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

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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.

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.[1–4] 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.[1–4]

Cumulative evidence suggests an association of diabetes mellitus (DM) with increased incidence and mortality of various cancers.[5] In urothelial carcinoma of the bladder (UCB), DM has been shown to be an independent predictor of disease recurrence- and progression-free survival.[6] 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.[7–9]

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.[10] 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.[11] 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).[10] Lymphovascular invasion (LVI) was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls.[10]

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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Table 1
Clinicopathologic characteristics of the 2492 patients who underwent nephroureterectomy for upper tract urothelial carcinoma.

Characteristics	Total	No DM	DM, No metformin	DM, metformin	*p* Value
Number of patients (*n*, %)	2492	2136 (85.7)	162 (6.5)	194 (7.8)	–
Gender (*n*, %)					
Male	1681 (67.5)	1430 (66.9)	116 (71.6)	135 (69.6)	0.38
Female	811 (32.5)	706 (33.1)	46 (28.4)	59 (30.4)	
Age (years)					
Mean (SD)	68.2 (10.7)	68.2 (10.6)	67.4 (11.2)	68.1 (11.8)	0.89
Median (IQR)	x69.2 (62–77)	69.0 (62–76)	69.6 (62–77)	70.2 (62–78)	
ECOG performance status (*n*, %)					
Missing information	841 (33.7)	726 (34.0)	47 (29.0)	68 (35.1)	0.83
0	1101 (44.2)	945 (44.2)	73 (45.1)	83 (42.8)	
1	410 (16.5)	349 (16.3)	31 (19.1)	30 (15.5)	
2	108 (4.3)	87 (4.1)	10 (6.2)	11 (5.7)	
3	9 (0.4)	8 (0.4)	0	1 (0.5)	
4	23 (0.9)	21 (1.0)	1 (0.6)	1 (0.5)	
Pathologic stage (*n*, %)					
pT0	15 (0.6)	14 (0.7)	0 (0)	1 (0.5)	0.16
pTa	527 (21.1)	442 (20.7)	35 (21.6)	50 (25.8)	
pTis	48 (1.9)	40 (1.9)	4 (2.5)	4 (2.1)	
pT1	555 (22.3)	480 (22.5)	35 (21.6)	40 (20.6)	
pT2	473 (19.0)	396 (18.5)	32 (19.8)	45 (23.2)	
pT3	754 (30.3)	662 (31.0)	42 (25.9)	50 (25.8)	
pT4	120 (4.8)	102 (4.8)	14 (8.6)	4 (2.1)	
Pathologic grade (*n*, %)					
No tumors	15 (0.6)	14 (0.7)	0 (0)	1 (0.5)	0.78
Low	389 (15.6)	331 (15.5)	29 (17.9)	29 (14.9)	
High	2088 (83.8)	1791 (83.8)	133 (82.1)	164 (84.5)	
Lymph node status					
pN0	595 (23.9)	515 (24.1)	41 (25.3)	39 (20.1)	0.41
pN1	222 (8.9)	197 (9.2)	11 (6.8)	14 (7.2)	
pN*x*	1675 (67.2)	1424 (66.7)	110 (67.9)	141 (72.7)	
Tumor necrosis (*n*, %)					
Absent	1912 (76.7)	1635 (76.5)	126 (77.8)	151 (77.8)	0.87
Present	580 (23.3)	501 (23.5)	36 (22.2)	43 (22.2)	
Tumor location (*n*, %)					
Pelvicaliceal system	1613 (64.7)	1380 (64.6)	103 (63.6)	130 (67.0)	0.76
Ureter	879 (35.3)	756 (35.4)	59 (36.4)	64 (33.0)	
Multifocal tumor (*n*, %)					
No	1902 (76.3)	1637 (76.6)	118 (72.8)	147 (75.8)	0.54
Yes	590 (23.7)	499 (23.4)	44 (27.2)	47 (24.2)	
Lymphovascular invasion (*n*, %)					
Absent	1905 (76.4)	1635 (76.5)	123 (75.9)	147 (75.8)	0.96
Present	587 (23.6)	501 (23.5)	39 (24.1)	47 (24.2)	
Concomitant Cis (*n*, %)					
Absent	1914 (76.8)	1640 (76.8)	125 (77.2)	149 (76.8)	0.99
Present	578 (23.2)	496 (23.2)	37 (22.8)	45 (23.2)	
Tumor architecture (*n*, %)					
Papillary	1890 (75.8)	1617 (85.6)	122 (75.3)	151 (77.8)	0.79
Sessile	602 (24.2)	519 (24.3)	40 (24.7)	43 (22.2)	
Surgical approach (*n*, %)					
Open	2042 (81.9)	1753 (82.1)	136 (84.0)	153 (78.9)	0.43
Laparoscopic	450 (18.1)	383 (17.9)	26 (16.0)	41 (21.1)	
Previous UCB (*n*, %)					
No	1839 (73.8)	1591 (74.5)	115 (71.0)	133 (68.6)	0.14
Yes	653 (26.2)	545 (25.5)	47 (29.0)	61 (31.4)	
Adjuvant chemotherapy (*n*, %)					
No	2245 (90.1)	1922 (90.0)	146 (90.1)	177 (91.2)	0.86
Yes	247 (9.9)	214 (10.0)	16 (9.9)	17 (8.8)	

CIS: Carcinoma in situ; DM: Diabetes mellitus; UCB: Urothelial cancer of the bladder.

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death was determined by treating physicians, by chart review corroborated by death certificates, or by death certificates alone.[12] All patients who were coded as dead of cancer had previous disease recurrence. Patients who died in the perioperative period (i.e., within 30 days of surgery) were censored at the time of death for UTUC-specific survival analyses.

Statistical analyses

Associations of DM and metformin use with categorical variables were assessed using chi-squared tests. Differences in continuous variables were analyzed using the Mann–Whitney *U* test. Recurrence-free, cancer-specific, and any-cause survival curves were generated using the Kaplan–Meier method; log rank test was used to compare survival. Univariable and multivariable Cox regression models addressed the association of DM and metformin use with disease recurrence, cancer-specific mortality and any-cause mortality after RNU. All *p*-values were two-sided and statistical significance was defined as a $p < 0.05$. Statistical analyses were performed using SPSS Statistics® 20 (SPSS®, IBM Corp, Armonk, NY, USA).

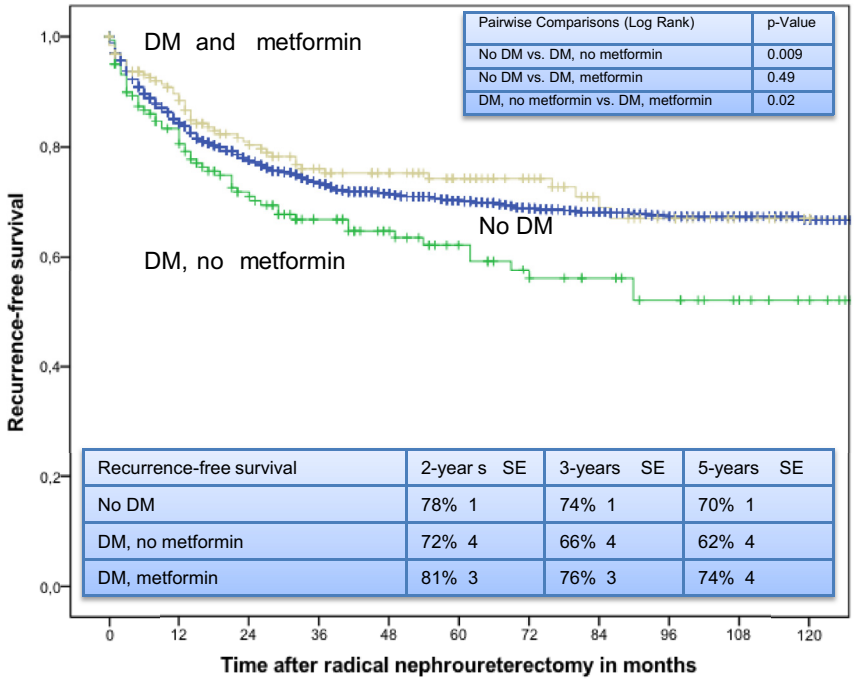
Results

Association of diabetes mellitus and metformin use with clinicopathologic features

Clinicopathologic characteristics of the patients and their association with DM and metformin use are shown in Table 1. A total of 356 patients (14.3%) had DM and 194 patients (7.8%) used metformin. There were no differences in clinicopathologic characteristics between patients without DM, those with DM who used metformin and those with DM who did not use metformin.

Association of diabetes mellitus and metformin use with disease recurrence

Within a median follow-up of 32 months (interquartile range, IQR: 56 months), 663 patients (26.6%) experienced disease recurrence after RNU. Median time to recurrence was 11 months (IQR: 19 months). Patients who had DM but did not use metformin were at significantly higher risk of disease recurrence than DM patients who used metformin ($p = 0.02$), who in turn were not at different risk



Pairwise Comparisons (Log Rank)	p-Value
No DM vs. DM, no metformin	0.009
No DM vs. DM, metformin	0.49
DM, no metformin vs. DM, metformin	0.02

Recurrence-free survival	2-year s SE	3-years SE	5-years SE
No DM	78% 1	74% 1	70% 1
DM, no metformin	72% 4	66% 4	62% 4
DM, metformin	81% 3	76% 3	74% 4

	Patient numbers at risk for disease recurrence										
Months	0	12	24	36	48	60	72	84	96	108	120
No DM	2136	1605	1257	988	802	649	503	400	327	259	189
DM, no metformin	162	121	92	68	54	43	35	30	25	19	15
DM, metformin	194	152	122	99	85	68	53	36	30	21	16

Figure 1. Kaplan–Meier curves depicting recurrence-free survival in 2492 patients treated with radical nephroureterectomy for upper tract urothelial carcinoma, according to diabetes mellitus (DM) and their metformin use.

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than non-DM patients ($p = 0.49$) (Fig. 1). In univariable Cox regression analyses (Table 2), DM without metformin use was associated with increased risk of disease recurrence (HR: 1.43, 95% CI 1.09–1.43, $p = 0.01$). In multivariable Cox regression analysis (Table 3), DM without metformin use remained independently associated with disease recurrence (HR: 1.44, 95% CI 1.10–1.90, $p = 0.009$).

Association of diabetes mellitus and metformin use with cancer-specific and any-cause mortality

Within the study period (median follow-up: 36 months, IQR: 55 months), 545 patients (21.9%) died from UTUC. Median time to cancer-specific death was 19 months (IQR: 26 months). Diabetic patients without metformin use were at significantly higher risk of cancer-specific mortality than DM patients who used metformin ($p = 0.004$) (Fig. 2). In univariable Cox regression analyses (Table 2), DM without metformin use ($p = 0.01$) was associated with increased risk of cancer-specific mortality (HR: 1.47, 95% CI 1.09–1.96, $p = 0.01$); this association remained significant in multivariable Cox regression analysis (HR: 1.49, 95% CI 1.11–2.00, $p = 0.008$, Table 3). During follow-up, 884 patients (35.5%) died from any cause. Median time to any-cause death was 25 months (IQR: 38 months). In univariable and multivariable (Table 3) analyses, DM without metformin use was not associated with any-cause mortality.

Discussion

In our multi-institutional UTUC study we found that diabetic patients who did not use metformin were more likely to experience disease recurrence than those who used metformin. While no one has reported on the influence of DM on UTUC, several studies reported an association of DM with disease recurrence in other cancer types. In a study on 251 patients with non-muscle-invasive UCB, DM was found to be an independent predictor for disease recurrence.[6] Similarly, Spratt et al. recently reported higher rates of biochemical recurrence in prostate cancer treated with

Table 2
Univariable Cox regression analyses predicting disease recurrence, cancer-specific mortality and any-cause mortality in 2492 patients treated with radical nephroureterectomy for upper urinary tract urothelial cancer.

Characteristics	Disease recurrence			Cancer-specific mortality			Any-cause mortality		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age (cont.)	1.01	1.01–1.02	<0.001	1.02	1.01–1.03	<0.001	1.04	1.03–1.05	<0.001
Female gender	1.09	0.93–1.28	0.30	1.04	0.87–1.24	0.66	1.07	0.93–1.23	0.32
ECOG performance status									
0	–	Referent	0.23	–	Referent	0.17	–	Referent	<0.001
1	0.96	0.80–1.15	0.68	1.01	0.83–1.22	0.94	0.84	0.72–0.98	0.03
2	1.21	0.97–1.51	0.10	1.27	0.99–1.63	0.06	1.41	1.17–1.70	<0.001
3	1.26	0.86–1.85	0.23	1.11	0.70–1.77	0.65	1.46	1.06–2.02	0.02
4	1.78	0.57–5.57	0.32	2.40	0.77–7.52	0.13	2.23	0.83–5.99	0.11
No data	1.31	0.65–2.65	0.46	1.60	0.79–3.24	0.19	1.13	0.60–2.13	0.70
DM status									
No DM	–	Referent	0.02	–	Referent	0.007	–	Referent	0.07
DM, no metformin	1.43	1.09–1.43	0.01	1.47	1.09–1.96	0.01	1.19	0.93–1.52	0.17
DM, metformin	0.90	0.67–1.21	0.49	0.75	0.53–1.07	0.12	0.78	0.60–1.03	0.07
pT stage									
pT0-pTa-pTis-pT1	–	Referent	<0.001	–	Referent	<0.001	–	Referent	<0.001
pT2	3.11	2.40–4.03	<0.001	3.56	2.65–4.79	<0.001	1.78	1.47–2.17	<0.001
pT3	6.71	5.39–8.35	<0.001	8.04	6.23–10.36	<0.001	3.35	2.85–3.93	<0.001
pT4	25.52	19.21–33.93	<0.001	31.66	23.02–43.55	<0.001	11.84	9.21–15.22	<0.001
High grade vs. low grade	6.05	4.04–9.08	<0.001	7.65	4.66–12.56	<0.001	2.51	1.99–3.15	<0.001
Previous UCB	1.08	0.91–1.27	0.41	1.13	0.94–1.36	0.21	1.30	1.12–1.50	<0.001
Tumor location	0.98	0.83–1.15	0.78	1.02	0.86–1.22	0.80	1.03	0.90–1.18	0.66
Multifocality	1.27	1.07–1.51	0.006	1.30	1.08–1.57	0.006	1.23	1.06–1.43	0.008
Technique laparoscopic vs. open	0.84	0.67–1.06	0.14	0.71	0.53–0.94	0.02	0.80	0.63–1.01	0.06
Presence of LVI	3.30	2.83–3.85	<0.001	3.53	2.98–4.19	<0.001	2.52	2.20–2.90	<0.001
Concomitant Cis	1.61	1.37–1.90	<0.001	1.50	1.25–1.81	<0.001	1.37	1.18–1.60	<0.001
Nodal status									
pN0	–	Referent	<0.001	–	Referent	<0.001	–	Referent	<0.001
pN1	4.53	3.60–5.71	<0.001	4.98	3.84–6.44	<0.001	3.16	2.54–3.94	<0.001
pN*x*	0.911	0.75–1.11	0.34	1.01	0.81–1.26	0.93	0.99	0.84–1.17	0.90
Sessile vs. papillary architecture	3.49	2.99–4.07	<0.001	3.57	3.01–4.23	<0.001	2.59	2.26–2.98	<0.001
Presence of necrosis	2.17	1.85–2.55	<0.001	2.23	1.87–2.67	<0.001	1.93	1.68–2.23	<0.001
Adjuvant chemotherapy	3.85	3.21–4.61	<0.001	3.45	2.83–4.22	<0.001	2.22	1.84–2.67	<0.001

CIS: Carcinoma in situ; cont.: continuous; DM: Diabetes mellitus; LVI: Lymphovascular invasion; UCB: Urothelial cancer of the bladder.

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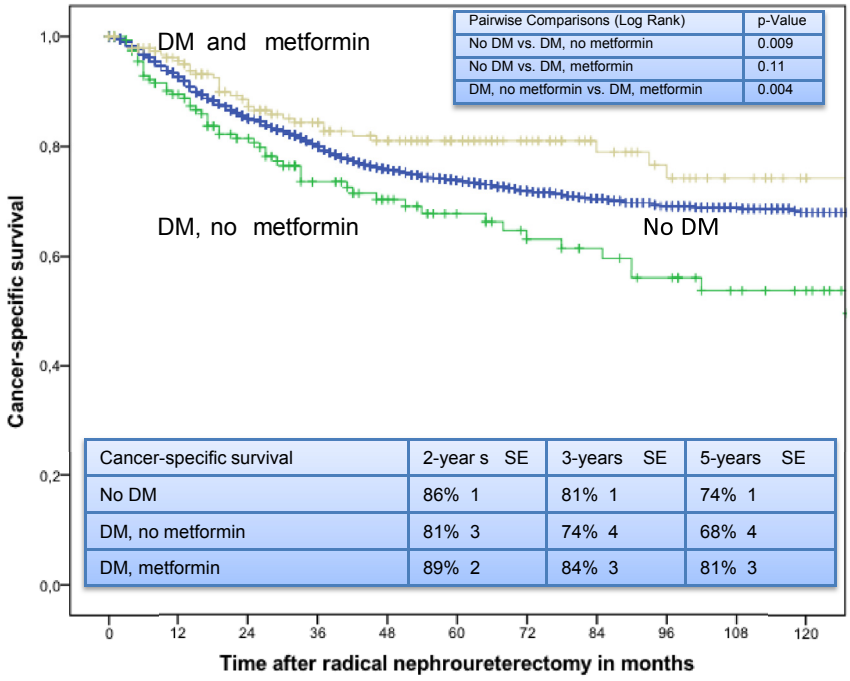
Table 3
Multivariable Cox regression analyses predicting disease recurrence, cancer-specific mortality and any-cause mortality in 2492 patients treated with radical nephroureterectomy for upper urinary tract urothelial cancer.

Characteristics	Disease recurrence			Cancer-specific mortality			Any-cause mortality		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age (continuous)	1.01	1.00–1.02	0.006	1.02	1.01–1.03	<0.001	1.04	1.03–1.05	<0.001
DM status									
No DM	–	Referent	0.03	–	Referent	0.01	–	Referent	0.09
DM, no metformin	1.44	1.10–1.90	0.009	1.49	1.11–2.00	0.008	1.21	0.94–1.55	0.14
DM, metformin	1.03	0.77–1.40	0.83	0.81	0.57–1.16	0.26	0.81	0.62–1.07	0.14
pT stage									
pT0-pTa-pTis-pT1	–	Referent	<0.001	–	Referent	<0.001	–	Referent	<0.001
pT2	2.31	1.74–3.06	<0.001	2.64	1.91–3.65	<0.001	1.54	1.24–1.91	<0.001
pT3	4.15	3.20–5.38	<0.001	4.98	3.70–6.71	<0.001	2.46	2.10–3.00	<0.001
pT4	10.93	7.72–15.48	<0.001	12.78	8.65–18.90	<0.001	6.15	4.51–8.37	<0.001
High grade vs. low grade	1.81	1.16–2.84	0.009	2.06	1.20–3.56	0.009	1.28	0.98–1.66	0.07
Multifocality	0.89	0.74–1.07	0.20	0.96	0.79–1.17	0.66	1.01	0.86–1.18	0.95
Presence of LVI	1.32	1.11–1.58	0.002	1.41	1.16–1.72	0.001	1.32	1.12–1.55	0.001
Concomitant Cis	1.22	1.02–1.45	0.03	1.08	0.88–1.31	0.46	1.09	0.93–1.28	0.28
Nodal status									
pN0	–	Referent	<0.001	–	Referent	<0.001	–	Referent	<0.001
pN1	2.09	1.63–2.68	<0.001	2.21	1.67–2.92	<0.001	1.65	1.30–2.10	<0.001
pN*x*	1.11	0.92–1.36	0.27	1.28	1.03–1.61	0.03	1.14	0.97–1.35	0.12
Sessile vs. papillary architecture	1.46	1.23–1.74	<0.001	1.37	1.13–1.67	0.001	1.28	1.09–1.51	0.003
Presence of necrosis	0.94	0.79–1.12	0.48	0.94	0.78–1.14	0.53	1.08	0.92–1.26	0.36

CIS: Carcinoma in situ; cont.: continuous; DM: Diabetes mellitus; LVI: Lymphovascular invasion; UCB: Urothelial cancer of the bladder.



Cancer-specific survival	2-year s	SE	3-years	SE	5-years	SE
No DM	86%	1	81%	1	74%	1
DM, no metformin	81%	3	74%	4	68%	4
DM, metformin	89%	2	84%	3	81%	3

	Patient numbers at risk for survival										
Months	0	12	24	36	48	60	72	84	96	108	120
No DM	2136	1767	1383	1079	852	681	527	414	337	266	193
DM, no metformin	162	129	104	74	59	47	40	34	29	21	18
DM, metformin	194	163	132	109	90	71	55	39	32	22	16

Figure 2. Kaplan–Meier curves depicting cancer-specific survival in 2492 patients treated with radical nephroureterectomy for upper tract urothelial carcinoma, according to diabetes mellitus (DM) and their metformin use.

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external-beam radiation therapy in diabetic patients who did not use metformin compared to those who used metformin.[13] An association of DM with disease recurrence has also been reported in other cancers such as stage I–III colorectal,[14] endometrial,[15] prostate,[16,17] hepatocellular[18] and non-small cell lung cancers.[19] The biology underlying the association of DM and its potential growth promoting effect on urothelial cells remains to be investigated. High doses of insulin have been shown to promote UCB cell proliferation in vitro.[20] Furthermore, the insulin-like growth factor receptor I (IGF-IR), which is activated by insulin-like growth factors and insulin and promotes cell growth and anti-apoptosis, has been shown to be overexpressed in invasive UCB.[21] The protective effect of metformin also needs further validation and testing. Metformin reduces the levels of insulin and insulin-like growth factors in vivo and has been shown to lead to mTOR inhibition, p53 activation and cell cycle arrest in vitro.[22] Whether these mechanisms are also in effect in UTUC remains to be investigated. Since disease recurrence in UTUC after RNU is strongly associated with survival,[1] we also sought to investigate the impact of DM and metformin on cancer-specific and overall-survival.

In our study, we found that diabetic patients who did not use metformin had a significantly shorter cancer-specific survival than diabetics who used metformin or non-diabetics. When adjusting for the effects of standard clinicopathologic features, DM without metformin remained independently associated with increased risk of cancer-specific mortality in comparison to non-diabetic patients with UTUC. Similarly, DM was positively associated with UCB mortality in a recent meta-analysis of 11 cohort studies.[23] Moreover, DM appears to be an independent predictor of cancer-specific mortality and any-cause mortality in patients receiving curative therapy for hepatocellular carcinoma.[24] Likewise, DM was independently associated with an increased risk of cancer-specific mortality compared with non-DM patients in colorectal cancer and early breast cancer.[25,26] In addition, long-term type-2 DM and insulin-use have been shown to be associated with the incidence of invasive UCB.[27] Furthermore, various studies show an association between long-term intake of pioglitazone and UCB.[28–30] However, this association has not been reported in UTUC. Further studies are necessary to assess whether DM is the cause of the worse outcome or whether anti-diabetic medication such as pioglitazone has a growth promoting effect on UTUC.

Our study has several limitations. First and foremost the limitations due its retrospective design which warrant further confirmation in a prospective study. As a multicenter study, the cohort of patients underwent RNU by several surgeons and several pathologists analyzed the pathological specimens. However, all physicians were dedicated to uro-oncology. We did not have any information on DM type or type, dose, length and cumulative exposure of use of anti-diabetic medication other than metformin. In addition, no data on baseline renal function, which affects outcomes in patients with DM were available. Moreover, no data on glycemic control like fasting glucose or HbA1C were available. Despite its limitations, this study is the first to assess the impact of DM and metformin use on oncologic outcomes of patients with UTUC undergoing RNU. Future studies have to evaluate the impact of DM duration and type, dosage and duration of intake of anti-diabetic medication on oncologic outcomes and cancer progression in UTUC.

To conclude, patients with DM not treated with metformin appear to be at higher risk for disease recurrence and cancer-specific mortality compared to patients without DM and with DM and metformin use. The mechanisms behind the impact of DM on UTUC patients undergoing RNU and the potential negative effect of anti-diabetic drugs other than metformin need to be further elucidated. Future studies need to focus on DM length, severity, anti-diabetic drug use, length of intake, cumulative exposure, and dosage to gain better understanding of the impact of DM and anti-diabetic drugs on UTUC recurrence, progression and outcome.

Conflict of interest statement

M. Rieken: Grant support from Swiss National Science Foundation.

A. Bachmann: Company consult for American Medical Systems, Orion Pharma, Schering, Olympus, Caris Life Sciences.

S.F. Shariat: Advisory board for Ferring Pharmaceutics.

All other authors have nothing to disclose.

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