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Impact of smoking status at diagnosis on disease recurrence and death in upper tract urothelial carcinoma

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Abstract

- To evaluate the impact of smoking exposure on oncological outcomes in patients with upper tract urothelial carcinoma (UTUC) treated with radical nephroureterectomy (RNU).
- Patient and disease characteristics from 288 patients with UTUC treated with RNU between 1995 and 2008 were collected from a prospectively maintained database at the Memorial Sloan-Kettering Cancer Center.
- Disease recurrence was defined as distant metastases, or local failure in the operative site or regional nodes.
- Factors associated with recurrence and death were determined.
- The prevalence of current, former and never smoking at diagnosis was 19.1%, 55.2%, and 25.7%, respectively.
- 71.0% of patients reported a ≥20 pack-year smoking history.
- With a median follow-up of 4.02 years, disease recurrence occurred in 27% (n = 79) of patients and 41% (n = 117) died during follow-up.
- While age at diagnosis, American Society of Anesthesiologists score, advanced stage, nodal involvement and high grade adversely affected recurrence-free survival, smoking status was not associated with risk of recurrence or death in multivariate analysis (P = 0.60).

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Conflict of Interest
None declared.

- Multivariate competing risks regression showed that current smokers faced a significantly higher risk of death than never smokers (hazard ratio 3.64, 95% confidence interval 1.59–8.34).
- While smoking status at diagnosis and cumulative smoking exposure were not associated with UTUC recurrence, our findings highlight the substantial risk of death in patients with UTUC who are active smokers.
- Treatment plans to promote smoking cessation are recommended for these patients.

Keywords

tobacco; smoking; urinary bladder neoplasms; outcome assessment; nephrectomy; prognosis

Introduction

Upper tract urothelial carcinoma (UTUC) is a rare cancer, accounting for 5–7% of all urothelial malignancies [1]. The 5-year survival rate is nearly 90% for patients with early-stage UTUC but decreases to <30% in patients with regional nodal metastases and <10% in patients with distant metastases [2]. Most strategies to reduce disease recurrence and progression have focused on optimizing diagnostic imaging and surgical techniques, with little attention given to addressing modifiable risk factors, such as cigarette smoking.

Cigarette smoking is the primary causative risk factor for both UTUC and lower tract urothelial carcinoma [3]. Cigarette smoking accounts for 50% of urothelial carcinoma cases in males and 30% in females [4,5], smokers are three times more likely to develop urothelial carcinoma than never smokers, and risk increases with lifetime duration of smoking and mean number of cigarettes smoked per day [5,6]. Smoking is also an important modifier of genetic risk, as smokers who carry variants in *NAT2* and *GSMT1* are at highest risk of developing urothelial carcinoma [7]. Although risk levels never return to those of never smokers [8], an immediate decrease in risk of ~40% is observed among those with high risk genetic polymorphisms who stop smoking, which implies that tobacco has a late-stage effect in urothelial carcinogenesis.

Despite evidence from animal models and cell lines suggesting that constituents in tobacco smoke may promote cancer growth by increasing cellular proliferation and decreasing apoptosis [9–13], previous clinical studies on the impact of smoking on the prognosis of lower tract urothelial carcinoma have yielded mixed results. In 2002, a systematic review of the effect of smoking on prognosis concluded that there was evidence to suggest that smoking cessation might favourably alter the course of bladder cancer [14]. Since then, one study reported that continued smoking after diagnosis was a significant predictor of shorter recurrence-free survival (RFS), while a second study found that smoking status at diagnosis was not associated with response to BCG therapy, disease recurrence, progression, all-cause mortality, or urothelial cancer-specific mortality [15,16]. For UTUC, only one study, based on 105 patients, has examined survival differences between ever and never smokers [17]. To inform clinical practice, more research is needed to elucidate the role of smoking on the prognosis of UTUC, particularly with respect to recency of smoking exposure.

In the present study, we examined the impact of smoking status and cumulative smoking exposure on the risk of recurrence and death among 288 patients with UTUC treated with radical nephroureterectomy (RNU) in a single high-volume referral center. We hypothesized that patients who were current smokers at the time of diagnosis would experience decreased RFS compared with patients who had stopped smoking before diagnosis (former smokers) or never smoked cigarettes.

Materials and Methods

Patient Selection

Data from 324 consecutive patients with UTUC who underwent RNU with ipsilateral bladder cuff resection from 1995 to 2008 were obtained from a prospectively maintained clinical database. Genitourinary surgeons performed surgery according to standard protocol for RNU, which involves excision of the kidney with the entire length of the ipsilateral ureter and adjacent bladder cuff. The hilar and regional lymph nodes adjacent to the ipsilateral great vessels were resected as needed, along with enlarged lymph nodes that were either identified on preoperative CT scans or palpable intraoperatively. The institutional review board reviewed and approved the request for exemption of this retrospective chart review of clinical data and approved waivers for Health Insurance Portability and Accountability Act authorization and informed consent. Patients were excluded if they were treated with neoadjuvant chemotherapy ($n = 30$) or had missing information regarding smoking history ($n = 6$), resulting in a total sample size of 288.

Pathological Evaluation

Surgical specimens were processed using standard pathological techniques and reviewed by genitourinary pathologists. All specimens were histologically confirmed to be urothelial carcinoma. Tumours were staged according to the 2002 American Joint Committee on Cancer TNM classification [18]. Tumour grading was assessed according to the 1998 WHO consensus classification [19].

Follow-Up Regimen

Patients were seen every 3 months for the first year after RNU, every 4 months for the second year, every 6 months for the third, fourth and fifth years, and annually thereafter. Follow-up consisted of history, physical examination, serum chemistry studies, urinary cytology, chest radiography, cystoscopic evaluation and radiographic evaluation of the contralateral upper urinary tract. Disease recurrence was defined by pathologically proven tumour in the operative site, regional nodes or distant metastasis. The cause of death was determined by chart review and corroborated by death certificates.

Smoking Exposure

Self-reported smoking data were routinely collected at the time of diagnosis on all urology patients. Available variables for analysis included smoking status (current, former, or never smoker), duration of smoking (<20, 20–39, and ≥40 years), and quantity smoked (1–10, 11–20, 21–30, and >30 CPD – cigarettes per day). Patients were considered current smokers if they reported smoking at the time of diagnosis or stopped smoking within 1 year of

diagnosis, and were considered former smokers if they had stopped smoking at least 1 year before diagnosis. Duration of smoking and CPD were used to construct pack-years smoked for all former and current smokers (<20 vs ≥20 pack-years) as a measure of cumulative smoking exposure.

Statistical Analyses

Descriptive statistics were calculated for demographic, disease and smoking characteristics. Associations between categorical variables were assessed using the chi-squared test and the Kruskal–Wallis test was used for continuous variables. Follow-up time was calculated from the date of diagnosis to the first of either recurrence or death. Patients alive and without disease recurrence were censored at the date of their last follow-up. RFS probabilities were estimated using the Kaplan–Meier method, in which recurrence and death were included as events. The log-rank test determined differences in survival function between groups. Because smoking is an established risk factor for common health problems that increase risk of death, we also conducted competing risks analyses. The cumulative incidence was estimated, where disease recurrence was treated as the primary event of interest, and death without recurrence as a competing event. Gray's test was used to determine differences in cumulative incidence function between groups [20]. Multivariate Cox regression and competing risks regression models were adjusted for traditional prognostic factors that were identified *a priori* and included age at diagnosis, American Society of Anesthesiologists (ASA) score, pathological stage and grade, and nodal status. A P value <0.05 was considered to indicate statistical significance. Statistical analyses were conducted using SAS (version 9.2. Cary, NC: SAS Institute; 2008) and R (version 2.11.0. R Development Core Team; 2010), including the 'SURVIVAL' and 'CMPRSK' packages.

Results

Table 1 shows the associations between demographic and disease characteristics by smoking status. The patient population was 92% white and 65% male, with a median (range) age at diagnosis of 71 (37–90) years. Forty-seven percent of patients had ASA scores ≥3, 26% had advanced disease based on pathological tumour stage (pT ≤ 2), and 10% had lymph node involvement based on nodal stage. High grade disease was seen in 77% of patients. Nineteen percent of patients were current smokers at the time of diagnosis and 55% were former smokers. Of the ever smokers, 71% smoked for ≥20 pack-years. Compared with never and former smokers, current smokers were significantly more likely to be younger, and have localized disease, and low grade disease (all $P < 0.05$). Never smokers were more likely than current and former smokers to be female ($P < 0.001$).

The median (range) follow-up for patients was 4.02 (0.03–14.65) years. During the follow-up period, 41% ($n = 117$) of the study population died. Of the 117 deaths, 56% ($n = 66$) were attributable to disease, 28% ($n = 33$) were attributable to other causes, and 15% ($n = 18$) resulted from an unknown cause. Disease recurrence occurred in 27% ($n = 79$) of patients, and 80% ($n = 63$) of the patients with disease recurrence ultimately died from disease.

Figure 1 presents survival probabilities by smoking status. Smoking status was not significantly associated with RFS in univariate analysis ($P = 0.684$, Fig. 1A), nor was pack-

years ($P = 0.622$; data not shown). In multivariate analysis, smoking status was not associated with risk of recurrence or death ($P = 0.600$, Table 2) after adjusting for traditional prognostic factors. Increased age at diagnosis, ASA score ≥3, advanced pT stage, positive nodal status, and high grade disease were all associated with decreased RFS probability in univariate analysis and remained associated with increased risk of recurrence or death in multivariate analysis.

Since smoking is associated with increased risk of death from other health problems such as heart disease, we used competing risks analyses to examine the cumulative incidence of recurrence where death without recurrence was treated as a competing event. Smoking status was significantly associated with cumulative incidence of recurrence in univariate analysis ($P = 0.009$), where never smokers had the highest cumulative incidence of recurrence and current smokers had the lowest. Smoking status was also significantly associated with the competing event of death without recurrence ($P = 0.014$), but the direction was reversed so that current smokers had the highest cumulative incidence of death without recurrence (Fig. 1B). Pack-years was not significantly associated with cumulative incidence of recurrence or death without recurrence ($P = 0.844$ and $P = 0.202$, respectively; data not shown). After adjusting for traditional prognostic factors in multivariate competing risks regression, smoking status was no longer associated with recurrence ($P = 0.180$, Table 3), but a strong association remained between smoking status and death without recurrence ($P < 0.001$), where current smokers had increased risk of death without recurrence compared with never smokers. Advanced pT stage, positive nodal status, and high grade disease were all associated with increased cumulative incidence of recurrence in univariate analysis and remained associated with increased risk of recurrence in multivariate analysis.

Discussion

The present findings suggest that smoking status at diagnosis and cumulative smoking exposure do not significantly increase risk of UTUC recurrence; however, these findings also highlight the substantial risk of death faced by patients with UTUC who are current smokers, and underscore the importance of promoting smoking cessation among patients with UTUC.

The only previous report to consider smoking exposure in the context of UTUC prognosis was conducted among 105 patients. In univariate analyses, Simsir *et al*. [17] found that ever smokers experienced shorter time to bladder recurrence than never smokers, but did not differ with respect to time to pelvic recurrence or distant metastasis. Importantly, recurrence of upper tract tumours in the bladder was not an endpoint in the present study, and we believe this may represent tumour seeding or multifocal disease as opposed to new tumour growth. Consistent with the present findings, Simsir *et al*. did not find that pack-years of smoking affected UTUC prognosis. The present study extends their report in several ways. First, we subdivided ever smokers into current and former smokers to better understand whether recency of smoking influences UTUC outcome. Second, we conducted multivariate analyses that showed that smoking status was not an independent predictor of recurrence when traditional prognostic factors were taken into account. Most notably, our competing risks analyses showed that, although current smoking did not increase the risk of recurrence,

it imparted a significant risk of dying compared with former and never smoking. Without the latter analyses, we would have erroneously concluded that smoking status is not relevant in UTUC survival.

Our hypothesis that current smoking adversely impacts recurrence risk was not supported. In fact, compared with never and former smokers, current smokers had lower proportions of advanced stage disease, nodal involvement, and high grade disease. It is possible that selection bias influenced our results since only patients who were healthy enough to undergo RNU were included in the present analysis. Current smokers with advanced disease may be less likely to be eligible for surgery and therefore be underrepresented in the study. This is indirectly supported by the significantly younger age of the current smokers compared with former and never smokers. Remarkably, current smokers selected for surgery and representing a younger and potentially healthier population, still died at a greater rate than former and never smokers during follow-up. Since effective smoking cessation treatments exist for patients with cancer [21], the promotion of smoking cessation among patients with UTUC who are current smokers at diagnosis is warranted.

Strengths of the present study include the multiple aspects of smoking status evaluated and an analytical approach that considered competing risks. Limitations are acknowledged. As prospective data on changes in smoking behaviour after diagnosis were not available, we considered only patients' smoking status at diagnosis. Recent findings from other cancers suggest that post-diagnosis smoking is an important factor to consider in prognostic studies [22,23]. In the present study, 20% of patients with UTUC reported being current smokers at diagnosis. This may be an underestimate since it was based on self-reporting, which is prone to recall bias and intentional false reporting [24]. Future studies should consider pre- and post-diagnosis smoking exposure and should biochemically verify smoking status among larger groups of patients with UTUC.

Cancer diagnosis and treatment present an excellent opportunity to encourage smoking cessation among patients [25–27]; however, a recent survey of 1821 American urologists found that more than half of them never discuss smoking cessation with their patients [28]. Given the frequency of contact between urologists and patients with bladder cancer, urologists are in a unique position to promote smoking cessation as part of comprehensive clinical care.

In conclusion, the present study of patients with UTUC treated with RNU found that the majority of patients had been exposed to cigarette smoking and 71% of these patients report smoking heavily (≥20 pack-years). While smoking status did not adversely affect UTUC recurrence, current smokers had a significantly higher risk of death without recurrence than never smokers. Given that cigarette smoking is a modifiable risk factor and effective smoking cessation treatments exist [29], physicians treating patients with cancer should provide smoking cessation advice and counselling as part of the comprehensive management of their disease [30].

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Abbreviations

CPD	cigarettes per day
UTUC	upper tract urothelial carcinoma
RNU	radical nephroureterectomy
RFS	recurrence-free survival
ASA	American Society of Anesthesiologists
HR	hazard ratio

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What's known on the subject? and What does the study add?

- Cigarette smoking is the leading cause of urothelial carcinoma; however, the impact of smoking on outcomes after surgery for upper tract urothelial carcinoma is unknown. One study suggests that patients with a smoking history have an increased risk of recurrence in the bladder compared with never smokers but these patients did not differ with respect to time to pelvic recurrence or distant metastasis.
- We subdivided smokers into current and former smokers and performed multivariate analyses that showed that smoking status was not an independent predictor of recurrence when traditional prognostic factors were taken into account. In addition, competing risks analyses showed that although current smoking did not increase the risk of recurrence, it imparted a significant risk of dying compared with former and never smoking.

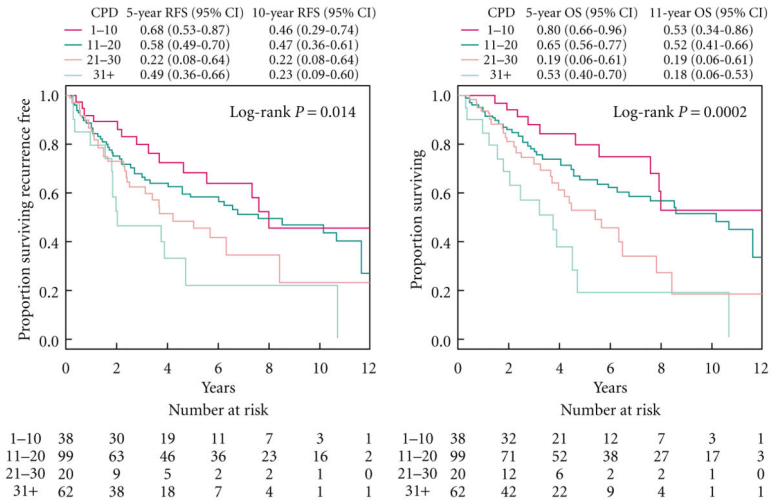

Fig. 1.

Kaplan-Meier estimates of recurrence-free survival probabilities (left) and overall free survival probabilities (right) stratified by cigarettes per day.

Table 1

Characteristics of 288 patients with UTUC by smoking status.

Characteristic	Smoking status				*P**
	Overall	**Never 74 (25.7)**	**Former 159 (55.2)**	**Current 55 (19.1)**	
Median (range) age at diagnosis	71.0 (37.0–90.0)	73.0 (43.0–88.0)	72.0 (38.0–90.0)	64.0 (37.0–82.0)	<0.001
Sex, *n* (%)					<0.001
Male	187 (64.9)	35 (47.3)	117 (73.6)	35 (63.6)	
Female	101 (35.1)	39 (52.7)	42 (26.4)	20 (36.4)	
Median (range) body mass index	26.9 (15.6–42.7)	26.6 (17.1–42.2)	27.3 (17.8–42.7)	26.9 (15.6–42.4)	0.318
Race, *n* (%)					0.795
White	266 (92.4)	68 (91.9)	146 (91.8)	52 (94.5)	
Other	22 (7.6)	6 (8.1)	13 (8.2)	3 (5.5)	
ASA score†, *n* (%)					0.167
Healthy	152 (52.8)	46 (62.2)	78 (49.1)	28 (50.9)	
Not healthy	136 (47.2)	28 (37.8)	81 (50.9)	27 (49.1)	
pT stage‡, *n* (%)					0.031
Localized	213 (74.0)	55 (74.3)	110 (69.2)	48 (87.3)	
Advanced	75 (26.0)	19 (25.7)	49 (30.8)	7 (12.7)	
N stage, *n* (%)					0.071
Nx or N0	260 (90.3)	64 (86.5)	142 (89.3)	54 (98.2)	
N1 or N2	28 (9.7)	10 (13.5)	17 (10.7)	1 (1.8)	
Grade, *n*(%)					0.025
Low	65 (22.6)	14 (18.9)	31 (19.5)	20 (36.4)	
High	223 (77.4)	60 (81.1)	128 (80.5)	35 (63.6)	
Pack-years, *n* (%)					<0.001
<20	62 (29.0)	NA	55 (34.6)	7 (12.7)	
≥20	152 (71.0)	NA	104 (65.4)	48 (87.3)	

* Chi-squared test when categorical and Kruskal–Wallis test when continuous.

† Healthy = healthy or mild systemic disease; Not healthy = severe systemic disease.

‡ Localized = Ta, T1, T2; Advanced = T3 or T4.

Table 2

Multivariate Cox regression for the association between smoking status and risk of recurrence or death.

	HR (95% CI)	*P*
Smoking status		0.600
Never	Ref	
Former	0.90 (0.59–1.37)	
Current	1.15 (0.66–1.99)	
Age at diagnosis	1.04 (1.01–1.06)	0.001
ASA score		0.023
Healthy	Ref	
Unhealthy	1.54 (1.06–2.24)	
pT stage		<0.001
Localized	Ref	
Advanced	2.24 (1.52–3.30)	
N stage		<0.001
Nx or N0	Ref	
N1 or N2	3.18 (1.87–5.39)	
Grade		0.048
Low	Ref	
High	1.62 (1.00–2.61)	

Table 3

Multivariate competing risks regression for the association between smoking status and risk of recurrence, with death as a competing event.

	Recurrence		Death without recurrence	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Smoking status		0.180		<0.001
Never	Ref		Ref	
Former	0.82 (0.47,1.42)		0.94 (0.48,1.85)	
Current	0.44 (0.19,1.06)		3.64 (1.59,8.34)	
Age at diagnosis	1.01 (0.99,1.03)	0.460	1.09 (1.05,1.13)	<0.001
ASA score		0.170		0.740
Healthy	Ref		Ref	
Unhealthy	1.44 (0.85,2.45)		1.11 (0.61,2.03)	
pT stage		<0.001		0.780
Localized	Ref		Ref	
Advanced	3.27 (1.92,5.59)		0.9 (0.44,1.85)	
N stage		0.005		0.320
Nx or N0	Ref		Ref	
N1 or N2	2.55 (1.34,4.86)		0.45 (0.09,2.19)	
Grade		0.009		0.410
Low	Ref		Ref	
High	3.57 (1.37,9.31)		0.77 (0.41,1.44)	