ORIGINAL ARTICLE

Risk Factors Leading to Radical Cystectomy in Patients Who Had Undergone Nephroureterectomy

Janghui Lee, Bumjin Lim, Dalsan You, In Gab Jeong, Cheryn Song, Jun Hyuk Hong, Choung-Soo Kim, Hanjong Ahn, Bumsik Hong

Department of Urology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Purpose: To identify the risk factors leading to radical cystectomy in patients who had undergone nephroureterectomy (NUx).

Materials and Methods: We retrospectively reviewed the medical records of patients with upper tract urothelial carcinoma who underwent NUx during 2011–2019 and excluded patients with metastatic cancer. In total 646 patients were included in this study; of these, 532 had no previous bladder cancer history. Follow-up was performed every 3 months for 2 years after NUx was administered, and recurrence was confirmed using cystoscopy, urine cytology, computed tomography, and chest radiography. Bladder recurrence was confirmed through biopsy, urine cytology, or radiologic examination. Univariate and multivariate Cox regression analyses were performed for statistical analysis of risk factors leading to radical cystectomy in patients undergoing NUx.

Results: Lymphovascular invasion (LVI) (hazard ratio [HR], 4.728; 95% confidence interval [CI], 1.463–15.570; $p=0.011$), previous transurethral resection of bladder tumor history (HR, 3.825; 95% CI, 1.164–12.571; $p=0.027$), and intravesical recurrence (IVR) within 6 months (HR, 3.733; 95% CI, 1.091–12.778; $p=0.036$) in patients undergoing NUx are predictors of radical cystectomy implementation. In a multivariate analysis of patients without bladder cancer history, bladder recurrence was identified as a predictor of radical cystectomy implementation, if it occurred within 6 months of NUx (HR, 8.608; 95% CI, 1.545–47.976; $p=0.014$).

Conclusions: LVI and IVR within 6 months and previous bladder cancer history are factors that can predict the need for radical cystectomy after NUx. Even in patients without bladder cancer history, early bladder recurrence within 6 months is a major predictor of radical cystectomy.

Key Words: Nephroureterectomy, Radical cystectomy, Ureter cancer, Bladder cancer, Intravesical recurrence

Received September 27, 2021

Revised October 15, 2021

Accepted October 17, 2021

Corresponding author:

Bumsik Hong

Email: bshong@amc.seoul.kr

<https://orcid.org/0000-0003-1991-1229>

INTRODUCTION

Upper tract urothelial carcinomas (UTUCs) account for 5%–10% of all urothelial cancers. With its rising incidence, it is the fifth most frequently diagnosed noncutaneous cancer in the US.^{1,2} UTUCs can be located in the whole urinary tracts, but upper urinary tract urothelial carcinoma is

a relatively rare entity.^{3–5} UTUCs, on an average, have the highest incidence rate at 65 years of age, and a few recent studies have shown their prevalence in the United States amongst those aged 70 years and older. The cause of UTUCs is unclear. However, according to previous studies, smoking, job-related factors, abuse of painkillers, Chinese herbs nephropathy, and lithiasis were

reported to be associated with the incidence of UTUCs.⁶

Radical nephroureterectomy (NUx) with bladder cuff excision is a standard treatment method for UTUCs⁷ and is performed using various procedures such as robotic surgery, laparoscopic surgery, hand-assisted laparoscopic surgery, or open NUx. The biggest problem in UTUCs is recurrence after surgery. Recurrences in the retroperitoneum, contralateral urinary tract, and bladder are common. Of these types of recurrences, intravesical recurrence (IVR) is the most common. A recent study reported that relapses occurred in about 22%–47% of UTUC patients.^{8,9}

There are many studies on factors that influence bladder recurrence rate. The multifocality of UTUCs, the presence of Carcinoma *in situ* (CIS), and laparoscopic surgery have been suggested as representative risk factors.¹⁰ In a few studies, factors influencing the incidence of muscle invasive bladder cancer after NUx were investigated. These studies identified bladder cancer history prior to NUx, pathologic T stage at the first transurethral resection of the bladder (TURB), presence of CIS, and previous intravesical therapy as important factors in the muscle invasive bladder cancer (MIBC)-occurrence group.^{11,12} Radical cystectomy is recognized as the most common and effective treatment when MIBC is confirmed.¹³ Cystectomy with recurred MIBC or a recurrent bladder tumor has a high risk of surgery and adversely affects the patients' quality of life (QoL) and life span.¹⁴

However, since there are very few studies conducted so far and the analysis is limited, a more detailed study is needed based on the data accumulated over a long period of time. Therefore, in this paper, we tried to identify the factors that predict the implementation of radical cystectomy according to IVR, in patients who underwent NUx.

MATERIALS AND METHODS

1. Patient Population

This retrospective study was approved by the Institutional Review Board of Seoul Asan Medical Center (S2020-2618-0001). We retrospectively screened the medical records of patients who underwent NUx at Seoul Asan Medical Center, from January 2011 to December 2019. A total of 646 patients underwent surgery during this period.

Patients included in this study were (1) those whose primary origin was ureter cancer, (2) those who underwent NUx for UTUC, (3) those who were followed up within 3 months, and (4) medical records are required for the study. The exclusion criteria were as follows: (1) metastatic cancer, (2) NUx performed for ureter cancer that occurred in patients who underwent radical cystectomy, and (3) cases with insufficient clinical data or loss of follow-up.

2. Diagnosis and Pathologic Evaluations

All patients underwent computed tomography (CT) and cystoscopy before surgery. Preoperative ureteroscopy was not performed as a routine, but was recommended based on CT and urine cytology results. Nine surgeons performed all the surgeries and the surgical methods were open and laparoscopic NUx with open-bladder cuff excision; there was no difference between the surgeons in any of the surgical methods.

The pathological examination of all specimens after surgery was performed using the same procedure. Tumors were classified according to the American Joint Committee on Cancer–Union Internationale Contre le Cancer TNM classification, 8th edition¹⁵ and the 1998 World Health Organization/International Society of Urologic Pathology consensus classification

grade.¹⁶ Multiplicity and location were reported by a pathologist.

3. Follow-up Protocols

For the first 2 years after surgery, the patients were followed up every 3 months, via cystoscopy, urine cytology, CT, and chest radiography. When no evidence of recurrence was observed, follow-up was performed at 6-month intervals over 2 years, followed by annual examinations. IVR was defined whenever a lesion was observed by follow-up cystoscopy and confirmed by biopsy or cytology, as well as by radiological examination. Most of the patients with confirmed bladder recurrence received TURB.

4. Statistical Analyses

Quantitative data are expressed as median (range) or mean (standard deviation) and categorical variables were expressed as absolute values (percentage). Univariate and multivariate Cox regression analyses were performed for the analysis of risk factors leading to radical cystectomy in patients undergoing NUx. Correlations between outcomes and the assessed variables were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs).

All statistical analyses were performed using IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA).

RESULTS

The clinical and pathological characteristics are summarized in Table 1. A total of 646 patients were evaluated and all patients underwent NUx for UTUCs. Their median age was 70 years (interquartile range [IQR], 62–71 years), and the median follow-up period was 45.1 months (IQR,

18–66 months) with 459 males (71.1%) and 187 females (29.4%).

Among the subjects, 114 (17.6%) had a previous history of bladder cancer before NUx. A total of 418 patients (64.7%) underwent laparoscopic surgery including hand-assisted laparoscopic surgery, and the other 228 (35.3%) underwent open NUx. Upon the analysis of the specimens of the subjects after surgery, the T stage was T3 or higher in 241 patients (37.3%), and node metastasis was identified in a total of 55 patients. Distal ureter tumors were observed in 190 patients (29.4%), and 164 patients (25.4%), and multiplicity was confirmed in 192 patients (29.7%). A total of 49 patients (7.6%) underwent neoadjuvant CTx, and 99 (15.3%) underwent adjuvant CTx. Further, 11 patients underwent radical cystectomy by bladder recurrence after NUx (1.7%).

To eliminate the effects of previous bladder cancer, we performed a subgroup analysis on patients without previous history of bladder cancer. A total of 532 patients (82.4%) had no previous bladder cancer history. Their median age was 68 years (IQR, 61–75.8 years) with 373 males (70.1%) and 159 females (29.9%), and the median follow-up period was 43.7 months (range, 18–63 months). Of these, 177 patients (33.3%) underwent open surgery, and 355 patients (66.7%) underwent laparoscopic surgery including hand-assisted laparoscopic surgery. The T stage of 201 patients (37.8%) was above T3, and node metastasis was confirmed in a total of 46 patients (8.5%). CIS was confirmed in 217 patients (40.8%) and high-grade tumors in 437 patients (82.1%). lymphovascular invasion (LVI) was observed in 132 patients (24.8%), and multiplicity was observed in 147 patients (27.6%). A total of 135 patients (25.4%) had distal ureter involvement, 40 patients (7.5%) underwent neoadjuvant CTx, and 74 patients (13.9%) underwent adjuvant CTx after NUx. Cystectomy according to bladder recurrence was confirmed in a

Table 1. Clinical characteristics of the study patients

Characteristic	Total patients (n=646)	Patients with no previous bladder cancer history (n=532)
Age (yr)	70 (62–76)	68.0 (61–75.8)
Sex		
Male	459 (71.1)	373 (70.1)
Female	187 (28.9)	159 (29.9)
Height (cm)	162.7±9.1	162.9±8.41
Weight (kg)	65.6±11.3	65.3±10.37
Body mass index (kg/m ²)	25.1±13.0	24.6±3.15
Diabetes mellitus	153 (23.7)	124 (23.3)
Hypertension	324 (50.2)	261 (49.1)
ASA PS classification		
I	37 (5.7)	64 (5.8)
II	554 (85.8)	456 (85.7)
III	55 (8.5)	45 (8.5)
Pre-NUx TURB history		
Positive	114 (17.6)	-
Negative	532 (82.4)	-
Operation type		
Laparoscopy	418 (64.7)	177 (33.3)
Open	228 (35.3)	355 (66.7)
NUx pathology		
Pathologic T		
pT0–pT2	405 (62.7)	331 (62.2)
pT3–pT4	241 (37.3)	201 (37.8)
Node metastasis	55 (8.5)	46 (8.6)
Carcinoma <i>in situ</i>	268 (41.5)	217 (40.8)
Tumor grade (WHO/ISUP)		
High grade	518 (80.2)	437 (82.1)
Low grade	128 (19.8)	95 (17.9)
LVI	164 (25.4)	132 (24.8)
Tumor location		
Distal	190 (29.4)	135 (25.4)
Other sites	456 (70.6)	397 (74.6)
Tumor multiplicity	192 (29.7)	147 (27.6)
Neoadjuvant chemotherapy	49 (7.6)	40 (7.5)
Adjuvant chemotherapy	99 (15.3)	74 (13.9)
Cystectomy after NUx	11 (1.7)	6 (1.1)
Follow-up (mo)	44.1 (18–66)	43.7 (17.9–62.5)

Values are presented as median (interquartile range), number (%), or mean±standard deviation.

ASA PS: American Society of Anesthesiologists physical status, NUx: nephroureterectomy, TURB: transurethral resection of the bladder, LVI: lymphovascular invasion, WHO: World Health Organization, ISUP: International Society of Urological Pathology.

total of 6 patients (1.1%) (Table 1).

A risk factor analysis for radical cystectomy after NUx was performed. The factors identified as independent predictors in the multivariable logistic regression analysis were LVI (HR, 4.728; 95% CI, 1.463–15.570; $p=0.011$), previous TURB history (HR, 3.825; 95% CI, 1.164–12.571; $p=0.027$), and IVR within 6 months (HR, 3.733; 95% CI, 1.091–12.778; $p=0.036$) (Table 2).

Univariate analysis revealed that a distal tumor location is a risk factor for performing radical cystectomy after NUx in patients without previous bladder cancer history. When the tumor is located distally (HR, 6.229; 95% CI, 1.140–34.029; $p=0.035$), an IVR within 6 months (HR, 10.799; 95% CI, 1.977–58.996; $p=0.006$) was confirmed. Multivariate analysis performed with these factors revealed bladder recurrence within 6 months (HR,

Table 2. Multivariate Cox proportional hazard regression analysis of risk factors for radical cystectomy after NUX

Variable	Univariate		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.041 (0.978–1.108)	0.212		
Sex	0.918 (0.244–3.463)	0.900		
Body mass index	0.960 (0.787–1.171)	0.689		
Diabetes mellitus	1.868 (0.512–6.810)	0.532		
Hypertension	1.682 (0.461–6.130)	0.129		
Operation type (open vs. laparoscopy)	0.490 (0.149–1.615)	0.241		
pT stage $\geq$ 3	1.414 (0.413–4.839)	0.581		
Node metastasis	2.421 (0.309–19.004)	0.400		
Carcinoma <i>in situ</i>	2.094 (0.638–6.866)	0.223		
Tumor grade	2.804 (0.359–21.909)	0.868		
LVI	4.968 (1.513–16.312)	0.008	4.728 (1.436–15.570)	0.011
Tumor multiplicity	1.272 (0.370–4.373)	0.703		
Distal ureter tumor	3.029 (0.924–9.929)	0.067		
Adj CTx	2.811 (0.745–10.609)	0.127		
Previous bladder cancer history	4.075 (1.243–13.359)	0.020	3.825 (1.164–12.571)	0.027
IVR within 6 months	3.733 (1.091–12.778)	0.036	10.014 (1.827–54.896)	0.008

NUx: nephroureterectomy, HR: hazard ratio, CI: confidence interval, pT: pathologic T, LVI: lymphovascular invasion, Adj CTx: adjuvant chemotherapy, IVR: intravesical recurrence.

Table 3. Multivariate Cox proportional hazard regression analysis of risk factors for radical cystectomy after NUX in patients with no previous bladder cancer history

Variable	Univariate		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.073 (0.980–1.175)	0.130		
Sex	0.471 (0.055–4.029)	0.491		
Body mass index	1.081 (0.846–1.383)	0.532		
Diabetes mellitus	1.918 (0.350–10.506)	0.453		
Hypertension	5.774 (0.673–49.508)	0.110		
Operation type (open vs. laparoscopy)	0.287 (0.052–1.583)	0.152		
pT stage $\geq$ 3	1.190 (0.218–6.505)	0.841		
Carcinoma <i>in situ</i>	1.795 (0.362–8.898)	0.474		
Tumor grade	1.224 (0.143–10.482)	0.854		
LVI	4.215 (0.850–20.906)	0.078		
Tumor multiplicity	0.987 (0.179–5.436)	0.988		
Distal ureter tumor	6.229 (1.140–34.029)	0.035	4.638 (0.831–25.889)	0.080
Adj CTx	1.725 (0.201–14.781)	0.619		
IVR within 6 months	10.799 (1.977–58.996)	0.006	8.608 (1.545–47.976)	0.014

NUx: nephroureterectomy, HR: hazard ratio, CI: confidence interval, pT: pathologic T, LVI: lymphovascular invasion, Adj CTx: adjuvant chemotherapy, IVR: intravesical recurrence.

8.608; 95% CI, 1.545–47.976; $p=0.014$) as a risk factor (Table 3).

We reported 11 patients who underwent radical cystectomy after NUX. Of these, 4 patients had a previous bladder cancer history, and 7 patients had tumor involvement in the distal ureter. Their

first IVR occurred at a median of 8.2 months (IQR, 2–24 months); cystectomy was performed due to IVR at a median of 27 months (IQR, 7–69 months). The median follow-up period was 43.7 months (IQR, 22–79 months). The pathology after NUX and the basis for cystectomy are shown in Table 4.

Table 4. Analysis of patients who underwent radical cystectomy after NUx

Case no.	Previous bladder cancer	Distal ureter tumor involvement	Nephroureterectomy pathology	First IVR (mo)	Postoperative bladder instillation	Time to cystectomy (mo)	Reason of cystectomy	Follow-up (mo)
1	Yes	Yes	pT2N0, HG	-	-	18	MIBC	56
2	Yes	Yes	pT1N0, HG	-	-	10	T1cHG whole bladder	22
3	Yes	Yes	pT1N0, HG	-	-	69	MIBC	79
4	Yes	No	pT2N1, HG	-	-	27	T1aHG whole bladder	35
5	No	Yes	pT3N0, HG	2	BCG failure	13	MIBC	23.5
6	No	Yes	pT3N0, HG	24	-	28	MIBC	55
7	No	Yes	pT2N0, HG	6	-	43	MIBC	52.5
8	No	Yes	pT1N0, HG	4	-	13	MIBC	42.9
9	No	No	pTaN0, LG	4	-	7	TaHG whole bladder	29.9
10	No	No	pT3N0, HG	13	-	48	TaHG whole bladder	53
11	No	No	pT1N0, HG	4	BCG failure	21	T1aHG whole bladder	31.8

NUx: nephroureterectomy, IVR: intravesical recurrence, pT: pathologic T, HG: high grade, LG: low grade, MIBC: muscle invasive bladder cancer, BCG: Bacillus Calmette-Guérin.

Table 5. Characteristics of patients with bladder recurrence within 6 months after NUx

Characteristic	Bladder recurrence within 6 months after NUx (n=81)	Patients with no bladder recurrence within 6 months (n=565)
Age	68.28 (66–70)	68.40 (62–76)
Sex		
Male	61 (74.4)	398 (70.4)
Female	21 (25.6)	167 (29.6)
Hypertension	45 (54.9)	280 (49.6)
Diabetes mellitus	23 (28.4)	130 (23)
ASA PS classification		
I	5 (6.1)	32 (5.7)
II	66 (80.5)	489 (86.5)
III	11 (13.4)	44 (7.8)
Operation type		
Laparoscopic surgery	49 (60.5)	361 (63.9)
Open surgery	32 (39.5)	204 (36.1)
pT stage≥3	24 (29.6)	217 (38.4)
Node metastasis	2 (2.4)	53 (9.4)
Carcinoma <i>in situ</i>	37 (45.1)	231 (40.9)
Tumor grade (WHO/ISUP)		
High grade	72 (87.8)	447 (79.1)
Low grade	10 (12.2)	118 (20.9)
Lymphovascular invasion	18 (22)	147 (26.0)
Tumor multiplicity		
Yes	33 (40.7)	172 (30.4)
No	48 (59.3)	393 (69.6)
Distal ureter tumor	33 (40.2)	159 (28.1)
Radical cystectomy	5 (6.1)	6 (1.06)
Adjuvant chemotherapy	6 (7.3)	94 (16.6)
Follow-up duration (mo)	49.20 (42.01–56.55)	43.10 (40.72–45.49)

Values are presented as median (range) or number (%).

Implementation in patients with no previous bladder cancer history.

NUx: nephroureterectomy, ASA PS: American Society of Anesthesiologists physical status, pT: pathologic T, WHO: World Health Organization, ISUP: International Society of Urological Pathology.

Table 5 presents the characteristics of 81 patients who developed IVR within 6 months. The

average age of the patients was 68.28 years (IQR, 66–70 years), and the gender was 61 males (74.4%)

Fig. 1. Kaplan-Meier survival curve according to time of bladder recurrence. IVR: intravesical recurrence.

and 21 females (25.6%). The T stage was T3 or higher in 24 patients (29.6%), and node metastasis was confirmed in 2 patients, corresponding to 2.4%. Thirty-three patients (40.2%) included distal ureter tumor. A total of 5 patients (6.1%) underwent radical cystectomy during the follow-up period. The median follow-up period was 49.2 months (range, 42.01–56.55 months). As a result of analysis using the Kaplan-Meier method, the group with IVR confirmed within 6 months showed a higher probability of performing cystectomy than the other group ($p=0.024$, log-lank test, Fig. 1).

DISCUSSION

The high bladder recurrence rate of UTUCs worsens patients' QoL¹⁷⁻¹⁹ after NUx and increases the economic burden.^{20,21} In addition, patients need to receive TURB repeatedly, exposing them to the possibility of operation-related risk and complications caused by surgery. The progression to MIBC should be scrutinized further as it directly relates to the patient's survival.^{22,23} Since the implementation of NUx, some studies have been conducted on the factors that affect IVR. However, a clear cause was not identified and the results were variable.

Seisen et al.²⁴ performed a meta-analysis based on a total of 18 previous studies. In this paper, IVR-specific predictors were identified in terms of patient-, tumor-, and treatment-related factors. Among the patient-specific predictors, male sex, previous bladder cancer history, and preoperative chronic kidney disease showed significant results, and preoperative urinary cytology, tumor location, tumor multifocality, pathologic T (pT) stage, and tumor necrosis were confirmed as tumor-specific predictors. Finally, management laparoscopic surgery, an extravesical approach, and a positive surgical margin were found to have significant results as specific predictors.²⁴

In the meta-analysis by Azémar et al.,²⁵ it was difficult to classify the tumor site as a risk factor for IVR, and it was confirmed that IVR was higher in males, but the limitations of not considering other patient characteristic factors were explained. Previous bladder tumor history was suggested to have an effect. Recently, Shigeta et al.¹¹ in a study conducted in Japan, confirmed the factors affecting IVR after the implementation of NUx and attempted to identify the risk factors leading to MIBC progression after IVR. In this study, tumor location, the pT stage, and tumor multifocality were identified as risk factors. As factors predicting the likelihood of progression to MIBC after IVR, the bladder recurred tumor was pT1, concomitant CIS was confirmed, and intravesical therapy was not performed.

In this study, the previously suggested predictors corroborated with data from our center, and the time of first occurrence of IVR was set as a new predictor, through the analysis of the risk of radical cystectomy implementation after NUx during the follow-up period.

For this study, factors affecting radical cystectomy implementation were identified in all patients who underwent NUx for UTUCs. The multivariate analysis revealed that with NUx and regular

follow-up, bladder recurrence within 6 months (HR, 10.014; 95% CI, 1.827–54.896; $p=0.008$), LVI (HR, 4.728; 95% CI, 1.436–15.570; $p=0.011$), and previous TURB history (HR, 3.825; 95% CI, 1.164–12.571; $p=0.027$) were factors predicting radical cystectomy after NUX.

We performed a subgroup analysis on patients with no bladder cancer history and tried to identify predictors through a multivariate analysis, which identified IVR occurring within 6 months (HR, 8.608; 95% CI, 1.545–47.976; $p=0.014$) as a significant predictor. The univariate analysis indicated tumor location in the distal ureter (HR, 6.229; 95% CI, 1.140–34.029; $p=0.035$) as a predictor, but it was difficult to obtain meaningful results for the same in the case of the multivariate analysis (HR, 4.638; 95% CI, 0.831–25.889; $p=0.080$).

As this was a retrospective study and used data from a single center, the possibility of there being a selection bias in the subject selection process could not be excluded and because of the lack of international implications for the benefit of lymph node dissection in UTUC, this study was excluded from the risk factor.²⁶

Previous studies aimed to determine the cause of IVR, but most of the preceding studies did not specify the follow-up period or did not analyze the time of occurrence.

Despite these limitations of the study and the small number of patients who underwent radical cystectomy, this study is meaningful in that it is the first one to confirm IVR occurring within the first 6 months of follow-up as a predictor of radical cystectomy implementation.

CONCLUSIONS

A confirmed LVI or an IVR occurrence within 6 months of NUX is a risk factor that can predict radical cystectomy implementation. For patients

without previous bladder cancer history, early bladder cancer recurrence within 6 months is a predictor of radical cystectomy implementation. Characterizing the importance of distal ureter involvement in UTUCs requires follow-up studies in a larger patient population.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

ORCID

Janghui Lee, <https://orcid.org/0000-0001-6552-169X>
 Bumjin Lim, <https://orcid.org/0000-0002-1746-6072>
 Dalsan You, <https://orcid.org/0000-0001-8152-847X>
 In Gab Jeong, <https://orcid.org/0000-0003-4093-832X>
 Cheryn Song, <https://orcid.org/0000-0002-1823-4281>
 Jun Hyuk Hong, <https://orcid.org/0000-0003-2705-0481>
 Choung-Soo Kim, <https://orcid.org/0000-0002-7464-3207>
 Hanjong Ahn, <https://orcid.org/0000-0001-7608-5352>
 Bumsik Hong, <https://orcid.org/0000-0003-1991-1229>

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7–30.
2. Andreassen BK, Aagnes B, Gislefoss R, Andreassen M, Wahlqvist R. Incidence and survival of urothelial carcinoma of the urinary bladder in Norway 1981–2014. *BMC Cancer* 2016;16:799.
3. Lonergan PE, Porten SP. Bladder tumor recurrence after urothelial carcinoma of the upper urinary tract. *Transl Androl Urol* 2020;9:1891–6.
4. Gross AJ, Netsch C, Stolzenburg JU, Becker B. Upper urinary tract urothelial cell carcinoma. *Urologe A* 2020;59:1265–74. (German).
5. Soria F, Shariat SF, Lerner SP, Fritsche HM, Rink M, Kassouf W, et al. Epidemiology, diagnosis, pre-operative evaluation and prognostic assessment of upper-tract urothelial carcinoma (UTUC). *World J*

- Urol 2017;35:379-87.
6. Colin P, Koenig P, Ouzzane A, Berthon N, Villers A, Biserte J, et al. Environmental factors involved in carcinogenesis of urothelial cell carcinomas of the upper urinary tract. *BJU Int* 2009;104:1436-40.
 7. Liu F, Guo W, Zhou X, Ding Y, Ma Y, Hou Y, et al. Laparoscopic versus open nephroureterectomy for upper urinary tract urothelial carcinoma: a systematic review and meta-analysis. *Medicine (Baltimore)* 2018;97:e11954.
 8. Chen CS, Li JR, Wang SS, Yang CK, Cheng CL, Yang CR, et al. Tumor multifocality is a significant risk factor of urinary bladder recurrence after nephroureterectomy in patients with upper tract urothelial carcinoma: a single-institutional study. *Diagnostics (Basel)* 2020;10:201.
 9. Roupert M, Babjuk M, Comperat E, Zigeuner R, Sylvester RJ, Burger M, et al. European Association of Urology guidelines on upper urinary tract urothelial carcinoma: 2017 update. *Eur Urol* 2018;73:111-22.
 10. Xylinas E, Colin P, Audenet F, Phe V, Cormier L, Cussenot O, 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.
 11. Shigeta K, Matsumoto K, Ogihara K, Murakami T, Anno T, Umeda K, et al. The clinicopathological characteristics of muscle-invasive bladder recurrence in upper tract urothelial carcinoma. *Cancer Sci* 2021;112:1084-94.
 12. Wu J, Xu PH, Luo WJ, Dai B, Shen YJ, Ye DW, et al. Intravesical recurrence after radical nephroureterectomy of upper urinary tract urothelial carcinoma: a large population-based investigation of clinicopathologic characteristics and survival outcomes. *Front Surg* 2021;8:590448.
 13. Witjes JA, Bruins HM, Cathomas R, Compérat EM, Cowan NC, Gakis G, et al. European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. *Eur Urol* 2021;79:82-104.
 14. Choi H, Park JY, Bae JH, Tae BS. Health-related quality of life after radical cystectomy. *Transl Androl Urol* 2020;9:2997-3006.
 15. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer International Publishing; 2017.
 16. Epstein JI, Amin MB, Reuter VR, Mostofi FK. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. *Bladder Consensus Conference Committee. Am J Surg Pathol* 1998;22:1435-48.
 17. Jung A, Nielsen ME, Crandell JL, Palmer MH, Smith SK, Bryant AL, et al. Health-related quality of life among non-muscle-invasive bladder cancer survivors: a population-based study. *BJU Int* 2020;125:38-48.
 18. Mason SJ, Downing A, Wright P, Hounscome L, Bottomley SE, Corner J, et al. Health-related quality of life after treatment for bladder cancer in England. *Br J Cancer* 2018;118:1518-28.
 19. Smith AB, Jaeger B, Pinheiro LC, Edwards LJ, Tan HJ, Nielsen ME, et al. Impact of bladder cancer on health-related quality of life. *BJU Int* 2018;121:549-57.
 20. Johnson DC, Greene PS, Nielsen ME. Surgical advances in bladder cancer: at what cost? *Urol Clin North Am* 2015;42:235-52, ix.
 21. Svatek RS, Hollenbeck BK, Holmang S, Lee R, Kim SP, Stenzl A, et al. The economics of bladder cancer: costs and considerations of caring for this disease. *Eur Urol* 2014;66:253-62.
 22. Malmström PU, Gårdmark T, Sherif A, Ströck V, Hosseini-Aliabad A, Jahnson S, et al. Incidence, survival and mortality trends of bladder cancer in Sweden 1997-2016. *Scand J Urol* 2019;53:193-9.
 23. Martinez Rodriguez RH, Buisan Rueda O, Ibarz L. Bladder cancer: present and future. *Med Clin (Barc)*

- 2017;149:449-55.
24. Seisen T, Granger B, Colin P, Leon P, Utard G, Renard-Penna R, 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;67:1122-33.
25. Azemar MD, Comperat E, Richard F, Cussenot O, Roupret M. Bladder recurrence after surgery for upper urinary tract urothelial cell carcinoma: frequency, risk factors, and surveillance. *Urol Oncol* 2011;29:130-6.
26. Dominguez-Escrig JL, Peyronnet B, Seisen T, Bruins HM, Yuan CY, Babjuk M, et al. Potential benefit of lymph node dissection during radical nephroureterectomy for upper tract urothelial carcinoma: a systematic review by the European Association of Urology Guidelines Panel on Non-muscle-invasive Bladder Cancer. *Eur Urol Focus* 2019;5:224-41.