

ARTICLE

Oncological outcomes of radical nephroureterectomy for upper urinary tract urothelial neoplasia in Denmark

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ABSTRACT

Objective: To report the oncological outcomes of radical nephroureterectomy for upper urinary tract urothelial neoplasia in a large study sample.

Materials and methods: This was a nationwide multicenter registry-based cohort study of all patients with upper urinary tract urothelial neoplasia in Denmark found to be eligible for nephroureterectomy between April 2004 and April 2017 ($N = 1384$). Primary endpoints were intravesical recurrence-free survival and overall survival. Survival probabilities were estimated with Kaplan–Meier and the log-rank test to compare survival curves. Association with clinical outcomes was studied using univariate and multivariate Cox proportional hazards.

Results: Intravesical recurrence-free survival was 72% [95% confidence interval (CI) 69–75%] at 5 years and 70% (95% CI 67–73%) at 10 years. Patients with muscle-invasive disease had a significantly lower rate of intravesical recurrence [hazard ratio (HR) = 0.46, $p < 0.0001$] and patients with high-grade tumors had a significantly higher rate of incident intravesical recurrence compared to low-grade tumors (HR = 1.65, $p = 0.001$). The overall survival was 76% (95% CI 74–79%) at 5 years and 64% (95% CI 60–70%) at 10 years. Patients with higher age ($p = 0.008$) and muscle-invasive disease ($p < 0.0001$) had worse overall survival. When comparing surgical approaches, laparoscopic nephroureterectomy versus open nephroureterectomy did not differ in intravesical recurrence-free survival but was associated with shorter postoperative hospital stay ($p < 0.0001$) and better overall survival ($p = 0.02$).

Conclusions: We report the oncological outcomes of radical nephroureterectomy for upper urinary tract urothelial neoplasia in a large sample and give insights into predictive factors with significant impact.

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Nephroureterectomy; laparoscopy; surgical oncology; Denmark

Introduction

Upper urinary tract urothelial neoplasia [upper urinary tract urothelial carcinoma (UTUC)] is a rare form of cancer. The annual incidence in Europe is estimated to be 1.2 cases per 100,000 inhabitants, accounting for only 5–10% of all urothelial neoplasias [1]. Studies report that up to 77% of UTUCs are invasive at the time of diagnosis, and a 57% 5 year overall survival rate has been described, being dramatically lower (<10%) for pT4 patients [2]. Hence, early diagnosis and treatment is important. Current gold-standard surgical treatment is radical nephroureterectomy, which can be performed as laparoscopic radical nephroureterectomy (LNU) or open radical nephroureterectomy (ONU). Most published reports on clinical experiences of radical nephroureterectomy for UTUC are based on single-center reports with small samples [1]. Thus, large multicenter studies are needed to better understand the oncological outcomes of nephroureterectomy for UTUC. The purpose of our study is to report Danish national

data for patients who underwent radical nephroureterectomy, in terms of hospitalization, intravesical recurrence-free survival and long-term oncological outcome.

Materials and methods

Study design

This was a nationwide registry-based retrospective observational cohort study. All Danish citizens are registered with a unique personal identification number [Central Personal Registration (CPR) number], which allows linkage with all national registries at an individual level. We included data from the National Patient Registry (NPR), which contains information on all hospitalizations [3], including surgical procedures coded according to the Nordic Classification of Surgical Procedures and diagnoses coded according to the International Classification of Diseases, 10th revision (ICD-10). All aspects of this study followed the principles in the

Declaration of Helsinki. The study was approved by the Danish Health Data Board (jr. no. 2008-58-0020).

Study cohort

All patients who underwent nephroureterectomy performed between April 2004 and April 2017 in Denmark (approximate total population of 5.5 million) were included. For each patient, we retrieved data from national registries on age, gender, length of hospital stay (hospital stay after surgery and any readmission within the first 30 days after surgery), recurrence or synchronous bladder tumor to the nephroureterectomy procedure, tumor, node, metastasis (TNM) classification for primary tumor and recurrences to bladder, death and reason for death. Patients with primary M+ status and patients who underwent nephroureterectomy procedures in conjugation with cystectomy, were excluded from the study. Neoadjuvant and/or adjuvant chemotherapy was not a standard treatment in Denmark during this period; therefore, we assume that no or very few patients were offered oncolological treatment in this series. Non-cancer-related nephroureterectomies were not included in the analyses. Data on late distant metastasis were not available. Data on T staging were missing for 133 patients (9.6%). [Supplementary Appendix 1](#) shows the algorithm and data codes used to retrieve data.

Data analysis and statistics

The primary endpoint was intravesical recurrence-free survival after radical nephroureterectomy and the secondary endpoint was overall survival after radical nephroureterectomy. Patients' clinical and demographic results were presented using descriptive statistics. We compared the clinical and pathological characteristics using Wilcoxon tests for continuous variables and the chi-squared test for categorical variables. Intravesical recurrence-free survival was defined as the time interval between the date of radical nephroureterectomy and the date of intravesical recurrence, while patients who died before the onset of recurrence were defined as censored. Overall survival was defined as the time interval between the date of radical nephroureterectomy and the date of patient death from any cause. Survival probabilities were estimated using the Kaplan–Meier method, and the log-rank test was applied to compare survival curves. Univariate and multivariate Cox proportional hazards regression analyses were performed to determine the associations between clinical outcomes. All tests were two sided and the significance level was set at $p < 0.05$. Statistical analyses were performed with R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Population characteristics

We identified a total of 1893 patients who underwent radical nephroureterectomy during the study period. In 234 out of

these 1893 cases (12%), patients had previously presented with bladder urothelial carcinoma. In 179 out of 1659 cases (11%), concurrent bladder cancer was present, and 96 out of 1480 patients (5.2%) had synchronized metastatic disease. These patient cohorts were excluded from the study. Analyses were thus performed on 1384 patients who underwent radical nephroureterectomy. We observed a significant temporal trend toward a persistent increase in the year 2009 and onwards in the number of radical nephroureterectomies ([Figure 1](#)). Median age was 70 years [interquartile range (IQR) 64–76 years] and 513 (37%) were females. T stage was missing in 133 patients (9.6%). In total, 829 (60%) tumors were stage pTa. In 267 cases (19.3%), patients had muscle-invasive disease (MID). The distribution of LNU versus ONU was 1063 (77%) versus 321 (23%). Sixty-nine patients (5%) underwent lymph-node dissection, and 20 (29%) of these patients had pathological stage N+. The estimated annual incidence in Denmark was 3.3 cases per 100,000 inhabitants in 2016–2017. Patient characteristics are summarized in [Table 1](#).

The total median follow-up time was 54 months (IQR 28–82 months). Median length of hospital stay was 5 days (IQR 3–7 days). LNU was associated with significantly shorter postoperative hospital stay (median 4 days; IQR 2–6 days) than ONU (median 8 days; IQR 6–10 days) ($p < 0.0001$).

Intravesical recurrences

A total of 292 out of 1384 patients (21%) had intravesical recurrence. The median time to intravesical recurrence was 9 months (IQR 5–19 months). Moreover, 247 (85%) of all intravesical recurrences occurred within the first 2 years after surgery. Intravesical 5 year recurrence-free survival after radical nephroureterectomy was 72% [95% confidence interval (CI) 69–75%] and 10 year intravesical recurrence-free survival was 70% (95% CI 67–73%) ([Figure 2](#)).

Choice of surgical approach (LNU vs ONU) did not influence the incidence of intravesical recurrences [hazard ratio (HR) = 1.0; 95% CI 0.79–1.33; $p = 0.832$]. Presence of MID was associated with a significantly lower incidence of intravesical recurrences (HR = 0.34; 95% CI 0.15–0.77; $p < 0.0001$). A pTa stage was associated with a significantly higher incidence of intravesical recurrences compared to other pT stages (HR = 1.6; 95% CI 1.04–2.43, $p = 0.031$). High-grade tumors were associated with a significantly higher incidence of intravesical recurrences (HR = 1.55; 95% CI 1.19–2.01; $p = 0.001$). Patients who had lymphadenectomy had a significantly lower incidence of intravesical recurrences (HR = 0.34; 95% CI 0.15–0.77; $p = 0.009$). Univariate analyses are summarized in [Table 2](#) together with multivariate analyses, which revealed that after adjustment for age, gender, surgical approach, tumor stage, tumor grade and performing lymphadenectomy, two important predictors remained significant: patients with MID had a significantly lower rate of intravesical recurrence (HR = 0.46; 95% CI 0.31–0.66; $p < 0.0001$) and patients with high-grade tumors had a significantly higher rate of incident intravesical recurrence compared to those with low-grade tumors (HR = 1.65; 95% CI 1.22–2.25; $p = 0.001$).

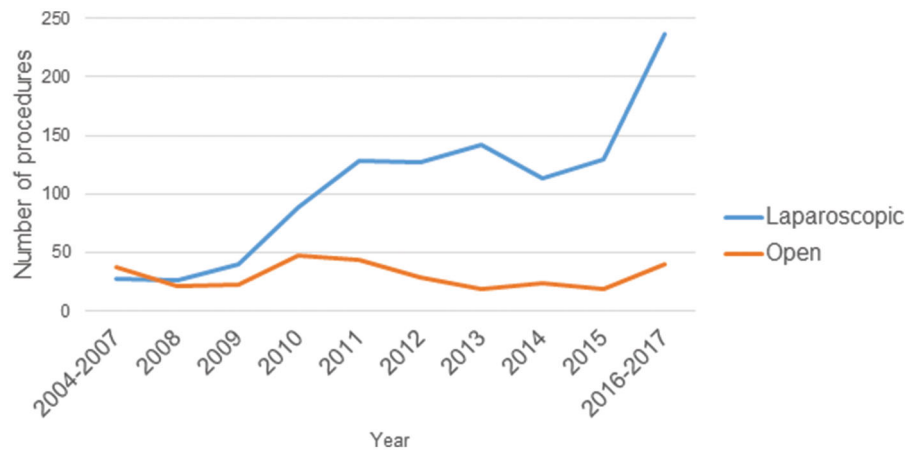


Figure 1. Distribution of nephroureterectomy procedures per year.

Table 1. Patient characteristics.

Characteristic	All	Open	Laparoscopic	<i>p</i>
<i>N</i>	1384	321	1063	
Age (years)				
<60	214 (15.46)	58 (18.07)	156 (14.68)	0.105
60–69	499 (36.05)	110 (34.27)	389 (36.59)	0.145
70–79	539 (38.95)	127 (39.56)	412 (38.76)	0.309
≥80	132 (9.54)	26 (8.10)	106 (9.97)	0.120
Gender				
Female	513 (37.10)	115 (35.82)	398 (37.44)	0.6445
Male	871 (62.90)	206 (64.18)	665 (62.56)	
T stage				
Missing	133 (9.61)	48 (14.95)	85 (7.10)	
T1	144 (10.40)	30 (9.35)	114 (10.72)	0.00521
T2	59 (4.26)	17 (5.30)	42 (3.95)	0.32659
T3	174 (12.57)	47 (14.64)	127 (11.95)	0.08902
T4	36 (2.61)	18 (5.61)	18 (1.69)	0.13170
Ta	838 (60.55)	161 (50.16)	677 (63.69)	<0.0001
Tumor grade				
High grade	971 (70.16)	172 (53.58)	799 (75.16)	<0.0001
Low grade	413 (29.84)	149 (46.42)	264 (24.84)	
T stage				
MID	269 (19.44)	82 (25.55)	187 (17.59)	0.0002
NMID	982 (70.95)	191 (59.50)	791 (74.41)	
Missing	133 (9.61)	48 (14.95)	85 (7.10)	
Intravesical recurrences				
Yes	292 (21.10)	64 (19.94)	228 (21.45)	0.058
No	1092 (78.90)	257 (80.06)	835 (78.55)	

Data are shown as *n* (%).

MID: muscle-invasive disease; NMID: non-muscle-invasive disease.

Overall survival

The overall survival was 76% (95% CI 74–79%) at 5 years and 64% (95% CI 60–70%) at 10 years (Figure 3). Patients with MID had a worse overall survival than those who had non-muscle-invasive disease (NMID) (HR = 2.51; 95% CI 1.96–3.22; $p < 0.0001$) at both 5 years (MID: 60%, 95% CI 54–68%; vs NMID: 81%, 95% CI 78–84%) and 10 years (MID: 46%, 95% CI 31–67%; NMID: 66%, 95% CI 59–75%) (Figure 4). Higher age was also associated with worse overall survival (Table 3). No significant differences in overall survival were observed according to lymphadenectomy status, gender or tumor grade (Table 3). In a multivariate analysis adjusting for other factors, we found that higher age, open approach and MID remained factors predictive of worse overall survival (Table 3).

Discussion

The estimated annual incidence of UTUC in Western countries is reported to be one to two cases per 100,000 inhabitants [1,4]. In Denmark, we found an incidence approximately twice as high as this, with 3.3 cases per 100,000 inhabitants. Patients with MID represented only 20%, which is less than previously reported in the literature and in European Association of Urology guidelines [2,4]. In general, there is a global trend toward earlier diagnosis of urothelial neoplasia leading to a relatively high proportion of patients with earlier stage disease [5,6]. Specifically for Denmark, the combination of high incidence and low MID may be due to the early detection and management strategy related to the nationwide implementation of standardized cancer patient pathways since 2007–2009 [7–11]. Cancer patient pathways were introduced to ensure earlier detection of cancer based on a set of alarm symptoms that raise cancer suspicion or a more diffuse but reasonable suspicion, after which the standardized referral system ensures time-efficient diagnostic pathways [7–11]. Temporal trends in our study, where we see a drastic increase in 2009, are likely to be explained by these standardized cancer patient pathways. We believe that these standardized cancer patient pathways, through earlier referral, standardized diagnostic approaches and earlier detection, have provided more patients with a diagnosis at a stage where it makes sense to intervene surgically.

Most patients experienced the recurrence during the first 2 years after nephroureterectomy. We did not find any differences in intravesical recurrence when comparing the surgical approach in terms of LNU versus ONU in univariate and multivariate analyses, which is in contrast to the findings of some studies [12,13], but in general in line with the majority of previously reported studies [1]. Intravesical recurrence occurred in 21% of patients, which is comparable to the lowest incidences previously reported (range 22–46%) [14,15]. Although the incidence of intravesical recurrence was generally low, we also found that patients with NMID had more incidences of intravesical recurrence compared to those with MID. One possible explanation may be that patients who had MID died earlier than those who had NMID, which may indicate that patients with MID died before experiencing

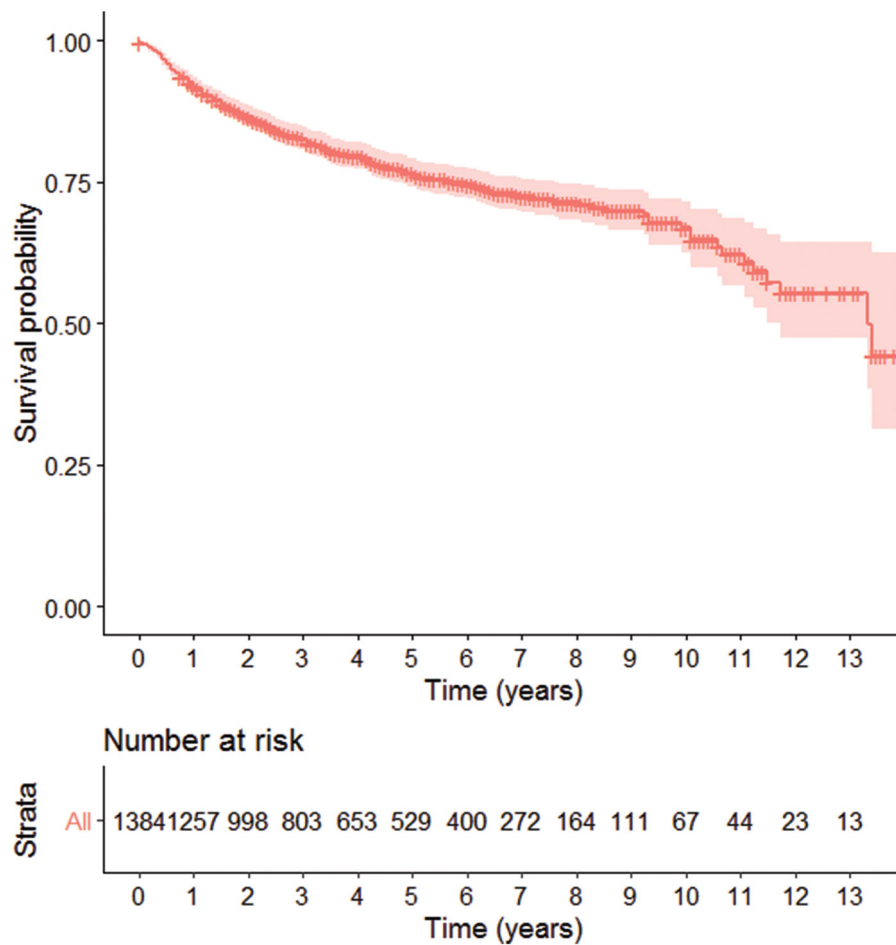


Figure 2. Intravesical recurrence-free survival after nephroureterectomy in patients with urothelial neoplasia: total patient population.

Table 2. Predictors of intravesical recurrences within the bladder after nephroureterectomy in patients with urothelial neoplasia.

	Univariate				Multivariate			
	Coef.	HR	95% CI	p	Coef.	HR	95% CI	p
Age (years)								
<60	Ref.				Ref.			
60–69	–0.07	0.68	0.68–1.30	0.7	–0.18	0.84	0.59–1.18	0.3
70–79	–0.02	0.71	0.71–1.36	0.9	–0.07	0.94	0.67–1.31	0.7
≥80	–0.54	0.35	0.35–0.98	0.04	–0.52	0.59	0.35–1.01	0.05
Gender								
Female	Ref.				Ref.			
Male	0.13	1.14	0.91–1.43	0.3	0.11	1.11	0.87–1.41	0.4
T stage								
NMID	Ref.				Ref.			
MID	–0.83	0.44	0.31–0.63	<0.0001	–0.81	0.46	0.31–0.66	<0.0001
Lymphadenectomy								
Not performed	Ref.				Ref.			
Performed	–1.07	0.34	0.15–0.77	0.009	–1.73	0.18	0.01–3.64	0.3
Tumor grade								
Low grade	Ref.				Ref.			
High grade	0.44	1.55	1.19–2.01	0.001	0.50	1.65	1.22–2.25	0.001
Surgical approach								
Open	Ref.				Ref.			
Laparoscopic	0.03	1.03	0.79–1.33	0.8	–0.14	0.87	0.66–1.15	0.3

Coef: coefficient; HR: hazard ratio; CI: confidence interval; NMID: non-muscle-invasive disease; MID: muscle-invasive disease; Ref: reference.

intravesical recurrences. As previously reported [16], we confirm that high-grade tumors were associated with an increased risk of intravesical recurrence.

From an etiological perspective, our findings suggest interesting relationships. It was previously shown that activating mutations of the fibroblast growth factor receptor-3

(FGFR3) are present at a more frequent rate in NMID than in MID [17]. FGFR3 plays a role in embryonic development, where growth, differentiation and establishment of metabolic functions are important [18]; hence, when this system is activated beyond the speed limit, a risk of cancer emerges [18]. Although only the minority of high-grade tumors possess the

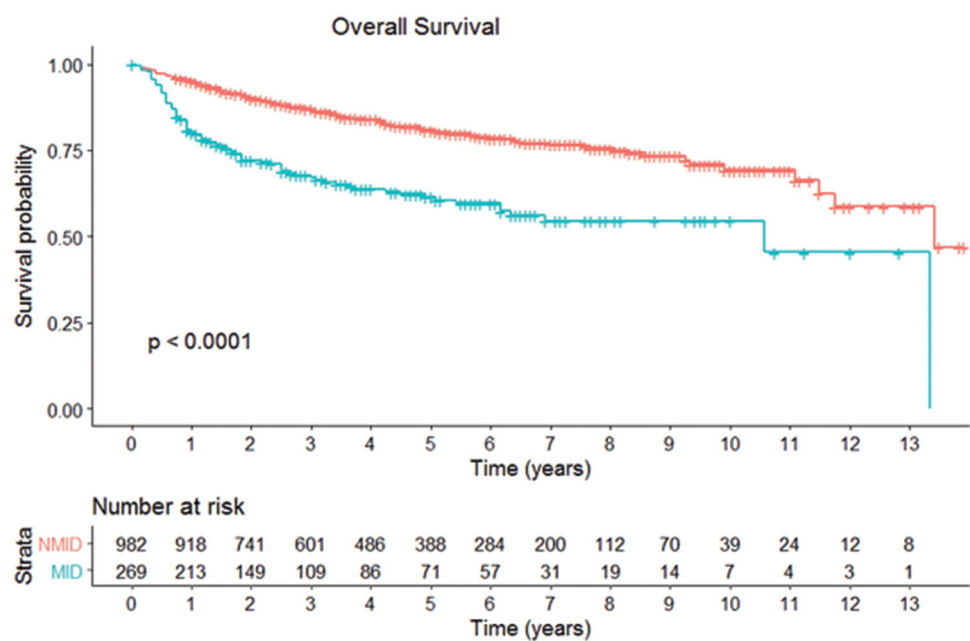


Figure 3. Overall survival after nephroureterectomy in patients with urothelial neoplasia: total patient population.

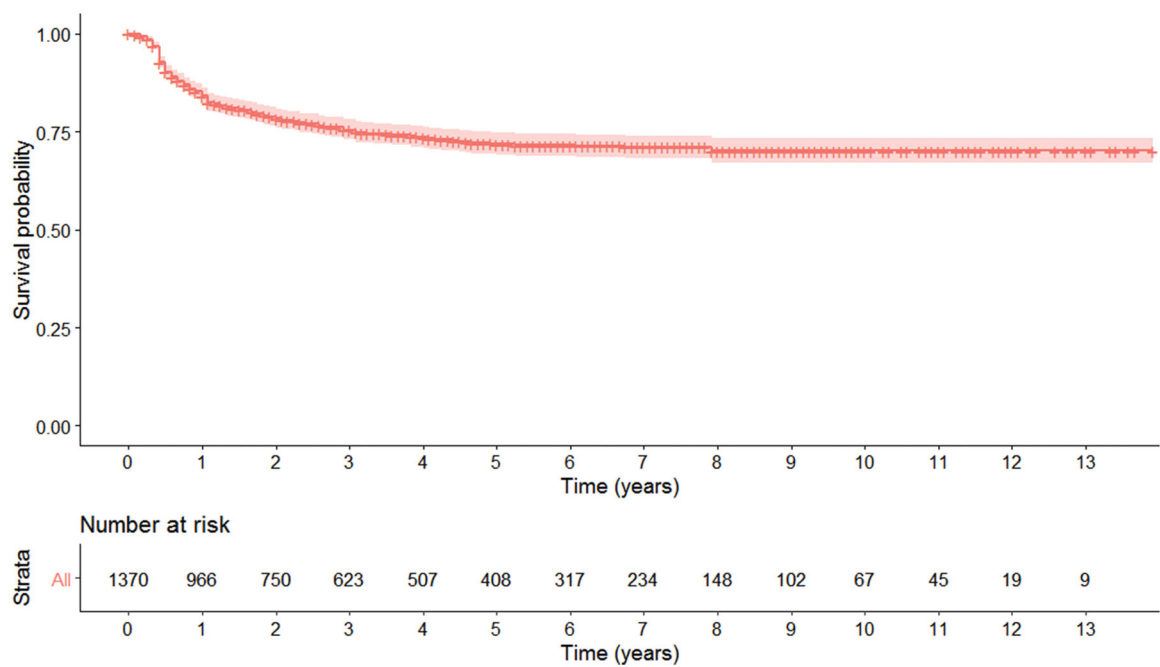


Figure 4. Overall survival after nephroureterectomy in patients with urothelial neoplasia: differences between those with muscle-invasive disease (MID, in blue) and those with non-muscle-invasive disease (NMID, in red).

tumor suppressor gene *TP53* inactivation mutations, patients with MID who have the *TP53* mutations are at risk of faster progression, more aggressive tissue invasion and therapeutic resistance [19,20]. Taken together, the genetic backgrounds of both NMID and high-grade tumors may partly explain the significant association with increased intravesical recurrences. Studies are warranted to shed further light on these genetic factors.

While cancer-specific survival measures give insight into death due to a specific disease, this analysis could not be performed in our cohort because of a lack of data regarding late distant metastases. Instead, we have included overall

survival, which is more representative of what the patients care most about: living longer regardless of the cause of death. Our results show that overall survival is comparable with some of the best results reported in the literature [1–27]. Unsurprisingly, patients with MID had a worse overall survival compared to those with NMID, and higher age was also associated with worse overall survival. However, we also found that LNU was associated with a better overall survival than ONU. One may suspect that this could be related to postoperative hospital stay and recovery, and indeed we found that LNU was associated with significantly shorter postoperative stay compared to ONU, but the survival curves

Table 3. Predictors of overall survival after nephroureterectomy in patients with urothelial neoplasia.

	Univariate				Multivariate			
	Coef.	HR	95% CI	p	Coef.	HR	95% CI	p
Age (years)								
<60	Ref.				Ref.			
60–69	0.53	1.70	1.15–2.50	0.007	0.55	1.74	1.16–2.61	0.008
70–79	0.64	1.90	1.30–2.79	0.001	0.67	1.94	1.31–2.92	0.001
≥80	0.87	2.38	1.48–3.85	<0.0001	0.86	2.37	1.43–3.95	0.001
Gender								
Female	Ref.				Ref.			
Male	−0.07	0.94	0.74–1.18	0.6	−0.05	0.95	0.74–1.21	0.7
T stage								
NMID	Ref.				Ref.			
MID	0.92	2.51	1.96–3.22	<0.0001	0.87	2.39	1.83–3.11	<0.0001
Lymphadenectomy								
Not performed	Ref.				Ref.			
Performed	0.38	1.47	0.90–2.40	0.1	−1.36	0.26	0.01–4.43	0.4
Tumor grade								
Low grade	Ref.				Ref.			
High grade	−0.20	0.82	0.65–1.28	0.09	−0.24	0.79	0.60–1.03	0.08
Surgical approach								
Open	Ref.				Ref.			
Laparoscopic	−0.42	0.66	0.52–0.83	<0.0001	−0.33	0.72	0.56–0.94	0.02

Coef: coefficient; HR: hazard ratio; CI: confidence interval; NMID: non-muscle-invasive disease; MID: muscle-invasive disease; Ref.: reference.

diverge on long-term follow-up, suggesting that the differences between LNU and ONU arise with time. Hence, differences in overall survival may be more strongly related to the differences in long-term complications between LNU and ONU. Our study data do not allow this issue to be explored and more studies are warranted.

The median hospital stay was 4 days for LNU, which is comparable to the literature, while there was prolonged hospital stay after ONU compared to the literature [13,28,29]. We reported a reduction in hospital stay by 50% in patients who underwent LNU compared to ONU; this should be taken into account when choosing the surgical approach, especially as the overall survival rate was comparable, if not better, for patients who underwent LNU. The fast-tract principle is well established in Denmark; therefore, a prolonged hospital stay was not reasonable.

Although this study provides the largest study sample to date with insight into long-term follow-up for this rare disease, several limitations to this study must be noted when interpreting its results. First, this is a retrospective study, and data were not collected for the purpose of conducting this study or comparing the two surgical approaches. Hence, there are some aspects that we could not explore in this study, e.g. the impact of local treatment of NMID. Second, we did not have detailed complete data allowing us to explore the impact of T staging or late distant metastases, which could have provided further insight into oncological outcomes.

In conclusion, in this large nationwide multicenter registry-based cohort study, we report that MID and low-grade tumors predict lower intravesical recurrence, and that high age, open approach and MID are predictors of worse overall survival.

Disclosure statement

The authors declare no potential conflicts of interest.

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