

## Diabetes mellitus without metformin intake is associated with worse oncologic outcomes after radical nephroureterectomy for upper tract urothelial carcinoma

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Accepted 10 September 2013

Available online 20 September 2013

### Abstract

**Aims:** Evidence suggests a detrimental effect of diabetes mellitus (DM) on cancer incidence and outcomes. To date, the effect of DM and its treatment on prognosis in upper tract urothelial carcinoma (UTUC) remains uninvestigated. We tested the hypothesis that DM and metformin use impact oncologic outcomes of patients treated with radical nephroureterectomy (RNU) for UTUC.

**Methods:** Retrospective analysis of 2492 patients with UTUC treated at 23 institutions with RNU without neoadjuvant therapy. Cox regression models addressed the association of DM and metformin use with disease recurrence, cancer-specific mortality and any-cause mortality.

**Results:** A total of 365 (14.3%) patients had DM and 194 (7.8%) patients used metformin. Within a median follow-up of 36 months, 663 (26.6%) patients experienced disease recurrence, 545 patients (21.9%) died of UTUC and 884 (35.5%) patients died from any cause. Diabetic patients who did not use metformin were at significantly higher risk of disease recurrence and cancer-specific death compared to non-diabetic patients and diabetic patients who used metformin. In multivariable Cox regression analyses, DM treated without metformin was associated with worse recurrence-free survival (HR: 1.44, 95% CI 1.10–1.90,  $p = 0.009$ ) and cancer-specific mortality (HR: 1.49, 95% CI 1.11–2.00,  $p = 0.008$ ).

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**Conclusions:** Diabetic UTUC patients without metformin use have significantly worse oncologic outcomes than diabetics who used metformin and non-diabetics. The possible mechanism behind the impact of DM on UTUC biology and the potentially protective effect of metformin need further elucidation.

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**Keywords:** Upper tract urothelial carcinoma; Diabetes mellitus; Metformin; Surgery

## Introduction

Upper tract urothelial carcinoma (UTUC) is a rare disease resulting in a high rate of morbidity and mortality.<sup>1–4</sup> Radical nephroureterectomy (RNU) with excision of a bladder cuff is the standard of care treatment for patients with normal contralateral kidney and high-grade and/or invasive tumors of the renal pelvicalyceal system and ureter.<sup>1–4</sup>

Cumulative evidence suggests an association of diabetes mellitus (DM) with increased incidence and mortality of various cancers.<sup>5</sup> In urothelial carcinoma of the bladder (UCB), DM has been shown to be an independent predictor of disease recurrence- and progression-free survival.<sup>6</sup> Moreover, studies suggest that metformin, a biguanide widely prescribed as first-line oral anti-diabetic therapy for type-2 DM, might reduce the incidence of cancer and cancer-related mortality in DM patients.<sup>7–9</sup>

To our knowledge, no study to date has evaluated the association of DM and metformin use with prognosis of UTUC patients. Therefore, we assessed the impact of DM and metformin use on oncologic outcomes of patients treated with RNU for UTUC. We hypothesized that DM would be associated with worse outcomes and that metformin might compensate this deleterious effect.

## Patients and methods

### *Patient selection and data collection*

This was an institutional review board approved study with all participating sites providing the necessary institutional data sharing agreements prior to initiation of the study. A total of 23 international centers provided data, which were submitted to a computerized databank. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication, resolution of all identified anomalies was achieved before analysis. Prior to final analysis, the database was frozen, and the final data set was produced. The study population comprised 2492 patients with UTUC who underwent RNU between 1987 and 2007. We excluded patients with a history of muscle-invasive UCB. Surgery was performed by surgeons according to the standard criteria for RNU, that is, extrafascial dissection of the kidney with the entire

length of ureter and adjacent segment of the bladder cuff.<sup>10</sup> The hilar and regional lymph nodes were generally resected if palpable intraoperatively or enlarged on preoperative imaging. The extent of lymphadenectomy performed was at the discretion of individual surgeons. No patient received neoadjuvant chemotherapy or radiotherapy. No patient had distant metastatic disease at the time of RNU. For the analysis, patients were assigned to three groups at the time of RNU: First, patients without history of DM; second, patients with DM and any anti-diabetic medication except metformin; third, patients with DM and metformin use. Data on DM and metformin use were acquired by chart review.

### *Pathological evaluation*

All surgical specimens were processed according to standard pathologic procedures at each institution. Tumors were staged according to the 2002 American Joint Committee on Cancer–Union Internationale Contre le Cancer (AJCC/UICC) TNM classification, tumor grade was assessed according to the 1998 WHO/International Society of Urologic Pathology (ISUP) consensus classification.<sup>11</sup> Tumor location was defined as either renal pelvic or ureteral. Tumor multifocality was defined as the synchronous presence of two or more pathologically confirmed tumors in any location (renal pelvicalyceal system or ureter).<sup>10</sup> Lymphovascular invasion (LVI) was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls.<sup>10</sup>

### *Follow-up*

Patients were 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 medical history taking, 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, or magnetic resonance imaging were performed when clinically indicated. Disease recurrence was defined as tumor relapse in the operative field, regional lymph nodes, and/or distant metastasis. Occurrences of UCB or contralateral upper tract were not coded as disease recurrence. Cause of

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