



Serum and tissue syndecan-1 levels in renal cell carcinoma

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Background: The proteoglycan syndecan-1 is involved in cell proliferation, adhesion and angiogenesis. It was shown to be involved in cancer progression in different tumor entities. So far, the role of syndecan-1 in renal cell carcinoma (RCC), one of the most common diseases in urologic oncology, was little described. Purpose of the present study was to obtain serum concentrations and tissue expression levels of syndecan-1 in a cohort of patients diagnosed with RCC.

Methods: Clinical and follow-up data were obtained from 413 RCC patients. SDC1 levels were determined in serum samples of 100 patients by enzyme-linked immunosorbent assay and tissue SDC1 expression was measured by immunohistochemistry (IHC) in 343 cases. Results were correlated with clinicopathological and follow-up data.

Results: Five and ten years overall and cancer specific survival were 67% and 56% [overall survival (OS)] and 79% and 76% [cancer-specific survival (CSS)]. In female patients and locally advanced disease ($\geq T3$), tissue SDC1 expression was decreased (female 85.6% *vs.* male 71.1% low tissue SDC1 expression, $P=0.0153$ and $\leq T2$ 70.0% *vs.* $\geq T3$ 87.2% low tissue SDC1 expression, $P=0.0055$) compared to male patients and organ confined disease. Locally advanced tumor stage, presence of lymph node or distant metastases, high Fuhrman grading and clear cell carcinoma as histopathological subtype were independent prognostic factors for reduced CSS and OS. There was no impact of serum SDC1 (sSDC1) serum concentration or SDC1 tissue protein expression on OS, CSS or recurrence free survival (RFS) in uni- or multivariable analysis.

Conclusions: sSDC1 concentration or SDC1 tissue protein expression levels had no influence on patients' prognosis in the present cohort of patients diagnosed with RCC.

Keywords: Renal cell carcinoma (RCC); syndecan; CD138; SDC1; kidney cancer

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Introduction

Renal cell carcinoma (RCC) is one of the most common urologic cancers with an estimated incidence of 4.4/100,000 worldwide (1). The standard treatment of localized

disease is surgery with the option of a nephron sparing approach, depending on tumor size and localization (2). In larger tumors or when the localization of the tumor is unfavorable, radical nephrectomy is recommended. Even

large tumors involving the vascular system can be surgically removed providing beneficial impact for tumor related prognosis. In metastatic disease, multiple pharmacological treatment options are available. Even in metastatic disease, nephrectomy and metastatectomy in selected cases can be performed in order to improve of cancer-specific survival (CSS) (3,4).

Syndecan-1 (SDC1, CD138) is one out of four members of the transmembrane heparan sulfate proteoglycan family (5). In mammals SDC1 is mainly expressed in epithelial and mesenchymal cells. The transmembrane structure implicates its significance in cell-cell- and cell-microenvironment interactions. Syndecans are involved in non-malignant processes like wound healing, inflammation and neovascularization (6) as well as in the development and progression of numerous cancer types (7-10). Various growth factors like tumor necrosis factor alpha (TNF- α), transforming growth factor beta (TGF- β) and basic fibroblast growth factor (bFGF) showed modulatory impact on SDC1 expression (11,12). SDC1 serves as co-receptor for various growth factors such as platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), bFGF and TGF- β (13,14). Substantial cell functions in the premalignant and malignant cell phenotype like altered migration, proliferation and cell motility, reduced adhesion and modified invasion capabilities were shown to be affected by SDC1 (7-10).

The extracellular domain of SDC1 can be shed resulting in a biological active ectodomain (15), which is able to trap the above-mentioned ligands acting as a competitive antagonist to the intact transmembrane protein, thus downregulating downstream receptor cascades (16).

In vitro studies demonstrated that reduced SDC1 expression levels are associated with altered cancer cell growth by modification of the microenvironment in a pro-malignant manner (17). It was shown that low SDC1 protein expression in tumor cells was associated with reduced prognosis and worse tumor related conditions in different solid tumor types including breast, head and neck, colorectal, bladder and prostate cancer as well as cholangiocarcinoma (18-20). On the other hand high SDC1 epithelial expression was associated with favorable outcome in squamous cell lung cancer (21). Furthermore, elevated serum concentration of shed SDC1 was associated with reduced survival in lung, bladder and prostate cancer (22,23).

Little is known about the role of SDC1 in RCC. Therefore, the aim of the present study was to assess

the correlation of serum/tissue levels of SDC1 with clinicopathological parameters and follow-up data in RCC.

We present the following article in accordance with the REMARK reporting checklist (available at <http://dx.doi.org/10.21037/tau-19-787>).

Methods

This retrospective study included 413 patients who underwent rule-based surgical therapy for RCC between 1990 and 2005. Preoperative serum samples were available for 100 patients, while formalin-fixed paraffin embedded (FFPE) tissue samples were available for 343 patients. In 52 cases, both FFPE tissue and serum samples were available. The study was performed according to the Declaration of Helsinki and the institutional ethics committee approved the study protocol (14-5738-BO). The primary endpoint of this study was overall survival (OS) and the secondary endpoints were CSS and recurrence free survival (RFS). All patients were followed from baseline (date of surgery) until December 2016. Clinical and pathological data was obtained from patients' medical reports.

Syndecan serum expression, ELISA

Data on serum SDC1 (sSDC1) serum concentration was available from 100 patients. sSDC1 serum levels were quantified by using a sandwich ELISA (Diacclone CD138, Gene-Probe San Diego CA USA; Cat.Nr.: 950.640.096) according to the manufacturer's instructions.

Histopathological work-up and immunohistochemistry (IHC)

Diagnosis was conducted in line with the WHO classification-scheme (24). FFPE tumor samples were available from 343 RCC patients. A tissue microarray (TMA) was constructed with three cores from each tumor sample after selection and labeling of the corresponding area on a hematoxylin & eosin slide.

Staining procedures for SDC1 were performed as described previously (25). Combined quantitative and qualitative evaluation of IHC results were performed by one pathologist blinded to clinical/follow-up data using a semiquantitative approach. Staining intensity was assessed as strong (3 points), moderate (2 points), weak (1 point) and no immunoreactivity (0 points) of all tumor cells.

Statistical analysis

Data are presented as medians \pm SEM. Statistical significance was assigned at the level of $P < 0.05$. Data lacking normal distribution were analyzed by the non-parametric two-tailed Wilcoxon rank sum test (Mann-Whitney) for paired group comparisons. Proportional distribution of the immunohistochemical results were analyzed using the Fisher's exact test. OS, CSS and RFS analyses were done by uni- and multivariable Cox proportional hazard survival regression analyses and Kaplan-Meier survival analyses with log-rank (Mantel-Cox) test, using the IBM® SPSS® (version 24.0, Chicago, IL, USA) and GraphPad Prism® (version 6, La Jolla, CA, USA). As cut-off for serum expression, the median serum expression value was chosen. In the IHC results, strong and moderate signal was compared to weak and no signal. Perioperative variables with a P value of at least 0.05 in the univariable Cox-regression analyses were included in the multivariable models.

Results

Study population

Median patient's age was 63 years (10–91 years), the male to female ratio was 2:1. Mean follow up time was 90.2 months. Median OS and RFS were 71.5 months (1–293 months) and 63.0 months (1–218 months). Five and 10 years OS were 67.1% and 56.0%, 5 and 10 years CSS were 78.5% and 75.8%. Data on local tumor stage was available from 307 patients (T1 38.4%, $n=118$, T2 23.8%, $n=73$, T3 36.2%, $n=111$ and T4 1.6%, $n=5$). Organ confined tumors ($\leq T2$) were found in 62.2% whereas 37.8% were locally advanced ($\geq T3$). Seven percent of the tumors were lymph node positive and in 9.8% metastatic disease was identified at the initial diagnosis.

Histopathological findings

Clear cell RCC was diagnosed in 78.7% of the tumors, papillary RCC in 16.4%, chromophobe RCC in 4.7% and sarcomatoid de-differentiated RCC in 0.5%. Distribution of Fuhrman nuclear grading 1–4 was 13.5%, 39.2%, 34.2% and 13.2%, respectively.

Beside membranous SDC1-reactivity in tumor cells, SDC1 (CD138) is typically positive in plasma cells and also in the plasma itself (Figure 1).

Correlation of sSDC1 concentration levels with clinicopathological parameters

SDC1 serum concentration levels showed no correlation with patients' age, gender, tumor stage, differentiation (Fuhrman nuclear grade), histological subtype, lymph node and/or metastasis status (Table 1). Median sSDC1 levels showed no difference between benign controls (11.0 ng/mL) and tumor patients (17.6 ng/mL; $P=0.0769$, $n=100$).

Correlation of tissue SDC1 expression with clinicopathological parameters

SDC1 protein expression showed no correlation with patients' age, differentiation (Fuhrman nuclear grade), histological subtype, lymph node and/or metastasis status. In contrast, in female patients the content of low SDC1 protein expression was elevated compared to male patients (85.6% vs. 71.1%, $P=0.0153$, $n=343$). In addition, the content of low SDC1 protein tissue expression was elevated in locally advanced compared to organ confined disease (87.2% in $\geq T3$ vs. 70.0% in $\leq T2$, $P=0.0055$, $n=243$) (Table 1).

In case of 52 patients both, serum and tumor tissue samples were available. We found no correlation between sSDC1 serum levels and tissue immunoreactivity ($P=0.7363$).

Survival analysis

There was no difference in OS, CSS or RFS stratified by serum sSDC1 or SDC1 tissue protein levels (OS serum: $P=0.1996$; OS protein: $P=0.8201$; CSS serum: $P=0.4900$; CSS protein: $P=0.2773$; RFS serum: $P=0.7837$; RFS protein: $P=0.1028$) as shown in Kaplan-Meier survival analysis (Figure 2).

Univariable Cox regression analysis identified locally advanced tumor stage $\geq T3$, positive lymph node and distant metastasis status, Fuhrman grade 3–4 and histological subtype clear-cell carcinoma as significant risk factors for reduced OS (T, N, M, Fuhrman grading $P < 0.001$, clear-cell carcinoma $P=0.005$) and CSS (T, N, M: $P < 0.001$, Fuhrman grading $P=0.001$, clear-cell carcinoma $P=0.011$). Locally advanced disease $\geq T3$ and positive lymph nodes were identified as risk factors for reduced RFS (T: $P=0.003$, N: $P < 0.001$) (Table 2). sSDC1 levels and SDC1 protein tissue expression had no impact on OS or CSS in univariable analyses (sSDC1 serum: OS: $P=0.157$; CSS: 0.311; SDC1 protein: OS: $P=0.787$; CSS: $P=0.280$).

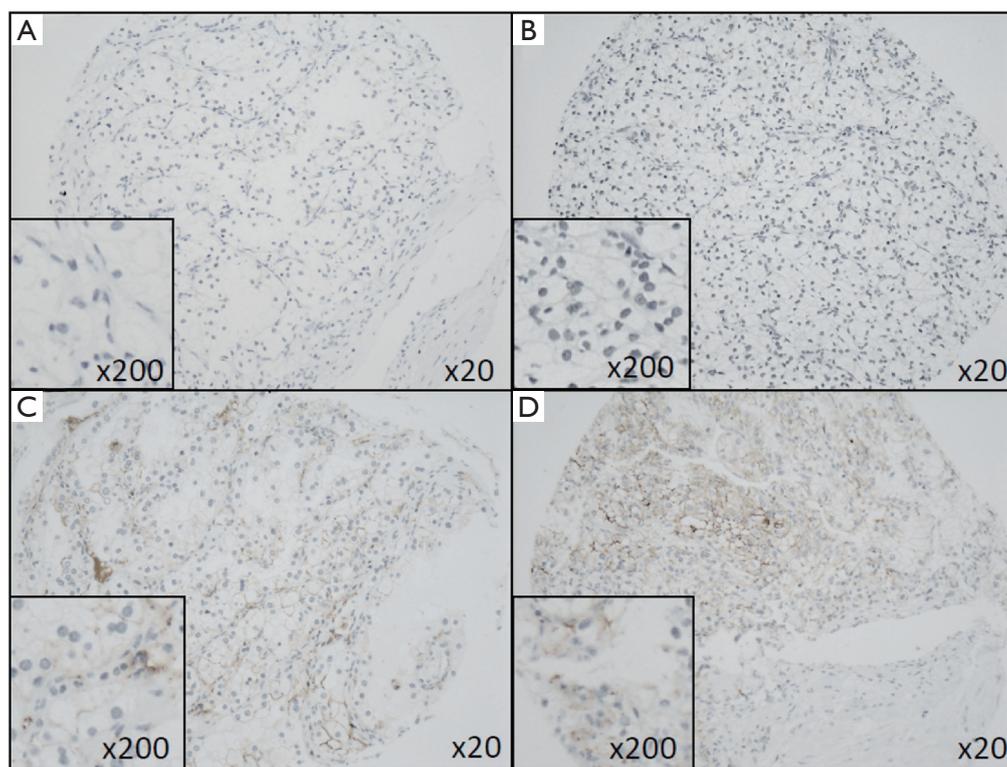


Figure 1 SDC1 (CD138) staining characteristics in RCC cases. In these cases with clear cell histology (original magnification 20 \times), no staining is detectable in (A) while in (B) a faint membranous SDC1-immunopositivity can be noted. In (C) a moderate and in (D) a focal strong SDC1-immunoreactivity can be seen. SDC1-reactivity can be identified in plasma cells and the plasma itself (C). RCC, renal cell carcinoma.

In the multivariable analyses locally advanced tumor stages $\geq T3$, positive lymph node and metastases status were shown to be independent risk factors for reduced OS (T: $P=0.003$, N and M: $P<0.001$) and CSS (T, N and M: $P<0.001$). Additionally, Fuhrman nuclear grading was shown to be an independent risk factor for reduced CSS ($P<0.001$). Locally advanced tumor stages $\geq T3$ and positive lymph node status proved to be independent prognostic factors for reduced RFS (T: $P=0.007$, N: $P=0.001$) (Table 3).

Discussion

Dysregulation of SDC1 expression was frequently observed in various cancers. Both enhanced and decreased tissue expressions were found to be associated with clinicopathological parameters and patients' prognosis in tissue-specific manner (17,18). For hematological tumors,

SDC1 seems to have a significant clinical potential, as its enhanced serum levels were consistently shown to be associated with poor prognosis in chronic lymphocytic leukemia (26), large B-cell lymphoma (27), Hodgkin's lymphoma (28) and multiple myeloma (29). Inconsistent results were shown for some solid tumors especially breast cancer, where dysregulation of SDC1 showed discrepant results. On the one hand elevated protein SDC1 expressions in immunohistochemical analyses showed reduced OS and CSS with reduced cancer related prognosis in advanced breast cancer (30-32). Other studies in contrast could not confirm this observation and showed no impact of SDC1 expression levels in ductal carcinoma of the breast (33) or adverse results with elevated numbers of high grade malignancies and reduced cancer related prognosis in invasive ductal breast cancer patients (34). A meta-analysis of ten studies with 888 colorectal carcinoma patients found decreased SDC1 expression levels in tumor compared

Table 1 SDC1 levels in serum and tissue of RCC patients. Higher amount of low SDC1 tissue expression in tumor tissue was more common in female (85.6%) than in male (71.1%) patients (P=0.0153) and in locally advanced (87.2%) compared to organ confined (70.0%) disease (P=0.0055)

Characteristic	SDC1 serum concentration			SDC1 protein expression (immunohistochemistry)					
	Number (n=100)	Median (range)	P	Number (n=343)	SDC1 low		SDC1 high		P
					n	%	n	%	
Age, year									
≤63	45	18.0 (3.0–82.0)		181	135	74.6	46	25.4	
>63	55	17.0 (2.0–359.0)	0.7604	162	127	78.4	35	21.6	0.7390
Gender									
Male	64	17.6 (2.3–219.5)		218	155	71.1	63	28.9	
Female	36	17.3 (3.1–358.7)	0.6304	125	107	85.6	18	14.4	0.0153
Stage									
Organ confined (T1-T2)	60	19.1 (2.3–191.0)		157	110	70.1	47	29.9	
Locally advanced (T3-4)	39	15.9 (3.9–358.7)	0.1999	86	75	87.2	11	12.8	0.0055
N.A.	1	–		100	–	–	–	–	
Fuhrmann grade									
Low (FG 1-2)	35	14.7 (3.9–191.0)		152	123	80.9	29	19.1	
High (FG 3-4)	13	16.2 (3.1–219.5)	0.5539	143	105	73.4	38	26.6	0.2393
N.A.	52	–		48	–	–	–	–	
Lymph node									
N0	92	16.6 (2.3–358.7)		233	178	76.4	55	23.6	
N+	7	14.7 (7.1–54.5)	0.8059	18	14	77.8	4	22.2	0.8667
N.A.	1	–		92	–	–	–	–	
Metastases									
M0	91	17.4 (2.3–358.7)		223	171	76.7	52	23.3	
M+	8	17.0 (6.1–47.4)	0.9949	28	21	75.0	7	25.0	0.8686
N.A.	1	–		92	–	–	–	–	
Histological subtype									
Clear cell carcinoma	69	16.8 (3.1–219.5)		278	215	77.3	63	22.7	
Non-clear cell carcinoma	26	19.8 (2.3–358.7)	0.6431	65	47	72.3	18	27.7	0.5166
N.A.	5	–		–	–	–	–	–	

RCC, renal cell carcinoma.

to normal tissue as well as in low grade and low stage compared to high grade and high stage disease. However, pooled data analyses revealed no impact for SDC1 on patients' survival (35).

In bladder cancer, decreased SDC1 expressions of tumor

cells and increased SDC1 staining in tumor neighboring stromal cells were associated with progressed tumor stages and poor patients' prognosis (36,37). Additionally, in our previous analysis, increased sSDC1 concentrations were associated with poor CSS in bladder cancer patients (36). In

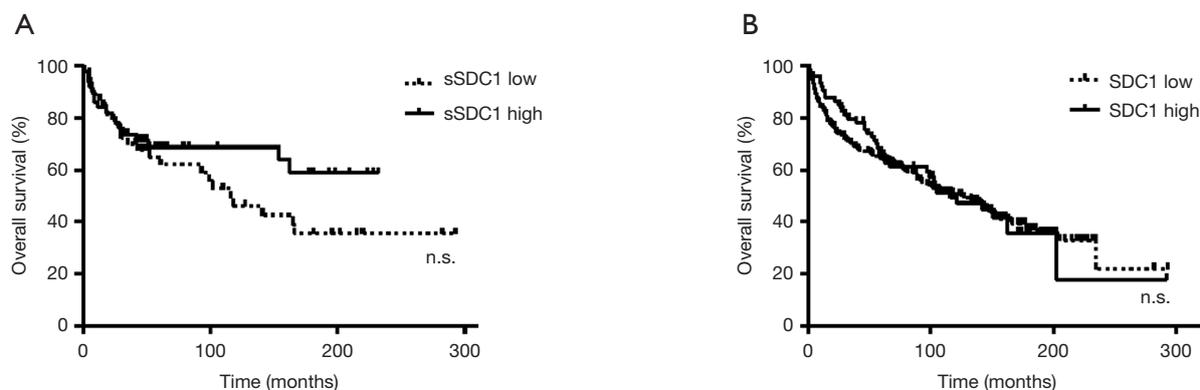


Figure 2 Kaplan-Meier survival curves for overall survival stratified by (A) sSDC1 serum levels and (B) SDC1 tissue expressions. SDC1 serum and tissue levels were not associated with OS, CSS and RFS. OS, overall survival; CSS, cancer-specific survival; RFS, recurrence free survival.

prostate cancer, SDC1 immunoreactivity showed no cancer related prognostic impact (23). Similar to bladder cancer, increased sSDC1 levels were found to be independently associated with poor CSS in advanced cases of prostate cancer, implicating the impact of shed SDC1-ectodomain as a preoperative risk-stratification parameter in prostate cancer (23). This thesis was underlined by the finding that SDC1 shedding seems to be involved in chemotherapy resistance in prostate cancer. In a cohort of 75 patients, increasing sSDC1 levels were associated with a declining therapeutic effect of docetaxel chemotherapy and worse cancer related prognosis (38).

SDC1 (also known as CD138) tissue expression is a well known marker for plasma cells in IHC. In a study with 50 RCC specimens (40 clear cell, 6 papillary and 4 chromophobe) SDC1 protein staining showed membranous immunoreactivity for clear-cell and chromophobe RCC whereas immunoreactivity was located at the basal cytoplasm in papillary RCC. Decreased SDC1 protein expression was associated with increasing nuclear grade. Correlations between SDC1 and tumor stage or histological subtypes could not be identified (39). In addition, our data on a larger number of RCC tumor samples showed a higher proportion of tumors with low SDC1 immunoreactivity in advanced stages of RCC. Interestingly, low SDC1 protein tissue expression was more often found in females compared to male patients.

None of the formerly published studies assessed the correlation between SDC1 and patients' prognosis in RCC. Thus, to best of our knowledge, the present study is

the first to assess this topic. Our data suggest that SDC1 tissue expression has no impact on OS, CSS or RFS in RCC. Similarly, analyzing the soluble SDC1 levels in preoperative serum samples of RCC patients for the first time, we found no correlation between SDC1 concentration and clinicopathological parameters or patients' outcome. In our study, multivariable Cox survival analyses confirmed that clinical parameters including tumor stage, presence of lymph node or distant metastases as well as histopathological features such as histological subtype and Fuhrman nuclear grade are independent prognostic factors for RCC.

The present study has some potential limitations. First, the retrospective character of the study limits its informative value as all data of retrospective investigations should be interpreted critically. Further, a semiquantitative immunohistochemical approach is associated with increased susceptibility of systemic bias as the choice of antibody, staining method and subjective nature of the evaluator can influence the results.

Conclusions

SDC1 tissue protein expression was higher in organ confined disease compared to locally advanced RCC and in males compared to female patients. There was no difference in sSDC1 expression levels stratified to age, gender, local tumor stage, lymph node and metastases status, nuclear grade and histological subtype. No significant impact on patients' prognosis could be identified for serum sSDC1

Table 2 Cox univariable analysis

Characteristic	Overall survival			Cancer specific survival			Recurrence free survival		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age									
≤63 years	ref.		0.074	ref.		0.373	ref.		0.348
>63 years	1.295	0.975–1.719		0.831	0.553–1.249		0.707	0.343–1.457	
Sex									
Male	ref.		0.255	ref.		0.478	ref.		0.794
Female	1.191	0.881–1.610		1.167	0.762–1.785		0.908	0.441–1.871	
T									
Organ confined (T1–T2)	ref.		<0.001	ref.		<0.001	ref.		0.003
Locally advanced (T3–4)	1.815	1.314–2.507		2.961	1.910–4.591		3.011	1.473–6.152	
N									
N–	ref.		<0.001	ref.		<0.001	ref.		<0.001
N+	5.343	3.236–8.821		7.878	4.524–13.719		6.167	2.437–15.606	
M									
M–	ref.		<0.001	ref.		<0.001	ref.		0.159
M+	4.802	3.139–7.346		7.320	4.488–11.940		2.143	0.741–6.197	
Fuhrman grading									
G1–2	ref.		<0.001	ref.		0.001	ref.		0.271
G3–4	1.885	1.380–2.575		2.106	1.365–3.250		1.642	0.679–3.972	
Histological subtype									
Clear cell carcinoma	ref.		0.005	ref.		0.011	ref.		0.119
Non-clear cell carcinoma	0.554	0.366–0.838		0.426	0.221–0.820		0.388	0.118–1.276	
sSDC1 serum									
≤17.6 ng/mL	ref.		0.157	ref.		0.311	ref.		0.526
>17.6 ng/mL	0.638	0.342–1.190		0.618	0.243–1.570		1.351	0.533–3.424	
SDC ICH									
Low	ref.		0.787	ref.		0.280	ref.		0.154
High	0.952	0.665–1.362		0.752	0.448–1.262		1.994	0.772–5.149	

Locally advanced tumor stage ≥T3, positive lymph nodes, metastatic disease, high Fuhrman grade 3–4 and histological confirmed non-clear cell carcinoma proved to be significant risk factors for reduced OS and CSS in univariable Cox regression analyses. Locally advanced tumor stage ≥T3 and positive lymph nodes were shown to be prognostic factors for poor RFS [sSDC1 serum: OS: HR 0.553 (0.287–1.065), P=0.076; CSS: HR 0.636 (0.247–1.643), P=0.350; SDC1 tissue: OS: HR 0.952 (0.665–1.362), P=0.787; CSS: HR 0.752 (0.448–1.262), P=0.280].

expression and SDC1 tissue protein expression in the present study. Locally advanced tumor stage and positive lymph node status were independent prognostic factors for

reduced OS, CSS and RFS. Additionally, positive metastases status was an independent prognostic factor for reduced OS and CSS and elevated nuclear grade for CSS.

Table 3 Cox multivariable analysis

Variable	Overall survival			Cancer specific survival			Recurrence free survival		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
T (organ confined vs. locally advanced)	1.714	1.199–2.452	0.003	2.937	1.843–4.679	<0.001	2.704	1.312–5.571	0.007
N– vs. N+	4.353	2.346–8.079	<0.001	6.272	3.287–11.969	<0.001	4.931	1.939–12.539	0.001
M– vs. M+	2.490	1.505–4.120	<0.001	3.403	1.978–5.854	<0.001	–	–	–
Fuhrman 1/2 vs. 3/4	1.334	0.932–1.909	0.115	1.355	0.851–2.157	<0.001	–	–	–
Histological subtype (clear cell vs. other)	0.610	0.223–1.667	0.336	0.699	0.169–2.892	0.622	–	–	–

Locally advanced tumor stage \geq T3 and positive lymph node status were shown to be independent risk factors for reduced OS, CSS and RFS. Metastatic disease proved to be an independent risk factor for reduced OS and CSS. High Fuhrman nuclear grade 3–4 was shown to be independent prognostic factor for CSS.

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Footnote

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Data Sharing Statement: Available at <http://dx.doi.org/10.21037/tau-19-787>

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Ethical Statement: The authors are 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. Written informed consent was obtained from the patients for publication of this Original Article. The principles of the Helsinki Declaration were followed during the study. Patients were treated according to the Treatment Guidelines of the European Association of Urology and approved by an interdisciplinary tumor board. The Committee for Research of the Faculty of Medicine, University Hospital Essen, University Duisburg-Essen approved the study protocol (ID 14-5738-BO). Confidentiality of the patients' data was guaranteed and all data was anonymized. Future management of the patients is not affected by the present study.

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