Research and Reports in Urology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

High frequency of bladder cancer after nephroureterectomy: justification for adjuvant intravesical treatment?

This article was published in the following Dove Press journal:
Research and Reports in Urology

Matan Mekayten
Vladimir Yutkin
Mordechai Duvdevani
Dov Pode
Guy Hidas
Ezekiel H Landau
Fadi Youssef
Ofer N Gofrit

Department of Urology, Hadassah Hebrew University Medical Center, Jerusalem, Israel

Background: Bladder recurrence after nephroureterectomy (NU) is common. However, there is no acceptable policy of adjuvant intravesical treatment after NU.

Objective: To assess the rate of bladder recurrence following NU and to identify the high-risk subgroups that may become candidates for adjuvant intravesical therapy after NU.

Patients and methods: Ninety-one patients (mean age 66.4 years) underwent NU. High-grade (HG) tumors were found in 63 patients and low-grade (LG) tumors in 28. Median follow-up was 72 months. The risk of bladder recurrence was assessed by uni- and multivariate analyses of patient and tumor characteristics.

Results: Bladder recurrence developed in 38 patients (41.8%) after a median period of 11 months. Among these, 25 patients with HG upper tract urothelial carcinoma (39.7%) and 13 patients with LG upper tract urothelial carcinoma (46.4%) developed recurrence. HG bladder recurrence developed in 24 patients (63.2%) and LG recurrence developed in 14 patients (36.8%). Stages pTa, pT1, pT2, or higher bladder recurrence developed in 26 (68.4%), 7 (18.4%), and 4 patients (10.5%), respectively, and pure pTis developed in 1 patient. On uni- and multivariate analyses, the risk of bladder recurrence was independent of any clinicopathologic characteristics.

Conclusion: High rate and short time interval of bladder recurrence after NU were found, with no specific subgroup of patients with increased risk. These findings support prescribing adjuvant intravesical therapy to all patients after NU.

Keywords: urothelial upper tract tumors, bladder recurrence, nephroureterectomy

Introduction

Urothelial carcinoma (UC) is the fourth most common solid malignancy and the eighth most fatal malignancy in men.[1] Most UCs arise in the bladder, but 5%–10% arise in the upper urinary tract.[1,2] Upper tract urothelial carcinoma (UTUC) poses diagnostic and therapeutic challenges: tissue-based diagnosis and follow-up are difficult compared to bladder cancer. The standard care in UTUC is nephroureterectomy (NU).[3,4] Kidney preserving treatments are reserved for selected low-risk patients.[5]

UCs are notorious for their high recurrence rate. After excision of a bladder cancer, up to 55% of the patients develop recurrence.[6] Following extirpative surgery for UTUC, 22%–47% of patients develop bladder recurrence.[1,3,5,7–9] Two main theories hypothesize to explain this high recurrence rate. The field cancerization theory suggests that multiplicity is due to carcinogenic exposure of the entire urothelium.[10,11] The seeding theory claims for intraluminal seeding of a single progenitor cancerous cell.[1,11–13]

Correspondence: Matan Mekayten
Department of Urology, Hadassah Hebrew University Medical Center, Jerusalem, Kiryat Hadassah P. O. B. 12000, Jerusalem 9112001, Israel
Tel +972 2 677 6874
Fax +972 2 643 0929
Email mci10matan@gmail.com

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/RRU.S164166

With the emergence of a new molecular-based studies, the intraluminal seeding theory gained the spotlight, though both mechanisms probably coexist.[14]

Following transurethral resection of bladder tumor, intravesical instillations of chemotherapy or immunotherapy are recommended according to the patient's risk group: for low- or intermediate-risk patients, a single postoperative intravesical instillation of chemotherapy is advisable; in the intermediate-risk patients, chemotherapy or immunotherapy is recommended with maintenance therapy up to 1 year; and in high-risk patients, a 3-year maintenance protocol is recommended.[1,15,16] Currently, there are no established recommendations for adjuvant treatments after NU.

In this study, we estimated the rate of bladder recurrence following NU in an attempt to identify subgroups that are at a higher risk for this type of recurrence.

Patients and methods

Surgery and follow-up protocols

Surgery was done either openly or laparoscopically. In either way, a bladder cuff was removed. Tumors were staged according to the tumor node metastasis (TNM) classification[17] and graded according to the World Health Organization classification.[18] Adjuvant intravesical treatment was not given to any patient. Follow-up was based on tumor grade. In patients with high-grade tumors, cystoscopy and urinary cytologic examination were done at 3-month intervals in the first year, at 6-month intervals for another 2 years, and annually for an additional 2 years. Annual ultrasonic examination of the urinary system was then done indefinitely. Computed tomography scan was performed at 6-month intervals for the first 3 years. For low-grade tumor, the same protocol was applied without computed tomography or cytology. Additional investigations were performed if clinically indicated. Patients included in the study were followed for at least 6 months or until disease recurrence or death. Median follow-up was 72 months (range 6–240 months). Data for all patients were available and none were lost to follow-up.

Data analysis

Disease-free and overall survival rates were calculated from the day of NU. The effect of the following parameters on recurrence and survival was assessed: age, gender, UTUC grade, stage, previous bladder UC, location in the urinary system, type of surgery (laparoscopic vs. open), and if diagnostic ureteroscopy was done prior to NU. A two-tailed $p<0.05$ was considered statistically significant. Vesical and extravesical tumor recurrences were analyzed separately. Statistical analysis was performed using SPSS v23.0 statistical software (IBM Corporation, Armonk, NY, USA) and Microsoft Excel 2016 (Microsoft Inc., Redmond, WA, USA).

The official institutional review committee which approved our study is the Ethics (Helsinki) Committee at Hadassah University Hospital for the conduct of clinical studies. The committee is in due compliance with the Public Health Regulations (Medical Experiments In Human Subjects) – 1980, the Governing Regulations of the Ministry of Health and the provisions of the current harmonized international guidelines for good clinical practice, namely, ICH-GCP. All data were kept secured with the relevant precautions. Committee approval number: HMO-16-0026. Patient consent was not required.

Results

Patients

Between January 1996 and December 2015, 91 patients (67 men and 24 women) underwent NU as the treatment of UTUC (Table 1). Mean patients' age was 66.4 years (SD 11.24, range 40–86 years, median age 67). UTUC was located in the renal pelvis in 52 patients (57.1%) and in the ureter in 39 (42.9%) patients. Tumor stages were pTa and pT1 in 22 (24.2%) and 27 patients (29.7%), respectively, pT2 in 19 patients (20.9%),

Table 1 Patients' characteristics

	N	Percentage
Gender		
Male	67	73.63
Female	24	26.37
Age (years)		
Average	66.4	(SD=11.24)
UTUC grade		
High	63	69.23
Low	28	30.77
Stage		
Ta	22	24.18
T1	27	29.67
T2	19	20.88
T3	23	25.27
Location		
Kidney	52	57.14
Ureter	39	42.86
Treatment		
Laparoscopic	43	47.25
Open	48	52.75
Previous bladder cancer		
Yes	12	13.19
No	79	86.81
Previous ureteroscopy		
Yes	37	40.66
No	54	59.34

Abbreviation: UTUC, upper tract urothelial carcinoma.

and pT3 in 23 patients (25.3%). Sixty-three patients (69.2%) had high-grade tumors and 28 (30.8%) had low-grade tumors. Twelve patients (12.8%) had prior bladder UC. Thirty-seven patients (39.4%) underwent diagnostic ureteroscopy before NU. Surgery was laparoscopic in 43 patients (47.3%) and open in 48 patients (52.7%). Ureteral margins were negative in all patients.

Recurrence and survival

During follow-up, 51 patients (56.0%) were diagnosed with cancer recurrence. Among them, 38 (74.5%) had bladder recurrence, 23 (25.5%) had extravesical recurrence without bladder recurrence, and 10 (19.6%) had both extra- and intravesical recurrences.

A total of 30 patients (33%) died during follow-up, after a median period of 43 months after surgery. In 20 patients (66.7%), death was disease specific (after a median period of 36.5 months) and in 10 patients (33.3%), death was non-disease specific (after a median period of 70 months). Overall survival rate at 5 years was 72.5% and was associated with tumor grade ($p<0.001$) and patients' age ($p<0.05$). High-grade tumor and advanced age were associated with lower survival rates with an odds ratio of 0.941 for every year, and having high-grade tumor had an odds ratio of 0.101. However, stage, previous ureteroscopy, gender, location, history of previous bladder cancer, and surgical approach showed no significant effect on overall survival.

Disease-specific survival rate was 79.9% and was not associated with age, gender, tumor location, and laparoscopic surgery, as opposed to open, location or previous bladder UC. Disease-specific survival rate was significantly lower among patients with high UTUC grade ($p<0.001$), advanced stage ($p<0.001$), and in the absence of previous ureteroscopy ($p<0.05$).

Bladder recurrence

Bladder recurrence occurred in 38 patients (41.8%) after a median period of 11 months (Figure 1). Three-quarters of the recurrences occurred during the first year after NU and 91.67% occurred within 2 years. pTa bladder recurrence developed in 26 patients (68.4%), pT1 tumor in 7 patients (18.4%), pT2 tumor in 4 patients (10.5%), and 1 patient developed pure pTis. High-grade bladder recurrence developed in 24 patients (63.2%) and low-grade recurrence developed in 14 patients (36.8%). Twenty-five patients with high-grade UTUC (39.7%) developed bladder recurrence. Of these, 20 (80%) were high grade and 5 (20%) were low grade. Thirteen patients with low-grade UTUC (46.4%) developed bladder recurrence, including 9 patients (69.2%) with low-grade recurrence and 4 (30.8%) with high-grade recurrence. Bladder recurrence was fatal in nine patients (disease-specific rate 23.7%).

The risk of bladder recurrence after UTUC was independent of patients' age, gender, UTUC grade, stage, location in the urinary system, surgery method, or the use of diagnostic ureteroscopy prior to NU in univariate analysis (Table 2). Bladder recurrence timing is depicted in Figure 1. The treatment of bladder recurrence was as for primary bladder tumors and included transurethral resection and further therapy and follow-up according to the pathologic findings. Two patients underwent radical cystectomy with ileal conduit and two had non-operable disease upon diagnosis.

A binary logistic regression analysis was conducted to predict bladder recurrence using gender, age, grade, stage, location of tumor, surgical method, previous bladder cancer, and previous ureteroscopy. The full model was not found to be statistically significant in comparison to the model using constant only, indicating that the predictors as a set did not reliably distinguish patients with and without bladder recurrence (chi-square=11.011, $p=0.201$ with degrees of freedom=8).

Discussion

This work demonstrates the high frequency of bladder recurrence after NU, which developed in 41.8% of the patients after a median period of 11 months and was fatal in nine patients (disease-specific rate 23.7%). In the current study, none of the patients received adjuvant intravesical therapy. This may explain the high rate of bladder recurrence after NU. Bladder recurrence rate was independent of patients' age, gender, UTUC grade, stage, location in the urinary system, and surgery type. Previous studies showed bladder recurrence rate of 22%–47% after NU. Various risk factors of bladder recurrence after NU that were reported in the past included gender, previous bladder cancer, preoperative chronic kidney disease, urinary cytology, location, multifocality, T stage, necrosis, laparoscopic approach, extravesical bladder cuff removal method, and surgical margins.[19,20] None of these factors were found to be a risk factor in consensus.[19]

This frequency of bladder recurrence after NU is similar to the frequency of recurrence after transurethral resection of bladder cancer (31%–78%).[8,9,21] Despite this similarity and its potential aggressive behavior, a well-established bladder adjuvant therapy protocol following NU has not been

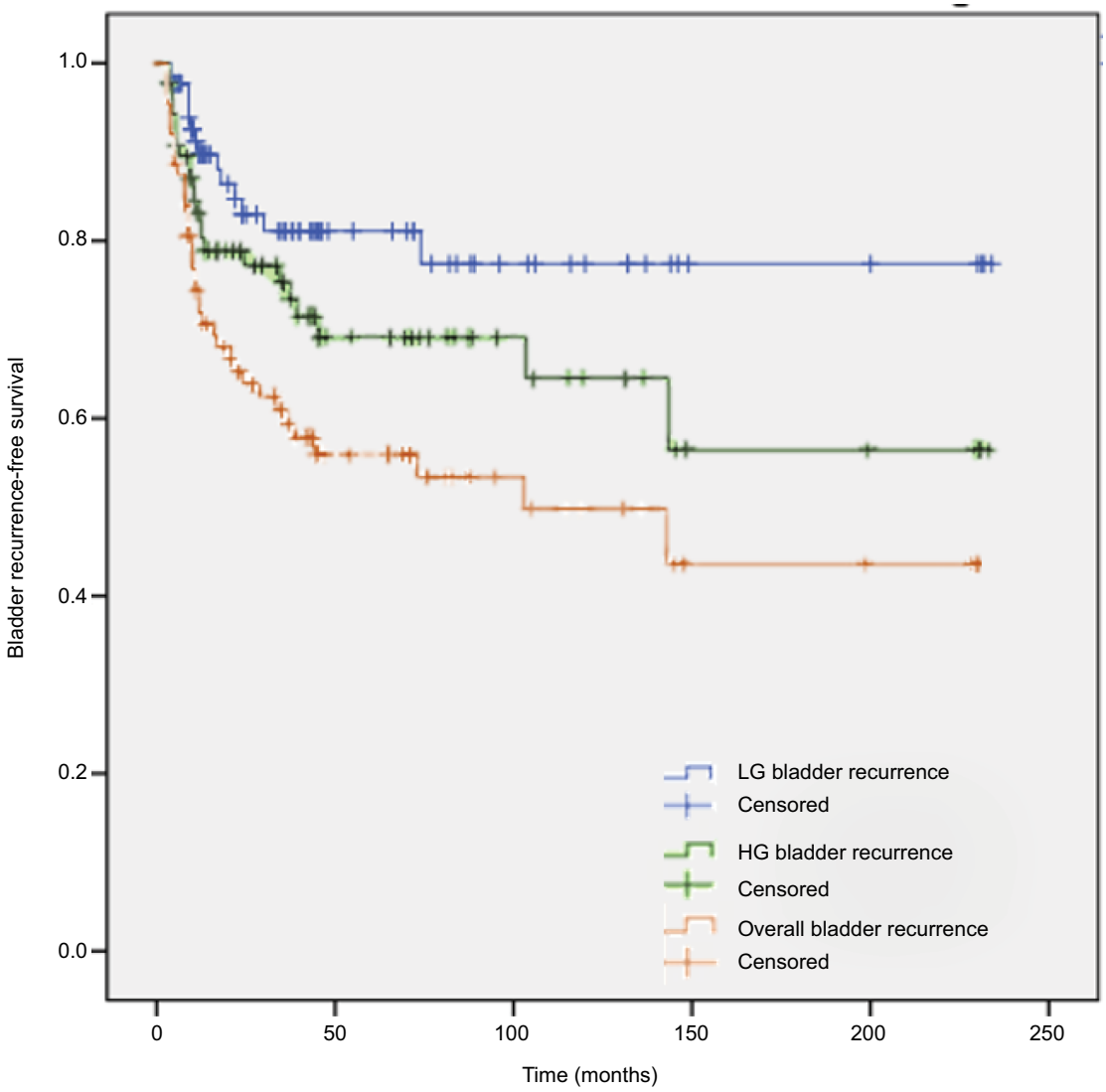

Figure 1 Bladder recurrence-free survival according to recurrence grade.
Abbreviations: HG, high grade; LG, low grade.

established. Several clinical trials have examined the efficacy of different protocols. Three large trials examined the effect of adjuvant intravesical therapy after NU.

The ODMIT-C trial was the first large-scale prospective, multicenter, randomized clinical trial addressing the efficacy of immediate adjuvant intravesical therapy after NU. A single postoperative intravesical dose of mitomycin C (MMC; 40 mg in 40 mL of saline; Kyowa, Hakko, Slough, UK) demonstrated an absolute risk reduction of 11% of bladder recurrence. Number needed to treat to prevent one bladder tumor was nine.[22] In another study including 196 patients, a significant vesical recurrence-free survival was demonstrated, but not in cancer-specific survival.[23] THP Monotherapy Study Group trial, which included 72 patients, demonstrated that intravesical instillation of pirarubicin within 48 hours after NU was associated with lower bladder tumor recurrence rates of 16.9% at 2 years vs. 42.2% at 2 years, with a hazard rate of 0.26.[24]

Several systematic reviews and meta-analyses demonstrated the efficacy of prophylactic intravesical instillation chemotherapy for preventing bladder tumor recurrence after NU. These studies suggest a preventive effect with an odds ratio of 0.45–0.48 and a progression-free interval prolongation of 38%. Furthermore, the first instillation that begins within 24 hours after surgery was more effective compared to instillation at 48 hours or 2 weeks, and a single instillation had similar effect to multiple instillations.[25] Despite these findings that were reported in the years 2010–2013, immediate intravesical instillation of chemotherapy has not become a common practice. This is probably due to the fear

Table 2 Bladder recurrence univariate model

	Bladder recurrence, n (%)	No bladder recurrence, n (%)	Exact significance (two sided)[a]
Total	38 (41.8)	53 (58.2)	
Gender			
Female	7 (29.2)	17 (70.8)	
Male	31 (46.3)	36 (53.7)	0.158
Age (years)			
<67	20 (45.5)	24 (54.5)	
≥67	18 (38.3)	29 (61.7)	0.529
Grade			
High	25 (39.7)	38 (60.3)	
Low	13 (46.4)	15 (53.6)	0.646
Stage			
Ta	13 (59.1)	9 (40.9)	
T1	9 (33.3)	18 (66.7)	
T2	7 (36.8)	12 (63.2)	
T3	9 (39.1)	14 (60.9)	0.289
Location			
Kidney	24 (46.2)	28 (53.8)	
Ureter	14 (35.9)	25 (64.1)	0.393
Surgical approach			
Laparoscopic	18 (41.9)	25 (58.1)	
Open	20 (41.7)	28 (58.3)	1
Previous bladder cancer			
Yes	5 (41.7)	7 (58.3)	
No	33 (41.8)	46 (58.2)	1
Previous ureteroscopy			
Yes	18 (48.6)	19 (51.4)	
No	20 (37.0)	34 (63.0)	0.288

Notes: [a]Chi-square Fisher's exact test was performed. For variables more than two categorical variables – the asymptotic significance (two-sided) was depicted instead of Fisher's exact significance.

from perivesical chemotherapy leak and its potential disastrous consequences.

In this study, we emphasize the high risk, the short time interval, and the absence of reliable predictive factors for bladder recurrence after NU. Thus, it seems reasonable to prescribe adjuvant intravesical therapy for most, if not all, patients after NU. This should be administered as if they had a resection of bladder tumor.

The main limitation of the study is its retrospective design. Despite the wide time range of follow-up, the follow-up and the treatment protocol were consistent and stable. Additionally, the effectiveness of adjuvant intravesical treatment recommended here is extrapolated from bladder cancer. There is no high-quality evidence in the literature to support it.

Conclusion

This study demonstrates the high frequency (41.8%), short time interval (median of 11 months), and substantial aggressive nature of bladder recurrence after NU. No specific subgroup of patients with higher risk of bladder recurrence was identified. Therefore, we suggest that adjuvant intravesical therapy be administered to all patients after NU, as is done after trans-urethral resection of bladder tumor.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Non-Muscle Invasive Bladder Cancer: American Urological Association. Available from: http://www.auanet.org/education/guidelines/non-muscle-invasive-bladder-cancer.cfm. Accessed June 15, 2016.
2. Munoz JJ, Ellison LM. Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. *J Urol*. 2000;164(5):1523–1525.
3. Fang D, Li X-S, Xiong G-Y, Yao L, He Z-S, Zhou L-Q. Prophylactic intravesical chemotherapy to prevent bladder tumors after nephroureterectomy for primary upper urinary tract urothelial carcinomas: a systematic review and meta-analysis. *Urol Int*. 2013;91(3):291–296.
4. Margulis V, Shariat SF, Matin SF, et al; Upper Tract Urothelial Carcinoma CollaborationThe Upper Tract Urothelial Carcinoma Collaboration. Outcomes of radical nephroureterectomy: a series from the upper tract urothelial carcinoma collaboration. *Cancer*. 2009;115(6):1224–1233.
5. Rouprêt M, Babjuk M, Compérat E, et al. European association of urology guidelines on upper urinary tract urothelial carcinoma: 2017 update. *Eur Urol*. 2018;73(1):111–122.
6. Leblanc B, Duclos AJ, Bénard F, et al. Long-term followup of initial Ta grade 1 transitional cell carcinoma of the bladder. *J Urol*. 1999;162(6):1946–1950.
7. Zigeuner RE, Hutterer G, Chromecki 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(6):1181–1186.
8. Novara G, De Marco V, Dalpiaz O, et al. Independent predictors of metachronous bladder transitional cell carcinoma (TCC) after nephroureterectomy for TCC of the upper urinary tract. *BJU Int*. 2008;101(11):1368–1374.
9. Xylinas E, Rink M, Margulis V, Karakiewicz P, Novara G, Shariat SF. Multifocal carcinoma In situ of the upper tract is associated with high risk of bladder cancer recurrence. *Eur Urol*. 2012;61(5):1069–1070.
10. MilláN-RodríGuez F, ChéChile-Toniolo G, Salvador-Bayarri J, Huguet-PéRez J, Vicente-RodríGuez J. Upper urinary tract tumors after primary superficial bladder tumors: prognostic factors and risk groups. *J Urol*. 2000;164(4):1183–1187.
11. Habuchi T. Metachronous multifocal development of urothelial cancers by intraluminal seeding. *Lancet*. 1993;342(8879):1087–1088.
12. Catto JWF, Hartmann A, Stoehr R, et al. Multifocal urothelial cancers with the mutator phenotype are of monoclonal origin and require panurothelial treatment for tumor clearance. *J Urol*. 2006;175(6):2323–2330.
13. Hafner C, Knuechel R, Zanardo L, et al. Evidence for oligoclonality and tumor spread by intraluminal seeding in multifocal urothelial carcinomas of the upper and lower urinary tract. *Oncogene*. 2001;20(35):4910–4915. Available from: http://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=09509232&AN=8911021&h=ILJ1sWCVqqV3Sw9Nbreemxkkty lKW8OoniW5BwJrYkI35JgFThDZWj9lfXwnGF92ye%2FpdtM1QG UYG35RAfk94w%3D%3D&crl=c. Accessed November 4, 2016.
14. Takahashi T, Kakehi Y, Mitsumori K, et al. Distinct microsatellite alterations in upper urinary tract tumors and subsequent bladder tumors. *J Urol*. 2001;165(2):672–677.

15. Badalament RA, Herr HW, Wong GY, et al. A prospective randomized trial of maintenance versus nonmaintenance intravesical bacillus Calmette-Guérin therapy of superficial bladder cancer. *J Clin Oncol*. 1987;5(3):441–449.
16. Sylvester RJ, Oosterlinck W, Witjes JA. The schedule and duration of intravesical chemotherapy in patients with non–muscle-invasive bladder cancer: a systematic review of the published results of randomized clinical trials. *Eur Urol*. 2008;53(4):709–719.
17. Sobin LH, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours*. 7th revised ed. Hoboken, USA: John Wiley & Sons; 2009.
18. Lopez-Beltran A, Gasser T, Hartmann A. Tumours of the urinary system. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA, editors. *World Health Organisation Classification of Tumors. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs*. Lyon, France: IARC Press. 2004:88–157.
19. Professionals S-O. Upper Urinary Tract Urothelial Cell Carcinoma. Uroweb. Available from: https://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/?type=summary-of-changes. Accessed June 15, 2016.
20. Seisen T, Granger B, Colin P, et al. A systematic review and meta-analysis of clinicopathologic factors linked to intravesical recurrence after radical nephroureterectomy to treat upper tract urothelial carcinoma. *Eur Urol*. 2015;67(6):1122–1133.
21. Sylvester RJ, van der Meijden APM, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol*. 2006;49(3):466–477.
22. O'Brien T, Ray E, Singh R, Coker B, Beard R, British Association of Urological Surgeons Section of Oncology. 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. *Eur Urol*. 2012;61(3):e14.
23. Wu W-J, Ke H-L, Yang Y-H, Li C-C, Chou Y-H, Huang C-H. Should patients with primary upper urinary tract cancer receive prophylactic intravesical chemotherapy after nephroureterectomy? *J Urol*. 2010;183(1):56–61.
24. Ito A, Shintaku I, Satoh M, et al. Prospective randomized Phase II trial of a single early intravesical instillation of pirarubicin (THP) in the prevention of bladder recurrence after nephroureterectomy for upper urinary tract urothelial carcinoma: the THP monotherapy study group trial. *J Clin Oncol*. 2013;31(11):1422–1427.
25. Wu P, Zhu G, Wei D, et al. Prophylactic intravesical chemotherapy decreases bladder tumor recurrence after nephroureterectomy for primary upper tract urothelial carcinoma: a systematic review and meta-analysis. *J BUON*. 2015;20(5):1229–1238.