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The role of diabetes mellitus in localized and metastatic renal cell carcinoma

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ABSTRACT

Introduction & Objectives: Until recently, the incidence of renal cell carcinoma (RCC) has been increasing worldwide, mainly in western countries, at a rate between 2% and 4% per year. However, the reason for this dramatic increase in number has not been fully understood. Diabetes mellitus (DM) is a known risk factor for RCC, but the impact of DM on the prognosis of RCC is unclear. In the present study, we investigated the potential influence of DM on clinicopathological features of localized and metastatic RCC. Material & Methods: We evaluated 863 patients with primary RCC who had undergone renal surgery between 1991 and 2005 in the University Hospital Hannover; the mean follow-up was 58 months. To test the association of DM with survival end-points, Kaplan-Meier Method and Cox multivariable logistic regression models were applied. Results: In total, we identified 123 diabetic patients who suffered from RCC, 9 patients with diabetes type 1 and 114 with type 2. Patients with DM type 2 presented significantly more often with pT1a tumours at diagnosis (40.0% vs 31.7%, $p = 0.02$), had less frequently high grade cancer (G3/4; 10.3% vs 16.2%, $p = 0.03$), were older (median, 65.3 vs 61.6 years; $p < 0.001$), and had a higher BMI at diagnosis (median, 27.6 vs 25.8, $p < 0.001$). However, there was no difference between diabetic and non-diabetic patients concerning sex, histological subtype, lymphatic and distant metastasis. In addition, there was no discrepancy in 5-year cancer specific survival between both groups (62.2% vs 64.9% for patients with and without DM type 2, respectively). Applying multivariable analysis, unlike age, tumour stage, grade and N/M status, diabetes was not identified as a significant independent prognostic factor. Conclusions: To our knowledge this is the first study to show that even though diabetes is a risk factor for RCC it does not seem to influence its prognoses even though it might be diagnosed earlier in diabetic patients.

Keywords: Renal Cell Cancer; Risk Factor; Diabetes Mellitus; Survival; Prognosis

1. INTRODUCTION

More than 40,000 new cases are diagnosed in the European Union every year and more than half of these patients will die from RCC [1]. Worldwide, the mortality from RCC exceeds 100,000 per year [2]. Despite increased health care facilities for imaging and consequent early diagnosis, still up to one third of all patients with RCC will have metastases at time of presentation [3-7]. Of the remaining two thirds, approximately 20% - 40% of those treated with (partial) nephrectomy in case of localized disease, will eventually develop metachronous metastasis or locally recurring cancer [8-11].

As patients' clinical courses vary and are difficult to predict, and as an increasing number of adjuvant and palliative agents has been and is currently being developed for the treatment of RCC, the stratifications of patients to different therapeutic strategies according to specific prognostic factors will become increasingly important. Favourable prognostic factors include complete resectability and a long interval between initial diagnosis and development of metastases [12,13].

An increased risk of kidney cancer has been reported for obese persons [14] as well as for diabetic patients

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[15-17]. Moreover, obesity is a major risk factor associated with diabetes mellitus (DM) [18,19]. Although the precise mechanism how obesity contributes to insulin resistance and DM has not yet been identified; both DM and obesity are associated with hyperinsulinemia [20]. As the incidence of DM increases with body mass [18, 19,21], and obesity has only recently been identified as an independent positive prognostic factor for patients with localized RCC [22], we investigated the role of DM on the prognosis of RCC.

2. MATERIAL AND METHODS

A total of 863 RCC patients treated from 1991 to 2005 by radical nephrectomy or nephron-sparing surgery and information whether they also suffered DM were included in this study. Information on patients' and tumour characteristics such as TNM stage, age and sex, histological differentiation, Fuhrman grade, presence of regional lymph node or distant metastases and type of surgery was obtained from our institutional database (MHH).

The duration of the follow-up was calculated from date of surgery to the date of death or last follow-up. Death was assessed as either cancer-related or unrelated. In case of patients' death, the cause was obtained from death certificates or correspondence with physicians.

Chi-square (or Fisher's exact) and T-tests were applied to evaluate patients' and tumour characteristics of potential importance for the postoperative clinical prognosis (**Table 1**). The cancer specific survival (CSS) was calculated according to Kaplan-Meier method. Likelihood of Cox proportional hazards regression model was used to compare the prognostic accuracy between the two classifications. SPSS 17.0 was used for statistical assessment. All tests were 2-sided, $p < 0.05$ was considered to indicate significance.

3. RESULTS

3.1. Patients' and Tumour Characteristics

In total, 123 out of 863 patients with RCC were identified as diabetic, 9 patients with DM type 1 and 114 with type 2. To compare homogeneous collectives, we excluded those patients with type 1 DM form all further calculation.

The median age for all 854 patients was 62.1 years and differed significantly between diabetic and non-dia- betic RCC patients (median, 65.3 vs 61.6 years; $p < 0.001$, t-test). In addition, patients with DM had a significantly higher median body mass index (BMI) of 27.6 vs 25.8 kg/m^2 ($p < 0.001$, t-test). In our cohort, those patients with DM type 2 presented significantly more often with pT1a tumours (40.0% vs 31.7%; $p = 0.018$, chi^2) and less often with poorly differentiated RCC (G3/4 cancer in 10.3% vs 16.2%, $p = 0.026$, chi^2).

Table 1. Diabetes mellitus (DM) related tumour and patient specific characteristics.

Variable	DM II	no DM	*p*-value	Test
Age in Years [mean; ± SD]	65.5 ± 8.7	60.9 ± 11.5	<0.001	t-test
BMI in kg/m^2 [mean; ± SD]	28.8 ± 6.7	26.6 ± 4.4	0.001	t-test
Histology			0.32	Fisher's Exact
Clear Cell	109 (95.6%)	680 (92.6%)		
Non Clear Cell	5 (4.4%)	54 (7.4%)		
Stage (TNM 2002)			0.018	Chi^2
pT1a	42 (40.0%)	222 (31.7%)		
pT1b	22 (21.0%)	156 (22.2%)		
pT2	3 (2.8%)	61 (8.7%)		
pT3a	7 (6.7%)	111 (15.8%)		
pT3b/c	28 (26.7%)	133 (19.0%)		
pT4	3 (2.8%)	18 (2.6%)		
LN metastasis[1]	6 (5.3%)	61 (8.2%)	0.35	Fisher's Exact
Pumonal/ Visceral Metastasis[1]	18 (15.8%)	124 (16.8%)	0.89	Fisher's Exact
Grade			0.026	Chi^2
G1	14 (13.1%)	106 (15.3%)		
G2	82 (76.6%)	474 (68.5%)		
G3	9 (8.4%)	110 (15.9%)		
G4	2 (1.9%)	2 (0.3%)		

[1]at time of renal surgery; [2]from time of renal surgery; Abbreviations: BMI = body mass index, DM = diabetes mellitus, SD = standard deviation, LN = lymph node.

However, there were no significant difference between diabetic and non-diabetic patients concerning nodal disease (5.3% vs 8.2%, $p = 0.35$) and visceral metastasis (15.8% vs 16.8%, $p = 0.89$) at diagnosis.

3.2. Cancer Specific Long-Term Survival (CSS)

After a mean follow-up of 5 years, 336 (39.3%) patients had died from tumour progression, 40.4 and 39.2% of all patients with and without DM type 2 ($p = 0.84$, Fishers' exact). With a 5-year-CSS rate of 62.2% and 64.9%, this difference among groups was not demonstrated to be statistically significant, either ($p = 0.67$, log rank; **Figure 1**).

In accordance, applying multivariable analysis, unlike age, tumour stage, grade and N/M status, diabetes could not be identified as a significant independent prognostic factor (HR 1.247 (95% CI 0.89-1.75, $p = 0.203$, Cox regression; **Table 2**).

4. DISCUSSION

To our knowledge this is the first study focusing on the association between DM and kidney cancer mortality.

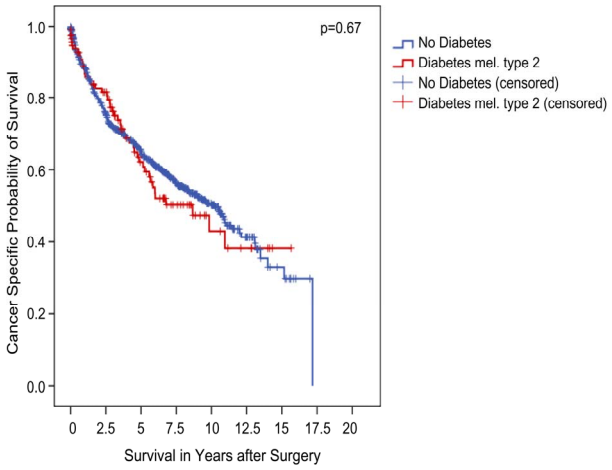

Figure 1. Association between diabetes type 2 and clinical outcome in all patients (Kaplan-Meier; n = 854 evaluable): the 5-year CSS was not different between both groups (62.2% vs 64.9% for patients with and without diabetes type 2, respectively; p = 0.67, log-rank test).

Table 2. Diabetes fails as an independent prognostic marker for cancer specific survival in patients with RCC (multivariable Cox regression analysis).

Variable	HR (95% CI)	*p*-value
Age	1.04 (1.03 - 1.05)	<0.001
Sex		0.39
Female	Reference	
Male	1.12 (0.87 - 1.44)	
Grade		<0.001
G1	Reference	
G2	1.29 (0.85 - 1.97)	0.24
G3/4	2.27 (1.38 - 3.75)	0.001
Stage		<0.001
pT1a	Reference	
pT1b	1.25 (0.84 - 1.85)	0.27
pT2	2.49 (1.56 - 3.97)	<0.001
pT3a	1.94 (1.30 - 2.91)	0.001
pT3b	2.20 (1.50 - 3.25)	<0.001
pT3c	7.28 (2.81 - 18.89)	<0.001
pT4	2.14 (1.01 - 4.18	0.026
LN Metastasis[1]		<0.001
Negative	Reference	
Positive	2.77 (1.93 - 3.96)	
Pumonal/Visceral Metastasis[1]		< 0.001
Negative	Reference	
Positive	2.71 (2.01 - 3.64)	
Diabetes Mellitus (DM)[1]		0.20
No DM	Reference	
DM II	1.25 (0.89 - 1.75)	

[1]At time of surgery.

The annual mortality-to-incidence ratio with RCC is significantly higher compared to other urological malignancies, and its incidence has been increasing steadily in recent decades [23]. Many risk factors may play a role in this increase, including nutritional and hormonal parameters, hypertension, and family history of RCC [16, 24-27]. A history of DM has also been associated with a modest increase in the risk of RCC in several studies [15-17].

This may be mediated through an increase in the incidence of hypertension or body mass [17]. Obesity is another widely accepted risk factor for the development of RCC [14]. Furthermore, in a survey of adults in the United States, overweight and obese individuals had a higher relative risk of hypertension, hypercholesterolemia, and DM, compared with normal weight individuals. In addition, the BMI has only recently been identified as an independent positive prognostic factor for patients with localized RCC [22].

More than 280 million people worldwide are known to suffer from DM (http://www.diabetesatlas.org), and this number is projected to grow to 438 million by 2030. DM can change the outcome of cancer either directly, through biological mechanisms, or indirectly, by affecting the use of screening and treatment allocation. Whereas the association between DM and pancreatic cancer is fairly well established from studies carried out to date [28], risks of death from cancers at other sites in diabetics are less well understood. However, DM is known to commonly occur together with breast cancer; and two of the major risk factors for type 2 DM, similar to RCC, older age and obesity are also associated with breast cancer [29]. In addition, clinical studies suggest an association between DM and an inferior outcome in women with breast cancer [29]. Interestingly, several anti-diabetic therapies, including the biguanides and the peroxisome proliferator-activated receptor ligands may also have activity against breast cancer and are being tested in clinical trials [29].

In this large retrospective analysis with a mean follow up period of 5 years we were able to show that patients with DM type 2 presented significantly more often with smaller tumours at diagnosis (pT1a) and had less frequently high-grade RCC. In addition, we found a significantly higher BMI in diabetic patients compared to those without diabetes. However, we did not reveal an influence of DM on the histological subtype as well as the prevalence of lymph node and distant metastasis at the time of diagnosis. The five-year tumour specific survival was similar in both groups and DM could not be identified as a significant independent prognostic marker applying multivariable analysis.

Previous studies have suggested that the development of renal cell cancer in obese, diabetic patients is related

to hormonal changes, showing that obese diabetic women have an increased risk of renal cell cancer compared to men [30]. In our study there was no difference between the incidence of RCC in diabetic and non-diabetic men and women.

Our study is not without limitations that need to be acknowledged including its retrospective design, its lack of central pathologic review as well as documentation of specific additional treatment modalities in case of relapse though at least subjectively we do not believe that the latter differed significantly between either groups.

In conclusion, to our knowledge this is the first study showing that even though diabetes is a risk factor for RCC and diabetic patients seem to be diagnosed earlier with RCC (lower stages and tumour grade) it does not influence the prognosis of RCC.

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