Advanced Age Impacts Survival After Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma

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ABSTRACT

Upper tract urothelial carcinoma continues to have a poor prognosis even after radical surgical treatment. In a significant sample size of 1387 patients treated with radical nephroureterectomy, we aimed to investigate commonly available factors predictive of recurrence and survival, with an emphasis on the effects of age on survival outcomes. Overall survival ($P = .0001$) and cancer-specific survival ($P = .0001$) has been found to be statistically significantly associated with age as independent predictors, and this research confirms that patients aged 70 and above may have worse outcomes compared to younger patients, and they are needing an improved care and management of UTUC to improve outcomes.

Introduction: Upper tract urothelial carcinoma is rare but has a poor prognosis. Prognostic factors have been extensively studied in order to provide the best possible management for patients. We have aimed to investigate commonly

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available factors predictive of recurrence and survival in this patient population at high risk of death and recurrence, with an emphasis on the effects of age (using a cutoff of 70 years) on survival outcomes. **Patients and Methods:** From 1387 patients with clinically nonmetastatic upper tract urothelial carcinoma treated with radical nephroureterectomy at 21 academic hospital centers between 2005 and 2021, 776 patients were eligible and included in the study. Univariable and multivariable Cox regression models were built to evaluate the independent prognosticators for intravesical and extravesical recurrence, overall survival, and cancer-specific survival according to age groups. A P value of $<.05$ was considered statistically significant. **Results:** We did not find an association between groups aged <70 and >70 years old and preoperatively clinical or histopathological characteristics. Kaplan-Meier analysis was found no statistical significance between the 2 age groups in terms of intravesical or extravesical recurrence ($P = .09$ and $P = .57$). Overall survival ($P = .0001$) and cancer-specific survival ($P = .0001$) have been found to be statistically significantly associated with age as independent predictors (confounding factors: gender, tumor size, tumor side, clinical T stage, localization, preoperative hydronephrosis, tumor localization, type of surgery, multifocality of the tumor, pathological grade, lymphovascular invasion, concomitant CIS, lymph node status, necrosis, or history of previous bladder cancer). **Conclusion:** This research confirms that patients aged 70 and above who undergo radical nephroureterectomy may have worse outcomes compared to younger patients, older patients needing an improved care and management of UTUC to improve their outcomes in the setting of an increase in this aged population group.

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Introduction

Upper tract urothelial carcinoma (UTUC) is a rare malignancy arising from the transitional cell lining of the renal pelvis and ureter.[1] It accounts for only 5% to 10% of all urothelial carcinomas[2] and has an annual incidence of 1 to 2 cases per 100,000 people in the general population.[3] UTUC is more commonly diagnosed in males than females and typically presents in the sixth or seventh decade of life.[2] The prognosis of UTUC is generally poor, with a 5-year survival rate ranging from 30% to 60% and a high recurrence rate, particularly in patients with high-grade tumors[4] or carcinoma in situ (CIS).[5] The prognosis is also influenced by the stage and location of the tumor, with a worse outcome associated with advanced stage and involvement of the renal pelvis. Furthermore, lymph node involvement is a strong predictor of survival, with a 5-year survival rate in the range of 20% to 30% in patients with positive lymph nodes at surgery.[3,4] Despite optimal treatment based on radical nephroureterectomy (RNU) with bladder cuff excision (BCE) and lymph node dissection,[4,5] with or without adjuvant chemotherapy,[6] the rates of intravesical and extravesical recurrence range from 9% to 73% and 8% to 53%, respectively.[7-10] While predictive factors for intravesical and extravesical recurrence after RNU for UTUC have been extensively studied, only a few have been validated and incorporated in clinical practice.[1] Several studies have identified tumor stage, grade, size, multifocality, lymphovascular invasion, and variant histology as important predictors of intravesical recurrence.[9,10] Other studies have also suggested that the presence of CIS, positive surgical margins, and delayed ureteral stump recurrence are associated with an increased risk of intravesical recurrence.[10,11] Additionally, some studies have investigated the role of molecular markers such as Ki-67 and P53 in predicting intravesical recurrence, but their clinical usefulness remains to be established.[12,13] Predictive factors of extravesical recurrence of urothelial cancer after nephrectomy for UTUC are less studied compared to those for intravesical recurrence.[14] Some of the identified risk factors include advanced tumor stage, positive surgical margins, lymph node involvement, high tumor grade, and tumor size >2 cm.[15,16] Additionally, the presence of CIS has been shown to be a significant predictor of both intravesical and extravesical recurrence.[17-20] Finally, lymph node involvement, high tumor grade and stage, lymphovascular invasion, and positive surgical margins are all prognostic factors associated with worse outcomes after RNU for UTUC.[18-20] Molecular markers, such as KI-67 and P53 expression, have also been found to be predictive of overall survival, respectively.[21-23]

In a multi-institutional study was showed that patients with advanced age >70 years were less likely to undergo lymphadenectomy and to receive adjuvant chemotherapy. Even more, in multivariable analyses, the authors showed that being older was associated with decrease overall survival (OS; cutoff >60 years) and cancer-specific survival (CSS; cutoff >80 years).[9] Nevertheless, it seems that when taking into consideration the Eastern Cooperative Oncology Group (ECOG) performance status age is an independent predictor only for OS.[24] However, until now there has been no cutoff recommendation in the European guidelines regarding age[1] as it is in respect to nonmuscle invasive bladder cancer (NMIBC), where a cutoff of 70 years is recommended to be used.[25]

In this study, we analyzed a large multi-institutional dataset of UTUC patients undergoing RNU for localized disease. Our main objective was to investigate commonly available factors, such as clinical and pathological variables, that are predictive of recurrence and survival in UTUC patient population at high risk of death and recurrence, with an emphasis on the effects of age (using a cutoff of 70 years as for urothelial carcinoma of the bladder) on survival outcomes.

Table 1 Association of Age With Clinicopathological Features

Variable	Patients No./(%)	Age <70 Years No./(%)	Age >70 Years No./(%)	*P* Value
Gender Male	543 (70)	261 (69.6)	282 (70.3)	.82
Female	233 (30)	114 (30.4)	119 (29.7)	
ECOG 0	396 (51)	234 (62.4)	162 (40.4)	**.001**
1	278 (35.8)	119 (31.8)	159 (39.6)	
2	86 (11.1)	20 (5.3)	66 (16.5)	
3	16 (2.1)	2 (0.5)	14 (3.5)	
Smoking status No	339 (43.7)	155 (41.3)	184 (45.9)	**.038**
Yes	286 (36.9)	133 (35.5)	153 (38.1)	
Former	151 (19.4)	87 (23.2)	64 (16)	
Tumor size <2 cm	184 (23.7)	91 (24.3)	93 (23.2)	.72
>2 cm	592 (76.3)	284 (75.7)	308 (76.8)	
Tumor side Right	387 (49.9)	174 (46.4)	213 (53.1)	.17
Left	383 (49.3)	198 (52.8)	185 (46.1)	
Both	6 (0.8)	3 (0.8)	3 (0.8)	
Clinical stage Ta	102 (13.2)	51 (13.6)	51 (12.7)	.06
Tis	5 (0.6)	4 (1.1)	1 (0.3)	
T1	324 (41.7)	161 (42.9)	163 (40.7)	
T2	216 (27.9)	106 (28.3)	110 (24.4)	
T3	105 (13.5)	38 (10.1)	67 (16.7)	
T4	24 (3.1)	15 (4)	9 (2.2)	
Hydronephrosis No	381 (49.1)	197 (52.5)	184 (45.9)	.06
Yes	395 (50.9)	178 (47.5)	217 (54.1)	
Localization Kidney	351 (45.2)	175 (46.7)	176 (43.9)	.64
Ureter	260 (33.5)	125 (33.3)	135 (33.7)	
Both	165 (21.3)	75 (20)	90 (22.4)	
Multifocality No	617 (79.5)	297 (79.2)	320 (79.8)	.83
Yes	159 (20.5)	78 (20.8)	81 (20.2)	
Type of surgery Open	440 (56.7)	213 (56.8)	227 (46.6)	.83
Laparoscopic	308 (39.7)	147 (39.2)	161 (40.2)	
Robotic	28 (3.6)	15 (4)	13 (3.2)	
Pathological stage Ta	121 (15.6)	64 (17.1)	57 (14.2)	**.022**
Tis	14 (1.8)	6 (1.6)	8 (2)	
T1	184 (23.7)	100 (26.6)	84 (20.9)	
T2	184 (23.7)	13 (24.8)	91 (22.7)	
T3	234 (30.2)	91 (24.3)	143 (35.7)	
T4	39 (5)	21 (5.6)	18 (4.5)	
Grade G1	44 (5.7)	25 (6.7)	19 (4.7)	.27
G2	640 (82.4)	311 (82.9)	329 (82)	
G3	92 (11.9)	39 (10.4)	53 (13.3)	
PSM	61 (7.9)	22 (5.9)	39 (9.7)	**.046**
LVI	136 (17.5)	59 (15.7)	77 (19.2)	.2
Concomitant CIS	102 (13.1)	47 (12.5)	55 (13.7)	.62
Sessile tumor architecture	99 (12.8)	51 (13.6)	48 (12)	.49
Necrosis	142 (18.3)	61 (16.3)	81 (20.2)	.15
Lymph node status Negative	284 (36.6)	148 (39.5)	136 (33.9)	.24
Positive	91 (11.7)	44 (11.7)	47 (11.7)	
Nx	401 (51.7)	183 (48.8)	218 (54.4)	
Previous bladder cancer, Yes	252 (32.5)	118 (31.5)	134 (33.4)	.56

Table 1 (*continued*)

Variable	Patients No./(%)	Age <70 Years No./(%)	Age >70 Years No./(%)	*P* Value
Adjuvant chemotherapy	106 (13.7)	66 (17.6)	40 (10)	**.002**
Intravesical recurrence	246 (31.7)	117 (31.2)	129 (31.2)	.77
Extravesical-recurrence	151 (19.5)	74 (19.7)	77 (19.2)	.85
Deaths	174 (22.4)	59 (15.7)	115 (28.7)	**.0001**
Death due to UTUC	151 (19.5)	54 (14.4)	97 (24.2)	**.001**

Abbreviations: LVI = lymphovascular invasion; PSM = positive surgical margins; UTUC = upper tract urothelial carcinoma.
Bold *P* values are statistical significant, No: number, yrs: years; Nx: not assessed.

Patients and Methods

Patients

We have reviewed a multicenter share database of 1387 patients with clinically nonmetastatic UTUC treated with RNU and histologically confirmed, at 21 academic hospital centers between 2005 and 2021. Patients were included in the study only if complete records for surgical, clinical (gender, age, tumor characteristics, and surgical treatment variables), pathological, and oncological outcomes of interest were available. Criteria for exclusion consist in lack of complete data, metastatic disease, other neoplasia, patient's refusal to enter the study, and lost to follow-up. In total 611 patients were excluded due to not meeting the inclusion criteria. The final cohort included 776 UTUC patients treated with RNU at 21 academic centers between 2005 and 2020. All patients signed a written informed consent.

Intervention and Follow-Up

RNU was performed with open, laparoscopic, or robotic approach at the discretion of the surgeon. BCE technique was not standardized, and lymph node dissection (LND) was performed at the discretion of the surgeon or when enlarged lymph nodes were present on staging imaging. All RNU specimens were analyzed by experienced uropathologists at each center and were staged based on the TNM classification, while tumor grade was based on the 2004/2016 World Health Organization classification. Follow-up was not standardized but was generally conducted according to international guidelines at that time. Follow-up usually consisted of physical examination, urinary cytology, abdomen computed tomography scan or abdomen magnetic resonance imaging, and chest radiography every 3 to 6 months during the first 12 months following RNU, every 6 months between the second and the fifth year after surgery, and yearly thereafter. Bladder cystoscopy was generally performed after 3 and 9 months from surgery and yearly thereafter.

Statistical Analysis

Categorical variables were reported as absolute numbers and percentages. Continuous variables were reported as medians and interquartile ranges (IQRs). χ^2 and Kruskal-Wallis tests were performed for categorical and continuous variables, respectively, to compare the populations. Kaplan-Meier curves were built to evaluate differences in overall survival (OS) rates between patients according to age category (cutoff 70 years as previously used in other urological malignancies[26] including urothelial carcinoma of the bladder[27]). The log-rank test was used to determine the statistical difference between groups. Univariable and multivariable Cox regression models were built to evaluate the independent prognosticators for intravesical recurrence, extravesical recurrence, overall survival, and CSS. Data were analyzed using STATA 11 (Stata Corp., College Station, TX), and a *P* value of <.05 was considered statistically significant.

Results

Patient's Characteristics

In total 776 patients were included in the study, of this 401 (53.7%) were aged >70 years at the time of the RNU. We analyzed associations with the clinic and pathological characteristics according age at the time of intervention and the groups of patients <70 years and >70 years did not differ in terms of gender, tumor size, tumor side, clinical T stage, localization, preoperative hydronephrosis, tumor localization, type of surgery, multifocality of the tumor, pathological grade, lymphovascular invasion, concomitant CIS, lymph node status, necrosis, or history of previous bladder cancer (BCa). There was a statistical significant difference between cohorts regarding: ECOG status with 20% of patients with ECOG 2 and 3 in the >70 years cohort compared to 6% in the <70 years cohort, $P = .001$; smoking status with more smokers in the >70 years. cohort, $P = .038$; pathological T stage with 40% of patients having T3 and T4 stage in the elderly cohort compared to 30% in younger patients, $P = .022$; positive surgical margins (PSM) up to 10% compared to 5.9%, $P = .046$ and less patients received adjuvant chemotherapy in the elderly cohort (10% vs. 17.6%, $P = .002$).

In terms of oncological outcomes there was no difference in intravesical recurrence and extravesical recurrence percentages, but more deaths (115/28.7% vs. 59/15.7%, $P = .0001$) and cancer-specific deaths (97/24.4% vs. 54/14.4%, $P = .001$) were reported in the >70 years cohort (Table 1).

Intravesical Recurrence After RNU

In a pre-RNU multivariable model age >70 years (HR 1.36, 95% CI 1.04-1.78, $P = .021$), CIS (HR 3.25, 95% CI 1.11-9.55, $P = .031$), previous BCa (HR 1.56, 95% CI 1.19-2.04, $P = .001$), and multifocality (HR 1.47, 95% CI 1.06-2.02, $P = .018$) were found predictive factors for intravesical recurrence (Table 2). However, in Kaplan-Meier analysis was found no statistical significance between groups in terms of intravesical recurrence, $P = .09$ (Figure 1a). The mean time to intravesical recurrence was

Table 2 Multivariable Presurgery Model to Predict Risk of Intravesical Recurrence of Upper Tract Urothelial Carcinoma

Variable	HR	95% CI	*P* Value
Gender male vs. female	0.9	0.66-1.21	.49
Age <70 vs. >70 years	1.36	1.04-1.78	**.021**
ECOG continuous	0.83	0.68-1.01	.064
Smoking status No		Ref.	
Yes	1.08	0.81-1.44	.57
Former	0.98	0.68-1.4	.91
Tumor size <2 cm vs. >2 cm	0.84	0.63-1.12	.24
Tumor side Right		Ref.	
Left	1.28	0.99-1.65	.056
Both	0.38	0.05-2.82	.31
Clinical stage Ta		Ref.	
Tis	3.25	1.11-9.55	**.031**
T1	1.13	0.77-1.66	.52
T2	0.73	0.47-1.14	.17
T3	0.46	0.25-0.85	**.014**
T4	0.59	0.2-1.69	.32
Hydronephrosis no vs. yes	1.15	0.88-1.52	.29
Localization Kidney		Ref.	
Ureter	0.93	0.67-1.3	.70
Both	1.01	0.7-1.46	.92
Multifocality no vs. yes	1.47	1.06-2.02	**.018**
Previous Bladder cancer no vs. yes	1.56	1.19-2.04	**.001**
Harrell's C index		**65.69**	

Abbreviations: CI = confidence interval; HR = hazard ratio; yrs = years.
Bold values represents statistically significant items.

23 months (SD 26.5). Mean time to intravesical recurrence 27.2 months (SD 30.2) in patients aged <70 years and 19.1 months (SD 21.8) in those aged >70 years, $P < .0001$.

Extravesical Recurrence After RNU

In a multivariable model age was not found to be associated with extravesical recurrence and also in the Kaplan-Meier survival analysis (Figure 1b). Independent predictive factors for extravesical recurrence after RNU were tumor size (HR 0.54 95%CI 0.35-0.84, $P = .007$), previous BCa (HR 1.69, 95% CI 1.18-2.42, $P = .004$), pathological a higher T stage, a higher grade (G2 or G3) (HR 1.73, 95% CI 1.03-2.91, $P = .0001$), PSMs (HR 1.65, 95% CI 1-2.71, $P = .046$), LVI (HR 1.55, 95% CI 1-2.4, $P = .047$) and positive lymph node status (HR 2.3, 95% CI 1.34-3.92, $P = .002$). The multivariable model had a C-index of 81.3% (Table 3). The mean time to extravesical recurrence was 28.3 months (SD 29.8). Mean time to extravesical recurrence 33.2 months (SD 34.3) in patients aged <70 years and 23.6 months (SD 21.2) in those aged >70 years, $P < .0001$.

Overall Survival After RNU

After a mean follow-up of 31 months, range 1 to 148 months, in Kaplan-Meier survival analysis age was found statistically significantly associated with OS, $P = .0001$ (Figure 1c); mean time to death 36.6 months (SD 34.6) in patients aged <70 years and 25.8 months (SD 24.9) in those aged >70 years, $P < .0001$. Furthermore, age was an independent predictor for worse OS (HR 2.18, 95% CI 1.52-3.12, $P = .0001$), together with a previous history of BCa (HR 1.42, 95% CI 1.01-2.01, $P = .04$), higher pathological T stage, higher histological grade and pathologically positive lymph nodes status (HR 1.88, 95% CI 1.13-3.12, $P = .014$). The model had a C-index of 77.06 (Table 4).

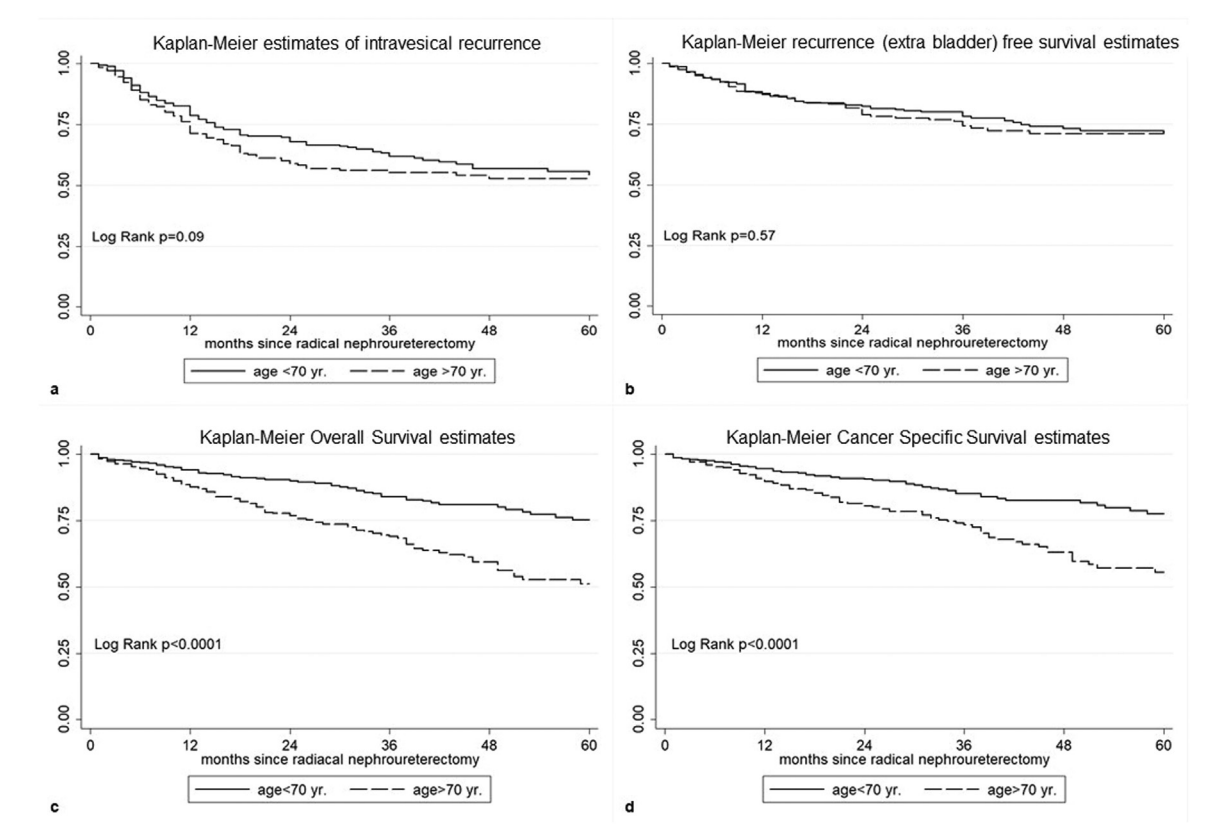
Cancer-Specific Death After RNU

In Kaplan-Meier survival analysis, age was statistically significantly associated with CSS, $P = .0001$ (Figure 1d). Furthermore, age was an independent predictor for worse CSS (HR 2.31, 95% CI 1.57-3.38, $P = .0001$), together with tumor size (HR 0.64, 95% CI 0.42-0.98, $P = .041$), previous history of BCa (HR 1.67, 95% CI 1.16-2.4, $P = .005$), higher pathological T stage, higher histological grade and pathologically positive lymph nodes status (HR 2.1, 95% CI 1.24-3.56, $P = .006$). The model had a C-index of 79.26 (Table 5).

Discussion

In this study, we analyzed the clinic and pathological characteristics of 776 patients who underwent RNU, with a focus on the differences between patients aged 70-years old and above and those under 70-years old. Significant differences in terms of ECOG performance status, smoking status, pathological T stage, positive surgical margins (PSM), and adjuvant chemotherapy received were found. Older patients were more likely to be smokers and they

Figure 1 Kaplan-Meier survival function and intravesical recurrence estimates in upper tract urothelial carcinoma patients after radical nephroureterectomy according to age; (a) Kaplan-Meier analysis comparing age <70 years and >70 years regarding intravesical recurrence; (b) Kaplan-Meier analysis comparing age <70 years and >70 years regarding extravesical recurrence free survival; (c) Kaplan-Meier analysis comparing age <70 years and >70 years regarding overall survival; (d) Kaplan-Meier analysis comparing age <70 years and >70 years regarding cancer-specific survival.



had a worse ECOG performance status and were less likely to have received adjuvant chemotherapy, which is consistent with routine clinical practice. No difference in intravesical recurrence and extravesical recurrence percentages between the 2 groups, although patients aged 70 and above showed a significantly worse overall (HR = 2.18; 95%CI = 1.52-3.12; $P < .01$) and CSS (HR = 2.31; 95%CI = 1.57-3.38; $P < .01$) compared to younger patients. However, elderly patients had a more advanced stage at diagnosis with 10% more patients expressing a T3 or T4 disease compared to the younger counterparts; more had PSM 9.7% vs. 5.9% and less received adjuvant treatment 10% vs. 17.6%, because up to 20% had an ECOG score of 2 and 3 compared to 6% in the younger fellows. Despite this, we noticed that this particular feature of elderly patients lead to worse survival and this requires maybe an intensive follow-up based on this age cutoff.

The association between age and clinical outcomes in UTUC patients has been investigated in several studies[9,24,28-30] (25-28). Shariat et al.[9] found an association between advanced age and shorter OS and CSS ($P \leq .006$), but the predictive accuracy of a base model has not been improved for recurrence, OS or CSS by adding age. Margulis et al.[4] identified that patient age ($P = .001$), is independently associated with CSS. Lately, a systematic review by Pallauf et al.[31] identified age as the most reliable predictive factor for CSS. One study by Chromecki et al.[24] confirmed that higher patient age at RNU is associated with worse clinical outcomes after surgery but ECOG performance has modified this association. Kim et al.[32] aimed to assess the prognostic significance of age, in UTUC patients treated with RNU through a systematic review and meta-analysis. The authors found that advanced age was significantly associated with worse progression free-survival (PFS) [HR 1.01] and OS (HR 1.05). For CSS age is also a significant predictor (HR 1.02). It seems that age is a demographic predictor of survival in UTUC.

Taken together, these studies consistently suggest that older age is associated with worse prognostic outcomes in patients with UTUC who undergo RNU, which is consistent with the results reported here. The use of age along with other commonly available factors with significant predictive value in our study cohort, including staging, grade and history of previous bladder cancer allowed achieving a C-index of 0.78 and of 0.79 for overall and CSS. These results compare favorably with those reported in the literature. Several nomograms have been developed to assess the disease recurrence, OS

Table 3 Multivariable Model to Predict Risk of Recurrence (Extra Bladder) of Upper Tract Urothelial Carcinoma

Variable	HR	95% CI	*P* Value
Gender male vs. female	0.91	0.6-1.38	.66
Age <70 vs. >70 years	0.88	0.6-1.28	.51
ECOG continuous	1.19	0.94-1.5	.14
Smoking status No		Ref.	
Yes	1.48	0.99-2.23	.56
Former	1.58	0.95-2.63	.07
Tumor size <2 cm vs. >2 cm	0.54	0.35-0.84	**.007**
Tumor side Right		Ref.	
Left	1.25	0.88-1.77	.2
Both	7.28	.	.
Hydronephrosis no vs. yes	1.42	0.98-2.07	.06
Localization Kidney		Ref.	
Ureter	0.88	0.54-1.43	.61
Both	1.39	0.87-2.22	.15
Multifocality no vs. yes	0.87	0.55-1.36	.54
Previous Bladder cancer no vs. yes	1.69	1.18-2.42	**.004**
Stage Ta		Ref.	
Tis	3.09	0.52-18.18	.21
T1	3.43	1.18-9.97	**.02**
T2	2.98	1-8.83	**.049**
T3	7.24	2.54-20.6	**.0001**
T4	11.3	3.49-36.6	**.0001**
Grade G1		Ref.	
G2	1.73	1.03-2.91	**.0001**
G3	3.35	.	**.0001**
Surgical Positive margins no vs. yes	1.65	1-2.71	**.046**
Lymphovascular invasion no vs. yes	1.55	1-2.4	**.047**
Concomitant CIS no vs. yes	1.53	0.98-2.37	.056
Tumor necrosis no vs. yes	1.39	0.9-2.15	.13
Tumor architecture	0.68	0.4-1.16	.16
Lymph node status Negative		Ref.	
Positive	2.3	1.34-3.92	**.002**
Nx	1.26	0.82-1.95	.28
Type of surgery Open		Ref.	
Laparoscopic	0.71	0.48-1.04	.08
Robotic	0.3	0.04-2.25	.24
Harrell's C index		**81.32**	

Abbreviations: CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio; Nx = not assessed; yrs = years.
Bold values represents statistically significant items.

or CSS, such as Ehdaie et al.[33] that found that the final nomogram models comprising of preoperative lymph node status, pathologic grade performed as previously published. The prediction of intravesical recurrence has been assessed through a nomogram model by Xylinas et al.[34] having good accuracy for predicting intravesical recurrence in the external validation cohort (C-index of 0.69), as well as the study of Freifeld et al.[35] achieving a C-index of 0.71, or the Hou et al.[36] nomogram achieving 1-, 3-, and 5-year predictive accuracies of 0.74, 0.70, and 0.71, respectively. In comparison, the prognostic model used in this study had a C-index of 0.78 to 0.79, indicating similar or slightly better discriminative ability than existing models for UTUC. However, direct comparisons between models are difficult due to differences in patient populations, inclusion criteria, and outcome measures. Taking into consideration that studies performed to assess oncological outcomes used age as a continuous variable[33,34] and some used it as a noncontinuous variable[35,37] but do not provide consistency of which aged category of patients influence OS and CSS. Zeng et al.[38] categorized patients as below 65 and over/equal to 65-years old with no statistically significance achieved for CSS (HR 1.46 95% CI 0.96−2.24 $P = .08$). Wu et al.[37] developed the decade's categorization <60, 60 to 69, and 70+ achieving statistical significance both for OS and CSS in multivariate analysis ($P < .001$). Also Qi et al.[39] identified significant association between different age groups (40-59, 60-79,

Table 4 Multivariable Model to Risk of Death of Any Causes After Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma

Variable	HR	95% CI	*P* Value
Gender male vs. female	1.06	0.74-1.51	.73
Age <70 vs. >70 years	2.18	1.52-3.12	**.0001**
ECOG continuous	1.15	0.92-1.43	.2
Smoking status No		Ref.	
Yes	0.99	0.68-1.44	.96
Former	1.2	0.76-1.88	.41
Tumor size <2 cm vs. >2 cm	0.77	0.51-1.15	.2
Tumor side Right		Ref.	
Left	1.09	0.79-1.5	.59
Both	2.99	.	.
Hydronephrosis no vs. yes	1.35	0.96-1.91	.08
Localization Kidney		Ref.	
Ureter	0.9	0.58-1.4	.65
Both	1.22	0.79-1.86	.35
Multifocality no vs. yes	0.9	0.58-1.39	.65
Previous Bladder cancer no vs. yes	1.42	1.01-2.01	**.04**
Stage Ta		Ref.	
Tis	0.76	0.09-6.39	.8
T1	1.94	0.88-4.28	.098
T2	1.78	0.78-4.06	.16
T3	4.13	1.92-8.88	**.0001**
T4	6.46	2.56-16.29	**.0001**
Grade G1		Ref.	
G2	3.27	2.09-5.11	**.0001**
G3	5.17	.	.
Surgical Positive margins no vs. yes	1.18	0.71-1.98	.5
Lymphovascular invasion no vs. yes	1.33	0.88-2.01	.17
Concomitant CIS no vs. yes	1.3	0.85-2	.22
Tumor necrosis no vs. yes	0.96	0.64-1.44	.85
Tumor architecture	1.08	0.66-1.78	.73
Lymph node status Negative		Ref.	
Positive	1.88	1.13-3.12	**.014**
Nx	1.28	0.86-1.9	.22
Type of surgery Open		Ref.	
Laparoscopic	0.79	0.55-1.13	.2
Robotic	1.15	0.41-3.24	.78
Harrell's C index		**77.06**	

Abbreviations: CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio; Nx = not assessed; yrs = years.
Bold values represents statistically significant items.

and ≥80) and OS and CSS ($P = .0001$) in multivariate analysis. Zhang et al.[40] spliced the age groups as <65 and ≥65 years and also achieved significant results in the association of age and OS and CSS ($P < .001$) in multivariate analysis. As we know to date categorizing patients as below or above 70 years of age has not been assessed in the literature. Results from most of the studies provide insights that advanced age is an independent predictor for OS and CSS. Especially, patients in the 8 decade have poor outcomes due to advanced age. It is worth mentioning that advancement in health care and the rise in life expectancy it is necessary to search in detail also for the impact of lower age categories that can influence oncological outcomes.

We recognize that this study has a number of limitations, including the heterogeneous follow-up duration and follow-up protocols, the nonstandardized surgical techniques as well as the study design, with no planned sample size, missing data. It is well known that there are differences in recurrence, CSS and OS for different groups of patients and in advanced age and the increasing number of patients in category >70-years old is pushing research to identify properly the risk factors for recurrence, CSS and OS. Our results point to the fact that in this advanced age category of patients that are going to rise in the coming years, in which the management is challenging and will have to be adapted. Nevertheless, we believe that our study had merit to explore commonly available factors in

Table 5 Multivariable Model to Risk of Cancer-Specific Death After Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma

Variable	HR	95% CI	*P* Value
Gender male vs. female	0.97	0.65-1.44	.9
Age <70 vs. >70 years	2.31	1.57-3.38	**.0001**
ECOG continuous	0.98	0.77-1.25	.89
Smoking status No		Ref.	
Yes	0.92	0.61-1.38	.69
Former	1.42	0.89-2.26	.13
Tumor size <2 cm vs. >2 cm	0.64	0.42-0.98	**.041**
Tumor side Right		Ref.	
Left	1.08	0.76-1.53	.63
Both	5.65	.	.
Hydronephrosis no vs. yes	1.38	0.95-2	.088
Localization Kidney		Ref.	
Ureter	1.06	0.66-1.7	.79
Both	1.12	0.7-1.79	.62
Multifocality no vs. yes	1.04	0.66-1.63	.86
Previous Bladder cancer no vs. yes	1.67	1.16-2.4	**.005**
Stage Ta		Ref.	
Tis	0.82	0.09-7.24	.86
T1	2.27	0.92-5.56	.073
T2	1.55	0.59-4.07	.36
T3	5.11	2.13-12.2	**.0001**
T4	9.52	3.41-26.5	**.0001**
Grade G1		Ref.	
G2	1.48	2.38-9.15	**.0001**
G3	2.2	.	.
Surgical Positive margins no vs. yes	1.32	0.78-2.23	.29
Lymphovascular invasion no vs. yes	1.27	0.78-2.23	.27
Concomitant CIS no vs. yes	1.39	0.89-2.18	.13
Tumor necrosis no vs. yes	1.11	0.72-1.71	.61
Tumor architecture	0.96	0.56-1.67	.9
Lymph node status Negative		Ref.	
Positive	2.1	1.24-3.56	**.006**
Nx	1.11	0.72-1.71	.61
Type of surgery Open			
Laparoscopic	0.8	0.54-1.18	.27
Robotic	1.34	0.47-3.83	.57
Harrell's C index		**79.26**	

Abbreviations: CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio; Nx = not assessed; yrs: years.
Bold values represents statistically significant items.

routine clinical practice in a large dataset of UTUC patients, thus providing results that can assist the decision-making process in this setting.

Conclusion

We can state that the study confirms that patients aged 70 and above who undergo RNU may have worse outcomes compared to younger patients, despite there being no significant differences in terms of most clinic and pathological characteristics. Therefore, older patients may require more attention and care in the management of urothelial carcinoma to improve their outcomes. The study also highlights the importance of considering multiple factors, such as age, tumor size, and pathological characteristics, in predicting recurrence and survival after RNU. Further validation of the prognostic model presented here in larger and diverse patient cohorts is needed to confirm its clinical utility.

Clinical Practice Points

- The poor prognosis of upper tract urothelial carcinoma must impose the best possible management in elderly patients.
- Advanced age (>70 years) impacts both overall survival and cancer-specific survival.

- Patients over 70 years of age at the time of diagnosis tend to have more aggressive disease with consecutive impact on survival outcomes.
- Personalized strategies should be discussed with patients at time of diagnosis and at every game-changer point during the follow-up.
- Elderly patients should be closely followed for disease recurrence to provide the best of care.

CRediT authorship contribution statement

Matteo Ferro and Sever Chiujdea: conceptualization, methodology, formal analysis, investigation, data curation, writing-original draft, visualization, writing – review & editing, project administration, supervision; **Mihai Dorin Vartolomei:** conceptualization, methodology, data collection, writing-original draft, statistical analysis, writing – review & editing; **Pierluigi Bove:** data collection, methodology, writing-original draft; writing – review & editing; **Angelo Porreca** data collection, methodology, writing – review & editing; Gian Maria Busetto**:** data collection, methodology, writing – review & editing; **Francesco del Giudice:** data collection, methodology, writing – review & editing; **Alessandro Antonelli:** data collection, methodology, writing – review & editing; **Nazario Foschi:** data collection, methodology, writing – review & editing; **Marco Racioppi:** data collection, methodology, writing – review & editing; **Riccardo Autorino:** data collection, methodology, writing – review & editing; **Francesco Chiancone:** data collection, methodology, writing – review & editing; Nicola Longo**:** data collection, methodology, writing – review & editing; **Biagio Barone:** data collection, methodology, writing – review & editing; **Felice Crocetto:** data collection, methodology, writing – review & editing; **Gennaro Musi:** data collection, methodology, writing – review & editing; **Stefano Luzzago:** data collection, methodology, writing – review & editing; **Mattia Luca Piccinelli:** data collection, methodology, writing – review & editing; **Francesco Alessandro Mistretta:** data collection, methodology, writing – review & editing; **Ottavio de Cobelli:** data collection, methodology, writing – review & editing; **Octavian Sabin Tataru:** data collection, methodology, writing-original draft, formal analysis, data curation, writing-original draft, writing – review & editing; **Rodolfo Hurle:** data collection, methodology, writing – review & editing; **Giovanni Liguori:** data collection, methodology, writing – review & editing; **Marco Borghesi:** data collection, methodology, writing – review & editing; **Alessandro Veccia:** data collection, methodology, writing – review & editing; **Francesco Greco:** data collection, methodology, writing – review & editing; **Luigi Schips:** data collection, methodology, writing – review & editing; **Michele Marchioni:** data collection, methodology, writing – review & editing; **Giuseppe Lucarelli:** data collection, methodology, writing – review & editing; **Daniele Dutto:** data collection, methodology, writing – review & editing; **Fulvia Colucci:** data collection, methodology, writing – review & editing; **Giorgio Ivan Russo:** data collection, methodology, writing – review & editing; **Arturo Lo Giudice:** data collection, methodology, writing – review & editing; **Emanuele Montanari:** data collection, methodology, writing – review & editing; **Luca Boeri:** data collection, methodology, writing – review & editing; **Giuseppe Simone:** data collection, methodology, writing – review & editing; **Matteo Rosazza:** data collection, methodology, writing – review & editing; **Simone Livoti:** data collection, methodology, writing – review & editing; **Paolo Gontero:** data collection, methodology, writing – review & editing; **Francesco Soria:** conceptualization, methodology, formal analysis, data collection, data curation, writing-original draft, writing – review & editing, project administration, supervision. All authors contributed to the drafting of the article and critical revision of scientific content, and approved the final article.

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References

1. Rouprêt M, Babjuk M, Burger M, et al. European Association of Urology guidelines on upper urinary tract urothelial carcinoma: 2020 update. *Eur Urol*. 2021;79:62–79. doi:10.1016/j.eururo.2020.05.042.
2. Soria F, Shariat SF, Lerner SP, et al. Epidemiology, diagnosis, preoperative evaluation and prognostic assessment of upper-tract urothelial carcinoma (UTUC). *World J Urol*. 2017;35:379–387. doi:10.1007/s00345-016-1928-x.
3. Lughezzani G, Jeldres C, Isbarn H, 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. doi:10.1016/j.ejca.2009.06.016.
4. Margulis V, Shariat SF, Matin SF, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. *Cancer*. 2009;115:1224–1233. doi:10.1002/cncr.24135.
5. 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;67:1122–1133. doi:10.1016/j.eururo.2014.11.035.
6. Birtle A, Johnson M, Chester J, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. *Lancet*. 2020;395:1268–1277. doi:10.1016/S0140-6736(20)30415-3.
7. Cutress ML, Stewart GD, Zakikhani P, Phipps S, Thomas BG, Tolley DA. Ureteroscopic and percutaneous management of upper tract urothelial carcinoma (UTUC): systematic review. *BJU Int*. 2012;110:614–628. doi:10.1111/j.1464-410X.2012.11068.x.
8. Yuan H, Chen X, Liu L, et al. Risk factors for intravesical recurrence after radical nephroureterectomy for upper tract urothelial carcinoma: a meta-analysis. 32. 2014:989–1002. Urol Oncol. doi:10.1016/j.urolonc.2014.01.022.
9. Shariat SF, Godoy G, Lotan Y, et al. Advanced patient age is associated with inferior cancer-specific survival after radical nephroureterectomy. *BJU Int*. 2010;105:1672–1677. doi:10.1111/j.1464-410X.2009.09072.x.
10. Kenigsberg AP, Meng X, Ghandour R, Margulis V. Oncologic outcomes of radical nephroureterectomy (RNU). *Transl Androl Urol*. 2020;9:1841–1852. doi:10.21037/tau.2019.12.29.
11. Rink M, Ehdaie B, Cha EK, et al. Stage-specific impact of tumor location on oncologic outcomes in patients with upper and lower tract urothelial carcinoma following radical surgery. *Eur Urol*. 2012;62:677–684. doi:10.1016/j.eururo.2012.02.018.
12. Shigeta K, Matsumoto K, Ogihara K, et al. The clinicopathological characteristics of muscle-invasive bladder recurrence in upper tract urothelial carcinoma. *Cancer Sci*. 2021;112:1084–1094. doi:10.1111/cas.14782.
13. Wu P, Liu S, Zhang W, et al. Low-level Ki-67 expression as an independent predictor of bladder tumour recurrence in patients with primary upper tract urothelial carcinoma after radical nephroureterectomy. *Jpn J Clin Oncol*. 2015;45:1175–1181. doi:10.1093/jjco/hyv139.
14. Peyronnet B, Seisen T, Dominguez-Escrig JL, et al. Oncological outcomes of laparoscopic nephroureterectomy versus open radical nephroureterectomy for upper tract urothelial carcinoma: an European Association of Urology guidelines systematic review. *Eur Urol Focus*. 2019;5:205–223. doi:10.1016/j.euf.2017.10.003.
15. Gust KM, Resch I, D'Andrea D, Shariat SF. Update on systemic treatment of upper tract urothelial carcinoma: a narrative review of the literature. *Transl Androl Urol*. 2021;10:4051–4061. doi:10.21037/tau-21-47.
16. Chung JH, Song W, Kang M, et al. Conditional intravesical recurrence-free survival rate after radical nephroureterectomy with bladder cuff excision for upper tract urothelial carcinoma. *Front Oncol*. 2021;11:730114. doi:10.3389/fonc.2021.730114.

17. Fang D, Xiong GY, Li XS, et al. Pattern and risk factors of intravesical recurrence after nephroureterectomy for upper tract urothelial carcinoma: a large Chinese center experience. *J Formos Med Assoc*. 2014;113:820–827. doi:10.1016/j.jfma.2013.11.004.
18. Xylinas E, Colin P, Audenet F, 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;31:61–68. doi:10.1007/s00345-012-0957-3.
19. Xylinas E, Rink M, Cha EK, et al. Impact of distal ureter management on oncologic outcomes following radical nephroureterectomy for upper tract urothelial carcinoma. *Eur Urol*. 2014;65:210–217. doi:10.1016/j.eururo.2012.04.052.
20. Youssef RF, Shariat SF, Lotan Y, et al. Prognostic effect of urinary bladder carcinoma in situ on clinical outcome of subsequent upper tract urothelial carcinoma. *Urology*. 2011;77:861–866. doi:10.1016/j.urology.2010.09.032.
21. Li Q, Bagrodia A, Cha EK, Coleman JA. Prognostic genetic signatures in upper tract urothelial carcinoma. *Curr Urol Rep*. 2016;17:12. doi:10.1007/s11934-015-0566-y.
22. Lughezzani G, Burger M, Margulis V, et al. Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. *Eur Urol*. 2012;62:100–114. doi:10.1016/j.eururo.2012.02.030.
23. Missaoui N, Bdioui A, Baccouche A, et al. Significance of p53, p27, Ki-67, E-cadherin, and HER2 expression in upper urinary tract urothelial carcinoma. *J Egypt Natl Canc Inst*. 2020;32:36. doi:10.1186/s43046-020-00047-z.
24. Chromecki TF, Ehdaie B, Novara G, et al. Chronological age is not an independent predictor of clinical outcomes after radical nephroureterectomy. *World J Urol*. 2011;29:473–480. doi:10.1007/s00345-011-0677-0.
25. Babjuk M, Burger M, Capoun O, et al. European Association of Urology guidelines on non-muscle-invasive bladder cancer (Ta, T1, and carcinoma in situ). *Eur Urol*. 2022;81:75–94. doi:10.1016/j.eururo.2021.08.010.
26. Vartolomei MD, Matei DV, Renne G, et al. Long-term oncologic and functional outcomes after robot-assisted partial nephrectomy in elderly patients. *Minerva Urol Nefrol*. 2019;71:31–37. doi:10.23736/S0393-2249.18.03006-0.
27. Ferro M, Chiujdea S, Musi G, et al. Impact of age on outcomes of patients with pure carcinoma in situ of the bladder: multi-institutional cohort analysis. *Clin Genitourin Cancer*. 2022;20:e166–e172. doi:10.1016/j.clgc.2021.12.005.
28. Yap SA, Schupp CW, Chamie K, Evans CP, Koppie TM. Effect of age on transitional cell carcinoma of the upper urinary tract: presentation, treatment, and outcomes. *Urology*. 2011;78:87–92. doi:10.1016/j.urology.2011.03.032.
29. Kobayashi H, Kikuchi E, Tanaka N, et al. Patient age was an independent predictor of cancer-specific survival in male patients with upper tract urothelial carcinoma treated by radical nephroureterectomy. *Jpn J Clin Oncol*. 2016;46:554–559. doi:10.1093/jjco/hyw028.
30. Chen IHA, Chang CH, Huang CP, et al. Factors predicting oncological outcomes of radical nephroureterectomy for upper tract urothelial carcinoma in Taiwan. *Front Oncol*. 2021;11:766576. doi:10.3389/fonc.2021.766576.
31. Pallauf M, König F, D'Andrea D, et al. A systematic review and meta-analysis of prognostic nomograms after UTUC surgery. *Front Oncol*. 2022;12:907975. doi:10.3389/fonc.2022.907975.
32. Kim HS, Jeong CW, Kwak C, Kim HH, Ku JH. Association between demographic factors and prognosis in urothelial carcinoma of the upper urinary tract: a systematic review and meta-analysis. *Oncotarget*. 2017;8:7464–7476. doi:10.18632/oncotarget.10708.
33. Ehdaie B, Shariat SF, Savage C, Coleman J, Dalbagni G, Postoperative nomogram for disease recurrence and cancer-specific death for upper tract urothelial carcinoma: comparison to American Joint Committee on Cancer staging classification. Urol J. 2014;11. Available at: https://pubmed.ncbi.nlm.nih.gov/24807756/ Accessed: March 18, 2023.
34. Xylinas E, Kluth L, Passoni N, et al. Prediction of intravesical recurrence after radical nephroureterectomy: development of a clinical decision-making tool. *Eur Urol*. 2014;65:650–658. doi:10.1016/j.eururo.2013.09.003.
35. Freifeld Y, Ghandour R, Singla N, et al. Preoperative predictive model and nomogram for disease recurrence following radical nephroureterectomy for high grade upper tract urothelial carcinoma. *Urol Oncol*. 2019;37:758–764. doi:10.1016/j.urolonc.2019.06.009.
36. Hou G, Zheng Y, Zhang L, et al. Development and validation of a prognostic nomogram for patients with intravesical recurrence after radical nephroureterectomy for non-metastatic upper tract urothelial carcinoma. *World J Urol*. 2020;38:1969–1975. doi:10.1007/s00345-019-02985-3.
37. Wu J, Chen S, Wu X, et al. Trends of incidence and prognosis of upper tract urothelial carcinoma. *Bosnian J Basic Med Sci*. 2021;21:607–619. doi:10.17305/bjbms.2020.5345.
38. Zeng S, Dai L, Yang J, et al. Development and external validation of a nomogram predicting prognosis of upper tract urothelial carcinoma after radical nephroureterectomy. *Urol Oncol*. 2019;37 290.e17-24. doi:10.1016/j.urolonc.2018.12.027.
39. Qi F, Wei X, Zheng Y, Sha Y, Lu Y, Li X. Nomograms to predict overall and cancer-specific survival in patients with upper tract urothelial carcinoma: a large population-based study. *Transl Androl Urol*. 2020;9:1177–1191. doi:10.21037/tau.2020.03.28.
40. Zhang GL, Zhou W. A model for the prediction of survival in patients with upper tract urothelial carcinoma after surgery. *Dose Response*. 2019;17:1559325819882872. doi:10.1177/1559325819882872.