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# Effects of Diabetes and Antidiabetics on the Obesity Paradox in Renal Cell Cancer: A Single-center Experience

Moustafa Elleisy[1], Heike Zettl[2], Desiree Louise Dräger[1], Oliver W. Hakenberg[1]

[1]Department of Urology, University Medical Center Rostock, Rostock, Germany
[2]Clinical Cancer Registry, University Medicine Rostock, Rostock, Germany

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

The prevalence of type 2 diabetes mellitus is increasing rapidly worldwide, and there is strong evidence suggesting that cancer incidence is increased in individuals with diabetes. In this study, the effects of different antidiabetic drugs and body weight on the treatment of renal cell carcinoma were investigated.

## Abstract

**Objective:** To determine the effect of diabetes and anti-diabetic treatments on the obesity paradox in renal cell cancer (RCC). We report preliminary results from a single centre study.

**Materials and Methods:** We retrospectively collected data from 294 patients treated between 2018 and 2023 for radical nephrectomy (RN) or partial nephrectomy (PN) for RCC. Age at diagnosis, histopathological data (pathological T-stage, lymph node involvement), tumor size, body mass index, length of hospital stay, death, recurrence, as well as type 2 diabetes mellitus and antidiabetic drugs were recorded and analyzed. A total of 232 (81%) patients were non-diabetic and 55 (19%) were diabetic patients. Patient data were assessed for differences related to bodyweight and the use of antidiabetics.

**Results:** In the diabetic cohort, a higher age at diagnosis of RN was observed when comparing patients treated with dipeptidyl peptidase-4 inhibitors to those treated with sodium glucose cotransporter 2 inhibitors (81 vs. 59 years, $p<0.01$), as well as when comparing patients treated with metformin to those treated with sulfonylureas (SU) (67 vs. 81 years, $p<0.05$). Furthermore, in diabetic patients with PN, compared to those treated with insulin, treated with metformin, no deaths occurred, which was significant (0% vs. 50%, $p<0.05$). The length of stay after PN for diabetic patients treated with metformin was significantly shorter than that of diabetic patients treated with insulin or SU ($p<0.05$).

**Conclusion:** In our study, an obesity paradox was observed for obese patients with RCC. However, the beneficial effects of certain antidiabetics should be considered as a potential cause of this paradox.

**Keywords:** Renal cell cancer, pathological outcomes, diabetes, metformin, antidiabetics

## Introduction

Renal cell carcinoma (RCC) accounts for 3% of all cancer incidence and is the 14th most prevalent oncological disease worldwide (1). In Europe, 138,611 diagnoses of RCC and 54,054 deaths were reported in 2020, with the deaths accounting for 30% of all RCC-related deaths worldwide. An increase in the RCC incidence rate in Europe was reported between 1990 and 2013, reflecting a 23% increase in the age-standardized incidence rate per 100,000 people (1).

### Diabetes Mellitus

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (2). [The specific disease] is emerging as one of the most prevalent human diseases after cardiovascular

**Correspondence:** Moustafa Elleisy MD, Department of Urology, University Medical Center Rostock, Rostock, Germany
**E-mail:** elleisy.moustafa@gmx.at **ORCID-ID:** orcid.org/0000-0001-7375-5357
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conditions and is the sixth leading cause of death worldwide (World Health Organization - WHO). The prevalence of type 2 diabetes mellitus (T2DM) is increasing rapidly worldwide (2). 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. T2DM accounts for about 90% of the total diabetes cases and its prevalence increases with age (3).

There is strong evidence suggesting that cancer incidence is increased in patients with T2DM (2,4). The pathophysiological hypotheses to explain the link between diabetes or hyperglycemia and cancers rely on biological, particularly endocrine mechanisms involving insulinresistance. Indeed, in the genesis of T2DM, reduced insulin sensitivity plays a key role, inducing compensatory hyperinsulinaemia, 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, and breast, all of which are organs with an increased risk of cancer in type 2 diabetic patients (2). T2DM may be considered a specific and independent risk factor for various forms of cancer, due to its particular metabolic characteristics of glucose intolerance and hyperinsulinemia (2,3).

Diabetes has also been significantly linked with an elevated risk of kidney cancer in a meta-analysis of 11 cohort studies (3). Women were observed to have a slightly greater risk ratio (3). Diabetes has also been associated with higher mortality after cancer, and survivors of some cancers have a higher incidence of developing subsequent diabetes (5). Finally, cancer and diabetes treatments have been shown to influence the relationship between diabetes and cancer-associated outcomes (5).

### The Effect of Antidiabetic Drugs on Cancer Risk

Metformin is an oral biguanide that is well established as the first-line treatment of T2DM (6). In a retrospective study, a significant association between metformin use and decreased RCC risk was described. Moreover, a decreased risk of RCC was reported with increased cumulative duration of metformin use (inverse dose-response pattern) (1).

Sulfonylureas (SU) are among the oldest drugs available for the treatment of T2DM. Although SU have been in clinical use for many years, their associations with cancer remain uncertain (6).

There was initially a concern that exogenous insulin was associated with an increased risk of cancer (5). After methodological concerns were carefully considered, however, more recent epidemiological studies have not consistently found an association between insulin, particularly insulin analogues, and cancer (5).

The role of thiazolidinediones (TZDs) in cancer treatment and prevention is uncertain (7). TZDs have been shown to be associated with approximately 20% to 40% lower prostate-specific antigen levels among patients with prostate cancer (6).

Incretin-based drugs include glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors (5). 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 (5).

Sodium glucose cotransporter 2 inhibitors (SGLT2-I) are the newest class of oral diabetes medications (5). In animal models, certain SGLT2-I have been associated with mammary, adrenal, testicular, and renal neoplasms. As SGLT2-I are relatively new in clinical practice, their effects on cancer incidence and mortality should be further elucidated in large-scale studies, with longer durations of follow-up (3,5,6).

### Obesity Paradox

Obesity is a well-known risk factor for RCC incidence. Nonetheless, in several studies, a favourable RCC prognosis in terms of survival benefit was reported in patients with elevated BMI, and this phenomenon is known as the "obesity paradox" (7). According to this paradox, obesity is associated with an increased risk of developing RCC, but after treatment, obese patients have better survival rates than their non-obese counterparts (7). The exact mechanisms behind this paradox are not fully understood, but might include differences in tumour biology, immune response or treatment response in obese patients (1). The risk of RCC was shown to increase by 4% to 6% per unit increase in body mass index (BMI) (per 1 kg/m$^2$). Early adult obesity and especially abdominal obesity (observed more frequently in males than females) have also been identified as risk factors of RCC (1).

The aim of this retrospective analysis was to assess the association between antidiabetic treatments as a potential protective factor and the obesity paradox in RCC, in patients treated at the Department of Urology, University of Rostock, between January 2018 and December 2023.

## Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the University Medical Center Rostock (approval number: A 2023-0174, date: 24.01.2025). The need for informed consent was waived by the Ethics Committee of the University Medical Center Rostock.

Institutional review board approval was obtained before the initiation of the study. This study included a total of 294 patients treated for nmRCC. We identified all patients newly

diagnosed with RCC at our institution according to the Clinical Cancer Registry (CCR) using the International Classification of Diseases, 10th Revision code C64 for renal cancer. 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 procedural episodes in German hospitals, was used to identify specific procedures. The 5-554 code was used to identify patients who underwent radical nephrectomy (RN) and the 5-553 code was used for partial nephrectomy (PN). Patients who underwent either open or laparoscopic surgery were included. Age at diagnosis, histopathological data (pathological T-stage, lymph node involvement), tumor size, BMI, length of hospital stay (LOS), death, and recurrence were recorded and analyzed. T2DM status was considered, if patients were under medical treatment prior to admission for surgical treatment. Patients with incomplete data were excluded.

### Statistical Analysis

We analyzed a BMI-based cohort according to the WHO's BMI categories: normal weight (BMI 18.5-24.9), overweight (BMI 25-29.9), obesity class 1 (BMI 30-34.9), obesity class 2 (BMI 35-39.9), and obesity class 3 (BMI ≥40). All patients were newly diagnosed with RCC at our institution between 1 January 2018 and 31 December 2023. Data were analyzed using SPSS (Version 29, IBM Corp., Armonk, NY, USA). Categorical variables were reported as absolute numbers and proportions, while continuous variables were reported as medians with interquartile ranges or means with standard deviations as appropriate. Comparisons of categorical variables between the cohorts were made using Pearson's chi-squared test, and Fisher's exact test and were reported according to the smallest theoretical frequency, with Fisher's exact test used if less than 5 and Pearson's chi-squared test if greater than 5. According to the distribution of the data, assessed by the Kolmogorov-Smirnov test, the t-test and the Mann-Whitney U test were used for group comparisons for continuous variables. A one-way ANOVA with Bonferroni multiple comparison test, was used for continuous variables. A p-value of $p<0.05$ was considered statistically significant.

## Results

A total of 287 (98%) patients were included in the study, while 7 (2%) were excluded due to missing diabetes status and/or incomplete data, as shown in Figure 1. Of the included patients, 232 (81%) were non-diabetic and 55 (19%) were diabetic. Antidiabetic treatments included metformin in 16 (29%) patients, insulin in 15 (27%) patients, diet in 9 (16%) patients, SLGT2-I in 6 (11%) patients, SU in 3 (5,5%) patients, DPP-4 in 3 (5,5%) patients, and glinide in 1 (1,8%) patient. In Figure 2, the patients are shown with their respective BMI cohorts.

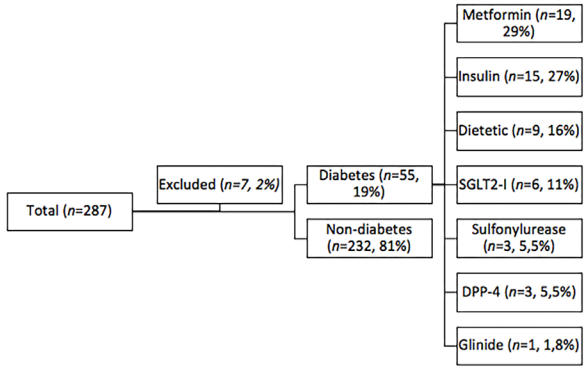


**Figure 1.** A graphic showing the treatment of patients and their antidiabetic medication

SGLT2-I: Sodium-glucose cotransporter type 2 inhibitors, DPP-4: dipeptidyl peptidase-4 inhibitor

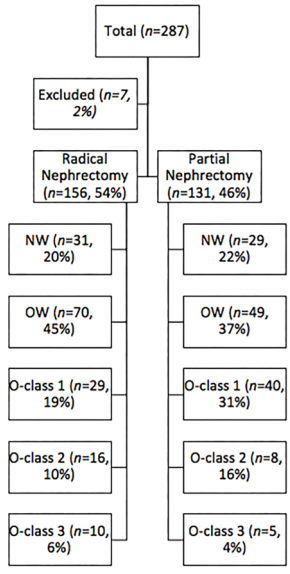


**Figure 2.** A graphic showing the patients with their respective BMI cohorts

BMI: Body mass index, NW: Normal weight (BMI: 18.5-24.9 kg/m$^2$), OW: Overweight (BMI 25-29.9 kg/m$^2$), O: Obesity (class 1: BMI 30-34.9 kg/m$^2$, class 2: BMI 35-39.9 kg/m$^2$, class 3: BMI ≥40 kg/m$^2$)

### Radical Nephrectomy

Overall, 156 patients underwent RN. Of these, 124 (79%) were non-diabetics and 32 (21%) were diabetics (Table 1). Fourteen patients (43.8%) were treated with metformin, 9 (28%) with insulin, 9 (28%) with dietary measures, 2 (6.3%) with SGLT2-I, 3 (9.4%) each with DPP-4 or SU, and only 1 (3.1%) patient with glinide. Additionally, a higher age at diagnosis was found in the diabetic cohort when comparing DPP-4 and SGLT2-I (81 vs. 59 years, $p<0.01$, as shown in Table 2), as well as when comparing metformin and SU (67 vs. 81 years, $p<0.05$). Of note, the diabetic cohort did not have a significantly higher BMI ($p>0.05$, data not shown).

**Table 1. Descriptive characteristics for the cohort of 156 patients treated with radical nephrectomy between January 2018 and December 2023**

| Variables | NW | OW | O-class 1 | O-class 2 | O-class 3 | p-value |
|---|---|---|---|---|---|---|
| Number of patients, n (%) | 31 (19.9) | 70 (44.9) | 29 (18.6) | 16 (10.3) | 10 (6.4) | |
| Diagnosis age, median (IQR), years | 69 (59-79) | 68 (62-77) | 65 (59-70) | 63 (51-76) | 59 (56-65) | 0.4[a,b]/0.6[c]/0.3[d] |
| **Gender, n (%)** | | | | | | |
| Female | 15 (48) | 23 (33) | 7 (24) | 7 (44) | 4 (40) | 0.1[a]/0.5[b,d]/0.8[c] |
| Male | 16 (52) | 47 (67) | 22 (76) | 9 (56) | 6 (60) | |
| Diabetes, n (%) | 4 (13) | 14 (20) | 5 (17) | 5 (31) | 4 (40) | 0.5[a]/0.9[b]/0.3[c]/0.1[d] |
| Length of stay, mean (SD), days | 7.7 (3.7) | 7.9 (5.7) | 7.9 (4.9) | 6.1 (1) | 7.5 (2.2) | 0.4[a]/0.5[b]/0.09[c]/0.7[d] |
| **Histology, n (%)** | | | | | | |
| Clear cell RCC | 21 (68) | 54 (77) | 23 (79) | 15 (94) | 8 (80) | 0.9[a]/0.1[b]/0.5[c]/0.7[d] |
| Papillary RCC | 1 (3) | 9 (13) | 4 (14) | | | |
| Chromophobe RCC | 3 (10) | 3 (4) | | 1 (6) | 1 (10) | |
| Sarcoamtoid RCC | 2 (6) | | | | | |
| Others | 2 (6) | 4 (6) | 2 (7) | | 1 (10) | |
| Unknown | 1 (3) | | | | | |
| **Pathological tumor stage, n (%)** | | | | | | |
| pT1a | 3 (10) | 6 (9) | 1 (3) | 4 (25) | 1 (10) | 0.2[a,c]/0.1[b]/0.09[d] |
| pT1b | | 9 (13) | 5 (17) | 2 (13) | 2 (20) | |
| pT2a | 4 (13) | 5 (7) | 2 (7) | | 1 (10) | |
| pT2b | 1 (3) | 2 (3) | | | | |
| pT3a | 18 (58) | 42 (60) | 19 (66) | 9 (56) | 4 (40) | |
| pT3b | 3 (10) | 6 (9) | 1 (3) | 1 (6) | | |
| pT3c | | | 1 (3) | | 1 (10) | |
| Unknown | 2 (6) | | | | 1 (10) | |
| **Nodal tumor stage, n (%)** | | | | | | |
| N0 | 23 (74) | 56 (80) | 27 (93) | 14 (88) | 9 (90) | 0.7[a]/0.1[b]/0.2[c,d] |
| N1 | 6 (19) | 9 (13) | 1 (3) | | | |
| NX | 2 (6) | 5 (7) | 1 (3) | 2 (13) | 1 (10) | |
| Recurrence, n (%) | 3 (10) | 12 (17) | 2 (7) | 2 (13) | 3 (30) | 0.4[a]/0.9[b,c]/0.1[d] |
| Death, n (%) | 10 (32) | 20 (29) | 4 (14) | 6 (38) | 2 (20) | 0.7[a]/0.09[b]/0.7[c,d] |
| **Tumor site, n (%)** | | | | | | |
| Right | 15 (48) | 35 (50) | 19 (66) | 11 (69) | 4 (40) | 0.9[a,d]/0.2[b,c] |
| Left | 16 (52) | 35 (50) | 10 (34) | 5 (31) | 6 (60) | |
| Tumor size, mean (SD), cm | 7.8 (4.5) | 7.1 (3.1) | 6.7 (2.3) | 5.8 (2.2) | 6 (3.4) | 0.3[a,d]/0.2[b]/0.07[c] |

(*) Statistically significant difference. (a) NW vs. OW, (b) NW vs. O-Class 1, (c) NW vs. O-Class 2, (d) NW vs. O-Class 3, BMI: Body mass index, RCC: Renal cell carcinoma, NW: Normal weight (BMI: 18.5-24.9 kg/m$^2$), OW: Overweight (BMI 25-29.9 kg/m$^2$), O: Obesity (class 1: BMI 30-34.9 kg/m$^2$, class 2: BMI 35-39.9 kg/m$^2$, class 3: BMI ≥40 kg/m$^2$), IQR: Interquartile range, SD: Standard deviation

**Table 2. Descriptive characteristics of the diabetes cohort of 29 patients treated with radical nephrectomy between January 2018 and December 2023**

| Variables | Metformin | Insulin | DPP-4 | SU | p-value |
|---|---|---|---|---|---|
| Number of patients, n (%) | 14 (48) | 9 (31) | 3 (10) | 3 (10) | |
| Diagnosis age, median (IQR), years | 67 (63-76) | 65 (63-81) | 59 (57-62) | 81 (78-84) | $0.7^{a,d}/0.08^{b}/<0.05^{*c}/0.09^{e}/<0.01^{*f}$ |
| **Gender, n (%)** | | | | | |
| Female | 4 (29) | 3 (33) | | 2 (67) | $0.9^{a}/0.5^{b,c,d,e}/0.3^{d,e}/0.4^{f}$ |
| Male | 10 (71) | 6 (67) | 3 (100) | 1 (33) | |
| BMI, mean (IQR), kg/m$^2$ | 30 (27-35) | 33 (28-38) | 35 (23-41) | 27 (24-28) | $0.3^{a,b,f}/0.2^{c}/0.8^{d}/0.1^{e}$ |
| Length of stay, mean (SD) days | 6.7 (2) | 8.3 (4.8) | 7.3 (1.5) | 6.3 (1.5) | $0.3^{a}/0.6^{b}/0.8^{c}/0.7^{d}/0.5^{e,f}$ |
| **Histology, n (%)** | | | | | |
| Clear cell RCC | 11 (79) | 8 (89) | 3 (100) | 3 (100) | $0.3^{a}/0.8^{b,c}/0.2^{d,e}/0.9^{f}$ |
| Papillary RCC | | 1 (11) | | | |
| Chromophobe RCC | 1 (7) | | | | |
| Others | 2 (14) | | | | |
| **Pathological tumor stage, n (%)** | | | | | |
| pT1a | | 1 (11) | | 1 (33) | $0.5^{a,e}/0.1^{b,d}/0.2^{c}/0.3^{f}$ |
| pT1b | 3 (21) | 2 (22) | | | |
| pT2a | 1 (7) | | 1 (33) | | |
| pT2b | | | | | |
| pT3a | 8 (57) | 6 (67) | 1 (33) | 2 (67) | |
| pT3b | 2 (14) | | | | |
| pT3c | | | 1 (33) | | |
| **Nodal tumor stage, n (%)** | | | | | |
| N0 | 12 (86) | 9 (100) | 3 (100) | 3 (100) | $0.5^{a}/0.8^{b,c}/0.9^{d,e,f}$ |
| N1 | 1 (7) | | | | |
| NX | 1 (7) | | | | |
| Recurrence, n (%) | 5 (36) | 3 (33) | 0 | 0 | $0.9^{a,f}/0.5^{b,c,d,e}$ |
| Death, n (%) | 5 (36) | 3 (33) | 0 | 2 (67) | $0.9^{a}/0.5^{b,c,d,e}/0.4^{f}$ |
| **Tumor site, n (%)** | | | | | |
| Right | 9 (64) | 5 (56) | 2 (67) | 3 (100) | $0.9^{a,b,d,f}/0.5^{b,c,e}$ |
| Left | 5 (36) | 4 (44) | 1 (33) | | |
| Tumor size, mean (SD), cm | 8.3 (3.8) | 6 (2.9) | 6.6 (3.2) | 6.7 (2.5) | $0.1^{a}/0.5^{b,c}/0.8^{d}/0.7^{e}/0.9^{f}$ |

(*) Statistically significant difference. (a) Metformin vs. Insulin, (b) Metformin vs. DPP-4, (c) Metformin vs. SU, (d) Insulin vs. DPP-4, (e) Insulin vs. SU, (f) DPP-4 vs. SU, BMI: Body mass index, RCC: Renal cell carcinoma, SGLT2-I: Sodium-glucose cotransporter type 2 inhibitor, DPP-4: Dipeptidyl peptidase-4 inhibitor, SU: Sulfonylureas, IQR: Interquartile range, SD: Standard deviation

**Table 3. Descriptive characteristics for the cohort of 131 patients treated with partial nephrectomy between January 2018 and December 2023**

| Variables | NW | OW | O-Class 1 | O-Class 2 | O-Class 3 | p-value |
|---|---|---|---|---|---|---|
| Number of patients, n (%) | 29 (22.1) | 49 (37.4) | 40 (30.5) | 8 (6.1) | 5 (3.8) | |
| Diagnosis age, median (IQR), years | 75 (64-81) | 69 (62-77) | 66 (61-74) | 75 (62-80) | 61 (59-65) | 0.7[a]/0.4[b]/0.9[c]/0.3[d] |
| Gender, n (%) | | | | | | |
| Female | 12 (41.4) | 16 (32.7) | 10 (25) | 4 (50) | 2 (40) | 0.4[a]/0.2[b]/0.7[c]/0.9[d] |
| Male | 17 (58.6) | 33 (67.3) | 30 (75) | 4 (50) | | |
| **Diabetes, n (%)** | | | | | | |
| Negative | 24 (82.8) | 38 (77.6) | 33 | 5 (62.5) | 1 (20) | 0.7[a]/0.4[b]/0.1[c]/<0.001*[d] |
| Positive | 5 (17.2) | 10 (20.4) | (82.5) | 2 (25) | 1 (20) | |
| Unknown | | 1 (2) | 5 (12.5)<br>2 (5) | 1 (12.5) | 3 (60) | |
| Length of stay, mean (SD), days | 7.2 (3.6) | 6.7 (2) | 6.8 (2.7) | 5.9 (1.5) | 9 (6.7) | 0.9[a]/0.7[b]/0.3[c]/0.4[d] |
| **Histology, n (%)** | | | | | | |
| Clear cell RCC | 18 (62) | 28 (57.1) | 32 (80) | 8 (100) | 4 (80) | 0.6[a]/0.1[b]/0.2[c]/0.5[d] |
| Papillary RCC | 8 (27.6) | 16 (32.7) | 3 (7.5) | | | |
| Chromophobe RCC | 2 (6.8) | 1 (2) | 4 (10) | | 1 (20) | |
| Others | 1 (3.4) | 3 (6.1) | 1 (2.5) | | | |
| Unknown | | 1 (2) | | | | |
| **Pathological tumor stage, n (%)** | | | | | | |
| pT1 | 1 (3.4) | 1 (2) | | | | 0.7[a]/0.6[b,c]/0.4[d] |
| pT1a | 15 (51.7) | 31 (63.3) | 20 (50) | 7 (87.5) | 1 (20) | |
| pT1b | 5 (17.2) | 6 (12.2) | 10 (21) | | 3 (60) | |
| pT2 | | | 1 (2.5) | | | |
| pT2a | 1 (3.4) | | | | | |
| pT3 | | 1 (2) | | | | |
| pT3a | 5 (17.2) | 5 (10.2) | 7 (17.5) | 1 (12.5) | 1 (20) | |
| pT4 | | 1 (2) | 1 (2.5) | | | |
| Unknown | 2 (6.9) | 4 (8.2) | 1 (2.5) | | | |
| **Nodal tumor stage, n (%)** | | | | | | |
| N0 | 27 (93.1) | 40 (81.6) | 35 (87.5) | 8 (100) | 5 (100) | 0.2[a]/0.6[b]/0.9[c,d] |
| N1 | | | 1 (2.5) | | | |
| NX | 2 (6.9) | 9 (18.4) | 4 (10) | | | |
| Recurrence, n (%) | 2 (6.9) | 7 (14.3) | 2 (5) | 0 | 0 | 0.5[a]/0.9[b,c,d] |
| Death, n (%) | 6 (20.7) | 4 (8.2) | 10 (25) | 0 | 1 (20) | 0.2[a]/0.7[b]/0.3[c]/0.9[d] |
| **Tumor site, n (%)** | | | | | | |
| Right | 12 (41.4) | 22 (44.9) | 17 (42.5) | 5 (62.5) | 3 (60) | 0.8[a]/0.9[b]/0.4[c]/0.6[d] |
| Left | 17 (58.6) | 27 (55.1) | 23 (57.5) | 3 (37.5) | 2 (40) | |
| Tumor size, mean (SD), cm | 3.5 (2.2) | 3.3 (2.4) | 3.5 (1.3) | 2.5 (0.6) | 3.9 (1.7) | 0.6[a,d]/0.9[b]/0.2[c] |

(*) Statistically significant difference. (a) NW vs. OW, (b) NW vs. O-Class 1, (c) NW vs. O-Class 2, (d) NW vs. O-Class 3, BMI: Body mass index, RCC: Renal cell carcinoma, NW: Normal weight (BMI: 18.5-24.9 kg/m²), OW: Overweight (BMI 25-29.9 kg/m²), O: Obesity (class 1: BMI 30-34.9 kg/m², class 2: BMI 35-39.9 kg/m², class 3: BMI ≥40 kg/m²), IQR: Interquartile range, SD: Standard deviation

**Table 4. Descriptive characteristics of the diabetes cohort of 22 patients treated with partial nephrectomy between January 2018 and December 2023**

| Variables | Metformin | Insulin | SGLT2-I | p-value |
|---|---|---|---|---|
| Number of patients, n (%) | 12 (55) | 6 (27) | 4 (18) | |
| Diagnosis age, median (IQR), years | 70 (64-77) | 75 (56-84) | 70 (63-79) | 0.8a,c/0.9b |
| **Gender, n (%)** | | | | |
| Female | 2 (16.7) | 3 (50) | | 0.3a/0.9b/0.2c |
| Male | 10 (83.3) | 3 (50) | 4 (100) | |
| BMI, mean (IQR), kg/m$^2$ | 29 (25-31) | 29 (22-36) | 28 (26-29) | 0.9a/0.5b/0.8c |
| Length of stay, mean (SD) days | 5.3 (0.8) | 8.7 (5.2) | 8.7 (4.7) | <0.05*a,b/0.9c |
| **Histology, n (%)** | | | | |
| Clear cell RCC | 8 (66.7) | | | 0.9a/0.6b/0.2c |
| Papillary RCC | 2 (16.7) | 6 (100) | 3 (75) | |
| Chromophobe RCC | 2 (16.7) | | 1 (25) | |
| **Pathological tumor stage, n (%)** | | | | |
| pT1a | 5 (41.7) | 2 (33.3) | 2 (50) | 0.3a/0.6b/0.4c |
| pT1b | 3 (25) | 2 (33.3) | | |
| pT2a | 1 (8.3) | | | |
| pT3a | 3 (25) | 2 (33.3) | 2 (50) | |
| **Nodal tumor stage, n (%)** | | | | |
| N0 | 10 (83.3) | | | 0.9a,b,c |
| NX | 2 (16.7) | 6 (100) | 4 (100) | |
| Recurrence, n (%) | 1 (8.3) | 2 (33.3) | 1 (25) | 0.07a/0.5b/0.9c |
| Death, n (%) | 0 | 3 (50) | 1 (25) | <0.05*a/0.3b/0.6c |
| **Tumor site, n (%)** | | | | |
| Right | 6 (50) | 4 (66.7) | 1 (25) | 0.7a/0.6b/0.5c |
| Left | 6 (50) | 2 (33.3) | 3 (75) | |
| Tumor size, mean (SD), cm | 3.7 (1.9) | 3.9 (1.7) | 3.4 (0.9) | 0.8a/0.7b/0.6c |

(*) Statistically significant difference. (a) Metformin vs. Insulin, (b) Metformin vs. SGLT2-I, (c) Insulin vs. SGLT2-I, BMI: Body mass index, RCC: Renal cell carcinoma, SGLT2-I: Sodium-glucose cotransporter type 2 inhibitor, IQR: Interquartile range, SD: Standard deviation

### Partial Nephrectomy

Overall, 131 patients underwent PN. Of these, 108 (82%) were non-diabetic and 23 (18%) were diabetic (Table 3). Twelve patients (52%) were treated with metformin, 6 (26%) with insulin, 4 (17%) with SGLT2-I, and 1 (4%) with a DPP-4 inhibitor. A significant difference in T2DM rates was found between normal weight and obesity class 3, but this is most likely due to a lack of data (Table 4). Interestingly, in the diabetic cohort undergoing PN, patients treated with metformin showed a significantly lower death rate compared to those treated with insulin (0% vs. 50%, $p<0.05$). Furthermore, the LOS for diabetic patients treated with metformin was significantly shorter than that of diabetic patients treated with insulin or SU ($p<0.05$). No differences in terms of pathological features or other baseline characteristics were found. Here, as well, the diabetic cohort did not show a significantly higher BMI ($p>0.05$, data not shown).

## Discussion

In this study, RCC patients were differentiated according to body weight and associated antidiabetic medications. For RN, a significantly higher age at diagnosis, was observed in the diabetic cohort, when comparing DPP-4 inhibitors and SGLT2-I inhibitors. Furthermore, patients with diabetes treated with metformin experienced no deaths, a result significantly different from those taking insulin. 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 people with diabetes taking metformin had a 23% lower overall risk of cancer compared to those not taking metformin. The study observed and reported a risk reduction for the longest metformin treatment period (8).

A number of factors have been proposed to contribute to the increased risk of cancer development and mortality in the setting of obesity and T2DM. These include hyperglycemia,

insulin resistance, hyperinsulinemia, increased insulin-like growth factor-1 (IGF-1) levels, dyslipidemia, inflammatory cytokines, increased leptin, and decreased adiponectin (6). Insulin resistance in metabolic tissues, such as fat, liver, and skeletal muscle, results in increased production of insulin from pancreatic β-cells, which leads to circulating hyperinsulinemia. Pancreatic β-cells eventually decompensate, and hyperglycemia develops. Hyperglycemia also develops as a result of increased hepatic glucose production secondary to insulin resistance in the liver and decreased uptake into skeletal muscle and adipose tissue (6). Endogenous insulin acting on the liver increases insulin-like growth factor-1 (IGF-1) synthesis and leads to decreased concentrations of IGF-binding proteins 1 and 2, thus potentially increasing local concentrations of bioavailable IGF-1. Adipose tissue inflammation occurs with insulin resistance, leading to the production of cytokines and changes in the circulating concentrations of adipokines, such as increased leptin and decreased adiponectin (6).

The mechanism by which obesity improves the survival of patients with RCC is not well understood. Patients with higher BMI may adequately preserve their fat and muscle mass, thus allowing a better nutritional status and a potential survival advantage, delaying the onset of cachexia. Another possible explanation is that RCCs arising in obese patients may be more indolent than those in normal-weight patients; they 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) (9,10). Although patients with obesity are characterized by a higher rate of tumor growth, they may have more indolent tumors, probably because they are diagnosed at earlier stages as they are at a higher likelihood of being screened for other diseases (10).

An alternative explanation for the obesity paradox 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. The 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 than those of normal-weight patients. The molecular profile of tumours of obese patients is characterized by the upregulation of genes associated with hypoxia, angiogenesis and epithelial-mesenchymal transition (10). Interestingly, Li et al. (11) also found an obesity paradox for lung cancer operations, where patients with higher BMI showed a significantly better long-term survival rate. Possible reasons for this are that obese patients have a greater ability to store nutrients to resist surgical interventions compared to normal/underweight patients. The protective effects of peripheral adipose tissues have been demonstrated in previous investigations, contributing to a better prognosis for surgical patients (11). Another conceivable cause could be that an increasing number of people are becoming obese at a young age with strong physiological functions and better recovery capabilities. because obese patients are considered at higher risk of cardiovascular disorders, they are generally treated at an early age with medicines to control blood pressure and prevent hyperglycemia. This situation may be another important reason for the obesity paradox (11).

We hypothesize that obese patients usually present with diabetes as part of a metabolic syndrome. It is possible, however, that the use of metformin and SGLT2-I, for example, suppresses the mTOR signaling pathway by reducing the circulating levels of insulin and IGF-1 in peripheral blood and activating liver kinase B1 signaling pathways, thus leading to decreased cell proliferation, reduced protein translation, and lower insulin levels (7). Nevertheless, the obesity paradox has not yet been fully clarified.

BMI is used in most studies that evaluate the influence of obesity on RCC (12). However, BMI has limitations that impact its utility in elucidating the biology underlying the impact of obesity on RCC (12). BMI is an imperfect surrogate for biologically distinct body composition compartments, such as visceral adipose tissue and muscle mass, and inferences about the global metabolic state based on BMI are incomplete (12). However, in recent studies, the BMI range associated with the lowest risk of mortality varies depending on secular trends, ethnicity, and population (12). Furthermore, adiposity traits are known to be sexually dimorphic. Females have higher single nucleotide variants-based (SNV-based) heritability for waist-to-hip ratio (WHR) and larger effect sizes in more than 90% of WHR (adjusted for BMI)-associated SNVs, compared with males. Since female adiposity distribution is drastically different from that in males, the relatively higher abdominal obesity in males may explain the sex-specific difference in risk (13). A previous study found that the BMI-all-cause mortality association weakened with older age. A possible reason why the BMI–all-cause mortality association attenuates might be that nutritional reserves become more important with age. Another cause could be reverse causality, as there is increased prevalence of major disease among older individuals, some of which impact BMI through muscle mass loss (13). Body composition can be measured indirectly using anthropometric measurements, such as BMI and abdominal circumference, or directly using computed tomography or dual-energy X-ray absorptiometry (12).

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 (3). Yet the link between diabetes and anti-diabetic medication, especially metformin, is compelling 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. Healthcare providers should follow certain guidelines for the care of diabetic individuals, including medical therapy and regular cancer screenings based on each patient's unique risk factor profile. Through these measures, the early detection of cancer can be prioritized, leading to more effective treatment and improved outcomes for diabetic patients (3).

Many studies suggest a potential positive effect of certain antidiabetics; however, prospective studies are needed to validate these findings. Currently, the lack of large, randomized controlled trials makes it difficult to provide a general recommendation. Nevertheless, for diabetic patients with RCC, one could consider using metformin and SGLT2-I rather than DPP-4 or SU.

### Study Limitations

This study is limited by its retrospective nature and single-center data collection, which restricts the generalizability of the findings. Other limitations are the relatively low number of diabetic patients and the lack of long-term follow-up. Further investigations with larger cohorts will be needed to establish the prognostic significance of DM and anti-diabetic 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, may be included in future clinical trials to better assess body fat.

## Conclusion

In this study, no significant differences were found regarding the obesity paradox in RCC. However, the findings indicate that certain antidiabetic treatments have beneficial effects on RCC for both RN and PN.

### Ethics

**Ethics Committee Approval:** The study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the University Medical Center Rostock (approval number: A 2023-0174, date: 24.01.2025).

**Informed Consent:** The need for informed consent was waived by the Ethics Committee of the University Medical Center Rostock.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: D.L.D., O.W.H., Concept: M.E., Design: M.E., Data Collection or Processing: H.Z., M.E., Analysis or Interpretation: M.E., Literature Search: M.E., Writing: M.E.

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