Gender-specific effect of smoking on upper tract urothelial carcinoma outcomes

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Objective

- To evaluate the gender-specific differential effects of smoking habits and cumulative smoking exposure on outcomes in patients with upper tract urothelial carcinoma (UTUC) treated with radical nephroureterectomy (RNU).

Patients and Methods

- A total of 864 consecutive patients, comprising 553 (64%) men and 311 (36%) women, from five international institutions underwent RNU without neoadjuvant chemotherapy.
- Smoking history included smoking status (current, former or never), quantity of cigarettes per day (CPD), smoking duration in years and years since smoking cessation. Cumulative smoking exposure was categorized as light short-term (≤19 CPD and ≤19.9 years), moderate (all combinations except light short-term and heavy long-term), and heavy long-term (≥20 CPD and ≥20 years).
- Uni- and multivariable competing risk regression models were used to assess the associations with outcomes.

Results

- Overall, 244 (28.2%), 297 (34.4%) and 323 (37.4%) patients were never, former and current smokers, respectively.
- There were no differences in smoking status, quantity and duration between the genders.
- In female ever smokers, 30 (9.6%), 121 (38.9%) and 67 (21.5%) were light short-term, moderate and heavy long-term smokers, respectively. Compared with men, female current smokers were more likely to experience disease recurrence in univariable analysis ($P = 0.013$).
- In heavy long-term smokers, female gender was significantly associated with disease recurrence (hazard ratio [HR] 1.7; $P = 0.03$) and cancer-specific mortality (HR 2.0; $P = 0.009$) in multivariable analysis that adjusted for standard clinico-pathological features.
- In female patients only, smoking quantity, duration and cumulative exposure were associated with disease recurrence and cancer-specific mortality on multivariable analyses ($P \leq 0.025$).

Conclusions

- The impact of smoking on UTUC outcomes after RNU is gender-specific.
- Females who are current and heavy long-term smokers experience worse outcomes than their male counterparts.
- Further research is needed to elucidate the molecular mechanisms underlying the gender-specific differential effect of smoking on UTUC outcomes.

Keywords

smoking, gender, urothelial carcinoma, transitional cell carcinoma, upper urinary tract, radical nephroureterectomy, dose relationship, recurrence, survival

Introduction

Radical nephroureterectomy (RNU) is the standard treatment for muscle-invasive and high-risk non-muscle-invasive upper tract urothelial carcinoma (UTUC) [1–3]. Smoking is the most established risk factor for UTUC development [3,4], with an estimated increase in relative risk of 2.5- to sevenfold in both genders [4–6]. The risk of developing UTUC has been shown to increase with increasing number cigarettes of smoked daily and smoking duration [7]. We have recently shown the detrimental impact of smoking on UTUC outcomes after RNU [8].

Interestingly, there is a gender-specific difference in the smoking-attributable risk of developing UTUC; an estimated seven of 10 UTUCs among men and four of 10 among women are caused by smoking [7]. Yet, although men have been estimated to be more than twice as likely to develop UTUC than women, there is no difference between genders with regard to prognosis after adjusting for tumour stage [9–11]. In lower tract urothelial carcinoma (i.e. urothelial carcinoma of the bladder), cumulative evidence suggests an association between smoking and more advanced disease stage and grade as well as disease recurrence [12–15]. Moreover, population-based and multicentre collaborative studies have shown that female gender is associated with a significantly higher rate of cancer-specific recurrence and mortality after radical cystectomy [16] but, to date, no study has assessed the gender-specific impact of smoking on UTUC outcomes in patients treated with RNU.

The aim of the present international, multi-institutional study was to assess the gender-specific effect of smoking habits as well as smoking cessation on outcomes of patients with UTUC treated with RNU.

Patients and Methods

Patient Selection

The present retrospective study was performed with the approval and oversight of each institution's respective institutional review board, with all participating sites providing the necessary data-sharing agreements before initiation of the study. A total of five centres provided data. The database was frozen in 2009, before the final analysis.

Complete data from 864 consecutive patients who underwent RNU between 1987 and 2007 for UTUC were available. No patient received preoperative systemic chemotherapy or perioperative radiotherapy. Patients with a history of urothelial carcinoma invading bladder muscle were excluded. RNU was performed according to previously reported standards [1]. Hilar or regional lymphadenectomy was generally performed in patients who had suspicious lymph nodes on preoperative imaging or who had suspicious intraoperative findings [17]. The indication and extent of lymphadenectomy performed was at the discretion of the individual surgeon. Tumour multifocality was defined as the synchronous presence of two or more pathologically confirmed tumours in any location (renal pelvicalyceal system or ureter) [18]. Adjuvant chemotherapy was administered at the investigator's discretion based on patients' tumour stage and overall health status [19].

Pathological Evaluation

All surgical specimens were processed according to the standard pathological procedures at each institution. Genitourinary pathologists, who were blinded to clinical outcomes, re-examined all specimens according to standardized criteria and confirmed UC histology. Tumours were staged according to the 2010 American Joint Committee on Cancer–Union Internationale Contre le Cancer TNM classification [20]. Tumour grading was performed according to the 2004 WHO/International Society of Urologic Pathology consensus classification [21]. Histopathological assessment included concomitant carcinoma *in situ* (CIS), tumour architecture (papillary or sessile, based on the predominant feature of the index lesion [22]), lymphovascular invasion ([LVI] defined as the presence of tumour cells within an endothelium-lined space without underlying muscular walls [23]), and tumour necrosis (defined as the presence of microscopic coagulative necrosis in >10% of the tumour [24]). Tumour location was defined as either renal pelvicalyceal or ureteric based on the index cancer [25,26].

Smoking Assessment

Smoking history was routinely assessed at a clinic visit within 1 year of RNU. Patients were only considered to be ever smokers if they had smoked 100 cigarettes during their lifetime. Data on self-reported cigarette smoking included smoking status (current, former or never smoker), mean number of cigarettes per day ([CPD] i.e. quantity; 1–9, 10–19, 20–29, ≥30 CPD), duration of smoking (≤9.9, 10–19.9, 20–29.9, 30–39.9, ≥40 years) and years since smoking cessation to RNU in former smokers (≤4.9, 5-9.9, ≥10 years). Patients reporting smoking cessation <1 year before surgery were considered current smokers. Patients reporting tobacco use other than cigarette smoking (e.g. tobacco chewing, cigars and pipes) were excluded ($n = 26$).

Follow-up Regimen

Patients were generally followed every 3–4 months for 1 year after RNU, every 6 months 2–5 years after RNU, and annually thereafter [1,2]. Follow-up consisted of a history, physical examination, routine blood evaluation, urinary

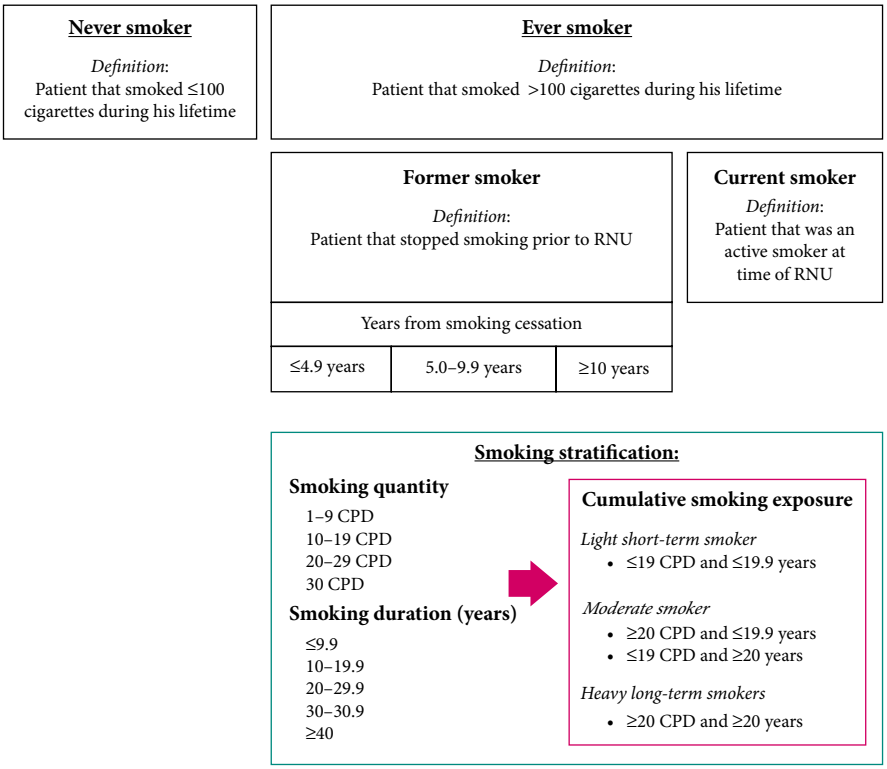


Fig. 1 Stratification of smoking behaviour used in the study.

Abbreviations:
RNU = Radical nephroureterectomy; CPD = Cigarettes per day

cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scans, chest CT, or MRI were performed when clinically indicated. Disease recurrence was defined as tumour relapse in the operative field, regional lymph nodes, and/or distant metastasis. Occurrences of urothelial carcinoma in the bladder or contralateral upper tract were not considered to be disease recurrence. Cause of death was determined by treating physicians, by chart review corroborated by death certificates, or by death certificates alone [27]. All patients who were coded as dead from cancer had previous disease recurrence. Peri-operative mortality (i.e. any death within 30 days of surgery or before discharge) was censored at time of death for cancer-specific survival analyses.

Statistical Analysis

An overview of the smoking stratifications used in the present study is shown in Fig. 1. For statistical analyses, smoking quantity (never vs ≤19 vs ≥20 CPD), duration (never vs ≤19 vs ≥20 years) and years since cessation (never vs ≤9.9 vs ≥10 years vs current smoking) were grouped based on preliminary analyses [8] and findings in other urological malignancies [28,29]. We categorized patients based on their cumulative smoking exposure into four groups: never smoker, light short-term smoker (≤19 CPD and ≤19.9 years), moderate smoker (≥20 CPD and ≤19.9 years or ≤19 CPD and ≥20 years) and heavy long-term smokers (≥20 CPD and ≥20 years). Preliminary analyses using different thresholds showed that this stratification offered the best discrimination for cumulative smoking exposure (data not shown).

The Kolmogorov–Smirnov test was used to assess the normality of variable distributions. Fisher's exact test and the chi-squared test were used to evaluate the association between categorical variables. Differences in variables with a continuous distribution across categories were assessed using the Mann–Whitney *U*-test (two categories) and Kruskal–Wallis test (three and more categories). In order to assess the impact of smoking on disease recurrence and cancer-specific mortality, univariable and multivariable competing risks regression analyses were conducted [30], since smoking is an established risk factor for common health problems that increase risk of death [31]. The cumulative incidence was estimated and graphically displayed; patients who died without experiencing the event of interest were treated as a competing event. Gray's test was used to determine differences in cumulative incidence function between groups [30]. First, we analysed the differences between men and women separately in every

smoking subgroup (smoking status, quantity and duration). Second, we analysed outcomes according to smoking status, quantity and duration separately in men and women. In multivariable analyses, potential interactions were tested using the likelihood ratio test. All reported *P* values are two-sided, and a *P* value < 0.05 was considered to indicate statistical significance. Statistical tests were performed using SPSS Statistics® 20 (IBM Corp, Armonk, NY, USA) and R (version 2.15.0; The R Foundation for Statistical Computing, Vienna, Austria).

Results

Association of Gender with Smoking and Clinico-pathological Characteristics

The present study comprised 553 (64%) men and 311 (36%) women. Female patients were older than their male counterparts (median: 72 vs 69 years; $P = 0.001$). Of 864 patients, 244 (28.2%) never smoked, 297 (34.4%) were former smokers, and 323 (37.4%) were current smokers. There were no differences in smoking status, quantity or duration between the genders. There was a difference in years from smoking cessation ($P = 0.047$) without a clear gender-specific trend regarding time from cessation. Overall, 57 (10.3%), 210 (38.0%) and 135 (24.4%) men were light short-term, moderate and heavy long-term smokers, respectively. In women, 30 (9.6%), 121 (38.9%) and 67 (21.5%) were light short-term, moderate and heavy long-term smokers, respectively. There were no differences in clinico-pathological features between men and women ($P > 0.05$; Table 1). Table 2 shows the gender-specific association of clinico-pathological features with smoking status and cumulative smoking exposure. In men (Table 2A) and women (Table 2B), current smokers were treated more often with open surgery ($P \leq 0.047$), had higher tumour stages ($P \leq 0.037$), more lymph node metastasis ($P \leq 0.003$) and more often received adjuvant chemotherapy ($P \leq 0.04$). In women, current smokers also had more high grade disease ($P = 0.007$) and more LVI ($P = 0.05$).

Gender-specific Differences in Survival Outcomes and Association with Smoking

There were no differences in disease recurrence and cancer-specific mortality between men and women. The median (interquartile range [IQR]) follow-up of patients alive at censorship was 50 (23, 90) months. During follow-up, disease recurred overall in 273 patients (31.6%), 359 (41.6%) died from any cause and 220 (25.5%) died from UTUC. Actuarial (SE) recurrence-free survival estimates at 2, 5 and 10 years after RNU were 69 (2)%, 64 (2)% and 60 (2)%, respectively. Actuarial (SE) cancer-specific survival estimates at 2, 5 and 10 years after RNU were 79 (2)%, 69 (2)%, and 62 (2)%, respectively.

On univariable analyses, there were no differences in disease recurrence and cancer-specific mortality between men and women in never and former smokers, those smoking ≤ 19 CPD or ≤19.9 years, and those with a light short-term or moderate cumulative exposure. In current smokers, women had a higher cumulative incidence of disease recurrence then their male counterparts ($P = 0.013$; Fig. 2). In patients smoking ≥20 CPD, ≥20 years or with a heavy-long-term cumulative exposure (all Fig. 2), women were more likely to experience disease recurrence (all $P \leq 0.016$) and die from UTUC (all $P \leq 0.014$).

On multivariable analysis that adjusted for the effects of age, tumour location, lymph node metastasis (pNx vs pN0 and pN+ vs pN0), adjuvant chemotherapy, pathological grade, pathological stage (pT2 vs pT0,a,is,1; pT3 vs pT0,a,is,1; pT4 vs pT0,a,is,1), tumour architecture, tumour necrosis, LVI, and concomitant CIS, female gender was significantly associated with disease recurrence (hazard ratio [HR]: 1.66; 95% CI: 1.04–2.64; $P = 0.032$) and cancer-specific mortality (HR: 2.03; 95%CI: 1.19–3.46; $P = 0.009$) in patients with a heavy long-term cumulative smoking exposure (Table 3A).

Association of Smoking with Survival Outcomes in Men

In the subgroup analyses of only male patients, current smokers ($P = 0.031$) and those smoking ≥20 years ($P = 0.043$) experienced more disease recurrence compared with never smokers. In addition, former smokers experienced more cancer-specific mortality ($P = 0.043$) compared with never smokers. On multivariable analyses that adjusted for standard clinico-pathological features smoking status, quantity, duration and cumulative exposure were not associated with disease recurrence or cancer-specific mortality (Table 3B).

Association of Smoking with Survival Outcomes in Women

Figure 3 shows the incidence plots for disease recurrence and cancer-specific mortality of female patients according to smoking habits. Compared with never smokers, current or heavy long-term smokers as well as those smoking ≥20 CPD or ≥20 years were at higher risk of disease recurrence (all $P \leq 0.003$) and cancer-specific mortality (all $P \leq 0.036$). Current, heavy long-term and smokers ≥20 years were also at higher risk of disease recurrence compared with former or moderate smokers as well as those smoking ≤ 19.9 years (all $P \leq 0.044$), who in turn did not differ from never smokers. The same findings were true for moderate smokers and those smoking <19 CPD and ≤19.9 years regarding cancer-specific survival. By contrast, former smokers were at higher risk of cancer-specific mortality compared with never smokers, but not current smokers.

Table 1 Descriptive characteristics of 864 patients treated with RNU for UTUC, stratified by gender.

Smoking characteristics	All: *N* = 864	Male: *N* = 553	Female: *N* = 311	*P*
Smoking status, *n* (%)				0.4
Never smoked	244 (28.2)	151 (27.3)	93 (29.9)	
Former smoker	297 (34.4)	199 (36.0)	98 (31.5)	
Current smoker	323 (37.4)	203 (36.7)	120 (38.6)	
Smoking quantity, *n* (%)				0.7
Never smoked	244 (28.2)	151 (27.3)	93 (29.9)	
1-9 CPD	125 (14.5)	76 (13.8)	49 (15.8)	
10-19 CPD	233 (27.0)	152 (27.5)	81 (26.0)	
20-29 CPD	156 (18.1)	101 (18.3)	55 (17.7)	
≥30 CPD	106 (12.3)	73 (13.2)	33 (10.6)	
Smoking duration*n* (%)				0.9
Never smoked	244 (28.2)	151 (27.3)	93 (29.9)	
10–19.9 years	147 (17.0)	96 (17.4)	51 (16.4)	
20–29.9 years	259 (30.0)	169 (30.6)	90 (28.9)	
30–30.9 years	135 (15.6)	86 (15.6)	49 (15.8)	
≥40 years	79 (9.1)	51 (9.2)	28 (9.0)	
Years from smoking cessation, *n* (%)				0.047
Never smoked	244 (28.2)	151 (27.3)	93 (29.9)	
≤4.9	94 (10.9)	65 (11.8)	28 (9.0)	
5-9.9	110 (12.7)	63 (11.4)	47 (15.1)	
≥10	93 (10.8)	71 (12.8)	23 (7.4)	
Current smoker	323 (37.4)	203 (36.7)	120 (38.6)	
Clinical and pathological characteristics				
Median age, Years (IQR)	70 (61; 76)	69 (61; 75)	72 (64; 77)	0.001
Tumour location, *n* (%)				0.2
Renal pelvicalyceal system	582 (67.4)	363 (65.6)	219 (70.4)	
Ureter	282 (32.6)	190 (34.4)	92 (29.6)	
Surgical approach, *n* (%)				0.9
Open	741 (85.8)	475 (85.9)	266 (85.5)	
Laparoscopic	123 (14.2)	78 (14.1)	45 (14.5)	
Pathological stage, *n* (%)				0.5
pT0	11 (1.3)	9 (1.6)	2 (0.6)	
pTa	146 (16.9)	99 (17.9)	47 (15.1)	
pTis	26 (3.0)	16 (2.9)	10 (3.2)	
pT1	191 (22.1)	125 (22.6)	66 (21.2)	
pT2	186 (21.5)	122 (22.1)	64 (20.6)	
pT3	268 (31.0)	161 (29.1)	107 (34.4)	
pT4	36 (4.2)	21 (3.8)	15 (4.8)	
Pathological grade, *n* (%)				0.6
No grade (pT0)	11 (1.3)	9 (1.6)	2 (0.6)	
Low grade	113 (13.1)	73 (13.2)	40 (12.9)	
High grade	740 (85.6)	471 (85.2)	269 (86.5)	
Lymph node status, *n* (%)				0.4
Negative (pN0)	341 (39.5)	217 (39.2)	124 (39.9)	
No dissection performed (pNx)	429 (49.7)	281 (50.8)	148 (47.6)	
Positive (pN+)	94 (10.9)	55 (9.9)	39 (12.5)	
Concomitant CIS, *n* (%)				0.08
Absent	606 (70.1)	376 (68.0)	230 (74.0)	
Present	258 (29.9)	177 (32.0)	81 (26.0)	
LVI, *n* (%)				0.5
Absent	576 (66.7)	364 (65.8)	212 (68.2)	
Present	288 (33.3)	189 (34.2)	99 (31.8)	
Tumour architecture, *n* (%)				0.3
Papillary	589 (68.2)	384 (69.4)	205 (65.9)	
Sessile	275 (31.8)	169 (30.6)	106 (34.1)	
Tumour necrosis, *n* (%)				0.4
Absent	606 (70.1)	394 (71.2)	212 (68.2)	
Present	258 (29.9)	159 (28.8)	99 (31.8)	
Adjuvant chemotherapy, *n* (%)				0.8
Not administered	801 (92.7)	514 (92.9)	287 (92.3)	
Administered	63 (7.3)	39 (7.1)	24 (7.7)	

Table 2A Association of clinico-pathological findings with smoking status and cumulative intensity in 553 male patients with UTUC treated with RNU.

Characteristics of male patients	Smoking status				Cumulative smoking exposure*			
	Never: *N* = 151	Former: *N* = 199	Current: *N* = 203	*P*	Light short-term: *N* = 57	Moderate: *N* = 210	Heavy long-term: *N* = 135	*P*
Median age, Years (IQR)	70 (59;76)	70 (63;75)	68 (61;74)	0.3	65 (60;73)	68 (60;75)	71 (65;76)	**0.02**
Tumour location, *n* (%)				0.3				0.09
Renal pelvicalyceal system	92 (61)	132 (66)	139 (68)		38 (67)	151 (72)	82 (61)	
Ureter	59 (39)	67 (34)	64 (32)		19 (33)	59 (28)	53 (39)	
Surgical approach, *n* (%)				**<0.001**				0.4
Open	127 (84)	153 (77)	195 (96)		48 (84)	178 (85)	122 (90)	
Laparoscopic	24 (16)	46 (23)	8 (4)		9 (16)	32 (15)	13 (10)	
Pathological stage, *n* (%)				**0.011**				0.07
pT0	2 (1)	5 (2)	2 (1)		1 (1)	6 (3)	0 (0)	
pTa	32 (21)	35 (18)	32 (16)		9 (16)	35 (17)	23 (17)	
pTis	5 (3)	10 (5)	1 (1)		2 (4)	8 (4)	1 (1)	
pT1	42 (28)	50 (25)	33 (16)		17 (30)	39 (19)	27 (20)	
pT2	30 (20)	40 (20)	52 (26)		8 (14)	49 (23)	35 (26)	
pT3	36 (24)	54 (27)	71 (35)		14 (25)	66 (31)	45 (33)	
pT4	4 (3)	5 (3)	12 (6)		6 (10)	7 (3)	4 (3)	
Pathological grade, *n* (%)				0.3				0.3
No (pT0) or Low grade	28 (18)	29 (15)	25 (12)		7 (12)	33 (16)	14 (10)	
High grade	123 (82)	170 (85)	178 (88)		50 (88)	177 (84)	121 (90)	
Lymph node status, *n* (%)				**0.001**				0.07
Negative (pN0)	68 (45)	86 (43)	63 (31)		20 (35)	81 (39)	48 (35)	
No dissection performed (pNx)	77 (51)	96 (48)	108 (53)		27 (47)	106 (51)	71 (53)	
Positive (pN+)	6 (4)	17 (9)	32 (16)		10 (18)	23 (10)	16 (12)	
Concomitant CIS, *n* (%)				0.1				0.5
Absent	102 (68)	126 (63)	148 (73)		41 (72)	148 (70)	85 (63)	
Present	49 (32)	73 (37)	55 (27)		16 (28)	62 (30)	50 (37)	
LVI, *n* (%)				0.8				0.3
Absent	101 (67)	127 64()	136 (67)		35 (61)	146 (70)	82 (61)	
Present	50 (33)	72 (36)	67 (33)		22 (38)	64 (30)	53 (39)	
Tumour architecture, *n* (%)				0.2				0.3
Papillary	102 (68)	147 (74)	135 (67)		45 (79)	149 (71)	88 (65)	
Sessile	49 (32)	52 (26)	68 (33)		12 (21)	61 (29)	47 (35)	
Tumour necrosis, *n* (%)				0.2				0.6
Absent	112 (74)	147 (74)	135 (67)		37 (65)	147 (70)	98 (73)	
Present	39 (26)	52 (26)	68 (33)		20 (35)	63 (30)	37 (27)	
Adjuvant chemotherapy, *n* (%)				**0.001**				0.07
Not administered	147 (97)	189 (95)	178 (88)		52 (91)	194 (92)	121 (90)	
Administered	4 (3)	10 (5)	25 (12)		5 (9)	16 (8)	14 (10)	

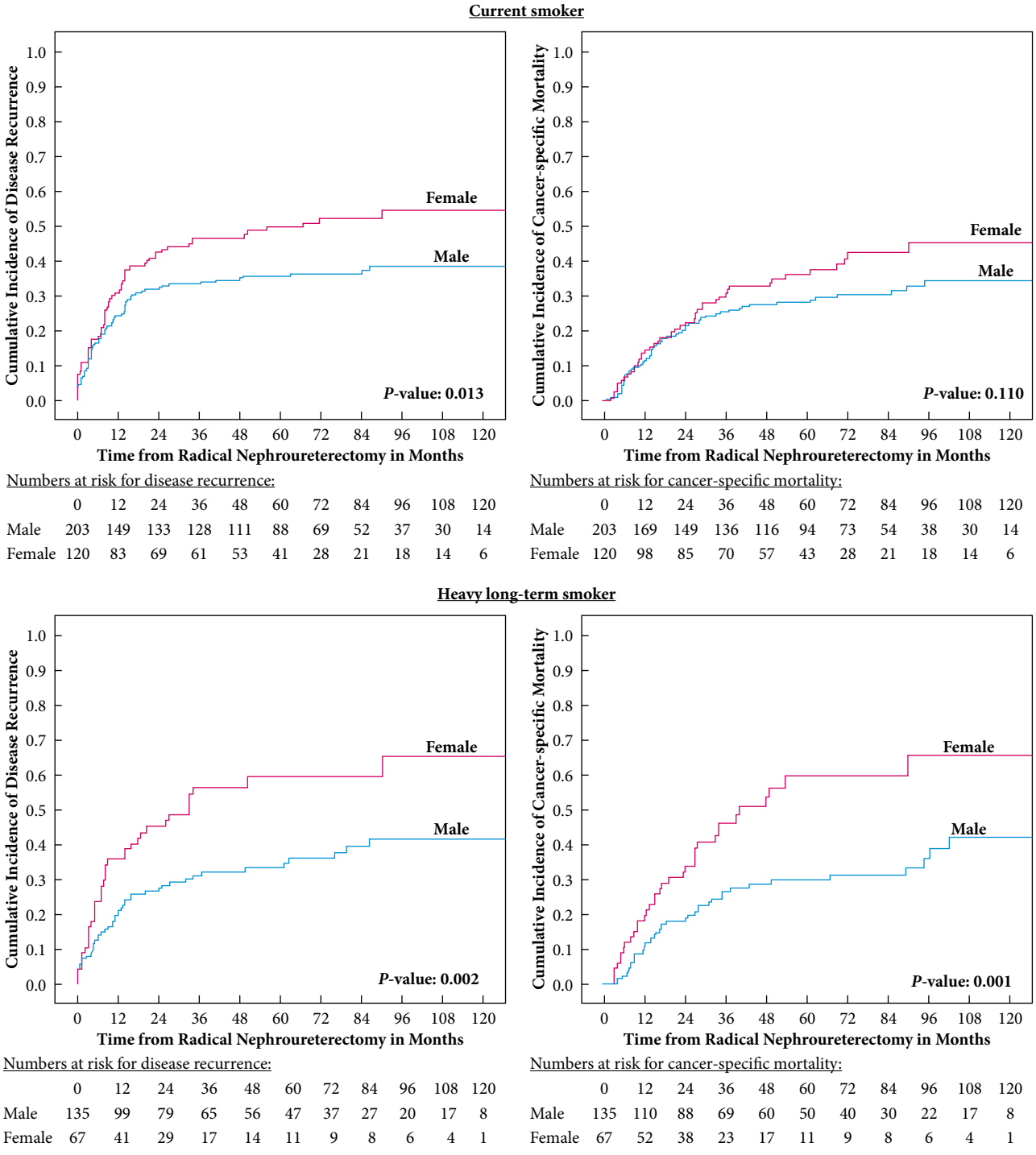
**Cumulative smoking exposure was compared with never smokers (reference group). Numbers for never smokers are displayed at smoking status.*

Table 2B Association of clinico-pathological findings with smoking status and cumulative intensity in 331 female patients with UTUC treated with RNU.

Characteristics of female patients	Smoking status (%)				Cumulative smoking exposure (%)*			
	Never: *N* = 93	Former: *N* = 98	Current: *N* = 120	*P*	Light short-term: *N* = 30	Moderate: *N* = 121	Heavy long-term: *N* = 67	*P*
Mean age, years (median; IQR)	72 (64;81)	75 (67;79)	71 (63;75)	**0.02**	70 (52;75)	73 (65;78)	71 (63;73)	0.2
Tumour location, *n* (%)				0.5				0.8
Renal pelvicalyceal system	62 (67)	68 (69)	89 (74)		21 (70)	87 (72)	49 (73)	
Ureter	31 (33)	30 (31)	31 (26)		9 (30)	34 (28)	18 (27)	
Surgical approach, *n* (%)				**0.047**				0.4
Open	77 (83)	79 (81)	110 (92)		24 (83)	104 (80)	61 (86)	
Laparoscopic	16 (17)	19 (19)	10 (8)		16 (17)	6 (20)	17 (14)	
Pathologic stage, *n* (%)				**0.037**				0.3
pT0	2 (2)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
pTa	16 (17)	19 (19)	12 (10)		5 (17)	19 (16)	7 (10)	
pTis	6 (7)	4 (4)	0 (0)		1 (3)	2 (1)	1 (2)	
pT1	20 (22)	23 (24)	23 (19)		3 (10)	29 (24)	14 (21)	
pT2	16 (17)	18 (18)	30 (25)		6 (20)	29 (24)	13 (19)	
pT3	29 (31)	32 (33)	46 (38)		15 (50)	36 (30)	27 (40)	
pT4	4 (4)	2 (2)	9 (8)		0 (0)	6 (5)	5 (8)	
Pathologic grade, *n* (%)				**0.007**				0.2
No (pT0) or Low grade	18 (19)	17 (17)	7 (6)		4 (13)	14 (12)	6 (9)	
High grade	75 (81)	81 (83)	113 (94)		26 (87)	107 (88)	61 (91)	
Lymph node status, *n* (%)				**0.003**				**0.003**
Negative (pN0)	50 (54)	39 (40)	35 (29)		12 (40)	41 (34)	21 (31)	
No dissection performed (pNx)	38 (41)	46 (47)	64 (53)		14 (47)	66 (54)	30 (45)	
Positive (pN+)	5 (5)	13 (13)	21 (18)		4 (13)	14 (12)	16 (24)	
Concomitant CIS, *n* (%)				0.5				0.3
Absent	67 (72)	70 (71)	93 (78)		22 (73)	96 (79)	45 (67)	
Present	26 (28)	28 (29)	27 (22)		8 (27)	25 (21)	22 (33)	
LVI, *n* (%)				**0.05**				0.1
Absent	71 (76)	68 (69)	73 (61)		21 (70)	81 (67)	39 (58)	
Present	22 (24)	30 (31)	47 (39)		9 (30)	40 (33)	28 (42)	
Tumour architecture, *n* (%)				0.2				0.2
Papillary	65 (70)	68 (69)	72 (60)		18 (60)	80 (66)	42 (63)	
Sessile	28 (30)	30 (31)	48 (40)		28 (40)	12 (34)	41 (37)	
Tumour necrosis, *n* (%)				0.2				0.2
Absent	63 (68)	73 (74)	76 (63)		18 (60)	90 (74)	41 (61)	
Present	30 (32)	25 (26)	44 (37)		12 (40)	31 (26)	26 (39)	
Adjuvant chemotherapy, *n* (%)				**0.04**				0.2
Not administered	89 (96)	93 (95)	105 (88)		27 (90)	113 (93)	58 (87)	
Administered	4 (4)	5 (5)	15 (13)		3 (10)	8 (7)	9 (13)	

**Cumulative smoking exposure was compared with never smokers (reference group). Numbers for never smokers are displayed at smoking status.*

Fig. 2 Cumulative incidence estimates of disease recurrence and cancer-specific mortality in 864 patients with UTUC treated with RNU, stratified by gender. The plots display the subgroups of current smokers, heavy long-term smokers (≥20 CPD and ≥20 years), smokers with ≥20 CPD and smokers with a smoking duration of ≥20 years.



Numbers at risk for disease recurrence:

	0	12	24	36	48	60	72	84	96	108	120
Male	203	149	133	128	111	88	69	52	37	30	14
Female	120	83	69	61	53	41	28	21	18	14	6

Numbers at risk for cancer-specific mortality:

	0	12	24	36	48	60	72	84	96	108	120
Male	203	169	149	136	116	94	73	54	38	30	14
Female	120	98	85	70	57	43	28	21	18	14	6

Numbers at risk for disease recurrence:

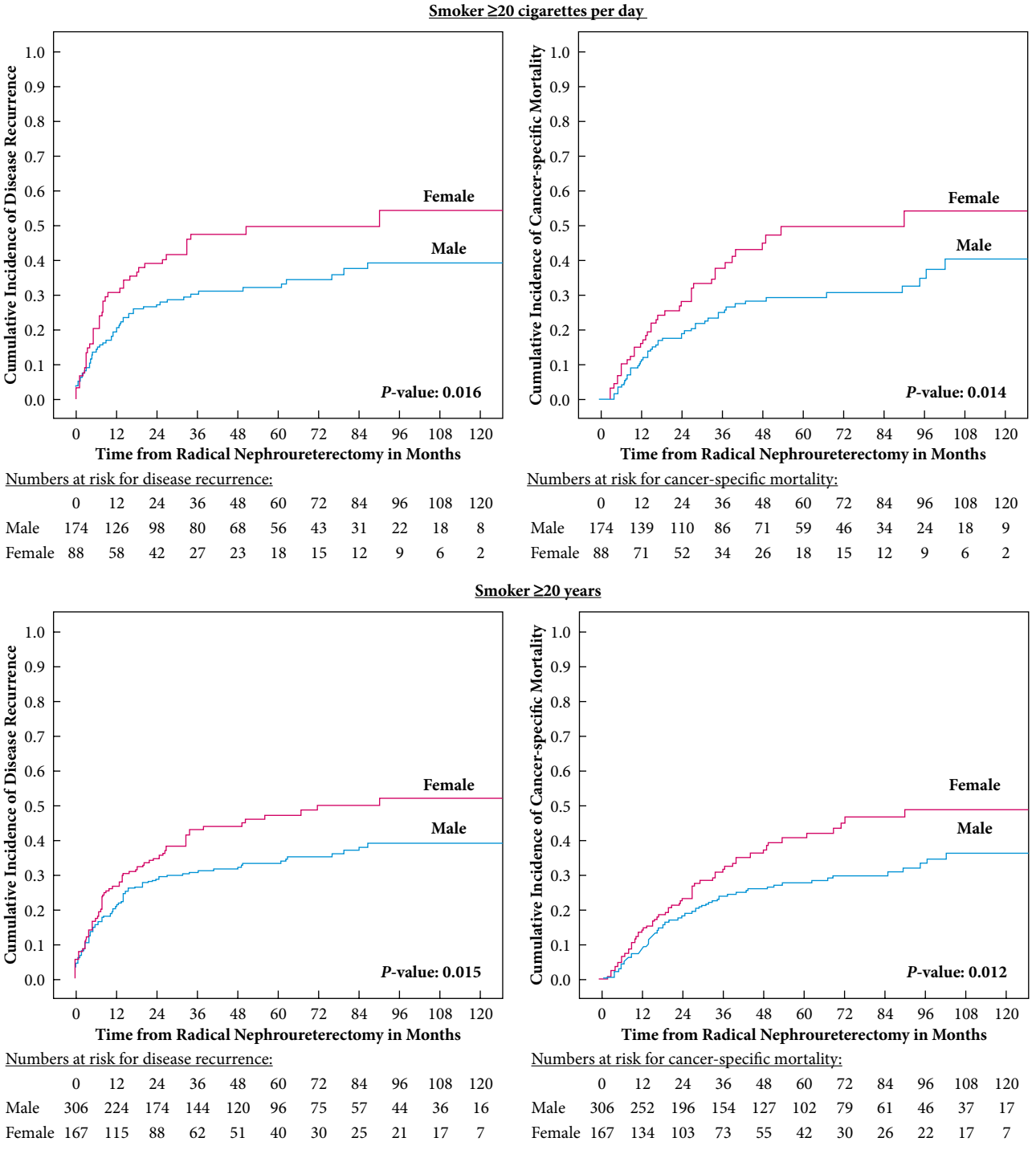
	0	12	24	36	48	60	72	84	96	108	120
Male	135	99	79	65	56	47	37	27	20	17	8
Female	67	41	29	17	14	11	9	8	6	4	1

Numbers at risk for cancer-specific mortality:

	0	12	24	36	48	60	72	84	96	108	120
Male	135	110	88	69	60	50	40	30	22	17	8
Female	67	52	38	23	17	11	9	8	6	4	1

On multivariable analyses that adjusted for standard clinico-pathological features, current smoking status was significantly associated with disease recurrence ($P = 0.012$; Table 3B). Moreover, heavy long-term smoking, smoking ≥20 CPD or ≥20 years were independent predictors for disease recurrence (all $P \leq 0.025$) and cancer-specific mortality (all $P \leq 0.019$; Table 3B). These findings remained true when the same

Fig. 2 Continued



Numbers at risk for disease recurrence:

	0	12	24	36	48	60	72	84	96	108	120
Male	174	126	98	80	68	56	43	31	22	18	8
Female	88	58	42	27	23	18	15	12	9	6	2

Numbers at risk for cancer-specific mortality:

	0	12	24	36	48	60	72	84	96	108	120
Male	174	139	110	86	71	59	46	34	24	18	9
Female	88	71	52	34	26	18	15	12	9	6	2

Numbers at risk for disease recurrence:

	0	12	24	36	48	60	72	84	96	108	120
Male	306	224	174	144	120	96	75	57	44	36	16
Female	167	115	88	62	51	40	30	25	21	17	7

Numbers at risk for cancer-specific mortality:

	0	12	24	36	48	60	72	84	96	108	120
Male	306	252	196	154	127	102	79	61	46	37	17
Female	167	134	103	73	55	42	30	26	22	17	7

analyses were performed in women without adjuvant chemotherapy ($n = 24$).

Association of Gender and Smoking Cessation with Outcomes

In men, 65 (11.8%) former smokers ceased smoking ≥10 years (distant former smoker) and 134 (24.2%) ceased smoking ≤9.9 years (recent former smoker) before RNU. Current ($P = 0.033$) and recent former smokers ($P = 0.015$) had a higher incidence of disease recurrence compared with never smokers, who in turn showed no difference from distant former smokers. Recent former smokers also had a higher risk of cancer-specific mortality compared with never smokers ($P = 0.010$). On multivariable analyses,

Table 3A Multivariable competing risk regression analyses predicting disease recurrence and cancer-specific mortality in 864 patients with UTUC treated with RNU according to smoking history subgroups.

Subgroups of patients	Female vs male							
	Disease recurrence				Cancer-specific mortality			
	HR	95% CI		*P*	HR	95% CI		*P*
		Lower	Upper			Lower	Upper	
Current smoker, $n = 323$	1.30	0.92	1.84	0.130	1.19	0.79	1.77	0.400
Smoking ≥ 20 CPD, $n = 262$	1.40	0.91	2.16	0.130	1.61	0.98	2.64	0.059
Smoking ≥ 20 years, $n = 473$	1.26	0.92	1.72	0.150	1.36	0.95	1.94	0.098
Heavy long-term smoker, $n = 202$	1.66	1.04	2.64	**0.032**	2.03	1.19	3.46	**0.009**

HRs and P *values represent the results for gender in the model. Each subgroup was adjusted in a separate multivariable model, that adjusted for the effects of centre, age (continuous), gender, tumour location, lymph node metastasis (pNx vs pN0 and pN+ vs pN0), adjuvant chemotherapy, pathological grade, pathological stage (pT2 vs pT0,a,is,1; pT3 vs pT0,a,is,1; pT4 vs pT0,a,is,1), tumour architecture, tumour necrosis, LVI, and concomitant CIS.*

years from smoking cessation were not associated with disease recurrence or cancer-specific mortality.

In women, 29 (9.3%) and 70 (22.5%) patients were distant and recent former smokers, respectively. Current smokers had a higher incidence of disease recurrence compared with never ($P < 0.001$), distant former ($P = 0.025$) and recent former smokers ($P = 0.031$), who in turn did not show any different incidence from each other. Current ($P = 0.001$) and distant former smokers ($P = 0.027$) also had a higher risk of cancer-specific mortality compared with never smokers. On multivariable analyses that adjusted for standard clinico-pathological factors, current smoking was associated with disease recurrence (HR:1.65; 95%CI 1.03–3.05; $P = 0.039$).

Discussion

A significant number of men (47%) and women (25%) treated with RNU for UTUC in the present study were former or current smokers, a rate that is in accordance with the literature [4,7]. Although smoking is a well established risk factor for UTUC development [3,4], no study has analysed the impact of gender on smoking association with UTUC outcomes.

We found that the detrimental effect of smoking on post-RNU outcomes was gender-specific. In female current smokers, those with the highest smoking quantity, duration and cumulative exposure experienced more disease recurrence and cancer-specific mortality compared with their male counterparts in univariable analyses. In patients with heavy long-term cumulative smoking exposure, female gender remained an independent risk factor for both endpoints in multivariable analyses. This finding is of particular importance since previous studies have not found differences in outcomes between men and women treated with RNU for UTUC [9–11]. Although there is no comparable study in UTUC, a previous study in urothelial carcinoma of the bladder found poor outcomes in smokers, particularly in male patients in univariable analysis [32].

In women, there was a distinct dose relationship between smoking intensity and the risk of disease recurrence and cancer-specific mortality after RNU. Heavy long-term cumulative smoking exposure, a high smoking quantity and long smoking duration were independent risk factors for both endpoints after adjusting for the effects of established clinico-pathological features in women. By contrast, we did not find these associations in men. Indeed, the odds for UTUC development among smokers are higher in men [7], but it seems that women have a more unfavourable response to the toxic effects of cigarette smoke. The exact mechanisms of smoking-induced urothelial carcinogenesis remain unknown, but accumulating evidence suggests that dose escalation and longer duration might increase not only the risk of urothelial carcinoma development, but also its aggressiveness [4,13,14,33]. Gender-specific differences in urothelial carcinoma outcomes might be also influenced by physiological factors such as differences in the sex-hormonal levels [34–37], or other inherent/genetic, environmental, behavioural or lifestyle factors (e.g. second-hand smoking) for which the present study, unfortunately, could not adjust [38].

Despite the relatively large sample size and the multiple aspects of smoking considered in the present study, it has several limitations. First and foremost are limitations inherent to its retrospective and multi-institutional nature, including surgeons' numbers, preferences and experience, or surgical techniques. Moreover, absence of lymphadenectomy as well as differences in the lymph node count and anatomical template of lymphadenectomy might have influenced our results. Another limitation includes possible interobserver variability between pathologists; a central pathology review was not performed. Nevertheless, all surgeons and pathologists operated at academic centres with experience in UTUC. Comorbidities might have

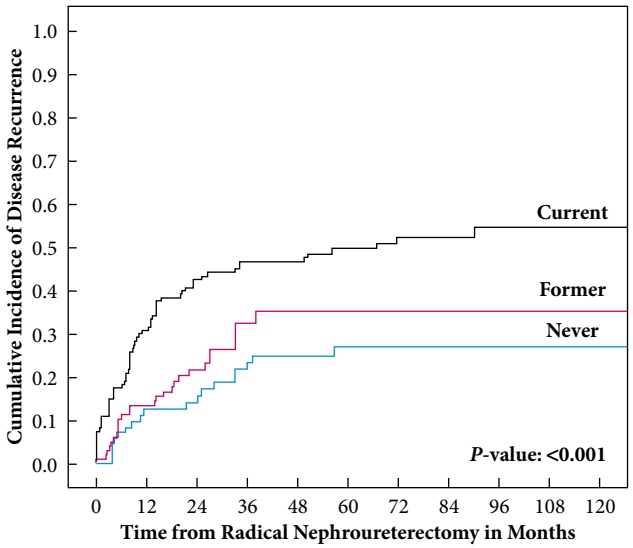
Table 3B Multivariable competing risk regression analyses predicting disease recurrence and cancer-specific mortality in the subgroups of 553 male and 331 female patients with UTUC treated with RNU according to smoking history.

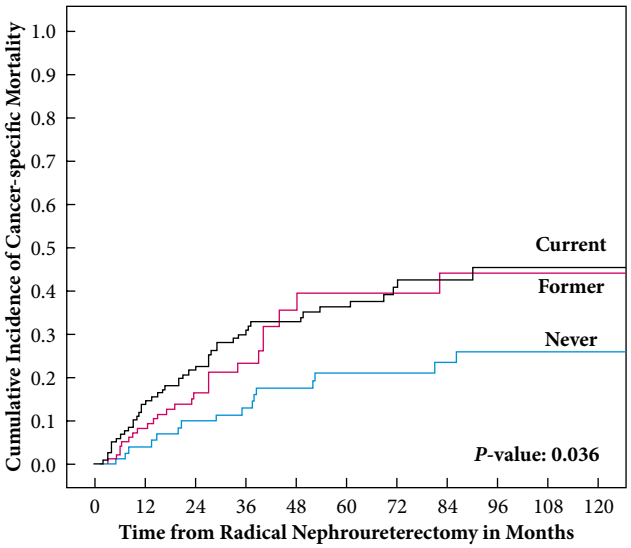
	Male								Female							
	Disease recurrence				Cancer-specific mortality				Disease recurrence				Cancer-specific mortality			
	HR	95% CI		*P*	HR	95% CI		*P*	HR	95% CI		*P*	HR	95% CI		*P*
		Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper	
Smoking status																
Never	Ref.	–	–	–	Ref.	–	–	–	Ref.	–	–	–	Ref.	–	–	–
Former	1.48	0.95	2.32	0.086	1.45	0.90	2.34	0.120	1.27	0.70	2.30	0.430	1.58	0.83	3.00	0.160
Current	1.47	0.93	2.30	0.096	1.25	0.77	2.03	0.360	1.98	1.17	3.37	**0.012**	1.74	0.97	3.12	0.063
Smoking quantity																
Never	Ref.	–	–	–	Ref.	–	–	–	Ref.	–	–	–	Ref.	–	–	–
≤19 CPD	1.50	0.97	2.33	0.068	1.32	0.83	2.09	0.250	1.50	0.89	2.55	0.130	1.29	0.72	2.34	0.39
≥20 CPD	1.43	0.90	2.27	0.130	1.38	0.84	2.28	0.210	2.00	1.09	3.66	**0.025**	2.38	1.24	4.57	**0.009**
Smoking duration																
Never	Ref.	–	–	–	Ref.	–	–	–	Ref.	–	–	–	Ref.	–	–	–
≤19.9 years	1.71	1.02	2.86	0.052	1.64	0.94	2.88	0.082	1.02	0.51	2.01	0.960	0.79	0.34	1.84	0.580
≥20 years	1.43	0.94	2.17	0.098	1.29	0.82	2.00	0.270	1.91	1.12	3.24	**0.017**	1.98	1.12	3.51	**0.019**
Cumulative smoking exposure																
Never	Ref.	–	–	–	Ref.	–	–	–	Ref.	–	–	–	Ref.	–	–	–
Light short-term	1.84	1.04	3.26	0.050	1.63	0.90	2.95	0.110	1.16	0.56	2.42	0.690	0.80	0.39	2.20	0.660
Moderate	1.43	0.91	2.24	0.120	1.29	0.80	2.09	0.300	1.51	0.86	2.64	0.150	1.33	0.72	2.47	0.360
Heavy long-term	1.43	0.89	2.31	0.140	1.33	0.80	2.24	0.270	2.38	1.29	4.42	**0.006**	3.00	1.53	5.91	**0.002**

Ref., referent. All models were adjusted for the effects of centre, age (continuous), tumour location, lymph node metastasis (pNx vs pN0 and pN+ vs pN0), adjuvant chemotherapy, pathological grade, pathological stage (pT2 vs pT0,a,is,1; pT3 vs pT0,a,is,1; pT4 vs pT0,a,is,1), tumour architecture, tumour necrosis, LVI, and concomitant CIS.

Fig. 3 Cumulative incidence estimates of disease recurrence and cancer-specific mortality according to cigarette smoking status, cumulative smoking exposure, smoking quantity and duration in 311 female patients with UTUC treated with RNU.

Smoking status





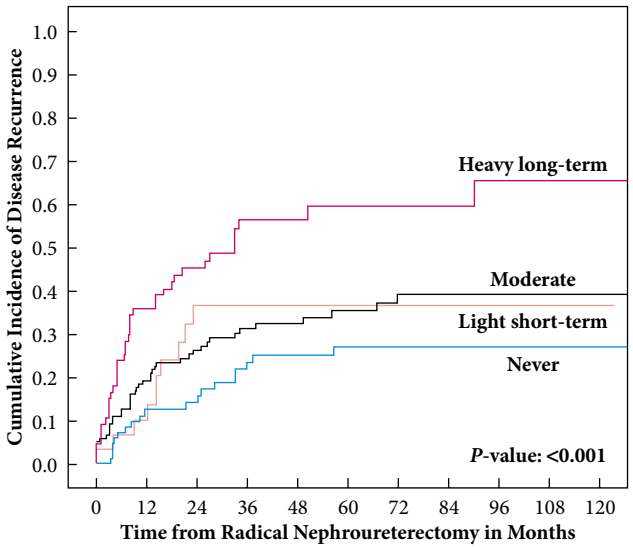
Numbers at risk for disease recurrence:

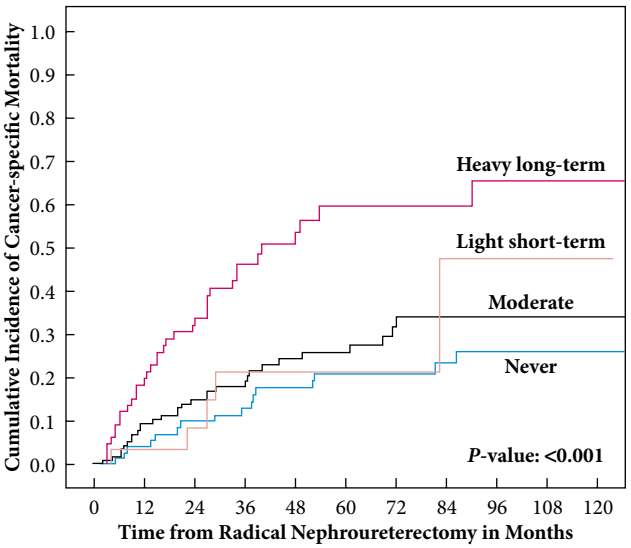
	0	12	24	36	48	60	72	84	96	108	120
Never	93	59	55	49	43	35	30	27	24	19	9
Former	98	73	44	21	15	14	13	11	8	7	3
Current	120	83	69	61	53	41	28	21	18	14	6

Numbers at risk for cancer-specific mortality:

	0	12	24	36	48	60	72	84	96	108	120
Never	93	66	59	56	48	39	34	30	25	19	9
Former	98	78	48	26	17	15	14	11	9	7	3
Current	120	98	85	70	57	43	28	21	18	14	6

Cumulative smoking exposure





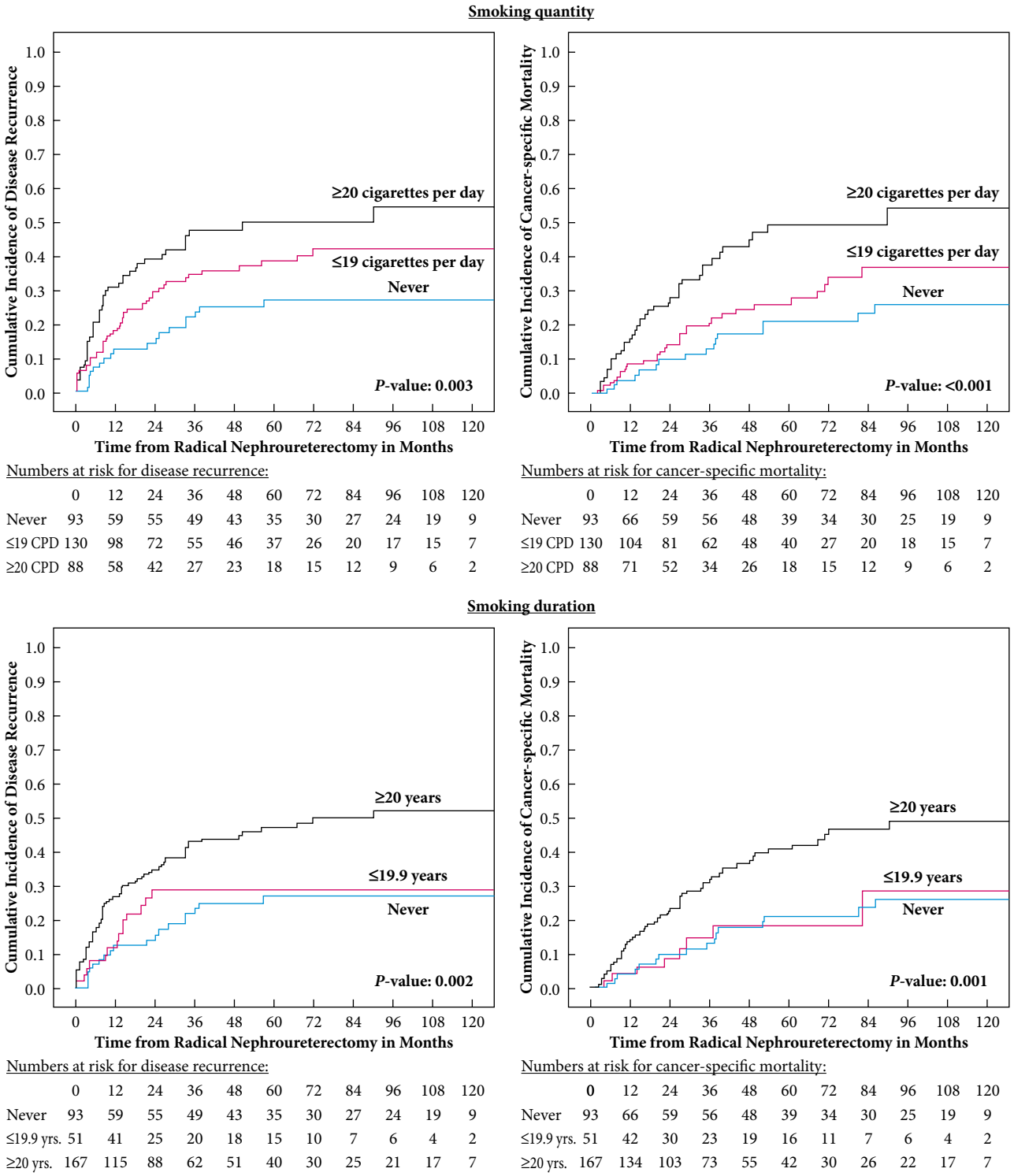
Numbers at risk for disease recurrence:

	0	12	24	36	48	60	72	84	96	108	120
Never	93	59	55	49	43	35	30	27	24	19	9
Light	30	24	13	10	9	8	5	2	2	2	1
Moderate	121	92	72	55	46	36	27	22	19	16	7
Heavy	67	41	29	17	14	11	9	8	6	4	1

Numbers at risk for cancer-specific mortality:

	0	12	24	36	48	60	72	84	96	108	120
Never	93	66	59	56	48	39	34	30	25	19	9
Light	30	23	16	11	10	9	6	2	2	2	1
Moderate	121	101	80	62	48	38	27	23	20	16	7
Heavy	67	52	38	23	17	11	9	8	6	4	1

Fig. 3 Continued



influenced the decision-making regarding surgical therapy, introducing a selection bias for which our analyses could not adjust. also In addition, we could not adjust our analyses for analgesia use, which may have influenced the incidence of UTUC. Another bias might be present because of the exclusion of other tobacco products (e.g. cigars, pipes or tobacco chewing) and different forms of tobacco exposure (e.g. second-hand smoking or occupational

exposure) and we could not adjust our analyses for different types of tobacco. Smoking history was self-reported and therefore subject to recall bias. Smoking status was not verified biochemically. Under-reporting of tobacco use (i.e. underestimation of the true number of current smokers and overestimation of former smokers as well as underestimation of smoking quantity and duration) might have biased our data. Finally, cultural and population-based differences in gender-specific smoking behaviour may have influenced our findings. The present results certainly need to be confirmed in robust, prospective studies.

In conclusion, cigarette smoking has a more detrimental effect on outcomes in females than in males. Females who are current smokers and have a heavy long-term cumulative smoking exposure are significantly more likely to experience disease recurrence and cancer-specific mortality than their male counterparts. The biological mechanisms underlying the gender-specific differential effect of smoking need to be investigated further. The results show that urologists, healthcare providers and society in general should focus on prevention and cessation of smoking, especially in females.

Acknowledgements

We thank all members of the Upper Tract Urothelial Carcinoma Collaboration (UTUCC):

Patrick J. Bastian, Karim Bensalah, Eugene K. Cha, Evi Comploj, Mario Fernández, Vincenzo Ficarra, Wareef Kabbani, Wassim Kassouf, Eiji Kikuchi, Theresa M. Koppie, Juan I. Martinez-Salamanca, Surena F. Matin, Kazumasa Matsumoto, Francesco Montorsi, Casey K. Ng, Giacomo Novara, Mototsuga Oya, Jean-Jacques Patard, Mesut Remzi, Marco Roscigno, Philipp Ströbel, Stefan Tritschler, Matthias Waldert, Thomas J. Walton, Alon Weizer, J. Stuart Wolf, and Richard Zigeuner

Source of Funding

Michael Rink is supported by The Frederick J. and Theresa Dow Wallace Fund of the New York Community Trust.

Conflict of Interest

Michael Rink is a Speaker for Pfizer Pharma and Shahrokh F. Shariat is an Advisory Board member of Ferring Pharma. All other authors declare no conflict of interest.

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Abbreviations: UTUC, upper tract urothelial carcinoma; RNU, radical nephroureterectomy; CPD, cigarettes per day; CIS, carcinoma in situ; LVI, lymphovascular invasion; HR, hazard ratio; IQR, interquartile range.