during follow-up were assessed and statistical analysis was performed with SPSS version 24 (IBM Corp.; Armonk, NY, USA).

### 3. Results

Seventy cases (94.6%) underwent open nephroureterectomy whereas four cases (5.4%) had laparoscopic nephroureterectomy. Thirty-eight (51.4%) tumors were located in the pelvis, 7 (9.5%) in the ureter, and 29 (39.2%) both in the pelvis and ureter. Sixty (81.1%) patients were male and 14 (18.9%) were female. The ages at the time of diagnosis ranged from 40 to 84 years with a median age of 63.8 years. The follow-up time of all patients was 43.5 months (±48.7) (min: 1 month–max: 204 months). Twenty-seven cases (36.5%) were ≥70 years of age whereas 47 cases (63.5%) were <70. Fifty-six (75.7%) cases were alive; however, 18 (24.3%) patients were found to be dead. The mean tumor size was 5.4 cm (0.3–17 cm). pTa, pT1, pT2, pT3, and pT4 tumors were reported in 16 (21.6%), 13 (17.6%), 4 (5.4%), 28 (37.8%), and 13 (17.6%) patients, respectively. Histopathologically, 17 cases (23%) were low-grade and 57 cases (77%) were high-grade (Table 1).

Twenty-two cases (29.7%) showed variant differentiation (19 squamous, 2 sarcomatoid, 1 glandular differentiation). Necrosis, LVI, PNI, and LNM was observed in 29 (39.2%), 25 (33.8%), 9 (12.2%), and 10 (13.5%) cases, respectively. Furthermore, 13 cases (17.6%) showed positive surgical margin (Table 1).

According to the follow-up data, 6.3% of cases with stage pTa, 23.1% of cases with stage pT1, 35.7% of cases with stage pT3, and 30.8% of the cases with stage pT4 were dead. All the cases with stage pT2 were alive. There was no statistically significant correlation between stage, tumor localization, positive surgical margin, and OS (P = 0.19, P = 0.324, P = 0.28, respectively).

Two of 17 low-grade carcinomas (11.8%) and 16 of 57 high-grade carcinomas (28.1%) were dead and no statistically significant correlation was found between tumor grade and OS (P = 0.14).

Concomitant bladder tumor was detected in 31 cases (41.9%). The tumor was located in bladder and contralateral kidney in one case (1.4%). However, the association between prognosis and concomitant urothelial cancer was not significant (P = 0.45).

In addition, no statistically significant correlation was found between sex, age over or under 70, tumor size, PNI, LVI, and OS (P = 0.11, P = 0.774, P = 0.21, P = 0.13, P = 0.74, respectively). However, statistically significant association was observed between OS and differentiation (Figure 1), necrosis (Figure 2), LNM (Figure 3), and distant metastasis (Figure 4) (P < 0.001, P < 0.001, P < 0.001, P = 0.042, respectively).

There was no significant correlation between synchronous tumor in the bladder (P = 0.45) and OS as well as distant metastasis, differentiation, necrosis, LNM, and LVI (P = 0.96, P = 0.43, P = 0.79, P = 0.64, P = 0.92, respectively). Only distant metastasis was statistically associated with OS by multivariate analysis (P = 0.037). Table 2 demonstrates the multivariate analysis of parameters affecting OS.

Six of 74 cases had recurrence and 2 of these 6 cases were dead. We observed no significant relationship between recurrence and OS (P = 0.57).

The pathological stages of these recurrent cases were found as pTa (n=1), pT3 (n=4), and pT4 (n=1). Five cases were high-grade whereas one case was low-grade. Two recurrent cases had LVI, concomitant bladder tumor and metastasis. None of them showed PNI. One case had tumor positive surgical margins.

We found no significant relationship between DFS and age (over/under 70), stage, tumor grade, LVI, PNI, surgical margin positivity, concomitant bladder tumor and metastasis. (P = 0.711, P = 0.436, P = 0.549, P = 0.918, P = 0.393, P = 0.900, P = 0.207, P = 0.100, respectively).

Three of 45 cases without necrosis had recurrence in addition to three cases with necrosis. Three of 52 cases without any additional differentiation had recurrence.
Table 1. Univariate analysis of demographic, clinical, and pathological characteristics for overall survival.

| Clinicopathologic factors                  | Category                                         | n (%)  | P-values |
|--------------------------------------------|--------------------------------------------------|--------|----------|
| Median age in years (range)                | 63.8 (min 40-max 84) (SD ± 8.9)                  | 74     |          |
|                                            | Age ≥ 70                                         | 27 (36.5) | 0.77    |
|                                            | Age <70                                          | 47 (63.5) |          |
| Tumor size                                 | 5.4 cm (min 0.3–max 17 cm)                      |         | 0.21    |
| Sex                                        | Male                                             | 60 (81.1) | 0.11    |
|                                            | Female                                           | 14 (18.9) |          |
| Survival                                   | Live                                             | 56 (75.7) |          |
|                                            | Ex                                               | 18 (24.3) |          |
| Initial surgery                            | Open nefroureterectomy                           | 70 (94.6) |          |
|                                            | Laparoscopic nefroureterectomy                    | 4 (5.4)  |          |
| Tumor location                             | Renal pelvis                                     | 38 (51.4) | 0.324   |
|                                            | Ureter                                           | 7 (9.5)  |          |
|                                            | Renal pelvis and ureter                          | 29 (39.2) |          |
| Pathological T stage                       | pTa                                              | 16 (21.6) | 0.19    |
|                                            | pT1                                              | 13 (17.6) |          |
|                                            | pT2                                              | 4 (5.4)   |          |
|                                            | pT3                                              | 28 (37.8) |          |
|                                            | pT4                                              | 13 (17.6) |          |
| Tumor grade                                | High                                             | 57 (77)   | 0.14    |
|                                            | Low                                              | 17 (23)   |          |
| Differentiation                            | Absence                                          | 52 (70.3) | <0.001  |
|                                            | Presence                                         | 22 (29.8) |          |
|                                            | Squamous                                         | 19 (25.7) |          |
|                                            | Sarcomatoid                                      | 2 (2.7)   |          |
|                                            | Glandular                                        | 1 (1.4)   |          |
| Lymph node metastasis                      | Absence                                          | 64 (86.5) | 0.042   |
|                                            | Presence                                         | 10 (13.5) |          |
| Lymphovascular invasion                    | Absence                                          | 49 (66.2) | 0.74    |
|                                            | Presence                                         | 25 (33.8) |          |
| Perineural invasion                        | Absence                                          | 65 (87.8) | 0.13    |
|                                            | Presence                                         | 9 (12.2)  |          |
| Tumor necrosis                             | Absence                                          | 45 (60.8) | <0.001  |
|                                            | Presence                                         | 29 (39.2) |          |
| Surgical margins                           | Negative                                         | 61 (82.4) | 0.28    |
|                                            | Positive                                         | 13 (17.6) |          |
| Synchronous tumor                          | Absence                                          | 42 (56.8) | 0.45    |
|                                            | Presence                                         | 32 (43.2) |          |
|                                            | Bladder                                          | 31 (41.9) |          |
|                                            | Bladder and contralateral kidney                 | 1 (1.4)   |          |
| Recurrent disease                          | Absence                                          | 68 (91.9) | 0.57    |
|                                            | Presence                                         | 6 (8.1)   |          |
| Metastasis                                 | Absence                                          | 58 (78.4) | <0.001  |
|                                            | Presence                                         | 16 (21.6) |          |
Figure 1. Kaplan–Meier curves of overall survival stratified according to the histological differentiation of tumors.

Figure 2. Kaplan–Meier curves of overall survival stratified according to tumor necrosis.
Figure 3. Kaplan–Meier curves of overall survival stratified according to lymph node metastasis (LNM).

Figure 4. Kaplan–Meier curves of overall survival stratified according to distant metastasis.
Three tumors with additional differentiation had recurrent disease. None of the cases with recurrent disease had lymph node metastasis. Four cases with no metastasis and 2 cases with metastasis had recurrent disease. No significant relationship was observed between DFS and necrosis, differentiation and lymph node involvement (P = 0.254, P = 0.103, P = 0.458, respectively).

4. Discussion

UUSUC is rare but a potentially lethal disease (7). Upper urinary system tumors are generally multifocal affecting all urinary system lined by urothelium (1,9). The mean age of patients is reported as 65 years and the disease is more common in men (8). Various studies focused on the effect of clinical and pathologic parameters on UUSUC outcomes (1,5,7,10,12,18–24). Several studies reported tumor stage and grade as prognostic predictors in UUSUC (1,5,7,10,12,18–24). In two different studies of Kikucki et al. and Bolenz et al., LVI was reported as an independent prognostic factor of DFS in UUSUCs (6,25). In our study, LVI was observed in 25 (33.8%) of 70 patients. There was no statistically significant correlation between LVI and OS. The presence of LVI should be stated in pathology reports in order to follow up the patients. (6).

Green et al. reported that the prognosis of bladder urothelial carcinoma is worse in women (10). Two multiinstitutional analyses performed by Fernandez et al. and Shariat et al. did not show any difference in pathologic characteristics and outcomes between sexes in UUSUC (1). Emamekho et al. reported that sex had no significant effect on OS and DFS of 454 cases (5). Most of our cases were men (n = 60) and no significant correlation was observed between sex and OS.

The studies about tumor localization and prognosis reported that ureteral tumors have a worse prognosis than renal pelvic tumors (1,5,7,18). The reason of this correlation is controversial while stage and treatment options may change (10). The protective effect of the renal parenchyma is thought to be associated with this finding. Also, the presence of a thin layer of adventitia surrounding the ureter, which contains an extensive plexus of blood and lymphatic vessels makes the invasion of tumor easier (21). However, several studies did not confirm the independent prognostic impact of tumor location on survival and showed the same recurrence-free survival and cancer-specific survival rates for renal pelvis and ureteral tumors (1,5). Similarly, we did not find a significant relation between OS and tumor localization. Nevertheless, this may be due to the unequal distribution of the cases for tumor localization.

Histopathologically, UUSUCs are generally high-grade tumors (9). Pathological tumor stage and histological grade are accepted as main indicators for prognosis similar to other malignant tumors (7,9,12,14,19–23). Most of the cases were high-grade in our study. Sixteen of 57 high-grade carcinomas were dead while only 2 of 17 low-grade carcinomas were found to be dead.

There was a correlation between grade or stage and OS; however, it was not statistically significant and this may be explained by the distribution numbers among the groups (P = 0.14, P = 0.19).

The presence of tumor necrosis is an indicator of aggressiveness in almost all malignancies (1,9,12). However, recent studies reported controversial results about the prognostic role of tumor necrosis in UUSUC (1). In the study of Zhang et al., tumor necrosis was found in 48 of 100 cases and was related to pathological stage, higher tumor grade, LNM, and LVI (12). Seitz et al. detected tumor necrosis in 165 of 754 cases (21.9%) from 9 different centers and showed that the prevalence of tumor necrosis increased as the pathological stage increased. Also, they reported that tumor necrosis was related to higher grade, LNM, LVI, sessile tumoral architecture and concomitant carcinoma in situ among UUSUC. However, tumor necrosis was not an independent predictor of clinical

|                  | Levels       | Hazard ratio | 95% CI Lower bound | 95% CI Upper bound | P-value |
|------------------|--------------|--------------|--------------------|--------------------|---------|
| Tumor necrosis   | Negative     | 5.483        | 0.895              | 33.583             | 0.066   |
|                  | Positive     |              |                    |                    |         |
| Tumor differentiation | Negative   | 1.825        | 0.627              | 5.314              | 0.270   |
|                  | Positive     |              |                    |                    |         |
| Lymph node metastasis | Negative  | 1.100        | 0.330              | 3.666              | 0.877   |
|                  | Positive     |              |                    |                    |         |
| Metastasis       | Negative     | 4.200        | 1.087              | 16.227             | 0.037   |
|                  | Positive     |              |                    |                    |         |
outcome (24). In our study, necrosis showed significant relation in univariate analysis; however, this relation was not proven by multivariate analysis (P < 0.001, P = 0.66, respectively). Larger studies are needed to prove this correlation.

Lymph node involvement is generally accepted as an important prognostic factor (1). The lymph node status remains unknown because no lymphadenectomy procedures were done in many nephroureterectomy operations (5). Our clinical approach is the excision of lymph nodes when palpable lymph nodes were observed during the operation or when preoperative radiological studies reported a suspect of lymph node positivity.

However, there are many studies showing that LNM is an independent prognostic factor of UUSUC (1,7,12). The effect of lymph node dissection on survival is still controversial in nephroureterectomy for UUSUCs (26,27). In the metaanalysis of Guo et al., patients with LNM had worse prognosis (3). On the other hand, in the same study, it was reported that lymphadenectomy showed no significant difference on survival and recurrence in pN0 or pNx cases (3).

We observed a significant association between lymph node involvement and OS in univariate analysis; however, this correlation was not proven by multivariate analysis (P = 0.042, P = 0.877).

In the literature, distant metastasis is related to prognosis in UUSUC (12,28). We also found a significant relation between distant metastasis and OS by univariate and multivariate analysis (P < 0.001, P = 0.037).

Even though the prognostic role of squamous differentiation is accepted in UUSUC, the clinical importance is still controversial (7,13,16). Most of the studies revealed that squamous differentiation was related to higher tumor grade and advanced tumor stage in univariate analysis (13). Makise et al. observed that squamous differentiation was the most common histological variant among 140 primary UUSUC and related with poor prognosis in univariate analysis (13). Qin et al. suggested that differentiation was a poor prognostic factor especially in ureteral tumors (7). We observed that squamous differentiation is the most common variant and it showed a statistically significant correlation with OS but this was not proven by multivariate analysis (P < 0.001, P = 0.27, respectively).

The history of a bladder tumor is reported as a poor prognostic factor in UUSUC in the literature and such cases must be under more stringent follow-up regimens or being treated more aggressively (1,29,30). There are studies suggesting the effect of synchronous or metachronous bladder cancer on recurrence and survival among UUSUC (7). Novara et al. also reported that the presence of concomitant muscle invasive bladder cancer is a poor prognostic factor (23). Bladder was the most common localization of concomitant tumors (n = 8) in our study. One case had tumor in both bladder and kidney. However, the presence of concomitant bladder tumor had no effect on prognosis.

It was reported that the presence of bladder cancer before the diagnosis of UUSUC has no significant effect on prognosis (31). We could not subgroup our cases according to the occurrence time of the previous bladder tumor.

There are some studies supporting that cisplatin-based additional treatments after surgery prolongs survival in UUSUCs (4). In another study, adjuvant chemotherapy after surgery was found to be associated with longer cancer specific and recurrence-free survival in patients with pT3N0M0 UUSUCs (32). The metastatic cases in our study group had chemotherapy.

This study has several limitations that need to be considered in interpreting the findings. The first limitation is the retrospective nature of the study. Additionally, the number of patients and the follow-up period are not enough to fully interpret the results. Finally, surgical procedures were performed by different surgeons at different institutions, explaining both the variability of intraoperative management and extent of lymph node dissection. Despite these limitations, this study showed that squamous differentiation, lymph node metastasis, distant organ metastasis, and tumor necrosis have statistically significant correlation with OS by univariate analysis in patients with UUSUC. Nevertheless, distant metastasis was the only statistically significant prognostic factor of OS observed in multivariate analysis.

Finally, well-designed and larger multiinstitutional studies are still needed to provide stronger evidence and to promote the use of these prognostic factors in the management of the treatment.

References

1. Lughezzani G, Burger M, Margulis V, Matin SF, Novara G, Roupret M, Shariat SF, Wood CG, Zigeuner R. Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. Eur Urol 2012; 62: 100-114.

2. Miyazaki J, Nishiyama H. Epidemiology of urothelial carcinoma. Int J Urol 2017; 24:730-734.

3. Guo R, Zhu Y, Xiong G, Li X, Zhang K, Zhou L. Role of lymph node dissection in the management of upper tract urothelial carcinomas: a meta-analysis. BMC Urol 2018; 18: 24.
4. Leow JJ, Martin-Doyle W, Fay AP, Choueiri TK, Chang SL, Bellmunt J. A systematic review and meta-analysis of adjuvant and neoadjuvant chemotherapy for upper tract urothelial carcinoma. Eur Urol 2014; 66: 529-541.

5. Emamekhoo H, Dhillon P, Gopalakrishnan D, Elson P, Stephenson A, Magi-Galluzzi C, McKenzie J, Harper H, Haber GP, Kauk J et al. Prognostic factors and risk stratification in invasive upper tract urothelial carcinoma. Clin Genitourin Cancer 2018; 16: e751-e760.

6. Bolenz C, Fernández MI, Trojan L, Herrmann E, Becker A, Weiss C, Alken P, Ströbel P, Michel MS. Lymphovascular invasion and pathologic tumor stage are significant outcome predictors for patients with upper tract urothelial carcinoma. Urology 2008;72:364-369.

7. Qin C, Dong EL, Du ZY, Qiu XY, Tang G, Chen FR, Zhang B, Tian DW, Hu HL, Wu CL. Prognostic significance of urothelial carcinoma with divergent differentiation in upper urinary tract after radical nephroureterectomy without metastatic diseases: A retrospective cohort study. Medicine (Baltimore) 2017; 96: e6945.

8. Gümuş E, Horasanlı K, Tanrıverdi O, Boylu U, Çevik C, Miroğlu C. Üst üriner sistem üretyal tümörlerinde 10 yıllık klinik deneyimimiz. Turk J Urol 2004; 30: 160-165 (in Turkish).

9. Humphrey PA. Urothelial carcinoma of the upper urinary tract. The Journal of Urology 2014; 192: 1223-1224.

10. Green DA, Rink M, Xylinas E, Matin SF, Stenzl A, Roupret M, Habuchi T, Kawauchi A, Uozumi J, Yokoi S, Tsujihata M et al. Laparoscopic radical nephroureterectomy: a multicenter analysis in Japan. Eur Urol 2009; 55: 1397-1409.

11. Kikuchi E, Oya M. Clinical practice patterns for upper tract urothelial carcinoma: a nationwide survey in Japan. Japanese Journal of Clinical Oncology. 2016; 46:768-774.

12. Zhang XK, Zhang ZL, Yang P, Cai MY, Hu WM, Yun JP, Zhou FJ, Qian CN, Cao Y. Tumor necrosis predicts poor clinical outcomes in patients with node-negative upper tract urothelial carcinoma. Jpn J Clin Oncol 2015; 45:1069-1075.

13. Makise N, Morikawa T, Kawai T, Nakagawa T, Kume H, Homma Y, Fukayama M. Squamous differentiation and prognosis in upper urinary tract urothelial carcinoma. Int J Clin Exp Pathol 2015; 8: 7203-7209.

14. Abdulmajed MI, Sancak EB, Reşorlu B, Al-chalaby GZ. What are the currently available and in development molecular markers for bladder cancer? Will they prove to be useful in the future? Turk J Urol 2014; 40: 228-232.

15. van Osch FH, Jochens SM, van Schooten FJ, Bryan RT, Zeegers MP. Significant role of lifetime cigarette smoking in worsening bladder cancer and upper tract urothelial carcinoma prognosis: a meta-analysis. J Urol 2016; 195: 872-879.

16. Kucuk U, Pala EE, Cakır E, Sezer O, Bayol U, Divrik RT, Cakmak O. Clinical, demographic and histopathological prognostic factors for urothelial carcinoma of the bladder. Cent European J Urol 2015; 68: 30-36.

17. Moch H, Humphrey PA, Ulbright TM, Reuter VE. WHO Classification of Tumours of the Urinary System and Male Genital Organs. 4th ed. Lyon, France: WHO Press; 2016.

18. Ziguenre RE, Hutterer G, Chromek T, Rehak P, Langner C. Bladder tumour development after urothelial carcinoma of the upper urinary tract is related to primary tumour location. BJU Int 2006; 98:1181-1186.

19. Lugehezzani G, Jeldres C, Ishbarn H, Sun M, Shariat SF, Alsaker A, Pharan D, Widmer H, Arjane P, Graeven M et al. Nephroureterectomy and segmental ureterectomy in the treatment of invasive upper tract urothelial carcinoma: a population-based study of 2299 patients. Eur J Cancer 2009; 45: 3291-3297.

20. Ackdogan 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. Park J, Ha SH, Min GE, Song C, Hong B, Hong JH, Kim CS, Ahn H. The protective role of renalparchenyma as a barrier to local tumor spread of upper tract transitional cell carcinoma and its impact on patient survival. J Urol 2009; 182: 894-899.

22. Kamihira O, Hattori R, Yamaguchi A, Kawa G, Ogawa O, Habuchi T, Kawauchi A, Uozumi J, Yokoi S, Tsujihata M et al. Laparoscopic radical nephroureterectomy: a multicenter institutional dataset from 3 European centers. Cancer 2007; 110: 1715-1722.

23. Novara G, De Marco V, Gottardo F, Dalpiaz O, Bouygues V, Galfano A, Martignoni G, Patard JJ, Artibani W, Ficarra V. Independent predictors of cancer-specific survival in transitional cell carcinoma of the upper urinary tract: multi-institutional study. J Urol 2017; 198: 895-1900.

24. Seitz C, Gupta A, Shariat SF, Matsumoto K, Kassouf W, Walton TJ, Fritsche HM, Otto W, Tritscher S, Bastian PJ et al. Association of tumor necrosis with pathological features and clinical outcome in 754 patients undergoing radical nephroureterectomy for upper tract urothelial carcinoma: an international validation study. J Urol 2010; 184: 1895-1900.

25. Kikuchi E, Horiguchi Y, Nakashima J, Hatakeyama N, Matsumoto M, Nishiyama T, Murai M. Lymphovascular invasion independently predicts increased disease specific survival in patients with transitional cell carcinoma of the upper urinary tract. J Urol 2005; 174: 2120-2123.

26. Mason RJ, Kassouf W, Bell DG, Lacombe L, Kapoor A, Jacobsen N, Fairey A, Izawa J, Black P, Tanguay S et al. The contemporary role of lymph node dissection during nephroureterectomy in the management of upper urinary tract urothelial carcinoma: the Canadian experience. Urology 2012; 79: 840-845.

27. Burger M, Shariat SF, Fritsche HM, Martinez-Salamanca JJ, Matsumoto K, Chromek TF, Ficarra V, Kassouf W, Seitz C, Pycha A et al. No overt influence of lymphadenectomy on cancer-specific survival in organ-confined versus locally advanced upper urinary tract urothelial carcinoma undergoing radical nephroureterectomy: a retrospective international, multi-institutional study. World J Urol 2011; 29: 465-472.
28. Li X, Ma X, Tang L, Wang B, Chen L, Zhang F, Zhang X. Prognostic value of neutrophil-to-lymphocyte ratio in urothelial carcinoma of the upper urinary tract and bladder: a systematic review and meta-analysis. Oncotarget 2016; 8: 62681-62692.

29. Mullerad M, Russo P, Goli Janin D, Chen HN, Tsai HH, Donat SM, Bochner BH, Herr HW, Sheinfeld J, Sogani PC, et al. Bladder cancer as a prognostic factor for upper tract transitional cell carcinoma. J Urol 2004; 172: 2177-2181.

30. Li WM, Li CC, Ke HL, Wu WJ, Huang CN, Huang CH. The prognostic predictors of primary ureteral transitional cell carcinoma after radical nephroureterectomy. J Urol 2009; 182: 451-458.

31. Cho DS, Hong SY, Kim YK, Kim SI, Kim SJ. Prognostic factors in transitional cell carcinoma of the upper urinary tract after radical nephroureterectomy. Korean J Urol 2011; 52: 310-316.

32. Huang YC, Chen MF, Shi CS, Shindel AW, Huang CE, Pang ST, Chuang CK, Chen CS, Chang YH, Lin WY et al. The efficacy of postoperative adjuvant chemotherapy for patients with pT3N0M0 upper tract urothelial carcinoma. J Urol 2015; 194: 323-329.