



Does diabetes mellitus play an independent prognostic role in kidney cancer?

Johannes Breyer

Department of Urology, University of Regensburg Caritas St. Josef Medical Center, Regensburg, Germany

Correspondence to: Johannes Breyer. Department of Urology, University of Regensburg Caritas St. Josef Medical Center, Landshuter Str. 65 93053 Regensburg, Germany. Email: johannes.breyer@ukr.de.

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Kidney cancer accounts for about 2% of all carcinomas with an incidence of 403,262 new cases in 2018 and 175,098 dying from the tumor (1). Due to the improved and more frequent use of imaging, incidence is rising about 2% over the last two decades with more small and localized tumors being diagnosed (2).

Smoking, obesity and hypertension have been identified as modifiable risk factors for renal cell carcinoma (RCC) (3,4).

The role of diabetes mellitus (DM) as an independent risk factor and prognostic factor of RCC remains unclear (3,4). There is evidence that diabetes may be a risk factor for RCC. Ribback *et al.* could show that long-term hyperglycemia can induce carcinogenesis in renal tubule cells *in vitro* (5). In a meta-analysis, Bao *et al.* described an increased risk for diabetic patients to develop RCC, independent of obesity, smoking and alcohol consumption (6). But there was no association to carcinoma-specific survival (CSS) in this meta-analysis. In a single-center propensity score analysis of over 1,000 patients with RCC, no correlation of DM with survival of RCC could be shown (7). In a retrospective analysis on the influence of metabolic syndrome on the outcome of localized RCC, DM as single component of metabolic syndrome had no independent influence on survival (8).

However, there is data that underlines a negative prognostic impact of diabetes in RCC patients. Chen *et al.* could show a worse recurrence-free survival (RFS), CSS and overall survival (OS) for diabetes in another meta-

analysis (9). Patel *et al.* could also show a significant worse survival for DM in patients with T1a kidney cancer (10). In a retrospective analysis of 571 patients with T1 RCC DM was the best predictor for worse long-term OS without influencing RFS or CSS (11).

Nayan *et al.* performed a multi-center propensity score analysis of patients with localized RCC undergoing surgical treatment in 16 centers in Canada between 1989 and 2017 (12). The entire cohort consists of a retrospective cohort (1989–2011) and a prospective cohort (2011–2017) with a median follow-up of 26.6 months. After excluding patients with previous RCC and with missing data, 4,828 patients could be included in the final analysis, 20% of those having DM. There were 901 deaths with 299 from RCC. Diabetic patients were older, had more comorbidities and a higher amount of clear cell carcinoma. After propensity score matching, all characteristics were balanced. No correlation between DM and CSS (HR 1.13, 95% CI: 0.78–1.62) and OS (HR 1.14, 95% CI: 0.94–1.38) after propensity score matching could be found (12).

There is substantial merit in this study. As outlined above, data concerning the prognostic role of DM in RCC is conflicting. Since DM is often accompanied by multiple other diseases such as hypertension, increased BMI and older age, it is very important to exclude this bias when analyzing survival in these patients. Kriegmair *et al.* showed that metabolic syndrome is associated with survival in RCC but not DM as a single factor (8). The strength of the

study at hand is that there is individual retrospective and prospective multi-center patient data of a large cohort over a large time span.

Another interesting finding of the analysis of Nayan *et al.* is that there is a correlation between DM and clear cell histology, which has been described earlier (7) and deserves a closer look on the underlying mechanisms in future studies.

However, there are a few limitations to this study. The median follow-up is rather short and it would be interesting, to determine how diabetes influences long-term survival. Furthermore, there is no information on the severity of the diabetes, i.e., Glucose and HbA1c levels. However, a previous study did not show any correlation with the severity of diabetes (7).

Furthermore, there is no information on the treatment of diabetes in this study. There is data on the effect of the antidiabetic drug metformin on the outcome of RCC (13-15). Metformin might influence prognosis via suppression of the mTOR-pathway (16). Hakimi *et al.* could find no impact on the use of metformin at the time of renal surgery for RCC on RFS and CSS (13). Hamieh *et al.* also did not find an effect of the use of metformin on OS in RCC (14). However, there may be a positive effect of metformin use in metastatic patients treated with sunitinib (15). Thus, the prognostic effect of metformin also remains unclear and seems not to have an independent prognostic effect.

To conclude, in clinical routine diabetic patients should be treated the same as non-diabetic patients concerning radicality and time of treatment.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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