

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

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Abstract

Objectives

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

A total of 519 patients underwent RNU at five institutions. Smoking history included smoking status, quantity of cigarettes per day (CPD), duration, and time from cessation. The 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). Univariable/multivariable cox regression analyses assessed the effects of smoking on IVR.

Results

A total of 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%) experienced IVR. Actuarial IVR-free-survival estimates at 2, 5, and 10 years were $72 \pm 2\%$ (standard error), $58 \pm 3\%$, and $51 \pm 4\%$, 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 (p values ≤ 0.01). Patients who quit smoking ≥ 10 years prior to RNU had better IVR outcomes than current smokers and those patients who quit smoking < 10 yr prior to RNU.

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 IVR. Smoking cessation >10 yr prior to RNU seems to mitigate these detrimental effects.

Introduction

Smoking is the most common risk factor for developing upper tract urothelial carcinoma (UTUC), increasing the relative risk by 5- to 7-fold [1-3]. We previously showed that smoking status and cumulative smoking exposure were associated with worse oncologic 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 of 10 and more years seemed to abrogate the detrimental effect of smoking on UTUC prognosis.

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

Similarly to our previous study [4], we hypothesized that there is a dose-response relationship between smoking intensity and occurrence of intravesical recurrence, 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

Patient selection

In this institutional review board-approved study, all participating sites provided necessary institutional data-sharing agreements prior to the initiation of the study. A total of five centers provided data. A computerized 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. Prior to 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 total, 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 clinicopathologic variables and 345 on follow-up and therefore were excluded from the analysis. Patients reporting tobacco use other than cigarette smoking (eg, tobacco chewing, cigars, and pipes) were excluded (n = 26). Complete data of 519 patients who underwent RNU between 1987 and 2007 for UTUC were available for 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 (n=53).

Pathologic evaluation

All surgical specimens were processed according to standard pathologic procedures at each institution [8, 13]. Genitourinary pathologists who were blinded to clinical outcomes

reexamined all specimens according to standardized criteria and confirmed UC histology.

Tumors were staged according to the 2010 American Joint Committee on Cancer/Union Internationale Contre le Cancer TNM classification. Tumor grading was performed according to the 2004 World Health Organization/International Society of Urologic Pathology consensus classification.

Smoking assessment

Smoking history was routinely assessed at a clinic visit within 1 yr 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; ie, quantity; never smoked, 1–9, 10–19, 20–29, ≥ 30), duration in years (never smoked, ≤ 9.9 , 10–19.9, 20–29.9, 30–39.9, ≥ 40), and years since smoking cessation to RNU in former smokers (≤ 4.9 , 5–9.9, ≥ 10 yr). Patients who reported smoking cessation within 1 yr prior to surgery were considered current smokers [4, 14, 15].

Follow-up regimen

Patients were generally followed every 3-4 months for the first year following RNU, every 6 months from the second through 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 urinary tract. Elective bone scans, chest computerized tomography, and/or magnetic resonance imaging were performed when clinically indicated. Bladder cancer occurrences were coded as intravesical recurrence; excluding tumor relapse in the operative

field, contralateral ureter and/or pyelocalyceal 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 yr), and years since cessation (never vs ≤ 9.9 vs ≥ 10 yr vs current smoking) were grouped based on previous publications [4, 14, 15]. We categorized patients based on their cumulative smoking exposure into four groups: never smoker, light-short-term smoker (≤ 19 CPD and ≤ 19.9 yr), moderate smoker (≥ 20 CPD and ≤ 19.9 yr or ≤ 19 CPD and ≥ 20 yr), and heavy-long-term smokers (≥ 20 CPD and ≥ 20 yr) [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 intravesical recurrence, univariable and multivariable cox regression analyses were conducted. All reported p values are two sided and statistical significance was set at $p < 0.05$. Statistical tests were performed with SPSS v.20 (SPSS, IBM Corp., Armonk, NY, USA).

Results

Clinicopathologic characteristics and smoking features

Table 1 shows the clinicopathologic 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 more than 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 clinicopathologic 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; p-values<0.03). Therefore, current smokers were more likely to have undergone open RNU and adjuvant chemotherapy administration (both p-values <0.001).

Association of smoking with intravesical recurrence in all patients (n=519)

Median follow-up of patients alive at censorship was 37 months (interquartile range: 19-73). Within the follow-up, 152 patients (29%) experienced intravesical recurrence. Actuarial intravesical recurrence-free survival estimates at 2, 5, and 10 yr after RNU were 72 ± 2% (standard error), 58 ± 3%, and 51 ± 4%, respectively. Information on the frequency of intravesical recurrence and on time to intravesical recurrence 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 intravesical recurrence when compared to never smokers (both p values ≤0.001). There was no difference between former and current smokers. Light-short-term, moderate, and heavy-long-term smokers had higher risks of intravesical recurrence compared with never smokers (all p

values ≤ 0.01). There was no difference between light-short-term and moderate smokers and, between light-short-term and heavy-long-term smokers.

When analyzing patients according to smoking quantity and duration separately, those who smoked ≥ 20 CPD or ≥ 20 yr had a higher risk of intravesical recurrence compared to never smokers (both p values ≤ 0.001).

The multivariable analyses investigating the association of smoking features with intravesical recurrence is shown in table 2. These analyses were adjusted for the effects of standard clinicopathologic parameters such as age, gender, previous history of bladder cancer, surgical approach, tumor location, tumor stage and grade, presence of lymphovascular invasion and concomitant cis. In multivariable analysis, current smoking status was associated with intravesical recurrence (hazard ratio (HR)): 1.69; 95% confidence interval (CI), 1.05–2.72; p = 0.03). Compared with never smokers, smokers with a smoking quantity ≥ 20 CPD, or smoking duration ≥ 20 yr, or heavy-long-term smokers had all a significantly higher risk of intravesical recurrence (all p values ≤ 0.04).

Association of smoking with intravesical recurrence in patients without history of previous bladder cancer (n=344)

When excluding patient with previous history of bladder cancer (n=175), within a median follow-up of 36 months, 73 patients (21%) experienced intravesical recurrence.

Actuarial intravesical recurrence-free survival estimates at 2, 5, and 10 yr after RNU were $80 \pm 3\%$ (standard error), $67 \pm 4\%$, and $63 \pm 4\%$, respectively. In multivariable analysis, current smoking status, smokers with a smoking quantity ≥ 20 CPD, or smoking duration ≥ 20 yr, or heavy-long-term smokers had all a significantly higher risk of intravesical recurrence compared to never smokers (all p values ≤ 0.01). Interestingly, former smokers, smokers with a smoking quantity < 20 CPD, or smoking duration < 20 yr, or light-short-term or moderate

smokers all had a significantly higher risk of intravesical recurrence compared to never smokers (all p-values ≤ 0.03).

Effect of smoking cessation on clinicopathologic characteristics and intravesical recurrence

In 204 former smokers, 136 (67%) quit smoking < 10 yr (recent former smokers) and 68 (33%) > 10 yr (distant former smokers) prior to RNU. Distant former smokers did not differ from never smokers with regards to intravesical recurrence rates on multivariable analyses (p values > 0.05), while recent former smokers had worse outcomes, when excluding patients with previous bladder cancer (p=0.03).

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].

Intravesical recurrence after RNU is a frequent event. Thus, a better understanding of the association between smoking exposure and intravesical recurrence could offer insights into the natural history of UTUC, as well as improve patient counseling and possibly outcomes through modification of smoking habits.

We confirmed that current smokers were at a significantly higher risk intravesical recurrence [12]. The odds of experiencing intravesical recurrence increased progressively from never to former to current smokers. However, the magnitude of the odds was higher for established prognostic factors of intravesical recurrence such as 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 intravesical recurrence 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 intravesical recurrence.

We found a dose relationship between cumulative smoking exposure and risk of developing intravesical recurrence. Although never smokers had the most favorable outcomes, heavy-long-term smokers had the worst. In addition, patients with the highest smoking quantity and duration presented with the worst outcomes. Similarly to our findings, Hagiwara et al. found that a cut-off of 50 cpd was predictive of intravesical recurrence [12]. 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 >10 yr could mitigate the unfavorable effects of smoking in UTUC patients. Distant former smokers had lower rates of intravesical recurrence compared with 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 our 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, behavioral, or lifestyle factors that our study could not adjust for might be another explanation.

Our study has several limitations. First and foremost are limitations inherent to the retrospective and multi-institutional nature of the study including surgical, pathological and follow-up differences among centers. However, all surgeons and pathologists operated at centers dedicated to the management of UTUC. Comorbidities might have influenced the decision-making regarding surgical therapy, introducing a selection bias. Another bias might be the exclusion of tobacco products other than cigarettes (eg, cigars, pipes, tobacco chewing) and different forms of tobacco exposure (eg, secondhand smoking, occupational exposure). We could also not adjust our analyses for different types of tobacco and its constituents. Finally, smoking history was self-reported and therefore subject to recall bias.

Conclusions

Cigarette smoking is significantly associated with intravesical recurrence in patients treated with RNU for UTUC. Current and heavy-long-term smokers have the highest risk for poor outcomes. Smoking cessation >10 yr prior to surgery seems to reduce the unfavorable effects of smoking on outcomes. Although our results need to be confirmed in a robust prospective study, these findings should further help urologists and general health care practitioners to counsel their patients regarding the benefits of smoking cessation and prevention programs. Heavy-long-term smokers should be considered for close follow-up and immediate instillation of mitomycin C after RNU.

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	All n (%) (n = 519)	Never smoked n (%) (n = 190)	Former smoker n (%) (n = 204)	Current smoker n (%) (n = 125)	p value
Smoking quantity					–
Never smoked	190 (36)	190 (100)	–	–	
1–9 CPD	64 (12)	–	37 (18)	27 (22)	
10–19 CPD	128 (25)	–	68 (33)	60 (48)	
20–29 CPD	76 (15)	–	52 (26)	24 (19)	
≥30 CPD	61 (12)	–	47 (23)	14 (11)	
Smoking duration, yr					–
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)	
Age, yr; median (IQR)	70 (61–76)	70 (61–77)	71 (63–77)	69 (61–74)	0.35
Gender					0.34
Male	330 (64)	114 (60)	137 (67)	79 (63)	
Female	189 (36)	76 (40)	67 (33)	46 (37)	
Tumor location					0.04
Renal pelvicaliceal 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)	
Pathologic 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	Variable	22 (4)	All patients 6 (3) (n=519)	4 (2)	Patients without previous bladder cancer (n=344) 12 (10) 0.16	
Pathologic grade						
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 carcinoma in situ						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 (n,%)						<0.001
Not administered		466 (90)	182 (96)	192 (94)	92 (74)	
Administered		53 (10)	8 (4)	12 (6)	33 (26)	
Occurrence of intravesical recurrence (n,%)						-
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)	
Time to intravesical recurrence (yr, median (IQR))						-
		27.3 (12-60)	44.9 (13-68)	32.7 (9-78)	23.9 (16-36)	

Table 1. Descriptive characteristics of 519 patients treated with radical nephroureterectomy for upper tract urothelial carcinoma according to smoking status.

CPD: Cigarettes per day.
IQR: Interquartile range.

	HR	95% CI Lower	95% CI Upper	p value	HR	95% CI Lower	95% CI Upper	p value
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
Ureteral tumor 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
Pathologic grade	0.68	0.37	1.30	0.28	1.03	0.35	3.25	0.87
Pathologic 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 carcinoma in situ	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
<20y vs never	1.56	0.89	2.76	0.12	2.95	1.34	6.47	0.01
>= 20y vs never	1.58	1.04	2.43	0.03	2.59	1.41	4.75	0.01
Cumulative				0.19				0.02

exposure								
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
>=10y vs never	1.49	0.91	2.45	0.11	1.35	0.77	2.38	0.29
<10y 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

Table 2. Multivariable cox regression analyses predicting intravesical recurrence in 519 patients with upper tract urothelial carcinoma treated with radical nephroureterectomy according to smoking status, quantity, duration and cumulative exposure.