Urologia Internationalis

Research Article

Urol Int 2025;109:361–371
DOI: 10.1159/000543757

Received: September 3, 2024
Accepted: January 16, 2025
Published online: January 24, 2025

The Impact of Diabetes and Antidiabetics on Uro-Oncological Disease Outcomes: A Single-Center Experience

Moustafa Elleisy[a] Heike Zettl[b] Desiree Louise Dräger[a] Oliver W. Hakenberg[a]

[a]Department of Urology, University Medical Center Rostock, Rostock, Germany; [b]Clinical Cancer Registry, University Medicine Rostock, Rostock, Germany

Keywords
Uro-oncology · Pathological outcomes · Diabetes · Metformin · Antidiabetics

Abstract

Introduction: The aim of this study was to determine the impact of diabetes and antidiabetic medications on referral and pathological outcomes in uro-oncology cases. We report preliminary results from a single-center study. ***Methods:*** We retrospectively collected data from 781 patients treated between 2018 and 2023 for radical prostatectomy (RP) for prostate cancer (PCa), radical cystectomy (RC) for bladder cancer, radical nephroureterectomy for upper tract urothelial carcinoma, partial nephrectomy and radical nephrectomy (RN) for renal cell carcinoma (RCC). A total of 617 (79%) patients were nondiabetics, and 164 (21%) were diabetics. Patient data were assessed for differences between diabetics and nondiabetics. ***Results:*** All diabetic patients had a significantly higher BMI than nondiabetic patients ($p < 0.05$ for PCa and $p = 0.006$ for RC, respectively). In diabetic patients with PCa, a lower proportion of ISUP grade 3 and 5 PCa was seen ($p = 0.047$). In diabetic RCC patients on antidiabetic medication, there was a significantly higher incidence of recurrence rates after RN ($p = 0.015$). Penile cancer was diagnosed in diabetic patients at an older age ($p = 0.019$). ***Conclusion:*** Significantly, higher BMI was observed for RP and RC in diabetic patients, as well as for RCC after RN. Diabetics showed a significantly higher occurrence of recurrence for RCC after RN.

Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is emerging as one of the most prevalent human diseases after cardiovascular diseases and is the sixth leading cause of death worldwide (WHO). The prevalence of type 2 diabetes mellitus (T2DM) is increasing rapidly worldwide [1]. In 2019, 11% of women and 12.3% of men in Germany had a documented diagnosis of diabetes, one of the highest prevalence rates in Europe [2].

There is strong evidence to suggest that cancer incidence is increased in patients with T2DM. The pathophysiological hypotheses to explain the link between diabetes or hyperglycemia and cancers rely on biological, particularly endocrine mechanisms involving insulin resistance. Indeed, in the genesis of T2DM, reduced insulin sensitivity plays a key role, inducing compensatory hyperinsulinemia with an increased level of circulating insulin-like growth factors (IGF). These are well known to stimulate cell proliferation in many organs, including the liver, pancreas, colon, ovary, breast, all of which are organs

karger@karger.com
www.karger.com/uin

Correspondence to:
Moustafa Elleisy, elleisy.moustafa@gmx.at

with an increased risk of cancer in type 2 diabetic patients [1]. T2DM may be considered as a specific and independent risk factor for various forms of cancer, due to its particular metabolic characteristics of glucose intolerance and hyperinsulinemia [1, 2].

Diabetes has also been significantly linked with an elevated risk of kidney cancer in a meta-analysis of 11 cohort studies [2]. According to the meta-analysis of 29 cohort studies, females with diabetes have a higher risk of bladder cancer (BCa) [2]. Surprisingly, individuals with diabetes tend to have a lower risk of prostate cancer (PCa). Low testosterone in diabetic individuals could be one reason because prostate cell development is aided by the conversion of testosterone to dihydrotestosterone [2]. Of note, PCa incidence has been found to be consistently lower among men with diabetes [3].

Diabetes has also been associated with higher mortality after cancer, and survivors of some cancers have a higher incidence of developing subsequent diabetes. Finally, both cancer and diabetes treatments have been shown to influence the relationship between diabetes and cancer-associated outcomes [4].

The Effect of Antidiabetic Drugs on Cancer Risk

Given the insulin- and glucose-modulating effects of antihyperglycemic medications, there have been numerous studies examining the potential impact of these drugs on the risk and prognosis of cancer [4]. Metformin is an oral biguanide that is well established as the first-line treatment of T2DM [3, 4]. Metformin use was also associated with a 24% lower rate of PCa-specific mortality and all-cause mortality among men with T2DM. Sulfonylureas (SUs) are among the oldest drugs available for the treatment of T2DM. Although SUs have been in clinical use for many years, their associations with cancer remain uncertain [3].

There are two thiazolidinediones (TZDs) in current clinical use, rosiglitazone and pioglitazone. The role of TZD in cancer treatment and prevention is uncertain. TZDs have been shown to be associated with approximately 20% to 40% lower prostate-specific antigen (PSA) levels among patients with PCa [3]. However, the Food and Drug Administration issued a warning in 2011 regarding pioglitazone after early studies showed a higher risk of BCa with pioglitazone, especially with more than 2 years of use. Since then, a multitude of studies have been conducted in this area and a recent meta-analysis reported a small but significantly increased risk of BCa with pioglitazone. Similarly, an increased risk of BCa has been associated with rosiglitazone [4].

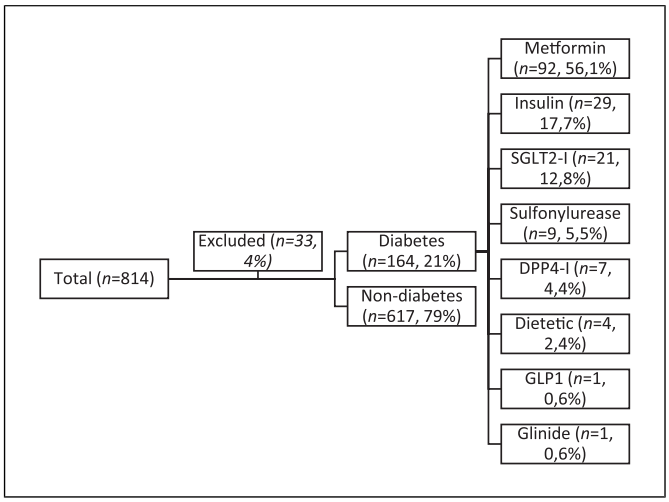

Fig. 1. A graphic showing the treatment of patients and their antidiabetic medication. SGLT2-I, sodium-glucose cotransporter type 2 inhibitors; DPP4-I, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1.

Incretin-based drugs include glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors [4]. While there were initial concerns about an increased risk of pancreatic cancer with incretin-based drugs and medullary thyroid cancer with GLP-1 receptor agonists, these effects have not been confirmed in recent studies.

Sodium-glucose cotransporter 2 inhibitors (SGLT2-I) are the newest class of oral diabetes medications [4]. SGLT2 has been found to be overexpressed in pancreatic, prostate, and colon cancer [3]. In animal models, certain SGLT2-I have been associated with mammary, adrenal, testicular, and renal neoplasms. An increased risk for BCa has been reported for empagliflozin, and there were concerns with an imbalance of BCa occurrences in clinical trials with dapagliflozin [2–4].

Urological Tumors

PCa is one of the leading causes of cancer-related death in men worldwide [5]. Several studies have shown that metformin may inhibit the growth of PCa cells in vitro and in vivo and reduce the risk of PCa. However, the evidence for the use of metformin as a treatment for PCa remains controversial [5–8].

BCa is a heterogeneous disease with a variable prognosis and natural history [9]. Approximately 75% of newly diagnosed BCa are non-muscle-invasive bladder cancers, and 50% of them are low-risk diseases [10, 11]. Recently, T2DM was found to be associated with a higher risk of recurrence and progression in patients

Table 1. Descriptive characteristics of the cohort of 200 patients treated with RP between January 2018 and February 2023

Variables	Nondiabetes	Diabetes	*p* value
Patients, *n* (%)	166 (83)	34 (17)	
Diagnosis age, median (IQR), years	67 (62–71)	67 (62–72)	0.5
PSA, mean (SD), ng/mL	17.3 (27.4)	9.1 (5.3)	0.2
BMI, mean (IQR), kg/m^2	28 (25–30)	29.8 (27–32)	**0.047***
Length of stay, mean (SD), days	14.7 (22.4)	16.4 (26.7)	0.4
ISUP grade at RP, *n* (%)			**0.047***
1	23 (13.9)	2 (5.9)	
2	66 (39.8)	19 (55.9)	
3	48 (28.9)	9 (23.5)	
4	3 (1.8)	3 (8.8)	
5	24 (14.5)	1 (3)	
Unknown	2 (1.2)		
Pathological tumor stage, *n* (%)			0.6
pT1a	2 (1.2)		
pT2a	9 (5.4)	1 (2.9)	
pT2b	3 (1.8)		
pT2c	53 (31.9)	11 (32)	
pT3	1 (0.6)	1 (2.9)	
pT3a	48 (28.9)	13 (38)	
pT3b	47 (28.3)	7 (21)	
pT4	2 (1.2)		
Unknown	1 (0.6)		
Nodal tumor stage, *n* (%)			0.2
N0	135 (81.3)	32 (94)	
N+	30 (18.1)	2 (6)	
NX	1 (0.6)		
Recurrence, *n* (%)	12 (7.2)	0	0.08
Death, *n* (%)	12 (7.2)	5 (2.5)	0.9

BMI, body mass index; PSA, prostate-specific antigen; ISUP, International Society of Urological Pathology; RP, radical prostatectomy; IQR, interquartile range; SD, standard deviation. *Statistically significant difference.

with T1 high-grade BCa compared to those without T2DM [10].

Renal cell carcinoma (RCC) is a common renal neoplasia that accounts for 2% to 3% of all adult malignancies. Several studies suggest that the incidence of a metabolic syndrome – abdominal obesity, insulin resistance, dyslipidemia and elevated blood pressure – significantly correlates with the occurrence and development of RCC [12, 13].

Patients and Methods

The aim of this retrospective study was to assess the association between diabetes and urological cancers in the patients treated at the Department of Urology of Rostock University between January 2018 and February 2023. Institutional Review Board approval was obtained before the initiation of the study. This study included a total of 781 patients treated for confirmed urological cancer. We identified all patients newly diagnosed with PCa at our institution according to the Clinical Cancer Registry (CCR) using the International Classification of Diseases, 10th Revision (ICD-10) code C61. The C67 code was used for BCa, C60 for penile cancer, C64 for renal cancer, and C65 for upper tract urothelial carcinoma. The CCR also provided information on age at diagnosis and tumor stage (TNM classification). The OPS Classification of Interventions and Procedures version 2023, an administrative dataset covering all episodes in German hospitals, was used to identify specific procedures. The 5-60 code was used to identify

Table 2. Descriptive characteristics of the cohort of 58 male patients treated with radical cystoprostatectomy for synchronous PCa between January 2018 and December 2022

Variables	Nondiabetes	Diabetes	*p* value
Patients, *n* (%)	41 (71)	17 (29)	
Diagnosis age, median (IQR), years	68 (62–76)	74.5 (64–80)	0.2
BMI, mean (IQR), kg/m^2	27 (24–29)	30 (27–34)	**0.006***
Length of stay, mean (SD), days	23.9 (18.4)	24.5 (17.7)	0.9
ISUP grade at RP, *n* (%)			0.8
1	31 (75.6)	12 (70.5)	
2	6 (14.6)	3 (17.6)	
3	2 (4.9)		
4	1 (2.4)		
5			
Unknown	1 (2.4)	2 (11.7)	
Pathological tumor stage, *n* (%)			0.3
pT2a	15 (36.6)	5 (29.4)	
pT2c	17 (41.5)	8 (47)	
pT3a	4 (9.7)	2 (11.7)	
pT3b		2 (11.7)	
pT4	1 (2.4)		
Nodal tumor stage, *n* (%)			0.8
N0	40 (97.6)	16 (94)	
N+	1 (2.4)	1 (6)	
Recurrence, *n* (%)	0	0	0.9
Death, *n* (%)	17 (41.5)	7 (41.2)	0.9

BMI, body mass index; ISUP, International Society of Urological Pathology; RP, radical prostatectomy; IQR, interquartile range; SD, standard deviation. *Statistically significant difference.

patients who underwent radical prostatectomy (RP), the 5-576 code for radical cystectomy (RC), the 5-554 code for radical nephrectomy, and the 5-553 code for partial nephrectomy. Age at diagnosis, preoperative PSA levels, histopathological data (pathological T-stage, International Society of Urological Pathology [ISUP] grade group, lymph node involvement), body mass index (BMI), length of hospital stay, death, recurrence, and tumor size were recorded and analyzed. T2DM status was considered if patients were under medical treatment for diabetes or had a positive medical history of diabetes prior to admission for surgical treatment. Patients with incomplete data were excluded.

Statistical Analysis

We analyzed a T2DM-based cohort; including patients with new diagnoses of PCa, BCa, RCC, upper tract urothelial carcinoma, and penile cancer at our institution between 1 January 2018 and 29 February 2023. Data were analyzed using SPSS (Version 29, IBM Corp., Armonk, NY, USA). Categorical variables were presented as absolute numbers and proportions, while continuous variables were expressed as medians with interquartile ranges or means with standard deviation when appropriate. Comparisons of categorical variables between the cohorts were made using Pearson's chi-square and Fisher's exact test, and specified according to the smallest theoretical frequency with Fisher's exact test used in case <5 and Pearson's chi-square test >5. Continuous variables were compared using the independent sample *t* test for normally distributed data, and the Mann-Whitney U test was applied to non-normally distributed data. A p value of < 0.05 was considered statistically significant.

Results

A total of 781 (96%) patients were included in the study, and 33 (4%) were excluded due to missing diabetes status and/or missing variables (shown in Fig. 1). Of the patients, 617 (79%) were nondiabetics and 164

Table 3. Descriptive characteristics of the cohort of 156 patients treated with RC between January 2018 and December 2023

Variables	Nondiabetes	Diabetes	*p* value
Patients, *n* (%)	118 (75)	38 (25)	
Diagnosis age, median (IQR), years	71 (63–78)	75 (66–79)	0.05
Gender, *n* (%)			0.4
Female	37 (34.4)	8 (21)	
Male	81 (68.6)	30 (79)	
BMI, mean (IQR), kg/m^2	28.8 (23–28)	29 (26–32)	<**0.001***
Length of stay, mean (SD), days	24.4 (20.7)	24.7 (16)	0.3
Pathological tumor stage, *n* (%)			0.9
pT1	19 (16.1)	8 (23.5)	
pT2	8 (6.8)	3 (8.8)	
pT2a	12 (10.2)	8 (23.5)	
pT2b	8 (6.8)	3 (7.9)	
pT3	1 (0.8)		
pT3a	20 (16.9)	3 (7.9)	
pT3b	27 (22.8)	7 (18.4)	
pT4a	19 (16.1)	7 (18.4)	
pT4b	3 (2.5)	1 (2.6)	
Unknown	1 (0.8)		
Nodal tumor stage, *n* (%)			0.5
N0	78 (66.1)	28 (73.7)	
N1	14 (11.9)	4 (10.5)	
N2	25 (21.2)	4 (10.5)	
NX	1 (0.8)	2 (5.3)	
Recurrence, *n* (%)	27 (22.9)	7 (18.4)	0.7
Death, *n* (%)	53 (44.9)	24 (63.2)	0.09
Concomitant Cis, *n* (%)	14 (11.9)	2 (5.3)	0.5
Urinary diversion, *n* (%)			0.9
Ureterocutaneostomy	7 (5.9)	1 (2.6)	
Ileum conduit	94 (79.7)	32 (84.2)	
Ileal neobladder	15 (12.7)	5 (13.2)	
Unknown	2 (1.7)		

BMI, body mass index; Cis, carcinoma in situ; IQR, interquartile range; SD, standard deviation. *Statistically significant difference.

(21%) were diabetics. Antidiabetic treatment included metformin in 92 (56.1%) patients, insulin in 29 (17.7%) patients, SGLT2-I in 21 (12.8%) patients, SUs in 9 (5.5%) patients, DPP-4 in 7 (4.3%) patients, diet in 4 (2.4%) patients, and GLP-1 and glinide in 1 (0.6%) patient each.

Radical Prostatectomy

Overall, 200 patients underwent RP, of whom 166 (78%) were nondiabetics and 34 (16%) were diabetics (Table 1). Of the 34 diabetic patients, 29 (85%) were treated with metformin, 2 (6%) each with insulin and SGLT2-I, and only 1 (3%) with SUs. Due to missing information on diabetes status, 12 (6%) patients were excluded. Patients with diabetes had a significantly higher BMI (28 vs. 29.8, $p = 0.047$). However, there was no difference between the different antidiabetic medications. Notably, a trend toward lower ISUP grade was observed in the diabetes cohort ($p = 0.047$).

Radical Cystoprostatectomy in Patients with BCa and Synchronous PCa

In a subgroup analysis, 58 patients with BCa and synchronous PCa were analyzed separately from 111 male patients (52%) after RC (Table 2). Again, 3 patients (5%) with missing information on their diabetes status were excluded. Of the patients, 41 (67%) were nondiabetics and 17 (28%) were diabetics. In particular, 10

Table 4. Descriptive characteristics of the cohort of 36 patients treated with nephroureterectomy between January 2018 and December 2022

Variables	Nondiabetes	Diabetes	*p* value
Patients, *n* (%)	29 (80.6)	7 (19.4)	
Diagnosis age, median (IQR), years	75.5 (66–81)	66 (56–81)	0.4
Gender, *n* (%)			0.9
Female	14 (48.3)	3 (42.9)	
Male	15 (51.7)	4 (57.1)	
BMI, mean (IQR), kg/m^2	25.6 (21–28)	27 (19–28)	0.5
Length of stay, mean (SD), days	10.5 (6.4)	16.9 (12.2)	0.1
Pathological tumor stage, *n* (%)			0.9
pT1	4 (13.8)	1 (14.3)	
pT2	1 (3.4)		
pT3	20 (69)	5 (71.4)	
pT4	4 (13.8)	1 (14.3)	
Nodal tumor stage, *n* (%)			0.4
N0	20 (69)	6 (85.7)	
N1	3 (10.3)	1 (14.3)	
N2	6 (20.7)		
Recurrence, *n* (%)	3 (10.3)	0	0.9
Death, *n* (%)	14 (48.3)	2 (28.6)	0.4
Tumor site, *n* (%)			0.3
Right	12 (41.4)	5 (71.4)	
Left	16 (55.2)	2 (28.6)	
Bilateral	1 (3.4)		

BMI, body mass index; IQR, interquartile range; SD, standard deviation.

(58.8%) patients were treated with metformin, 5 (29.4) patients with SGLT2-I, and 1 (5.9) patient each with insulin and SUs. Diabetic patients had a significantly higher BMI (27 vs. 30, $p = 0.006$).

Radical Cystectomy

Overall, 156 patients underwent RC for BCa. Of the patients, 118 (75%) had no diabetes and 38 (24%) had diabetes. Seventeen patients (44.7%) were treated with metformin, 8 (21.1) with insulin, 7 (18.4%) with SGLT2-I, and 3 (7.9%) each with SU and diet (Table 3). The diabetes cohort had a significantly higher BMI (28.8 vs. 29, $p < 0.001$). There was no age difference between patients with diabetes and those without (71 vs. 75 years, $p = 0.05$). There was a higher incidence of recurrence rates in the diabetes cohort ($p < 0.001$) when patients were treated with diet only (data not shown).

Nephroureterectomy

A total of 36 patients underwent NUE. Of the patients, 29 (80.6%) were nondiabetics and 7 (19.4%) were diabetics (Table 4). Two patients (28.6%) each were treated with metformin and insulin and 1 (14.3%) patient each with SGLT2-I, DPP-4 and SUs. The length of hospital stay was not significantly longer in the diabetes cohort (16.9 days vs. 10.5 days, respectively, $p = 0.1$).

Radical Nephrectomy

Overall, 151 patients underwent radical nephrectomy. Of the patients, 119 (74.4%) were nondiabetics and 32 (20%) were diabetics (Table 5). Fourteen patients (43.8%) were treated with metformin, 9 (28.1%) with insulin, 2 (6.3%) with SGLT2-I, 3 (9.4%) each with DPP-4 and SU, and only 1 (3.1) patient with glinide. Nine (5.6%) patients were excluded because their diabetes status was not known. Of note, the diabetic cohort had not a significantly higher BMI (28.4 vs. 30.9, $p = 0.05$). A significantly lower recurrence rate was observed in nondiabetics compared to diabetics (13 vs. 9, respectively, $p = 0.015$). There was a higher incidence of right-sided renal cancer in the diabetic cohort ($p = 0.045$).

Partial Nephrectomy

Overall, 130 patients underwent partial nephrectomy. Of the patients, 103 (82%) were nondiabetics and 23 (18%) were diabetics (Table 6). Twelve patients (52%)

Table 5. Descriptive characteristics of the cohort of 151 patients treated with RN between January 2018 and March 2023

Variables	Nondiabetes	Diabetes	*p* value
Patients, *n* (%)	119 (78.8)	32 (21.2)	
Diagnosis age, median (IQR), years	66 (58–76)	66.5 (63–79)	0.07
Gender, *n* (%)			0.6
Female	43 (36.1)	10 (31)	
Male	76 (63.9)	22 (69)	
BMI, mean (IQR), kg/m^2	28.4 (25–31)	30.9 (27–35)	0.05
Length of stay, mean (SD), days	7.8 (4.8)	7.3 (3)	0.9
Histology, *n* (%)			0.6
Clear cell RCC	93 (78.2)	26 (81.3)	
Papillary RCC	12 (10.1)	1 (3.1)	
Chromophobe RCC	7 (5.9)	1 (3.1)	
Sarcomatoid RCC	1 (0.8)	1 (3.1)	
Others	5 (4.2)	3 (9.4)	
Unknown	1 (0.8)		
Pathological tumor stage, *n* (%)			0.8
pT1a	12 (10.1)	3 (9.4)	
pT1b	13 (10.9)	5 (15.6)	
pT2a	8 (6.7)	3 (9.4)	
pT2b	3 (2.5)		
pT3a	72 (60.5)	17 (53.1)	
pT3b	7 (5.9)	3 (9.4)	
pT3c	1 (0.8)	1 (3.1)	
Unknown	3 (2.5)		
Nodal tumor stage, *n* (%)			0.5
N0	99 (83.2)	29 (90.6)	
N1	12 (10.1)	2 (6.3)	
NX	8 (6.7)	1 (3.1)	
Recurrence, *n* (%)	13 (10.9)	9 (28.1)	**0.015***
Death, *n* (%)	29 (24.4)	11 (34.4)	0.3
Tumor site, *n* (%)			**0.045***
Right	58 (48.7)	22 (68.8)	
Left	61 (51.3)	10 (31.2)	
Tumor size, mean (SD), cm	7 (3.3)	7.7 (3.4)	0.9

BMI, body mass index; RCC, renal cell carcinoma; RN, radical nephrectomy; IQR, interquartile range; SD, standard deviation. *Statistically significant difference.

were treated with metformin, 6 (26%) with insulin, 4 (17%) with SGLT2-I, and 1 (4%) patient with DPP-4. A total of 7 (5%) patients were excluded because their diabetes status was not known.

Penile Cancer

Overall, 39 patients were diagnosed with penile cancer between January 2018 and December 2022. Of the patients, 30 (76.9%) were nondiabetics and 9 (23.1%) were diabetics (Table 7). Five patients (55.6%) were treated with metformin, 2 (22%) with DPP-4, 1 (11.1%) each with GLP-1 or diet. A higher age at diagnosis was observed in diabetic patients (75 years vs. 64 years in nondiabetic patients, $p = 0.09$). In addition, a higher recurrence rate was observed in the nondiabetic cohort (33.3% vs. 0% in nondiabetics, $p = 0.08$).

Discussion

In this study, the major uro-oncological diseases were differentiated according to diabetes status and associated antidiabetic medication. For PCa, a lower recurrence rate after RP was observed. In a prospective multicenter study,

Table 6. Descriptive characteristics of the cohort of 126 patients treated with PN between January 2018 and March 2023

Variables	Nondiabetes	Diabetes	*p* value
Patients, *n* (%)	103 (82)	23 (18)	
Diagnosis age, median (IQR), years	69 (61–77)	71 (64–80)	0.3
Gender, *n* (%)			0.2
Female	37 (35.9)	5 (21.7)	
Male	66 (64.1)	18 (78.3)	
BMI, mean (IQR), kg/m^2	28.1 (24–31)	28.6 (25–30)	0.7
Length of stay, mean (SD), days	6.9 (2.7)	6.9 (3.5)	0.9
Histology, *n* (%)			0.8
Clear cell RCC	68 (66)	17 (74)	
Papillary RCC	22 (21.4)	5 (21.7)	
Chromophobe RCC	7 (6.8)	1 (4.3)	
Sarcomatoid RCC	1 (1)		
Others	5 (4.9)		
Pathological tumor stage, *n* (%)			0.08
pT1	2 (1.9)		
pT1a	63 (61.2)	10 (43.5)	
pT1b	16 (15.5)	5 (21.7)	
pT2	1 (1)		
pT2a		1 (4.3)	
pT3	1 (1)		
pT3a	11 (10.7)	5 (21.7)	
pT4	2 (1.9)		
Unknown	7 (6.8)		
Nodal tumor stage, *n* (%)			0.8
N0	90 (87.4)	21 (91.3)	
N1	1 (1)		
NX	12 (11.7)	2 (8.7)	
Recurrence, *n* (%)	7 (6.8)	4 (17.4)	0.1
Death, *n* (%)	16 (15.5)	4 (17.4)	0.8
Tumor site, *n* (%)			0.9
Right	49 (47.6)	11 (48)	
Left	54 (52.4)	12 (52)	
Tumor size, mean (SD), cm	3.3 (2.1)	3.7 (1.6)	0.2

BMI, body mass index; RCC, renal cell carcinoma; PN, partial nephrectomy; IQR, interquartile range; SD, standard deviation.

it was shown that obesity is associated with higher R1 resection rates, resulting in increased recurrence rates [14]. Therefore, we compared the recurrence rate for normal-weight patients between the two cohorts to minimize the possible protective effect of obesity. There was no significant difference between diabetic and nondiabetic patients ($p = 0.8$).

This corresponds to studies which have shown that diabetics treated with metformin have a reduced risk of PCa by 44% [8]. A Scottish study reported that diabetics taking metformin had a 23% lower overall risk of cancer compared to those not taking metformin. The study observed and reported risk reduction for the longest metformin treatment period [8]. Pencik et al. [5] were able to show a frequent genomic co-deletion of PTEN, one of the most frequently deleted genes in mPCa, and STAT3 in patients with mPCa. Loss of stat3 in a Pten-null mouse prostate model leads to a reduction of LKB1/pAMPK with simultaneous activation of mTOR/CREB, resulting in metastatic disease. However, constitutive activation of stat3 led to high LKB1/pAMPK levels and suppressed mTORC1/CREB pathway, preventing mPCa development. Metformin inhibits mTORC1 in liver and requires LKB1 to mediate glucose homeostasis with

Table 7. Descriptive characteristics of the cohort of 39 diagnosed with penile cancer between January 2018 and December 2022

Variables	Nondiabetes	Diabetes	*p* value
Patients, *n* (%)	30 (77)	9 (23)	
Diagnosis age, median (IQR), years	64 (59–73)	75 (70–79)	**0.019***
BMI, mean (IQR), kg/m^2	28.3 (26–32)	32.3 (26–37)	0.06
Histology, *n* (%)	29 (96.7)	8 (89)	0.2
Squamous cell carcinoma			
Others			
Unknown	1 (3.3)	1 (11)	
Pathological tumor stage, *n* (%)			0.6
pT1a	9 (30)		
pT1b	4 (13.3)	2 (22)	
pT2	13 (43.3)		
pT3	2 (6.7)	5 (56)	
pT4b	1 (3.3)	2 (22)	
Unknown	1 (3.3)		
Nodal tumor stage, *n* (%)			0.7
N0	23 (76.7)	7 (78)	
N1	3 (10)		
N2	1 (3.3)		
N3	1 (3.3)	1 (11)	
NX	2 (6.7)	1 (11)	
Recurrence, *n* (%)	10 (33.3)	0	0.08
Death, *n* (%)	5 (16.7)	4 (44.4)	0.2
Concomitant Cis, *n* (%)	8 (26.7)	0	0.2
Tumor size, mean (SD), cm	2.1 (1.7)	2.5 (2.1)	0.6

BMI, body mass index; Cis, carcinoma in situ; IQR, interquartile range; SD, standard deviation. *Statistically significant difference.

significantly reducing tumor growth accompanied by diminished mTORC1/CREB, AR, and PSA levels. Moreover, metformin treatment of PCa patients with high Gleason grade resulted in undetectable mTORC1 levels and upregulated STAT3 expression [5].

Regarding BCa, in our data metformin or other antidiabetic treatment was not associated with BCa outcome. This goes with the observation of Wissing et al. [15]. Where metformin was also not associated with BCa outcome, a major factor for the varying impact of diabetes on different tumor entities is probably related to obesity. In most cases, obesity is also associated with T2DM in the context of metabolic syndrome. Depending on how significant the risk factor for the occurrence of the particular tumor entity is (e.g., high for RCC), T2DM and obesity play a significant role.

In our cohort, diabetics with RCC had a higher BMI and, above all, a higher recurrence rate after surgery. Also here, a comparison between the normal-weight nondiabetics and normal-weight diabetics showed no difference in recurrence rate (p = 0.8). Similarly, Kriegmair et al. [16] reported that MetS negatively impacted the progression-free survival of patients with localized RCC, while it did not influence cancer-specific survival or overall survival. A possible explanation is that patients with higher BMI may adequately preserve their fat and muscle mass, thus allowing a better nutritional status and potential survival advantage delaying the onset of cachexia. On the other is that RCCs arising in obese patients may be more indolent than those in normal-weight patients; patients with obesity have favorable clinical and pathologic conditions at diagnosis when compared with normal-weight patients (lower stage, lower Fuhrman grade, smaller tumor size, and absence of symptoms and distant metastasis) [15]. Although patients with obesity are characterized by a higher rate of tumor growth, they may have more indolent tumors probably because they may be diagnosed at earlier stages as they are at a higher likelihood of being screened for other diseases [17].

Remarkably, a diabetes status or use of metformin has been shown to be a protective factor in penile cancer. Diabetic patients with penile cancer in our study had a significantly higher age at diagnosis and a lower recurrence rate. To our knowledge, this is the first study to suggest a protective link between penile cancer and diabetes status, respectively, antidiabetic drugs. An explanation may be a different gene expression involving fatty acid metabolism genes. Fatty acid synthase (FASN) is a gene that regulates de novo biosynthesis of fatty acids, an essential process for tumor growth. FASN is downregulated in patients with obesity, and higher FASN expression is associated with worse survival. An upregulation of FASN gives cancer cells a survival advantage, making it a potential metabolic oncogene. Lastly, obese and normal-weight patients could have different transcriptomic profiles: tumors of patients with obesity have a different molecular profile compared to those of normal-weight patients. The molecular profile of tumors of obese patients is characterized by the upregulation of genes associated with hypoxia, angiogenesis, and epithelial-mesenchymal transition [17].

However, research on the relationship between diabetes and cancer risk is limited. Most studies have poor sensitivity to detect small associations, especially for specific cancer types. The use of various antihyperglycemic drugs in diabetic patients also complicates research, as adjustments to medication over time make it challenging to evaluate long-term outcomes [2]. Yet, the link between diabetes and antidiabetic medication, especially metformin, seems to be definite and well worth further exploration. The prevention and early detection of cancer in diabetic patients should be a top priority in clinical practice. Additionally, hyperglycemia may create an environment that favors cancer cell growth [2].

This study is limited by its retrospective nature and single-center experience, which may limit the generalizability of the findings. Another limitation is the relatively low number of diabetic patients and absence of long-term investigations. Further investigations with larger cohorts will be needed to establish the prognostic significance of T2DM and antidiabetic medication in cancer patients. Although BMI is largely used to replace the term "obesity" in clinical practice, BMI does not effectively reflect body fat distribution. Other parameters describing body fat distribution such as abdominal circumference and subcutaneous fat thickness should perhaps be included in future clinical trials to better assess body fat.

Conclusion

This study suggests that diabetes status and/or antidiabetic treatment may have beneficial effects in PCa, RCC, and penile cancer.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the University Medical Center Rostock (Approval No. A 2023-0174). The need for informed consent was waived by the Ethics Committee of the University Medical Center Rostock.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

M.E.: project development, data analysis, and manuscript writing. H.Z.: data collection. D.L.D.: data generating. O.W.H.: manuscript editing.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy restrictions but are available from the corresponding author M.E. upon reasonable request.

References

1 Zhang K, Bai P, Dai H, Deng Z. Metformin and risk of cancer among patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Prim Care Diabetes. 2021;15(1):52–8. https://doi.org/10.1016/j.pcd.2020.06.001

2 Ahmad I, Suhail M, Ahmad A, Alhosin M, Tabrez S. Interlinking of diabetes mellitus and cancer: an overview. Cell Biochem Funct. 2023;41(5):506–16. https://doi.org/10.1002/cbf.3802

3 Shlomai G, Neel B, LeRoith D, Gallagher EJ. Type 2 diabetes mellitus and cancer: the role of pharmacotherapy. J Clin Oncol. 2016;34(35):4261–9. https://doi.org/10.1200/JCO.2016.67.4044

4 Lega IC, Lipscombe LL. Review: diabetes, obesity, and cancer-pathophysiology and clinical implications. Endocr Rev. 2020;41(1):bnz014. https://doi.org/10.1210/endrev/bnz014
5 Pencik J, Philippe C, Schlederer M, Atas E, Pecoraro M, Grund-Gröschke S, et al. STAT3/LKB1 controls metastatic prostate cancer by regulating mTORC1/CREB pathway. Mol Cancer. 2023;22(1):133. https://doi.org/10.1186/s12943-023-01825-8
6 Cai H, Zhang B, Ahrenfeldt J, Joseph JV, Riedel M, Gao Z, et al. CRISPR/Cas9 model of prostate cancer identifies Kmt2c deficiency as a metastatic driver by Odam/Cabs1 gene cluster expression. Nat Commun. 2024;15(1):2088. https://doi.org/10.1038/s41467-024-46370-0
7 Ye J, Cai S, Feng Y, Li J, Cai Z, Deng Y, et al. Metformin escape in prostate cancer by activating the PTGR1 transcriptional program through a novel super-enhancer. Signal Transduct Target Ther. 2023;8(1):303. https://doi.org/10.1038/s41392-023-01516-2
8 Jo JK, Song HK, Heo Y, Kim MJ, Kim YJ. Risk analysis of metformin use in prostate cancer: a national population-based study. Aging Male. 2023;26(1):2156497. https://doi.org/10.1080/13685538.2022.2156497
9 Barone B, Finati M, Cinelli F, Fanelli A, Del Giudice F, De Berardinis E, et al. Bladder cancer and risk factors: data from a multi-institutional long-term analysis on cardiovascular disease and cancer incidence. J Pers Med. 2023;13(3):512. https://doi.org/10.3390/jpm13030512
10 Frego N, Contieri R, Diana P, Mancon S, Colombo P, Lazzeri M, et al. Inflammatory markers and Type 2 diabetes mellitus as prognostic risk factors in low-risk bladder cancer. BJU Int. 2023;132:154–6. https://doi.org/10.1111/bju.16026
11 Wong MCS, Huang J, Wang HHX, Yau STY, Teoh JYC, Chiu PKF, et al. Risk prediction of bladder cancer among person with diabetes: a derivation and validation study. Diabet Med. 2024;41(3):e15199. https://doi.org/10.1111/dme.15199
12 Liang Y, Zhang C, Luo J, He Y, Zhang Y, Quan Z, et al. Influence of metabolic syndrome on survival of patients with localized renal clear cell carcinoma: a retrospective cohort study in China. Urol Oncol. 2023;41(5):257.e19–e26. https://doi.org/10.1016/j.urolonc.2023.01.023
13 Li S, Ruan B, Wang Z, Xia J, Lin Q, Xu R, et al. Glucose dysregulation promotes oncogenesis in human bladder cancer by regulating autophagy and YAP1/TAZ expression. J Cell Mol Med. 2023;27(23):3744–59. https://doi.org/10.1111/jcmm.17943
14 Goßler C, May M, Rosenhammer B, Breyer J, Stojanoski G, Weikert S, et al. Obesity leads to a higher rate of positive surgical margins in the context of robot-assisted radical prostatectomy. Results of a prospective multicenter study. Cent Eur J Urol. 2020;73(4):457–65. https://doi.org/10.5173/ceju.2020.0265.R1
15 Wissing MD, O'Flaherty A, Dragomir A, Tanguay S, Kassouf W, Aprikian AG. Chronic prednisone, metformin, and non-steroidal anti-inflammatory drug use and clinical outcome in a cohort of bladder cancer patients undergoing radical cystectomy in Québec, Canada. BMC Urol. 2023;23(1):119. https://doi.org/10.1186/s12894-023-01287-6
16 Kriegmair MC, Mandel P, Porubsky S, Dürr J, Huck N, Nuhn P, et al. Metabolic syndrome negatively impacts the outcome of localized renal cell carcinoma. Horm Cancer. 2017;8(2):127–34. https://doi.org/10.1007/s12672-017-0289-2
17 Turco F, Tucci M, Di Stefano RF, Samuelly A, Bungaro M, Audisio M, et al. Renal cell carcinoma (RCC): fatter is better? A review on the role of obesity in RCC. Endocr Relat Cancer. 2021;28(7):R207–16. https://doi.org/10.1530/ERC-20-0457