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Urothelial Cancer

Impact of Smoking on Oncologic Outcomes of Upper Tract Urothelial Carcinoma After Radical Nephroureterectomy

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Abstract

Background: Cigarette smoking is a common risk factor for developing upper tract urothelial carcinoma (UTUC).
Objective: To assess the impact of cigarette smoking status, cumulative smoking exposure, and time from cessation on oncologic UTUC outcomes in patients treated with radical nephroureterectomy (RNU).
Design, setting, and participants: A total of 864 patients underwent RNU at five institutions. The median follow-up in this retrospective study was 50 mo. Smoking history included smoking status, quantity of cigarettes per day (CPD), duration in years, and years from smoking cessation. The cumulative smoking exposure was categorized as light-short-term ($\leq$19 CPD and $\leq$19.9 yr), moderate (all combinations except light-short-term and heavy-long-term), and heavy-long-term ($\geq$20 CPD and $\geq$20 yr).
Interventions: RNU with or without lymph node dissection. No patient received neoadjuvant chemotherapy.
Outcome measurements and statistical analysis: Univariable and multivariable logistic regression and competing risk regression analyses assessed the effects of smoking on oncologic outcomes.
Results and limitations: A total of 244 patients (28.2%) never smoked; 297 (34.4%) and 323 (37.4%) were former and current smokers, respectively. Among smokers, 87 (10.1%), 331 (38.3%), and 202 (23.4%) were light-short-term, moderate, and heavy-long-term smokers, respectively. Current smoking status, smoking $\geq$20 CPD, $\geq$20 yr, and heavy-long-term smoking were associated with advanced disease (p values $\leq$0.004), greater likelihood of disease recurrence (p values $\leq$0.01), and cancer-specific mortality (p values $\leq$0.05) on multivariable analyses that adjusted for standard features. Patients

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who quit smoking ≥10 yr prior to RNU did not differ from never smokers regarding advanced tumor stages, disease recurrence, and cancer-specific mortality, but they had better oncologic outcomes then current smokers and those patients who quit smoking <10 yr prior to RNU. The study is limited by its retrospective nature.

Conclusions: Cigarette smoking is significantly associated with advanced disease stages, disease recurrence, and cancer-specific mortality in patients treated with RNU for UTUC. Current smokers and those with a heavy and long-term smoking exposure have the highest risk for poor oncologic outcomes. Smoking cessation >10 yr prior to RNU seems to mitigate some detrimental effects. These results underscore the need for smoking cessation and prevention programs.

1. Introduction

Smoking is one of the most common risk factors for developing urothelial carcinoma (UC), including upper tract urothelial carcinoma (UTUC) [1]. Smoking increases the relative risk of developing this rare but potentially lethal disease by 2.5- to 7-fold [2–4]. One previous study of 502 UTUC patients showed that the risk of developing UTUC increases with an increasing number of daily smoked cigarettes and years of smoking, even when controlling for the effects of age and gender [5]. Smoking cessation >10 yr earlier seems to decrease the effect of smoking on UTUC development [5].

Radical nephroureterectomy (RNU) with excision of a bladder cuff is the standard of care for patients with high-grade and/or invasive tumors of the renal pelvicalyceal system or ureters with a normal contralateral kidney [1,6]. At the time of RNU, up to 50% of patients have non–organ-confined disease or lymph node metastasis; 50–70% of these patients eventually die of UTUC within 5 yr of their RNU [6–8]. Cumulative evidence suggests an association between smoking and more advanced disease stage and grade as well as disease recurrence in urothelial carcinoma of the bladder (UCB) [9–13]. However, to the best of our knowledge, no study has yet assessed the impact of different aspects of smoking behavior on UTUC outcomes in patients treated with RNU.

We hypothesized that smoking is associated with biologically more aggressive tumors as reflected by pathologic features and survival outcomes. We also hypothesized that there is a dose–response relationship between smoking intensity and adverse outcomes and that smoking cessation may reduce these effects. To address these hypotheses, we investigated smoking habits and intensity as well as cessation from smoking in a large international multi-institutional cohort of patients treated with RNU for UTUC.

2. Patients and methods

2.1. Patient selection

This was a retrospective study approved by the institutional review board, with all participating sites providing the necessary data-sharing agreements prior to initiation. 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. 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, duration, or time from cessation, and 111 patients had missing data on clinicopathologic variables or 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 864 consecutive patients who underwent RNU (open: 741 [85.8%]; laparoscopic: 123 [14.2%]) between 1987 and 2007 for UTUC were available. No patient received preoperative systemic chemotherapy or perioperative radiotherapy. RNU was performed according to techniques previously described [14]. Hilar or regional lymphadenectomy was generally performed in patients with suspicious lymph nodes on preoperative imaging or with suspicious intraoperative findings [15]. The indication and extent of lymphadenectomy performed was at the discretion of the individual surgeons. Tumor multifocality was defined as the synchronous presence of two or more pathologically confirmed tumors in any location (renal pelvicalyceal system or ureter). Adjuvant chemotherapy was administered at the investigator's discretion.

2.2. Pathologic evaluation

All surgical specimens were processed according to standard pathologic procedures at each institution. 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 [16]. Tumor grading was performed according to the 2004 World Health Organization/International Society of Urologic Pathology consensus classification [17]. Histopathologic assessment included concomitant carcinoma in situ, tumor architecture (papillary or sessile based on the predominant feature of the index lesion [18]), lymphovascular invasion (defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls [8]), and tumor necrosis (defined as the presence of microscopic coagulative necrosis in >10% of the tumor [19]). Tumor location was defined as either renal pelvicalyceal or ureteral based on the index cancer [14].

2.3. 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 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.