EUROPEAN JOURNAL OF CANCER 45 (2009) 3291–3297

available at www.sciencedirect.com

journal homepage: www.ejconline.com

Nephroureterectomy and segmental ureterectomy in the treatment of invasive upper tract urothelial carcinoma: A population-based study of 2299 patients

Giovanni Lughezzani[a,b], *Claudio Jeldres*[a], *Hendrik Isbarn*[a,c], *Maxine Sun*[a], *Shahrokh F. Shariat*[a], *Ahmed Alasker*[a], *Daniel Pharand*[d], *Hugues Widmer*[d], *Philippe Arjane*[d], *Markus Graefen*[c], *Francesco Montorsi*[b], *Paul Perrotte*[d], *Pierre I. Karakiewicz*[a,d,*]

[a]*Cancer Prognosis and Health Outcomes Unit, University of Montreal Health Center, Montreal, QC, Canada, H2X 3J4*
[b]*Department of Urology, Vita-Salute San Raffaele University, Milan, Italy*
[c]*Martini-Clinic, Prostate Cancer Center Hamburg-Eppendorf, Hamburg, Germany*
[d]*Department of Urology, University of Montreal, Montreal, QC, Canada*

ARTICLE INFO

Article history:
Received 29 April 2009
Received in revised form 7 June 2009
Accepted 12 June 2009
Available online 15 July 2009

Keywords:
Carcinoma
Transitional cell
Renal pelvis
Ureter
TNM classification
Lymph node metastases
Cancer-specific mortality
Prognosis

ABSTRACT

Purpose: The TNM staging system represents the cornerstone for classifying patients with upper tract urothelial carcinoma (UTUC). We tested the prognostic impact of pT and pN stages on cancer-specific mortality (CSM) in a large population-based cohort of surgically treated patients with UTUC.

Methods: Our analyses relied on 2299 patients treated with nephroureterectomy (NU) or segmental ureterectomy (SU) for UTUC within nine Surveillance, Epidemiology and End Results registries between 1988 and 2004. CSM rates after surgery were graphically explored using Kaplan–Meier plots. Univariable and multivariable Cox regression models tested the effect of pT and pN stages on CSM, after adjusting for tumour grade, age, gender, primary tumour location, type and year of surgery.

Results: Five years after surgery, the overall CSM-free survival rate was 77.6%. The 5-year CSM-free survival rates of pT_1N_0 ($n = 739$), pT_2N_0 ($n = 422$), pT_3N_0 ($n = 691$), pT_4N_0 ($n = 190$) and any T N_{1-3} ($n = 257$) were, respectively, 93.5 versus 86.2 versus 64.5 versus 54.7 versus 35.0%. The 5-year CSM-free survival rates of $pT_{1-2}N_{1-3}$ ($n = 41$) and $pT_{3-4}N_{1-3}$ ($n = 216$) patients were, respectively, 68.9% and 28.7% ($p = 0.006$). In multivariable analyses, pT and pN stages ($p < 0.001$), as well as tumour grade ($p < 0.001$), achieved independent predictor status. Advanced age adversely affected CSM-free survival ($p = 0.001$). Conversely, tumour location, gender, year and type of surgery did not exert independent predictor status.

Conclusion: Durable cancer control can be expected in patients treated with NU or SU for organ-confined (pT_{1-2}) UTUC. Conversely, the presence of non-organ-confined (pT_{3-4}) disease and/or of nodal metastases (pN_{1-3}) exerts a profound detrimental effect on CSM-free survival.

* *Corresponding author:* Address: Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center (CHUM), 1058, rue St-Denis, Montréal, Québec, Canada, H2X 3J4. Tel.: +1 514 890 8000 35336; fax: +1 514 412 7363.
E-mail address: pierre.karakiewicz@umontreal.ca (P.I. Karakiewicz).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.06.016

1. Introduction

Upper tract urothelial carcinoma (UTUC) accounts for approximately 10% of all renal tumours and for 5–6% of urothelial tumours, with an incidence of 0.7/100.000 person-years.[1–3] The standard of care for invasive, non-metastatic UTUC is nephroureterectomy (NU).[1,4,5] Segmental ureterectomy (SU) may be performed in select patients.[1,3,6,7] Pathologic TNM staging represents the cornerstone for classifying the prognosis of patients with UTUC.[1,8,9] As in other disease models, patients with higher pT stages and/or the presence of nodal metastases are expected to have less favourable prognoses.[5,10–12]

However, to the best of our knowledge, only one large-scale study that relied on tertiary care centres data examined the ability of the TNM staging system to predict cancer-specific mortality (CSM) in patients with UTUC.[13] Therefore, we performed a population-based analysis that focused on the ability of pT and pN stages to stratify CSM risk after NU or SU in patients with UTUC.

2. Materials and methods

2.1. Study population

Patients diagnosed with UTUC (ICD-O-2 C65.9 and C66.9 codes) with available TNM stage,[9] who underwent either a NU or a SU between 1988 and 2004 were identified within nine Surveillance, Epidemiology and End Results (SEER) cancer registries ($n = 2547$).[14] These include the Atlanta, Detroit, San Francisco-Oakland and Seattle-Puget Sound metropolitan areas, as well as the states of Connecticut, Hawaii, Iowa, New Mexico and Utah. The characteristics of the SEER population are comparable to those of the general population of the United States.[14]

The cause of death was defined according to SEER-specific cause of death code (code 29020). For the purpose of this analysis, deaths from UTUC were coded as cancer-specific events. All other deaths were considered as other-cause mortality. Exclusions consisted of patients with distant metastases ($n = 112$) and of patients with unavailable tumour grade ($n = 136$). Finally, patients with unknown nodal status (pN_x; $n = 839$) were excluded from the survival analyses. The rationale for the exclusion of pN_x patients was based on the inability to know whether these individuals did or did not harbour lymph node metastases. In consequence, the pN stage could not have been validated in these individuals.

2.2. Statistical analysis

The Chi-square test and the student *t*-test were, respectively, used for comparison of means and proportions. CSM rates after NU or SU were graphically explored in Kaplan–Meier plots, after stratification according to pathologically determined T (pT_1N_0 versus pT_2N_0 versus pT_3N_0 versus pT_4N_0) and N stages (pN_0 versus $pN_{1–3}$), as was previously done for UC of the urinary bladder.[15] The log-rank test was used for comparison of CSM rates between different groups.

Univariable and multivariable Cox regression models addressed CSM after NU or SU. Covariates consisted of pathologically determined T stage (pT_1 versus pT_2 versus pT_3 versus pT_4), N stage (N_0 versus $N_{1–3}$), tumour grade (I versus II versus III versus IV), primary tumour location (ureter versus renal pelvis), type of surgery (NU with bladder cuff versus NU without bladder cuff versus SU), year of surgery, gender (male versus female) and age. Since pT and pN stages, as well as tumour grade, may contribute to a multiplicative increase in CSM rate, we tested three first-degree interactions between these variables. Specifically, multivariable interaction tests were performed between pT and pN stages, between T stage and tumour grade and between N stage and tumour grade. All reported *p*-values are two-sided and statistical significance was set at $\leqslant 0.05$. Statistical analyses were performed with S-Plus Professional software (MathSoft Inc., Seattle, Washington).

3. Results

The study population consisted of 2299 patients who underwent either a NU ($n = 2077$) or a SU ($n = 222$) for UTUC between 1988 and 2004 (Table 1). The majority were male (60.5%) and Caucasian (88.9%). Overall, 1424 (61.9%) and 875 (38.1%) patients had, respectively, renal pelvic and ureteral tumours. Stage pT_1 was recorded in 32.7% of patients at NU or SU. Conversely, stage pT_4 was recorded in the 11.0% of cases. The proportion of patients with nodal metastases was 11.2%. Most patients had grade III UTUC (41.8%), followed by grade II UTUC (33.8%). The majority of patients underwent a NU with bladder cuff removal (60.9%). NU without bladder cuff removal was performed in 29.4% of patients. Finally, 9.7% of patients underwent a SU.

The characteristics of excluded patients (pN_x; $n = 839$) are given in Table 1. Overall, significant differences between the study population (pN_0 and $pN_{1–3}$ patients) and patients with unknown nodal status (pN_x) were recorded relative to SEER registries ($p < 0.001$), race ($p = 0.01$), type and year of surgery ($p = 0.003$ and $p < 0.001$, respectively), tumour grade distribution ($p = 0.005$) and length of follow-up ($p < 0.001$).

When data were stratified according to primary tumour location (renal pelvis versus ureter), statistically significant differences were observed in pT stage distribution (Table 1). For example, 44.2% of patients with renal pelvic tumours had pT_3 disease versus 24.7% of patients with ureteral tumours ($p < 0.001$). Similar differences were recorded for pN stage distribution. Specifically, 13.1% of patients with renal pelvic tumours had nodal metastases versus 8.0% of patients with ureteral tumour ($p < 0.001$). Interestingly, a larger proportion of males had ureteral tumours (40.5%), relative to females (34.4%; $p = 0.003$). Finally, ureteral tumours were in general treated surgically at more advanced age than renal pelvic tumours ($p = 0.002$).

When data were stratified according to surgery type (NU with bladder cuff removal versus NU without bladder cuff removal versus SU), statistically significant differences were observed in pT stage distribution (54.0 versus 41.1 versus 75.7% of $pT_{1–2}$ UTUC; $p < 0.001$), in tumour grade distribution (57.9 versus 68.3 versus 53.6% of grades III–IV tumours; $p < 0.001$) and in gender distribution (58.4 versus 61.6 versus 70.7% of males; $p = 0.002$).

Table 1 – Characteristics of the study population of patients diagnosed with upper tract urothelial carcinoma who were treated with nephroureterectomy or segmental ureterectomy with (n = 2299) or without (n = 839) lymphadenectomy between 1988 and 2004. Patients with known nodal stage (pN_0 and $pN_{1–3}$) were stratified according to primary tumour location (renal pelvis versus ureter).

	Study population (known nodal stage; pN_0 and $pN_{1–3}$)	Renal pelvis UC	Ureteral UC	*p*-Value[a]	Excluded patients (unknown nodal stage; pN_x)	*p*-Value[b]
Number of patients	2299	1424	875	–	839	–
Age (years)						
Mean (Median)	71.0 (72.0)	70.5 (71.0)	71.9 (73.0)	0.002[d]	72.2 (73.0)	0.3[d]
Range	27–99	27–99	29–94		37–98	
Age group						
<49	82 (3.6%)	66 (4.6%)	16 (1.8%)	<0.001[c]	23 (2.7%)	0.1[c]
50–59	237 (10.3%)	163 (11.4%)	74 (8.5%)		69 (8.2%)	
60–69	600 (26.1%)	374 (26.3%)	226 (25.8%)		212 (25.3%)	
70–79	882 (38.4%)	517 (36.3%)	365 (41.7%)		326 (38.9%)	
>80	498 (21.7%)	304 (21.3%)	194 (22.2%)		209 (24.9%)	
Gender						
Male	1391 (60.5%)	828 (58.1%)	563 (64.3%)	0.003[c]	496 (59.1%)	0.5[c]
Female	908 (39.5%)	596 (41.9%)	312 (35.7%)		343 (40.9%)	
SEER registries						
San Francisco-Oakland	331 (14.4%)	251 (13.1%)	181 (14.8%)	0.06[c]	101 (12.0%)	<0.001[c]
Connecticut	372 (16.2%)	283 (14.8%)	197 (16.1%)		108 (12.9%)	
Metropolitan Detroit	453 (19.7%)	368 (19.2%)	214 (17.5%)		129 (15.4%)	
Hawaii	142 (6.2%)	91 (4.8%)	76 (6.2%)		25 (3.0%)	
Iowa	292 (12.7%)	278 (14.5%)	177 (14.4%)		163 (19.4%)	
New Mexico	122 (5.3%)	75 (3.9%)	63 (5.1%)		16 (1.9%)	
Seattle	364 (15.8%)	355 (18.6%)	193 (15.0%)		184 (21.9%)	
Utah	59 (2.6%)	85 (4.4%)	40 (3.3%)		66 (7.9%)	
Metropolitan Atlanta	164 (7.1%)	127 (6.6%)	84 (6.9%)		47 (5.6%)	
Race						
Caucasian	2004 (88.9%)	1255 (88.1%)	789 (90.2%)	0.1[c]	772 (92.0%)	0.01[c]
Other	255 (11.1%)	169 (11.9%)	86 (9.8%)		67 (8.0%)	
Type of surgery						
NU with bladder cuff	1400 (60.9%)	859 (60.3%)	541 (61.8%)	<0.001[c]	551 (65.7%)	0.003[c]
NU without bladder cuff	677 (29.4%)	565 (39.7%)	112 (12.8%)		196 (23.4%)	
Segmental ureterectomy	222 (9.7%)	0 (0)	222 (25.4%)		92 (11.0%)	
Year of surgery						
1988–1994	801 (34.8%)	512 (36.0%)	289 (33.0%)	0.03[c]	403 (48.0%)	<0.001[c]
1995–1999	655 (28.5%)	419 (29.4%)	236 (27.0%)		277 (33.0%)	
2000–2004	843 (36.7%)	493 (34.6%)	350 (40.0%)		159 (19.0%)	
pT stage						
pT_1	752 (32.7%)	428 (30.1%)	324 (37.0%)	<0.001[c]	258 (30.8%)	0.3[c]
pT_2	450 (19.6%)	196 (13.8%)	254 (29.0%)		149 (17.8%)	
pT_3	845 (36.7%)	629 (44.2%)	216 (24.7%)		332 (39.6%)	
pT_4	252(11.0%)	171 (12.0%)	81 (9.3%)		100 (11.9%)	
pN stage						
pN_0	2042 (88.8%)	1237 (86.9%)	805 (92.0%)	<0.001[c]	–	–
$pN_{1–3}$	257 (11.2%)	187 (13.1%)	70 (8.0%)		–	
Tumour grade						
Grade I	129(5.6%)	72 (5.1%)	57 (6.5%)	0.2[c]	48 (5.7%)	0.005[c]
Grade II	778 (33.8%)	467 (32.8%)	311 (35.5%)		286 (34.1%)	
Grade III	961 (41.8%)	612 (43.0%)	349 (39.9%)		391 (46.6%)	
Grade IV	431 (18.7%)	273 (19.2%)	158 (18.1%)		114 (13.6%)	
Follow-up (months) of censored patients						
Mean (Median)	55.9 (39.0)	61.3(45.0)	55.4 (39.0)	0.05[d]	67.1 (50.5)	<0.001[d]
Range	0.1–203	0.1–203	0.1–203		0.1–201	

UC: urothelial carcinoma; NU: nephroureterectomy and SEER: Surveillance, Epidemiology and End Results.
a Comparisons were made between patients with renal pelvis UC and patients with ureteral UC.
b Comparisons were made between patients with known nodal stage (pN_0 and $pN_{1–3}$) and patients with unknown nodal stage (pN_x).
c Chi-square test.
d Student *t*-test.

In the overall population, the CSM-free rates at 1, 3 and 5 years were, respectively, 91.0%, 80.6% and 77.6% (Fig. 1A). After stratification for pT and pN stages, the 5-year CSM-free survival rates were 93.5 versus 86.2 versus 64.5 versus 54.7

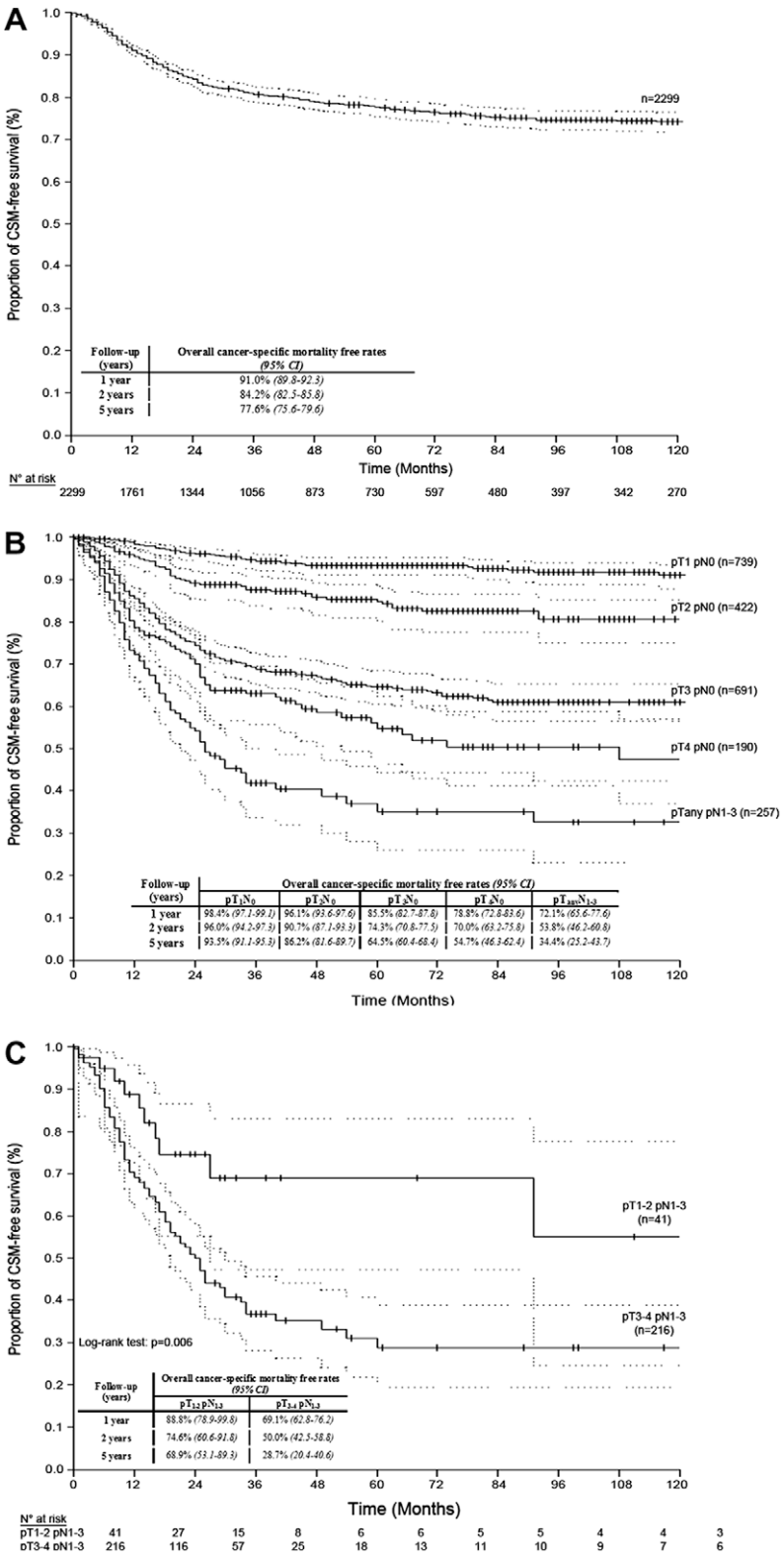

Fig. 1 – Kaplan–Meier plots assessing cancer-specific mortality (CSM) rates in surgically treated patients with upper tract urothelial carcinoma. (A) Illustrates the CSM-free survival in the entire cohort of 2299 patients. (B) Stratifies the CSM-free rates according to pT stages and the presence of nodal metastases ($pN_{1–3}$). Log-rank tests comparing CSM-free survival rates were all significant (all *p*-values <0.001, except for comparison between pT_3 and pT_4: $p = 0.02$). (C) Stratifies the CSM-free rates according to $pT_{1–2}$ versus $pT_{3–4}$ stage in patients with established nodal metastases ($pN_{1–3}$).

versus 35.0% for, respectively, pT_1N_0, pT_2N_0, pT_3N_0, pT_4N_0 and any pT $N_{1–3}$ patients (log-rank test: all *p*-values <0.001, except for the comparison between pT_3 and pT_4 tumours: $p = 0.3$) (Fig. 1B). Of all patients, 257 (11.3%) had nodal metastases

Table 2 – Univariable and multivariable analyses addressing cancer-specific mortality in the population of surgically treated patients with upper tract urothelial carcinoma with known T and N stages (n = 2299).

Variables	Patients with known T and N stages (n = 2299)	
	UVA analysis	MVA analysis
	HR; p-value	
T stage	$p < 0.001$	$p < 0.001$
pT_2 versus pT_1	2.35; <0.001	1.99; 0.001
pT_3 versus pT_1	6.09; <0.001	4.06; <0.001
pT_4 versus pT_1	8.27; <0.001	5.49; <0.001
N stage		
$pN_{1–3}$ versus pN_0	4.78; <0.001	2.59; <0.001
Tumour grade	$p < 0.001$	$p < 0.001$
II versus I	2.43; 0.03	1.72; 0.2
III versus I	6.42; <0.001	2.97; 0.009
IV versus I	7.48; <0.001	3.14; 0.008
Age group	$p < 0.001$	$p = 0.001$
50–59 versus <49	1.02; 0.1	1.55; 0.2
60–69 versus <49	2.51; 0.01	2.00; 0.05
70–79 versus <49	2.56; 0.01	2.01; 0.05
>80 versus <49	3.56; 0.001	2.92; 0.003
Year of diagnosis	$p = 0.12$	$p = 0.07$
1995–1999 versus 1988–1994	1.21; 0.09	1.08; 0.5
2000–2004 versus 1988–1994	0.96; 0.8	0.80; 0.09
Surgery type	$p < 0.001$	$p = 0.2$
NU without bladder cuff versus NU with bladder cuff	1.63; <0.001	1.21; 0.08
Segmental ureterectomy versus NU with bladder cuff	0.74; 0.1	1.01; 0.9
Gender		
Female versus male	1.20; 0.06	0.99; 0.9
Primary tumour location		
Ureter versus Renal pelvis	0.70; 0.001	0.97; 0.8

UVA: univariable, MVA: multivariable, HR: hazard ratio and NU: nephroureterectomy.

($pN_{1–3}$). Of those, 41 (16%) had organ-confined ($pT_{1–2}$) UTUC and 216 (84.0%) had non-organ-confined ($pT_{3–4}$) UTUC. The 5-year CSM-free survival rate of $pT_{1–2}N_{1–3}$ patients was 68.9% versus 28.7% for $pT_{3–4}N_{1–3}$ patients (log-rank test: $p = 0.006$) (Fig. 1C).

In multivariable Cox regression analyses, the rate of CSM increased according to pT stage (Table 2). Specifically, patients with pT_2, pT_3 and pT_4 UTUC were 2.0 ($p = 0.001$), 4.1 ($p < 0.001$) and 5.5 ($p < 0.001$) times more likely to succumb to UTUC than patients with pT_1 UTUC. Patients with nodal metastases ($pN_{1–3}$) were 2.6 times ($p < 0.001$) more likely to die of UTUC, relative to their counterparts without nodal metastases. Interestingly, the location of the primary tumour failed to achieve independent predictor status (HR: 0.97; $p = 0.8$). Conversely, elevated tumour grade was associated with higher likelihood of CSM. For example, patients with grade III UTUC were 3.0 times ($p = 0.009$) more likely to die of UTUC than patients with grade I tumours. Increasing age was also associated with more elevated CSM rates. For example, patients aged 70–79 years were 2.0 times ($p = 0.05$) more likely to die of UTUC than their counterparts aged less than 49 years. Finally, the surgery type (NU with bladder cuff removal versus NU without bladder cuff removal versus SU) did not affect the CSM-free rates, after controlling for other covariables. All tests of first-degree interactions (pT stage and pN stage, pT stage and tumour grade, and pN stage and tumour grade) failed to achieve statistical significance.

4. Discussion

Nephroureterectomy (NU) represents the treatment modality of choice for patients with UTUC.[1,4,5] Segmental ureterectomy (SU) may be performed in select patients.[1,3,6,7] To date, only one large-scale series from a multi-institutional tertiary care centres database assessed the survival rates after NU for UTUC.[13] In the current series of 2299 patients, we examined the CSM rates after NU or SU. The overall rate of CSM-free survival was 77.6% 5 years after surgery. Since most cancer-related deaths occur within 2–3 years after surgery, a 77.6% survival rate confirms the validity of NU and SU as effective cancer control measures.

Our study also demonstrated that the pathologically determined T and N stages can accurately discriminate the CSM-free survival of patients with UTUC. Of 2299 patients, 739 had pT_1N_0 versus 422 had pT_2N_0 versus 691 had pT_3N_0 versus 190 had pT_4N_0 versus 257 had any T $N_{1–3}$ disease. The 5-year CSM-free survival rates of these four mutually exclusive categories were, respectively, 93.5 versus 86.2

versus 64.5 versus 54.7 versus 35.0%. This demonstrated that pathological T stage is a powerful discriminant of CSM-free survival. Moreover, our data indicated that the presence of established nodal metastases strongly predisposes to higher CSM rates than pT_3 or pT_4 stage. It is of interest that all pT stages are statistically significantly different from one another, when CSM is considered. This even applies to pT_3 and pT_4 tumours, which confirms the validity of current pT substages.

When analyses were restricted to patients with established nodal metastases (pN_{1-3}, $n = 257$), the presence of organ-confined T stage (pT_{1-2}) exerted a protective effect on CSM rates, relative to patients with non-organ-confined (pT_{3-4}) UTUC (log-rank test: $p = 0.006$). Therefore, non-organ-confined disease is also an important determinant of prognosis, even in the presence of nodal metastases.

The importance of pT and pN stages was confirmed in multivariable models, where, for example, pT_3 stage increased the rate of CSM in a 4.1-fold fashion, and the presence of nodal metastases (pN_{1-3}) increased the rate of CSM in a 2.6-fold fashion. Although it may be suspected that the combination of pT and pN stages, or the combination of pT stage and grade, or the combination of pN stage and grade may increase the rate of CSM in a multiplicative fashion, this was not the case as evidenced by the lack of statistical significance between the three tested first-degree interactions.

Younger age exerted a protective effect on CSM rates. It is possible that older patients had more aggressive tumours, since our analysis did adjust for stage and grade. This phenomenon may be explained by greater reluctance to perform NU or SU in elderly patients.[5,16] Finally, our results indicated that grade is a powerful predictor of CSM, which is consistent with previous data.[5,8,12] It is noteworthy that, in multivariable Cox regression models, there was no difference in CSM rates between grade 1 and grade 2 tumours, as well as between grade 3 and grade 4 tumours. Conversely, there was an important CSM difference between grades 1–2 and grades 3–4 tumours. This observation supports the currently recommended two-tiered World Health Organisation-International Society of Urological Pathology (WHO-ISUP) grading system, which divides urothelial tumours into low grade versus high grade.[17]

It is also noteworthy that the effect of NU with bladder cuff removal versus NU without bladder cuff removal on CSM was relatively weak in the current analysis (HR: 1.2; $p = 0.08$). The same limitation was recently reported by Capitanio and colleagues in a large-scale tertiary care centres dataset, where patients who underwent a NU with bladder cuff removal fared no differently from NU patients.[18] Lack of important effect on CSM may result from selection biases, whereby high-risk patients are treated with NU with bladder cuff removal and low-risk patients are treated with NU alone. Only a randomised-controlled trial addressing NU with bladder cuff removal versus NU without bladder cuff removal may validly assess the benefit of this procedure at NU.

Besides the main findings, our results also demonstrated statistically significant differences in pT and pN stages distribution ($p < 0.001$), in median age at diagnosis ($p = 0.002$) and in gender distribution ($p = 0.003$), when patients were stratified according to primary tumour location (renal pelvis versus ureter). Unfortunately, the scope and the significance of these differences cannot be examined in greater detail, due to the population-based nature of our study. Nonetheless, these associations warrant closer examination in future studies and may represent surgical selection biases.

Several limitations apply to our study. It is possible that some individuals who were censored may have moved out of the SEER registry and died of their disease. Unfortunately, the effect of this type of loss to follow-up is not known in either this or any other previous SEER database study. Moreover, the SEER database lacks details about pathological specimen handling. Tumour evaluations may have been performed with some variability, according to centres. Therefore, the stage findings are representative of a real-life phenomenon, but cannot be compared to clinical trials or prospective studies, where detailed pathologic review is performed. Additionally, UTUC tends to be multifocal.[19] Unfortunately, the SEER database provides no information about disease focality. Similarly, we did not have information about previous bladder cancer diagnoses and eventual recurrences.[20–22] The lack of this information prevents us to adjust the incidence of UTUCs according to a monoclonal origin assumption, as suggested by Aben and colleagues.[23] We also lacked information about previous surgical treatments. For example, the survival of patients treated with cystectomy previously may be different from that of patients treated with upfront NU.[22] Similarly, patients treated with endourologic surgeries previously may have different natural history than patients who were treated with immediate NU or SU.[24,25] Finally, the SEER database contains no information about the extent of the lymph node dissection that was performed at NU or SU. It is possible that some patients underwent more extensive lymph node dissections than others. Therefore, this variability in lymph node dissection extent may undermine the value of the current pN stage. Standardisation of lymph node dissection may therefore improve the prognostic ability of pN stage and should represent a focus of future prospective trials.

In conclusion, durable cancer control can be expected in patients with organ-confined (pT_{1-2}) UTUC. Conversely, the presence of non-organ-confined (pT_{3-4}) disease and/or of nodal metastases (pN_{1-3}) exerts a profound detrimental effect on CSM-free survival of patients treated with NU or SU for UTUC.

Conflict of interest statement

None declared

Acknowledgements

Dr. Pierre I. Karakiewicz was partially supported by the University of Montreal Urology Associates, Fonds de la Recherche en Santé du Québec, the University of Montreal Department of Surgery and the University of Montreal Foundation.

REFERENCES

1. Oosterlinck W, Solsona E, van der Meijden AP, et al. EAU guidelines on diagnosis and treatment of upper urinary tract transitional cell carcinoma. *Eur Urol* 2004;**46**(2):147–54.
2. Munoz JJ, Ellison LM. Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. *J Urol* 2000;**164**(5):1523–5.
3. Oosterlinck W. Ureteral tumour: a specific upper urinary tract transitional cell carcinoma. *Eur Urol* 2007;**51**(5):1164–5.
4. Zigeuner R, Pummer K. Urothelial carcinoma of the upper urinary tract: surgical approach and prognostic factors. *Eur Urol* 2008;**53**(4):720–31.
5. Hall MC, Womack S, Sagalowsky AI, Carmody T, Erickstad MD, Roehrborn CG. Prognostic factors, recurrence, and survival in transitional cell carcinoma of the upper urinary tract: a 30-year experience in 252 patients. *Urology* 1998;**52**(4):594–601.
6. Anderstrom C, Johansson SL, Pettersson S, Wahlqvist L. Carcinoma of the ureter: a clinicopathologic study of 49 cases. *J Urol* 1989;**142**(2 Pt 1):280–3.
7. Zungri E, Chechile G, Algaba F, Diaz I, Vila F, Castro C. Treatment of transitional cell carcinoma of the ureter: is the controversy justified? *Eur Urol* 1990;**17**(4):276–80.
8. Huben RP, Mounzer AM, Murphy GP. Tumor grade and stage as prognostic variables in upper tract urothelial tumors. *Cancer* 1988;**62**(9):2016–20.
9. TNM classification of malignant tumors. UICC, 2002.
10. Krogh J, Kvist E, Rye B. Transitional cell carcinoma of the upper urinary tract: prognostic variables and post-operative recurrences. *Br J Urol* 1991;**67**(1):32–6.
11. Langner C, Hutterer G, Chromecki T, Winkelmayer I, Rehak P, Zigeuner R. pT classification, grade, and vascular invasion as prognostic indicators in urothelial carcinoma of the upper urinary tract. *Mod Pathol* 2006;**19**(2):272–9.
12. Novara G, De Marco V, Gottardo F, et al. Independent predictors of cancer-specific survival in transitional cell carcinoma of the upper urinary tract: multi-institutional dataset from 3 European centers. *Cancer* 2007;**110**(8):1715–22.
13. Margulis V, Shariat SF, Matin SF, et al. Outcomes of radical nephroureterectomy: a series from the upper tract urothelial carcinoma collaboration. *Cancer* 2009;**115**(6):1224–33.
14. Ries LAG, Melbert D, Krapcho M, et al. *SEER cancer statistics review, 1975–2004*. Bethesda, MD: National Cancer Institute; 2006. <http://seer.cancer.gov/csr/1975-2004/>, based on November 2006 SEER data submission, posted to SEER website, [last accessed: January 2007].
15. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1054 patients. *J Clin Oncol* 2001;**19**(3):666–75.
16. Cozad SC, Smalley SR, Austenfeld M, Noble M, Jennings S, Raymond R. Transitional cell carcinoma of the renal pelvis or ureter: patterns of failure. *Urology* 1995;**46**(6):796–800.
17. Eble JN, Sauter G, Epstein JI, Sesterhenn IAE. *World health organization classification of tumours. Pathology and genetics of tumours of the urinary system and male genital organs*. Lyon, France: IARC Press; 2004. pp. 89–158.
18. Capitanio U, Shariat SF, Isbarn H, et al. Comparison of oncologic outcomes for open and laparoscopic nephroureterectomy: a multi-institutional analysis of 1249 cases. *Eur Urol* 2009(April 3).
19. Gupta R, Paner GP, Amin MB. Neoplasms of the upper urinary tract: a review with focus on urothelial carcinoma of the pelvicalyceal system and aspects related to its diagnosis and reporting. *Adv Anat Pathol* 2008;**15**(3):127–39.
20. Kang CH, Yu TJ, Hsieh HH, et al. The development of bladder tumors and contralateral upper urinary tract tumors after primary transitional cell carcinoma of the upper urinary tract. *Cancer* 2003;**98**(8):1620–6.
21. Mullerad M, Russo P, Golijanin D, et al. Bladder cancer as a prognostic factor for upper tract transitional cell carcinoma. *J Urol* 2004;**172**(6 Pt 1):2177–81.
22. Sanderson KM, Cai J, Miranda G, Skinner DG, Stein JP. Upper tract urothelial recurrence following radical cystectomy for transitional cell carcinoma of the bladder: an analysis of 1069 patients with 10-year followup. *J Urol* 2007;**177**(6):2088–94.
23. Aben KK, Witjes JA, van Dijck JA, Schalken JA, Verbeek AL, Kiemeney LA. Lower incidence of urothelial cell carcinoma due to the concept of a clonal origin. *Eur J Cancer* 2000;**36**(18):2385–9.
24. Lucas SM, Svatek RS, Olgin G, et al. Conservative management in selected patients with upper tract urothelial carcinoma compares favourably with early radical surgery. *BJU Int* 2008;**102**(2):172–6.
25. Bader MJ, Sroka R, Gratzke C, et al. Laser therapy for upper urinary tract transitional cell carcinoma: indications and management. *Eur Urol* 2008(December 17).