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ORIGINAL PAPER

Metabolic Syndrome Negatively Impacts the Outcome of Localized Renal Cell Carcinoma

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Abstract The aim of this study was to analyze the impact of metabolic syndrome (MetS) on outcome of patients with localized renal cell carcinoma (RCC). A retrospective database was compiled consisting of 646 patients who underwent surgery for localized RCC between 2005 and 2014. A total of 439 patients were eligible for final analysis. For diagnosis of MetS, the WHO criteria of 1998 were used. Median follow-up was 32 months (ranging from 2 to 119). Kaplan-Meier and log-rank analyses were performed to compare patients with and without MetS or its components. Univariate and multivariate logistic regression identified prognostic factors for progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS). In our cohort, 9.8% (n = 43) of patients were diagnosed with MetS. There were no differences between patients with and without MetS regarding clinicopathological parameters with the exception of patients' age (p = 0.002). Kaplan-Meier and log-rank analyses revealed a shorter PFS for patients with MetS (p = 0.018), whereas no differences were found for each of the single components of MetS, namely, diabetes mellitus (DM) (p = 0.332), BMI >30 kg/m^2 (p = 0.753), hypertension (p = 0.451), and hypertriglyceridemia (p = 0.891). Logistic regression identified age (HR = 1.92, p = 0.03), tumor stage (HR = 4.37, p < 0.001), grading (HR = 4.57, p < 0.001), nodal status (HR = 3.73, p = 0.04), surgical margin (HR = 1.96, p = 0.04), concomitant sarcomatoid differentiation (HR = 5.06, p < 0.001), and MetS (HR = 1.98, p = 0.04) as independent factors for PFS. For CSS, only age (HR = 2.62, p = 0.035), tumor stage (HR = 3.06, p < 0.02), and grading (HR = 6.83, p < 0.001) were significant. In conclusion, patients with localized RCC and MetS show significantly reduced PFS and might profit from specific consultation and follow-up.

Keywords Diabetes mellitus · Dyslipidemia · Hypertension · Metabolic syndrome · Obesity · Renal cell carcinoma · Survival

Introduction

Renal cell carcinoma (RCC) is the second most lethal of the urological cancers, with at least 62,700 new cases and more than 14,000 cancer-related deaths in the USA in 2016 [1]. Several verified risk factors for RCC have been identified, including smoking, obesity, and hypertension [2]. Thus, for primary prevention of RCC, the European Association of Urology (EAU) Guidelines on RCC recommend elimination of cigarette smoking and weight reduction [2]. As well as disease prevention, certain prognostic factors can help clinicians to decide on therapy and follow-up of RCC patients. Here, clinical prognostic factors, such as performance status and symptoms, have been included in prognostic systems and nomograms of localized disease [3, 4] and are used in clinical practice.

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RCC has been linked to various metabolic alterations that go far beyond the mutation of the *VHL* gene in clear-cell RCC (ccRCC) [5, 6]. In addition, growing evidence suggests that metabolic syndrome (MetS)—a combination of impaired glucose tolerance, obesity, hypertension, and dyslipidemia—has a strong association with increased RCC risk [7]. Among others, hormonal changes including insulin, insulin-like growth factor (IGF), and leptin have been suggested as underlying mechanisms for this observation [8]. However, the impact of MetS on prognosis of RCC is less investigated and seems to be more complex. Diabetes mellitus (DM) [9] and hypertriglyceridemia [10] have been associated with worse progression-free survival (PFS) and/or cancer-specific survival (CSS)/OS, whereas obesity has been associated with improved RCC outcome [11]. Until now, to our knowledge, no study on the survival outcome of RCC patients with concomitant MetS exists.

Given the diversity of data on oncological outcome of RCC in the presence of various components of MetS and the lack of data on outcome of RCC in patients with the manifestation of MetS, the aim of our work was to assess the effects of MetS on RCC in a comprehensive cohort study.

Patients and Methods

Design and Patients

Clinical data of patients (n = 646) who underwent radical or partial nephrectomy for localized RCC at our institution between 2005 and 2014 were consecutively pooled in a retrospective database. Patients with synchronous bilateral disease (n = 12), previous metachronous RCC (n = 36), or a history of a malignant tumor diagnosis before RCC (n = 159) were excluded. Furthermore, patients were censored at the time of occurrence of a second malignancy or metachronous RCC. Finally, clinicopathological data from 439 patients were analyzed.

MetS was diagnosed according to the WHO criteria of 1998, which defines MetS as impaired glucose tolerance, impaired fasting glucose or DM and/or insulin resistance together with two or more additional components from hypertension (blood pressure ≥ 160/90 mmHg), raised plasma triglycerides (≥150 mg/dl) and/or low HDL cholesterol (<35 mg/dl for men, <39 mg/dl for women), central obesity (body mass index (BMI) >30 kg/m^2 or waist-to-hip ratio >0.9 for males, >0.85 for females), and microalbuminuria [12]. Surgical specimens were evaluated by experienced genitourinary pathologists, according to the current classification of renal tumors [5, 13]. Tumor stage was readjusted to the TNM staging system of 2009 [14]. Preoperative staging of patients included abdominal computed tomography or magnetic resonance imaging, chest imaging, serum chemistry, and bone scans. Brain imaging was performed when indicated by symptoms. None of the patients received (neo)adjuvant therapy. In cases of recurrence and/or metastatic disease, surgical removal, administration of immunotherapy or targeted therapy was used as therapeutic approach. Cause of death was determined by the physician or by chart review. Before inclusion of parameters into the database, local ethics committee approval (No. 2014-811R-MA) was obtained.

Outcome Measurements and Statistical Analysis

Statistical analysis was performed with JMP 11.0 (SAS Institute, Cary, NC, USA). PFS (time to relapse, progression, or death from any cause, whichever occurred first), CSS (time to death due to cancer), and OS (time to death, irrespective of the cause) were the endpoints of the study. For comparison of patient and tumor characteristics of RCC patients with or without MetS or its components, t tests and two-sided exact Fisher tests were used. To illustrate CSS, Kaplan-Meier curves and univariate Cox models were computed. To investigate the role of MetS or its components as independent prognostic factors, we used multivariate Cox models, adjusting for age (<65 years vs. ≥65 years), sex, Fuhrman grade (G1–2 vs. G3–4), tumor stage (pT1–2 vs. pT3–4), nodal stage (pN0 vs. pN+), surgical margin (R0 vs. R+), histology (ccRCC vs. non-ccRCC), and concomitant sarcomatoid differentiation as nominal variables. In the logistic regression models, either the parameter MetS or one single component (hypertension, BMI >30 kg/m^2, hypertriglyceridemia) was regarded. Finally, we checked for multicollinearity between the predictors by calculating the corresponding variance inflation factors and the respective condition number. A p value <0.05 was considered significant.

Results

Patient characteristics of the cohort are shown in Table 1. Median age was 63 years (range 27–88) and male gender was predominant (72.4%, n = 318). Radical and partial nephrectomy balanced each other as the surgical approach for RCC (46.2%, n = 203 and 53.1%, n = 233). Overall, 85 (19.4%) patients had a recurrence (n = 15) and/or metastasis (n = 79) during the follow-up period. Median time to progression was 13.5 months (range 0.5–96). At the time of analysis, 54 patients in the cohort had died and 53.8% (n = 29) of the deaths were cancer related. DM was identified in 74 (16.9%) patients. Altogether, MetS was diagnosed in 43 (9.8%) of the patients, mostly due to the presence of hypertension and a BMI >30 kg/m^2 in addition to DM (n = 26, 5.9%). Only 5 patients had the combination of DM, hypertension, hypertriglyceridemia, and a BMI >30 kg/m^2 (Table 1). The medical treatment details of the patients with MetS and DM are

Table 1 Characteristics of the cohort of 439 patients undergoing surgery for localized renal cell carcinoma

	Number	Percent
Patient		
Age ≥65 years	198	45.1
Male	318	72.4
BMI >30 kg/m^2	104	23.7
Diabetes mellitus (DM)	74	16.9
Hypertension	288	65.6
Metabolic syndrome	43	9.8
DM + hypertension and BMI >30 kg/m^2	26	5.9
DM + hypertension and hypertriglyceridemia	12	2.7
DM + BMI >30 kg/m^2 and hypertriglyceridemia	0	0
DM + Hypertension and hypertriglyceridemia and BMI >30 kg/m^2	5	1.1
Surgery		
Radical nephrectomy	203	46.2
Partial nephrectomy	233	53.8
Tumor stage		
pT1a	165	37.5
pT1b	112	25.5
pT2a	32	7.3
pT2b	11	2.5
pT3a	67	15.2
pT3b	41	9.3
pT3c	0	0
pT4	6	1.3
N+	13	2.9
R+	18	4.1
R+ (RN)[a]	14	6.9
R+ (PN)	4	1.7
Grading		
G1	72	16.4
G2	288	65.6
G3	57	13.0
G4	4	0.9
Concomitant sarcomatoid differentiation	9	2.0
Histology		
Clear cell	310	70.6
Papillary	79	18.0
Chromophobe	28	6.4
Other	9	2.0

[a] Includes 10 pT3b-c cases

Table 2 Medical treatment of the patients with diabetes mellitus and metabolic syndrome

	Metabolic syndrome	Diabetes mellitus
N	43	74
Insulin	8 (18.6)	16 (21.6)
Oral antidiabetics	27 (62.8)	50 (67.6)
Metformin	14 (32.6)	16 (21.6)
Metformin + other oral antidiabetics	8 (18.6)	13 (17.6)
Other oral antidiabetics	5 (11.6)	11 (14.9)
Antilipemics	15 (34.9)	32 (43.2)
Statine	15 (34.9)	29 (39.2)
Statine + other antilipemics	0	2 (2.7)
Other antilipemics	0	1 (1.4)
Antihypertensives	35 (81.4)	56 (75.7)
ACE-inhibitor only	3 (7.0)	8 (10.8)
ACE-inhibitor + other antihypertensives	16 (37.2)	21 (28.4)
Other antihypertensives	14 (32.6)	27 (36.5)
Other		
ASS	16 (37.2)	25 (33.8)
Xanthinoxidase inhibitors	5 (11.6)	7 (9.5)

displayed in Table 2. An insulin-dependent impaired glucose tolerance was found in 8 (18.6%) and 16 (21.6%) patients, and oral antidiabetics were taken by 27 (62.6%) and 50 (67.6%) patients, respectively.

As shown in Table 3, patient and tumor characteristics did not differ between patients with and without MetS except for age. The proportion of patients ≥65 years was significantly higher in the group with MetS (65.1 vs. 40.4%, $p = 0.002$). In addition, patients were stratified by the MetS components DM, hypertension, high BMI, and dyslipidemia. Similar to patients with MetS, diabetic patients (68.9 vs. 40.3%, $p = 0.001$), and patients with hypertension (56.2 vs. 23.8%, $p = 0.001$) were significantly older (age ≥ 65 years). The proportion of male patients was significantly higher in patients with a BMI >30 kg/m^2 (77.0 vs. 61.5%, $p = 0.003$). and the respective patients were more likely to have a clear-cell histology (79.8 vs. 67.7%, $p = 0.016$). In contrast, patients with hypertriglyceridemia had a reduction in the frequency of ccRCC (53.8 vs. 75.6%, $p = 0.006$) and a lower frequency of higher grading (G3-G4) (53.8 vs. 75.6%, $p = 0.006$).

As displayed in Fig. 1a, Kaplan-Meier analysis showed a significantly decreased PFS in patients with MetS. Only 67.8% of the patients with MetS had no disease progression after 35 months compared to 83.1% of the patients without MetS ($p = 0.018$). No differences were observed when stratified for the various components of MetS individually (Fig. 1b–d). Kaplan-Meier analyses for CSS or OS showed no significant differences when stratified to MetS. However, OS was impaired in patients with DM ($p = 0.021$) and improved in patients with BMI >30 kg/m^2 ($p = 0.051$) (Fig. S1 and S2).

To further assess factors involved in disease progression and survival, we performed uni- and multivariate

Table 3 Stratification of selected patient and tumor characteristics regarding the presence of metabolic syndrome or its subconditions

	Metabolic Syndrome		*p*	Diabetes mellitus		*p*	BMI >30 kg/m^2		*p*	Hypertension		*p*	Triglycerides >150 mg/dl		*p*
	Yes	No		Yes	No		Yes	No		Yes	No		Yes	No	
Age ≥ 65 years	65.1	40.4	0.002	68.9	40.3	0.001	41.4	46.0	0.427	56.2	23.8	0.001	35.4	46.6	0.188
Male (%)	62.8	73.7	0.148	68.9	73.6	0.473	77.0	61.5	0.003	71.8	74.8	0.510	72.3	70.0	0.098
T-stage															
pT1–2	62.8	75.6	0.095	67.6	75.6	0.152	78.9	74.4	0.695	71.5	78.9	0.106	81.5	73.3	0.253
T-stage															
pT3–4	37.2	24.4	0.095	32.4	24.4	0.152	23.1	25.6	0.695	28.5	21.1	0.106	18.5	26.7	0.253
Grading (G1–2)	83.7	86.2	0.645	85.1	86.4	0.853	85.6	86.9	0.741	86.8	85.1	0.659	95.4	81.1	**0.006**
Grading (G3–4)	16.3	13.8	0.645	14.9	13.6	0.853	14.4	13.1	0.741	13.2	14.9	0.659	4.6	18.9	0.572
Concomitant sarcomatoid diff.	2.3	2.2	0.999	1.3	2.2	0.999	0	2.6	0.210	2.8	0.7	0.283	3.1	1.1	0.572
ccRCC vs. non-ccRCC	69.7	72.3	0.721	64.9	72.5	0.205	79.8	67.7	**0.016**	71.3	70.7	0.910	53.8	75.6	**0.006**

Bold indicates significant differences ($p < 0.05$)

analyses. As shown in Table 4, MetS was a significant factor in PFS using both uni- and multivariate regression (HR = 2.01, $p = 0.032$ and HR = 1.98, $p = 0.047$). Furthermore, independent factors for PFS were age (HR = 1.92, $p = 0.031$), tumor stage (HR = 4.37, $p < 0.001$), grading (HR = 4.57, $p < 0.001$), surgical margin (HR = 1.96, $p = 0.042$), nodal status (HR = 3.73, $p = 0.038$), and concomitant sarcomatoid differentiation (HR = 5.06, $p = 0.002$). In addition, we performed separate multivariate models including single components (DM, hypertension, high BMI, and hypertriglyceridemia) instead of MetS controlling for the same confounders. Here, no impact of the respective parameters on PFS was observed, although hypertriglyceridemia showed a tendency toward significance in multivariate analysis regarding PFS (HR = 2.84, $p = 0.074$). Respective analyses for CSS and OS are illustrated in Tables S1 and S2. Age (HR = 2.62, $p = 0.035$), tumor stage (HR = 3.06, $p = 0.010$), and grading (HR = 6.83, $p < 0.001$) were independent predictors of CSS, whereas only tumor stage (HR = 2.44, $p = 0.016$) and grading (HR = 4.36, $p < 0.001$) independently influenced OS. Finally, the variance inflation factors for all covariates were sufficiently small with a condition number of 5.4. Hence, any relevant collinearity effects can be ruled out.

Discussion

Our study demonstrates a significantly shorter PFS for RCC patients with MetS, whereas no differences in PFS were found for the single components of MetS when analyzed individually. To our knowledge, no study has yet analyzed the survival outcome of RCC patients who suffer from the complete spectrum of MetS factors. Whereas two previous studies described the association of MetS or its components with pathologic RCC features such as tumor size or grade [15, 16], the question of whether MetS itself influences the prognosis of RCC patients has not been resolved. In contrast, the single components of MetS have already been examined in relation to survival of RCC patients; in a recent meta-analysis, DM was associated with poor OS, CSS, and RFS [9]. However, several publications showed that the relation of DM and worse outcome was not significant, which is in accordance to our results [17–19]. Hypertension was shown to negatively affect cancer-specific and overall mortality in one study [20], whereas other studies revealed a non-significant coherence between hypertension and CSS/OS [21] or even a favorable outcome of RCC patients with a history of hypertension [22]. The only study on dyslipidemia showed that elevated serum triglycerides >250 mg/dl were independently associated with worse PFS [10]. Here, a trend toward significance regarding PFS was seen in our multivariate analysis (HR = 2.84, $p = 0.074$), with a cutoff of ≥150 mg/dl according to the WHO criteria of 1998 [12]. Interestingly, despite being one of the major risk factors for RCC development, numerous studies found obese RCC patients to have improved outcome compared to patients with normal weight [11, 23, 24]. No clear explanation has been brought forward for this paradox. However, some researchers question the "obesity paradox" hypothesis due to possible reverse causation, selection bias, or other forms of bias rather than being a true biological association [25, 26]. Regardless of these possible explanations, our study suggests that the obesity

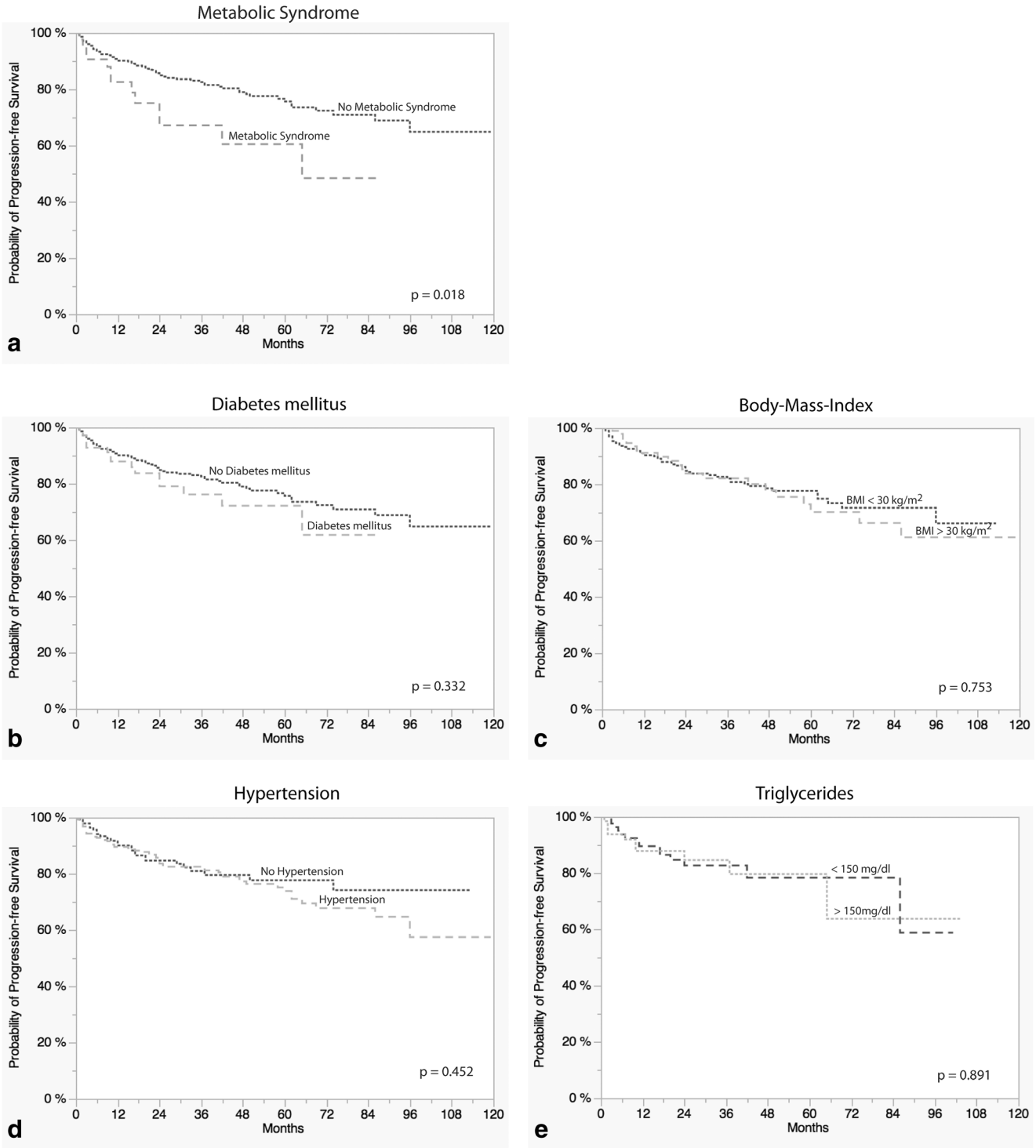

Fig. 1 Kaplan-Meier curves for progression-free survival probabilities stratified by metabolic syndrome (**a**) or its underlying components diabetes mellitus (**b**), high BMI (>30 kg/m2) (**c**), hypertension (**d**), or hypertriglyceridemia (>150 mg/dl) (**e**)

paradox does not implicitly apply and remains questionable especially in the context of the MetS.

Our study found a significant reduction in OS in patients with DM and improved OS in patients with BMI >30 kg/m^2 in the Kaplan-Meier analyses in accordance to previous studies in patients with RCC [9, 11, 23]. However, in contrast to PFS, CSS and OS were not independently influenced by MetS in our study population. This can possibly be explained by the relatively short median follow-up of patients in our study and the limited number of events due to localized disease. Nevertheless, the reduced PFS in patients with MetS in combination with the lack of influence on PFS of the single

Table 4 Uni- and multivariate Cox-regression for progression-free survival

	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*	HR	95%CI	*p*
Progression free survival						
Age (<65 vs. ≥65 years)	1.11	0.33–3.83	0.898	1.92	1.20–3.21	0.031
Sex (male vs. female)	0.85	0.54–1.39	0.524	1.11	0.65–1.81	0.658
T-stadium (pT1–2 vs. p3–4)	8.05	4.88–13.97	<0.001	4.37	2.57–7.43	<0.001
Grade (G1–2 vs. 3–4)	7.49	4.71–11.74	<0.001	4.57	2.62–7.78	<0.001
R status (R0 vs. R+)	3.47	1.8–5.98	<0.002	1.96	1.02–3.53	0.042
Nodal status (pN0 vs. pN+)	6.69	3.23–12.41	<0.001	3.73	1.08–9.83	0.038
Concomitant sarcomatoid differentiation	17.01	7.43–33.96	<0.001	5.06	1.91–12.41	0.002
ccRCC vs. non-ccRCC	1.01	0.61–1.61	0.965	0.9	0.52–1.57	0.722
Metabolic Syndrome	2.01	1.06–3.54	0.032	1.98	1.01–3.61	0.047
Results of separate multivariate models each with inclusion of one single component of metabolic syndrome together with parameters of the original model						
Diabetes mellitus	1.31	0.72–2.24	0.349	1.47	0.78–2.61	0.681
BMI >30 kg/m^2	0.92	0.56–1.55	0.642	0.91	0.52–1.57	0.762
Hypertension	1.19	0.75–1.94	0.449	1.16	0.69–2.00	0.691
Triglycerides >150 mg/dl	1.04	0.44–2.33	0.920	2.84	0.10–1.10	0.074

components of MetS highlights the importance of including the complete picture of MetS in the assessment of RCC patients. Furthermore, this emphasizes the requirement to specially assign comprehensive therapy and follow-up for this patient population. Therapeutic options for patients with MetS in general include lifestyle modifications with diet, exercise, and behavioral therapy, optionally accompanied by a pharmacological approach (e.g. appetite suppressants, antidiabetic agents, antihypertensive drugs, lipid lowering medications) and/or bariatric surgery [27, 28]. In other entities such as breast cancer, a positive effect of diet and weight loss has already been reported [29], and in diabetic RCC patients, cholesterol-lowering pharmacotherapy use was associated with a borderline significant RCC survival benefit [30]. Furthermore, bariatric surgery is associated with a significant reduction of cancer incidence and mortality and this cancer-protective role is strongest for female obesity-related tumors [31]. The question of whether therapeutic intervention for MetS can generate improved survival for RCC patients should be evaluated in randomized prospective trials.

Furthermore, our results emphasize the need for more investigation of the molecular mechanisms underlying our findings. This may not only increase our understanding about RCC biology but might also help to prevent its progression and identify possible targets of new cancer therapies. Various mechanisms have been put forward as explanation for the link between MetS and cancer progression. These include alterations in various hormone-regulated pathways such as insulin signaling or imbalances in the insulin-like growth factor (IGF) axis, and also altered adiponectin, leptin, and estrogen levels [8]. Since agents that modulate these respective hormonal signaling cascades are available, they should be considered as possible treatment strategies in patients with RCC and MetS. For example, in vitro experiments suggest that clinical application of anti-IGF antibodies may be effective in combination with mTOR inhibitors [32]. Besides endocrine disorders, the release of proinflammatory cytokines such as TNF-α or IL-6 by adipose tissue promotes angiogenesis and cell proliferation or hyperglycemia allowing fast tumor growth [8]. In RCC, the situation is even more complex. Its various biological features result in metabolic dysfunctions involving almost every metabolic pathway [6]. Many metabolic abnormalities of RCC can be linked to VHL loss, which causes alterations in pathways including glycolysis and oxidative phosphorylation [33]. Generally, a shift toward a Warburg-effect like state with dependency of anaerobic metabolism can be observed in RCC [34]. In addition, downregulation of AMP-activated kinase and increased acetyl CoA carboxylase is another frequent metabolic change causing increased fatty acid synthesis [35]. Hence, through metabolic reprogramming, RCC cells experience an anaerobic and thus less efficient catabolism with increased anabolism using alternative substrates. Therefore, tumor cells may extensively profit from the oversupply of metabolic substrates found in patients with MetS allowing faster disease progression. Consequently, a combined approach with cutting off the nutrient supply (by dietary or medical approaches e.g. metformin, bariatric surgery) and molecular inhibition of relevant metabolic pathways (e.g., mTOR inhibitors) should be the subject of prospective studies [36, 37]. In

addition, targeting alternative sources of energy or lipogenesis may be promising and should be further investigated [38].

Our work is based on retrospective data with a relatively short median follow-up, which certainly has an impact on our findings regarding CSS and OS. However, our strict exclusion criteria provided a well-selected study cohort and reduced the risk of underlying biases. This work is to date the first study on outcome of localized RCC in the presence of MetS. Our results add to the understanding of RCC prognosis in this highly prevalent situation and will help to assign improved therapies and follow-up for RCC patients with concomitant MetS.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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