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Impact of smoking status and cumulative exposure on intravesical recurrence of upper tract urothelial carcinoma after radical nephroureterectomy

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Objective

- To assess the impact of cigarette smoking status, cumulative smoking exposure, and time from cessation on intravesical recurrence (IVR) outcomes in patients treated with radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC).

Patients and Methods

- In all, 519 patients underwent RNU at five institutions. Smoking history included smoking status, quantity of cigarettes smoked per day (cpd), duration, and time from cessation.
- The cumulative smoking exposure was categorised 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).
- Univariable/multivariable cox regression analyses assessed the effects of smoking on IVR.

Results

- In all, 190 patients (36%) never smoked; 205 (40%) and 125 (24%) were former and current smokers, respectively.
- Among smokers, 42 (8%), 185 (36%), and 102 (20%) patients were light-short-term, moderate, and heavy-long-term smokers, respectively.
- Within a median follow-up of 37 months, 152 patients (29%) had IVR. Actuarial IVR-free-survival estimates (standard error) at 2, 5, and 10 years were 72 (2)%, 58 (3)%, and 51 (4)%, respectively.
- In multivariable analyses, current smoking status, smoking intensity (≥20 cpd), smoking duration (≥20 years), and heavy-long-term smoking were associated with higher risk of IVR (all $P \leq 0.01$).
- Patients who quit smoking ≥10 years before RNU had better IVR outcomes than current smokers and those patients who quit smoking <10 years before RNU.

Conclusions

- Cigarette smoking is significantly associated with IVR in patients treated with RNU for UTUC.
- Current and heavy-long-term smokers have the highest risk of IVR.
- Smoking cessation for >10 years before RNU seems to mitigate these detrimental effects.

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Keywords

smoking, upper tract urothelial carcinoma, radical nephroureterectomy, intravesical recurrence

Introduction

Smoking is the most common risk factor for developing upper tract urothelial carcinoma (UTUC), increasing the relative risk by five- to seven-fold [1–3]. We previously showed that smoking status and cumulative smoking exposure were associated with worse oncological survival in patients with UTUC treated with radical nephroureterectomy (RNU). Current and heavy-long-term smokers had higher risks of disease recurrence and cancer-specific mortality [3,4]. Moreover, smoking cessation for ≥10 years seemed to abrogate the detrimental effect of smoking on UTUC prognosis.

Intravesical recurrence (IVR) after RNU is a frequent event, occurring in 30–50% of patients in the first 5 years after RNU, with most tumours occurring within the first year [5–9]. Prognostic factors for IVR are needed to help clinical decision-making for follow-up scheduling (e.g. cystoscopy) and postoperative administration of one instillation of chemotherapy to prevent IVR [10,11]. Recently a retrospective single centre study reported that current smoking status and a smoking quantity of >50 cigarettes per day (cpd) were independently associated with the occurrence of IVR in 245 patients who underwent RNU for UTUC [12]. However, that study did not report on the effect of cumulative smoking exposure and time from smoking cessation [12].

Similarly to our previous study [4], we hypothesised that there is a dose–response relationship between smoking intensity and occurrence of IVR, and that smoking cessation may reduce this effect. To address these hypotheses, we investigated smoking habits and intensity, as well as impact of cessation in a large international multi-institutional cohort of patients treated with RNU for UTUC.

Patients and Methods

In this Institutional Review Board-approved study, all participating sites provided necessary institutional data-sharing agreements before the initiation of the study. In all, five centres provided data. A computerised databank was generated for data transfer. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Before final analysis, the database was frozen.

The Upper Tract Urothelial Carcinoma Collaboration collected data on 2492 patients with UTUC treated with RNU. Patients with a history of radical cystectomy for treatment of muscle-invasive or high-risk non-muscle-invasive bladder cancer were excluded from data collection. In all, 564 had missing data on smoking status; 927 patients had missing data on smoking quantity, smoking duration, or time from smoking cessation; 111 patients had missing data on clinicopathological variables, and 345 on follow-up and therefore were excluded from the analysis. Patients reporting tobacco use other than cigarette smoking (e.g. tobacco chewing, cigars, and pipes) were excluded (26 patients). Complete data for 519 patients who underwent RNU between 1987 and 2007 for UTUC were available for the analyses. No patient received preoperative systemic chemotherapy or perioperative radiotherapy. RNU was performed according to techniques previously described [8,13]. Adjuvant chemotherapy was administered at the investigator's discretion (53 patients).

Pathological Evaluation

All surgical specimens were processed according to standard pathological procedures at each institution [8,13]. Genitourinary pathologists who were 'blinded' to clinical outcomes re-examined all specimens according to standardised criteria and confirmed UC histology. Tumours were staged according to the 2010 American Joint Committee on Cancer/Union Internationale Contre le Cancer TNM classification. Tumour grading was performed according to the 2004 WHO/International Society of Urologic Pathology consensus classification.

Smoking Assessment

Smoking history was routinely assessed at a clinic visit at ≤1 year of RNU. Patients were only considered ever smokers if they had smoked at least 100 cigarettes during their lifetime. Data on self-reported cigarette smoking included smoking status (current, former, or never smoker), average number of cigarettes per day (cpd; i.e. quantity; never smoked, 1–9, 10–19, 20–29, ≥30 cpd), duration in years (never smoked, ≤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 who reported smoking cessation at ≤1 year before RNU were considered current smokers [4,14,15].

Follow-up Regimen

Patients were generally followed every 3–4 months for the first year after RNU, every 6 months from the second to the fifth year, and annually thereafter. Follow-up consisted of a history, physical examination, routine blood work, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper

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urinary tract. Elective bone scans, chest CT, and/or MRI were performed when clinically indicated. Bladder cancer occurrences were coded as IVR; excluding tumour relapse in the operative field, contralateral ureter and/or pyelo-calyceal system, regional lymph nodes, and/or distant metastasis.

Statistical Analysis

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 previous publications [4,14,15]. We categorised 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) [4,14,15].

The chi-square test was used to evaluate the association between categorical variables. Differences in variables with a continuous distribution across categories were assessed using the Kruskal–Wallis test. To assess the impact of smoking on IVR, univariable and multivariable Cox regression analyses were conducted. All reported *P* values are two-sided and statistical significance was set at $P < 0.05$.

Results

Clinicopathological Characteristics and Smoking Features

Table 1 shows the clinicopathological characteristics of the study cohort. Of the 519 patients, 190 (36%) never smoked, 204 (40%) were former smokers, and 125 (24%) were current smokers. Most of the former and current smokers smoked for >20 years. Among ever smokers, 42 (8%), 185 (36%), and 102 (20%) were light-short-term, moderate, and heavy-long-term smokers, respectively.

Association of Smoking with Clinicopathological Characteristics

Current smokers were more likely to have an aggressive disease than former and never smokers (higher rates of pT3–T4 disease, pN+ and lymphovascular invasion; all $P < 0.03$). Therefore, current smokers were more likely to have undergone open RNU and adjuvant chemotherapy administration (both $P < 0.001$).

Association of Smoking with IVR in all 519 Patients

The median (interquartile range) follow-up of patients alive at censorship was 37 (19–73) months. Within the follow-up, 152 patients (29%) had IVR. Actuarial IVR-free survival estimates (standard error) at 2, 5, and 10 years after RNU were 72 (2)%, 58 (3)%, and 51 (4)%, respectively. Information on the frequency of IVR and on time to IVR in the entire cohort and stratified by smoking status is shown in Table 1.

In univariable analyses, current and former smokers had a higher risk of IVR than never smokers (both $P \leq 0.001$). There was no difference between former and current smokers. Light-short-term, moderate, and heavy-long-term smokers had higher risks of IVR than never smokers (all $P \leq 0.01$). There was no difference between light-short-term and moderate smokers and, between light-short-term and heavy-long-term smokers.

When analysing patients according to smoking quantity and duration separately, those who smoked ≥20 cpd or ≥20 years had a higher risk of IVR than never smokers (both $P \leq 0.001$).

The multivariable analyses investigating the association of smoking features with IVR are shown in Table 2. These analyses were adjusted for the effects of standard clinicopathological parameters, e.g. age, gender, previous history of bladder cancer, surgical approach, tumour location, tumour stage and grade, presence of lymphovascular invasion and concomitant carcinoma *in situ* (CIS). In multivariable analysis, current smoking status was associated with IVR (hazard ratio [HR] 1.69; 95% CI, 1.05–2.72; $P = 0.03$). Compared with never smokers, smokers with a smoking quantity of ≥20 cpd, or smoking duration of ≥20 years, or heavy-long-term smokers all had a significantly higher risk of IVR (all $P \leq 0.04$).

Association of Smoking with IVR in Patients without History of Previous Bladder Cancer (344 Patients)

When excluding patient with previous history of bladder cancer (175 patients), within a median follow-up of 36 months, 73 patients (21%) had IVR. Actuarial IVR-free survival estimates (standard error) at 2, 5, and 10 years after RNU were 80 (3)%, 67 (4)%, and 63 (4)%, respectively. In multivariable analysis, current smoking status, smokers with a smoking quantity of ≥20 cpd, or smoking duration of ≥20 years, or heavy-long-term smokers all had a significantly higher risk of IVR than never smokers (all $P \leq 0.01$). Interestingly, former smokers, smokers with a smoking quantity of <20 cpd, or smoking duration of <20 years, or light-short-term or moderate smokers all had a significantly higher risk of IVR than never smokers (all $P \leq 0.03$).

Effect of Smoking Cessation on Clinicopathological Characteristics and IVR

In 204 former smokers, 136 (67%) quit smoking at <10 years (recent former smokers) and 68 (33%) at >10 years (distant former smokers) before RNU. Distant former smokers did not differ from never smokers for IVR rates on multivariable analyses ($P > 0.05$), while recent former smokers had worse outcomes, when excluding patients with previous bladder cancer ($P = 0.03$).

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Table 1 Descriptive characteristics of 519 patients treated with RNU for UTUC according to smoking status.

Variable	All (*n* = 519)	Never smoked (*n* = 190)	Former smoker (*n* = 204)	Current smoker (*n* = 125)	*P*
N (%) :					
Smoking quantity, cpd:					–
Never smoked	190 (36)	190 (100)	–	–	
1–9	64 (12)	–	37 (18)	27 (22)	
10–19	128 (25)	–	68 (33)	60 (48)	
20–29	76 (15)	–	52 (26)	24 (19)	
≥30	61 (12)	–	47 (23)	14 (11)	
Smoking duration, years:					–
Never smoked	190 (36)	190 (100)	–	–	
10–19.9	78 (15)	–	50 (25)	27 (22)	
20–29.9	135 (26)	–	77 (38)	58 (46)	
30–30.9	74 (14)	–	48 (23)	26 (21)	
≥40	43 (9)	–	29 (14)	14 (11)	
Years from smoking cessation:					–
Never smoked	190 (36)	190 (100)	–	–	
<10	136 (26)	–	136 (67)	–	
≥10	68 (14)	–	68 (33)	–	
Current smoker	125 (24)	–	–	323 (100)	
Median (IQR) age, years	70 (61–76)	70 (61–77)	71 (63–77)	69 (61–74)	0.35
N (%):					
Gender:					0.34
Male	330 (64)	114 (60)	137 (67)	79 (63)	
Female	189 (36)	76 (40)	67 (33)	46 (37)	
Tumour location:					0.04
Renal pelvi-calyceal system	352 (68)	116 (61)	145 (71)	91 (73)	
Ureter	167 (32)	74 (39)	59 (29)	34 (27)	
Surgical approach:					
Open	397 (77)	150 (79)	139 (68)	108 (86)	<0.001
Laparoscopic	122 (23)	40 (21)	65 (32)	17 (14)	
Pathological stage:					0.01
pT0, Ta, Tis, T1	256 (49)	102 (54)	110 (54)	44 (35)	
pT2	101 (20)	35 (18)	38 (19)	28 (22)	
pT3	140 (27)	47 (25)	52 (25)	41 (33)	
pT4	22 (4)	6 (3)	4 (2)	12 (10)	
Pathological grade:					0.16
Low grade	88 (17)	35 (18)	37 (18)	16 (13)	
High grade	431 (83)	155 (82)	167 (82)	109 (87)	
Lymph node status:					<0.001
pN0	194 (37)	72 (38)	82 (40)	40 (32)	
pNx	260 (50)	108 (57)	103 (51)	49 (39)	
pN+	65 (13)	10 (5)	19 (9)	36 (29)	
Concomitant CIS:					0.46
Absent	344 (66)	126 (66)	130 (64)	88 (70)	
Present	175 (34)	64 (34)	74 (36)	37 (30)	
Lymphovascular invasion:					0.03
Absent	347 (67)	136 (72)	139 (68)	72 (58)	
Present	172 (33)	54 (28)	65 (32)	53 (42)	
Adjuvant chemotherapy:					<0.001
Not administered	466 (90)	182 (96)	192 (94)	92 (74)	
Administered	53 (10)	8 (4)	12 (6)	33 (26)	
Occurrence of IVR:					–
Yes	152 (29.3)	33 (17.4)	70 (34.3)	49 (39.2)	
No	367 (70.3)	157 (82.6)	134 (65.7)	76 (60.8)	
Median (IQR) time to IVR, years	27.3 (12-60)	44.9 (13-68)	32.7 (9-78)	23.9 (16-36)	–

IQR, Interquartile range.

Discussion

Cigarette smoking is an established risk factor for UTUC development and prognosis, in terms of disease recurrence (local and distant) and cancer-specific mortality [3,4,16]. IVR after RNU is a frequent event. Thus, a better understanding of the association between smoking exposure and IVR could offer insights into the natural history of UTUC, as well as improve patient counselling and possibly outcomes through modification of smoking habits.

We confirmed that current smokers were at a significantly higher risk of IVR [12]. The odds of IVR increased progressively from never to former to current smokers.

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Table 2 Multivariable cox regression analyses predicting IVR in 519 patients with UTUC treated with RNU according to smoking status, quantity, duration and cumulative exposure.

Variable	All patients (n = 519)				Patients without previous bladder cancer (n = 344)			
	HR	95% CI lower	95% CI upper	*P*	HR	95% CI lower	95% CI upper	*P*
Age	1.02	1.01	1.04	0.02	1.02	0.99	1.04	0.07
Female gender	0.98	0.68	1.40	0.91	1.23	0.75	2.01	0.41
Ureteric tumour location	0.99	0.69	1.42	0.94	1.00	0.57	1.76	0.98
Previous history of bladder cancer	2.51	1.74	3.62	<0.001	–	–	–	–
Laparoscopic vs open RNU	1.89	1.22	2.93	0.01	1.50	0.81	2.79	0.20
Lymph node metastasis:				0.08				0.30
pNx vs pN0	1.20	0.83	1.73	0.34	1.52	0.87	2.67	0.15
pN+ vs pN0	1.98	1.08	3.64	<0.03	1.63	0.66	4.06	0.29
Pathological grade	0.68	0.37	1.30	0.28	1.03	0.35	3.25	0.87
Pathological stage:				0.25				0.01
pT2 vs pT0/a/is/1	1.15	0.68	1.92	0.61	0.58	0.27	1.27	0.18
pT3 vs pT0/a/is/1	1.41	0.80	2.49	0.24	0.80	0.35	1.84	0.60
pT4 vs pT0/a/is/1	2.67	1.02	7.01	0.04	3.43	1.01	11.79	0.04
Lymphovascular invasion	1.38	0.85	2.24	0.20	1.29	0.61	2.71	0.51
Concomitant CIS	3.93	2.72	5.67	<0.001	4.17	2.48	7.02	<0.001
Smoking status:				0.08				0.01
Former vs never	1.50	0.95	2.38	0.08	2.81	1.41	5.59	0.01
Current vs never	1.69	1.05	2.72	0.03	2.55	1.33	4.89	0.01
Smoking quantity:				0.09				0.01
<20 cpd vs never	1.52	0.97	2.38	0.07	2.59	1.38	4.86	0.01
≥20 cpd vs never	1.67	1.04	2.68	0.03	2.78	1.40	5.53	0.01
Smoking duration:				0.10				0.01
<20 years vs never	1.56	0.89	2.76	0.12	2.95	1.34	6.47	0.01
≥20 years vs never	1.58	1.04	2.43	0.03	2.59	1.41	4.75	0.01
Cumulative exposure:				0.19				0.02
Light short-term vs never	1.50	0.75	2.98	0.25	2.74	1.11	6.78	0.03
Moderate vs never	1.54	0.98	2.42	0.06	2.65	1.40	5.01	0.01
Heavy long-term vs never	1.67	1.01	2.76	0.04	2.66	1.28	5.51	0.01
Time from cessation:				0.12				0.09
≥10 years vs never	1.49	0.91	2.45	0.11	1.35	0.77	2.38	0.29
<10 years vs never	1.74	0.97	3.11	0.06	1.72	1.04	2.83	0.03
Current smoker	1.73	1.07	2.80	0.03	1.72	1.06	2.79	0.03

However, the magnitude of the odds was higher for established prognostic factors of IVR, e.g. concomitant CIS and previous history of bladder cancer than for smoking, which is similar to previous findings in UTUC [5–8,17,18]. The failure to detect a statistical significant association between former smoking status and IVR in multivariable analyses might be explained due to the strength of these covariables. In addition, controlling for patients with previous bladder cancer confirmed the expected association between former smoking status and IVR.

We found a dose relationship between cumulative smoking exposure and risk of developing IVR. Although never smokers had the most favourable outcomes, heavy-long-term smokers had the worst. In addition, patients with the highest smoking quantity and duration presented with the worst outcomes. Similar to the present findings, Hagiwara et al. [12] found that a threshold of 50 cpd was predictive of IVR. Although the exact mechanisms of smoking-induced urothelial carcinogenesis remain unknown, accumulating evidence suggests that dose escalation and longer duration might increase not only the risk of development of UC but also its aggressiveness and thus impact disease recurrence. Thus, heavy-long-term smokers should be considered for close follow-up and immediate instillation of intravesical chemotherapy after RNU [10,11].

We found that smoking cessation for >10 years could mitigate the unfavourable effects of smoking in patients with UTUC. Distant former smokers had lower rates of IVR than recent former or current smokers. This beneficial effect in patients with long-term smoking cessation may be due to minor field damage effects or better-retained repair mechanisms. Although the present results confirmed the need of long-term smoking cessation to reduce the effect of smoking in UTUC, this effect was not present in all former smokers (when considering all patients). Smoking intensity seems to have an important impact on outcomes; a combination of smoking with other inherent/genetic, environmental, behavioural, or lifestyle factors that the present study could not adjust for might be another explanation.

The present study has several limitations. First and foremost are limitations inherent to the retrospective and

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multi-institutional nature of the study including surgical, pathological and follow-up differences among centres. However, all surgeons and pathologists operated at centres dedicated to the management of UTUC. Comorbidities might have influenced the decision-making for surgical therapy, introducing a selection bias. Another bias might be the exclusion of tobacco products other than cigarettes (e.g. cigars, pipes, tobacco chewing) and different forms of tobacco exposure (e.g. second-hand smoking, occupational exposure). We could also not adjust the present analyses for different types of tobacco and its constituents. Finally, smoking history was self-reported and therefore subject to recall bias.

In conclusion, cigarette smoking is significantly associated with IVR in patients treated with RNU for UTUC. Current and heavy-long-term smokers have the highest risk of poor outcomes. Smoking cessation for >10 years before RNU seems to reduce the unfavourable effects of smoking on outcomes. Although the present results need to be confirmed in a robust prospective study, these findings should further help urologists and general healthcare practitioners to counsel their patients about the benefits of smoking cessation and prevention programmes. Heavy-long-term smokers should be considered for close follow-up and immediate instillation of mitomycin C after RNU.

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Conflict of Interest

E.X. is a recipient of a grant from the French Association of Urology (Association Française d'Urologie, AFU). The other authors do not have any conflict of interest to disclose.

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Abbreviations: CIS, carcinoma in situ; cpd, cigarettes per day; IVR, intravesical recurrence; RNU, radical nephroureterectomy; UTUC, upper tract urothelial carcinoma.

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